OPTIMISATION OF CORNEAL BIOMECHANICAL CHARACTERISTICS IN ORTHOKERATOLOGY FOR MYOPIA CONTROL

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Summary

The rapid increase in myopia prevalence has escalated a wealth of research interest in the prevention mechanisms of myopia. Orthokeratology (ortho-k) is among the most promising approaches. A reluctance to employ this modality has been observed, owing to the selective treatment outcome and the long-term effects to the corneal tissue.

This thesis investigates the attitudes of clinicians towards various myopia control interventions, including ortho-k within a cross-sectional internet-based survey; long-term effects of ortho-k lens wear on corneal biomechanical properties in myopic school-children over a two year period; short-term corneal biomechanical changes over the first 7 nights of lens wear; and the influence of factors (age, ethnicity, eye/body size and nutrition) on corneal biomechanical properties in healthy adults. The aim of this thesis is to aid a deeper understanding of the role of corneal biomechanical properties in ortho-k lens wear, specifically for myopia control.

The findings within the thesis demonstrate that surveyed eye-care practitioners are aware of the scientific findings within the field of myopia control; two thirds would still prescribe single vision glasses to their patients, owing to a lack of clear guidelines and the selective treatment outcome. Results of the ortho-k studies suggest that the corneal biomechanical characteristics are affected by long term ortho-k wear, having a stabilising effect to the components of the anterior eye in progressing myopia. Short term ortho- k lens wear study reveals marked changes in corneal biomechanical parameters within the first seven nights of lens wear. Ortho-k itself and the anterior segment changes observed cannot explain all the variation in treatment response. The final study demonstrates the relationship between corneal biomechanical parameters and nutrition, ocular biometry and body size, suggesting that individual factors, although non-substantially, contribute towards the treatment outcome.

It, is therefore, suggested to establish an internationally acknowledged guideline for myopia control. Further studies should be designed to understand the complex mechanisms underlying ortho-k in myopia control.

Keywords: orthokeratology, myopia control, corneal biomechanics, short and long-term changes, factors.

Dedication

To my grandfather who has taught me so many things, but most importantly the courage to reach for the stars.

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List of abbreviations and acronyms

7MX	7-methylxanthine
AC	Anterior Chamber
AC/A ratio	Accommodative Convergence to Accommodation Ratio
ACD	Anterior Chamber Depth
AL	Axial Length
ANOVA	Analysis of Variance
AS-OCT	Anterior Segment Optical Coherence Tomography
ASL	Anterior Segment Lenght
AUC	Area Under the Curve
BL	Baseline
BMI	Body Mass Index
BOS	Berkley Orthokeratology Study
BOZD	Back Optic Zone Diameter
BVS	Best Vision Sphere
CCT	Central Corneal Thickness
CH	Corneal Hysteresis
CI	Confidence Interval
CLEERE	Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error Study
cm	Centimetres
COMET	Correction for Myopia Evaluation Trial

CRF	Corneal Resistance Factor
D	Dioptre
DA	Deformation Amplitude
Delta K	Corneal Astigmatism Measured by Corneal Topography
Dk	Oxygen Permeability
Dk/t	Oxygen Transmissibility
e	Eccentricity
END	Endothelium
FFQ	Food Frequency Questionnaire
Flat e	Eccentricity of the Flattest Corneal Meridian
Flat K	Keratometry Reading of the Flattest Corneal Meridian
h	Height
HC	Highest Concavity
HM-PRO	High Myopia – Partial Reduction Ortho-k: a 2 Year Randomized Study
ICC	Interclass Correlation Coefficient
IOL	Intraocular Lens
IOP	Intraocular Pressure
IOP_{cc}	Corneal Compensated Intraocular Pressure
IOP_{g}	Goldmann Correlated Intraocular Pressure
kg	Kilograms
K-S test	Kolmogorov–Smirnov Test

LCI	Low Coherence Interferometry
LD	Laser Diode
LE	Left Eye
LT	Crystalline Lens Thickness
M	Month(s)
MC	Myopia Control
MK	Microbial Keratitis
mm	Millimetres
mmHg	Millimetres of Mercury
MRI	Magnetic Resonance Imaging
MSE	Mean Spherical Equivalent
n	Sample Size
NITM	Near Work Induced Transient Myopia
NY	New York
OK	Orthokeratology
ORA	Ocular Response Analyzer
Ortho-K	Orthokeratology
p	Probability
PALs	Progressive Addition Lenses
PCA	Principal Component Analysis
PCI	Partial Coherence Interferometry

PMMA	Polymethylmethacrylate
QS	Quality Score
RE	Right Eye
RGPs	Rigid Gas Permeable Contact Lenses
ROMIO	Retardation of Myopia in Orthokeratology
RPE	Retinal Pigment Epithelium
r_s	Spearman Rank Order Coefficient
SD	Standard Deviation
SNR	Signal to Noise Ratio
Steep e	Eccentricity of the Steepest Corneal Meridian
Steep K	Keratometry Reading of the Steepest Corneal Meridian
SVS	Single Vision Spectacles
S-W test	Shapiro-Wilk Test
TO-SEE	Myopia Control Using Toric Orthokeratology
TR	Tear Reservoir
UK	United Kingdom
USA	United States of America
VA	Visual Acuity
vs	Versus
WS	Waveform Score
YM	Young's Modulus

X^2	Chi Square
Λ	Wavelength
&	And
^{O}	Degrees
Δ	Delta
>	Greater than
≥	Greater than or Equal to
<	Less than
≤	Less than or Equal to
%	Percentage
±	Plus or Minus
^{2}	Square

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Chapter 1. Introduction

1.1 General overview

The rapid increase in myopia prevalence has escalated an amplified interest in this research area (Pan *et el.* 2012). The multifactorial nature of this condition has set challenges for the researchers and clinicians on how to manage this condition more effectively (Flitcroft 2012). Orthokeratology (ortho-k) is among the most promising methods for slowing down myopia progression (Holden *et al.* 2014). However, a reluctance towards this intervention has been seen over the years owing to the individually selective treatment outcome, which frequently has been linked to the corneal response to the treatment (Swarbrick *et al*. 1998; Swarbrick 2006). This chapter introduces the findings on myopia development, progression, myopia control (MC) and, in detail, one of the MC interventions, ortho-k, currently available in the scientific literature. Ortho-k is reviewed particularly in relation to the corneal structure and biomechanical properties. Subsequently this chapter outlines the research rationale and aims for the experimental chapters included in the thesis.

1.2 Myopia

1.2.1 Definition of myopia

Myopia is an ametropic condition in which a mismatch exists between the optical power of the eye and its axial length. The parallel light entering the myopic eye forms a sharp image in front of the retinal plane, resulting in the perception of a blurred visual image.The imbalance may arise from an eye either having a relatively long axial length or increased optical power of one or more of its refractive elements (Rosenfield 2006). Studies indicate that myopia is mostly axial in nature, resulting from the increase in vitreous chamber depth and that the contribution of the cornea is relatively small (Wallman and Adams 1987; Grosvenor and Scott 1994; Grosvenor and Goss 1998; Strang *et al.* 1998; Logan *et al.* 2004). As a result, the far point of an eye, a point conjugating to the fovea when accommodation is fully relaxed, is located in front of the eye. Therefore, it is difficult for one to see distant objects clearly. Visual acuity (VA) in myopia can be restored with the use of

corrective lenses. Normal vision is restored by the introduction of a divergent optical element in front of the eye matching the degree of myopic refractive error (Rabbetts 2007; Sankaridurg and Holden 2014).

1.2.2 Prevalence of myopia

The prevalence of myopia has increased globally in the last few decades reaching epidemic levels in some parts of the world. For example, a study conducted by Vitale *et al.* (2009), comparing the incidence of myopia in 12-54 year old population in the United States of America between 1971-1972 and 1999-2004, showed that the levels of myopia increased from 25% to 46.1% respectively. In a population of Taiwanese school-children (aged 16 to 18 years) an increase in myopia from 74% to 84% between 1983 and 2000 was reported (Lin *et al.* 2004). In a recent study McCullough *et al.* (2016) reported a doubled rate of myopia prevalence amongst white British school children when compared to last 50 years.

Regional differences exist in prevalence of myopia (Pan *et al.* 2012). High myopia prevalence has been associated with the region of South-East Asia. In a study conducted by Lam *et al.* (2004), 87.2% of children between 13 to 15 years of age, attending local schools in Hong Kong, were found to be myopic. Correspondingly, 81% of Taiwanese school children aged 15 years were found to be myopic (Lin *et al.* 2004). In other parts of the world, myopia prevalence is much lower, for example, in teenage children it was found to be 27.4% in Europe (Williams *et al.* 2015) and 29.4% in Australia (French *et al.* 2013); however a clear trend of increase can be seen (Williams *et al.* 2015; Mccullough *et al.* 2016). In the United States of America prevalence of 20% in a group of 13 year old children was reported (Zadnik 1997), whilst in the UK it was reported to be 14.6% of the same age (McCullough *et al.* 2016).

Myopia prevalence varies with age (Grosvenor 1987; Mutti and Zadnik 2000; Pan *et al.* 2012), reaching its peak in the second or third decade of life and decreasing gradually afterwards (Vitale *et al.* 2008; Vitale *et al.* 2009; Williams *et al.* 2015). For example, Williams *et al.* (2015) reported that the prevalence of myopia was 47.2% and 27.5% amongst adults

aged 25 to 29 years and 55-59 years respectively. This may reflect the the increasing prevelance of myopia among younger generations (Williams *et al.* 2015) but, most likely, the well documented hyperopic shift associated with normal aging (Mutti and Zadnik 2000a; Lee *et al.* 2002; Vitale *et al.* 2009). Studies of refractive error in childhood are indicating that myopia is an increasingly prevalent condition thoughrout the school years and is reaching into early adulthood more frequently (Goh and Lam 1994; Kinge *et al.* 2000; Saw *et al.* 2002; Jorge *et al.* 2007)

A systematic review and meta-analysis conducted by Holden and colleagues suggested that half of the world's population (~5 billion people) will be myopic by 2050 (Holden *et al.* 2015; Holden *et al.* 2016). It is estimated that one fifth of these myopic individuals will be highly myopic (≥ -5.00 D) (Holden *et al.* 2015). Currently the rates of high myopia vary grately across the globe. Population based surveys, comparing the rates of high myopia among Australin, American and Wester European adults (≤ 40 years), have reported relatilively low prevelance of 2% to 4% (Kempen *et al.* 2004). The rate is slighty higher in the region of South East Asia. Prevelence of 7% of high myopia amoung adults (40 to 79 years) has been reported (Wong *et al*. 2000). Contrary the prevalence of high myopia within the cohort of Singeporean schoolchildren (age 7-9 years) was found to fall within a rage of 15% to 18% (Saw *et al.* 2005a). The information regarding the rates of high myopia prevalence within American and Europian children is scarce, however trends of increasing rate in myopia have been reported (McCullough *et al.* 2016). Myopia and especially high myopia have been negatively associated with various medical, social and financial factors (Flitcroft, 2012; Foster and Jiang, 2014). The increased risk between high myopia and ocular pathology not only amplifies the menace of vision loss but also has demonstrated a measurable decrease in the quality of life that was comparable with that of patients with keratoconus (Rose *et al.* 2000; Takashima *et al*. 2001). Moreover, the financial implications and the burden on the healthcare system by uncorrected distance vision, mostly caused by myopia, have been estimated to be over 200 billion US dollars per annum (Smith *et al*. 2009). These factors have affected the overall attitude towards myopia as not a simple

refractive inconvenience that can be easly corrected with spectacle lenses (Flitcroft, 2012; Holden *et. al* 2014).

1.2.3 Emmetropisation

Emmetropsation is described as the diminishment of neonatal refractive error (Troilo 1992). It is postulated that both active and passive processes drive the process of emmetropisation and subsequently preserve it (Troilo 1992; Brown *et al.* 1999). Passive emmetropisation is associated with a normal eye growth (eye enlargement) whilst active emmetropisation is dependent on a visual feedback (Troilo 1992; Brown *et al.* 1999).

At birth, refractive error is typically hyperopic (Banks 1980; Wood *et al.* 1995; Kuo *et al.* 2003; Varughese *et al.* 2005) and generally falls within a range of +2.00 ± 2.00 D (Banks 1980) or +2.40 ± 2.62 D (Varughese *et al.* 2005). Approximately 50% of the new-born population have a spherical refractive error (>2.50 D) (Cook and Glasscock 1951). During the first year of life rapid eye growth occurs and a decline in hyperopia to a mean level of +1.50 D is observed (Saunders *et al.* 1995; Wood *et al.* 1995). This phase is associated with significant changes in axial length (Mutti *et al.* 2005) and corneal (Inagaki 1986; Mutti *et al.* 2005) and crystalline lens (Mutti *et al.* 2005) power. The axial elongination is is mostly associated with the the enlargement of the vitreous chamber and to a lesser exten with the growth in the anterior chamber (Mutti *et al.* 2005). Crystalline lens thins significantly during this period and flattening is observed in both anterior and posterior lens radii (Mutti *et al.* 2005). Simultaneously an increase in the equivalent crystalline lens refractive index can be seen, which in turn results in a large decrease in the power of the crystalline lens (Mutti *et al.* 2005). It is estimated that at this stage crystalline lens decreseases in power three times as much the cornea does (Mutti *et al.* 2005). The lens streching in the equatorial plane during the rapid phase of emmetropisation has been suggested to be a vital factor for maintaining emmetropia in a growing eye (Mutti 2010). Mutti *et al.* (2013) demonstrated that around one year before myopia onset crystalline lens lost its compensatory mechanism for maintainnig emmetropisation – changing it power in tandem with axial elongination.

Crystalline lens ceased thinning, flattening and loosing power in a cohort of 732 ethnically diverse schoolchildren (6-14 years of age) (Mutti *et al*. 2013).

The process of emmetropisation continues at slower rate until six years of age, when emmetropia is commonly achieved (Flitcroft 2014). Morgan *et al.* (2010), however, suggests that mild hyperopia instead of emmetropia is the preferred end point of emmetropisation. In the study, gathering data from children (n=38811; age 5 to 15 years) in eight study sites around the globe to provide a representative population-based sample, Morgan and colleagues (2010) demonstrated that cohorts with a low rate of myopia prevalence, tend to remain mildly hypermetropoc even at age of fifteen. In a recent study Zadnik *et al.* (2015) proposed a model for prediction of juvenile-onset myopia and identified cycloplegic spherical equivalent (SE) refractive error as the best single predictor for future myopia development. Refractive error of <+0.75 D of hyperopia at age of 6 years is associated with an increased risk of myopia development (Zadnik *et al.* 2015).

After six years of age a divergent pattern in the distribution of human refractive error can be seen (Flitcroft 2014). A mean refraction of -0.50 ± 0.67 D was observed in a group of 7 to 9-year-old Chinese children (n=1043) (Saw *et al.* 2004a) and +0.17 ± 1.00 D in 7 year old Taiwanese children (Lin *et al.* 2004), whilst by the age of 11 it was observed to be –1.20 ± 1.93 D in Taiwanese school-children (Lin *et al.* 2004). Whereas in the United Kingdom it was +1.23 D (lying in the range of +0.97 to +1.49 D) amongst 6 to 7 years children and +0.45 (laying in the range of +0.21 to +0.69 D) amongst 12 to 13 year old children of European ethnicity (Logan *et al.* 2011).

1.2.4 Mechanisms of myopia development

The complex multifactorial nature of myopia has been widely discussed (Mutti *et al.* 2002; Morgan and Rose 2005; Rose, Morgan, Smith*, et al.* 2008a; Flitcroft 2014; Goldschmidt and Jacobsen 2014). However, the exact mechanisms driving the disproportional relationship between the axial length and dioptric power of the eye, are not yet fully understood.

1.2.4.1 Genetic factors

As emphasised in the reviews by Saw *et al.* (2000) and Goldschmidt and Jacobsen (2014), genetics play a role in myopia development. Twin studies have revealed a high heritability of refractive error (Lyhne *et al.* 2001) with greater prevalence among monozygotic twins than dizygotic twins (Hammond *et al.* 2001; Dirani *et al.* 2006)

The role of parental myopia has been established. Pacella *et al.* (1999) reported that the risk of myopia development in a child with two myopic parents is 5.09 times higher than it would be for a child with non-myopic parents. Mutti *et al.* (2002) reported odds ratios of 3.31 and 7.29 for a child to develop myopia in cases where one or both parents were myopic respectively. Jones-Jordan *et al.* (2010) conducted a discrete-time survival model analysis in a cohort of 1854 non-myopic first graders and followed them until the eighth grade. The risk of a child becoming myopic based on parental myopia and cycloplegic autorefraction was evaluated. Authors concluded that refractive error at first grade level and the number of myopic parents can be used as a predictor for myopia development. However, sensitivity of these factors was reported to be low and other factors, which might be more reliable, should be taken into an account. In another study Jones-Jordan and colleagues (2014) reported results of the effect of near work, outdoor activity and myopia in a cohort of 700 families. Heredity was the strongest contributor to the similarities in refractive error between siblings.

More than 40 genetic loci linked to myopia have been identified (Paluru *et al.* 2003; Hammond *et al.* 2004; Zhang *et al.* 2006; Zadnik *et al.* 2015). Autosomal dominant (AD) high myopia, for example, has been associated with 18p, 12q and 17q, with MYP3 locus on 12q accounting for approximately 25% of cases in the United Kingdom (Farbrother *et al.* 2004). Furthermore, 9 loci affecting the axial length of an eye solely, as well as overall refractive error of an eye have been identified, emphasising the complex genetic nature of myopia (Cheng *et al.* 2013).

1.2.4.2 Educational level and near work

An association between parental educational level/occupation and myopia prevalence was reported by the COMET study group: higher levels of education were associated with higher myopia prevalence (Gwiazda *et al.* 2011a).

Mutti *et al.* (2002) investigated various factors associated with myopia development. Myopic children demonstrated a higher ability in reading tests. Similarly, correlations between intelligence and myopia development have been drawn by Ashton (1985) and Saw and co-workers (Saw *et al.* 2001; Saw *et al.* 2004a).

Mutti *et al.* (2002) reported an association between near work and myopia, however, heredity was found to be more pronounced risk factor. The link between near work and myopia has also been investigated by Ip *et al.* (2008) and, similar to the findings of Mutti *et al.* (2002), a vague correlation was drawn between time children spent engaged in near work related activities and myopia. Nevertheless, the intensity of the near work was proposed as a relevant factor, especially when comparing children of Caucasian and Asian ethnicity. This difference in ethnicity has suggested that the diverse mode of education encountered among different countries is a possible triggering factor for myopia development (Ip *et al.* 2008). A study conducted by Lam *et al.* (2004) compared the prevalence of myopia among two groups of schoolchildren in Hong Kong: one attending local schools, where academic activities are more demanding and near work intensive, and the other attending international schools, which are less demanding and near work intensive. The age of schoolchildren (13 to 15 years) was selected so that children would have been enrolled in the educational system long enough for the influence of each mode of education to be evaluated. Higher prevalence of myopia was observed amongst local schoolchildren rather than international schoolchildren (87.2% and 62% respectively). However, when ethnicity was taken into an account, higher rates of myopia were observed amongst Chinese schoolchildren regardless of the type of school they attended. When the lifestyle and academic demands of Australian and Singaporean schoolchildren of Chinese

ethnicity (age 6 to 7 years) were compared, higher rates of myopia were found in Singaporean than Australian children (29.1% compared to 3.3%) (Rose *et al.* 2008a). Interestingly, the Australian schoolchildren spent more time engaged in near work-related activities outside the school, but more time outdoors, compared to the other group. However, Singaporean children are enrolled in the educational system at a younger age, hence, being exposed to close-up work for a longer period in total (Rose *et al.* 2008a). An association between near work and myopia was also found in a recent study conducted by Li *et al.* (2015). Authors reported that a close reading distance and prolonged periods of reading were correlated with myopia in a large cohort (n=1770) of children (age 10 to 15 years) of Chinese ethnicity (Li *et al.* 2015).

Jones-Jordan *et al.* (2012) also studied the impact of near work on refractive error development and annual myopia progression in a large cohort of ethnically diverse myopic children as a part of CLEERE Study and found a small clinical effect on annual myopia progression related to the near work. Moreover, when the effect of near work on myopia progression was investigated amongst siblings from 700 families (n=1522), no significant effect was found and heritability was the main contributor (Jones-Jordan *et al.* 2014).

However, overall a recen meta-analysis by Huang *et al.* (2015) suggests that near work activity is a relevant factor in myopia development and progression and, based on the evidence available, should be considered a moderately important to outcome (level B) – risk factor for myopia development. Meta-analysis demonstrated that schoolchildren who engage in near work activities significantly more, had an 80% higher risk of developimg myopia at some point of their lives (Huang *et al.* 2015). Moreover, the association between near work and myopia indicated a 2% increased odds of myopia per additional dioptre-hour of time spent engaging in near work related activities per week (Huang *et al.* 2015).

1.2.4.3 Accommodative factors: lag of accommodation, AC/A ratio and the role of esophoria

Reduction in accommodative response to various stimuli have been noted in myopic individuals, inducing blur during near work stimulating axial growth (McBrien and Millodot 1986; Gwiazda *et al.* 1993; Gwiazda *et al.* 1999; Mutti *et al.* 2000a). Woodman *et al.* (2010) demonstrated that prolonged accommodative tasks induce transient changes in axial length (AL) in young myopes and emmetropes, causing a temporary shift towards a more myopic refraction. Mallen *et al*. (2006) reported an increase of 0.058 ± 0.037 mm and 0.037 ± 0.027 mm in AL in young early-onset myopes and emmetropes matched for age and amplitude of accommodation for a 6.00 D accommodative demand, respectively. Later studies supported findings by Mallen *et al.* (2006). In a similar study set-up Read *et al.* (2010) demonstrated mean axial elongation of 0.023 ± 0.023 mm in a group of young myopes and 0.025 ± 0.015 mm in emmetropes. Results published by Woodman *et al.* (2010) also sustained the magnitude of axial elongation reported previously with a mean increase in AL of 0.027 ± 0.021 mm amongst early-onset myopes and 0.010 ± 0.015 mm amongst emmetropes, respectively. The slight variations between the results might have arisen from the differences in study populations (myopia onset and age range of the cohort), instrumentation used and corrections applied for the changes in crystalline lens thickness (Read *et al.* 2010; Woodman *et al.* 2010).

Ciuffreda and Wallis (1998) introduced the term ‘near work induced transient myopia’ (NITM) and showed that myopes exhibit an accommodative inaccuracy (0.35 D), when shifting focus to distant object after a prolonged period of near work. NITM has also been observed in other studies (Ferree *et al.* 1931; Vera-Diaz *et al.* 2002; Wolffsohn *et al.* 2003; Vasudevan and Ciuffreda 2008). In addition, the response of the vergence system is altered in both myopic children (Gwiazda *et al.* 1999) and myopic adults (Jiang 1995), when compared to emmetropes. Gwiazda *et al.* (1999), for example, reported a higher accommodative convergence to accommodation ratio (AC/A ratio) and an increased amount of accommodative convergence in myopic children, supporting the assumption that

myopic children accommodate excessively during prolonged near vision tasks. This subsequently triggers an elevated accommodative convergence response. High AC/A ratios have been associated with early stages of myopia development, however these tend to stabilise and reach similar values to those of emmetropic individuals in later stages of myopia onset (Gwiazda *et al.* 1993; Gwiazda *et al.* 1995; Gwiazda *et al.* 1999). Furthermore, a shift towards a more esophoric state at near has been reported among myopic children, as well as the tendency to under-accommodate if esophoria is present (Gwiazda *et al.* 1993; Gwiazda *et al.* 1995; Gwiazda *et al.* 1999). Therefore, it is speculated that esophoric myopes must relax their accommodation to reduce excessive accommodative convergence in order to maintain single binocular vision (Gwiazda *et al.* 1999). Alterations in accommodation and vergence response can be observed as early as 2 years before the onset of myopia (Gwiazda *et al.* 2005).

1.2.4.4 Outdoor activity and lighting levels

Studies reviewing the influence of lifestyle on myopia development have highlighted the importance of outdoor activities (Jones *et al.* 2007; Rose*, et al.* 2008a; Rose *et al.* 2008b). Jones *et al.* (2007) investigated outdoor activity, in tandem with the history of parental myopia, in 514 schoolchildren and concluded that lower amounts of outdoor activity increased the risk of child becoming myopic in the eighth grade (the mean estimated age of the commencement of myopia onset was 11.4 ± 1.5 years), if a child had two myopic parents rather than none or one myopic parent. Moreover, the chances of developing myopia decreased in children who were highly engaged in outdoor activities and had no history of parental myopia in comparison to those with both parents being myopic (Jones *et al.* 2007).

Subsequently Rose *et al.* (2008a) compared the influence of time spent outdoors between Australian and Singaporean schoolchildren of Chinese ethnicity (n=124 and n=628 respectively). On average, Singaporean schoolchildren were four times less engaged in outdoor and sports activities than Australian schoolchildren of Chinese ethnicity (3.05 hours

per week compared to 13.75 hours per week respectively), with the myopia prevalence being almost ten times higher in the Singaporean schoolchildren. It was speculated that the higher levels of educational pressure in Singapore leads to prolonged near work and, in combination with a reduction in time spent outdoors, could trigger myopia development (Rose *et al.* 2008a).

Furthermore, Rose *et al.* (2008b) investigated the influence of outdoor activity in groups of 6 and 12-year-old Australian schoolchildren (n=1765 and n=2367 respectively) over a period of 2 years, as a part of Sydney Myopia study. Rose *et al.* (2008b) reported lower rates of myopia in children, who were more engaged in outdoor activities and did less near work, than in children, who spent more time indoors engaged in near work-related activities. Authors speculated that the higher luminance levels of outdoors compared to those of indoors, trigger biochemical processes, which might contribute to more hyperopic refraction (Rose *et. al* 2008b). Also, in higher luminance pupil diameter is smaller and, hence, ensures a greater depth of focus (Rose *et. al* 2008b).

The findings of Rose and colleagues (2008a, 2008b) are supported by a similar study investigating the associations between outdoor activity and myopia development in a population of Singaporean children and adolescents (11 to 20 years of age) (Dirani *et al.* 2009). Guggenheim *et al.* (2012) investigated the influence of time spent outdoors and physical activity in 13,988 English school-children living in the former Avon health authority over a period of 7 years. The results supported the hypothesis that increased time spent outdoors has a protective effect on myopia development. The amount of time spent outdoors was found to be independent of the level of physical activity. A study following a cohort of Chinese schoolchildren (n=382, mean age 6.3 ± 0.4 years) further supported the hypothesis of the protective effects of increased outdoor activity (Guo *et al.* 2017).

Urbanisation, although not directly, has been linked to myopia development and, when studied in an association with outdoor activities, has been shown to be a risk factor as children in urban areas spend significantly less time outdoors and more time engaged in

near work-related indoor activities compared to children in the rural areas who spend more time outdoors (Wu *et al.* 2010; Guo *et al.* 2013).

Jones-Jordan and colleagues from the CLEERE Study Group on several occasions have demonstrated that the protective effectt of outdoor activities after the onset of myopia is negligible. In 2012 Jones-Jordan et al. studied the association between myopia progression and time spent outdoors and in various visual activities in a cohort of 835 ethnicaly diverse myopic children (6 to 14 years of age at baseline). The clinical effect on myopia progression was found to be small and did not reduce annual myopia progression. Furthermore Jones-Jordan *et al.* (2014) investigated the contribution of near work and outdoor activity towards refrective development in a cohort of 700 families and 1522 children (mean age 13.3 ± 0.90 years at the last visit) of different ethnical over a period of 20 years (1989-2009). Although outdoor activity and other shared environmental factors did have an impact on the myopia progression among the siblings, it was slight and major effect was attributed to genetic factors (Jones-Jordan *et al.* 2014). This may suggest that time spent outdoors may not exert a general inhibitory effect on ocular growth and the protective mechanisms before and after the myopia onset could be driven by different underlaying processes (Jones-Jordan *et al.* 2012).

A recent meta-analysis conducted by Xiong *et al.* (2017) also after systematically analysing the available information on time spent outdoors and its association with myopia, supported the hypothesis proposed by Jones-Jordan and colleagues (2012). The protective effect of outdoor activities could be observed before/at onset of myopia but not for myopia progression. Likewise, increased time spent outdoors had a positive effect towards incident myopia but not myopia progression (Xiong *et al.* 2017). Nevertheless, the pooled data demonstrated that time spent outdoors prevents a shift towards myopic shift in refraction in the entire study population (Xiong *et al.* 2017).

The exact mechanism behind the protective effect of outdoor activities is still uncertain, however, animal studies support the assumptions drawn by Rose *et al.* (2008b) discussed

previously. Moreover, myopia progression is shown to be slower during the summer months compared to with winter months, emphasising the importance of lighting levels (Fulk *et al.* 2002; Donovan *et al.* 2012; Gwiazda *et al.* 2014). A study conducted by Ashby *et al.* (2009) using chicks as an experimental model suggests that natural daylight conditions (approximately 30 000 lx) are correlated with shorter axial lengths and more hyperopic refractions than, for example, exposure to normal laboratory lightning (approximately 500 lx). Cohen *et al.* (2011) and Smith *et al.* (2012) have also demonstrated the protective nature of high luminance levels on myopia development, using chick and rhesus monkey models respectively. Moreover, Ashby and Schaeffel (2010) demonstrated the possible involvement of dopamine, a light-dependant retinal neuro-modulator in the retardation of myopia development, by exposing chicks with induced myopia to different ambient lightning levels and then injecting them with spiperone, a dopamine antagonist, which overcomes the protective nature of higher ambient light levels and, once again, enhances the progression of deprivation myopia.

Zadnik *et al.* (2000) investigated the effects of night-time nursery light effects on myopia progression in a CLEERE study cohort of ethnically diverse 1200 schoolchildren. Authors concluded that night-time lighting is not a risk factor for myopia development (Zadnik *et al.* 2000). Simiilar findings were reported by Gwiazda *et al.* (2000) and no influene of light cycles were found to influence myopia development and ocular growth.

Lower levels of vitamin D have been associated with myopia development (Mutti *et al.* 2011a; Mutti and Marks 2011; Yazar *et al.* 2014; Gardner *et al.* 2015). Myopic individuals have notably significantly lower concentrations of 25(OH)D3 in their blood compared to non-myopes. Contrary Williams *et al.* (2016) did not find lower levels of serum vitamin D_3 in a cohort of 3168 myopic individuals (age 72.4 ± 5.0 years) of Southern and Northen European background. Nevertheless, study findings supported the protective effect of UVB exposure during lifetime, especially between 14 to 29 years of age, and myopia development (Williams *et al.* 2016). Therefore, more studies are required to investigate the relationship between vitamin D levels and sun exposure as the two factors are closely linked and could

potentially aid in designing a more effectibve intervention for slowing down myopia progression (Yazar *et al.* 2014; Williams *et al.* 2016).

1.2.4.5 The role of the retinal periphery in myopia development

The aforementioned genetic and environmental factors highlight the multifaceted nature of myopia; however, they do not fully address the issue of its unknown underlying mechanism. Studies using animal models have demonstrated the influence of optical blur on the refractive development of the eye and the importance of visual feedback and stimulated a vast interest in human ocular development (Smith *et al.* 1994; Smith 1998; Smith and Hung 1999; Smith *et al.* 1999; Stone and Flitcroft 2004). Deprivation of form vision (form deprivation), which is achieved, for example, by eyelid suture or rearing vision with translucent occluders, in early stages of life, stimulates rapid axial eye growth and, hence, myopia progression (Wiesel and Raviola 1977; Wallman *et al.* 1978; Smith *et al.* 1987). Once the form deprivation is ceased, the eye experiences myopic defocus, which is then overcome by slowing the growth of vitreous chamber (Wallman and Adams 1987).

Optical defocus in animal models most commonly is induced by spectacle or contact lenses (Wildsoet and Wallman 1995; Smith *et al.* 1994; Smith *et al*. 1999; Benavent-Perez *et al.* 2012). For example myopic defocus, imposed by positive spectacle lenses in chicks, is eliminated by the thickening of the choroid which moves the retina closer to the image plane, as demonstrated by Wildsoet and Wallman (1995). Whereas hyperopic defocus, induced by negative lenses, is compensated for by axial elongation (Wildsoet and Wallman 1995). Subsequent recovery, following the removal of the spectacle lens, includes changes in chick choroidal thickness and normalisation of their eye's axial length (Wildsoet and Wallman 1995). Most of the animal studies and also human studies conducted until recently have been focused on the central part of retina and fovea, neglecting most of the retina, the periphery (Stone and Flitcroft 2004; Wallman and Winawer 2004).

1.2.4.5.1 Animal studies

A series of animal studies have been conducted to investigate the possible involvement of the peripheral retina in the development of myopic refractive error (Smith *et al.* 2005; Smith *et al.* 2007; Huang *et al.* 2009; Smith *et al.* 2009a; Smith *et al.* 2009b). Smith *et al.* (2005) restricted peripheral vision using specially designed binocular goggles with a small central aperture in 12 infant monkeys for a year. It was observed that the absence of peripheral vision disrupted the emmetropisation process. A myopic shift in refraction was noted in the experimental group when compared to the control group (which did not undergo treatment; +0.03 ± 2.39 D vs +2.39 ± 0.92 D respectively). The vitreous chamber was elongated in the treatment group compared to the control group; therefore, it was assumed that the deprivation of peripheral vision accelerates the rate of axial growth. When unrestricted vision was re-introduced after the goggle rearing period, a recovery and shift towards a refractive state laying within the normal range was observed, even if the fovea was ablated (Smith *et al.* 2005). However, Schippert and Schaeffel (2006) contradicted these findings by demonstrating that the restriction of peripheral vision does not necessarily result in axial growth in chicks. The authors hypothesised that the field of restricted vision could be linked to the myopisation and that they restricted too little of the peripheral vision. Schippert and Schaeffel speculated that, if only 2 to 3 mm of central vision had been left unrestricted, a shift towards myopic refraction could have resulted (Schippert and Schaeffel 2006).

In a landmark study, Smith and colleagues demonstrated that the fovea is not required for normal eye growth (Smith *et al.* 2007). Monocular foveal ablation in 13 young rhesus monkeys was induced by photocoagulation. Subsequently, 3 monkeys were chosen as control animals and were allowed an unrestricted vision, whilst the remaining monkeys were fitted with form-deprivation goggles. Monocular foveal ablation had no effect on the process of emmetropisation in the control monkeys as the refractive error was within the normal range in both eyes. Whereas in the treatment group, where ablation was combined with form deprivation, intraocular differences between the refractive status of eyes were

observed, and foveal ablation did not prevent the development of form deprivation myopia (Smith *et al.* 2007).

More recently, Smith *et al.* (2009a) demonstrated that the retinal mechanisms contributing towards myopia development are regionally selective, using a monkey model. When monocular form deprivation of the nasal visual field of 9 infant monkeys was introduced, axial growth in the treated portion of the visual field was observed in 6 monkeys (Smith, Huang*, et al.* 2009). This selective involvement of local retinal regions has also been observed in chicks (Wallman *et al.* 1987; Diether and Schaeffel 1997). Wallman *et al.* (1987) reported a selective development of form deprivation myopia in chicks, when part or all of the retina was restricted with white translucent occluders. The position of the myopia induced corresponded to the retinal region deprived, i.e. temporal, nasal or the whole retina, whilst the unrestricted area remained emmetropic or nearly emmetropic (Wallman *et al.* 1987).

Smith and colleagues (2009b), supported their previous findings (2007) pertaining to peripheral retinal involvement in the process of myopia development, using a monkey model (Smith, *et al.* 2009b). Peripheral hyperopic defocus was induced in 8 monkeys, using -3.00 D lenses with 6.00 mm central apertures, allowing binocular vision. Simultaneously, 6 monkeys underwent monocular foveal ablation with photocoagulation and were subsequently fitted with -3.00 D lenses that induced hyperopic defocus across the entire visual field. Twenty-four monkeys were used as controls and were allowed unrestricted vision, whilst 4 monkeys wore plano lenses binocularly from 3 weeks till approximately 5 months of age. At the end of the rearing period, the control monkeys were hyperopic (mean refraction +2.57 ± 1.07 D), whilst monkeys in both experimental groups developed myopia. The mean refraction in the -3.00 D aperture group was +0.36 ± 2.69 D compared to +0.46 ± 2.49 D in the foveal ablation/-3.00 D full-field hyperopic defocus group. Although he standard deviation are large and refractive error is scattered in both groups and, therefore, should be viewed cautiously, Smith *et al.* (2009b) concluded that peripheral hyperopic defocus can trigger myopia development, either in the presence or absence of clear central

vision. The authors also proposed the possibility of spatial distribution across all the retina and the mechanisms underlying form deprivation are alike, because two different rearing strategies (deprivation with -3.00 D aperture lenses and combination of -3.00 D lenses and foveal ablation with photocoagulation respectively) gave similar results (Smith*, et al.* 2009b).

Huang *et al.* (2009) reported that monkeys undergoing form deprivation demonstrated a relatively hyperopic peripheral refraction. Ten rhesus monkeys were fitted with diffuser lenses to impose monocular form deprivation. The fellow eye of the form deprived monkeys was used as a control. An additional 6 monkeys were allowed unrestricted vision and were also used as controls. After the rearing period 7 monkeys in experimental group developed myopia in the form deprived eye. Six of form deprived monkeys developed a relative hyperopic refraction in the treated eye, whilst in the control eye it was similar to the central refraction. Two of the form deprived monkeys developed relative hyperopia in the treated eye and peripheral refraction tended to become less hyperopic with the increasing eccentricity.

Study conducted by Benavente-Perez and colleagues (2012) using a marmoset model to investigate the effect of multizone contact lenses, which imposed a hyperopic and myopic defocus simultaneously, demonstrated the possible benefit of such intervention for myopia control and possible regulatory effect of myopia development. Authors fitted 10 marmosets with specifically designed multifzone contact lenses, consisting of six concentring rings of opposite power (+5.00 D and -5.00 D), in one eye and plano contact lens in the contralateralr eye, using it as a control. The simultaneous imposal of myopic and hyperopic defocus resulted in more hyperopic refraction and ocular growth in treated eyes compared to the control ones. The mean hyperopic shift (MSE of treated eyes – MSE of control eyes) was + 1.44 ± 0.45 D (Benavent-Perez *et al.* 2012). Three of six treated animals, one of which were myopic at baseline, and that had myopia in both eyes at the end of the study period, were less myopic in their treated eye compared to the control one (Benavent-Perez *et al.* 2012). These results were in agreement with a previous study by Trolio *et al.* (2009)

and another study conducted in 2014 by Benavent-Perez *et al,* in which marmosets were also used as the experimental model.

In response to the aforementioned findings, in a retrospective review describing peripheral management strategies for myopia, Smith (2011) and Wallman and Winawer (2004) speculated that signals from the periphery can dominate those generated by fovea, owing to the large summation area available across peripheral retina when compared to the centrally located fovea.

1.2.4.5.2 Peripheral refraction in humans

The involvement of the retinal periphery cannot be assessed in the same manner in human studies, however, certain observations can be made by evaluating peripheral refractive error. Hoogerheide *et al.* (1971) evaluated refractive error across the horizontal visual field (± 60^{o} from the centre of fixation) in young adults (18-20 years old) undergoing training to become pilots. They found that emmetropic or mildly hyperopic pilots, who developed myopia over a course of unspecified time, had at least one hyperopic semi-field meridian when compared to the axial refraction. Mutti and colleagues (2000b) studied central refractive error and peripheral refractive error in nasal visual field (30^{o} form the primary gaze in nasal meridian only) in a group of 5 to 14 year old children under cycloplegia, using an auto refractor (Mutti *et al.* 2000b). Myopic children were found to have a slightly hyperopic peripheral refraction (+0.80 ± 1.29 D) compared to emmetropes and hyperopes (-0.41 ± 0.75 D and -1.09 ± 1.02 D respectively). Subsequently Mutti *et al.* (2007) measured the peripheral refractive error before and after the onset of myopia in a cohort of 605 children (6 to 14 years) and observed changes in peripheral refraction with an accelerated shift towards a more hyperopic refraction (30^{o} from the primary gaze) a year before onset of myopia. Interestingly, Atchison *et al.* (2006) found meridional differences in peripheral refraction with hyperopia being more pronounced across horizontal rather than vertical meridian in adult myopes.

Other studies investigated peripheral refraction in various individual groups, for example in emmetropic, hyperopic and myopic individuals between the age of 18 and 57 years (n=32) (Millodot 1981), emmetropic, hyperopic and myopic individuals between the age of 21 to 33 years (n=31) (Seidemann *et al.* 2002), myopic individuals between the age of 14 to 26 years old (n=56) (Logan *et al.* 2004) and found a link between hyperopic peripheral refraction and myopia (Ferree *et al.* 1931; Rempt *et al.* 1971; Millodot 1981; Seidemann *et al.* 2002; Schmid 2003; Logan *et al.* 2004; Kang *et al.* 2010; Mutti *et al.* 2011b).

Contrary to the findings listed beforehand, Sng (2011) did not observe a correlation between hyperopic peripheral refraction and the development or progression of myopia, in a cohort of 187 Singaporean children of Chinese ethnicity (7.2 ± 3.0 years of age), questioning the hypothesis of hyperopic peripheral refraction being a predictive factor for myopia development. Atchinson *et al.* (2015) also did not support the hypothesis of relative peripheral hyperopia as a predictor factor for myopia development or progression in a cohort of >1700 children of Chinese ethnicity (7 years of age at baseline) and >1000 children of Chinese ethnicity (14 years of age at baseline) over a two year period along the horizontal visual field. If this hypothesis would be ideally describe myopia development and progression, the central refractive error should become more myopic, whilst the relative peripheral refraction become more hyperopic. Study data, however, show, an opposite relationship – the larger the myopic shift in the central refraction in developing/progressive myopes, the more myopic (negative) the relative peripheral refraction was (Atchinson *et al.* 2015). However, authors did not present their findings as absolute and suggested that retinal periphery might have role in myopia development/progression and central refractive error owing to other factors, such as retinal/ocular shape (Atchinson *et al.* 2015).

Sng and colleagues proposed that a hyperopic peripheral refraction is a characteristic of an eye with developed refractive error (Sng *et al.* 2011). This view has been supported by Huang et al (2009) in primates. Moreover, observations of individuals with ocular conditions such as congenital cataracts and ptosis supports the theory of the involvement of both central and peripheral retina in the formation of eye's refractive status (Weiss 2003).

1.2.4.5.3 Peripheral refraction and ocular shape

Human peripheral refraction studies have shown relative peripheral hyperopia in myopes, relative peripheral myopia in hyperopes and relative peripheral myopia or near-emmetropia in emmetropes (Mutti *et al.* 2000; Seidemann *et al.* 2002; Calver *et al.* 2007), suggesting a more prolate eye shape in myopes, a more oblate shape in hyperopes and a spherical or slightly oblate shape in emmetropes, which is a classic characterisation of the shape of an eyeball in relation to refractive error (Ferree *et al.* 1931; Deller *et al.* 1947; Rempt *et al.* 1971; Mutti *et al.* 2000b). These hypotheses, however, must be approached with caution (Cheng *et al.* 1992; Stone and Flitcroft 2004). When form deprivation myopia is induced in animal models and ocular shape is assessed, a more prolate ocular shape owing to axial elongation and, hence, posterior globe dimensions are found, nevertheless, individual variations exist (Wallman *et al.* 1987; Huang *et al.* 2009). The results obtained from human studies highlight the individual variations (Cheng *et al.* 1992; Singh *et al.* 2006).

Cheng *et al.* (1992) measured ocular shape in 6 emmetropic, 8 hyperopic and 7 myopic eyes, using magnetic resonance imaging (MRI) and did not find a correlation between refractive error and eye shape. They concluded that emmetropic, hyperopic and myopic eyes vary in overall size, but not in the shape, describing vast majority of eyes as being sphero-elliptical (Cheng *et al.* 1992). Only two myopic eyes (-5.50 D and -8.00 D) were observed to be asymmetrical and distorted in shape (authors did not discuss shape changes in detail). MRI measurements showed that mean ocular dimensions of emmetropic eyes were slightly longer than those of hyperopic eyes, but shorter than those of myopic eyes (Cheng *et al.* 1992). Singh *et al.* (2006) used a 3 dimensional approach of MRI to measure ocular shape in a group of 7 individuals (refractive error range -16.25 D to +3.50 D). MRI measurements showed differences in eye size, symmetry and shape contradicting the overall correlations between eye shape and refractive error. Two eyes with refractive error of -7.00 differed greatly in axial length (25.00 mm and 28.00 mm respectively) and correspondingly in shape, while 3 eyes, with similar axial lengths had a variety of refractive errors, ranging from -3.00 to +3.25 D, and two nearly emmetropic eyes (refractive error -

0.12 D and +0.50 D) were oblate and spherical respectively (Singh *et al.* 2006). Results from the study conducted by Atchison and colleagues (Atchison *et al.* 2004) assessing eye shape in 88 emmetropic and myopic subjects suggested that most myopic eyes tend to expand more in the horizontal dimension than the vertical dimension, but less than in axial dimension (global expansion), therefore justifying observations reported by Singh *et al.* (2006) and proposition made by Stone and Flitcroft (2004). Stone and Flitcroft suggested (2004) that ocular shape should not be classified as prolate, oblate or spherical as unique characteristics of refractive error, but rather could be used in the treatment strategies for myopia progression by modifying the spherical image shell (i.e. how image is projected onto retina) which would mimic the retinal shape of the eye and eliminate peripheral hyperopic defocus (Figure 1.1.).

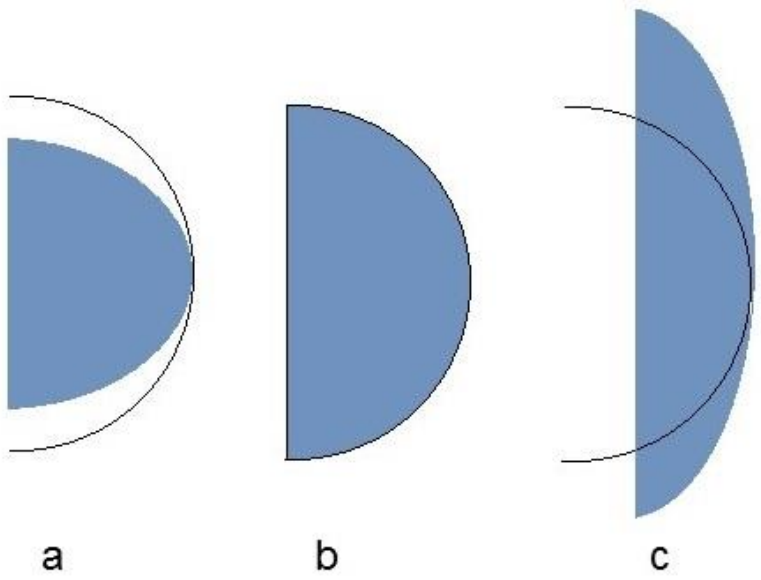

Figure 1.1 Schematic drawing of the relationship between image shell (black hemi-sphere), which is assumed to be spherical, and approximated eyeball shapes (blue half-sphere and ellipsoids) based on peripheral refraction; a. prolate, image shell is displaced posteriorly form the retina at periphery, b. spherical, image shell mimics retinal shape c. oblate, image shell is displaced anteriorly from the retina. Adapted from Stone and Flitcroft (2004).

1.2.5 Myopia control

An increase in hyperopic peripheral defocus has been observed in a cohort of Chinese children wearing SVS (n=28) (Lin *et al.* 2010). Peripheral defocus has been found to trigger

development of myopia even in the absence of foveal vision in the monkey model, even if clear central vision is present (Smith *et al.* 2009b). Various alternatives have been proposed to manage myopia more effectively and counter the mechanisms driving myopia progression (Sankaridurg and Holden 2014). Treatment strategies include undercorrection (Chung *et al.* 2002; Adler and Millodot 2006), progressive addition (PALs) and bifocal spectacle lenses (Goss and Uyesugi 1995; Fulk *et al.* 2000; Gwiazda *et al.* 2003), soft and rigid single vision and multifocal contact lenses (Walline *et al.* 2013), as well as specially designed spectacle and contact lenses (Sankaridurg *et al.* 2010; Sankaridurg *et al.* 2011), orthokeratology (ortho-k) (Cho and Cheung 2012; Chen *et al.* 2013), pharmaceuticals (Tan *et al.* 2005; Chia *et al.* 2012b) and increased outdoor activity (Wu *et al.* 2013). These management strategies target various factors linked to the development of progressive myopia with variable success (Goss and Uyesugi 1995; Leung and Brown 1999; Fulk *et al.* 2000; Chung *et al.* 2002; Gwiazda *et al.* 2003; Tan *et al.* 2005; Adler and Millodot 2006; Walline *et al.* 2009; Yang *et al.* 2009; Sankaridurg *et al.* 2010; Anstice and Phillips 2011; Sankaridurg *et al.* 2011; Chia *et al.* 2012a; Cho and Cheung 2012; Walline *et al.* 2013; Hasebe *et al.* 2014), using traditional spectacle lenses as a reference point to their relative efficacy (Figure 1.2).

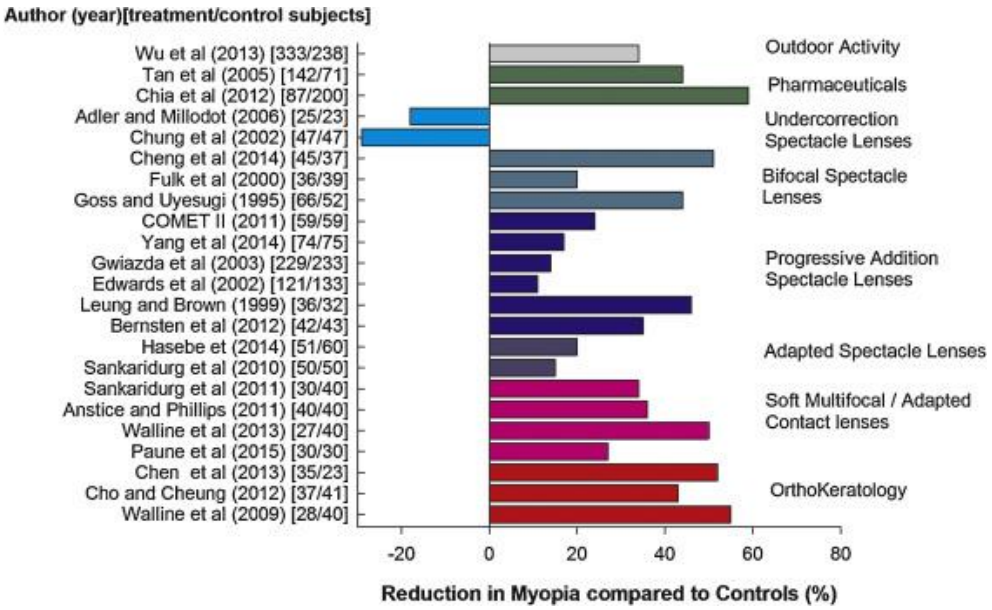

Figure 1.2 Summary of studies investigating the efficacy of myopia control strategies (Wolffsohn *et al.* 2016).

1.2.5.1 Management strategies designed to reduce accommodative demand

1.2.5.1.1 Progressive addition and bifocal spectacle lenses

Traditional progressive addition and bifocal lenses have been prescribed to reduce the demand of accommodation, as well as mitigate the blur associated with increased lag of accommodation in myopia (Gwiazda *et al.* 1995; Gwiazda *et al.* 1999; Gwiazda *et al.* 2003). Bifocal lenses are hypothesised to impose a slight myopic defocus on the peripheral retina within the pus segment of the lens and also attribute towards slowing down myopia progression in such way (Aller and Wildsoet 2008; Sankaridurg and Holden 2014)

The success rate of studies employing PALs and bifocals have varied greatly from no effect (Shih *et al.* 2001; Edwards *et al.* 2002) to up to around 26% for PALs (Hasabe *et al.* 2008). One of the earliest studies employing PALs as a treatment strategy achieved reduction of 46% of myopia progressionn, dependidng on the treatment additive power chosen and its interaction to the accommodative system (Leung and Brown 1999). Meanwhile, some studies employing bifocols and executive bifocals have shown efficacy around 44-56% (Goss and Uyesugi 1995; Cheng *et al.* 2014). However, overall findings reported by other studies have shown more modest retardation rates, around 14% to 24% (Fulk *et al.* 2000; Gwiazda *et al.* 2003; Hasebe *et al.* 2008; Yang *et al.* 2009; Gwiazda *et al.* 2011b).

Interestingly undercorrection, which was believed not only to reduce accommodative demand, but also induce not only foveal but peripheral myopic defocus too, which has been hypothesised to act as a halting signal to myopia development in animal studies (Shaikh *et al.* 1999; Smith and Hung 1999), has been found to rather accelerate the rate of myopia progression for 17-23% (Chung *et al.* 2002; Adler and Millodot 2006).

1.2.5.1.2 Conventional soft and rigid bifocal contact lenses

Various approaches of adjusted fitting methods of conventional soft and rigid single vision and bifocal contact lenses have been found to have no effect on myopia progression (Horner *et al.* 1999), however, on individual occasions, they can even arrest the progression of myopia (Aller and Wildsoet 2008). The rationale behind prescribing contact lenses is the

same as for PALs and bifocal spectacle lenses, nevertheless, the bifocal or multifocal optics are always aligned with the position of gaze as the lens moves with the eye and there would be an improvement in the retinal image quality as the contact lens is positioned directly onto the eye (Gwiazda *et al.* 2003; Aller and Wildsoet 2008; Gifford and Gifford 2016).

1.2.5.1.3 Pharmaceutical approaches

The premise of introducing pharmaceutical agents for myopia control (MC) was to reduce the accommodative demand. Conversely, animal models and human trials suggest that the mechanism of action could be non-accommodative in nature and involve retinal and scleral factors (McBrien *et al.* 1993; Trier *et al.* 2008).

Pharmaceutical treatment strategies, such as low dose atropine (0.01% – 0.5%) and 1% atropine in the earlier studies, pirenzepine and 7-methylxanthine (7MX) have shown high success rates (46% to 76%), however, there has been a lack of consensus for the optimum concentration to prevent adverse effects and regression once treatment is ceased, as well as the commercial availability of the product (Tan *et al.* 2005; Chua *et al.* 2006; Tong *et al.* 2009; Chia *et al.* 2012b).

1.2.5.2 Management strategies designed to modify peripheral refraction

The growing evidence of the involvement of peripheral retina in myopia development (Smith *et al.* 2005; Smith *et al.* 2007) and the impact of optical defocus (Smith 1998; Shaikh *et al.* 1999; Smith and Hung 1999; Whatham and Judge 2001) have remodelled the concept of the optimal optical treatment strategy for MC. Smith (2011) proposed a model that would provide clear vision in the fovea and induce myopic defocus in the periphery (Figure 1.3). This model of correction can be applied for myopia management with multifocal soft contact lenses (Walline *et al.* 2013), specially designed spectacle (Sankaridurg *et al.* 2010; Hasebe *et al.* 2014) and contact lenses (Sankaridurg *et al.* 2011) and ortho-k, an overnight application of special lenses (Swarbrick 2006; Walline *et al.* 2009).

The relative efficacy of multifocal lens (Walline *et al.* 2013), and specially designed spectacle (Sankaridurg *et al.* 2010; Hasebe *et al.* 2014) and contact lenses (Sankaridurg *et*

al. 2011) compared to single vision spectacle controls has been reported to be 50%, 20-30% and 34% respectively, whereas for ortho-k the relative efficacy is ~50% (Cho and Cheung 2012; Walline 2012; Chen *et al.* 2013; Si *et al.* 2015; Sun *et al.* 2015).

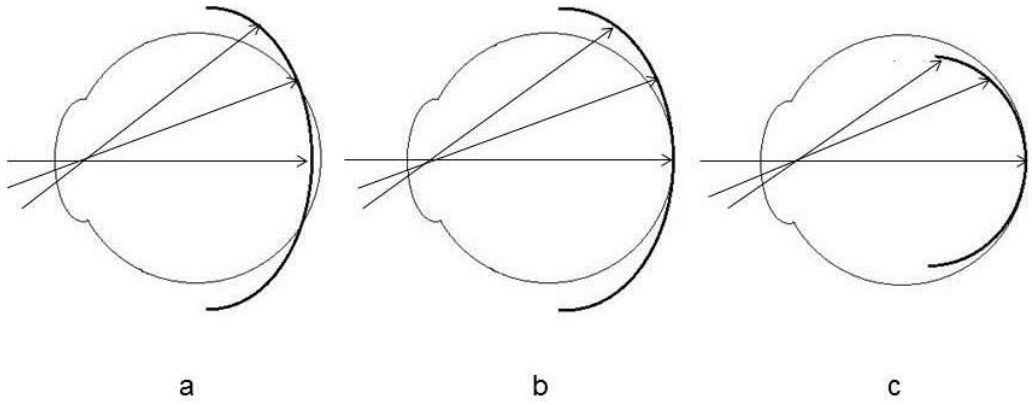

Figure 1.3 Schematic drawing of different correction approaches used for myopia control and the location of image shell (thicker black line); a. undercorrection, image shell is displaced posteriorly form the retina, b. classical approach to myopia correction, image shell is placed onto the retina centrally, but located posteriorly in the periphery c. perceived optimal correction, image shell is placed onto the retina centrally, but located anteriorly in the periphery. Adapted and reprinted with premission from Smith (2011).

Methods employing the modification of peripheral refraction are still evolving, exploring the adequate amount of peripheral defocus for an optimal treatment outcome (Sankaridurg and Holden 2014; Gifford and Gifford 2016). They have showed their potential by slowing down the progression of myopia by 30 to 50% (Sankaridurg *et al.* 2010; Cho and Cheung 2012; Walline *et al.* 2013).

However, out of all optical management strategies discussed above, ortho-k offers a great advantage by providing clear spectacle or contact lens-free vision to a patient during the day (Swarbrick 2006). It is believed that the change in the corneal thickness and the corneal topgrraphical changes induced by the reverse geometry (ortho-k) lens (Swarbrick *et al.*, 1998) creates an optimum peripheral retinal image as proposed by Smith (2011). Also, the mechanisms involving increased positive spherical aberration have been proposed to

contribute towards the optimal ocular environment for MC. (Joslin et al, 2003; Berntsen et al. 2005; Gifford *et al.* 2013; Gifford and Gifford 2016). Sperical abberations do not impact the optical quality of the central vision; however with an increasing pupil size (5 mm), spherical aberations are the driving force for the visual quality and could have influence on peripheral refraction (Berntsen et al. 2005; Smoth 2011); for further information on ortho-k please refer to Section 1.3). Longitudinal studies conducted by various authors (Cho *et al.* 2005; Walline *et al.* 2009; Kakita *et al.* 2011; Cho and Cheung 2012; Chen *et al.* 2013) have proven the efficiency of ortho-k for MC by reducing myopia up to -5.00 centrally, whilst inducing a myopic shift in the periphery (Charman *et al.* 2006; Queiros *et al.* 2010; Kang and Swarbrick 2013). It is hypothesised that modification of ortho-k lens parameters and design could enhance the myopia control effect; however, as noted by Kang *et al.* (2013) it is a difficult task and various aspects remain to be studied. A pilot study conducted by Loertscher (2013) introduced a multifocal ortho-k lens design and over a 26 day period was able to observe anti-myopic changes. Thirty children (10 to 14 years of age) were randomly fitted with a standard ortho-k lens in one eye and a multifocal ortho-k lens in the fellow eye overa an average period of 26 ± 16 days. An equal VA and peripheral refraction was developed over the time, however only in the eyes fitted with the multifocal ortho-k lens, a significant decrese in axial elongination, vitreous chamber depth and thickening of choroid were seen (Loertscher 2013). Therefore, it was suggested that simultenious myopic defocus in the central retina, rather than the refractive changes in the peripheral retina, are the probable cause of MC effect in the short term ortho-k lens wear (Loertscher 2013). However, not only this but other work should be extended in order to create an optimal myopia control intervention (Gifford and Gifford 2016).

1.3 Orthokeratology

Orthokeratology (also known as ortho-k or corneal reshaping or corneal refractive therapy) is defined as a transient mitigation of refractive error usually by overnight application of specially designed rigid gas permeable contact lenses, inducing corneal shape changes (Swarbrick 2006).

The clinical application of ortho-k is not a novel approach (Jessen 1962; Kerns 1976a; Polse 1977) and has primarily, although not widely, been used for mild to moderate myopia correction (Jessen 1962; Kerns 1976c; Polse *et al.* 1982; Brand *et al.* 1983). However, over the last two decades ortho-k has recaptured the interest of practitioners and scientists owing to innovations in lens designs (Wlodyga and Bryla 1989; Harris and Stoyan 1992) and materials (MacKeen *et al.* 1992), as well as instrumentation (Klyce 2000), making the outcome of treatment more persistent and predictable (Mountford 1997), but mostly, due to its promising halting effect of myopia progression (Cho *et al.* 2005; Walline *et al.* 2009; Cho and Cheung 2012).

1.3.1 Evolution of orthokeratology

Jessen (1962) was the first to describe an application of contact lenses to intentionally change corneal curvature and, therefore, the refractive status of an eye. His technique, which he named 'orthofocus', was designed based on his own previous clinical observations pertaining to myopic patients fitted with flatter micro type lenses (maximum total diameter 9.0 mm, which was later increased to 9.5 - 10.5 mm to improve the centration and to stabilise the fit). An improvement in unaided visual acuity after a year of lens wear was seen. To correct myopia, a flattening of the central cornea was desired. Hence, a conventional plano-powered hard contact lens made of a polymethyl methacrylate (PMMA) was fitted flatter than the flattest keratometry (flattest K) reading by the amount of patient's refractive error in a high-riding position. This lens fitting position was chosen, so that it would interact with the upper eyelid, which then would act as a lever enhancing the flattening effect. Conversely, in hyperopia, this method required steepening of the cornea and, hence, a lens with a small diameter (usually between 7.6 and 8.6 mm) and steeper curvature than the flattest K was fitted centrally onto cornea. Astigmatism was corrected by fitting a low-riding lens in such a manner that the upper lid was resting above the superior margin of the contact lens, eliminating its pressure being exerted on the eye. Jessen (1962) hypothesised that eyelid-cornea interaction has a major role in the development of the refractive status of an eye. The bi-curve design with an edge lift was preferred, however,

for larger myopic and hyperopic refractive errors, a tri-curve design was introduced. In addition, a toric lens with prism ballast enhanced the treatment outcome of an astigmatic patient as it allowed better lens centration. Notably, the orthofocus technique was more easily applied in case of hyperopia and astigmatism owing to the lens position on the cornea and relatively small lens size. On contrary, in myopia, larger lens diameter was required (usually 9.5 to 10.5 mm), causing discomfort during the lens wear and increasing the risk of ocular complications due to hypoxia. Nonetheless, in the paper discussing orthofocus techniques (Jessen, 1962), a successful treatment outcome of a patient with -3.00 dioptres of bilateral myopia, a relatively high refractive error to be corrected by this method, was reported. The full correction of myopia was achieved gradually over a period of two months of lens wear on daily basis with an unaided visual acuity ranging between 20/20 and 20/25. Lens wear for several hours a day was required to maintain the treatment effect. Overall, Jessen suggested that the method was promising, and tended to give a permanent effect if the treatment is commenced in an early age in cases of hyperopia and astigmatism. In cases of myopia, the effect tended to be more temporary. Nevertheless, the long lasting effects of this technique remained to be studied (Jessen 1962).

Later Jessen (1964) suggested the use of de Carle bifocal lens design for correction of hyperopia and reverse de Carle bifocal lens design for correction of myopia to stabilise lens centration and increase comfort during lens wear. The de Carle bifocal lens design consisted of a steep central base curve that corrected vision in distance and flatter peripheral zone to produce the near addition. Jessen also concluded that children up to +3.50 D of hyperopia respond well to lens wear and, after a year, refractive error tends to diminish by half (Jessen 1964).

Over the next several years, studies investigating various fitting philosophies and aspects of ortho-k were conducted. Emmetropisation through contact lenses was proposed by Neilson, May and Grant (1964). They discussed the importance of the cornea-contact lens relationship, suggesting that the optimal fit regarding lens centration and comfort was 0.12-0.37 D flatter than the flattest K, as a flatter fit than this might, on the contrary, promote

steepening of the cornea. Furthermore, once the reduction of myopia was observed, new keratometric readings were obtained and a lens 0.25 D flatter than the flattest K reading was chosen. The length of treatment was patient-dependent, defining the endpoint of treatment as a state when 20/20 visual acuity is reached and plano lenses are used to retain the effect achieved (Neilson *et al.* 1964).

In 1968, Ziff (1968a; 1968b) discussed his approach of gradually fitting increasingly flatter contact lenses over a period of 1 to 3 years to halt the progression of myopia, emphasising the importance of the patient's age on the course of treatment. Age was found to have an impact on eye growth. Ziff also proposed the use of retainer lenses for a few hours a day to preserve the effect achieved. His extrinsic suggestion of overnight application of ortho-k to retain a good visual acuity during daytime in the later stages of treatment programme, when the visual maturity (18-22 years as defined by Ziff) is reached, however, was perceived as controversial. He reported 41 cases out of which 39 cases demonstrated an improvement in visual acuity after removal of the lenses and the optimum result of the course of treatment was defined as 1.00 D or greater change in the aspect of corneal curvature (Ziff 1968a; 1968b).

However, the inconsistency, and in many cases anecdotal nature of clinical trials (Kerns 1976a; Coon 1982), indicated the need for controlled studies to be conducted in order to establish orthokeratology as a clinical technique.

Kerns (1976a, 1976b, 1976c, 1977a, 1977b, 1977c, 1977d, 1978) carried out a study investigating the corneal response to ortho-k and rigid contact lenses in general, dividing myopic subjects in two control groups (3 non-contact lens wearers and 13 conventional rigid lens wears respectively) and one experimental group (18 subjects) that underwent ortho-k treatment over a period of 946 ± 158 days. Lenses in the control contact lens wearer group were fitted in accordance to keratometry readings and remained unchanged during the study period, whilst in experimental group, lenses were initially fitted in accordance to keratometry readings or up to 0.50 dioptre flatter than the flattest keratometry reading and

worn on a daily basis. The fit in orthokeratology group was gradually adjusted, when flattening of the cornea or reduction in myopia was observed. The initial refractive error in spherical equivalent form was -3.50 D or less. In order to assess corneal changes, and safety and recovery aspects of the procedure, refraction and over-refraction were measured, and keratometry and central/peripheral pachimetry were performed. Lens centration and lag, and corneal integrity were also assessed by biomicroscopic examination during every visit (Kerns 1976b). The results indicated an average reduction in myopia of 1.06 ± 0.98 D (ranging between 3.00 D decrease to 0.75 D increase in refraction) in the horizontal meridian and 0.68 ± 0.90 D (ranging between 3.25 D decrease to 1.00 D increase) in the vertical meridian, with changes in vertical meridian being more unpredictable and fluctuating, especially if lens was fitted more than 0.59 D flatter than keratometry reading, and were speculatively linked to the different pressure distribution under the lens in both meridians. Hence, concerns of induced with-the-rule astigmatism were expressed. The changes observed in both control groups did not exceed those relating to diurnal fluctuations (Kerns 1976c). Also, contact lenses in the experimental group had a tendency to decentre and ride high as the cornea changed its curvature and underwent sphericalisation, emphasising the importance of corneal shape factor. Therefore, in order to maintain an acceptable cornea-lens relationship and achieve good centration, most of the lens parameters were manipulated on an individual basis. Corneal integrity, as observed by fluorescein pattern and keratometry, was maintained in acceptable limits in most of the subjects (Kerns 1977a). Kerns (1978) concluded that, although most of the factors involved in this procedure are individual and 20/20 visual acuity is not reached, and once a full understanding of mechanisms involved in corneal reshaping is achieved, especially the aspects of corneal rigidity, the procedure could become more widely used.

A study conducted by Binder *et al.* (1980) affirmed conclusions drawn by Kerns (1978) on the unpredictably and variability of ortho-k and the corneal response to it, as there was no clear correlation between keratometric changes and treatment process. In its design and

fitting philosophy, this study was similar to the one carried out by Kerns (1976b). Of 20 subjects that underwent treatment, 9 responded well to corneal reshaping, 6 showed an unpredictable and variable response, and 5 did not respond to treatment at all. The flatness of the fit, similar to studies mentioned beforehand, was adjusted during the course of study on an individual basis and varied between 0.50 to 2.75 D flatter than the flattest corneal meridian. Overall, an average reduction in myopia of 1.50 D was achieved when moderate myopia was present. Whilst, low myopes showed either no response or a negligible response to the treatment (Binder *et al.* 1980).

The Berkley orthokeratology study (BOS) was a single centre masked randomized study carried out over a period of 2 years that monitored corneal changes, and the safety and efficiency of ortho-k in 40 subjects (Polse *et al.* 1982; Brand *et al.* 1983; Polse *et al.* 1983). A group of 40 conventional contact lens wearers were chosen as controls. The refractive error of the participants varied between 1 D and 4 D of myopia, with initial flattest keratometric readings falling into the range of 40.50 to 47.00 D. Initially, all participants were fitted with PMMA material lenses, however, at later stages of study they were refitted with PMMA-silicon combination, if oedema occurred. Measurements of visual acuity, keratometry, and endothelial cell density were obtained and a slit lamp examination was performed. Over the course of study, the lens fit was gradually adjusted and lens wearing time was moderately reduced in the experimental group to investigate the rebound effect (the reduction of effect achieved once the treatment is ceased), with greater changes occurring at the first 132 days from the baseline measures. The mean refractive change achieved in the treatment group by the end of the study was 1.01 D reduction of myopia, compared to 0.54 D refractive change in conventional contact lens wearer group. As the wear of lenses was reduced to 4 hours per day, the refractive changes achieved mitigation rapidly (an average decrease of 45% was observed). However, although not clinically significant, 26% of changes achieved did not reduce even after 79.6 days, suggesting that this procedure could have a small permanent impact on the cornea. No clinically significant adverse corneal response to the treatment was observed. The authors concluded that the

results obtained in this study are in agreement with those of previous studies conducted by Kerns (1978) and Binder *et al.* (1980), regarding the average refractive changes achieved and the fluctuating nature of them. However, it was implied that patients with myopia of 1.50 D could succeed from ortho-k treatment.

Soon afterwards Coon (1984) investigated different approach to ortho-k by fitting PMMA lenses slightly steeper (+0.25 – +0.50 D depending on the astigmatism present) than the actual corneal curvature in the flattest meridian, in order to mitigate the risk of induced astigmatism over a period of 80 weeks. The lenses were fitted with an apical clearance which enhanced the reshaping effect of orthokeratology by manipulating the tear reservoir (TR), a percentage of posterior lens surface inhabited by peripheral and intermediate curves. He speculated that forces acting underneath the lens surface are crucial to the refractive changes achieved by this technique. The TR was gradually increased from initial 32.5% up to 45% or more over the course of study to promote corneal reshaping. However, when the TR reached 45%, the lens centration became unstable and was compensated for by increasing the total diameter of the lens. The results showed a reduction in myopia among both groups, with a slightly greater reduction in the experimental group (0.49 D @ 180/ 0.43 D @ 90 and 0.56 @ 180/ 0.60 @ 90 respectively), and the equal reduction of myopia along both meridians indicated that no with-the-rule astigmatism was induced over the course of study. No clinically significant adverse effects were observed. Interestingly, changes in corneal thickness in the experimental group were noted. Central thinning and peripheral thickening of the cornea was observed, prompting speculation on the mechanisms involved in the process of corneal reshaping. Coon concluded that orthokeratology is clinically safe method which does not induce more complications than conventional PMMA lens wear (Coon 1984).

To summarise, the studies listed above are not the only ones discussing early attempts of development of corneal reshaping, however, they highlight the problems encountered in the primary stages of this procedure, such as the lack of a consistent fitting protocol, the poor lens centration with the fit gradually becoming flatter, the length of treatment

compared to the improvement in visual acuity, but most importantly, the unpredictably of the outcome of treatment. In many cases there was no clear correlation between keratometric readings and the improvement in visual acuity. Factors that were more dominant than the possible gains of the procedure, impacting its further clinical use, however, were gradually overcome in later stages of method development as more suitable lens designs were established.

1.3.2 Reverse geometry lens design

Jessen (1964) noted the optimal lens centration observed in his orthofocus techniques was achieved using the de Carle bifocal design, containing relatively flat peripheral curve (approximately 12.50 mm), an intermediate zone ranging in-between 0.50-0.75 D flatter than the central keratometric reading of a patient and central zone that was 3 times steeper the required reading add than the intermediate zone. Jessen speculated that a modified reverse design de Carle bifocal could be suitable for myopia correction and could overcome the superior centration observed with conventional contact lenses. He described the desired design as a lens with a concave back surface that has a flatter centre, which would flatten the corneal apex, and a steeper periphery, which would enhance tear exchange, whilst the intermediate curve would provide a good lens centration. Typically, for myopia correction, this lens was 9.8 mm in diameter horizontally and 8.8 mm vertically respectively, and truncated in shape, having a central zone 5.50 mm wide and a peripheral curve of 11 mm radius.

Later Fontana (1972) introduced a new approach to ortho-k by fitting myopic patients with a one-piece bifocal. He described this lens as consisting of a central zone (6 mm) that had a 1 D flatter base curve than the paracentral area, which was chosen in accordance with the keratometric readings to fit the flattest corneal meridian, and having 8 mm wide optic zone and 9.6 mm total diameter. It was implied that changes occur within the first six weeks and that three to four pairs of lens are needed over the course of treatment, the latter pair serving as a retainer lenses. Reflecting on 78 patients, Fontana concluded that in 96% of

cases an improvement in visual acuity was noted and that there is no limitation in patient selection. Nevertheless, to achieve a full correction of refractive error, it was advisable to select patients with up to 3 D of myopia (Fontana 1972).

However, it was not until 1989 that accelerated orthokeratology and a novel reverse lens design was introduced by Wlodyga and Bryla(1989) The use of temporal keratometric readings was highlighted as a crucial part of their fitting approach. Only horizontal temporal readings were measured and they were recorded by asking patient to fixate nasally on the '+' sign of the keratometer ring. The difference between central and temporal K readings was used as a predictor for the success of treatment, assuming that a flatter temporal K reading than the central one is a good indicator. The lens, referred to as Ortho-K 60, had a 6-mm wide primary base curve, 1 mm wide peripheral secondary base curve, which was 0.6 mm steeper than primary base curve, and 0.7 mm wide peripheral curve with a total diameter ranging from 8.5 to 11.0 mm. Over the course of treatment, which was suggested to be 6 weeks long, three to four pairs of lenses were required with each lens set being 1 D flatter than the flattest K reading. The first set was worn for a few hours over a period of one to two days, whereas set two was worn up to one week. The third set was worn for one to three weeks, and, finally, the fourth set was worn for a period of three to six weeks. A retainer pair of lenses were used afterwards on a daily basis until a stable 20/20 level at vision was reached, gradually reducing wearing time to a few hours in the mornings and evenings. Data from 15 patients, undergoing their treatment programme, were presented. The amount of myopia reduced, varied between 1 to 4 dioptres with several patients achieving plano refraction.

Harris and Stoyan (1992) investigated the effects of the OK-3 lens design in 80 myopic patients, using the fitting approach described by Wlodyga and Bryla (1989). Harris and Stoyan predicted that the maximum amount of myopia corrected with this procedure is twice the difference between central and temporal K readings, emphasising the importance of corneal eccentricity (e), the amount by which corneal shape diverges from a sphere. The lens design used was described as having a 6-mm wide optic zone diameter and tear

reservoir or intermediate zone of 3.00 D dioptres steeper than the base curve of optic zone to enhance tear exchange, which was then followed by flatter aspheric peripheral zone. The total diameter of the lens was 9.5 mm. The procedure consisted of 4 to 5 steps and was proposed to last from 3 months to a year. The first pair of lenses was prescribed 1.00 to 1.50 D flatter than the flattest K reading and was worn for 2 to 7 days, when rapid corneal flattening within the first hours of lens wear occurred. When central pooling in the fluorescein pattern could not be seen and no lens movement was observed, a new lens 0.50 D flatter than the previous lens was prescribed. After 1 to 3 weeks a third lens, again 0.50 flatter than the previous lens, was prescribed and the lens diameter was increased, if needed. Subsequent lenses maintaining the same regression in base curve were prescribed at one-month intervals until an unaided vision of 20/20 was achieved. To retain the achieved effect, a retainer lens of same design was typically worn for two-to-three hours in the mornings and evenings. The authors suggested that the optimum myopia range was up to 6.00 D and astigmatism up to 3.00 D. The average reduction of myopia achieved in the study, however, was 2.62 D (Harris and Stoyan 1992).

The lens designs described above have contributed towards the establishment of modern ortho-k and the four/five zone reverse geometry lens design commonly used nowadays. Various lens designs are currently available, with their parameters being specified by the manufacturer (Tahhan *et al.* 2003). Nevertheless, Swarbrick (2006) describes a typical reverse geometry lens for myopia reduction as being composed of a relatively flat central treatment zone (usually 6 mm wide), adjoined by one or few slightly steeper reverse curves, which stabilise the fit. The outer boarder of the reverse curve is surrounded by an alignment curve, designed to improve lens centration, which then is followed by a peripheral curve to ensure edge clearance (Figure 1.4).

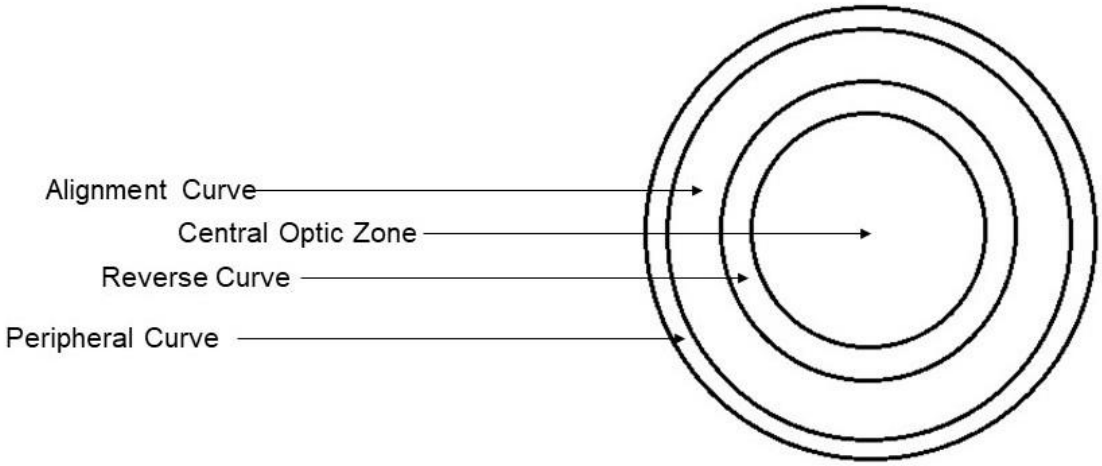

Figure 1.4 Schematic drawing of a reverse geometry lens. Adapted from Swarbrick (2006).

1.3.3 Current state of orthokeratology

Innovations in contact lens materials and the approval of rigid gas permeable contact lenses for overnight use (MacKeen *et al.* 1992; Gleason and Albright 2003) have re-established interest in ortho-k, which offers spectacle or contact lens free vision during the day and is speculated to have a halting effect on myopia progression (Fan *et al.* 1999; Cho, *et al.* 2002; Cho *et al.* 2003a; Cho *et al.* 2003b; Walline *et al.* 2004a). For further information on MC and ortho-k refer to section 1.5.2.

Various reverse geometry lens designs have been evaluated and are proven to reduce myopia effectively by an overnight application and achieve the refractive changes required within a week (Cho *et al.* 2003a; Tahhan *et al.* 2003; Maldonado-Codina *et al.* 2005; Marcotte-Collard *et al.2018*). The fitting guidelines are specified by individual manufacturers and the optimal effect achieved varies between studies and the optimum lens design eliciting maximum myopia reduction remains undefined. However, it is generally agreed that ortho-k can effectively reduce up to 4.00-5.00 D of myopia and 1.50-2.00 D of with-the-rule astigmatism (Mountford 1997; Fan *et al.* 1999; Nichols *et al.* 2000; Rah *et al.* 2002; Cho *et al.* 2003b; Tahhan *et al.* 2003; Walline, Rah*, et al.* 2004; Cho *et al.* 2005; Maldonado-Codina *et al.* 2005). Swarbrick *et al.* (1998) and Alharbi and Swarbrick (2003) associated the

maximum amount of myopia reducible with reverse geometry lenses with corneal epithelial thickness changes occurring in orthokeratology (up to 20 µm). For detailed discussion of mechanisms underlying ortho-k please see Section 1.5.

The standard reverse geometry lens design have four to five curves (Swarbrick 2006). An example of a five curve ortho-k lens design is DremLens reverse geometry lens. DreamLens is available under various names in different countries. In the UK DreamLens ortho-k lenses are provided by the No7 Contact Lenses (Hastings, United Kingdom) and were employed for conducting study described in Chapter 5. DreamLens ortho-k lens design is a five curve reverse geometry lens design. The zones are devided in a central zone, a reverse zone, two distinct aligment zones and a peripheral edge curve (please see Figure 1.4 for illustration of the reverse geometry lens zone composition). The central curve is flatter and exert a positive pressure to the central cornea. The back optic zone radius (BOZR) usually ranges from 6.0 to 8.0 mm depending on the specific design and creates a treatment zone of around 5.0 mm). The central zone is then rounded by a steeper reverse curve, aligning with the mid periphery of the cornea and creating a negative pressure owing to the tear film annularlry pooling under the zone. This curve has a radius of 0.5 to 1.0 mm or is manufactured 3.0 to 5.0 D steper than the back optic zone radius and provides an area for the corneal epithelial cells and intracellular fluid to expand to. The third to fourth zone is the aligment curve that is again flatter than reverse curve and its main purpose is to aid with the lens centration. The curve lands on the corneal periphery and it is generally 1.0 to 1.5 mm wide dependidng on the lens design. The final outer zone is the peripheral edge curve that is flatter than the aligment curve and provides and edge lift for an adequate lens movement, ocular comfort and the tear-debris exchange (Bauch and Lomb 2004; http://www.no7contactlenses.com/eyedream.html#philosophy; accessed 13.12.2018).

An example of the four curve lens is Paragon CRT reverse geometry lens (Paragon Vision Sciences, Gilbert, Arizona, USA). The lens have congruent anterior and posterior surfaces each consisting of central zone, a mathematically designed sigmoidal corneal proximity

return zone, a noncurving tangent landing zone and a convex elliptical edge zone that joins both surfaces (Paragon Z package insert, Paragon Vision Sciences. Available at: https://www.accessdata.fda.gov/cdrh_docs/pdf5/P050031c.pdf; accessed 13.12.2018). The overall diameter range from 9.5 mm to 12.0 mm. The central base curve radius can be manufactured within range of 6.50 mm to 10.5 mm. The return zone is typically smaller and is 0.75 mm to 1.5 mm wide, whilst the landing zone is 0.5 mm to 2.75 mm (radius: to infinity). Peripheral edge curve width depends on the size of the landing zone and can be manufactured within a range of 0.04 mm to landing zone width.

The lenses are usually fitted based on topographic maps. Any further adjustments to the lens fit are made using the original BL map and the map obtained after the overnight lens wear.

Reverse geometry lenses were designed to reduce myopia, however, attempts to apply ortho-k for correction of hyperopia (Gifford and Swarbrick 2008; Gifford *et al.* 2009) and also presbyopia (Gifford and Swarbrick 2013) have been made. The effect achieved, however, is approximately three times less than that of a myopic ortho-k (Gifford and Swarbrick 2008; Gifford *et al.* 2009; Gifford and Swarbrick 2009, 2013).

1.4 Corneal biomechanics

Aspects discussed previously (Section1.3) demonstrate that a strong cornea-tear film-contact lens interaction is present in ortho-k. The hypothesis proposed by Kerns (1978) on corneal rigidity and observations made by Coon (1984) regarding corneal thickness changes, indicate that the cornea itself plays an important role towards a successful treatment outcome. Hence, an appropriate lens design is not the only determining factor for a successful treatment outcome. Close relationship between corneal tissue, tear film and the ortho-k lens exists. Therefore study of its biomechanical properties could provide a deeper understanding of the underlying mechanisms of this technique.

1.4.1 Cornea

The cornea is a highly specialised transparent avascular tissue that, together with the sclera, forms the outer tunic of the eye. The mechanical properties of the cornea to withstand internal and external forces to maintain the shape of an eyeball, as well as its optical features, which provide two thirds of eye's refractive power, are well established (Klyce and Beuerman 1998; Klyce 2005; Ruberti *et al.* 2011). The cornea is elliptic in shape with an average horizontal diameter of 12.6 mm and 11.7 mm vertically (Klyce and Beuerman 1998) (Figure 1.5). The central thickness of the cornea is approximately 520 µm, which gradually increases towards the periphery, reaching approximately 650 µm (Klyce and Beuerman 1998; González-Méijome *et al.* 2003). Microscopically, the cornea is composed of five distinct layers (Klyce and Beuerman 1998). Recently, however, it has been proposed that the sixth Dua's layer of cornea in the posterior part of stroma exist (Dua *et al.* 2013). Nevertheless, the classic five-layer composition of the cornea will be discussed in structural order: epithelium, Bowman's layer, stroma, Descemet's membrane and endothelium (Klyce and Beuerman 1998).

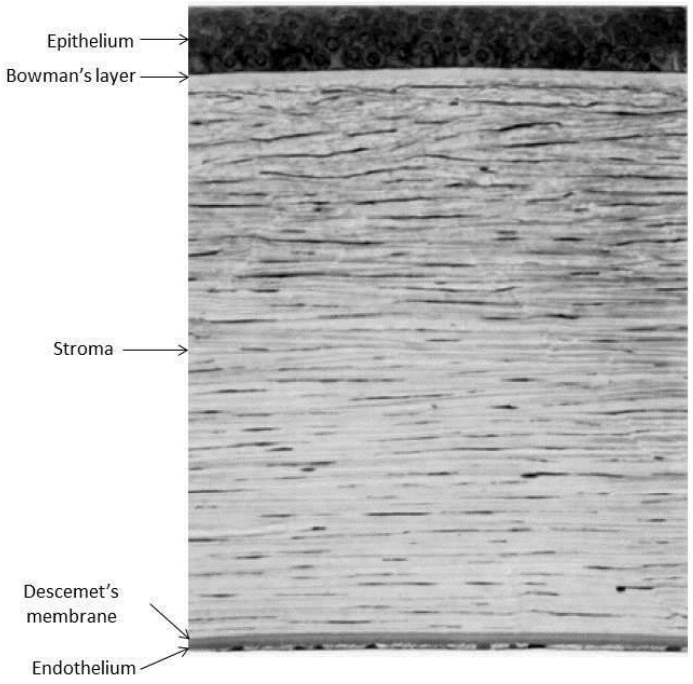

Figure 1.5 Microscopic structure of the cornea. Adapted from Klyce and Beuerman (1998).

1.4.1.1 Epithelium

The corneal epithelium is a stratified squamous non-keratinized epithelium, around 50 µm in thickness, and is the most regularly arranged of all squamous epithelia in the body (Ehlers 1969; Hogan *et al.* 1971). The epithelium is mainly composed of three types of cells, which are arranged in 5 to 6 layers and compose ~10% of the overall corneal thickness. The number of epithelial layers increase towards the limbus (Hogan *et al.* 1971).

The two layers of superficial cells, which are the outermost layer of epithelial cells, interact with the tear film directly, providing a smooth ocular surface and enhancing active transport and diffusion (Hogan *et al.* 1971). Superficial cells are are wide and thin, measuring around 20 to 45 µm in width and around 4 µm in thickness. The tear-side surface of them is covered with a large number of microplicae and microvilli that enhance the surface area of epithelium and anchors tear film to it.The inner surface of these cells are in a direct contact with the wing cells (Hogan *et al.* 1971; Fatt and Weissman, 1992). Superficial cells are the only epithelial cells have the tight cell junctions, zonula occludentes that decrease the possibility of harmful substances from entering into the intraocular tissue. Other tight cell junction types, that are present in the superficial layer and closely interlinks these cells, are desmosomal attachments and maculae occludentes (Pedler 1962; Hogan *et al.* 1971).

Wing cells are ordered in two to three layers and are connected to basal cells, the only cells capable of mitosis (Hogan *et al.* 1971; Gipson *et al.* 2005). Wing cells are derived from basal cells and are pushed towards the epithelial surface. They are polygonal in shape with wing-like extensions and are firmly interconnected with each other and the surrounding epithelial cell layers (Hogan *et al.* 1971; Fatt and Weissman, 1992). They are connected with desmosomal junctions and maculae occludentes. Wing cells do not proliferate frequently, however, they have a role in the process of re-epitelhelazion and they passively take part in tear spreading (Pedler 1962; Dohlman 1971; Hogan *et al.* 1971; Klyce 2005).

The single layered basal cells lay on epithelial basement membrane, an anchor like structure involved in the process of epithelial wound healing and regeneration (Vracko 1974;

Gipson *et al.* 1987; Torricelli *et al.* 2013). Basal cells are columnar shaped and small. They compose one third of epithelial thiclness and are ~20 µm tall and 10 µm wide (Hogan *et al.* 1971; Fatt and Weissman, 1992; Klyce 2005). The cells are joined by desmosomes and maculae occludentes (Perera 1969; Hogan *et al.* 1971). They are the only epithelial cells capable of mitosis and play an important role in the regeneration of corneal epithelium (Dohlman 1971; Fatt and Weissman, 1992). The epithelial basment membrane is ~0.05 µm thick granular layer that separates epithelium from Bowman's layer. It has an important role in cell migration, adhesion, differentiation and signal transduction (Dohlman 1971; Vracko 1974; Gipson *et al.* 1987; Torricelli *et al.* 2013). Mechnically epithelium is very easy mouldable and, unlike stroma, which defines corneal biomechanical response, does not contribute to the corneal mechanical properties as much (Elsheikh 2010).

The average lifespan of epithelial cells is 7 days, rapid cell turnover being a crucial component of its protective nature and helping maintain a smooth ocular surface (Hanna and O'Brien 1960; Klyce 2005).

1.4.1.2 Bowman's layer

Bowman's layer is a ~8-12 µm thick acellular non-regenerative layer, composed of randomly arranged collagen fibrils that condensates into the underlying stroma (Tisdale *et al.* 1988; Komai and Ushiki 1991; Kenyon and Chaves 2005). The function of it is still a controversial topic, however, it is hypothesised that it might serve as a bounding element to maintain corneal structure and a biological barrier against viruses (Fite and Chodosh 1998; Wilson and Hong 2000; Lagali *et al.* 2009).

1.4.1.3 Stroma

The corneal stroma or *Substantia Propria* contributes ~ 90%, approximately 500 µm, of corneal thickness and is mainly composed of collagen type I (Klyce and Beuerman 1998). The collagen is ordered in uniform sized, closely and strictly packed fibrils that further are arranged into sheets of 200-250 lamellae (Komai and Ushiki 1991). This elegant organisation is crucial for corneal transparency and optical performance (Maurice 1957;

Meek and Boote 2004). The relatively small cellular part of the stroma is composed of keratocytes, initially quiescent fibroblast cells that have a crucial role in synthesis and renewal of stromal collagen (Jester *et al.* 1987; Klyce 2005). Whilst the ground substance of stroma consists of proteoglycans, macromolecules that helps to stabilise and organise collagen fibrils (Gipson *et al.* 2005). The primary role of the stroma is to provide a transparent pathway for light and, secondary together with the sclera, helps to maintain intraocular pressure (Gipson *et al.* 2005).

1.4.1.4 Descemet's membrane

Descemet's membrane is an elastic, homogeneous ~6-13 μm thick structure that lies between the stroma and endothelium and has a tendency to thicken during life (Johnson *et al.* 1982; Klyce and Beuerman 1998; Hayashi *et al.* 2002). It is considered the basement membrane of the corneal endothelium and is mainly composed of different types of collagen. Descemet's membrane is able to regenerate if damaged (Hayashi *et al.* 2002; Klyce 2005; Kabosova *et al.* 2007). The function of Descemet's membrane is not well understood; nevertheless, it has been hypothesised that it may have a role in endothelial cell differentiation and proliferation (Joyce 2012). Furthermore, it could be crucial for preservation of corneal curvature and radius (Danielsen 2004).

1.4.1.5 Endothelium

The corneal endothelium, a monolayer of polygonal cells, lines the posterior corneal surface. It mostly consists of hexagonal, ~4-6 μm thick, metabolically active cells (Rao *et al.* 1982; Waring *et al.* 1982). Endothelial cells have limited capacity of proliferation and they tend to reduce in number with age (Klyce and Beuerman 1998; Joyce 2012). In order to maintain a continuous cell layer, for example in response to injury, endothelial cells change in shape (polymorphism) and size (polymegathism) (Klyce and Beuerman 1998). The primary function of the endothelium is to fulfil its role as a pump to ensure corneal transparency by regulation of corneal hydration (Klyce 2005).

1.4.1.6 Corneal metabolism

The cornea is an avascular tissue. Therefore, most of the nutrition needed for the vital processes of corneal tissue is supplied by the surrounding environment, with the cellular layers of the cornea being responsible for the vast majority of the metabolic activity (Riley 1969; Freeman 1972). In open-eye conditions, the oxygen is supplied to the cornea by diffusion through the tear film with small amounts of oxygen being acquired from the aqueous humor, a clear fluid that fills the anterior and posterior chambers (Goel *et al.* 2010), and limbar capillaries (Cogan and Kinsley 1942; Fatt and Bieber 1968; Fatt *et al.* 1969). Glucose and most of the amino acids are supplied by the aqueous humor (Riley 1969; Klyce and Beuerman 1998). During closed-eye conditions, vital processes of the cornea are highly dependent on the aqueous humor. The oxygen pressure in tears decreases from approximately 155 mmHg to 55 mmHg and two thirds of the oxygen required is supplied from the palpebral capillaries (Smelser and Ozanics 1952; Fatt and Bieber 1968; Fatt *et al.* 1969).

Glucose is one of the most important nutrients required by the cornea. The metabolism of glucose involves aerobic and anaerobic pathways. Fifteen percent of glucose is oxidized and 85% is converted into lactate respectively, with lactate production increasing in anaerobic environments (Fatt and Bieber 1968; Klyce 1981). Lactate is eliminated from the cornea through diffusion into the aqueous humor. An excessive accumulation of lactate in the corneal tissue can induce epithelial and stromal oedema (Riley 1969; Klyce 1981).

Therefore, when a contact lens is introduced to an eye for an overnight application as is in case of ortho-k, it is crucial that it does not interfere with normal corneal metabolism. An oxygen tension ranging between 11.4-37.0 mmHg has been found to be the critical threshold for intact corneal metabolism to be preserved (Polse and Mandell 1970; Mandell and Farrell 1980). Also, it is important for undisturbed endothelial function as the corneal endothelium does not posses capacity of cell proliferation and has an important role in the

maintenance of corneal metabolism and transparency (Klyce and Beuerman 1998; Joyce 2012).

1.4.2 Corneal biomechanical characteristics

The cornea is a viscoelastic tissue, possessing both elastic and viscous properties (Dupps 2007; Elsheikh 2010). Elastic materials regain their initial shape in a reversible linear manner once the sheer-stress or the external load or force has been removed (Figure 1.6-A). Viscous materials, on the other hand, flow under a load and do not return to their initial shape Figure 1.6-B). Corneal layers possess different biomechanical properties (Elsheikh *et al.* 2007; Elsheikh *et al.* 2008a; Elsheikh 2010). However, the viscoelastic nature is dominated by its bulk component, the stroma, which inhibits two phase stress-strain (deformation) relationship (extracellular matrix driven and collagen driven phase respectively) (Elsheikh *et al.* 2008a; Elsheikh 2010). Additionally, regional differences in the corneal response to external stress have been reported (Hjortdal 1996; Anderson *et al.* 2004; Elsheikh *et al.* 2007; Elsheikh 2010; Thomasy *et al.* 2014; Whitford *et al.* 2015).

The energy that viscoelastic material absorbs within itself due to its mechanical properties (in this case corneal tissue) in a stress-strain cycle is referred to as hysteresis, a characteristic often used for descriptive purposes of corneal biomechanics and a direct measure of the viscoelastic nature of the corneal tissue (Figure 1.6-B) (Elsheikh 2010). Young's modulus (YM) is classic measure of corneal elastic properties in a laboratory setting (Elsheikh *et al.* 2008b; Elsheikh 2010). It is defined as a ratio of an applied stress or force to a cross sectional area to a resultant strain or deformation (Elsheikh 2010). Creep, another biomechanical characteristic, is defined as a ratio of stress and strain change material exhibits under a constant load, with a tendency to increase under the same amount of load (Elsheikh 2010). Once the load is removed, especially if the stress-strain cycle is repeated multiple times, the deformation to some extent is permanent (Elsheikh 2010). Conversely, the stress relaxation is the decrease in deformation under the same amount of load (Elsheikh 2010). Therefore, material does not return to its original shape instantly when

load is removed. Unlike creep, stress relaxation is only visible when the load is completely removed. Also, in stress relaxation the strain or force decreases, whilst the strain or deformation remains constant (Elsheikh 2010).

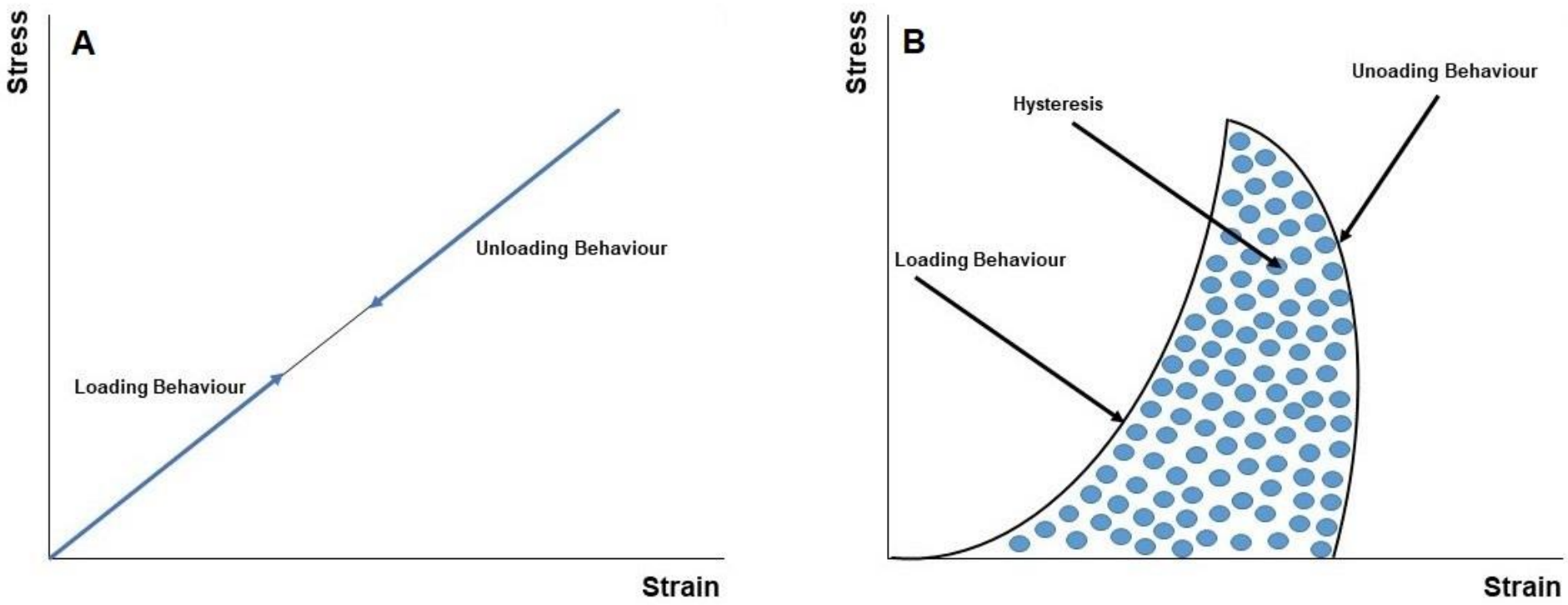

Figure 1.6 Typical stress-strain behaviour of a perfectly elastic material (A) and corneal tissue (viscoelastic material) (B). Adapted from (Elsheikh 2010).

1.4.2.1 *In-vitro* versus *in-vivo* testing

Knowledge available on corneal biomechanics at present is mostly based on tests conducted in a laboratory environment with donor tissue or using numerical simulation (Anderson *et al.* 2004; Elsheikh *et al.* 2008b; Elsheikh *et al.* 2009; Elsheikh 2010; Whitford *et al.* 2015). These tests have deepened understanding of corneal tissue changes within normal aging and disease (Elsheikh 2010). However, as they remove the cornea from its normal environment, are highly dependent on the availability of donor tissue and donors' age (Elsheikh 2010),

The advances in instrumentation (Luce 2005; Hon and Lam 2013) over the recent years have enable *in-vivo* testing, under more physical conditions than previously possible. Therefore, allowing dynamic structural analysis and observation of the anterior eye and ocular globe in various clinical settings and ocular pathologies (Luce 2005; Gonzalez-Meijome *et al.* 2008; Kirwan and O'Keefe 2008; Chen *et al.* 2009; Frings *et al.* 2015; Koprowski *et al.* 2015; Perez-Rico *et al.* 2015; Wang *et al.* 2015). The devices that are most frequently used and are available for clinical application, are the Ocular Response Analyzer (ORA) (Reichert Ophthalmic Instruments, Buffalo, NY, USA) (Corvis ST (Oculus, Wetzlar, Germany). Both devices use an air puff to temporarily deform the cornea to enable dynamic monitoring and by using bespoke technologies and mathematical calculations, records the mechanical nature of the cornea (Luce 2005; Hon and Lam 2013). The ORA and Corvis ST and their specific parameters are described extensively in Chapter 2.

The parameters of the corneal biomechanical response (for detailed list of the parameters, please refer to Section Chapter 2) are not an exact comparison to the biomechanical measures obtained by the methods used in the classical mechanical setting (Elsheikh 2010). Therefore, classical descriptors of the corneal tissue such as stiffness or elasticity should be applied with caution and a prefix 'ORA derived/specific'

and ‘Corvis ST derived/specific’ should be always used, especially in the context of hysteresis.

1.4.3 Factors affecting corneal biomechanics

It has been found that corneal biomechanics, measured *in-vivo*, are affected by age, intraocular pressure (IOP), central corneal thickness (CCT) (Kotecha *et al.* 2006; Shen, Wang*, et al.* 2008; Kotecha *et al.* 2014) and, controversially, refractive error (Chang *et al.* 2001; Shen *et al.* 2008). As discussed before, corneal biomechanical properties *in-vivo* setting are mainly messured using an air-puff applanation (Luce 2005; Hon and Lam 2013). The energy absorption in corneal tissue during rapid corneal deformation delays induced by the air-puff, results in a difference between the applanation pressures. The difference between these inward and outward motion applanation pressures is called corneal hysteresis (CH) (Luce 2005).

The cornea undergoes age-related changes as does all the tissue in the human body. A study investigating ageing of the human corneal stroma (Malik *et al.* 1992) revealed that over a life span (birth to 90 years) there is an increase in spacing between collagen molecules possibly owing to the increasing crosslinking between collagen over the time. In addition, a decrease in the inter-fibrillar spacing, presumably due to changes in proteoglycan arrangement, is present, resulting into corneal stiffening with age (Malik *et al.* 1992). The mechanism of corneal tissue stiffening has been questioned (Elsheikh *et al.* 2007). Recently, an updated biomechanical model of the human cornea was proposed and age-related stiffening of corneal tissue was linked to changes in fibril behaviour not fibril layout (Whitford *et al.* 2015).

The well-established ORA derived parameter CH, which is a measure of viscous damping properties of the cornea (Luce 2005; Kotecha *et al.* 2006; Kotecha *et al.* 2014), for example, has a tendency to decrease with age. Huang *et al.* (2011) measured CH in a population of Chinese school-children (aged 7-12 years) and found it to be 10.4 ± 2.2

mmHg. Foster *et al.* (2011) investigated CH in British adult population (aged 48 to 91 years) and found it to be 10.0 ± 1.67 mmHg. A study conducted in 2006 showed a 0.28 mmHg decrease in CH per decade (Kotecha *et al.* 2006), whereas Shen *et al.* (2008) found no significant correlation between age and CH in 45 highly myopic (-6.00 to -15.00 D) subjects and 90 healthy individuals (0.00 to -3.00 D). Foster and colleagues (2011) reported an average decrease of 0.31 mmHg in CH per decade as well as 0.34 mmHg decrease in CRF per decade (Foster *et al.* 2011).

1.4.4 Corneal biomechanics and orthokeratology

Ortho-k utilises the viscoelastic nature of corneal tissue (Elsheikh 2010). Creep and stress relaxation are the effects predominantly seen in the eyes undergoing ortho-k treatment from the classic mechanics point of view (Elsheikh 2010). Kerns (1978) speculated that corneal rigidity could influence the corneal response to orthokeratology as a large individual variability in response to treatment was observed. A pilot study conducted by Gonzalez-Meijome and his colleagues (2008) investigated the influence of short term ortho-k on the corneal biomechanical properties measured with ORA in 8 subjects with moderate myopia. ORA measurements showed that corneas with lower CH and corneal resistance factor (CRF), which is believed to described the overall rigidity of the cornea (Luce 2005), responded more rapidly to treatment and also had a tendency to recover more quickly. Chen *et al.* (2009) reported a reduction in CRF after an overnight wear of ortho-k lenses from 10.7 to 10.1 mmHg in 20 mild to moderate myopic subjects. Interestingly, no strong trends in the CH were detected. Unsurprisingly, age has been observed to influence the corneal response to ortho-k lens wear, as the cornea has a tendency to become more rigid with increasing age (Jayakumar and Swarbrick 2005).

1.5 Mechanisms of orthokeratology

The mechanisms underlying ortho-k are still not fully understood. In the early stages of orthokeratology development, an overall bending, or moulding, of the cornea was

proposed to be the mechanism of action (Jessen 1962; Kerns 1978). However, the central corneal thickness changes noted by Coon (1984), using the hydraulic fitting approach established by Tabb, and later studied in detail by Swarbrick *et al.* (1998) in myopic individuals, has suggested a theory of individual, mostly anterior corneal layer contribution towards the refractive change achieved. Swarbick *et al.* (1998) reported a central epithelial thinning of 7.1 ± 7.1 µm (corresponding to 30%) over a period of 28 days. Mid-peripheral corneal thickening of 11.0 ± 8.6 µm was found to be stromal in origin. Swarbrick and co-workers (1998) proposed a redistribution of epithelial and stromal tissue, first noted by Greenberg and Hill (1973), to induce the refractive changes and underpinned their statement by mathematical calculations using customised Munnerlyn's formula. Munnerlyn's formula is primarily used to predict the outcome of refractive surgery (Munnerlyn *et al.* 1988):

$$\boldsymbol{t = \frac{-S^2 D}{8(n-1)}},$$

were t originally is ablation depth, but in the case of ortho-k is change in sagittal height, S originally is ablation diameter but in case of ortho-k is flattened corneal zone, D is desired refractive change and n is refractive index of cornea (1.377).

Swarbrick and colleagues (1998) presumed that the tear film forces acting under the lens could enhance the corneal thickness changes observed. They also assumed that the stromal changes induced by orthokeratology cannot alter stromal structure and that the posterior part of cornea is not involved in the reshaping process. The finding of anterior corneal thickness changes was later confirmed by Alharbi and Swarbrick (2003) and others (Reinstein *et al.* 2009; Nieto-Bona *et al.* 2011a, 2011b; Qian *et al.* 2013). However, in 2004, Owens *et al.* reported curvature changes in the posterior cornea and supported a theory involving overall bending of the cornea in the initial stages of ortho-k. They observed flattening of the posterior corneal radii within the first week that

diminished with time (Owens *et al.* 2004). Therefore, theory proposing a mechanism involving initial overall bending of the cornea combined with anterior corneal tissue redistribution that, in later stages of the ortho-k treatment, is dominated by the theory of redistribution of anterior corneal tissue (Owens *et al.* 2004).

Interestingly, opposite corneal thickness changes, to those seen in myopic ortho-k, were observed in hyperopic ortho-k. Gifford *et al.* (2009a, 2009b) investigated short time effects of overnight ortho-k in hyperopia and reported central corneal steepening and para-central flattening. Later studies by Gifford *et al.* (2011) supported the finding of para-central epithelial thinning, which in return triggers the overall corneal thickness changes.

1.5.1.1 Mechanical forces acting under reverse geometry lens

Mountford (2004) proposed that a model of mechanical forces induced by reverse geometry lens is involved in ortho-k. In his model, Mountford (2004) incorporated the idea of hydraulic tear film force model, proposed by Tabb and evaluated by Coon (1984), and eyelid pressure. When a reverse geometry lens is introduced to the eye, an imbalance between forces exists. The central part of the cornea, corresponding to treatment zone of the reverse geometry lens, is exposed to compressive forces, whilst tensile forces are present at the very edge of treatment zone. The tangential stress, arising from the interaction between the viscoelastic cornea and incompressible tear film across the corneal surface, triggers the corneal shape changes until the equilibrium in the post-lens tear film is reached (Mountford 2004). Kwok (1984) presented a model of the anterior surface of the human cornea and reported that the smallest surface area of the cornea, for example, for discordant forces to reach the balance as in case of orthokeratology (Mountford 2004), is spherical. The cornea is aspheric in its nature and is characterised by eccentricity, undergoing shape changes until spherical shape or zero eccentricity is reached. The role of lid pressure involvement has been viewed cautiously

as the impact is minimal under closed eye conditions and there are no surface tension forces present (Allaire and Flack 1980; Hayashi and Fatt 1980; Mountford 2004).

1.5.1.2 Morphological changes of the cornea in orthokeratology

Animal studies support the clinical findings of myopic ortho-k (please refer to Section 1.5.1.21.2). Matsubara *et al.* (2004) used a rabbit model to investigate the effects of ortho-k-lens wear at microscopic level over a period of 28 days. In the central part of the cornea, the basal cells were flattened with higher mitotic activity. Also, the number of cell layers was unchanged. In the mid-peripheral region, which corresponded to the alignment zone of the lens, the number of epithelial cell layers increased, the basal cells were elongated, the wing cells were stratified, and the mitotic activity of basal cells was reduced here. No stromal changes were reported (Matsubara *et al.* 2004).

Choo *et al.* (2008) used a cat model to investigate morphological changes induced by ortho-k. Compression of central epithelial basal cells and elongation of mid-peripheral basal cells was noted as soon as 4 hours after ortho-k lens wear in the cat model mimicking myopia. After two weeks of lens wear, morphological changes in the epithelium became more pronounced and relative stromal thinning was observed. Centrally, changes in the number of epithelial cell layers was hard to assess, however, in mid-peripheral regions an increase in cell layers was observed (Choo *et al.* 2008). The authors speculated that morphological changes seen in early stages of treatment (e.g. cell compression) are accompanied by alteration in the cell metabolic processes, which take place at later stages. Hence, providing a possible explanation for the enhanced cell proliferation in mid-peripheral regions of epithelium and stromal thinning encountered. In the same study the effects of hyperopic ortho-k were also investigated. In hyperopic animals, central epithelial thickening was reported after 4 hours of lens wear. Initially, an elongation of central basal cells with slight changes in mid-peripheral region was observed. However, in later stages of treatment central epithelial basal cells regained

their usual appearance, whilst basal cells in mid-periphery appeared to be compressed (Choo *et al.* 2008).

Cheah *et al.* (2008) reported changes induced by ortho-k lenses over a period of 24 hours in a primate model. The number of epithelial cell layers remained unchanged across the whole surface area of the cornea. A central epithelial thinning together with compression of basal cells was reported. In the mid-peripheral region, the basal cells were elongated and the superficial cell nuclei were enlarged. No morphological alterations in stromal and endothelial structure were detected. Authors presumed that changes in cell shape, especially in surface cells, indicated that epithelial renewal rate is slower and highlighted the ambiguous nature of stromal thickness changes as no morphological alterations were observed (Cheah *et al.* 2008).

Conversely, other studies investigating morphological changes induced by short and long-term wear of orthokeratology lenses in human corneas, using confocal microscopy (Nieto-Bona *et al.* 2011a, 2011b) reviled the theory of central epithelial thinning and mid-peripheral corneal thickening, as well as decrease in basal cell density. Keratocyte density in stroma decreased at the initial stages of lens wear, but returned to baseline measures after 1 month. A thinning of Bowman's layer and sub-basal nerve plexus was also noted (Nieto-Bona *et al.* 2011b). After 1 year of ortho-k lens wear, central epithelial thinning and reduction in basal cell density of 12-15% were still present, however, stromal keratocyte density was closer to baseline measurements (Nieto-Bona *et al.* 2011a). These findings indicate that corneal response to ortho-k may involve various cell processes, mostly located in epithelial layer of the cornea, presumably triggering stromal response similar to that observed in the process of injury in the initial stages of treatment (Wilson *et al.* 1996). Corneal epithelial response to injury involves a three phase process of cell migration, proliferation and cell adhesion in the affected area (Dua *et al.* 1994). Corneal epithelium also triggers stromal response to injury that involves keratocyte apoptosis, migration and subsequently decrease in their density (Wilson *et al.* 2001).

Nieto-Bona *et al.* (2011a) also reported significant changes in endothelial cell density after a 1 year of ortho-k lens wear. Increase in the endothelial cell polymegathism (change in cell size) reversed after ceasation of ortho-k treatment; however, it did not return to baseline (BL). No changes were reported after a month of ortho-k lens wear (Nieto-Bona *et al.* 2011b). Authors noted that the area of visualisation for an image is relatively small and the quality of the image is highly dependant on the subject corporation.These factors limit the possibility of imaging the whole area corresponding to the ortho-k lens, therefore, number of images were taken averaged to obtain an accurate cell count of different corneal layers. Also, if corneal oedema is present, it affects the visualisation of the corneal layers and leads to an underestimation of cell count (Nieto-Bona *et al.* 2011a).

Qian *et al.* (2013) supported the previously found evidence of central epithelial thinning and indicated that the inconsistency in mid-peripheral corneal thickness may arise due to the assessment in different locations as regional differences in corneal thickness and biomechanical properties have been observed previously (Hjortdal 1996; Shin *et al.* 1997).

1.6 Retention and reversibility of orthokeratology

The reversibility of refractive changes achieved by ortho-k has been studied, both in short and long term ortho-k. For example, it was reported by Sridharan and Swarbrick (2003) that as little as 10 minutes of reverse geometry lens wear can induce significant refractive changes. However, 8 hours of lens wear was suggested to reach the optimal effect. Mountford (1998) investigated the effect of retention and regression of accelerated ortho-k over a period of 90 days. The greatest reduction in refractive error occurred during the first week after the commencement of ortho-k. The daily regression (0.50 – 0.75 D), however, was observed to stabilise and decrease towards the end of the study period (Mountford 1998). Sorbara *et al.* (2005) studied regression of ortho-k effect after 72-hour

long wash-put period after a month of ortho-k lens wear. A recovery of approximately 60% of initial refractive error was observed. Barr and colleagues studied aspects of recovery after 6 to 9 months of daily ortho-k in 96 myopic individuals (Barr *et al.* 2004). The refractive error tended to return to baseline measures within 72 hours. However, they speculated that the recovery aspects are patient and refractive error dependant and complete and stable return to the initial state can take a longer time (Barr *et al.* 2004). Soni *et al.* (2004) reported that corneal thickness returned to baseline measures within 24 hours, but full corneal recovery, after one month of overnight ortho-k, occurred within two weeks. Wu *et al.* (2009) reported a corneal flattening of 0.27 D in the spherical component and an increase in with-the-rule astigmatism of 0.17 D after cessation of lens wear in myopic children, who underwent ortho-k treatment for 4 years. The authors speculated that wash-out period might have been insufficient; however, as the trend was seen in all individuals, they also concluded that the residual 'permanent' changes are mild but clinically insignificant (Wu *et al.* 2009).

Nieto-Bona and co-workers observed the recovery aspects on morphological basis after a 1 month wash-out period in myopes who underwent ortho-k treatment for one year (Nieto-Bona *et al.* 2011a). The epithelium and stroma returned to baseline measures within the wash-out period. However, the 3% reduction in Bowman's layer and sub-basal nerve plexus thickness did not recover. The authors, however, recommended that a larger study cohort would be required to establish this statement as it was difficult to distinguish between epithelial and stromal layer border under confocal microscopy during the treatment phase owing to epithelial thinning and cell compression (Nieto-Bona *et al.* 2011a).

1.7 Corneal insults associated with orthokeratology

Early studies focusing on safety aspects of ortho-k indicated that orthokeratology is relatively safe and concluded that it does not create more complications than conventional rigid contact lens wear (Kerns 1978; Polse *et al.* 1983).

Nevertheless, until a deeper understanding of the mechanisms underlying ortho-k and corneal changes induced by it is acquired, the safety aspects of ortho-k must be evaluated more intensely. Swarbrick and co-workers (1998) speculated that the epithelial thinning induced by ortho-k might compromise the permeability of epithelium and, therefore, its barrier function. The observations of confocal microscopy have questioned the stromal response to ortho-k as activation of keratocytes was observed (Nieto-Bona *et al.* 2011a). A change in tear film composition after ortho-k lens wear has also been noted (Choy *et al.* 2004).

Microbial keratitis (MK), although rare, is one of the most severe complications associated with contact lens wear, causing severe complications and vision loss (Dart 1988; Cheng *et al.* 1999; Stapleton *et al.* 2008) and has been associated with orthokeratology (Watt and Swarbrick 2007). In a review focusing on the occurrence of MK, Watt and Swarbick (2007) summarised 123 cases of MK induced by ortho-k from 2001 to 2007. The vast majority of MK occurred in the region of East Asia (85 cases) and was associated with the lack of regulations regarding ortho-k technique. Sixty four cases originated from China, reaching the peak in prevelance around 2001, when the ortho-k market in China was unregulated. Lenses were fitted by untrained professionals using unsuitable lens materials for overnight wear (Watt and Swarbrick 2007). Good practice guidelines have since been established to promote patient compliance and standardise the routine of prescribing procedure for practitioners (Cho *et al.* 2008). The guidelines outline practitioner and supporting staff education, minimal requirments of instrumentation needed for ortho-k lens fitting, trial fitting, patient eductation (in practice

and with patient information sheets), patient consent for the ortho-k treatment and follow up. Bullimore *et al.* (2013) reviewed 50 cases of MK from 27 practitioners, which represented one third of all practices providing data for the study. Each practice was adjusted and stratified depending on the number of patients in total and those fitted with ortho-k lenses to diminish any bias. Limiting the sample to those patients with at least 3 months of documented contact lens wear since 2005, resulted in a smaller sample of 1317 patients; 640 adults (49%) and 677 children (51%) representing 2599 patient-years of wear (adults = 1164; children = 1435). It was estimated that the incidence of MK among adults was 0 per 10,000 patients-years of wear (95% CI=0 to 31.7) and 13.9 per 10,000 patient-years of wear (95% CI = 1.7 to 50.4) with an overall estimated incidence of 7.7 per 10,000 patients-years of wear (95% CI = 0.9 to 27.8).

The permeability of the epithelium was found to be unaffected in study conducted by Yeah and co-workers in 39 myopic individuals after 30 days of ortho-k lens wear, indicating that the thickness and morphological changes observed in the previous studies (Swarbrick *et al.* 1998; Alharbi and Swarbrick 2003) do not compromise epithelial barrier function (Yeh *et al.* 2013). Moreover, no clinically significant fluorescein staining was observed.

Clinical case reports have indicated an occurrence of fibrillary lines and iron rings in ortho-k lens wear (Cho, Chui*, et al.* 2002; Lum and Swarbrick 2007; Gonzalez-Meijome *et al.* 2012). Fibrillary lines reported by Lum and Swarbrick (2007), in a 39 year old woman, and in 3 out of 150 patients over a period of 2 years by Cheung *et al.* (2006), were presumed to represent the changes in sub-basal nerve plexus owing to the migration of epithelium. It was later confirmed by Lum *et al.* (2012) that these lines represent altered nerve fibres. However, as they are also observed in a healthy non-contact lens wearing individuals (Bron 1975), they are not regarded as complication of ortho-k lens wear.

In addition, iron rings, first observed by Cho and colleges (Cho *et al.* 2002b) and later detected by others (Liang *et al.* 2003; Gonzalez-Meijome *et al.* 2012), have not been regarded as an ortho-k complication. It has been reported that the rings can resolve themselves within two months after cessation of ortho-k lens wear (Cho *et al.* 2003). However, they have a tendency to increase in occurrence with the length of ortho-k lens wear (Cho *et al.* 2005). Cho *et al.* (2002) associated iron rings with rapid corneal curvature changes induced by ortho-k and tear pooling under the reverse geometry lens and presumed them being epithelial in origin.

1.8 Research rationale and aims

Myopia is a global health problem, which is a major cause of visual impairment and blindness across the globe (Pan *et al.* 2012; Holden *et al.* 2014; Holden *et al.* 2016). The rapid increase in myopia has heralded a significant amount of interest in the development mechanisms and interventions to slow down this condition (Holden *et al.* 2014; Sankaridurg and Holden 2014; Holden *et al.* 2016). The wealth of research has shown that myopia is not solely a refractive condition or a simple inconvenience (Flitcroft 2012; Holden *et al.* 2014). It is a life-long condition, that increases the risk of ocular pathology in a similar manner as hypertension increases the risk of cardiovascular disease (Flitcroft 2012). However, at present no consensus exists on how to manage this condition effectively and numerous questions remain unanswered. The various myopia control (MC) methods available are off-label and not available within a standard clinical setting (Johnson 2014; Gifford and Gifford 2016). The clinical efficacy versus the statistically significant efficacy of MC interventions has been questioned both by researchers and clinicians (Fulk *et al.* 2000; Johnson 2014).

One of the most promising optical MC interventions, ortho-k, despite its relative success in slowing down myopia progression by up to 50% (Cho and Cheung 2012; Chen *et al.* 2013), has been met with reluctance for adaptation into general clinical practice owing to the selective treatment outcome, the unclear mechanism by which the treatment outcome is achieved and long term effect to corneal tissue (Kwok *et al.* 2005; Swarbrick 2006; Johnson 2014). New instrumentation able to dynamically assess corneal biomechanical properties *in-vivo* (Luce 2005; Hon and Lam 2013) have shown promising results in pilot studies, investigating corneal biomechanical response in ortho-k lens wear (Gonzalez-Meijome *et al.* 2008; Chen *et al.* 2009). Nevertheless, further research of corneal tissue and the anterior segment of the eye response to ortho-k lens wear, especially in progressing myopia, is required.

The aim of the work presented in this thesis is to aid a better understanding of the current clinical management of MC and in particular the application of ortho-k. Therefore, the following research studies were be conducted:

1. Investigation of the attitudes of eye-care practitioners across the globe towards myopia control via a cross-sectional survey.
2. A retrospective data analysis investigating corneal biomechanics in a cohort of progressing myopic schoolchildren undergoing ortho-k treatment over a two-year period.
3. A study of short term corneal biomechanical effects of an ortho-k lens wear over the first 7 nights of treatment.
4. A cross-sectional study in healthy individuals investigating factors such as age, ethnicity, eye and body size, and nutrition and subsequently their influence on the corneal biomechanical properties.

Chapter 2. Instrumentation

2.1 General overview

This chapter describes the instrumentation and general methodology used for acquiring measurements in Chapters 4-6. Specific details of the methodology employed within the experimental chapters (Chapters 3-6) are described in the methods section of each individual chapter.

Several of the instruments described in this chapter and employed in the experimental chapters have the ability to obtain the same measurements. Part of the thesis is focusing on retrospective data analysis (Chapter 4). Therefore, when developing methodology for other chapters (Chapters 5-6), the same instruments or instruments using similar measurement techniques, were utilised. Summary of the instruments used in the study are presented in Table 2.1.

Initially Corvis ST (Oculus, Wetzlar, Germany) was selected for the assessment of central corneal thickness (CCT), due to the similar imaging technique employed by the Pentacam (Oculus, Wetzlar, Germany), from which data were extracted for the retrospective analysis. The use of Corvis ST reduced the appointment time as corneal biomechanical response and CCT could be obtained in a single measurement. Corvis ST was reported to be a reliable instrument for the assessment of CCT (Hon and Lam 2013; Hong *et al.* 2013). Issues experienced whilst using the instrument for data collection for the experimental Chapter 6 (instrument not firing up or not taking measurements), led to reconsideration of its use for CCT assessment. Aladdin (Topcon, Tokyo, Japan), which also measures CCT, had been used for measurements taken simultaneously for another study not included in the thesis. These measurements were, therefore, used instead. Later, at the data analysis stage for Chapter 5, ocular biometric parameters such as anterior chamber depth (ACD) and crystalline lens thickness (LT) became relevant for studies discussed in experimental Chapters 4 and 5 and were

extracted from Pentacam for the retrospective analysis and Aladdin for the prospective study.

Instrument:	Used for measuring:	Used in Chapter:
ORA (Reichert Ophthalmic Instruments, Buffalo, NY, USA)	Corneal biomechanical properties	Chapter 4 to Chapter 6
Corvis ST (Oculus, Wetzlar, Germany)	Corneal biomechanical properties	Chapter 5 to Chapter 6
Shin Nippon SRW-5000	Refractive error	Chapter 5 to Chapter 6
IOL Master 500 (Carl Zeiss, Jena, Germany)	Axial length (AL)	Chapter 4 to Chapter 6
Aladdin (Topcon, Tokyo, Japan)	CCT	Chapter 5 to Chapter 6
Pentacam (Oculus, Wetzlar, Germany)	CCT	Chapter 4
Corneal Topographer Medmont E300 (Medmont Ltd, Melbourne, Australia)	Corneal topography	Chapter 4 to Chapter 6
Specular microscope SP 3000P (Topcon, Tokyo, Japan)	Corneal endothelial imaging	Chapter 4 to Chapter 6

Table 2.1: Summary of instrumentation used in the experimental chapters of the thesis.

2.2 Assessment of corneal biomechanical properties

2.2.1 Ocular Response Analyzer

The Ocular Response Analyzer (ORA) (Reichert Ophthalmic Instruments, Buffalo, NY, USA) is a non-contact tonometer (NCT) that uses a rapid air pulse to indent the cornea and assesses its biomechanical response through a force-displacement relationship (Figure 2.1-A) (Luce 2005).

The measurement takes place within a 20 ms interval and can be described by two separate applanation events – one that displaces the cornea inward (inward applanation) and the second resulting from the outwards rebound as the cornea returns to its initial shape (outward applanation) (Figure 2.2) (Luce 2005). During the first inward applanation, a controlled amount of air pressure pulse (P1), forces the cornea inwards past the applanation point (peak 1) into a concave shape. The first applanation event acts as a trigger to gradually switch off the air pressure pulse in a symmetrical time-inverse manner after a further increase in air pressure (Pmax) has taken place. The cornea then returns to a convex shape past the second (outward) applanation point (peak 2) and pressure (P2) is recorded. P1 and P2 are determined by drawing a line down from each of the applanation peaks to the intersection of the pressure curve (Figure 2.2). An electro-optical detection system monitors the corneal curvature changes, using an infrared light reflected from the central 3 mm of the cornea. The resulting voltage change during the measurement process is recorded to create an air-pressure deformation with time waveform curve (Figure 2.1-B and Figure 2.2). The P2 value is lower than the initial P1 value, which results from the viscous damping properties of the cornea and is termed corneal hysteresis (CH=P1-P2) (Figure 2.2) (Luce 2005; Kotecha *et al.* 2006; Elsheikh, Alhasso*, et al.* 2009).

CH is thought to be a measure of the cornea's ability to absorb and dissipate energy (Luce 2005; Kotecha *et al.* 2006). Corneal resistance factor (CRF), which is believed to

describe the overall resistance of the cornea, is derived from CH and is calculated as a linear function of the two applanation pressures, using a proprietary algorithm (CRF= k1 x (P1 - 0.7 x P2) + k2; k1 and k2 are constants that are non-disclosed by the manufacturer) (Kotecha *et al.* 2006; Shah *et al.* 2006; Ortiz *et al.* 2007; Reinstein *et al.* 2011). As a non-contact tonometer, the ORA also displays two intraocular pressure (IOP) measurements. Goldmann correlated IOP (IOPg) is a mean of two IOP measurements and corneal-compensated IOP (IOPcc), which is less affected by the corneal properties such as central corneal thickness (CCT) and CH Figure 2.2 (Ortiz *et al.* 2007; Elsheikh, Alhasso*, et al.* 2009; Reinstein *et al.* 2011).

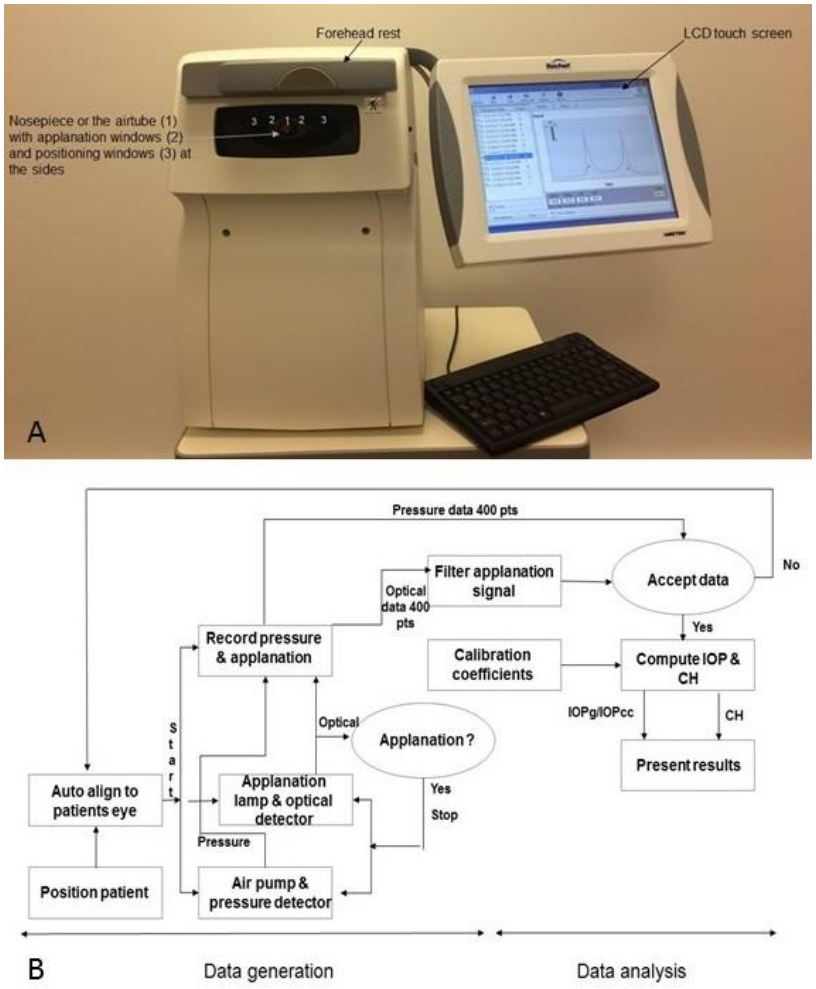

Figure 2.1 (A) The set-up of the second generation ORA; (B) Schematic representation of measurement and data generation process, scheme redrawn from Luce (2005).

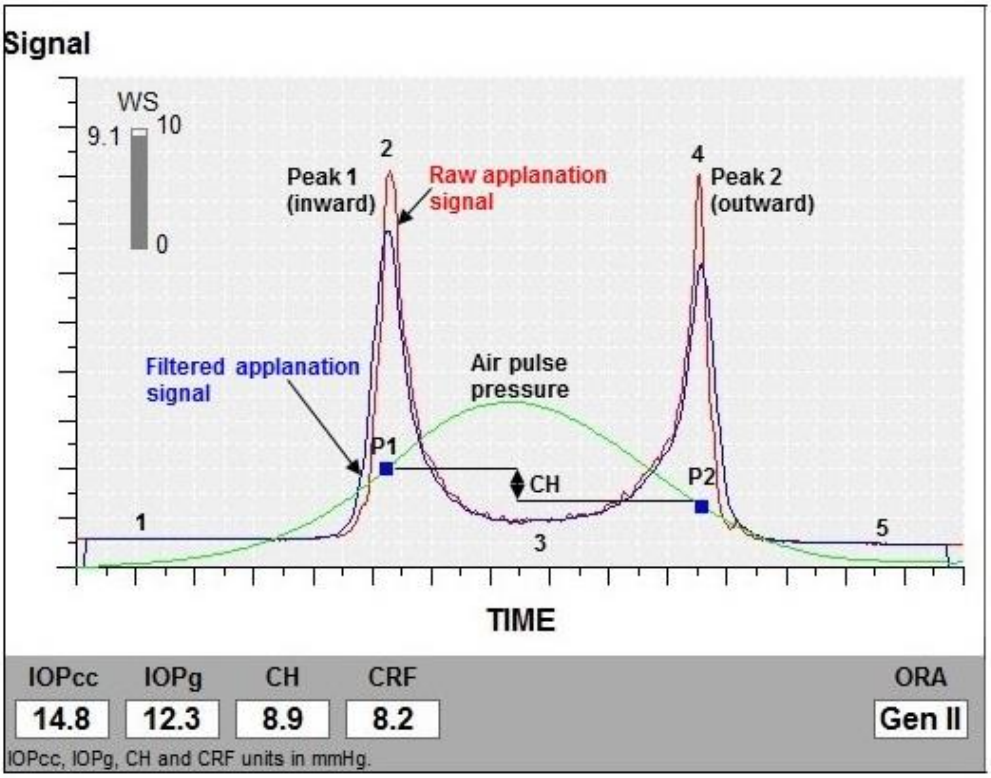

Figure 2.2 The output of the ORA measurement. (1,5) convex cornea, (2, 4) flat cornea, (3) concave cornea; peak 1 representing the initial inward applanation, peak 2 representing the subsequent rebound applanation; P1 – pressure of the first applanation, P2 – pressure at the point of the outward applanation; WS – waveform score represents the measurement signal quality (Kotecha *et al.* 2006; Shah *et al.* 2006; Ehrlich *et al.* 2010).

CH and CRF are purely empirical parameters and should be evaluated cautiously (Reinstein *et al.* 2011). No correlation between the ORA-derived parameters CH and CRF and the standard mechanical parameters, for example, hysteresis and Young's modulus have been found; these parameters are not expected to show any correlation as they are obtained in two very different experimental settings (Elsheikh 2010; Lau and Pye 2011). Moreover, conflicting reports exist regarding the application of CH and CRF in different clinical situations, especially in normal aging of human eye (Malik *et al.* 1992; Kotecha *et al.* 2006; Kotecha *et al.* 2014). The cornea has been found to stiffen with age (Malik *et al.* 1992), whilst ORA-derived CH has been demonstrated to decrease with age (Kotecha *et al.* 2006; Kotecha *et al.* 2014). The prefix 'ORA-derived' should always be

used, when describing corneal biomechanical response using the ORA. Furthermore, studies in keratoconic (Fry *et al.* 2008; Saad *et al.* 2010; Mikielewicz *et al.* 2011; Wolffsohn *et al.* 2012) and post-Lasik patients (Kerautret *et al.* 2008; Landoulsi *et al.* 2013) have shown that CH and CRF have low sensitivity and specificity in discriminating between healthy and ectatic eyes (Saad *et al.* 2010; Reinstein *et al.* 2011). An additional 37 parameters have been derived and found to be better indicators of corneal biomechanical response than CH and CRF alone (Reinstein *et al.* 2011; Landoulsi *et al.* 2013). Additional parameters are based on the results of studies, which have investigated the applanation signal morphology in detail and have derived their own applanation curve descriptive parameters (Fry *et al.* 2008; Kerautret *et al.* 2008; Saad *et al.* 2010). The waveform signal morphology and the standardised parameters developed for and incorporated in the Reichert ORA-Generation II will be discussed in section 2.2.1.1.

2.2.1.1 Signal morphology and the additional ORA-derived parameters from the waveform curve

An applanation curve in normal eyes is nearly symmetrical, with its height dependent on the pressure needed to applanate a specific eye (Figure 2.2). The applanation signal or waveform, especially the raw signal (Figure 2.2) may vary in appearance between measurements. However, the height of the both inward and outward applanation signal peaks should be above the air-pressure curve (Figure 2.2). Both applanation peaks should have a well-defined high or end point (Figure 2.2). Also, the signal peaks should be similar in amplitude, approximately symmetrical and relatively free from noise (Luce 2005; Saad *et al.* 2010).

The filtered waveform is an improved version of the raw applanation signal and is designed to detect the optimal point of applanation in less than ideal signals. A parameter called waveform score (WS), with its values ranging from 0 to 10, has been incorporated

in the measurement process of the ORA-Generation II (version 2.04) to monitor the quality of the signal and subsequently the measurement itself (Ehrlich *et al.* 2010; Lam *et al.* 2010; Ayala and Chen 2012; Mandalos *et al.* 2013). Studies have recommended only selecting measurements when the cut-off value of WS is at least 3.5, to ensure reliability (Ehrlich *et al.* 2010; Lam *et al.* 2010; Ayala and Chen 2012; Mandalos *et al.* 2013). The vast majority of studies are in agreement that a cut-off value for WS between 6.0 to 7.0 and above for a reliable measurement should be chosen (Ehrlich *et al.* 2010; Ayala and Chen 2012; Mandalos *et al.* 2013). It is recommended to take several measurements with a reliable WS score and the ORA device itself will present the best measurement based on an internal undisclosed algorithm (Ayala and Chen 2012).

The 37 standardised ORA-derived parameters, derived by Reichert, are intended to provide a detailed description of the waveform, resulting from the two applanation events in relation to the air pulse pressure curve (Figure 2.2). These are summarised in Table 2.2. The interpretation of the parameters derived from the waveform needs to be applied to each clinical situation individually (Mikielewicz *et al.* 2011). A graphical representation of these parameters has been demonstrated in Figure 2.3. The waveform curve (referred to as applanation curve) has been divided into the upper 75% and upper 50% with regards to its height (Figure 2.3). The additional parameters are divided into two groups. The first group consists of 24 parameters and describes the upper 75% of each peak and the curve in general (slew1, slew2, mslew1, mslew2, dive1, dive2, aindex, bindex and alphf), whilst the second set, consisting of 13 parameters, describes the upper 50% of each peak (Table 2.2).

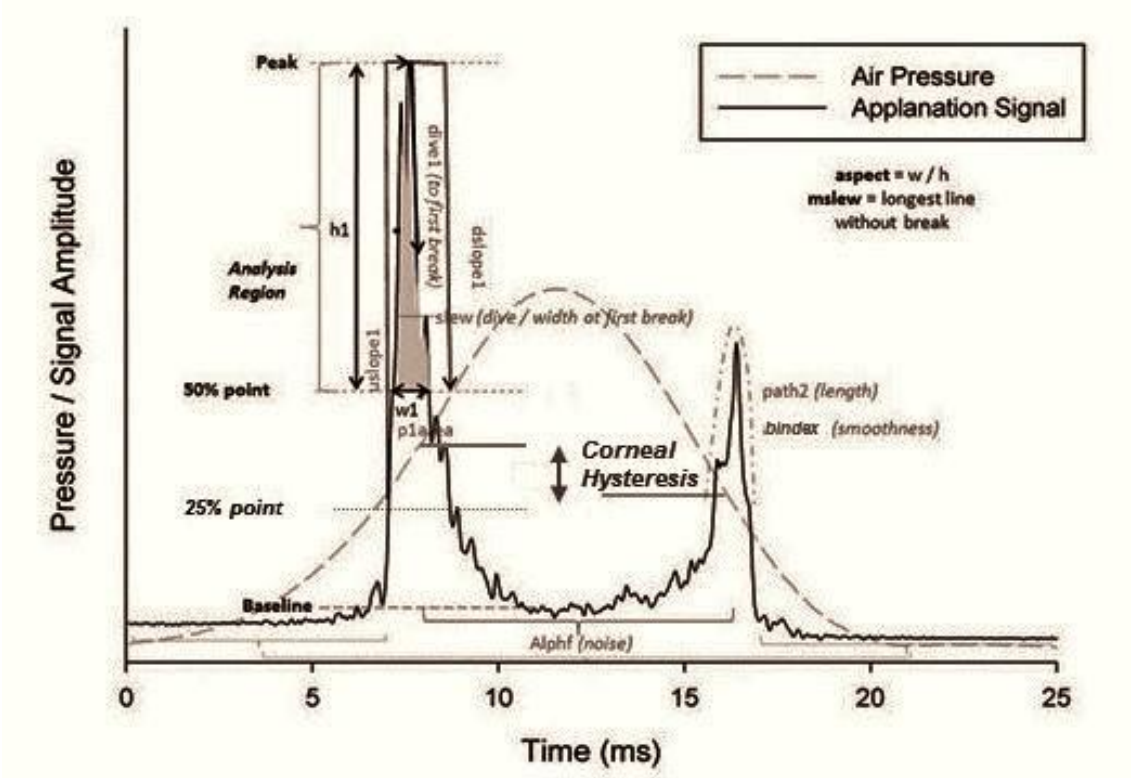

Figure 2.3 Graphical representation of the 37 ORA-derived parameters from the applanation signal. Definition of individual parameters has been provided in Table 2.2 Summary and definition of the 37 additional parameters derived from the ORA applanation signal. Adapted and reprinted with permission from Wolffsohn *et al.* (2012).

The repeatability and reliability of the four original parameters (CH, CRF, IOPg and IOPcc) have been widely studied and have been found to range from moderate to good in adult (Moreno-Montanés *et al.* 2008; Wasielica-Poslednik *et al.* 2010; Xu *et al.* 2011; Landoulsi *et al.* 2013) and child populations (Hon *et al.* 2012). However, only one study to date has investigated the repeatability of the waveform parameters (Landoulsi *et al.* 2013). Landoulsi *et al.* (2013) found that the additional parameters were variable, and only six parameters (p1area and p2area from the upper 50% and 75% of the applanation peak and h1 from the upper 50% and 75% from applanation peak) were repeatable. They enrolled 100 patients in their study and conducted analyses of both eyes of each participant. Participants were divided into five subgroups: patients under 30 years of age with a good ocular health; patients with good ocular health between the age of 30 to 50

years; patients with good ocular health 50 years and older; patients who had undergone LASIK refractive surgery and patients with a history of photorefractive surgery. No information regarding the number of participants in each subgroup were provided by the authors. Ten consecutive ORA measurements in a single session were taken and interclass correlation coefficients (ICCs) were evaluated. If all ten measurements were analysed, 9 parameters showed substantial to perfect agreement (ICC≥0.61), 4 parameters showed moderate agreement (ICC 0.41-0.60) and 28 parameters showed slight to fair agreement (ICC 0.10 to 0.40). If only three measurements with the best WS were selected for analysis, 10 parameters achieved substantial to perfect agreement, 7 parameters showed moderate agreement and 24 parameters were in fair to slight agreement. Age had a minor effect on the repeatability of measurements (Landoulsi *et al.* 2013). Eight parameters showed substantial to perfect agreement in the subgroup of patients with good ocular health older than 50 years, whilst only four and five parameters achieved the same ICC values in the subgroup of patients younger than 30 years and subgroup of patients between 30 to 50 years of age (Landoulsi *et al.* 2013). Nevertheless, the final conclusions were based on the analysis of the whole group rather than each subgroup individually. The authors suggested that clinical decisions should be made based on the parameters with the highest repeatability and based on the initial (inward) applanation peak in order to reach consistent conclusions (Landoulsi *et al.* 2013) (Table 2.2 and Figure 2.3).

The ORA-Generation II was used in the experimental chapters (Chapters 4 to Chapters 6). It is recommended by the manifactuer to take several measurments per eye in order for the ORA to select the best measurement based on WS and the applanation signal quality. No more than 5 measurements were taken per eye (Ehrlich *et al.* 2010). The best measurement selected by the ORA was used for the analysis. A cut-off value of 3.6 for WS was selected for the retrospective data analysis described in Chapter 4, which included a child population. Children have a tendency to fixate and co-operate with the

examiners less effectively (Hon *et al.* 2012). A cut-off value for WS of 6.5 was chosen in experimental Chapters 5-6 (Ehrlich *et al.* 2010).

Applanation peak 1 (inward applanation)	Applanation peak 2 (outward applanation)	Definition
slew1	slew 2	aspect ratio of dive2 where dive2 is divided by width
mslew1	mslew2	maximum single increase in the rise of the peak (longest continuous line without a break)
dive1	dive2	backside of downslope of peak (absolute value of peak until the first break)
aindex	bindex	the smoothness of the peak (related to the noise of the measurement aka how many times peak changes the direction and represent local imperfections in the cornea, respectively softness of the cornea)
alphf		the smoothness of the region between the peaks (related to the noise of the measurement and represent local imperfections in the cornea, respectively softness of the cornea)
Parameters derived from the upper 50% and 75% of the peak		
p1area	p2area	area under the curve (AUC) (proportional estimate of the time needed for the cornea to change from the convex/concave to the concave/convex form; smaller values indicate that the cornea is less dampable)
h1	h2	height from the lowest to the highest point in peak
w1	w2	width at the base of the peak region (descriptor of the time course)
aspect 1	aspect 2	aspect ratio of the peak (height/width)
uslope1	uslope2	rate of increase from base to peak
dslope1	dslope2	rate of decrease from peak to base
path1	path2	the absolute value of path length around the peak

Table 2.2 Summary and definition of the 37 additional parameters derived from the ORA applanation signal. Parameters are assembled in two groups – the first group contains parameters describing the whole applanation curve; the second group contains parametrs that are specific for both, the upper 50% and 75% of the peak. The definitions of the parameters have been adopted from Mikielewicz *et al.* (2011), Wolffsohn *et al.* (2012) Luz *et al.* (2012; 2013; 2016). Note: parameters with the highest repeatability based on which clinical decisions should be made, according to the study conducted by Landoulsi *et al.* (2013).

2.2.2 Corvis ST

The Corvis ST (Oculus, Wetzlar, Germany) is a non-contact tonometer combined with Scheimpflug imaging to allow a dynamic investigation of the corneal response to an air pulse (Hon and Lam 2013; Hong *et al.* 2013) (Figure 2.4.).

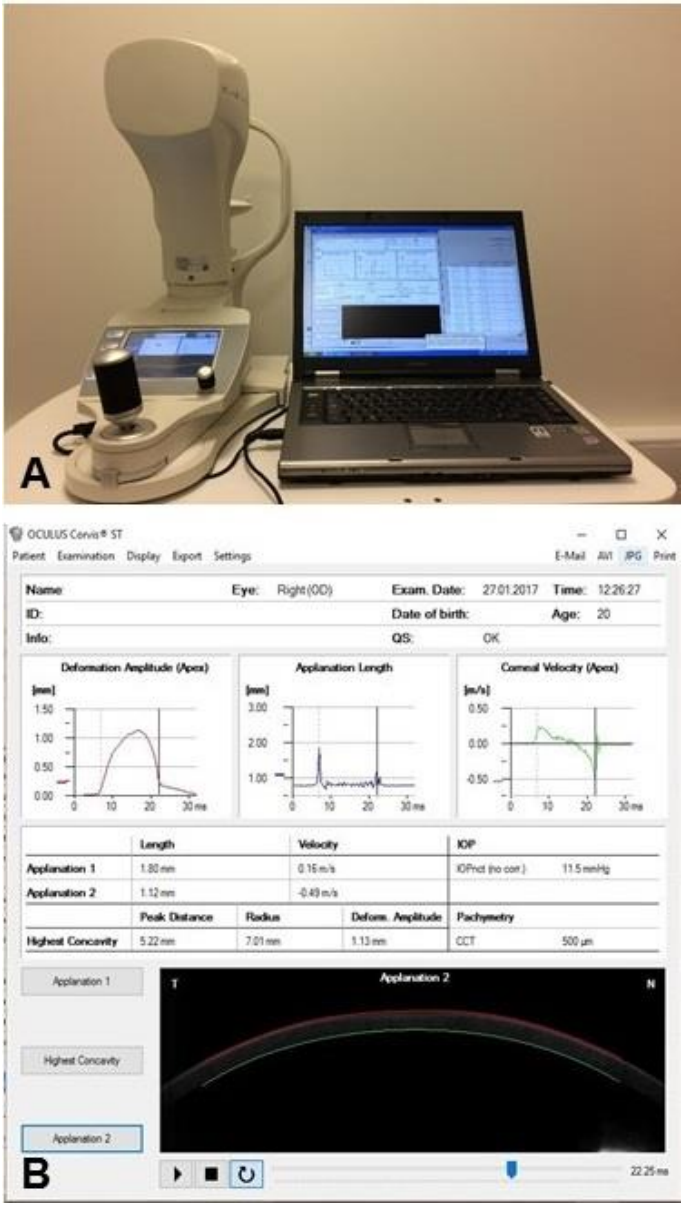

Figure 2.4 (A) Corvis ST setup. The Corvis ST device is connected to a laptop with an installed patient management software for easier patient management and observation of corneal response to the air puff, (B) The home screen of the measurement output.

A high-speed camera, alongside a slit light source, which illuminates a sectional plane of the cornea, is incorporated within the instrument. The camera gathers 4330 frames per second and produces 140 images per measurement. Subsequently, a 30 ms long video output is displayed. The image plane of the camera is tilted 45^{o} to the optical axis of the camera lens. It allows the observation of a real time dynamic deformation of the cornea, particularly its cross-section, over an 8.5 mm diameter of coverage (Figure 2.4-B). A measurement of IOP and assessment of corneal biomechanical response is acquired by quantifying the video output (Oliveira *et al.* 2011; Hon and Lam 2013; Hong *et al.* 2013; Lanza *et al.* 2016). The instrument is operated by a joystick and 'fires' automatically, once an optimal alignment, which can be monitored through a display, is achieved (Figure 2.4-A).

The cornea is exposed to a controlled amount of the air-puff (30.3 kPa) and goes through three separate phases (Hon and Lam 2013; Hong *et al.* 2013). The initial response of the cornea to the air pulse is the first applanation, with the cornea then subsequently moving inwards and reaching the point of highest concavity (point in time in which cornea has reached the longest distance from its original position and shape). Thereafter, the cornea rebounds and returns to its original shape through the second applanation (Hong *et al.* 2013; Reznicek *et al.* 2013; Perez-Rico *et al.* 2015). A graphical representation of the video output and the applanation process is presented in Figure 2.5.

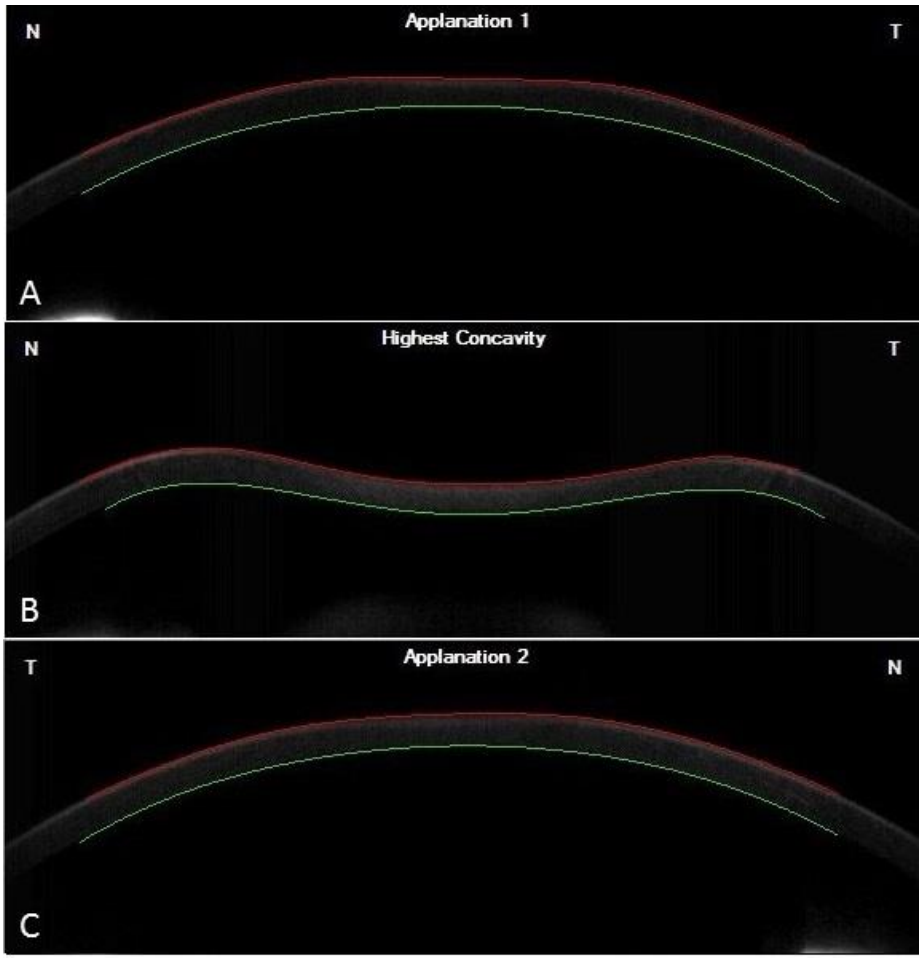

Figure 2.5 Corvis ST deformation profile. (A) Applanation 1, when a controlled amount of air pulse is directed onto the cornea, (B) point of highest concavity (HC), (C) rebound or second applanation, thorough which the cornea regains its convex shape.

The quantification of the video output allows several Corvis ST specific parameters, which describe corneal displacement with respect to time, length (Figure 2.6-A) and amplitude (Figure 2.6-B), to be derived from the applanation process. These parameters and their definitions are summarised in Table 2.3 and a graphical representation is presented in Figure 2.6.

Parameter	Definition
IOP (mmHg)	IOP base on the first applanation response
Central corneal thickness (CCT) (μm)	CCT based on the optical image analysis
Deformation Amplitude (DA)	maximum deformation amplitude (from the commencement of the delivery of air puff to the highest concavity) at the corneal apex
A1 time (ms)	time from the start of the measurement until the first applanation
A1 length (mm)	length of the flattened cornea during the first applanation
A1 velocity (m/s)	corneal velocity during the first applanation moment
A2 time (ms)	time from the start of the measurement until the second applanation
A2 length (mm)	length of the flattened cornea during the second applanation
A2 velocity (m/s)	corneal velocity during the second applanation moment
HC time (ms)	time from the start of the measurement until the cornea reaches the point of highest concavity
Peak distance (mm)	the distance between the highest point of non-deformed cornea
Radius of curvature (mm)	the curvature of non-deformed cornea
A1 deformation amplitude (mm)	amplitude of the deformation during the first applanation
HC deformation amplitude (mm)	amplitude of the deformation during at highest concavity
A2 deformation amplitude (mm)	amplitude of the deformation during the first applanation

Table 2.3 The Corvis ST derived parameters (software version 102.r1260) and their definition. Definitions were adopted from Hon and Lam (2013), Matsuura *et al.* (2016) and Lanza *et al.* (2016).

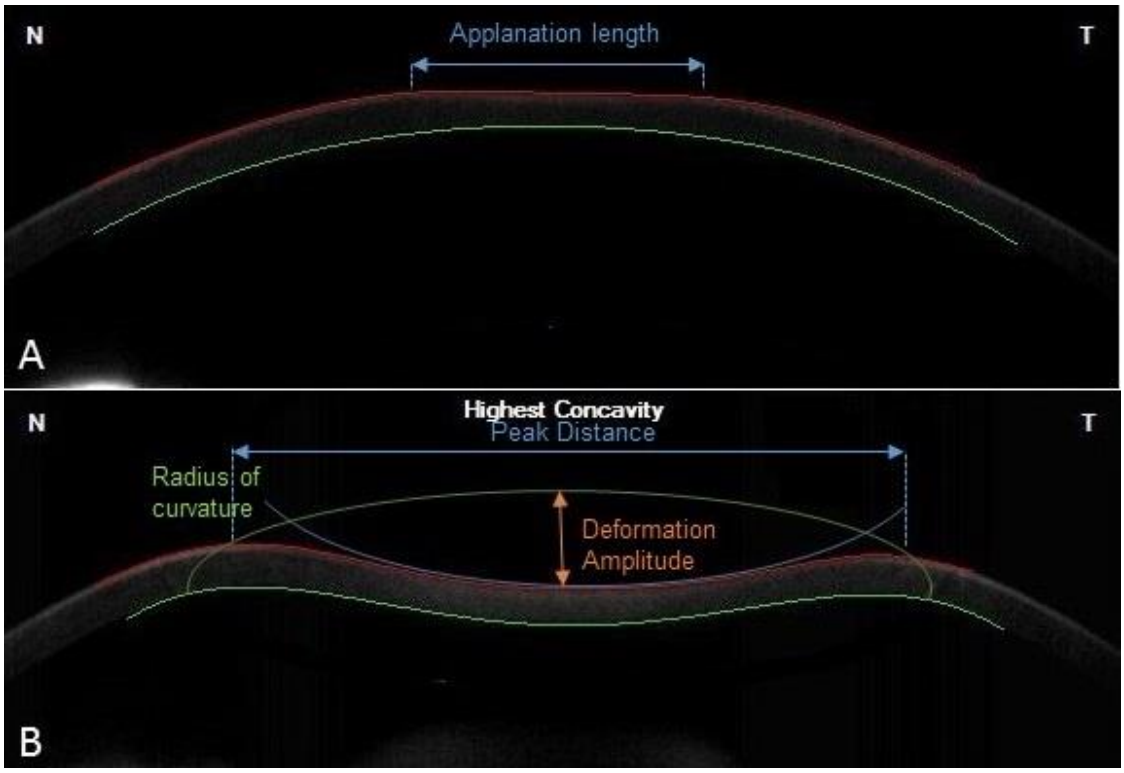

Figure 2.6 Graphic representation of the Corvis ST parameters summarised in Table 2.3.

IOP measurements acquired with Corvis ST were found to be repeatable in a healthy adult population (Hong *et al.* 2013). The repeatability coefficient of CCT measurements was also found to be ±15.3 µm (95% confidence interval) (Hon and Lam 2013). The influence of IOP and CCT on the corneal biomechanical parameters measured by the Corvis ST were reported to be low (Valbon *et al.* 2014). Although specific modifications can be applied to calculate elastic modulus from the data provided by the Corvis ST (Roberts *et al.* 2011), the parameters derived from the Corvis ST are device-specific and have demonstrated a great variability (Hon and Lam 2013; Lanza *et al.* 2016; Matsuura *et al.* 2016). DA and applanation 1 time are reported to be the most repeatable parameters (Hon and Lam 2013; Matsuura *et al.* 2016).

The accuracy and repeatability of the Corvis ST and the ORA (CH, CRF) have been evaluated (Matsuura *et al.* 2016). The ORA has shown higher reproducibility than the Corvis ST (Matsuura *et al.* 2016). The relationship between CH, CRF and Corvis ST

parameters is weak to moderate (Matsuura *et al.* 2016). Theoretically, both the ORA and Corvis ST measure corneal deformation. However, the ORA output is the signal intensity of the reflected infrared light that represented in scalar arbitrary units. Therefore, it does not account for direction of corneal motion. Corvis ST reports the corneal displacement in real time. Magnitude and direction of motion is measured (Tejwani *et al.* 2014). Application of specific algorithms have shown that not only a corneal response, but also the reaction of the eyeball can be evaluated, using the same Corvis ST measurement (Koprowski *et al.* 2015; Shih *et al.* 2015). Therefore both instruments were used for investigation of corneal biomechanical properties.

The Corvis ST was used in Chapters 5-6 for the evaluation of corneal biomechanical response. The newest patient management software to date (version 102.r1260) was used and 3 measurements per eye were taken (Hon and Lam 2013; Nemeth *et al.* 2013). Only one measurement with a quality score (QS) reading 'OK' was selected for analysis (Lanza *et al.* 2016; Matsuura *et al.* 2016).

2.3 Refractive error

2.4 Shin Nippon SRW-5000

Objective refractive data were obtained using an open field infrared autorefractor Shin Nippon SRW-5000 (Anjiomato Trading Inc., Tokyo, Japan). Autorefraction, specifically, using open field devices, has been found to be an appropriate method for studying refractive error, as it is more repeatable than retinoscopy and subjective refraction (Zadnik *et al.* 1992; Bullimore *et al.* 1998; Walline *et al.* 1999; Davies *et al.* 2003; Sheppard and Davies 2010). The open field setting ensures that the myopic shift, induced by the proximal accommodation, is reduced (Sheppard and Davies 2010).

The Shin Nippon SRW 5000 employs an infrared light and calculates refractive error in two stages (Mallen *et al.* 2001). A target of infrared light is projected through the entrance pupil of the eye and subsequently reflected by the retina. A motorised lens track is used

to place the infrared ring in approximate focus and a digital analysis of the ring target in multiple meridians is used to calculate the toroidal prescription. The image analysis is conducted in 0.15 seconds, allowing 45 static prescription measurements to be taken within 1 minute. The instrument can determine a wide range of refractive error (± 22.00 D sphere; ± 10.00 D cylinder), in 0.125 D steps. Cylinder axis is reported with 1^{o} precision. The vertex distance can be altered. The alignment of the infrared ring can be monitored through a display and a hard copy of the measurements can be obtained (Mallen *et al.* 2001).

The accuracy and repeatability of Shin Nippon SRW-5000 autorefractor have been studied previously, both in adult (Mallen *et al.* 2001) and child populations (Chat and Edwards 2001). The instrument has demonstrated a high repeatability and accuracy (Chat and Edwards 2001; Mallen *et al.* 2001). The instrument had a tendency to underestimate myopia, but showed a good repeatability (± 0.14 D for refractive sphere and ± 0.16 D for cylinder) in an adult population (Mallen *et al.* 2001). In children, improved repeatability was achieved under cycloplegic conditions (Chat and Edwards 2001).

The Shin Nippon SRW autorefractor was used in experimental Chapter 5 for screening purposes, and Chapter 6 for determination of mean spherical equivalent (MSE). A modification of a Badal lens system was attached to the instrument. A +5.00 D lens set at a distance of 20 cm to the eye was used to induce zero accommodative demand. A Maltese cross was selected as a fixation target. (Rabbetts 2007) (Figure 2.7). Measurements were taken monocularly with one eye occluded.

Figure 2.7 Shin Nippon SRW setup with a Badal lens system modification.

2.5 Ocular Biometry

2.5.1 IOLMaster 500

The IOLMaster 500 (Carl Zeiss, Jena, Germany), a commercially available optical biometer, was used to measure axial length (AL) in experimental Chapters 4-6.

The IOLMaster 500 is a non-contact instrument (Figure 2.8-A), which was principally developed to aid with intraocular lens (IOL) calculations prior to cataract extraction (Santodomingo-Rubido *et al.* 2002). Owing to its fast, precise and non-invasive measurement technique, it has been widely used in the field of myopia research (Mallen *et al.* 2006; Logan *et al.* 2011; Cho and Cheung 2012; Gardner *et al.* 2015; Swarbrick *et al.* 2015).

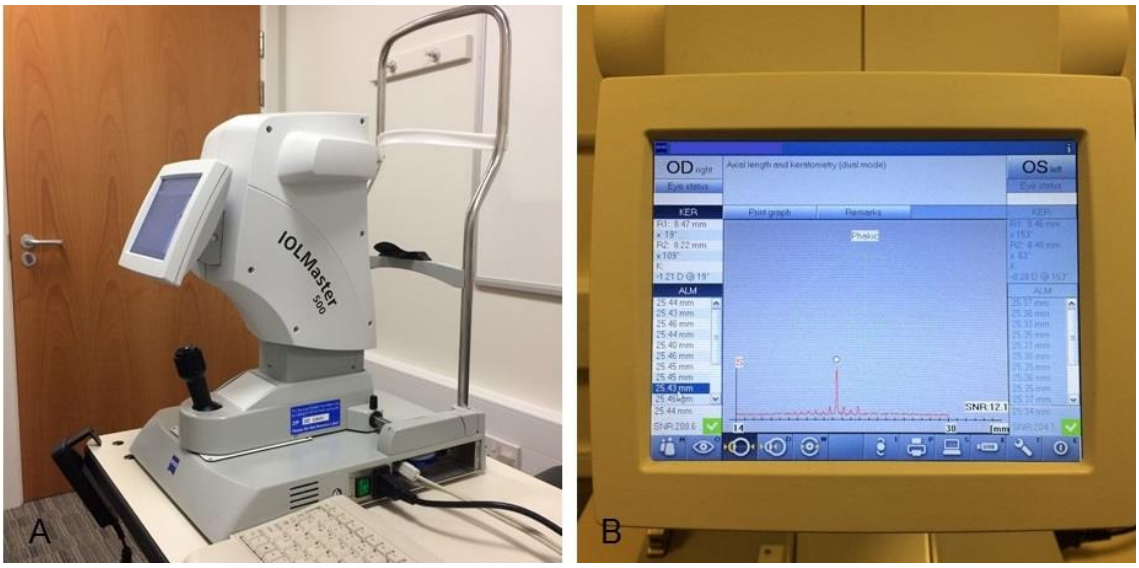

Figure 2.8 (A) IOLMaster 500, (B) The display of the AL measurement with the signal to noise ratio (SNR) as an indicator of the measurement quality.

The IOLMaster 500 employs dual beam partial coherence interferometry (PCI) to acquire AL length measurements (Santodomingo-Rubido *et al.* 2002; Chen *et al.* 2011) (Figure 2.9). An incorporated infrared laser diode (LD) with a wavelength (λ) of 780 µm is used to measure the distance between the corneal apex and retinal pigment epithelium (RPE). Light emitted from the diode is split into two equal co-axial beams (CB1 and CB2) by a beam splitter (BS1), reflected by two mirrors (M1 and M2), and enters the eye. It is then reflected from the corneal (C) and retinal (R) interfaces (CBC1, CBC2 and CBR1, CBR2, respectively). Upon leaving the eye, the four light beams pass through a second beam splitter (BS2) and the differences in their frequencies, due to the reflection from the two interfaces, are detected by a photodetector (PHD). The mirror (M1) is moved at a constant speed to yield a particular interference pattern during the measurement process. The exact extent of the mirror (M1) displacement (d) can be measured and related to the signals received at the PHD enabling a precise estimation of the distance between cornea and retina (Santodomingo-Rubido *et al.* 2002). A resolution of 0.01 mm of AL measurements is achieved (Drexler *et al.* 1998; Mallen *et al.* 2006). Additionally to AL measurements, anterior chamber depth (ACD), corneal curvature, corneal diameter

and the optimal IOL calculations can be acquired with the IOLMaster 500 using image analysis (Eleftheriadis 2003).

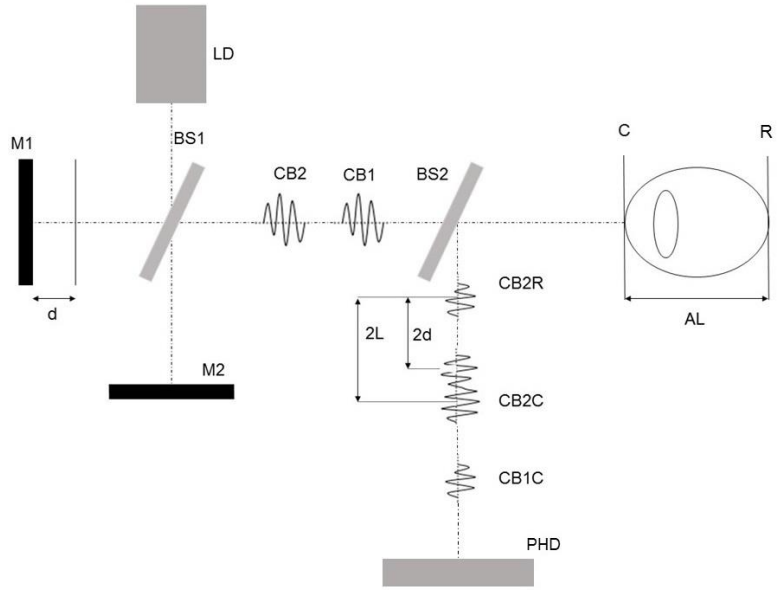

Figure 2.9 The operating principle of IOLMaster 500. Figure redrawn and reprinted with premission from Santodomingo-Rubido (2002).

The IOLMaster has been found to be a safe and reliable instrument for measuring AL in children (Carkeet *et al.* 2004; Hussin *et al.* 2006) and adults (Santodomingo-Rubido *et al.* 2002; Rose and Moshegov 2003; Chen *et al.* 2011). Signal to noise ratio (SNR) is an indicator of measurement quality, and a value of 2.0-2.1 has been suggested as a cut-off value for a reliable measurement (Olsen 2007; Suto *et al.* 2007) (Figure 2.8-B).

The first five measurements with SNR value above 3.5, with a maximum difference of 0.02 mm between any two readings, were averaged and selected for analysis in experimental Chapter 4 for retrospective data analysis (Cho and Cheung 2012). The first ten measurements with SNR value above 2.2, and a maximum difference of 0.02 mm between any two readings, were averaged and selected for analysis in experimental Chapters 5-6.

2.5.2 Aladdin

The Aladdin (v.HW3.0, Topcon, Tokyo, Japan) is a commercially available optical biometry and topography system (Figure 2.10). The Aladdin device employs a low coherence interferometry (LCI) to acquire multiple biometry measures (AL, ACD, corneal curvature and topography, lens thickness, pupillometry and CCT) in 5 seconds (Mandal *et al.* 2013; Rozema *et al.* 2014). The Aladdin was used to measure ACD, LT and CCT in experimental Chapter 5 and CCT in Chapter 6.

An 830 nm super luminescent diode is employed to measure AL, whilst anterior chamber depth is achieved in a similar manner to that of the IOLMaster (Wolffsohn *et al.* 2013; Huang *et al.* 2015; Hoffer *et al.* 2016) (please refer to 2.5.1). A horizontal slit of a 473-nm blue light-emitting diode is projected onto the anterior chamber and the distance between the anterior corneal pole and the anterior crystalline lens is measured (Santodomingo-Rubido *et al.* 2002; Wolffsohn *et al.* 2013; Huang *et al.* 2015). A resolution of 0.01 mm for AL and ACD measurements is achieved.

There is limited information available on how LT and CCT are measured by the Aladdin, however, the principle of employing a super luminescent diode to acquire AL measurements suggests that the measurement principle is also based on optical LCI and uses the change in signal frequencies reflected from the ocular interfaces to calculate the exact distance in a similar manner to the Lenstar 900 (Haag Streit AG, Koeniz, Switzerland). Lenstar 900 also uses a broadband light source, allowing measurements of AL, ACD, LT ad CCT (Cruysberg *et al.* 2010).

The Aladdin has been validated (Mandal *et al.* 2013) and has shown a good repeatability and agreement with other ocular biometers for AL and ACD measurements (Mandal *et al.* 2013; Huang *et al.* 2015; Hoffer *et al.* 2016; McAlinden *et al.* 2017).

Four measurements were acquired for each patient in experimental Chapters 5-6 (Huang *et al.* 2015; Hoffer *et al.* 2016). The instrument allows automatic data export via Microsoft Excel file and displays the data as an average of all the measurements.

Figure 2.10 Aladdin ocular biometry and topography system based on Placido disc principle (please see Section 2.6.1 for more detailed information of Placido disc principle).

2.5.3 Pentacam

The Pentacam (Oculus, Wetzlar, Germany) is a non-contact anterior segment tomographer that uses Scheimpflug imaging technique to acquire measurements of anterior and posterior corneal topographies, corneal thickness, corneal wavefront aberrations and densitometry, ACD and LT (McAlinden *et al.* 2011; Oliveira *et al.* 2011).

A rotating Scheimpflug camera is coupled with a static camera and a rotating slit light source. The rotating system moves around the optical axis from 0^{o} to 180^{o} and scans the cornea at a specific angle, providing cross sectional images due to the transparent and reflective composition of the anterior eye (Buehl *et al.* 2006; Oliveira *et al.* 2011) (for Scheimpflug cross sectional images please refer to Section 2.1.2). The static camera controls the fixation, corrects for eye movements and detects pupil contour (Oliveira *et al.* 2011).

The Pentacam has shown a good repeatability (McAlinden *et al.* 2011; Oliveira *et al.* 2011) and is in agreement with other ocular biometric devices. Nevertheless, caution should be taken when interpreting data from different devices (Rozema *et al.* 2014). No direct comparison between the Pentacam and the Aladdin has been published to date. Repeatability studies between Sirius (CSO, Costruzione Strumenti Oftalmici, Florence, Italy), an optical biometer combining Scheimpflug imaging technique with topography system, and Pentacam (Nasser *et al.* 2012; Anayol *et al.* 2014; Shetty *et al.* 2014), and Sirius and Aladdin (Polat *et al.* 2016) have been conducted. Clinically insignificant differences were found between Aladdin and Sirius data (Polat *et al.* 2016). It was advised to analyse the data obtained with Pentacam and Sirius with caution and not to use them interchangeably (Nasser *et al.* 2012; Anayol *et al.* 2014; Shetty *et al.* 2014).

The Pentacam was used in the experimental Chapter 4 for CCT, ACD and LT measurements. Three measurements were acquired, averaged and used for the analysis (Khoramnia *et al.* 2007; Miranda *et al.* 2009).

2.6 Corneal topography

2.6.1 Medmont E300

Medmont E300 (v. 5.4.0 Beta 4, Medmont Ltd, Melbourne, Australia) is an automated videokeratoscope that uses Placido rings to map the front surface of the cornea. It employs 32 Placido rings (ranging from 0.25 mm to 11.0 mm in diameter) and analyses more than 1000 points on the corneal surface (http://www.medmont.com/products/e300-topographer/).

The Placido disc-based systems use the cornea as a convex mirror, reflecting the rings off the tear film overlying the cornea and measuring the size of a reflection of a given light source at known distance. A camera records the reflected image, which is subsequently analysed, using a Medmont-specific algorithm (Figure 2.11-A) (Cho, Lam *et al.* 2002; Wolffsohn and Peterson 2006).

An automated range-finder is incorporated within the videokeratoscope system, ensuring a precise determination from the corneal apex to the instrument's camera, ensuring only images with a good focus and alignment are captured (Read *et al.* 2009). A quality score from 0 to 100 is available to aid with the measurement process. A quality score above 75 is advised as a cut-off value for a good measurement (Chui and Cho 2005).

Figure 2.11 Medmont E300 setup. (A) The videokeratoscope with the Placido rings, (B) the display of the data in a form of tangential map.

The instrument provides simulated keratometry (K) readings in steep and flat meridian over the central 3 mm of the cornea, corneal astigmatism (ΔK), eccentricity (e), apical radius, corneal shape profile, and displays various types of topographical maps (axial, tangential and difference). In addition, tear film stability and contact lens fit can be monitored with incorporated software (Figure 2.11-B) (Cho, Lam *et al.* 2002; González-Méijome *et al.* 2007; Read *et al.* 2009).

The instrument has been shown to be accurate and repeatable on test surfaces (Tang *et al.* 2000), in child (Chui and Cho 2005) and adult (Cho, Lam *et al.* 2002; Wang *et al.* 2012; Hamer *et al.* 2016) populations.

Three simulated K and eccentricity readings, in flat and steep meridian, were taken and analysed in experimental Chapters 4-6 (González-Méijome *et al.* 2004; Wang *et al.* 2012). Tangential and difference maps were acquired to monitor lens fit in experimental Chapters 5-6. A quality score of 98 was choose as a cut-off value for a reliable measurement in Chapters 4-6 (Read *et al.* 2009).

2.7 Endothelial health

2.7.1 SP3000P

The SP3000P (Topcon Corporation, Tokyo, Japan) is an automated non-contact specular microscope which allows acquisition of corneal endothelium images and measurement of CCT (Bao *et al.* 2014) (Figure 2.12). It succeeded the SP2000P (Topcon Corporation, Tokyo, Japan), which was studied in detail to improve the measurement process and the automated cell analysis (Cheung and Cho 2000; Cho and Cheung 2000; Bao *et al.* 2014).

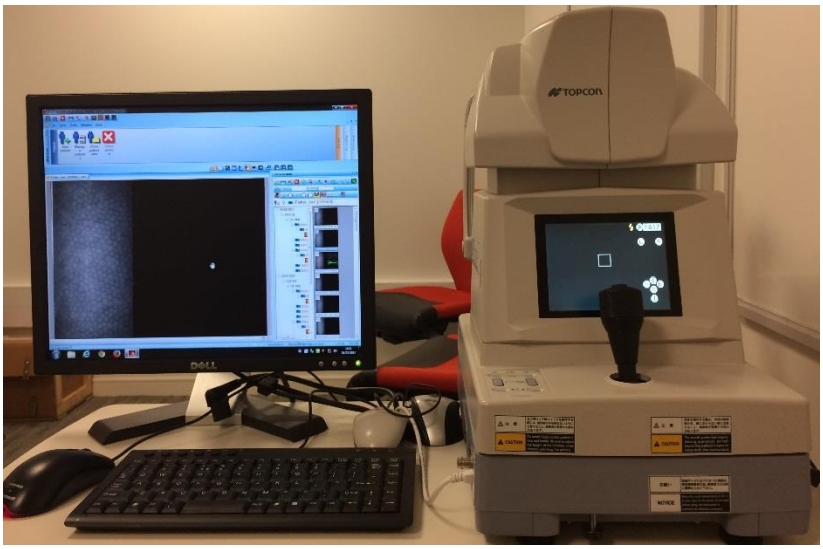

Figure 2.12 Specular microscope Topcon SP3000P with IMAGEnet software for detailed endothelial cell analysis.

Non-contact specular microscopes have experienced various modifications (Bourne and Kaufman 1976; Olsen 1979; Cheung and Cho 1998; McCarey *et al.* 2008). They still employ the principle introduced by Maurice (1968) (McCarey *et al.* 2008): a high magnification view of specularly reflected light is necessary to image the corneal endothelium and is obtained by incorporating a concave lens in the instrument (Figure 2.13). The specular reflex is achieved by light reflecting off two refractive interfaces with different refractive indices (endothelium-aqueous humour, air-tear film/epithelium). The incident angle of the light must be equal to the angle of reflection. The endothelial surface

is less reflective, whilst the epithelial surface is highly reflective due to the large air-epithelium refractive index difference. The relatively close proximity of the epithelium and endothelium restricts the light reflex and together with the radius of curvature determines the rectangular shape of the viewable/imaged area. The size of this area is further affected by corneal thickness and the width of the beam (Figure 2.13-A). As the light beam passes through the epithelium to the endothelium and then, subsequently, back through the corneal stroma, light scatter occurs due to the collagen fibril and keratocyte arrangement. The width of the beam is increased from narrow to wide in order to allow the epithelial reflex to encroach on the endothelial reflex. The endothelium can then be observed and captured. The acquired image has a different contrast due to the light scatter (Figure 2.13-B) (McCarey *et al.* 2008).

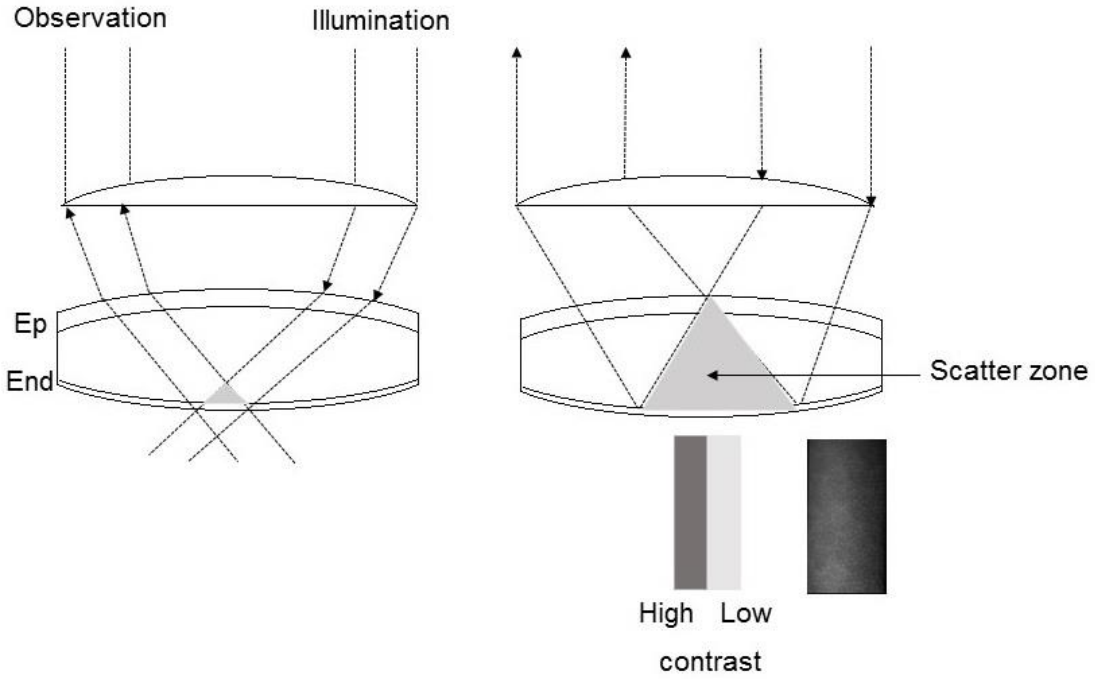

Figure 2.13 The principle of specular microscopy (Ep - epithelium, end – endothelium). The observation and illumination angles are equal. When the light beam passes through the Ep to the End and then, subsequently, is reversed back to Ep, light scatter occurs due to the structure of stroma. The width of the beam is increased in order to allow the Ep reflex to encroach on the End reflex. The End can then be observed and captured. Image adapted and reprinted with permission from McCarey *et al.*(2008).

In addition to the central endothelium, the SP3000P allows for nasal, temporal, inferior and superior endothelium views 30^{o} away from the horizontal axis. The instrument saves up to 5 images per eye and provides a quick cell count and shape analysis for screening purposes (Cho and Cheung 2000). An automated, semi-automated or manual mode can be selected for image capture. The images from the specular microscope are transferred to a computer with an automated cell analysis software (IMAGEnet ibase, Topcon Corporation, Tokyo, Japan) for a detailed analysis. Cell count, hexagonality and average cell size are displayed (Cheung and Cho 2000; Cho and Cheung 2000) (Figure 2.12).

The Topcon SP specular microscope series has been shown to produce reliable measurements (Cheung and Cho 1998; Cheung and Cho 2000; Cho and Cheung 2000; Mccarey *et al.* 2008), which are in agreement with other commercially available instruments for CCT and corneal endothelial assessment (McCarey *et al.* 2008; Bao *et al.* 2014; Gasser *et al.* 2015).

The automated image capture mode was employed in the studies described in Chapter 4, 5 and 6. IMAGEnet ibase v. 3.18. software was used for the cell analysis. Three images of central endothelium per eye were captured and saved. Using the grading system validated before (Cheung and Cho 2000; Cho and Cheung 2000), the clearest images with a minimum of 100 cells were selected for the analysis (Doughty and Aakre 2008; Doughty 2013).

Chapter 3. Current trends of myopia management in clinical practice

3.1 General overview

This chapter describes the purpose, design and findings of the 'Global trends in myopis management attitudes and strategies in clinical practice' (Wolffsohn *et al.* 2016). In total nine hundred seventy one responses from the eye care practitoners across the globe were received, analaysed and reflect on the current state of myopia management in clinical practice. The survey also tidentifies problems associated with myopia control (MC) interventions.

3.2 Introduction

The prevalence of myopia has doubled in the last three decades (Lin *et al.* 2004; Vitale *et al.* 2009; Pan *et al.* 2012; Holden *et al.* 2016; Mccullough *et al.* 2016), reaching 20-50% in America and Europe (Sperduto *et al.* 1983; Vitale *et al.* 2008; Logan *et al.* 2011; Williams *et al.* 2015; Mccullough *et al.* 2016) and approaching 70-90% in regions of South East Asia (Lin *et al.* 1988; Goh and Lam 1994; Edwards and Lam 2004; Lin *et al.* 2004; Ting *et al.* 2004) amongst schoolchildren and young adults (for more detailed prevalence rates of myopia, please refer to Section 1.2.2). If myopia prevalence continues to increase at the same rate, evidence-based models predict that half of the world's population will be myopic by 2050 (Holden *et al.* 2016). Moreover, a shift towards a more myopic refraction has been observed in the last two generations (Lin *et al.* 2004; Liang *et al.* 2013), leading to an increased level of high myopia (≥-6.00 D). Lin *et al.* (2004) compared the age of onset and prevalence of myopia amongst schoolchildren between 1983 and 2000. The mean age of myopia onset was 11 years in 1983, whereas it was 8 years in 2000 (Lin *et al.*, 2004). The mean refractive status at 8 years was 0.45 ± 1.03 D and -0.15 ± 1.40 D, in 1983 and 2000, respectively; whereas, at 11 years it was -0.27 ± 1.72 D and -1.20 ± 1.93 D, in 1983 and 2000 respectively. An evidence-based model of progression rates of myopia in Asian countries, introduced by Sankaridurg and

Holden (Holden *et al.* 2014; Sankaridurg and Holden 2014), predicts that a child with -1.00 D of myopia at 6 years of age will be expected to progress to -7.00 D on average by the age of 15. Therefore, more people at a younger age will encounter the economic and health burdens associated with this condition (Holden *et al.* 2014). High myopia is strongly linked to ocular pathologies, such as retinal detachment, glaucoma and cataracts (Brown and Hill 1987; Leske *et al.* 1995; Mitchell *et al.* 1999; Vongphanit *et al.* 2002; Saw *et al.* 2005; Flitcroft 2012). Flitcroft (2012) demonstrated that the risk of developing ocular pathology increases with the level of myopia. For example, compared to emmetropes, the odds ratio of developing retinal detachment is 21.5 (95% confidence interval: 17.3-26.7) for myopia -5.00 to -6.99 D, and increases to 44.2 (34.2-57.2) for myopia -7.00-8.99 D (Ogawa and Tanaka 1987; Flitcroft 2012). The risk of developing myopic maculopathy is 40.6 (13.3-124.4) for myopia of -5.00 to -6.99 D, but increases to 126.8 (34.0-472.3) for myopia of -7.00 to -8.99 D (Vongphanit *et al.* 2002; Flitcroft 2012). However, even lower levels of myopia (-1.00 to -3.00 D) have been found to have an increased risk of developing these conditions, when compared to emmetropes (Flitcroft 2012). The odds of developing myopic maculopathy is doubled (Vongphanit *et al.* 2002; Flitcroft 2012) and the odds of developing retinal detachment is tripled (Li *et al.* 2003; Flitcroft 2012). Thus, similarly to Holden (2014), Flitcroft (2012) highlighted the need to slow down the progression of myopia and reduce the levels of high myopia.

Brennan (2012), Holden (2014) and Sarkanidurg and Holden (Sankaridurg and Holden 2014) have discussed the potential benefit of reducing the rate of myopia progression. Brennan estimated that slowing down the progression of myopia by 33%, would lead to a reduction of 73% of high myopia (>-5.00 D), but if a retardation rate of 50% was achieved, 90% of high myopia would be eliminated (Brennan 2012). Sarkanidurg and Holden used an evidence-based model to demonstrate that if myopia could be retarded by 30% over a time span of 8 years, myopia progression would be reduced from an average of -7.00 D to -5.50 D (Holden *et al.* 2014; Sankaridurg and Holden 2014).

Perhaps, the most challenging aspect of myopia management, is its multifaceted aetiology. A range of factors including genetic predisposition (Zadnik, Karla 1997; Pacella *et al.* 1999; Mutti *et al.* 2002; Farbrother *et al.* 2004; Kurtz *et al.* 2007; Cheng *et al.* 2013), inadequate accommodation response (Gwiazda *et al.* 1993; Gwiazda *et al.* 1995), elevated accommodative convergence to accommodation, the AC/A ratio and/or esophoria (Drobe and Desaintandre 1995; Gwiazda *et al.* 1999), excessive time spent undertaking near work (Mutti *et al.* 2002; Ip *et al.* 2008; Vasudevan and Ciuffreda 2008; Woodman *et al.* 2010), low levels of outdoor activity (Jones *et al.* 2007; Rose, Morgan, Ip*, et al.* 2008; Wu *et al.* 2010; Guggenheim *et al.* 2012; Guo *et al.* 2013; Wu *et al.* 2013), lightning levels (Ashby *et al.* 2009; Ashby and Schaeffel 2010; Cohen *et al.* 2011; Smith *et al.* 2012) and magnitude of hyperopic peripheral defocus (Hoogerheide *et al.* 1971; Rempt *et al.* 1971; Millodot 1981; Mutti *et al.* 2000; Seidemann *et al.* 2002; Schmid 2003; Logan *et al.* 2004; Charman *et al.* 2006; Mutti *et al.* 2007; Kang *et al.* 2010; Mutti *et al.* 2011) have been linked to the development and/or progression of myopic refractive error. However, the exact mechanisms surrounding myopia development and progression are not yet fully understood (for the factors of myopia development please refer to Section 1.2.4).

Although it is not yet possible to prevent the onset of myopia, extensive research in the area of myopia control (MC) has yielded promise in the reduction in myopia progression. Optical interventions, most predominantly contact lenses, pharmaceutical treatment and behavioural approaches, targeting various aspects of the underlying mechanisms of myopia development, have demonstrated retardation rates of 14 to 72% in longitudinal clinical studies and trials (Goss and Uyesugi 1995; Leung and Brown 1999; Fulk *et al.* 2000; Chung *et al.* 2002; Edwards *et al.* 2002; Gwiazda *et al.* 2003; Tan *et al.* 2005; Adler and Millodot 2006; Walline *et al.* 2009; Yang *et al.* 2009; Anstice and Phillips 2011; Gwiazda *et al.* 2011; Sankaridurg *et al.* 2011; Berntsen *et al.* 2012; Chia *et al.* 2012b;

Cho and Cheung 2012; Chen *et al.* 2013; Walline *et al.* 2013; Wu *et al.* 2013; Cheung *et al.* 2014; Hasebe *et al.* 2014; Paune *et al.* 2015).

Conventional single vision spectacle lenses seem to be ineffective for MC as they induce peripheral hyperopic defocus, a factor speculated to promote eye growth. (Smith, Huang*, et al.* 2009; Smith, Hung*, et al.* 2009; Lin *et al.* 2010; Smith 2011). However, some authors have questioned whether peripheral defocus is the primary mechanism driving eye growth, having reported that some myopic children wearing single vision spectacles were actually exposed to greater relative myopic defocus. Thus, myopia progression was less in these children than it was in those wearing single vision spectacles with relatively greater hyperopic defocus (Berntsen *et al.* 2012; Atchison *et al.* 2015). Other large scale human studies have also found peripheral refraction to neither affect myopia onset or development (Gwiazda *et al.* 2003; Mutti *et al.* 2011). Progressive addition (PALs) and bifocal lenses have been prescribed to reduce accommodative demand, and mitigate the blur associated with increased lag of accommodation in myopia (Gwiazda *et al.* 1993; Gwiazda *et al.* 1995; Gwiazda *et al.* 1999; Gwiazda *et al.* 2003). It is presumed that an insufficient amount of accommodation might cause a relative retinal blur and, hence, be a triggering factor for axial elongation. The success rate of studies employing PALs and bifocals have varied from no effect (Shih *et al.* 2001; Edwards *et al.* 2002), to 46% for PALs (although this study was not randomised; Leung and Brown 1999); and 44 to 56 % for bifocals and executive bifocals, respectively (Goss and Uyesugi 1995; Cheng *et al.* 2014). However, other studies have reported retardation rates of 14% to 24% (Leung and Brown 1999; Fulk *et al.* 2000; Gwiazda *et al.* 2003; Hasebe *et al.* 2008; Yang *et al.* 2009) which are less convincing (Wolffsohn *et al.* 2016).

Undercorrection, which was believed not only to reduce accommodative demand, but induce myopic defocus, has been hypothesised to act as a halting signal to myopia development in animal studies (Shaikh *et al.* 1999; Smith *et al.* 1999). Contrarily, undercorrection has been found to accelerate the rate of myopia progression by 17 to

29% in human clinical studies (Chung *et al.* 2002; Adler and Millodot 2006; Wolffsohn *et al.* 2016).

Soft single vision contact lenses (Horner *et al.* 1999; Walline, Jones*, et al.* 2004; Walline *et al.* 2008), and conventional rigid gas permeable (RGP) contact lenses (Khoo *et al.* 1999; Katz *et al.* 2003; Walline, Jones*, et al.* 2004) have been found to have no effect on myopia progression. However, multifocal contact lens designs appear to be effective in reducing myopia progression by 34 to 50%; it may result from the optics of a contact lens, including the near portion, being consistently aligned with the position of gaze as the lens moves with the eye, (Gwiazda *et al.* 2003; Aller and Wildsoet 2008; Anstice and Phillips 2011) and possibly more consistency in wearing time, which seems to be an important factor for efficacy (Lam *et al.* 2014). Orthokeratology (ortho-k), on the other hand, has been consistent in the level of myopia retardation shown and is able to slow the progression of myopia by 50%, (Walline *et al.* 2009; Cho and Cheung 2012; Chen *et al.* 2013). Therefore, it is considered the optical treatment with the strongest accumulated evidence to date (Gonzalez-Meijome *et al.* 2016; Wolffsohn *et al.* 2016).

Pharmaceutical treatment strategies, such as atropine (Shih *et al.* 2001; Chua *et al.* 2006; Chia *et al.* 2012b), and pirenzepine (Siatkowski *et al.* 2004; Tan *et al.* 2005; Siatkowski *et al.* 2008), have shown high success rates (32% to 72%). However, the limited commercial availability of the low dose atropine and the unlicensed status of pirenzepine for medical use, and also the unknown effects of long term use and the rebound effect following cessation of treatment (Tan *et al.* 2005; Tong *et al.* 2009; Yang *et al.* 2009; Cheng *et al.* 2014; Chia *et al.* 2015; Wolffsohn *et al.* 2016) limit the clinical use of them.

Epidemiology studies in the general population and in monozygotic twins, have generally demonstrated that time spent outdoors reduces the likelihood of myopia onset (Sherwin *et al.* 2012; Lee *et al.* 2013; Parssinen *et al.* 2014; Ramessur *et al.* 2015). The behavioural approach of increased outdoor activity has been shown to retard the onset

of myopia by 11-34%. (Wu *et al.* 2013) It is postulated that the higher luminance levels, which exist outdoors compared to indoors, trigger the release of the retinal transmitter, dopamine, which is believed to prevent axial growth and myopia development. (Ashby *et al.* 2009; Ashby and Schaeffel 2010; French *et al.* 2013) In addition, it has been suggested that components of sunlight itself, could activate vitamin D, which could play a potential role in preventing eye growth. (Mutti *et al.* 2011; French *et al.* 2013) Additional factors like increased viewing distance that reduces the accommodation demand and improved image quality due to the smaller pupil in bright light conditions and, hence, increased depth of focus, when compared to indoor conditions, could further contribute towards the protective effects of increased outdoor activity (Rose, Morgan, Ip*, et al.* 2008) (for MC interventions please refer to Section 1.2.5).

However, if and how these approaches are employed in clinical practice is still unclear, and the information in scientific literature on this topic is sparse. In 2013 the Vision Research Institute (Ferris State University Michigan Collage of Optometry) conducted a survey with 700 eye care professionals (ophthalmologists, optometrists, opticians, ophthalmic technicians) concerning the increasing rates of myopia prevalence (available online: http://www.myopiacontrol.org/how-do-you-myopia-control-.html; accessed 01.10.2015). The results showed that practitioners in United States of America were aware of the growing issue and tended to familiarise themselves with the current literature in the field. Also, they chose to prescribe ortho-k as the main option for MC. However, their rationale for prescribing different MC strategies was not included in the survey. Similarly, Contact Lens Spectrum has also surveyed over 400 practitioners in the United States of America, in both 2014 and 2015, showing that, in both years, 24% of practitioners report using contact lenses to control myopia. Practitioners reported using soft multifocal and orthokeratology contact lens designs predominantly, with very few reporting that they used rigid multifocal contact lenses (Nichols 2016).

Johnson (2014) and Holden (2014) stressed the need for more scientific studies as most of them have looked at retardation rates of myopia progression over the period of two years, and little is known about the rebound effects. Moreover, Johnson (2014) doubted clinicians' ability to see the bigger picture – do clinicians understand the benefit of annual retardation rates, when they are converted into dioptres, the most commonly used measure of refraction in optometric practice, and the long term effect of myopia progression and the potential risks of developing ocular pathologies? Several studies have reported statistically, but not clinically, significant reductions in the rates of myopia progression retardation (Edwards *et al.* 2002; Gwiazda *et al.* 2003; Gwiazda *et al.* 2011), and some authors doubt the retardation effect achieved (Fulk *et al.* 2000), presumably leaving practitioners confused and sceptical about the various management strategies available. Therefore, a better understanding of current trends of myopia management in clinical practice is required before targeted education and recommended criteria for intervention can be introduced (Wolffsohn *et al.* 2016).

3.3 Method

A self-administrated, internet-based, cross-sectional survey in 6 languages (English, French, Spanish, Italian, Portuguese and Chinese) was distributed using online software SurveyMonkey (www.surveymonkey.com; SurveyMonkey Inc. San Mateo, California, USA) through various professional bodies across the world to target eye care professionals (optometrists, dispensing opticians, ophthalmologists and others) globally. Before the global distribution, survey was piloted internally on a small number of eye care professionals (n=5).

The survey comprised of nine questions (forced choice and multiple choice), relating to the self-reported clinical management behaviours of practitioners for progressive myopia and practitioner's current opinions on MC related clinical care including:

- How concerned are you about the increasing frequency of paediatric myopia in your practice? (rated as ‘not at all,’ to ‘extremely,’ on a 10-point scale);
- From what you have heard/read about the effectiveness of myopia control options to date, what % reduction do you think the following options can achieve? (modalities provided: undercorrection, single vision spectacles, bifocal spectacles, progressive addition spectacles, RGP (alignment fit), single vision contact lenses, standard multifocal contact lenses, specific myopia control contact lenses, orthokeratology, pharmaceuticals such as atropine, refractive surgery, increased time spent outdoors; rated as a percentage from 0 to 100%);
- How active would you consider your clinical practice in the area of myopia control? (rated as ‘Not at all,’ to ‘fully,’ on a 10-point scale);
- How many times have you prescribed the following correction options for progressing/young myopes over an average month (please consider the total number of progressing/young myopes and include all in your response)? (modalities provided: single vision spectacles, bifocal spectacles, progressive addition spectacles, RGPs (alignment fit), single vision soft contact lenses, standard multifocal contact lenses, specific myopia control contact lenses, orthokeratology, pharmaceuticals such as atropine, refractive surgery);
- How old (in years) would the patient have to be for you to consider each of the following options (not just for myopia control and assuming average handling skills and child/parent motivation)? (modalities provided single vision spectacles, bifocal spectacles, progressive addition spectacles, RGPs (alignment fit), single vision soft contact lenses, standard multifocal contact lenses, specific myopia control contact lenses, orthokeratology, pharmaceuticals such as atropine, refractive surgery; prescribing age

listed starting from 5 years up to 18 years in one-year steps with an option 'would not prescribe this' available);

- What would be the minimum amount of myopia (in dioptres) for you to consider each of the following correction options for a patient? (modalities provided single vision spectacles, bifocal spectacles, progressive addition spectacles, RGPs (alignment fit), single vision soft contact lenses, standard multifocal contact lenses, specific myopia control contact lenses, orthokeratology, pharmaceuticals such as atropine, refractive surgery; level of myopia to consider specific modality provided in half dioptre steps from -0.50D to >-5.00D with an option 'would not prescribe this' available);
- What is the minimum level of myopia progression you consider necessitates a myopia control approach? (level of myopia progression listed in quarter dioptre steps per year from 0D/year up to >1.00D/year with an option 'myopia control is not warranted' available);
- Do you use undercorrection as a strategy to slow myopia progression? (options provided: 'no', 'sometimes', or 'always');
- If you have only ever fitted single vision spectacles/contact lenses for myopic patients, what has prevented you prescribing an alternative method? (options specified: 'I don't think they are more effective', 'the outcome is unpredictable', 'safety concerns', 'cost to the patient makes it uneconomic', 'additional chair time', 'inadequate information/knowledge', 'benefit/risk ratio').

An option to add further comments to each of the questions and the topic as a whole was available (for the full questionnaire in English please refer to Appendix 1.2).

Following an explanation of the research via email, in which participants were invited to devote 5 minutes of their time and complete an international survey, regarding their

opinion on the currently available myopia management strategies to enhance the knowledge of how well myopia is managed in everyday practice by them and their colleagues across the globe, participants consented to take part in it by clicking a link that re-directed them to the survey (for invitation email please refer to Appendix 1.1). Participation in the survey was voluntary and anonymous, however respondents were asked to provide basic demographic information about themselves (highest qualification, number of years since qualification, everyday working environment and their geographical location) before submitting their responses.

A sample size of 1000 respondents was targeted as it is the suggested size for a general purpose survey, and allows a fairly reliable comparison up to 3 subgroups (Ornstein 2013). Moreover, in this case, the target population was profession-specific, therefore, around 1000 responses were considered to be a reliable representation of eye care professionals' opinion around the globe. Power analysis was not conducted as the survey was predicted to have more than one definite outcome and sample size would be strongly affected by the size of the subgroups, that could not be easily predicted (Ornstein 2013). The data was collected between January and June 2015. For full questionnaire, please refer to Appendix 1.2. The methodology and survey itself has already been published (Wolffsohn *et al.* 2016).

3.3.1 Statistical Analysis

Statistical analysis was conducted using SPSS (IBM SPSS Statistics for Windows, Version 21.0. IBM Corp. Armonk, New York, USA). Median, confidence intervals (CI, where applicable), mean and standard deviations were calculated for each question response. The results were grouped by continent (Asia, Australasia, Europe, North America and South America; Africa was excluded as only 7 responses were received), and countries within a continent, where response rate allowed ($n \geq 30$). Kruskal-Wallis test was applied to determinate the differences (taken as $p<0.05$) between the groups (using bootstrapping approach, where applicable), due to the non-parametric nature of the data.

For conciseness, only significant comparisons have been reported (non-significant comparisons are listed, if relevant). For full list of comparisons and results please refer to Appendix 1.3.

3.4 Results

3.4.1 Responses

A total number of 971 complete survey responses from Africa (n=7; not included in further analysis), Asia (n=291), Australasia (n=119), Europe (n=339), North America (n=133), and South America (n=82) were received. Country-specific responses could be extracted from:

- Europe: France (n=34), Italy (n=72), Netherlands (n=38) Portugal (n=48), Spain (n=34) and United Kingdom (UK)/Ireland (EIRE) (n=52)
- Asia: China (n=137), Hong Kong (n=61) and India (n=37)
- North America: Canada (n=33) and USA (n=100).

The response rate could not be estimated exactly as the survey was distributed via various professional bodies and the overall denominator population was unknown. However, it is likely that the response rate of this survey corresponds to the lower limit of those reported previously for email/internet based surveys (9-32%, with mean response rate of 20% (Deutskens *et al.* 2004; Kaplowitz *et al.* 2004; Nulty 2008)).

Of the study participants, 72.4% (n=698) were optometrists, 18.6% (n=180) were ophthalmologists, 5.8% (n=56) were contact lens opticians and 3.2% (n=31) were other types of eye care specialists. The principal working environment for 84.4% was in clinical practice (n=814), 11.3% worked in academia (n=109), 1.6% worked within industry (n=16) and 2.7% (n=26) worked in other environments. However, all study participants were registered eye care practitioners. The vast majority of the practitioners that took part in the survey have been qualified professionals for 11-20 years (calculated as median).

3.4.2 Self-reported concern about the increasing frequency of paediatric myopia in their practice

Practitioners' concern about increasing frequencies of paediatric myopia in their practices on a global scale was 8/10 (median) (Appendix 1.3). Continental division revealed that practitioner concern was higher (9/10) in Asia than any of the other continents ($p<0.001$), with a similar level of concern (all with a median of 7/10; $p>0.05$) across Australasia, Europe, North and South America (Figure 3.1).

In Asia, Chinese practitioners were more concerned (10/10) than those in Hong Kong (8/10; $p=0.001$) or India (8/10; $p=0.002$). In Europe, Portuguese (8/10) and Spanish (9/10) practitioners were more concerned than those in Italy (7/10, $p=0.046$, $p=0.027$ respectively), the Netherlands (7/10, $p=0.002$, $p=0.001$ respectively) or the UK/EIRE (6/10, $p<0.001$, $p<0.001$ respectively). In the North American continent, practitioners from the USA (7/10) were more concerned than Canadian practitioners (6/10, $p=0.005$) (Appendix 1.3).

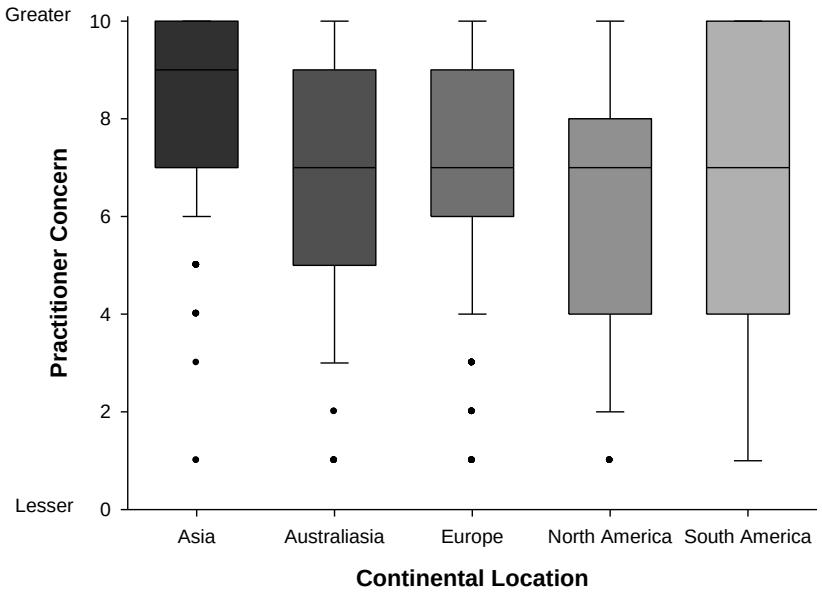

Figure 3.1 Concern regarding increasing myopia amongst paediatric patients for practitioners located in different continents (n=964), (Wolffsohn *et al.* 2016). Note: line within the box represent median, error bars represent 95% CI.

3.4.3 Perceived efficacy of myopia control options

Practitioners self-reported relative efficacy of various myopia management strategies to slow down the myopia progression was the highest for orthokeratology. They perceived that ortho-k slows down myopia progression by 44% (on average across the globe). It was followed by increased time spent outdoors (32%) and pharmaceutical approaches (28%). Single vision distance undercorrection and single vision spectacles were perceived to be the least effective method (6% and 11%, respectively). These findings were consistent across all continents except for South America ($p<0.05$), where all the interventions had similar perceived efficacy (12-24%), apart for increased outdoor activity (35%). Compared with practitioners from all other continents, practitioners from Asia considered single vision, bifocal spectacle lenses and PALs to be relatively more effective for reducing childhood myopia progression ($p<0.01$). Australian and North American practitioners perceived single vision contact lenses as less effective than practitioners from other continents ($p<0.01$). North American practitioners were less convinced by ortho-k and pharmaceutical treatment as appropriate methods for MC than those from Asia or Australasia ($p=0.001$). Similarly, European practitioners were less convinced by the effect of pharmaceutical pharmaceuticals ($p<0.001$). North American practitioners were also more sceptical about the potential benefit of increasing time spent outdoors on myopia progression compared with practitioners from other continents ($p<0.05$).

Country-specific comparisons showed that there were variations in the perceived effectiveness across all MC options, especially among French practitioners and their European colleagues (please refer to Table 3.1 and Appendix 1.3).

Continent		Asia	Australasia	Europe	North America	South America
Intervention		Perceived efficacy (%)				
Spectacles	Undercorrection	6.5±13.9	2.5±7.4	6.4±15.8	2.9±7.9	13.4±23.1
	Single Vision	16.0±23.6	4.2±12.5	10.0±21.8	4.0±14.0	18.1±30.7
	Bifocals	18.4±21.1	14.1±14.8	12.4±17.5	11.6±14.4	12.3±24.2
	Progressive Addition (PALs)	21.3±21.2	16.0±14.0	14.7±18.6	11.3±13.5	12.8±24.8
Contact Lenses	Rigid Gas Permeable (RGP), alignment fit	23.9±26.9	9.6±13.8	14.1±20.8	9.9±15.4	13.6±27.0
	Single Vision Soft	11.9±20.6	4.1±11.5	10.1±20.5	2.9±10.5	16.0±29.0
	Multifocal Soft	15.5±20.2	22.5±19.3	16.4±25.7	18.4±20.5	11.5±19.7
	Novel Myopia Control Soft	24.4±26.0	29.1±19.3	25.2±25.7	21.5±23.1	18.8±28.5
	Ortho-k	48.6±29.6	47.8±25.3	44.3±29.0	36.9±30.1	23.9±32.3
Pharmaceutical		31.7±27.8	39.0±32.4	24.2±29.4	21.8±27.0	14.6±23.3
Refractive Surgery		17.4±29.7	11.4±24.3	12.8±25.6	13.5±30.6	18.0±29.4
Increased Time Spent Outdoors		38.7±27.5	29.7±22.0	29.4±26.2	20.5±17.9	35.3±32.0

Table 3.1 Perceived effectiveness (defined as the expected level of reduction in childhood myopia progression in percent) of myopia control interventions by practitioners in different continents. Note: data are presented as mean±SD.

3.4.4 Perceived level of clinical activity in the area of myopia control

Overall, practitioners rated their level of clinical activity as 7 out of 10 (median value) in the area of MC across the globe. Practitioners in Asia considered their clinical activity in MC to be more active (median 8/10) than practitioners in Australasia (median 7/10; p=0.028), Europe (median 7/10; p<0.001), North America (median 4/10; p<0.001) and South America (median 5/10, p<0.001). North American practitioners perceived themselves to be less active in this area of practice than those from Europe (p<0.001) and Australasia (p<0.001). Within Europe there were no differences between countries, however, within Asia, practitioners from India (6/10) considered themselves less active than practitioners in China (8/10, p<0.001) or Hong Kong (8/10, p=0.002) practitioners. Similarly, regional differences within North America could be observed. Canadian practitioners (2/10) reported themselves to be less active than those from the USA (5/10, p=0.034) (Figure 3.2 and Appendix 1.3).

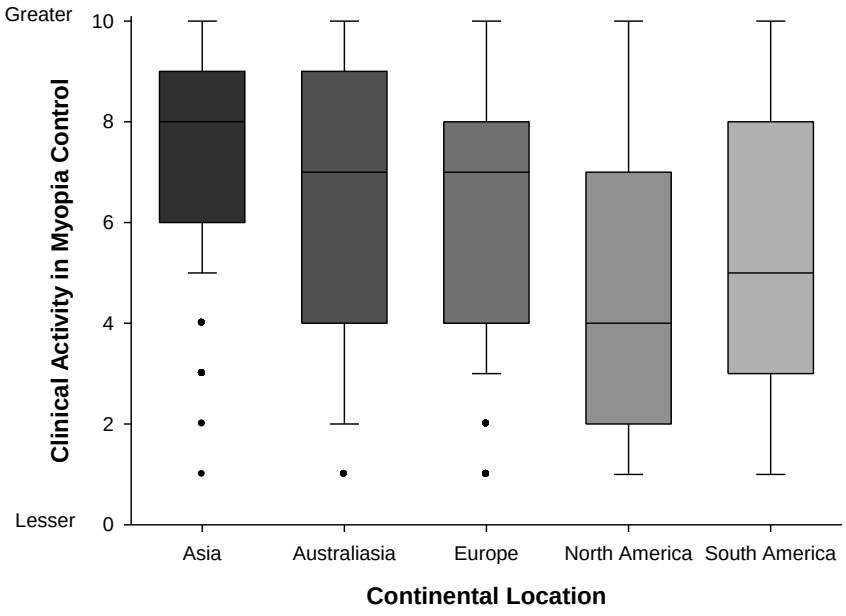

Figure 3.2 Perceived level of clinical activity in the area of myopia control for practitioners located in different continents (n=964), (Wolffsohn *et al.* 2016). Note: lines within the box represent median, error bars represent 95% CI.

3.4.5 Frequency of prescribing different myopia correction options for progressing/young myopes

The majority of progressing myopic patients across the globe were being prescribed either single vision (full correction) spectacles (47.8 ± 31.7%), or single vision contact lenses (15.2±17.3%). Whereas, ortho-k (14.3 ± 24.3%), PALs (6.5 ± 14.3%), RGPs (4.5 ± 10.5%), multifocal contact lenses (4.1 ± 11.3%), bifocal spectacles (2.6 ± 8.2%), novel MC contact lenses (2.1 ± 7.9%), pharmaceuticals (1.9 ± 8.7%) and refractive surgery (1.0 ± 5.4%) were utilised less frequently (Appendix 1.3).

Practitioners in Asia reported prescribing single vision (full correction) spectacles most frequently, whereas those from Australia prescribed them least often ($p<0.001$). Similarly, European practitioners were more reluctant to prescribe single vision spectacles than Asian practitioners ($p<0.001$). North American practitioners indicated prescribing bifocal spectacles most frequently ($p<0.001$) for progressing/young myopes. Australian practitioners, and to a lesser degree, practitioners in Asia, prescribed PALs more frequently ($p<0.001$) than those from other continents. Australian and North American practitioners prescribed RGPs (alignment fit) ($p<0.001$) more for progressing myopic patients than those in Asia, Europe or South America. Single vision contact lenses were prescribed less in Asia than in any other continent, whilst standard multifocal contact lenses were prescribed more in North America ($p<0.001$) than anywhere else.

Practitioners in Europe, however, tended to prescribe this modality more often than those in Asia. Whereas, specific MC contact lens designs were not utilised in any of the continents (Table 3.2 and Appendix 1.3).

Ortho-k was utilised less frequently by the practitioners in South America ($p<0.001$) than by those in Asia, Australasia, Europe or North America. Practitioners in Asia prescribed pharmaceutical treatment more frequently ($p<0.001$) than practitioners from other continents for young myopic patients. Refractive surgery was advised more in the

regions of South America and Australasia than in any other continent ($p<0.001$) for these patients, however, the prescribing frequency was still low (2.8 ± 7.6% and 0.3 ± 1.3% respectively; expressed as mean ± SD) (Table 3.2).

Intra-region comparisons showed large variations in prescribing habits for all MC options (Appendix 1.3). Within Europe practitioners in the Netherlands, and to a lesser extent in Italy, prescribed single vison spectacles less than in other European countries ($p<0.001$) for progressing myopes. Similarly, in Asia, practitioners in India prescribed single vision spectacles to a lesser extent than those in China or Hong Kong ($p<0.001$). Whereas, in Northern America, Canadian practitioners prescribed single vision spectacles more frequently than their colleagues from the USA ($p=0.028$). Bifocal spectacles and PALs were prescribed with a similar frequency across Europe, but differences existed among practitioners in Asia (all $p<0.001$ and all $p=0.007$ respectively) and Northern America ($p=0.023$ and $p=0.032$ respectively). Practitioners in the UK chose RGP contact lenses less frequently for their progressing myopic patients than their European colleagues ($p<0.001$). Whereas, within Asia, Indian practitioners prescribed this type of correction more frequently than those in Hong Kong and China ($p<0.001$). Single vision contact lenses were prescribed at similar rates among European and Northern American practitioners, whilst, within Asia, they were prescribed relatively more frequently in India than other countries ($p<0.001$). Within Europe, ortho-k was chosen more often by practitioners in the Netherlands than any other country in Europe ($p\leq0.001$), whereas in Asia, practitioners in China chose this modality for progressing/young myopes more frequently than their colleagues in India ($p<0.001$), and relatively more frequent than their neighbours in Hong Kong ($p<0.001$).

Great inter-regional variations were reported for prescribing of standard multifocal and specific M contact lenses, pharmaceutical treatment and refractive surgery (Appendix 1.3).

Continent		Asia	Australasia	Europe	North America	South America
Technique		Prescribing frequency (%)				
Spectacles	Single Vision	57.6±31.3	36.8±30.2	42.2±30.7	49.6±31.3	52.1±30.5
	Bifocals	2.9±7.3	1.3±4.4	2.1±7.0	5.1±13.6	1.9±7.0
	Progressive Addition (PALs)	7.4±13.3	17.4±23.0	4.1±12.2	3.7±9.2	1.8±5.2
Contact Lenses	Rigid Gas Permeable (RGP)	4.9±8.5	0.6±2.1	6.1±13.6	2.4±8.3	6.8±10.8
	Single Vision Soft	5.7±9.9	13.9±13.4	20.2±18.8	18.8±16.5	21.0±20.3
	Multifocal Soft	0.8±2.9	6.2±11.9	4.3±11.0	8.5±17.5	2.1±7.2
	Novel Myopia Control Soft	2.2±8.1	1.5±4.7	2.4±8.8	0.9±5.1	3.0±10.6
	Ortho-k	11.1±17.6	21.2±29.1	18.3±27.6	9.4±18.5	7.9±25.2
Pharmaceutical		5.6±14.5	0.8±3.3	0.1±1.2	1.1±6.8	0.7±5.0
Refractive Surgery		2.0±8.3	0.3±1.3	0.3±1.6	0.6±4.5	2.8±7.6

Table 3.2 Frequency of prescribing myopia correction options for progressing/young myopes by practitioners in different continents for progressing/young myopes. Note: data are expressed as mean±SD.

3.4.6 Minimum patient age that practitioners consider myopia correction options

Globally, single vision spectacles were prescribed from the youngest age (5.4 ± 1.5 years). Multifocal spectacles (bifocal: 6.3 ± 2.3 years; PALs: 7.3 ± 2.8 years) and pharmaceuticals (6.4 ± 2.6 years) were considered from an older age. Contact lenses were prescribed for older children, especially those with a novel MC design (single vision: 6.5 ± 3.4 years; novel MC soft: 8.8 ± 3.1 years; ortho-k: 8.8 ± 3.1 years; multifocal: 8.9 ± 3.1 years; RGPs: 9.9 ± 3.3 years). Most practitioners did not recommend refractive surgery to patients under 18 years of age (Appendix 1.3.).

Continental comparisons revealed that single vision spectacles, bifocal spectacles and PALs were prescribed for relatively older ages in Asia and Europe than in Australasia or North America ($p<0.05$). Whereas, all soft contact lens modalities were fitted from older age in Asia and South America than in Australasia, Europe or North America ($p<0.01$). No difference in the minimum age between practitioners in different continental locations who would consider prescribing RGP contact lenses, ortho-k, pharmaceuticals or refractive surgery correction options was observed ($p>0.05$) (Table 3.3).

Country-specific comparisons showed that within Europe, practitioners from the Netherlands fitted single vision spectacles from an older age (5.9 ± 1.7 years, $p<0.001$) than their colleagues across the continent. French practitioners considered fitting single vision contact lenses from an older age compared to those from the rest of the continent, with the exception of Portuguese practitioners, who were conservative with their minimum fitting age of all types of contact lenses ($p<0.05$). Within Asia, practitioners in India fitted RGPs from an older age than their colleagues in China (11.7 ± 3.4 years; $p=0.003$), whereas practitioners in China were more conservative in their minimum fitting age for single vision soft contact lenses than those from either Hong Kong or India ($p<0.05$). Ortho-k was prescribed at an earlier age in Hong Kong than India or China ($p<0.001$) and in the USA than in Canada ($p=0.029$). Pharmaceuticals were considered at an earlier age in China than in Hong Kong or India ($p=0.001$). Variations in the

appropriate age for refractive surgery existed among European practitioners (p=0.295), whereas practitioners in North America and Asia were in agreement with the recommended age for refractive surgery (p=0.241 and p=0.574 respectively) (Appendix 1.3.).

Continent		Asia	Australasia	Europe	North America	South America
Intervention		Age (years)				
Spectacles	Single Vision	5.9±3.9	5.3±0.5	7.4±3.0	5.2±0.6	5.5±1.2
	Bifocals	6.6±2.6	6.0±1.3	7.4±2.6	5.1±0.5	7.5±2.9
	Progressive Addition (PALs)	7.8±3.0	6.5±1.4	7.8±2.8	6.7±2.9	8.0±3.2
Contact Lenses	Rigid Gas Permeable (RGP)	10.1±3.3	9.0±1.7	7.9±2.4	9.3±3.0	10.2±4.3
	Single Vision Soft	10.9±3.8	8.3±0.8	7.8±2.7	7.9±2.4	10.3±3.7
	Multifocal Soft	11.1±4.0	8.3±0.8	7.4±2.5	8.1±2.7	11.0±3.6
	Specific Myopia Control Soft	10.8±3.5	8.3±0.8	7.3±2.5	7.9±2.6	10.3±3.9
	Ortho-k	9.6±3.2	8.0±1.1	8.1±2.3	8.0±3.1	12.3±4.8
Pharmaceuticals		6.4±2.6	6.7±3.9	7.9±3.6	6.4±3.3	6.3±2.2
Refractive Surgery		16.9±2.9	18.0±0.0	12.8±4.5	18.0±0.0	15.5±5.2

Table 3.3 Minimum patient age considered necessary by practitioners (from different continents who prescribed these options for different myopia correction options). Note: data are represented as mean±SD years.

3.4.7 Minimum degree of myopia that needs to be present for practitioners to consider myopia control options

Global comparisons showed that practitioners indicated that myopia would be corrected with single vision spectacles at a lower degree (-1.07 ± 0.90 D) than it would with refractive surgery (-3.06 ± 1.62 D). All other modalities would be considered at approximately -2.00 D (Appendix 1.3.).

Continent specific comparisons revealed that practitioners in Asia required a higher level of myopic refractive error before they would consider single vision spectacles than their colleagues in other continents ($p<0.01$). Australasian practitioners were willing to fit bifocals and PALs at a lower level of myopia than clinicians in Asia, Europe or South America ($p<0.01$). North American practitioners prescribed bifocal and PALs to children with a lower degree of myopia than those from Asia ($p=0.001$). However, practitioners from Asia were willing to consider single vision soft contact lenses, MC specific contact lenses, ortho-k and pharmaceutical intervention at a lower level of myopia than those from Australasia or Europe ($p<0.01$), and single vision soft contact lenses and pharmaceutical treatment than those from North and South America ($p<0.01$). Multifocal contact lenses were considered at a lower level of myopia by Australasian practitioners than those from Asia, Europe or South America ($p<0.01$). In Asia, practitioners fitted RGPs at higher level of myopia than those from Europe and North America ($p<0.01$). Practitioners in Asia and Europe would consider recommending refractive surgery at a significantly higher level of myopia than those from Australasia, North or South America ($p<0.05$) (Table 3.4).

Within Europe, Portuguese and French practitioners required a higher level of refractive error before they would consider fitting RGPs than their colleagues across the continent ($p<0.05$). Higher level of refractive error was required in Portugal before ortho-k ($p<0.01$) or refractive surgery ($p<0.001$) was considered in contrast to other European countries. In Asia, practitioners in India considered prescribing bifocals ($p<0.05$), PALs ($p<0.01$) or

ortho-k ($p=0.001$) at higher levels of myopia than practitioners from China or Hong Kong. Practitioners in China considered prescribing pharmaceuticals to patients with a lower level of myopia (-0.66 ± 0.4D) compared to practitioners from India (-2.86 ± 1.01D) or Hong Kong (-2.39 ± 1.75D; $p<0.001$). Within North America, practitioners from Canada and USA were in agreement with the levels of myopia required to prescribe all modalities except for PALs ($p=0.012$), which were fitted at higher levels of myopia by Canadian practitioners (Appendix 1.3).

Continent		Asia	Australasia	Europe	North America	South America
Intervention		Level of myopia (D)				
Spectacles	Single Vision	-1.2±1.0	-0.8±0.3	-0.8±0.9	-0.8±0.7	-1.3±0.4
	Bifocals	-1.8±1.1	-0.8±0.4	-1.8±1.4	-1.1±0.7	1.5±0.0
	Progressive Addition (PALs)	-2.1±1.4	-0.9±0.6	-1.8±1.4	-1.1±0.7	-1.5±0.0
Contact Lenses	Rigid Gas Permeable (RGP)	-3.1±1.9	-2.8±1.4	-2.2±1.8	-1.5±1.4	-1.8±0.4
	Single Vision Soft	-2.6±1.8	-1.8±0.9	-1.1±0.8	-0.9±0.7	-1.5±0.0
	Multifocal Soft	-2.6±1.7	-1.8±1.0	-1.9±1.5	-1.1±0.7	-1.5±0.0
	Novel Myopia Control Soft	-2.7±1.8	-1.7±0.9	-1.9±1.5	-1.5±1.2	-1.5±0.0
	Orthokeratology	-2.4±1.5	-1.6±0.8	-2.3±1.6	-1.5±1.2	-1.5±0.0
Pharmaceuticals		-1.6±1.5	-2.1±0.9	-3.1±1.6	-1.5±1.3	-2.5±2.1
Refractive Surgery		-3.5±1.6	-2.9±1.5	-2.9±1.5	-1.7±1.3	-2.8±1.8

Table 3.4 Minimum level of patient myopia (in dioptres) before myopia correction options would be considered by practitioners. Note: data are presented as mean±SD**.**

3.4.8 Minimum annual amount of patient myopia progression that would prompt a practitioner to specifically adopted a myopia control approach

Globally, the minimum myopia progression rate that practitioners considered required a MC approach was 0.51 to 0.75 D/year for the majority of respondents (31.1%), with 74% indicating a level between 0.25 and 1.00 D/year (Appendix 1.3).

Continental comparisons showed that Australian practitioners adopted MC strategies for myopia progressing at slower rates than practitioners from Asia, North or South American ($p<0.001$). In Europe, practitioners were willing to treat myopia progression at slower rates than those from Asia ($p<0.001$) or South America ($p=0.003$). No differences in the minimum annual myopia progression rate, requiring MC intervention, between Europe ($p=0.090$), Asia ($p=0.365$) or North America ($p=0.057$) were reported (Figure 3.3).

Free text responses (40 in total) identified other factors, apart from the annual progression rate of myopia that would prompt clinicians to consider MC intervention, including family history of myopia (6 respondents), age of myopia onset (10 respondents), absolute degree of refractive error at the time (2 respondents), ocular biometry (3 respondents), environmental factors/lifestyle (6 respondents), lighting exposure (3 respondents) and parental decisions (3 respondents) (Appendix 1.3).

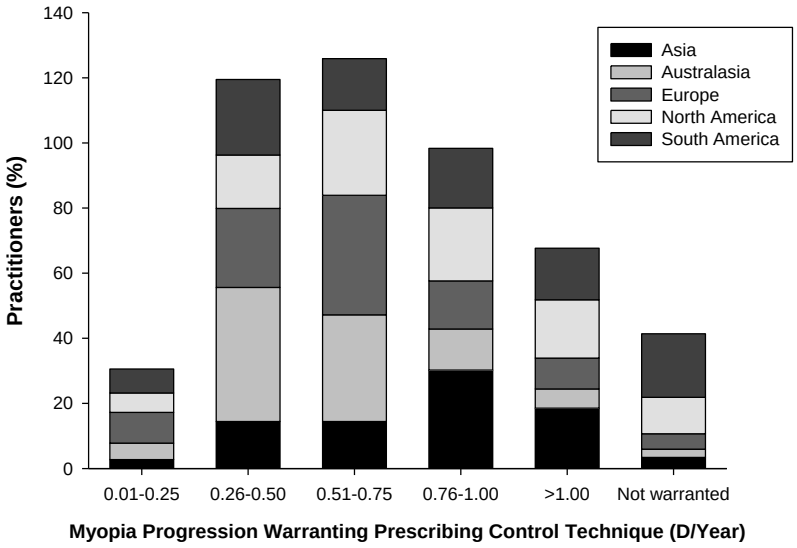

Figure 3.3 Minimum myopia progression in dioptres per year (D/year) that necessitates use of a myopia control approach for practitioners located in different continents (n=964; presented as percentage of practitioners that would prescribe myopia control intervention), (Wolffsohn *et al.* 2016).

3.4.9 Use of single-vision undercorrection as a strategy to slow myopia progression

Most practitioners across the globe did not consider single-vision distance undercorrection to be an effective strategy for slowing down myopia progression (72.7%) (Appendix 1.3.). Continent specific comparisons revealed undercorrection was utilised relatively more often in South America than Australia, Asia or North America ($p<0.01$) (Appendix 1.3).

Within Europe, no differences apart from Spanish and Portuguese practitioners, who reported using undercorrection as a strategy to control myopia more often than their colleagues from the UK and Ireland ($p<0.05$), were observed. Within Asia, practitioners in India employed undercorrection more than those from China or Hong Kong ($p<0.001$). Within North America, there was no difference in the use of undercorrection between the USA and Canada ($p=0.719$) (Figure 3.4 and Appendix 1.3).

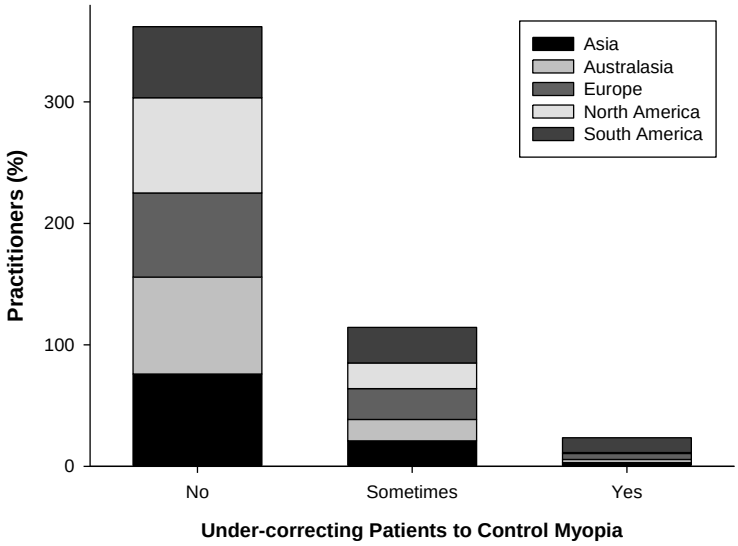

Figure 3.4 Use of undercorrection as a strategy to slow myopia progression by practitioners located in different continents (n=964), (Wolffsohn *et al.* 2016).

3.4.10 Factors preventing the prescription of a myopia control approach

The most common reason reported by the practitioners that would prevent them from adapting MC strategies was the increased cost (35.6%) and the inadequate information about the modalities available (33.3%). Practitioners also felt that the treatment outcomes were unpredictable (28.2%) and were concerned about the safety aspects of MC modalities (25.3%). The ineffectiveness of MC modalities for slowing down myopia progression (23.8%); and the low risk/benefit ratio (20.5%) were also considered as strong arguments not to consider MC interventions. No significant difference in the distribution of these factors between or within continents (p=1.00) was observed (Figure 3.5 and Appendix 1.3).

Free text comments identified other factors affecting the prescription of these strategies to relate to the relative availability of the MC treatments and the instrumentation necessary to prescribe them, and the need for consistent regulations and informational materials (Appendix 1.3).

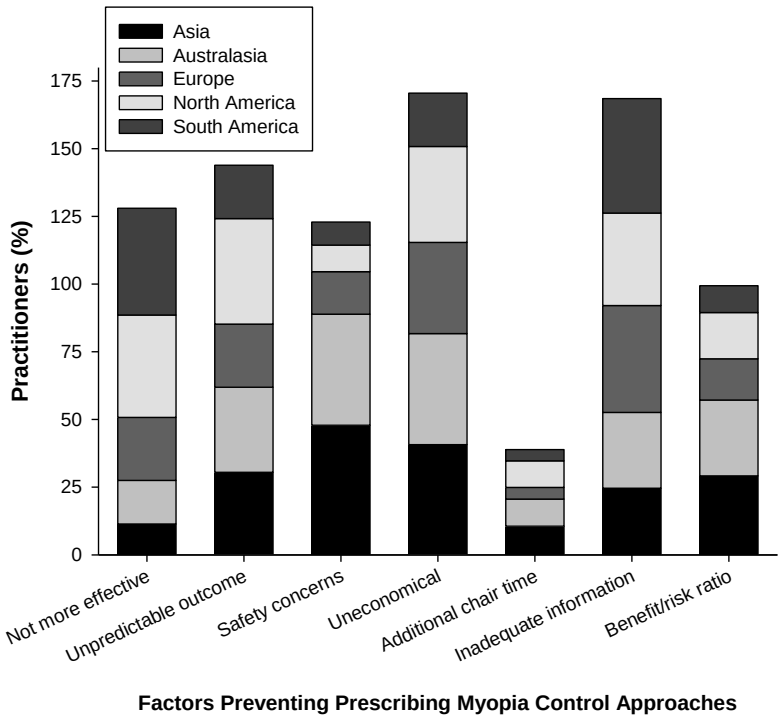

Figure 3.5 Factors prevent prescribing a myopia control approach by practitioners located in different continents (n=964), (Wolffsohn *et al.* 2016).

3.5 Discussion

This is the first study to date to investigate the self-reported attitudes of eye care practitioners towards myopia management and control interventions across the globe. The number of responses, the principal spread of them across, and within five continents, and the professional qualification of the respondents (91% were optometrists and ophthalmologists) provided professional, yet cynical and enthusiastic opinion on the topic. Overall, the survey provides an insight into a challenging field of research that has flourished in recent years, addresses the questions raised before by people working in a clinical and/or research environment (Johnson 2014), and highlights issues in the field of MC.

Unsurprisingly, practitioners in Asia, especially those from China, were more concerned about the increasing prevalence of paediatric myopia in clinical practice than their colleagues from other continents. Similarly, practitioners in the region of Asia reported themselves to be more active in the area of MC. It is undeniable, that the prevalence rates of myopia are reaching

epidemic levels in Asia (Lin *et al.* 2004; Pan *et al.* 2012). However, recent studies have showed that, within Europe and the United States of America, the prevalence of myopia has doubled over the past three to four decades (Vitale *et al.* 2009; Mccullough *et al.* 2016), showing similar trends to Asia, where higher levels of myopia are observed in younger cohorts (Williams *et al.* 2015), reaching levels of 30% among schoolchildren and young adults (Montes-Mico and Ferrer-Blasco 2000; Jorge *et al.* 2007; Vitale *et al.* 2008; Hendricks *et al.* 2009; Williams *et al.* 2015; McCullough *et al.* 2016). Therefore, practitioners from other parts of the world should not be ignorant to myopia management approaches, and myopia should be addressed as a world-wide issue.

When asked to identify the relative efficacy of various MC approaches, practitioners correctly identified ortho-k as one of the most effective methods for attenuating childhood myopia progression, which was in accordance with the current evidence of retardation rates of 45-50% (Si *et al.* 2015; Wen *et al.* 2015). However, despite its relative efficacy, ortho-k only constitutes of only 1% of all the contact lens fits world-wide (Efron *et al.* 2013). The relative efficacy of behavioural approaches of increased outdoor activity was slightly overestimated and pharmaceutical treatment was underestimated (32% and 28% on average) in comparison to 11-34% (Wu *et al.* 2010; Wu *et al.* 2013) and 32-72% (Tan *et al.* 2005; Chua *et al.* 2006; Chia *et al.* 2012b; Chia *et al.* 2015), based on scientific evidence. Single vision spectacles and single vision undercorrection, which has been reported to increase rather than decrease the progression of myopia (Chung *et al.* 2002; Adler and Millodot 2006), were considered to be least effective. However, some practitioners, particularly those in South America, Spain and Portugal within Europe and India within Asia (Figure 3.4 and Appendix 1.3.), were more willing to employ distance undercorrection in their practice for young and progressive myopes.

Interestingly, even though most of the practitioners would consider themselves to be active in the field of MC within their practices, two thirds of them reported prescribing single vision spectacles or contact lenses (68%) to young or progressing myopes, with the uptake of more effective methods varying between and within the continents.

One third of the practitioners not adopting any of the more effective MC approaches reported their reluctance to be linked with the increased costs and (or) an inadequate amount of information was available to them. Around one quarter of the practitioners felt that the outcome of MC approaches is unpredictable, and that these methods are not effective. Relative safety of these procedures also was considered, albeit to a lesser extent. Free text responses further revealed the possible reasons for not employing MC approaches, and were linked to the relative availability of various MC options, especially specific MC contact lens designs, and the lack of regulatory guidelines as most of the currently available interventions are still 'off-label'. Furthermore, the availability of specific instrumentation required to fit more sophisticated contact lens designs, such as a corneal topographer for fitting orthokeratology contact lenses, in most practices is limited. Also, if the modification of peripheral refraction is to be successfully employed in human trials more often, rather than only in animal trials (Smith, Hung*, et al.* 2009; Mutti *et al.* 2011; Atchison *et al.* 2015), instrumentation to rapidly assess the peripheral eye shape and refraction would be required.

When asked to describe how their preferences for prescribing different MC options would vary according to patient's age, degree of myopia and the annual progression of this condition, practitioners were comfortable to prescribe refractive corrections with a simpler optic design and pharmaceuticals from an earlier age (5-6 years). Whereas, they tended to wait until a child is older to prescribe more sophisticated optical designs, including bifocals, PALs, RGPs, multifocal and specific MC contact lenses and ortho-k. Similarly, more complex modalities were considered appropriate for mild to moderate myopia, whilst single vison glasses were fitted at lower levels. The rate of myopia progression that would trigger practitioners to consider MC approach largely mirrored the prevalence rates in the specific region or country. In addition to the rate of myopia progression, practitioners indicated family history, age of onset, the level of myopia, ocular biometry, lightning levels, lifestyle effects and environmental factors and also parental involvement (Cheung *et al.* 2014) to play a role in the decision making of most suitable type of intervention. Research suggests that a lower level of hyperopia (<6

years old) is a good predictor of subsequent myopia development and correlates well with the age (Thorn *et al.* 2005; Zadnik *et al.* 2015). Also, myopia progresses at a faster rate in children compared to adolescents (Dong *et al.* 2013), therefore suggesting that young progressing myopes would benefit more, if the MC interventions would be employed earlier.

More research on the relative benefits of MC interventions, especially on contact lens modalities, that have shown the most promising effects of all optical interventions, in children, adolescents and young adults, is needed. This, in return, will encourage practitioners to employ these approaches at an earlier age. Practitioners in Hong Kong can be considered the pioneers of ortho-k lens fitting and, unsurprisingly, fitted this modality from an earlier age than any other country or continent. Hong Kong is a good example how, with a simple procedure of establishing guidelines for a safe ortho-k practice (Cho *et al.* 2008) , both practitioners and parents of young myopic patients, can be encouraged to employ ortho-k for MC.

Several limitations of the present study exist. The survey was piloted on a very small number of eye care practitioners (n=5) at the initial stage of the study; this phase should have been more extensive. Although survey was distributed globally and similar regional respose level was aimed for, the fact that more proactive eyecare practitoners took part in the survey and, therefore, possibly slightly overestimated the true situation of MC adaptation in clinical enviroment. Also, the fact that not all practices are equipped the same should be acknowledged. The availability of clinical instrumentation required for fitting different MC modalities, time constraints and the policy of employer might affect their decision to uptake MC in their daily routine.

In summary, this survey, investigating practitioners' self-reported attitudes towards MC, shows that, despite the growing evidence of the sight threatening and social-economic aspects of myopia, the moderate level of practitioners' concern and perceived activity in the area of MC and the uptake of appropriate techniques in clinical practice, is insufficient. It is clear, that the research findings do not translate well into a clinical setting. Furthermore, practitioners do not

apply MC techniques early enough in a child's ocular development to achieve the optimal effect. Adequate education of practitioners is lacking, whilst MC interventions are still unapproved by professional bodies. Therefore, safety regulations and appropriate guidelines for myopia management in clinical practice, which would address the epidemic nature of this lifelong condition, and highlight the benefits of myopia retardation strategies, needs to be established in order to enhance patient care and protect patients from the risks, costs and quality of life issues associated with myopia.

In order to provide a further education for practitioners and establish internationally acknowledged guidelines further, a large-scale longitudinal study investigating the effects of MC interventions and their application in a clinical setting, should be designed and conducted. The scope of this thesis is to investigate the biomechanical aspects of ortho-k, which is one of the most promising optical approaches for slowing down myopia progression at present.

Chapter 4. Long term corneal biomechanical response to orthokeratology and the role of anterior eye segment in myopic schoolchildren

4.1 General overview

This chapter describes a retrospective data analysis of corneal biomechanical properties measured by the ORA after 2 years of ortho-k lens wear in Chinese children that were collected as a part of three studies ['Retardation of myopia in orthokeratology' (ROMIO) (Cho and Cheung 2012), 'Myopia control using toric orthokeratology' (TO-SEE) (Chen *et al.* 2013) and 'High myopia – partial reduction ortho-k: a 2-year randomized study' (HM-PRO) (Charm and Cho 2013)] primaly investigating the efficacy of ortho-k lens wear for MC and were conducted by collaborators at the Hong Kong Politechincal University but not published before.

4.2 Introduction

The ability of orthokeratology (ortho-k) to achieve consistent myopia retardation rates of 40% to 50% (Cho, Pauline *et al.* 2005; Walline *et al.* 2009; Cho and Cheung 2012; Charm and Cho 2013; Chen *et al.* 2013; Swarbrick *et al.* 2015) has established the method as one of the most promising approaches for myopia control (MC) (Holden *et al.* 2014; Huang *et al.* 2016). However, the inter-individual variations in treatment response (Cho *et al.* 2005; Walline *et al.* 2009; Kakita *et al.* 2011; Hiraoka *et al.* 2012; Santodomingo-Rubido *et al.* 2012; Swarbrick *et al.* 2015), a lack of consensus on the underlying mechanisms of ortho-k (Swarbrick *et al.* 1998; Owens *et al.* 2004; Cheah *et al.* 2008; Tsukiyama *et al.* 2008) and, subsequently, the mechanisms by which it inhibits myopia progression (Berntsen *et al.* 2005; Kang and Swarbrick 2011; Hiraoka *et al.* 2015; Swarbrick *et al.* 2015; Santodomingo-Rubido, Villa-Collar, Gilmartin, Gutiérrez-Ortega*, et al.* 2016), have highlighted the need to better understand the corneal response to ortho-k lens wear and, subsequently, the contribution of the anterior eye to myopia progression.

The transient alteration of corneal shape by the ortho-k lens, to temporarily eliminate myopic refractive error, achieved by the the topographical changes induced by the ortho-k lens

(Mountford 2004; Chan *et al.* 2010), is either attained by tissue re-distribution induced by the interaction between tangential forces exerted by the lens and their interaction with the tear film (Swarbrick *et al.* 1998; Alharbi and Swarbrick 2003; Mountford 2004; Swarbrick 2004; Swarbrick *et al.* 2015), or the interaction between the tear film, the compressive forces exerted at the centre of the lens and tensile forces exerted at the edge of the lens (Mountford 1997; Mountford 1998, 2004). The optical effects of topographical chages achieved by the ortho-k lens are believed to underpin the mechanisms, by which the reduction in myopia progression is attained. The thinning of the central cornea and thickening of the mid-peripheral cornea induced by ortho-k lens has been proposed to create an environment which alters peripheral refraction and eliminates hyperopic defocus, thereby slowing down myopia progression (Walline *et al.* 2009; Kang and Swarbrick 2011; Swarbrick *et al.* 2015; Kang and Swarbrick 2016). Peripheral hyperopic defocus has been found to act as a stimulus for axial elongation in animal models (Smith, Hung*, et al.* 2009; Liu and Wildsoet 2011) and, therefore, presumably, affect the refractive development in children (Sng *et al.* 2011; Berntsen *et al.* 2013) (for detailed information on mechanisms underlying ortho-k, please refer to Section 1.5).

However, this theory is under debate as a recent study has shown no correlation between peripheral refraction and myopia progression (Atchinson *et al.* 2015) and also demonstrated that axial elongation and changes in corneal power in Caucasian schoolchildren undergoing ortho-k therapy for 2 years (Santodomingo-Rubido, Villa-Collar, Gilmartin and Gutiérrez-Ortega 2016). Furthermore, correlation between corneal aberrations and changes in axial length (AL) has been observed, suggesting that other optical phenomena can contribute to the MC effect of ortho-k (Berntsen *et al.* 2005; Hiraoka *et al.* 2015; Santodomingo-Rubido, Villa-Collar, Gilmartin, Gutiérrez-Ortega*, et al.* 2016). Hiraoka *et al.* (2015) hypothesised that the higher order aberrations (especially spherical aberration) observed in adults, undergoing ortho-k therapy (Joslin *et al.* 2003; Berntsen *et al.* 2005), could act as an inhibitory factor to axial elongation and myopia progression in children. Hiraoka's study investigated Japanese schoolchildren over a period of one year and did not find a correlation between axial elongation

and the altered corneal shape of the flattened central zone surrounded by a steepened annular area in the mid-periphery. This has been reported to induce spherical aberrations and simultaneously reduce hyperopic defocus (Berntsen *et al.* 2005). Instead, a correlation between coma-like aberrations, corneal multifocality and axial elongation was found, suggesting that asymmetric components of optics contributed towards the 'MC' effect of the ortho-k (Hiraoka *et al.* 2015).

The inter-individual variability in treatment outcome of ortho-k in MC has been associated with age, sex, age of myopia onset, rate of myopia progression and level of parental myopia, anterior chamber depth (ACD), corneal power and shape, and iris and pupil diameter (Santodomingo-Rubido *et al.* 2013). Ortho-k was found to be more successful in comparison to single vision spectacles (SVS) in white European children of older age (range 6 to 12 years) with earlier onset of myopia, lower level of parental myopia, larger iris and pupil diameter, longer anterior chamber (AC), greater corneal power and a more prolate corneal shape at baseline, over a two-year study period (Santodomingo-Rubido *et al.* 2013). However, these factors together could only account for 50.6% of total variance in AL changes in ortho-k wearing children and 49.5% of total variance in SVS wearing children (Santodomingo-Rubido *et al.* 2013). Interestingly, no change in ACD of ortho-k wearing schoolchildren of Chinese ethnicity (7-10 years of age) was observed over the same time period, compared to SVS wearing children, whose ACD increased significantly (Cheung and Cho 2016). Regardless of the modality prescribed, no change in overall anterior segment length (ASL) and crystalline lens, was seen in both SVS and ortho-k wearing children. However, authors concluded that no firm conclusion can be drawn form the study and further research in the area should be warranted due to the small sample size (37 ortho-k wearing children vs 41 SVS wearing children), the relatively small changes in the anteriror segment over the period of 2 years and possibly different accommodative demand in the two groups. Also, the changes seen in the control group (SVS wearing children) accounted for a small amount of overall axial elongination (Cheung and Cho 2016). In the same cohort, a reduction in CCT was detected

over the first six months of ortho-k lens wear, which subsequently stabilised (Cheung and Cho 2013, 2016).

Studies investigating the efficacy of ortho-k for MC have shown similar reduction rates by employing various lens designs in children of different ethnicities (Kakita *et al.* 2011; Cho and Cheung 2012; Hiraoka *et al.* 2012; Charm and Cho 2013; Chen *et al.* 2013; Swarbrick *et al.* 2015). It is highly unlikely that ethnicity and lens design would explain much of the total variance of successful treatment outcome and myopia progression. Therefore, the anterior eye segment, particularly the corneal response to ortho-k lens wear in long term, is of interest. A synchronised interaction between all optical components and AL of the eye is required for the process of emmetropisation to be successful (Mutti 2010; Mutti *et al.* 2013). In case of myopia this vital ocular equilibriumis disrputed (Mutti *et al.* 2013). In order to better understand the driving forces behind myopia development and to find an optimal intervation for MC, it is crucal to comprehend the involvement of anterior segment in the process of slowing down myopia progression and the role of its components in process of the axial elongination.

Ortho-k therapy is a dynamic process whereby short and long-term responses to ortho-k lens wear differ (Zhong *et al.* 2009; Nieto-Bona *et al.* 2011a, 2011b). The treatment effect is achieved within the first seven to ten nights of lens wear, but stabilises within the first thirty to ninety nights (Mountford 1998; Sridharan and Swarbrick 2003), suggesting that initial adaptation is followed by the retention of the achieved treatment effect. Studies of long term corneal response to ortho-k wear provide evidence of the technique's safety, efficacy, effect on corneal adaptation and reversibility (Zhong *et al.* 2009; Nieto-Bona *et al.* 2011a). However, in the context of MC, long term studies are required to understand the factors by which ortho-k regulates and stabilises myopia progression. If the changed corneal morphology induced by the reverse geometry lens is crucial for slowing down myopia progression, then stabilisation and adaptation to the new corneal shape is necessary before the 'MC' effect can take place. If the primary inhibitory factor, by which ortho-k slows down myopia progression could be

elucidated, the method could be optimised and the underlying mechanisms could presumably be applied to other MC interventions.

The Ocular Response Analyser (ORA, Reichert Ophthalmic Instruments, Buffalo, NY, USA) has enabled the assessment of corneal biomechanical properties in-vivo (Luce 2005) (for more information on the ORA and corneal biomechanical measures, please refer to 2.2.1). Corneal hysteresis (CH) and corneal resistance factor (CRF), which are ORA specific parameters and describe the viscous damping properties and the overall resistance of the cornea respectively (Luce 2005), have been found to be affected by ortho-k lens wear (Gonzalez-Meijome *et al.* 2008; Chen *et al.* 2009; Mao *et al.* 2010; Yeh *et al.* 2013). CRF (Chen *et al.* 2009; Mao *et al.* 2010; Yeh *et al.* 2013) and CH (Mao *et al.* 2010; Yeh *et al.* 2013) both decrease over the first thirty nights of lens wear and return to baseline levels within 3 months of lens wear (Mao *et al.* 2010). However, CH and CRF on their own are not able to fully discriminate between healthy and ectatic corneas (Kerautret *et al.* 2008; Saad *et al.* 2010; Mikielewicz *et al.* 2011). Saad *et al.* (2010) reported CH and CRF values in normal, keratoconic and keratoconus suspect corneas and concluded that in all three groups a large scatter of CH and CRF values was seen. Similar CH and CRF values but different air-pressure characteristics were not a rarity, therefore, suggesting that the signal from the applanation curve should also be analysed when evaluating corneal biomechanical response. The morphological changes induced by the ortho-k lens reported in animal (Matsubara *et al.* 2004; Cheah *et al.* 2008; Choo *et al.* 2008) and human (Zhong, XW *et al.* 2009; Nieto-Bona *et al.* 2011a, 2011b) studies are not as severe as the ones observed in advanced keratoconus (Saad *et al.* 2010). A detailed analysis of the applanation curve could provide more information about the corneal biomechanical changes occurring in ortho-k than CH and CRF alone.

None of the previous studies investigating corneal biomechanical response to ortho-k have been conducted for longer than six months, and no comparison of corneal biomechanical response in healthy control individuals not undergoing ortho-k therapy has been reported (Gonzalez-Meijome *et al.* 2008; Chen *et al.* 2009; Mao *et al.* 2010; Yeh *et al.* 2013). Therefore,

studies following both individuals undergoing and not undergoing ortho-k therapy, and investigating the ORA applanation peak in detail, over a longer study period, are required as they would provide a better understanding of corneal biomechanical response to ortho-k and the role of anterior eye segment in myopia progression.

The purpose of this study was to conduct a retrospective analysis of yet unpublished data obtained as a part of three studies (ROMIO, TO-SEE and HM-PRO studies, a two-year randomized clinical trials evaluating the effectiveness of myopia control using ortho-k) conducted by collabrators at The Hong Kong Polytechnic University (Cho and Cheung 2012; Chen *et al.* 2013; Charm and Cho 2013), monitoring corneal biomechanical response to ortho-k lens wear in comparison to naturally progressing myopia in myopic schoolchildren fitted with single vision spectacles over a two-year period. The investigation of long term corneal biomechanical response to would aid to a better understanding of the involvement of anterior segment in myopia progression and to evaluate the role of corneal tissue in ortho-k.

4.3 Methods

4.3.1 Subjects and study protocol

A retrospective analysis of data pooled from three studies ['Retardation of myopia in orthokeratology' (ROMIO) (Cho and Cheung 2012), 'Myopia control using toric orthokeratology' (TO-SEE) (Chen *et al.* 2013) and 'High myopia – partial reduction ortho-k: a 2-year randomized study' (HM-PRO) (Charm and Cho 2013)] was conducted to investigate the corneal biomechanical response to ortho-k lens wear and the contribution of the anterior eye to myopia progression over a two year period.

Data from 164 subjects (83 ortho-k wearing children, 81 single vision spectacles wearing children) were retrieved from the participants of the three aforementioned studies and combained for the analysis (Table 4.2). Participants who attended all study visits were included in analysis.Sudy design, refraction and axial length data have been reported previously (Cho and Cheung 2012; Charm and Cho 2013; Chen *et al.* 2013).

In summary, Chinese children living in Hong Kong, China (6 to 12 years old) with refraction between -0.50 to -8.00 D, with-the-rule astigmatism up to -3.50 D, and good ocular and general health were assigned either to treatment (ortho-k) or control (single vision spectacle group). Subject recruitment was adjusted for age, sex and manifest refraction to minimise systematic bias. Subjects in the ortho-k group were fitted with reverse geometry lenses (for lens specifications please refer to Table 4.2) by experienced orthokeratology practitioners, and asked to wear the lenses overnight, adhering to an 8-10 hour sleeping schedule.

For ROMIO and TO-SEE Menicon Z Night (NKL Contactlenzen B.V., Emen, Netherlands) and Menicon Z toric (NKL Contactlenzen B.V., Emen, Netherlands) ortho-k lenses were used, respectively. These are four zone reverese geometry lenses (Table 4.2, Section 1.3.3).The total lens diameter was ordered in three steps – 10.20 mm, 10.60 mm (standard) and 11.0 mm. Treatment zone was 6 mm in diameter (Cho and Cheung 2012; Charm and Cho 2013). The base curve ranged from 7.20 mm to 10 mm in 0.05 mm steps. Tangential angle (50^{o} – 65^{o} (1^{o} step) and sagittal depth (0.50 – 0.99 mm (0.01 mm step) were adjusted depending on the topography readings. The lens fitting and ordering was based on topography maps and Easyfit software (http://www.menicon.com/pro/our-products/gp-lens/menicon-z-night/; accessed 13.12.2018; Cho and Cheung 2012; Charm and Cho 2013). For the HM-Pro Procornea DreamLite (Pro Cornea Ltd., Eerbeek, Netherlands) ortho-k lenses were used (Table 4.2). Procornea DreamLite is a four zone reverse geopmetry lens (Table 4.2, Section 1.3.30 THAT has a 10.50 mm total diameter, treatment zone (optic zone) of 6 mm and back optic zone radius from 7.20 mm to 9.50 mm in 0.05 mm steps (Chen *et al.* 2013).

Lens adjustments (maximum 3 times) to reach an optimal fit (good centration and 'bull's eye' pattern) were made if necessary. Subjects in the spectacle group were provided with single vision spectacles and asked to wear them during waking hours. No significant adverse events were reported in any of the studies (Cho and Cheung 2012; Charm and Cho 2013; Chen *et al.* 2013). Double masking in the study could not be achieved do to the vast differencies in the

both modalities for myopia control. However, one study investigator, who took AL measurments could be masked as ortho-k do not present manifest signs during the estimation of AL. Other examiners who did the slit lamp assessment and assessed the lens fit could not be masked as manifest signs of ortho-k wear were present during these procedures (Cho and Cheung 2012). The demographic and refractive data of the pooled cohort are summarised in Table 4.1. For individual specifications of study design, cohort demographic and refractive data of each study please refer to Table 4.2.

All studies complied with the Declaration of Helsinki and were approved by the Departmental Research Committee of the School of Optometry of the Hong Kong Polytechnic University. All three studies were registered at ClinicalTrials.gov (ROMIO: NCT00962208, TO-SEE: NCT00978692, HM PRO: NCT00977236).

		Control	Ortho-k
Number of participants (male:female)		81 (35:45)	83 (43:40)
Age (years)		9.0 ± 1.4 (Mean ± SD), range (6 to 12)	9.0 ± 1.2 (Mean ± SD), range (6 to 12)
Refractive Error	Sphere (D)	-3.15 ± 1.95, range (-0.50 to -8.00)	-2.86 ± 1.95, range (-0.50 to -7.75)
	Cylinder (D)	-0.95 ± 0.85, range (0 to -3.50)	-1.00 ± 0.89, range (0 to -3.50)

Table 4.1 Cohort demographics and refractive data.

	ROMIO	TO-SEE	HM-PRO
Study design	Randomised	Non-randomised	Randomised
Masking	Examiners masked to axial length measurements		
Ethnicity	Chinese		
Age (years)	6-10	6-12	8-12
Myopia (D)	-0.50 to -4.00	-0.50 to -5.00	-5.00 to -8.00
With-the-rule astigmatism (D)	up to -1.25	-1.25 to -3.50	up to -1.50
Astigmatism axis (degrees)	180 ± 30	180 ± 20	180 ± 20
Ortho-k group (n=)	37	43	26
Control group (n=)	41	37	26
Ortho-k lens Type	Menicon Z Night (NKL Contactlenzen B.V., Emen, Netherlands)	Menicon Z Night Toric (NKL Contactlenzen B.V., Emen, Netherlands)	Procornea DreamLite (Pro Cornea Ltd., Eerbeek, Netherlands)
Ortho-k lens material (Dk $[cm^2 \bullet mLO_2]/(s \bullet mL \bullet mmHg]$)	Tisilfocon A (163×10^{-11})	Tisilfocon A (163×10^{-11})	Hexafocon A (100×10^{-11})
Control group	Single vision spectacles (CR-39 material, Hong Kong Optical Lens Co., Hong Kong, China)		
Data collection	Baseline, 6, 12, 18 and 24 months		
Refraction method	Cycloplegic subjective refraction		
AL measurement	IOLMaster 500 (Zeiss Humphrey Systems, Dublin, CA, USA)		
Anterior eye structure measurements	Pentacam (Oculus Inc., Jena, Germany)		
Corneal topography measurements	Medmont E300 (Version 3.9.3 Medmont Pty. Ltd., Camberwell, Australia)		
Corneal biomechanical measurements	Ocular Response Analyser (2nd generation ORA, Reichert Inc., Buffalo, NY, USA)		

Table 4.2 Summary of ROMIO (Cho and Cheung 2012), TO-SEE (Chen *et al.* 2013) and HM-PRO study design (Charm and Cho 2013).

4.3.2 Measurements

Data were collected at baseline (BL), 6, 12, 18 and 24 months after commencement of the study. Subjective refraction was conducted under cycloplegia. AL was measured, using partial coherence interferometry (IOLMaster 500), by taking an average of the first 5 measurements with a signal-to-noise ratio above 3.5, and a maximum difference of 0.02 mm between any two readings (Cho and Cheung 2012). Corneal topography in the steep and flat meridian, using Medmont E300 was assessed by selecting the best of four images captured (image score above 98) (Cho and Cheung 2012). CCT at the thinnest point of the cornea, and ACD were determined using a Scheimpflug imaging system, by taking an average of three measurements per eye. The ORA was used to assess corneal biomechanical properties, by selecting the best of four measurements (waveform score of 3.6 or above and true best signal value) (Lam *et al.* 2010; Hon *et al.* 2012). Table 4.2 provides an overview of the instrumentation used in these three studies.

Detailed information on instrumentation used in all studies is discussed in Chapter 2.

4.3.3 Data analysis

Data were recorded using Microsoft Excel (Microsoft Office Professional Plus 2013, Microsoft Corp. Redmond, Washington, USA). Statistical analysis was conducted using SPSS (IBM SPSS Statistics for Windows, Version 21.0. IBM Corp. Armonk, New York, USA).

Data were tested for normality using the Kolmogorov-Smirnov (K-S) test ($p>0.05$). Repeated measures analysis of variance (ANOVA) was employed to examine the changes in response variables over time, when data were normally distributed. Friedman analysis of variance was used for non-normally distributed data. Statistically significant changes from baseline were further investigated, using post hoc tests with Bonferroni correction.

Multivariate regression analysis (stepwise) was used to further examine the relationship between refractive changes, simulated keratometry readings, corneal eccentricity in the

steepest and flattest meridian, CCT, AL and corneal biomechanical properties over the two-year period of ortho-k lens or spectacle wear.

A critical p-value of 0.05 was chosen to denote statistical significance, and only data from the right eye were analysed.

The study was designed to achieve 80% power (α=0.05, Cohen's d=0.25) to detect at least 0.4 mmHg change in CRF (Cohen's d=0.27) (Hon *et al.* 2012), based on the repeated measures ANOVA with correlation coefficient between the repetitions set to 0.5, and required a minimum of 25 participants in each group. Study power was determined, using statistical power program G*Power 3.0 (version 3.0.10) (Faul *et al.* 2007; Faul *et al.* 2009).

4.4 Results

4.4.1 Changes in refractive error, corneal curvature and central corneal thickness

Ortho-k lens wear reduced the initial mean myopic spherical refractive error of -2.86 ± 1.78 D (mean ± SD) to -0.39 ± 0.94 D by the six-month appointment ($p<0.001$), and this remained stable throughout the rest of the study period ($p>0.05$). Mean corneal astigmatism significantly decreased between BL and the six-month appointment ($p<0.001$), and remained stable thereafter ($p>0.05$) (Table 4.3).

Conversely, myopia progressed in the spectacle wearing group, with mean spherical refractive error increasing from -3.15 ± 1.95 D to -4.09 ± 1.91 D over the two-year period ($p<0.001$). A similar increase was observed in mean corneal astigmatism ($p=0.039$) (Table 4.3).

In the ortho-k group, a decrease in flat and steep eccentricity ('e') was seen between BL and the six-month appointment (both $p<0.001$), then both flat and steep 'e' remained stable over the remaining eighteen months of the study ($p>0.05$) (Table 4.3). Similarly, a flattening in the flattest and steepest meridian between the BL and six-month visit (both $p<0.001$) was detected, which stabilised thereafter ($p>0.05$) (Table 4.3). Keratometric astigmatism (ΔK) did not change over the two-year period ($p=0.245$) (Table 4.3).

In the spectacle wearing group, steep and flat ‘e’, simulated keratometry in the flattest meridian, and keratometric astigmatism remained stable throughout the study period (all $p>0.05$), with the exception of fluctuations in the simulated keratometry in the steepest meridian, which could not be described as consistently increasing or decreasing ($p<0.001$), (Table 4.3).

The effect of group (ortho-k vs spectacle) was significant for all parameters ($p<0.05$), except for steep ‘e’ ($p=0.951$) (Table 4.3).

Parameter (Mean±SD)	Group	Visit					K-S test for normality	Effect of time (Repeated Measure ANOVA)		Effect of group (Repeated Measure ANOVA)	
		BL	6 months	12 months	18 months	24 months	p	p	F	p	F
Refractive sphere (D)	**SVS**	-3.15±1.95	-3.25±1.85	-3.52±1.78	-3.85±1.87	-4.09±1.91	0.031*	<0.001	184.02	<0.001	273.28
	OK	-2.81±1.78	-0.39±0.94	-0.43±0.97	-0.35±0.97	-0.27±0.89	0.029*	<0.001	69.68		
Refractive astigmatism (D)	**SVS**	-0.95±0.85	-0.98±0.81	-1.02±0.73	-1.02±0.83	-1.10±0.83	0.120	0.039	2.709	<0.001	37.7
	OK	-1.00±0.89	-0.43±0.45	-0.50±0.47	-0.52±0.41	0.52±0.51	0.006*	<0.001	58.667		
Steep e	**SVS**	0.40±0.12	0.41±0.16	0.40±0.13	0.40±0.14	0.38±0.11	0.218	0.587	0.708	0.951	0.004
	OK	0.46±1.21	0.35±0.13	0.35±0.12	0.36±0.12	0.39±0.11	0.399	<0.001	5.424		
Flat e	**SVS**	0.63±0.09	0.63±0.09	0.62±0.09	0.63±0.09	0.64±0.09	0.889	0.373	1.058	<0.001	153.09
	OK	0.66±0.09	0.36±0.16	0.32±0.15	0.33±0.14	0.32±0.14	0.792	<0.001	90.459		
Steep K (D)	**SVS**	44.77±1.67	44.89±1.59	44.91±1.67	44.89±1.73	44.90±1.66	0.900	<0.001	11.458	<0.001	44.10
	OK	44.74±1.61	42.80±1.44	43.07±1.51	43.03±1.50	43.04±1.46	0.692	<0.001	61.655		
Flat K (D)	**SVS**	43.31±1.40	43.34±1.37	43.32±1.40	43.29±1.42	43.30±1.61	0.694	0.303	1.131	<0.001	40.30
	OK	43.12±1.25	41.57±1.34	41.75±1.29	41.70±1.37	41.64±1.24	0.978	<0.001	70.877		
ΔK (D)	**SVS**	1.46±0.64	1.55±0.62	1.59±0.66	1.59±0.65	1.60±0.89	0.153	0.116	2.314	0.016	6.02
	OK	1.62±0.75	1.23±0.70	1.32±0.63	1.33±0.57	1.40±0.65	0.385	0.245	1.37		

Table 4.3 Changes in refractive sphere, astigmatism and corneal topography over the two-year study period in spectacle (SVS) and ortho-k (OK) wearing groups. *If p<0.05, Friedman's test procedures were carried out. Note: statistically significant p values (p<0.05) are underlined.

The CCT, measured using Pentacam (Oculus Wetzlar, Germany), in the ortho-k group reduced initially ($F_{(1.345, 49.752)}$=6.051, p<0.001) and was significantly thinner between BL and the 6-month visit (568 ± 36 µm vs 565 ± 32 µm; p<0.001), and BL and the 18-month visit (568 ± 36 µm vs 564 ± 31 µm; p=0.002). However, CCT returned to BL levels after two years of ortho-k lens wear (568 ± 36 µm vs 569 ± 31 µm; p=0.269) (Figure 4.1).

In the spectacle group, a slight, but significant, increase in the CCT was observed between BL and the 24-month visit (576 ± 28 µm vs 584 ± 28 µm respectively; $F_{(2.421, 104.108)}$=6.846, p<0.001) (Figure 4.1).

The effect of treatment (ortho-k lens wear) on CCT was significant (F=5.0, p=0.028).

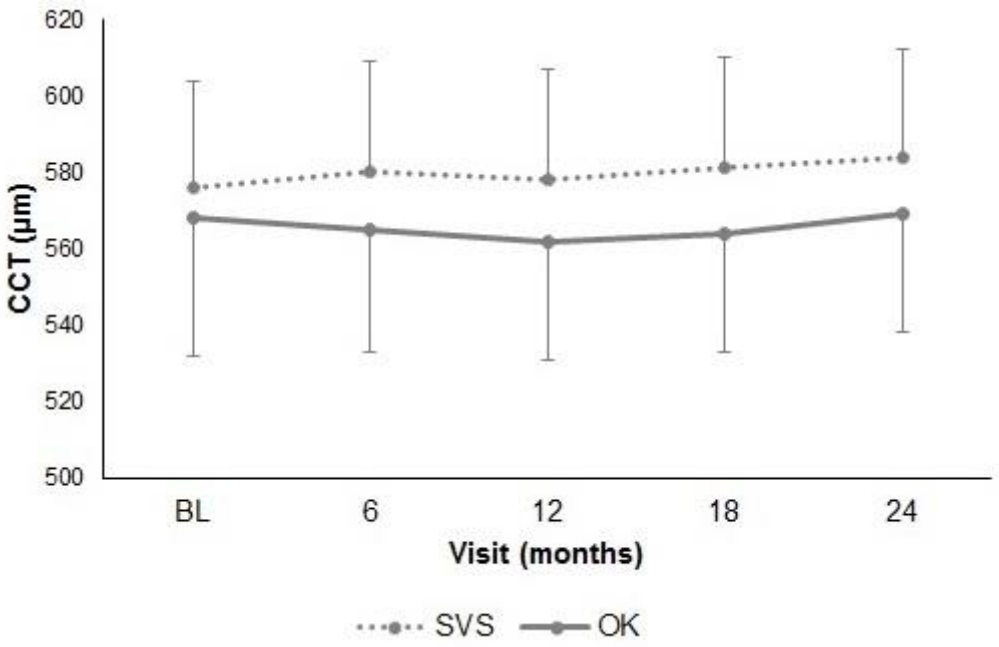

Figure 4.1 Changes in CCT over the two-year study period in the ortho-k wearing group (OK) and single vision spectacle wearing group (SVS). Note: data are presented as mean ± SD (n_{OK}=83 and n_{SVS}=81), error bars represent 1 SD.

4.4.2 Corneal biomechanical response measured with the Ocular Response Analyzer

The ORA derived parameters that changed significantly over the two-year study period are summarised in Table 4.4 and Table 4.5. The non-significant parameters are presented in Table 4.6 and Appendix 2).

Goldmann correlated intraocular pressure (IOPg), corneal biomechanics corrected intraocular pressure (IOPcc), CH and CRF did not change significantly over the study period in the ortho-k wearing group (p_{IOPg}=0.536, p_{IOPcc}=0.603, p_{CH}=0.933 and p_{CRF}=0.912 respectively; Appendix 2). Decrease in CH and CRF, as well as in IOPg and IOPcc have been reported after one week of ortho-k lens wear that stabilises thereafter (at 3 and 6 month follow-up) in a group of schoolchildren of similar age (Mao *et al.* 2010). Also changes in CH (Gonzalez-Meijome *et al.* 2008) and CRF (Chen *et al.* 2009) have been reported in an adult population after just a few hours of ortho-k lens wear, whilst decrese CRF has been reported after one night of lens wear (Chen *et al.* 2009). Therefore, it is possible that the initial corneal response to ortho-k lens wear is different to that of a long term as the cornea adjust to the reshaping effect induced by the lens (Gonzalez-Meijome *et al.* 2008; Chen *et al.* 2009; Mao *et al.* 2010).

In contrast, IOPg, IOPcc and CH fluctuated significantly in the spectacle wearing group; however, they did not consistently increase or decrease (Table 4.5). CRF remained stable (p=0.515). The effect of treatment was significant for IOPg, CH and CRF (p_{IOPg}=0.032, p_{CH}=0.012 and p_{CRF}=0.005 respectively; Appendix 2).

Some of the 37 additional ORA-derived metrics appeared to be more sensitive in both groups, with the initial applanation peak affected the most (Figure 4.2 and Figure 4.3). The corneal biomechanical response in the spectacle wearing group was more varied than it was in the ortho-k wearing group (Figure 4.3 and Table 4.5). There was no effect of time for some parameters (path1 from the upper 50% of the initial applanation peak

or the absolute value of the path around the peak), but the effect of group (ortho-k wear) was significant ($p_{OK\ time}$=0.238, $p_{SVS\ time}$=0.535, $p_{effect\ of\ group}$=0.018; Table 4.6 and Appendix 3).

In the ortho-k group, significant changes in corneal biomechanical response were seen between BL and the 6-month appointment ($p>0.05$, post-hoc pairwise comparisons), but this stabilised thereafter ($p>0.05$).

In the spectacle wearing group, some fluctuations in the corneal biomechanical response occurred between BL and 12-month appointment ($p<0.05$) (Figure 4.2).

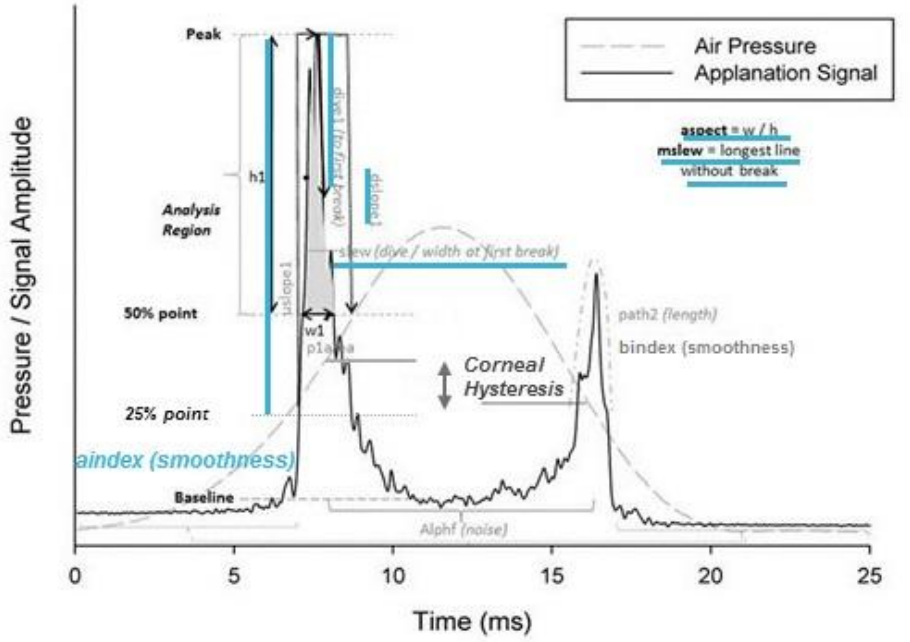

Figure 4.2 The significant changes in the ORA applanation curve in the ortho-k group over the two-year period are highlighted with a blue line. Figure adapted and reprinted with permission from Wolffsohn *et al.* (2012).

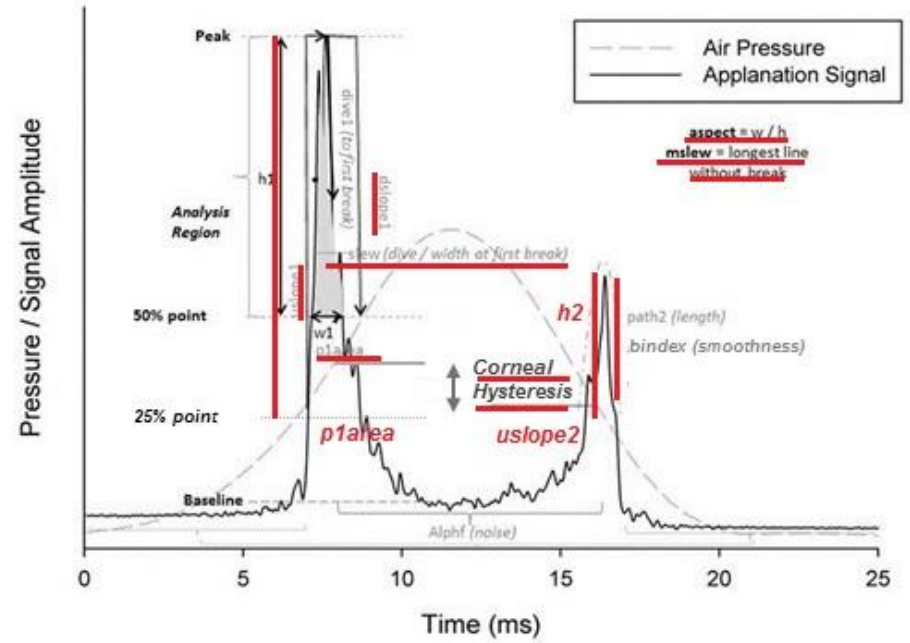

Figure 4.3 The significant changes in the ORA applanation curve in the spectacle group over the two-year period are highlighted with a blue line. Figure adapted and reprinted with permission from Wolffsohn *et al.* (2012).

ORA parameter (Mean±SD)	Visit					K-S test for normality	Effect of time (Repeated Measure ANOVA)	
	BL	6 months	12 months	18 months	24 months	p	p	F
slew1	64.45±22.90	61.19±21.81	61.27±24.53	58.13±19.12	60.89±23.18	0.705	0.05	2.418
mslew1	100.3±28.5	97.2±26.2	99.4±33.4	92.9±28.3	93.5±29.1	0.402	0.003	4.087
dive1	322.3±101.4	296.5±104.8	302.9±108.9	302.3±101.6	305.2±101.2	0.152	0.042	2.537
aindex	9.49±0.63	9.31±0.82	9.50±0.73	9.40±0.83	9.48±0.65	<0.001*	0.032	10.53
Values from upper 75% of peak								
h1	244.5±54.4	239.9±54.2	236.1±60.2	232.7±55.6	230.4±61.8	0.515	0.013	3.254
aspect1	17.13±4.28	16.35±4.04	16.53±5.32	16.05±4.35	15.75±4.77	0.397	0.021	2.966
dslope1	24.13±6.29	23.14±6.30	23.52±7.99	22.93±6.77	22.21±7.14	0.622	0.027	2.807
Values from upper 50% of peak								
h1	244.5±54.4	239.9±54.2	236.1±60.2	232.7±55.6	230.4±61.8	0.515	0.013	3.254
aspect1	23.22±6.64	22.16±6.87	22.51±9.74	22.17±7.70	21.58±8.18	0.904	0.026	2.826

Table 4.4 The ORA derived metrics that reached statistical significance over the two-year study period in the ortho-kgroup. *If p<0.05, Friedman's test procedures were carried out.

ORA parameter (Mean±SD)	Visit					K-S test for normality	Effect of time (Repeated Measure ANOVA)	
	BL	6 months	12 months	18 months	24 months	p	p	F
IOPg (mmHg)	15.40±2.78	15.67±3.35	15.11±3.03	15.40±3.26	15.11±3.16	0.340	0.046	2.465
IOPcc (mmHg)	15.07±2.88	15.44±3.21	14.66±2.94	14.74±3.39	14.64±2.92	0.868	0.005	3.891
CH (mmHg)	11.17±1.55	11.05±1.52	11.30±1.37	11.48±1.61	11.34±1.50	0.847	0.019	3.028
slew1	62.03±18.39	59.55±20.64	56.82±16.60	61.37±24.65	66.79±26.53	0.946	0.049	2.43
slew2	82.07±30.73	89.28±30.95	76.31±31.64	86.21±35.56	88.92±36.43	0.604	0.036	2.622
mslew1	100.5±28.4	92.59±30.89	88.54±22.25	98.89±34.03	105.4±36.3	0.982	0.007	3.619
dive2	246.2±82	233.5±76.3	219.5±68	243.3±92.6	255.7±107	0.868	0.03	2.746
Values from upper 75% of peak								
p1area	3456±838	3293±859	3020±777	3412±1113	3475±1087	0.833	0.012	3.599
h1	371.5±78.01	348.3±90.5	326.1±70.2	365.1±110	376.2±108.2	0.458	0.003	4.722
h2	307.3±89.8	292.5±76.7	278.4±64.9	307.9±86.8	322.3±94.1	0.745	0.013	3.533
uslope1	62.24±18.05	58.87±20.22	56.74±16.16	61.78±23.62	66.90±26.60	0.893	0.046	2.476
uslope2	81.28±30.74	85.74±30.68	76.11±31.71	85.57±36.33	89.42±35.51	0.550	0.026	2.818
dslope1	24.07±6.24	22.12±6.71	21.09±6.46	23.85±8.25	24.01±7.42	0.241	0.03	2.742
Values from upper 50% of peak								
p1area	1495±414	1407±382	1296±363	1465±541	1462±469	0.920	0.023	3.176
h1	247.7±52	232.2±60.3	217.4±46.8	243.4±73.3	250.8±72.1	0.458	0.003	4.722
h2	204.9±59.9	195±51.1	185.8±43.3	205.2±57.9	214.8±62.7	0.745	0.013	3.533
aspect1	16.97±3.96	15.57±4.50	14.95±3.98	16.81±5.52	17.23±5.41	0.927	0.009	3.461

Table 4.5 The ORA derived metrics that reached statistical significance over the two-year study period in the spectacle group. *If $p<0.05$, Friedman's test procedures were carried out.

Additional ORA-derived parameter	Definition of the metric in relation to the changes induced by the ortho-k lens wear	Group	
		SVS	OK
		p value	p value
slew2	aspect ratio of dive2 where dive2 is divided by width		0.262
mslew2	maximum single increase in the rise of the peak (longest continuous line without a break)		0.109
dive1	backside of downslope of peak (absolute value of peak until the first break)	0.146	
dive2			0.299
aindex	the smoothness of the peak (related to the noise of the measurement aka how many times peak changes the direction and represent local imperfections in the cornea, respectively softness of the cornea)	0.337	
bindex		0.365	0.507
aplhf	the smoothness of the region between the peaks (related to the noise of the measurement and represent local imperfections in the cornea, respectively softness of the cornea)	0.847	0.750
Values from upper 75% of peak			
p1area	area under the curve (proportional estimate of the time needed for the cornea to change from the concave to the convex form)		0.17
p2area	area under the curve (proportional estimate of the time needed for the cornea to change from the concave to the convex form)	0.178	0.108
h2	height from the lowest to the highest point in peak		0.053
w1	width at the base of the peak region (descriptor of the time course)	0.802	0.24
w2		0.276	0.088
aspect2	aspect ratio of the peak (height/width)	0.069	0.08
uslope1	rate of increase from base to peak		0.08
uslope2			0.257
dslope2	rate of decrease from peak to base	0.147	0.09
path1	the absolute value of path length around the peak	0.845	0.309
path2		0.636	0.962
Values from upper 50% of peak			
p1area	area under the curve (proportional estimate of the time needed for the cornea to change from the convex to the concave form)		0.341
p2area	area under the curve (proportional estimate of the time needed for the cornea to change from the concave to the convex form)	0.207	0.084
h2	height from the lowest to the highest point in peak		0.053
w1	width at the base of the peak region (descriptor of the time course)	0.972	0.674
w2		0.872	0.420
aspect1	aspect ratio of the peak (height/width)	0.08	
aspect2		0.421	0.421
uslope1	rate of increase from base to peak	0.089	0.06
uslope2		0.123	0.177
dslope1	rate of decrease from peak to base	0.221	0.058
dslope2		0.992	0.458
path1	the absolute value of path length around the peak	0.535	0.238
path2		0.472	0.476

Table 4.6 Summary of the additional ORA-derived parameters that did not significantly change over the two-year study period in ortho-k (OK) and spectacle (SVS) group.

4.4.3 Axial length, anterior chamber depth and endothelial cell count

AL increased in the ortho-k group over the two-year period ($p<0.001$), but at a slower rate than in the spectacle wearing group ($p<0.001$) (Table 4.7).

ACD did not increase in the ortho-k group over the study period ($p=0.836$), whereas it did in the spectacle wearing group ($p<0.001$). ACD increased steadily over the first 18 months of the study period ($p\leq0.013$), but stabilised thereafter ($p=0.295$) (Table 4.7).

The endothelial cell count fluctuated significantly between BL and the six months visit in the ortho-k group ($p=0.046$), but stabilised thereafter ($p>0.05$). No significant changes in the spectacle group over the two-year period occurred ($p=0.216$) (Table 4.7).

Parameter (Mean±SD)	Group	Visit					K-S test for normality	Effect of time (Repeated Measure ANOVA)		Effect of group (Repeated Measure ANOVA)	
		BL	6 months	12 months	18 months	24 months	p	p	F	p	F
AL (mm)	SVS	24.72±1.12	24.85±1.08	25.02±1.09	25.18±1.09	25.25±1.03	0.998	<0.001	201.40	0.178	1.835
	OK	24.68±0.97	24.73±0.93	24.80±0.91	24.87±0.88	24.90±0.87	0.623	<0.001	45.08		
ACD (mm)	SVS	3.33±0.24	3.34±0.23	3.36±0.23	3.37±0.24	3.38±0.24	0.998	<0.001	7.065	0.195	1.70
	OK	3.33±0.21	3.31±0.21	3.31±0.21	3.32±0.20	3.32±0.21	0.632	0.836	0.361		
END cell count (cells/mm^2)	SVS	3563.73±260.14	3602.04±304.64	3596.70±275.63	3595.28±276.11	3531.83±263.06	0.821	0.216	1.48	0.29	0.589
	OK	3570.40±250.63	3689.14±300.62	3636.31±251.12	3631.34±256.61	3608.82±302.49	0.200	0.046	2.453		

Table 4.7 Changes in AL, ACD, LT and endothelial (END) cell count over the two-year study period of ortho-k lens wear compared to baseline. *If p<0.05, Friedman's test procedures were carried out.

4.4.4 Relationship between axial, refractive, topographic and corneal thickness changes and corneal biomechanics

The changes in AL, myopic refractive error and astigmatism, corneal topography and thickness have been summarised in Table 4.8 and Table 4.9. In both groups, corneal biomechanical parameters, measured with the ORA, contributed towards the change in AL, refractive sphere and astigmatism, corneal topography and CCT over the two-year period, explaining 1% to 75% of the total variance.

Corneal biomechanical parameters contributed most towards the variance in CCT between BL and the 6 month appointment in the ortho-k group (43.4%) (Table 4.8), whereas in the spectacle group they contributed most to refractive astigmatism between BL and the 6 month appointment (74.9%) (Table 4.9).

The changes in refractive sphere in both groups were mostly accounted for by the change in AL. The changes in refractive astigmatism were explained by the variance in the topographic astigmatism ΔK. The variance in CCT was accounted for by the changes in corneal biomechanics, whilst most of the topographic changes observed were influenced by the variance in other topographic parameters. No multicollinearity between different topographic parameters occurred within the presented models (Table 4.8 and Table 4.9).

In the ortho-k group, the variance in AL was mostly explained by the change in refractive sphere (Table 4.8), whereas in the spectacle group, changes in AL were mostly accounted for by the increase in refractive sphere and ACD (Table 4.9).

Parameter	Visit ‘x’ vs visit ‘y’	Multiple regression equation	p values	Total variance explained by the MR model (%)	Variance explained by the corneal biomechanical parameters (%)
Refractive sphere (D)	6M vs BL	∆sphere = 2.76 – 2.86 x ∆AL + 0.18 x ∆CH + 2.00 x ∆e steep	<0.05	29	7.3
	12M vs BL	∆sphere = 1.27 – 0.16 x ΔAL – 3.89 x Δflat e + 0.07 x Δsteep K	≤0.006	42.6	–
	18M vs BL	∆sphere = 1.59 – 0.14 x ΔAL – 2.98 x Δflat e + Δsteep K	≤0.021	29.2	–
	24M vs BL	∆sphere = 3.12 – 2.77 x ΔAL – 0.02 x path21 – 0.04 x Δflat K	≤0.035	35.6	11.2
Refractive astigmatism (D)	6M vs BL	∆refractive astigmatism = 0.36 – 0.46 x Δdelta K	<0.005	27.1	–
	12M vs BL	∆refractive astigmatism = 0.30 – 0.57 x Δdelta K	≤0.004	30.1	–
	18M vs BL	∆refractive astigmatism = 0.27 – 0.46 x Δdelta K – 0.04 x Δdslope1 + 0.01 x Δmslew2	≤0.001	42.1	18.4
	24M vs BL	∆refractive astigmatism = 0.37 – 0.39 x Δdelta K	≤0.011	13	–
CCT (µm)	6M vs BL	∆CCT = -5.41 + 7.11 x ΔACD + 0.31 x Δpath2 – 5.16 x Δrefractive astigmatism – 0.14 x Δdslope11	<0.04	49.4	43.4
	12M vs BL	∆CCT = -7.09 + 3.22 x ΔACD	≤0.013	12.3	–

	18M vs BL	∆CCT = 75.24 + 83.09 x ΔACD – 28.83 x Δsphere	≤0.044	24.4	–
	24M vs BL	None of the variance explained by the model			
Steep e	6M vs BL	None of the variance explained by the model			
	12M vs BL	Δsteep e = -0.08 + 0.01 x Δflat K	≤0.006	17.7	–
	18M vs BL	Δsteep e = -0.08 + 0.01 x Δflat K – 0.003 x Δdslope2	≤0.002	41.5	6.9
	24M vs BL	Δsteep e = -0.04 + 0.01 x Δflat K	<0.001	30.6	–
Flat e	6M vs BL	Δflat e = -0.32 +0.12 x ΔIOPcc	≤0.035	0.1	0.1
	12M vs BL	Δflat e = -0.16 +0.01 x Δsteep K – 0.05 x Δsphere – 0.08 x Δ aplhf	≤0.028	40.2	12.6
	18M vs BL	Δflat e = -0.12 +0.01 x Δsteep K – 0.05 x Δsphere – 0.01 x ΔAL + 0.05 x Δdelta K	≤0.008	47.5	–
	24M vs BL	Δflat e = -0.29 + 0.01 x Δsteep K	<0.001	27.9	–
Steep K (D)	6M vs BL	Δsteep K = -0.36 + 1.028 x Δflat K +0.99 x Δdelta K	<0.001	99.9	–
	12M vs BL	Δsteep K = 0.15 + 1.0 x Δflat K +0.99 x Δdelta K + 0.02 x ΔCCT	<0.001	100	–
	18M vs BL	Δsteep K = -0.01 + 1.0 x Δflat K +0.96 x Δdelta K	≤0.001	100	–
	24M vs BL	Δsteep K = 0.03 – 1.0 x Δ flat K + 0.98 x Δdelta K – 0.04 x ACD – 0.09 x ΔAL + 0.02 x Δpath2 – 0.01 x Δslew2	<0.001	100	0.6
Flat K (D)	6M vs BL	Δflat K = -0.36 + 0.97 x Δsteep K +0.98 x Δdelta K	<0.001	99.9	–

	12M vs BL	Δflat K = 0.15 + 1.0 x Δflat K +0.99 x Δdelta K + 0.03 x ΔCCT	<0.001	100	–
	18M vs BL	Δflat K = 0.01 + 0.99 x Δflat K - 0.96 x Δdelta K	≤0.001	100	–
	24M vs BL	Δflat K = 0.03 -0.99 x Δsteep K – 0.98 x Δdelta K + 0.42 x ΔACD – 0.9 x ΔAL – 0.01 x Δpath2 + 0.001 x Δslew1	<0.001	100	0.6
ΔK (D)	6M vs BL	Δdelta K = -0.81 -0.56 x Δrefractive astigmatism	<0.001	27.1	–
	12M vs BL	Δdelta K = -0.31 -0.54 x Δrefractive astigmatism + 0.28 x Δsteep K	<0.001	38.9	–
	18M vs BL	Δdelta K = -0.33 -0.49 x Δrefractive astigmatism +1.79 x Δ e flat - 0.49 x Δaplhf + 0.001 x Δdive2		42.8	6.7
	24M vs BL	Δdelta K = -0.01 + 1.02 x Δsteep K	<0.001	100	–
AL (mm)	6M vs BL	ΔAL = 0.19 – 0.05 x Δsphere	<0.05	13.3	–
	12M vs BL	ΔAL = 2.84 – 1.39 x Δsphere + 0.09 x Δbindex	≤0.016	28.8	10.5
	18M vs BL	ΔAL = 1.09 – 1.43 x Δsphere + 0.09 x Δpath2 – 6.68 x Δflat e	≤0.003	34.7	10.3
	24M vs BL	ΔAL = 0.49 – 0.07 x Δsphere	≤0.002	18.2	–

Table 4.8 Changes in AL, refractive sphere, astigmatism, CCT, steep e, flat e, steep k and flat K explained by the contribution of corneal biomechanical parameters measured by the ORA and other metrics in the ortho-k group over the two-year period. Note: when a parameter from the upper 50% of the curve is entered in equation, '1' is added to the parameter name, to distinguish it from the parameters from upper 75% of the peak; if no β value is entered in the equation, SPSS output displayed it as '<0.001'.

Parameter	Visit ‘x’ vs visit ‘y’	Multiple regression equation	p values	Total variance explained by the MR model (%)	Variance explained by the corneal biomechanical parameters (%)
Refractive sphere (D)	6M vs BL	∆sphere = 0.23 + 0.83 x ∆ACD – 2.53 x ∆AL – 0.21 x ∆aindex + 0.15 x ∆w11 + 0.02 x ∆dslope11 + 0.03 x ∆w2	<0.05	73	23.5
	12M vs BL	∆sphere = -0.41 – 0.24 x ∆AL – 0.001 x ΔCCT	≤0.022	59.4	–
	18M vs BL	∆sphere = -0.67 – 0.21 x ∆AL – 0.04 x Δflat K -0.001 x Δh1	≤0.013	73.4	2.1
	24M vs BL	∆sphere = 0.13 – 2.0 x ∆AL	<0.001	70.1	–
Refractive astigmatism (D)	6M vs BL	∆refractive astigmatism = 1.26 + 0.003 x Δh2 – 0.56 x Δaplhf + 0.03 x Δpath21 +0.08 x Δaspect21 – 0.06 x Δpath1	≤0.002	74.9	74.9
	12M vs BL	∆refractive astigmatism = -0.01 - 0.05 x ΔAL +0.001 ΔCCT – 0.36 x Δdelta K	≤0.024	35.8	–
	18M vs BL	∆refractive astigmatism = -0.03 - 0.03 x ΔAL - 0.21 Δdelta K – 0.01 x ΔIOPg	≤0.035	42	9.3
	24M vs BL	∆refractive astigmatism = -0.23 – 1.51 x Δflat e + 0.003 x ΔCCT – 0.13 x ΔACD	≤0.038	37.5	–
CCT (µm)	6M vs BL	None of the variance explained by the model			
	12M vs BL	∆CCT = -1.14 +141.42.88 x ΔACD – 1.08 x Δh2 – 20.83 x ΔCH	≤0.029	39	8.7
	18M vs BL	∆CCT = 7.82 +133.63 x ΔACD – 1.99 x Δmslew1 – 11.56 x ΔIOPg	≤0.013	46.4	9.5

	24M vs BL	ΔCCT = 42.19 + 59.88 x ΔACD – 0.52 x Δh11 + 8.86 x Δaindex	<0.001	87.6	31.6
Steep e	6M vs BL	Δsteep e = -0.02 + 0.01 x Δflat K + 0.01 x Δdslope1 – 0.08 x Δaplhf	≤0.047	65.7	11.8
	12M vs BL	Δsteep e = -0.01 + 0.64 x Δflat e	≤0.007	16.1	–
	18M vs BL	Δsteep e = -0.01 + 0.54 x Δflat e	<0.001	47.4	–
	24M vs BL	Δsteep e = -0.02 + 0.59 x Δflat e	≤0.007	18.5	–
Flat e	6M vs BL	Δflat e =-0.18 + 0.01 x Δsteep K -0.05 x Δsphere	≤0.036	43.4	–
	12M vs BL	Δflat e = -0.17 +0.26 x Δsteep e – 0.02 x Δsphere – 0.001 x ΔCCT	≤0.044	32.5	–
	18M vs BL	Δflat e = -0.26 +0.09 x Δsteep K – 0.02 x Δsphere – 0.001 x ΔCCT +Δdive2	≤0.043	81.9	1
	24M vs BL	Δflat e = -0.04 +0.29 x Δsteep e – 0.08 x Δrefractive astigmatism	≤0.018	31.8	–
Steep K (D)	6M vs BL	Δsteep K = -0.02 + 1.0 x Δflat K +1.01 x Δdelta K + 0.001 x Δh21	<0.001	100	0.3
	12M vs BL	Δsteep K = 0.15 + 1.0 x Δflat K +1.0 x Δdelta K	<0.001	100	–
	18M vs BL	Δsteep K = 0.15 + 1.0 x Δflat K	<0.001	99.9	–
	24M vs BL	None of the variance explained by the model			
Flat K (D)	6M vs BL	Δflat K = 0.15 + 1.0 x Δsteep K +1.02 x Δdelta K + 0.001 x Δh21	<0.001	100	0.3
	12M vs BL	Δflat K = 0.001 + 1.0 x Δsteep K -1.0 x Δdelta K	<0.001	100	–
	18M vs BL	Δflat K = -0.15 + 0.95 x Δsteep K	<0.001	99.9	–

	24M vs BL	Δflat K = 0.01 - 1.0 x Δdelta K +1.05 x Δsteep K+ 0.001 x ΔCCT	<0.001	100	–
ΔK (D)	6M vs BL	Δdelta K = -0.29 + 1.75 x Δflat e – 0.01 x Δuslope21	≤0.007	36.4	7.8
	12M vs BL	Δdelta K = 0.09 – 0.97 x Δflat K + 1.00 x Δsteep K	<0.001	100	–
	18M vs BL	Δdelta K = 0.15 + 0.05 x Δflat K	<0.001	68.2	–
	24M vs BL	Δdelta K = 0.09 – 0.97 x Δflat K – 0.99 x Δsteep K + 0.001 x ΔCCT	<0.001	100	–
AL (mm)	6M vs BL	∆AL = 0.15 – 0.13 x ∆sphere + 0.09 x ∆ACD + 0.04 x ∆w11 + 0.02 x ∆path1	<0.05	43.8	22.1
	12M vs BL	∆AL = -1.01 – 1.07 x ∆sphere + 14.17 x ∆flat e -2.77 x ∆refractive astigmatism - 0.64 x ∆ACD + 0.05 x Δpath11	≤0.019	73.7	2
	18M vs BL	∆AL = -1.93 – 2.31 x ∆sphere -2.18 x ∆refractive astigmatism - 0.18 x ∆flat K	0.014	69.5	–
	24M vs BL	∆AL = 0.23 – 0.35 x ∆sphere	<0.01	70.1	–

Table 4.9 Changes in AL, refractive sphere, astigmatism, CCT, steep ‘e’, flat ‘e’, steep ‘k’ and flat ‘k’ explained by the contribution of corneal biomechanical parameters measured by the ORA and other metrics in the spectacle group over the two-year period. Note: when a parameter from the upper 50% of the curve is entered in equation, ‘1’ is added to the parameter name, to distinguish it from the parameters from upper 75% of the peak; if no β value is entered in the equation, SPSS output displayed it as ‘<0.001’.

4.5 Discussion

This study investigated the long-term effects of ortho-k wear on corneal biomechanical properties and the possible contribution of the anterior eye to myopia progression in myopic schoolchildren.

Ortho-k lens wear effectively reduced refractive sphere and astigmatism, slowing down myopia progression and axial elongation by 42%. Ortho-k also slowed down the ACD growth. In contrast, in the spectacle wearing (control) group, refractive sphere, astigmatism, AL and ACD increased significantly over the two-year period. These results are in agreement with the previous work on which they are expanding (Cho and Cheung 2012; Charm and Cho 2013; Chen *et al.* 2013).

The topographic changes observed in the present study are also in agreement with previous work (Cho *et al.* 2005; Santodomingo-Rubido *et al.* 2012). Ortho-k lens wear initially induced a corneal flattening in both meridians, which stabilised within 6 months of lens wear. Previously reported results in similar cohorts also suggested that significant flattening and changes in the eccentricity occur during the first six months of ortho-k lens wear (Cho *et al.* 2005; Santodomingo-Rubido *et al.* 2012).

The small fluctuations in corneal topographic parameters seen in the spectacle group have been reported before. In a study of similar design, investigating the efficacy of ortho-k for MC, all of the topographical parameters in the spectacle group, except for steep simulated keratometry readings, remained the same (Santodomingo-Rubido *et al.* 2012). A longitudinal study conducted in Portuguese university students over the course of three years showed that, regardless of the refractive status and progression of myopia, topographic changes remained stable (Jorge *et al.* 2007).

Changes in CCT support the previously reported results of the ROMIO cohort data (Cheung and Cho 2016), in which a significant thinning was observed within the first six months of the ortho-k lens wear, with stability thereafter. In the present study, CCT in the

ortho-k group thinned significantly over the first six months, remained stable between the 6 and 18-month appointments, but returned to baseline level at 24 months (Figure 4.1). However, these findings contradict the results of a significant central corneal thinning after 5 years of ortho-k lens wear reported by Zhong and colleagues (2009), and the well established evidence of central epithelial thinning and mid-peripheral thickening of the cornea underlying the mechanisms of ortho-k (Swarbrick *et al.* 1998; Swarbrick 2006). Cheung and colleagues (2016) suggested that caution must be taken when interpreting results, owing to the relatively small sample size. The current study is expanding the cohort (Cheung and Cho 2016) and obtaining similar results. Fluctuations seen in the spectacle group, however, still raise questions. Zhong and colleagues (2009) measured CCT using confocal microscopy and suggested that other methods, such as anterior segment optical coherence tomography (AS-OCT) could be more sensitive in detecting thickness changes. Nieto-Bona *et al.* (2011a) contradicted this theory by comparing corneal thickness measurements obtained by confocal microscopy with the ones from optical coherence tomography and found no difference between the two methods. CCT was measured using the Pentacam in this study. It has been shown that devices based on Scheimpflug imaging like Pentacam and optical coherence tomography can be used interchangeably for measuring CCT (Bayhan *et al.* 2014). It is, therefore, unlikely that differences in instrumentation could cause these discrepancies. It is more likely that mechanical forces exerted by the lens and the duration of the ortho-k therapy could account for these variations (Swarbrick *et al.* 1998; Owens *et al.* 2004; Cheah *et al.* 2008; Choo *et al.* 2008; Zhong *et al.* 2009; Elsheikh 2010).

Zhong *et al.* (2009) proposed that short term and long term corneal morphological changes are different. The mid-peripheral thickening observed after the first night of lens wear was thought to be mainly caused by temporary oedema induced by overnight wear and mechanical pressure exerted by the lens. On the other hand, thickness changes (central thinning and mid-peripheral thickening) observed after years are thought to be

mainly caused by changes in topography and cell morphology. Animal work investigating the effects of ortho-k lens wear support these findings, but suggest that the plasticity of epithelium, cell compression and inter-cell processes, especially in the first days of ortho-k lens, should be taken into account (Matsubara *et al.* 2004; Cheah *et al.* 2008; Choo *et al.* 2008). The changes in the current study may reflect the processes described above. The initial changes (formation of the treatment zone, mechanical stress exerted by the lens and reorganisation of the corneal topography) all stabilise within the first six months of the treatment and could be mostly accounted for by the re-modelling of the corneal epithelium. At later stages, adaptation to lens wear has occurred, and the treatment outcome is not so much reliant on central corneal thickness, but on other aspects, such as mid-peripheral corneal thickening or the overall corneal shape. Furthermore, most of the studies looking at thickness changes have been conducted in an adult population (Swarbrick *et al.* 1998; Alharbi and Swarbrick 2003; Owens *et al.* 2004; Yeh *et al.* 2013). Significant changes seen in the spectacle group (Figure 4.1) may indicate that fluctuations in CCT are normal in a myopic child population. Shorter and long-term studies monitoring corneal thickness changes and the mechanical impact of ortho-k lens wear to the cornea are required to gain a deeper understanding of the underlying mechanisms of ortho-k. However, diurnal changes in CCT have been reported before. A trend of gradual corneal thinning throughout are normal, with cornea being the thickest upon awakening (Kiely *et al.* 1982; Harper *et al.* 1996). Although visits were aimed to be schedualed at the same time of the day, it was not always possible due to the busy scheduale of schoolchildren and their parents. Therefore, diurnal fluctuations in CCT could also account for some variance seen in the results.

This is the first study to examine ORA-derived applanation peak in response to ortho-k lens wear in detail, and to examine corneal biomechanics over a two-year period. Saad and colleagues (2010) and Kerautret *et al.* (2008) demonstrated the importance of signal morphology analysis of applanation curves alongside CH and CRF, both of which have

a limited discriminatory ability. Since then parameters derived from applanation curves have proven to be a useful tool in the detection of keratoconus (Mikielewicz *et al.* 2011; Wolffsohn *et al.* 2012). Previous studies have only considered CH and CRF as the descriptors of corneal biomechanical response to ortho-k wear (Gonzalez-Meijome *et al.* 2008; Chen *et al.* 2009; Mao *et al.* 2010; Yeh *et al.* 2013). The longest running study investigating the influence of ortho-k lens wear was conducted over a six month period (Mao *et al.* 2010). Reduction of myopic refractive error, changes in corneal thickness and morphology do not occur simultaneously (Swarbrick *et al.* 1998; Alharbi and Swarbrick 2003; Zhong *et al.* 2009; Nieto-Bona *et al.* 2011a; Cheung and Cho 2016). Alharbi and Swarbrick (2003) suggested that the first 10 nights of ortho-k lens wear are critical, as the vast majority of corneal thickness changes take place over this period and stabilise thereafter. Other studies have demonstrated that initial thickness changes and the subsequent morphological changes in corneal structure are different from long term changes (Zhong *et al.* 2009; Nieto-Bona *et al.* 2011a, 2011b; Cheung and Cho 2016). Alterations in keratocyte density and morphology (Zhong *et al.* 2009; Nieto-Bona *et al.* 2011a, 2011b) indicate that the mechanical stress induced by the lens account for the initial corneal thickness changes (1 night to 1 month of lens wear). These are predominantly epithelial in origin (Alharbi and Swarbrick 2003; Matsubara *et al.* 2004; Cheah *et al.* 2008). Kerotocyte density tends to return to BL levels at later stages of treatment (1 year to 5 years of lens wear) (Zhong *et al.* 2009; Nieto-Bona *et al.* 2011a), suggesting that corneal response to ortho-k lens wear is a dynamic process and should be evaluated for longer than for six months.

CH, which is a descriptor of the viscous damping properties of the cornea (Luce 2005), did not change over the study period in the ortho-k group, but fluctuated significantly in the spectacle group. CRF, which characterises the overall resistance of the cornea (Luce 2005; Lau and Pye 2011), remained stable in both groups. These findings are in general agreement with an earlier study conducted over a period of 6 months, which reported a

decrease in CH and CRF after one week of ortho-k lens wear. These values were found to return to BL level at three and six month follow up visits (Mao *et al.* 2010). Mao *et al.* (2010) concluded that the initial changes in CH and CRF can be explained by the reshaping effect of the cornea, and that ortho-k does not cause damage to corneal microstructure. The current study did not assess the initial response to ortho-k lens and cannot confirm these findings. However, such assumptions need to be made cautiously. The ORA assesses the mechanical properties of the cornea based on an applanation signal (Luce 2005; Lau and Pye 2011) and does not directly assess corneal structure at a microscopic level. Studies investigating the effects of ortho-k at a microscopic level have shown that lens wear induces changes in the corneal structure (Matsubara *et al.* 2004; Cheah *et al.* 2008; Choo *et al.* 2008; Zhong *et al.* 2009; Nieto-Bona *et al.* 2011a). The statistically significant fluctuations seen in the spectacle group in the present study also suggest that CH and CRF describe the overall corneal mechanical behaviour, rather than structural changes at microscopic level, as no treatment apart form conventiel SV glasses that did not interact with the corneal tissue directly, was applied to control group. The cornea reaches adult size during the first two years of life and does not undergo major structural changes thereafter (Kaufman 1998). Myopia development has been linked to changes in corneal shape (Davis *et al.* 2005). A less prolate corneal shape has been associated with myopia and increased AC growth during myopia development, suggesting that deeper AC may require less flattening of the peripheral cornea to preserve its junction at the limbus (Davis *et al.* 2005). There are other corneal biomechanical parameters derived from the ORA applanation curve that need to be considered.

Detailed analysis of the applanation curve demonstrated that, in both groups, significant changes were mostly limited to the initial applanation peak, but the corneal biomechanical response in the spectacle group was much more varied (Figure 4.2 and Figure 4.3). Ortho-k lens wear affected 9 of the additional ORA-derived parameters

during the first 18 months of lens wear, whilst 14 of the parameters changed significantly over the two-year study period in the spectacle group. Nevertheless, datapresented in this chapter are skewed and with large SDs. Moreover, children are les corporative with the ORA and the acceptable waveform score (WS) for children is lower (3.6≥) (Hon *et al.* 2012) and these factors could account for some of the variations observed.

Parameters like slew1 (an aspect ratio of the absolute value of the initial applanation peak to the first break), mslew1 (the maximum single increase of in the rise of the initial applanation peak), h1 from the upper 50% and 75% of the initial applanation peak (the height from the lowest to the highest point of the peak) and aspect1 from the upper 50% of the initial applanation peak (aspect ratio of the peak height/width) underwent significant changes in both groups. In the ortho-k group these parameters followed a certain trend of decrease over the study period, whereas in the spectacle group fluctuations in the parameters were observed. However, no consistent trends were identified.

Parameters such as slew2 (an aspect ratio of the absolute value of the rebound peak to the first break); dive2 (the absolute value of the rebound peak until the first break); p1area or the area under the curve of the upper 50% and 75% of the initial applanation curve (proportional estimate of the time needed for the cornea to change from the convex to the concave form), h2 (the height from the lowest to the highest point) of the upper 50% and 75% of the rebound peak and others that underwent changes over the two year period in the spectacle group (Table 4.5) also fluctuated and did not follow a certain trend. These fluctuations could reflect the ocular biometric changes occurring in progressing myopia (Lam *et al.* 1999; Saw *et al.* 2005). Cornea together with sclera forms the outer shell of the eye. Corneal and scleral biomechanical and structural changes (namely weaking of the tissue and preservation of the limbar junction) during myopia development and the subsequent stretching of an eyball have been reported before (McBrien and Gentle 2003; Davis 2005). Therfore, these observations might indicate that

certain parameters of the ORA applanation peak could be used as predictors, or descriptors, of myopia progression, and that ortho-k has a stabilising effect on the cornea. However, more work is needed to support this theory. Researchers have questioned the ORA's ability to purely assess the corneal biomechanical response and have proposed that it might measure the whole globe response instead (Iomdina *et al.* 2009; Elsheikh 2010). Studies investigating corneal response in emmetropes, stable and progressive myopes could provide a new perspective for the application of the ORA and its specific parameters in the field of myopia research.

The other parameters that were affected in the ortho-k group, but not in the spectacle group, could reflect on the mechanical effects of the lens wear and the corneal structural changes previously reported (Choo *et al.*, 2008, Matsubara *et al.*, 2004, Cheah *et al.*, 2008, Zhong *et al.*, 2009, Nieto-Bona *et al.*, 2011). Aindex represents the smoothness of the peak which, in turn, represent the softness and the local imperfections in the cornea (Table 4.6). The changes seen in this parameter could mirror the long term effects of ortho-k lens wear to corneal structure. Elsheikh (2010) suggested that both epithelial remodelling and creep (persistant deformation or in the context of ortho-k, the response of further time-dependent increase in deformation or corneal flattening after lens removal (Mountford 1998)), take place simultaneously in ortho-k wear. Epithelial remodelling is an important contributor towards the thickness changes induced by ortho-k lens wear (Swarbrick *et al.* 1998; Alharbi and Swarbrick 2003; Cheah *et al.* 2008; Choo *et al.* 2008; Zhong *et al.* 2009). Aindex could, therefore, represent the re-modelling effect achieved by the reverse geometry lens on the epithelium. However, as collagen fibrils are the main carriers of the load, they dominate corneal mechanical behaviour and, subsequently, its response to ortho-k, (Boote *et al.* 2005; Elsheikh 2010). Hence, it is more likely that the significant changes in this ORA-derived parameter could be a result of alterations in collagen fibril architecture induced by the repeated application of the reverse geometry lens. The decrease in dive1 (the absolute value of initial applanation peak until the first

break), dislope 1 (the rate of decrease from initial applanation peak to base from the upper 75% of the peak) and aspect1 (the aspect ratio of the initial applanation peak height/width from the upper 75% of the peak) could reflect the flattening effect of the reverse geometry lens or suggest that the cornea becomes more pliable (the basic methodology of the ORA) and less resistant as a result of the ortho-k lens wear (Elsheikh, Ross*, et al.* 2009; Terai *et al.* 2012).

Endothelial cell count remained stable over the study period in the spectacle wearing group, however, this fluctuated in the ortho-k group. Endothelial cells have a limited capacity of proliferation, and they tend to decrease in number with every decade (Klyce and Beuerman 1998; Joyce 2012). The apparent increase between BL and six-month appointment in the ortho-k group is likely to be due to enhanced visibility of the endothelium following corneal reshaping.

Multiple regression analysis further supported the hypothesis of the stabilising effect of ortho-k on the anterior eye, and revealed the complex relationship between axial, refractive, topographical, corneal thickness and biomechanical changes over the two year period (Table 4.8 and Table 4.9). Over the first six months of the study period, corneal biomechanical properties contributed significantly towards the changes observed in the spectacle wearing group (1-75%), but diminished thereafter. In the ortho-k group corneal biomechanical parameters explained 1%-18% of the total variance in the selected parameters, except for CCT, in which they accounted for 44.6%. Interestingly, the variance in CCT in the ortho-k group was mainly accounted for by the additional ORA-derived parameters within the first six months, but they did not account for any of the subsequent variance. As this is the first study to investigate corneal response to ortho-k lens wear in progressing myopes in detail, no comparisons can be made. However, presumably, the first six months are crucial for the treatment effect of the ortho-k to stabilise. These findings, together with the analysis of the effect of time on the ORA-derived applanation curve, provide a new insight to the mechanisms by which

ortho-k slows down myopia progression, suggesting not only contribution of optical factors (Berntsen *et al.* 2005; Kang and Swarbrick 2011; Hiraoka *et al.* 2015; Swarbrick *et al.* 2015), but also of mechanical factors.

Although all three studies followed the same recruitment, inclusion/exclusion and overall study model (Cho and Cheung 2012; Charm and Cho 2013; Chen *et al.* 2013), the limitations of the current study include different lens types used (the fitting parameters were kept similar) and the fact that for HM-PRO study myopia was corrected only partially (up to 4.00 D). Also, not all children could attend the visits as schedualed and diurnal variations could affect the trends seen in this study (Kieley *et al.* 1982; Harper *et al.* 1996). Moreover, children are less complient with the ORA (Hon *et al.* 2012), which also could have had an impact on the overall results, considering that the data are relatively scattered and have large standard deviations.

In summary, this study demonstrates that the corneal biomechanical characteristics of the cornea are affected by long term ortho-k wear. It also shows that ortho-k has a stabilising effect to the components of the anterior eye in progressing myopia and raises interesting questions regarding the mechanisms by which ortho-k slows down myopia progression. Further short and long-term studies are needed to support these findings. They should specifically investigate corneal biomechanical response to ortho-k lens wear within the first six months of the treatment, which has been found to be the critical time period. These studies could contribute towards a deeper understanding of the mechanisms underlying ortho-k and potentially their contribution in slowing down myopia progression.

Chapter 5. Short-term corneal biomechanical changes in orthokeratology

5.1 General overview

This chapter describes a study designed to investigate the corneal biomechanical response over the first seven nights of ortho-k lens wear in a cohort of young adults using the Ocular Response Analayzer (ORA) (Reichert Ophthalmic Instruments, Buffalo, NY, USA) and Corvis ST (Oculus, Wetzlar, Germany); and observe if the short term corneal biomechanical response is different from that of a long one discussed in Chapter 4.

5.2 Introduction

One of major limitations that orthokeratology (ortho-k) as a clinical procedure has encountered over the years, is the large inter-individual variability in treatment response (Kerns 1976c; Sridharan and Swarbrick 2003; Swarbrick 2006; Gonzalez-Meijome *et al.* 2008). Different clinical outcomes in patients with similar topography measurements, refractive errors and the same amount of desired refractive changes, is not a rarity (Sridharan and Swarbrick 2003; Gonzalez-Meijome *et al.* 2008). Subsequently, it has raised questions regarding the corneal tissue response to ortho-k (Gonzalez-Meijome *et al.* 2008).

Previous long-term studies have focoused on the ability of ortho-k to slow down myopia progression (Cho, *et al.* 2005; Walline *et al.* 2009; Cho and Cheung 2012; Chen *et al.* 2013; Lin *et al.* 2014; Si *et al.* 2015; Sun *et al.* 2015; Swarbrick *et al.* 2015), and also the reversibility (Sorbara *et al.* 2005) and safety aspects (Kerns 1978; Polse *et al.* 1983; Walline, Rah*, et al.* 2004; Van Meter *et al.* 2008) of the method. In contrast, previous short-term studies have principally investigated the refractive and corneal profile changes, induced by reverse geometry lenses in the open- and closed-eye environments (Mountford 1998; Swarbrick *et al.* 1998; Alharbi and Swarbrick 2003; Sridharan and Swarbrick 2003; Owens *et al.* 2004; Soni *et al.* 2004; Yoon and Swarbrick 2013), reversibility (Barr *et al.* 2004; Soni *et al.* 2004; Wu *et al.* 2009; Santodomingo-Rubido *et*

al. 2014) and the efficacy of various lens designs, which have proven to not affect the treatment outcome (Cho Cheung, Sin and Edwards, 2003; Soni *et al.* 2003; Tahhan *et al.* 2003; Soni *et al.* 2004; Maldonado-Codina *et al.* 2005). These studies in tandem with the investigation of mechanical forces acting under the reverse geometry lens (Coon 1984; Kwok 1984; Mountford 2004) have helped to establish a standardised clinical profile of ortho-k. The method is effective for correcting mild to moderate myopia (Mountford 1997; Mountford 1998; Nichols *et al.* 2000; Rah *et al.* 2002; Alharbi and Swarbrick 2003; Tahhan *et al.* 2003; Swarbrick 2006), achieving the refractive changes required, by reshaping the anterior corneal tissue (Swarbrick *et al.* 1998; Alharbi and Swarbrick 2003; Swarbrick 2006; Chen *et al.* 2010). On average up to forty per cent of the refraction can be corrected within the first 8 hours of overnight lens wear (Mountford 1998; Swarbrick *et al.* 1998; Nichols *et al.* 2000; Alharbi and Swarbrick 2003; Soni *et al.* 2004; Swarbrick 2006). The treatment effect tends to reach the optimum within the first 7-10 days of overnight lens wear and stabilise within the first 30 days (Mountford 1998; Swarbrick *et al.* 1998; Nichols *et al.* 2000; Alharbi and Swarbrick 2003; Soni *et al.* 2004; Swarbrick 2006).

The central epithelial thinning and mid-peripheral stromal thickening, first reported by Swarbrick and colleagues (1998), that reached statistical significance by day 7, and stabilised after 28 days of lens wear, suggested that the refractive changes are achieved by the re-distribution of the anterior corneal tissue. However, the tissue re-distribution did not account for the refractive changes achieved during the first day of ortho-k lens wear (Swarbrick *et al.* 1998). Therefore, a transient overall bending of the cornea as the initial corneal response to lens wear, which is then followed by tissue re-distribution, was suggested (Swarbrick *et al.* 1998; Owens *et al.* 2004). The involvement of posterior corneal surface, which would support the hypothesis of overall bending of the cornea in the initial stages of the treatment, however, is still unclear (Owens *et al.* 2004; Tsukiyama *et al.* 2008; Chen *et al.* 2010; Yoon and Swarbrick 2013) and the theory of the shape

change of the anterior corneal tissue is favoured (Chen *et al.* 2010). Moreover, several studies (Tsukiyama *et al.* 2008; Santodomingo-Rubido *et al.* 2014; Santodomingo-Rubido, Villa-Collar, Gilmartin and Gutiérrez-Ortega 2016), investigating the contribution of other ocular parameters (axial length and anterior chamber depth) to the treatment effect of ortho-k, have strengthened the latter assumption and have concluded that refractive changes are attributed to changes in anterior corneal shape.

Studies investigating the effects of ortho-k lens wear at a cellular level, using animal models (Matsubara *et al.* 2004; Cheah *et al.* 2008; Choo *et al.* 2008) and confocal microscopy in the human population (Zhong *et al.* 2009; Nieto-Bona *et al.* 2011a, 2011b) to reflect the short- and long-term behaviour of the cornea in ortho-k lens wear, support the clinical observations of the corneal profile changes, induced by ortho-k. Animal models suggest that the compression of the easily mouldable epithelium, due to the mechanical stress exerted by the reverse geometry lens, is the major contributor to the refractive changes achieved in the first hours and nights of ortho-k lens wear (Cheah *et al.* 2008; Choo *et al.* 2008) (for more information on mechanisms of ortho-k, please refer to Section 1.5).

From the viewpoint of classic mechanics, the cornea is a viscoelastic material, the behaviour of which is dominated by its bulk component, the stroma (Boote *et al.* 2005; Elsheikh *et al.* 2007; Elsheikh *et al.* 2008a, 2008b; Elsheikh 2010; Whitford *et al.* 2015). The stroma is fibrous and hence possess high mechanical stiffness (Boote *et al.* 2005; Elsheikh 2010). In contrast, the epithelium (Elsheikh *et al.* 2008a; Thomasy *et al.* 2014), and similarly the endothelium (Thomasy *et al.* 2014), have low mechanical stiffness and are easily re-modelled due to their cellular composition (Elsheikh *et al.* 2008a). The cornea's biomechanical response to the external forces is both time- and load-dependant (Boote *et al.* 2005; Elsheikh *et al.* 2008b; Elsheikh 2010). If corneal tissue is exposed to the external loads repeatedly, as in the case of overnight application of ortho-k lenses, a mild creep (or permanent deformation) (Wu *et al.* 2009; Elsheikh 2010) in response to

mechanical stress of the reverse geometry lens, in combination with strain and epithelium re-modelling, occurs (Elsheikh 2010) (for more information on corneal biomechanics, please refer to Section 1.4.2).

Nevertheless, few studies (Cheah *et al.* 2008; Choo *et al.* 2008; Gonzalez-Meijome *et al.* 2008; Chen *et al.* 2009) have considered the corneal thickness, profile and morphological changes observed in ortho-k lens wear in the context of corneal mechanical behaviour. Clinical researchers should not be ignorant of this aspect, as it could enhance the understanding of the underlying mechanisms of ortho-k. Instrumentation, such as Ocular Response Analyser (ORA, Reichert Ophthalmic Instruments, Buffalo, NY, USA) and Corvis ST (Oculus Opticgeraete, Wetzlar, Germany) are available to monitor corneal biomechanical response dynamically and non-destructible *in-vivo* (Luce 2005; Hon and Lam 2013). Studies investigating the corneal biomechanical properties *in-vivo,* using ORA and its specific biomechanical parameters corneal hysteresis (CH) and corneal resistance factor (CRF), which describe the viscous damping properties and overall rigidity of the cornea, respectively (Luce 2005; Shah *et al.* 2006; Ortiz *et al.* 2007; McMonnies 2012), have reported changes in corneal biomechanical behaviour induced by short-term ortho-k (Gonzalez-Meijome *et al.* 2008; Chen *et al.* 2009). However, none of the studies have examined the 37 additional ORA-derived parameters which have been found to be better descriptors of corneal biomechanical response, rather than CH and CRF alone (Kerautret *et al.* 2008; Mikielewicz *et al.* 2011; Wolffsohn *et al.* 2012). The Corvis ST has not yet been employed in the field of ortho-k (for detailed information about the ORA along with its specific parameters and the Corvis ST, please refer to Sections 2.2.1 and 2.1.2.

The purpose of this study was to investigate corneal biomechanical changes over the first seven subsequent nights of ortho-k lens wear. The study will provide a deeper understanding of the initial corneal response to ortho-k lens wear during the first night

and the adoption, stabilisation and deformation processes that take place over the first 7 nights, in which the optimal treatment effect is achieved.

5.3 Methods

5.3.1 Subjects and study protocol

Twenty-five mild to moderate myopic volunteers (refractive error between -1.00D and –4.75D, with refractive with-the-rule astigmatism of less than 1.50D or against-the-rule astigmatism of less than 1.00D) with good ocular and general health were recruited from the population of Aston University optometry students. Exclusion criteria were any history of ocular trauma, surgery or disease, rigid contact lens wear and any contradiction to ortho-k lens wear. The risks and benefits of ortho-k were explained and written consent was obtained before the commencement of the study.

Participants were invited to attend a 60-minute baseline assessment at the Aston University Health Clinic to obtain the required measurements for ortho-k lens manufacturing and the baseline measurements of corneal biomechanics. After the initial visit they were asked to return for the lens fitting and teaching session, which then was followed by a visit after the first night of ortho-k lens wear and subsequent 30 minutes follow up visits for the next 6 days, when all the necessary measurements were taken.

Initial appointments were scheduled at least 2 hours after waking to diminish the impact of overnight and contact lens wear induced oedema (Armitage and Schoessler 1988; Harper *et al.* 1996; Fonn *et al.* 1999; Du Toit *et al.* 2003). Participants were also advised to cease soft contact lens wear at least 24 hours before the initial appointment. Subsequently, they were advised to adhere to a healthy 6-8 hour sleeping schedule to achieve optimal treatment effect, once the ortho-k lenses were dispensed (Mountford 1998; Alharbi and Swarbrick 2003). The visits were scheduled during the first half of the day after the first night of lens wear, whilst the rest of the follow up visits took place during the working day.

Twenty-one participants completed the study. Two participants dropped out before the commencement of the ortho-k lens wear. One participant could not cope with lens handling and dropped out after the first night of lens wear, whilst another participant, who was atopic, discontinued lens wear after 3 nights due to an allergic reaction (giant papillary conjunctivitis). Two participants could not attend one of eight schedualed visits due to family and work emergency. Average data for the absent appointment were used for analysis in these two cases. For the cohort demographics please refer to Table 5.1.

The study was conducted in accordance with the tenets of the Declaration of Helsinki and approved by the Aston University Research Ethics Committee (Appendix 6.1). Data were collected from November 2016 to February 2017.

Number of participants (male:female)	21 (6:15)	
Age (years)	21.04 ± 2.67 (Mean ± SD; range 18 to 28)	
Refractive Error (MSE, dioptres)	-2.83 ± 1.11 D; range -1.00 to -5.25)	
Ethnicity	Asian	13
	Black	1
	Caucasian	7

Table 5.1 Cohort demographics

5.3.2 Lens design and fitting philosophy

Ortho-k reverse geometry lenses (DreamLens lens design, Eyedream, No7 Contact Lenses, Hastings, UK), tailored in Boston XO (hexafocon A; nominal Dk=100 x 10^{-11} [cm^2•mLO_2]/(s•mL•mmHg]) material (Bauch & Lomb, Rochester, New York, USA), were ordered and fitted based on the manufacturers guidelines and specifications. The lenses were suitable for correction of myopic refractive error from -0.75D to -4.50D (although up to -5.00D can be corrected), with refractive with-the-rule astigmatism up to 1.50D or against-the-rule astigmatism up 1.00D. Topography maps (Medmont E300, Medmont

Ltd, Melbourne, Australia) and up to date subjective refraction were required for the lens to be manufactured, both of which were acquired at the baseline appointment.

Lenses were available in three diameters (10.10mm, 10.50mm and 10.90mm), had aspheric blend curves and the typical DreamLens reverse geometry lens profile (Swarbrick 2006; please refer to Section 1.3.3). The treatment zone was 6 mm wide. Lens fit and fluorescein pattern were assessed upon lens dispensing, after the first night of lens wear and on day seven. Images of the lens fit were captured at the same stages of the study (CSO digital slit-lamp biomicroscope; camera Digital Vision, Epsilon Lyrae image software, Epsilon imaging Inc., Ann Arbor, Michigan, USA). Between nights 2 to 7 corneal topography was used to monitor the fit.

No modifications or adjustments to the lens initially dispensed were made during the study, even if the fit was acceptable, but not optimal (Nichols *et al.* 2000) as the main aim of the study was to investigate the initial changes in corneal biomechanics, induced by ortho-k lens wear. If the fit was not acceptable, lens wear would be discontinued.

A sterile saline, Boston Simplus multi-action solution (Bauch & Lomb, Rochester, New York, USA) for lens cleaning and storage and Biotrue re-wetting eye drops (Bauch & Lomb, Rochester, New York, USA) to aid with the lens insertion and removal were provided.

If an over-correction was required to achieve optimal vision during the day within the study period, Acuvue Moist daily disposable contact lenses (Johnson & Johnson Vision Car Inc., Jacksonwille, Florida, USA) were fitted and dispensed.

5.3.3 Measurements

At baseline appointments, full sphere-cylinder refraction together with a thorough slit lamp examination and corneal topography readings (Medmont E300, software version 5.4.0 Beta 4, Medmont Ltd, Melbourne, Australia) to measure corneal shape, specifically eccentricity (e) and simulated keratometry (K) readings, were conducted. The

biomechanical properties of the cornea were measured, using the ORA (Reichert Ophthalmic Instruments, Buffalo, USA) and Corvis ST (Oculus Opticgeraete, Wetzlar, Germany) (for detailed list of instrument specific corneal biomechanical parameters, please refer to 2.2.1) Central corneal thickness (CCT), anterior chamber depth (ACD) and lens thickness (LT) were measured, using the Aladdin ocular biometer and topography system (Topcon, Tokyo, Japan). Axial length (AL) was measured, using the IOL Master 500 (Carl Zeiss Meditec Ltd, Jena, Germany). The health of the central corneal endothelium was assessed, using the Topcon specular microscope SP-3000P (Topcon Corporation, Tokyo Japan). IMAGEnet ibase software (version 3.18., Topcon Corporation, Tokyo, Japan) was used for cell count.

Lens fit was assessed and a thorough slit-lamp biomicroscope examination was conducted at the lens dispensing visit.

The same battery of tests as in baseline appointment were performed after the first and seventh night of the lens wear, except for the full sphere-cylinder refraction. A subjective spherical over-refraction (the results will be presented as best vision sphere, BVS) was performed instead. Also, the lens fit was assessed.

During the follow up visits (second to sixth night of lens wear) the same battery of test as in the appointment after the first night of the lens wear, except for the assessment of the lens fit and health of the central endothelium, were conducted. The tests performed at each visit are summarised in Table 5.2.

For detailed information on all instrumentation used in the study, measurement recording and quality assessment protocol, please refer to Chapter 2 and Sections 2.5.1 - 2.5.2, 2.6 - 2.7.

Measurement performed (instrument used)	Visit								
	BL	**Lens dispensing**	**Night 1**	**Night 2**	**Night 3**	**Night 4**	**Night 5**	**Night 6**	**Night 7**
Sphere-cylinder refraction	x								
Subjective over-refraction		x	x	x	x	x	x	x	x
Topography (Medmont E300)	x		x	x	x	x	x	x	x
Corneal biomechanical properties (ORA/Corvis ST)	x		x	x	x	x	x	x	x
CCT (Aladdin)	x		x	x	x	x	x	x	x
ACD (Aladdin)	x		x	x	x	x	x	x	x
AL (IOL Master 500)	x		x	x	x	x	x	x	x
Endothelial health (SP-3000P)	x		x						x
Lens fit assessment		x	x						x
Slit lamp examination	x	x	x	x	x	x	x	x	x

Table 5.2 Summary of the measurements taken at each visit. Note: ‘x’ indicates the measurement was performed.

5.3.4 Statistical analysis

Data were recorded, using Microsoft Excel (Microsoft Office Professional Plus 2013, Microsoft Corp. Redmond, Washington, USA). Statistical analysis was conducted using SPSS (IBM SPSS Statistics for Windows, Version 21.0. IBM Corp. Armonk, New York, USA).

Data were tested for normality, using the Shapiro-Wilk (S-W) test ($p>0.05$). Repeated measures analysis of variance (ANOVA) was employed to examine the changes in response variables over the time when data were normally distributed, and Friedman analysis of variance was used, when they were not. Statistically significant changes from baseline were further investigated, using post hoc tests with Bonferroni correction.

Multivariate regression analysis (stepwise) was used to further examine the relationship between refractive changes, simulated keratometry readings, corneal eccentricity in the steepest and flattest meridian, CCT and corneal biomechanical properties over the seven-day period of ortho-k lens wear.

A critical p-value of 0.05 was chosen to denote statistical significance and only data from the right eye were analysed.

Study was designed to achieve 80% power ($\alpha=0.05$, Cohen's $d=0.25$) to detect at least 0.6 mmHg change in CRF after overnight ortho-k lens wear (Cohen's $d=0.46$) (Chen *et al.* 2009), based on the repeated measures ANOVA with correlation coefficient between the repetitions set to 0.5, and required 16 participants. However, nine additional participants were recruited to account for the drop out and unsuccessful initial fits. The power design calculations and subsequently the sample size was based on the results of previous studies (Moreno-Montanés *et al.* 2008; Wasielica-Poslednik *et al.* 2010; Hon and Lam 2013; Hong *et al.* 2013). Study power was determined, using statistical power program G*Power 3.0 (version 3.0.10) (Faul *et al.* 2007; Faul *et al.* 2009).

5.4 Results

5.4.1 Changes in refractive error, corneal curvature and central corneal thickness

Ortho-k lens wear effectively reduced myopic refractive error over the seven-day period ($F_{(2.716,51.599)}$=50.145, p<0.001). The average refraction was -2.83 ± 1.11 D at the BL, reducing to -1.69 ± 0.69 D and -0.64 ± 0.65 D, after the first and seventh night of lens wear, respectively (Figure 5.1). Post hoc pairwise comparisons showed that refraction was significantly different from the BL and the first night of lens wear (p≤0.001), but stabilised after the second night (p>0.05).

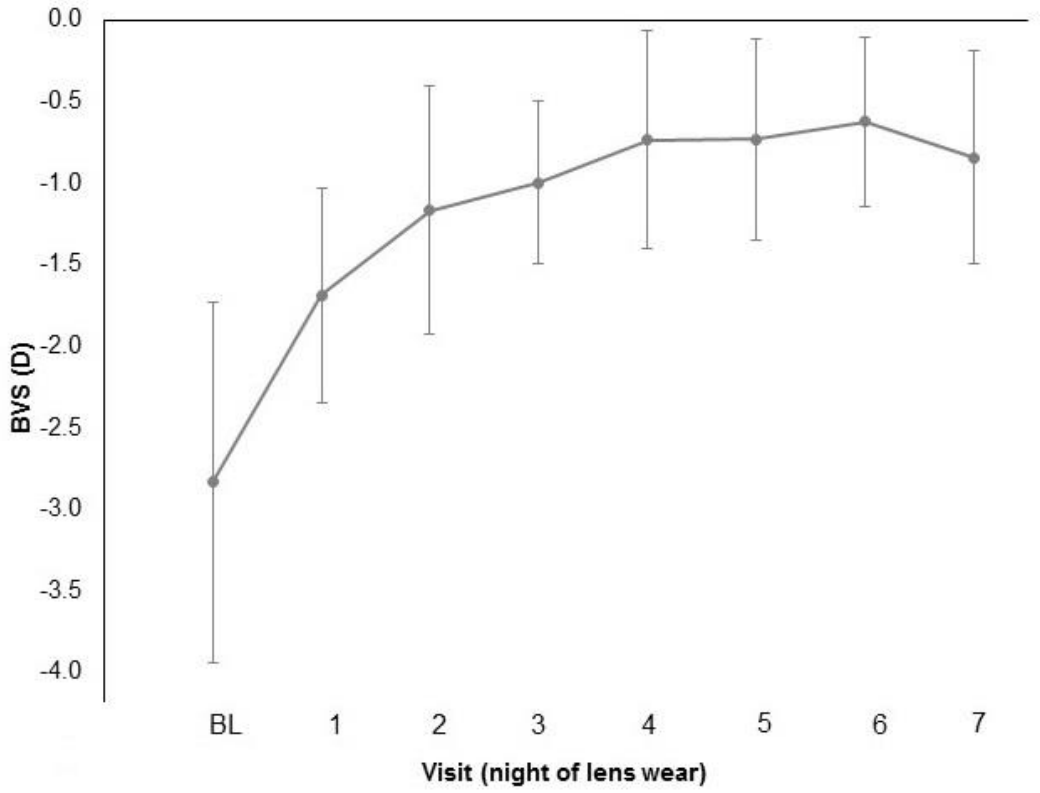

Figure 5.1 Refractive changes over the seven-day period of ortho-k lens wear compared to baseline. Note: refraction is presented as BVS and plotted as mean ± SD (n=21), error bars represent 1 SD.

A similar pattern could be seen within the topography readings (Table 5.3). Steep and flat eccentricity (e) changed within the first night of ortho-k lens wear (BL vs first night

p<0.001; all nights p<0.05) and stabilised thereafter (p>0.05). Also, a gradual corneal flattening, in both the steep and flat meridians, was observed (Table 5.3) and reached statistical significance after the seventh night of lens wear in the steep meridian (p=0.01) and second night in the flat meridian (p=0.06).

A gradual thinning of the central cornea ($F_{(2.155,43.098)}$=1.971, p=0.035), that reached statistical significance after the seventh night (p=0.008), occurred during the study period. CCT at BL was 545 ± 41 µm, 545 ± 42 µm after the first night and 539 ± 43 µm after the seventh night of lens wear (Figure 5.2).

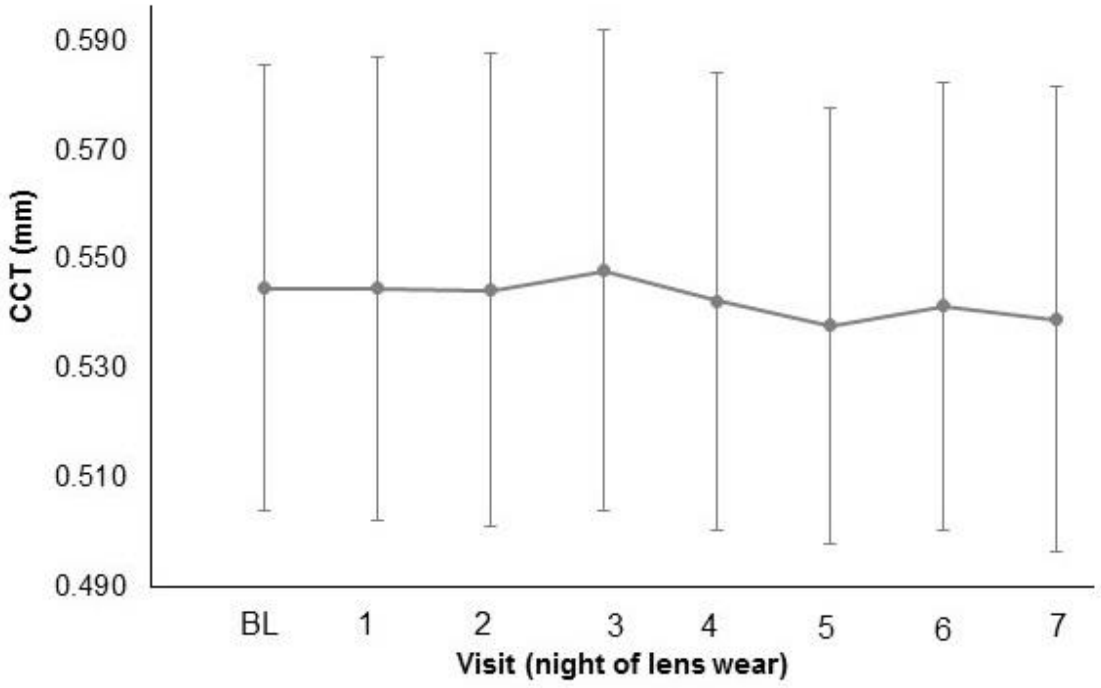

Figure 5.2 Changes in CCT over the seven-day period of ortho-k lens wear compared to baseline. Note: data are presented as mean ± SD (n=21), error bars represent 1 SD.

Ocular parameter (Mean±SD)	Visit								S-W test for normality	Effect of time (Repeated Measure ANOVA)	
	BL	Night 1	Night 2	Night 3	Night 4	Night 5	Night 6	Night 7	p	p	F
Steep e	0.42±0.14	0.29±0.11	0.29±0.13	0.28±0.11	0.27±0.06	0.27±0.08	0.26±0.11	0.28±0.09	0.181	<0.001	6.117
Flat e	0.65±0.10	0.53±0.12	0.47±0.16	0.50±0.13	0.43±0.15	0.39±0.16	0.39±0.17	0.42±0.16	0.986	<0.001	15.692
Steep K (D)	43.90±1.51	43.80±1.52	43.67±1.54	44.24±1.53	43.57±1.55	43.72±1.63	43.38±1.52	43.50±1.51	0.723	0.003	3.27
Flat K (D)	42.86±1.39	42.70±1.39	42.54±1.38	43.03±1.22	42.51±1.40	42.46±1.35	42.40±1.40	42.39±1.40	0.310	0.017	3.774
ΔK (D)	1.00±0.42	1.11±0.45	1.11±0.50	1.19±0.64	1.05±0.54	1.26±0.86	0.99±0.59	1.09±0.62	0.150	0.342	1.281

Table 5.3 Changes in corneal topography over the seven-day period of ortho-k lens wear compared to baseline. *If $p<0.05$, Friedman's test procedures were carried out, statistically significant ($p<0.05$).

5.4.2 Changes in corneal biomechanical properties

5.4.2.1 Corneal biomechanical properties measured with Ocular Response Analyser

The main ORA parameters, Goldman correlated intraocular pressure IOPg ($F_{(7,133)}$=0.792, p=0.595), intraocular pressure adjusted for corneal thickness IOPcc ($F_{(7,133)}$=1.211, p=0.306), CH ($F_{(4.373,83.087)}$=1.824, p=0.126) and CRF ($F_{(7,133)}$=1.03, p=0.413) were unaffected by the ortho-k lens wear over the 7-day period. The average CH was 10.42 ± 1.29 mmHg at the baseline appointment, 10.26 ± 1.19 mmHg after the first night of lens wear, and 10.04 ± 1.50 mmHg after seven nights of lens wear. CRF was 9.35 ± 1.71 mmHg, 9.42 ± 1.51 mmHg and 9.13 ± 2.00 mmHg, respectively at the same time points (please refer to Appendix 3 for the full ORA results table).

Conversely, the additional ORA derived parameters were affected by the lens wear. Twelve of thirty-seven parameters that reached statistical significance over the seven-day period are summarised in Table 5.4. The ortho-k lens wear mostly affected the first (initial applanation) peak (Figure 5.3), rather than the second (rebound peak) with the vast majority of changes occurring during the first four nights (Table 5.5). The metrics of the initial applanation peak and rebound peak that were unaffected by the ortho-k lens wear are summarised in Table 5.6 (please refer to Appendix 3 for full table and results). For the full explanation of the applanation peak, please refer to Section 2.2.1.

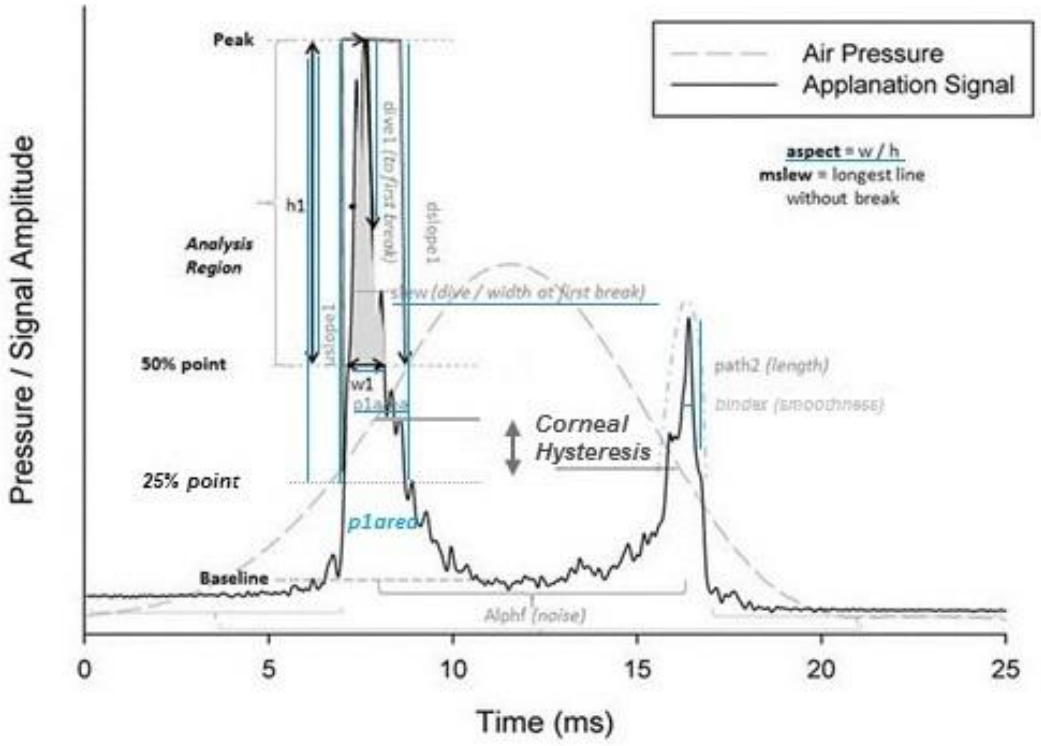

Figure 5.3 The affected regions by the ortho-k lens wear of the ORA applanation curve marked with a blue line and letters. Figure adapted and reprinted with permission from (Wolffsohn *et al.* 2012).

ORA parameter (Mean±SD)	Visit								S-W test for normality	Effect of time (Repeated Measure ANOVA)	
	BL	Night 1	Night 2	Night 3	Night 4	Night 5	Night 6	Night 7	p	p	F
dive1	421.30±138.39	454.50±74.90	414.70±118.93	412.47±66.46	380.32±81.60	384.32±131.61	416.93±107.87	379.63±129.80	0.001*	0.021	2.619
Values from upper 75% of peak											
p1area	4817.07±783.76	4833.19±1233.09	4585.91±983.69	4558.19±834.29	4464.56±6.16.58	4753.93±1162.44	4691.06±977.86	4582.30±1168.29	0.574	0.033	2.265
h1	486.36±68.28	479.43±80.69	462.74±81.74	439.52±59.70	420.25±51.42	446.88±81.52	458.16±87.52	438.19±76.59	0.512	0.008	2.892
aspect1	22.56±3.91	21.70±3.75	21.87±4.72	19.60±2.97	19.00±3.39	20.21±4.47	21.46±4.98	19.92±3.59	0.225	0.007	2.994
uslope1	69.15±14.77	70.14±14.05	65.59±17.81	62.16±14.03	58.35±12.50	60.43±16.15	67.27±17.18	57.18±15.05	0.032*	0.015	2.592
dslope1	34.66±7.17	32.41±6.12	34.20±8.13	29.52±4.94	28.94±5.96	30.99±6.77	32.64±8.39	31.62±5.47	0.342	0.049	2.086
Values from upper 50% of peak											
h1	324.24±45.52	319.62±53.79	308.49±54.49	293.02±39.80	280.136±34.28	297.92±54.35	305.44±58.34	292.13±51.06	0.512	0.001	3.692
h2	305.01±31.91	286.96±50.16	286.60±46.80	248.64±50.16	282.81±41.90	273.46±44.80	278.88±41.35	273.03±36.04	0.645	<0.001	21.152
w1	12.14±1.65	12.14±1.74	11.71±1.87	12.33±1.59	13.33±1.59	12.84±2.29	12.43±1.80	12.90±2.57	0.007*	0.007	2.548
w2	11.86±2.35	12.71±3.59	12.57±3.43	13.53±3.98	13.00±3.26	12.89±2.66	13.14±3.21	12.14±2.92	0.312	<0.001	11.367
aspect1	27.20±5.43	26.58±4.24	26.96±6.36	24.14±4.39	21.38±4.09	24.06±6.28	25.23±6.39	23.53±6.04	0.437	0.003	3.224
dslope1	46.78±11.87	44.75±11.13	48.24±12.62	41.51±10.20	36.95±9.35	42.08±12.01	41.73±12.77	40.23±9.78	0.414	0.026	2.36

Table 5.4 The twelve additional ORA derived metrics that reached the statistical significance over the 7-day period of ortho-k lens wear compared to BL. *If p<0.05, Friedman's test procedures were carried out.

ORA parameter (Mean ± SD)	When effect of time is significant (post hoc test with Bonferroni corrections)	
	night 'x' vs night 'y'	**p value**
dive1	night 1 vs night 4	0.015
Values from upper 75% of peak		
p1area	BL vs night 1	0.005
h1	BL vs night 4	0.006
aspect1	BL vs night 4	0.048
uslope1	night 1 vs night 7	0.010
dslope1	BL vs night 4	0.014
Values from upper 50% of peak		
h1	BL vs night 4	0.006
	night 7 vs BL and all nights	<0.001
h2	BL vs night 4	0.022
	BL vs night 7	0.033
	night 1 vs BL and all nights	<0.001
w1	night 2 vs night 4	0.021
w2	night 1 vs BL and all nights	<0.001
aspect1	BL vs night 2	0.027
	BL vs night 4	0.01
	night 1 vs night 4	0.04
dslope1	BL vs night 1	<0.001
	night 1 vs night 2	0.001
	night 1 vs night 3	0.004
	BL vs night 4	0.004

Table 5.5 Statistically significant pairwise post hoc (with Bonferroni correction) comparisons, showing the effects ortho-k lens wear on ORA-derived metrics after each night.

ORA parameter (Mean ± SD)	Explanation of the metric in relation to the changes induced by the ortho-k lens wear	p value
slew1	aspect ratio of dive2 where dive2 is divided by width	0.510
slew2		0.938
mslew1	maximum single increase in the rise of the peak (longest continuous line without a break)	0.157
mslew2		0.151
dive2	backside of downslope of peak (absolute value of peak until the first break)	0.475
aindex	the smoothness of the peak (related to the noise of the measurement aka how many times peak changes the direction and represent local imperfections in the cornea, respectively softness of the cornea)	0.731
bindex		0.352
aplhf	the smoothness of the region between the peaks (related to the noise of the measurement and represent local imperfections in the cornea, respectively softness of the cornea)	0.339
Values from upper 75% of peak		
p2area	area under the curve (proportional estimate of the time needed for the cornea to change from the concave to the convex form)	0.117
h2	height from the lowest to the highest point in peak	0.08
w1	width at the base of the peak region (descriptor of the time course)	0.348
w2		0.377
aspect2	aspect ratio of the peak (height/width)	0.540
uslope2	rate of increase from base to peak	0.915
dslope2	rate of decrease from peak to base	0.264
path1	the absolute value of path length around the peak	0.088
path2		0.471
Values from upper 50% of peak		
p1area	area under the curve (proportional estimate of the time needed for the cornea to change from the convex to the concave form)	0.889
p2area	area under the curve (proportional estimate of the time needed for the cornea to change from the concave to the convex form)	0.247
aspect2	aspect ratio of the peak (height/width)	0.896
uslope1	rate of increase from base to peak	0.204
uslope2		0.934
dslope2	rate of decrease from peak to base	0.243
path1	the absolute value of path length around the peak	0.521
path2		0.492

Table 5.6 Summary of the additional ORA-derived parameters that did not significantly change over the study period.

5.4.2.2 Corneal biomechanical properties measured with Corvis ST

All parameters measured with the Corvis ST over the seven-day period have been summarised in Table 5.7. None of the parameters, except for the A1 length (the cord length of the initial applanation), $\chi^2(7)=39.214$, $p<0.001$ and A2 length ($\chi^2(7)=39.214$, $p<0.001$), reached statistical significance. When outliers were removed (identified, using Box and Whisker plots and normality plots), A1 length approached statistical significance ($\chi^2(7)=13.037$, $p=0.007$), whilst A2 length remained significant (Figure 5.4). The post hoc tests revealed that A2 length was significantly different between baseline appointment and all 7 nights of lens wear (all $p<0.001$, except for BL vs 5th day – $p=0.017$). For the full explanation of the applanation metrics, please refer to Section 2.2.2.

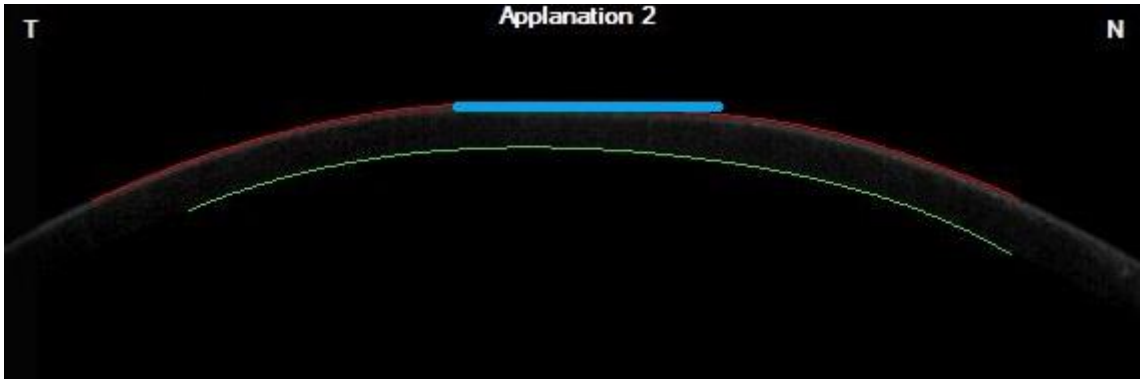

Figure 5.4 The affected region – Corvis ST derived metric (A2 length) by the ortho-k lens wear marked with a blue line.

5.4.3 Axial length, anterior chamber depth, lens thickness and endothelial cell count

No significant changes in AL, ACD or LT were observed over the 7-day period of lens wear (Table 5.8). Also, no changes in endothelial (END) cell count or shape were found, when adjusted for age (Table 5.8). However, significant changes in shape were found between BL and first night of lens wear ($F_{(2,40)}=4.703$, $p=0.015$; post hoc $p=0.025$) when results were not adjusted for age.

Corvis ST parameter (Mean±SD)	Visit								S-W test for normality	Effect of time (Repeated Measure ANOVA)	
	BL	Night 1	Night 2	Night 3	Night 4	Night 5	Night 6	Night 7	p	p	F
IOP	13.38±1.82	13.37±2.04	13.17±1.93	13.87±2.07	13.31±1.84	13.19±1.55	13.36±2.18	13.36±2.16	0.784	0.866	0.66
Def. Amp.	1.09±0.12	1.07±0.08	1.08±0.09	1.05±0.11	1.07±0.10	1.07±0.08	1.07±0.11	1.05±0.10	0.656	0.685	0.317
A1 time (ms)	7.24±0.22	7.26±0.24	7.22±0.24	7.31±0.26	7.24±0.22	7.22±0.19	7.24±0.27	7.25±0.27	0.618	0.689	0.191
A1 length (mm)	1.75±0.09	1.78±0.03	1.78±0.03	1.74±0.12	1.79±0.03	1.74±0.11	1.78±0.04	1.73±0.14	<0.001*	0.002	22.205
A1 velocity (m/s)	0.16±0.01	0.15±0.02	0.16±0.02	0.16±0.02	0.16±0.01	0.16±0.01	0.15±0.02	0.15±0.02	0.112	0.112	0.368
A2 time (ms)	22.17±0.42	22.10±0.27	22.16±0.32	22.0±0.38	22.06±0.34	22.07±0.31	22.01±0.39	22.05±0.37	0.075	0.657	0.717
A2 length (mm)	1.78±0.24	1.73±0.29	1.74±0.23	1.71±0.24	1.70±0.31	1.62±0.28	1.62±0.32	1.73±0.28	<0.001*	<0.001	39.214
A2 velocity (m/s)	-0.38±0.07	-0.38±0.06	-0.38±0.06	-0.37±0.06	-0.38±0.08	-0.38±0.05	-0.38±0.06	-0.38±0.07	0.386	0.844	0.484
HC time (ms)	16.89±0.38	16.89±0.30	16.93±0.42	16.82±0.32	16.78±0.35	16.85±0.26	16.82±0.47	16.73±0.40	0.129	0.331	1.165
Peak dist (mm)	3.07±1.04	3.59±1.24	4.23±1.17	4.06±1.18	4.34±1.10	3.98±1.18	3.82±1.21	3.88±1.31	<0.001*	10.428	0.166
Radius (mm)	7.27±0.81	7.25±0.61	7.09±0.71	7.20±0.60	7.01±0.58	6.99±0.72	6.94±0.63	7.21±0.69	0.662	0.119	1.700
A1 Def. Amp. (mm)	0.13±0.01	0.12±0.01	0.12±0.01	0.13±0.01	0.12±0.01	0.12±0.01	0.12±0.01	0.12±0.01	0.754	0.456	0.719
HC Def. Amp.	1.09±0.12	1.07±0.08	1.08±0.09	1.05±0.11	1.07±0.10	1.07±0.08	1.07±0.11	1.05±0.10	0.656	0.560	0.0.461
A2 Def. Amp. (mm)	0.40±0.03	0.38±0.04	0.38±0.05	0.38±0.04	0.38±0.05	0.38±0.04	0.39±0.04	0.37±0.05	0.658	0.435	0.916

Table 5.7 Changes in corneal biomechanical properties measured with Corvis ST over the seven-day period of ortho-k lens wear compared to baseline. *If $p<0.05$, Friedman's test procedures were carried out, statistically significant ($p<0.05$).

Ocular parameter (Mean±SD)	Visit								S-W test for normality	Effect of time (Repeated Measure ANOVA)	
	BL	Night 1	Night 2	Night 3	Night 4	Night 5	Night 6	Night 7	p	p	F
AL (mm)	24.67±0.72	24.65±0.73	24.65±0.72	24.64±0.69	24.65±0.72	24.68±0.72	24.63±0.71	24.64±0.72	0.331	0.185	1.914
ACD (mm)	3.79±0.18	3.77±0.18	3.77±0.19	3.78±0.22	3.77±0.19	3.75±0.29	3.77±0.19	3.78±0.17	0.708	0.351	1.036
LT (mm).	3.51±0.20	3.53±0.18	3.53±0.21	3.54±0.20	3.53±0.21	3.53±0.21	3.52±0.21	3.51±0.22	0.267	0.452	0.897
END cell count (cells/mm^2)	2693.45± 298.33	2556.23± 588.21						2684.07± 296.61	0.006*	0.446	1.614
END cell hexagonality (%)	62.38±8.82	56.81±8.81						60.3±9.24	0.895	0.129	0.88

Table 5.8 Changes in AL, ACD, LT and endothelial cell count over the seven-day period of ortho-k lens wear compared to baseline. *If p<0.05, Friedman's test procedures were carried out.

5.4.4 Relationship between refractive, topographic and corneal thickness changes and corneal biomechanics

After the first night of lens wear multiple modelling revealed that changes in the ORA-derived parameter h2 compared to BL explained 28.3% of total variance in BVS (ΔBVS = 1.04 + 0.06 x Δh2; p_{h2}=0.023). Whereas after 7 night of lens wear compared to BL 94.5% of total variance in BVS was accounted for by the flat e (52.7%), age (13%), flat K (11.2%), Corvis ST-derived parameter A1 length (7.2%), delta K and ORA-derived parameter CH (6.5%); (ΔBVS = -5.16 – 7.27 x Δflat e + 0.26 x age -0.84 x Δflat K – 4.71 x ΔA1 length – 0.57 x Δdelta K + 0.27 x ΔCH; p_{all}<0.001).

Around 28% of changes in steep e after first night of lens wear were accounted by changes in BVS (Δsteep e = -0.56 - 0.62 x ΔBVS; p_{BSV}=0.024). After the seven nights of lens wear compared to BL, 23% of changes were explained by the variance in the ORA-derived parameter aspect2 from the upper 50% (entered in equation as aspect21) of the peak; (Δsteep e = -0.19 - 0.02 x Δaspect21; $p_{aspect21}$=0.024).

Variance in flat e was partially accounted for (22.5%) by changes in ORA-derived parameter w1 from the upper 50% of the peak (Δflat e = 2.53 + 3.96 x Δw11; p_{w11}=0.047). After seven nights of lens wear 82.4% of the total variance in flat e was explained by age (17.9%), changes in BVS (52.9%) and Corvis ST-derived parameter A2 Def. Ampl. (11.6%); (Δflat e = -0.47 – 0.81 x ΔBVS + 0.21 x age + 0.99 x ΔA2 Def. Amp.; p_{BVS}<0.001, p_{age}=0.002, $p_{A2\ De.\ Amp.}$=0.005).

No other variables were found to contribute towards the multiple regression model, apart from flat K, which explained 69.4% of total variance in steep K after the first night of lens wear (Δsteep K = 0.04 +0.88 x Δflat K, $p_{flat\ K}$<0.001). Similarly, 69.4% of variance in the flat K was explained by the changes in steep K (Δflat K = -0.08 +0.78 x Δsteep K, $p_{steep\ K}$<0.001). After seven nights of lens wear, however, 89.8% of the variance observed in the steep K was accounted for flat K (37.6%), CCT (21.1%), ORA-derived parameters

path2 (10.2%) aspect2 from the upper 50% of the peak (6.1%) and CRF (7.2%) and the Corvis ST derived parameter Peak Dist. (7.6%) (Δsteep K = -0.02 +0.66 x Δflat K + 0.02 x ΔCCT + 0.18 x Δpath2 + 0.16 x ΔPeak Dist. -0.08 x Δaspect21 -0.15x ΔCRF, $p_{all} \leq 0.001$). Whereas, the variance in flat K at the same time point (55.2%) was explained by changes in BVS (26.8%) and the ORA-derived parameter dslope2 (28.4%) (Δflat K = 0.17 -0.37 x ΔBVS – 0.06 x Δdslope2; $p_{BVS}=0.001$, $p_{dslope2}=0.004$).

Twenty-two per cent of total variation in CCT after the first night lens wear was accounted for by changes in Corvis ST derived metric Peak Dist. (ΔCCT = -0.002 x ΔPeak Dist.; $p_{Peak\ Dist.}=0.049$). After seven nights of lens wear 75.5% of the changes in CCT were explained by the variation in the ORA-derived parameters path2 from the upper 50% of the curve (20.2%), mslew1 (19.1%), steep e (17.3%) and age (18.9%) (ΔCCT = 0.05 + 0.01 x Δpath21 + 0.03 x Δsteep e – 0.002 x age + Δmslew1; $p_{path21}=0.007$, $p_{steep\ e}<0.001$, $p_{age}<0.001$, $p_{mslew1}=0.004$).

The daily variations over the study period that could be explained by corneal biomechanics, and the other ocular parameters, are summarised in Table 5.9.

Parameter	Night ‘x’ vs night ‘y’	Multiple regression equation	p values	Total variance explained by the MR model (%)	Variance explained by the corneal biomechanical parameters (%)
BVS (D)	2 vs 1	ΔBVS = 0.58 -0.02 x Δslew2	0.017	34.3	34.3
	3 vs 2	ΔBVS = 1.74 - 0.79 x age – 27.72 x ΔA2 Def. Ampl. – 0.02 x Δdive2 + Δp2area – 16.22 x ΔA1 velocity -6.27 x ΔACD	≤0.005	85.3	50.5
	4 vs 3	ΔBVS = 0.41 – 0.04 x Δdslope2 – 0.17 x ΔCH	≤0.028	54.2	54.2
	5 vs 4	ΔBVS = -0.21 – 2.06 x Δflat e – 0.03 x Δaspect11	≤0.019	58	19.3
	6 vs 5	ΔBVS = 0.13 -1.70 x Δflat e	0.019	25.6	–
	7 vs 6	ΔBVS = -5.16 – 7.27 x Δflat e + 0.26 x age – 0.84 x Δflat K – 4.71 x ΔA1 length – 0.57 x Δdelta K + 0.27 ΔCH	<0.001	94.5	15.3
CCT (µm)	2 vs 1	None of the variance explained by the model			
	3 vs 2	ΔCCT= -0.01 – 0.01 x ΔIOP – 0.26 x ΔA1 Def. Amp.	≤0.004	64.4	64.4
	4 vs 3	ΔCCT= -0.02 + 0.02 x ΔCRF – 0.02 x Δaindex	≤0.006	64.8	64.8
	5 vs 4	ΔCCT= -0.002 + 0.01 x Δsteep K	0.018	30.4	–
	6 vs 5	ΔCCT= 0.11 + 0.13 x Δflat K – 0.12 x Δpath1 + 0.21 x ΔRadius + 0.01 x Δdelta K + 0.02 x Δpath11 + Δp1area	≤0.009	100	99.1
	7 vs 6	ΔCCT= 0.05 + 0.01 x Δpath21 + 0.03 x Δsteep e – 0.002 x age + Δmslew1	≤0.007	75.7	39.3
Steep e	2 vs 1	None of the variance explained by the model			
	3 vs 2	Δsteep e = 0.17– 10.16 x ΔA1 Def. Ampl.	<0.001	52.9	52.9
	4 vs 3	Δsteep e = -0.01 - 0.01 x Δdslope1	<0.001	51.5	51.5
	5 vs 4	Δsteep e = -0.01+ 0.01 x Δsteep K	0.049	22.1	–
	6 vs 5	Δsteep e = -0.01+ 0.42 x ΔCCT – 0.03 x Δdslope11	≤0.04	55.2	12.2
	7 vs 6	Δsteep e = -0.19+ 0.02 x Δaspect21	0.033	23	23
Flat e	2 vs 1	Δflat e = -0.75 + 0.03 x Δdive2 + 3.16 x ΔCH + 130.84 x ΔLT + 0.03 x Δp1area	<0.05	97.3	72.4
	3 vs 2	None of the variance explained by the model			
	4 vs 3	Δflat e = 0.05 + 0.01 x Δdslope11 + 0.03 x ΔIOP_g + 0.15 x ΔA2lenght + 0.65 x Δsteep e - 0.16 x Δalphf + 0.02 x ΔPeak Dist.	≤0.025	88.7	75.7
	5 vs 4	Δflat e = -0.06 – 0.15 x ΔBVS	0.06	38.7	–

	6 vs 5	Δflat e = 0.01 – 0.01 x Δflat K	<0.001	48.5	–
	7 vs 6	Δflat e = 0.01 – 0.01 x Δflat K	<0.001	48.5	–
Steep K	2 vs 1	None of the variance explained by the model			
	3 vs 2	Δsteep K = -0.01 + 0.92 x Δflat K - 0.87 x ΔBVS + 0.58 x ΔA2 velocity	<0.05	99.1	1.1
	4 vs 3	Δsteep K = 2.01 – 0.09 x age + 0.92 x Δflat k + Δparea	≤0.01	84.4	8.3
	5 vs 4	Δsteep K = 0.07 – 94.41 x ΔCCT – 1.66 x ΔA2 length – 1.54 x Δaindex	≤0.006	69.8	39.4
	6 vs 5	Δsteep K = -0.27 + 7.33 x ΔCCT+ 0.93 x Δflat K OR Δsteep K = -0.27 + 1.04 x Δflat K - 0.91 x Δw21 – 0.09 x ΔIOP_{cc}	<0.05	99.9	1
	7 vs 6	Δsteep K = -0.84 + 0.68 x Δflat K	0.04	37.6	–
Flat K	2 vs 1	Δflat e = -0.15 – 0.41 x Δsteep K	<0.001	60.4	–
	3 vs 2	Δflat K = -0.10 + 0.23 x Δ alphf – 0.09 x Δaspect21 + 0.002 x Δdive2 + 0.04 x Δdslope21 + 0.08 x Δbindex -0.33 x Δsteep e – 0.01 x Δpath11	≤0.036	94.1	84.9
	4 vs 3	Δflat K = 0.16 + 0.95 x Δflat e + 0.52 x Δsteep K	≤0.05	76.9	–
	5 vs 4	Δflat K = -1.72 + 0.75 x age + 0.31 x Δsteep K	≤0.019	55.9	–
	6 vs 5	Δflat K = 0.21 + 20.71 x ΔCCT + 0.67 x Δsteep K – 0.01 x Δuslope21	<0.05	99.9	1
	7 vs 6	Δflat K = -0.73 + 0.35 x ΔBVS – 0.06 x Δdslope2	≤0.004	55.2	28.4

Table 5.9 Daily variations in BVS, CCT, steep e, flat e, steep k and flat K explained by contributions of corneal biomechanical parameters measured by the ORA and Corvis ST and other metrics. Note: when a parameter from the upper 50% of the curve is entered in equation, '1' is added to the parameter name, to distinguish it from the parameters from upper 75% of the peak; if no β value is entered in equation, SPSS output displayed it as '0'.

5.5 Discussion

This is the first study to date to investigate the corneal biomechanical response to ortho-k lens wear in detail, utilising the ORA and Corvis ST and examining the first seven days of the lens wear, when the vast majority of the refractive changes occur (Mountford 1998; Swarbrick *et al.* 1998; Nichols *et al.* 2000; Alharbi and Swarbrick 2003; Soni *et al.* 2004; Swarbrick 2006).

As expected, ortho-k lens wear, effectively reduced myopic refractive error over the seven-day period and corrected around 60% of initial myopic refractive error within one night of lens wear, which is in agreement with previous work (Mountford 1998; Swarbrick *et al.* 1998; Nichols *et al.* 2000; Alharbi and Swarbrick 2003; Soni *et al.* 2004). Also, a gradual flattening of the corneal curvature, with significant changes occurring in the flattest corneal meridian first, was observed. This finding is supported by the previous findings of Swarbrick and colleagues (1998) and others (Soni *et al.* 2003; Sorbara *et al.* 2005). The observations of central corneal thinning that reached significance after the seventh night of lens wear, however, contradicts the work by Swarbrick and co-workers (1998). Although they reported central corneal thinning, it failed to reach statistical significance even after 28 days of ortho-k lens wear. The changes in CCT reported in the present study also contradicts the findings of Alharbi and Swarbrick (2003) and Haque *et al.* (2004), but are in agreement with Nichols and colleagues (2000) and others (Owens *et al.* 2004; Yoon and Swarbrick 2013), who postulated that the vast majority of epithelial thinning occurs between the first and seventh night of lens wear. These discrepancies between studies could arise from different techniques employed to measure corneal thickness (Swarbrick *et al.*, 1998, Nichols *et al.*, 2000, Owens *et al.*, 2004) or experiment conditions (closed- vs open-eye environment) (Swarbrick *et al.*, 1998, Alharbi and Swarbrick, 2003, Owens *et al.*, 2004, Yoon and Swarbrick, 2013). Swarbrick and colleagues(1998) used modified Holden-Payor optical micropachometer at eight different locations (central, 0.5 mm, 1.25 mm, 2.75 mm and 4.25 mm nasal and

0.25 mm, 1.00 mm, 2.50 and 4.00 mm temporal). Later Alharbi and Swarbrick (2003) used the same approach, but different corneal locations (centre (0.25 mm nasal), 3.50 mm and 5.00 mm nasal and 3.25 mm and 4.75 mm temporal). Whilst, Nichols (2000) employed Orbtek Orbiscan (Salt Lake City, UT, USA) to measure centrally and 3mm from the centre nasally, temporally, inferiorly and superiorly. Owens *et al.* (2004) used the EyeSys corneal topographer (EySys Technologies, Huston, TX, USA) to measure corneal thickness at 1.25 mm radius from the centre for central readings and at 2.5 mm radius for the mid-periphery. Although authors justify their choice of locations as instrument specific (Nichols *et al.* 2000; Owens *et al.* 2004) or corresponding to the reverse geometry lens zones (Nichols *et al.* 2000; Alharbi and Swarbrick 2003; Owens *et al.* 2004; Yoon and Swarbrick 2013),

Also, it could account for the assumptions made by various researchers that different mechanisms and complex interactions within the cornea take place in the initial stages of ortho-k lens wear (Swarbrick *et al.*, 1998, Owens *et al.*, 2004, Yoon and Swarbrick, 2013). The flattening of the anterior cornea, central epithelial thinning and mid-peripheral thickening is well documented in the literature (Swarbrick *et al.* 1998; Alharbi and Swarbrick 2003; Tsukiyama *et al.* 2008); however, the overall mechanisms of these changes are still obscure. Swarbrick *et al.* (1998) was the first group to demonstrate the central corneal thinning and mid-peripheral stromal thickening and hypothesised it could be due to the tissue re-distribution of the anterior cornea. A study conducted later (Owens *et al.* 2004), however, questioned the involvement of the anterior corneal tissue and demonstrated that transient changes in posterior corneal curvature can be observed in the first week of ortho-k lens wear. Other studies (Tsukiyama *et al.* 2008; Chen *et al.* 2010; Yoon and Swarbrick 2013), have failed to support the findings by Owens *et al.* (2004) and support the theory of anterior corneal shape changes as the main attributor of the refractive changes achieved by ortho-k. The observations at microscopic level in animal models (Matsubara *et al.* 2004; Cheah *et al.* 2008; Choo *et al.* 2008) support the

findings of the corneal thickness changes. However, they question the tissue re-distribution as the main mechanism of these changes and consider the mechanical effects of the lens, the plasticity of epithelium, cell compression and inter-cell processes, especially in the first days of ortho-k lens, instead (Matsubara *et al.* 2004; Cheah *et al.* 2008; Choo *et al.* 2008).

In terms of corneal biomechanics, CH (descriptor of the viscous damping properties) and CRF (the overall resistance of the cornea) measured by the ORA were not affected by the ortho-k lens wear. Previous work suggests that significant changes in CH (Mao *et al.* 2010) and CRF (Chen *et al.*, 2009, Mao *et al.*, 2010) can be observed after as little as one night of ortho-k lens wear. Furthermore, work presented by Yeh and colleagues (2013) demonstrates, that changes in both parameters become significantly apparent after 30 nights of ortho-k lens wear. Age (Kotecha *et al.* 2006; Shen, Fan*, et al.* 2008; Kotecha *et al.* 2014) and ethnicity (Yeh *et al.*, 2013) have both been linked to the corneal biomechanical properties measured by the ORA. However, it is unlikely that these factors could account for the discrepancy between the results of the previous work and the results reported in the present study as both the age (range 18-36 years) and ethnicity (predominantly Asian or Asian ethnicity) of the cohorts were similar (Chen *et al.*, 2009, Yeh *et al.*, 2013), with the exception of the study conducted by Mao and colleagues (2010), in which Chinese children (mean ± SD, 11.67 ± 2.56) participated.

It is more likely that the differences between the findings of the present study and previous work (Kerautret *et al.* 2008; Saad *et al.* 2010; Mikielewicz *et al.* 2011) could be explained by other factors. Researchers have previously questioned the CH and CRF ability to discriminate between normal and ectatic corneas, and demonstrated that CH and CRF should not be the only corneal biomechanical factors considered. Moreover, CH and, subsequently, CRF (as it is derived from CH) are suggested to be descriptors of the viscosity of the extracellular matrix components proteoglycans and glycoproteins and their interaction with collagen fibrils, (Nishimura *et al.* 1998; Spörl *et al.* 2009; Terai

et al. 2012), rather than collagen fibrils themselves. Collagen fibrils dominate the corneal mechanical behaviour and, subsequently, its response to ortho-k, as they are the main carriers of the load (Boote *et al.* 2005; Elsheikh 2010). Also, if the refractive changes during the first days of ortho-k lens wear are predominately achieved by epithelium (Matsubara *et al.* 2004; Cheah *et al.* 2008; Choo *et al.* 2008), CH and CRF could not reflect these changes, as both of these parameters are descriptors of stromal behaviour. The epithelium has been found to account for only 3% of the overall mechanical behaviour of the cornea (Elsheikh *et al.* 2008a). It is established that corneal behaviour is time and load-dependent (Elsheikh, 2010) and, therefore, changes in CH and CRF could become significant within a longer study period, as demonstrated by Yeh and co-workers (2013).

Detailed analysis of the air-pressure curve revealed that 12 of the additional 37 ORA-derived parameters were affected by ortho-k lens wear. The vast majority of the changes occurred during the initial applanation and were more pronounced in the upper 50% of the applanation peak, suggesting that ortho-k lens wear affects the transition of the cornea from the convex to concave form more than the original applanation phase (Figure 5.3). A time-dependent variability in the different ORA-derived metrics was observed with most of the significant changes occurring during the first four nights of the ortho-k lens wear.

A reduction in the absolute value of the first break of the initial applanation peak, which is a descriptor of the speed of the deformation past the concave phase, was observed. It might reflect the corneal shape changes induced by ortho-k lens wear. Ortho-k treated cornea might be deformed or flattened more easily as it is already undergoing flattening induced by the reverse geometry lens. The area under the curve (AUC), p1area decreased over the 7 nights, alongside with the height (h1 and h2 from upper 50% and h1 from upper 75% of the curve). AUC is the proportional estimate of the time needed for the cornea to change from the convex to concave form and is dependent on the peak

height and width. Therefore, the ortho-k treated cornea again could be more easily flattened due to the changes induced by the reverse geometry lens. Decrease in the AUC over the time could also reflect the increasing deformation (Elsheikh 2010) and epithelial remodelling (Cheah *et al.* 2008; Choo *et al.* 2008; Elsheikh 2010), induced by the repeated exposure to the ortho-k lens. Also, the upward slope from the upper 75% of the peak, downward slope (dslope1) from the upper 75% and 50% (uslope1) and width (w1) from the upper 50% and, subsequently, aspect 1 or the aspect ratio of the peak height/width from the upper 75 and 50% of the applanation peak, were reduced. This may indicate that the cornea becomes more bendable (the basic methodology of the ORA) and less resistant as a result of the ortho-k lens wear (Elsheikh, Ross*, et al.* 2009; Terai *et al.* 2012), or yet again it could reflect the flattening effect of the reverse geometry lens. The latter assumption could help to explain the changes in the height (h2) from the upper 50% of the rebound peak, reflecting the reshaping effect of the ortho-k lens wear (Cheah *et al.* 2008; Choo *et al.* 2008; Elsheikh 2010).

The fact that aindex, bindex and aplhf or the descriptors of the smoothness of the applanation curve and, subsequently, the local imperfections of the corneal structure, suggest that short term ortho-k lens wear does not disrupt the structure stromal extracellular matrix. Observations at microscopic level in primates have shown that even 4 hours of reverse geometry lens wear induces marked changes in the central corneal epithelial and stromal thickness (Cheah *et al.* 2008). Therefore, this assumption needs to be viewed cautiously and more work is needed to support this theory. Also, the role and, subsequently, the interpretation of the specific ORA-parameters (aindex, bindex and aplhf) need to be investigated more thoroughly.

From the 14 parameters provided by the Corvis ST, only applanation 1 length (A1 length) and applanation 2 length (A2 length) were found to be affected by the ortho-k lens wear. Applanation length is an estimate of the cord or length of the area of the cornea that is flattened by the air puff. An apparent decrease in the A2 length was seen and it most

likely reflects the changes in formation of central treatment zone, induced by the reverse geometry lens (Figure 5.4). However, contrary to the findings of the ORA, the parameters of the Corvis ST, relating to the speed of the deformation (A1, A2 velocity) and the deformation amplitude (deformation amplitude (DA), deformation amplitude of the first (A1 Def. Ampl,) and second (A2 Def. Ampl.) applanation and highest concavity (HC Def. Ampl.)), remained unchanged. Although, a weak to moderate correlation between different Corvis ST and ORA (specifically CH and CRF) parameters, has been found (Matsuura *et al.* 2016), Corvis ST measures the actual corneal movement (Hon and Lam 2013; Koprowski 2014; Matsuura *et al.* 2016), induced by the air puff, whilst the ORA analyses the change in reflectance angle of the light incident on the central cornea (Luce 2005; Matsuura *et al.* 2016). No papers to date have investigated the correlation between the Corvis ST and the additional ORA-derived parameters, however, as they are derived from the same applanation signal as CH and CRF, the differences between findings of the Corvis-ST and ORA are not surprising.The different measurement approaches between instruments makes it difficult to make direct comparisons between findings of the ORA and Corvis ST (Tejwani *et al.* 2014). The arbitrary technique employed by the ORA and the measurement of horizontal corneal displacement in real time by the Corvis ST provides a significant information about corneal response *in vivo*, however, further studies are required to better establish all parameters from each device to ease the clinical application of them in different scenarios. The fact that Corvis ST did detect less changes than the ORA in the current application could indicate either that the ortho-k lens does not induce significant corneal displacement in horizontal plane or the time period of the current study was too short for the Corvis ST to detect any changes induced by the reverse geometry lens. As this is the first study investigating corneal biomechanical response in ortho-k, using Corvis ST, it is diffucult to make any comparisons or assumptions.

As expected, AL, ACD and LT were not affected by the ortho-k lens wear over the study period, suggesting that mechanisms underlying ortho-k therapy are corneal in origin. This finding is supported by Santodomingo-Rubido and colleagues (2014) who studied short-time changes in axial elongation and other ocular biometric parameters after 1 week of discontinuation of long term ortho-k lens wear in Caucasian schoolchildren and concluded that refractive changes were primarily accounted by the recovery of corneal shape. Subsequently Santodomingo-Rubido and colleagues (2016) investigated the corneal power changes over 3 and 24 months of ortho-k lens wear in the same cohort and concluded that the changes in corneal power (central, peri- and para- central) were not correlated with the increasing AL. A study, investigating ACD in a cohort of myopic adults (mean age ± SD, 29.6 ± 3.8 years) also concluded that the refractive changes, induced by the ortho-k lens are primarily attributed to the changes in the anterior corneal shape (Tsukiyama *et al.* 2008).

Multiple regression analysis revealed complex interactions between refractive, corneal curvature, thickness and biomechanical changes over the initial seven nights of ortho-k therapy (Table 5.9). After the first night of the lens wear only up to 30% of the total variance in the changes of BVS, CCT and steep and flat meridian eccentricity could be explained by the fitted model, with little or no contribution of corneal biomechanical properties. However, as the treatment effect progressed over the subsequent days, 50-99% of the total variance were accounted for by the multiple regression modelling. Corneal biomechanical characteristics contributed significantly to the model and on average explained around 45% of the total variance in BVS, CCT, simulated keratometry readings and eccentricity. These interactions, presumably, reflect the stress, strain, shear and creep processes occurring within the corneal tissue in response to the static deformation induced by the ortho-k lens and the ability of the dynamic deformation, induced by the ORA and Corvis ST to detect these changes (Elsheikh, Ross*, et al.* 2009; Elsheikh 2010; Terai *et al.* 2012).

The study has several limitations. Although study reached the required power not all participants were able to attend both study visits. Also, not all participants could attend the schedualed appointments at the same time of the day, therefore, diurnal variances could have had an influence on the results summarised in this chapter (Kiely *et al.* 1982; Harper *et al.* 1996). Initial inclusion criteria of myopia -2.00D to -4.00D with with-the-rule-astigmatism of up to 1.50D were also changed due to available participant pool. Subjects with these parameters of refractive error have been found to respond to ortho-k treatment better (Swarbrick 2006) and would have provided a more controlled environment for the investigation of corneal biomechnical properties.

To conclude, this study demonstrates marked changes in corneal biomechanical parameters measured by the ORA and Corvis ST, occurring over the initial 7 nights of ortho-k lens wear. The refractive and curvature changes take place during the first night of the lens wear, whilst thickness changes of the central cornea and biomechanical parameters measured by ORA and Corvis ST happen more gradually, occurring over the first seven nights of ortho-k lens wear. It highlights the complex processes underlying the mechanisms of ortho-k, providing further evidence for the corneal involvement in the treatment response. However, ortho-k itself and the anterior segment structures undergoing changes during the corneal reshaping process are unable to explain all of the variation in treatment response, indicating that other patient specific factors could affect treatment outcome. Therefore, a better understanding of corneal biomechanical parameters in healthy individuals is required to potentially establish a list of predictors that would enhance the chances of achieving desired treatment effect.

Chapter 6. Factors influencing corneal biomechanics

6.1 General overview

This chapter describes a study investigating corneal biomechanical response in cohort of 158 healthy individuals by using the Ocular Response Analayzer (ORA) (Reichert Ophthalmic Instruments, Buffalo, NY, USA) and Corvis ST (Oculus, Wetzlar, Germany); in relation to various factors like age, ethnicity, diet, eye and body size. The aim of this study is to aid a better understanding to factors that might influence corneal biomechanical response in healthy population and if any of these factors could act as predictors for treatment outcome in different clinical scenarios, for example in case of application of ortho-k and myopia control (MC).

6.2 Introduction

The cornea is a unique structure that, together with sclera, forms the outer tunic of the eye and provides two thirds of eye's optical power (Hogan *et al.* 1971; Fatt and Weissman 1992; Klyce and Beuerman 1998). As the anterior surface and primary optical element of the eye, the cornea can be compromised by several conditions such as: keratoconus, in which a progressive, non-inflammatory thinning of the corneal stroma occurs (Rabinowitz 1998; Ruberti *et al.* 2011); Fuchs endothelial dystrophy, which is characterised by the formation of cornea guttae and increased loss of corneal endothelial cells (Repp *et al.* 2013); and trauma, which may result in reduced visual acuity. Likewise, the cornea can be re-shaped to correct the mismatch between eye's axial length (AL) and optical power, and the resulting refractive error. Techniques to address such issues include: refractive surgery, in which the required refractive changes are achieved by the ablation of corneal tissue (Roberts 2000; Ruberti *et al.* 2011); and orthokeratology (ortho-k), in which a specific reverse geometry lens is worn overnight to induce the desired corneal shape changes (Swarbrick 2006) (as discussed in more detail in Chapter 1). Regardless of whether the changes are caused by pathology or induced artificially,

corneal structure and material properties, factors which are crucial for the eye's optical performance, are altered (Fatt and Weissman 1992; Swarbrick *et al.* 1998; Roberts 2000; Ruberti *et al.* 2011). Therefore, a close and dynamic monitoring of the corneal tissue is required to predict the course of disease and the treatment outcome.

Until recently, the monitoring and follow-up of disease progression, procedure outcomes, or corneal behaviour mostly relied upon the geometrical and biometrical measurements of the cornea (namely topography and corneal thickness), mathematical modelling, and observations of destructive *in-vitro* testing (Ethier *et al.* 2004; Elsheikh 2010; Ruberti *et al.* 2011). Destructive *in-vitro* testing has provided a detailed understanding of the different biomechanical properties possessed by corneal layers (Elsheikh *et al.* 2008a; Thomasy *et al.* 2014). It has also identified the viscoelastic nature of corneal tissue, which is dominated by its bulk component, the stroma, which exhibits a two phase stress-strain relationship (Anderson *et al.* 2004; Boyce *et al.* 2008), and regional differences of corneal response to external stress (Hjortdal 1996; Anderson *et al.* 2004; Elsheikh *et al.* 2007; Whitford *et al.* 2015). Age-related stiffening of the cornea, presumably due to the changes in collagen fibril behaviour and distribution, has also been reported (Malik *et al.* 1992; Elsheikh *et al.* 2007). These studies highlight the contributing factors in the varied progression of disease and the selective treatment outcome. *In-vitro* testing is limited by a range of factors, such as the availability of donor tissue (Myung *et al.* 2008); the suitability of an appropriate experimental model (Boyce *et al.* 2008; Elsheikh *et al.* 2008b); and, its inability to mimic *in-vivo* conditions (Elsheikh *et al.* 2007), which are also multifactorial (for example the impact of lifestyle or ethnicity). Measurements which were easily obtainable *in-vivo*, such as pachymetry and corneal topography, are incapable of detecting such biomechanical changes.

The introduction of the Ocular Response Analyser (ORA, Reichert Technologies, NY, USA) in 2005 (Luce 2005) and the Corvis ST (Oculus, Wetzlar, Germany) in 2011 (Hon and Lam 2013) have allowed corneal biomechanics to be clinically examined (the

working principles of and parameters derived from both instruments have been discussed in detail in Section Chapter 2).

ORA-specific parameters corneal hysteresis (CH) and corneal resistance factor (CRF) have been studied in association with age (Kotecha *et al.* 2006; Kamiya *et al.* 2009; Landoulsi *et al.* 2013), ethnicity (Detry-Morel *et al.* 2012), a range of ocular conditions (Luce 2005; Sullivan-Mee *et al.* 2008; Abitbol *et al.* 2010; Fontes *et al.* 2010; Saad *et al.* 2010; Wolffsohn *et al.* 2012), and several procedures, including ortho-k and refractive surgery (Gonzalez-Meijome *et al.* 2008; Kirwan and O'keefe 2008; Chen *et al.* 2009). The Corvis ST has been shown to be effective for examining the effect of ocular clinical conditions such as diabetes mellitus (Perez-Rico *et al.* 2015) and glaucoma (Salvetat *et al.* 2015; Wang *et al.* 2015), and procedures such as refractive surgery (Frings, A. *et al.* 2015; Frings, Andreas *et al.* 2015). However, there is a distinct lack of population based studies investigating the biomechanical properties of the cornea in healthy individuals (Kamiya *et al.* 2009; Landoulsi *et al.* 2013; Valbon *et al.* 2014). Moreover, only a few studies (Kerautret *et al.* 2008; Mikielewicz *et al.* 2011; Wolffsohn *et al.* 2012; Landoulsi *et al.* 2013) have examined the additional 37 parameters of applanation curve provided by the second generation ORA, which are believed to be better descriptors of the corneal mechanical behaviour than CH and CRF alone (Saad *et al.* 2010; Mikielewicz *et al.* 2011).

The aim of this study was, therefore, to investigate the applanation curve provided by the ORA and the Corvis ST specific parameters in healthy individuals in association with age, ethnicity, nutrition, and eye and body size. This would provide a deeper understanding of corneal biomechanical response, not only observed in normal aging, but also from the viewpoint of lifestyle effects, which have not yet been studied widely.

6.3 Methods

6.3.1 Subjects and study protocol

One hundred and fifty-eight volunteers with good ocular and general health were recruited from the population of Aston University's students, staff, and their families and friends. Exclusion criteria were: any history of ocular trauma, surgery, disease, and rigid contact lens wear. Written consent was obtained before the examination in accordance with the tenets of the Declaration of Helsinki. The study was approved by the Aston University Research Ethics Committee (included in Appendix 6.2).

Participants were invited to attend a 60-minute appointment at the Aston University Health Clinic. They were advised to cease soft contact lens wear 24 hours before the appointment. Appointments were scheduled at least 2 hours after waking to diminish the impact of overnight and contact lens wear induced oedema (Armitage and Schoessler 1988; Harper *et al.* 1996; Fonn *et al.* 1999; Du Toit *et al.* 2003). All participants filled out personal details sheet specifying their age and ethnicity based on the recommendations from the Office of National Statistics (https://www.ons.gov.uk/methodology/classificationsandstandards/measuringequality/ethnicgroupnationalidentityandreligion; accessed 01.10.2015).

6.3.2 Measurements

Participants were optimally positioned in front of each instrument and asked to fixate on an appropriate target. Manufacturer recommendations (if any) were taken into account in order to obtain optimum readings. Both eyes were examined during the appointments, however, only the readings of the right eye (RE) for all measurements taken were included in the analysis. Refraction was measured monocularly using an open-field autorefractor (Shin-Nippon SRW, Anjiomato Trading Inc., Tokyo, Japan) with accommodation relaxed using a (+5.00D) Badal lens system. Ten measurements were averaged to calculate mean spherical equivalent (MSE).

A corneal topographer (Medmont E300, Medmont Ltd, Melbourne, Australia) was used to measure corneal shape, specifically eccentricity and keratometry (K) readings. The corneal endothelium was assessed using the Topcon SP3000P specular microscope (Topcon, Tokyo Japan). Central corneal thickness (CCT) was measured using ocular biometer and topography system Aladdin (Topcon, Tokyo Japan). Axial length, the assessment taken to represent eye size, was measured, using an optical biometer (IOL Master 500, Carl Zeiss Meditec Ltd, Jena, Germany).

Height and weight measurements were taken using a stadiometer (Seca, Birmingham, UK) and a mechanical scale (Boots UK Ltd, Nottingham, UK). Three subsequent height measurements were taken to the closest 0.1 cm (Taylor *et al.* 2006) to establish observers' standard deviation (SD), as suggested by Voss (1990), and were in agreement with a typical SD range of 0.2 to 0.3 cm (Voss *et al.* 1990). Weight was measured to the closest 0.5 kg, and 1 kg was taken away from the final reading to account for the participant's clothing (Taylor *et al.* 2006). Subsequently, body mass index (BMI=$\mathrm{weight\ (kg)}/(\mathrm{height\ (m)})^2$) was calculated (Must and Anderson 2006).

The biomechanical properties of the cornea were measured using ORA (ORA, Reichert Ophthalmic Instruments, Buffalo, USA) Corvis ST (Oculus, Wetzlar, Germany). For the ORA, 4 measurements with a waveform score (WS) ≥ 6.5 were obtained. The instrument automatically selected the best reading or best signal value (BSV). The WS cut-off value was chosen arbitrarily (Ehrlich *et al.* 2010; Lam *et al.* 2010; Ayala and Chen 2012; Mandalos *et al.* 2013). For Corvis ST three measurements with quality core (QS) were obtained and one reading was selected for analysis (Matsuura *et al.* 2016) (for specific details on instrumentation please refer to Chapter 2).

6.3.2.1 Food frequency questionnaire

Food consumption data concerning average frequency and portion sizes over the prior year were obtained using a 90 item Food Frequency Questionnaire (FFQ, included in

Appendix 4), adapted to include food items commonly consumed in the UK (Chiu *et al.* 2014). For each food item, the average intake frequency (9 categories ranging from 'never', or 'less than once per month', up to '6 or more times per day') in specified portion sizes (3 categories: small, medium and large) was recorded. For estimation purposes, 'medium' portion size was considered to be the natural portion of each food item (e.g., one apple), standard weight (e.g., one handful of berries or rice) or volume measures (e.g., one glass of milk) commonly used in the UK. A 'small' portion was considered to be half of a medium portion size, and a large portion was considered to be 1.5 times that of a medium portion. Subsequently, all intakes and portion sizes were broken down to a daily intake in a medium portion size (e.g., an average intake of a large serving 5-6 times per week was converted to ([5.5/7]x1.5)=1.18 medium portions/day). The 90 food items were then divided into 37 pre-defined food groups (Table 6.1), as identified by Chiu *et al.*, (2014) to minimise within-person variations and to perceive the possible influence of diet as whole (Hu 2002) on the corneal biomechanics. Subsequently the 90 food items were separated into categories of specified food groups/nutrients to evaluate the possible influence of specific products (Table 6.2).

Food group	Food items
Processed meat	*Hotdogs, ham, bacon, sausage*
Red meat	*Hamburgers. beef, beef stew, pork or lamb*
Organ meat	*Liver, liverwurst*
Fish and other seafood	*Fried fish, tuna, oysters, shrimp, other fish*
Poultry	*Fried chicken, chicken or turkey*
Pizza	*Pizza*
Soup	*Vegetable and tomato soup, other soup*
Eggs	*Eggs*
Butter or margarine	*Butter added to vegetables, butter on bread, margarine on bread*
Peanuts	*Peanuts or peanut butter*
Gravies	*Gravies*
Cold breakfast cereal	*Milk on cereal, other cold breakfast cereal*
Whole grains	*High-fibre cereals, fortified cereals, cooked cereals, brown bread*
Refined grains	*Biscuits, white bread, corn bread, pasta or, spaghetti, noodles*
Rice	*Rice*
Snacks	*Crisps*
High-energy drinks	*Regular soft drinks, fruit drinks, sugar in coffee or tea*
Sweets and desserts	*Doughnuts, chocolate, candy, other candy*
Chips	*Chips*
Liquor	*Liquor*
Beer	*Beer*
Wine	*Wine*
High-fat dairy products	*Whole milk, ice cream, other cheese, macaroni and*
Low-fat dairy products	*Semi-skimmed milk, skimmed milk, yogurt, cottage cheese*
Condiments	*Red chili sauce*
Salad dressings	*Salad dressings*
Fruit	*Apples, bananas, peaches, melon, watermelon, strawberries, Oranges, grapefruit, other fruit*
Fruit juice	*Orange or grapefruit juice*
Cruciferous vegetables	*Broccoli, coleslaw, cauliflower, cooked greens*
Dark yellow vegetables	*Butternut squash, carrots, sweet potatoes*
Tomatoes	*Tomatoes*
Green leafy vegetables	*Raw spinach, cooked spinach, green salad*
Legumes	*String beans, peas, other beans, chili with beans*
Other vegetables	*Corn, any other vegetable*
Potatoes	*Potatoes*
Coffee or tea	*Coffee or tea*
Non-dairy creamer in coffee or tea	*Non-dairy creamer in coffee or tea*

Table 6.1 Summary of the 37 food groups extracted from 90 item FFQ. Adapted from Chiu *et al.* (2014).

Food group/nutrients	Food items
Fruit, Vegetables, Soup	*Apples, bananas, peaches, melon, watermelon, strawberries, Oranges, grapefruit, other fruit, broccoli, coleslaw, cauliflower, cooked greens, butternut squash, carrots, sweet potatoes, potatoes, raw and cooked spinach, cooked greens, string beans, other beans, tomatoes, other vegetables*
Meat	*Hotdogs, ham, bacon, sausage, hamburgers. beef, beef stew, pork or lamb, liver, liverwurst, fried chicken, chicken or turkey*
Dairy products	*Whole milk, ice cream, other cheese, milk in coffee or tea, semi-skimmed milk, skimmed milk, yogurt, cottage cheese*
Carbohydrates	*High-fibre cereals, fortified cereals, other cold cereals, cooked cereals, brown bread, white bread, corn bread, biscuits, doughnuts, chocolate, other candy, pasta or spaghetti, rice, noodles, crisps, pizza, chips*
Drinks	*Regular soft drinks, coffee or tea*
Sauces	*Gravies, red chili sauce, salad dressings*
Fish/ Omega 3 rich products	*Fired fish, tuna, oysters, shrimp, other fish*
Alcoholic drinks	*Beer, wine, liquor*
Vitamin E rich products	*Broccoli, raw spinach, cooked spinach, tomatoes, peanuts and peanut butter, margarine*

Table 6.2 Summary of the food groups/ nutrients subsequently extracted from 90 item FFQ.

6.3.3 Statistical Analysis

The study was designed to achieve 80% power (α=0.05) to detect a minimum association of r=0.25 between the variables based on the results of similar studies previously published (Kotecha *et al.* 2006; Kotecha *et al.* 2014), and required a minimum of 120 participants. More participants were considered to be beneficial due to the study population being restricted to the university environment, and a larger sample size could be advantageous when analysing the association between corneal biomechanical properties and age. Statistical power software G*Power 3.0 (Faul *et al.* 2007) was used for the sample size calculations.

During the data collection process, Corvis ST was not able to consistently achieve a measurement due to alignment issues, therefore obtaining valid measurements with QS 'OK' status was difficult. As a result, data from 89 participants could be retrieved for

analysis, achieving 68% power. Whilst the unit was analysed for defects, the manufacturer did not find the instrument to be faulty.

All data were organised using Excel (Microsoft Corporation, Redmond, USA) and subsequently transferred to SPSS (IBM SPSS Statistics for Windows, v. 21.0. IBM Corporation, Armonk, USA) for statistical analysis. Data were tested for normality ($p>0.05$) using Kolmogorov-Smirnov (K-S) test.

As most of the data were not normally distributed, and some of the factors were dichotomous and ranked, Spearman's correlation coefficient was used to investigate the possible association between the variables. Confidence intervals were bootstrapped. Multiple regression analysis (stepwise) was used to determine the relationship between demographic variables, dietary components, ocular biometric parameters and multiple potentially dependent corneal biomechanical variables, to determine the total variance that could be explained.

For food consumption data, a factor or Principal Component Analysis (PCA) was conducted to extract the most important information (dietary components) from the given data set (Abdi and Williams 2010).

6.4 Results

6.4.1 Cohort demographics and ethnicity

The mean age (± SD) of the participants (99 women and 59 men) was 32.4 ± 12.3 years (range 19 to 67). The mean spherical equivalent (MSE, ± SD) refractive error was -1.46 ± 2.25 dioptres (range -11.81 to 3.60). Forty nine percent (n=77) of the participants were of an Asian background (mostly from India and Pakistan), 43% (n=68) were Caucasian, 4% (n=7) were of mixed ethnicity, 2% (n=3) of black and 2% (n=3) of another ethnicity. Hence only Caucasian and South West Asian ethnicities were compared in this element of the analysis.

6.4.2 Daily food consumption

Two dietary patterns, based on eigenvalues, parameters extracted from the data set after it has been linearly transformed, and similar to those reported previously (Hu *et al.* 1999; Chiu *et al.* 2014), were identified from the data set and classified as 'British oriental' or 'British Western' patterns, respectively. To identify which dietary pattern each participant had, a final score was obtained based on daily food consumption and weighted by the individual factor loadings. The highest score determined the dietary pattern. Individual factor loadings for both patterns of food items groups are summarized in Table 6.3. For more details please refer to Chiu *et al.* (2014). The 'British Oriental' pattern was associated with a higher intake of vegetables, fruit, low fat dairy products, peanuts, fish and poultry, whereas the 'British Western' pattern was associated with higher intake of refined grains, vegetables, rice, potatoes, red meat and high energy drinks.

The British Oriental pattern explained 11.6% of the total variance or differences between participants in daily food consumption, whilst British Western Pattern accounted for 8.4% of total variance. Therefore, diet classification was not considered as an appropriate method to assess food intake, alternatively the consumption of specific food groups (Table 6.2) was investigated (Table 6.4 and Table 6.5).

Moreover, the diet of 72.8% (n=115) of the study participants mainly consisted of vegetables, fruit, low fat dairy products, peanuts, poultry and fish, and therefore aligned more closely with the British Oriental pattern. Whereas 27.8% of participants were identified to have British Western pattern as their diet type.

Food item or food group	Factor 1: British Oriental pattern	Factor 2: British Western pattern
Tomatoes	0.64	-
Green leafy vegetables	0.62	-
Fruit	0.60	-
Legumes	0.59	-
Dark yellow vegetables	0.54	-
Low fat dairy products	0.46	-
Cruciferous vegetables	0.46	-
Peanuts	0.44	-
Fish and other seafood	0.44	-
Whole grains	0.36	-
Soup	0.33	-
Poultry	0.31	-
Coffee or tea	0.30	-
Refined grains	-	0.70
Other vegetables	0.42	0.58
Potatoes	0.31	0.55
Rice	-	0.52
Red meat	-	0.46
Chips	-	0.45
High energy drinks	-	0.45
Processed meat	-	0.42
Sweets and desserts	-	0.42
Snacks	-	0.42
Organ meat	-	0.38
Pizza	-	0.37
Butter or margarine	-	0.35

Table 6.3 Individual factor loadings for two major dietary patterns identified. Food items or groups with factor loading less than 0.3 were not listed and included in the subsequent dietary pattern calculation.

6.4.3 Corneal biomechanical properties in association with age, ethnicity, daily food consumption, eye and body size and ocular biometry

6.4.3.1 Ocular Response Analyser

Statistically significant correlations are summarised in Table 6.4. A full list of correlations is included in Appendix 5. Age had no influence on the main ORA parameters CH (r_s=0.094, p=0.298) and CRF (r_s=0.097, p=0.284) or any other ORA derived parameter (all p>0.05, Appendix 5). Similarly, ethnicity had no effect on the ORA specific corneal biomechanical parameters CH (r_s=0.010, p=0.091), CRF (r_s =-0.008, p=0.926) or any other parameter (all p>0.05, Appendix 5, Table A).

Eye size (measured as AL) and body size (BMI) both had an effect on corneal biomechanical properties measured with the ORA. Eye size was positively correlated (all p<0.05) with 8 of 41 ORA specific parameters, mostly from the second rebound applanation (Table 6.4). An inverse relationship existed between body size and 5 of the ORA corneal biomechanical parameters (all p<0.05). Four of the parameters were from the initial applanation peak (Table 6.4).

Dietary patterns extracted with the PCA analysis had no influence on CH (r_s=0.125, p=0.116), CRF (r=0.091, p=0.314) or any other ORA specific parameter (p>0.05, Appendix 5, Table A). However, specific dietary components like meat (p<0.05) and fish (p<0.05) were correlated with 4 of the additional 37 ORA specific parameters. No consistent pattern in the relationship between the intake of a specific dietary component and the corneal biomechanical properties was observed (Table 6.4). An inverse relationship between CCT and only one of the forty-one ORA specific parameter alph (r_s=-0.234, p=0.026) was observed. Similarly, endothelial cell count was positively correlated with only one parameter: p1area from the upper 50% of the peak (r_s=0.176, p=0.05) (Table 6.4).

The relationship between corneal biomechanics and both steep and flat K did not appear follow a particular trend, however, the significant associations between these topographic parameters and ORA specific parameters were observed at the initial applanation peak (Table 6.4). Detailed information on the ORA applanation curve can be found in Section 2.2.1 and Figure 2.3 (page 95).

Parameter	Spearman's correlation coefficient (r_s) (p value)																	
						Diet						Topography parameters						
	Eye size/Axial length (mm)	Endothelial cell count (cells/mm^2)	Age (years)	Ethnicity	Body size (BMI)	Fruit, vegetables etc.	Meat	Dairy products	Carbo-hydrates	Fish	Vitamin E	Steep e	Flat e	Steep K (D)	Flat K (D)	∆ K	CCT (µm)
IOPg (mmHg)	-	-	-	-	-	-	0.194 (0.030)	-	-	-	-	-	-	-	-	-	
IOPcc (mmHg)	0.187 (0.037)																
slew1	-	-	-	-	-0.214 (0.017)	-	-	-	-	-	-	-	-	-	-	-	
mslew1	-	-	-	-	-0.208 (0.020)	-	-	-	-	-	-	-	-	-	-	-	
mslew2	0.188 (0.036)	-	-	-	-	-	-	-	-0.225 (0.012)	-	-	-	-	-	-	-	
dive1	0.190 (0.034)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0.195 (0.030)	
dive2	-	-	-	-	-0.216 (0.016)	-	-	-	-	-	-	-	-	-	-		
alph																	-0.234 (0.026)
Values from upper 75% of the peak																	
p1area														0.330 (<0.001)	0.038 (<0.001)		
p2area	-	-	-	-	-	-	-0.184 (0.039)	-	-	-	-			-0.365 (<0.001)	0.409 (<0.001)	-	
h1	-	-	-	-	-	-	-0.184 (0.039)	-	-	-	-	-	-	-	-	-	
h2	0.189 (0.035)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
aspect1	0.189 (0.035)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
aspect2	0.189 (0.035)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
uslope1				-0.216 (0.016)													

Continued

Values from upper 50% of the peak																	
p1area	-	0.176 (0.050)	-	-	-	-	-	-	-	-0.190 (0.034)	-	-	-	-0.354 (<0.001)	0.397 (<0.001)	-	
p2area	-	-	-	-	-	-	-0.179 (0.045)	-	-	-	-	-	-	-	-	-	
h2	0.204 (0.023)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
aspect1	-	-	-	-	-0.224 (0.012)	-	-	-	-	-	-	-	-	-		-	
aspect2	-	-	-	-		-	-	-	-	-	-	-	-	-	-	0.290 (0.025)	
uslope1	-	-	-	-	-0241 (0.007)	-	-	-	-	-	-	-	-	-	-	-	
uslope2	0.196 (0.028)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
path1	-	-	-	-	-	-	-	-	-	0.225 (0.012)	-	-	-	-0.317 (<0.001)	0.424 (<0.001)-	-	

Table 6.4 Summary of statistically significant correlations between the ORA derived metrics and age, ethnicity, specific dietary components, eye and body size and ocular biometric parameters.

6.4.3.2 Corvis ST

Statistically significant correlations are summarised in Table 6.5. A full list of correlations is included in Appendix X. Age and body size had no influence on the corneal biomechanical parameters measured with the Corvis ST ($p>0.05$, Appendix 5, Table B).

Ethnicity was negatively associated with the time of the second applanation (A2 time, r_s= -0.418, $p<0.001$). The A2 time was significantly slower in participants of Caucasian background (22.04 ± 0.39 s, mean ± SD) than in participants of Asian ethnicity (22.52 ± 0.52 s) ($p<0.001$, one-way ANOVA). Ethnicity was also positively correlated with radius, however, no differences in pair-wise comparisons was ($p=0.077$, Kruskal-Wallis test).

Eye size was correlated with four Corvis ST parameters (A1 time, A1 length and A1 velocity), three of which were positively associated with the first applanation event (Table 6.5).

Dietary pattern had no influence on corneal biomechanics (all $p>0.05$, Appendix 5, Table B). Specific dietary components (meat, fish, carbohydrates and Vitamin E rich food), however, were positively associated (all $p<0.05$) with certain Corvis ST parameters (Table 6.5).

CCT and endothelial cell count were negatively associated with only one Corvis ST parameter A2 velocity (r_s=-0.029, $p=0.039$) (Table 6.5).

The relationship between corneal topography and parameters derived from the Corvis ST were moderate to strong and were associated with the initial applanation event; however, no apparent trend was obvious (Table 6.5).

For detailed explanation of Corvis ST parameters, please refer to Section 2.2.2).

Parameter	Spearman's correlation coefficient (r_s) (p)																
	Eye size/Axial length (mm)	Endothelial cell count (cells/mm^2)	Age (years)	Ethnicity	Body size (BMI)	Diet						Topography parameters					CCT (µm)
						Fruit, vegetables etc.	Meat	Dairy products	Carbo-hydrates	Fish	Vitamin E	Steep e	Flat e	Steep K	Flat K	Δ K	
Def. Amp.(mm)	-	-	-	-	-	-	-	-	0.285 (0.007)	-	-	-	-	-	-	-	-
A1 time (ms)	0.217 (0.041)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
A1 length (mm)	0.260 (0.014)	-	-	-	-	-	0.229 (0.033)	-	-	-	-	-	0.309 (0.003)	0.534 (<0.001)	0.612 (<0.001)	-	-
A1 velocity (m/s)	-0.318 (0.02)	-	-	-	-	-	-	-	-	-	0.246 (0.022)	-	-	-0.320 (0.02)	-0.323 (0.02)	-	-
A2 time (ms)	-	-	-	-0.418 (<0.001)	-	-	-	-	-	-	-	-	-	-	-	-	-
A2 velocity (m/s)	-0.219 (0.039)	-0.229 (0.039)	-	-	-	-	-	0.292 (0.006)	-	-	-	-	-	-	-	-	-
Peak dist (mm)	-	-	-	-	-	-	-	-	-	-	-	-	-0.516 (0.017)	-	-	-	-
Radius (mm)	-	-	-	0.467 (0.033)	-	-	-	-	-	0.478 (0.028)	-	-	-	-	-	-	-
HC Def. Amp.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-0.478 (0.029)
A2 Def. Amp. (mm)	-	-	-	-	-	-	-	-	-	-	0.651 (0.001)	-	-	-0.491 (0.0224)	-	-	-

Table 6.5 Summary of statistically significant correlations between the ORA derived metrics and age, ethnicity, specific dietary components, eye and body size and ocular biometric parameters.

6.4.4 Multiple regression

6.4.4.1 Ocular Response Analyser

For multiple regression, CCT, topographic parameters (steep e, flat e, steep K, flat K and ΔK), MSE, dietary pattern and specific dietary components (fruit, meat, dairy, products, carbohydrates, fish and Vitamin E rich dietary components), eye and body size, alongside demographic variables (age and ethnicity) were selected as predictors and entered into the model. The model was designed to fit stepwise selection criteria for the independent variables with a significance level of p=0.05 and inclusion criteria of 2 standard deviations (SD).

The predictors accounted for 7% to 27% of the total variance in the ORA specific corneal biomechanical parameters (Table 6.6). From all predictors, the most significant contributors towards the various corneal biomechanical parameters were dietary pattern and specific food components (carbohydrates and meat), which explained variance of 16 ORA specific parameters (Table 6.6). If dietary pattern was not included in the multiple regression model, higher intake of meat and steep K explained most of the variance (7-11%) in the corneal biomechanical parameters measured with the ORA.

6.4.4.2 Corvis ST

The same predictors as for the ORA were chosen to execute multiple regression analysis for the Corvis ST specific parameters.

Predictors explained 20% to 54% of the total variance in the corneal biomechanical properties measured by the Corvis ST. Contrary to the ORA, multiple regression analysis revealed that predominantly ethnicity rather than food intake is accountable for the most variance in the corneal biomechanics Table 6.7).

Parameter	Equation	Variance explained (%)	p values	Standardized β
IOPg (mmHg)	15.363 – 1.862 x dietary pattern	7.5	$p_{\text{dietary pattern}}$=0.047	$\beta_{\text{dietary pattern}}$=-0.247
IOPcc (mmHg)	54.407 – 0.026 x CCT – 3.43 x steep K	11.5	p_{CCT}=0.037, $p_{\text{steep K=0.040}}$	β_{CCT}=-0.278, $\beta_{\text{steep K}}$=-0.274
CH (mmHg)	–	–	–	–
CRF (mmHg)	11.018 – 1.137 x dietary pattern	10.1	$p_{\text{dietary pattern}}$=0.020	$\beta_{\text{dietary pattern}}$=-0.319
slew1	–	–	–	–
slew2	–	–	–	–
mslew1	–	–	–	–
mslew2	–	–	–	–
dive1	548.683 – 2.134 x age	10.5	p_{age}=0.018	β_{age}=-0.324
dive2	11.93.375 – 99.556 x steep K	8.4	$p_{\text{steep K=0.035}}$	$\beta_{\text{steep K}}$=-0.290
aindex	–	–	–	–
bindex	9.651 – 0.048 x MSE + 0.018 x dairy products	21.7	p_{MSE}=0.002, $p_{\text{dairy products}}$=0.028	β_{MSE}=-0.417, $\beta_{\text{dairy products}}$=0.287
aplhf	2.106 – 0.002 x CCT + 0.022 x carbohydrates	20.8	p_{CCT}=0.037, $p_{\text{steep K}}$=0.040	β_{CCT}=-0.278, $\beta_{\text{steep K}}$=-0.274
Values from upper 75% of peak				
p1area	7584.824 – 1170.889 x dietary pattern – 10.487 x fruit	16.0	$p_{\text{dietary pattern}}$=0.005, p_{fruit}=0.049	$\beta_{\text{dietary pattern}}$=-0.441, β_{fruit}=-0.284
p2area	6032.208 – 732.661 x dietary pattern	8.7	$p_{\text{dietary pattern}}$=0.032	$\beta_{\text{dietary pattern}}$=-0.295
h1	–	–	–	–
h2	456.351 + 123.312 x steep e – 38.889 x dietary pattern	20.9	$p_{\text{steep e}}$=0.009, $p_{\text{dietary pattern}}$=0.012	$\beta_{\text{steep e}}$=0.342, $\beta_{\text{dietary pattern}}$=-0.329
w1	20.323 + 0.779 x BMI	9	p_{BMI}=0.029	β_{BMI}=0.301
w2	–	–	–	–
aspect1	–	–	–	–
aspect2	17.468 + 0.406 x carbohydrates	7.4	$p_{\text{carbohydrates}}$=0.049	$\beta_{\text{carbohydrates}}$=0.271
uslope1	–	–	–	–
uslope2	71.898 + 4.332 x Vitamin E	7.6	$p_{\text{Vitamin E}}$=0.046	$\beta_{\text{Vitamin E}}$=0.0.276
dslope1	32.487 + 15.776 x ΔK	7.6	$p_{\Delta K}$=0.046	$\beta_{\Delta K}$=0.276
dslope2	78.219 – 18.338 x steep K + 13.204 x flat K – 0.005 x endothelial cell count	26.9	$p_{\text{steep K}}$=0.001, $p_{\text{flat K}}$=0.004, $p_{\text{endothelial cell count}}$=0.025	$\beta_{\text{steep K}}$=-0.776, $\beta_{\text{flat K}}$=0.673, $\beta_{\text{endothelial cell count}}$=-0.296
path1	17.613 + 0.304 x carbohydrates	7.4	$p_{\text{carbohydrates}}$=0.049	$\beta_{\text{carbohydrates}}$=0.272
path2	31.792 + 0.467 x carbohydrates – 0.029 x CCT	17.5	$p_{\text{carbohydrates}}$=0.010, p_{CCT}=0.032	$\beta_{\text{carbohydrates}}$=0.346, β_{CCT}=-0.286

Continued

Values from upper 50% of peak				
p1area	3168.023 – 518.191 x dietary pattern	10	$p_{dietary\ pattern}$=0.021	$\beta_{dietary\ pattern}$=-0.317
p2area	2657.113 – 335.692 x dietary pattern	8.2	$p_{dietary\ pattern}$=0.037	$\beta_{dietary\ pattern}$=-0.287
h1	–	–	–	–
h2				
w1	–	–	–	–
w2	–	–	–	–
aspect1	29.1666 + 1.488 x meat – 0.0985 x age	14.8	p_{meat}=0.033, p_{age}=0.044	β_{meat}=0.287, β_{age}=-0.270
aspect2	16.539 – 0.695 x carbohydrates + 10.275 x steep e	16.6	$p_{carboydrates}$=0.027, $p_{steep\ e}$=0.036	$\beta_{carboydrates}$=0.295, $\beta_{steep\ e}$=0.278
uslope1	–	–	–	–
uslope2	–	–	–	–
dslope1	–	–	–	–
dslope2	23.326 + 1.171 x carbohydrates + 18.345 x steep e	14.9	$p_{carboydrates}$=0.042, $p_{steep\ e}$=0.042	$\beta_{carboydrates}$=0.272, $\beta_{steep\ e}$=0.272
path1	20.558 + 1.198 x Vitamin E + 3.091 x dietary pattern	18.5	$p_{Vitamin\ E}$=0.018, $p_{dietary\ pattern}$=0.031	$\beta_{Vitamin\ E}$=0.018, $\beta_{dietary\ pattern}$=0.031
path2	23.145 + 0.684 x carbohydrates	9.6	$p_{carboydrates}$=0.024	$\beta_{carboydrates}$=0.310
aspect2	16.539 – 0.695 x carbohydrates + 10.275 x steep e	16.6	$p_{carboydrates}$=0.027, $p_{steep\ e}$=0.036	$\beta_{carboydrates}$=0.295, $\beta_{steep\ e}$=0.278
uslope1	–	–	–	–
uslope2	–	–	–	–
dslope1	–	–	–	–
dslope2	23.326 + 1.171 x carbohydrates + 18.345 x steep e	14.9	$p_{carboydrates}$=0.042, $p_{steep\ e}$=0.042	$\beta_{carboydrates}$=0.272, $\beta_{steep\ e}$=0.272
path1	20.558 + 1.198 x Vitamin E + 3.091 x dietary pattern	18.5	$p_{Vitamin\ E}$=0.018, $p_{dietary\ pattern}$=0.031	$\beta_{Vitamin\ E}$=0.018, $\beta_{dietary\ pattern}$=0.031
path2	23.145 + 0.684 x carbohydrates	9.6	$p_{carboydrates}$=0.024	$\beta_{carboydrates}$=0.310
aspect2	16.539 – 0.695 x carbohydrates + 10.275 x steep e	16.6	$p_{carboydrates}$=0.027, $p_{steep\ e}$=0.036	$\beta_{carboydrates}$=0.295, $\beta_{steep\ e}$=0.278
uslope1	–	–	–	–
uslope2	–	–	–	–
dslope1	–	–	–	–
dslope2	23.326 + 1.171 x carbohydrates + 18.345 x steep e	14.9	$p_{carboydrates}$=0.042, $p_{steep\ e}$=0.042	$\beta_{carboydrates}$=0.272, $\beta_{steep\ e}$=0.272
path1	20.558 + 1.198 x Vitamin E + 3.091 x dietary pattern	18.5	$p_{Vitamin\ E}$=0.018, $p_{dietary\ pattern}$=0.031	$\beta_{Vitamin\ E}$=0.018, $\beta_{dietary\ pattern}$=0.031
path2	23.145 + 0.684 x carbohydrates	9.6	$p_{carboydrates}$=0.024	$\beta_{carboydrates}$=0.310

Table 6.6 Summary of multivariate regression analysis for ORA parameters.

Parameter	Equation	Variance explained (R^2 x 100%)	p values	Standardised β
IOP (mmHg)	–	–	–	–
Def. Amp.(mm)	1.177 – 0.205 x steep e - 0.001 x CCT	40.8	$p_{steep\ e}$=0.031, $p_{CCT=}$0.034	$\beta_{steep\ e}$=0.429, β_{CCT}=-0.419
A1 time (ms)	7.914 – 0.861 x steep e	19.2	$p_{steep\ e}$=0.047	$\beta_{steep\ e}$=-0.439
A1 length (mm)	1.747 + 0.019 x MSE + 0.001 x age	48.6	p_{MSE}=0.002, p_{age}=0.040	β_{MSE}=0.0.627, β_{age}=0.0.367
A1 velocity (m/s)	–	–	–	–
A2 time (ms)	22.792 – 0.276 x ethnicity	20.4	$p_{ethnicity}$=0.040	$\beta_{ethnicity}$=0.367
A2 length (mm)	-1.979 + 0.319 x ethnicity + 0.078 x carbohydrates +0.346 x flat K	54.1	$p_{ethnicity}$=0.001, $p_{carbohydrates}$=0.012, $p_{flat\ K}$=0.048	$\beta_{ethnicity}$=0.721, $\beta_{carbohydrates}$=0.469, $\beta_{flat\ K}$=0.374
A2 velocity (m/s)	–	–	–	–
HC time (ms)	17.532 – 2.850 x endothelial cell count	19.6	$p_{endothelial\ cell\ count}$=0.045	$\beta_{endothelial\ cell\ count}$=-0.442
Peak Dist. (mm)	5.420 – 3.474 x flat e	22.8	$p_{flat\ e}$=0.029	$\beta_{flat\ e}$=-0.447
Radius (mm)	6.531 + 0.458 x ethnicity	22.9	$p_{ethnicity}$=0.028	$\beta_{ethnicity}$=0.478
A1 Def. Amp. (mm)	–	–	–	–
HC Def. Amp. (mm)	1.177 + 0.205 x steep e – 0.001 x CCT	40.8	$p_{steep\ e}$=0.031, $p_{CCT=}$0.034	$\beta_{steep\ e}$=0.429, β_{CCT}=-0.419
A2 Def. Amp. (mm)	0.400 + 0.017 x Vitamin E + 0.015 x MSE	48.8	$p_{Vitamin\ E}$=0.004, $p_{MSE=}$0.015	$\beta_{Vitamin\ E}$=0.564, β_{CCT}=-0.455

Table 6.7 Summary of multivariate regression analysis for Corvis ST parameters.

6.5 Discussion

6.5.1 Introduction

Ocular Response Analyser and Corvis ST have been a helpful tool for dynamic monitoring of corneal biomechanical response from their inception. The ORA specific parameters, corneal hysteresis (CH) and corneal resistance factor (CRF), similarly to Corvis ST parameters, have broadened the clinical knowledge of glaucoma management (Martinez-De-La-Casa *et al.* 2006; Salvetat *et al.* 2015), and keratoconus progression (Shah *et al.* 2007; Wolffsohn *et al.* 2012; Ali *et al.* 2014). Despite this, few studies have investigated the full range of metrics that can be extracted by the ORA in relation to various lifestyle, ocular globe, and disease-related factors (Kerautret *et al.* 2008; Mikielewicz *et al.* 2011; Wolffsohn *et al.* 2012) or Corvis ST parameters in relation of any other aspect than ocular condition (Ali *et al.* 2014; Wang *et al.* 2015) or repeatability (Bak-Nielsen *et al.* 2015).

In a recent case report, Kerautret *et al.* (2008) discussed the possible interpretation of the ORA applanation peak and how it may relate to the corneal biomechanical response; CH and CRF should not be the only ORA-derived parameters considered. They found that normal and ectatic corneas could provide the same CRF and CH values, however, a closer examination of applanation peak and signal morphology showed variations in corneal biomechanical behaviour. Likewise Bak-Nielsen *et al.* (2015) provided an interesting insight on several Corvis ST parameters related to the highest concavity and its relation to age. Therefore, deeper knowledge of the corneal biomechanical response would be invaluable when dealing with clinical situations where the biomechanical aspects of an eye are important, as it could enable the prediction of a successful treatment outcome or course of a disease. This study investigated the relationship between age, ethnicity, diet, eye and body size, and 41 metrics extracted from the ORA and Corvis ST parameters in healthy individuals.

6.5.2 Ocular Response Analyser

From all factors listed above, age is the most extensively studied in relationship to the corneal biomechanical properties *in-vivo* (Kotecha *et al.* 2006; Kamiya *et al.* 2009; Kotecha *et al.* 2014; Bak-Nielsen *et al.* 2015). The ORA parameter CH is thought to represent the viscoelastic nature of the corneal tissue, and, similarly to CRF, has been found to negatively correlate with age (Kotecha *et al.* 2006; Kotecha *et al.* 2014). These findings appear to support ex-vivo experimental observations of the changes in collagen fibril spacing and behaviour with the increasing age (Malik *et al.* 1992; Whitford *et al.* 2015) resulting in, stiffening of the cornea. However, the assumption that CRF supposedly represents the overall resistance of the cornea needs to be viewed cautiously. CRF has a tendency to reduce with age and, therefore, it could misleadingly suggest that the cornea becomes less resistant. Hence, it should be assumed that CRF may also, to some extent, account for the elastic properties of the cornea. The metrics derived from the air applanation curve could further strengthen this assumption, as they describe the cornea's ability to deform or regain its initial shape after the displacement by the air jet. Variations in these parameters could further account for the age-related structural changes reported previously (Malik *et al.* 1992; Whitford *et al.* 2015), and may represent the corneal stroma-driven stress-strain relationship (Hjortdal 1996; Thomasy *et al.* 2014; Whitford *et al.* 2015). Whilst no significant relationship appears between CH, CRF or any other ORA derived parameter and age was observed in this study, similarly to the results reported by Bak-Nielsen and colleagues (2015), it appears that the cornea does not undergo age-related structural changes.

It is unlikely that the ORA or Corvis ST is unable to detect the age-related changes reported previously (Kotecha *et al.* 2006; Valbon *et al.* 2013; Kotecha *et al.* 2014; Bak-Nielsen *et al.* 2015), or that there would be a need to question the ability of the instrumentation to measure the true biomechanical response *in-vivo* (Lau and Pye 2011). However, in context of the current study, a larger cohort of adult participants with a wider

age distribution would be required to establish the relationship between age and corneal biomechanical response. CH and CRF have been reported to decrease slightly with every decade of human life (Kotecha *et al.* 2006; Foster *et al.* 2011), however the vast majority of the participants in this study were at the end of their second decade (18%) or in their third decade of life (33%), whilst only 9% of the participants represented sixth and seventh decade of human life span. Therefore, the results of the current study could not be considered to be truly representative of a wide age cohort.

In a recent study, Kotecha and colleagues (2014) discussed the relationship observed between CH, CRF, age, central corneal thickness and AL. They highlighted that these factors do not fully explain the variations observed in CH and CRF, and that the corneal biomechanical response is more complex, with additional contributors involved. The authors suggested that CH and CRF should be looked at along with additional ORA parameters. The current study alongside age, investigated the influence of CCT and the effects of the eye size (measured as AL). CCT was not associated to CH or CRF in the current study, whilst Kotecha *et al.* (2014) reported a strong positive correlation between CH, CRF and CCT (partial least squares regression, scaled coefficients CCT_{CH} 0.62, $p<0.001$; CCT_{CRF} 0.62, $p < 0.0001$). Kotecha *et al.* (2014), used an ultrasound pachymeter (Altair, Optikron 2000, Roma, Italy) to measure CCT, whilst non-contact measurement was obtained in the present study using an ocular biometry and topography system, the Aladdin (Topcon, Tokyo, Japan). The Aladdin employs a similar measurement technique to the Lenstar 900 (Haag Streit AG, Koeniz, Switzerland), which has shown a good agreement with ultrasound pachymetry (Borrego-Sanz *et al.* 2014). Previous studies, using ultrasound pachymetry to determinate CCT have reported weak to moderate associations between CH, CRF and CCT in a population with a similar age range (Medeiros and Weinreb 2006; Touboul *et al.* 2008). Therefore, it is likely that other factors (e.g., selection of the data analysis method) rather than instrumentation or patient age affected the significance of associations between ORA variables and CCT. Only one

of the additional ORA specific parameter alpfh which describes the smoothness of the peak, was negatively correlated with CCT.

Contrasting to the negative association between CRF and AL reported by Kotecha and colleagues (2014), no significant relationship between CRF, CH and AL was found. Other studies, similarly to current results, have also not found a significant relationship between CH (Lim *et al.* 2008; Xu *et al.* 2011) or CRF (Narayanaswamy *et al.* 2011; Xu *et al.* 2011) and AL.

Interestingly, Kotecha and colleagues (2014) suggested that ethnicity may account for the discrepancy between the study results. Their study reported the association between corneal biomechanical properties and AL in a Caucasian cohort, whereas most of the results reported previously were obtained from Asia (Lim *et al.* 2008; Shen, Fan*, et al.* 2008; Chang *et al.* 2010; Narayanaswamy *et al.* 2011). However, that hypothesis is not supported by the results from this study.

A relationship was observed between AL and dive1, aspect1 from upper 75% of the peak (metrics that describe the corneal response to the air jet deformation during the initial applanation event), and mslew2, aspect2 from the upper 75% of the peak, h2 and uslope2 of the upper 50% of the peak, (metrics that describe the cornea's ability to regain its initial shape after the air-pressure deformation) as shown in Table 6.4 (a graphical representation of the curve are presented in Figure 2.3, page 95). Given an increase in peak height (h2), along the ratio of peak width/height (aspect1 and aspect2), and the changes in upward slope (uslope2) which mostly affected the second rebound peak, appears to suggest that the signal morphology – and therefore – corneal deformation is influenced by eye length. However, when multivariate stepwise modelling was applied, AL did not account for the variance observed.

The associations between additional ORA parameters and AL have not been reported previously. Despite this, a decrease in CH along with increasing AL has been reported

previously (Narayanaswamy *et al.* 2011; Bueno-Gimeno *et al.* 2014). It has been suggested that this may be an indicator of structural changes of the anterior eye in myopia (Shen, Fan*, et al.* 2008). Another study has reported the same relationship between CRF and AL (Chang *et al.* 2010), which also would support Shen *et al.*'s hypothesis of structural alterations of the anterior eye occurring in myopia (Shen, Fan*, et al.* 2008). The statistically significant positive associations between the additional ORA parameters and AL observed in the current study could support this hypothesis, however further investigation is required to provide evidence for a relationship beyond 'random' association.

Corneal curvature was not found to correlate with the any of the main four ORA parameters (CH, CRF, IOPg and IOPcc), but was found to have a moderate relationship with the additional ORA metrics, p1area and p2area from the upper 75% and 50% of the peak. Studies conducted previously have reported no relationship between corneal curvature and CH or CRF (Kamiya *et al.* 2008; Xu *et al.* 2011), and found it to be a non-significant predictor in multiple regression analysis (Xu *et al.* 2011). The significance of the additional parameters, in relation to the corneal curvature could further support the changes of the structural alterations of the anterior eye, as proposed by Shen *et al.* (2008). Nevertheless, further studies are required and a careful interpretation of the associations between AL, corneal curvature and the additional ORA generated parameters – which appears to be positive in the present study – needs to be conducted.

As discussed previously, the relationship between corneal biomechanical properties and ethnicity have not been investigated widely. One study investigating CH and CRF in a bi-racial cohort of healthy and glaucomatous individuals has reported significant differences in corneal biomechanical properties amongst African and Caucasian cohorts (Detry-Morel *et al.* 2012), however no such association between ethnicity and CH, CRF (or any other biomechanical metric) was found in this study, although the study population was primarily composed of individuals of Caucasian and British Asian origin.

Group specific differences in ocular globe dimensions and components between ethnic groups have been noted previously (Shimmyo *et al.* 2003; Dai and Gunderson 2006; Twelker *et al.* 2009). For example, central corneal thickness (CCT) – which has been found to strongly correlate with CH and CRF (Kotecha *et al.* 2006; Shah *et al.* 2006; Kotecha *et al.* 2014) – has been associated with ethnicity in both a paediatric population of Afro-Americans and Caucasians (Dai and Gunderson 2006), and in a healthy adult population of the same ethnical background (Shimmyo *et al.* 2003). However, there were no differences observed between individuals of Asian, Caucasian, or Hispanic origin (Shimmyo *et al.* 2003). Considering the positive correlation between CH, CRF, and CCT, corneal biomechanical properties could inherit a similar relationship to ethnicity. Therefore, further research amongst various ethical groups would be required to test this assumption.

Lifestyle influences have been of interest to epidemiological researchers in recent years, and have been associated with ocular health (Appel *et al.* 2003; Pasquale and Kang 2009), however this is the first study to date to investigate the possible association of lifestyle (specifically food intake and body mass index (BMI)), with corneal biomechanical properties. Specific dietary components, such as Vitamin E, have been shown to have a protective effect on corneal and conjunctival health at a cellular level in a rat model (Fujikawa *et al.* 2003), and therefore, could be expected to affect corneal biomechanics. Whilst nutrition and increased intake of specific dietary components have been linked to conditions such as age-related macular degeneration (Chiu *et al.* 2014), glaucoma (Coleman *et al.* 2008), and cataracts (Hosseini *et al.* 2008), it has not yet been associated to corneal health directly. No significant relationship has previously been found between dietary patterns (Chiu, Chang *et al.*, 2014), or individual foods or dietary components (e.g., Vitamin E). Nevertheless, a higher intake of meat and fish (and also adherence to a food pattern such as British Western), were found to account for some of the variance observed in corneal biomechanical response, and to correlate negatively with the

additional ORA derived metrics (Table 6.4). This is in agreement with previous work, which linked higher meat intake to an increased risk of cataracts (Appleby, Allen *et al.*, 2011). In the context of the negative associations found in this study, higher meat intake could reflect the structural changes at the tissue level, since p2area describes the area under the curve (AUC), whereas h2 describes the height of the curve in time and hence the cornea's ability to regain its initial shape after the air-jet induced deformation.

BMI or body size was found to be negatively correlated with the corneal biomechanical properties. BMI was one of the three predictors (alongside steep K and adherence to British Western dietary pattern) that mostly accounted for some variance within the metrics derived from the ORA. Alongside higher meat intake, BMI accounted for variations in aspect1 and uslope1 derived from the upper 50% of the initial applanation curve. From a structural and anatomical aspect, a higher BMI has been linked with a thicker retina (Wong *et al.* 2005) and the development of conditions such as cataract, glaucoma and diabetic retinopathy (Cheung and Wong 2007). The negative associations in the current study suggests that after the first applanation has taken place, the height and weight of the peak is affected by the BMI, presumably indicating that cornea is more easily deformed as the BMI increases.

6.5.3 Corvis ST

Corvis ST is a relatively new instrument to the optical industry and information regarding its association to various ocular parameters is still sparse (Hon and Lam 2013; Asaoka *et al.* 2015). In a study conducted by Bak-Nielsen *et al.* (2015), age was found to be associated with highest concavity (HC) and parameters derived from this event. Participants were divided into two groups: young (average age 25.4 years, range: 22 to 30 years) and old (average age 75.8 years, range: 66 to 86 years). Older participants had a longer HC, deformation amplitude, HC deflection length (defined as horizontal length of the deformed cornea) and HC deflection amplitude (deformation amplitude corrected for the whole eye movement). In a different study, age was found to be a

significant predictor for first and second applanation time (A1 time and A2 time), length (A2 length) and velocity (A2 velocity). In addition, maximum deformation amplitude increased with increasing age (Asaoka *et al.* 2015). However, no association between age and any of the Corvis ST generated parameters was found in the present study. This may be due to the age distribution between participants, the relatively small sample size and the different software versions employed in each study.

Asaoka *et al.* (2015) also reported AL to be a significant predictor for the same output measures as for subject age. AL was found to be positively related to A1 time and maximum deformation amplitude. A1 velocity, A2 time and peak distance exhibited a negative relationship with AL (Asaoka *et al.* 2015). In the present study, A1 time and length were positively correlated to AL, whilst A1 and A2 velocity was negatively correlated. This might suggest that longer eyes are more resistant during the initial applanation (resulting in longer A1 time), but once the applanation event has commenced, they are deformed more easily and recover quicker than shorter eyes (supported by the moderate inverse relationship between A1 and A2 velocity and AL). Despite this, AL was not found to be a significant predictor in the multiple regression model.

The relationship between corneal curvature and corneal biomechanical parameters was also studied by Asaoka *et al.* (2015). The authors reported that the average corneal curvature was a significant predictor for the same Corvis ST specific parameters as for AL. The relationship, except for A1 time, was positive. The associations observed on the current study were significant for A1 length, A1 velocity and HC deformation amplitude. Corneal curvature was one of the most frequent parameters that accounted for some of the variance.

No comparisons between different ethnicities have been made to date with the Corvis ST. In the present study, the velocity of the second applanation (A2 velocity) was

significantly slower among participants of Caucasian background than those of British Asian background, indicating that require more time to regain their initial shape following deformation.

CCT has been found to influence the velocity and length of the second applanation (A2 length and velocity), and the curvature of HC (Asaoka *et al.* 2015), suggesting that thicker corneas are more resistant to deformation. The results of this study did not find a correlation between any of the Corvis ST generated parameters, except for negative moderate associations of HC deformation amplitude. This could further support the hypothesis of thicker corneas' ability to resist the deformation more than thinner ones.

BMI and daily food consumption has not yet been studied in relation to Corvis ST parameters. The associations between BMI and any of the Corvis ST generated metrics, in contrast to the ORA parameters, were non-significant. Daily food consumption of meat, fish, carbohydrates, dairy products and Vitamin E had a positive effect on the first and second applanation events. Similar assumptions as in the case of the results obtained from the ORA could be made (please refer to section 6.5.2).

6.5.4 Study limitations

Although the inclusioun criteria for the study were not strict, current study had some limitations. The study was conducted on university campus, therefore, not all age groups were represented equally and participant recruitment of 55 years and older was difficult. The restricted patient pool together with the ethnical dominance of individuals of British Asian background influenced the diet component of the study and is not a representative of the population in general.

Also, due to difficulties with instrumentation, Corvis ST data for all individuals could not be retrieved. Each of the instruments employed in the study for the investigation of corneal biomechanical parameters had more than ten paramaters to investigate in associaciation to the selected factors, therefore, other aspects that could potentially have

an influence to corneal tissue, such as smoking, UV exposure, blod type and others, could not studied and further research in this area is warranted.

6.5.5 Conclusion

The present study does not support an association between the ORA specific parameters of CH, CRF and age, ethnicity, daily food consumption or eye and BMI. The investigation of the additional ORA-derived parameters does, however, provide an interesting insight into their relationship with daily food consumption, ocular biometry and eye and body size. The proportion of the variation in the additional ORA parameters could not be explained by the ocular and demographic characteristics alone. Daily food consumption accounted for some of the variations observed, therefore suggesting that there are other factors contributing to the corneal biomechanical response. Analysis of the Corvis ST generated parameters provided further evidence of the influence of different factors on corneal biomechanics. Further work is required to investigate the additional parameters of the ORA and Corvis ST generated metrics in healthy individuals (and their relation to ocular and lifestyle effects) to enhance the understanding of corneal biomechanical response and aid with a prediction of treatment outcome in diferent clinical applications like ortho-k and MC.

Chapter 7. Conclusion and future work

7.1 General conclusions

The work presented in this thesis investigates the management of myopia in a clinical setting; aims to ameliorate the application of orthokeratology (ortho-k) by studying the corneal biomechanical response to the ortho-k lens wear and also looking at the various factors that may affect corneal tissue and, therefore, contribute towards a more predictable treatment outcome.

The review of the literature (Chapter 1) identified the current challenges in the field of myopia control (MC) and the clinical application of ortho-k. Myopia is not a simple inconvenience but rather a major public health problem that is a cause of blindness and visual impairment worldwide (Flitcroft 2012; Pan *et al.* 2012; Holden *et al.* 2014). The multifaceted nature of this condition complicates the management of myopia. Genetics, behaviour and the environment have been identified as the causative and inherited factors of myopia (Wojciechowski 2011; Flitcroft 2012; Goldschmidt and Jacobsen 2014). The optical and pharmaceutical interventions tailored to target the factors contributing towards myopia development are able to limit myopia progression to a certain level (Sankaridurg and Holden 2014). However, the clinical versus statistical significance has been questioned (Fulk *et al.* 2000; Johnson 2014).

Only recently has the long term benefit of the application of MC interventions been elegantly demonstrated using evidence based models (Sankaridurg and Holden 2014), thus emphasising the lifelong and progressing nature of myopia and the need of adequate management strategy of this condition. Myopia usually manifests in childhood and progresses through early adolescence. At present, it is not possible to prevent myopia from developing, however it is possible to limit its progrssion and subsequently reduce the risk of associated pathologies (Flitcroft 2012). Research studies addressing the clinical application of the MC modalities would be beneficial to aid with raising

awareness of myopia and the complications and risks associated with it, as well as the importance of limiting the progression of myopia (Holden *et al.* 2016).

Ortho-k, which is one of the most promising MC interventions (Sankaridurg and Holden 2014), is not a new approach for myopia correction; however, reluctance to employ this modality has been observed mostly owing to the selective treatment outcome. Over recent years the approach of using the corneal topographer as the main assessment and fitting tool in addition to the adoptation reverse geometry lens as the treatment tool has enhanced the treatment outcome (Swarbrick 2004; Swarbrick 2006; Si *et al.* 2015; Sun *et al.* 2015). Nevertheless, some factors such as the role of corneal tissue mechanical properties are still widely unaccounted for. The advent of *in-vivo* corneal biomechanical assessment (described in detail in Section Chapter 2) has opened new avenues for the study of the anterior segment of the eye, not only in the context of ortho-k, but also of other clinical applications. By better understanding the role of corneal mechanical behaviour in ortho-k lens wear it may be possible to improve the treatment outcome and optimise the application of ortho-k for MC.

7.1.1 Current trends of myopia management strategies in clinical practice

The results of the global myopia survey (Chapter 3), which investigated the attitudes of the eye-care professionals towards MC, revealed that there is a preceived lack of information available to practitioners; although they are aware of the recent scientific findings in the field, the research outcomes do not translate well into the clinical setting. The questionnaire was designed to cover aspects of the perceived efficacy of various MC modalities by the clinicians, the frequency of prescribing particular interventions in the everyday clinical setting, the patient's age and degree of myopia required for practitioner to consider each of the correction options and the limiting factors of prescribing various interventions. Two thirds (68%) of the 964 surveyed eye-care practitioners, regardless of the geographical location, chose to prescribe single vision glasses rather than evidence-based more effective modalities for MC, identifying the lack

of clear guidelines (33.3% of 964 practitioners) and unpredictability and safety (~25%) of the treatment outcome, achieved by the MC modalities as their main inhibiting factors. Interestingly, patient's age, annual progression rate and the degree of myopia were not the pre-dominant factors in the decision making for the most appropriate MC intervention. Age is identified as a good predictor for myopia development (Thorn *et al.* 2005; Zadnik *et al.* 2015). The regional differences in the response to some extent mirrored the activity of MC research in the given area. For example, practitioners in Hong Kong and China considered themselves more active in the field of MC (9/10 vs all the other regions~7/10; median) and prescribed ortho-k more frequently than their colleges across the globe.

To date, this is the only self-reported survey, exploring the attitudes of the eye-care professionals on a global scale, therefore no comparison can be made. Nevertheless, these findings support the concerns expressed previously in the research community regarding the underrated status of myopia within the clinical setting (Choo *et al.* 2008; Holden *et al.* 2014; Johnson 2014; Sankaridurg and Holden 2014; Gifford and Gifford 2016; Holden *et al.* 2016). Results suggest, that a clear internationally acknowledged guidelines and safety regulations should be issued by the expertise in the field. Also, educational materials should be provided to clinicians, patients and if appropriate, patients' parents. Clinical research studies that would address and evaluate issues identified in this survey and similar studies conducted in the future would be beneficial and could aid toward establishment of MC guidelines.

7.1.2 Long term corneal biomechanical response to orthokeratology and the role of anterior eye segment in myopic schoolchildren

The work presented in Chapter 4, in which a retrospective data analysis of myopic schoolchildren undergoing ortho-k treatment for a period of 2 years using the ORA to monitor corneal biomechanical response, was carried out, provided interesting findings of the corneal tissue response and metrics of the anterior segment of the eye. Also, it

indirectly addressed some of the problematic points identified by the eye-care practitioners in the global myopia survey in Chapter 3.

This is the first study to investigate corneal biomechanical response in progressing myopic schoolchildren. Data from 83 ortho-k wearing children and 81 single vision spectacle (SVS) wearing children, who attended 5 study visits with a 6-month (M) interval (BL, 6 M, 12 M, 18 M and 24 M), were analysed. SVS wearing children, who were age matched, acted as controls for an observation of the natural progressing myopia.

The results compare favourably with the studies conducted previously, on which the Hong Kong reseach group are expanding (Cho and Cheung 2012; Charm and Cho 2013; Chen *et al.* 2013) regarding the efficacy of ortho-k's ability to limit myopia progression by ~40%, slowing down AL and AC growth. These findings were also in agreement with the eye-care practitioners'' subjective assessment of the efficacy of ortho-k of 45% (Chapter 3, Section 3.4.3).

The corneal topographical changes likewise support the previous work both in ortho-k wearing children (Cho, Pauline *et al.* 2005; Santodomingo-Rubido *et al.* 2012) and single vision spectacles wearing control group (Jorge *et al.* 2007; Santodomingo-Rubido *et al.* 2012). The topography changes occur during the first six months of lens wear, stabilising thereafter. Fluctuations within topographical parameters in individuals with a natural myopia progression are to be expected and presumably describe a typical gait of myopia development.

The changes in central corneal thickness (CCT) followed a similar pattern to the topographical changes seen within the ortho-k group, further supporting the hypothesis that the first six months may be the critical period for this technique for the treatment effect to take place. Swarbrick and colleagues (2015) however stated that a period of six months is insufficient to achieve a stabilisation of a progressive myopia, therefore a

period of 18 months or more could be beneficial for the treatment effect of MC to be achieved.

Reduction in myopia, changes in CCT and corneal morphology do not occur simultaneously (Swarbrick *et al.* 1998; Zhong *et al.* 2015; Cheung and Cho 2016). Analysis of the ORA data revealed that CH (descriptor of viscous damping properties) was not affected by the ortho-k lens, however this parameter fluctuated significantly in the SVS group. CRF (characteristic of the overall resistance of the cornea) did not undergo significant changes in any of the study groups. These findings favourably support previous work of Mao *et al.* (2010) who observed initial changes in CH and CRF over the first week of the lens wear, which then return to BL within 3 to 6 months. These changes could reflect the classical descriptors (YM, creep and stress relaxation); however, they cannot be assessed in the *in-vivo* environment with the current instrumentation and only a hypothesis or premise can be made.

The detailed analysis of the applanation curve demonstrated that significant changes in both groups were limited to the initial applanation peak. The critical period for the corneal biomechanical changes were the first 18 months of the ortho-k lens wear, stabilising thereafter. Several parameters (slew1, mslew1, h1 from the upper 50% and 75% of the initial appanation peak; for full list of the parameters please refer to Chapter 4, Section 4.4.2, page 163) were affected, but the response in SVS group was more varied. As this is the first study of a kind investigating the ORA applanation peak in detail both in ortho-k wearing children and SVS wearing children, no direct comparison can be made. Moreover, all of the biomechanical parameters are ORA-specific (Dupps 2007) and do not necessarily translate well into a clinical setting. Premises that can be drawn from these results are: the stabilising effect of the ortho-k lens wear in progressing myopia; both optical and mechanical factors contribute towards limiting myopia progression in ortho-k; the ORA-derived parameters reflect mechanical effects of the reverse geometry lens imposed on the corneal tissue; and the ORA could potentially be used as a tool for

monitoring the anterior segment of the eye in naturally progressing myopia. Nevertheless, a further work that would expand these observations, such as longitudianal studies of myopia development and the role of corneal biomechanical parameters, is required.

7.1.3 Short-term corneal biomechanical changes in orthokeratology

The work presented in Chapter 5 explores the critical period of ortho-k lens wear during the first 7 nights of treatment (Swarbrick *et al.* 1998; Nichols *et al.* 2000; Mao *et al.* 2010). Twenty one healthy individuals wore ortho-k lenses for a period of a 7 nights and attended a daily study visit after each night of lens wear.

The refractive changes, changes in corneal curvature and in CCT were in agreement with the research conducted previously (Swarbrick *et al.* 1998; Nichols *et al.* 2000; Alharbi and Swarbrick 2003; Soni *et al.* 2003; Sorbara *et al.* 2005; Yoon and Swarbrick 2013). Sixty per cent of the initial myopic refractive error was corrected over the first night of the lens wear. The thinning of CCT reached significance by the seventh night of lens wear. No anti-myopic changes in AL, ACD and LT were seen over the study period, comfirming that the mechanisms underlying ortho-k are corneal in nature. Also, these findings suggest that a longer period (months to years) of ortho-k lens wear is necessary if this technique is applied as a MC intervention, which is in agreement with the work presented in the Chapter 4.

A detailed analysis of the ORA-derived metrics did not support the previous work in regard to CH and CRF (Chen *et al.* 2009; Mao *et al.* 2010). Yeah *et al.* (2013) reported significant changes in CH and CRF only after 30 night of lens wear. The CH and CRF remained stable during the study period in this experiment. The ability of CH and CRF have enough discriminative power to detect changes has been questioned before (Kerautret *et al.* 2008; Saad *et al.* 2010; Mikielewicz *et al.* 2011).

Other ORA-derived parameters did undergo significant changes over the study period and were limited to the initial applanation peak. In contrast to CCT changes, most of the changes in corneal biomechanical parameters occurred over the first 4 nights of the lens wear. The height of the initial applanation peak (h1) was reduced. The same observation was made in the results presented in Chapter 4. Height (h1) along other parameters affected by the ortho-k leans wear suggests that corneas undergoing ortho-k treatment are more easily deformed by the air puff (Chapter 5, Section 5.4.2.1, page 200). However, ORA-derived parameters (aindex, bindex and aplhf; characteristics of the smoothest of the curve) did not change over the course of the study, hence it can be speculated that short term ortho-k does not affect the corneal tissue at microscopic level.

Although differences in the corneal movement in response to the air puff were seen in the video output of Corvis ST, only two parameters being applanation length 1 and applanation length 2 were affected by the ortho-k lens wear. Both of these parameters are direct measures of the flattened area of the air puff, therefore, most likely reflect the formation of treatment zones, imposed by the reverse geometry lens.

These results support the groundwork conducted to date and provide a further evidence for the corneal involvement in the treatment response.

7.1.4 Factors influencing corneal biomechanics

Differences in the ocular globe dimensions due to age and body height have been reported previously (Wong *et al.* 2005; Ahmadi *et al.* 2007). For example, taller individuals are more likely to have longer eyes, deeper ACs, thinner crystalline lenses and flatter corneas (Wong *et al.* 2001). These are only a few factors that could affect treatment outcome of different conditions or techniques, but more specifically those involving manipulations of ocular structures such as corneas undergoing refractive surgery or ortho-k treatment. In order to optimise any technique and predict the treatment

outcome, factors that may increase inter-individual variations in treatment outcome must be identified.

A cohort of 158 healthy individuals were recruited to study the influence of age, ethnicity, eye and body size, and nutrition, in relation to corneal biomechanical properties for the study presented in Chapter 6.

The results of the study do not support an association between the ORA specific parameters of CH, CRF and age, ethnicity, daily food consumption or eye size and BMI. The relationship between age, ethnicity and eye size (AL) have been studied before (Kotecha *et al.* 2014) and contradicts the findings of the present study. CH and CRF have been found to negatively associated with age. A negative association between CRF and AL has also been identified (Kotecha *et al.* 2014).

A detailed investigation of the additional ORA-derived parameters does, however, provided an interesting insight into their relationship with daily food consumption, ocular biometry and eye and body size. The additional ORA parameters did not increase the percentage of variance that could be explained by the ocular and demographic characteristics. Daily food consumption accounted for some of the variations observed, therefore suggesting that there still are undetermined other factors contributing to the corneal biomechanical response.

Corvis ST is a relatively novel instrument and only a few studies have addressed the influence of age and AL to its output parameters (Asaoka *et al.* 2015; Bak-Nielsen *et al.* 2015). No association between age or eye size (AL) and any of the Corvis ST specific parameters was found in the present study. The only significant factor that was found to affect corneal biomechanical properties measured by the Corvis ST was dietery components.

Diet, in particular higher intake of meat, fish, carbohydrates, Vitamin E rich foods and dairy products showed a positive correlation between the ORA and Corvis ST

parameters opening new avenues for interesting future research. Further studies could test the hypothesis of nutrition and its effects on corneal tissue strength, which could be beneficial for ocular conditions such as keratoconus.

Although participants with a wide variety of ALs and BMIs were included in the study, the research could have benefited from a wider age range.

7.1.5 Future work and concluding remarks

The collection of studies presented in this thesis explore the clinical application of MC strategies and investigates the corneal biomechanical properties in the eyes undergoing ortho-k treatment, addressing some of the research questions raised previously and concerns expressed within the community of eye-care practitioners (Johnson 2014; Sankaridurg and Holden 2014; Gifford and Gifford 2016).

Premises and conclusions drawn from this thesis suggest that internationally acknowledged guidelines for MC could benefit the eye-care practitioners and subsequently their patients worldwide. Also, the clinical community should be further educated on the topic of myopia and its management. In recent years, the research community have openly spoken about the alarming rates of myopia progression, the earlier onset of this condition and the various ways in which clinicians can approach myopia more effectively (Sankaridurg and Holden 2014; Holden *et al.* 2015; Gifford and Gifford 2016). More clinical and survey based research, which would explore the clinical setting of myopia management, should be conducted. An updated version of the global myopia re-issued within the next few years could provide an insight of the progress in the field of MC.

The work presented here, investigating both short and long-term changes in ortho-k, suggests that further investigation of the role of corneal biomechanical properties is required. Studies closely monitoring the corneal biomechanical response of the patients undergoing ortho-k treatment over the first six months with regular intervals (1 week, 2

weeks, 1, month, 2 months etc.) are required to understand the underlying mechanisms of ortho-k and the mechanical phenomena taking place at each point along the treatment cycle. Furthermore, these studies should be longitudinal in nature to understand the long term corneal biomechanical response to lens wear. Corneal factors are the main contributors to the treatment outcome of ortho-k; however, more factors (e.g. the role of sclera) in relation to corneal biomechanical properties should be investigated.

Also, studies monitoring naturally progressing myopes and individuals wearing the ortho-k modality should be designed. Results in this thesis suggest that the ORA could be a useful tool to for monitoring the course of the anterior segments of eye with myopia progression.

Research presented here attempts to explain the 37 additional parameters derived from the ORA applanation curve and relate them to the clinical setting and classical mechanics. Further studies should be conducted to explore these parameters to incorporate them in a clinical setting. This in return would ameliorate the understanding of the processes underlying numerous ocular conditions and techniques including ortho-k.

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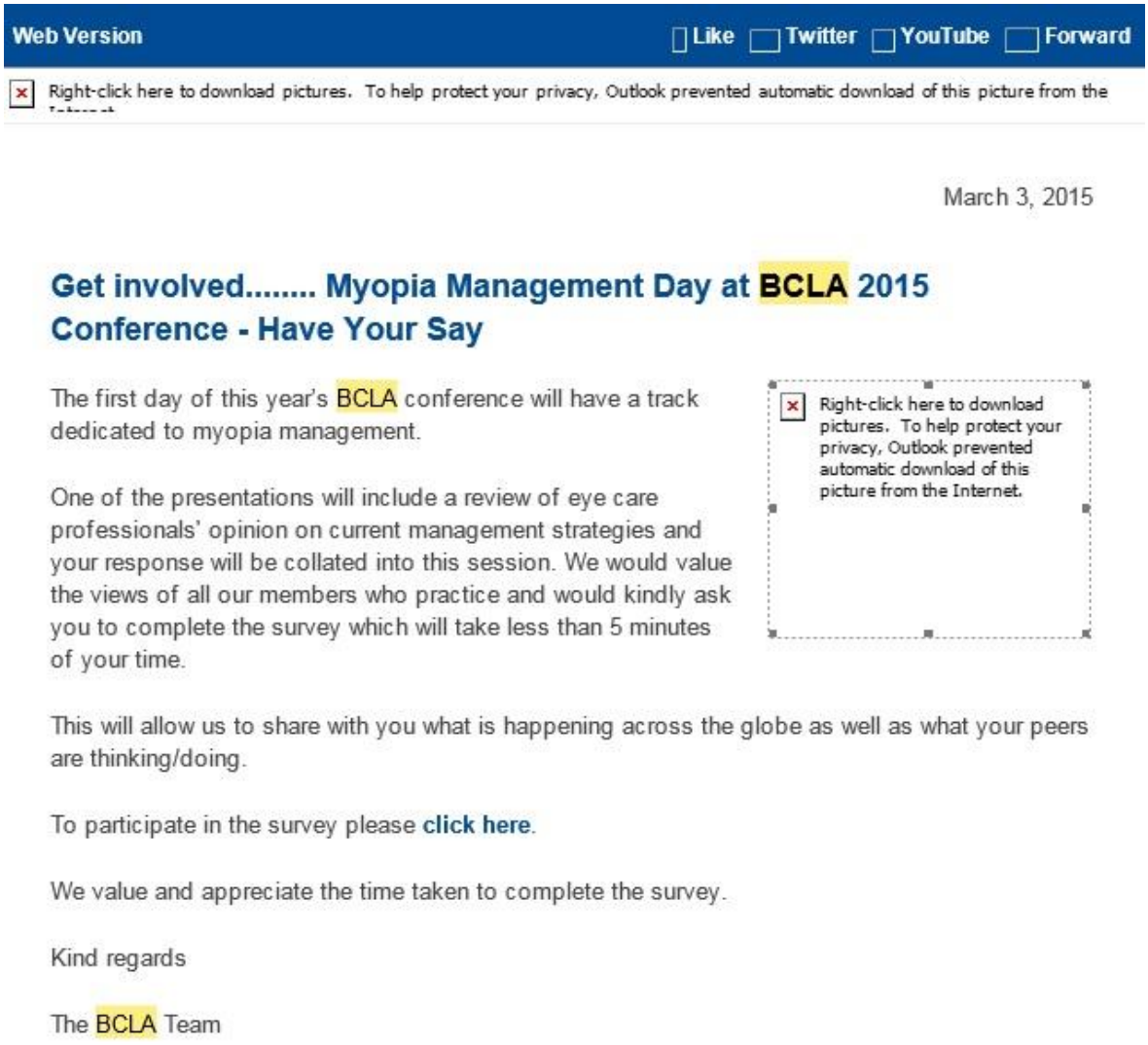
Appendix 1: Current trends of myopia management strategies in clinical practice

1.1 An example of email, inviting eye care professionals to take part in the study



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March 3, 2015

Get involved..... Myopia Management Day at BCLA 2015 Conference - Have Your Say

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The first day of this year's BCLA conference will have a track dedicated to myopia management.

One of the presentations will include a review of eye care professionals' opinion on current management strategies and your response will be collated into this session. We would value the views of all our members who practice and would kindly ask you to complete the survey which will take less than 5 minutes of your time.

This will allow us to share with you what is happening across the globe as well as what your peers are thinking/doing.

To participate in the survey please **click here**.

We value and appreciate the time taken to complete the survey.

Kind regards

The BCLA Team

1.2 Questionnaire

1. How concerned are you about the increasing frequency of paediatric myopia in your practice?

   Not at all

   Extremely

2. From what you have heard/read about the effectiveness of myopia control options to date, what % reduction do you think the following options can achieve (just type in a number without %)?

Undercorrection	
Single vision spectacles	
Bifocal spectacles	
Progressive spectacles	
RGP (alignment fit)	
Single vision soft contact lenses	
Standard multifocal soft contact lenses (even if off-label use)	
Specific myopia control soft contact lenses	
Orthokeratology	
Pharmaceuticals such as atropine	
Refractive Surgery	
Increased time spent outdoors	

3. How active would you consider your clinical practice in the area of myopia control?

   Not at all

   Extremely

Any comments?

4. How many times have you prescribed the following correction options for progressing/young myopes over an average month (please consider the total number of progressing/young myopes and include all in your response)?

Single vision spectacles	
Bifocal spectacles	
Progressive spectacles	
RGPs (alignment fit)	
Single vision soft contact lenses	
Standard multifocal soft contact lenses (even if off-label use)	
Specific myopia control soft contact lenses	
Orthokeratology	
Pharmaceuticals such as atropine	
Refractive surgery	

5. How old (in years) would the patient have to be for you to consider each of the following options (not just for myopia control and assuming average handling skills and child/parent motivation)?

	5	6	7	8	9	10	11	12	13	14	15	16	17	18	Would not prescribe this
Single vision spectacles	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
Bifocal spectacles	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
Progressive spectacles	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
RGPs (alignment fit)	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
Single vision soft contact lenses	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
Standard multifocal soft contact lenses (even if off-label use)	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
Specific myopia control soft contact lenses	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
Orthokeratology	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
Pharmaceuticals such as atropine	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
Refractive surgery	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○

6. What would be the minimum amount of myopia (in dioptres) for you to consider each of the following correction options for a patient?

	-0.50	-1,00	-1,50	-2,00	-2,50	-3,00	-3,50	-4,00	-4,50	-5,00	>-5,00	Would not prescribe this
Single vision spectacles	○	○	○	○	○	○	○	○	○	○	○	○
Bifocal spectacles	○	○	○	○	○	○	○	○	○	○	○	○
Progressive spectacles	○	○	○	○	○	○	○	○	○	○	○	○
RGP (alignment fit)	○	○	○	○	○	○	○	○	○	○	○	○
Single vision soft contact lenses	○	○	○	○	○	○	○	○	○	○	○	○
Standard multifocal soft contact lenses (even if off-label use)	○	○	○	○	○	○	○	○	○	○	○	○
Specific myopia control soft contact lenses	○	○	○	○	○	○	○	○	○	○	○	○
Orthokeratology	○	○	○	○	○	○	○	○	○	○	○	○
Pharmaceuticals such as atropine	○	○	○	○	○	○	○	○	○	○	○	○
Refractive surgery	○	○	○	○	○	○	○	○	○	○	○	○

7. What is the minimum level of myopia progression you consider necessitates a myopia control approach?

- ○ 0.01-0.25D/year
- ○ 0.26-0.50D/year
- ○ 0.51-0.75D/year
- ○ 0.76-1.00D/year
- ○ >1.00D/year
- ○ Myopia control is not warranted

Other (please specify)

8. Do you use undercorrection as a strategy to slow myopia progression?

No	Sometimes	Always
○	○	○

9. If you have only ever fitted single vision spectacles/contact lenses for myopic patients, what has prevented you prescribing an alternative method?

- [ ] I don't think they are any more effective
- [ ] The outcome is not predictable
- [ ] Safety concerns
- [ ] Cost to the patient makes it uneconomic
- [ ] Additional chair time
- [ ] Inadequate information / knowledge
- [ ] Benefit / risk ratio

Other (please specify)

10. Demographics

	Profession	Principal working environment	Years qualified	Geographical location
About you:				

Any further comments on myopia control?

Profession: optometrist, contact lens (dispensing) optician, ophthalmologist, other.

Principal working environment: practice, academic, industry, other.

Years qualified: 0; 1-5; 6-10; 11-20; 20-30; 31≤

1.3 Results

NB: Africa has been excluded from the analysis.

Bold = statistically significant

1. **How concerned are you about the increasing frequency of paediatric myopia in your practice?**

Globally:

Mean ± STDEV	**Median, CI []**
7.28 ± 2.50	**8.00, [8.00 8.00]**

Continents:

Continent	**Mean ± STDEV**	**Median, CI []**
Asia	8.37±1.80	9.00 [8.00, 9.00]
Australasia	6.83±2.71	7.00 [7.00, 8.00]
Europe	7.05 ±2.37	7.00 [7.00, 8.00]
North America	6.43 ±2.63	7.00 [6.00, 7.00]
South America	6.53 ±3.16	7.00 [6.00, 8.96]

Kruskal-Wallis test:

North-America - Asia	p<0.001
South America - Asia	p<0.001
Australasia - Asia	p<0.001
Europe - Asia	p<0.001

Countries:

Country	**Mean ± STDEV**	**Median, CI 95% []**
UK, EIRE	5.84 ± 2.57	6.00 [5.00,7.00]
Netherlands	6.34 ± 2.11	7.00 [Bigger sample needed]
Spain	8.26±2.25	9.00 [Bigger sample needed]
France	7.26 ±2.29	7.00 [Bigger sample needed]
Portugal	8.18 ± 3.22	8.00 [8.00, 9.37]
Italy	6.86 ± 2.47	7.00 [7.00,8.00]
India	7.32±2.64	8.00 [Bigger sample needed}
Hong Kong	7.89 ±1.68	8.00 [7.00, 9.00]
China	8.78 ± 1.53	10.00 [8.71, 10.00]
Canada	5.42 ± 2.65	6.00 [Bigger sample needed]
USA	6.75 ± 2.65	7.00 [7.00.8.00]

Significant differences (Kruskal-Wallis test):

UK, EIRE-Portugal	p<0.001
UK, EIRE-Spain	p<0.001
Netherlands-Portugal	p=0.002
Netherlands-Spain	p=0.001
Italy-Portugal	p=0.046
Italy-Spain	p=0.027
India-China	p=0.002
Hong Kong-China	p=0.001
USA-Canada	p=0.005

2. **From what you have heard/ read about the effectiveness of myopia control options to date, what % reduction do you think the following options can achieve?**

Globally:

	Under-correction	SVS	Bifocals	PALs	RGP (AF)	SV CL	Standard multifocal CL	Specific MC soft CL	Ortho-K	Pharmaceuticals	Refractive surgery	Increased time spent outdoors
Mean ± STDEV	6.07 ± 14.55	10.94 ± 21.95	14.50 ± 18.70	16.23 ± 19.21	15.85 ± 22.74	9.37 ± 19.78	16.77 ± 20.25	24.41 ± 25.07	43.89 ± 30.06	27.93 ± 29.58	14.55 ± 27.89	31.48 ±26.30
Median, CI 95% []	0 [0,0]	0 [0,0]	10 [6,10]	10.00 [10,10]	5.00 [5,8]	0 [0,0]	10.00 [8,10]	20.00 [15,20]	50.00 [50,50]	20.00 [10, 20]	0 [0,0]	25.00 [22.91, 30.00]

Continents:

Continent		Under-correction	SVS	Bifocals	PALs	RGP (AF)	SV CL	Standard multifocal CL	Specific MC soft CL	Ortho-K	Pharma-ceuticals	Refracti-ve surgery	Increas-ed time spent outdoors
Asia	**Mean ± STDEV**	6.53 ± 13.88	16.04 ± 23.56	18.38 ± 21.05	21.26 ± 21.16	23.87 ± 26.92	11.87 ± 20.64	15.51 ± 20.24	24.37 ± 25.96	48.57 ± 29.61	31.73 ± 27.82	17.38 ± 29.69	38.66 ± 27.53
	Median, CI 95% []	0.00 [0,0]	5.00 [1,10]	10.00 [10,15]	20.00 [15,20]	10.00 [10,20]	0.00 [0,4]	5.00 [2, 10]	20.00 [10,25]	50.00 [50,50]	30.00 [20,30]	0.00 [0,0]	40.00 [30.00,48 .44]
Australasia	**Mean ± STDEV**	2.53 ± 7.43	4.21 ± 12.51	14.05 ± 14.81	16.00 ± 14.01	9.61 ± 13.79	4.14 ± 11.52	22.47 ± 19.26	29.14 ± 19.34	47.82 ± 25.32	38.99 ± 32.38	11.36 ± 24.26	29.67 ± 22.01
	Median, CI 95% []	0.00 [0.,0]	0.00 [0,0]	10.00 [10,10]	10.00 [10,15]	2.00 [0,10]	0.00 [0,0]	20.00 [15,20]	30.00 [25,30]	50.00 [50,50]	40.00 [30,60]	0.00 [0,0]	25.00 [20,30]
Europe	**Mean ± STDEV**	6.401 ± 15.76	10.00 ± 21.77	12.94 ± 17.54	14.69 ± 18.64	14.09 ± 20.84	10.10 ± 20.54	16.37 ± 25.71	25.22 ± 25.72	44.29 ± 29.03	24.22 ± 29.43	12.79 ± 25.60	29.41 ± 26.21

	Median, CI 95% []	0 [0,0]	0 [0,0]	5.00 [5,10]	10.00 [5,10]	5.00 [5,10]	0.00 [0,0]	20.00 [10,20]	20.00 [10,20]	50.00 [40,50]	10.00 [9,10]	0 [0,0]	20.00 [20,25]
North America	**Mean ± STDEV**	2.93 ± 7.90	3.95 ± 14.04	11.62 ± 14.41	11.31 ± 13.52	9.85 ± 15.44	2.85 ± 10.50	18.42 ± 20.45	21.46 ± 23.14	36.94 ± 30.08	21.79 ± 26.97	13.51 ± 30.59	20.46 ± 17.93
	Median, CI 95% []	0.00 [0,0]	0.00 [0,0]	10.00 [5,10]	10.00 [5,10]	2.00 [0,5]	0.00 [0,0]	10.00 [5,20]	10.00 [7.00, 21.49]	30.00 [25,40]	10.00 [5,10]	0.00 [0.0]	20.00 [10,20]
South America	**Mean ± STDEV**	13.43 ± 23.05	18.11 ± 30.67	12.25 ± 24.24	12.76 ± 24.80	13.64 ± 26.99	15.96 ± 28.97	11.48 ± 19.65	18.76 ± 28.47	23.90 ± 32.26	14.60 ± 23.27	17.99 ± 29.43	35.25 ± 31.95
	Median, CI 95% []	0.00 [0,5]	0.00 [0,0]	0.00 [0.00, 0.46]	0.00 [0,1]	0.00 [0.00, 0.46]	0.00 [0,0]	0.00, [0,5]	0.00 [0.00. 14.12]	0.00 [0.00, 19.56]	0.00[0,5]	0.00 [0.00, 0.46]	25.00 [20,50]

Significant differences (Kruskal-Wallis test):

Myopia management modality		p value
Undercorrection	North-America –South America	0.028
	Australasia-South America	0.001
SVS	North-America America-Europe	0.026
	North America –South America	0.007
	North America-Asia	p<0.001
	Australasia-South America	0.021
	Australasia-Asia	p<0.001
	Europe-Asia	p<0.001
Bifocals	South America-Australasia	0.001
	South America-Asia	p<0.001
	Europe - Asia	0.008
PALs	South America-Europe	0.033
	South America-Australasia	p<0.001
	South America-Asia	p<0.001
	North America-Asia	p<0.001
	Europe-Asia	p<0.001
RGP (AF)	South America-Asia	p<0.001
	North America-Asia	p<0.001

	Australasia-Asia	p<0.001
	Europe-Asia	p<0.001
SV CL	North America-Europe	0.001
	North America-South America	0.014
	North America-Asia	p<0.001
	Australasia-Europe	0.016
	Australasia-Asia	p<0.001
Standard multifocal CL	South America-North America	0.008
	South America-Australasia	p<0.001
	Asia-North America	p<0.001
	Europe-Australasia	0.001
Specific MC CL	South America-Europe	0.013
	South America-Australasia	p<0.001
	North America-Australasia	0.011
	Asia-Australasia	p<0.001
Ortho K	South America-North America	0.023
	South America-Europe	p<0.001
	South America-Asia	p<0.001
	South America -Australasia	p<0.001
	North America-Asia	0.001
	North America-Australasia	0.001
Pharmaceuticals	South America-Europe	0.05
	South America-Asia	p<0.001
	South America-Australasia	p<0.001
	North America-Asia	0.003
	North America-Australasia	p<0.001
	Europe-Asia	p<0.001
	Europe-Australasia	p<0.001
	Asia-Australasia	0.006
Refractive surgery	No significant differences	No significant differences
Increased outdoor activity	North America-Europe	0.028
	North America-Australasia	0.016
	North America-South America	0.014
	North America-Asia	p<0.001
	Europe-Asia	p<0.001

Countries:

Country		Under-correction	SVS	Bifocals	PALs	RGP (AF)	SV CL	Standard multifocal CL	Specific MC soft CL	Ortho-K	Pharma-ceuticals	Refractive surgery	Increased time spent outdoors
UK, EIRE	Mean ± STDEV	2.16 ± 4.82	8.14 ± 20.59	13.78 ± 15.16	16.39 ± 18.07	14.14 ± 23.82	9.80 ± 21.86	26.37 ± 23.00	31.88 ± 24.45	44.90 ± 27.76	27.69 ± 28.81	18.49 ± 31.92	31.90 ± 24.42
	Median, CI 95% []	0.00 [0,0]	0.00 [0,0]	10.00 [5,15]	10.00 [5.00, 18.04]	5.00 [0,10]	0 [0,0]	30.00 [15,30]	30.00 [20,50]	50.00 [40,50]	20.00 [10,40]	0.00 [0.00, 8.04]	25.00 [20.00, 36.08]
Netherlands	Mean ± STDEV	6.13 ± 13.77	2.13 ± 5.64	12.00 ± 17.33	13.24 ± 18.53	7.87 ± 10.59	2.32 ± 7.14	13.53 ± 15.76	21.26 ± 21.44	48.15 ± 25.54	29.71 ± 26.62	11.45 ± 27.41	23.74 ±24.79
	Median, CI 95% []	0.00 [bigger sample]	0.00	8.00	5.50	5.00	0.00	10.00	10.00	50.00	21.00	0.00	27.50
Spain	Mean ± STDEV	9.79 ± 17.23	11.32 ± 23.30	16.65 ± 17.55	14.29 ± 16.23	17.24 ± 23.44	9.94 ± 20.13	17.35 ± 18.18	37.18 ± 26.48	56.76 ± 28.90	37.94 ± 35.78	19.23 ± 30.60	26.52 ± 26.08
	Median, CI 95% []	0.00 [bigger sample]	0.00	10.00	8.00	8.00	0.0	10.00	40.00	60.00	40.00	0.00	20.00
France	Mean ± STDEV	0.74 ± 2.50	10.88 ± 24.54	2.02 ± 4.61	4.53 ± 7.82	18.23 ± 14.35	2.06 ± 4.94	0.74 ± 2.50	2.35 ± 5.40	29.32 ± 26.49	5.47 ± 11.69	2.06 ± 5.24	18.65 ± 21.87
	Median, CI 95% []	0.00 [bigger sample]	0.00	0.00	0.00	20.00	0.00	0.00	0.00	22.5	0.00	0.00	10.00
Portugal	Mean ± STDEV	14.52 ±24.76	22.13 ± 24.05	10.38 ± 20.76	14.85 ± 22.70	17.83 ± 28.08	23.27 ± 28.08	16.08 ± 25.11	30.40 ± 33.93	38.96 ± 36.29	13.00 ± 25.09	26.10 ± 33.84	39.15 ± 31.92
	Median, CI 95% []	0.50 [0.00, 6.79]	10.00 [0.00, 18.60]	0.00 [0,3]	1.00 [0.00, 14.30]	10.00 [0,20]	10.00 [0,20]	0.00 [0.00, 6.80]	17.50 [5,35]	35.00 [13.91, 50.00]	0.00 [0.00, 8.03]	7.50 [0.00, 32.19]	35.00 [20,50]
Italy	Mean ± STDEV	8.91 ± 19.04	11.71 ± 21.86	12.40 ± 18.35	16.61 ± 21.30	12.91 ± 21.66	13.22 ± 21.80	13.85 ± 19.95	23.30 ± 26.69	42.78 ± 29.94	17.31 ± 26.14	10.98 ± 23.70	28.13 ± 27.15

	Median, CI 95% []	0.00 [0,2]	0.00 [0,5]	5.00 [0,10]	10.00 [4.86, 15.69]	5.00 [0,6]	5.00 [0,8]	5.00 [2,10]	10.00 [5.00, 20.69]	50.00 [38.72, 50.00]	4.00 [0,10]	0.00 [0,0]	20.00 [10,30]
India	Mean ± STDEV	20.27 ± 24.21	35.19 ± 31.11	16.40 ± 21.09	22.14 ± 25.18	29.68 ± 30.54	30.24 ± 33.74	17.57 ± 24.31	29.08 ± 32.37	26.57 ± 30.43	16.45 ± 19.96	23.43 ± 30.62	28.38 ± 24.55
	Median, CI 95% []	10.00 [bigger sample]	25.00	10.00	15.00	20.00	15.00	5.00	15.00	15.00	10.00	5.00	30.00
Hon Kong	Mean ± STDEV	3.94 ± 7.68	7.83 ± 15.83	21.06 ± 17.69	24.81 ± 18.35	15.13 ± 23.25	6.63 ± 15.19	15.29 ± 17.14	32.26 ± 22.85	56.84 ± 24.56	39.40 ± 23.98	9.03 ± 21.89	36.26 ± 22.76
	Median, CI 95% []	0.00 [0,0]	0.00 [0.00, 0.82]	20.00 [10.00, 25.89]	22.50 [20,30]	5.00 [0.00, 9.36]	0.00 [0,0]	10.00 [0,20]	30.00 [20.00, 32.68]	50.00 [50.00, 66.79]	40.00 [30,50]	0.00 [0,0]	40.00 [27.50, 50.00]
China	Mean ± STDEV	2.65 ± 7.21	14.42 ±22.41	10.94 ± 17.39	13.65 ± 17.71	23.21 ± 25.58	8.99 ± 16.72	12.20 ± 19.83	16.28 ± 23.39	45.12 ± 28.38	28.65 ± 27.97	17.48 ± 30.78	39.57 ± 30.05
	Median, CI 95% []	0.00 [0,0]	6.00 [0.23, 10.00]	[2.50, 9.54]	7.00 [5,10]	10.00 [7.46, 20.00]	0.00 [0.00, 1.09]	0.00 [0,2]	0.00 [0.00, 8.40]	50.00 [50,50]	20.00 [10,30]	0.00 [0.00, 0.77]	40.00 [30,50]
Canada	Mean ± STDEV	2.90	11.68 ± 5.13	10.19 ± 25.97	9.87 ± 18.40	3.58 ± 6.92	5.80 ± 18.29	11.80 ± 20.49	10.68 ± 17.81	26.29 ± 28.61	9.10 ± 15.03	18.03 ± 35.06	17.52 ±17.32
	Median, CI 95% []	0.00 [bigger sample]	0.00	5.00	5.00	0.00	0.00	0.00	0.00	20.00	2.00	0.00	10.00
USA	Mean ± STDEV	3.03 ± 8.70	1.67 ± 6.02	12.37 ± 13.11	11.84 ± 11.71	11.50 ± 6.53	2.02 ± 6.57	20.17 ± 20.06	24.14 ± 23.76	39.75 ± 30.26	25.43 ± 28.91	12.51 ± 29.52	21.24 ± 8.32
	Median, CI 95% []	0.00 [0,0]	0.00 [0,0]	10.00 [5,10]	10.00 [7.83, 10.00]	5.00 [0,10]	0.00 [0,0]	15.00 [10,20]	20.00 [10.00, 27.50]	37.50 [25,50]	10.00 [5.00, 27.17]	0.00 [0,0]	20.00 [12.83, 20.00]

Significant differences (Kruskal-Wallis test):

Myopia management modality		p value
Undercorrection	France -Italy	0.044
	France - Spain	0.034
	France - Portugal	0.001
	UK/EIRE - Portugal	0.016
SVS	Netherlands - Portugal	p<0.001
	UK/EIRE - Portugal	0.001
	Spain - Portugal	0.050
Bifocals	France - Netherlands	0.009
	France - Italy	0.001
	France – UK/EIRE	p<0.001
	France - Spain	p<0.001
	Portugal - Spain	0.013
PALs	France - Spain	0.027
	France - Italy	0.002
	France – UK/EIRE	0.002
RGP (AF)	Italy - France	0.005
	Netherlands- France	0.025
	UK/EIRE - France	0.029
SV CL	France - Portugal	p<0.001
	Netherlands - Portugal	p<0.001
	UK/EIRE - Portugal	0.015
Standard multifocal CL	France - Portugal	0.003
	France - Italy	p<0.001
	France – Netherlands	p<0.001
	France - Spain	p<0.001
	France – UK/EIRE	p<0.001
	Portugal – UK/EIRE	0.013
	Italy - UK/EIRE	0.049
Specific MC CL	France - Italy	p<0.001
	France - Netherlands	0.001
	France - Portugal	p<0.001
	France – UK/EIRE	p<0.001
	France - Spain	p<0.001

	Italy - Spain	0.032
Ortho K	France - Spain	0.003
Pharmaceuticals	France – UK/EIRE	p<0.001
	France - Spain	p<0.001
	France - Netherlands	p<0.001
	Portugal – UK/EIRE	0.027
	Portugal - Spain	0.009
	Portugal - Netherlands	0.004
Refractive surgery	France - Portugal	0.001
	Italy - Portugal	p<0.001
	Netherlands - Portugal	0.048
Increased outdoor activity	France - Portugal	0.019

3. How active would you consider your clinical practice in the area of myopia control?

Globally:

Mean ± STDEV	Median, CI []
6.35 ± 2.73	7.00 [7,7]

Continents:

Continent	Mean ± STDEV	Median, CI []
Asia	7.45 ± 2.07	8.00 [8,8]
Australasia	6.46 ± 2.81	7.00 [6,8]
Europe	6.27 ± 2.58	7.00 [6,7]
North America	4.72 ± 2.99	4.00 [3,5]
South America	5.45 ± 3.06	5.00 [4,6]

Kruskal-Wallis test (p<0.001):

Australasia-North America	**p<0.001**
Australasia - Asia	**0.028**
Australasia-Europe	1.00
Australasia-South America	0.214
North America-Asia	**p<0.001**
North America-Europe	**p<0.001**
North America-South America	1.00
Asia-Europe	**p<0.001**
Asia-South America	**p<0.001**
Europe-South America	0.589

Countries:

Country	Mean ± STDEV	Median, CI 95% []
UK, EIRE	5.19 ± 3.07	5.00 [4.00,6.80]
Netherlands	6.16 ± 2.05	7.00 [bigger sample]
Spain	6.88 ± 2.61	7.00 [bigger sample]
France	6.65 ± 2.59	7.50 [bigger sample]
Portugal	6.25 ± 1.99	6.00 [5,7]
Italy	6.58 ± 2.68	7.00 [5.93,8.00]
India	6.05 ± 1.99	6.00 [bigger sample]
Hong Kong	7.31 ± 2.20	8.00 [6.64,8.00]
China	7.96 ± 1.96	8.00 [8,8]
Canada	3.97 ± 3.42	2.00 [bigger sample]
USA	4.96 ± 2.83	5.00 [4,6]

Kruskal-Wallis test (Europe p=0.046, Asia p<0.001):

UK/EIRE-France	0.269
UK/EIRE-Netherlands	1.00
UK/EIRE-Italy	0.112
UK/EIRE-Spain	0.091
UK/EIRE-Portugal	1.00
France-Netherlands	1.00
France-Italy	1.00
France-Spain	0.345
France-Portugal	1.00
Netherlands-Italy	1.00
Netherlands-Spain	1.00
Netherlands-Portugal	1.00
Italy-Spain	1.00

Italy-Portugal	1.00
Spain-Portugal	1.00
Hong Kong-China	0.365
Hong Kong-India	**0.002**
China-India	**p<0.001**
Canada-USA	**0.034**

One hundred sixty-three respondents left comments.

Category	Number of responses
Myopia control is not actively employed or is not of a concern owing to the lack of myopic patients owing to e.g. practice location, patient demographics or patient's poor awareness of myopia control or lack of access to myopia control interventions	**33 (mostly due to patient demographics)**
Myopia control is ineffective or not worth the effort, considering the increased cost, inconsistent information and individually selective outcome.	8
Myopia control would be employed more in the clinical practice, if unite and consistent regulations and informational materials (e.g. leaflets) existed and different methods would be certified for MC use:	20
Multifocal lenses/Myopia spectacles	3
Practice is new in myopia control.	4
Currently active in myopia control and employing one or more of the myopia control approaches available;	**68**
From them (if specified) X employ:	
Orthokeratology (actively prescribing or suggesting and referring to a practice in which it is employed).	**50 (popular within Asia, Australasia, Europe)**
PALs/bifocals	**13 (pronounced in Australasia)**
Soft multifocal contact lenses	**13**
Increased outdoor activity	**6**
RGPs	**3**
Atropine	**1**
Specialised MC spectacle lenses	**1**
Undercorrection	**2**
Patient education	2

Two of the respondents criticised second question as being not well constructed: the first implied that undercorrection could not be viewed at as a method of MC, and the second implied that all MC methods are 'off-label' not only multifocal contact lenses.

4. **How many times have you prescribed the following correction options for progressing/ young myopes over an average month?**

Globally:

	SVS (%)	Bifocals (%)	PALs (%)	RGP (AF) (%)	SV CL (%)	Standard multifocal CL (%)	Specific MC soft CL (%)	Ortho-K (%)	Pharma-ceuticals (%)	Refracti-ve surgery (%)
Mean ± STDEV	47.78 ± 31.70	2.63 ± 8.16	6.45 ± 14.29	4.54 ± 10.48	15.22 ± 17.28	4.05 ± 11.33	2.07 ± 7.88	14.32 ± 24.25	1.95 ± 8.67	1.01 ± 5.41
Median, CI 95% []	50.00 [50.00, 53.96]	0.00 [0,0]	0.00 [0,0]	0.00 [0,0]	10.00 [8.70,12.50]	0.00 [0,0]	0.00 [0,0]	2.00 [0.56,2.9]	0.00 [0,0]	0.00 [0,0]

Continents:

Continent		SVS	Bifocals	PALs	RGP (AF)	SV CL	Standard multifocal CL	Specific MC soft CL	Ortho-K	Pharma-ceuticals	Refractive surgery
Asia	**Mean ± STDEV**	57.59 ± 31.26	2.89 ± 7.27	7.42 ± 13.33	4.85 ± 8.51	5.66 ± 9.92	0.78 ± 2.94	2.19 ± 8.12	11.08 ± 17.57	5.57 ± 14.46	1.96 ± 8.28
	Median, CI 95% []	65.14 [60.98,70.00]	0.00 [0,0]	1.39 [0.13,2.78]	0.00 [0.00,11.40]	0.00 [0,0]	0.00 [0,0]	0.00 [0,0]	2.90 [2.00,5.09]	0.00 [0,0]	0.00 [0,0]
Australasia	**Mean ± STDEV**	36.79 ± 30.15	1.27 ± 4.42	17.35 ± 23.03	0.61 ± 2.05	13.93 ± 13.35	6.24 ± 11.93	1.53 ± 4.65	21.21 ± 29.05	0.81 ± 3.29	0.25 ± 1.28
	Median, CI 95% []	33.33 [25,40]	0.00 [0,0]	7.14 [2.56,11.11]	0.00 [0,0]	12.50 [7.58, 18.18]	0.00 [0,0]	0.00 [0,0]	9.09 [4.76, 13.33]	0.00 [0,0]	0.00 [0,0]
Europe	**Mean ± STDEV**	42.17 ± 30.68	2.10 ± 6.99	4.12 ± 12.17	6.09 ± 13.58	20.17 ± 18.82	4.27 ± 10.95	2.44 ± 8.79	18.26 ± 27.64	0.13 ± 1.18	0.25 ± 1.58

	Median, CI 95% []	45.45 [40,50]	0.00 [0,0]	0.00 [0,0]	0.00 [0,0]	20.00 [15.38, 22.81]	0.00 [0,0]	0.00 [0,0]	46.50 [11.10, 82.00]	0.00 [0,0]	0.00 [0,0]
North America	**Mean ± STDEV**	49.56 ± 31.29	5.11 ± 13.57	3.65 ± 9.21	2.41 ± 8.34	18.80 ± 16.50	8.46 ± 17.51	0.91 ± 5.08	9.42 ± 18.49	1.08 ± 6.78	0.59 ± 4.50
	Median, CI 95% []	56.60 [50.00,58 .82]	0.00 [0,0]	0.00 [0,0]	0.00 [0,0]	19.76 [14.04,22 .96]	0.00 [0,1.38]	0.00 [0,0]	0.00 [0,0]	0.00 [0,0]	0.00 [0,0]
South America	**Mean ± STDEV**	52.10 ± 30.48	1.89 ± 6.97	1.77 ± 5.20	6.82 ± 10.78	20.99 ± 20.34	2.05 ± 7.24	3.04 ± 10.56	7.86 ± 25.22	0.68 ± 5.03	2.80 ± 7.62
	Median, CI 95% []	52.33 [45.11,63 .30]	0.00 [0,0]	0.00 [0,0]	0.00 [0.00,5.7 4]	17.20 [14.29,25 .00]	0.00 [0,0]	0.00 [0,0]	0.00 [0,0]	0.00 [0,0]	0.00 [0,0]

Kruskal-Wallis test:

Myopia management modality		p value
SVS	Australasia-Europe	1.00
	Australasia-North America	**0.028**
	Australasia-South America	**0.021**
	Australasia-Asia	**p<0.001**
	Europe-North America	**0.485**
	Europe-South America	0.309
	Europe-Asia	**p<0.001**
	North America-South America	1.00
	North America-Asia	0.161
	South America-Asia	1.00
Bifocals	Australasia-Europe	1.00
	Australasia-North America	**p<0.001**
	Australasia-South America	1.00
	Australasia-Asia	**0.018**
	Europe-North America	**p<0.001**
	Europe-South America	1.00
	Europe-Asia	0.159
	North America-South America	**0.025**

	North America-Asia	0.264
	South America-Asia	1.00
PALs	Australasia-Europe	**p<0.001**
	Australasia-North America	**p<0.001**
	Australasia-South America	**p<0.001**
	Australasia-Asia	0.102
	Europe-North America	1.00
	Europe-South America	1.00
	Europe-Asia	**p<0.001**
	North America-South America	0.680
	North America-Asia	**0.002**
	South America-Asia	**p<0.001**
RGP (AF)	Australasia-Europe	**p<0.001**
	Australasia-North America	1.00
	Australasia-South America	**p<0.001**
	Australasia-Asia	**p<0.001**
	Europe-North America	**0.008**
	Europe-South America	0.655
	Europe-Asia	0.760
	North America-South America	**p<0.001**
	North America-Asia	**p<0.001**
	South America-Asia	1.00
SV CL	Australasia-Europe	0.149
	Australasia-North America	0.987
	Australasia-South America	0.435
	Australasia-Asia	**p<0.001**
	Europe-North America	1.00
	Europe-South America	1.00
	Europe-Asia	**p<0.001**
	North America-South America	1.00
	North America-Asia	**p<0.001**
	South America-Asia	**p<0.001**
Standard multifocal CL	Australasia-Europe	1.00
	Australasia-North America	0.767
	Australasia-South America	0.108

	Australasia-Asia	**p<0.001**
	Europe-North America	**p<0.001**
	Europe-South America	1.00
	Europe-Asia	**p<0.001**
	North America-South America	**p<0.001**
	North America-Asia	**p<0.001**
	South America-Asia	1.00
Specific MC CL	Australasia-Europe	1.00
	Australasia-North America	0.730
	Australasia-South America	1.00
	Australasia-Asia	0.759
	Europe-North America	0.069
	Europe-South America	1.00
	Europe-Asia	0.507
	North America-South America	0.436
	North America-Asia	**p<0.001**
	South America-Asia	1.00
Ortho K	Australasia-Europe	1.00
	Australasia-North America	**0.006**
	Australasia-South America	**p<0.001**
	Australasia-Asia	1.00
	Europe-North America	**0.02**
	Europe-South America	**p<0.001**
	Europe-Asia	1.00
	North America-South America	**0.048**
	North America-Asia	0.160
	South America-Asia	**p<0.001**
Pharmaceuticals	Australasia-Europe	1.00
	Australasia-North America	1.00
	Australasia-South America	1.00
	Australasia-Asia	**p<0.001**
	Europe-North America	1.00
	Europe-South America	1.00
	Europe-Asia	**p<0.001**
	North America-South America	1.00

	North America-Asia	**p<0.001**
	South America-Asia	**p<0.001**
Refractive surgery	Australasia-Europe	1.00
	Australasia-North America	1.00
	Australasia-South America	**p<0.001**
	Australasia-Asia	**0.02**
	Europe-North America	1.00
	Europe-South America	**p<0.001**
	Europe-Asia	**p<0.001**
	North America-South America	**p<0.001**
	North America-Asia	0.061
	South America-Asia	0.25

Countries:

Country		**SVS**	**Bifocals**	**PALs**	**RGP (AF)**	**SV CL**	**Standard multifocal CL**	**Specific MC soft CL**	**Ortho-K**	**Pharma-ceuticals**	**Refracti-ve surgery**
UK, EIRE	Mean ± STDEV	56.43 ± 29.65	4.11 ± 10.14	2.89 ± 8.18	2.68 ± 8.35	20.56 ± 19.02	4.30 ± 14.80	1.03 ± 3.67	7.18 ± 17.41	0.51 ± 2.56	0.42 ± 2.01
	Median, CI 95% []	63.29 [57.30,71.43]	0.00 [0,0]	0.00 [0,0]	0.00 [0,0]	19.61 [13.16,22.53]	0.00 [0,0]	0.00 [0,0]	0.00 [0.00,1.9]	0.00 [0,0]	0.00 [0,0]
Netherlands	Mean ± STDEV	23.28 ± 23.93	1.04 ± 3.51	1.26 ± 4.99	8.64 ± 13.07	22.07 ± 22.40	5.02 ± 12.98	0.43 ± 2.56	37.85 ± 35.71	0.28 ± 1.67	0.13 ± 0.79
	Median, CI 95% []	21.40 [bigger sample]	0.00 [bigger sample]	0.00 [bigger sample]	2.45 [bigger sample]	21.90 [bigger sample]	0.00 [bigger sample]	0.00 [bigger sample]	23.14 [bigger sample]	0.00 [bigger sample]	0.00 [bigger sample]
Spain	Mean ± STDEV	44.56 ± 24.26	1.53 ± 3.18	0.93 ± 2.41	9.44 ± 21.04	22.7 ± 17.20	1.66 ± 4.19	3.85 ± 9.46	14.57 ± 23.53	0.00 ± 0.00	0.76 ± 3.51

	Median, CI 95% []	43.86 [bigger sample]	0.00 [bigger sample]	0.00 [bigger sample]	0.00 [bigger sample]	25.00 [bigger sample]	0.00 [bigger sample]	0.00 [bigger sample]	4.88 [bigger sample]	0.00 [bigger sample]	0.00 [bigger sample]
France	Mean ± STDEV	56.43 ± 30.53	0.81 ± 4.49	5.34 ± 19.04	15.15 ± 23.33	11.70 ±14.83	0.31 ± 1.51	0.37 ± 2.05	9.67 ± 21.10	0.05 ± 0.27	0.17 ± 0.62
	Median, CI 95% []	60.24 [bigger sample]	0.00 [bigger sample]	0.00 [bigger sample]	5.66 [bigger sample]	0.00 [bigger sample]	0.00 [bigger sample]	0.00 [bigger sample]	0.00 [bigger sample]	0.00 [bigger sample]	0.00 [bigger sample]
Portugal	Mean ± STDEV	62.42 ± 21.62	0.63 ± 4.42	1.93 ± 5.16	1.31 ± 4.49	25.99 ± 15.05	1.83 ± 5.26	1.36 ± 5.38	4.49 ± 18.18	0.00 ± 0.00	0.04 ± 0.26
	Median, CI 95% []	62.50 [61.25,69.53]	0.00 [0,0]	0.00 [0,0]	0.00 [0,0]	29.29 [23.18,33.33]	0.00 [0,0]	0.00 [0,0]	0.00 [0,0]	0.00 [0,0]	0.00 [0,0]
Italy	Mean ± STDEV	31.00 ± 28.60	3.00 ± 10.2	10.00 ± 19.6	5.00 ± 9.50	19.00 ± 16.90	4.00 ± 7.10	4.00 ± 13.50	23.00 ± 29.30	0.00 ± 0.00	0.00 ± 0.00
	Median, CI 95% []	27.00 [10,43]	0.00 [0,0]	0.00 [0,4]	0.00 [0,0]	17.00 [10,25]	0.00 [0,0]	0.00 [0,0]	13.00 [5,20]	0.00 [0,0]	0.00 [0,0]
India	Mean ± STDEV	51.70 ± 43.31	9.42 ± 21.69	4.31 ± 11.15	6.30 ± 16.67	19.11 ± 2.44	1.25 ± 0.54	2.39 ± 0.97	0.34 ± 0.21	0.88 ± 0.42	4.30 ± 11.89
	Median, CI 95% []	47.37 [bigger sample]	3.45 [bigger sample]	1.33 [bigger sample]	14.30 [bigger sample]	17.65 [bigger sample]	0.00 [bigger sample]	0.00 [bigger sample]	0.00 [bigger sample]	0.00 [bigger sample]	0.00 [bigger sample]
Hon Kong	Mean ± STDEV	60.80 ± 30.57	1.73 ± 7.16	11.32 ± 16.32	1.44 ± 5.44	5.71 ± 9.34	0.86 ± 3.78	5.86 ± 15.14	10.78 ± 13.12	1.03 ± 4.27	0.46 ± 0.36
	Median, CI 95% []	65.59 [59.41,75.52]	0.00 [0,0]	4.39 [0.00,12.50]	0.00 [0,0]	0.00 [0,0]	0.00 [0,0]	0.00 [0.00,2.82]	5.28 [1.37,10.95]	0.00 [0,0]	0.00 [0,0]
China	Mean ± STDEV	56.33 ± 34.04	1.32 ± 3.61	3.80 ± 11.20	7.38 ± 9.42	2.34 ± 4.82	0.43 ± 2.19	0.32 ± 1.54	14.04 ± 20.51	11.18 ± 18.99	2.88 ± 11.57
	Median, CI 95% []	66.23 [60.98,75.41]	0.00 [0,0]	0.00 [0,0]	4.29 [1.37,5.13]	0.00 [0,0]	0.00 [0,0]	0.00 [0,0]	5.36 [2.39,9.68]	0.00 [0.00,5.20]	0.00 [0,0]
Canada	Mean ± STDEV	60.40 ± 32.66	4.70 ± 13.69	4.98 ± 14.46	0.40 ± 1.34	16.93 ± 18.50	5.02 ± 13.75	0.52 ± 2.95	4.05 ± 11.16	0.95 ± 4.50	2.05 ± 8.93

	Median, CI 95% []	64.36 [bigger sample]	0.00 [bigger sample]	0.00 [bigger sample]	0.00 [bigger sample]	12.50 [bigger sample]	0.00 [bigger sample]	0.00 [bigger sample]	0.00 [bigger sample]	0.00 [bigger sample]	0.00 [bigger sample]
USA	Mean ± STDEV	45.98 ± 30.14	5.25 ± 13.60	3.21 ± 6.70	3.07 ± 9.51	19.42 ± 15.84	9.60 ± 18.51	1.04 ± 5.62	11.19 ± 20.07	1.12 ± 7.41	0.11 ± 0.56
	Median, CI 95% []	51.72 [44.12,58.19]	0.00 [0.00,1.22]	0.00 [0,0]	0.00 [0,0]	20.00 [14.61,25.00]	1.00 [0.00,3.33]	0.00 [0,0]	0.86 [0.00,4.63]	0.00 [0,0]	0.00 [0,0]

Kruskal-Wallis test:

Myopia management modality		p value
SVS	Netherlands-Italy	1.00
	Netherlands-Spain	0.072
	Netherlands-France	**p<0.001**
	Netherlands-UK/EIRE	**p<0.001**
	Netherlands-Portugal	**p<0.001**
	Italy-Spain	1.00
	Italy-France	**0.003**
	Italy-UK/EIRE	**p<0.001**
	Italy-Portugal	**p<0.001**
	Spain-France	1.00
	Spain-UK/EIRE	0.622
	Spain/Portugal	0.077
	France-UK/EIRE	1.00
	France-Portugal	1.00
	UK/EIRE-Portugal	1.00
	India-Hong Kong	**All p=0.164**
	India-China	
	China-Hong Kong	
	Canada-USA	**0.028**
Bifocals	Netherlands-Italy	1.00
	Netherlands-Spain	0.872
	Netherlands-France	1.00
	Netherlands-UK/EIRE	0.214

	Netherlands-Portugal	1.00
	Italy-Spain	1.00
	Italy-France	0.563
	Italy-UK/EIRE	1.00
	Italy-Portugal	0.203
	Spain-France	0.263
	Spain-UK/EIRE	1.00
	Spain-Portugal	0.103
	France-UK/EIRE	**0.047**
	France-Portugal	1.00
	UK/EIRE-Portugal	**0.010**
	India-Hong Kong	**All p<0.001**
	India-China	
	China-Hong Kong	
	Canada-USA	**0.023**
PALs	Netherlands-Italy	**p<0.001**
	Netherlands-Spain	1.00
	Netherlands-France	1.00
	Netherlands-UK/EIRE	0.746
	Netherlands-Portugal	1.00
	Italy-Spain	**0.004**
	Italy-France	**0.038**
	Italy-UK/EIRE	0.078
	Italy-Portugal	**0.003**
	Spain-France	1.00
	Spain-UK/EIRE	1.00
	Spain/Portugal	1.00
	France-UK/EIRE	1.00
	France-Portugal	1.00
	UK/EIRE-Portugal	1.00
	India-Hong Kong	**All p=0.007**
	India-China	
	China-Hong Kong	
	Canada-USA	**0.032**
RGP (AF)	Netherlands-Italy	0.339
	Netherlands-Spain	1.00

	Netherlands-France	1.00
	Netherlands-UK/EIRE	**0.017**
	Netherlands-Portugal	**0.001**
	Italy-Spain	1.00
	Italy-France	**0.001**
	Italy-UK/EIRE	1.00
	Italy-Portugal	0.568
	Spain-France	0.259
	Spain-UK/EIRE	0.246
	Spain/Portugal	**0.034**
	France-UK/EIRE	**p<0.001**
	France-Portugal	**p<0.001**
	UK/EIRE-Portugal	1.00
	India-Hong Kong	**All p<0.001**
	India-China	
	China-Hong Kong	
	Canada-USA	0.053
SV CL	Netherlands-Italy	1.00
	Netherlands-Spain	1.00
	Netherlands-France	0.550
	Netherlands-UK/EIRE	1.00
	Netherlands-Portugal	1.00
	Italy-Spain	1.00
	Italy-France	0.655
	Italy-UK/EIRE	1.00
	Italy-Portugal	0.308
	Spain-France	0.143
	Spain-UK/EIRE	1.00
	Spain-Portugal	1.00
	France-UK/EIRE	0.358
	France-Portugal	**0.002**
	UK/EIRE-Portugal	1.00
	India-Hong Kong	**All p<0.001**
	India-China	
	China-Hong Kong	
	Canada-USA	0.402

Standard multifocal contact lenses	Netherlands-Italy	**(Europe all p=0.055)**
	Netherlands-Spain	
	Netherlands-France	
	Netherlands-UK/EIRE	
	Netherlands-Portugal	
	Italy-Spain	
	Italy-France	
	Italy-UK/EIRE	
	Italy-Portugal	
	Spain-France	
	Spain-UK/EIRE	
	Spain/Portugal	
	France-UK/EIRE	
	France-Portugal	
	UK/EIRE-Portugal	
	India-Hong Kong	**All p=0.001**
	India-China	
	China-Hong Kong	
	Canada-USA	**0.010**
Specific myopia control CL	Netherlands-Italy	0.160
	Netherlands-Spain	**0.001**
	Netherlands-France	1.00
	Netherlands-UK/EIRE	1.00
	Netherlands-Portugal	1.00
	Italy-Spain	0.309
	Italy-France	0.640
	Italy-UK/EIRE	1.00
	Italy-Portugal	0.502
	Spain-France	**0.002**
	Spain-UK/EIRE	**0.034**
	Spain/Portugal	**0.003**
	France-UK/EIRE	1.00
	France-Portugal	1.00
	UK/EIRE-Portugal	1.00
	India-Hong Kong	**All p<0.001**
	India-China	

	China-Hong Kong	
	Canada-USA	0.643
Orthokeratology	Netherlands-Italy	0.089
	Netherlands-Spain	0.132
	Netherlands-France	**p<0.001**
	Netherlands-UK/EIRE	**p<0.001**
	Netherlands-Portugal	**p<0.001**
	Italy-Spain	1.00
	Italy-France	0.190
	Italy-UK/EIRE	**0.001**
	Italy-Portugal	**p<0.001**
	Spain-France	0.781
	Spain-UK/EIRE	**0.040**
	Spain-Portugal	**p<0.001**
	France-UK/EIRE	1.00
	France-Portugal	0.263
	UK/EIRE-Portugal	1.00
	India-Hong Kong	**All p<0.001**
	India-China	
	China-Hong Kong	
	Canada-USA	**0.004**
Pharmaceuticals	Netherlands-Italy	All p=0.679
	Netherlands-Spain	
	Netherlands-France	
	Netherlands-UK/EIRE	
	Netherlands-Portugal	
	Italy-Spain	
	Italy-France	
	Italy-UK/EIRE	
	Italy-Portugal	
	Spain-France	
	Spain-UK/EIRE	
	Spain/Portugal	
	France-UK/EIRE	
	France-Portugal	
	UK/EIRE-Portugal	

	India-Hong Kong	**All p<0.001**
	India-China	
	China-Hong Kong	
	Canada-USA	0.742
Refractive surgery	Netherlands-Italy	All p=0.654
	Netherlands-Spain	
	Netherlands-France	
	Netherlands-UK/EIRE	
	Netherlands-Portugal	
	Italy-Spain	
	Italy-France	
	Italy-UK/EIRE	
	Italy-Portugal	
	Spain-France	
	Spain-UK/EIRE	
	Spain/Portugal	
	France-UK/EIRE	
	France-Portugal	
	UK/EIRE-Portugal	
	India-Hong Kong	**All p<0.001**
	India-China	
	China-Hong Kong	
	Canada-USA	0.135

5. **How old (in years) would the patient have to be for you to consider each of the following options (not just for myopia control and assuming average handling skills and child/ parent motivation)?**

Globally:

	SVS (years)	Bifocals (years)	PALs (years)	RGP (AF) (years)	SV CL (years)	Standard multifocal CL (years)	Specific MC soft CL (years)	Ortho-K (years)	Pharma-ceuticals (years)	Refracti-ve surgery (years)
Mean ± STDEV	5.44 ± 1.52	6.30 ± 2.25	7.31 ± 2.83	9.87 ± 3.28	8.51 ± 3.44	8.90 ± 3.08	8.78 ± 3.11	8.82 ± 3.10	6.41 ± 2.55	17.11± 2.91
Median, CI 95% []	5.00 [5,5]	5.00 [5,5]	7.00 [6,8]	10.00 [8,10]	9.00 [8,10]	9.00 [8,10]	9.00 [8,10]	9.00 [8,10]	5.00 [5,6]	18.00 [18,18]

Continents:

Continent		SVS (yrs)	Bifocals (yrs)	PALs (yrs)	RGP (AF) (yrs)	SV CL (yrs)	Standard multifocal CL (yrs)	Specific MC soft CL (yrs)	Ortho-K (yrs)	Pharma-ceuticals (yrs)	Refractive surgery (yrs)
Asia	**Mean ± STDEV**	5.90 ± 3.86	6.60 ± 2.57	7.83 ± 3.04	10.08 ± 3.32	10.90 ± 3.78	11.13 ± 4.03	10.76 ± 3.52	9.58 ± 3.24	6.40 ± 2.61	16.85 ± 2.86
	Median, CI 95% []	5.00 [5,5]	5.00 [5,6]	7.50 [6.50,8.00]	10.00 [8,10]	10.00 [8.50,11.50]	10.00 [8,12]	10.00 [9,10]	8.00 [8,10]	5.00 [5.00,5.50]	18.00 [18,18]
Australasia	**Mean ± STDEV**	5.33 ± 0.51	6.00 ± 1.26	6.50 ± 1.38	9.00 ± 1.67	8.33 ± 0.82	8.33 ± 0.82	8.33 ± 0.82	8.00 ± 1.10	6.67 ± 3.87	18.00 ± 0.00
	Median, CI 95% []	5.00 [5,6]	5.50 [5,7]	6.50 [5,8]	8.00 [8,11]	8.00 [8,9]	8.00 [8,9]	8.00 [8,9]	8.00 [7,9]	6.00 [5,9]	18.00 [18,18]

Europe	**Mean ± STDEV**	7.41± 3.04	7.44 ± 2.60	7.78 ± 2.82	7.89 ± 2.42	7.78 ±2.73	7.44 ± 2.46	7.33 ± 2.45	8.11 ± 2.32	7.89 ± 3.62	12.78 ± 4.49
	Median, CI 95% []	5.00 [5,11]	8.00 [5,10]	8.00 [5,10]	8.00 [5,11]	8.00 [5,10]	8.00 [5,10]	7.00 [5,10]	8.00 [5,10]	5.00 [5,12]	12.00 [10,18]
North America	**Mean ± STDEV**	5.20 ± 0.56	5.13 ± 0.52	6.67 ± 2.85	9.33 ± 3.02	7.87 ± 2.42	8.07 ± 2.71	7.93 ±2.55	8.00 ± 3.07	6.40 ± 3.33	18.00 ± 0.00
	Median, CI 95% []	5.00 [5,5]	5.00 [5,5]	5.00 [5,8]	10.00 [7,12]	8.00 [6,10]	8.00 [6,10]	8.00 [6,10]	7.00 [6,9]	5.00 [5,6]	18.00 [18,18]
South America	**Mean ± STDEV**	5.50 ± 1.22	7.50 ± 2.88	8.00 ± 3.22	10.17 ± 4.26	10.33 ± 3.72	11.00 ± 3.58	10.33 ± 3.88	12.33 ± 4.84	6.33 ± 2.16	15.50 ± 5.21
	Median, CI 95% []	5.00 [5.00, 7.18]	6.50 [5,11]	7.00 [5,12]	11.50 [5,14]	10.00 [6.59,14.00]	10.00 [7.58,14.00]	10.50 [6.09,14.00]	12.50 [7.50,16.00]	5.00 [5.00,9.04]	18.00 [10.73,18.00]

Kruskal-Wallis test:

Myopia management modality		p value
SVS	Australasia-Europe	0.999
	Australasia-North America	1.00
	Australasia-South America	1.00
	Australasia-Asia	**0.057**
	Europe-North America	0.251
	Europe-South America	1.00
	Europe-Asia	1.00
	North America-South America	1.00
	North America-Asia	**0.007**
	South America-Asia	0.147
Bifocals	Australasia-Europe	0.099
	Australasia-North America	1.00
	Australasia-South America	0.945
	Australasia-Asia	**p<0.001**

	Europe-North America	**0.001**
	Europe-South America	1.00
	Europe-Asia	**0.031**
	North America-South America	0.212
	North America-Asia	**p<0.001**
	South America-Asia	1.00
PALs	Australasia-Europe	**0.001**
	Australasia-North America	1.00
	Australasia-South America	0.784
	Australasia-Asia	**p<0.001**
	Europe-North America	0.268
	Europe-South America	1.00
	Europe-Asia	**0.327**
	North America-South America	1.00
	North America-Asia	**p<0.001**
	South America-Asia	0.933
RGP (AF)	Australasia-Europe	1.00
	Australasia-North America	1.00
	Australasia-South America	0.803
	Australasia-Asia	1.00
	Europe-North America	1.00
	Europe-South America	**0.029**
	Europe-Asia	1.00
	North America-South America	1.00
	North America-Asia	1.00
	South America-Asia	0.253
SV CL	Australasia-Europe	1.00
	Australasia-North America	1.00
	Australasia-South America	0.157
	Australasia-Asia	**p<0.001**
	Europe-North America	1.00
	Europe-South America	**0.004**
	Europe-Asia	**p<0.001**
	North America-South America	**0.015**
	North America-Asia	**p<0.001**

	South America-Asia	0.241
Standard multifocal CL	Australasia-Europe	1.00
	Australasia-North America	1.00
	Australasia-South America	1.00
	Australasia-Asia	**p<0.001**
	Europe-North America	1.00
	Europe-South America	1.00
	Europe-Asia	**p<0.001**
	North America-South America	1.00
	North America-Asia	**p<0.001**
	South America-Asia	0.632
Specific MC CL	Australasia-Europe	1.00
	Australasia-North America	1.00
	Australasia-South America	1.00
	Australasia-Asia	**0.045**
	Europe-North America	1.00
	Europe-South America	1.00
	Europe-Asia	**p<0.001**
	North America-South America	1.00
	North America-Asia	**p<0.001**
	South America-Asia	0.512
Ortho K **(p=0.002)**	Australasia-Europe	**0.004**
	Australasia-North America	1.00
	Australasia-South America	1.00
	Australasia-Asia	1.00
	Europe-North America	0.230
	Europe-South America	0.153
	Europe-Asia	0.131
	North America-South America	1.00
	North America-Asia	1.00
	South America-Asia	1.00
Pharmaceuticals	Australasia-Europe	All p=0.814
	Australasia-North America	
	Australasia-South America	
	Australasia-Asia	

	Europe-North America	
	Europe-South America	
	Europe-Asia	
	North America-South America	
	North America-Asia	
	South America-Asia	
Refractive surgery	Australasia-Europe	All p=0.148
	Australasia-North America	
	Australasia-South America	
	Australasia-Asia	
	Europe-North America	
	Europe-South America	
	Europe-Asia	
	North America-South America	
	North America-Asia	
	South America-Asia	

Countries:

Country		**SVS**	**Bifocals**	**PALs**	**RGP (AF)**	**SV CL**	**Standard multifocal CL**	**Specific MC soft CL**	**Ortho-K**	**Pharma-ceuticals**	**Refracti-ve surgery**
UK, EIRE	Mean ± STDEV	4.96± 0.82	4.30 ± 3.09	4.20 ± 4.31	6.55 ± 4.13	7.37 ± 2.08	5.18 ± 4.42	5.86 ± 3.97	5.49 ± 4.75	0.8 ± 2.07	18.49 ± 5.57
	Median, CI 95% []	5.00 [5,8]	10.00 [5.11]	5.00 [5, 18]	8.00 [5,14]	8.00 [5,11]	7.00 [5,14]	7.00 [5,14]	7.00 [5,18]	0.00 [0,9]	15.00 [15,18]
Netherlands	Mean ± STDEV	5.94 ± 1.65	7.86 ± 2.25	8.83 ± 2.85	8.94 ± 3.01	8.11 ± 1.95	9.15 ± 2.14	8.53 ± 2.14	8.62 ± 1.93	6.55 ± 2.17	15.29 ± 5.06

	Median, CI 95% []	5.00	8.00	8.00	8.00	8.00	9.00	8.00	8.00	6.00	18.00
Spain	Mean ± STDEV	5.35 ± 1.47	6.06 ± 2.09	8.06 ± 2.99	10.00 ± 3.73	7.67 ± 2.76	7.73 ± 2.40	7.90 ± 3.42	8.30 ± 3.11	5.00 ± 0.00	18.00 ± 0.00
	Median, CI 95% []	5.00	5.00	7.50	10.00	7.00	8.00	7.00	8.00	5.00	18.00
France	Mean ± STDEV	5.31 ± 1.06	5.60 ± 0.89	8.11± 3.89	8.20 ± 2.54	10.80 ± 3.21	8.50 ± 4.04	7.00 ± 2.45	9.36 ± 2.75	8.00 ± 4.24	16.38 ± 4.59
	Median, CI 95% []	5.00	5.00	7.00	8.00	11.00	8.50	6.50	9.00	6.50	18.00
Portugal	Mean ± STDEV	5.46 ± 1.96	5.79 ± 1.63	7.52 ± 3.19	13.19 ± 4.59	10.48 ± 3.94	8.95 ± 3.95	10.83 ± 4.42	11.83 ± 4.47	5.33 ± 0.58	18.00 ± 0.00
	Median, CI 95% []	5.00	5.00	6.00	15.00	11.00	7.50	10.00	12.50	5.00	18.00
Italy	Mean ± STDEV	5.36 ± 1.25	6.13 ± 1.81	7.49 ± 3.21	9.74 ± 3.45	8.16 ± 2.83	7.84 ± 2.84	7.82 ± 2.91	10.00 ± 3.85	8.60 ± 3.58	16.50 ± 2.83
	Median, CI 95% []	5.00	5.00	6.00	10.00	8.00	7.00 [2,10]	7.00	9.00	8.00	18.00
India	Mean ± STDEV	6.16 ± 2.29	7.56 ± 3.07	8.17 ± 2.76	11.69 ± 3.41	11.06 ± 3.61	11.80 ± 2.91	10.63 ± 3.37	13.16 ± 3.82	7.72 ± 4.08	16.90 ± 3.01
	Median, CI 95% []	5.00	7.00	8.00	12.00	11.00	12.00	10.00	15.00	6.00	18.00
Hon Kong	Mean ± STDEV	5.50 ± 1.43	7.18 ± 1.93	7.81 ± 2.21	10.41 ± 2.85	10.02 ± 2.73	9.96 ± 2.96	8.71 ± 2.30	7.43 ± 1.61	7.31 ± 2.15	17.00 ± 2.45
	Median, CI 95% []	5.00	7.00	8.00	10.00	10.00	10.00	8.00	7.00	7.00	18.00
China	Mean ± STDEV	5.46 ± 1.46	6.88 ± 2.79	8.46 ± 3.24	9.49 ± 3.24	13.57 ± 4.32	11.53 ± 4.43	10.76 ± 3.94	8.69 ± 2.41	5.79 ± 1.85	17.57 ± 2.01

	Median, CI 95% []	5.00	5.00	8.00	8.00	15.00	10.00 [0,2]	10.00	8.00	5.00	18.00
Canada	Mean ± STDEV	5.43 ± 1.38	5.95 ± 1.96	7.30 ± 2.45	11.56 ± 2.28	8.58 ± 2.23	8.42 ± 2.24	8.33 ± 2.28	10.00 ± 3.48	6.83 ± 2.79	17.82 ± 0.60
	Median, CI 95% []	5.00	5.00	7.00	11.00	8.00	8.00	8.00	10.00	5.50	18.00
USA	Mean ± STDEV	5.16 ± 1.01	5.34 ± 0.89	6.65 ± 2.50	9.53 ± 2.67	8.44 ± 2.39	8.04 ± 2.45	7.97 ± 2.21	7.97 ± 2.13	6.19 ± 2.75	17.48 ± 2.60
	Median, CI 95% []	5.00	5.00	5.00	10.00	8.00	8.00	8.00	8.00	5.00	18.00

Kruskal-Wallis test:

Myopia management modality		p value
SVS	Netherlands-Italy	**0.029**
	Netherlands-Spain	**0.035**
	Netherlands-France	**0.031**
	Netherlands-UK/EIRE	**p<0.001**
	Netherlands-Portugal	**0.050**
	Italy-Spain	1.00
	Italy-France	1.00
	Italy-UK/EIRE	1.00
	Italy-Portugal	1.00
	Spain-France	1.00
	Spain-UK/EIRE	1.00
	Spain/Portugal	1.00
	France-UK/EIRE	1.00
	France-Portugal	1.00
	UK/EIRE-Portugal	1.00
	India-Hong Kong	0.218
	India-China	**0.025**
	China-Hong Kong	1.00

	Canada-USA	0.074
Bifocals	Netherlands-Italy	0.064
	Netherlands-Spain	0.072
	Netherlands-France	0.759
	Netherlands-UK/EIRE	**0.011**
	Netherlands-Portugal	**0.047**
	Italy-Spain	1.00
	Italy-France	1.00
	Italy-UK/EIRE	1.00
	Italy-Portugal	1.00
	Spain-France	1.00
	Spain-UK/EIRE	1.00
	Spain-Portugal	1.00
	France-UK/EIRE	1.00
	France-Portugal	1.00
	UK/EIRE-Portugal	1.00
	India-Hong Kong	All p=0.162
	India-China	
	China-Hong Kong	
	Canada-USA	0.226
PALs	Netherlands-Italy	0.417
	Netherlands-Spain	
	Netherlands-France	
	Netherlands-UK/EIRE	
	Netherlands-Portugal	
	Italy-Spain	
	Italy-France	
	Italy-UK/EIRE	
	Italy-Portugal	
	Spain-France	
	Spain-UK/EIRE	
	Spain/Portugal	
	France-UK/EIRE	
	France-Portugal	
	UK/EIRE-Portugal	
	India-Hong Kong	All p=0.828

	India-China	
	China-Hong Kong	
	Canada-USA	0.191
RGP (AF)	Netherlands-Italy	1.00
	Netherlands-Spain	1.00
	Netherlands-France	1.00
	Netherlands-UK/EIRE	1.00
	Netherlands-Portugal	**0.004**
	Italy-Spain	1.00
	Italy-France	1.00
	Italy-UK/EIRE	1.00
	Italy-Portugal	**0.044**
	Spain-France	1.00
	Spain-UK/EIRE	1.00
	Spain/Portugal	0.295
	France-UK/EIRE	1.00
	France-Portugal	**p<0.001**
	UK/EIRE-Portugal	**0.003**
	India-Hong Kong	0.679
	India-China	**0.003**
	China-Hong Kong	0.248
	Canada-USA	**0.04**
SV CL	Netherlands-Italy	1.00
	Netherlands-Spain	1.00
	Netherlands-France	0.054
	Netherlands-UK/EIRE	1.00
	Netherlands-Portugal	0.211
	Italy-Spain	1.00
	Italy-France	**0.008**
	Italy-UK/EIRE	1.00
	Italy-Portugal	**0.027**
	Spain-France	**0.003**
	Spain-UK/EIRE	1.00
	Spain-Portugal	**0.011**
	France-UK/EIRE	**0.001**
	France-Portugal	1.00

	UK/EIRE-Portugal	**0.002**
	India-Hong Kong	0.797
	India-China	**0.013**
	China-Hong Kong	**p<0.001**
	Canada-USA	0.636
Standard multifocal contact lenses	Netherlands-Italy	All p=0.367
	Netherlands-Spain	
	Netherlands-France	
	Netherlands-UK/EIRE	
	Netherlands-Portugal	
	Italy-Spain	
	Italy-France	
	Italy-UK/EIRE	
	Italy-Portugal	
	Spain-France	
	Spain-UK/EIRE	
	Spain/Portugal	
	France-UK/EIRE	
	France-Portugal	
	UK/EIRE-Portugal	
	India-Hong Kong	All p=0.208
	India-China	
	China-Hong Kong	
	Canada-USA	0.349
Specific myopia control CL	Netherlands-Italy	1.00
	Netherlands-Spain	1.00
	Netherlands-France	1.00
	Netherlands-UK/EIRE	1.00
	Netherlands-Portugal	1.00
	Italy-Spain	1.00
	Italy-France	1.00
	Italy-UK/EIRE	1.00
	Italy-Portugal	**0.016**
	Spain-France	1.00
	Spain-UK/EIRE	1.00
	Spain/Portugal	**0.036**

	France-UK/EIRE	1.00
	France-Portugal	1.00
	UK/EIRE-Portugal	**0.244**
	India-Hong Kong	**0.035**
	India-China	1.00
	China-Hong Kong	**0.024**
	Canada-USA	0.326
Orthokeratology	Netherlands-Italy	1.00
	Netherlands-Spain	1.00
	Netherlands-France	1.00
	Netherlands-UK/EIRE	1.00
	Netherlands-Portugal	0.140
	Italy-Spain	0.313
	Italy-France	1.00
	Italy-UK/EIRE	1.00
	Italy-Portugal	0.970
	Spain-France	0.982
	Spain-UK/EIRE	1.00
	Spain-Portugal	**0.005**
	France-UK/EIRE	1.00
	France-Portugal	1.00
	UK/EIRE-Portugal	**0.093**
	India-Hong Kong	**p<0.001**
	India-China	**p<0.001**
	China-Hong Kong	**p<0.001**
	Canada-USA	**0.029**
Pharmaceuticals	Netherlands-Italy	All p=0.218
	Netherlands-Spain	
	Netherlands-France	
	Netherlands-UK/EIRE	
	Netherlands-Portugal	
	Italy-Spain	
	Italy-France	
	Italy-UK/EIRE	
	Italy-Portugal	
	Spain-France	

	Spain-UK/EIRE	
	Spain/Portugal	
	France-UK/EIRE	
	France-Portugal	
	UK/EIRE-Portugal	
	India-Hong Kong	0.954
	India-China	**0.027**
	China-Hong Kong	**0.001**
	Canada-USA	0.454
Refractive surgery	Netherlands-Italy	All p=0.295
	Netherlands-Spain	
	Netherlands-France	
	Netherlands-UK/EIRE	
	Netherlands-Portugal	
	Italy-Spain	
	Italy-France	
	Italy-UK/EIRE	
	Italy-Portugal	
	Spain-France	
	Spain-UK/EIRE	
	Spain/Portugal	
	France-UK/EIRE	
	France-Portugal	
	UK/EIRE-Portugal	
	India-Hong Kong	All p=0.241
	India-China	
	China-Hong Kong	
	Canada-USA	0.574

6. What would be the minimum amount of myopia (in dioptres) for you to consider each of the following correction options for a patient?

Globally:

	SVS (D)	Bifocals (D)	PALs (D)	RGP (AF) (D)	SV CL (D)	Standard multifocal CL (D)	Specific MC soft CL (D)	Ortho-K (D)	Pharma-ceuticals (D)	Refractive surgery (D)
Mean ± STDEV	-0.83 ± 0.55	-1.65 ± 1.17	1.71 ± 1.20	-2.40 ± 1.62	-1.44 ± 1.06	-1.77± 1.55	-1.79 ± 1.25	-1.73 ± 1.10	-1.72 ± 1.45	-2.77 ± 1.59
Median, CI 95% []	-1.00 [-1.00, -0.50]	-1.50 [-2.00, -1.00]	-1.50 [-2.00, -1.00]	-2.50 [-3.00, -1.50]	-1.00 [-2.0, -1.00]	-1.50 [-2.50, -1.00]	-1.50 [-2.50, -1.00]	-1.50 [-2.50, -1.00]	-1.00 [-2.0, -1.00]	-3.00 [-3.50, -2.50]

Continents:

Continent		SVS (D)	Bifocals (D)	PALs (D)	RGP (AF) (D)	SV CL (D)	Standard multifocal CL (D)	Specific MC soft CL (D)	Ortho-K (D)	Pharma-ceuticals (D)	Refractive surgery (D)
Asia	**Mean ± STDEV**	-1.20 ± 1.00	-1.84 ± 1.09	-2.13 ± 1.36	-3.14 ± 1.90	-2.63 ± 1.78	-2.64 ± 1.71	-2.69 ± 1.80	-2.37 ± 1.48	-1.64 ± 1.51	-3.53 ± 1.55
	Median, CI 95% []	-1.00 [-1,-1]	2.00 [-2.00,-1.50]	-2.00 [-2.50,-1.00]	-3.00 [-5.00,-1.50]	-2.00 [-3.50,-1.00]	-2.50 [-3,-1]	-2.00 [-3.50,-1.00]	-2.50 [-1,-3]	-1.00 [-2.00,-0.50]	-3.50 [-4,-3]
Australasia	**Mean ± STDEV**	-0.79 ± 0.27	-0.79 ± 0.39	-0.92 ± 0.61	-2.79 ± 1.38	-1.79 ± 0.91	-1.79 ± 1.04	-1.71 ± 0.91	-1.64 ± 0.75	-2.14 ± 0.90	-2.93 ± 1.51
	Median, CI 95% []	-1.00 [-1.00,-0.50]	-0.50 [-1.50,-0.50]	-0.50 [-1.50,-0.50]	-3.00 [-3.00,-1.50]	-1.50 [-3,-1]	-1.50 [-3,-1]	-1.50 [-3,-1]	-1.50 [-3,-1]	-2.50 [-3.00,-1.50]	-3.00 [-5.50,-1.50]
Europe	**Mean ± STDEV**	0.81 ± 0.88	-1.75 ± 1.44	-1.81 ± 1.39	-2.19 ± 1.75	-1.06 ± 0.82	-1.94 ± 1.52	-1.94 ± 1.52	-2.31 ± 1.56	-3.13 ± 1.55	-2.93 ± 1.45

	Median, CI 95% []	-0.50 [-1.75,-0.50]	-1.25 [-3.00,-0.50]	-1.50 [-3.00,-0.50]	-1.00 [-1.00,-0.50]	-1.00 [-1.00,-0.50]	-1.75 [-3.00,-0.50]	-1.75 [-3.00,-0.50]	-2.25 [-3.25,-1.00]	-3.00 [-4.50,-1.75]	-3.00 [-3.75,-1.50]
North America	**Mean ± STDEV**	-0.83 ± 0.69	-1.05 ± 0.69	-1.08 ± 0.73	-1.54 ± 1.39	-0.88 ± 0.68	-1.08 ± 0.73	-1.50 ± 1.17	-1.50 ± 1.15	-1.50 ± 1.30	-1.71 ± 1.32
	Median, CI 95% []	-0.50 [-0.68,-0.50]	-0.75 [-1.50,-0.50]	-0.75 [-1.75,-0.50]	-1.00 [-2.00,-0.50]	-0.50 [-1.00,-0.50]	-0.75[-1.75,-0.50]	-1.25 [-2.00,-0.50]	-1.00 [-2.00,-0.50]	-1.00 [-2.00,-0.50]	-1.25 [-2.62,-0.50]
South America	**Mean ± STDEV**	-1.25 ± 0.35	1.50 ± 0.00	-1.50 ± 0.00	-1.75 ± 0.35	-1.50 ± 0.00	-1.50 ± 0.00	-1.50 ± 0.00	-1.50 ± 0.00	-2.50 ± 2.12	-2.75 ± 1.77
	Median, CI 95% []	-1.25 [bigger sample]	-1.50 [bigger sample]	-1.50 [bigger sample]	-1.75 [bigger sample]	-1.50 [bigger sample]	-1.50 [bigger sample]	-1.50 [bigger sample]	-1.50 [bigger sample]	-2.50 [bigger sample]	-2.75 [bigger sample]

Kruskal-Wallis test:

Myopia management modality		p value
SVS	Australasia-Europe	1.00
	Australasia-North America	1.00
	Australasia-South America	0.468
	Australasia-Asia	**0.005**
	Europe-North America	1.00
	Europe-South America	1.00
	Europe-Asia	**p<0.001**
	North America-South America	1.00
	North America-Asia	**p<0.001**
	South America-Asia	**p<0.001**
Bifocals	Australasia-Europe	**p<0.001**
	Australasia-North America	0.131
	Australasia-South America	**0.010**
	Australasia-Asia	**p<0.001**
	Europe-North America	1.00
	Europe-South America	1.00

	Europe-Asia	0.065
	North America-South America	0.992
	North America-Asia	**0.001**
	South America-Asia	1.00
PALs	Australasia-Europe	**p<0.001**
	Australasia-North America	**0.026**
	Australasia-South America	**0.003**
	Australasia-Asia	**p<0.001**
	Europe-North America	1.00
	Europe-South America	1.00
	Europe-Asia	**0.007**
	North America-South America	1.00
	North America-Asia	**p<0.001**
	South America-Asia	1.00
RGP (AF)	Australasia-Europe	0.074
	Australasia-North America	0.318
	Australasia-South America	1.00
	Australasia-Asia	1.00
	Europe-North America	1.00
	Europe-South America	1.00
	Europe-Asia	**p<0.001**
	North America-South America	1.00
	North America-Asia	**0.004**
	South America-Asia	1.00
SV CL	Australasia-Europe	1.00
	Australasia-North America	1.00
	Australasia-South America	1.00
	Australasia-Asia	**p<0.001**
	Europe-North America	1.00
	Europe-South America	1.00
	Europe-Asia	**p<0.001**
	North America-South America	0.559
	North America-Asia	**p<0.001**
	South America-Asia	**0.002**
Standard multifocal CL	Australasia-Europe	**0.022**

	Australasia-North America	0.942
	Australasia-South America	**0.022**
	Australasia-Asia	**p<0.001**
	Europe-North America	1.00
	Europe-South America	0.547
	Europe-Asia	**0.005**
	North America-South America	0.130
	North America-Asia	**0.001**
	South America-Asia	1.00
Specific MC CL	Australasia-Europe	0.233
	Australasia-North America	0.761
	Australasia-South America	0.972
	Australasia-Asia	**p<0.001**
	Europe-North America	1.00
	Europe-South America	1.00
	Europe-Asia	**0.010**
	North America-South America	1.00
	North America-Asia	0.102
	South America-Asia	0.789
Ortho K **(p=0.001)**	Australasia-Europe	0.106
	Australasia-North America	**0.017**
	Australasia-South America	0.042
	Australasia-Asia	**p<0.001**
	Europe-North America	1.00
	Europe-South America	1.00
	Europe-Asia	**0.004**
	North America-South America	1.00
	North America-Asia	1.00
	South America-Asia	1.00
Pharmaceuticals	Australasia-Europe	1.00
	Australasia-North America	1.00
	Australasia-South America	1.00
	Australasia-Asia	**0.001**
	Europe-North America	1.00
	Europe-South America	1.00

	Europe-Asia	**p<0.001**
	North America-South America	1.00
	North America-Asia	**0.025**
	South America-Asia	**0.001**
Refractive surgery	Australasia-Europe	**0.042**
	Australasia-North America	1.00
	Australasia-South America	1.00
	Australasia-Asia	**0.001**
	Europe-North America	**0.002**
	Europe-South America	**0.007**
	Europe-Asia	1.00
	North America-South America	1.00
	North America-Asia	**p<0.001**
	South America-Asia	**p<0.001**

Countries:

Country		**SVS**	**Bifocals**	**PALs**	**RGP (AF)**	**SV CL**	**Standard multifocal CL**	**Specific MC soft CL**	**Ortho-K**	**Pharma-ceuticals**	**Refracti-ve surgery**
UK, EIRE	Mean ± STDEV	-0.78± 0.51	-1.64 ± 1.01	-1.86 ± 1.21	-1.80 ± 1.12	-1.23 ± 0.80	-1.58 ± 0.80	-1.63 ± 1.01	-1.61 ± 1.11	-2.39 ± 1.87	-2.83 ± 1.37
	Median, CI 95% []	-0.50	-1.50	-2.00	-1.50	-1.00	-1.50	-1.50	-1.50	-1.50	-3.00
Netherlands	Mean ± STDEV	-0.74 ± 0.33	-1.93 ± 1.62	-1.64 ± 1.66	--1.32 ± 0.92	-0.98 ± 0.59	-1.73 ± 1.29	-1.75 ± 1.22	-1.38 ± 1.02	-2.50 ± 2.36	-3.46 ± 1.80
	Median, CI 95% []	-0.50	-1.50	-1.00	-1.00	-1.00	-2.00	-1.75	-1.00	-2.00	-1.50

Spain	Mean ± STDEV	-0.79 ± 0.33	-1.69 ± 1.18	-1.75 ± 1.22	-1.66 ± 1.16	-1.50 ± 1.33	-1.82 ± 0.98	-1.65 ± 1.13	-1.42 ± 0.90	-2.63 ± 2.14	-1.93 ± 0.83
	Median, CI 95% []	-0.75	-1.50	-1.50	-1.50	-1.00	-2.00	-1.00	-1.00	-2.00	-2.00
France	Mean ± STDEV	-0.53 ± 0.19	-2.50 ± 0.50	-2.75 ± 0.88	-2.73 ± 1.25	-1.29 ± 0.91	-2.33 ± 1.75	-1.83 ± 0.76	-1.64 ± 0.77	-2.50 ± 2.12	-2.00 ± 1.00
	Median, CI 95% []	-0.50	-2.50	-2.50	-3.00	-1.00	-2.50	-2.00	-1.50	-2.50	-1.50
Portugal	Mean ± STDEV	-0.72 ± 0.34	-1.88 ± 0.97	-2.19 ± 1.53	-2.83 ± 1.52	-1.34 ± 0.89	-2.12 ± 1.46	-2.05 ± 1.42	-2.54 ± 1.42	-2.25 ± 1.06	-4.36 ± 1.57
	Median, CI 95% []	-0.50	-1.75	-2.00	-2.50	-1.00	-1.50	-1.50	-2.00	-2.25	-5.50
Italy	Mean ± STDEV	-0.74 ± 0.36	-1.58 ± 1.03	-1.52 ± 1.08	-1.98 ± 1.42	-1.23 ± 0.90	-1.55 ± 0.98	1.55 ± 1.13	-1.58 ± 0.93	-3.00 ± 0.00	-4.17 ± 1.08
	Median, CI 95% []	-0.50	-1.50	-1.00	-1.50	-1.00	-1.00	-1.00	-1.50	-3.00	-3.75
India	Mean ± STDEV	-1.05 ± 104	-2.83 ± 1.37	-2.85 ± 1.32	-3.14 ± 1.70	-1.92 ± 1.27	-2.83 ± 1.15	-2.48 ± 1.61	-3.06 ± 1.56	-2.86 ± 1.00	-3.70 ± 1.56
	Median, CI 95% []	-0.50	-3.00	-3.00	-3.00	-1.50	-3.00	-1.75	-3.00	-3.00	-3.50
Hon Kong	Mean ± STDEV	-1.03 ± 0.54	-1.90 ± 0.92	-1.83 ± 0.87	-2.67 ± 1.69	-1.73 ± 1.15	-1.93 ± 1.29	-1.77 ± 1.07	-1.66 ± 0.86	-2.39 ± 1.75	-3.71 ± 1.07
	Median, CI 95% []	-1.00	-2.00	-1.75	-2.00	-1.00	-1.50	-1.50	-1.50	-2.00	-4.00
China	Mean ± STDEV	-0.89 ± 0.51	-1.64 ± 1.07	-1.91 ± 1.17	-2.85 ± 1.87	-2.15 ± 1.47	-2.24 ± 1.67	-2.32 ± 1.66	-1.74 ± 0.98	-0.66 ± 0.39	-3.23 ± 1.59
	Median, CI 95% []	-1.00	-1.00	-1.50	-2.00	-2.00	-2.00	-2.00	-1.50	-0.50	-3.00
Canada	Mean ± STDEV	-0.84 ± 10.57	-1.94 ± 1.27	-2.09 ± 1.22	-2.70 ± 1.75	-1.28 ± 0.99	-1.78 ± 0.81	-1.96 ± - 1.22	2.12 ± 0.64	-3.00 ± 2.79	-1.53 ± 0.59

	Median, CI 95% []	-0.50	-1.75	-2.00	-2.00	-1.00	-1.50	-1.75	-2.00	-3.00	-1.50
USA	Mean ± STDEV	-0.81 ± 0.62	-1.39 ± 1.09	-1.39 ± 1.09	-1.99 ± 1.40	-1.13 ± 0.78	-1.53 ± 1.16	-1.62 ± 1.17	-1.76 ± 1.15	-1.75 ± 1.48	-2.11 ± 1.21
	Median, CI 95% []	-0.50	-1.00	-1.00	-1.50	-1.00	-1.00	-1.00	-1.50	-1.00	-2.00

Kruskal-Wallis test:

Myopia management modality		p value
SVS	Netherlands-Italy	1.00
	Netherlands-Spain	1.00
	Netherlands-France	0.078
	Netherlands-UK/EIRE	1.00
	Netherlands-Portugal	1.00
	Italy-Spain	1.00
	Italy-France	**0.042**
	Italy-UK/EIRE	1.00
	Italy-Portugal	1.00
	Spain-France	**0.002**
	Spain-UK/EIRE	1.00
	Spain/Portugal	1.00
	France-UK/EIRE	**0.044**
	France-Portugal	0.102
	UK/EIRE-Portugal	1.00
	India-Hong Kong	All p=0.50
	India-China	
	China-Hong Kong	
	Canada-USA	0.942
Bifocals	Netherlands-Italy	All p=0.547
	Netherlands-Spain	
	Netherlands-France	
	Netherlands-UK/EIRE	

	Netherlands-Portugal	
	Italy-Spain	
	Italy-France	
	Italy-UK/EIRE	
	Italy-Portugal	
	Spain-France	
	Spain-UK/EIRE	
	Spain-Portugal	
	France-UK/EIRE	
	France-Portugal	
	UK/EIRE-Portugal	
	India-Hong Kong	**0.024**
	India-China	**p<0.01**
	China-Hong Kong	0.541
	Canada-USA	**0.038**
PALs	Netherlands-Italy	All p=0.071
	Netherlands-Spain	
	Netherlands-France	
	Netherlands-UK/EIRE	
	Netherlands-Portugal	
	Italy-Spain	
	Italy-France	
	Italy-UK/EIRE	
	Italy-Portugal	
	Spain-France	
	Spain-UK/EIRE	
	Spain/Portugal	
	France-UK/EIRE	
	France-Portugal	
	UK/EIRE-Portugal	
	India-Hong Kong	**0.002**
	India-China	**0.001**
	China-Hong Kong	1.00
	Canada-USA	**0.012**
RGP (AF)	Netherlands-Italy	0.418
	Netherlands-Spain	1.00

	Netherlands-France	**p<0.001**
	Netherlands-UK/EIRE	0.866
	Netherlands-Portugal	**p<0.001**
	Italy-Spain	1.00
	Italy-France	**0.046**
	Italy-UK/EIRE	1.00
	Italy-Portugal	0.087
	Spain-France	**0.005**
	Spain-UK/EIRE	1.00
	Spain/Portugal	**0.011**
	France-UK/EIRE	**0.024**
	France-Portugal	1.00
	UK/EIRE-Portugal	**0.047**
	India-Hong Kong	All p=0.525
	India-China	
	China-Hong Kong	
	Canada-USA	0.108
SV CL	Netherlands-Italy	All p=0.096
	Netherlands-Spain	
	Netherlands-France	
	Netherlands-UK/EIRE	
	Netherlands-Portugal	
	Italy-Spain	
	Italy-France	
	Italy-UK/EIRE	
	Italy-Portugal	
	Spain-France	
	Spain-UK/EIRE	
	Spain-Portugal	
	France-UK/EIRE	
	France-Portugal	
	UK/EIRE-Portugal	
	India-Hong Kong	0.308
	India-China	
	China-Hong Kong	
	Canada-USA	0.301

Standard multifocal contact lenses	Netherlands-Italy	All p=0.426
	Netherlands-Spain	
	Netherlands-France	
	Netherlands-UK/EIRE	
	Netherlands-Portugal	
	Italy-Spain	
	Italy-France	
	Italy-UK/EIRE	
	Italy-Portugal	
	Spain-France	
	Spain-UK/EIRE	
	Spain/Portugal	
	France-UK/EIRE	
	France-Portugal	
	UK/EIRE-Portugal	
	India-Hong Kong	0.058
	India-China	0.090
	China-Hong Kong	1.00
	Canada-USA	0.086
Specific myopia control CL	Netherlands-Italy	All p=0.458
	Netherlands-Spain	
	Netherlands-France	
	Netherlands-UK/EIRE	
	Netherlands-Portugal	
	Italy-Spain	
	Italy-France	
	Italy-UK/EIRE	
	Italy-Portugal	
	Spain-France	
	Spain-UK/EIRE	
	Spain/Portugal	
	France-UK/EIRE	
	France-Portugal	
	UK/EIRE-Portugal	
	India-Hong Kong	All p=0.232

	India-China	
	China-Hong Kong	
	Canada-USA	0.149
Orthokeratology	Netherlands-Italy	1.00
	Netherlands-Spain	1.00
	Netherlands-France	0.961
	Netherlands-UK/EIRE	1.00
	Netherlands-Portugal	**p<0.001**
	Italy-Spain	1.00
	Italy-France	1.00
	Italy-UK/EIRE	1.00
	Italy-Portugal	**0.005**
	Spain-France	1.00
	Spain-UK/EIRE	1.00
	Spain-Portugal	**0.002**
	France-UK/EIRE	1.00
	France-Portugal	0.431
	UK/EIRE-Portugal	**0.09**
	India-Hong Kong	**p<0.001**
	India-China	**p=0.001**
	China-Hong Kong	1.00
	Canada-USA	**0.028**
Pharmaceuticals	Netherlands-Italy	All p=0.986
	Netherlands-Spain	
	Netherlands-France	
	Netherlands-UK/EIRE	
	Netherlands-Portugal	
	Italy-Spain	
	Italy-France	
	Italy-UK/EIRE	
	Italy-Portugal	
	Spain-France	
	Spain-UK/EIRE	
	Spain/Portugal	
	France-UK/EIRE	
	France-Portugal	

	UK/EIRE-Portugal	
	India-Hong Kong	0.643
	India-China	**p<0.001**
	China-Hong Kong	**p<0.001**
	Canada-USA	0.059
Refractive surgery	Netherlands-Italy	**0.043**
	Netherlands-Spain	1.00
	Netherlands-France	1.00
	Netherlands-UK/EIRE	1.00
	Netherlands-Portugal	**0.001**
	Italy-Spain	0.322
	Italy-France	0.139
	Italy-UK/EIRE	1.00
	Italy-Portugal	1.00
	Spain-France	1.00
	Spain-UK/EIRE	1.00
	Spain-Portugal	0.075
	France-UK/EIRE	1.00
	France-Portugal	**0.015**
	UK/EIRE-Portugal	0.436
	India-Hong Kong	All p=0.354
	India-China	
	China-Hong Kong	
	Canada-USA	0.117

7. **What is the minimum level of myopia progression you consider necessitates a myopia control approach?**

Globally:

0.01-0.25 D/per year	0.26-0.50 D/per year	0.51-0.75 D/per year	0.76-1.00 D/per year	>1.00 D/per year	MC is not warranted
60	216	301	199	132	60
6.2	22.3	31.1	20.6	13.6	6.2

Continent:

Continent	0.01-0.25 D/per year		0.26-0.50 D/per year		0.51-0.75 D/per year		0.76-1.00 D/per year		>1.00 D/per year		MC is not warranted	
	Number	%	Number	%	Number	%	Number	%	Number	%	Number	%
Asia	8	2.8	42	14.4	89	30.6	88	30.2	54	18.6	10	3.4
Australasia	6	5	49	41.2	39	73.9	15	12.6	7	5.6	3	2.5
Europe	32	9.5	82	24.4	124	36.9	50	14.9	32	9.5	16	4.8
North America	8	6	22	16.5	34	25.6	30	22.6	24	18	15	11.3
South America	6	7.3	19	23.2	13	15.9	15	18.3	13	15.9	16	19.5

Kruskal-Wallis test:

Australasia-North America	**p<0.001**
Australasia - Asia	**p<0.001**
Australasia-Europe	0.854
Australasia-South America	**p<0.001**
North America-Asia	1.00
North America-Europe	**p<0.001**
North America-South America	1.00
Asia-Europe	**p<0.001**
Asia-South America	1.00
Europe-South America	**0.003**

Countries:

Countries	0.01-0.25 D/per year		0.26-0.50 D/per year		0.51-0.75 D/per year		0.76-1.00 D/per year		>1.00 D/per year		MC is not warranted	
	Number	%	Number	%	Number	%	Number	%	Number	%	Number	%
UK/EIRE	6	11.8	12	23.5	16	31.4	9	17.6	5	15.7	3	5.9
Netherlands	5	13.2	4	10.5	19	50	4	10.5	4	10.5	2	5.3
Spain	1	2.9	15	44.1	13	38.2	4	11.8	1	2.9	0	0
France	1	3	4	12.1	13	39.4	5	15.2	7	21.2	1	3
Portugal	3	6.3	6	12.5	21	43.8	8	16.7	8	16.7	2	4.2
Italy	10	13.9	23	31.9	16	22.2	11	15.3	4	5.6	8	11.1
India	0	0	7	18.9	10	27	7	18.9	10	27	3	11.1
Hong Kong	2	3.2	9	14.5	16	25.8	20	32.3	10	16.1	5	8.1
China3	3	2.2	15	11	55	40.4	40	29.4	22	16.2	1	0.7
Canada	0	0	3	9.1	9	27.3	10	30.3	5	15.2	6	18.2
USA	8	8	19	19	25	25	20	20	19	19	9	9

Kruskal-Wallis test: Europe distribution is not significantly different (p=0.09), Asia distribution is not significantly different (p=0.365), North America distribution is not significantly different (p=0.057).

Other (specify) - 40 responses

- Subjective to patients refractive error, family history and lifestyle (2) and other combination (3)
- Age of myopia onset (10 or 25%)
- Refractive error of patient (2)
- Environmental factors/lifestyle (6)
- Family history of myopia (6)
- Depending on preferred myopia management strategy (1)
- Depending on parent's decision (e.g. financial considerations) (3)
- Lightning levels/time spent outdoors (3)
- Not sure as abnormal progression rates of myopia are not defined (1)
- No experience in controlling myopia progression (1)
- Esophoria (1)

- K readings (1)
- Axial length (2)
- Motivation of patient (1)
- Body posture 2
- % of relative growth in body height 1

8. Do you use undercorrection as a strategy to slow myopia progression?

Globally:

No	Sometimes	Always
705	223	41
72.7%	23%	4.2%

Regionally:

Continent	No		Sometimes		Always	
	Number	%	Number	%	Number	%
Asia	221	75.9	61	20.96	9	3.09
Australasia	95	79.8	21	17.64	3	2.52
Europe	236	69.3	86	25.4	17	5
North America	104	78.2	28	21.1	1	0.7
South America	48	58.5	24	29.27	10	12.19

Kruskal-Wallis test:

Australasia-North America	1.00
Australasia - Asia	1.00
Australasia-Europe	0.267
Australasia-South America	**0.003**
North America-Asia	1.00
North America-Europe	0.350
North America-South America	**0.004**
Asia-Europe	0.618
Asia-South America	**0.006**
Europe-South America	0.234

Countries:

Countries	No		Sometimes		Always	
	Number	%	Number	%	Number	%
UK/EIRE	46	88.5	6	11.5	0	0
Netherlands	28	73.7	9	23.7	1	2.6
Spain	19	55.9	14	41.2	1	2.9
France	27	81.8	6	17.6	0	0
Portugal	26	54.2	16	33.3	6	12.5
Italy	47	65.3	22	30.5	3	4.2
India	16	43.2	18	48.7	3	8.1
Hong Kong	55	88.7	6	9.7	1	1.6
China	114	83.8	19	14	3	2.2
Canada	25	75.8	8	24.2	0	0
USA	79	79	20	20	1	1

Kruskal-Wallis test:

UK/EIRE-France	1.00
UK/EIRE-Netherlands	1.00
UK/EIRE-Italy	0.92
UK/EIRE-Spain	**0.028**
UK/EIRE-Portugal	**0.001**

France-Netherlands	1.00
France-Italy	1.00
France-Spain	0.345
France-Portugal	0.058
Netherlands-Italy	1.00
Netherlands-Spain	1.00
Netherlands-Portugal	0.466
Italy-Spain	1.00
Italy-Portugal	1.00
Spain-Portugal	1.00
Hong Kong-China	1.00
Hong Kong-India	**p<0.001**
China-India	**p<0.001**
Canada-USA	0.719

9. **If you have ever fitted single vision spectacles/ contact lenses for myopic patients, what has prevented you prescribing an alternative method?**

Globally:

Reason	%
Not more effective	23.8
Unpredictable outcome	28.2
Safety concerns	25.3
Uneconomical	35.6
Additional chair time	7.9
Inadequate information	33.3
Benefit/risk ratio	20.5

Asia:

Reason	%
Not more effective	11.4
Unpredictable outcome	30.5
Safety concerns	47.9
Uneconomical	40.7
Additional chair time	10.6
Inadequate information	24.6
Benefit/risk ratio	29.2

Australasia:

Reason	%
Not more effective	16.1
Unpredictable outcome	31.4
Safety concerns	41
Uneconomical	41
Additional chair time	10
Inadequate information	28
Benefit/risk ratio	28

Europe:

Reason	%
Not more effective	23.3
Unpredictable outcome	23.3
Safety concerns	15.7
Uneconomical	33.7
Additional chair time	4.3
Inadequate information	39.5
Benefit/risk ratio	15.2

North America:

Reason	%
Not more effective	37.8
Unpredictable outcome	39
Safety concerns	9.8

Uneconomical	35.4
Additional chair time	9.8
Inadequate information	34.1
Benefit/risk ratio	17.1

South America:

Reason	%
Not more effective	39.4
Unpredictable outcome	19.7
Safety concerns	8.5
Uneconomical	19.7
Additional chair time	4.2
Inadequate information	42.3
Benefit/risk ratio	9.9

23.68Kruskal-Wallis test for continents: distribution between continents is the same (all p=1.00)

UK/EIRE:

Reason	%
Not more effective	31
Unpredictable outcome	34.5
Safety concerns	6.9
Uneconomical	24.1
Additional chair time	10.3
Inadequate information	65.5
Benefit/risk ratio	6.9

Netherlands:

Reason	%
Not more effective	19.2
Unpredictable outcome	34.6
Safety concerns	34.6
Uneconomical	38.5
Additional chair time	0
Inadequate information	19.2
Benefit/risk ratio	23.1

Spain:

Reason	%
Not more effective	11.8
Unpredictable outcome	23.5
Safety concerns	17.6
Uneconomical	52.9
Additional chair time	5.9
Inadequate information	11.8
Benefit/risk ratio	17.6

France:

Reason	%
Not more effective	29.6
Unpredictable outcome	7.4
Safety concerns	11.1
Uneconomical	11.1
Additional chair time	3.7
Inadequate information	29.6
Benefit/risk ratio	20.5

Portugal:

Reason	%
Not more effective	21.4
Unpredictable outcome	16.7
Safety concerns	14.3
Uneconomical	28.6
Additional chair time	2.4
Inadequate information	64.3
Benefit/risk ratio	26.2

Italy:

Reason	%
Not more effective	13.3
Unpredictable outcome	36.7
Safety concerns	20
Uneconomical	40
Additional chair time	10
Inadequate information	40
Benefit/risk ratio	6.7

Kruskal-Wallis test for Europe: distribution between countries is the same (all p=1.00)

India:

Reason	%
Not more effective	10.8
Unpredictable outcome	48.6
Safety concerns	35.1
Uneconomical	40.5
Additional chair time	5.4
Inadequate information	21.6
Benefit/risk ratio	32.4

Hong Kong:

Reason	%
Not more effective	11.1
Unpredictable outcome	20
Safety concerns	53.3
Uneconomical	40
Additional chair time	8.9
Inadequate information	11.1

Benefit/risk ratio	33.3

China:

Reason	%
Not more effective	7.1
Unpredictable outcome	29.5
Safety concerns	52.7
Uneconomical	41.1
Additional chair time	10.7
Inadequate information	31.3
Benefit/risk ratio	25.9

Kruskal-Wallis test for Asia: distribution between countries is the same (all p=1.00)

Canada:

Reason	%
Not more effective	52
Unpredictable outcome	52
Safety concerns	20
Uneconomical	40
Additional chair time	16
Inadequate information	52
Benefit/risk ratio	24

USA:

Reason	%
Not more effective	31.6
Unpredictable outcome	33.3
Safety concerns	5.3
Uneconomical	33.3
Additional chair time	7
Inadequate information	26.3
Benefit/risk ratio	14

Kruskal-Wallis test for North America: distribution between countries is the same (all p=1.00)

Other (specify) – 95 responses

- **N/A or e.g. is fitting Ortho-K or using other methods (36 or 37,89%)**
- Insufficient amount of myopic patients to make it profitable/financially profitable (3)
- Not actual due to e.g. practice location or patients' demographics (2)
- Inadequate information/contradictory information, no clear standards or regulations (19)
- Decision of parents/patients (financial consideration, lack of knowledge about MC, motivation) or wish not to slow but stop myopia progression (20)

- Confusing question construction (1); maybe should have been paraphrased as ‘If you mostly prescribe SVS….’(M.Z.)
- The predictability of outcome and clinical relevance (4)
- Vision therapy as an alternative (2)
- Availability of MC interventions and required optometric instrumentation (6)
- Rate of progression (1)
- Role of genetics (cannot be change with optical means) (1)
- No experience in controlling myopia progression (1)
- Age of myopia onset (1)
- Outdoor activity (2)

10. Demographics

Geographical distribution:

Continent	Number of responses	%
Africa	6	0.6
Asia	291	30
Australasia	119	12.3
Europe	339	34.9
North America	133	13.8
South America	82	8.4
Total	970	

Country	Number of responses	%
UK, EIRE	52	5.36
Netherlands	38	3.91
Spain	34	3.50
France	34	3.50
Portugal	48	4.94
Italy	72	7.42
India	37	3.91
Hong Kong	61	6.28
China	137	14.12
Canada	33	3.40
USA	100	10.40

Profession:

Globally:

Optometrist	703	72.4%
Ophthalmologist	181	18.6%
Contact lens optician	56	5.8%
Other	31	3.2%

Africa:

Optometrist	5	83.3%
Ophthalmologist	1	16.7%
Contact lens optician	0	0%
Other	0	0%
Total	6	

Asia:

Optometrist	178	61.2%
Ophthalmologist	84	28.9%
Contact lens optician	1	0.3%
Other	28	9.6%
Total	291	

Australasia:

Optometrist	118	99.2%
Ophthalmologist	1	0.8%
Contact lens optician	0	0%
Other	0	0%
Total	119	

Europe:

Optometrist	244	72%
Ophthalmologist	41	12.1%
Contact lens optician	51	15%
Other	3	0.9%
Total	331	

North America:

Optometrist	103	99%
Ophthalmologist	0	0%
Contact lens optician	1	1%
Other	0	0%
Total	104	

South America:

Optometrist	26	31.7%
Ophthalmologist	54	65.9%
Contact lens optician	2	2.4%
Other	0	0%
Total	82	

UK/EIRE:

Optometrist	40	76.9%
Ophthalmologist	0	0%
Contact lens optician	12	23.1%
Other	0	0%
Total	52	

Netherlands:

Optometrist	28	73.7%
Ophthalmologist	0	0%
Contact lens optician	9	23.7%
Other	1	2.6%
Total	38	

Spain:

Optometrist	29	85.3%
Ophthalmologist	0	0%
Contact lens optician	5	14.7%
Other	0	0%
Total	34	

France:

Optometrist	0	0%
Ophthalmologist	33	97.1%
Contact lens optician	0	0%
Other	1	2.9%

Total	34	

Portugal:

Optometrist	45	93.8%
Ophthalmologist	2	4.2%
Contact lens optician	0	0%
Other	1	2.1%
Total	48	

Italy:

Optometrist	58	80.6%
Ophthalmologist	0	0%
Contact lens optician	14	19.4%
Other	0	0%
Total	72	

Hong Kong:

Optometrist	59	95.2%
Ophthalmologist	1	1.6%
Contact lens optician	0	0%
Other	2	3.2%
Total	62	

China:

Optometrist	28	20.6%
Ophthalmologist	82	60.3%
Contact lens optician	1	0.7%
Other	25	18.4%
Total	148	

India:

Optometrist	36	97.3%
Ophthalmologist	0	0%
Contact lens optician	0	0%
Other	1	2.7%
Total	37	

USA:

Optometrist	99	99%
Ophthalmologist	0	0%
Contact lens optician	1	1%
Other	0	0%
Total	100	

Canada:

Optometrist	33	100%
Ophthalmologist	0	0%

Contact lens optician	0	0%
Other	0	0%
Total	33	

Principal working environment:

Globally:

Practice	816	84%
Academic	110	11.3%
Industry	19	2%
Other	26	2.7%

Africa:

Practice	2	33.3%
Academic	1	16.7%
Industry	3	50%
Other	0	0%

Asia:

Practice	255	87.6%
Academic	20	6.9%
Industry	7	2.4%
Other	9	3.1%

Australasia:

Practice	110	92.4%
Academic	6	5%
Industry	0	0%
Other	3	2.5%

Europe:

Practice	307	90.6%
Academic	13	3.8%
Industry	7	2.1%
Other	10	2.9%

North America:

Practice	117	88%
Academic	12	9.0%
Industry	2	1.5%
Other	2	1.5%

South America:

Practice	24	29.3%
Academic	58	70.7%
industry	0	0%

Other	0	0%

UK/EIRE:

Practice	46	88.5%
Academic	2	3.8%
Industry	4	0%
Other	52	0%

Netherlands:

Practice	33	86.8%
Academic	0	0%
Industry	3	7.9%
Other	2	5.3%

Spain:

Practice	29	85.3%
Academic	4	11.8%
Industry	0	0%
Other	1	2.9%

France:

Practice	32	94.1%
Academic	0	0%
industry	0	0%
Other	2	5.9%

Portugal:

Practice	42	87.5%
Academic	3	6.3%
Industry	1	2.1%
Other	2	4.2%

Italy:

Practice	69	95.8%
Academic	1	1.4%
industry	1	1.4%
Other	1	1.4%

India:

Practice	29	78.4%
Academic	5	13.5%
industry	1	2.7%
Other	2	5.4%

Hong Kong:

Practice	57	91.9%
Academic	5	8.1%
industry	0	0%

Other	0	0%

China:

Practice	126	92.6%
Academic	2	1.5%
industry	2	1.5%
Other	6	4.4%

Canada:

Practice	32	97%
Academic	1	3%
industry	0	0%
Other	0	0%

USA:

Practice	85	85%
Academic	11	11%
industry	2	2%
Other	2	2%

Years being qualified:

Globally:

0	13	1.3%
1-5	161	16.6%
6-10	153	15.8%
11-20	252	26 5%
21-30	220	22.7%
31 or more	172	17.7%

Africa:

0	13	1.3%
1-5	161	16.6%
6-10	153	15.8%
11-20	252	26 5%
21-30	220	22.7%
31 or more	172	17.7%

Asia:

0	13	1.4%
1-5	80	27.5%
6-10	65	22.3%
11-20	76	26.1%
21-30	45	15.5%
31 or more	21	7.2%

Australasia:

0	5	4.2%

1-5	14	11.8%
6-10	16	13.4%
11-20	24	20.2%
21-30	32	26.9%
31 or more	28	23.5%

Europe:

0	2	0.6%
1-5	46	13.6%
6-10	35	10.3%
11-20	92	27.1%
21-30	92	27.1%
31 or more	72	21.2%

North America

0	1	0.7%
1-5	13	9.7%
6-10	21	15.7%
11-20	31	23.1%
21-30	35	26.1%
31 or more	33	24.6%

South America:

0	1	1.2%
1-5	8	9.8%
6-10	15	18.3%
11-20	26	31.7%
21-30	16	19.5%
31 or more	16	19.5%

UK/EIRE:

0	0	0%
1-5	3	5.8%
6-10	2	3.8%
11-20	9	17.3%
21-30	16	30.8%
31 or more	22	42.3%

Netherlands:

0	0	0%
1-5	6	15.8%
6-10	5	13.2%
11-20	14	36.8%
21-30	6	15.8%
31 or more	7	18.4%

Spain:

0	0	0%
1-5	2	5.9%
6-10	1	2.9%
11-20	13	38.2%
21-30	16	47.1%
31 or more	2	5.9%

France:

0	1	2.9%
1-5	1	2.9%
6-10	2	5.9%
11-20	6	17.6%
21-30	14	41.2%
31 or more	10	29.4%

Portugal:

0	0	0%
1-5	18	37.5%
6-10	11	22.9%
11-20	17	35.4%
21-30	1	2.1%
31 or more	1	2.1%

Italy:

0	1	1.4%
1-5	6	8.3%
6-10	5	6.9%
11-20	14	19.4%
21-30	28	38.9%
31 or more	18	25%

India:

0	2	5.4%
1-5	8	21.6%
6-10	7	18.9%
11-20	12	32.4%
21-30	5	13.5%
31 or more	3	8.1%

Hong Kong:

0	0	0%
1-5	18	29%
6-10	15	24.2%
11-20	14	22.6%
21-30	14	22.6%
31 or more	1	1.6%

China:

0	2	1.5%
1-5	36	26.5%
6-10	34	25%
11-20	37	27.2%
21-30	17	12.5%
31 or more	10	7.4%

Canada:

0	1	3%
1-5	5	15.2%
6-10	8	24.2%
11-20	7	21.2%
21-30	4	12.1%
31 or more	8	24.2%

USA:

0	0	0%
1-5	8	8%
6-10	13	13%
11-20	24	24%
21-30	31	31%
31 or more	24	24%

Any further comments.
148 comments left.

- Skull size/body physiology/relative speed of growth should be taken into consideration (3)
- Axial length/peripheral refraction (3)
- Not actual due to e.g. practice location or patients' demographics (3)
- **Immediate action is required/promotion of public/professional awareness (32 or 21.16%)**
- Availability of funding form government health funding organisations (1)
- Current approaches are not effective (3)
- Management approach depends of patient's age (1)
- Specialisation of practice (e.g. high street/independent) (2)
- **Inadequate information/contradictory/ insufficient information, no clear standards or regulations, availability of certified MC interventions (27 or 18.24%)**
- **Ortho-K has been proven to be most effective form clinical observations in everyday practice (13 or 8.78%)**
- **Lifestyle/the role of outdoor/visual habits/individually selective outcome (18 or 12.16%)**
- Decision of parents/patients (financial consideration, lack of knowledge about MC, motivation) or wish not to slow but stop myopia progression (9)
- The role of accommodation/vergence system (4)
- **Age of myopia onset (34 or 22.97%)**
- Actively prescribing MC interventions 5 to 10 years (6)

- Criticised questions 4, 5 and 6 – the way questions are formulated will give skewed results, negative percentage would not be accepted (as in case of undercorrection), …not only for myopic patients was misleading, found the inclusion of refractive surgery ‘silly’ (6)
- Vision therapy as an alternative (4)
- Full correction at distance, none for near work (remove glasses at near or put reading glasses on SV CL (2)
- The predictability of outcome and clinical relevance (4)
- Diluted atropine (1)

Appendix 2: Long term corneal biomechanical response to orthokeratology and the role of anterior eye segment in myopic schoolchildren

ORA parameter (Mean±SD)	Group	Visit					K-S test for normality	Effect of time (Repeated Measure ANOVA)		Effect of group (Repeated Measure ANOVA)	
		BL	6 months	12 months	18 months	24 months	p	p	F	p	F
IOPg (mmHg)	SVS	15.40±2.78	15.67±3.35	15.11±3.03	15.40±3.26	15.11±3.16	0.340	0.046	2.465	0.032	4.71
	OK	14.66±2.89	14.93±2.72	14.30±2.71	14.68±2.80	14.52±3.02	0.389	0.536	0.748		
IOPcc (mmHg)	SVS	15.07±2.88	15.44±3.21	14.66±2.94	14.74±3.39	14.64±2.92	0.868	0.005	3.891	0.589	0.29
	OK	14.73±3.26	14.97±2.54	14.50±2.93	14.88±2.98	14.66±3.06	0.150	0.603	0.686		
CH (mmHg)	SVS	11.17±1.55	11.05±1.52	11.30±1.37	11.48±1.61	11.34±1.50	0.847	0.019	3.028	0.012	6.64
	OK	10.90±1.59	10.88±1.43	10.82±1.52	10.76±1.77	10.85±1.79	0.740	0.933	0.13		
CRF (mmHg)	SVS	11.03±1.58	11.00±1.69	11.07±1.51	11.29±1.64	11.09±1.72	0.958	0.515	0.818	0.005	8.22
	OK	10.59±1.46	10.65±1.59	10.41±1.48	10.47±1.77	10.51±1.86	0.899	0.912	0.168		
slew1:	SVS	62.03±18.39	59.55±20.64	56.82±16.60	61.37±24.65	66.79±26.53	0.946	0.049	2.43	0.945	0.005
	OK	64.45±22.90	61.19±21.81	61.27±24.53	58.13±19.12	60.89±23.18	0.705	0.05	2.418		
slew2:	SVS	82.07±30.73	89.28±30.95	76.31±31.64	86.21±35.56	88.92±36.43	0.604	0.036	2.622	0.734	0.12
	OK	86.64±33.80	87.11±30.56	83.55±26.23	82.12±29.59	82.68±30.65	0.759	0.262	1.34		
mslew1:	SVS	100.5±28.4	92.59±30.89	88.54±22.25	98.89±34.03	105.4±36.3	0.982	0.007	3.619	0.753	0.10
	OK	100.3±28.5	97.2±26.2	99.4±33.4	92.9±28.3	93.5±29.1	0.402	0.003	4.087		
mslew2:	SVS	122.7±40.5	120.8±37	115.9±35.8	127.7±45.8	133.4±45.4	0.890	0.025	2.858	0.871	0.03

	OK	127.3±43.3	126.1±36.6	121.7±33.3	123.1±44.7	121.8±37.5	0.490	0.109	1.918		
dive1:	**SVS**	325.8±97.8	300.8±111.3	298.4±77	309±130.3	329.3±118.1	0.836	0.146	1.725	0.222	1.51
	OK	322.3±101.4	296.5±104.8	302.9±108.9	302.3±101.6	305.2±101.2	0.152	2.537	0.042		
dive2:	**SVS**	246.2±82	233.5±76.3	219.5±68	243.3±92.6	255.7±107	0.868	2.746	0.03	0.418	0.66
	OK	252.3±79.4	248.6±76.5	226.2±70	231±79.3	246.7±91.1	0.801	1.231	0.299		
aindex:	**SVS**	9.46±0.95	9.45±0.76	9.68±0.41	9.57±0.67	9.62±0.62	<0.001*	4.545	0.337	0.255	1.31
	OK	9.49±0.63	9.31±0.82	9.50±0.73	9.40±0.83	9.48±0.65	<0.001*	10.53	0.032		
bindex:	**SVS**	9.41±1.50	9.59±0.99	9.33±1.46	9.54±1.02	9.69±0.68	<0.001*	4.313	0.365	0.652	0.20
	OK	9.65±0.88	9.72±0.66	9.58±0.85	9.47±1.00	9.71±0.63	<0.001*	3.31	0.507		
aplhf:	**SVS**	1.37±0.74	1.27±0.37	1.27±0.36	1.28±0.34	1.23±0.33	0.001*	1.382	0.847	0.719	0.13
	OK	1.30±0.36	1.28±0.33	1.25±0.30	1.35±0.43	1.25±0.31	0.028*	1.92	0.750		
Values from upper 75% of peak											
p1area:	**SVS**	3456±838	3293±859	3020±777	3412±1113	3475±1087	0.833	3.599	0.012	0.155	2.05
	OK	3305±854	3332±971	3215±876	3146±786	3167±861	0.818	1.673	0.17		
p2area:	**SVS**	2155±731	1961±718	1940±591	2058±712	2241±814	0.974	1.64	0.178	0.232	1.45
	OK	2201±776	2113±702	2089±753	1958±765	2123±762	0.610	2.016	0.108		
h1:	**SVS**	371.5±78.01	348.3±90.5	326.1±70.2	365.1±110	376.2±108.2	0.458	4.722	0.003	0.455	0.56
	OK	366.8±81.7	359.8±81.4	354.2±90.2	349±83.4	345.5±92.7	0.515	3.254	0.013		
h2:	**SVS**	307.3±89.8	292.5±76.7	278.4±64.9	307.9±86.8	322.3±94.1	0.745	3.533	0.013	0.492	0.48
	OK	316.8±80.8	310.9±80.6	298.1±71.8	291.4±83.1	303.3±84	0.948	2.385	0.053		
w1:	**SVS**	22.13±2.19	22.63±2.31	22.12±7.64	22.11±2.75	22.15±2.55	0.123	0.409	0.802	0.696	0.15
	OK	21.77±2.83	22.31±2.67	21.96±3.07	22.04±2.33	22.42±2.71	0.308	1.387	0.24		
w2:	**SVS**	16.94±3.63	16.43±4.08	22.15±2.65	16.08±3.83	16.71±4.50	0.287	1.289	0.276	0.159	2.02
	OK	16.58±4.27	16.28±3.81	16.78±3.82	16.18±4.49	17.11±3.89	0.139	0.982	0.088		

aspect1:	**SVS**	16.97±3.96	15.57±4.50	14.95±3.98	16.81±5.52	17.23±5.41	0.927	3.461	0.009	0.663	0.191
	OK	17.13±4.28	16.35±4.04	16.53±5.32	16.05±4.35	15.75±4.77	0.397	2.966	0.021		
aspect2:	**SVS**	18.99±6.79	19.20±8.06	16.73±5.48	20.32±8.29	20.94±9.29	0.238	2.356	0.069	0.661	0.193
	OK	20.41±7.58	20.25±7.43	18.71±6.18	19.26±7.91	18.67±6.67	0.051	2.123	0.08		
uslope1:	**SVS**	62.24±18.05	58.87±20.22	56.74±16.16	61.78±23.62	66.90±26.60	0.893	2.476	0.046	0.971	0.001
	OK	64.34±22.14	61.78±20.66	61.46±22.24	58.27±18.58	60.27±22.58	0.373	2.12	0.08		
uslope2:	**SVS**	81.28±30.74	85.74±30.68	76.11±31.71	85.57±36.33	89.42±35.51	0.550	2.818	0.026	0.641	0.22
	OK	86.70±33.68	87.11±30.56	83.55±26.23	81.78±30.07	83.14±29.88	0.740	1.353	0.257		
dslope1:	**SVS**	24.07±6.24	22.12±6.71	21.09±6.46	23.85±8.25	24.01±7.42	0.241	2.742	0.03	0.669	0.184
	OK	24.13±6.29	23.14±6.30	23.52±7.99	22.93±6.77	22.21±7.14	0.622	2.807	0.027		
dslope2:	**SVS**	25.70±10.59	26.23±14.50	22.12±7.64	27.75±12.58	28.56±15.17	0.129	1.789	0.147	0.922	0.01
	OK	27.86±11.92	26.88±10.19	24.39±9.36	26.36±13.24	24.84±10	0.058	2.046	0.09		
path1:	**SVS**	21.29±3.62	20.99±2.79	21.44±4.07	20.91±2.95	21.22±2.87	0.537	0.348	0.845	0.233	1.44
	OK	21.93±3.27	21.69±3.47	21.85±4.32	21.82±3.26	21.49±3.93	0.992	1.208	0.309		
path2:	**SVS**	27.22±7.32	29.03±9.05	27.80±8.46	28.88±8.30	27.28±6.75	0.207	0.638	0.636	0.333	0.95
	OK	27.90±8.39	27.85±6.24	26.93±7.06	28.69±7.16	27.08±5.32	0.187	0.153	0.962		
Values from upper 50% of peak											
p1area:	**SVS**	1495±414	1407±382	1296±363	1465±541	1462±469	0.920	3.176	0.023	0.115	2.54
	OK	1389±390	1411±455	1376±424	1328±367	1328±401	0.973	1.129	0.341		
p2area:	**SVS**	930±315	840±310	837±267	908±330	988±357	0.955	1.517	0.207	0.379	0.78
	OK	972±340	921±310	919±356	854±331	927±340	0.738	2.192	0.084		
h1:	**SVS**	247.7±52	232.2±60.3	217.4±46.8	243.4±73.3	250.8±72.1	0.458	4.722	0.003	0.455	0.56
	OK	244.5±54.4	239.9±54.2	236.1±60.2	232.7±55.6	230.4±61.8	0.515	3.254	0.013		
	SVS	204.9±59.9	195±51.1	185.8±43.3	205.2±57.9	214.8±62.7	0.745	3.533	0.013		

h2	**OK**	211.2±53.9	207.3±53.7	198.8±47.9	194.3±55.4	202.2±56	0.948	2.385	0.053	0.492	0.475
w1:	**SVS**	11.22±2.16	11.73±1.96	11.24±2.00	11.37±2.16	11.63±1.91	0.388	0.128	0.972	0.393	0.74
	OK	10.95±2.20	11.31±2.28	11.23±2.32	11±2.11	11.31±2.18	0.007*	2.34	0.674		
w2:	**SVS**	8.5±2.28	7.91±2.14	8.29±2.68	7.93±2.31	8.35±2.14	0.025*	1.239	0.872	0.203	1.65
	OK	8.31±2.58	8.11±2.09	8.26±2.38	7.89±2.20	8.13±1.87	0.045*	3.89	0.420		
aspect1:	**SVS**	23.09±7.36	20.49±7.53	20.13±6.38	22.13±7.36	22.29±7.62	0.218	2.114	0.08	0.93	0.008
	OK	23.22±6.64	22.16±6.87	22.51±9.74	22.17±7.70	21.58±8.18	0.904	2.826	0.026		
aspect2:	**SVS**	26.24±12.14	26.90±12.18	25.13±10.81	27.92±11.33	27.59±10.79	0.200	0.977	0.421	0.865	0.03
	OK	27.76±10.91	27.26±9.70	25.87±9.17	26.46±11.95	26.05±9.04	0.402	0.979	0.421		
uslope1:	**SVS**	59.08±23.27	53.83±21.71	55.60±20.09	58.28±23.81	63.26±28.89	0.538	2.046	0.089	0.821	0.05
	OK	62.98±24.10	57.60±23.29	58.12±24.86	55.85±23.84	58.70±24.19	0.699	2.308	0.06		
uslope2:	**SVS**	68.64±26.63	69.01±29.83	62.23±29.30	70.48±28.71	72.33±30.99	0.516	1.838	0.123	0.973	0.001
	OK	70.99±28.71	70.59±28.91	69.64±27.72	64.82±24.80	65.23±25.84	0.622	1.596	0.177		
dslope1:	**SVS**	37.88±14.14	33.64±14.64	32.10±12.84	35.99±14.09	34.97±12.05	0.225	1.443	0.221	0.36	0.83
	OK	38.39±13.49	37.86±15.61	38.68±22.12	38.75±16.15	34.75±14.84	0.297	2.323	0.058		
dslope2:	**SVS**	42.52±23.70	40.37±17.14	39.32±16.76	43.05±18.67	42.64±19.28	0.046*	0.268	0.992	0.85	0.04
	OK	44.04±19.96	41.80±16.71	39.98±17.60	42.65±20.98	38.34±14.17	0.481	0.9	0.458		
path1:	**SVS**	30.25±6.25	30.35±5.83	30.74±6.89	30.35±6.54	31.33±6.60	0.576	0.786	0.535	0.018	5.82
	OK	32.70±7.04	32.04±7.05	31.89±8.29	32.46±6.29	31.72±6.97	0.792	1.393	0.238		
path2:	**SVS**	38.49±10.61	39.03±11.48	37.64±9.53	37.49± 8.77	36.49±10.38	0.388	0.889	0.472	0.916	0.01
	OK	36.81±9.74	37.41±10.27	37.39±10.67	38.52±10.57	34.69±7.75	0.958	0.881	0.476		

Corneal biomechanical properties measured with the ORA. *If $p<0.05$, Friedman's test procedures were carried out, statistically signifycant ($p<0.05$).

Appendix 3: Short term corneal biomechanical changes ORA-derived parameters over the seven-day period of ortho-k lens wear compared to baseline

ORA parameter (Mean ± SD)	Visit								S-W test for normality	Effect of time (Repeated Measure ANOVA)	
	BL	Night 1	Night 2	Night 3	Night 4	Night 6	Night 8	Night 7	p	p	F
IOPg (mmHg)	11.95±2.89	12.52±3.11	11.18±2.91	12.39±3.38	12.55±2.46	11.98±2.41	12.07±2.84	12.27±3.57	0.782	0.595	0.792
IOPcc (mmHg)	12.90±2.22	13.67±2.70	12.41±2.38	13.71±2.66	13.72±2.14	13.40±2.02	13.53±2.33	13.58±2.73	0.733	0.306	1.211
CH (mmHg)	10.42±1.29	10.26±1.19	10.25±1.29	10.02±1.47	10.15±1.14	10.00±1.21	9.93±1.36	10.04±1.50	0.715	0.126	1.824
CRF (mmHg)	9.35±1.71	9.42±1.51	8.99±1.64	9.15±1.92	9.31±1.38	9.02±1.46	8.98±1.66	9.13±2.00	0.957	0.413	1.03
slew1	69.73±19.53	70.14±14.05	64.51±20.03	62.16±14.03	58.23±12.75	58.55±19.91	66.72±18.83	55.50±17.83	0.038*	0.510	6.254
slew2	74.95±19.63	70.77±24.57	74.22±18.81	57.37±25.47	71.90±21.76	64.81±27.38	6.16±26.97	66.18±14.55	0.094	0.938	0.332
mslew1	109.31±19.84	109.19±20.28	103.69±27.74	98.42±19.23	91.32±18.57	95.72±17.55	105.32±21.78	97.35±19.73	0.419	0.157	1.545
mslew2	112.01±26.081	106.49±30.78	108.71±22.11	92.32±29.34	106.92±29.87	103.64±32.48	105.20±27.79	105.18±23.50	0.410	0.151	1.687
dive1	421.30±138.39	454.50±74.90	414.70±118.93	412.47±66.48	380.32±81.60	384.32±131.61	416.93±107.87	379.63±129.80	0.001*	0.021	2.619
dive2	424.87±58.44	393.98±93.29	390.14±76.25	291.30±117.67	377.06±72.44	350.13±122.13	359.37±90.70	363.99±57.86	0.189	0.475	0.944
sindex	9.91±0.28	9.97±0.11	9.97±0.11	9.96±0.09	9.95±0.12	9.90±0.26	9.91±0.37	9.76±0.64	0.001*	0.731	4.411
bindex	9.89±0.27	9.82±0.40	9.82±0.37	9.55±1.26	9.93±0.18	9.84±0.47	9.83±0.43	9.86±0.15	0.001*	0.352	7.787
aplint	0.89±0.12	0.99±0.15	0.90±0.23	0.94±0.18	0.90±0.15	0.90±0.16	0.88±0.21	0.92±0.19	0.033*	0.339	7.927
Values from upper 75% of peak											
p1area	4817.07±783.76	4833.19±1233.09	4585.91±983.89	4558.19±834.29	4464.56±6.16.58	4753.93±1162.44	4691.06±977.86	4582.30±1168.29	0.547	0.033	2.265
p2area	44.78.11±854.22	4563.98±977.87	4534.69±1462.56	4043.83±1440.31	4551.86±883.43	4385.79±975.01	4443.75±1131.25	4077.18±802.88	0.094	0.117	1.688
h1	486.36±68.28	479.43±80.69	462.74±81.74	439.52±59.70	420.25±51.42	446.88±81.52	458.16±87.52	438.19±76.59	0.512	0.008	2.892
h2	457.52±47.86	430.45±75.23	429.91±70.20	372.96±75.24	424.21±62.85	410.19±67.20	418.32±62.02	412.55±54.06	0.645	0.080	1.868
w1	21.76±1.97	22.29±2.47	21.38±2.16	22.53±1.55	22.38±1.94	22.53±2.96	21.67±2.35	22.19±2.69	0.155	0.348	1.131
w2	23.19±3.54	24.67±5.07	24.10±6.11	24.40±4.69	24.43±4.70	23.79±3.83	23.33±4.09	22.57±4.76	0.524	0.377	1.054
aspect1	22.56±3.91	21.70±3.75	21.87±4.72	19.60±2.97	19.00±3.39	20.21±4.47	21.46±4.98	19.92±3.59	0.225	0.007	2.994
aspect2	20.27±4.10	18.40±5.53	18.86±4.96	15.96±4.65	18.11±4.73	17.98±5.07	18.56±4.79	18.26±4.59	0.448	0.540	0.860
uslope1	69.15±14.77	70.14±14.05	65.59±17.81	62.16±14.03	58.35±12.50	60.43±16.15	67.27±17.18	57.18±15.05	0.032*	0.015	2.592
uslope2	74.95±19.63	70.86±24.39	74.22±18.81	58.70±22.53	71.90±21.76	66.04±25.24	67.33±24.80	66.18±14.55	0.094	0.915	0.376
dslope1	34.66±7.17	32.41±6.12	34.20±8.13	29.52±4.94	28.94±5.96	30.99±6.77	32.64±8.39	31.62±5.47	0.342	0.049	2.086
dslope2	28.89±6.90	25.77±8.03	26.17±8.08	22.98±7.05	24.64±6.56	26.09±7.67	26.38±6.69	25.90±7.90	0.024*	0.264	8.841
path1	19.67±2.47	19.62±2.64	19.68±2.62	18.70±1.93	18.14±2.07	18.45±3.07	18.99±3.04	19.19±3.42	0.139	0.088	1.821
path2	20.23±3.70	19.00±4.98	19.69±5.63	18.97±4.74	18.04±3.90	18.73±4.67	18.87±4.84	19.67±3.96	0.763	0.471	0.902
Values from upper 50% of peak											
p1area	2183.11±416.28	2190.18±648.28	2117.22±499.99	2089.67±444.50	2065.20±336.98	2206.03±283.20	2169.99±485.95	2092.93±578.35	0.031*	0.889	2.841
p2area	1977.93±413.52	2039.07±474.84	2003.33±717.68	1791.01±788.71	2039.50±427.04	2017.35±474.41	1987.97±636.29	1791.71±352.92	0.747	0.247	1.317
h1	324.24±45.52	319.62±53.79	308.49±54.49	293.02±39.80	280.136±34.28	297.92±54.35	305.44±58.34	292.13±51.06	0.512	0.001	3.692
h2	305.01±31.91	286.96±50.16	286.60±46.80	248.64±50.16	282.81±41.90	273.46±44.80	278.88±41.35	273.03±36.04	0.645	p<0.001	21.152
w1	12.14±1.65	12.14±1.74	11.71±1.87	12.33±1.59	13.33±1.59	12.84±2.29	12.43±1.80	12.90±2.57	0.007*	0.007	2.548
w2	11.86±2.35	12.71±3.59	12.57±3.43	13.53±3.98	13.00±3.26	12.89±2.66	13.14±3.21	12.14±2.92	0.437	p<0.001	11.367
aspect1	27.20±5.43	26.58±4.24	26.96±6.36	24.14±4.39	21.38±4.09	24.06±6.28	25.23±6.39	23.53±6.04	0.255	0.003	3.224
aspect2	26.76±6.28	24.55±8.23	24.22±6.35	19.82±6.78	23.52±8.19	22.57±7.11	22.53±6.79	24.09±7.02	0.166	0.896	0.408
uslope1	66.13±14.17	66.41±15.14	57.29±15.97	55.39±13.87	52.86±12.10	58.01±17.76	63.54±18.97	55.86±19.01	0.851	0.204	1.417
uslope2	66.74±15.47	59.33±18.71	67.45±18.35	50.79±21.83	62.70±18.74	57.84±23.74	60.64±24.79	28.13±13.51	0.414	0.934	0.34

dslope1	46.78±11.87	44.75±11.13	48.24±12.62	41.51±10.20	36.95±9.35	42.08±12.01	41.73±12.77	40.23±9.78	0.086	0.026	2.36
dslope2	42.09±6.20	39.88±13.61	36.92±11.78	34.24±14.08	36.06±13.97	36.06±13.97	36.82±10.57	39.85±16.68	0.086	0.243	1.325
path1	27.52±5.17	26.99±5.11	25.98±5.05	24.89±2.91	24.98±3.57	25.70±608	25.69±5.04	26.49±5.67	0.894	0.521	0.884
path2	27.49±4.72	25.81±6.77	27.63±8.84	28.28±10.22	24.50±5.42	25.18±6.72	26.83±7.64	27.0±5.52	0.947	0.492	0.870

Corneal biomechanical properties measured with the ORA over the 7-night period (statistically significant ($p<0.05$)).

Appendix 4: Food Frequency Questionnaire

Participant ID:	Date: / /2016	Researcher initials:

Corneal Biomechanics Nutrition Survey

Please choose **one** of the nine categories that best describes how many times over the past year have you eaten each food type and indicate whether you typically ate a small (S), medium (M) or large (L) serving. A medium serving size describes the natural or standard portion size e.g., 1 banana = medium portion size or 2 slices of pizza = medium portion size.

Food	Never or <1 per month	1-3 per month	1 per week	2-4 per week	5-6 per week	1 per day	2-3 per day	4-5 per day	6+ per day
E.G., PIZZA			M						
Salads, vegetables & soup									
Apples									
Bananas									
Peaches									
Cantaloupe									
Watermelon									
Strawberries									
Oranges									
Grapefruit									
Other fruit									
Orange or grapefruit juice									
Broccoli									
Coleslaw									
Cauliflower									
Cooked greens									
Squash									
Carrots									
Sweet potatoes									
Tomatoes									
Raw spinach									
Cooked spinach									
Green salad									
String beans									
Other beans									
Peas									
Chilli with beans									
Corn									
Potatoes									
Any other vegetable									

Vegetable and tomato soup									
Other soup									
Food	Never or <1 per month	1-3 per month	1 per week	2-4 per week	5-6 per week	1 per day	2-3 per day	4-5 per day	6+ per day
Meat & fish									
Hotdogs									
Ham									
Bacon									
Sausage									
Hamburgers									
Beef									
Beef stew									
Pork or lamb									
Liver									
Liverwurst									
Fried fish									
Tuna									
Oysters									
Shrimp									
Other fish									
Fried chicken									
Chicken or Turkey									
Dairy & eggs									
Ice cream									
Cottage cheese									
Other cheese									
Macaroni and cheese									
Milk in coffee or tea									
Milk on cereal									
Whole milk									
2% milk (semi-skimmed)									
1% milk (skimmed)									
Yogurt									
Eggs									
Butter added to vegetables									
Butter on bread									
Margarine on bread									
Cereal foods, sweets & biscuits									
High-fibre cereals									

Fortified cereals									
Other cold cereals									
Cooked cereals									
Dark bread									
White bread									
Corn bread									
Biscuits									
Food	Never or <1 per month	1-3 per month	1 per week	2-4 per week	5-6 per week	1 per day	2-3 per day	4-5 per day	6+ per day
Doughnuts									
Chocolate									
Other candy									
Pasta or spaghetti									
Rice									
Noodles									
Crisps									
Pizza									
Chips									
Beverages & condiments									
Regular soft drink									
Fruit drinks									
Coffee or tea									
Sugar in coffee or tea									
Non-dairy creamer in coffee or tea									
Liquor									
Beer									
Wine									
Gravies									
Red chili sauce									
Salad dressings									
Peanuts or peanut butter									

Appendix 5: Factors influencing corneal biomechanics

			Spearman's correlation coefficient (r_s)																	
Parameter	Mean±SD	K-S test for normal distribution	Eye size/Axial length (mm)	Endothelial cell count (cells/mm^2)	Age (years)	Ethnicity	Body size (BMI)	Diet						Topography parameters						
								Fruit, vegetables etc.	Meat	Dairy products	Carbohydrates	Fish	Vitamin E	Steep e	Flat e	Steep K	Flat K	∆ K	CCT (µm)
IOPg (mmHg)	12.86±3.16	0.027	0.127	0.101	0.095	0.051	-0.034	0.078	0.194*	0.027	0.009	0.143	0.018	0.053	-0.003	0.019	0.093	0.111	-0.44
IOPcc (mmHg)	13.93±2.80	0.2	0.1087*	0.088	0.036	0.001	0.014	0.050	0.165	-0.058	-0.022	0.125	-0.022	0.044	0.044	0.014	0.126	0.003	-0.101
CH (mmHg)	10.20±1.39	0.03	-0.12	0.056	0.094	0.010	-0.095	0.013	0.039	0.125	0.013	0.025	-0.037	0.076	0.008	0.154	0.144	-0.022	0.002
CRF (mmHg)	9.45±1.67	0.039	-0.15	0.119	0.123	0.062	-0.077	0.043	0.115	0.077	0.0005	0.075	-0.028	-0.076	0.013	0.007	-0.060	0.016	0.069
slew1	72.78± 19.42	0.08	0.117	0.091	-0.142	-0.084	-0.214*	-0.35	-0.095	0.132	0.094	-0.020	0.069	-0.023	-0.09	-0.036	0.009	0.88	-0.05
slew2	78.61± 21.37	0.2	0.151	-0.092	-0.025	-0.124	-0.024	-0.051	-0.115	-0.54	-0.107	-0.136	0.062	-0.029	0.38	0.156	0.166	0.25	0.108
mslew1	113.69± 25.15	0.04	0.134	0.092	-0.056	-0.150	-0.208*	0.88	-0.125	0.131	-0.024	-0.062	0.152	-0.029	0.38	0.156	0.166	0.25	-0.024
mslew2	118.88± 25.62	0.2	0.188*	-0.160	0.049	-0.1049	-0.032	-0.057	-0.121	-0.029	-0.225*	-0.0.79	0.123	0.010	-0.086	0.0115	0.145	-0.009	0.085
dive1	454.6± 114.76	<0.001	0.190*	-0.003	0.082	-0.074	-0.004	-0.065	-0.080	0.043	-0.04	-0.020	0.077	0.026	-0.054	0.003	0.144	0.195*	0.017
dive2	413..80± 79.60	0.001	0.133	0.079	-0.132	-0.102	-0.216*	-0.44	-1.05	0.117	0.076	-0.022	-0.032	-0.015	0.016	-0.017	0.04	0.070	0.04
aindex	9.93±0.26	<0.001	-0.063	0	0.034	-0.098	-0.026	-0.094	-0.050	0.86	0.063	-0.066	-0.160	0.034	-0.170	-0.009	0.002	-0.060	0.164
bindex	9.79±0.47	<0.001	0.107	0.043	0.036	0.062	0.012	-0.012	-0.038	0.051	0.028	0.062	0.053	0.036	-0.001	0.003	0.058	0.090	-0.08
aplhf	0.92±0.18	<0.001	-0.007	0.034	-0.016	-0.050	-0.059	0.005	0.078	-0.172	-0.091	0.037	-0.065	0.019	-0.077	-0.022	-0.065	-0.073	-0.234*

Values from upper 75% of peak																			
p1area	5277.84±1383.64	<0.001	0.164	0.153	0.014	-0.003	0.010	0.030	-0.010	-0.024	-0.046	-0.174	0.053	0.086	0.114	0.365**	0.409**	0.078	-0.035
p2area	4822.19±1139.57	0.2	0.067	0.055	0.097	-0.019	0.075	-0.109	-0.184*	0.104	-0.013	-0.129	0.03	0.026	0.01	0.330*	0.338*	-0.1	0.077
h1	510.95±76.44	0.092	0.067	0.055	0.097	-0.19	0.075	-0.109	-0.184*	0.104	-0.13	-0.129	0.03	0.018	0.034	0.330	0.338	-0.39	-0.048
h2	460.79±68.73	0.023	0.189*	0.031	-0.058	-0.162	*-0.239*	0.114	0	0.087	-0.019	0.077	0.131	0.073	-0.036	0.031	0.081	0.029	0.101
w1	22.06±2.36	<0.001	0.024	0.141	0.028	0.089	0.111	-0.036	-0.068	-0.047	0.08	-0.166	-0.002	-0.036	0.108	0.216	0.230	0.083	-0.144
w2	24.03±4.39	<0.001	-0.126	0.41	-0.004	0.054	0.024	0.002	-0.036	0.059	0.037	-0.041	0.006	-0.041	0.094	0.129	0.087	-0.165	0.049
aspect1	23.33±3.72	0.2	0.189*	0.031	-0.058	*-0.162*	*-0.239*	0.114	0	0.087	-0.019	0.077	0.131	0.073	-0.036	0.031	0.081	0.029	0.049
aspect2	19.79±4.46	0.2	0.189*	0.031	-0.058	*-0.162*	*-0.239*	0.114	0	0.087	-0.019	0.077	0.131	0.089	-0.036	-0.002	0.064	0.031	0.069
uslope1	73.98±16.89	0.2	0.133	0.079	-0.132	-0.102	-0.216*	-0.04	-0.105	0.117	0.076	-0.022	0.071	0.038	0.046	0.043	0.077	0.052	-0.005
uslope2	78.55±21.51	0.05	0.151	-0.093	-0.026	-0.123	0.025	-0.051	-0.113	-0.053	-0.110	-0.134	0.063	-0.027	0.037	0.157	0.166	0.024	0.110
dslope1	35.25±6.21	0.2	0.106	-0.032	-0.002	-0.124	-0.162	0.115	0.05	0.038	-0.081	0.104	0.124	0.115	-0.066	0.007	0.66	-0.009	0.062
dslope2	27.62±7.46	0.05	0.130	0.042	0.099	-0.045	0.027	-0.019	-0.055	0.035	0.030	-0.008	0.027	0.078	-0.049	0.014	0.083	0.204	-0.035
path1	19.11±2.82	0.2	0.151	-0.093	-0.026	-0.123	-0.025	-0.051	-0.113	-0.053	-0.11	-0.134	0.063	-0.027	-0.027	0.157	0.166	0.024	-0.052
path2	18.88±3.46	0.06	0.096	-0.088	-0.049	-0.060	-0.134	-0.086	-0.134	0.073	-0.040	0.023	0.142	0.075	-0.079	-0.004	0.37	-0.09	-0.136
Values from upper 50% of peak																			
p1area	2429.52±776.85	<0.001	0.151	0.176*	0.008	0.025	0.020	0.026	-0.142	-0.023	-0.095	-0.190*	0.059	0.1	-0.10	0.354**	0.397**	0.012	0.01
p2area	2132.08±542.28	0.2	0.080	0.075	0.089	-0.001	0.036	-0.107	-0.179*	0.095	-0.030	-0.139	0.004	0.034	0.047	*0.341*	*0.345*	-0.37	0.055
h1	340.63±50.96	0.09	*0.274*	0.077	-0.058	-0.113	-0.168	0.106	-0.44	0.043	0.012	-0.21	0.097	0.117	0.021	*0.253*	0.319	0.08	-0.048
h2	307.19±45.82	0.033	0.204*	0.045	0.095	-0.066	0.092	-0.118	-0.211	0.102	0.041	-0.145	0.099	0.070	0.018	*0.339*	*0.361*	0.23	0.101
w1	12.46±2.17	<0.001	-0.024	0.074	0.101	0.104	0.124	-0.025	-0.095	-0.064	-0.129	-0.159	-0.042	0.117	0.021	*0.253*	0.319	0.08	0.010
w2	12.76±2.70	<0.001	0.015	-0.006	0.078	0.002	-0.224*	0.23	0.002	0.023	-0.055	-0.009	-0.109	0.104	0.015	0.154	0.177	0.018	0.045
aspect1	28.02±5.88	0.2	0.157	0.002	-0.129	-0.145	-0.224	0.063	0.059	0.075	0.096	0.111	0.133	-0..011	0.050	0.188	0.146	0.290*	-0.087
aspect2	25.18±6.4	0.04	0.039	0.047	0.017	-0.28	0.006	-0.105	-0.108	-0.43	0.026	-0.047	0.154	-0.037	0.016	-0.021	0.06	0.040	-0.042

	4																		
uslope1	68.80± 17.98	0.2	0.093	0.026	-0.080	-0.102	-0241*	0.008	-0.098	0.126	0.105	0.016	0.083	0	-0.001	-0.001	0.045	0.145	-0.092
uslope2	69.83±19. 17	0.032	0.196*	0.111	-0.055	- 0.0002	-0.137	0.038	-0.039	0.099	0.022	-0.66	0.098	0.001	-0.058	-0.060	-0.041	0.084	-0.011
dslope1	47.62± 12.02	0.2	0.196	0.059	-0.001	0.010	0.036	-0.083	0.065	-0.049	-0.077	-0.005	-0.057	-0.102	-0.057	-0.136	0.073	-0.073	-0.095
dslope2	39.21± 12.43	0.051	-0.007	0.094	0.056	-0.002	0.093	-0.106	-0.087	0.074	0.04	0.033	0.109	-0.008	0.159	0.217	0.247	0.016	-0.053
path1	26.40±5.4 9	0.2	-0.051	-0.170	-0.14	-0.075	-0.093	-0.017	0.141	-0.006	0.09	0.225*	0.027	0.009	0.006	-0.054	-0.012	0.165	-0.118
path2	26.31±5.4 2	<0.00 1	0.06	-0.069	-0.002	0.053	0.104	-0.029	0.087	-0.039	-0.09	0.081	-0.078	0.028	- 0.0112	-0.169	-0.157	0.032	-0.093

Table A1: Summary of the association between the ORA parameters and age, ethnicity, dietary components, eye and body size and ocular biometric parameters. Note: *correlation significant at <0.05 level, ** correlation significant at <0.01 level.

			Spearman's correlation coefficient (r_s)																	
								Diet						Topography parameters					
Parameter	**Mean±SD**	**K-S test for normal distribution**	**Eye size/Axial length (mm)**	**Endothelial cell count (cells/mm²)**	**Age (years)**	**Ethnicity**	**Body size (BMI)**	**Fruit, vegetables etc.**	**Meat**	**Dairy products**	**Carbo-hydrates**	**Fish**	**Vitamin E**	**Steep e**	**Flat e**	**Steep K**	**Flat K**	**Δ K**	**CCT (µm)**
IOP (mmHg)	13.65±1.92	0.161	0.204	0.011	-0.224	0.201	-0.100	0.157	-0.023	0.094	-0.153	0.117	0.099	-0.149	-0.088	0.093	0.112	-0.127	-0.057
Def. Amp.(mm)	1.07±0.09	0.200	0.013	0.130	0.116	-0.114	0.012	0.067	0.147	-0.052	0.285**	0.029	0.015	0.184	-0.025	-0.079	-0.022	0.196	-0.167
A1 time (ms)	7.44±0.32	<0.001	0.217*	-0.079	-0.071	-0.175	-0.192	-0.016	-0.030	0.020	-0.080	-0.062	0.068	-0.109	0.003	0.137	0.168	-0.171	0.181
A1 length (mm)	1.77±0.07	0.009	0.260*	0.146	0.264	-0.121	-0.024	0.113	0.229*	0.109	-0.115	-0.016	0.070	0.105	0.309**	0.534**	0.612**	-0.148	0.162
A1 velocity (m/s)	0.16±0.02	0.200	-0.318**	0.126	-0.063	0.021	-0.036	-0.028	0.002	0.040	0.207	0.162	0.246*	0.150	0.174	-0.321**	-0.323**	-0.197	-0.098
A2 time (ms)	22.21±0.53	0.077	-0.082	-0.078	0.200	-0.418**	-0.061	-0.207	0.038	-0.048	0.161	-0.119	-0.122	0.085	0.051	-0.032	-0.034	0.061	0.159
A2 length (mm)	1.74±0.27	<0.001	-0.074	-0.021	0.158	0.166	0.078	0.090	-0.086	-0.092	0.028	-0.071	0.085	0.153	0.033	0.103	0.107	-0.052	0.145
A2 velocity (m/s)	-0.36±0.06	0.169	-0.219*	-0.229*	0.026	-0.053	-0.088	0.075	-0.144	0.292**	-0.009	0.012	0.092	-0.194	-0.076	-0.049	-0.114	0.128	-0.002
HC time (ms)	17.07±0.57	<0.001	-0.200	-0.365	-0.202	-0.144	-0.011	-0.387	0.080	0.070	-0.112	-0.019	-0.160	-0.075	0.044	-0.08	-0.197	0.012	-0.033
Peak Dist. (mm)	3.3±1.01	<0.001	0.282	0.188	-0.035	0.126	-0.016	0.265	0.037	-0.084	0.061	-0.374	-0.027	0.323	-0.516*	0.135	0.117	0.340	-0.351

Radius (mm)	7.46±0.82	0.024	-0.168	0.093	0.008	0.467*	0.066	0.295	0.214	0.149	0.162	0.478*	0.007	0.169	-0.245	-0.076	-0.033	-0.076	0.244
A1 Def. Amp. (mm)	0.13±0.01	0.042	-0.215	-0.010	-0.396	0.348	-0.227	0.078	-0.230	0.057	-0.088	0.063	0.056	0.145	-0.108	-0.170	-0.113	-0.126	0.108
HC Def. Amp. (mm)	1.07±0.09	0.200	0.112	0.137	0.062	-0.171	0.070	0.088	0.049	0.001	0.313	-0.202	0.142	0.338	-0.132	-0.212	-0.110	-0.282	-0.478**
A2 Def. Amp. (mm)	0.42±0.07	0.200	-0.349	0.181	-0.181	0.058	0.024	0.340	0.018	0.429	0.379	0.1312	0.651**	0.204	-0.146	-0.491*	-0.325	0.144	-0.245

Table A2: Summary of the association between the Corvis ST parameters and age, ethnicity, dietary components, eye and body size and ocular biometric parameters. Note: *correlation significant at <0.05 level, ** correlation significant at <0.01 level.

Appendix 6: Ethical approvals for the studies (Chapter 5 and Chapter 6)

6.1. Short term corneal biomechanical changes in orthokeratology (amended version) (Chapter 5)

No: Orr, Janis
Nosūtīts: pirmdiena, 2016. gada 5. decembrī 7:21
Kam: Zvirgzdina, Madara (Research Student)
Kopija: Wolffsohn, James S W
Tēma: Fwd: Ethics Amendment Request
FYI

Begin forwarded message:
From: "Seare, Nichola" [redacted]
Date: 4 December 2016 at 17:22:05 GMT
To: "Orr, Janis" [redacted]
Cc: "Wolffsohn, James S W" [redacted], **"Birdi, Gurkiran"** [redacted], **"Seare, Nichola"** [redacted]
Subject: RE: Ethics Amendment Request
Hi Janis

Apologies for the slower than normal response to this amendment request – we have had a change of admin support for UREC and Gurkiran and I are still catching up.

I am happy to give a favourable opinion to the amendment on behalf of UREC for which Gurkiran will send formal confirmation next week.

Best wishes

Nichola

Dr Nichola Seare
[redacted]

Personal Assistant: Gurkiran Birdi [redacted]

From: Orr, Janis
Sent: 18 November 2016 12:18
To: Seare, Nichola [redacted]
Cc: Wolffsohn, James S W [redacted]
Subject: Ethics Amendment Request

Dear Dr Seare,

I am writing to request an ethics amendment for an orthokeratology contact lens study ('Presbyopic Corneal Reshaping') I received ethical approval for on 5th August 2015 (attached).

Initially, we intended to investigate whether or not it is feasible to correct presbyopia using a novel orthokeratology lens. Due to problems with comfort and stability of this contact lens design, it has been necessary to adapt the study. Instead we will investigate

the short term (1 week) corneal response to standard commercially available CE marked orthokeratology lenses, fitted to correct myopia (the refractive condition it was designed to correct). Although this technique is established in optometric practice, the exact mechanism by which it achieves its effect is not fully understood. We believe that by closely monitoring the corneal response to orthokeratology over a short period of time, we will understand how orthokeratology achieves its effect, and how individual corneal characteristics influence its success.

I have attached the original documentation and the amended versions.

As the measurements that we will be performing / contact lens types we will be fitting are all included within the original ethics application, and the proposed study design is more straightforward than the original design, we hoped that it would be possible to amend the original application.

Kind regards,

Janis Orr

Research protocol

Short time corneal biomechanical changes in corneal reshaping therapy

Myopia is a global public health issue however no consensus on an appropriate, safe, and effective management strategy has yet been reached, despite its rapidly increasing prevalence (Pan *et al.* 2012). Orthokeratology or corneal reshaping therapy, an overnight application of a specially designed contact lens to temporary reduce mild to moderate myopia, presumably through a tissue redistribution, providing patients with clear spectacle- and contact lens-free vision during the walking hours, has become more popular method for myopia management over the recent years, owing to its non-surgical nature (Swarbrick 2006) and the ability to slow down myopia progression in children by 50% (Si *et al.* 2015). The individually selective treatment outcome and corneal tissue involvement (Swarbrick *et al.* 1998; Choo *et al.* 2008) have highlighted the importance of understanding corneal response in orthokeratology.
Until recently, most of the knowledge about biomechanical properties of corneal tissue was gained from destructive *ex vivo* testing or ocular biometric parameters (corneal thickness and curvature) alone. Introduction of instrumentation such as Ocular Response Analyzer (ORA, Reichert Technologies) and Corvis ST (Oculus GmbH, Germany) has allowed corneal biomechanical response to be clinically examined (Luce 2005; Hon and Lam 2013). Both instruments use an air-puff displacement to evaluate corneal response. ORA specific parameters corneal hysteresis (CH) and corneal resistance factor (CRF), that describes the viscoelastic damping properties and overall resistance of the corneal tissue, have been found to be useful tools in keratoconus and glaucoma management (Luce 2005; Sullivan-Mee *et al.* 2008; Abitbol *et al.* 2010; Fontes *et al.* 2010; Wolffsohn *et al.* 2012). Also, they have been reported to be affected by short time orthokeratology (Gonzalez-Meijome *et al.* 2008; Chen *et al.* 2009). However, rarely any study has looked at detailed corneal biomechanical response provided by the ORA (Kerautret *et al.* 2008; Mikielewicz *et al.* 2011; Wolffsohn *et al.* 2012) or investigated corneal biomechanical response in orthokeratology, using Corvis ST.
The aim of this study is to investigate corneal biomechanical response to orthokeratology lens wear over a time span of 7 days, when the vast majority of refractive changes occur. Myopic patients (preferably 19-24 years of age) will be fitted with an orthokeratology lens and the refractive and corneal biomechanical changes, occurring during the first seven days of lens wear will be monitored. Visits will involve initial assessment, lens fitting visit, 1 day after the first night of the lens wear and then 6 subsequent visits over the course of a week. At each visit following measurements will be taken:

Refractive error (Shin-Nippon NVision K 500, subjective refraction)
Monocular and binocular distance visual acuity)
Corneal topography (Medmont E300 topographer)
Corneal biomechanical response (ORA, Corvis ST)
Endothelial effects (Specular Microscope, Topcon SP3000P)
Epithelial effects (thickness changes, tissue redistribution) (OCT, ALADDIN, Topcon, Medmont E300 topographer)
Corneal profile changes (Corvis ST (Scheimpflug imaging), Medmont E300 topographer

6.2. Factors influencing corneal biomechanics (Chapter 6)

> From: University REC Enquiries
> Sent: 06 August 2015 16:46
> To: Orr, Janis
> Subject: RE: Revised documentation for ethics applications
>
> **Dear Janis**
> **Please find favourable opinion letters for Projects 833 and 834 attached.**
> **Regards**
> **Martin Johnson**
> **Governance Support Team**
> **Aston University**
> **Aston Triangle**
> **Birmingham**
> **B4 7ET**
> [redacted]
> [redacted]
>
> From: Orr, Janis
> Sent: 09 July 2015 16:40
> To: University REC Enquiries
> Subject: RE: Revised documentation for ethics applications
>
> Dear Martin,
>
> Attached are the documents containing the suggested amendments.
>
> Kind regards,
>
> Janis
>
>
> Dr Janis B. Orr PhD BSc(Hons) MCOptom DipTp(IP)
> Lecturer in Optometry
> Aston University
> Aston Triangle
> Birmingham
> B4 7ET
> [redacted]
> [redacted]
> www.aston.ac.uk/lhs/research/centres-facilities/ophthalmic-research-group/<http://www.aston.ac.uk/lhs/research/centres-facilities/ophthalmic-research-group/>
>
> [Logo-for-Aston-University-001]
>
> [cid:image002.png@01D0D067.0BDC9A00]
>
> From: University REC Enquiries
> Sent: 09 July 2015 14:05

> To: Orr, Janis
> Subject: RE: Revised documentation for ethics applications
>
> Good afternoon Janis
>
> We have reviewed your resubmitted documents and request you address the following two points:
>
>
> • Project 833 - Please include some further detail to explain what a ‘bespoke aberrometer’ is and does.
>
>
> • Project 834 – Amend Consent Form to include a line asking participants if they are happy to take part in the second part of the study.
>
>
> Thank you
>
> Regards
>
> Martin

Aston University

MEMORANDUM

DATE: 15 June 2015

TO: Dr Janis Orr,
School of Life and Health Sciences

FROM: Dr Nichola Seare,
Chair of the Aston University Research Ethics Committee

SUBJECT: Ethics Application 834: 'Factors Influencing Corneal Biomechanics'

Following a meeting of the Sub-Group of the University's Ethics Committee to consider the above project proposal, on behalf of the Committee. The Sub-Group asked the project team to address the following points and to submit appropriate revised documentation:

Research Participant Information Sheet

Members felt that you did not require the last two sentences under the heading *'What will happen to me if I decide to take part?'.*

Members recommend that you have two separate Participant Information Sheets. One for people in the first part of the study and another for the small number of subjects who will be asked to return.

Please add a line in the information sheet stating that you will talk to the participants about anything you see that could affect their health.

Consent Form

Please add a line on the consent form asking participants if they are happy to take part in the second part of the study.

The revised documentation should be submitted to Martin Johnson (urec_queries@aston.ac.uk) who will then arrange asap for the Sub-Group to consider its approval on behalf of the Ethics Committee.

Chair of the Ethics Committee

Appendix 7: Patient information sheets and consent forms (Chapter 5 and Chapter 6)

7.2 Short term corneal biomechanical changes in orthokeratology (Chapter 5)

RESEARCH PARTICIPANT INFORMATION SHEET

Aston University
Life & Health Sciences

Short term corneal biomechanical changes in orthokeratology

Invitation

You are being invited to take part in a research project that will be conducted at Aston University. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. Thank you for reading this.

What is the purpose of the project?

The purpose of this study is to find how an overnight application of specially designed lens, which provides a clear vision during the day without the need for additional spectacles or contact lenses (clinically referred to as orthokeratology), affects the biomechanical properties of the cornea (the transparent front surface of your eye) over the period of seven days. The results of this research project will inform the contact lens industry and practitioners of the biomechanical changes occurring during the first week of the lens wear, when most of the treatment effects take place.

Why have I been chosen?

You have been invited to take part because you are over 18, have healthy eyes and require corrective lenses for distance.

What will happen to me if I decide to take part?

After the study has been explained to you and consent given, you will be asked about your ocular history (which will include the completion of a short questionnaire) and your eye health will be assessed and photographed using a clinical microscope. The shape of the front of your eye will be assessed using light reflected from the front surface and the biomechanics of your eye will be assessed with a puff of air (a clinical test used to evaluate the pressure in your eyes). Your refraction will be checked with clinical instrumentation and your vision will be measured over a range of distances.

You will then be fitted with made-to-measure rigid contact lenses by a qualified optometrist to be worn overnight only. These lenses will make subtle, reversible changes to the shape of your cornea (the transparent layer at the front of your eye) which will allow you to have clear vision during the day without wearing spectacles or other contact lenses. You will be asked to return the morning after fitting for assessment using the same procedures and then 6 subsequent mornings. We will also ask you to fill out a questionnaire on how satisfied you are with the lens. The lenses will be worn in both eyes. If the initial lens does not give optimum vision, adjustments may need to be made the new lens type in order to achieve this.

The duration of the tests will be approximately 20-25 minutes at a single appointment. By volunteering to participate you will be giving anybody in the research team consent to access your results and compare them to other participants involved in the project, as well as confirming your past refractive correction.

What are the possible disadvantages and risks of taking part?

You will need to attend the Aston University Eye Clinic on several occasions in order to be fitted for the lenses and for follow-up. The tests do not make contact with your eyes and have been tested to ensure they are safe. Your data will be anonymised before stORAge.

It may take time to get used to wearing the lenses, particularly if you haven't worn contact lenses before. It may also take some time for your vision to improve following the fitting of the lenses. If you decide to stop wearing the lenses, your eyes will go back to normal.

What are the possible benefits of taking part?

You may be able to see well at all distances during waking hours without the need for glasses or contact lenses. This is the only non-surgical way to achieve this. The lenses will be provided to you free of charge.

Do I have to take part?

No, you do not have to participate if you do not wish to do so. This information sheet is yours to keep. If you would like to participate, you will be required to sign the enclosed consent form. You are free to withdraw at any time. No sanctions will be taken against any patient who refuses to participate in or withdraws from this project. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

What if new information becomes available?

New information will be used to guide the study.

What happens when the research study stops?

When your participation in the study stops (you have worn the lenses in both eyes for 1 week) you will be able to continue lens wear, if you wish to, and your care will be transferred to the Aston University Health Clinic.

What if something goes wrong?

You will be in the hands of fully qualified optometrists at Aston University Optometry Clinic. In the unlikely event that there are any complications, these will be managed in an appropriate, timely fashion. You will also be told what action to take should this happen out of hours.

Will my taking part in this project be kept confidential?

Yes. Your participation in this study will be strictly confidential. There will be no way to link any research data to any individual participant.

What will happen to the results of the research project and how will participant anonymity be protected?

The results of the study will be available to the named investigators only and data files will be named in such a way that your identity is protected. We aim to publish the results of this project. However, there will be no reference to any individual's performance in any publication. Details of any publication will be conveyed to participants on request.

Who has reviewed the project?

The research has been reviewed by Aston University's Ethics Committee.

Contacts for further information

Dr Janis B. Orr (Principal Investigator) [redacted]

Ms Madara Zvirgzdina (Research Student) [redacted]

Who do I contact if I wish to make a complaint about the way in which the research is conducted.

If you have any concerns about the way in which the study has been conducted, then you should contact Secretary of the University Research Ethics Committee: [redacted]

Personal Identification Number for this study: _____

Aston University
Life & Health Sciences

CONSENT FORM

Title of Project: Short term biomechanical changes in orthokeratology

Research Venue: Aston University Optometry Clinic

Aston University Investigators: Janis Orr PhD DipTp(IP)

James Wolffsohn PhD PgDipAdvClinOptom PgCHE MBA

Madara Zvirgzdina MSc BSc

Please initial box

I confirm that I have read and understand the information sheet dated ..... ☐

for the above study and have had the opportunity to ask questions.

I understand that my participation is voluntary; the study tests are not part of any medical treatment or negate the need for regular eye examination. ☐

I understand that I am free to withdraw at any time, without giving any reason, without my legal rights being affected. ☐

I agree to take part in the above study. ☐

_____ _____ _____

Name of Research Participant Date Signature

_____ _____ _____

Name of Person taking Consent Date Signature

1 copy for research participant; 1 copy for Aston University

7.3 Factors influencing corneal biomechanics (Chapter 6)

RESEARCH PARTICIPANT INFORMATION SHEET Aston University Life & Health Sciences

Factors Influencing Corneal Biomechanics

Invitation

You are being invited to take part in a research project that will be conducted at Aston University. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. Thank you for reading this

What is the purpose of the project?

To find out which factors influence how rigid the cornea (the transparent part of the front of your eye) is. The results of this study will have important implications for several clinical situations including glaucoma diagnosis, refractive surgery and corneal reshaping therapy (also known as orthokeratology).

Why have I been chosen?

You have been chosen because you are over 18 and have healthy eyes.

What will happen to me if I decide to take part?

After the study has been explained to you and consent given, you will be asked about your ocular history and diet (including the completion of a short questionnaire) and your eye health will be assessed and photographed using a clinical microscope. Your height and weight may also be measured in order to investigate the influence of eye/body size on the rigidity of the cornea only. The shape of the front of your eye will be assessed using light reflected from the front surface and the biomechanics of your eye will be assessed with a puff of air (a clinical test used to evaluate the pressure in your eyes). The duration of the tests will be 45-60 minutes at a single appointment.

What are the possible disadvantages and risks of taking part?

You will need to attend the Aston University Eye Clinic on one occasion in order to participate.

What are the possible benefits of taking part?

You will be providing us with important information on the cornea, a vital part of the eye, which has implications for many clinical areas.

Do I have to take part?

No, you do not have to participate if you do not wish to do so. This information sheet is yours to keep. If you would like to participate, you will be required to sign the enclosed consent form. You are free to withdraw at any time from the project. No sanctions will be taken against any patient who refuses to participate in or withdraws from this project. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

What if new information becomes available?

New information will be used to guide the study.

What if something goes wrong?

It is extremely unlikely that anything will go wrong during your participation in this study. However if an adverse event occurs, you will be in the hands of fully qualified optometrists at Aston University Optometry Clinic. We are happy to discuss anything that could affect your health.

Will my taking part in this project be kept confidential?

Yes. Your participation in this study will be strictly confidential. There will be no way to link any research data to any individual participant.

What will happen to the results of the research project and how will participant anonymity be protected?

The results of the study will be available to the named investigators only and data files will be named in such a way that your identity is protected. We aim to publish the results of this project. However, there will be no reference to any individual's performance in any publication. Details of any publication will be conveyed to participants on request.

Who has reviewed the project?

The research has been reviewed by Aston University's Ethics Committee.

Contacts for further information

Dr Janis B. Orr (Principal Investigator) [redacted]

Ms Madara Zvirgzdina (Research Student) [redacted]

Who do I contact if I wish to make a complaint about the way in which the research is conducted?

If you have any concerns about the way in which the study has been conducted, then you should contact Secretary of the University Research Ethics Committee: [redacted]

Personal Identification Number for this study: _____

Aston University
Life & Health Sciences

CONSENT FORM

Title of Project:	Factors Influencing Corneal Biomechanics
Research Venue:	Aston University Optometry Clinic
Aston University Investigators:	Janis Orr PhD DipTp(IP)
	James Wolffsohn PhD PgDipAdvClinOptom PgCHE MBA,
	Madara Zvirgzdina MSc BSc

Please initial box

I confirm that I have read and understand the information sheet dated ..... ☐

for the above study and have had the opportunity to ask questions.

I understand that my participation is voluntary; the study tests are not part of any medical treatment or negate the need for regular eye examination. ☐

I understand that I am free to withdraw at any time, without giving any reason, without my legal rights being affected. ☐

I agree to take part in the above study. ☐

_____ _____ _____

Name of Research Participant Date Signature

_____ _____ _____

Name of Person taking Consent Date Signature

1 copy for research participant; 1 copy for Aston University

Appendix 8: List of publications

1. Wolffsohn J.S., Calossi A., Cho P., Gifford K., Jones L., Li M., Lipener C., Logan N.S., Malet F., Matos S., Meijome J.M.G., Nichols J.J., Orr J.B., Santodomingo-Rubido J., Schaefer T., Thite N., van der Worp E., **Zvirgzdina M.**, 2016. Global trends in myopia management attitudes and strategies in clinical practice.*Contact Lens & Anterior Eye*, *39*(2), pp.106-116.

2. **Zvirgzdina M.,** Orr J.B., Wolffsohn J.S., 2016 “Are we being short sighted about shortsightedness?” *Atlas of Science,* (https://atlasofscience.org/are-we-being-shortsighted-about-shortsightedness/); accessed on 23rd Jully 2018.