PERIPHERAL REFRACTION AND PERIPHERAL EYE LENGTH IN MYOPIC PROGRESSION AND MYOPIC CONTROL

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Peripheral Refraction and Peripheral Eye Length in Myopic Progression and Myopic Control

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CERTIFICATE OF ORIGINALITY

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Lee Tsui Tsui

This thesis is dedicated to

the memory of my father

Abstract

A number of animal studies have shown that optical input of hyperopic defocus into the retina other than the foveal area would alter central refractive changes. Some researchers therefore proposed that peripheral refraction might also play a role in the regulation of eye growth in human eyes. However, clinical studies on peripheral refraction have yet provided a conclusive answer to this. Certain myopic control treatments have also been devised in attempt to arrest myopia progression through the manipulation of peripheral refraction of an eye. Because of its ability in reducing and even converting relative peripheral hyperiopia into relative myopia in myopic eyes, orthokeratology (ortho-k) was thought to have exerted its myopic control effect through reducing the hyperopic defocus in the peripheral retina. Despite the extensive work done, it is still unclear how these treatments were able to arrest myopic progression. The current study set out to investigate the characteristics and changes of field curvatures and retinal contour in children eyes which are more prone to refractive changes and in eyes which have undertaken ortho-k treatment.

Longitudinal monitoring of peripheral refraction and peripheral eye length were performed on fifty seven untreated children with different ametropia and twenty eight ortho-k-treated children every six-monthly for twelve months. The baseline and 12-month changes in field curvatures and retinal contours were compared between different refractive groups and between eyes with different rate of myopic progression in both untreated and ortho-k-treated subjects.

Although significantly different peripheral refraction and retinal contour were found in different ametropias, the current study was unable to find any association between field curvature, retinal contour and myopic progression. Nor there was an association between the changes in these parameters and central refractive changes. Eyes with different rates of myopic progression did not showed significant differences in both parameters, in both untreated and ortho-k-treated subjects.

Comparing the field curvature and retina contour in the ortho-k-treated eyes and in the untreated myopic eyes did not find any significant difference. In a pilot investigation with six of the ortho-k-treated eyes, changes in field curvature and retina contour during the spectacle-wearing phase did not differ significantly from those changes during the ortho-k-wearing phase. Therefore, results from the current study did not show that relative peripheral refraction and eye length have potential in the regulation of eye growth.

In the current study, we also determine the variability of measurement methods commonly used in current research on peripheral refraction or peripheral eye length. Future studies on the risks factors on eye growth and mechanism of myopic control effect with ortho-k are still need.

Publications arising from the thesis

Journal articles

Lee TT and Cho P (2012). Repeatability of relative peripheral refraction in untreated and orthokeratology-treated eyes. Optom Vis Sci 89(10):1477-1486.

Lee TT and Cho P (2013). Relative peripheral refraction in children: twelve-month changes in eyes with different ametropias. Ophthalmic Physiol Opt 33(3):283-293

Lee TT, Yap M and Cho P. Changes in relative peripheral refraction and peripheral eye length in orthokeratology-treated eyes. (Sumitted to Clin Exp Optom)

Conference papers

Lee TT and Cho P. A pilot study on peripheral refraction on myopic eyes. Oral presentation at the 5th Asia Cornea and Contact Lens Conference (ACCLC), 2008, Singapore

Lee TT and Cho P. Changes in peripheral refraction in children of different refractive errors and rates of myopic progression – 6-month results. Poster presentation at the 13th International Myopia Conference (IMC 2010), Tuebingen, Germany.

Lee TT and Cho P. Changes in relative peripheral refraction in children after 13 months of ortho-k lens wear. Oral presentation at the 3rd Asia Orthokeratology and Specialty Lens Conference (AOSLC), 2012, Hangzhou, People's Republic of China

Lee TT and Cho P. Changes in peripheral eye length in children. Oral presentation at American Academy of Optometry 2013 Meeting (AAO), Seattle, the USA

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Table of Contents

Abbreviations

ACD	Anterior chamber depth
AL	Axial length
CC	Corneal thickness
CHASE	The Child Heart and Health Study in England
CLEERE	The Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error Study
COMET	The Correction of Myopia Evaluation Trial Study
CR	Central refraction
CRAYON	The Corneal Reshaping and yearly Observation of Nearsightedness Study
CR-M	M factor of central refraction
DF	Dual focus
DISC	The Defocus Incorporated Soft Contact
DZ	Dyzygotic twins
GEM	The Genes in Myopia Study
IE	Initially emmetropic group
IE-FAST	Initially emmetropic fast-progressing group
IE-SLOW	Initially emmetropic slow-progressing group
IH	Initially hyperopic group
IH-FAST	Initially hyperopic fast-progressing group
IH-SLOW	Initially hyperopic slow-progressing group
IM	Initially myopic group
IM-FAST	Initially myopic fast-progressing group
IM-SLOW	Initially myopic slow-progressing group

J_0	Cylindrical component along the horizontal or vertical meridian
J_{45}	Cylindrical component along the 45° or 135° meridian
LORIC	The Longitudinal Orthokeratology Research in Children
LT	Lens thickness
M	Spherical equivalent refraction
MCOS	The Study on Myopic Control with Orthokeratology Contact Lenses in Spain
MRI	Magnetic resonance imaging
MZ	Monozygotic twins
OK-12M	12^{th}-month visit after the OK-S visit
OK-1M	1^{st}-month visit after the OK-S visit
OK-6M	6^{th}-month visit after the OK-S visit
OK-S	Visit after the stabilization of orthokeratology responses
OLSM	The Orinda Longitudinal Study of Myopia
Ortho-K	Orthokeratology
PEL	Peripheral eye length
PR	Peripheral refraction
Pre-OK	Pre-orthokeratology treatment visit
PR-J_0	J_0 cylindrical component of peripheral refraction
PR-J_{45}	J_{45} cylindrical component of peripheral refraction
PR-M	M component of peripheral refraction
RCT	Randomized control trial
RESC	The Refractive Error Study in Children
RGP	Rigid gas permeable lenses

ROMIO	The Retardation of Myopia in Orthokeratology Study
RPEL	Relative peripheral eye length
RPR	Relative peripheral refraction
RPR-J_0	J_0 cylindrical component of relative peripheral refraction
RPR-J_{45}	J_{45} cylindrical component of relative peripheral refraction
RPR-M	M component of relative peripheral refraction
RRG	Radial refractive gradient
SCL	Soft contact lenses
SCORM	The Singapore Cohort study of the Risk factors for Myopia
SER	Spherical equivalent refraction
SMS	The Sydney Myopia Study
STAMP	The Study of Theories about Myopia Progression
STARTS	The Strabismus Amblyopia and Refractive Error in Singaporean Children Study
Subj-J_0	J_0 cylindrical component of subjective refraction
Subj-J_{45}	J_{45} cylindrical component of subjective refraction
Subj-M	M component of subjective refraction
SVL	Single vision lenses
VCD	Vitreous chamber depth
WHO	World Health Organization
XPRES	The Xichang Pediatric Refractive Error Study

Chapter One

Myopia and Myopic Control

1.1 Prevalence of myopia in children

The World Health Organization (WHO) recorded a worldwide visually-impaired population of 285 million, of which 80% were avoidable or curable (Pascolini and Mariotti, 2012). The major cause of visual impairment (43%) has been found to be uncorrected refractive errors (Pascolini and Mariotti, 2012). There was also an estimate of 12 million children aged below 15 suffering from visual impairment due to uncorrected refractive errors including myopia, hyperopia and astigmatism (Pascolini and Mariotti, 2012). Although myopia is relatively less risky for the development of amblyopia in children compared to hyperopia and astigmatism (Doshi and Rodriguez, 2007), it still impedes the quality of life if untreated. It is also associated with higher risks of developing complications from high myopia (such as retinal detachment, glaucoma and cataract) in adulthood (Saw *et al.*, 2005b). Therefore, investigating the prevalence of myopia will not only help us to understand the epidemic of the disease, but also to facilitate the health departments and researchers to develop strategies in order to prevent as well as to control the disease and its associated complications.

1.1.1 Worldwide prevalence of myopia in children

The prevalence of myopia experiences some regional, racial and socioeconomic differences (Pan *et al.*, 2012). It also varies with age of the population being surveyed.

About 70 published reports, dated end of the last century or onwards, prescribing population based information on prevalence of myopia have

been retrieved through online search (the majority was from PubMED search) and reviewed. Figures 1.1 and 1.2 show the prevalence of myopia with age in Asian and non-Asian countries, respectively. Information was based on 36 reports from which the prevalence of myopia was clearly stated or could be retrieved or estimated from the presented figures.

1.1.1.1 Racial and regional differences

A. Prevalence in east and south-eastern Asian countries

It is well recognized that Asian countries are more epidemiologic in myopia than western countries (Figure 1.1). In Taiwan, the nationwide prevalence of myopia was 20% for 7-year-olds and up to 85% for 18-year-olds in 2000 (Lin *et al.*, 2001). While in 2005, in a southern city, Kaohsiung, it was 3 – 5% for the 3-6-year-olds (Lai *et al.*, 2009). The myopic population from the aboriginal area of Kaoshiung around the same year ranged from 7% for the seven-year-olds to 37%for the 13-year-olds (Hsu *et al.*, 2008).

In Singapore, the Singapore Cohort study of the Risk factors for Myopia (SCORM) recorded a 28% to 52% of myopic population in the 7-9-year-olds from 1999 to 2001 (Saw *et al.*, 2006). It was also reported that 74% of the Grade 9 and 10 school students (14–19 years) were myopic in 2002 (Quek *et al.*, 2004).

In Kuala Lumbar of Malaysia, the Refractive Error Study in Children (RESC) reported the myopic prevalence to be 10% to 32% for the seven- to 15-year-olds during 2003 (Goh *et al.*, 2005).

In China, 78% of the 15-year-olds in Guangzhou (a south-eastern city of Guangdong province on the south-eastern coast of China)

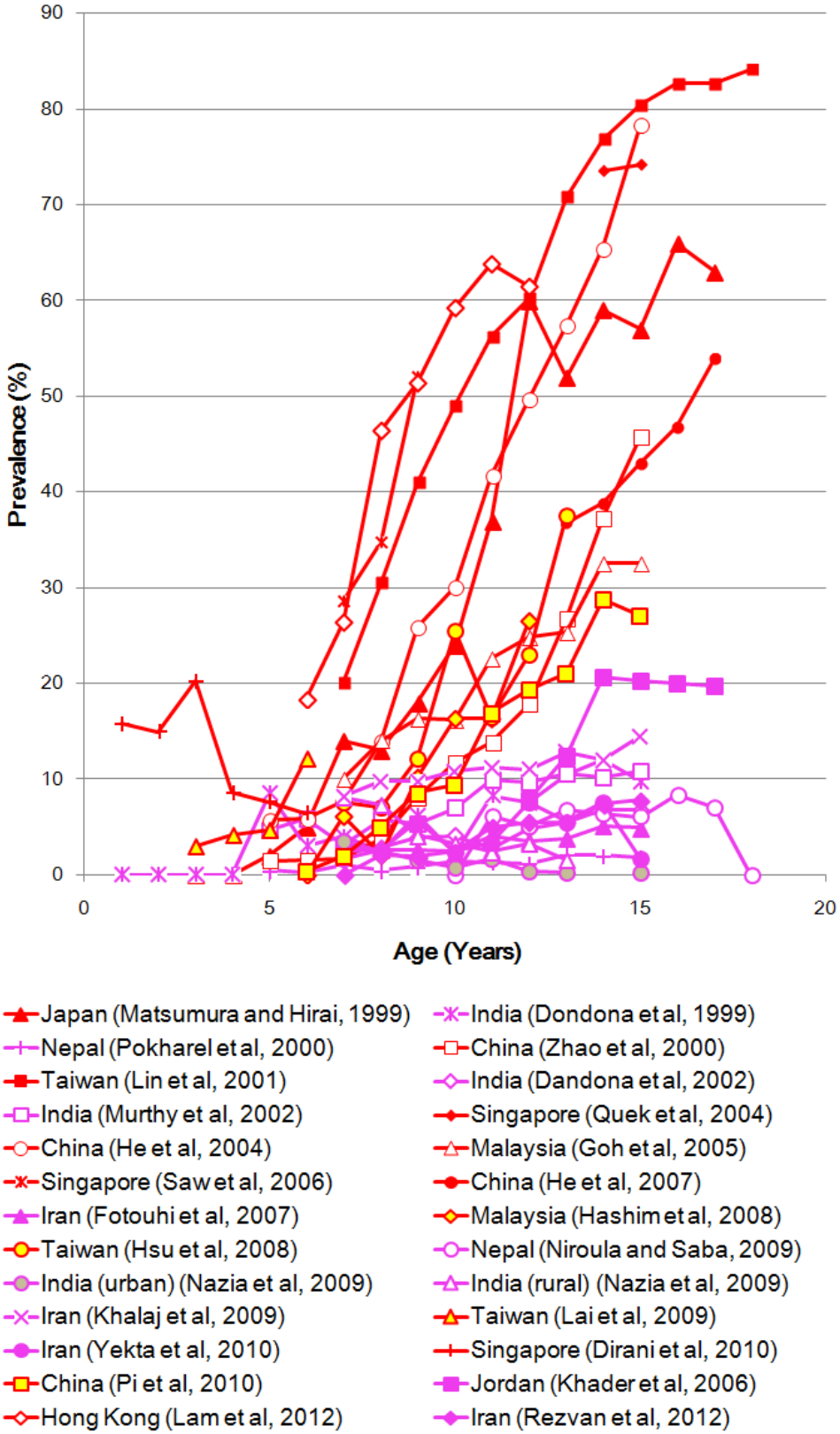


Figure 1.1. Prevalence of myopia by age in Asian countries. Symbols in red represent countries in the South-east Asia while those in pink represent countries in the Middle East and Southern Asia.

were found to be myopic (He *et al.*, 2004), compared to a 27% myopic population in Youngchuan of Chongqin city (west of China) (Pi *et al.*, 2010) and a 43% myopic population in Yangxi of Yangjiang (a south-western city of Guangdong province) (He *et al.*, 2007) for the same age group. The difference in myopic population between rural and urban areas observed in the Chinese reports was consistent with those found in India (Dandona *et al.*, 2002; Murthy *et al.*, 2002; Uzma *et al.*, 2009), Nepal (Pokharel *et al.*, 2000; Niroula and Saha, 2009; Shresha *et al.*, 2011) and Poland (Czepita *et al.*, 2008). The western cities are less urbanized than the eastern cities in China. The majority of the Youngchuan population studied was from rural area of the township in the western city, Chongqin, while the Yangxi population was from a relatively more rural area compared to Guangzhou, the most urbanized city of the Guangdong province. The rural-urban differences suggested the influence of environmental factors such as near work and living environment on the development of myopia. It was believed that schooling was more intensive in the more urban areas, and the students were subjected to longer hours of near work both during and after school (Morgan and Rose, 2013). The association of near work and myopia has been well established (see Section 1.2.2.2). The population density and the living spaces differed between rural and urban areas. It has been shown that the higher population density in cities were associated with the higher prevalence of myopia (Zhang *et al.*, 2010).

In Hong Kong, 6% of the pre-school children (2 – 6 years) were myopic (Fan *et al.*, 2011). Recently, Lam et al (2012) found a high

prevalence for school children in Hong Kong aged between six (18%) and twelve years (>60%).

B. Prevalence in south Asian and the Middle East countries

Unlike those east and south-eastern Asian countries, countries in the south Asia (e.g. Nepal and India) and the Middle East (e.g. Iran and Jordan) reported a much lower myopic prevalence in children. Their myopic population for below-18-year-olds was not more than 20% (Pokharel *et al.*, 2000; Dandona *et al.*, 2002; Murthy *et al.*, 2002; Hashemi *et al.*, 2004; Khader *et al.*, 2006; Fotouhi *et al.*, 2007; Khalaj *et al.*, 2009; Krishnaiah *et al.*, 2009; Niroula and Saha, 2009; Yekta *et al.*, 2010; Ostadimoghaddam *et al.*, 2011; Shresha *et al.*, 2011; Rezvan *et al.*, 2012).

C. Prevalence in other countries

For Caucasians, the prevalence of myopia is much lower (Figure 1.2). In Europe, the myopic population was between 2 and 20% in children at 6-15 years old in Poland (Czepita *et al.*, 2007a; Czepita *et al.*, 2007b), less than 20% for below 17-year-olds in Germany (Jobke *et al.*, 2008), and was about 9% for the 6- to 7-year-olds and 29% for the 12- to 13-year-olds (Logan *et al.*, 2011) in the UK. In the US, 7% of 6-year-olds (Giordano *et al.*, 2009) and 34% of the 12- to 17-year-olds (Vitale *et al.*, 2009) were myopic. In Australia, the prevalence of myopia in schoolchildren was lower, giving a 2 to 15% in the 6- to 12-year-olds (Junghans and Crewther, 2003; Junghans and Crewther, 2005). In some African countries, the rate of

myopia was found to be less than 13% in teenagers (Naidoo *et al.*, 2003; Ahuama and Atowa, 2004; Anera *et al.*, 2009; Jimenez *et al.*, 2012; Mehari and Yimer, 2012).

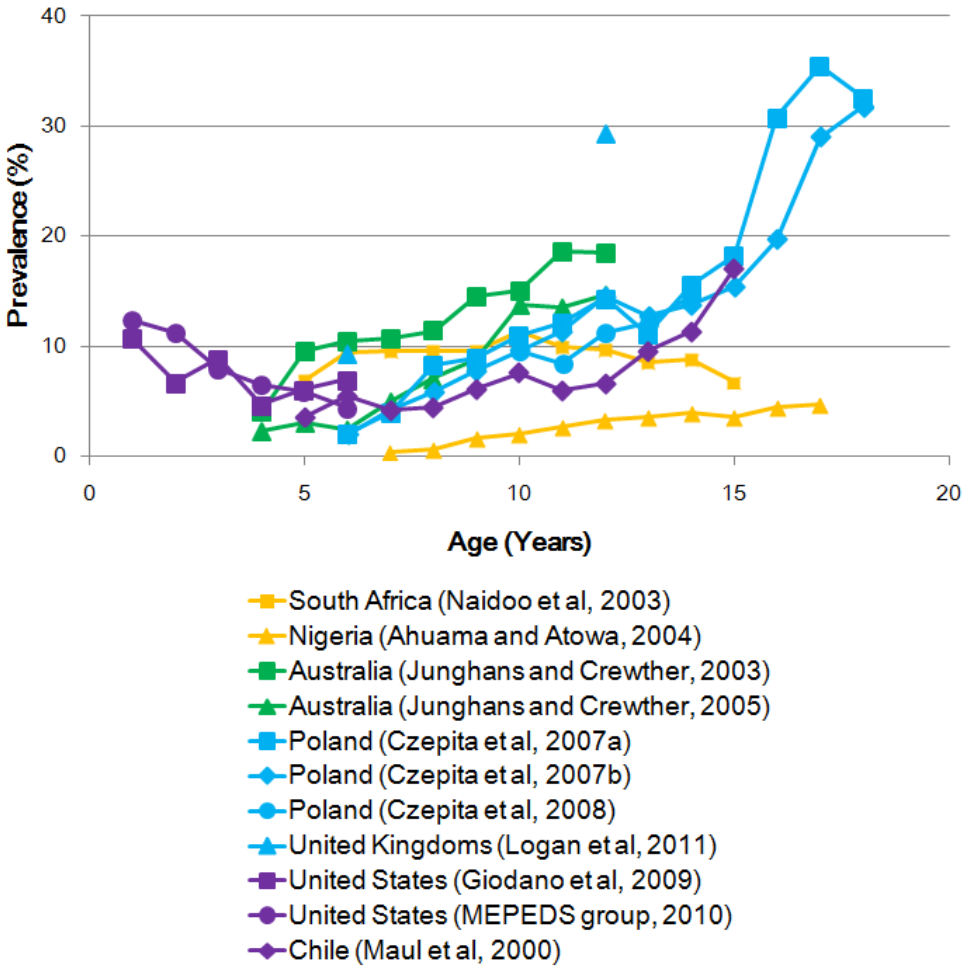


Figure 1.2. Prevalence of myopia in non-Asian countries. Yellow symbols represent African countries, green represent Australia, blue represent European countries and purple represent American countries.

D. Ethnicity difference within a studied population

Not only has myopic prevalence demonstrated geographical variations, it has also shown racial differences within a studied country. The Aston Eye Study in the UK has found higher

prevalence of myopia in South Asian and Black African children than in white European children (Logan *et al.*, 2011). This was consistent with the earlier Child Heart and Health Study in England (CHASE) (Rudnicka *et al.*, 2010). Being consistent with those found in the UK, results from the Baltimore Pediatric Eye Disease Study (Giordano *et al.*, 2009) and the Multi-Ethnic Pediatric Eye Disease Study (MEPEDS-Group, 2010) on 6–72 month-olds in America showed that Africa-American children had a six-folded and Hispanic Whites had three-folded higher risk of myopia than non-Hispanic Whites did (Borchert *et al.*, 2011). As it was unclear how many of the studied population were immigrants to the studied countries, these prevalence information could only be treated as ethnicity differences with environmental factors controlled to a certain extent. Singapore and Malaysia are neighboring nations with similar composition of ethnicity groups. The myopic prevalence was highest in Chinese, followed by Indian and was the lowest in Malay children (Saw *et al.*, 2006). The myopic prevalence was, however, shown to be different between the two nations, with Singapore having a three-folded higher myopic rate in the 7-9 year-olds (Saw *et al.*, 2006). This, again, shows the combined influence of environmental and genetic risk factors on myopia.

In China, there was scarce information on myopic prevalence in different clans. Of the available reports, the minority clans such as the Tibetan, Mongolian and Uygur were compared against the majority clan, the Han population. Higher myopic prevalence was found in Han schoolchildren than in Tibetan (Ge *et al.*, 2007) and

Uygur (Wang *et al.*, 2007). It was believed that the Han culture had more emphasis on the academic achievement, so Han students may spend longer hours in close work even after school. In another study investigating the vision and refractive status of Mongolia and Han students, Dong and colleagues (2007) claimed that 69% of the Han students with sub-normal acuity suffered from myopia, compared to 57% in the Mongolian students. These figures were, however, misinterpreted. If the number of myopic students were compared to the total number of students with the same clan, the myopic prevalence obtained would be 8.1% for the Hans and 14.7% for the Mongolians. The representativeness of these reports were, nevertheless, limited by their sampling methods, incomplete reporting of surveyed statistics, improper prevalence calculation, which have signified the need of a more systematic nationwide study design.

In short, Asian countries, particularly those in the South-eastern Asia, showed higher prevalence of myopia than Western countries. Ethnicity also played a part in the epidemiology of myopia.

1.1.1.2 Age differences

Figures 1.1 and 1.2 show the age-dependent myopic prevalence in different countries. Below six years of age, the prevalence of myopia is low and it varies with age slightly. Several studies even found that myopic rate decreased with age during the first few years of life (Giordano *et al.*, 2009; Dirani *et al.*, 2010; MEPEDS-Group, 2010). This was suggested to be an evidence of active emmetropization

during the first few years of life in the human eye. It has been speculated that the sensitive period in human eyes for emmetropization was within the first year of life (Zadnik and Mutti, 1995). However, consistent observations on the decreasing trend in mean spherical equivalent refraction (SER) by age (Twelker *et al.*, 2009) (Figure 1.3) was unable to explain the increasing myopia prevalence with age during the first few years of life (Figures 1.1 and 1.2). It was noted that the number of subjects refracted in the younger infants (usually the groups under 12 months of age) was almost half the number of the subjects in the other age groups in these studies. With consideration on the possibility that those whose parents were more willing to have their children received cycloplegic refraction were more likely to have eye problems, the prevalence of myopia in this younger infants might have been over-estimated. However, from six years onwards, the prevalence of myopia increases more rapidly with age and these changes could be more drastic in some Asian countries, such as Taiwan, Hong Kong, Singapore and China. Even within Asia, the epidemic of myopia is more serious in south-eastern Asian countries (e.g. Taiwan, Singapore, China and Hong Kong) than in the central or south Asian countries (e.g. Iran, India and Nepal). Figure 1.3 shows the mean SER by age in different countries. Children from south-eastern Asian countries, such as China, Japan, Hong Kong and Taiwan, develop myopia at a younger age than children from many other countries do. Mean SER of Caucasian children remains hyperopic throughout the childhood. The greater slopes of the curves for most south-eastern

countries also suggest a faster myopic progression rate in their children than in Caucasian children.

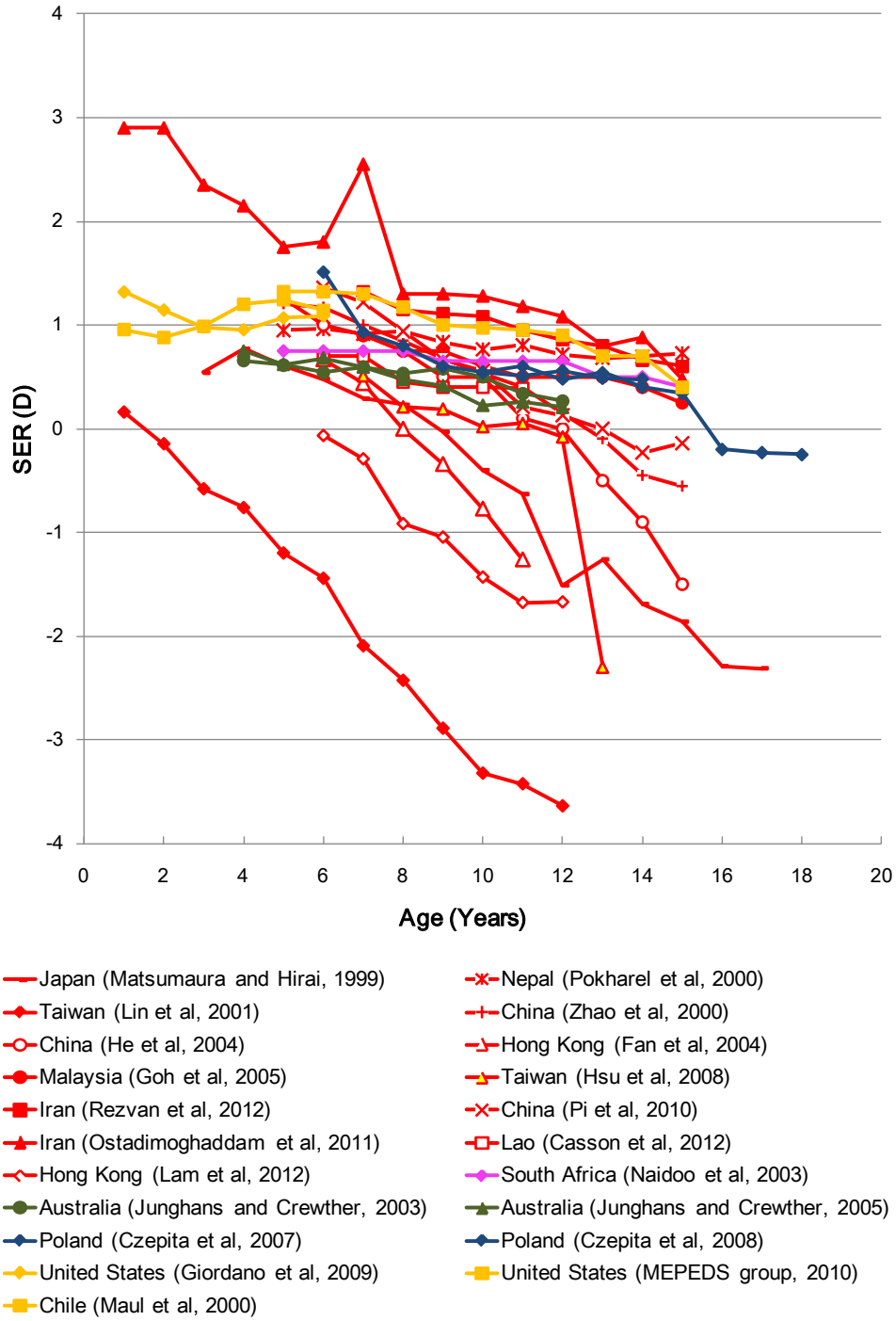


Figure 1.3. Mean spherical equivalent refraction (SER) by age in different countries. Red symbols represent Asian, Green for Australia, Blue for European, pink for African, yellow for the American countries.

1.1.1.3 Socioeconomic differences

Saw et al (2006) reported significantly higher myopic prevalence in Singapore than in Malaysia for the same ethnic groups. Similarly, a higher myopic prevalence in Middle Eastern children living in Australia was reported than that found in Middle Eastern countries (Azizoglu *et al.*, 2011). Similar report has also shown different prevalence of myopia in European Cacausians living in North Ireland and Sydney (French *et al.*, 2012). The prevalence of myopia was also found to be different between rural and urban areas which encompass the same ethnicity (Dandona *et al.*, 2002; Murthy *et al.*, 2002; Czepita *et al.*, 2008; He *et al.*, 2009). These differences may infer that other than ethnicity, environmental factors such as lifestyle, cultural background, education, near work and parental myopia. also play an important role in the epidemiology of myopia (see Section 1.2).

1.1.2 Changes of prevalence of myopia

While cross-sectional studies on myopic prevalence in many countries are widely available, longitudinal studies on the change of prevalence over time for any individual country or city are scarce. In Hong Kong, it has been reported that the myopic prevalence has increased from 2.7% in 1996-97 to 6.3% in 2006-07 in preschool children (2 – 6 years) (Fan *et al.*, 2011), while Lam et al (2012) did not observe a noticeable increase in myopia prevalence in older children. In Australia, the myopic rate for 4 – 12 year-olds in 2000s was found to be 6.9%, which was similar to an earlier cohort 10 years before (Junghans and Crewther, 2005). In Japan, the prevalence of myopia

in 17-year-olds was found to increase from 45% in 1984 to 65% in 1996 (Matsumura and Hirai, 1999). In the US, the prevalence of myopia in 12-17-year-olds rose from 24% in the 1970s to 34% in the 2000s (Vitale *et al.*, 2009). In Taiwan, the myopic population was found to increase from 38% in 1990 to 61% in 2000 for 12-year-olds and from 75% in 1990 to 84% in 2000 for 18-year-olds (Lin *et al.*, 2004).

The change in myopic prevalence over time varies from place to place. The underlying causes of these changes were not clear. Increased education, increased immigrants of Asian ethnicity and increased genetic susceptibility have been postulated to be risk factors for the change of myopic prevalence with time (Vitale *et al.*, 2009; Parssinen, 2012). Regardless of what the underlying causes are, a major challenge to such reports would be the consistency of research protocol and examination procedures used to collect the data.

1.1.3 Prevalence of high myopia

In practice, myopia of 6.00 D or more is considered as high myopia. Reports on the prevalence of high myopia during the early years of life are scarce (Lin *et al.*, 2001; Dirani *et al.*, 2010; Mohammad, 2010; Lam *et al.*, 2012). FitzGerald et al (2005) reported that 5% of the pediatric myopic population less than 10 years in New York had myopia of -6.00 D or more. About 2.5% of the 12-13-year-olds were found to have high myopia (≤ -5.00 D) in Sweden (Villarreal *et al.*, 2000). In Mexico, 1.4% of the 12-13 year-old population were found to have high myopia (≤ -5.00 D) (Villarreal *et al.*, 2003). In Iran, less than 1% of the adolescent population was high myopes (Hashemi *et al.*, 2004; Ostadimoghaddam *et al.*, 2011; Rezvan *et al.*, 2012).

Insignificant prevalence of high myopia was also observed in Nepal (Shresha *et al.*, 2011). In Hong Kong, the average prevalence of high myopia for 6–12-year-olds was 1.8% and that for the 12-year-olds alone was 3.8% (Lam *et al.*, 2012). The prevalence of high myopia of an earlier cohort in Hong Kong was similar (Fan *et al.*, 2004). In Singapore, the prevalence of high myopia was estimated to 5.7% for 15-19 year-olds (Quek *et al.*, 2004). In Taiwan, about 2% of the 12-year-olds and 17% of the 18-year-olds in 2000 were high myopes (Lin *et al.*, 2004). Compared to less than 1% and 7%, respectively, in an earlier cohort in 1990 (Lin *et al.*, 2004), the increase in prevalence of high myopia in Taiwan in 2000 was of concern. It is of no surprise that in places where the prevalence of myopia is higher, the prevalence of high myopes is also higher.

1.1.4 Consequences of high prevalence of myopia

Myopia imposes a considerable burden on the society. It has been estimated that US$3.9 to US$7.2 billion were spent on correcting refractive errors in the United States (Rein *et al.*, 2006; Vitale *et al.*, 2006). A recent study reviewed an annual individual expense of US$148 on eye examination and spectacles for 12–17-year-old children in Singapore (Lim *et al.*, 2009). The increase in the prevalence of myopia, accompanied by the increased need of treating the associated vision-threatening diseases, exacerbates its societal burden. If myopia is left untreated or allowed to progress into severity, the deprived vision and increased risks of developing permanently visually-impairing diseases such as glaucoma, retinal detachment and macular degenerative diseases, will eventually hamper the quality of life of the myopic population (Jones and Luensmann, 2012).

In view of the threats to the quality of life and increased societal burden by myopia, preventive measures to reduce the prevalence of myopia, as well as to stop myopia from progressing during childhood are essential. In order to tackle the problem, current myopia research follows different directions: 1) to recognize the mechanisms of myopic development and the associated risk factors; 2) to develop means to avoid the development of myopia in the early years of life; 3) to develop effective measures to arrest myopic progression on eyes which has become myopic.

1.1.5 Limitations of the epidemiology studies

Direct comparison among reported prevalence figures from various studies retained some difficulties. There existed differences in the sampling methods, age groups studied, examination protocols and instrumentation used, cycloplegic procedures and definition of ametropia adopted. At the end of the last century, WHO has launched the Refractive Error Study in Children (RESC) project and conducted a series of epidemiologic studies in different countries using the same protocol (Negrel *et al.*, 2000). In RESC project, children from five to 15 years were sampled from each geographically divided cluster of approximately equal population sizes. Sample size calculation was based on the estimated 22% prevalence in 15-year-olds with an error bound of 20% at 95% confidence intervals, adjusted by a 10% absence or non-participation rate and finally an arbitrary 25% allowance for invalid data. Examination procedures included lensometry, VA measurements, ocular motility, alignment evaluation, cycloplegic retinoscopy and autorefraction, external and internal ocular health evaluation. The RESC project defined ametropia by cycloplegic SER

(Twelker *et al.*, 2009). Hyperopia was defined by an SER ≥ 0.50 D while myopia was defined by an SER ≤ -0.50 D. With the RESC protocol, the comparison of myopic prevalence from various reports has received fewer challenges (Morgan *et al.*, 2010). It will further facilitate the investigation of environmental risk factors in the epidemiology of myopia. An increasing number of studies have undertaken the same definition for ametropia and similar procedures as the RESC project.

A major limitation which has made the current epidemiologic study on myopia less representative is the sampling method of individual study. For example, the samples in the Hong Kong studies might not be representing the whole picture of the schoolchildren as the examination was conducted primarily in a few schools which the authors believed were representative for the local schools within the education system. Further impedance on the accuracy of these epidemiology studies were from the use or not of cycloplegia for refraction and the choice of refractive methods. Cycloplegic refraction is crucial especially on children who have more active accommodation and are less cooperative during refraction (Fotedar *et al.*, 2007). Autorefraction would be a useful objective measurement in most cases. However, when refracting children at young ages, such as infants below one year, the use of streak retinoscopy was more successful (Guyton and O'Connor, 1991). However, it will require experienced practitioners in order to minimize bias.

1.2 Risk factors of early onset myopia

The cause of myopia is multifactorial. The causes for myopia development in early-onset myopia and late-onset myopia are thought to be of different

origins (Wu *et al.*, 2005) but they may have certain risk factors in common. A number of studies have shown that late-onset myopia in young adults was related to near work, which had put certain occupations into higher risk of myopia development and progression (Simensen and Thorud, 1994; McBrien and Adams, 1997; Wu *et al.*, 1999; Ting *et al.*, 2004; Cortinez *et al.*, 2008) . Several reports on myopia prevalence among microscopists have consistently shown that the prevalence among this profession was significantly higher than the population-based prevalence (McBrien and Adams, 1997; Ting *et al.*, 2004). Both genetic and environmental risk factors coexist to leave an eye more myopia-prone. Parental myopia has been shown to be a risk factor for higher prevalence of myopia in children (Mutti *et al.*, 2002; Kurtz *et al.*, 2007; Lam *et al.*, 2008; Jones-Jordan *et al.*, 2010; Xiang *et al.*, 2012a; Xiang *et al.*, 2012b) and twin studies have also supported the heritability of myopia (Dirani *et al.*, 2006; Dirani *et al.*, 2008a; Tsai *et al.*, 2009; Baird *et al.*, 2010; Zhang *et al.*, 2011). However, the interactions from environmental factors in these familial analyses (e.g. siblings sharing similar living environment, education, nutrition) have indicated some importance of environmental factors (Chen *et al.*, 2007; Czepita *et al.*, 2011) Opinion on whether there is a stronger effect of genetic or environmental risk factors has not yet been determined. Mutti et al (2002) concluded that the heredity was of a strong influence than environmental factors, while Morgan et al (2012) has recently suggested that “school myopia is multifactorial, possibly involving a large number of genes of small effect, and major environmental factors”.

1.2.1 Genetic risk factors

1.2.1.1 Parental myopia

In one of the epidemic populations, Taiwanese, Liang et al (2004) have shown, in a group of young adults, that the number of highly myopic parents would increase the risk of high myopia development, and that those having highly myopic parents were likely to have an earlier onset of myopia. Although the mean age of myopia onset in their study indicated that in general, respondents had early-onset myopia, those with late-onset myopia were not excluded from the analysis. As the causative factors were not the same between early- and late-onset myopia, they may have over-estimated the influence of parental myopia.

It would have been more valuable to investigate parental effect on early-onset myopia in children than in older subjects. In a population based study, Lam et al (2008) found that refractive errors of Hong Kong teenagers was negatively associated with the number of myopic parents (SER of children with two myopic parents was the least hyperopic while SER of those without myopic parents was the most hyperopic). Axial length (AL) was, on the other hand, positively related to the number of myopic parents (the more the number of myopic parents, the longer the axial length). It was because the more myopic eyes tended to have longer axial lengths (Meng *et al.*, 2011). Moreover, in the same study refractive changes and axial elongation were most rapid in children with two myopic parents in their initially non-myopic cohort. In the Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error (CLEERE)

Study, the incidence of myopia in the originally non-myopic children in their first grade was found highest in children with two myopic parents and lowest in children whose parents were both non-myopic (Jones-Jordan *et al.*, 2010). These findings were in agreement with the Correction of Myopia Evaluation Trial study (COMET2-Study-Group, 2011) in the US where the progression of myopia and axial length changes in the myopic children of the control group increased with the number of myopic parents (Kurtz *et al.*, 2007). However, at the end of the 12-month longitudinal observation in Lam and colleagues' study (2008), regardless the change in refractive errors was the greatest, mean SER of children with two myopic parents remained emmetropic. Furthermore, the 12-month change in SER was not of clinical significance. In an earlier study, Fan et al (2005) found no significant differences in the AL of preschool children (who were overwhelmingly emmetropic) with different number of myopic parents. However, the sampling method was less representative for kindergarteners in Fan and co-workers' study.

It would be of interest to see how different the myopic progression and axial elongation of these emmetropic cohorts (pre-school or school children) would be in relation to the number of myopic parents when they developed myopia. Further investigation with unbiased sampling is warranted on how the parental myopia will be in association with the SER and axial lengths in emmetropic kindergarteners and with the pattern of myopia onset. In addition, a comparison between myopic and non-myopic patterns would add

extra value to these reports. Low and colleagues (2010) have provided some insight on this issue. They evaluated the information from the STrabismus, Amblyopia and Refractive error in Singaporean children (STARTS) study, and found that about 45% of myopic preschool children had both parents with myopia, compared to 22% of the myopic peers with neither parent myopic. However, the emmetropic subjects in the same study did not show any particular pattern on parental myopia. Parental refractive status seems to have no particular relationship in emmetropia.

From a Chinese cohort, Xiang et al (2012b) found that the prevalence of myopia, as well as high myopia in children, were positively related to the severity of myopia in their parents. Their work had augmented Liang and colleagues' findings (2004) that the prevalence of high myopia in a group of young adults was associated with parental high myopia, although the latter did not exclude the influence of late-onset myopia as previously discussed.

Opinion about the impact of parental myopia is consistent across various studies. However, these studies commonly experienced a major limitation with respect to the method of evaluating parental refractive status. The most commonly used method was self-reporting by questionnaires. Although some reports have tried to ensure the reliability of the questionnaire by conducting validity cross-check through performing subjective refraction on a number of the participating parents (Liang *et al.*, 2004; Xiang *et al.*, 2012b), faulty estimations on the prevalence as well as severity of parental myopia should not be overlooked. The GEnes in Myopia (Madsen *et*

al.) study, on the other hand, has measured the ocular biometrics in 132 pedigrees for an investigation on the familial correlation of myopia (Chen *et al.*, 2007). The estimated correlations in the parent-offspring pairs were 0.25, 0.38, 0.37 and 0.30 for SER, AL, anterior chamber depth (ACD) and corneal curvature (CC), respectively (Rein *et al.*). The stronger correlation in AL was, however, not explained by the correlation in SER but by ACD. Unfortunately, the GEM study did not measure the lens curvatures and thickness, lenticular power or vitreous chamber depth (VCD), which would possibly provide more information for the parent-offspring familial correlations.

1.2.1.2 Siblings

Compared to the parent-offspring correlations, the sib-pair (between siblings) correlations in the GEM study were higher in all parameters (Chen *et al.*, 2007). The correlations for SER, AL, ACD and CC were approximately 0.78, 0.40, 0.62 and 0.34, respectively. The strongest correlation was found in SER, which was not explained by a correspondingly higher correlation in AL. However, the heritability index for each parameter showed a different pattern from that of the correlations, with 0.50, 0.73, 0.78 and 0.16 for SER, AL, ACD and CC, respectively. It is believed that the parameters measured were insufficient to explain the differences between the refractive and biometric correlations in myopia inheritance analysis. Lens curvatures and thickness, lens power and VCD measurement may provide additional insight in such studies.

The correlations for the sib-pairs were consistently higher than those for the parent-offspring pairs in the GEM study. It indicated that the heritance of myopia in the two familial relationships were different, with the parent-offspring heritability being more prone to environmental impacts, while the sib-pairs were more heritable. Czepita et al (2011) also found significant association between early-onset myopia and parental myopia as well as sibling myopia in 5533 Polish students aged six to 18 years. However, the risk factors were not adjusted for age and gender or educational levels. Notwithstanding, there were no information showing the level of correlations between parent-children and between-siblings myopia, nor were there information on the impact of the severity of parental myopia or sibling myopia on the subject's SER.

1.2.1.3 Twin studies

The twin studies provided evidence of heritability of refractive errors from another perspective. Stronger correlations in monozygotic (MZ) than in dyzygotic (Lehembre *et al.*) twins for myopia and biometry data have been consistently reported by a number of twin studies (Tsai *et al.*, 2009; Baird *et al.*, 2010; Zhang *et al.*, 2011). With a sample size of 58 twin pairs, Tsai et al (2009) showed very strong correlations in MZ twins for all the measured parameters, namely SER, AL, ACD and lens thickness (LT), compared to relatively smaller but significant correlations in DZ twins. Their study reported a heritability index of 0.33 and 0.67 for SER and AL, respectively. The trend was similar to those observed in the sibling studies (see

Section 1.2.1.2). The GEM study investigated the prevalence and characteristics of myopia in 612 pairs of both MZ and DZ twins and found that both twins in MZ pairs had 78% chance of developing myopia, compared to 47% in the DZ pairs (Baird *et al.*, 2010). The risk of both twins developing myopia in the MZ was ~1.6 times greater than those in the DZ twins. In addition, the higher intra-pair correlations found in MZ than in the DZ twins with respect to refractive errors and axial lengths have reflected a high genetic component in refractive development. In 565 twin pairs (359 MZ pairs and 206 DZ pairs) in the Guangzhou Twin Eye study, Zhang et al (2011) found a very strong correlation of 0.89 in AL between MZ twins, compared to a weaker correlation of 0.38 between DZ twins. However, in the Guangzhou study, no analysis was performed on the correlations of SER or other biometric data. As shown by the Taiwanese twin study (Tsai *et al.*, 2009), LT also demonstrated a strong heritability. Hence, considerations on the lenticular biometry are warranted in future studies.

1.2.1.4 Age of myopia onset

It has been established that the earlier the age of first myopia onset, the higher the risk of developing high myopia (Saw *et al.*, 2001; Liang *et al.*, 2004). Almost half of the myopic participants in Liang and co-workers study (2004) had myopia of 6.00 D or more, and had onset of myopia at the age between six and 12 years. Their results also showed that participants whose parents were highly myopic would develop myopia at an earlier age.

1.2.2 Environmental risk factors

1.2.2.1 Education

There has been very limited study on the risk of myopia in Hong Kong. In an earlier report, the myopia prevalence in local and international schools was compared (Lam *et al.*, 2004). No difference in prevalence of myopia in children attending local or international schools was found. It was generally thought that the curriculum of international schools were less demanding than local schools, so a higher prevalence would have been expected in children attending local schools. However, the lifestyle, such as extra-curriculum activities, reading habits, TV/computer game hours of Chinese children would be expected to be similar regardless of the types of school they attended. Nowadays, school children in Hong Kong have to attend many different extra-curriculum courses and extra tuition classes after school and the use of computers, tablets or personal digital assistants have became more popular among the younger ages. These environmental factors were, however, not taken into consideration in Lam et al.'s study (2004). Although that Chinese children in international school having a higher prevalence of myopia than their Caucasian classmates indicated that ethnicity played an important role in myopia, contribution of after-school lifestyle (such as extra-curriculum activities and extra tuition classes) was not studied. A similar study with additional consideration on the after-school activities and daily-life visual habits is warranted to have a more up-to-date and comprehensive investigation.

Liang et al (2004) have reported that higher education level was

associated with the development of high myopia in Taiwanese adults. However, their study was subjected to some bias as most of their subjects were high school senior students and university students who had higher education levels compared to the general populations. Myopic prevalence surveys on military conscripts have consistently shown that the higher prevalence of myopia was observed in young adults who spent more years at school or had achieved higher level of education (Saw *et al.*, 2001; Vannas *et al.*, 2003; Konstantopoulos *et al.*, 2008; Jung *et al.*, 2012). These reports were more representative of the nation's population, although usually only male conscripts were considered. In Singapore, the conscript survey had also indicated that the stream of education attended and the tuition lessons in primary school were associated with myopia among young servicemen (Saw *et al.*, 2001). It is of interested to expect a causal effect among these three parameters: the number of tuition lessons might increase the opportunity for the children to enter the more gifted education stream which in turn would promote the highest level of education achieved. It was, however, suggested by the GEM study that educational attainment was of a strong genetic influence, rather than environmental (Dirani *et al.*, 2008b). Moreover, younger age of myopia onset has been shown to be a risk factor for developing high myopia in the Singaporean survey (Saw *et al.*, 2001). The increased close-work activities in the Singaporean conscripts (as indicated by the extra tuition lessons attended in primary schools) might also prompt the onset of myopia at a younger age (Saw *et al.*, 2001), which in turn enhanced the prevalence of

high myopia (almost half of the conscripts had myopia of 6.00 D or more) in the study group.

Parental education was also investigated in some reports, but opinions were inconclusive. It was previously thought that the level of education received by parents did not correlate significantly with the prevalence of myopia or age of onset of myopia in their offspring (Saw *et al.*, 2001; Mutti *et al.*, 2002; French *et al.*, 2012). On the contrary, Xiang et al (2012a) has recently found a higher risk of myopia development in children with higher parental education levels. However, it was noted that in Xiang and colleague's sample, almost 80% of the parents had highest education at secondary level and 17% at tertiary level, leaving 3% of the parents in the no formal or primary level group. The unequal sample size may have introduced bias on the effect of parental education level on the prevalence of child myopia.

1.2.2.2 Near work

The association between near work and myopia has been well documented in numerous studies (Hepsen *et al.*, 2001; Saw *et al.*, 2001; Mutti *et al.*, 2002; Ip *et al.*, 2008; Konstantopoulos *et al.*, 2008; Saw *et al.*, 2008; Lu *et al.*, 2009a; Low *et al.*, 2010). The duration of continuous reading, reading distance and the number of books read per week or chapters per day, has been used as quantifiers of near work in different studies. Other indirect quantifiers or markers for the loading of near work, such as the age of first attending school, the stream of schools attended and the amount of extra tuition

lessons attended, have also been employed. That below the age of six and near work seemed to be less likely a risk factor for myopic development (Fan *et al.*, 2005; Low *et al.*, 2010). Low and co-authors (2010) postulated that it was because the total number of near work in preschool children was relatively smaller and the curriculum in kindergartens was less intensive, compared to elementary school children who had to spend significantly longer hours in near work and the curriculum in elementary schools were much more intensive. Moreover, reading material of kindergarteners are usually more pictorial, compared to the more literal material for the primary schoolchildren which would further increase the loading of near work for older children. Hepsen et al (2001) found significant myopic progression in a group of 41 initially emmetropic schoolboys (13 years old on average), compared to another group of 38 boys who were skilled laborers (apprentices of furniture makers, hairdressers and shoemakers). They postulated that the larger myopic shift was due to the more intensive daily close work attained by the schoolboys (average close work / reading time = 6 hours; average working distance = 36 ± 5 cm) while no intensive close work were required by the apprentices. Hepsen and colleagues' work did show some association between close work and myopic progression. However, they had neglected the close work nature of the apprentices (especially for the shoemakers); their working distance was at arm length or closer for 8 hours a day. In addition, other environmental risk factors, such as outdoor activity hours and lighting of working or studying environment were not considered as

covariates in this study.

Myopic subjects studying in the eighth grade in the Orinda Longitudinal Study of Myopia (OLSM) were found to have significantly longer near work diopters hours per week (i.e. number of hours performing near task per week per working distance for near) but shorter time spent on sports compared to their emmetropic counterparts (Mutti *et al.*, 2002). This was consistent with another population-based study in China (Zhang *et al.*, 2010).

However, the association between near work and myopia might be different in rural areas, compared to urban regions. In the Xichang Pediatric Refractive Error Study (X-PRES), Lu et al (2009a) conducted a multiple univariate analysis on the self-reported near work (e.g. homework and reading) and working distance by 998 middle school children (aged 14.6 years on average) in the rural area. They did not find any association between myopia and the number of hours spent per week on near work. They only observed a consistently shorter near working distance in myopic subjects than in non-myopic ones. Students studying in schools in cities face more challenges in their academic performance than students going to village schools. The near work habits in children differed between urban and rural areas as well. For example, in Hyperabad, India, the number of hours spent on near work activities by urban students was 8 hours per day compared to 5 hours per day by urban students (Dandona *et al.*, 1999). Another possible explanation on the urban-rural difference might be due to the higher population density in the urban area. Zhang et al (2010) evaluated the population

density of area of residence in 2480 children and suggested it would be a potential factor leading to higher myopia. Their findings suggested that living and activity spaces available for the general population may interact with lifestyles concerning studying, schooling and outdoor activities.

The association of myopia with near work has put certain occupations at risk of developing or progressing myopia. Jobs requiring working with the microscopes have aroused research interest in myopia risk factors. Ting et al. (2004) found a greater myopic prevalence (87%) among Chinese microscopists working in a hospital laboratory in Hong Kong than that in the United Kingdom (71%). The only difference between a group of 22 microscopists with progressing myopia and another group of 19 peers with stable myopia was AC/A ratio (4.59 Δ/D vs 3.34 Δ/D) in the Hong Kong study. A two-year follow-up study on the UK microscopists had shown that there were 39% and 48% of the initially emmetropic and myopic participants, respectively, who progressed into myopia with mean changes of 0.58D and 0.77D, respectively, over 2 years (McBrien and Adams, 1997). McBrien and Adams (1997) reported that the myopic shift was associated with an increase in VCD in both groups. This phenomenon was similar to those observed in near-work-induced transient myopia (Drexler *et al.*, 1998; Mallen *et al.*, 2006; Woodman *et al.*, 2011) where there was a transient increase in axial length.

The potential physiological basis for the association between myopia and near work lies in accommodative status, as some authors

suggested, more specifically on the lag of accommodation (Gwiazda *et al.*, 2004; Vasudevan *et al.*, 2009) while some suggested on the variability of accommodation (Langaas *et al.*, 2008). Recent study has demonstrated that optical defocus were able to cause small but significant transient changes in axial length (Read *et al.*, 2010). However, the role of accommodative lag in myopic progression was not advocated by recent longitudinal studies in which accommodative lag was found not associated with the progression of early-onset myopia (Mutti *et al.*, 2006; Weizhong *et al.*, 2008; Berntsen *et al.*, 2011).

1.2.2.3 Outdoor activities

It was not until recently that outdoor activity was considered a preventive measure for myopic progression. Rose et al (2008) analyzed the pattern of near work and outdoor activities in 1740 Year One and 2353 Year Seven students from the Sydney Myopia Study (SMS), and found that the greater the number of hours spent outdoor, the more hyperopic the mean SER were in both groups. Concurrently, the impact of near work alone on the mean SER was not as significant as in other studies (see Section 1.2.2.2). However, the interaction between the number of longer hours spent on outdoor activities but less on near work would have a preventive effect on myopia development. Rose et al. (2008)found that there was a 2- to 3-fold increase in risk with less outdoor activities and long near work hours. They postulated that the higher light intensity outdoors constricted the pupil, thus leading to a greater depth of focus and less

retinal blur. In addition, they further hypothesized that the increase in dopamine release by increased intensity outdoors might have suppressed the eye growth. The importance of light in the recovery from induced myopia in chicks (Stone *et al.*, 1995; Norton *et al.*, 2006a) and the protective effect of high ambient lighting in primates (Smith *et al.*, 2012) advocated this hypothesis.

1.2.3 Others

1.2.3.1 Natural lighting experienced in neonatal period

Animal studies have shown that light/dark cycles during the neonatal growth were able to affect refractive development (Stone *et al.*, 1995; Norton *et al.*, 2006a; Smith *et al.*, 2012). Mandel et al (2008) divided 276911 adolescents into four photo-period categories (Category I: 10.1 – 10.8 hours, Category II: 10.81 – 12.2 hours, Category III: 12.21 – 13.57 hours and Category IV: 13.58 – 14.23 hours), according to the average number of daylight hours during the 30 days from their date of birth, and found that more light exposure during the neonatal period was associated with moderate to severe myopia in adolescents. The exact reason was unknown; however, melantonin-dopamine balance was postulated to have been influenced by the neonatal phase of light exposure. Similar investigation was done on the Finnish army conscripts but there was no association between myopia and month of birth (Vannas *et al.*, 2003). Notwithstanding, a higher myopia prevalence was found in the region above the Arctic Circle, where there was extreme day light.

Further elaboration of the ambient light hypothesis into adolescent age will, however, lead to a contradiction to the hypothesis in which longer hours of outdoor activities would become a protective factor in myopic progression due to exposure of daylight. Smith et al (2012) found that monkeys reared in bright light intensity were able to remain hyperopic in spite of form deprivation treatment, while another group of form-deprived monkeys which were reared in normal lighting developed myopia at the end of the rearing period. If the primate model could be applied to humans, the prevalence of myopia would be relatively lower in the area where light intensity was high. Consideration on the applicability of animal models onto human eyes should also be taken. It was speculated that the animal models were applicable in human eyes for a sensitive period from birth to the first few year of life (or less) (Zadnik and Mutti, 1995). At the time of the juvenile-onset myopia takes place, the emmetropization animal model may not be fully applicable in human eyes. It would be of interest to re-evaluate the prevalence of myopia in the population studies by Mandel and co-workers (2008) and Vannas and colleagues (2003), by taking into consideration the effect of covariates such as age and the trend of prevalence in different age groups.

1.2.3.2 Peripheral refraction

Animal studies have shown that the relative peripheral hyperopia may be a potential cause of myopia while relative peripheral myopia could be protective against myopia development (Smith *et al.*, 2005;

Smith *et al.*, 2007; Smith *et al.*, 2009a; Smith *et al.*, 2009b). Moreover, from a number of clinical studies which measured the peripheral refraction of eyes before and after orthokeratology (ortho-k) treatment, it has been consistently shown that ortho-k treatment could convert the initial relative peripheral hyperopia into relative peripheral myopia (Charman *et al.*, 2006; Queirós *et al.*, 2010a; Kang and Swarbrick, 2011). It was then postulated that the changes in relative peripheral refraction by ortho-k could be a potential mechanism (Charman *et al.*, 2006) through which ortho-k was able to arrest myopic progression in children (Cho *et al.*, 2005; Walline *et al.*, 2009; Kakita *et al.*, 2011; Cho and Cheung, 2012; Santodomingo-Rubido *et al.*, 2012) (Details in Chapter 2).

1.3 Hypothesis of Myopia Development

1.3.1 Theory of emmetropization

Emmetropization is a process in which an eye grows to match the focal plane with the retina, in order to attain emmetropia. It is thought of as a combined process through both passive and active mechanisms. The passive mechanism relates to the proportional changes in the size of the globe. Concurrently, it is accompanied by a series of changes in corneal and lenticular lens powers and lens thickness to compensate for the increase in axial length. The active mechanism is a visually-driven modulation of the axial length, which is adjusted in response to defocused signals received by the retina (Norton and Siegwart, 1995; Brown *et al.*, 1999; Norton, 1999; Wallman and Winawer, 2004).

Animal models with chickens (Wallman *et al.*, 1978; Yinon *et al.*, 1980; Yinon *et al.*, 1982; Hodos and Kuenzel, 1984; Pickett-Seltner *et al.*, 1988; Irving *et al.*, 1992; Guo *et al.*, 1996; Schmid and Wildsoet, 1996; Winawer *et al.*, 2005; Schmid *et al.*, 2006), kittens (Smith *et al.*, 1980; Kirby *et al.*, 1982; Cremieux *et al.*, 1989; Ni and Smith, 1989), monkeys (Troilo and Judge, 1993; Smith *et al.*, 1994; Graham and Judge, 1999; Smith and Hung, 1999; Troilo *et al.*, 2000; Smith *et al.*, 2001), mouse (Tejedor and de la Villa, 2003; Schaeffel *et al.*, 2004; Faulkner *et al.*, 2007; Barathi *et al.*, 2008; Tkatchenko *et al.*, 2010; Zhou *et al.*, 2010), guinea pigs (Howlett and McFadden, 2006; Howlett and McFadden, 2009; Lu *et al.*, 2009b) and tree shrews (Sherman *et al.*, 1977; Marsh-Tootle and Norton, 1989; McBrien *et al.*, 1999; Shaikh *et al.*, 1999; Norton *et al.*, 2006b) have provided evidence to support the active feedback process in emmetropization. The vision-dependent modulation of axial length was successfully demonstrated with variation in light illumination and vision alteration by changing the focal plane or information removal or degradation from the foveal region (Norton and Siegwart, 1995; Wildsoet, 1997).

1.3.1.1 Lens induced ametropia

Positive lenses are able to bring the focal plane of an emmetropic eye to the front of the retina, inducing a positive or myopic defocus (Smith *et al.*, 1980; Pickett-Seltner *et al.*, 1988; Smith *et al.*, 1994; Hung *et al.*, 1995). Negative lenses will take the focal plane further away behind the retina, producing a negative or hyperopic defocus. The animal eyes could respond to the optical defocus produced by the lenses by changing the axial length. Albeit the power of the

inducing lenses used varied in different animals, animal eyes became shorter and hyperopic in magnitude similar to the inducing power when positive lenses were used while the eyes grew longer and became as myopic as the inducing power when the negative lenses were in place. It was also demonstrated that once the inducing lenses were removed and free vision was allowed, the eyes with induced ametropia were able to recover and to resume emmetropic (Smith *et al.*, 1994). Recent work from Zhu and colleagues (2013) have also shown that animals could shorten their eyes axially in response to myopic defocus. All these lens-induced responses observed in animals were experimented during the early developing period of individual species. Whether the implications from these animal studies would apply in human is still unknown. In human, the growth period during which myopia onsets is around the end of the first decade of life (Figure 1.3). How similar is the growth pattern during this period compared to that during the first few years of life in human is not known. Although it has been shown that axial length could be altered transiently by optical defocus in human (Read *et al.*, 2010; Chakraborty *et al.*, 2012), the change was relatively small and could be recovered shortly after the removal of defocus. More evidence is needed to confirm the long-term effect of optical defocus on axial length changes in human, and during the myopia-prone age, in particular.

1.3.1.2 Form deprivation myopia

Treated eyes in lid-sutured animals were found to be more myopic

than the fellow untreated eyes or other control animals (Sherman *et al.*, 1977; von Noorden and Crawford, 1978; Yinon *et al.*, 1980; Kirby *et al.*, 1982). Change in refractive errors was found to be correlated with greater increases in axial length, which indicated that the changes in refraction were mainly axial. However, the magnitude of myopia induced varied among species. The replacement of lid-suture procedures with translucent occluders or diffusers in later animal experiments was able to produce similar results and some of these studies showed that form-deprivation myopia was a graded phenomenon (Smith and Hung, 2000; Schmid *et al.*, 2006). It was also found that the modulation of spatial frequency, contrast and illumination was responsible for causing form-deprivation myopia (Feldkaemper *et al.*, 1999; Schmid *et al.*, 2006; Tran *et al.*, 2008).

1.3.2 Human eye growth

With the assumption that the human eye is not largely different from animal eyes, the growth of the human eye is thought to be, by itself, a genetically-guided process, and it is further modulated by a visually-guided mechanism (Zadnik and Mutti, 1995). That the refractive errors, axial lengths, corneal and lenticular powers of human eye at birth were distributed normally are believed to be genetic characteristics of eye growth (Ojaimi *et al.*, 2005). In general, the human eye is hyperopic at birth (Mayer *et al.*, 2001; Snir *et al.*, 2004). Hyperopia decreases and axial length increases with age during the early postnatal years (Mayer *et al.*, 2001). These changes are believed to be visually driven. The eye emmetropizes in an attempt to move its focal plane towards the retina, consequently to

achieve emmetropia. However, in human, the endpoint for this feedback mechanism seems to be slightly hyperopic (Morgan *et al.*, 2010).

Like many other organs, the eye has its own growing curve. The course of emmetropization had an exponential relationship with age, showing the most rapid growth rate at infancy (Mayer *et al.*, 2001). Significant reduction in hyperopia is found in the first nine months of life. It is brought about by pronounced reductions in corneal and lenticular powers with a substantial increase in vitreous chamber depth which results in a significant axial elongation thereafter (Isenberg *et al.*, 2004; Mutti *et al.*, 2004; Mutti *et al.*, 2005). The corneal and lenticular toricity also decrease during this major period of emmetropization. From the first twelve months of life onwards, although there are significant changes in refraction and ocular components with age, the ocular growth rate slows down from preschool age to puberty (Mayer *et al.*, 2001; Zadnik *et al.*, 2003; Jones *et al.*, 2005; Twelker *et al.*, 2009).

Although results from many population studies have shown that the function of mean refractive errors with age plateaus around mild hyperopia starting from the age of five or six years, higher prevalence of myopia and higher myopia are noted in some populations, such as Taiwan, Singapore and Hong Kong (Pan *et al.*, 2012). .

1.3.3 Axial elongation and global expansion

1.3.3.1 Axial elongation

Animal studies on lens-induced and form-deprivation myopia have shown that the induced myopia was axial in nature (Norton and Siegwart, 1995). In addition, various human studies have ascertained

the association of axial elongation with myopic progression (Lin *et al.*, 1988; Jones *et al.*, 2005; Saw *et al.*, 2005a; Ip *et al.*, 2007; Gonzalez Blanco *et al.*, 2008). Axial length and vitreous chamber depth are two biometric measurements which correlate significantly with myopic progression, while the others, including corneal and lenticular powers, anterior chamber depth, and lens thickness do not. The negative correlation between axial length and myopia is well accepted. Every one millimeter axial elongation corresponds to ~2.7 D increase in myopia (Rabbetts, 1998).

1.3.3.2 Evidence of global expansion

Magnetic resonance imaging (MRI) studies have suggested that ocular dimensional changes during eye growth were not only confined to antero-posterior elongation, but also involved equatorial and vertical expansions (Cheng *et al.*, 1992; Atchison *et al.*, 2004; Atchison *et al.*, 2005a; Ishii *et al.*, 2011). Cheng et al. (1992) measured the axial, coronal-horizontal (superimposed with the axial equatorial) and coronal vertical dimensions from MRI of 21 adult eyes. They found that the myopic eyes were the longest among all in all dimensions. They also proposed that the eye expands radially during myopia progression. Atchison et al. (2004) also found that myopic eyes were greater in length, height and width when compared with emmetropic eyes. In a later study, Atchison et al. (2005a) quantified the shape of the retinal surface and found that both emmetropic and myopic eyes were oblate in shape, with the myopic eyes being less so. However, they were unable to conclude

from their dimensional data whether eye growth fitted the axial elongation model or global expansion model. Ishii et al. (2011), using fourier descriptors, demonstrated that changes before the age of six years fitted better with axial elongation model while thereafter eye growth fitted better with the global expansion model.

1.3.4 Emmetropization and peripheral refraction

Assuming the animal models of emmetropization is applicable in human eyes, the development of myopia suggests a failure of the mechanism in human. The genetically programmed growth seems to be faulty since early childhood. Zadnik et al. (2003) found little changes in the corneal power, lens thinning and lens flattening between 6 and 14 years of age. The development of myopia was also found to be associated with a "stop" in lens thinning and flattening (Mutti *et al.*, 2012). This further suggests that failure of the active feedback may have resulted in a defect of the emmetropization process. What have caused the failure is still unknown, but there have been various speculations (Refer to Section 1.2.2 Environmental risk factors).

Central vision constitutes only a small portion of vision. It would be too simplistic to explain the etiology of myopia with emmetropization exclusively with axial optics. Some forty years ago, it was firstly proposed that certain peripheral refraction characteristics had made a group of young pilots more prone to myopia when compared to their counterparts who remained emmetropic (Hoogerheide *et al.*, 1971). Animal studies with deprived central vision and deprived peripheral vision followed to provide new insight about the influence of peripheral image on central refraction

development (Smith *et al.*, 2007; Huang *et al.*, 2009; Huang *et al.*, 2011). Numerous human studies and clinical trials have mushroomed to evaluate the role of peripheral refraction in myopia (see Chapter 2).

1.4 Myopic Control Interventions

Prevention is always better than a cure. In order to alleviate the social and health burden brought about by high myopia, the priority is to prevent myopia from developing or progressing during childhood. Although the etiology of myopia and the associated risk factors of its rapid progression are not fully understood, a number of myopic control interventions have been explored and employed in clinical practice in the hope of arresting myopic progression. In this section, the two major types of myopic control interventions, optical and pharmaceutical, are reviewed.

1.4.1 Optical interventions

The efficacies of various optical interventions have been well studied. Among these are spectacle lenses and contact lenses. Most of them are worn during waking hours while some are worn during sleep; some aim to relax accommodation during near work while some others to correct optical imperfectness on the peripheral retina, which are thought to cause myopic progression, other than central refractive errors.

1.4.1.1 Spectacle lenses

A. Undercorrection with single vision lenses

The rationale of undercorrection in retarding myopic progression

originated from the fact that myopes have a larger and more variable accommodative lag than emmetropes (Nakatsuka *et al.*, 2005; Langaas *et al.*, 2008), and the established hyperopic defocus at near during close work is thought to have stimulated myopic progression (Rosenfield and Gilmartin, 1999). The lag of accommodation was found to be reduced by undercorrection (Nakatsuka *et al.*, 2005). A few studies have shown that the lag of accommodation at near is correlated with myopic progression (Gwiazda *et al.*, 2004; Allen and O'Leary, 2006). However, it was not supported by others (Rosenfield *et al.*, 2002; Weizhong *et al.*, 2008; Berntsen *et al.*, 2011; Berntsen *et al.*, 2012). Mutti et al (2006) did not find significant increase in accommodative lag before and during the onset of myopia. Their observation of increased accommodative lag found only after the onset of myopia suggested that greater lag of accommodation in myopes was likely to be a consequence rather than a risk factor of myopic progression. Moreover, constant wear of single vision lenses (SVL) with full correction in myopes did not show significant difference in myopic progression from myopes wearing full correction only for distance (Parssinen *et al.*, 1989). In an randomized clinical trial (RCT), Chung et al (2002) compared the myopic progression of 47 myopic children (9-14 years) with under-correction of about +0.75 D to that of 47 control wearing full corrections. Myopia of the under-correction group progressed by 1.00 D during the 2-year study period, while that of the full correction group was 0.77 D. In a similar comparison on myopic progression between 25 myopes (6-15 years) who wore

under-corrections of 0.50 D and 23 myopes wearing full corrections, Adler and Millodot (2006) found a faster myopic progression in the under-correction group than in the full correction group by 0.17D over the 18-month study period. Contrary to what was suggested by the accommodative lag theory, myopes with full correction showed slower myopic progression than those with under-correction in their studies.

B. Bifocal and progressive addition lenses

Bifocals and progressive addition lenses (PAL) shared the same rationale as undercorrection does for myopic control intervention. Although the history of using bifocal lens to arrest myopic progression can be traced back to more than half a century ago (Cheng *et al.*, 2011), the efficacy of its use (and later with PAL) has received a lot of debate. The Houston Myopia Control Study was the first RCT to evaluate the effect of bifocals on retarding juvenile-onset myopia in the 1980s (Grosvenor *et al.*, 1987). Children between the ages of six and 15 years were randomly assigned to control (wearing SVL, n = 39) and treatment (wearing bifocals of +1.00 D, n = 41 and wearing +2.00 D, n = 44) groups. No significant difference in myopic progression rate was found among control (wearing SVL) and treatment groups (wearing executive bifocals with +1.00 D and +2.00 D addition) during the three-year study period. In a group of 82 myopes with esophoria at near aged between six and 13 years, Fulk et al (2000) found the myopic progression of the treatment group of 42 children wearing bifocals with +1.50 D addition was 0.99 ± 0.68 D in 30 months, compared to

that observed in the control (SVL) groups of 40 children whose myopic progression was 1.24 ± 0.65 D in 30 months. The treatment effect was only statistically but not clinically significant. The Correction of Myopia Evaluation Trial (COMET2-Study-Group) study compared the myopic progression of 233 children between six and 11 years wearing single vision lenses, with 229 children wearing PAL with +2.00 D addition for three years (Gwiazda *et al.*, 2003). A statistically significant effect of PAL on myopia control (mean difference in myopia progression of 0.18 D between treatment and control groups) during the first year of study was found. However, the difference was not clinically significant and no increase in treatment effect was observed during the second and the third year of study. Later, the COMET 2 study evaluated the use of PAL (+2.00 D addition) on children (8-12 years) with high accommodative lag (1.00 D at least at 33 cm) (COMET2-Study-Group, 2011). The treatment group in which 52 children were fitted with PAL lenses, showed a statistically significant treatment effect of 0.28 D over the 3-year when compared to the control group in which 58 children wore SVL for the whole period. The treatment effect was, however, considered clinically insignificant.

Recently, Berntsen et al (2012) reported a treatment effect of 0.18 D myopic progression by PAL over SVL during the first year of the Study of Theories about Myopia Porgression (STAMP). In this study, 42 subjects (6-11 year-olds) wore PALs with +2.00 D addition while 43 control subjects wore SVL lenses during the 2-year study period. The treatment effect was found clinically insignificant as well. In

another crossover design RCT with 92 Japanese children aged between six and 12 years, Hasebe and colleagues (2008) demonstrated a mean 18-month treatment effect of 0.17 D with statistical significance during the PAL lens-wearing periods. Yang et al (2009) compared the myopic progression in 74 Chinese children (7-13 year-olds) who wore PAL with +1.50 D addition with that in 75 controls wearing SVL lenses over two years, and reported a treatment effect of 0.26 D slower myopic progression in 2 years in the treatment group. The effect was, however, considered to be of no clinical significance. Unlike the others, Edwards et al (2002) found no statistically significant difference between PAL and SVL wearers in myopic progression over two years in Hong Kong Chinese children. In Edwards and colleagues' study, the PAL wearing group showed a myopic progression of 1.12 D, compared the SVL wearing group which showed 1.26 D for two years.

Because positive lenses can reduce the lag of accommodation and esophoria in esophoric subjects at near, the incorporation of additional power for near work in esophoric children was believed to benefit more in reducing myopic progression (Cheng *et al.*, 2011). Cheng et al (2010) evaluated the use of executive bifocals with and without base-in prisms in a group of Chinese Canadian children aged about 10 years. The subjects were randomly assigned to wear SVL, bifocals with +1.50 D addition and prismatic bifocals of +1.50 D addition incorporated with a 3^{Δ} base-in prism for 24 months. They found a significant treatment effect with bifocals (0.59 D) and prismatic bifocals (0.85 D) over SVL during the study period.

From the numerous work on bifocal and PAL spectacle lenses, it seems that the potential of these lens types in myopic control might only be confined to a particular group of children with near esophoria. However, evidence is still frail. Further evaluations on the use of prismatic designs are also needed.

C. Peripheral defocus or gradient design lenses

With the published evidence from animal studies that relative peripheral hyperopia could be a potential signal to initiate eye growth in primates and chicks, novel spectacle lens designs which aimed to eliminate the lens-induced relative peripheral hyperopic defocus, which are common with traditional SVL, have been established. One of them is a radial refractive gradient (RRG) design with plano power at the central zone of 6 mm in diameter, accompanied by a steadily and radially increasing SER of 1.00 D every 10° towards the lens periphery (Tabernero *et al.*, 2009). In contrary to the traditional SVL which were found to have elevated the relative peripheral hyperopia to 2.00 D in the peripheral 40° field, the RRG spectacles were able to cause a mean reduction of 1.00 D in relative peripheral hyperopia in six emmetropes and four myopic young adults. (Tabernero *et al.*, 2009).

Sankaridurg and co-workers (2010) evaluated three types of RRG lens designs on 201 Chinese children between six and 16 years of age. Type I lens came with a larger clear central zone of 20 mm diameter which was accompanied by a rotationally symmetrical ramped zone of increasing positive relative powers up to 1.00D at 25 mm from the lens center. Type II lens was also of a rotationally

symmetrical design, but came with a smaller central clear zone of 14 mm diameter and a higher positive relative power of 2.00 D at 25 mm from the lens center. Type III lens was an asymmetrical design whose central clear zone extended to 10mm in distance from the lens center to the nasal, temporal and inferior periphery. The maximum positive relative power was about 1.90 D in Type III lenses. Sankaridurg and colleagues (2010) could only find a statistically significant effect with Type III lenses in a sub-group of children with parental history of myopia, showing a mean treatment effect of 0.29 ± 0.11 D over conventional SVL during the 12-month study period. This lens became the blueprint of a myopic control spectacle lens lately available in the market.

Similar lens design was evaluated on chicks to evaluate its effect on inhibiting eye growth (Tepelus *et al.*, 2012). Tepelus and colleagues (2012) tested two RRG lens designs with different optical zone diameters and peripheral lens power profiles on chicks. The first design (RRG1) came with a wider central plano optical zone, a steeper gradient of power changes at the lens periphery and effectively imposed a high relatively positive power (~7.5D) on the peripheral visual field in the chick eyes. The second lens design (RRG2) came with a smaller central plano zone and a modest relative power in the periphery (~2.75D), leaving a greater increase in gradient of power change in the more central visual field of the chick eyes. The inhibitory effect on chicks was found to be more significant with the RRG2 design. This suggested that an RRG lens with a smaller plano optical zone would be more favorable to give

more prominent effects on myopic control.

1.4.1.2 Contact lenses

A. Soft lenses and rigid gas permeable lenses

Initial suspicions on soft contact lenses (SCL) to produce myopic progression in adults (Grosvenor, 1975; Harris *et al.*, 1975) had led to hesitation in the prescription of soft contact lenses for adolescents for years. Myopic creep with long-term soft contact lens wear was found to be a transient response of the cornea to hypoxia (Jalbert *et al.*, 2004; Blacker *et al.*, 2009). Furthermore, it has been shown that adolescent soft contact lens wearers did not have significant increase in myopic progression over others who were wearing spectacles (Horner *et al.*, 1999; Walline *et al.*, 2008). In a three-year RCT enrolling children at 8-11 years, Walline and colleagues (2008) compared the 3-year myopic progression in 237 contact-lens wearers to that in 230 spectacles wearers. The unadjusted mean changes in SER were -1.29 ± 0.71 D and -1.10 ± 0.71 D in the contact lens and the spectacles groups, respectively. When adjusted for age and sex, the differences in myopic progression, AL and corneal curvature did not show any significant differences between the two groups.

There are controversies on the effect of rigid gas permeable lenses (RGP) on myopic progression. Previous studies reported that RGP-wearing children showed a slower progression in axial myopia than the spectacle-wearing children by about 0.35 D per year (Perrigin *et al.*, 1990; Khoo *et al.*, 1999). Further evaluation from these studies have shown that corneal flattening brought about by the

alignment-fit lenses could only account for 1/3 of the treatment effect, and it was suggested that the rest of the refractive change had an axial origin. However, these results were challenged for their large dropout rate and subject bias without randomization. Katz et al (2003) reported a faster 24-month increase of 0.05D in myopia in a group of 105 RGP-wearing children (aged six to 12) than in another group of 192 spectacle-wearing controls. In another 3-year RCT involving 8-11 year-olds, Walline et al (2004) reported that although the RGP group (n = 53) showed a significantly greater myopic progression of 0.63 D over 3 years than the SCL control group (n = 41), axial elongation did not account for the difference. Rather, the transient corneal flattening in RGP group and the transient corneal steepening in SCL group were more likely to be the cause of the difference in refractive changes. Results from these RCTs, therefore, did not advocate RGP as an effective myopic control option.

B. Bifocal contact lenses and simultaneous designs

While numerous studies of myopic control effect using bifocal or multifocal spectacle lenses have been published, limited reports on the efficacy of bifocal contact lenses on myopic control could be found. Aller et al (2006) reported that multizone bifocal SCL exerted an inhibitory effect of about 0.50 D over single-vision SCL in one year. On the contrary, in a group of children wearing the center-distance Proclear Multifocals (CooperVision USA, Fairport, NY), McVey (2010) did not find any significant difference in the myopic progression rates in these children when compared with the control group from another clinical study wearing single vision SCL.

Although information was scant and available literature was equivocal, it has been proposed that bifocal designs might achieve myopic progression inhibitory effect through imposing accommodation lead (Tarrant *et al.*, 2008) and reducing relative peripheral hyperopia (or imposing relative peripheral myopia) (Lopes-Ferreira *et al.*, 2011) in myopic eyes.

In 10 emmetropic and 25 myopic young adults, Tarrant and co-workers (2008) reported that the simultaneous bifocal SCL (with a 2-mm center-distance zone surrounded by alternate rings of +1.50 D addition and distance correction) were able to cause an over response in accommodation in both emmetropes and myopes, while the single vision SCL with distance correction caused an under response in accommodation. In both lens wearing conditions, the accommodative response was greater in emmetropes than in myopes at all near working distances, which was consistent with previous studies with myopes showing greater accommodative lags (Nakatsuka *et al.*, 2005; Allen and O'Leary, 2006). They further speculated that bifocal SCL might be able to arrest myopic progression through inducing accommodation lead during near work. Notwithstanding, recent reports of longitudinal studies did not find any association between accommodation lag and myopic progression (Mutti *et al.*, 2006; Weizhong *et al.*, 2008; Berntsen *et al.*, 2011). It seems less likely that the bifocal SCL exerted effect on myopic progression through an accommodative channel.

A recent work by Rosen and colleagues (2012) evaluated the relative peripheral myopia induced by contact lenses (monofocal,

center-distance and center-near multifocals) on three emmetropic and one low myopic young adults, using a fast scanning Hartmann-Shack instrument to measure the peripheral aberration of these subjects with and without contact lenses. It was found that the center-distance multifocal lenses with 2.00 D addition were able to induce a small amount of relative myopia (about 0.50 D) in the 30° nasal field in tested eyes only. They concluded that the small increase in relative peripheral myopia induced by multifocal SCL was too small to exert myopic control effect. Their findings with the +2.00 D addition was consistent with those previously reported by Lopes-Ferreira and colleagues (2011). However, Lopes-Ferreria and colleagues (2011) found also that the increases in relative peripheral myopia were significant using +3.00 D and +4.00 D lenses of the same design. They reported that the increase in relative myopia could reach 3.00 D and 4.00 D in the nasal 35° field and reach 5.00 D and almost 6.00 D in the temporal field using the +3.00 D and +4.00 D additions, respectively. Further investigation is warranted on whether the amount of relative peripheral myopia induced in the peripheral field by the multifocal SCL would affect myopic progression in children. Sharing a similar concentric design as the bifocal SCL, simultaneous-design or dual-focus design lenses have been put forward for clinical trials (HKPU, 2011). The rationale of this design is to ensure myopic defocus at all times when the eye is either fixating at distance or at near. Animal studies have shown that simultaneous designs could interfere with the emmetropization of eye growth and serve as a rational method in retarding myopic

progression (Tse *et al.*, 2007; Benavente-Perez *et al.*, 2012). In a two-phased clinical trial, Anstice and Philips (2011) evaluated the myopic control effect of a dual focus (Turner *et al.*) SCL design, which comprised a central correction zone surrounded by a series of treatment and correction zones, on 40 children at 11-14 years for 20 months. The treatment zones were able to produce 2.00D of simultaneous myopic defocus. Their results demonstrated that the mean changes in spherical equivalent and axial elongation on eyes wearing a DF design were less than contralateral eyes wearing single-vision lenses (control eyes) by 0.25 D in 10 months. Another clinical evaluation on the Defocus Incorporated Soft Contact (DISC) lens was being undertaken in Hong Kong Chinese children and there is yet no published report on the efficacy of this simultaneous design on human.

C. Lenses with relative peripheral hyperopia design

Sankaridurg and colleagues (2011) also evaluated a contact lens variant of peripheral defocus design for myopic control. The contact lens attained a central zone for correcting for distance vision, followed by a peripheral zone of relatively more positive power reaching a maximum of +2.0 D at the edge of the optical zone. The rationale of this novel design was to reduce the relative peripheral hyperopic defocus in a myopic eye, which was believed to have caused the failure of emmetropization in human eyes as previously established in animal models (Smith *et al.*, 2005; Smith *et al.*, 2009b). The lens was able to cause a significant reduction in relative hyperopia in the nasal field of the myopic eyes while that in the

temporal field was found to be unaffected by wearing this lens design. In a one-year follow-up, Sankaridurg and colleagues (2011) found a treatment effect of 0.29 D less progression (or a 34% reduction in the rate of progression) in the contact lens group when compared with the spectacle-wearing controls. See also Section 1.4.1.1.C.

D. Reverse geometry lenses

Reserve geometry lenses (also called orthokeratology or ortho-k lenses) flattened the cornea and caused a temporary myopic reduction. The corneal-reshaping effect of these lenses has been confirmed to be effective in arresting myopic progression i (Cho *et al.*, 2005; Walline *et al.*, 2009; Kakita *et al.*, 2011; Cho and Cheung, 2012; Santodomingo-Rubido *et al.*, 2012). The reported reduction in the rate of axial elongation was 0.11 to 0.16 mm per year when compared to the control groups which either wore SVL or SCL. These results indicated that ortho-k could reduce myopic progression by 36% to 66%. In the Retardation of Myopia in Orthokeratology (ROMIO) study with children at 6-10 years, the only RCT in similar ortho-k studies, Cho and Cheung (2012) reported that the axial elongation during the two year study period in the ortho-k group (n=37) was 0.36 ± 0.24 mm, compared to 0.63 ± 0.26 mm in the spectacles-wearing control group (n=41). They demonstrated that the myopic progression in children could be retarded by 43% with ortho-k lens wear.

Albeit the myopic control effect by ortho-k is unambiguous, the

mechanism by which it exerts the effect is still unclear. Several studies advocated that ortho-k achieves myopic control by reducing the relative peripheral hyperopic defocus (or converting it into relative myopia) in ortho-k-treated eyes (Charman *et al.*, 2006; Kang and Swarbrick, 2011). (See Chapter 3)

1.4.2 Pharmaceutical interventions

The pharmacokinetics of antimuscarinic drugs such as atropine and pirenzepine and dopamine agonists such as apomorphine in different animal models have suggested their potentials in restricting myopic development. The use of antimascarinic drugs for myopic control was subsequent to a previous hypothesis on linking excessive near work and accommodation with myopic progression. However, animal study has shown that atropine worked well via a non-accommodative mechanism (McBrien *et al.*, 1993). Among all pharmaceutical interventions, atropine has received extensive investigations on various animal models as well as human studies, and has become a widely used prescription for myopic control by ophthalmologists. Several RCTs have shown consistent results on myopic progression inhibition by atropine (Yen *et al.*, 1989; Shih *et al.*, 1999; Chua *et al.*, 2006; Brown, 2009; Tong *et al.*, 2009; Chia *et al.*, 2012). The treatment effect of less myopic progression from these studies ranged from 0.36 D to 1.02 D per year compared to the control groups. Concentrations of 0.01% - 0.5% have been investigated and found to produce significant effect in different studies (Shih *et al.*, 1999; Chia *et al.*, 2012). However, atropine studies had to employ the use of near addition or multifocals for daily visual activities. This had interfered with the effect of eye drop on myopic progression.

Furthermore, the disadvantages of pupil dilation, such as photophobia and increased aberration have added further limitation to the therapy. Tropicamide was prescribed off-labeled for myopia prophylaxis (Iribarren, 2008). Its nightly administration is advantageous as its dilation and cycloplegic effect will not affect reading or cause photophobia in the waking hours. However, results from clinical trials on myopic progression with this eye-drop were scant. Other pharmaceutical agents such as pirenzepine and dopamine agonists were also potential interventions for myopia (Ganesan and Wildsoet, 2010). Pirenzepine, a selectively muscarinic antagonist, has also been found to cause 50% reduction in myopic progression in a two-year RCT in which 53 children were administered with Pirenzepine gel 2% twice daily for two years, compared to another group of 31 children administered with placebos (Siatkowski *et al.*, 2008). The administration of pirenzepine gel on children was found safe, and it has advantages of not dilating the pupils as well as causing less accommodation loss than atropine does. It is, however, less commonly used in myopic control treatment due to its unavailability in the market.

1.4.3 Efficacy of different myopic control interventions

Reporting the statistical differences between treatment and control methods does not reflect directly the practical importance of the treatment effects. Although a number of methods to determine clinical significance have been suggested (Jacobson *et al.*, 1999), there is yet a conclusive agreement. Most of the myopic control interventions reviewed above attained statistical significance. However, when looking into the magnitude of the treatment effect, a few of these studies may not be of clinical significance.

Another unresolved limitation in myopic control studies is to ensure if the target groups are undergoing a period of rapid myopic progression within and across different studies. The variability can only be minimized through robust research design making use of randomization, age-, gender- or initial refraction-matching at baseline visits.

Several systematic reviews have been made on the efficacy of various myopic control interventions (Saw *et al.*, 2002; Leo and Young, 2011; Walline *et al.*, 2011). From these reports, atropine showed the largest treatment effect. Unfortunately, there is no systematic review which compared the efficacies of all myopic control methods, including the ortho-k and other newly designed optical interventions.

Summary

The prevalence of myopia in children has demonstrated geographical, ethnicity, age and environmental differences. The progression of myopia prevalence varies from country to country. The prevalence of high myopia seems to attain similar trends. The increase in the prevalence of high myopia is of serious concern in some countries, as the socio-economical and health burden will be further increased. Children with parental myopia, involved in intensive near work and lack out-door activities are subjected to higher risks of developing myopia. To understand the increasing prevalence of myopia in different parts of the world, it is important to have a standard protocol for data collection. The development of myopia indicates a failure of the emmetropization in human eyes. However, the factors triggering the break-down of the mechanism are still unclear. Peripheral refraction has been one of the hypotheses proposed to have cause myopic development.

However, more work has to be done before a conclusion can be drawn. Various myopic control interventions have been investigated to arrest myopic progression. Among them, atropine and orthokeratology are the two which have received consistent supports on their treatment effects. However, the mechanisms through which who these interventions work are still unknown. Future works were needed on the development of a standard protocol for epidemiology study, on the etiology of myopia development and its progression, and the prevention of myopic progression through safe and effective interventions.

Chapter Two

Peripheral Refraction

2.1 History of peripheral refraction

2.1.1 Animal studies

There has been a long history for emmetropization in animal studies (Troilo, 1990; van Alphen, 1990; Wallman and Winawer, 2004). The development of myopia has been regarded as a failure of the emmetropization process in which form deprivation and defocus were found to be capable of disrupting the regulation of eye growth (Norton and Siegwart, 1995; Wildsoet, 1997). Apart from via the foveal experience in the post-natal eyes, the regulation of eye growth was also found possible through some non-foveal visual experience of the retina. Further studies have shown that eye growth could also be regulated by other local retinal regions (Smith *et al.*, 2005; Smith *et al.*, 2007; Smith *et al.*, 2009a; Smith *et al.*, 2009b). Studies involving hemi-field deprivation and defocus which induced myopia in the corresponding visual field have given rise to the development of the peripheral refraction (PR) theory (Smith *et al.*, 2009a). Studies in primates have further shown that the peripheral retina also played an important role in regulating eye growth, rather than the foveal retina alone (Smith *et al.*, 2005; Smith *et al.*, 2007; Smith *et al.*, 2009b). The following sections will focus on primate studies on PR investigations.

2.1.1.1 Peripheral refraction in infant monkeys

At three weeks of age, PR in the nasal and the inferior fields of infant monkeys were more myopic than the central refraction, while those in the temporal and superior fields were similar to the central refraction (Hung *et al.*, 2008). Relative myopia in the nasal field also

varied with central refraction in hyperopic primate eyes. The less hyperopic eyes demonstrated less relative myopia in the periphery, while the more hyperopic eyes had greater relative myopia. At 300 days, the primate eyes became less hyperopic both centrally and peripherally. The reduction in hyperopia was greater in the more hyperopic eyes and in the temporal field. These resulted in the RPR of the initially more hyperopic eyes becoming less myopic in the nasal field with no significant change in the temporal field. On the contrary, in the less hyperopic eyes the RPR in the nasal field remained relatively stable while that in the temporal field became more myopic.

Bradley and co-workers (1999) have shown that in primate eyes, the endpoint of emmetropization was slightly hyperopic. The 300th day PR profile with different degree of hyperopia being similar in shape suggested that similar characteristics were found in PR patterns. If it is so, this may further suggest, at least in primates, that emmetropization, being present in both central and peripheral retina, is a programmed change in ocular growth. However, investigation was limited to the animal in the first year of life. An analogy to juvenile-onset myopia in human might not be as appropriate as suggested by other studies (Mutti *et al.*, 2007; Schmid, 2011; Faria-Ribeiro *et al.*, 2012).

2.1.1.2 Effects of peripheral form deprivation and hyperopic defocus on central refraction in monkeys

It has been found that form deprivation and optical defocus myopia

could be produced when form deprivation and hyperopic defocus were restricted to the peripheral field while the central field was spared (Smith *et al.*, 2005; Smith *et al.*, 2007; Smith *et al.*, 2009b). Smith and colleagues (2005) applied peripheral form deprivation to 12 experimental monkeys from three weeks to 18 weeks of age, using a diffuser with central aperture of either 4 mm (six animals) or 8 mm (six animals) to provide clear central vision. Monkeys reared in clear plano lenses were used as control animals. At the end of the lens-rearing period, the refractive errors of the experimental animals were more myopic than those at the beginning of the lens-rearing period. They also became more myopic than the control animals. Those animals wearing smaller apertures of clear vision (i.e. greater area of peripheral form deprivation) were found to have greater central myopic shift. After the removal of the rearing lenses, seven of the experimental animals were further deprived of the foveal vision. Only one eye was deprived and deprivation of foveal vision was done with photocoagulation. At the end of the experimental period, both eyes recovered from the induced relative myopia and the central refractive errors returned to the normal range for primates. The recovery from form-deprived myopia was unaffected by the application of foveal ablation. This indicated that foveal region did not monopolize the active regulation of eye growth. That smaller aperture diffuser showed greater amount of induced myopic shift suggested that the more retinal area receiving hyperopic defocus, the greater the induced effect. It would be plausible if form deprivation could be localized to the foveal vision and the change in central

refraction be compared with that when the form deprivation was applied to the peripheral retina, and with the recovery rate in eyes receiving foveal ablation.

In another experiment, Smith and coworkers (2007) photocoagulated the foveal and perifoveal areas in one eye of 13 experimental monkeys, while leaving the fellow eye intact. Five of these treated monkeys were allowed unrestricted vision while the other eight were further form-deprived in the ablated eye by diffuser lenses. The animals which were allowed unrestricted vision did not show significant interocular differences in refractive errors while those which received monocular form deprivation after foveal ablation in the treated eyes have significant interocular differences. This indicated that the peripheral retina also played a role in the regulation of eye growth. That the animals which were allowed unrestricted vision did not show significant interocular differences suggested that the foveal vision was not essential in the determination of central refraction. Compared to a group of six historical control monkeys which received full field form deprivation, the centrally-ablated and peripherally form-deprived animals showed less induced myopia. These might augment the previously observed greater form deprivation myopia in eyes receiving clear central vision through a smaller aperture, suggesting that the development of myopia in the form deprivation model might be dependent on an integrative effect of signals received across the whole retina (Smith *et al.*, 2005).

In order to investigate the effect of the peripheral hyperopic defocus

on central refractive changes, Smith and colleagues (2009b) induced binocular hyperopic defocus by applying -3D lenses with 6 mm central circular aperture on eight infant monkeys. The aperture allowed unrestricted vision covering 10.3° of the central field. In another six animals, they ablated the foveal and perifoveal area in one eye of each monkey before inducing binocular full field hyperopic defocus (using full field -3.00 D lenses). This aimed to isolate the function of the foveal area in the regulation of eye growth in response to peripheral hyperopic defocus. The lens-rearing period for both treatment groups (-3D-aperture group and -3D-ablation group) was from three weeks to about five months of age. At the beginning of the lens-rearing period, both treatment groups and the control animals, which had intact retina and received unrestricted vision throughout the experiment, were moderately hyperopic (around +4.00 D) and there were no between-group differences in refractive errors. At the end of the lens-rearing period, the control group remained slightly hyperopic (around +2.00 D), while both treatment groups showed less hyperopic central refraction (Figure 2.1). Compared to those in the -3D-aperture group, central refraction in the -3D-ablation group showed less myopic shift. The difference suggested that the amount of myopic shift in central refraction induced by hyperopic defocus may be dependent on the integrative effects of the visual signals received across the retina (Smith *et al.*, 2005).

By applying relative peripheral defocus to the nasal hemi-field to the monkeys, Smith and colleagues (2010) showed that hyperopic

defocus exerted local and regional effects on the development of axial myopia. In this experiment, eight experimental monkeys were reared with lenses which imposed +3.00 D hyperoic defocus on the nasal field in one eye, while the fellow eye wore zero power lenses. Six other monkeys wore full field -3.00 D lenses over the treated eyes with the fellow eyes wearing zero power lenses. Full field hyperopic defocus was imposed on the treated eyes in the latter group. The lens-rearing period was from three weeks to 21 weeks of age in both groups. At the end of the lens-rearing period, the treated eyes were found to be more myopic, compared to the fellow untreated eye. The relative myopia in the treated eyes was found to be greater in the full-field-treated monkeys than in the nasal-field-treated ones (Figure 2.2). In the nasal-field-treated group, PR became more myopic in the nasal field and remained relatively stable in most animals (Figure 2.3). In the full-field-treated group, myopic shift was generally observed in both nasal and temporal fields. Across the tested field, the greatest change was observed within the more central eccentricities. The change in refraction attenuated with increasing eccentricity. This suggested that the central retina might be responsible for a larger response to hyperopic defocus when compared to the peripheral retina. These changes were found to be axial in nature, in both nasal-field- and full-field-treated animals. This experiment suggested that hyperopic defocus could cause local changes in eye length, which in turn changed the peripheral refraction in the primate eyes.

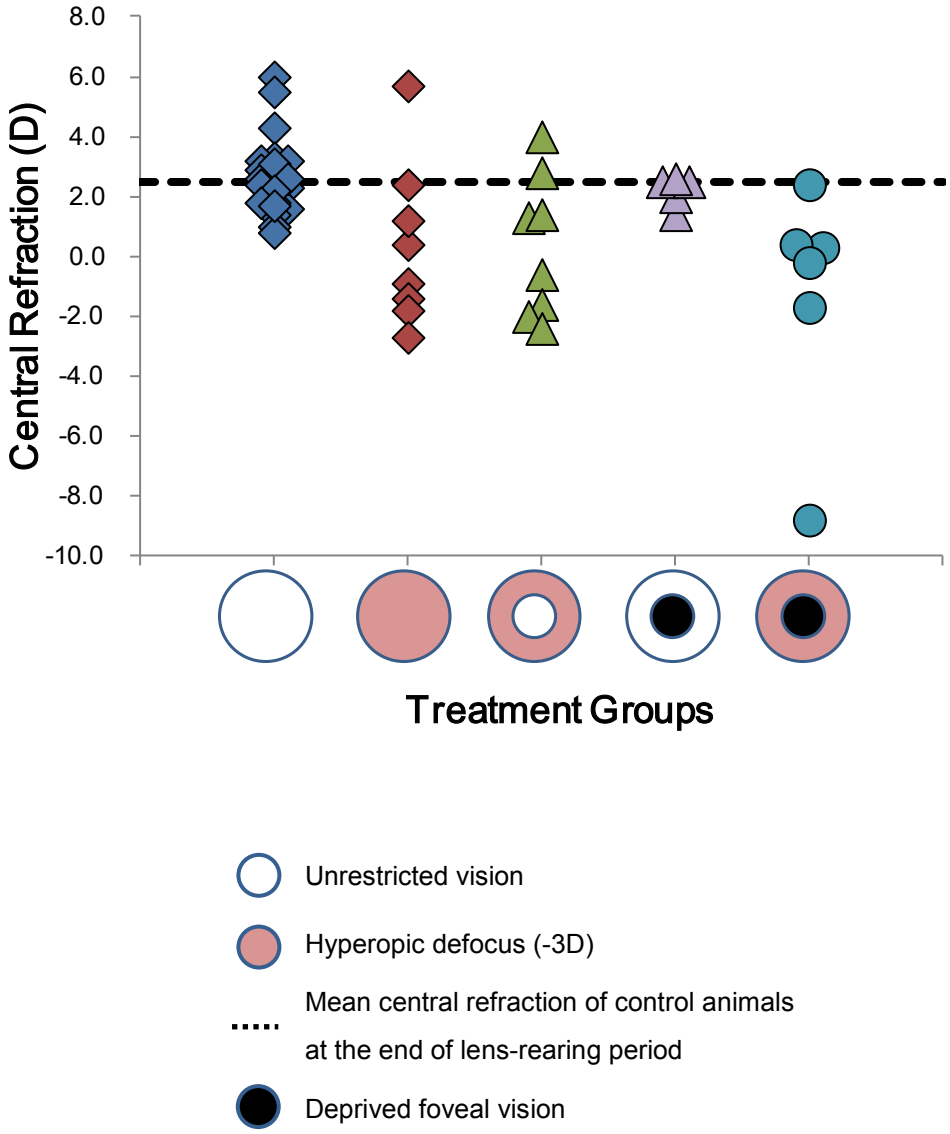


Figure 2.1. Central refraction at the end of a 3-month lens-rearing period in primate eyes receiving different treatments. The large (or outer) circle represents the visual field of a primate eye, while the inner circle represents the foveal and parafoveal vision [adapted from Smith et al (2009b)].

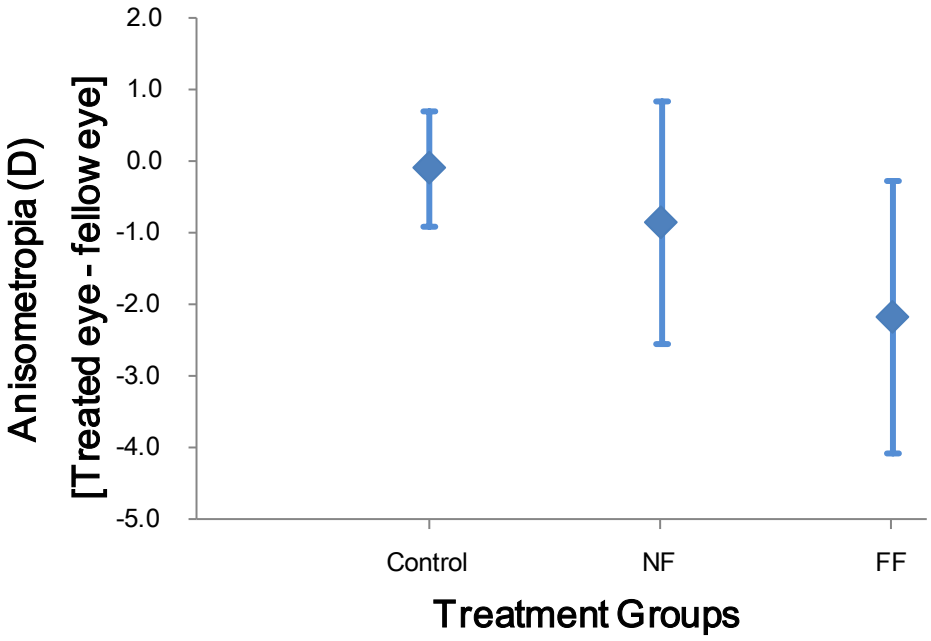


Figure 2.2. Anisometropia in central refraction at the end of the lens-rearing period in primate eyes receiving no treatment (Control) nasal-field hyperopic defocus (NF) and full-field hyperopic defocus (FF) [adapted from Smith et al (2010)]. Error bar = 1SD.

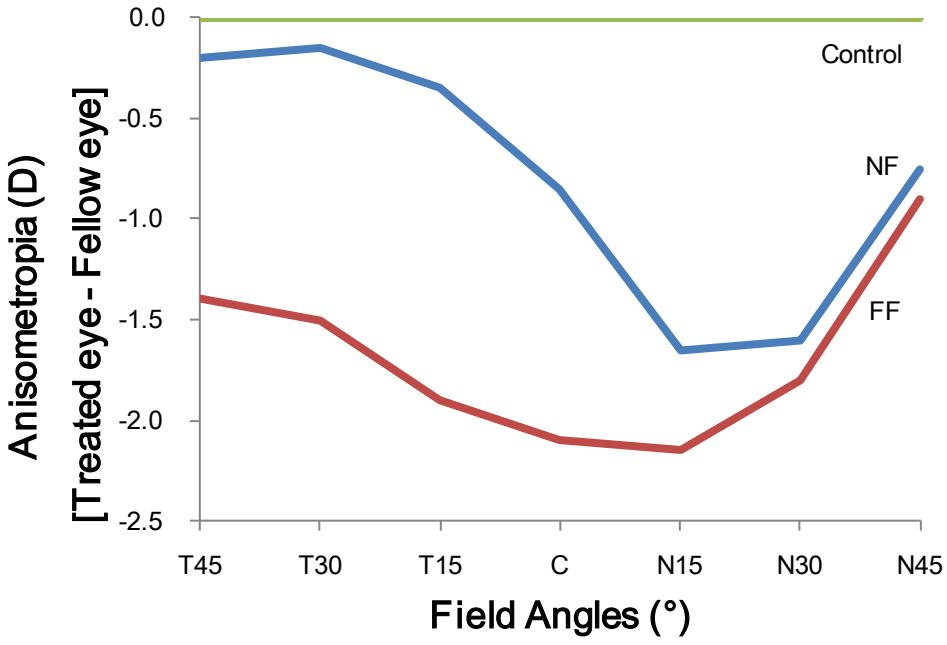


Figure 2.3. Anisometropia (D) in peripheral refraction at different field angles at the end of the treatment period in primate eyes receiving no treatment (Control), nasal-field hyperopic defocus (NF) and full-field hyperopic defocus (FF) [adapted from Smith et al (2010)].

2.1.2 Human studies

PR studies in human eyes could be traced back to the 1970s. Hoogerheide and colleagues (1971) measured the PR of young pilots using retinoscopy, looking for pre-disposing factor for the development of myopia. Rempt and colleagues (1971) categorized the shell of defocus into five types and represented them in skiagrams (Figure 2.4). They measured the refraction of subjects along the horizontal field by retinoscopy. At each eccentric angle, power along the horizontal meridian and vertical meridian were measured and presented separately in a skiagram. Types 1 and 3 indicate eyes showing relative peripheral hyperopia while Types 2, 4 and 5 indicate those with relative peripheral myopia or emmetropia. At each angle, the more distant the two meridians are apart from each other, the greater the astigmatism is at that eccentricity. Millodot (1981; 1984) investigated the PR profiles in different ametropic groups and aphakic eyes using auto-refraction, and found that relative peripheral hyperopia was associated with central myopia while peripheral myopia was associated with central hyperopia. Human studies on PR was left unattended for some time until a number of animal studies reported more evidence in support of the PR hypothesis in myopic development in 1990s. In the 2000s, PR studies in human eyes in relation to myopic progression gained interests and numerous studies have been conducted. The rest of this chapter will focus on these human studies.

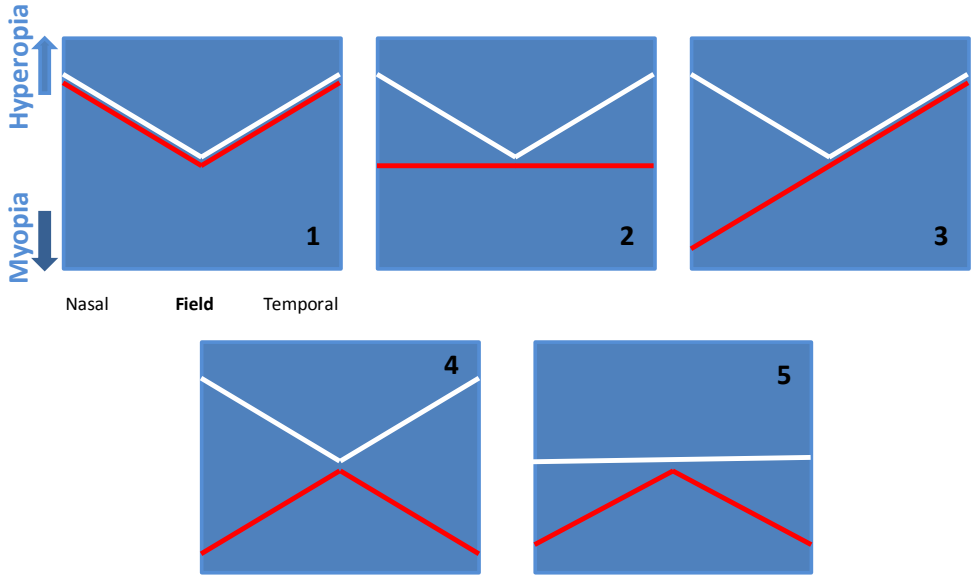


Figure 2.4. Five types of skiagrams were identified from the retinoscopic peripheral refraction across the horizontal field in a group of young pilots [adapted from Rempt et al (1971)]. White line: refraction of the vertical meridian at individual eccentricity of the horizontal field. Red line: refraction of the horizontal meridian at individual eccentricity of the horizontal field. All refraction was presented relative to the central refraction. Types 1 and 3 represent eyes with relative hyperopia. Types 2, 4 and 5 represent eyes with relative myopia or emmetropia.

2.2 Different methods for peripheral refraction measurements

PR is an indirect method used for determining the in vivo field curvatures in human eyes. There are a number of techniques with which PR could be assessed.

The commonly used techniques include both subjective refraction and objective methods such as retinoscopy, autorefraction, photorefraction, scanning photoretinoscopy and aberrometry. These common PR measurement methods require an individual to fixate at different eccentric fixation points, either by head turn or eye turn, while the instrument takes

measurements from a fixed position.

Retinosocopy is the earliest objective method used for the determination of PR. Hoogerheide and colleagues (1971) and Rempt and colleagues (1971) were the earliest to report PR measurements using retinoscopy. Refraction along the horizontal and the vertical meridians at each horizontal field angle were presented separately in a skiagram. From the analysis of the skiagram, the ocular shape was categorized into five different types (Figure 2.4). However, accuracy with retinoscopy is subject to the experience of the examiner.

Subjective refraction could also be used in PR measurements. With the examinee fixating eccentrically at a target, the examiner performed subjective refraction with trial lenses with the same procedures as in standard subjective foveal refraction. The accuracy of subjective PR would be dependent on the size and contrast of the stimuli, resolution of targets stimuli and the detection of the end point by the subject. Like standard subjective refraction, subjective PR will also require a high level of patience and concentration of the subject.

Aberrometry measures the aberration of an optical system. A number of instruments with different measuring principles have been used in aberrometry, including ray-tracing, Hartman-Shack, Tscherning and automatic retinoscopy (Rozema *et al.*, 2005). In PR studies, the most commonly used is the Hartman-Shack instruments, such as the COAS (Wavefront Science Inc. USA) and the WASCA (Carl Zeiss Meditec, Germany). The wavefront information is expressed in the form of Zernike polynomials or coefficients, which are dependent on pupil size and which require a circular aperture. In PR measurements, the instrument measures

aberration of an eye eccentrically when the pupil becomes elliptical in shape. Further manipulation of the obtained aberration data will transform them into information based on circular pupil. In addition, referencing with the pupil axis is crucial in the expression of Zernike values.

Photorefraction determines refractive errors by evaluating the illumination of the reflection of a point light source from the retina. This technique has been shown to have limitations when measurements were taken from large eccentric angles (Lundstrom *et al.*, 2005).

Auto-refraction is believed to be the most popular method used PR study. To determine PR, the auto-refractor has to allow unrestricted vision. The most commonly used instrument nowadays were the open-view auto-refractors, such as Shin-Nippon NVision K5001 (Ajinomoto Trading, Inc., Tokyo, Japan) which allows PR measurements across up to ±35° along the horizontal field and ±15° along the vertical.

Recent advancement attempted to measure PR continuously along a specified field. Instruments such as the EyeMapper (Fedtke *et al.*, 2014) and the scanning photorefractor (Tabernero and Schaeffel, 2009b; Tabernero *et al.*, 2011; Tabernero *et al.*, 2012) have been developed.

2.3 Ocular shape and retinal contour in human eyes

Results from magnetic resonance imaging (MRI) studies have provided more information on the association between eye shapes and ametropia than optical instruments did. These studies provide more information to support how well the myopia models, including the global, equatorial, posterior polar and axial expansion models (see section 2.3.3), could be applied in

human eyes (Verkicharla *et al.*, 2012). Both the physical contour of the retinal surface and the optical shell of the retinal focus are found to be different in different ametropias. The following sections review the relationship between eye shape, retinal shape and peripheral refraction.

2.3.1 Ocular shape

The sizes of eyes with different ametropias are not the same (Atchison *et al.*, 2004; Lim *et al.*, 2011). The three dimensions, the length, height and width, of eyes were significantly correlated with their refraction (Figure 2.5) (Atchison *et al.*, 2004). Myopic eyes are longer axially, vertically and horizontally (i.e. in length, height and width, respectively) compared to non-myopic eyes (Cheng *et al.*, 1992; Atchison *et al.*, 2004). The ocular dimensions as measured from the axial and the sagittal MRI images of eyes with different ametropia in Cheng et al.'s study (1992) were replicated in Figure 2.6 and Table 2.1. In another MRI study on the ocular shapes of 22 young emmetropes and 66 young myopes, Atchison and colleagues (2004) found that both emmetropic and myopic eyes had longer axial lengths than sagittal heights. They also found that the difference between axial length and sagittal heights was greater in myopic eyes than in emmetropic eyes.

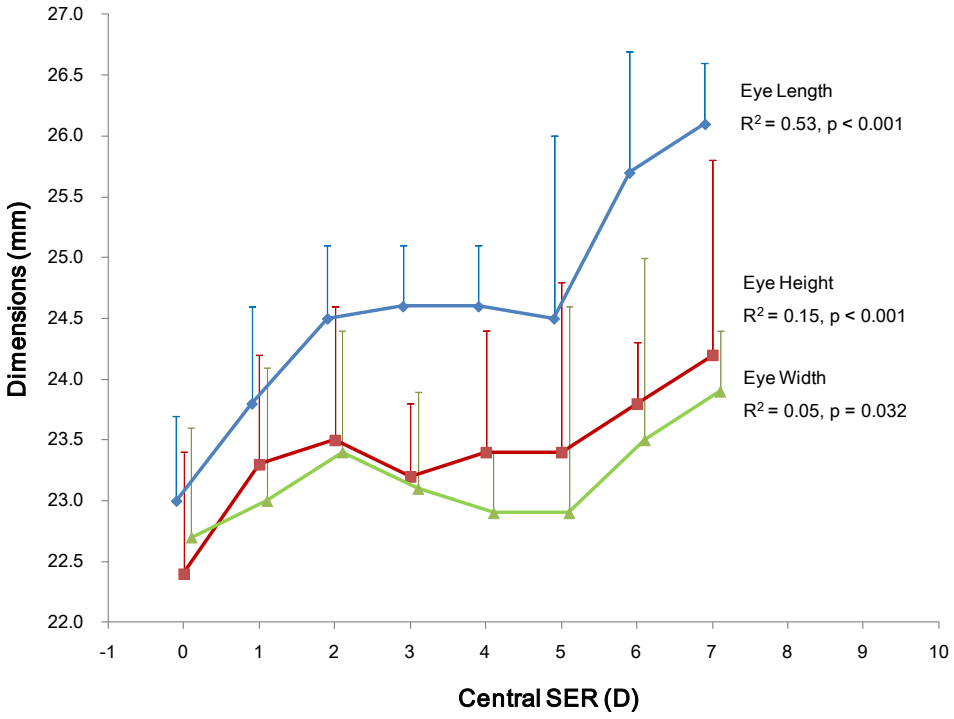


Figure 2.5. Eye length, height and width by spherical equivalent refraction [adapted from Atchison et al (2004)]. R^2 = coefficient of correlation.

The height and width were not significantly different in emmetropic eyes while in myopic eyes, the height was significantly greater than the width. Lim et al. (2011) evaluated the associations between the ocular dimensions and the SER of 134 eyes in 67 Chinese boys at six years of age using MRI analysis. They found that in both myopic and non-myopic eyes, more myopic (or less hyperopic) SER was associated with a longer AL and width of the eyes. Less hyperopic SER was associated with a greater height of the non-myopic eyes only, whereas a similar association was not found in myopic eyes.

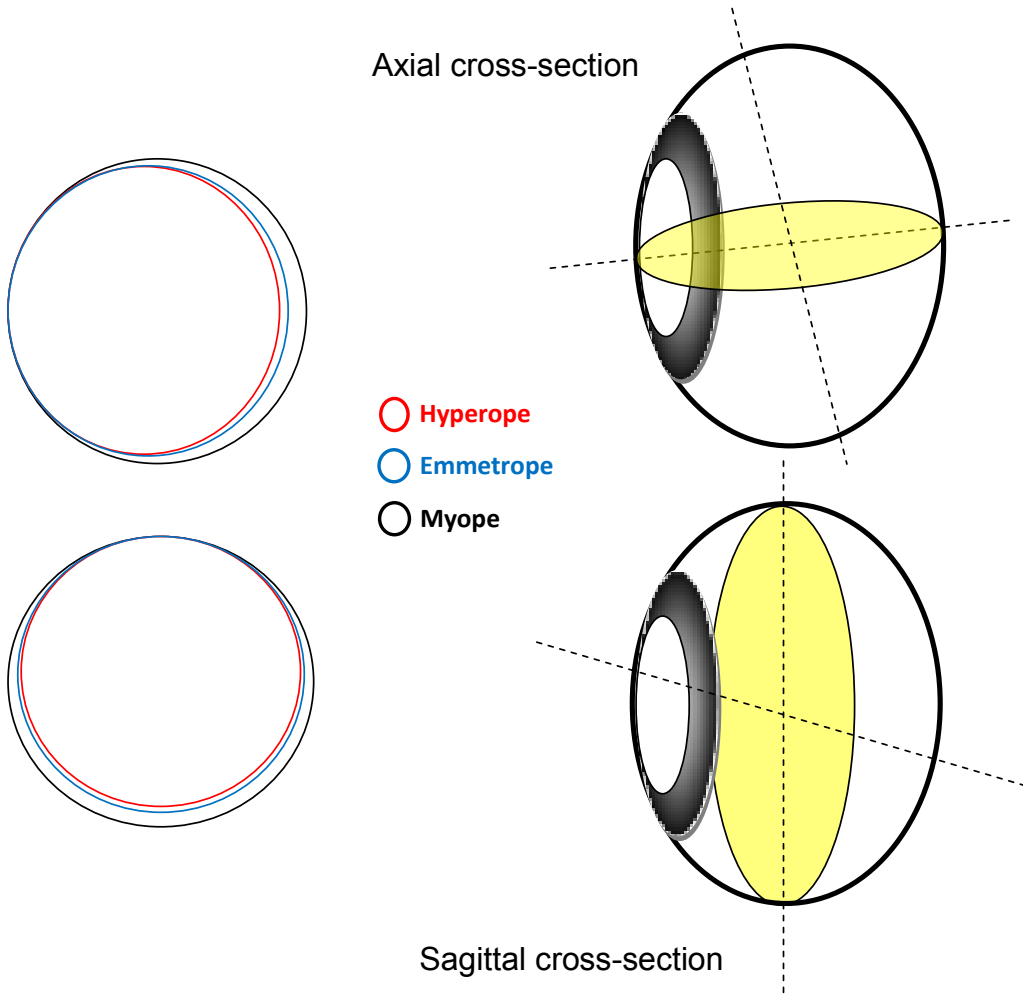


Figure 2.6. Ocular dimensions measured in different ametropias [adapted from Cheng et al (1992)].

Table 2.1. Ocular dimensions (mean ± SD) in eyes with different ametropias (Cheng *et al.*, 1992)

	Ocular dimensions (mean ± SD) in mm			
	Axial cross-section		Sagittal cross-section	
Ametropia	AL (AA')	Equator (BB')	Equator (CC')	Vertical (DD')
Hyperopia	22.3 ± 1.1	23.7 ± 1.1	23.3 ± 0.8	22.6 ± 1.4
Emmetropia	23.0 ± 1.2	23.9 ± 1.1	23.9 ± 1.4	23.1 ± 1.7
Myopia	24.5 ± 1.6	25.1 ± 0.9	25.5 ± 1.5	24.3 ± 1.2

2.3.2 Retinal contour

Information from ocular dimensional reports alone is not adequate to show how eye shape varies with different ametropias. A closer look into the retinal profile is able to give more insight. Retinal profiles gave more information on how retinal images were related to the image plane. Ellipsoids have been used to describe different retinal contours of eyes. With reference to the PR, the retinal contour of myopic eyes is thought to attain the shape of a prolate ellipse, while that of the non-myopic eyes is more oblate in shape. However, Atchison and colleagues (2005a) fitted different ellipsoidal curves to the retinal surface of 21 emmetropic and 66 myopic eyes of young adults, and reported that both emmetropic and myopic eyes were oblate in shapes, but the myopic eyes were more prolate than emmetropic eyes.

Using an optical low coherence reflectometer, Schmid (2003) measured the peripheral eye length (PEL) at 15° nasal, temporal, inferior and superior to the axial length in 63 7-15-year-olds with different ametropias. He found that the relative peripheral eye length (RPEL) was significantly greater in myopes than in emmetropes, which in turn was significantly greater than in hyperopes. This suggested that the retinal steepness was the greatest in myopes while it was the least in hyperopes. However, this earlier report did not depict the retinal contour in a more continuous manner. The lack of information on the nasal retinal measurements due to measurement imprecision around the optic disc might further limit the implications of the results. Although there was a strong correlation between RPEL and relative peripheral refraction, Schmid (2003) was unable to show whether myopic progression was associated with retinal steepness. Later, Schmid (2011)

monitored the PEL (at 20° nasally, temporally, superiorly and inferiorly from the fovea) and central refractive changes in 92 emmetropic or near-emmetropic children between seven and 11 years at baseline and at a 2-year follow-up visit. The mean changes in central SER and AL over the study period were -0.21 ± 0.56 D and 0.33 ± 0.21 mm, respectively. Baseline RPEL in the temporal retina was found to have a statistically significant but relatively weak correlation with the change in central SER, while those at other meridians did not have significant correlation with central refractive changes. The changes in RPEL measured nasally, temporally , superiorly and inferiorly were -0.049 ± 0.322 mm, -0.032 ± 0.263 mm, -0.053 ± 0.250 mm and +0.002 ± 0.230 mm, respectively. Changes were significant in the superior quadrant, but not in the others. Schmid (2011) further suggested that the steep temporal retinal surface was a likely predisposing factor in central myopic shift. As the reported correlation was relatively weak and the investigation was restricted to central and 20° in the four semi-meridians only, stronger evidence from investigations over a wider retinal area with more measurement points are needed. In addition, how the change in RPEL is correlated with any change in central SER and PR is not understood.

The use of the optical low coherence reflectometer, which is not commercially available, has restricted its popularity in clinical studies. The introduction of the IOLMaster (Carl Zeiss Meditec, Germany) has allowed more researchers to assess PEL in general clinical settings (Mallen and Kashyap, 2007; Ding and He, 2012; Ehsaei *et al.*, 2012; Faria-Ribeiro *et al.*, 2012).

Recent works have evaluated the retinal contour across a wider retinal area

and more field angles (Ehsaei *et al.*, 2012; Faria-Ribeiro *et al.*, 2012). It has been reported that myopic eyes had steeper retinal contours than emmetropic eyes at all meridians (Figure 2.7) and the eyeball is more prolate in the axial plane than in the sagittal plane (Ehsaei *et al.*, 2012). It was also reported that there was a significant asymmetry between the nasal and temporal retina in myopic eyes which was not observed in emmetropic eyes (Ehsaei *et al.*, 2012; Faria-Ribeiro *et al.*, 2012). However, these reports were cross-sectional studies and the retinal shapes were depicted in emmetropic and myopic adult eyes only. Further study on children's eyes with all types of ametropias would give more insight on how the retinal contour is related to early-onset myopia.

Associations between the rates of myopic progression and PR as well as RPEL on the nasal retina were reported in Faria-Ribeiro and colleagues' work (2012). They compared the PR and retinal steepness between a group of 32 young adults with non-progressing myopia (less than a change of 0.25 D in SER in the previous two years) against another group of 30 with progressing myopia (with myopic progression of at least 0.50 D in the previous year), and found that the progressing myopes had a steeper retina and a more hyperopic refraction on the nasal retina than in the non-progressing myopes. Their study, however, did not report the baseline PR and PEL, and therefore failed to relate the baseline characteristics with the rate of myopic progression. Their report did not provide evidence to support whether a more hyperopic defocus in the peripheral retina or a steeper retina would predispose an eye to progressing myopia.

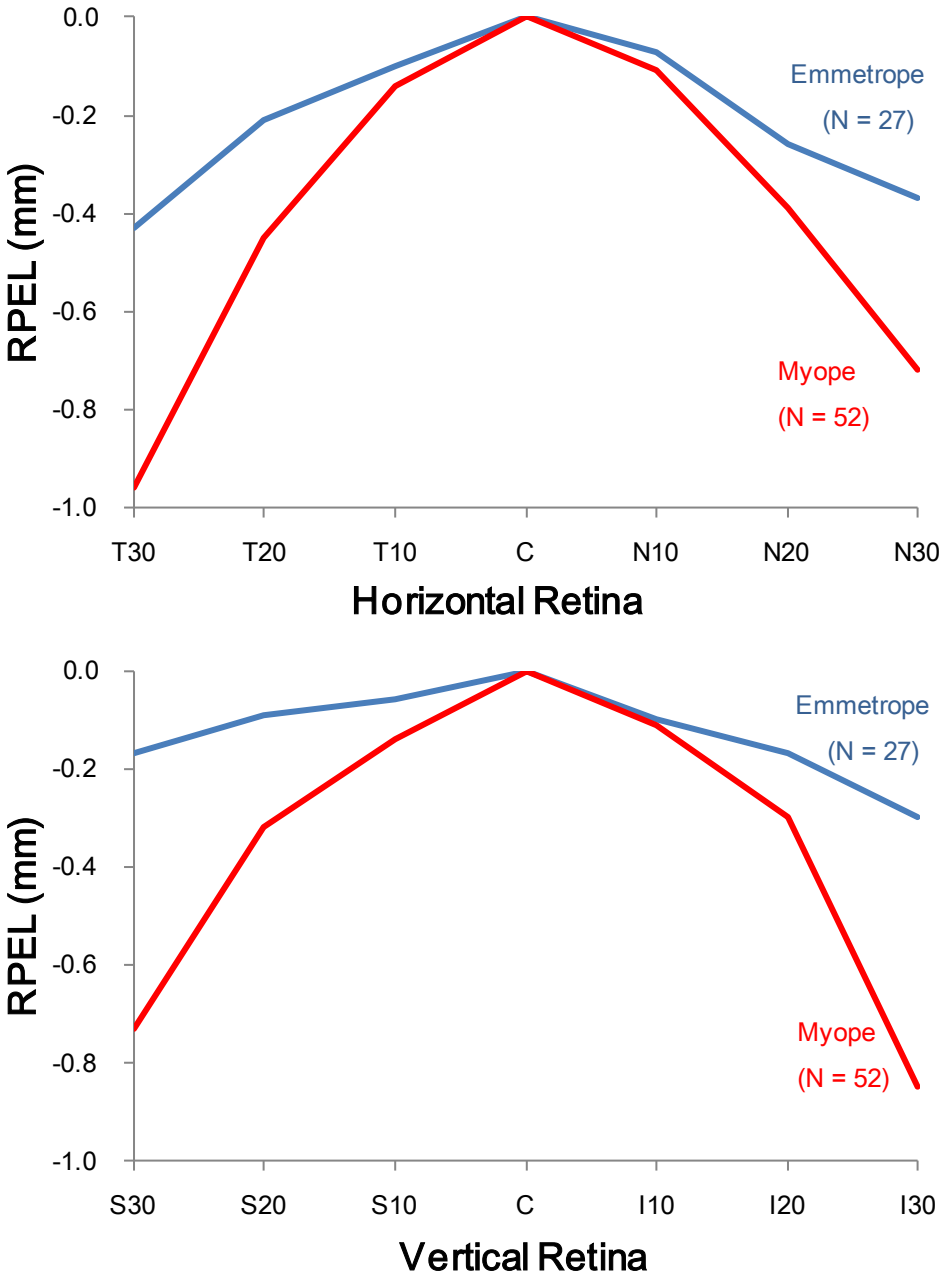


Figure 2.7. Retinal contour of emmetropic and myopic eyes [adapted from Ehsaei et al (2012)]. RPEL: relative peripheral eye length; T: temporal retina; N: nasal retina; S: superior retina; I: inferior retina; C: central retina)

2.3.3 Myopia models

Four models of ocular expansion in response to myopic progression have been proposed (Figure 2.8). It has been shown that there is no single model

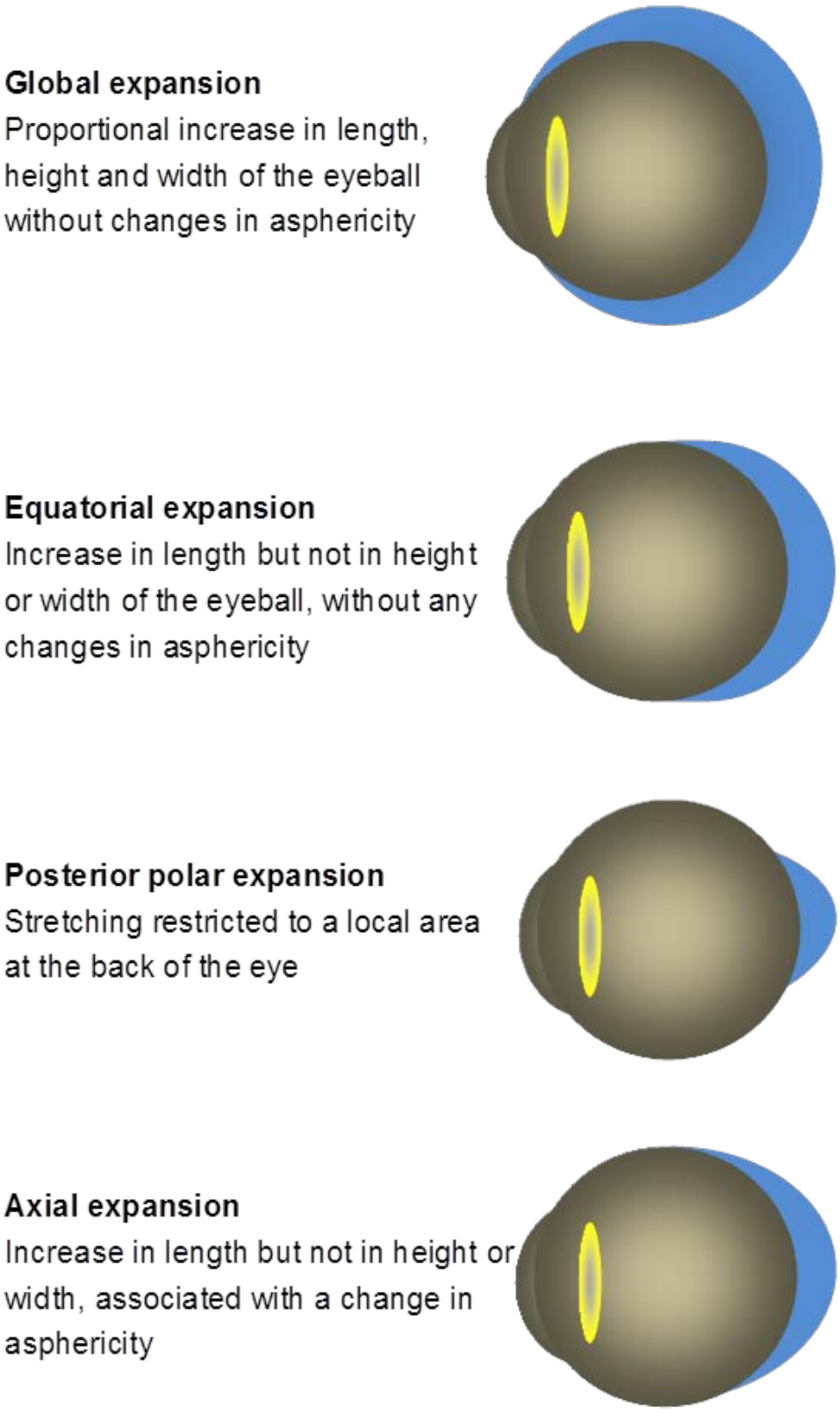


Figure 2.8. Four myopia models showing different patterns of retinal stretching [adapted from Atchison et al (2004)].

which could exclusively explain an individual ametropic population. By comparing the ocular dimensions of the myopic eyes to those of the emmetropic eyes, Atchison and colleagues (Atchison *et al.*, 2004) found that the axial expansion model and the global expansion model were not able to fit the myopic population exclusively. They have found evidence showing that the emmetropic eyes were more elongated in length than in height and more in height than in width. On the other hand, Lim and colleagues (2011) suggested that myopic eyes, particularly those with more myopic SER, elongated more axially than horizontally and vertically. The greatest change laid in the axial dimension, resulting in a more prolate shape of the retina. Hence, they suggested that myopic eyes fitted well into the axial elongation model. Non-myopic eyes, especially those with less hyperopic SER, elongated more proportionally in all three dimensions without significant changes in the asphericity of the retinal contour. Thus, they could be fitted into the global expansion model.

However, it would be imprudent to propose that a certain ametropia is confined to one of the models. The classification into four unique models over-simplifies the ocular shapes. In fact, animal studies have demonstrated that the retinal contour could be locally modulated to give a hemi field induced response to defocus and form deprivations (Chu *et al.*, 2012). Moreover, the asymmetrical retinal contour detected directly with optical low coherence reflectometer or partial coherence interferonmeter, and indirectly with PR measurements have shown that a combination of more than one model would better explain the ocular shape changes in different ametropias.

Current published studies investigating ocular dimensions in different

ametropias and their associations with myopic development have not provided longitudinal information on how the dimensions change with central SER changes. Further, longitudinal studies on the retinal contour changes in children who are prone to myopic development would allow a better understanding of whether retinal steepness would predispose an eye to a higher risk of myopic development or progression.

2.3.4 The relationship between ocular shape, retinal contour and peripheral refraction

The dimensional measurements of ocular length, height and width, the measurement of PEL, and the mathematical methods in fitting ellipsoidal curves onto retinal cross-sectional images are direct measurements of the ocular shape. PR, on the other hand, is an indirect alternative for describing ocular shape. It also provides information about the nature of the optics of the retinal images – whether there is a positive or negative defocus with respect to the central focus. Verkicharla et al. (2012) have recently pointed out that “myopic eyes are prolate in shape” would become a misconception, unless it is clearly stated whether the “shape” referred to the ocular shape, the retinal contour or the shape of the optical focus. For example, a prolate shape defined by ocular dimensions may not necessarily infer a prolate shape in the shell of the optical defocus (i.e. relative peripheral myopia). It should be clearly indicated whenever the “shape of an eye” is referred to.

2.4 Factors affecting peripheral refraction in human eyes

This last section reviews the ocular dimensions and retinal surface profiles

across different ametropias. In this section, variations of ocular shape as indirectly assessed by PR are reviewed.

2.4.1 Ametropias

Curves fitted on MRI images of retinal surfaces and PEL measurements using optical low coherence reflectometry and partial coherence interferonmetry techniques have indicated that the retinal contour of myopic eyes are more prolate than those of non-myopic eyes (Schmid, 2003; Atchison *et al.*, 2005a; Ehsaei *et al.*, 2012; Faria-Ribeiro *et al.*, 2012). How the refraction will be affected when it is measured off-axially will also depend on the refractive surfaces through which the light ray is refracted. The optical profiles of the corneal and the lenticular surfaces do not assume a spherical shape. They are rather referred to as conical surfaces (Smith *et al.*, 2009c; Chan *et al.*, 2012). In addition, off-axial light rays do not pass through the refracting surfaces at right angles. Therefore, off-axial refraction is expected to be quite different from the foveal refraction.

2.4.1.1 Types of ametropia

Despite the presence of within-type variabilities, different ametropic groups are characterized by particular patterns of peripheral defocus (Tabernero and Schaeffel, 2009b). Results from the PR studies are in agreement (Millodot, 1981; Seidemann *et al.*, 2002; Calver *et al.*, 2007; Berntsen *et al.*, 2010; Chen *et al.*, 2010b; Ehsaei *et al.*, 2011b; Sng *et al.*, 2011a; Tabernero *et al.*, 2011). Most of the these studies took measurements along the horizontal fields, while only a few assessed PR along the vertical or the oblique meridians as well. Earlier reports on PR in emmetropic and different ametropic eyes

can be traced back to the 1980s. Millodot (1981) auto-refracted 62 eyes along 120° horizontal field in 10° intervals in adults using Topcon Refractometer Type III. Of the 62 eyes, 19 were hyperopic (SER = +0.75 D to +4.00 D), 13 were near-emmetropic (SER = -0.99 D to +0.74 D) and 30 were myopic (SER = -1.00 D to -7.87 D). For each field angle, PR was represented in their most myopic and most hyperopic meridians in the original report. For better understanding, the results of both meridians are remapped relative to the central refraction in the current review and the relative peripheral SER of the three groups are compared in Figure 2.9. Millodot's (1981) results demonstrated relative peripheral hyperopia in myopic eyes but relative peripheral myopia in hyperopic ones. The differences were significant beyond 20° in both hemi-fields. Emmetropic eyes had relative peripheral hyperopia in the temporal field but relative peripheral myopia in the nasal field. Axis of astigmatism changed from with-the-rule to against-the-rule with eccentricities. A marked asymmetry between the hemi-fields was also noted.

Seidemann et al. (2002) measured PR on 31 young adults in the superior, inferior, nasal and temporal fields up to 22° from the central fixation using the Power-Refractor (Plusoptix, Nuremberg, Germany), and also further to 45° in the nasal field using the double-pass method on another group of 25 adults. Of the 31 adults measured with the Power-Refractor, five were hyperopic (SER = +4.50 D ± 2.21 D),

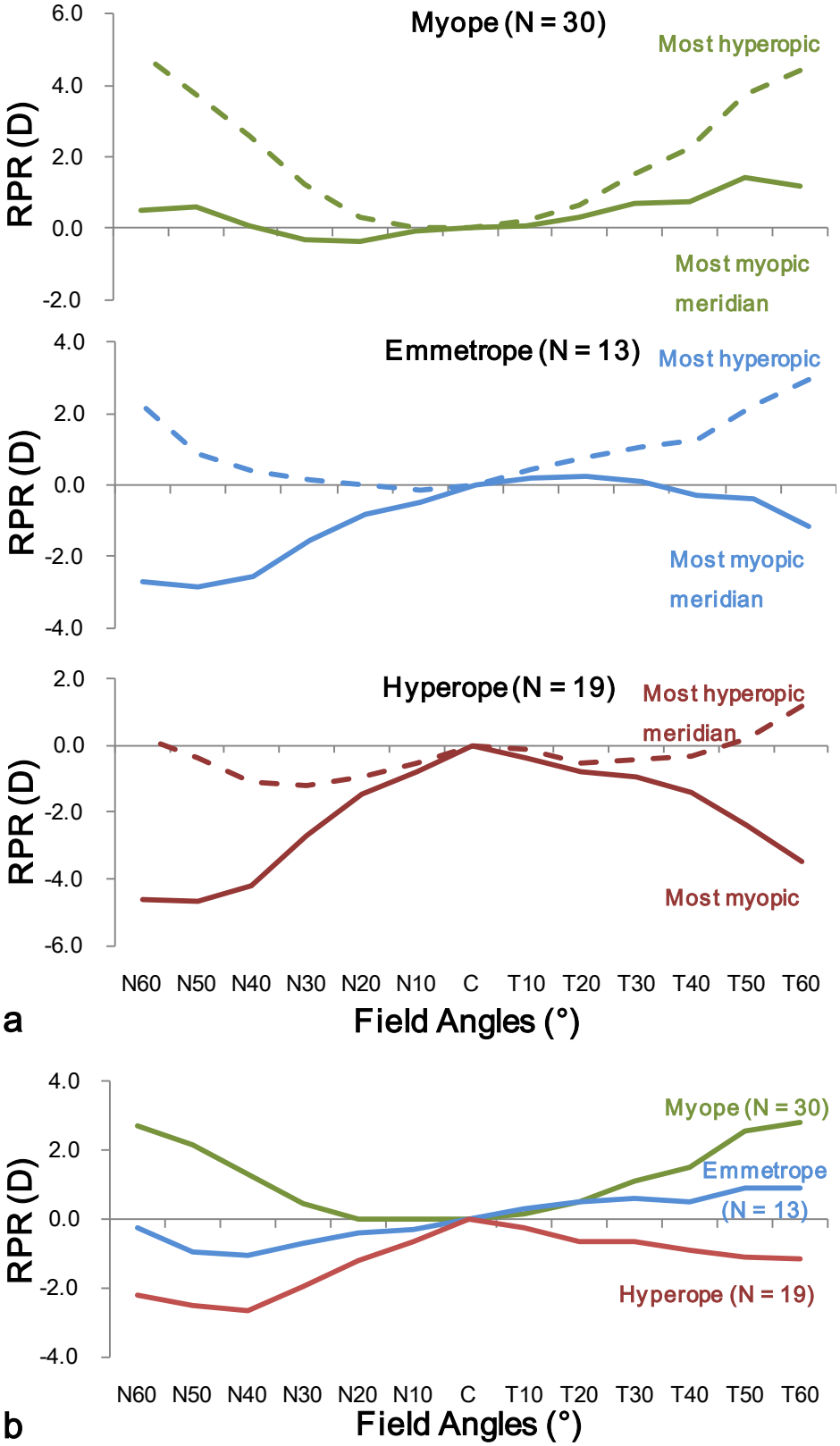


Figure 2.9. (a) Relative peripheral refraction of the major and the minor meridians in myopic, emmetropic and hyperopic eyes. (b) Relative peripheral refraction (SER) in different ametropias in adults [adapted from Millodot (1981)].

eight were emmetropic (SER = -0.17 ± 0.49 D) and 18 were myopic (-3.06 ± 1.62 D). Results from the Power-refractor method showed that PR on the horizontal meridian was mostly myopic relative to central refraction in all groups. The hyperopic eyes were markedly more myopic (~1.0 D) at 22° in the nasal field only than the myopic eyes. Differences in relative peripheral refraction (RPR) were not significant between any pairs of refractive groups at the other horizontal field angles. Along the vertical meridian, a marked relative hyperopia (~1.0 D) was noted at 22° in the superior field in the myopic eyes. At the same peripheral angle, difference among the three refractive groups became more significant. In the inferior field, all refractive groups had relative myopia. However, in this study the measurements were taken with subjects wearing their spectacle correction if they had habitual distance correction, and with the subject turning their eyes to view the eccentric fixation targets while keeping their head still during the examination. Therefore, the results did not take into account the influence of the spectacle correction. In addition, spectacle correction was not needed by all subjects; hence the influence of spectacle correction was not consistent across all refractive groups. Results from the double-pass method also showed relative peripheral myopia within the 45° nasal field in all refractive groups. RPR was not significantly different among the three groups with 30° field. With this method, the subjects were allowed to move their head to view the peripheral targets at primary gaze when taking measurements. Although a later report has evidenced that PR measurements were not affected by either the head-turn or the

eye-turn methods using an open-field auto-refractor (Mathur *et al.*, 2009b), it was unknown if this would apply to other instruments. These uncertainties have made Seidelmann and colleagues' (2002) results less comparable to those reported in other studies.

The RPR patterns in different ametropias were more discrete in children (Chen *et al.*, 2010b; Sng *et al.*, 2011a). Chen et al (2010b) compared the RPR between 40 children (11.1 ± 1.5 years) and 42 adults (21.6 ± 3.6 years). PR across the central 80° horizontal and 64° vertical field were measured under cycloplegia using an open-view auto-refractor. Both groups were sub-divided into four refractive groups according to their central refractive errors: hyoperopes (+0.50 D ≤ SER ≤ +2.00 D), emmetropes (-0.50 D < SER < +0.50 D), low myopes (-3.00 D ≤ SER ≤ -0.50 D) and moderate myopes (-6.00 D ≤ SER < -3.00 D). The myopic children had relative peripheral hyperopia at most angles (except at 22° in the nasal for low myopes and at 22° in the temporal for high myopes) (Figure 2.10). RPR in the myopic children were more hyperopic than in the emmetropic and hyperopic children, which demonstrated relative myopia in the peripheral field (except at 32° and 40° in the nasal for emmetropes). In the superior and the inferior fields, all children showed relative peripheral myopia up to 32°. RPR of the high myopes were less myopic than the other groups in the superior field.

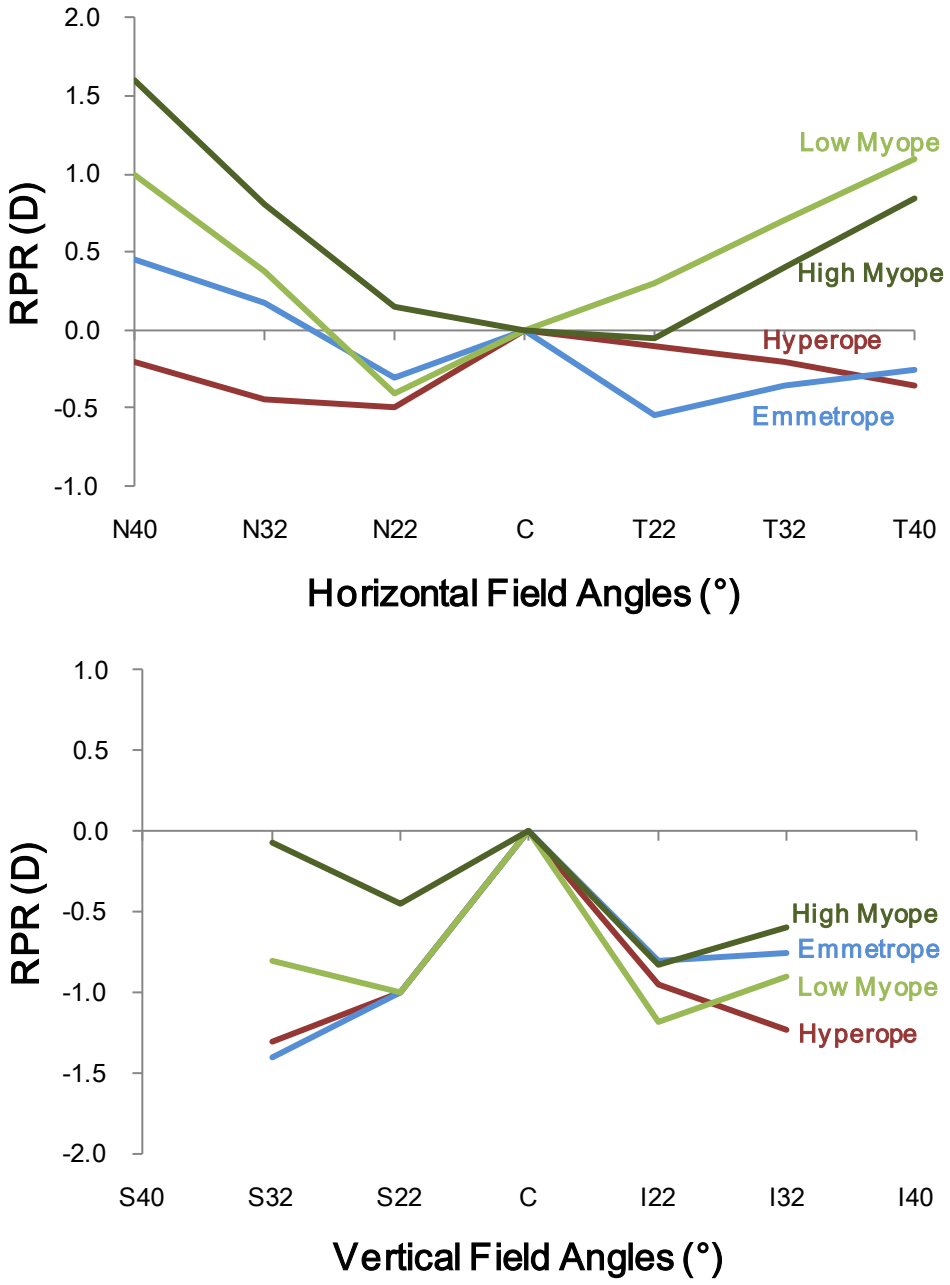


Figure 2.10. Relative peripheral refraction along the vertical and horizontal fields in Chinese children [adapted from Chen et al (2010b)]. N: nasal; T: temporal; S: superior; I: inferior and C: central).

Two hundred and fifty children (83 ± 36 months) from the Strabismus, Amblyopia, and Refractive Error in Young Singaporean Children study had PR of the central 60° horizontal field measured under cycloplegia at 15° intervals (Sng *et al.*, 2011a). The subjects were divided into four groups according to their central SER: hyperopes (SER > 1.00 D), emmetropes (-0.50 D < SER ≤ 1.00 D), low myopes (-3.00 D < SER ≤ -0.50 D) and high and moderate myopes (SER ≤ -3.00 D). The moderate and high myopes had relative hyperopia across the tested field, while the low myopic group had relative myopia at the 15° angles and relative hyperopia at 30° angles (Figure 2.11).

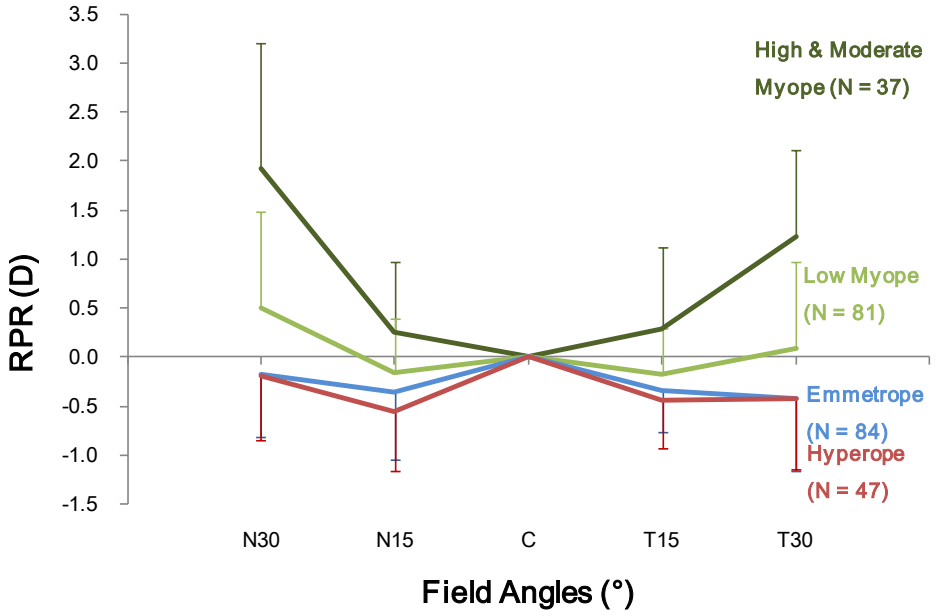


Figure 2.11. Relative peripheral refraction in Singapore Chinese children [adapted from Sng et al (2011a)]. N: nasal ; T: temporal; C: central. Error bar = 1SD.

RPR was significantly more hyperopic at all field angles in the

moderate and high myopic group than those in the emmetropic and the hyperopic groups, both of which demonstrated relative myopia at all peripheral angles. The RPR between the hemi-fields were asymmetrical and the asymmetry tended to increase with central refractive errors.

Ehsaei and colleagues (2011b) measured the non-cycloplegic PR of 49 young adults along the horizontal, vertical, 45°- and 135°-oblique fields using an open-view auto-refractor. The width of each field covered the central 60° and measurements were made at 10° intervals. Eighteen subjects were emmetropes (SER = 0.07 D ± 0.34 D) and 31 were myopes (SER = -5.73 D ± 1.80 D). Figure 2.12 illustrates the results of their study. Unlike previous studies (Seidemann *et al.*, 2002; Chen *et al.*, 2010b), the myopic eyes in Ehsaei et al's (2011b) study consistently demonstrated relative peripheral hyperopia along all fields measured, showing also a variability with the superior-temporal field being most hyperopic and inferior field being most myopic. The emmetropes demonstrated variabilities mainly along the vertical field with the superior field showing more hyperopic RPR than the inferior field. RPR in other fields of the emmetropic eyes did not vary significantly from central refraction.

Larger variability observed in PR and eye shapes of emmetropes have also been reported in other studies (Atchison *et al.*, 2004; Atchison *et al.*, 2005a; Tabernero and Schaeffel, 2009a)

2.4.1.2 Magnitude of ametropia

In multiple linear regression models on PR at 30° in both nasal and temporal fields, Sng et al (2011a) reported that for every one diopter increase in central SER, PR increased by 0.85 D at temporal 30° and 0.91 D at nasal 30°. This would lead one to expect an increase of about 0.10 D to 0.15 D relative peripheral hyperopia for every diopter increase in central myopia. Figure 2.13 summarizes the RPR at nasal 30° by central SER from different studies. It shows that for every one diopter increases in central myopia, the RPR at 30° in the nasal field will become more hyperopic by 0.41 D. This suggests a greater increase relative hyperopia per diopter central myopic shift than Sng and co-workers' study (2011a) suggested.

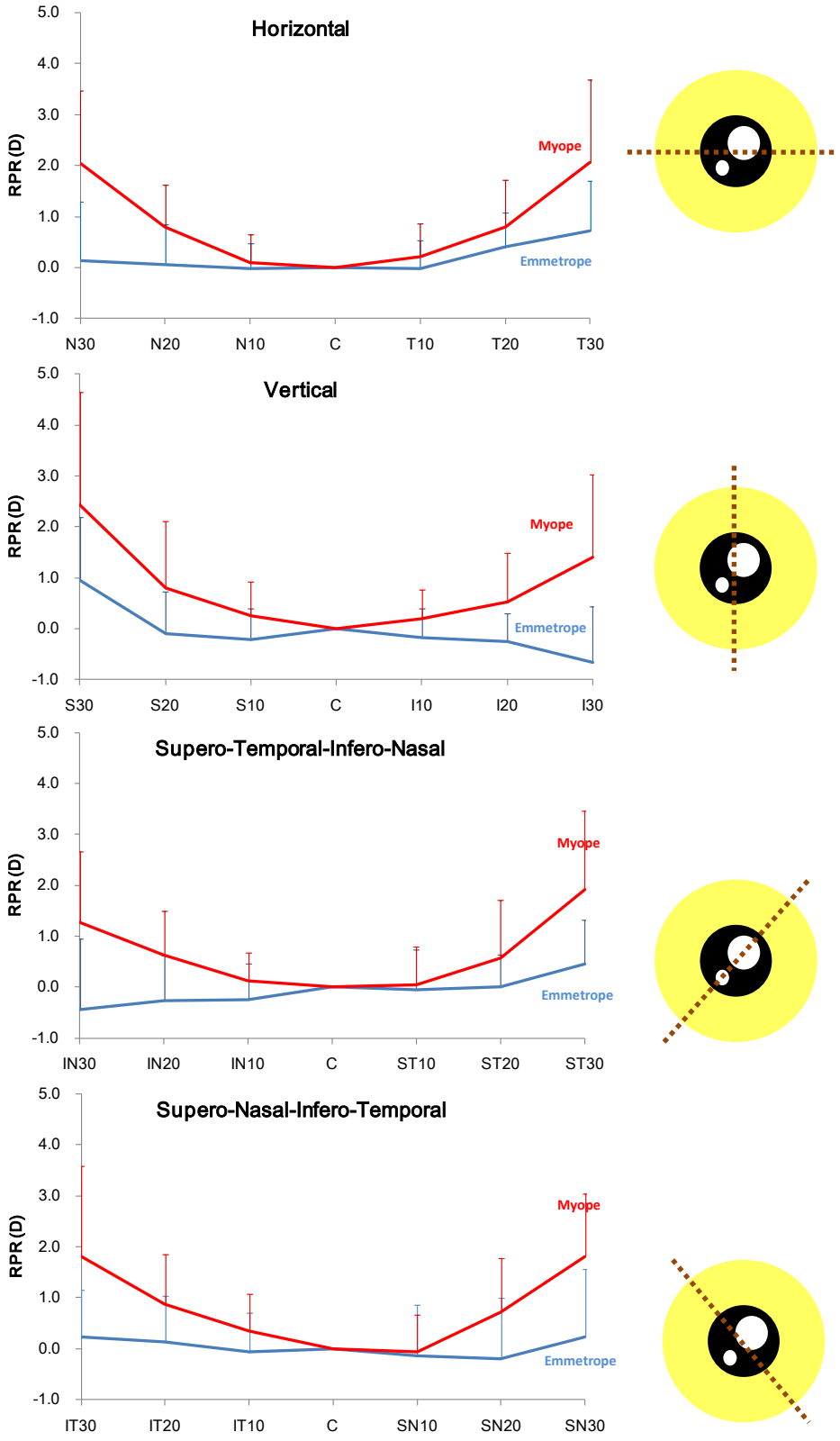


Figure 2.12. Relative peripheral refraction of adults along the horizontal, vertical, supero-temporal-infero-nasal and supero-nasal-infero-temporal fields [adapted from Ehsaei et al (2011b)]. The figures on the right show the field (dotted line) measured on a right eye. N: nasal; T: temporal; S: superior; I: inferior; IN: infero-nasal; ST: supero-temporal; IT: infero-temporal; SN: supero-nasal. Error bar = 1SD

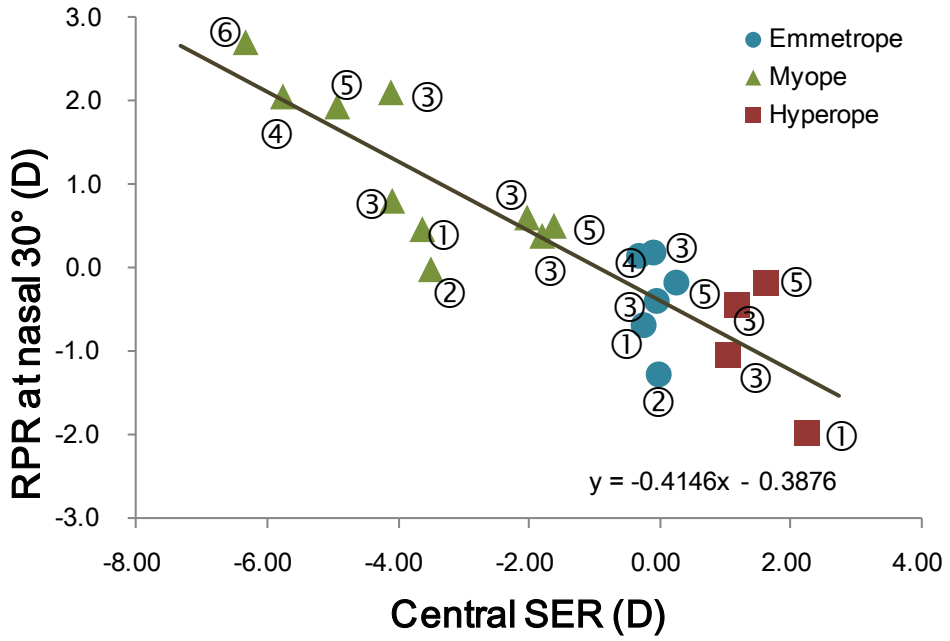


Figure 2.13. Relative peripheral refraction at nasal 30° field against central SER from different studies ① Millodot (1981); ② Calver et al (2007); ③ Chen et al (2010b); ④ Ehsaei et al (2011b); ⑤Sng et al (2011a); ⑥ Backhouse et al (2012)

One of the available PR studies on high myopes with myopia greater than 6.00 D (range: -12.50 D to -6.50 D), however, did not report large amount of relative peripheral hyperopia up to 20° towards the nasal and the temporal fields (Kwok *et al.*, 2012). Contrary to this results, Ehsaei et al (2011b) reported an RPR of 2.05 D at nasal 30° in a group of young adults with moderate myopia (SER = -5.76 ± 1.82 D). More recently, Backhouse and colleagues (2012) had reported the PR profile of 10 high myopes (SER = -6.33 ± 0.31 D) corrected with spherical soft contact lenses. They measured the subjects' PR with an open-view auto-refractor with the subjects turning their heads to view the eccentric fixations. Figure 2.14 shows the RPR measured when the subjects were refracted without any corrections.

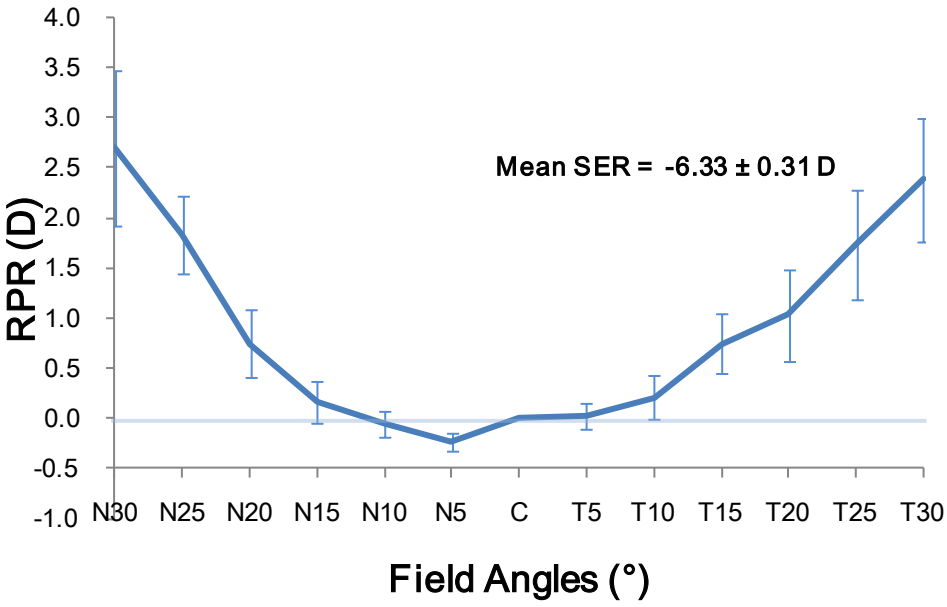


Figure 2.14. Relative peripheral refraction of high myopes [adapted from Backhouse et al (2012)]. N: nasal; T: temporal; C: central. Error bar = 1 SD.

However, there are no other reports on PR characteristics in high myopia. Further PR investigation on high myopes covering a wider range of field and on meridians other than the horizontal is warranted.

2.4.2 Ethnicity

Mutti and colleagues (2011) investigated the association of RPR (measured at nasal 30° only) and the risk of onset and progression of myopia in 2043 subjects (8.8 ± 5.5 years) who were initially non-myopia. These subjects included Native American (14.5%), Asian (11.2%), African American (18.6%), Hispanic (23.7%) , White (31.3%) and others (0.7%). Central SER and RPR were found to vary with ethnicity; Asians, African Americans, and Hispanics had a less hyperopic central refraction and a less myopic RPR, while Native Americans and Whites had a more hyperopic central refraction and a more myopic RPR (Figure 2.15).

During the evaluation of the risk of onset of myopia, they also found a greater risk of myopia onset in Asian subjects with every unit increase in RPR than in the African American subjects. There was no significant association found in other ethnicities. It should be noted, however, that when all subjects were considered as a whole and variations across ethnicities were taken into consideration, RPR did not appear to be a risk factor for myopia onset. Mutti and colleagues (2011) also investigated the association of RPR with myopic progression in the same study, and did not find any evidence for RPR as a potential causative factor for myopic progression. One limitation of their study was that they only measured

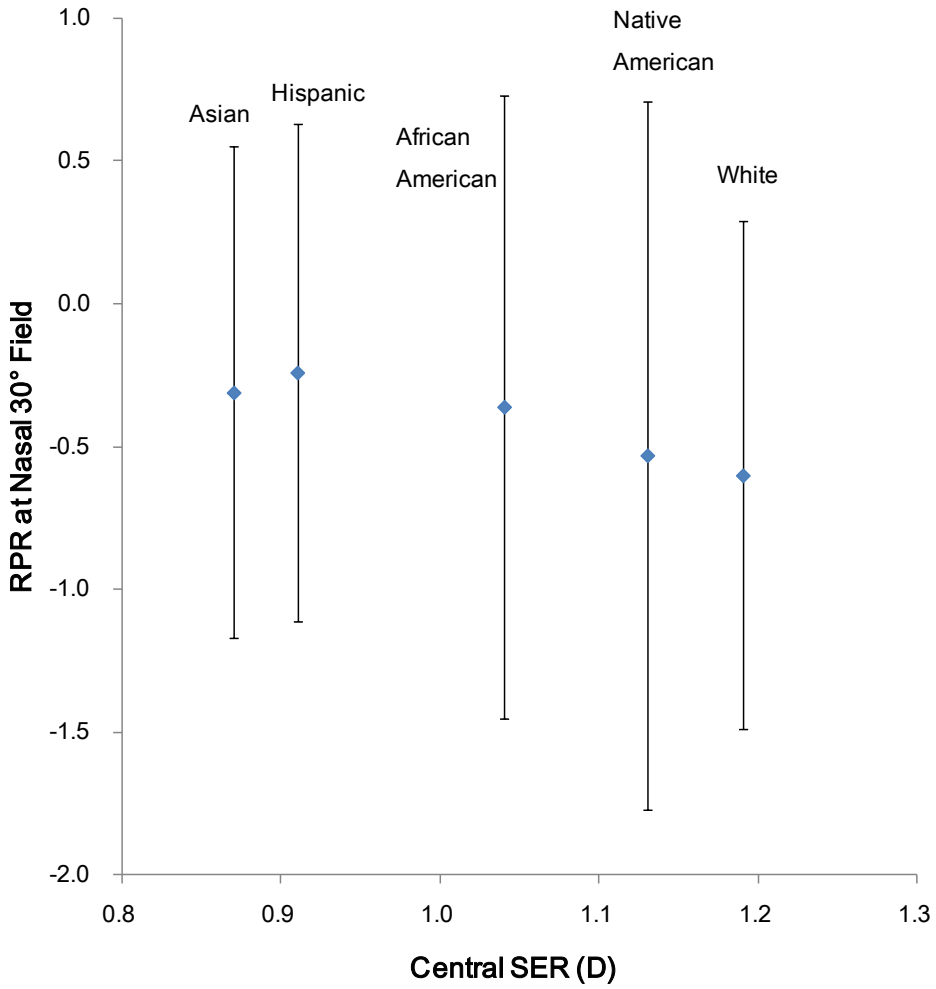


Figure 2.15. Relative peripheral refraction at nasal 30° field as a function of central spherical equivalent refraction in different ethnic groups [adapted from Mutti et al (2011)]. Error bar = 1 SD.

one eccentricity for RPR. It would be more comprehensive and convincing if RPR at more field angles were investigated in the analysis of association with the risk of onset and progression of myopia.

Kang and co-workers (2010) compared the RPR across the central 70° in the horizontal field in 35 White and 37 East Asian adults. They divided the subjects into emmetropes (-0.50 D < SER < +1.00D), low myopes (-2.50 D < SER ≤ -0.50 D) and moderate myopes (-5.50 D ≤ SER < -2.50) in both ethnic groups. In the emmetropic and the low myopic groups, ethnical

difference in RPR was not significant across the horizontal field. In the moderate myopic group, RPR was found to be more hyperopic in East Asians than in the Whites at angles beyond 25° in both of the nasal and the temporal fields.

2.4.3 Age

Atchison and co-workers (2005b) compared the PR profiles between 55 younger (24 ± 3 years) and 41 older subjects (59 ± 3 years). In the emmetropic emmetropes (-0.50 D < SER ≤ 0.50 D), low myopic (-1.50 D < SER ≤ -0.50 D) and moderately myopic (-2.50 D ≤ SER ≤ -2.50 D) groups, they did not find significant differences between the younger and the older subjects. However, the subject number in each refractive group was small for comparison between the two age groups. The ratios of the older to younger subjects were 8:20, 8:17 and 8:16 in the emmetropic, low myopic and moderately myopic groups, respectively. In addition, their report did not provide information on the effect of age on PR profiles by central refractive errors in children. Further understanding on the age effect in the year of onset of myopia may give more insight on how PR is involved in the development of myopia.

Of the 250 children whose PR were measured in the Strabismus, Amblyopia and Refractive Error in Singaporean Children Study, 103 were older than 72 months (Sng *et al.*, 2011a). When the whole group was divided into two age-groups (≤ six years vs > six years), central refraction and PR at each eccentricity were significantly more myopic in the older group than in the younger group. Relative hyperopia was found at 30° in both of the nasal and the temporal fields in the older group, while PR were more or less similar to

the central refraction within the central 30° (Figure 2.16). In the younger group, relative peripheral myopia was found across the central 60° horizontal field. The age difference seems to be significant (~ 1.0 D) at the most peripheral angles on both sides. However, it should not be overlooked that the central refraction between the two age-groups were significantly different (≤ 6-year-old-group = 0.27 ± 1.28 D; > 6-year-old-group = -2.5 ± 2.18 D). The demographics of the younger group consisted of a higher proportion of hyperopic eyes. On the contrary, the majority of older group tended to be moderate to high myopes. Furthermore, multiple logistic regression analysis for PR showed that age was not a significant factor that would have influenced PR at either 30° angle. Therefore, the age difference in PR observed in a sub-group of the Singaporean study may be due to the influence of the central ametropia rather than the age.

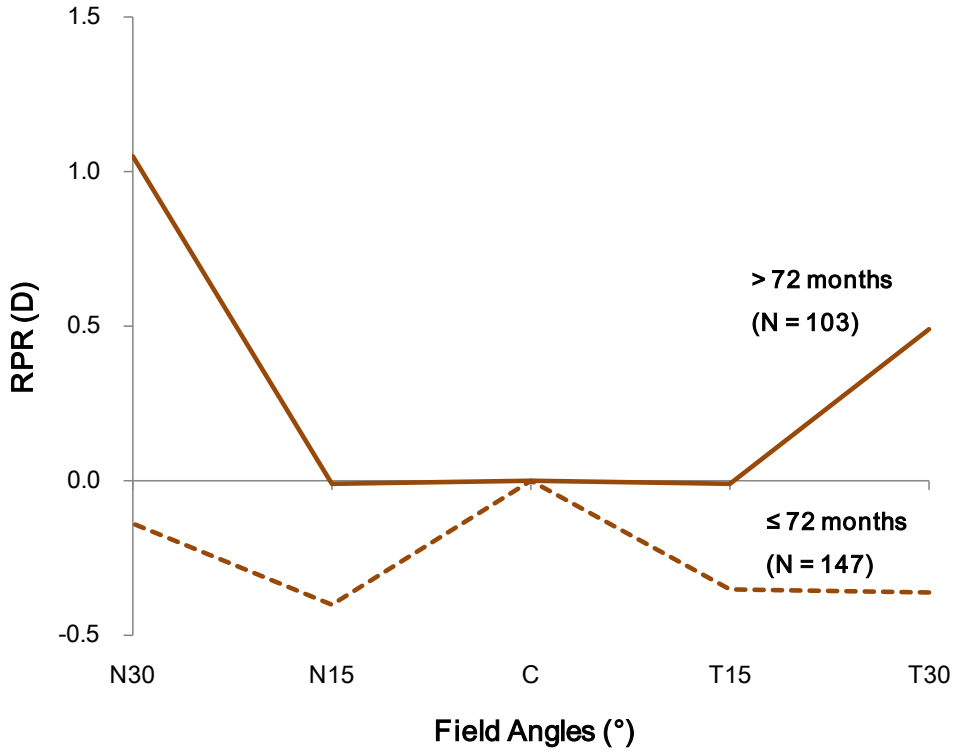


Figure 2.16 Relative peripheral refraction of children below and above six years old [adapted from Sng et al (2011a)]

In Chen and colleagues' study (2010b), where RPR of 40 children (11.08 ± 1.49 years) were compared against those of 42 adults (21.55 ± 3.63 years), it was shown that RPR only differed significantly between the two age groups in moderate myopes (Figure 2.17).

RPR in adults were more hyperopic across the horizontal field, with the age-difference being greater in the temporal field. Increases in relative

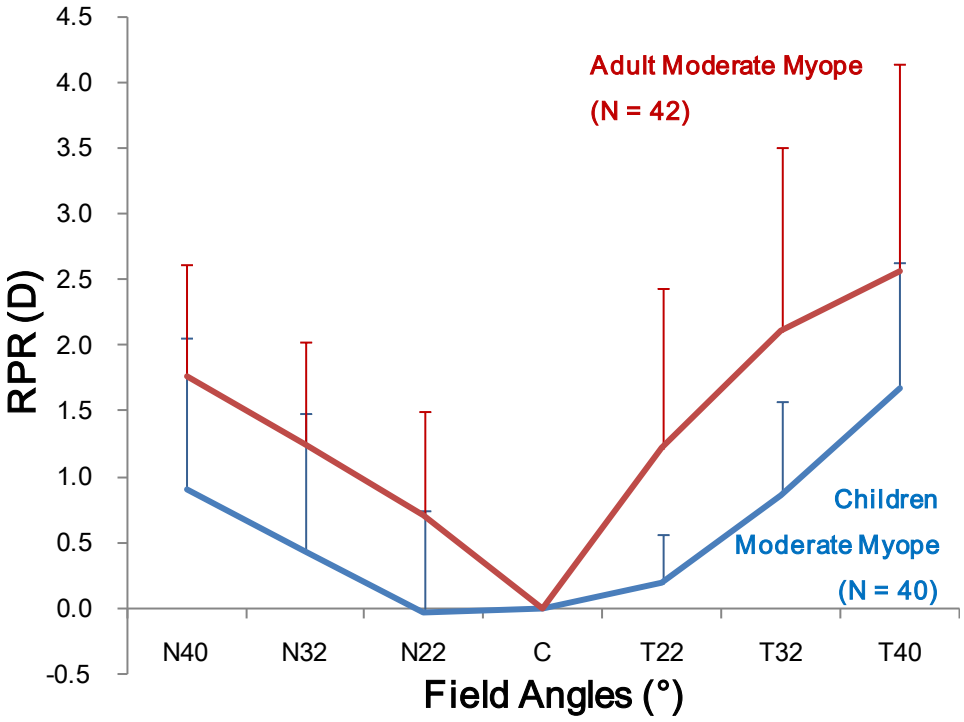


Figure 2.17. Relative peripheral refraction of children (N = 40) and adults (N = 42) with moderate myopia [adapted from Chen et al (2010b)]. Error bar = 1SD.

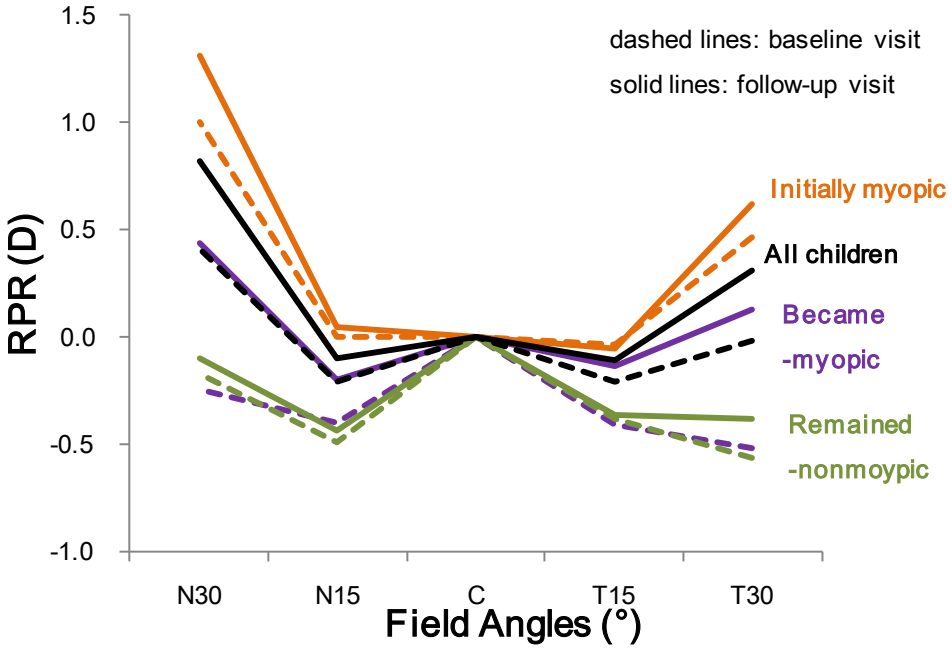


Figure 2.18. Changes in RPR of children with different baseline ametropias and their changes after about one year [adapted from Sng et al (2011b)]. Subject numbers: 67, 96 and 24 for became myopic, myopic at baseline and remained non-myopic groups, respectively.

peripheral hyperopia with eccentricities were also found to be more rapid in adults than in children. However, these differences were not accounted for by the AL or central SER in the moderate myopes.

In a longitudinal study comparing PR changes between baseline and a follow-up visit in about 12 months later in 187 Singapore Chinese children (7.2 ± 1.7 years at baseline), Sng and co-workers (2011b) found that the overall RPR became more hyperopic with time. Ninety-six children were myopic at baseline (initially-myopic group). Of those who were either hyperopic or emmetropic at baseline, 67 became myopic (became-myopic group) and 24 remained non-myopic (remained-non-myopic group) at the follow-up visit. Analysis of individual groups showed that the changes in RPR was significant in the became-myopic group only, while the

remained-non-myopic and initially-myopic groups did not show much changes over time (Figure 2.18). The changes of RPR with time, or age, should therefore be carefully interpreted, particularly since central refraction changed with age. That RPR changes were associated with central refractive changes would likely impede the interpretation of age changes is supported by a previous study of Mutti and colleagues (2007). They found different patterns of RPR changes before and after the onset of myopia between the became-myopic eyes and the remained-emmetropic eyes. The latter showed relatively stable relative peripheral myopia over time. The RPR of the became-myopic eyes were initially myopic. They started to change to relative hyperopia about 2 years before the onset of myopia.

2.4.4 Accommodation

The effect of accommodation has also been discussed from different perspectives: effect of accommodative tasks on PR, field curvature difference between distance and near viewing, and PR with and without corrections.

Walker and Mutti (2002) investigated the effect of prolong near work on PR in 22 young subjects (SER = 3.48 ± 1.76 D) who were either corrected with SCL or spectacles. PR at nasal 30° field were measured using an auto-refractor (Canon AutoRef R-1) before, during and after two hours of near work sustained at 30cm. The measurements were taken while the subject fixated at a target with their accommodation relaxed. At baseline, the mean RPR was found to be hyperopic. At the onset of near work, RPR became more hyperopic. It regressed with time during the two hours of sustained near work but remained more hyperopic than the baseline RPR.

Upon cessation of near work, the subjects were asked to change to a distance viewing task for recovery of accommodation. Upon the onset of recovery, RPR became significantly less hyperopic than baseline RPR and remained so during the first 30 minutes of the recovery period. After 30 minutes of recovery, the RPR resumed a similar level of relative hyperopia as that at baseline and remained so till the end of the recovery period. Walker and Mutti's (2002) study demonstrated that sustained near work would temporarily induce more hyperopic RPR during the near work, while the relaxation of accommodation would transiently lead to a more myopic RPR than the usual status.

During the investigation on their effect on PR profiles, accommodative stimuli could be provided by either altering the vergence (Davies and Mallen, 2009; Mathur *et al.*, 2009a) or the distance of the fixation targets (Lundstrom *et al.*, 2009; Tabernero and Schaeffel, 2009a; Whatham *et al.*, 2009). Results were, however, not consistent across studies.

Mathur and colleagues (2009a) evaluated the peripheral aberration of nine emmetropic (SER = 0.20 ± 0.30 D) young adults when they were asked to fixate targets which provided accommodative stimulus of 0.03D and 4.00 D. Measurement were made across the central 40° horizontal and vertical fields. RPR did not differ significantly between the two accommodative conditions across the horizontal and the vertical fields, although the RPR under higher accommodative demands appeared more hyperopic towards the peripheral angles observed in the nasal, superior and inferior fields.

Making use of a scanning infrared photoretinoscope, Tabernero and Schaeffel (2009a) evaluated the RPR patterns of 10 young emmetropes (sphere and cylindrical corrections < 0.50 D each) at different fixation

distances. The subjects were asked to fixate monocularly at a cross-hair which was placed 0.25 m, 0.50 m and 2.00 m away, corresponding to accommodative stimuli of 4.00 D, 2.00 D and 0.50 D. The photoretinoscope then swept across the horizontal 90° field to assess the PR profile while the subject steadily fixated at the target ahead. The PR profiles did not differ significantly by accommodative status in all subjects, but larger variability was observed during measurements under higher accommodative demands (i.e. 4.00 D).

Davies and Mallen (2009) measured the PR across the horizontal 60 ° field of 21 young emmetropes (SER = -0.13 ± 0.29 D) and 19 young myopes (SER = -2.95 ± 1.76 D) with accommodative stimuli from 0.00 D to 3.00 D (at 1.00 D intervals), using an open-view auto-refractor. The ametropic subjects wore spherical SCL for central refractive correction during the examination, while the emmetropic subjects underwent the examination with naked eyes. Accommodation did not alter the PR profiles in either emmetropic or myopic eyes.

On the contrary, Whatham et al. (2009) and Lundstrom et al. (2009) reported changes in PR profiles under different accommodative demands across the central 80° horizontal field in myopes. Whatham and co-workers (2009) assessed the changes in PR profiles with different accommodation stimuli on 20 young myopic subjects (SER = -2.17 ± 1.18 D) using an open-view auto-refractor. During the measurements, the subjects were corrected with spherical SCL and were asked to turn their head to fixate at primary gazes at the peripheral targets set at 30 cm, 40 cm and at distance to give accommodation stimuli of 3.00 D, 2.50 D and 0.00 D, respectively. On the other hand, Lundstrom and colleagues (2009) measured the off-axis

aberration of five emmetropes and five myopes, using a Hartmann-Shack wavefront sensor. Their subjects fixated with eye-turns at targets at 2 m and 40 cm away, giving accommodation stimuli of 0.50 D and 2.50 D, respectively. Whatham and colleagues (2009) found that RPR with distance viewing was more hyperopic than that with near viewing. They also found that the field curvature at distance viewing was significantly asymmetric while that at near was not. Lundstrom and colleagues (2009) did not find a difference in symmetry in RPR with accommodative stimuli, although they noted a more asymmetrical profile in myopes than in emmetropes. Their results showed a significantly more hyperopic RPR with distance viewing than with near beyond 20° temporal field only. RPR in emmetropic eyes did not seem to be affected by accommodative demands. In both studies, the differences between distance and near RPR profiles did not exceed 1.00 D and the differences were found to increase with eccentricities.

Although how RPR changes (i.e. increased, decreased or remains unchanged) with accommodation is yet to be confirmed, published reports have demonstrated that changes found were transient and were subject to variability. One suspected cause was the transient changes in choroidal thickness at near work (Woodman *et al.*, 2012; Ghosh *et al.*, 2014). In addition, these reports have not investigated the effect of corrective lenses on the changes observed.

2.4.5 Optical corrections

2.4.5.1 Spectacle correction

Spectacle correction with SVL was found to increase relative peripheral hyperopia in myopes in the horizontal field, although the

significance of the level of induced changes varied across studies (Calver *et al.*, 2007; Lin *et al.*, 2010; Backhouse *et al.*, 2012). Lin and colleagues (2010) measured the PR across the central 80° horizontal field on 17 children with low myopia (-3.00 D ≤ SER ≤ -0.75 D) and 11 with moderate myopia (-6.00 D ≤ SER ≤ -3.25 D) using an open-view auto-refractor. Measurements were made under cycloplegia with the subjects wearing spectacle corrections (spherical SVL) for central refractive errors with vertex distance of 12 mm. The subjects were asked to turn their head towards the peripheral target with eyes fixating at primary gaze during the peripheral measurements. They found that spectacles lens wear induced a larger increase in relative peripheral hyperopia in moderate myopes than in low myopes. In eyes with moderate myopia, the relative peripheral hyperopia was found to increase by 1.00 D and 1.25 D at temporal and nasal 40°, respectively, compared to 0.25D and 0.50 D, respectively, in low myopes (Figure 2.19). Their results suggested that the increase in relative peripheral hyperopia with spectacle lens wear depended on central refraction. However, results from another study by Backhouse and colleagues (2012) on high myopes did not seem to support the dependency on myopia levels. They measured the non-cycloplegic PR across the central 60° horizontal field on 10 high myopes (-5.00 D ≤ SER ≤ -8.00 D) with best sphere corrections using both spectacles and contact lenses. During the peripheral measurements, the subjects also turned their head and fixated the peripheral targets at primary gaze binocularly. Their results showed that the relative peripheral

hyperopia with spectacle lens wear was not significantly different from the uncorrected state across the horizontal field (Figure 2.20).

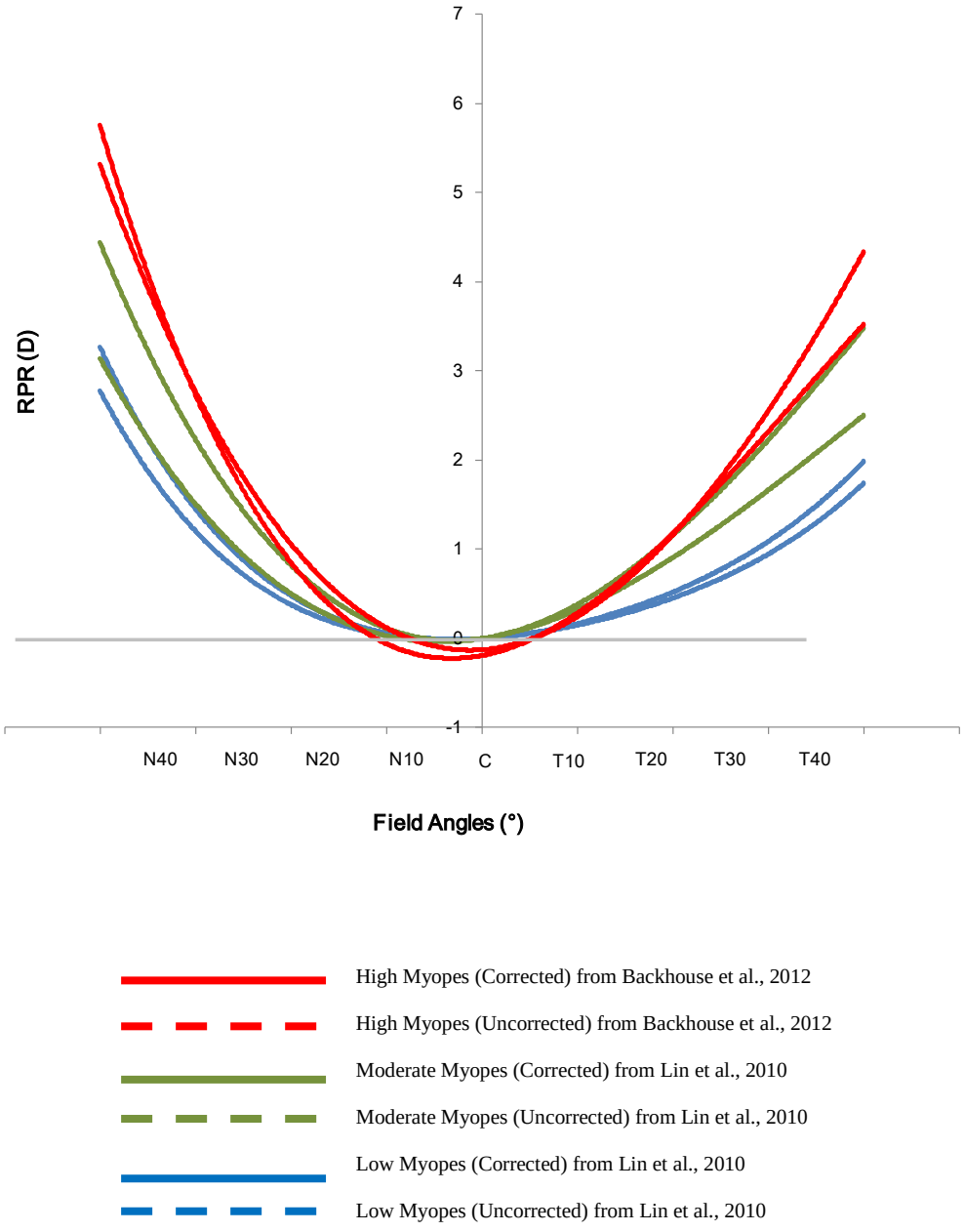


Figure 2.19. Change in relative peripheral refraction with and without spectacle correction [adapted from Lin et al (2010) and Backhouse et al (2012)].

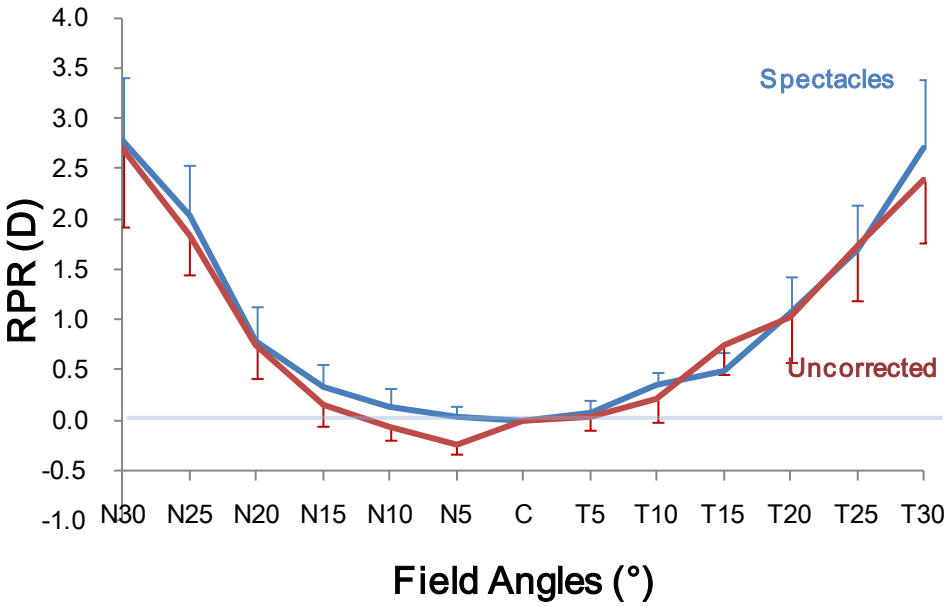


Figure 2.20. Relative peripheral refraction with and without spectacle corrections in high myopes [adapted from Backhouse et al (2012)]. N = nasal; T = temporal, C = central. Error bar = 1 SD.

However, in both studies, the pantoscopic tilt of spectacles was not controlled. Using ray-tracing method on eye models with central myopia of -3.00 D, -6.00 D and -9.00 D, it was shown that the larger the tilt on higher myopic corrections, the higher the induced relative peripheral hyperopia and variability also increased (Bakaraju *et al.*, 2008).

2.4.5.2 Contact lens correction

A. Soft contact lenses and RGP

The effect of SCL wear on PR have been reported by a number of studies (Davies and Mallen, 2009; Shen *et al.*, 2010; Shen and Thibos, 2011; Backhouse *et al.*, 2012; Kang *et al.*, 2012; Kwok *et al.*, 2012).

In 10 young myopic subjects, Davies and colleagues (2009) found no significant differences in RPR between eyes with and without SCL correction for distance. Shen et al (2010) found that both SCL and RGP could reduce relative peripheral hyperopia of the myopic eyes, with RGP being more effective in reducing the RPR, making the field of curvatures more consistent across the central 70° horizontal field. The average change in RPR by SCL was about 0.20 D at each eccentricity while that by RGP was almost doubled. Greater reduction with eccentricities could be observed using both lens types. However, Kang and colleagues (2012) found the opposite results. Seventeen low myopes (-2.00 D ≤ SER ≤ -0.75 D) and 17 moderate myopes (-6.00 D ≤ SER ≤ -2.25 D) were fitted, one at a time, with spherical SCL for full, 0.75 D-under-correction and 0.75 D over-correction on the right eye. The non-cycloplegic PR was measured with the lenses in situ using an open-view auto-refractor using the eye-turn method. Their results showed, unexpectedly and contradictory to previous findings, that full correction with SCL induced a significant increase in relative peripheral hyperopia compared to the naked eyes. However, the average increase in RPR with SCL was less than 0.50 D in both of Shen et al.'s (2010) and Kang et al.'s (2012)studies at any eccentricity and these might not be of any clinical significance.

Different results were reported in high myopes (Backhouse *et al.*, 2012; Kwok *et al.*, 2012). In a group of 10 high myopic (-12.50 D ≤ SER ≤ -6.50 D) young adults who were fitted with spherical disposable SCL, Kwok and colleagues (2012) measured their PR

with an open-view auto-refractor using the head turn method. They found that the relative peripheral hyperopia across the central 40° horizontal field was not only reduced by SCL wear, but was also converted into relative peripheral myopia at most peripheral angles. The amount of change was also found to increase with eccentricities. In a similar protocol, Backhouse and colleagues (2012) reported similar results with the central 60° horizontal field. They also compared RPR changes with SCL wear with those with spectacle lens wear. The latter was not found to be significantly different from naked eyes. SCL used in these studies were of ordinary spherical designs which were not expected to alter peripheral optics. However, since lens thickness increased towards the lens edge, some manufacturers may have slabbed off lens edge to reduce lens sensation and improve comfort. How the change in thickness from central to periphery of the lens affected the PR was not considered in these studies.

Contact lenses move with eye movement. During PR measurement with contact lenses in-situ, it is advisable to use the head turn method, so that the eye is at its primary gaze position to fixate at the PR target, causing the least lens lag.

B. Ortho-k and other contact lens designs

The effect on PR by ortho-k lens and other contact lens designs such as the radial refractive gradient and bifocal/multifocal SCL will be discussed in Section 2.5.

2.4.5.3 Post LASIK treatment

Laser in situ keratomileusis (LASIK) treatment on myopic eyes flattens the central cornea while steepens the mid-periphery (3 – 4 mm from center of the cornea) (Queirós *et al.*, 2010b). As a result of the changes in corneal optics, PR of the eye was also found to be altered. The post-LASIK RPR became markedly more myopic and the change was associated with a more reduction in myopia and an increase in against-the-rule astigmatism. The induced changes in RPR were also found to increase with eccentricities (Ma *et al.*, 2005; Queirós *et al.*, 2012).

2.5 Peripheral refraction and myopic control interventions

A number of myopic control interventions have been proposed with respect to their potential for inducing relative peripheral myopia which was believed to have the potential to arrest myopic progression (Tabernero *et al.*, 2009; Sankaridurg *et al.*, 2010; Sankaridurg *et al.*, 2011). Ortho-k has been shown to be effective for myopic control in children in different populations (Cho *et al.*, 2005; Walline *et al.*, 2009; Kakita *et al.*, 2011; Cho and Cheung, 2012; Santodomingo-Rubido *et al.*, 2012). The mechanism by which ortho-k effected myopic control was suggested to be PR-related (Charman *et al.*, 2006). This section reviews the changes in image shells induced by ortho-k lenses.

2.5.1 Orthokeratology

It has been shown that ortho-k lens wear is able to reshape the cornea and in turn convert relative peripheral hyperopia into relative myopia in eyes

undergoing ortho-k treatment for myopic reduction (Charman *et al.*, 2006; Queirós *et al.*, 2010a; Kang and Swarbrick, 2011). Charman and colleagues (2006) investigated ortho-k-induced profile changes in four young myopic adults (SER ranged from -2.00 D to -3.75 D). All subjects had similar mean SER and relative peripheral hyperopia across the horizontal peripheral field up to ±34°. At both 7- and 14-day post-ortho-k visits, the myopic reduction in all eyes was significant within the central ±10° (mean reduction in SER ranged from 1.5 D to 2.0 D), resulting in significant changes in RPR (mean change ~ 2.0 D at ±30°). All eyes attained relative peripheral myopia from 10° and beyond after ortho-k treatment.

In another large scale study, Queirós et al (2010a) measured the PR of 28 young adults (mean SER = -1.95 ± 1.27 D) before and at about five weeks after ortho-k treatment. They reported a mean myopic reduction of 1.50 D in central refraction which was accompanied by maximum changes of 2.50 D and 1.00 D in relative peripheral SER and J_0 component, respectively, at ±30° horizontal field (Figure 2.21). The mean post-treatment optical profile was symmetrical between the two hemi-fields, with increasing relative peripheral myopia towards the periphery. Similar changes were also found in children (Kang and Swarbrick, 2011). Kang and Swarbrick (2011) measured the horizontal PR of 16 children (aged between 11 and 16 years) who were fitted with ortho-k lenses on one eye and RGP lenses on the other eye for three months. The pre- and post-treatment SER reduction in the ortho-k-treated eyes was 1.83 ± 1.18 D for the central refraction, compared to 1.50 D and 2.50 D changes in RPR at 35° in the temporal and nasal field, respectively. The change in J_0 component was about 1.00 D to 1.50 D in the periphery (Figure 2.22).

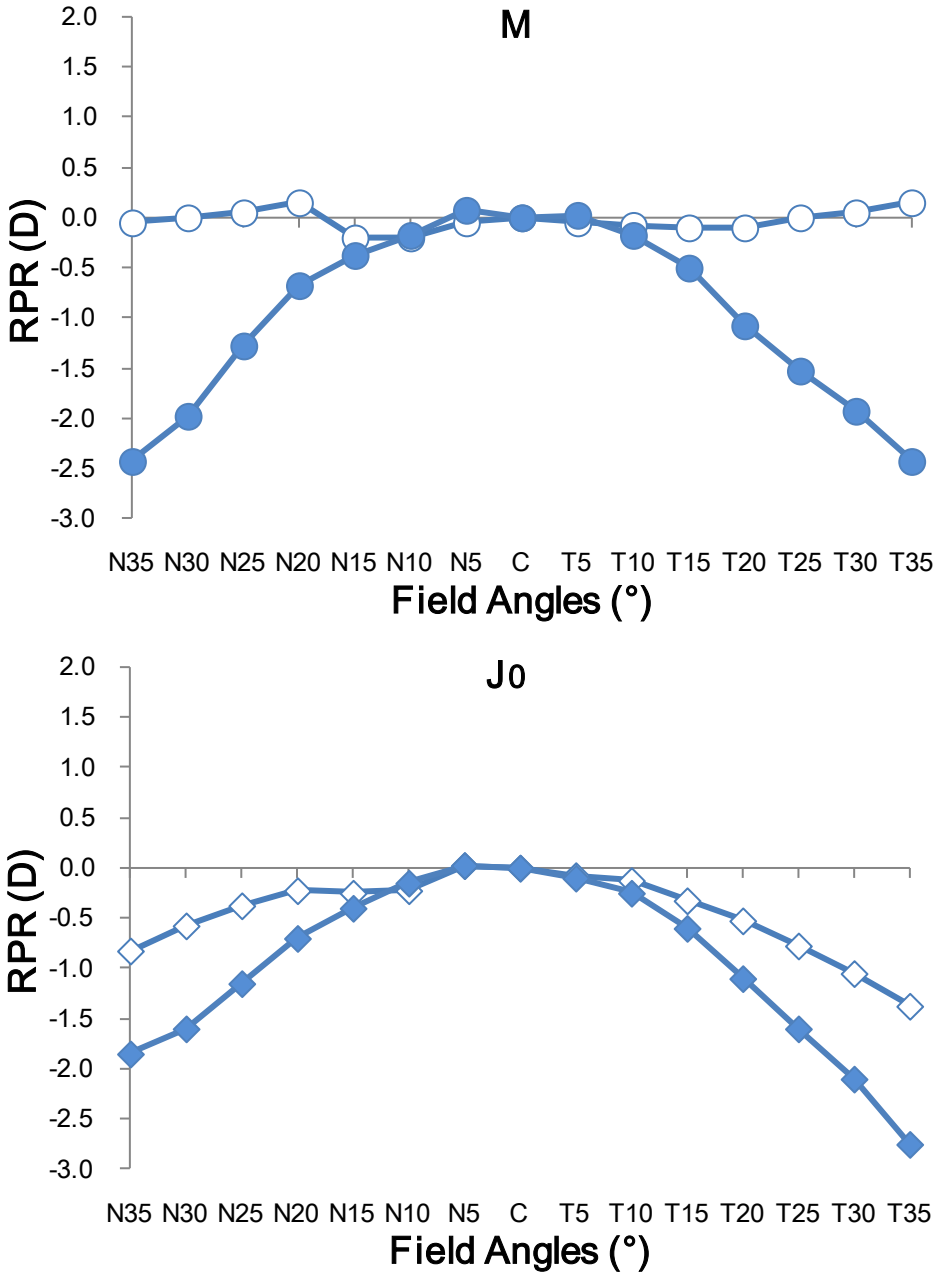


Figure 2.21. Relative peripheral refraction (RPR) (M and J_0) before and after orthokeratology in young adults (mean reduction in central refraction = -1.95 ± 1.27 D) [adapted from Queirós et al (2010a)]. N: nasal; T: temporal; C: central.

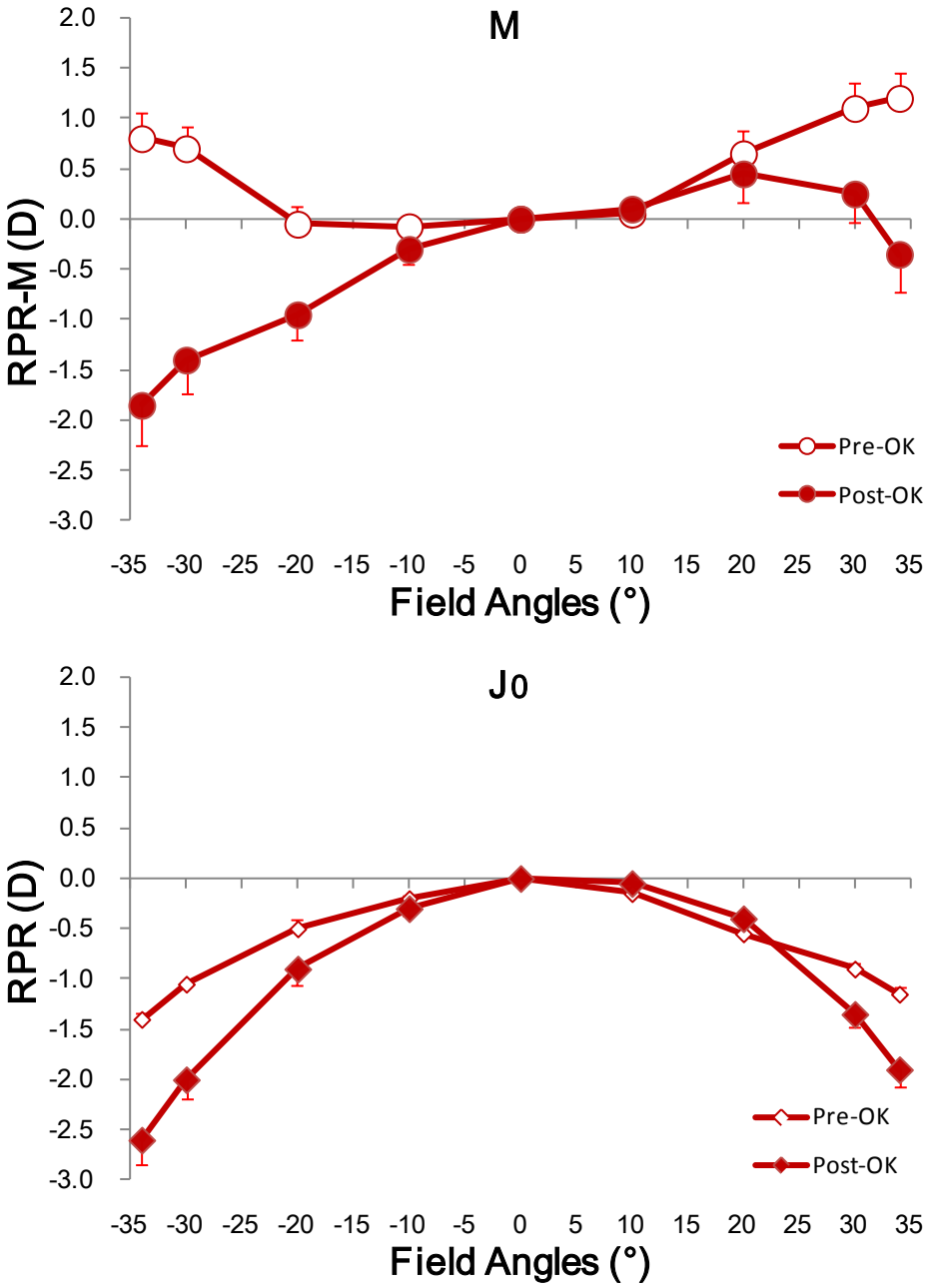


Figure 2.22. Relative peripheral refraction (M and J_0) in children (mean SER reduction in CR = 1.83 ± 1.18 D) [adapted from Kang and Swarbrick (2011)]. Negative field angles denote nasal field angles while positive angles denote temporal field angles. Error bar = 1 SD.

These studies have consistently shown that the myopic reduction happened mainly within ±10° in both hemi-fields and diminished towards the periphery. This has resulted in a significant reduction in relative peripheral hyperopia. The induced changes in optical profiles took place and stabilized within a few weeks of ortho-k lens wear. The peripheral optical profile of the myopic eyes eventually became relatively myopic after ortho-k treatment. The amount of the changes in RPR at 30° - 35° in both nasal and temporal fields were inconsistent with the central myopic reduction, even though had a high correlation with the baseline SER (Queirós *et al.*, 2010a). The mean changes in relative peripheral J_0 reported by these studies ranged from -0.50 D to -1.50 D in the periphery, showing that the change in PR was partially contributed by an increase in peripheral against-the-rule astigmatism.

The subjects in the above mentioned studies were low to moderate myopes (less than 4.00 D) only. Manufacturers of certain ortho-k lenses claimed that certain designs can reduce even higher amount of myopia [such as the Vipok lenses (Bloom, 2010)]. It is, therefore, important to know if the induced changes in optical profiles will be different in higher myopic eyes undergoing ortho-k treatment and in cases where partial correction is used on high myopes. This would give further insight on ortho-k for high myopes for myopic control. Correlation between the changes in central refraction and PR in both low/moderate and high myopes should also be investigated. The post-ortho-k profiles were not consistent among different studies in terms of their symmetry (Queirós *et al.*, 2010a; Kang and Swarbrick, 2011). Although it was postulated that lens centration would be a crucial

contributing factor (Queirós *et al.*, 2010a), further investigation with detailed analysis of the topographical profiles is needed. A recent study reported that the temporal cornea flattened more than the nasal cornea within the central circular zone (i.e. 5 mm diameter of the central cornea), while the former steepened more than the latter in the para-central annular zone (the zone ranging between 5 and 8 mm diameter) (Maseedupally *et al.*, 2013). These non-uniform corneal changes have caused a subsequence asymmetrical PR profile in the ortho-k-treated eyes.

2.5.2 Novel and bifocal/multifocal contact lens designs

Multifocal contact lenses and simultaneous design contact lenses have been investigated for their efficacy in myopic control (Tse *et al.*, 2007; Lopes-Ferreira *et al.*, 2011; Sankaridurg *et al.*, 2011; Benavente-Perez *et al.*, 2012; Rosen *et al.*, 2012). Their rationale as proposed for myopic control was linked to defocus, referring to the off-axial rays in particular.

Results from Lopes-Ferreira et al.'s (2011) and Rosen et al.'s (2012) studies have shown that multifocal SCL with additions less than 2.00 D were unable to induce significant relative peripheral myopia, on young adults who were near emmetropes or low myopes. Twenty eight young near emmetropes were fitted with the distance-centre design of the Proclear Multifocal (Cooper Vision) SCL with plano distance power and additions from +1.00 D to +4.00 D (in 1.00 D steps) in an investigation by Lopes-Ferreira and colleagues (2011). They found that the RPR with lower additions (+1.00 D and +2.00D) were not different from those when no lenses were worn, while the relative myopia induced by the higher additions (+3.00 D and +4.00D) became more significant, particularly in the temporal periphery. Central

refraction with the higher addition lenses became significantly more myopic, indicating a potential drop in visual acuity, which was however not discussed in the study. Moreover, this study was limited to emmetropic eyes. The lens performance, in terms of both visual acuity and the RPR induced, is however unable to be predicted from their study.

Rosen and colleagues (2012) investigated both centre-near and centre-distance designs of the Proclear Multifocal (Cooper Vision) with low (+1.00 D) and high (+2.00D) additions in three near emmetropes and one low myope, using a fast-scanning Hartmann-Shack aberrometer. Their findings have augmented Lopes-Ferreira et al.'s study (2011) to a certain extent. The tested contact lenses were to correct the central refraction in each subject. Within 15° in the nasal and 25° in the temporal fields, RPR changes by lens wear were not significantly different from those without any lens wear. The relative peripheral myopia induced by centre-distance design was greater in magnitude than by centre-near designs, and was greater with higher additions than with lower additions. Although the relative peripheral myopia induced was relatively more significant in the low myopic subject on the nasal peripheral field, the changes was still considered too small. Moreover, the subject number was too small in this study. A further study with larger subject numbers and different addition powers on myopic eyes is warranted.

The rationale of the simultaneous design is to concurrently impose focal images and myopic defocused images on the retina through a series of concentric zones with alternating refractive powers. Animal studies with chicks have shown that a simultaneous design with +10.00 D/-10.00 D dual powers in 50:50 for the negative-to-positive defocus annuli have

successfully modulated the refractive development of the eye and significantly reduced the inter-ocular difference in refraction after six days of lens wear (Tse *et al.*, 2007).

Compared to the final refraction of +9.70 D and -11.10 D in the eyes wearing +10.00 D and -10.00 D lenses, respectively, the eyes with the +10.00 D/-10.00 D dual power lens were found to be +4.70 D with retinoscopy at the end of the lens wearing period. An increase in the proportion of the negative defocus annuli demonstrated an increasing trend of developing myopia in the avian eyes. It was also demonstrated that the avian eyes, which had previously developed lens-induced myopia with -10.00 D lens wear for six days, were able to recover by switching to wear the +10.00 D/-10.00 D dual power lens for another six days. This design forms the basis of a clinical design, the DISC lens, which has been being evaluated for its myopic control efficacy in Hong Kong (HKPU, 2011).

In monkeys, Benavente-Perez and colleagues (2012) have recently demonstrated that the use of a +5.00 D/-5.00 D dual power design with 50:50 negative-to-positive power was able to retard myopic progression in monkeys. The animals wore the test lens on the right eye and a plano lens on the fellow eye for 12 weeks. The experimental eyes tended to be more hyperopic and smaller in size than the control eyes at the end of the lens wearing period. Compared to historical control animals wearing either +5.00 D or -5.00 D lenses on the experimental eye which became similar in refraction and size and became more myopic and bigger in size respectively, the dual power lens was thought to be effective in modulating the refractive development in monkeys.

Anstice and Philips (2011) investigated another dual focus contact lens

design on 40 children between 11 and 14 years. The lens corrected the refractive errors with the correction zones and provided a simultaneous defocus of 2.00 D in the treatment zones. The correction and the treatment zones were arranged in concentric annuli and the zone diameters were chosen in accordance with the pupil sizes in different lighting conditions. The subjects were divided into two groups with one group wearing the dual focus lens on the dominant eye and the single vision contact lens on the non-dominant eye in the first 10-month study period. The lenses were then swapped in the second 10-month study period. In the other group, the subjects wore the single vision contact lens on their dominant eyes and the dual-focus lens on the non-dominant eyes in the first study period then swapped in the second period. Although myopic progression during the second 10-month study period was not consistent in both groups, the relative increase in myopia in the eye wearing the dual focus lens (-0.44± 0.33 D) was significantly less than that in the eye wearing single vision contact lenses (-0.69 ± 0.38 D) in the first 10-month study period. The myopic control effect was however, not clinically significant. This clinically insignificant effect was likely a result of relatively slower myopic progression in older children. Moreover, the treatment-to-correction ratio might also have some influence on the myopic control efficacy of the dual power design.

The impositions of negative defocus together with focused images on the retina would, however, be affected by pupil size. If the pupil size was smaller than expected, the weight of the negative defocus will be less (Benavente-Perez *et al.*, 2012). This would also cause a different performance between distance and near viewing activities. Although this

problem may be minimized by incorporating more annuli with a thinner width of each annulus, image quality will be degraded by too many multifocal zones.

Although the treatment zone optics in CL is able to cause myopic defocus in the peripheral field, it is difficult to measure the profile of the images shells in eyes wearing these lenses (Benavente-Perez *et al.*, 2012). The two major limitations were the centration of the CL during peripheral measurement and the measurement area over which auto-refraction was taken. The head-turn method should be employed for PR measurement with CL as this would reduce lens decentration with fixation at primary gaze. The commonly used open-view auto-refractors measured refraction over an area of about 2.3 – 2.9 mm in diameter. This would cover more than one optical zone of the multi-zone CL designs and hence reduce the accuracy of PR measurement. Therefore, little is known about how much peripheral myopia was imposed on the peripheral retina and how the retinal images were affected by such lens designs.

Sankaridurg and colleagues (2011) evaluated a radial refractive gradient contact lens design on 60 Chinese children aged 7 to 14 years. The test lens had a central optical zone which was used to correct central refractive errors, and a peripheral treatment zone in which the power became progressively more positive than the central zone, reaching a maximum of +2.00 D more positive at the edge of the treatment zone (Figure 2.23).

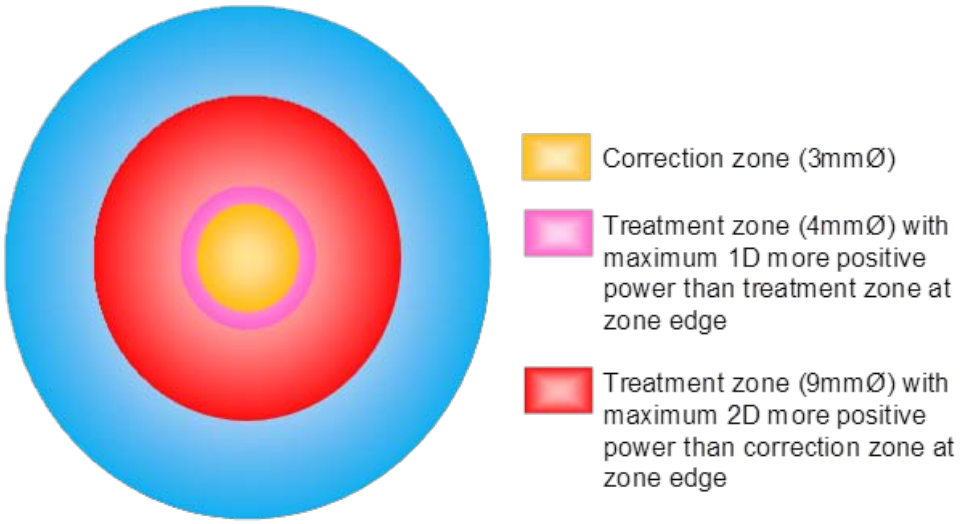


Figure 2.23. Schematics of the radial refractive gradient lens [adapted from Sankaridurg et al (2011)].

The treatment group had relative hyperopia in both nasal and temporal fields without contact lens wear. The RRG lens was able to reduce the relative hyperopia by as much as +2.00 D up to 40° in the nasal field, and to convert it into relative myopia within 30°. On the contrary, spectacle lens wear enhanced the relative hyperopia in the control group. The changes on the temporal field were not significant in either group.

The reason for the changes being localized to the nasal field was not understood. A potential cause might be due to lens decentration. Assuming this is the case, should the lens be more centered the reduction in relative peripheral hyperopia might not have been as significant as demonstrated.

At the end of 12-month study period, the RRG lens-wearing subjects showed a significantly slower axial elongation (0.27 mm), compared to an axial elongation of 0.40 mm in the spectacle-wearing subjects. Although this lens was able to cause a significant reduction in relative peripheral

hyperopia, the changes being localized in the nasal field and leaving the overall relative peripheral hyperopia at most of the peripheral field. Only the nasal 10° to 30° field showed a small amount of relative peripheral myopia (< 0.50 D) after lens wear. Further evidence would be needed to support the efficacy of these lenses in myopic control.

2.5.3 Spectacle lens novel designs

Three types of novel design spectacle lenses were evaluated by Sankaridurg and colleagues (2010) in a randomized control study with 210 Chinese children aged between six and 16 years. The Type I lens was a rotationally symmetrical design and had a 20 mm clear correction zone surrounded by a progressively ramped zone with relative positive powers up to +1.00 D at the edge of the treatment zone which was 25mm from the optical centre of the correction zone. The Type II lens, another rotationally symmetrical design, had a 14mm correction zone, which was surrounded by a ramped zone with maximum +2.00 D more positive power at 25 mm from correction zone centre. The Type III lens was an asymmetrical design whose correction zone extended to 10mm away from the centre along either side of the horizontal meridian and the inferior meridian. The treatment zone was optimized for minimal astigmatism along the horizontal meridian, attaining 1.90 D more positive power at 25mm from the lens centre. Only the Type II lens was shown to reduce the baseline relative hyperopia in the periphery. However, there was no significant treatment effect in arresting the myopic progression in this group. It was, however, found that in a sub-group analysis on the 6-12 year-old children with parental myopia and who wore Type III lenses showed least myopic progression over the 12 months period.

This observation was not explained by the change in RPR by the Type III lens in the sub-group.

2.5.4 Comparison of different interventions

It is yet to be decided how comparable each of the studied designs is to the others in terms of their efficacy in arresting myopic progression. As it is thought that relative peripheral myopia may prevent myopia from developing or progressing, the way in which and the extent by which different optical interventions would change RPR in an eye is thought to be related to its efficacy. Among them, ortho-k lens and the multifocal SCL with centre distance design and high addition powers (+3.00 D and +4.00 D) were more able to reduce a larger amount of relative peripheral hyperopia in myopic eyes. Ortho-k may be the only design which could convert relative hyperopia into relative myopia. Although Lopes-Ferrira and colleagues (2011) showed that multifocal SCL with higher addition powers had increased the relative peripheral myopia significantly in the near-emmetropic eyes, it is yet to be demonstrated that how the lenses would change the profiles in myopic eyes which tend to have relative hyperopia in the periphery. A recent report has compared the effect of ortho-k lenses and multifocal SCL in changing optical profiles in myopic eyes (Ticak and Walline, 2012). Ticak and Walline (2012) found that the multifocal design resulted in a more myopic central refraction than ortho-k lens did. The eye wearing the multifocal SCL remained relatively hyperopic while the eye undergoing ortho-k treatment became relatively myopic in all meridians. However, they used lenses with +2.00 D additions only, which have been found to cause smaller and yet significant changes in RPR

(Lopes-Ferreira *et al.*, 2011; Rosen *et al.*, 2012). In addition, some of the novel designs, such as the RRG lenses, caused asymmetrical changes between the hemi-fields only, while in ortho-k-treated eyes, relative peripheral myopia, though asymmetric, was found on both fields. If relative peripheral myopia is a crucial condition in preventing myopic progression as hypothesized, ortho-k may be the best candidate.

Summary

Primate studies have demonstrated that eye growth could be regulated by visual signals received from retinal areas other than the foveal region. Imposed relative peripheral hyperopic defocus was found to cause axial elongation as well as localized elongation over the semi-field receiving the signals in animals. Results from animal studies indicate that relative peripheral hyperopia is a potential stimulus for myopic development. The PR hypothesis on myopic development has encouraged numerous PR investigations in human. Human studies have shown that PR varies between ametropias. Myopic eyes tend to have relative peripheral hyperopia while hyperopic and emmetropic eyes tend to have relative peripheral myopia. Some studies have also suggested that relative peripheral myopia in the near-emmetropic eyes started to diminished and relative peripheral hyperopia started to appear before these eyes became myopic. These have led to further thoughts which suggest that relative peripheral hyperopia is associated with myopic progression. This has made researchers become more excited about the PR hypothesis in human myopia. However, the role of RPR in myopia development in human eyes is still unclear. Results from a number of longitudinal studies were even unable to show the association

between RPR and myopic development in children. Of the various factors being evaluated, ametropias and optical corrections used for correcting refractive errors are those which appear to alter PR significantly. Other factors, such as age, ethnicity and accommodation were either to have minimal effect or yet to show conclusive results from published reports. Base on the PR hypothesis, certain novel lens designs, including spectacle and contact lenses, have been proposed for myopic control. Their effectiveness in arresting myopia is, however, yet to be confirmed and would need further investigation and supports from larger scale clinical trials. Ortho-k, in which myopic reduction is brought about by the reverse geometry lens design, is confirmed to be an effective intervention for myopic control in children. It has been shown that ortho-k can largely reduce relative peripheral hyperopia and even convert it into relative peripheral myopia in the myopic eyes. Based on this observation, it is postulated that ortho-k effect myopic control through the alteration of RPR. However, there is yet evidence to prove the association between RPR and the effectiveness of myopic control by ortho-k.

Apart from PR, PEL was another parameter under investigation in the understanding of eye growth and eye shape changes during growth. We have also discussed briefly on ocular shape with respect to PEL. Moreover, common methods used for measuring PR and PEL were reviewed in this chapter.

Chapter Three

Orthokeratology

3.1 Overview of orthokeratology and current status

Myopic orthokeratology (ortho-k) is a programmed therapy which aims to temporarily reduce myopia through a series of reverse geometry design contact lenses. It is an alternative to refractive correction for low to moderate myopes. Its transient nature has allowed reversibility to wearers in case of unsatisfactory responses. The corneal reshaping therapy is also able to arrest myopia progression.

3.1.1 Popularity of orthokeratology lens wear

With the advancement on lens material and the improvement in the reverse-geometry design, ortho-k is now used as a night therapy and it is capable of reducing myopia of about 5 D within a few weeks(Swarbrick, 2006). This has also resulted in an increase in the popularity of ortho-k treatment. The use of ortho-k lenses as a myopic treatment is, however, not the sole reason for its popularity in areas where a high prevalence of myopia has been reported. The effectiveness in retarding myopic progression in children undergoing ortho-k treatment has become a major reason for its popularity among the young populations. With the many promising treatment effects found from a number of clinical trials (Cho *et al.*, 2005; Walline *et al.*, 2009; Kakita *et al.*, 2011; Cho and Cheung, 2012; Santodomingo-Rubido *et al.*, 2012), enrollment into ortho-k treatment for myopic control has been increasingly popular among children in Asian countries where school myopia is a prominent concern (Efron *et al.*, 2011).

3.1.2 Fitting philosophies

The principle of ortho-k lens fitting is based on the lens sag fitting philosophy. In ortho-k fitting, the goal is to look for optimal lens sag which creates a post-lens tear layer with varying thickness over different corneal areas. This tear lens should produce an optimal compressive force which primarily flattens the central cornea without compromising the corneal physiology (Figure 3.1.).

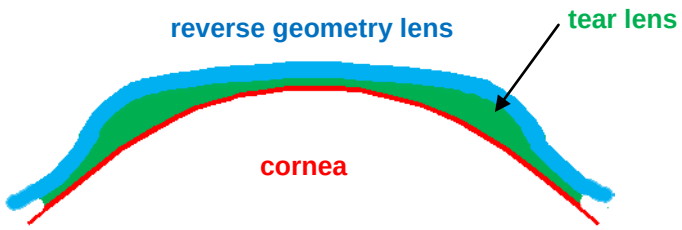


Figure 3.1. The relationship between an ortho-k lens and the cornea

Today, there are numerous designs owing their own proprietary. Regardless of the proprietary protection different designs may have, the reverse geometry lenses are generally composed of three to five curves (or zones in cases where multiple curves are employed to generate the profile of individual zones). A reverse geometry lens should have a base curve, a reverse curve, an alignment curve and a peripheral curve. The base curve is responsible for the corneal flattening. The reverse curve is responsible for generating the gradient needed to build up the tear film force for the central flattening and to allow space for the corneal tissue during the mid-peripheral steepening of the cornea. The alignment curve is responsible for the centration of the treatment zone. The peripheral curve is responsible for proper edge lift which facilitates tear exchange (Mountford *et al.*, 2004).

Nowadays, there are a number of principles for ortho-k fitting, and different ortho-k lens brand may employ different strategies in fitting.

3.2 Orthokeratology-induced corneal changes

The changes brought about by ortho-k to the cornea are marked and prompt. Corneal flattening, though transient, can be induced shortly after 10 minutes of lens wear (Sridharan and Swarbrick, 2003). A single overnight wear can already cause significant changes in the corneal curvatures and total thickness (Swarbrick *et al.*, 1998; Zhong *et al.*, 2009). This section reviews the short- and long-term corneal changes induced by myopic ortho-k.

3.2.1 Changes in corneal profiles

Reverse-geometry lens wear causes a central flattening together with a mid-peripheral steepening to the cornea (Lui and Edwards, 2000; Mountford and Pesudovs, 2002; Queirós *et al.*, 2010b). The majority of myopic reduction is explained by the central flattening of the cornea (Mountford and Pesudovs, 2002; Chan *et al.*, 2010). In a retrospective study which retrieve data on the topographical changes and subjective refractive errors after two weeks of ortho-k lens wear in 128 children , Chan and colleagues (2010) showed that the changes in apical corneal power was responsible for about 90% of the total myopic reduction.

A concurrent shape change can be found with lens wear. The shape of a cornea is referred to as an ellipse and can be quantified by shape factor (P), eccentricity (e) and asphericity (Q). The relationship between e, P and Q are as follows (Figure 3.2):

$$e = \sqrt{1 - \frac{b^2}{a^2}}$$

$$P = \frac{b^2}{a^2}$$

$$Q = P - 1$$

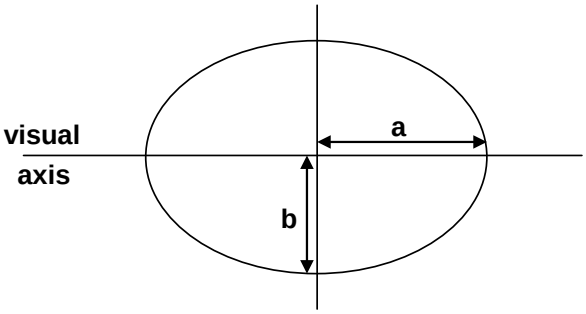


Figure 3.2. The cornea is treated as an elliptical surface with semi-major axis a, and semi-minor (a: semi-major axis; b: semi-minor axis)

Reduction in eccentricity values were reported in a number of studies (Coon, 1984; Nichols *et al.*, 2000; Mountford and Pesudovs, 2002; Stillitano *et al.*, 2007). The changes of eccentricity towards a zero value indicated sphericalization of the cornea by ortho-k. However, the post-treatment eccentricity measured by topographers might not be as correctly depicting the post-treatment corneal shape as it did before treatment. It was because the computation of quantifiers of corneal shape was based on the assumption that the cornea ascertained a conical shape. After ortho-k lens wear, the corneal surface was, nevertheless, abruptly changed, and the changes varied across the corneal regions. Within the treatment zone area, the central area was flattened more than the para-central area was. The central cornea was sphericalized by ortho-k treatment. In the para-central

annular zone, the anterior cornea was steepened by ortho-k treatment. Following the para-central annular zone, there was the mid-peripheral annual zone with corneal flattening. The difference in corneal shape changes in different zones had made the estimation of the corneal eccentricity after ortho-k treatment difficult if the topographical data was interpreted directly. Reconstruction of an ellipse curve using the topographical data has been used in the determination of post-ortho-k treatment corneal asphericity (Yoon and Swarbrick, 2013).

While the ortho-k-induced changes in the anterior cornea have been well-documented, opinion on the changes in the posterior cornea is not yet conclusive. Owens (2004) reported a transient flattening of the posterior cornea both centrally and mid-peripherally at a point 2.5 mm from the central cornea only one week after lens wear. The changes did not persist through the four weeks of lens wear period. Unlike the posterior cornea, the anterior cornea demonstrated a persistent central and mid-peripheral flattening in the same group of subjects. Chen and co-workers (2010a) found a significant, yet transient flattening of the posterior corneal curvature on the morning after the first overnight wear, which was not found at other visits throughout the 6-month study period. They further evaluated the day changes in the corneal curvatures with time after lens removal and found significant steeping in both of the anterior and posterior cornea immediately after lens removal only. No significant steepening was found at other times of the day. The diurnal changes in curvatures reported in their study, being consistent with those found in non-ortho-k lens wearers (Read and Collins, 2009) , suggested that the transient changes at the first morning visit might be resulted from the residual corneal edema which had caused significant

steepening in both anterior and posterior cornea soon after lens removal. Recent findings showing that there were no significant changes in posterior corneal elevation after ortho-k in 20 young adults with low to moderate myopia (Queirós *et al.*, 2011) has further supported that the posterior cornea is rarely altered by ortho-k treatment. By calculating the posterior ellipse curve using topographical data, Yoon and Swarbrick (2013) found no short-term changes in posterior corneal radii within 14 days of ortho-k lens wear, but a transient increase in Q which recover after 7 days of ortho-k lens wear. It was believed to be resulted from acumination of errors during the calculation of the ellipse curves and some suspected subtle peripheral corneal changes. Tsukiyama and colleagues (2008) investigated the long-term effect of ortho-k lens wear on the posterior cornea over 12 months and did not find any significant changes in posterior corneal radii at any week after ortho-k treatment.

3.2.2 Thickness of different corneal layers

Central cornea thinning and mid-peripheral thickening were observed in ortho-k treated corneas (Swarbrick *et al.*, 1998; Alharbi and Swarbrick, 2003; Zhong *et al.*, 2009; Nieto-Bona *et al.*, 2011b). In 18 young adults undertaking ortho-k, Alharbi and Swarbrick (2003) measured their total corneal thickness and stromal thickness with an optical pachometer then computed the epithelial thickness by subtraction. They concluded that that central corneal thinning had an epithelial origin while mid-peripheral thickening had a stromal origin. The induced changes and their origins were persistent over a 90-day period.

Zhong and colleagues (2009) attempted to compare the short- and long-term

effect of ortho-k, by comparing the corneal biometry and morphology between a group of adults who had worn ortho-k lens a single over-night and another group of adults who had worn ortho-k lens for five years. With corneal topography and confocal microscopy, they have successfully shown a short-term effect of central corneal thinning with mid-peripheral thickening. However, the long term effect did not review a central thinning though the mid-peripheral thickening was found. Since their pre-lens data of the short-term wearer was used as the baseline for both group, the changes in corneal biometry derived for the long-term group was not representative and thus the reported long-term changes in both central and mid-peripheral cornea might not be as convincing as those reported by others (Nieto-Bona *et al.*, 2011a). With confocal microscopy, Zhong and colleagues (2009), however, reported an increase in stromal thickness in the central cornea in the morning after the first overnight wear in the short-term group.

Nieto-Bona and colleagues (2011a) also observed a stromal thickening in the central cornea in eyes which had underwent ortho-k treatment for one year, using Visante OCT (Carl Zeiss, Germany) and confocal microscopy. They also observed significant reduction in both Bowman's membrane and sub-basal nerve plexus thickness. The discrepancies so observed among studies were likely resulted from the different measurement instruments used. Alharbi and Swarbrick (2003) used optical pachometer, Zhong and colleagues (2009) used confocal microscopy while Nieto-Bona and colleagues (2011a)used both confocal microscopy. These instruments measured thickness with different principles and the interpretation of thickness might be subject to bias of the examiner to different extent with different instrument and protocols. Neito-Bona and co-workers (2011a) had

already demonstrated the measurement difference between confocal microscopy and anterior OCT. Further study with standardized measurement methods, time of the day for data collection, and protocol on the measurement visits, and preferably together with a longitudinal study is warranted.

3.2.3 Cellular changes

Previously, little was known about the cellular changes to human cornea brought about by ortho-k lens wear except limited information from animal studies (Matsubara *et al.*, 2004; Cheah *et al.*, 2008; Choo *et al.*, 2008; Ding *et al.*, 2012). Confocal microscopic analysis of the post-ortho-k cornea has provided new insight on the ortho-k-induced corneal changes and on the safety of ortho-k treatment.

In the epithelial layer, eyes undergoing ortho-k treatment for one month or more were found to have significant reduction in basal cell density (Zhong *et al.*, 2009; Nieto-Bona *et al.*, 2011b; Nieto-Bona *et al.*, 2011a), and increased in height and width in superficial wing cells (Nieto-Bona *et al.*, 2011b; Nieto-Bona *et al.*, 2011a).

Stromal cell densities were not affected by ortho-k lens wear in the both short- and long-term responses, while increase in polymegethism in the endothelium and increase in the number of activated keratocytes in the stroma were reported (Nieto-Bona *et al.*, 2011a; Nieto-Bona *et al.*, 2011b). Zhong and colleagues (2009) however, reported a decrease in anterior and posterior stromal cell density for the short-term response. They also noticed smaller cell densities in stromal layers in subjects who had undertaken ortho-k for five years, compared to the control subjects without ortho-k

treatment.

Consistent findings from these reports indicated that the short-term changes in the endothelial cell density and hexagonicity, and the long-term change in cell density alone were insignificant. However, the changes in the long-term in terms of polymegethism in the endothelial cells were inconclusive (Hiraoka *et al.*, 2004; Zhong *et al.*, 2009; Nieto-Bona *et al.*, 2011b; Nieto-Bona *et al.*, 2011a)

3.3 Efficacy of orthokeratology in myopic control

There are a number of clinical trials which attempted to determine the myopic control effect of ortho-k in children. In this section, five major studies are reviewed.

1. The Longitudinal Orthokeratology Research in Children (LORIC)

Cho and colleagues (2005) recruited 43 children (7 – 12 years) with low to moderate myopia (-0.25 D to -4.50 D) and refractive astigmatism not greater than -2.00 D for ortho-k treatment for a two-year study period. All subjects were fitted with four to five-zone reverse geometry lenses made of Boston XO or HDS 100 material for myopic reduction. They were asked to attend the research data collection visits in the Optometry Clinic of the Hong Kong Polytechnic University before treatment (baseline) and every six months after commencement of the treatment for two years. The major outcome variables, including subjective refraction, AL and VCD, were measured under cycloplegia every six months. Ultrasound measurements were used to determine AL and VCD. In this study, historical control subjects were selected from another study (Edwards *et al.*, 2002) in which the age-,

gender- and baseline SER-matched subjects were corrected with single vision spectacle lenses. Of the 35 subjects (9.6 ± 1.5 years, SER = -2.27 ± 1.09 D, AL = 24.50 ± 0.71 mm) who finished the 24-month study period, the 24-month axial elongation in the ortho-k-treated subjects was 0.29 ± 0.27 mm, compared to 0.54 ± 0.27 mm for the 35 historical controls (9.6 ± 0.69 years, SER = -2.55 ± 0.98 D, AL = 24.64 ± 0.58). There were no significant between-group differences in baseline data and the retardation in myopic progression by ortho-k (myopic progression was 46% in ortho-k subjects than in controls) was significant.

This study suffered from a number of limitations. Firstly, the subjects were recruited from private optometry clinic and the lens fitting followed their practitioners' routine. The fitting protocol in lens selection, modification and retainer lens decision was not standardized, although the private practitioners were required to have achieved a certain standard of experience in ortho-k prescription. Secondly, the treatment groups were self-selected, and therefore subject randomization was not allowed. This reduced the power of the study. Thirdly, the measurement for the major outcomes, AL and VCD, was performed by ultrasound technique (Sonomed A-5500, Sonomed Inc., New York, USA) by taking five repeated readings with less than 0.1 mm as standard deviation for each eye. Results from the study have suffered from large measurement variability and would require both of the practitioner and the subject being stable.

2. The Corneal Reshaping and Yearly Observation of Nearsightedness (CRAYON) Pilot Study

Walline and colleagues (2009) recruited 40 subjects (8 – 11 years) with

myopia between -0.50 D and -4.00 D with refractive astigmatism of not more than -1.00 D to participate into a 2-year longitudinal study. They were fitted with CRT lenses (Paragon Vision Sciences, Mesa, Arizona) made of HDS 100 material. The fitting protocol and procedures followed the manufacturer's recommendation. Major outcome variable, AL, was measured by A-scan ultrasound annually. Historical controls were also employed in this study. They were SCL wearers from another study. Of the 28 subjects (10.5 ± 1.1 years, baseline AL = 24.30 ± 0.73 mm) who completed the 2-year study, AL increased by 0.25 ± 0.19 mm in 24 months, compared an axial elongation of 0.57 ± 0.20 mm in the controls (10.5 ± 1.0 years, baseline AL = 24.20 ± 0.63 mm). The ortho-k-treated eyes were found to have 0.22 mm less axial elongation (i.e. 39% reduction) over two years than the control subjects has. The study suffered from the same limitations as the LORIC study with the use of historical controls and ultrasound techniques in AL and VCD measurements. Although previous studies (Grosvenor, 1975; Harris *et al.*, 1975; Perrigin *et al.*, 1990; Dumbleton *et al.*, 1999; Horner *et al.*, 1999; Jalbert *et al.*, 2004) have different opinions on that SCL might caused myopic creep which might contraindicate SCL as a control treatment, it was shown in another randomized control that it was unlikely to cause myopic creep (Walline *et al.*, 2008).

3. Study on myopic control with orthokeratology contact lenses in Spain (MCOS)

Santodomingo-Rubido and colleagues (2012) conducted a non-randomized controlled study to determine the myopic control efficacy of ortho-k lens

wear against SVL wear in spectacle group for 24 months. There were 31 (9.6 ± 1.6 years) and 30 (9.9 ± 1.9 years) subjects recruited for the ortho-k and the control, respectively. The allocation of grouping was volunteered by the parents of the subjects. All ortho-k subjects were fitted with Menicon Z Night contact lenses in Menicon Z material, by computerized fitting using the Easy Fit software provided by the manufacturer. AL was measured with the IOLMaster (Carl Zeiss, Germany) under cycloplegia every six-monthly. 29 ortho-k subjects (Sphere = -2.20 ± 1.09 D, Cylinder = -0.29 ± 0.29 D, AL = 24.49 ± 0.78 mm) and 24 (Sphere = -2.35 ± 1.17 D, Cylinder = -0.35 ± 0.34 D, AL = 24.26 ± 1.01 mm) control subjects completed the study. The 24-month axial elongation in ortho-k subjects was 0.47 ± 0.21 mm while in controls was 0.69 ± 0.27 mm. Ortho-k was found to have significantly reduced myopic progression by 32%. The major limitation of this study was the non-randomized grouping strategy and that parents were allowed to opt for either treatment. Parents of children who had history of rapid progression might have higher tendency to choose to enroll their children into the treatment group than into the control group.

4. Japan study on the influence of orthokeratology on axial elongation in childhood myopia

Kakita and colleagues (2011) recruited 45 ortho-k subjects and 60 control subjects in a 2-year controlled study. 42 ortho-k subjects (12.0 ± 2.6 years, SER = -2.55 ± 1.82 D, AL = 24.66 ± 1.11 mm) and 50 control subjects (11.9 ± 2.1 years, SER = -2.59 ± 1.66 D, AL = 24.79 ± 0.80 mm) completed the study. The ortho-k subjects were fitted with Emerald lenses (Euclid Systems Corp., Herndon VA) in Boston XO materials while the controls were

corrected with SVL in spectacles. AL was monitored every 3-monthly in the treatment group and every 6-monthly in the control group, using the IOLMaster (Carl Zeiss Meditec, Germany) by the same examiner who was masked for the treatment method of each subject. At the end of the 2-year period, the increase in AL was 0.39 ± 0.27 mm and 0.61 ± 0.24 mm in the ortho-k and the control groups, respectively. The myopic progression was significantly reduced by 36% with ortho-k lens wear. The major limitation of this study was the large range of baseline SER and relatively older subject age. In addition, there was no disclosure of the grouping strategy.

5. The Retardation of Myopia in Orthokeratology (ROMIO) Study

Cho and Cheung (2012) conducted a 2-year randomized, single-masked controlled study to compare the ortho-k effect against spectacles on myopic control. They randomized 102 children into the ortho-k and the control groups, in which 37 ortho-k subjects (9.2 ± 1.1 years, Sphere = -2.05 ± 0.72 D, AL = 24.48 ± 0.71 mm) and 41 control subjects (9.4 ± 1.0 years, Sphere = -2.23 ± 0.84 D, AL = 24.40 ± 0.84 mm) completed the 2-year study. The ortho-k subjects were fitted with the Menicon Z Night lenses in Menicon Z material (NKL Contactlenze B.V., the Netherlands) using the Easy Fit Software provided by the manufacturer. All subjects were monitored every 6-monthly for cycloplegic AL using the IOLMaster. At the end of the 24-month study, the axial length increased by 0.36 ± 0.24 mm in the ortho-k group and 0.63 ± 0.26 mm in the control group. The efficacy of the ortho-k in the retardation of myopic progression was 43%. The ROMIO study was the only one published randomized clinical trial in myopic control study with ortho-k lenses. As in other ortho-k studies, the ROMIO study did not

perform AL measurement after stabilization of ortho-k effect. Lee and Cho (2010) observed subtle changes (subtle increase from lens wearing to lens discontinuation while subtle decrease from lens-discontinuation to lens wearing) in AL in a child during the transition period between the lens-wearing and the lens-discontinuation phases. In order to avoid over- or under-estimation of axial elongation due to ortho-k lens wear, it is advisable to perform AL measurement after stabilization of ortho-k responses are confirmed. .

Table 3.1 summarizes these ortho-k studies. As could be seen from the table, the drop-out rate was generally large in all studies, ranging from 7% to 30% for the ortho-k group and from 17% to 20% for the control groups. These studies only determined the myopic control effect of ortho-k on low to moderate myopes. It was probably due to that ortho-k treatment was considered more suitable for low to moderate myopes for a higher proficiency in full myopic reduction. It is, therefore, a need to study how the efficacy of myopic control by ortho-k differed in higher myopes.

In addition, with the advancement of corneal reshaping into possible correction for higher astigmatism, there is also a need to investigate its efficacy in arresting myopic progression in higher astigmats.

Moreover, the variation in myopic control effect within a study was large. As reflected from the standard deviation of the 24-month axial elongation in each study, some of the candidates progressed more rapidly while some progressed more slowly in both of the ortho-k and the control groups. The 95% confidence intervals would have some overlapping between the treatment and the control groups. Further investigation is needed to explore

Table 3.1 Comparison of different myopic control study with ortho-k

Study	LORIC	CRAYON	JAPAN [§]	MCOS	ROMIO
Authors (Year)	Cho et al. (2005)	Walline et al. (2009)	Kakita et al. (2011)	Santodomingo -Rubido (2012)	Cho and Cheung (2012)
Years of study conducted	N/A	2004 – 2005	2002 - 2007	2007 – 2008 [¶]	2008 – 2009 [¶]
Monitoring period (months)	24	24	24	24	24
Subjects at recruitment:	43:35 [▾]	40:28 [▾]	45:60 [▾]	31:30 [▾]	51:51 [▾]
Subjects at completion	35:35 [▾]	28:28 [▾]	42:50 [▾]	29:24 [▾]	37:41 [▾]
Age (years)					
Ortho-k	9.6 ± 1.5	10.5 ± 1.1	12.0 ± 2.6	9.6 ± 1.6 *	9.2 ± 1.1
Control	9.6 ± 0.7	10.5 ± 1.0	11.9 ± 2.1	9.9 ± 1.9 *	9.4 ± 1.0
Baseline SER (D)					
Ortho-k	-2.27 ± 1.09	N/A #	-2.55 ± 1.82	-2.20 ± 1.09 [η]	-2.05 ± 0.72 [η]
Control	-2.55 ± 0.98	N/A	-2.59 ± 1.66	-2.35 ± 1.17 [η]	-2.23 ± 0.84 [η]
Baseline AL (mm)					
Ortho-k	24.50 ± 0.71	24.3 ± 0.73	24.66 ± 1.11	24.49 ± 0.78	24.48 ± 0.71
Control	24.64 ± 0.58	24.20 ± 0.63	24.79 ± 0.80	24.26 ± 1.01	24.40 ± 0.84
Axial elongation at the end of study					
Ortho-k	0.29 ± 0.27	0.25	0.39 ± 0.27	0.47	0.36 ± 0.24
Control	0.54 ± 0.27	0.57	0.61 ± 0.24	0.69	0.63 ± 0.26
Efficacy of myopic control [ξ]	46%	39%	36%	32%	43%
Ortho-k lenses used	4 or 5-curve designs	Paragon CRT	Euclid Emerald	Menicon Z Night	Menicon Z Night
Measurement for AL	Contact A-Scan ultrasound under cycloplegia	Contact A-Scan ultrasound	IOLMaster	IOLMaster under cycloplegia	IOLMaster under cyclopelgia
Examiner blinding	Unknown	Unknown	Yes	Unknown	Yes
Randomization	No	No	No	No	Yes
Control methods	Historical controls wearing SV spectacles	Historical controls wearing SCL	SV spectacles	SV spectacles	SV spectacles

[§] Country in which study was conducted
[¶] Year of subject recruitment
[▾] Number of ortho-k subjects : number of control subjects
[η] Spherical component only
* information including drop-outs
# inclusion criterior for ortho-k subjects on refraction: Sphere: -0.75 D to -4.00 D; Cylinder < -1.00 D
[ξ] calculated by Difference in axial elongation between groups ÷ axial elongation in control groups)

why ortho-k effect varies and what factors determine its variability in myopic control efficacy.

3.4 Mechanism of orthokeratology in myopic control

While the efficacy of ortho-k effects has received extensive investigation, the mechanism through which it exerts myopic control effect was unknown. Although previous studies have shown ortho-k was able to reduce the initially relative peripheral hyperopia drastically in myopic eyes (see Chapter 2.5.1), there was scant evidence to support the link between reduced relative hyperopia following ortho-k treatment and retarded axial elongation in ortho-k wearing children. In addition, the PR hypotheses has only received support from animal studies which suggested that relative peripheral hyperopia would be a potential visual input for myopia progression. Association between RPR and myopic progression was, however, yet established or even challenged by some longitudinal PR studies (Mutti *et al.*, 2011; Sng *et al.*, 2011b). It would be too early to conclude if the alteration on the peripheral optics was responsible for the myopic control effect in ortho-k.

Summary

Orthokeratology is an effective alternative to refractive correction for low to moderate myopes. With the use of reverse-geometry design worn during sleep, it exerts transient myopic reduction by the alteration of the anterior cornea – flattening and thinning of the central anterior cornea together with a steepening and thickening in the mid-periphery. Posterior cornea was not altered by ortho-k. At cellular level, current evidence preliminary suggests that the anterior layers of the cornea are more likely to be changed, while the posterior layers are least affected. The popularity of ortho-k in areas

where a high prevalence of myopia was found is mainly due to its effectiveness in arresting myopic progression in children. The effectiveness of ortho-k when used as a myopic control intervention have been widely investigated and recently confirmed with an RCT conducted on Hong Kong Chinese. While the mechanism of myopic reduction in ortho-k has been well documented, the mechanism of myopic control in ortho-k remains unclear. Although it has been well documented that ortho-k is able to reduce relative peripheral hyperopia or even convert it into relative myopia in myopic eyes, the linkage between the reduction in relative peripheral hyperopia (or conversion into relative myopia) and the myopic progression has not been confirmed. PR studies with controversy results suggesting that PR might not be an influential factor for myopic progression impose additional challenges on the PR hypothesis in the myopic control mechanism with ortho-k.

Chapter Four

Niche Areas and Research Questions

4.1 Niche Areas

The PR hypothesis in myopia remains unclear and there are issues with this hypothesis.

1. There are inconclusive evidence that defocus is a potential factor stimulating active eye growth in human eyes.
2. Available information on human PR characteristics only shows that eyes with different ametropia may attain particular field curvatures; whether it is an effect or a cause of eye growth is still unclear.
3. Previous studies have focused more on PR in the description of eye shape, while PEL and its changes with myopic shift are less studied.
4. The application of research findings from animal models to humans may not be appropriate as the critical period for eye growth and the behavior during this period in the human eye are not the same in animals and humans. Indeed, there exist large variations across species in animal models.
5. To date, the myopic control effects of different interventions based on the PR hypothesis have not provided strong evidence to support PR as a cause of myopic progression. Although ortho-k has been shown to be effective in reducing relative peripheral hyperopia and even converting it into relative myopia in myopic eyes, the relationship, if any, between PR and myopic control remains unclear.
6. Although the effectiveness of ortho-k for myopic control has been confirmed, there are large variations in treatment effect among subjects. The reasons for the variations and factors that would predispose effective ortho-k treatment are still unclear.

4.2 Research Questions

The purpose of this PhD study is to conduct further investigation on the role of PR in myopic progression and myopic control. The field curvatures and the retinal contour are the two ocular characteristics to be investigated, and would be determined through PR and PEL, respectively. The current study set out to answer the following questions:

1. Are there any differences in PR and PEL between eyes with different myopic progression?
2. Are there any differences in PR and PEL changes between different ametropias or eyes with different rates of myopic progression?
3. Are there any differences in PR and PEL between ortho-k-treated and spectacle-wearing eyes?
4. Are there any differences in PR and PEL between eyes with different levels of ortho-k effects?

4.3 Null hypotheses

The designed experiments attempted to test against the following null hypotheses:

1. There were no differences in PR or PEL between eyes with fast and slow myopic progression.
2. There were no differences in changes of PR or PEL between eyes with different ametropias.
3. There were no differences in changes in PR or PEL between eyes with fast and slow myopic progression.

4. There were no difference in PR or PEL between ortho-k-treated and spectacle-wearing eyes.
5. There were no differences in PR or PEL between ortho-k-treated eyes showing fast and slow myopic progression during the treatment period.

Chapter Five

Subjects and Examination Procedures

This chapter gives detailed description on the subject recruitment and the examination procedures used in the current study. A detailed presentation of the study design and methodology of individual experiments conducted in this study is included in the Method sections of Chapters 6 – 10.

5.1 Study design overview

Experiments were designed to determine the repeatability of RPR and PEL measurements in spectacle-wearing and ortho-k-treated eyes. Children who enrolled into the longitudinal study on RPR and PEL were invited to join the repeatability study. In order to determine the changes in optical and retinal profile with central refractive errors in both spectacle-wearing and ortho-k-treated eyes, longitudinal studies investigating the changes in RPR and PEL in both spectacle-wearing and ortho-k-treated eyes were designed. Moreover, a pilot study which compared the changes in RPR and PEL before and after ortho-k treatment on the ortho-k-treated eyes was also designed.

There are five experiments in the current study:

Experiment 1 – Repeatability of peripheral refraction measurements (Chapter 6)

Experiment 2 – Repeatability of peripheral eye length measurements (Chapter 7)

Experiment 3 – Changes in peripheral refraction and peripheral eye length in spectacle-wearing eyes (Chapter 8)

Experiment 4 – Changes in peripheral refraction and peripheral eye length in ortho-k-treated eyes (Chapter 9)

Experiment 5 – Changes in peripheral refraction and peripheral eye length before and after ortho-k treatment (Chapter 10)

5.2 Subject recruitment

5.2.1 Ethics Clearance

All the experiments in the current study complied with the tenets of the Declaration of Helsinki of 2002, and the ethics clearance was approved by the Departmental Research Committee of the School of Optometry of The Hong Kong Polytechnic University. Written parental consent was obtained after a detailed explanation of the examination procedures and complete disclosure of the effects of topical cycloplegics and potential risks of ortho-k lens wear. Separate informed consents were obtained for the repeatability study and the longitudinal study.

5.2.2 Subject enrollment

Children aged between six and nine years were recruited. Experiment 3 (longitudinal study on spectacle-wearing eyes) commenced first while Experiment 4 and 5 (longitudinal study on ortho-k-treated eyes) commenced about one year later. A detailed eye examination was performed in each subject to confirm normal ocular condition and eligibility for the individual experiment before enrollment.

5.2.2.1 Longitudinal study on peripheral refraction and peripheral eye length in spectacle-wearing eyes (Experiment 3)

A total of 122 children were screened and 79 children who fulfilled the criteria listed in Table 5.1 were recruited. Nine withdrew from

the study after the baseline visit due to non-compliance to measurement procedures and refusal to receive cycloplegic eye drops. Twelve subjects decided to enroll in another ortho-k treatment and were unable to complete the 12-month study. Only 58 subjects who were able to complete the study and their data were used for analysis.

Table 5.1. Inclusion criteria for the longitudinal study on peripheral refraction and peripheral eye length in spectacle-wearing eyes

Inclusion criteria	Description
Age	6 – 9 years
Gender	Any
Ethnicity	Chinese
Ocular health	Free from any ocular pathologies or abnormal functional conditions such as tropia, amblyopia and pseudomyopia. No known allergies to eye drops used in this study
General health	Free from any long-term systemic condition or medications
Correction for ametropia	Spectacle correction with single vision lenses with no previous experience in contact lens wear or myopic control interventions
Subjective refraction	Sphere: no limitation Cylinder: not more than 1.50 DC
Best-corrected acuity (Snellen)	6/7.5 or better in each eye

5.2.2.2 Longitudinal study on peripheral refraction and peripheral eye length in ortho-k-treated eyes (Experiment 4)

Thirty-three children who satisfied the inclusion criteria listed in Table 5.2 were recruited. Two subjects were excluded as their manifest refraction at the delivery visit (of ortho-k lenses) exceeded the criteria. Two withdrew from the study after the initiation of ortho-k treatment. One of them decided to withdraw because of parental concerns on the child's ocular health after an episode of lid inflammation which was found unrelated to lens wear, while the other one withdrew because of concerns on frequent aftercare visits. One was excluded as he was unable to meet the time limit for the final data collection visit. Therefore, only 28 subjects remained and completed the 12-month study.

5.2.2.3 Difference in peripheral refraction and peripheral eye length changes before and after the ortho-k treatment (Experiment 5)

Six subjects from the longitudinal study on spectacle-wearing eyes (Experiment 3) switched to the longitudinal study on ortho-k-treated eyes (Experiment 4) 6-12 months after participating in the former study. They were included in Experiment 5, which aimed to compare the difference in PR changes with central refraction before and after ortho-k treatment.

Table 5.2. Inclusion criteria for the longitudinal study on peripheral refraction and peripheral eye length in ortho-k-treated eyes

Inclusion criteria	Description
Age	6 – 9 years
Gender	Any
Ethnicity	Chinese
Ocular health	● Free from any ocular pathologies or abnormal functional conditions such as tropia, amblyopia and pseudomyopia. ● No known allergies to eye drops used in this study ● No contraindications to contact lens wear
General health	Free from any long-term systemic condition or medications
Previous correction for ammetropia	no previous experience in contact lenses or myopic control interventions
Subjective refraction	* Myopia less than 6.00 D * Refractive cylinder not more than 1.50 DC with WTR axis, or not more than 1.00 DC with ATR axis
Topographical astigmatism	No limbus-to-limbus astigmatism
Visual acuity	6/7.5 or better in each eye

5.3 Measurement techniques

5.3.1 Subjective refraction

5.3.1.1 Instrumentation

Subjective sphero-cylindrical refraction was performed by the same practitioner at every visit, using trial lenses, Jackson's cross-cylinders and trial frames before and after cycloplegia. The trial frames were secured on the subject leaving a vertex distance of about 12 mm. Subjects were asked to read the Snellen letter chart at 6 meters for the determination of acuity. The chart was reflected by a mirror such that it was viewed from an optical distance of six meters. Subjective refraction followed the general procedures used in clinical practice. The end-point of subjective refraction was determined according to the maximum-plus-maximum-acuity principle in 0.25 D steps.

5.3.1.2 Correction for ametropias or residual refraction

Subjects with any ametropia (including hyperopia, myopia and astigmatism) in the spectacle-wearing group were corrected with normal single vision lenses made in plastic. In the ortho-k group, subjects with any residual refraction which could affect their day-time vision were corrected with normal single vision plastic spectacle lenses.

5.3.2 Peripheral refraction

5.3.2.1 Instrumentation

After cycloplegia, PR across the central 60° field were determined by an open-view auto-refractor, Shin-Nippon NVision K5001 (Ajinomoto Trading, Inc., Tokyo, Japan) with a self-fabricated external fixation system. The fixation system consisted of two components: a swinging arm and an optical system (Figure 5.1). The swinging arm had its center of rotation 15 mm behind the head rest and it was attached to a slider such that the center of rotation of the swinging arm could be aligned with the center of rotation of the tested eye. The optical system, attached to the other end of the swinging arm and comprised a 45°-inclined plane mirror and a condensing lens, was made to project the image of a 3-mm flashing red light-emitting diodes (LEDs) (3V) at 1 m from the eye. A protractor was used to ensure the optical system was swung to the correct angle of fixation.

Figure 5.1. Shin-Nippon NVision K5001 with the self-fabricated fixation system

5.3.2.2 Measurement procedures

After cycloplegia, the subject was asked to sit behind the auto-refractor with the chin and forehead resting firmly against the chin and the forehead rests, respectively. The eye level was aligned to the canthus indicator of the instrument, such that it was at the same level as the plane mirror of the optical system.

Measurements were taken from the right eye only, with the left eye being occluded. Central refraction was assessed first, with the subject looked straight ahead at the LED which was set at 0° position (C). The LED was then swung sideway to different peripheral field

angles accordingly for measurements of PR. The subject turned his/her eye to fixate the LED, while his/her head was held firmly by the examiner. When the subject was directed to fixate temporal, refraction was taken from the nasal field and vice versa.

PR measurements were made sequentially from the nasal field at 10° (N10), 20° (N20) and 30° (N30) and then from the temporal field at 10° (T10), 20° (T20) and 30° (T30). Each measurement was made manually, with the instrument being realigned each time along the instrument axis to obtain clear focus of the mire and laterally to the pupil center.

5.3.2.3 Data treatment

Previous study has shown that the mean difference between repeated measurements on central refraction using the same instrument was 0.11 D and 0.13 D for the spherical and cylindrical components, respectively (Davies *et al.*, 2003). With additional consideration on an allowance of ± 0.25 D from the mean difference and potentially larger variations in off-axis measurements, criteria were preset for the selection on the Shin-Nippon measurements (Table 5.3). For each field angle, 5 – 10 measurements were made to include at least five readings within the preset criteria. The first five readings which fulfilled the preset criteria were selected for the computation of mean (representative) values of the measurement.

Table 5.3. Preset criteria for the five auto-refractor measurements

	Maximum differences between any two readings			
Field angles (°)	**0**	**10**	**20**	**30**
Sphere	0.50 D	0.50 D	0.50 D	0.75 D
Cylinder	0.75 D	0.75 D	0.75 D	1.00 D

Each sphero-cylindrical reading, expressed in negative cylinders [Sphere (S) / Cylinder (Cyl) x Axis (Θ)], was transposed into vector components M, J_0 and J_{45}, using the following formula (Deal and Toop, 1993; Thibos *et al.*, 1997):

$M = S + \frac{Cyl}{2}$ (M = spherical equivalent)

$J_0 = -\frac{Cyl}{2} \times \cos 2\theta$ (J_0 = horizontal and vertical astigmatism)

$J_{45} = -\frac{Cyl}{2} \times \sin 2\theta$ (J_{45} = oblique astigmatism)

Transposed vectors from every five readings were averaged for each angle to give a representative reading. RPR were computed by subtracting central refraction from PR measurements for each vector. A complete set of data included M, J_0 and J_{45} components for central refraction and PR at six peripheral field angles.

5.3.3 Peripheral eye length measurement

5.3.3.1 Instrumentation

PEL across the central 60° horizontal field angles were measured using a PCI unit, the IOLMaster (Carl Zeiss, Germany) with a self-fabricated external fixation unit (Figure 5.2). The fixation unit comprised a 45°-inclined 50R/50T beam splitter and a series of

seven 3-mm LEDs mounted horizontally on an adjustable lever, which was placed right above the beam splitter. The beam splitter allowed the subject to view the LED as if they were placed in front of them. The distance of the LED from the beam splitter was adjusted for each eye such that every consecutive pairs of LEDs subtended an angle of 10°, with the assumption that the center of eye rotation was 15 mm behind the corneal surface. The central LED was aligned with the internal fixation light of the IOLMaster. Therefore, PEL were measured at the specified angles from the fixation axis.

5.3.3.2 Measurement procedures

The subject sat behind the instrument with the chin and forehead resting firmly against the chin and the head rests. The examiner also held his/her head firmly against the forehead rest to ensure the subject did not turn his/her head sideways during the measurements. Only the right eye of each subject was measured, while the left eye was occluded. The subject fixated at the internal fixation target first for target distance adjustment. The middle LED was used for AL measurement while the other six LEDs were used for PEL measurements.

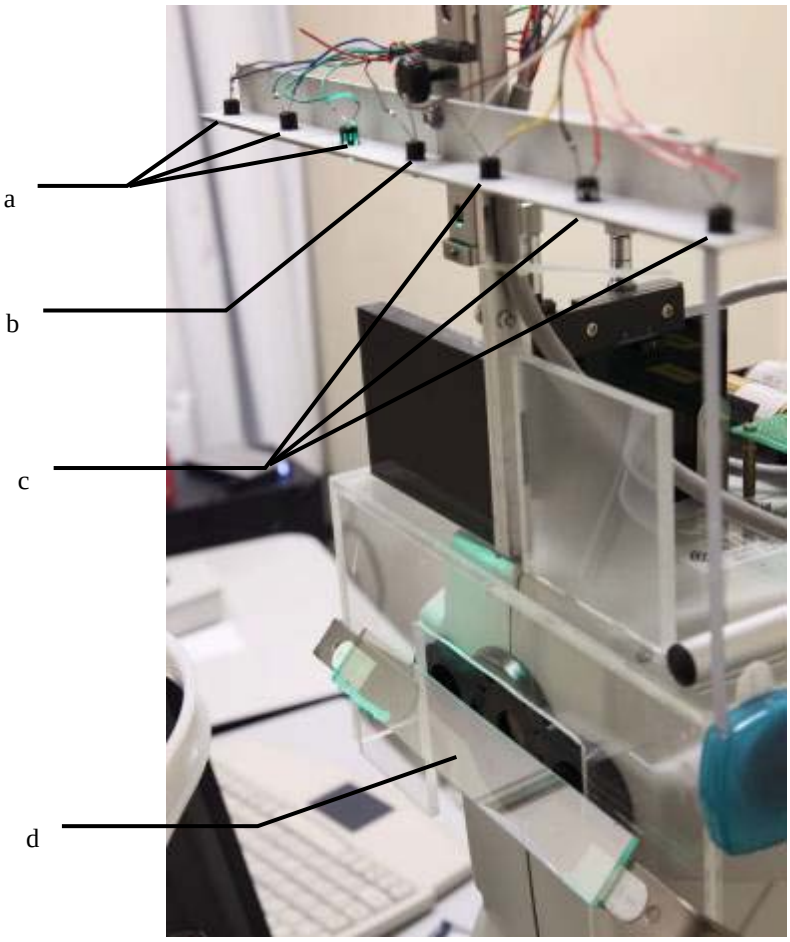


Figure 5.2. The IOLMaster with a self-fabricated fixation unit for PEL measurements. (a) LED for nasal fixation (right eye), (b) middle LED, (c) LED for temporal fixation (right eye), (d) beam splitter reflecting the images of LED and allowing lights from the instrument to pass through.

AL measurement was made while the subject fixated at the middle LED and the instrument was aligned such that the corneal spot was centered on the cross-hair on the IOLMaster screen. During PEL measurements, the subject turned the eyes while keeping his/her head still. The instrument needed to be realigned in order to obtain a sharp focus of the corneal spot on the cross-hair on the screen. PEL were measured while the subject fixated at the other LEDs,

temporally at 10°, 20° and 30°, and then nasally at 10°, 20° and 30°, in that order. When the subject fixated temporally at the LED, the IOLMaster measured PEL from the nasal cornea to the temporal retina or from the nasal field, and vice versa. In order to avoid confusion with the notations used in PR measurements, field angles were used to indicate the eccentricities of the PEL measurements. Therefore, N10, N20 and N30 represented PEL measurements taken from the nasal field (i.e. measuring from the nasal cornea to the temporal retina) while T10, T20 and T30 represented measurements taken from the temporal field (i.e. measuring from the temporal cornea to the nasal retina).

5.3.3.3 Data treatment

For each eccentricity, three readings were obtained and averaged (except at T30 where only two readings were obtained due to the limitation of 20 measurements on each eye per day as recommended by the manufacturer). Each measurement was considered valid if they had a signal-to-noise ratio of two or above. RPEL was computed by subtracting AL from the PEL for each eccentricity. The IOLMaster uses a grouped refractive index of 1.3375 in the calculation of optical distance.

5.3.4 Cycloplegia

Cycloplegia was achieved by the instillation of one drop of Alcaine 0.4% and one drop of Tropicamide 1.0%, followed by another drop of Cyclopentolate 1.0% with five minutes between each drop. Cycloplegic

refraction, PR and PEL measurement were performed at least 45 minutes after the application of the last drop and cycloplegia was confirmed by checking the pupil responses and accommodation.

5.4 Ortho-k technique and treatment protocol

5.4.1 Fitting philosophy

All ortho-k subjects were fitted with Z Night Lenses or Z Night Toric Lenses (NKL Contactlenzen B.V., Emmen, The Netherlands) on both eyes. After an initial evaluation to rule out any contraindication for ortho-k treatment, the initial trial lens was determined using the Easy Fit Software (version 2006, NKL Contactlenzen B.V.) based on topographical information taken with the Medmont E300 topographer (Medmont Pty Ltd., Vermont, VIC, Australia). The specifications of the contact lenses are listed in Table 5.4.

Lens modification was based on the lens centration as shown on the topographical maps (i.e. the difference map) comparing the pre- and post-treatment corneal topographies.

A bull eye detected with the difference map did not require lens modification unless under-response in myopic reduction was found. Modification in response to under-correction was achieved by further flattening the base curves of the lens with the use of the software. The software automatically adjusted the sagittal depth of the lens whenever the change made to the base curve was significant. A central island within the treatment zone or a downward decentration of the treatment ring (frowny face) indicated a steep fit lens. Modification was made by a reduction on the

sagittal depth in steps of 0.01 mm. An upward decentration of the treatment ring (smiley face) was indicative of a flat fit lens. Lens modification was achieved by a concurrent increase in the sagittal depth in steps of 0.01 mm together with a reduction in tangential angle in steps of 1°. Every unit of reduction in tangential angle approximately increased in the lens sag by 7 μm.

Table 5.4. Parameters of the Z Night Lens and Z Night Toric Lens

Parameters	Descriptions
Base curve	7.20 mm to 9.50 mm (0.05 mm / step)
Lens diameter	10.20 mm / 10.60 mm / 11.00 mm
Tangential angle	50° to 65° (1° / step) *
Sagittal depth	0.50 to 0.99 mm (0.01 mm / step) *
Material	Menicon Z
Oxygen permeability	Dk = 163 ISO / 189 Fatt
Nominal thickness	0.24 mm
Others	Three fenestrations on the reverse curve forming an equidistant triangle

* 2 meridians in Z Night Toric

5.4.2 Treatment protocol

At the delivery visit, the dynamic (lens movement, lens centration and tear exchange) and static fitting (alignment of different curves onto the cornea as shown by the fluorescein pattern) of lens was evaluated to ensure suitability for overnight wear. If the lenses were considered suitable, they were delivered for an overnight trial. On the next day, after the first overnight wear, the subject had to come back for an aftercare visit with lenses in situ within two hours after waking up. This was to ensure that any signs of compromised cornea had not recovered before the visit. Lens fitting, signs of lens binding, VA with lenses, over-refraction with contact lenses were evaluated before lens removal. After lens removal, corneal topography with Medmont E300 topographer, residual refraction with subjective refraction using trial lenses at vertex distance of 12 mm, ocular health evaluation were performed. The lenses were considered suitable for the continuation of overnight wear only if a bull's eye topographical response was obtained without any compromise on the external ocular health.

Follow-up visits at the first week, second week and fourth week were arranged to ensure the stability of ortho-k response. Lens modification was initiated once lens decentration or under-response of myopic reduction was found. In cases of lens decentration, a new pair of lenses with modified parameters would be ordered and the subject had to stop lens wear until the delivery of the new lenses. When the lenses which showed good centration and maximum myopic reduction without compromising the cornea are confirmed, they would be treated as the retainer lenses which the subject had to use till the end of the study. After the retainer lens was confirmed, regular 3-monthly aftercares were arranged.

The current study defined stabilization of lens wear as a bull's eye topographical response with no significant topographical change between two consecutive visits and maximum myopic reduction without any compromise on corneal health.

5.5 Data analysis methods

Unless specified, all statistical analysis was performed with PASW Statistics for Windows (Version 18.0 released in 2009, SPSS Inc., Chicago, US). The other statistic package used was the Instat+ v 3.36 (Statistical Services Centre, University of Reading, Reading, UK). All data were tested for any difference from the Gaussian normal distribution using the Kolmogorov-Smirnov or the Shapiro-Wilk tests. Detailed statistical methods are included in Chapters 6 – 10.

Chapter Six

Repeatability of Peripheral Refraction Measurements

Declaration

Contents of this chapter have been previously published and permission is obtained from the publisher to reuse contents of the paper in this chapter. Citation of the related publication is as follows:
Lee TT and Cho P (2012). Repeatability of relative peripheral refraction in untreated and orthokeratology-treated eyes. Optom Vis Sci 89(10):1477-1486.

6.1 Introduction

Among the many methods employed for the determination of field curvatures in human eyes (see Chapter 2.3), auto-refraction has been the most common and easily accessible objective assessment. Because of unrestricted peripheral vision, the open-view auto-refractors are the most popular for taking peripheral measurements. There are a number of models which serve this purpose: Canon Autoref R-1 (Canon USA, Lake Success, New York, USA), Shin-Nippon SRW5000 (Ajinomoto Trading Inc., Japan)/Grand Seiko WV-500 (Grand Seiko Co., Ltd., Japan, Shin-Nippon NVision K5001 (Ajinomoto Trading Inc., Japan) / Grand Seiko WR-5100K (Grand Seiko Co., Ltd., Japan) and Grand Seiko WAM-5500 (Grand Seiko Co., Ltd., Japan). Apart from the Canon Autoref R-1 which has been discontinued, the others are still commonly used in clinical practice and research studies. They are able to take peripheral measurements from the horizontal field up to ±40° and from the vertical field up to ±15°.
The repeatability of central refraction with these instruments is well documented (Chat and Edwards, 2001; Mallen *et al.*, 2001; Davies *et al.*,

2003), while that of peripheral refraction is not as clear. The Shin-Nippon SRW5000 has been evaluated for its repeatability of PR measurements in adults before and after ortho-k treatment (Charman *et al.*, 2006). However, this study was limited by a small sample size and that data treatment was not separated between pre- and post-ortho-k treatment. In view of the increasing application of the open-view auto-refractors in PR studies and that PR has been hypothesized to have a potential effect on myopic control with ortho-k, the current study aimed to determine the repeatability of RPR measurements using Shin-Nippon NVision K5001 auto-refractor in spectacle-wearing and ortho-k-treated eyes of children. It also investigated the difference between the two methods of averaging measurements for data treatment. In the following text, it is referred to as data treatment method.

6.2 Methods

6.2.1 Study design

Two experiments were designed to determine the repeatability of RPR in children: the first was for spectacle-wearing eyes while the second one was for ortho-k-treated eyes.

Experiment I – Repeatability of relative peripheral refraction in spectacle-wearing eyes

Spectacle-wearing subjects participating in the longitudinal study on RPR and PEL (Chapter 8) were invited to enroll in this experiment. Two sets of cycloplegic PR measurements (S1 and S2) were taken at the same visit by the same examiner to determine the repeatability of RPR. After collecting the first set of PR data, the subject was asked to retreat from the instrument,

which was reset before the second set of data was taken. (See Sections 6.2.2 and 6.2.4 below for determination of RPR)

Experiment II – Repeatability of relative peripheral refraction in orthokeratology-treated eyes

Ortho-k-treated subjects participating in the longitudinal study on RPR and PEL (Chapter 9) were invited to enroll in this experiment. All subjects were new to ortho-k treatment. Measurements were performed only after ortho-k treatment had stabilized. Consistencies of lens centration, topographical responses and residual refraction between two consecutive visits were used to confirmed stabilization.

Subjects attended two data collection visits on separate days which were 1 to 2 weeks apart. In order to determine the intra-visit repeatability, two complete sets of cycloplegic PR data (S1 and S2) were collected in the first visit as in Experiment I. To determine the inter-visit repeatability, a third set of PR data (S3) was collected in the second visit. On both visits, the treatment zone centre was required to be within a 0.5 mm distance from the pupil centre, and the inter-visit difference in subjective refraction was required to be not more than 0.50 D in either spherical or cylindrical components. To minimize the effect of diurnal variation in ocular biometrics and regression of ortho-k responses, measurements were made about the same time of day at each visit.

6.2.2 Examination procedures

Cycloplegic central refraction (CR) and PR across the central 60° horizontal field was measured in 10° intervals from the right eye of each subject using Shin-Nippon NVision K5001 auto-refractor. Detailed cycloplegia and PR

measurement procedures can be found in Chapter 5 (See Sections 5.3.2 and 5.3.4).

6.2.3 Subject number

Davies and colleagues (2003) reported that the mean difference ± SD between repeated measurements in foveal refraction using the Shin-Nippon NVision K5001 instrument was 0.03 ± 0.32 D. Based on a clinically acceptable level of 0.25 D for the mean difference between measurements, and with reference to the reported SD in foveal refraction, the computed subject number for achieving a power of 90% at a statistical significance level of 5% was 20.

6.2.4 Treatment of data

For each field angles, five to 10 measurements were made to include at least five readings that satisfy the preset criteria (Table 5.3). Measurements from T20 were excluded from data analysis owing to its proximity to the optic nerve head. Therefore, a complete set of data included CR and five PR data (from N10, N20, N30, T10 and T30) only.

Two methods were used in the determination of repeatability. Method 1 was to determine RPR from the average of the first five consecutive PR measurements, while Method 2 used the average of the first five PR measurements which satisfied the preset criteria.

All sphero-cylindrical readings were transposed into vector components M, J_0 and J_{45} before averaging as described in Chapter 5. RPR was determined by subtracting CR from the PR values for each angle.

6.2.5 Data analysis

Because the distribution of RPR data were not significantly different from a normal distribution [Kolmogorov-Smirnov tests, M and J_0: $p \geq 0.07$; J_{45}: $p \geq 0.06$ in spectacle-wearing eyes; M and $J_0 \geq 0.07$; J_{45}: $p \geq 0.12$ in ortho-k-treated eyes (exceptions: second measurement of M along T10 and first measurement of J_{45} along T10 in spectacle-wearing eyes; second measurement of M along T30, second measurement of J_0 along N10, and third measurement of J0 along N20 in ortho-k-treated eyes)], parametric tests were used in the remaining statistical analysis. Paired t-tests (in spectacle-wearing eyes) and repeated-measures analysis of variance (ANOVA; in ortho-k-treated eyes) were used to test for the presence of intra- and inter-visit differences in RPR at each field angle. Where significance of t-tests or ANOVA was tested among different refractive groups or eccentricities, Bonferroni corrections were applied. The adjusted p-values were indicated in these cases. If there were no significant differences between the data sets, Pearson correlations were used to investigate the relationship between the differences and their means. If there was no significant correlation, 95% limits of agreement (LoA) were computed and Bland and Altman plots were constructed. Coefficients of repeatability (COR = ±1.96 x SD of differences in RPR) were determined to supplement the comparison of measurement variabilities between eccentricities or subject groups. Comparison on measurement variability between CR and RPR was performed by analyzing the equality of variances (F tests) for M factor in each group. Comparisons of measurement variability between the spectacle-wearing and ortho-k-treated eyes (intra-visit measurements only) and between the intra- and inter-visit in

ortho-k-treated eyes were performed in the same way for CR as well as RPR for each of the peripheral field angles. All statistical tests were performed using SPSS 18.0 for Windows (SPSS Inc., Chicago, IL) unless otherwise specified.

6.3 Results

Fifty-nine children [8.0 ± 0.8 years] were enrolled in Experiment I. All data were included in the statistical analysis. The mean SER ± SD of the selected eyes was -1.86 ± 1.95 D. Eleven of these (right) eyes were hyperopic (spherical power ≥ 0.75 D), eight were emmetropic (-0.75 D < spherical power < 0.75 D), and 40 were myopic (spherical power ≤ -0.75 D). Twenty-eight subjects who had been wearing ortho-k lenses for ≥1 month were enrolled in Experiment II. Topographical responses in four of these subjects showed significant decentration [centre of treatment zone being >0.5 mm from pupil centre as shown on the topographical difference map using the Medmont Studio, version 4.12.0.5 (Medmont Int. Pty Ltd., Vermont, Australia)] in either visit; therefore, their data were not included in the analysis. The remaining 24 subjects [8.4 ± 0.8 years] had worn ortho-k lenses for 4 to 14 weeks before the first measurements were taken. The mean SER ± SD of the residual refractive errors of the right eyes of the remaining 24 eligible ortho-k-treated subjects was -0.53 ± 0.30 D.

6.3.1 Differences between the two methods used in the determination of relative peripheral refraction repeatability

Paired t-tests showed no significant differences between the two data

treatment methods in the determination of repeatability of RPR [$p > 0.14$ (with Bonferroni correction]. Because there were no significant differences between the two methods, only the results from Method 2 are presented and discussed in the rest of this chapter. In Method 2, the five measurements fulfilling the preset criteria could usually be obtained from six to eight consecutive measurements made for both spectacle-wearing and ortho-k-treated eyes.

6.3.2 Repeatability of central refraction in spectacle-wearing and orthokeratology-treated eyes

Objective CR measurements and the intra-visit differences in spectacle-wearing eyes are summarized in Table 6.1. There were no significant intra-visit differences in central M, J_0, or J_{45} (paired t-tests, $p \geq 0.19$). Intra-visit differences of the various power vectors were not significantly different in the spectacle-wearing eyes among different refractive groups (two-way repeated-measures ANOVA, $p = 0.93$ and $p = 0.83$, respectively).

The objective CR measurements and the intra- and inter-visit differences in ortho-k-treated eyes are summarized in Table 6.2. There were no significant differences in central M, J_0, and J_{45} among the three sets of measurements (repeated-measures ANOVA, $p \geq 0.23$).

The intra-visit differences in CR between spectacle-wearing and ortho-k-treated eyes were not statistically significant (unpaired t-tests, $p \geq 0.34$). The variability of mean measurement differences, as expressed by COR, is summarized in Table 6.3. The COR were <0.51 D in M and <0.37 D in J_0 and J_{45} in both treated and spectacle-wearing eyes.

The COR for CR were not significantly different between the spectacle-wearing and the ortho-k-treated eyes in M and J_0 (M: $F = 1.89$, $p = 0.05$; J_0: $F = 2.14$, $p = 0.08$). The COR for J_{45} were significantly different between spectacle-wearing and ortho-k-treated eyes ($F = 2.64$, $p < 0.01$). No significant differences in the COR for M, J_0, and J_{45} were found between intra- and inter-visit measurements in ortho-k-treated eyes ($1.17 \leq F \leq 2.14$, $0.08 \leq p \leq 0.74$). Only statistical results of M are presented in Table 6.4.

Table 6.1. Summary of central refraction and relative peripheral refraction results [mean (SD)] on spectacle-wearing eyes (Sets 1 and 2 measurements were made on the same visit. (Results from Method 2 only)

M factor	**CR**	**Relative peripheral refraction**					
Field angles (°)	**0**	**N30**	**N20**	**N10**	**T10**	**T20**	**T30**
1st Set	-2.07	0.87	0.16	0.02	-0.05		0.87
(S1)	(1.90)	(0.90)	(0.59)	(0.26)	(0.34)		(0.95)
2nd Set	-2.04	0.88	0.16	-0.03	-0.08	**Results**	0.86
(S2)	(1.88)	(0.91)	(0.59)	(0.30)	(0.37)	**excluded**	(0.97)
Intra-visit differences (S1 – S2)							
	-0.04	-0.01	0.00	0.05	0.04		0.01
	(0.16)*	(0.36)	(0.30)	(0.22)*	(0.28)#		(0.28)
J_0 factor	**CR**	**Relative peripheral refraction**					
Field angles (°)	**0**	**N30**	**N20**	**N10**	**T10**	**T20**	**T30**
1st Set	0.24	-1.13	-0.59	-0.18	-0.15		-0.77
(S1)	(0.21)	(0.27)	(0.21)	(0.17)	(0.20)		(0.29)
2nd Set	0.25	-1.12	-0.61	-0.18	-0.18	**Results**	-0.81
(S2)	(0.19)	(0.26)	(0.16)	(0.13)	(0.19)	**excluded**	(0.26)
Intra-visit differences (S1 – S2)							
	-0.01	-0.01	0.01	0.01	0.05		0.05
	(0.15)	(0.21)	(0.17)#	(0.18)#	(0.23)#		(0.24)
J_{45} factor	**CR**	**Relative peripheral refraction**					
Field angles (°)	**0**	**N30**	**N20**	**N10**	**T10**	**T20**	**T30**
1st Set	0,00	0.15	0.06	-0.02	-0.03		-0.12
(S1)	(0.13)	(0.26)	(0.21)	(0.11)	(0.15)		(0.25)
2nd Set	0.00	0.15	0.05	0.01	-0.04		-0.14
(S2)	(0.15)	(0.30)	(0.19)	(0.10)	(0.16)	**Results excluded**	(0.28)
Intra-visit differences (S1 – S2)							
	0.00	0.01	0.00	-0.03	0.01		0.01
	(0.08)	(0.16)#	(0.12)#	(0.09)#	(0.15)		(0.19)

N: nasal; T: temporal; CR: objective central refraction

#one outlier excluded

*two outliers excluded

Table 6.2. Summary of central refraction and relative peripheral refraction results [mean (SD)] on orthokeratology-treated eyes (Sets 1 and 2 measurements were made on the same visit. Set 3 measurements were made within two weeks after S1 and S2.

(A) M factor	CR	Relative peripheral refraction					
Field angle (°)	**0**	**N30**	**N20**	**N10**	**T10**	**T20**	**T30**
Visit 1							
1st Set (S1)	-1.00	-3.30	-1.45	-0.22	0.07		-0.72
	(0.23)	(1.53)	(0.83)	(0.36)	(0.30)		(1.35)
2nd Set (S2)	-0.94	-3.23	-1.49	-0.32	0.06		-0.81
	(0.31)	(1.57)	(1.09)	(0.44)	(0.33)		(1.51)
Visit 2							
3rd Set (S3)	-0.91	-3.34	-1.47	-0.34	0.04		-1.04
	(0.29)	(1.49)	(1.17)	(0.41)	(0.38)	Result	(1.45)
Intra-visit differences (S1 – S2)						excluded	
	-0.06	-0.02	0.04	0.16	0.00		0.09
	(0.22)	(0.48)#	(0.64)	(0.29)	(0.23)		(0.52)
Inter-visit differences							
S1 – S3	-0.09	0.04	-0.08	0.13	0.03		0.32
	(0.26)	(1.53)	(0.58)#	(0.32)	(0.25)		(0.91)
S2 – S3	-0.03	0.10	-0.03	0.02	0.02		0.23
	(0.31)	(1.52)	(0.72)	(0.25)	(0.31)		(1.15)
(B) J_0 factor	**CR**	**Relative peripheral refraction**					
Field angle (°)	**0**	**N30**	**N20**	**N10**	**T10**	**T20**	**T30**
Visit 1							
1st Set (S1)	0.23	-3.81	-1.66	-0.37	-0.19		-2.09
	(0.28)	(1.04)	(0.60)	(0.27)	(0.18)		(0.64)
2nd Set (S2)	0.23	-3.71	-1.71	-0.40	-0.17		-2.06
	(0.26)	(1.04)	(0.68)	(0.20)	(0.17)		(0.67)
Visit 2						Results	
3rd Set (S3)	0.25	-3.74	-1.68	-0.43	-0.11	excluded	-2.23
	(0.30)	(0.84)	(0.80)	(0.28)	(0.22)		(0.75)
Intra-visit differences (S1 – S2)							
	0.00	-0.11	0.05	0.03	-0.02		-0.03
	(0.13)	(0.54)	(0.32)	(0.27)	(0.23)		(0.26)

(Table 6.2 continued)							
Inter-visit differences							
S1 – S3	-0.02	-0.07	0.02	0.06	-0.08		0.14
	(0.19)	(0.87)	(0.57)	(0.35)	(0.27)		(0.65)
S2 – S3	-0.01	0.03	-0.03	0.03	-0.06		0.17
	(0.17)	(0.93)	(0.54)	(0.23)	(0.26)		(0.65)
(C) J_{45} factor	**CR**	**Relative peripheral refraction**					
Field angle (°)	**0**	**N30**	**N20**	**N10**	**T10**	**T20**	**T30**
Visit 1							
1st Set (S1)	0.05	0.29	0.05	0.00	-0.01		-0.14
	(0.16)	(0.68)	(0.34)	(0.11)	(0.18)		(0.44)
2nd Set (S2)	0.05	0.44	0.13	0.01	-0.01		-0.13
	(0.20)	(0.67)	(0.39)	(0.17)	(0.17)		(0.54)
Vist 2	0.06	0.33	0.11	-0.02	-0.01		-0.13
3rd Set (S3)	(0.16)	(0.41)	(0.22)	(0.11)	(0.15)		(0.37)
Intra-visit differences (S1 – S2)						Results excluded	
	0.00	-0.06	-0.07	-0.01	-0.01		-0.01
	(0.13)	(0.41)#	(0.24)	(0.17)	(0.16)		(0.32)
Inter-visit differences							
S1 – S3	-0.02	-0.04	-0.01	0.02	-0.01		0.00
	(0.12)	(0.56)	(0.26)	(0.11)	(0.19)		(0.44)
S2 – S3	-0.02	0.11	0.02	0.03	0.00		0.08
	(0.16)	(0.52)	(0.37)	(0.16)	(0.18)		(0.36)#

N: nasal; T: temporal; CR: objective central refraction

#one outlier excluded

Table 6.3. Summary of coefficient of repeatability (COR) for M, J_0 and J_{45} in spectacle-wearing and ortho-k-treated eyes

COR	CR	Relative peripheral refraction					
Field angle (°)	**0**	**N30**	**N20**	**N10**	**T10**	**T20**	**T30**
Spectacle-wearing eyes							
M factor	0.30*	0.70	0.58	0.42*	0.54#		0.56
J_0 factor	0.29	0.41	0.34#	0.36#	0.45#		0.48
J_{45} factor	0.17	0.31#	0.24#	0.19#	0.29		0.38
Orthokeratology-treated eyes (intra-visit)							
M factor	0.44	0.95#	1.26	0.56#	0.46	Results	1.02
J_0 factor	0.26	1.05	0.62	0.53	0.45	excluded	0.50
J_{45} factor	0.25	0.80	0.47	0.34	0.31		0.64
Orthokeratology-treated eyes (inter-visit)							
M factor	0.52	3.00	1.13	0.62	0.50		1.78
J_0 factor	0.36	1.71	1.12	0.68	0.53		1.28
J_{45} factor	0.23	1.10	0.52	0.22	0.37		0.85

N: nasal; T: temporal; CR: objective central refraction

#one outlier excluded

*two outliers excluded

Table 6.4. Analysis of equality of variances of measurement bias in M factor between spectacle-wearing and orthokeratology-treated eyes (intra-visit) and between intra-visit and inter-visit measurements in orthokeratology-treated eyes

	CR	Peripheral field angles					
		N30	**N20**	**N10**	**T10**	**T20**	**T30**
Spectacle-wearing vs Orthokeratology-treated eyes (intra-visit)							
F-statistics	1.89	1.78	4.55	1.74	1.48		3.45
p-value	0.05	0.08	<0.001	0.10	0.30	Results excluded	<0.001
Orthokeratology-treated eyes (intra-visit vs inter-visit)							
F- statistics	1.40	10.16	1.22	1.22	1.18		3.06
p-value	0.43	<0.001	0.65	0.65	0.69		0.06

N: nasal; T: temporal; CR: objective central refraction

6.3.3 Repeatability of relative peripheral refraction in spectacle-wearing eyes

RPR (M, J_0, and J_{45}) results in spectacle-wearing eyes are also shown in Table 6.1. There were no significant intra-visit differences in M, J_0, and J_{45} at any of the field angles (paired t-tests, $p \geq 0.10$). There were no significant differences found in the intra-visit differences among different power vectors and among different refractive groups (two-way repeated measures ANOVA, $p \geq 0.49$ and $p \geq 0.42$, respectively) at all peripheral field angles. The mean difference between any pair of CR and RPR at any angle was <0.05 D. The intra-visit differences in CR and RPR did not differ significantly across the horizontal 60° field (repeated-measures ANOVA, $p \geq 0.51$).

No significant correlation was found between the differences and their means for each parameter (Pearson correlation, M: $-0.16 \leq r \leq -0.01$, J0: $0.03 \leq r \leq 0.31$, J_{45}: $-0.21 \leq r \leq 0.18$). The COR ranged from ±0.42 D (N10) to ±0.70 D (N30) for M, from ±0.34 D (N20) to ±0.48 D (T30) for J0, and from ±0.19 D (N10) to ±0.38 D (T30) for J_{45} (Table 6.3). Figure 6.1 shows the Bland and Altman plots of the measurement variabilities in M factors of the CR and RPR. The COR of RPR measurements were compared with those of CR measurements, and the statistical results are shown in Table 6.5. The COR of RPR measurements were significantly different from those of CR measurements in spectacle-wearing eyes ($p < 0.02$) at all angles.

Table 6.5. Analysis of equality of variances in measurement bias in M factor between central refraction and relative peripheral refraction at different field angles

	Peripheral field angles					
	N30	**N20**	**N10**	**T10**	**T20**	**T30**
Spectacle-wearing eyes						
F-statistics	5.06	3.52	1.89	3.06		3.06
p-value	<0.01	<0.01	0.02	<0.01		<0.001
Orthokeratology-treated eyes (intra-visit)					Results	
F- statistics	4.76	8.46	1.74	1.09	excluded	5.59
p-value	<0.01	<0.01	0.39	0.83		<0.01
Orthokeratology-treated eyes (inter-visit)						
F-statistics	34.63	4.98	1.51	1.08		12.25
p-value	<0.01	<0.01	0.65	0.85		<0.01

N: nasal; T: temporal

6.3.4 Repeatability of relative peripheral refraction in orthokeratology-treated eyes

Table 6.2 summarizes the RPR results of the ortho-k-treated eyes (M, J_0, and J_{45}). No intra- or inter-visit RPR differences at any of the field angles were found (repeated-measures ANOVA, $p \geq 0.13$). The mean intra-visit difference was <0.16 D at any angle for M, J_0, and J_{45} (Table 6.2). The inter-visit differences were <0.17 D at any angle, except for M at T30. Since the mean inter-visit differences from S1 – S3 and S2 – S3 were not significantly different at any angle or vector ($p \geq 0.18$), the inter-visit difference from S1 – S3 were used for the following statistical analyses for simplicity. No significant differences in both intra- and inter-visit differences were found between CR and RPR or across the horizontal 60° fields (repeated measures ANOVA, $p \geq 0.486$).

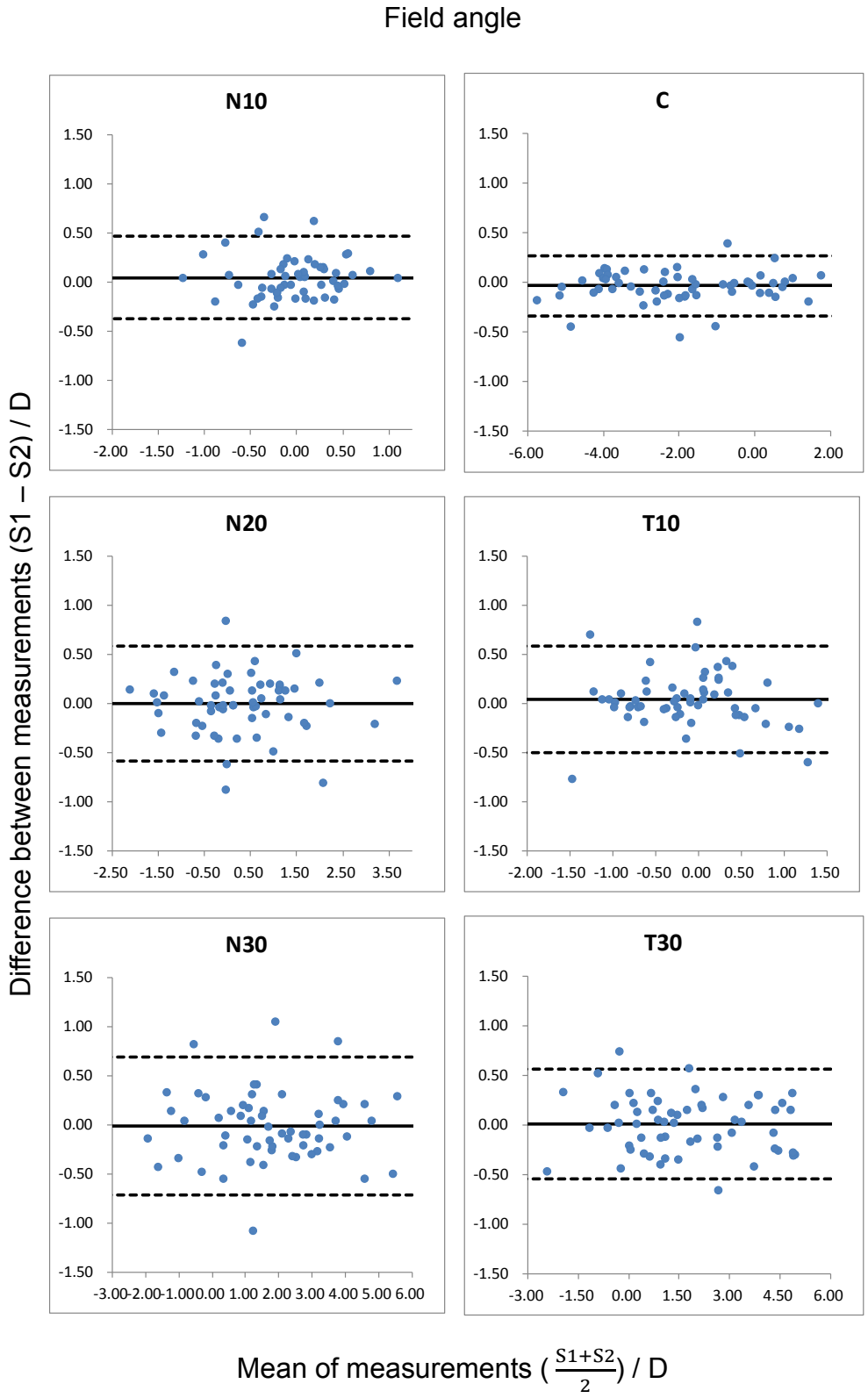


Figure 6.1. Bland and Altman plot of the repeated measurements in central refraction and relative peripheral refraction (M vector only) on spectacle-wearing eyes. Result of T20 was excluded. S1: 1st set of measurement; S2: 2nd set of measurement; C: central; N: nasal; T: temporal.

No significant correlations (Pearson correlations, M: $-0.49 \leq r \leq 0.32$; J_0: $-0.38 \leq r \leq 0.31$; J_{45}: $-0.42 \leq r \leq 0.55$) were found between the differences and their means. The intra- and inter-visit COR for ortho-k-treated eyes are summarized in Table 6.3. Only results S1 – S3 were presented in the inter-visit COR. Figure 6.2 shows the Bland and Altman plots of the measurement variability of CR and RPR in the ortho-k-treated eyes. The intra-visit COR of RPR (except for N10 and T10, $p > 0.39$) were significantly different from those of CR ($p < 0.01$), whereas the inter-visit COR of RPR were significantly different from those of CR beyond the central 20° field ($p < 0.01$; Table 6.5). At the same field angle, the intra-visit COR were generally smaller than the inter-visit COR in ortho-k-treated eyes for any of the vectors (Table 6.3). Within the central 40° field, the scatter of inter-visit measurements was approximately 20% wider than those of the intra-visit measurements. Such differences were, however, insignificant ($0.42 \leq p \leq 0.69$). Beyond the central 40°, the inter-visit measurement variabilities were significantly greater than the intra-visit ones ($p \leq 0.01$) by a factor of 2.5 times at most (Tables 6.4 and 6.5).

The mean measurement differences in ortho-k-treated eyes were not significantly different when compared with the results from spectacle-wearing eyes (unpaired t-tests, $p \geq 0.09$). However, beyond the central 10°, significant differences in measurement variability were found between the two groups across the horizontal field ($p \leq 0.04$; Table 6.4). The ortho-k-treated eyes show a twofold greater scatter of measurement bias toward the peripheral field when compared with the spectacle-wearing eyes (Table 6.3).

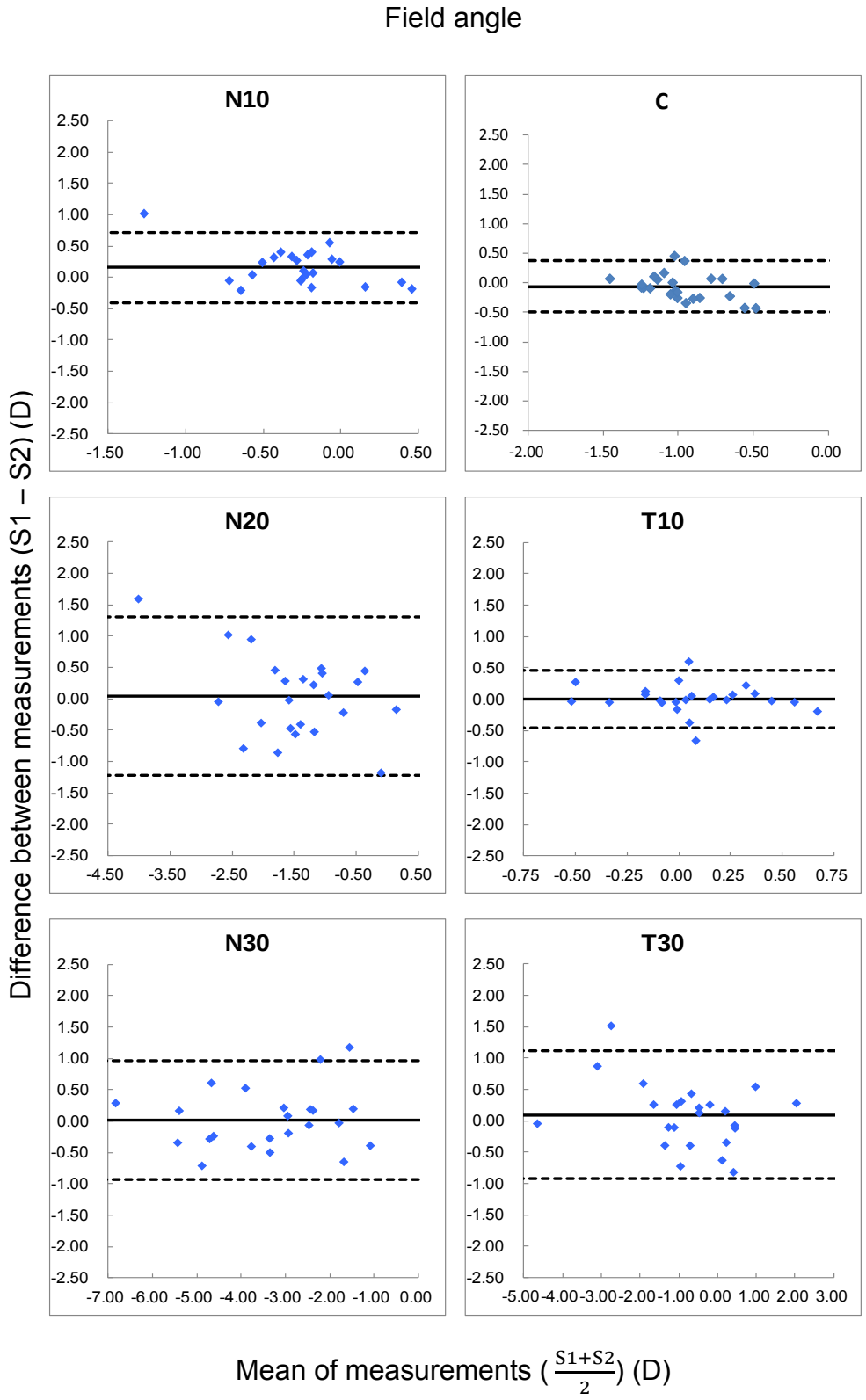


Figure 6.2. Bland and Altman plot of the intra-visit repeated measurements in central refraction and relative peripheral refraction (M vector only) on ortho-k-treated eyes. Result of T20 was excluded. S1 and S2: 1st and 2nd sets of measurements, respectively; C: central; N: nasal; T: temporal.

6.4 Discussion

In the current study, we determined repeatability of RPR from five consecutive PR measurements (Method 1) as well as the first five PR measurements that satisfied the preset criteria limiting the maximum difference in sphere and cylinder (Method 2). During our pilot study on PR measurements, we found that the variations in auto-refraction, particularly for the cylindrical component and in ortho-k-treated eyes, could be large. Measurements at more peripheral angles were more prone to such variations. This might be the result of larger values of cylinder being seen in ortho-k-treated eyes, and being seen more consistently between successive readings of each measurement. The current study showed that both methods gave similar RPR results and levels of repeatability in both spectacle-wearing and ortho-k-treated eyes. Although Method 1 is the common method reported in published papers on PR, we prefer to restrict the internal variability of the five measurements by using Method 2. Previous studies have investigated the validity and repeatability of non-cycloplegic CR made by the Shin-Nippon NVision K5001 in adults only (Davies *et al.*, 2003; Cleary *et al.*, 2009). The mean ± SD intersession differences in M, J_0, and J_{45} reported by Davies and colleagues (2003) were 0.03 ± 0.32 D, -0.02 ± 0.27 D, and -0.00 ± 0.11 D, respectively, for CR. Cleary and co-workers (2009) also reported good levels of repeatability, although measurements were not taken under cycloplegia. Both studies included adults aged from 18 to 60 years. The age of the majority of their subject groups were in the range of 20 to 40 years. Cleary and colleagues (2009) reported a more scattered test-retest variability, although the

measurements were made using a Badal optometer for better control of accommodation. The more scattered results may be due to monocular fixation during measurements. Davies and colleagues (2003), in contrast, allowed their subjects to fixate binocularly. Monocular fixation may induce relatively more accommodative responses compared with binocular fixation (Tan and O'Leary, 1985), and monocular viewing may lead to larger accommodation errors than in binocular viewing (Seidel *et al.,* 2005).

Our results on CR in spectacle-wearing eyes of children are in agreement with those reported by Davies and colleagues (2003) [unpaired t-tests, $p \geq 0.05$ for all parameters, Instat v3.3 (GraphPad Software, Inc., La Jolla, CA)] and Cleary and colleagues (2009) (unpaired t-tests, $p \geq 0.56$ for all parameters, Instat v3.36) in adults. Our study also shows a smaller scattering of the mean differences in children. Therefore, the repeatability of CR measurements is not worse in children, although their attention and fixation may be more variable.

Charman and colleagues (2006) reported the repeatability of PR in four ortho-k-treated eyes using Shin-Nippon SRW5000 and commented that the inter-set differences in PR measurements increased with peripheral field angle. They performed two sets of PR measurements at the pre-treatment and 7-day and 14-day post-treatment visits and combined the pre- and post-treatment data for the inter-set difference investigation. Because they combined pre- and post-ortho-k data and NVision SRW5000 measures refractive errors over a wider area (2.9mm) (Mallen *et al.,* 2001) than the NVision K5001 does (~2.3mm) (Davies *et al.,* 2003), direct comparison of the current results with theirs was not performed. In the current study, the mean intra-visit differences in RPR were < 0.05 D and < 0.32 D in

spectacle-wearing and ortho-k-treated eyes, respectively. The mean measurement differences found for RPR were not significantly different from those found for CR in both treated (intra-visit) and spectacle-wearing eyes (intra- and inter-visits).

Although the mean intra- and inter-visit differences were insignificant among different field angles, COR of RPR beyond the central 20° field were significantly greater than those of CR in both treated and spectacle-wearing eyes. Moreover, COR increased with field angles and were generally larger in the nasal than in the temporal fields (Table 6.3). This was observed for both spectacle-wearing and treated eyes and is in agreement with the findings reported by Charman and co-workers (2006). COR were significantly larger in ortho-k-treated eyes than in spectacle-wearing eyes (Table 6.3). Ortho-k results in a flattening of the central cornea and a steepening of mid-peripheral cornea. The deviation of the anterior corneal profile from a normal prolate elliptical shape is a likely source of error when the instrument is used to measure the modified corneal surface. Larger variations (COR) were observed for nasal than temporal fields in ortho-k-treated eyes. There might be asymmetrical corneal eccentricities (or shape factor) between the half fields, which results in differences in repeatability. Angle alpha has been suggested to be a potential source of asymmetry between the nasal and the temporal field in PR (Dunne *et al.*, 1993). Effectively, if we take angle alpha into account, we were actually assessing a wider nasal peripheral field, and this may be a reason for poorer repeatability of data in the nasal field angles because variability increased with field angle. However, the current study did not make further investigation on these factors.

During the off-axial auto-refraction, in both of the eye-turn or head-turn methods, the instrument had to be translated laterally to realign the pupil center. The cornea area over which the auto-refraction was taken was different from that when on-axis measurement was taken. Moreover, the open-view auto-refractor performed refraction over a 2.3mm diameter area. The corneal profile over which might experience a great variation in radii of curvature in ortho-k-treated eyes (Maseedupally *et al.*, 2013).

It is not clear how the altered corneal profile, after corneal reshaping, affects PR measurements, particularly at more extreme angles (e.g., 30° to the periphery) where measurement beam passes through corneal area with abruptly changing profiles over the treatment zone. However, an analysis of such effect on PR measurement is beyond the scope of the current study.

In ortho-k-treated eyes, inter-visits COR were significantly greater than intra-visit COR, when measurements were made beyond the central 40° field. As mentioned before, diurnal variation in ocular biometrics was minimized by taking measurements around the same time of the day for the inter-visits repeatability (not more than 1 hour difference). All subjects were instructed to wear ortho-k lenses during sleep for a minimum of 8 hours every night. They were also required to mark the time of lens insertion and removal every day in a logbook. The larger inter-visit variations in ortho-k-treated eyes are probably due to the regression of corneal shape and smaller day to day variation of topographical responses, although inter-visit measurements were made at about the same time of day. Ortho-k lens wear induces transient corneal shape changes, which may affect the refractive state of the eye and thus are more prone to day to day changes such as under- or overcorrection, lens decentration, binding and so forth. Although

usually small, these changes may affect the repeatability of PR measurements. In the current study, measurements in ortho-k-treated eyes were only taken after confirmation of stabilization of ortho-k treatment. Fedtke and colleagues (2011) have recently investigated the influence of lateral pupil misalignment on PR measurement. Their findings suggested that pupil alignment is very critical for the accuracy of PR measurements. They also observed a smaller tolerance on misalignment in the nasal field then in the temporal field. This may explain the larger COR in the nasal field than in the temporal field as observed in the current study. At 30° nasal field, Fedtke and colleagues (2011) reported that a 0.20 mm misalignment of the instrument axis from the pupil centre would give a clinically significant error of 0.25 D and 0.125 D for M and J_0, respectively. Ehsaei and colleagues (2011a) reported tolerance of translational misalignment from the centre of pupil of ~1.0 mm and ~0.5 mm for the 10° and 20° field angles, respectively, which gave a ±0.50 D variability in M factors. Hence, pupil misalignment during PR measurement may also contribute to the variations observed particularly at more extreme angles in ortho-k-treated eyes.

Cycloplegia is not routinely used in PR measurements. Some studies measured PR without paralyzing the accommodation. It is generally accepted that accommodation of < 2.00 D only had a limited effect on peripheral astigmatism within the central 60° horizontal field (Smith *et al.*, 1988; Calver *et al.*, 2007). However, Lundstrom and colleagues (2009) reported that the changes in RPR due to accommodation were not similar between emmetropic and myopic eyes. Without cycloplegia, the pupil size has to be controlled with ambient room lighting because measurements

made by Shin-Nippon open-view auto-refractors are valid for a minimum pupil size of 2.3 mm. If cycloplegia is not used, potential fluctuation in pupil size and crystalline lens thickness may result in more variability in the PR measurements in children. Further studies on PR measurements could include investigation of the influence of pupil size and accommodation.

6.5 Conclusions

The current study found that the mean intra-visit difference in RPR was < 0.05 D in spectacle-wearing eyes, whereas the mean intra- and inter-visits differences were < 0.32 D in ortho-k-treated eyes. Although mean measurement bias did not show significant differences in the current study, a larger variability was observed for measurements made beyond the central 20° field in both spectacle-wearing and ortho-k-treated eyes. Larger variations (wider 95% LoA and larger COR) were found in ortho-k-treated eyes than in spectacle-wearing eyes at most angles (except T10), and larger variations in inter-visit measurements than in intra-visit measurements beyond the central 40° field were found for ortho-k-treated eyes. In addition, greater variability was found at more peripheral angles and in the nasal field than in the temporal field.

Chapter Seven

Repeatability of Peripheral Eye Length Measurements

7.1 Introduction

IOLMaster is currently a commonly used measuring instrument for axial length measurements in research (Chapter 2, Section 2.3.2). It has also been previously shown to be feasible for measuring off-axis eye length (Tepelus *et al.*, 2012) with the use of a Badal optometer for external fixation (Mallen and Kashyap, 2007). In view of the recent research focus on the relationship between peripheral refraction and myopic progression, using the IOLMaster to measure PEL will add useful information to the understanding of eye growth in the course of myopic development.

Repeatability of AL measurements using IOLMaster has been well documented (Lam *et al.*, 2001; Carkeet *et al.*, 2004; Chan *et al.*, 2006; Hussin *et al.*, 2006). The reported COR in AL measurements were about 0.04 mm. Measuring AL in a group of 37 children in two sessions on the same day, Carkeet and colleagues (2004) found that the test-retest repeatability of AL measurements with the IOLMaster was 0.006 ± 0.022 mm. In another group of children aged 11.4 years, Hussin and colleagues (2006) reported inter-visits measurement variability of 0.004 ± 0.019 mm. However, the inter-visit time intervals in their study varied widely, from 4 to 98 days. In general, the variability in AL measurements using the IOLMaster was consistent across studies reported.

With the increased interest in PEL measurements, the repeatability of PEL measurements using the IOLMaster has also been investigated. However, these repeatability studies were conducted on adults only (Ding and He, 2012; Noble, 2012; Verkicharla *et al.*, 2013) Results have been shown to be comparable with that for AL measurements. Ding and colleagues (2012)

measured PEL at 40° in the nasal and the temporal fields while Noble (2012) measured PEL at 20° in superior, inferior, nasal and temporal fields. None of these studies evaluated the repeatability of PEL measurements at different intervals (eccentricities) across the central field, which was the case in most reported peripheral refraction studies. The more recent repeatability study by Verkicharla and colleagues (2013) measured out to 30° in the vertical and the nasal fields and out to 35° in the temporal field at 5° intervals. Their results however, were limited by small subject number (seven subjects) and all the peripheral measurements along the same meridian were grouped together for the determination of repeatability.

In myopic research and interventional myopic control studies which involve repeated measurements of peripheral ocular dimensions at intervals over months or even years, it is crucial to adopt procedures with high precision or good repeatability to detect real changes at different intervals. However, to our knowledge, there is limited information on the repeatability of peripheral eyeball length measurements using the IOLMaster in children. Compared to adults, children may have difficulties with the more peripheral fixations. Moreover, it is unclear whether the instrument can give repeatable measurements of the PEL of a 'distorted' cornea from orthokeratology (ortho-k) or LASIK surgery. Our study on the repeatability of peripheral refraction using an open-field auto-refractor found that repeatability of peripheral refraction was relatively worse in ortho-k-treated eyes compared to the spectacle-wearing eyes of children (Chapter 6). However, there has been no study evaluating repeatability of PEL measurements in eyes with reshaped corneas.

In view of the increased interest in the change in retinal shape during

myopic development and myopic intervention with ortho-k treatment for children, the current study aimed to determine the repeatability of PEL measurements from the IOLMaster in children and to compare the results between children who had received ortho-k treatment and those who had wore spectacles.

7.2 Methods

7.2.1 Study design

Two experiments were designed to determine the repeatability of PEL measurements in spectacle-wearing and ortho-k-treated eyes, respectively.

Experiment I – Repeatability of PEL measurements in spectacle-wearing eyes

Spectacle-wearing children who were enrolled in the longitudinal study were invited to participate in this study. Each subject had to attend two data collection visits. At each visit, AL and PEL across the central 60° horizontal field at 10° intervals were measured with the IOLMaster (Carl Zeiss, Germany) after cycloplegia. Repeated PEL measurements were performed at the second visit within two weeks to minimize the effect of time on axial elongation in this age group. Subjects had to remove their spectacles during measurements. Both visits were arranged at approximately the same time of the day to avoid possible diurnal variation. All PEL measurements were performed by the same examiner.

Experiment II – Repeatability of PEL measurements in ortho-k-treated eyes

Ortho-k-treated children who participated in a longitudinal study (Chapter 9)

were invited to participate in this study. Enrolled subjects had undergone ortho-k treatment for at least one month (after stabilization of treatment) and with satisfactory ortho-k responses (good lens centration as indicated by a bull's eye topographical map, no adverse corneal or external ocular health responses after ortho-k lens wear). Measurement procedures and conditions were the same as those in Experiment 1 and as described in Chapter 5. The first and the second visits were arranged not more than two weeks apart and at roughly the same time of the day. The ortho-k responses should be consistent at both visits in that the center of the treatment zone should be within 0.5 mm from the pupil center, the difference in subjective refraction between visits should not be more than 0.50 D in both sphere and cylinder.

7.2.2 Examination procedures

Every subject in both experiments had to attend two data collection visits. At each visit, the procedures for PEL measurements, as described in Chapter 5, were performed after cycloplegia. Cycloplegia was confirmed by papillary reflex testing and a near point of accommodation of less than two diopters. Only the right eye was measured for all subjects (see Sections 5.3.3).

7.2.3 Treatment of data

Apart from T30, three readings were obtained and averaged for all other eccentricities. At T30˚, only two readings were obtained due to the limitation of 20 measurements on each eye per day, according to the manufacturer's recommendation. The notations of the eccentric measurements refer to the field angles being measured. RPEL was

calculated by subtracting the AL measurement from the PEL measurement at each eccentricity.

7.2.4 Subject number

Since there was no similar study when this experiment was planned, we did not perform a priori subject number calculation. As this experiment recruited subjects from the one-year longitudinal studies on PR and PEL on spectacle-wearing and ortho-k-treated eyes, it was therefore we tried to recruit all these eligible subjects.

7.2.5 Data analysis

Since the distribution of the data obtained were not significantly different from normal distributions (Shapiro-Wilk tests, $0.14 < p < 0.92$), parametric tests were used for the analysis. Student t-tests and repeated measures (RM-) ANOVA were used to compare inter-visit differences for each eccentric angle and among different eccentricities, respectively. Bonferroni corrections were applied where appropriate and the p-values after correction are shown in the results. For measurements collected at each eccentricity, the 95% limits of agreement (LoA) were computed only if there was no significant difference in measurements between visits. The limits were calculated by mean inter-visit difference $\pm$ 1.96 SD. Bland and Altman's plots are also presented. Comparisons of repeatability among eccentric angles or between treatment groups were performed by analysis on the equality of variance using Instat+ version 3.03 (University of Reading, UK). Other statistical analyses were performed using PASW Statistics 18 (IBM Inc., Chicago, IL).

7.3 Results

Since not all subjects who volunteered for the longitudinal study were willing to come back on a second visit, only 25 spectacle-wearing and 20 ortho-k-treated subjects were recruited in Experiments I and II, respectively. However, some subjects did not return within two weeks for the second visit, so their data were excluded, leaving 14 [age = 7.51 (0.83) years] and 18 [age = 8.44 (0.85) years] eligible subjects in Experiments I and II, respectively. Table 7.1 presents the refractive errors of the subjects at recruitment and Tables 7.2 and 7.3 show the mean AL, PEL and RPEL measurements and the mean inter-visit differences in RPEL measurements, respectively.

7.3.1 Repeatability of PEL measurements in spectacle-wearing eyes

The mean AL, PEL and RPEL of the spectacle-wearing eyes at both visits are summarized in Table 7.2. There were no significant differences between inter-visit measurements at any eccentricity for PEL ($0.25 < p < 0.79$, with Bonferroni corrections). The mean inter-visit difference was not more than 0.04 mm for each of the tested eccentricities (Table 7.3). Mean inter-visit differences did not differ significantly with eccentricity ($p = 0.17$).

The 95% LoA was the smallest at N20 (-0.08 – 0.08) and largest at T20 (-0.29 – 0.32) (Table 7.3). The repeatability of PEL measurements at each eccentricity did not differ significantly from that of AL measurements ($0.16 < p < 1.00$), except at T10 and T20 ($p < 0.001$).

Table 7. 1. Refractive errors ± SD of subjects at recruitment (*residual correction)

Subjective refraction components	Groups	
	Spectacle-wearing (N=14)	Ortho-k-treated* (N=18)
Sphere / D	-0.86 ± 1.72	-0.25 ± 0.30
M / D	-0.93 ± 1.76	-0.49 ± 0.32
J_0 / D	0.05 ± 0.09	0.15 ± 0.18
J_{45} /D	0.01 ± 0.15	0.03 ± 0.07

Table 7.2. Repeated measurements of axial and peripheral eyeball lengths (mean ± SD mm) within 2 weeks.

	Spectacle-wearing group (N = 14)		Ortho-k-group (N = 18)	
Axial and peripheral eyeball lengths				
Field angles	V1	V2	V1	V2
N30	22.72 ± 0.75	22.7 ± 0.76	23.33 ± 0.58	23.32 ± 0.54
N20	23.19 ± 0.85	23.18 ± 0.85	24.03 ± 0.59	24.01 ± 0.58
N10	23.41 ± 0.90	23.39 ± 0.92	24.36 ± 0.60	24.36 ± 0.64
AL	23.50 ± 0.96	23.53 ± 0.96	24.47 ± 0.60	24.47 ± 0.61
T10	23.49 ± 0.92	23.45 ± 0.92	24.28 ± 0.58	24.27 ± 0.57
T20	23.25 ± 0.93	23.18 ± 0.90	23.81 ± 0.71	23.74 ± 0.65
T30	23.01 ± 0.80	23.00 ± 0.80	23.45 ± 0.63	23.46 ± 0.60
Relative peripheral eyeball lengths				
Field angles	V1	V2	V1	V2
N30	-0.79 ± 0.27	-0.82 ± 0.25	-1.13 ± 0.18	-1.15 ± 0.24
N20	-0.32 ± 0.16	-0.35 ± 0.15	-0.44 ± 0.15	-0.46 ± 0.16
N10	-0.01 ± 0.09	-0.14 ± 0.08	-0.10 ± 0.08	-0.10 ± 0.07
T10	-0.01 ± 0.12	-0.08 ± 0.13	-0.19 ± 0.14	-0.20 ± 0.15
T20	-0.25 ± 0.18	-0.35 ± 0.17	-0.65 ± 0.30	-0.73 ± 0.27
T30	-0.50 ± 0.23	-0.53 ± 0.23	-1.02 ± 0.25	-1.01 ± 0.24

No significant inter-visit difference at any eccentricity (Spectacle-wearing group: $-2.34 < t < 1.12$, $0.04 < p < 0.79$; Ortho-k-treated group: $-0.26 < t < 1.96$, $0.07 < p < 0.97$, with Bonferroni correction)

(V1 = first visit, V2 = second visit; N = nasal field, AL = axial length; T = temporal field)

Table 7.3. Inter-visit differences (mean ± SD mm) in axial and peripheral eyeball length measurements and 95% limits of agreement (95% LoA) in spectacle-wearing and ortho-k-treated eyes.

	Groups			
	Spectacle-wearing (N = 14)		Ortho-k-treated (N = 18)	
Axial length and peripheral eyeball lengths				
Field angles	Inter-visit differences	95% LoA	Inter-visit differences	95% LoA
N30	0.00 ± 0.05	-0.10 - 0.10	-0.01 ± 0.06*	-0.13 – 0.11*
N20	0.00 ± 0.04	-0.08 – 0.08	0.02 ± 0.05	-0.08 – 0.12
N10	0.01 ± 0.06	-0.11 – 0.13	0.00 ± 0.09	-0.18 – 0.18
AL	-0.03 ± 0.04	-0.11 – 0.05	-0.00 ± 0.03	-0.06 – 0.06
T10	0.04 ± 0.15	-0.25 – 0.33	0.01 ± 0.16	-0.30 – 0.32
T20	0.02 ± 0.16*	-0.29 – 0.32*	0.07 ± 0.16	-0.24 – 0.38
T30	0.01 ± 0.06	-0.11 – 0.13	-0.01 ± 0.08	-0.17 – 0.15
Relative peripheral eyeball lengths				
Field angles	Inter-visit differences	95% LoA	Inter-visit differences	95% LoA
N30	0.03 ± 0.07	-0.10 – 0.16	0.02 ± 0.13*	-0.24 – 0.28*
N20	0.03 ± 0.05	-0.07 – 0.13	0.02 ± 0.06	-0.09 – 0.13
N10	0.04 ± 0.06	-0.07 – 0.15	0.00 ± 0.09	-0.17 – 0.17
T10	0.07 ± 0.15	-0.23 – 0.37	0.01 ± 0.16)	-0.30 – 0.32
T20	0.04 ± 0.16*	-0.28 – 0.36*	0.07 ± 0.16	-0.24 – 0.38
T30	0.04 ± 0.07	-0.10 – 0.17	0.00 ± 0.08	-0.17 – 0.16

(N = nasal field; AL = axial length; T = temporal field)

*after exclusion of one outlier, i.e. mean ± 3SD

7.3.2 Repeatability of RPEL measurements in spectacle-wearing eyes

There was no significant inter-visit difference in RPEL measurements at any eccentricity in the spectacle-wearing eyes ($p > 0.15$, with Bonferroni correction). The mean inter-visit difference was not more than 0.07mm across the horizontal 60°. Figure 7.1 presents the Bland and Altman's plots of 95% limits of agreement of inter-visit measurements for AL and RPEL at each eccentricity in the spectacle-wearing eyes. The 95% LoA was the smallest at N20 (-0.07 – 0.13) and largest at T20 (-0.28 – 0.36). Repeatability of RPEL measurements at each eccentricity was not significantly different from that of AL measurements ($p > 0.053$), except at T20 and T30 ($p < 0.001$) (Table 7.4).

7.3.3 Repeatability of PEL measurements in ortho-k-treated eyes

The mean inter-visit difference was not more than 0.07 mm at each eccentricity (Table 7.3). There were no significant inter-visit differences in PEL measurements at any eccentricity ($0.07 < p < 0.97$), and the inter-visit differences did not differ significantly by eccentricities ($p = 0.70$). The 95% LoA was smallest at N20 (-0.08 – 0.12) and largest at T10 (-0.30 – 0.32) and T20 (-0.24 – 0.38) (Table 7.3). Repeatability of PEL measurements at each eccentricity was worse than that of AL measurements in ortho-k-treated eyes ($p < 0.04$).

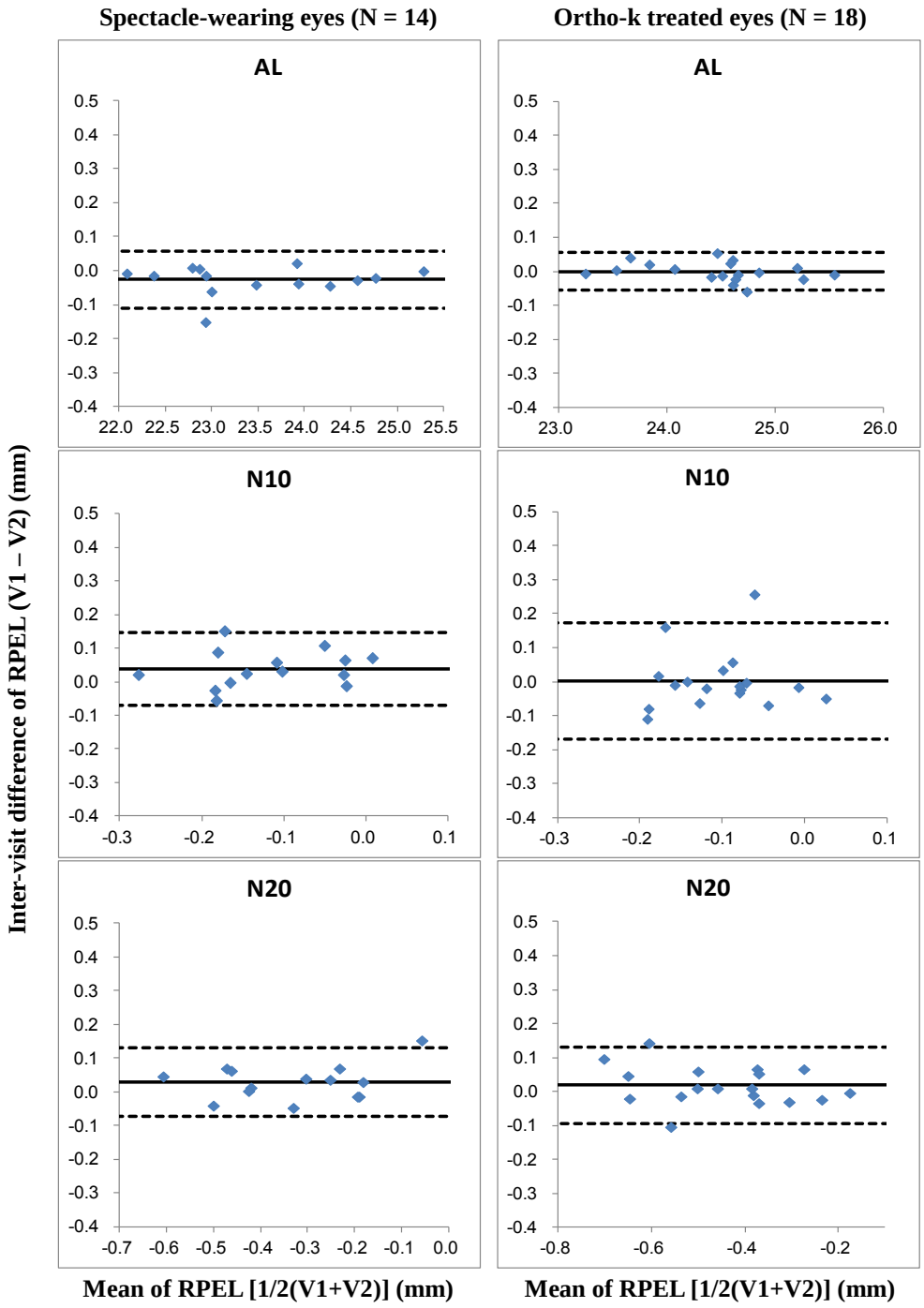


Figure 7.1 Bland and Altman's plots of 95% limits of agreement between measurements taken in two separate visits for axial length (AL) and relative peripheral eye length (RPEL). N = nasal field; T = temporal field. V1 and V2 = measurements taken from the 1st and 2nd visits, respectively. (* one outlier excluded)

(Figure 7.1 continued)

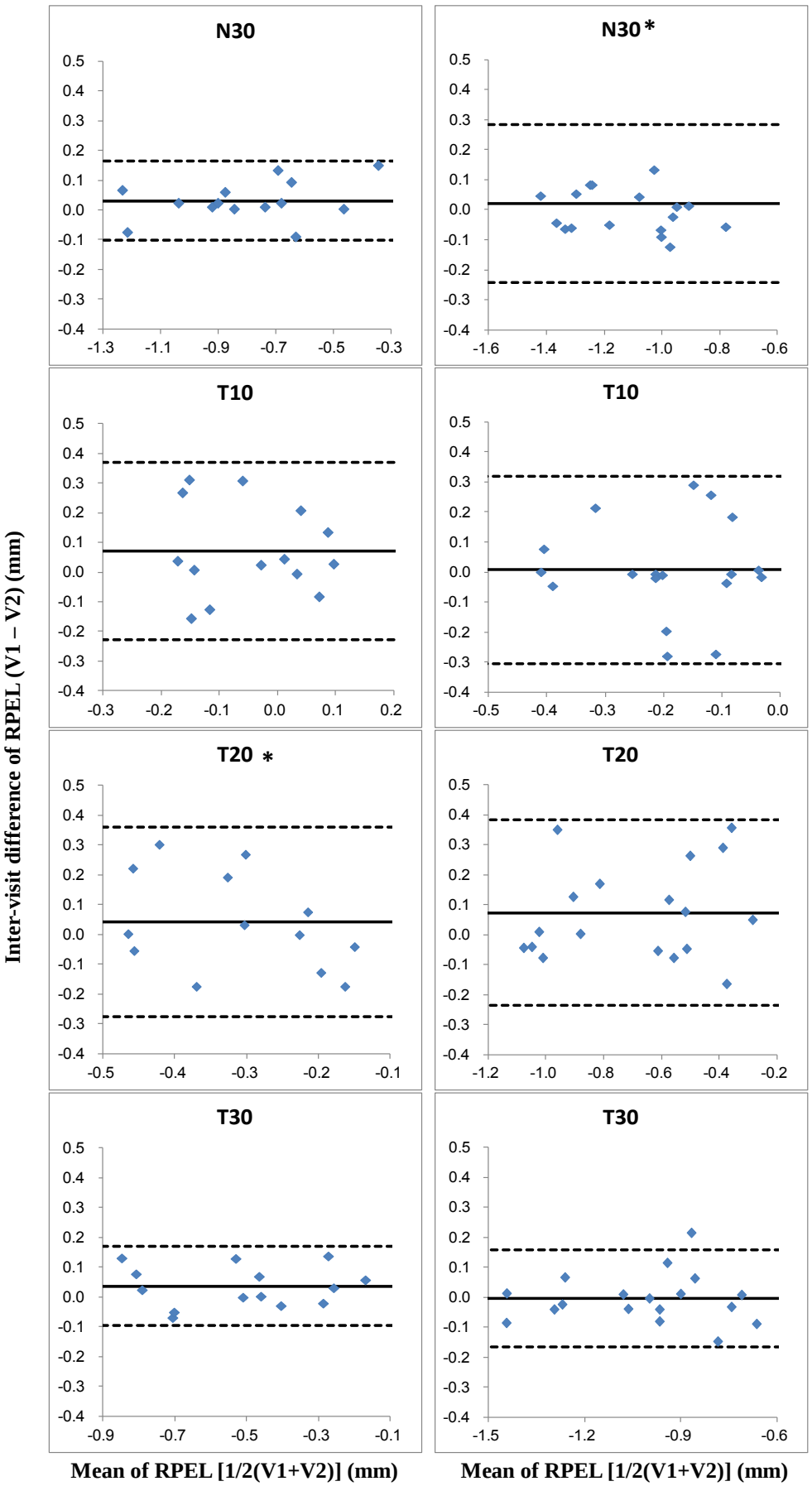


Table 7. 4. Analysis of equality of variances of measurement bias between axial length and relative peripheral eyeball length at different field angles in spectacle-wearing and ortho-k-treated eyes

	Relative field angles					
	N30	**N20**	**N10**	**T10**	**T20**	**T30**
Spectacle-wearing eyes						
F statistics	3.06	1.56	2.25	14.06	16.00	3.06
p-value	0.05	0.43	0.16	<0.001	<0.001	0.05
Ortho-k-treated eyes						
F-statistics	18.78	4.00	9.00	28.44	28.44	7.11
p-value	<0.001	<0.01	<0.001	<0.001	,0.001	<0.001

7.3.4 Repeatability of RPEL measurements in ortho-k-treated eyes

The mean inter-visit difference was not more than 0.07 mm at any eccentricity in ortho-k-treated eyes (Table 7.3). No significant inter-visit differences in RPEL measurements were found at any eccentricity ($0.07 < p < 0.93$). The 95% LoA was the smallest at N20 (-0.09 – 0.13) and the largest at T10 (-0.30 -0.32) and (-0.24 – 0.38) (Table 7.3). The Bland and Alman's plots of 95% LoA between the repeated RPEL measurements are shown in Figure 7.1 and the analysis on the equality of variances of the measurement bias between RPEL and AL are shown in Table 7.4. The repeatability of RPEL measurements was significantly greater than that of AL measurements at each eccentricity ($p < 0.001$).

7.3.5 Comparison of repeatability of PEL measurements between spectacle-wearing and ortho-k-treated eyes

The mean inter-visit differences in AL and PEL measurements were not significantly different between spectacle-wearing and ortho-k-treated eyes at any eccentricity ($0.05 < p < 0.97$). Repeatability of AL and PEL measurements (COR) were not significantly different between spectacle-wearing and ortho-k-treated eyes ($0.09 < p < 0.83$). The 95% LoA were comparable between the two groups at all eccentricities (Figure 7.1).

7.3.6 Comparison of repeatability of RPEL measurements between spectacle-wearing and ortho-k-treated eyes

The mean inter-visit difference in RPEL measurements were not significantly different between spectacle-wearing and ortho-k-treated eyes at any eccentricity ($0.16 < p < 0.80$). No significant difference in the repeatability of RPEL measurements between the two subject groups were found ($p > 0.18$). The Bland and Alman's plots for RPEL measurements show that the variability of measurement bias was comparable between the spectacle-wearing and ortho-k-treated eyes at each eccentricity (Figure 7.1).

7.4 Discussion

Compared to previous studies (Lam *et al.*, 2001; Carkeet *et al.*, 2004; Chan *et al.*, 2006; Hussin *et al.*, 2006), the current study found a larger measurement variability in AL measurements in spectacle-wearing eyes ($0.004 < p < 0.009$). This may be because the second measurement in the current study was taken on a different day (7.43 ± 3.39 days after the first

measurement), while in most of the other studies, the second measurement was taken on the same day. However, this different-day variation should be taken into consideration when PEL are to be monitored longitudinally. While previous studies measured only a limited number of eccentricities (Ding and He, 2012; Noble, 2012) and/or with smaller sample size (Hussin *et al.*, 2006), our study evaluated the measurement repeatability of PEL across the central 60° horizontal field at 10° intervals in children. We also investigated the effect of ortho-k treatment on the variability of PEL measurements. To our knowledge, our study is the first to report repeatability of PEL measurements at different eccentricities across the central 60º field in both spectacle-wearing and ortho-k-treated subjects. Our results show that the variabilities of PEL measurements at most of the tested eccentricities were comparable to AL measurements in spectacle-wearing eyes. Only those at T10 and T20 were significantly greater than those at other eccentricities. This was also observed in ortho-k-treated eyes. It is spectulated that this might be because the profile of the retina changes more rapidly in the para-disc area, leaving the repeated measurements (between days) more prone to variations. Compared to the results from Noble's study (2012) where the 95% LoA were -0.14 – 0.12 and -0.24 – 0.23 in the nasal and temporal 20º field, respectively, our results at N20 ($p = 0.04$) showed less variability while those at T20 were similar ($p = 0.19$). Since the age of the subjects in Noble's study was similar to the age of the children in the current study, the difference in the reported results may be because measurements around the para-optic disc region gave larger variations in PEL measurements. This was further evidence by the significantly greater 95% LoA at T10 and T20 than those at other field

angles. This is also a potential cause for the significant nasal-temporal difference in measurement variability observed in the N10-T10 and N20-T20 pairs in both spectacle-wearing and ortho-k-treated eyes.

Variability in PEL measurements was unaffected by ortho-k treatment across the central retina. Although the 95% LoA were slightly larger in ortho-k-treated eyes than in spectacle-wearing eyes, the differences were not significant.

Unlike PR measurements, PEL measurements were not affected by ortho-k treatment. One possible reason is that corneal reshaping largely alters the optics of the anterior ocular surface, while the biometry of the whole optical system is virtually unaffected.

Our design of the adaptation unit fixed the distance between consecutive LEDs and required the central LED to be at 25 cm away from the center of eye rotation in order to ensure the LEDs are subtending angles at 10° apart at the tested eye. The determination of the test distance was affected by the alignment by examiner and would eventually affect the actual angle of the LEDs subtending at the tested eye. We assumed a ± 2 cm error in the test distance (i.e. 23 cm to 27 cm) and calculated its influence on the angle subtended by each LED by substituting the fixed distance between consecutive LEDs into a tangent function. The error induced in the angle subtended at each eccentricity ranged from 0.7° (at 10°eccentric field) to 2.1° (at 30° eccentric field). We believe that the influence of alignment by the examiner in fixing the test distance on the angle subtended for the tested eccentricities was not significant.

That only three repeated readings were taken for each PEL measurement

added another limitation to the current study. It would be advisable to introduce other procedures or instruments with lower laser energy power which would overcome the laser safety issue in *in-vivo* measurements. Alternatives such as choosing beam splitters which would cover infra-red up to 760 nm would effectively reduce the dosage of laser reaching the retina.

7.5 Conclusions

Repeatability of PEL measurements, except at regions proximal to the para-optic disc, was found to be comparable to those of AL measurements using the IOLMaster. Ortho-k treatment did not affect the repeatability of PEL measurements. PEL measurements made by the current set-up showed good repeatability.

Chapter Eight

Changes in Peripheral Refraction and Peripheral Eye Length in Spectacle-wearing Eyes

Declaration

Parts of the contents of this chapter have been previously published and permission is obtained from the publisher to reuse contents of the paper in this chapter. Citation of the related publication is as follows:
Lee TT and Cho P (2013). Relative peripheral refraction in children: twelve-month changes in eyes with different ametropias. Ophthalmic Physiol Opt 33(3):283-293

8.1 Introduction

Evidence from animal studies has suggested that relative peripheral hyperopia may be a potential risk factor for myopic development (see Section 2.1). This has led researchers to consider a similar effect of relative peripheral hyperopia in human myopia. In humans, PR patterns were found to differ by ametropia. Mutti and colleagues (2007) reported that relative peripheral hyperopia developed before the onset of myopia. However, results from some longitudinal studies did not find significant correlations between baseline RPR and myopia progression (see Section 2.4). Hence, whether RPR plays a role in human myopia is still unclear.
This chapter reports a study examining the optical (i.e. PR) and biometric (i.e. PEL) characteristics of children with different ametropias. The aim of this study was to evaluate the relationship between central refractive changes, baseline PR and PEL, and the changes in PR and PEL of the young subjects during the study period.

8.2 Methods

Children aged six to nine years, meeting the inclusion criteria listed in Table 5.1 in Chapter 5, were recruited.

Written consent was obtained from their parents or guardians and the study was compliant with the Declaration of Helsinki. Subjects with any ocular pathologies or functional disabilities were excluded. Spectacle correction with single vision lenses was prescribed where indicated.

Central refraction (CR) and PR were monitored biannually for 12 months. Each subject received a detailed eye examination by the same examiner at each biannual data collection visit. At each visit, the outcome variables including subjective refraction, PR and PEL were measured, following cycloplegia. Other examinations included corneal topography, external and internal ocular health evaluation and non-contact tonometry. Cycloplegia was achieved by applying one drop of Alcaine 0.4% and one drop of Tropicamide 1.0%, followed by another drop of Cyclopentolate 1.0% five minutes later. Refraction was performed at least 45 minutes after the instillation of the last drop, and after cycloplegia was confirmed by checking the pupil responses and accommodation.

8.2.1 Examination procedures

Examinations performed before cycloplegia included subjective refraction, visual acuity in LogMAR, external ocular health evaluation, corneal topography with Medmont E300 topographer and non-contact tonometry. Examinations performed after cycloplegia included subjective refraction, PR and PEL measurements, corneal topography and internal ocular health

evaluation. Detailed procedures are described in Chapter 5.

8.2.2 Definitions

Ametropia referred to the M vector (i.e. SER) of cycloplegic subjective refraction (Subj-M) at each visit. Refractive grouping was made according to the Subj-M at the baseline visit (IH = initial hyperopes, IE = initial emmetropes and IM = initial myopes). Myopia was defined by SER $\leq$ -0.50 D, while emmetropia was defined by -0.50 D < SER < 0.50 D, and hyperopia by SER $\geq$ 0.50 D in Subj-M. CR referred to the cycloplegic objective central refraction measured by an auto-refractor.

8.2.3 Treatment of data

All refractive data were transposed into vector components M, J_0 and J_{45} (see Section 5.3.2.3). RPR was computed by subtracting CR from PR measurements for each vector. RPEL was computed by subtracting AL from PEL measurements. All eccentricities were expressed in terms of visual field angles.

8.2.4 Data analysis

Cycloplegic subjective refraction (Subj-M, $-J_0$ and $-J_{45}$), PR (PR-M, $-J_0$ and $-J_{45}$), RPR (RPR-M, $-J_0$ and $-J_{45}$), PEL and RPEL measurements were tested for normal distribution using Kolmogorov-Smirnov tests (Appendix I). Since most parameters were normally distributed, parametric statistical tests were employed for the rest of the analyses:

Differences among refractive groups

One-way ANOVA was used to compare the baseline PR among different

refractive groups.

Time effect on PR and PEL characteristics

The time effect on PR and PEL were determined using repeated measures (RM)-ANOVA for each refractive group.

Associations between parameters

Pearson coefficients (r) were used to show the association between the tested parameters. The following pairs of association were reported:

(a) baseline PR-M - baseline PEL

(b) changes in PR-M - changes in PEL

(c) baseline RPR-M - baseline RPEL

(d) changes in RPR-M - changes in RPEL

(e) changes in Subj-M and baseline RPR

(f) changes in Subj-M and changes in PR-M

(g) changes in Subj-M and changes in RPR-M

(h) axial elongation and baseline PEL

(g) changes in Subj-M and baseline PEL

(i) axial elongation and baseline RPEL

(j) changes in Subj-M and baseline RPEL

(k) axial elongation and changes in PEL

(l) changes in Subj-M and changes in PEL

(m) axial elongation and changes in RPEL

(n) changes in Subj-M and changes in RPEL

Subgroup analyses

Subgroup analyses were performed according to the central myopic shift (changes in Subj-M) in 12 months. Subjects with 1.00 D or less central

myopic progression were considered as SLOW progressors while those with a myopic shift >1.00 D were grouped as FAST progressors. Since the IH group had only one subject who showed fast progression and five who did not show a myopic shift at all, only a SLOW progressing subgroup was formed. A total of five subgroups (IH-SLOW, IE-FAST, IE-SLOW, IM-FAST and IM-SLOW) were formed. Comparisons between (1) IE-FAST and IE-SLOW, (COMET2-Study-Group) IM-FAST and IM-SLOW and (3) IH-SLOW and IE-SLOW subgroups were made to determine if RPR and RPEL were related to the rate of central myopic shift.

Where applicable, a Bonferroni correction was employed to adjust the critical values and the adjusted critical value (α) will be specified. All statistical tests were performed with PASW Statistics 18 (SPSS Inc., New York, USA).

8.3 Results

A total of 58 subjects met the criteria and were recruited. All subjects completed the study. The numbers of IH, IE and IM subjects were 23, 16 and 19, respectively. Their initial subjective refraction and AL are summarized in Table 8.1. Baseline Subj-M were significantly different among the three groups ($p < 0.001$), while AL were significantly larger in the IM than in the IE and IH groups ($p \leq 0.001$), but not between IE and IH groups ($p = 0.05$) The mean difference ± SD between the Subj-M and CR-M was 0.24 ± 0.22 D, with Subj-M being less myopic ($p < 0.001$).

Table 8.1. Baseline mean cycloplegic subjective refraction ± SD and axial length ± SD of each refractive group

Groups / N	Age ± SD /Years	Cycloplegic subjective refraction ± SD /D			Axial Length ± SD /mm
		M	J_0	J_{45}	
IH / 23	7.56 ± 0.88	1.15 ± 0.56	0.15 ± 0.23	0.010 ± 0.10	22.74 ± 0.90
IE / 16	8.09 ± 0.66	-0.18 ±0.22	0.11 ± 0.21	-0.01 ± 0.07	23.11 ± 0.70
IM / 19	7.87 ± 0.80	-1.79 ± 0.75	0.12 ± 0.16	0.01 ± 0.07	24.08 ± 0.78

IH (initially hyperopic): SER ≥ 0.50 D; IE (Initially emmetropic): -0.50 D < SER < 0.50 D; IM (Initially myopic): SER ≤ -0.50 D;

All groups became more myopic over the 12-month study period with significant changes in mean Subj-M ± SD of -0.28 ± 0.34 D, -0.82 ± 0.53 D and -1.13 ± 0.41 D for IH, IE and IM groups, respectively ($p < 0.002$). However, changes in Subj-J_0 and -J_{45} were not significant in any of the refractive groups ($0.08 < p < 0.70$).

8.3.1 Peripheral refraction

8.3.1.1 Baseline peripheral refraction

Baseline PR-M was significantly different among the three refractive groups ($p < 0.001$) (Figure 8.1), while PR-J_0 and PR-J_{45} did not differ significantly by refractive groups ($0.21 < p < 0.94$, with Bonferroni corrections).

8.3.1.2 Twelve-month changes in peripheral refraction

Over the study period, PR-M became more myopic (or less hyperopic) at all angles in all groups (Figure 8.1). The largest changes were observed in the IM group (0.56 D – 1.15 D) while the smallest changes were observed in the IH group (0.03 D – 0.34 D). In the IH group, PR-M changed significantly with time only at T10 ($p < 0.001$). In the IE group, PR-M changed significantly with time for angles from N30 to T10 ($p < 0.001$). All angles across the central 60° field in the IM group showed significant changes in PR-M with time ($p < 0.001$, RM-ANOVA).

Except PR-J_0 showed significant changes with time at T30 in the IE group ($p = 0.006$), PR-J_0 and PR-J_{45} did not change significantly in all groups (PR-J_0: $0.06 < p < 0.97$; PR-J_{45}: $0.14 < p < 0.98$, with Bonferroni correction).

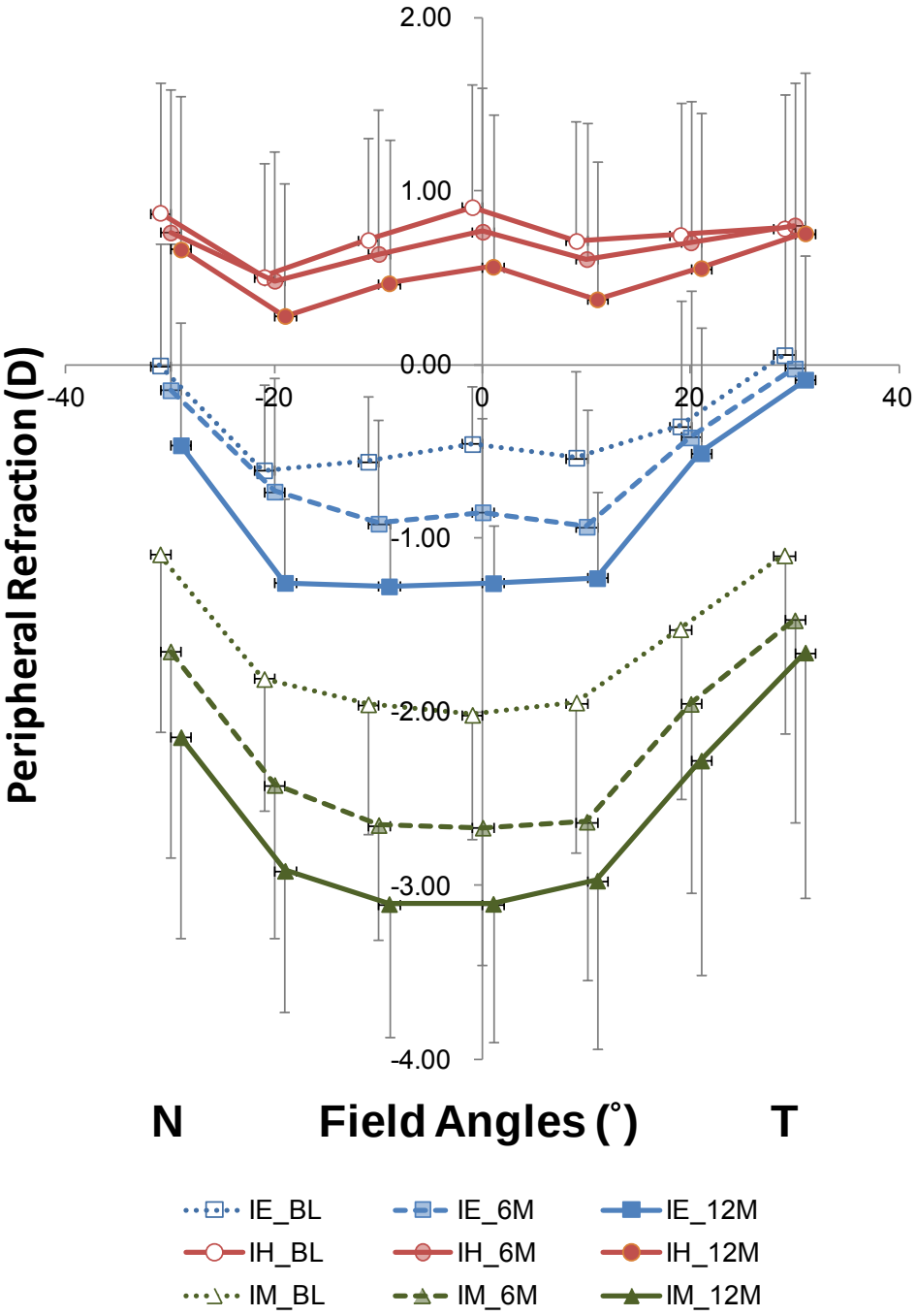


Figure 8.1. Peripheral refraction in different refractive groups over 12 months [PR-M: M vector of peripheral refraction; Baseline data are presented by open symbols with dotted lines, 6-month visit data by semi-filled symbols with broken lines and 12-month visit data by closed symbols with solid). IH (initially hyperopic): SER ≥ 0.50 D; IE (Initially emmetropic): -0.50 D < SER < 0.50 D; IM (Initially myopic): SER ≤ -0.50 D; N: nasal; T: temporal; C: central; Error bar = 1 SD]

8.3.2 Relative peripheral refraction

The biannual data for RPR-M, $-J_0$ and $-J_{45}$ are shown in Figures 8.2-8.4. .

8.3.2.1 Baseline relative peripheral refraction

At baseline, mean RPR-M of the IH group was found to be myopic (< 0.00 D) across the central 60° field. In the IE group, mean relative myopia (to a lesser extent than that in the IH group) was observed across the N20 to T10 field only, with relative hyperopia (RPR-M > 0.00 D) beyond. In the IM group, the peripheral field was found to be relatively hyperopic and the relative hyperopia increased with field angles. Pair-wise comparisons of RPR-M showed that IH and IM groups differed significantly at all angles while IE and IM did not show any difference. IH and IE groups only differed at T30. RPR-J_0 decreased (i.e. became more negative) towards the peripheral fields in all groups while RPR-J_{45} was close to zero across the central 60° field. RPR-M were significantly different among groups ($p < 0.0023$) at all angles, whereas there were no significant differences among groups for RPR-J_0 and $-J_{45}$ ($0.06 < p < 0.96$).

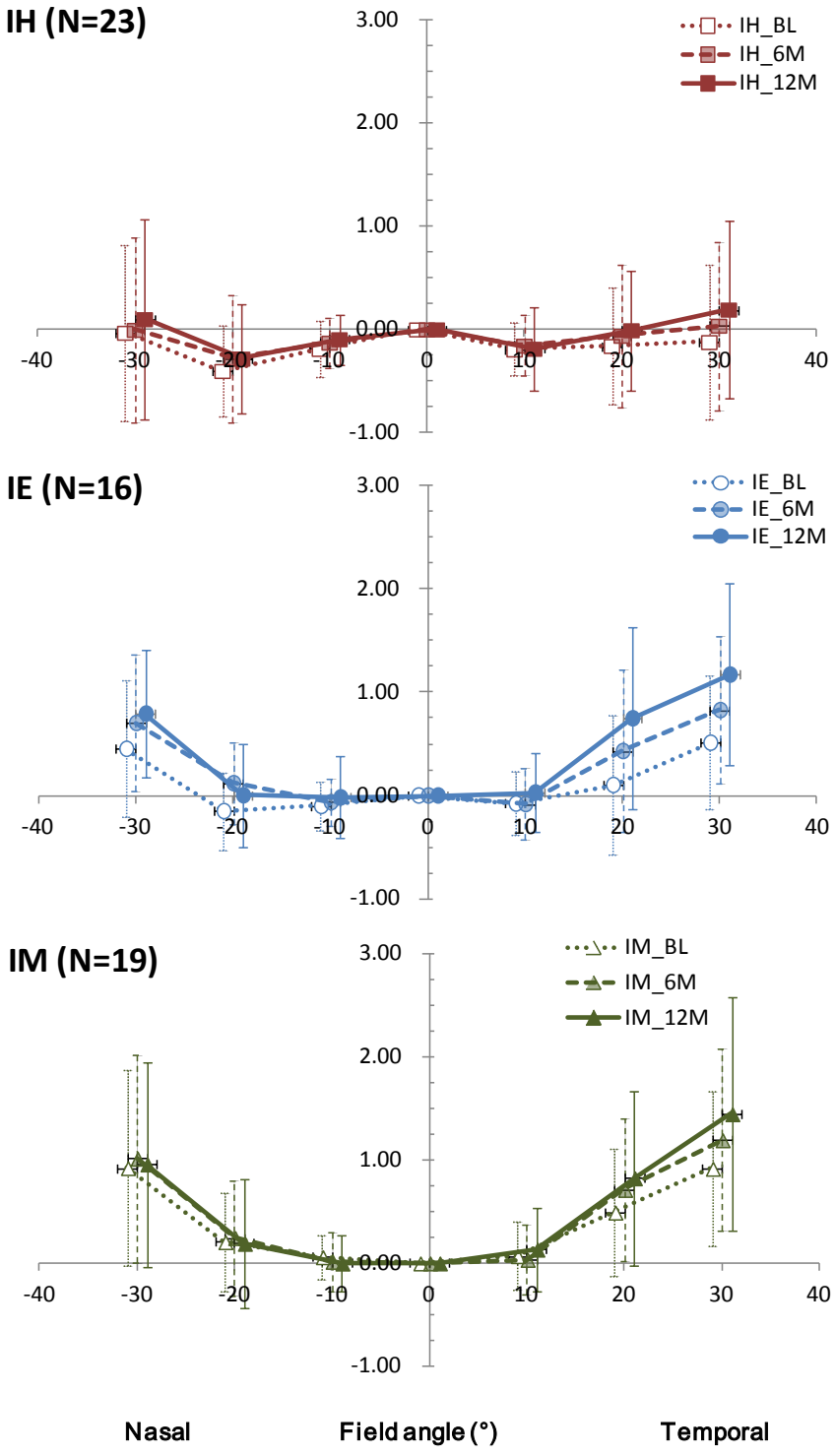


Figure 8.2. M factor of relative peripheral refraction (D) in different refractive groups over 12 months. Baseline data are presented by open symbols with dotted lines, 6-month visit data by semi-filled symbols with broken lines and 12-month visit data by closed symbols with solid). IH (initially hyperopic): SER ≥ 0.50 D; IE (Initially emmetropic): -0.50 D < SER < 0.50 D; IM (Initially myopic): SER ≤ -0.50 D; N: nasal; T: temporal; C: central. Error bar = 1 SD

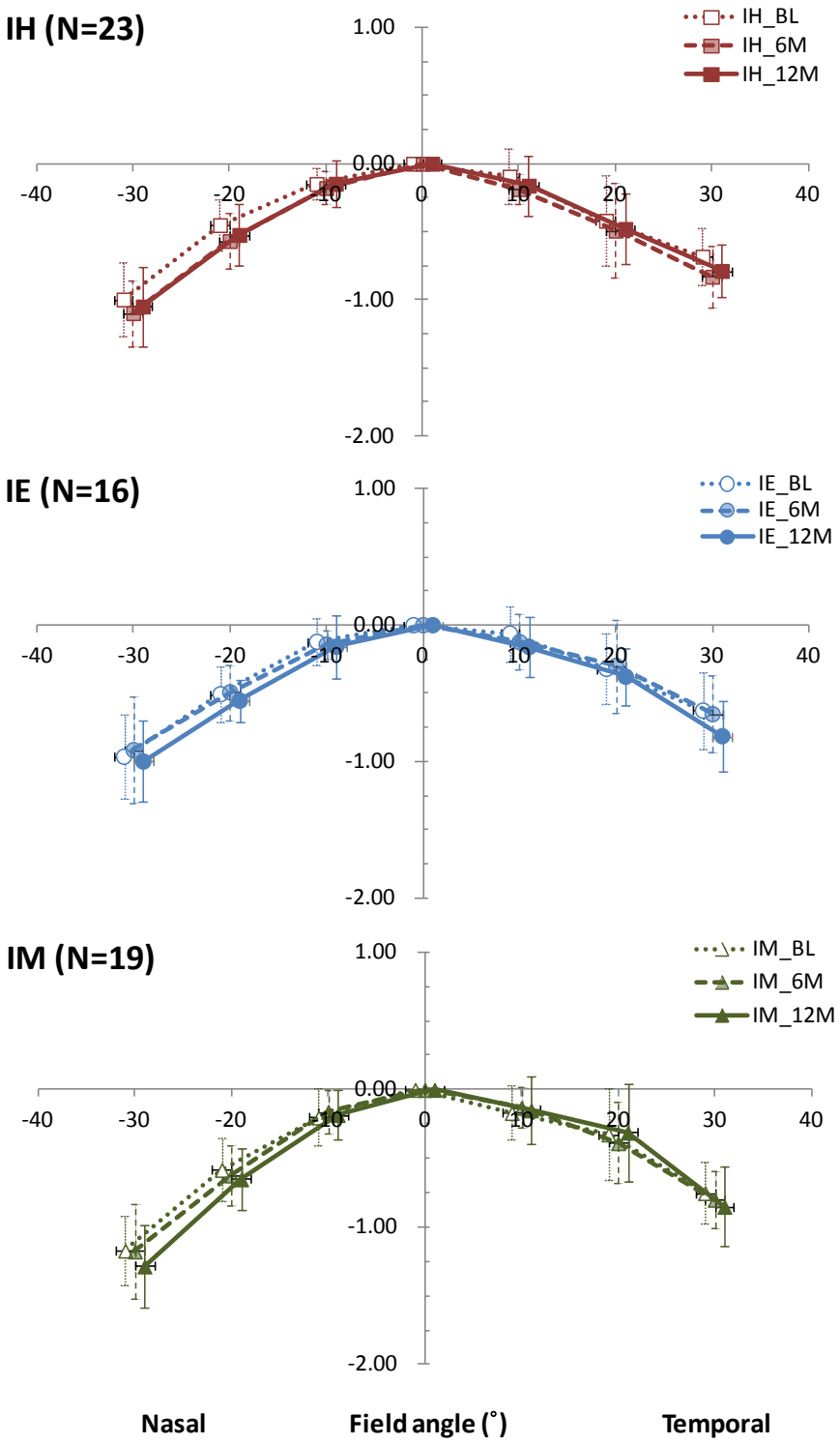


Figure 8.3. J_0 factor of relative peripheral refraction (D) in different refractive groups over 12 months. Baseline data are presented by open symbols with dotted lines, 6-month visit data by semi-filled symbols with broken lines and 12-month visit data by closed symbols with solid). IH (initially hyperopic): SER ≥ 0.50 D; IE (Initially emmetropic): -0.50 D < SER < 0.50 D; IM (Initially myopic): SER ≤ -0.50 D; N: nasal; T: temporal; C: central. Error bar = 1 SD.

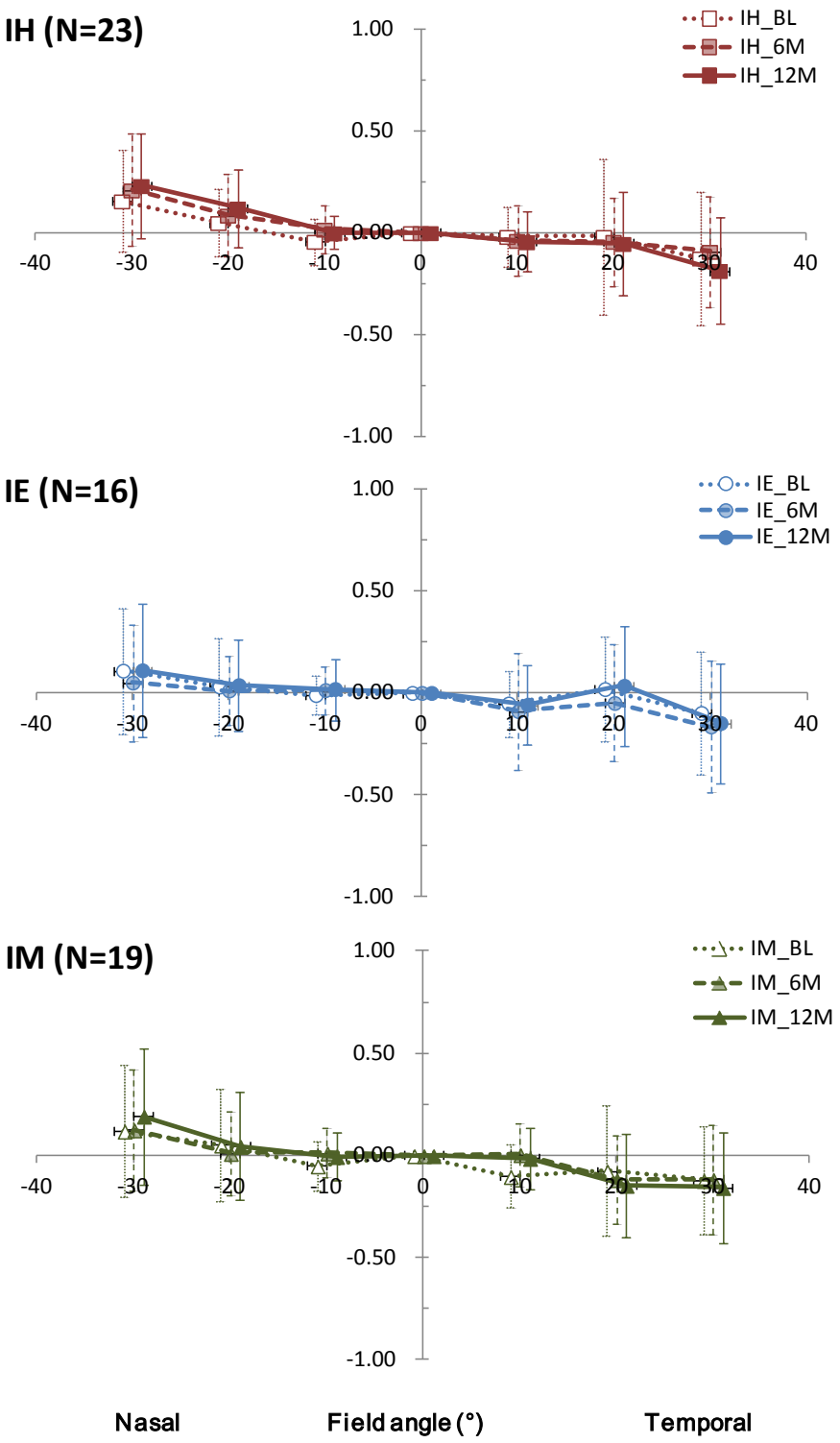


Figure 8.4. J_{45} factor of relative peripheral refraction in different refractive groups over 12 months. Baseline data are presented by open symbols with dotted lines, 6-month visit data by semi-filled symbols with broken lines and 12-month visit data by closed symbols with solid). IH (initially hyperopic): SER ≥ 0.50 D; IE (Initially emmetropic): -0.50 D < SER < 0.50 D; IM (Initially myopic): SER ≤ -0.50 D; N: nasal; T: temporal; C: central. Error bar = 1 SD.

8.3.2.2 Twelve-month changes in relative peripheral refraction

In the IH and IM groups, the changes of RPR-M with time were significant only at T30 ($0.001 < p < 0.004$). In the IE group, the RPR changes with time were significant at N20, T20 and T30 ($p < 0.003$, Bonferroni corrected). Changes in RPR-J_0 and -J_{45} with time were not significant at any angle in any group ($0.05 < p < 0.99$, with Bonferroni correction), except for J_0 at T30 in the IE group ($p < 0.001$).

8.3.3 Peripheral eye length

8.3.3.1 Baseline peripheral eye length

Figures 8.5 and 8.6 show the PEL and RPEL, respectively, of each refractive group over 12 months. Baseline AL and PEL were significantly different among different refractive groups ($p < 0.001$). Subjects in the IM group had significantly longer AL and PEL than those in the IH and IE groups ($p \leq 0.01$) while the IE and IH groups did not differ significantly from each other at any angle.

8.3.3.2 Twelve-month changes in peripheral eye length

There were significant increases in AL and PEL over 12 months in all groups (IH: $p \leq 0.005$; IE: $p < 0.001$; IM: $p < 0.001$). The increase was significantly different among refractive groups from N30 to T10. Post-hoc comparisons showed that significant differences were due to differences between the IH and IM at all angles while the IE and IM groups differed significantly only at T20 to T30.

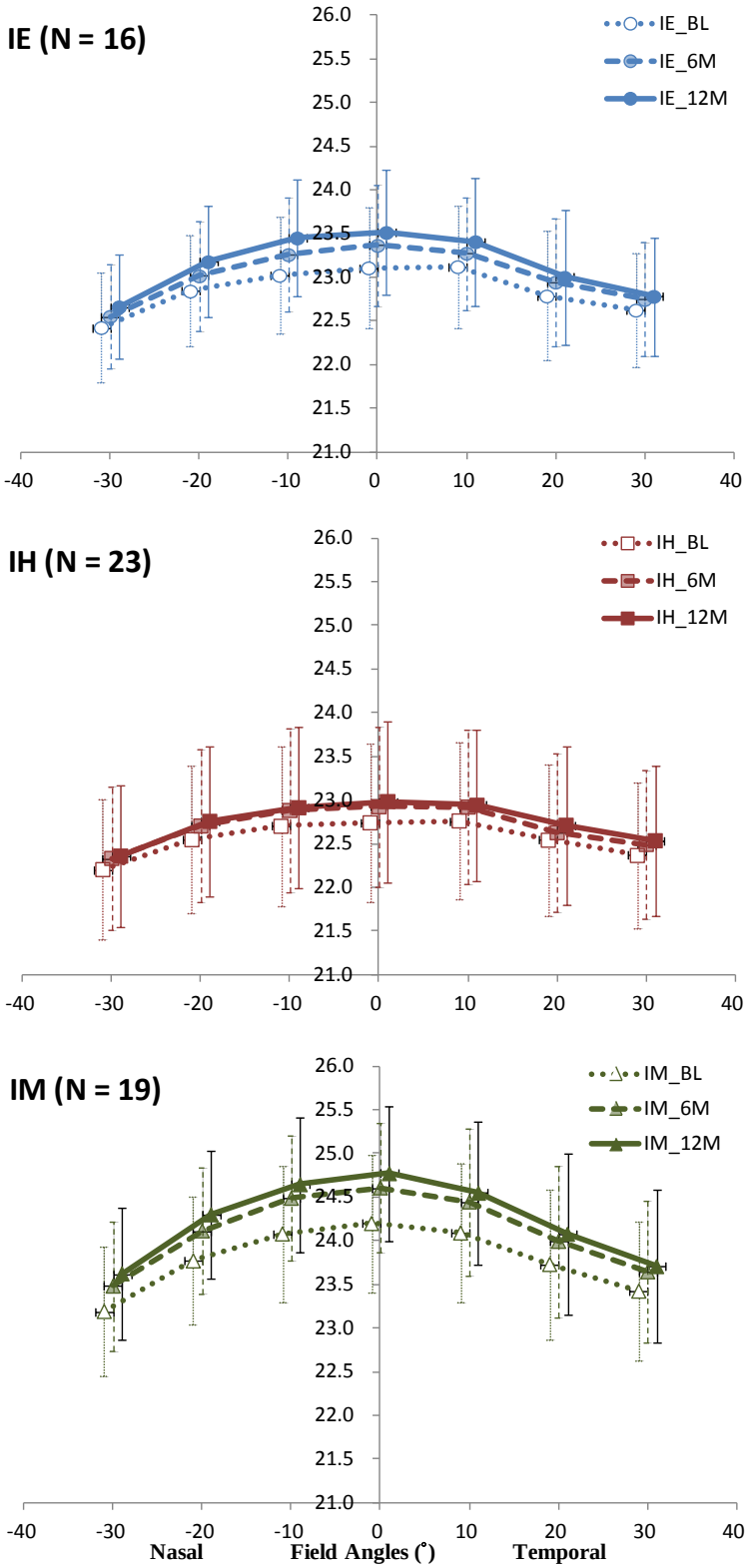


Figure 8.5. Peripheral eye length (mm) in different refractive groups over 12 months [Baseline data are presented by open symbols with dotted lines, 6-month visit data by semi-filled symbols with broken lines and 12-month visit data by closed symbols with solid). IH (Initially hyperopic): SER ≥ 0.50 D; IE (Initially emmetropic): -0.50 D < SER < 0.50 D; IM (Initially myopic): SER ≤ -0.50 D; N: nasal; T: temporal; C: central; Error bar = 1 SD].

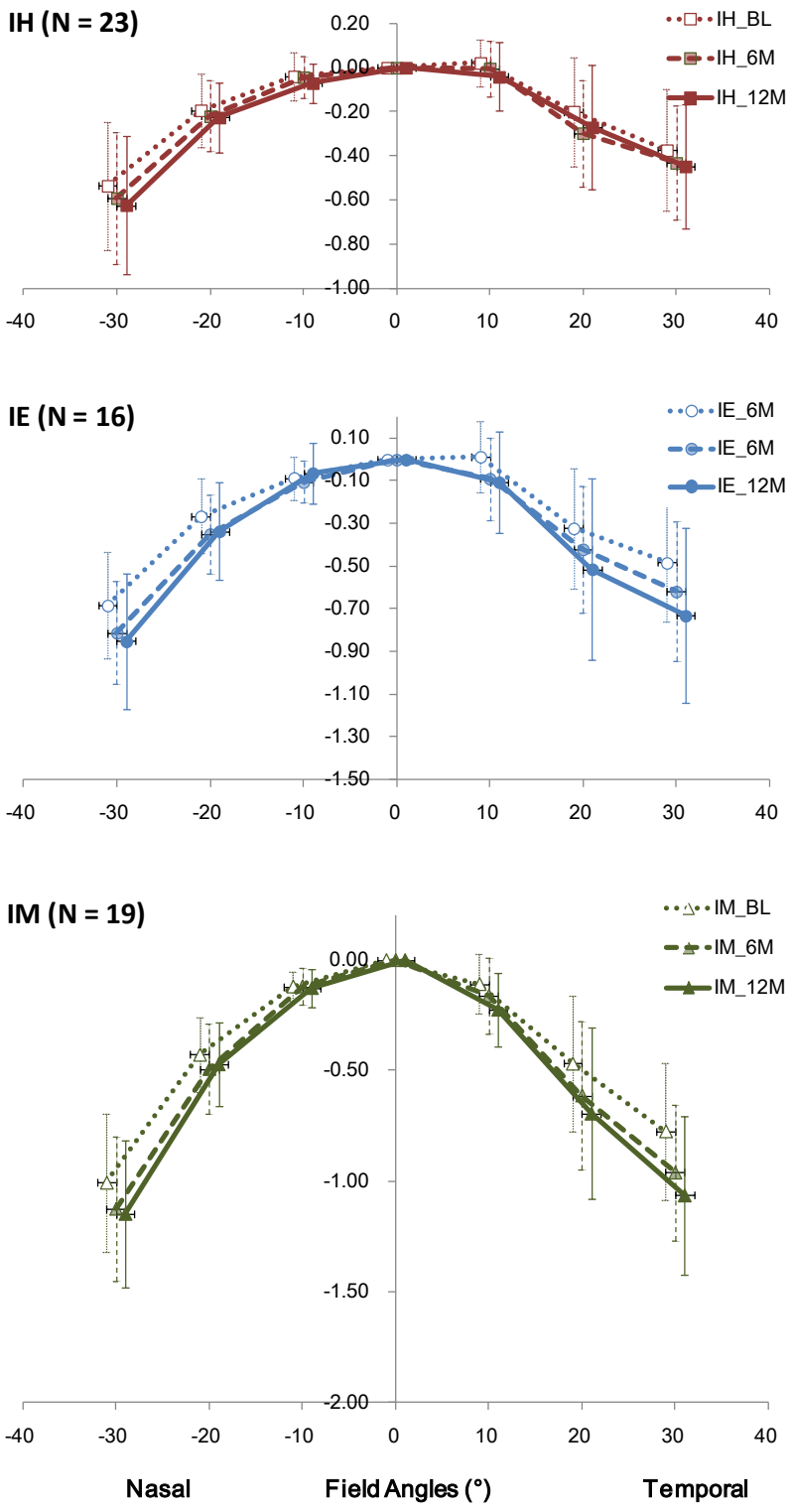


Figure 8.6. Relative peripheral eye length (mm) in different refractive groups over 12 months [Baseline data are presented by open symbols with dotted lines, 6-month visit data by semi-filled symbols with broken lines and 12-month visit data by closed symbols with solid). IH (Initially hyperopic): SER ≥ 0.50 D; IE (Initially emmetropic): -0.50 D < SER < 0.50 D; IM (Initially myopic): SER ≤ -0.50 D; N: nasal; T: temporal; C: central; Error bar = 1 SD].

8.3.4 Relative peripheral eye length

(A) Baseline RPEL

RPEL was significantly different among the three refractive groups ($p < 0.03$). RPEL was significantly different between the IH and IM groups (IM group being more negative in RPEL) at all angles ($p < 0.03$) while the IE and IM groups differ significantly at N30 only ($p = 0.005$). No significant difference was found in RPEL between the IH and IE groups at any field angle ($0.36 < p < 1.00$).

(B) Twelve-month changes in RPEL

In the IH group, RPEL changed significantly with time at N30 and T30 ($p < 0.002$). In the IE group, significant changes in RPEL were found at N30, T20 and T30 ($p < 0.005$). In IM group, except for N10, RPEL changed significantly over the study period at other angles ($p < 0.024$). However, the 12-month change in RPEL did not show significant between-group differences at other angles, except for T30 ($p < 0.001$).

8.3.5 Correlations between peripheral refraction and peripheral eye length

Since PR-J_0 and PR-J_{45} did not change significantly with time in any refractive group, correlation analyses were performed between PR-M and PEL only. This also applies in other correlations.

(A) Baseline PR and baseline PEL

Table 8.2 summarizes the Pearson coefficients (p-values) between baseline PR-M and baseline PEL.

Table 8.2. Correlations (p-values) between baseline M vector of peripheral refraction and baseline peripheral eye length

Groups	Field angles						
	N30	**N20**	**N10**	**C**	**T10**	**T20**	**T30**
All	-0.47¶	-0.57¶	-0.63¶	-0.68¶	-0.62¶	-0.64¶	-0.58¶
	(<0.001)	(<0.001)	(<0.001)	(<0.001)	(<0.001)	(<0.001)	(<0.001)
IH	-0.10	-0.23	-0.24	-0.39	-0.33	-0.38	-0.26
	(0.644)	(0.303)	(0.265)	(0.063)	(0.129)	(0.071)	(0.225)
IE	0.27	0.45	0.30	0.27	0.14	-0.06	0.04
	(0.321)	(0.077)	(0.254)	(0.318)	(0.612)	(0.815)	(0.877)
IM	-0.49	-0.51¶	-0.58¶	-0.59¶	-0.49	-0.71¶	-0.68¶
	(0.066)	(0.027)	(0.036)	(0.035)	(0.099)	(0.007)	(0.012)

IH (Initially hyperopic): SER ≥ 0.50D; IE (Initially emmetropic): -0.50D < SER < 0.50D; IM (Initially myopic); SER ≤ -0.50D

N: nasal; T: temporal; C: central

¶ significant correlations found

Considering all subjects, there were significant correlations between baseline PR-M and baseline PEL. Individual group analyses showed that there were no significant correlations between baseline PR-M and baseline PEL at any angle in either IH or IE group. In the IM group, there were significant correlations between baseline PR-M and baseline PEL from C to N20 and from T20 to T30.

(B) Changes in PR and changes in PEL

Table 8.3 summarizes the Pearson coefficients (p-values) between changes in PR-M and changes in PEL in 12 months.

Considering all subjects, there were significant correlations between changes in PR-M and changes in PEL at all angles. Individual group analyses showed significant correlations at C and N10 only in the IH group. In the IE group, significant correlations were found between N30 and T10.

In the IM group, significant correlations were found at all angles except T20.

Table 8.3. Correlations (p-values) between changes in M vector of peripheral refraction and changes in peripheral eye length.

Groups	Field angles						
	N30	**N20**	**N10**	**C**	**T10**	**T20**	**T30**
All	-0.81¶	-0.81¶	-0.83¶	-0.84¶	-0.65¶	-0.52¶	-0.65¶
	(<0.001)	(<0.001)	(<0.001)	(<0.001)	(<0.001)	(<0.001)	(<0.001)
IH	-0.52	-0.45	-0.67¶	-0.67¶	-0.36	-0.50	-0.36
	(0.055)	(0.09)	(0.006)	(<0.007)	(0.18)	(0.064)	(0.09)
IE	-0.52¶	-0.69¶	-0.70¶	-0.63¶	-0.65¶	-0.56	-0.36
	(0.076)	(0.021)	(0.018)	(0.036)	(0.030)	(0.075)	(0.17)
IM	-0.82¶	-0.77¶	-0.77¶	-0.84¶	-0.58¶	-0.37	-0.80¶
	(<0.001)	(<0.001)	(<0.001)	(<0.001)	(0.018)	(0.12)	(<0.001)

IH (Initially hyperopic): SER ≥ 0.50D; IE (Initially emmetropic): -0.50D < SER < 0.50D; IM (Initially myopic); SER ≤ -0.50D

N: nasal; T: temporal; C: central

¶ significant correlations found

8.3.6 Correlations between relative peripheral refraction and relative peripheral eye length

Since the 12-month changes in RPR-J_0 and RPR-J_{45} did not differ significantly between refractive groups, correlation analyses were performed between RPR-M and PEL only. This applies to all other correlations.

(A) Baseline RPR and baseline RPEL

Table 8.4 summarizes the Pearson coefficients (p-values) between baseline RPR-M and baseline RPEL.

Table 8.4. Correlations between baseline M vector of relative peripheral refraction and baseline peripheral eye length

Groups	Field angles					
	N30	**N20**	**N10**	**T10**	**T20**	**T30**
All	-0.83¶	-0.79¶	-0.48¶	-0.50¶	-0.74¶	-0.85¶
	(<0.001)	(<0.001)	(<0.001)	(<0.001)	(<0.001)	(<0.001)
IH	-0.86¶	-0.71¶	-0.23	-0.47	-0.61¶	-0.84¶
	(<0.001)	(<0.001)	(0.30)	(0.050)	(0.006)	(<0.001)
IE	-0.51	-0.61¶	-0.80¶	-0.43	-0.82¶	-0.80¶
	(0.08)	(0.039)	(<0.001)	(0.10)	(<0.001)	(<0.001)
IM	-0.84¶	-0.81¶	-0.27	-0.39	-0.67¶	-0.80¶
	(<0.001)	(<0.001)	(0.27)	(0.10)	(0.002)	(<0.001)

IH (Initially hyperopic): SER ≥ 0.50D; IE (Initially emmetropic): -0.50D < SER < 0.50D; IM (Initially myopic); SER ≤ -0.50D

N: nasal; T: temporal

¶ significant correlations found

Considering all subjects, there were significant correlations at all angles. Individual group analyses showed significant correlations at N20 - N30 and T20 - T30 in both IH and IM groups. In the IE group, significant correlations were found at N10 - N20 and T20 - T30.

(B) Changes in RPR and changes in RPEL

Table 8.5 summarizes the Pearson coefficients (p-values) between changes in RPR-M and changes in RPEL. Considering all subjects, significant correlations between changes in RPR-M and changes in RPEL could only be found at N30, T20 and T30. Individual group analyses showed no significant correlation at any angle in IH and IE groups. In the IM group, significant correlations were found at T30 only.

Table 8.5. Correlations between changes in M vector of relative peripheral refraction and changes in peripheral eye length

Groups	Field angles					
	N30	**N20**	**N10**	**T10**	**T20**	**T30**
All	-0.42¶	-0.23	-0.06	-0.24	-0.51¶	-0.71¶
	(0.001)	(0.08)	(0.67)	(0.08)	(<0.001)	(<0.001)
IH	-0.37	-0.09	-0.003	-0.17	-0.48	-0.41
	(0.08)	(0.67)	(0.99)	(0.45)	(0.12)	(0.05)
IE	-0.48	-0.41	-0.24	-0.18	-0.59	-0.62
	(0.24)	(0.33)	(0.74)	(0.50)	(0.10)	(0.06)
IM	-0.41	-0.27	0.06	-0.31	-0.50	-0.86¶
	(0.32)	(0.54)	(0.80)	(0.60)	(0.15)	(<0.001)

IH (Initially hyperopic): SER ≥ 0.50D; IE (Initially emmetropic): -0.50D < SER < 0.50D; IM (Initially myopic); SER ≤ -0.50D

N: nasal; T: temporal;

¶ significant correlations found

8.3.7 Correlations between changes in subjective refraction and baseline relative peripheral refraction

There were no statistically significant correlations between changes in Subj-M and baseline RPR (-M, $-J_0$ and $-J_{45}$) at any field angle in any refractive groups (detailed statistics are summarized in Table 8.6).

Post-hoc statistical powers of correlation tests were more than 0.98 considering all subjects and in the IH group. In the IE and IM groups, they ranged from 0.48 to 0.88 and from 0.70 to 0.99, respectively (Table 8.7).

Table 8.6. Pearson coefficients (p-values*) of changes in M vector of subjective refraction and baseline relative peripheral refraction [-M, $-J_0$ and $-J_{45}$] at each angle

Vectors	Groups (N)	Field angles					
		N30	N20	N10	T10	T20	T30
M	**ALL**	-0.25	-0.28	-0.34	-0.13	-0.19	-0.30
	(58)	(0.18)	(0.12)	(0.06)	(0.33)	(0.32)	(0.10)
	IH	-0.25	-0.21	-0.41	-0.19	-0.12	-0.04
	(23)	(0.26)	(0.33)	(0.05)	(0.38)	(0.58)	(0.86)
	IE	0.23	0.24	0.31	0.34	0.20	0.03
	(16)	(0.39)	(0.37)	(0.25)	(0.19)	(0.47)	(0.92)
	IM	0.26	0.24	-0.21	0.22	0.25	0.26
	(19)	(0.28)	(0.32)	(0.39)	(0.36)	(0.31)	(0.28)
J_0	**ALL**	0.15	0.09	-0.01	0.19	-0.17	0.02
	(58)	(0.27)	(0.50)	(0.94)	(0.16)	(0.20)	(0.91)
	IH	0.17	-0.25	0.40	0.02	0.16	-0.08
	(23)	(0.44)	(0.24)	(0.06)	(0.92)	(0.46)	(0.72)
	IE	-0.14	0.08	-0.38	0.29	-0.44	0.05
	(16)	(0.60)	(0.77)	(0.14)	(0.27)	(0.09)	(0.84)
	IM	-0.01	-0.15	-0.20	0.14	-0.14	-0.17
	(19)	(0.97)	(0.55)	(0.41)	(0.57)	(0.57)	(0.49)
J_{45}	**ALL**	-0.24	-0.27	-0.18	0.18	0.12	0.10
	(58)	(0.35)	(0.24)	(0.57)	(0.68)	(0.78)	(0.47)
	IH	-0.33	-0.24	-0.07	-0.01	0.01	0.05
	(23)	(0.12)	(0.26)	(0.76)	(0.95)	(0.96)	(0.83)
	IE	-0.22	-0.25	-0.25	-0.12	0.24	0.11
	(16)	(0.42)	(0.35)	(0.35)	(0.66)	(0.37)	(0.69)
	IM	-0.58	-0.55	-0.41	0.32	0.13	0.31
	(19)	(0.01)	(0.01)	(0.08)	(0.18)	(0.59)	(0.19)

IH (Initially hyperopic): SER ≥ 0.50D; IE (Initially emmetropic): -0.50D < SER < 0.50D; IM (Initially myopic); SER ≤ -0.50D

N: nasal; T: temporal

*No significant correlations found

Table 8.7. Statistical power of correlations between changes in M vector of subjective refraction and baseline relative peripheral refraction

Groups (N)	Field angles					
	N30	N20	N10	T10	T20	T30
ALL (58)	1.00	1.00	1.00	0.99	1.00	1.00
IH (23)	0.99	0.99	0.99	0.99	0.99	0.98
IE (16)	0.66	0.64	0.53	0.48	0.70	0.88
IM (19)	0.70	0.73	0.99	0.75	0.71	0.93

8.3.8 Correlations between changes in subjective refraction and changes in peripheral refraction

(A) Changes in Subj-M and changes in PR-M

Considering all subjects, changes in PR-M were significantly correlated with changes in Subj-M. Considering individual refractive group, significant correlations were found across the nasal field in the IH group, at N10 and N20 in the IE group and only at N10 in the IM group (Table 8.8). There was, however, no correlation across the temporal field in any group.

(B) Changes in Subj-M and changes in RPR-M

When all subjects were considered, significant correlations were found between changes in Subj-M and changes in RPR-M at N10, T20 and T30. However, when considering individual refractive group, changes in Subj-M were not significantly correlated with changes in RPR-M at any angle in any group (Table 8.8).

Table 8.8. Pearson coefficients (p-values) between changes in M vector of subjective refraction and changes in peripheral refraction (M vector) at each angle.

Groups	Field angles					
	N30	**N20**	**N10**	**T10**	**T20**	**T30**
ALL	0.70	0.78	0.86	0.70	0.39	0.46
(58)	(<0.001) ¶	(<0.001) ¶	(<0.001) ¶	(<0.001) ¶	(0.002) ¶	(<0.001) ¶
IH	0.72¶	0.73¶	0.78¶	0.43	0.51	0.36
(23)	(<0.001)	(<0.001)	(<0.001)	(0.08)	(0.03) ¶	(0.09)
IE	0.36	0.69¶	0.70¶	0.53	0.15	0.14
(16)	(0.54)	(0.015)	(0.006)	(0.12)	(0.58)	(0.61)
IM	0.56	0.46	0.83¶	0.58	0.07	0.26
(19)	(0.04)	(0.15)	(<0.001)	(0.05)	(0.16)	(0.28)

IH (Initially hyperopic): SER ≥ 0.50D; IE (Initially emmetropic): -0.50D < SER < 0.50D; IM (Initially myopic); SER ≤ -0.50D; N: nasal; T: temporal ; ¶ significant correlations

Table 8. 9. Pearson coefficients (p-values*) between changes in M vector of subjective refraction and changes in M vector of relative peripheral refraction at each angle.

Groups	Field angles					
(N)	**N30**	**N20**	**N10**	**T10**	**T20**	**T30**
ALL	-0.01	0.03	0.41	-0.24	-0.35	-0.41
(58)	(0.97)	(0.83)	(0.01) ¶	(0.21)	(0.028) ¶	(0.006) ¶
IH	0.22	0.11	0.39	-0.25	-0.10	-0.26
(23)	(0.32)	(0.63)	(0.07)	(0.26)	(0.66)	(0.23)
IE	-0.31	-0.07	0.27	-0.27	-0.34	-0.49
(16)	(0.24)	(0.80)	(0.31)	(0.31)	(0.21)	(0.06)
IM	-0.02	-0.27	0.47	-0.21	-0.45	-0.33
(19)	(0.94)	(0.78)	(0.24)	(0.80)	(0.30)	(0.64)

IH (Initially hyperopic): SER ≥ 0.50D; IE (Initially emmetropic): -0.50D < SER < 0.50D; IM (Initially myopic); SER ≤ -0.50D; **N: nasal; T: temporal**

*No significant correlations were found

8.3.9 Correlations between axial elongation, subjective refraction and peripheral eye length

(A) Baseline PEL, changes in Subj-M, and axial elongation

Considering all subjects, baseline PEL significantly correlated with changes

in Subj-M and axial elongation. However, in each individual refractive group, baseline PEL did not correlate significantly with axial elongation or changes in Subj-M (Table 8.10).

Table 8.10. Pearson coefficients (p-values*) between baseline peripheral eyeball length and (A) axial elongation and (B) changes in M vectors of subjective refraction [Subj-M]

Groups	Field angles						
(N)	**N30**	**N20**	**N10**	**C**	**T10**	**T20**	**T30**
(A) Axial elongation							
ALL	0.34	0.35	0.34	0.35	0.32	0.33	0.32
(58)	(0.036) ¶	(0.042) ¶	(0.045) ¶	(0.049) ¶	(0.042) ¶	(0.012) ¶	(0.028) ¶
IH	0.06	0.07	0.08	0.08	0.06	0.14	0.08
(23)	(0.79)	(0.75)	(0.72)	(0.72)	(0.77)	(0.54)	(0.74)
IE	0.08	0.02	0.01	-0.01	-0.06	-0.11	-0.09
(16)	(0.76)	(0.95)	(0.99)	(0.97)	(0.82)	(0.67)	(0.75)
IM	-0.02	-0.13	-0.21	-0.22	-0.21	-0.04	-0.01
(19)	(0.95)	(0.61)	(0.38)	(0.37)	(0.39)	(0.88)	(0.96)
(B) Changes in Subj-M							
ALL	-0.33	-0.36	-0.35	-0.36	-0.33	-0.34	-0.32
(58)	(0.02) ¶	(0.03) ¶	(0.04) ¶	(0.01) ¶	(0.03) ¶	(0.04) ¶	(0.02) ¶
IH	-0.34	-0.39	-0.36	-0.39	-0.36	-0.37	-0.33
(23)	(0.11)	(0.07)	(0.09)	(0.07)	(0.09)	(0.08)	(0.13)
IE	0.10	0.17	0.20	0.24	0.23	0.17	0.21
(16)	(0.71)	(0.52)	(0.45)	(0.37)	(0.39)	(0.52)	(0.44)
IM	0.18	0.26	0.33	0.34	0.35	0.17	0.18
(19)	(0.45)	(0.28)	(0.17)	(0.15)	(0.14)	(0.48)	(0.47)

IH (Initially hyperopic): SER ≥ 0.50D; IE (Initially emmetropic): -0.50D < SER < 0.50D; IM (Initially myopic); SER ≤ -0.50D

N: nasal; T: temporal; C: Central

*No significant correlations were found

(B) Baseline RPEL, changes in Subj-M and axial elongation

Baseline RPEL did not correlate significantly with axial elongation or

changes in Subj-M at any angle in any group (Table 8.11). The post-hoc power analyses of the correlation tests are shown in Table 8.12.

Table 8.11. Correlations (p value*) between baseline relative peripheral eyeball length and (A) changes in axial length and (B) changes in M vector of subjective refraction [Subj-M]

Groups	Field angles					
	N30	**N20**	**N10**	**T10**	**T20**	**T30**
(A) Axial elongation						
ALL	-0.21	-0.20	-0.18	-0.30	-0.14	-0.23
(58)	(0.44)	(0.36)	(0.36)	(0.16)	(0.31)	(0.45)
IH	-0.08	-0.07	0.01	-0.12	0.21	-0.02
(23)	(0.72)	(0.74)	(0.96)	(0.60)	(0.34)	(0.94)
IE	0.24	0.10	0.10	-0.20	-0.27	-0.17
(16)	(0.38)	(0.71)	(0.72)	(0.45)	(0.31)	(0.52)
IM	0.51	0.48	0.10	0.06	0.47	0.52
(19)	(0.15)	(0.16)	(0.68)	(0.81)	(0.15)	(0.12)
(B) Changes in Subj-M						
ALL	0.26	0.19	0.19	0.28	0.15	0.27
(58)	(0.20)	(0.45)	(0.32)	(0.18)	(0.27)	(0.20)
IH	0.27	0.15	0.23	0.26	0.11	0.29
(23)	(0.22)	(0.49)	(0.30)	(0.23)	(0.60)	(0.18)
IE	-0.42	-0.33	-0.33	-0.04	-0.14	-0.12
(16)	(0.11)	(0.22)	(0.21)	(0.89)	(0.60)	(0.67)
IM	-0.42	-0.45	-0.15	0.10	-0.39	-0.41
(19)	(0.07)	(0.05)	(0.53)	(0.69)	(0.10)	(0.08)

IH (Initially hyperopic): SER ≥ 0.50D; IE (Initially emmetropic): -0.50D < SER < 0.50D; IM (Initially myopic); SER ≤ -0.50D

N – nasal field; T – temporal field

* No significant correlations were found after Bonferroni correction

Table 8.12. Post-hoc power analyses of the Pearson correlations between (A) baseline relative peripheral eye length (RPEL) and (changes in axial length, and (B) between RPEL and changes in M vector of subjective refraction (Subj-M)

Groups	Field angles					
(N)	N30	N20	N10	T10	T20	T30
(A) Axial elongation						
ALL (58)	1.00	1.00	1.00	1.00	1.00	1.00
IH (23)	0.99	0.98	0.97	0.99	0.85	0.98
IE (16)	0.64	0.82	0.82	0.98	0.99	0.97
IM (19)	0.24	0.29	0.88	0.92	0.31	0.22
(B) Changes in Subj-M						
ALL (58)	0.99	0.99	0.99	0.99	0.99	0.99
IH (23)	0.77	0.91	0.83	0.79	0.93	0.74
IE (16)	0.99	0.99	0.99	0.92	0.96	0.96
IM (19)	0.99	0.99	0.98	0.88	0.99	0.99

(C) Changes in PEL, changes in Subj-M and axial elongation

Table 8.13 summarizes the correlations between changes in PEL, axial elongation and changes in Subj-M.

Considering all subjects, changes in PEL were significantly correlated with axial elongation and changes in Sujb-M. However, when considering the IH group only, significant correlations were found between changes in PEL and axial elongation at all angles, except T20, but the correlation between changes in PEL and changes in Subj-M was insignificant, except at N10.

In the IE group, significant correlations between changes in PEL and axial elongation as well as between changes in PEL and changes in Subj-M were found at N10 and N20 only.

In the IM group, significant correlations between changes in PEL and axial elongation as well as changes in PEL and changes in Subj-M were found

between N30 and T10

Table 8.13. Correlations (p value) between changes in peripheral eyeball length and (A) changes in axial length and (B) changes in M vector of cycloplegic subjective refraction [Subj-M]

Groups	Field angles						
(N)	**N30**	**N20**	**N10**	**C**	**T10**	**T20**	**T30**
(A) Axial elongation							
ALL	0.79¶	0.90¶	0.92¶	N/A	0.70¶	0.45¶	0.54¶
(58)	(<0.001)	(<0.001)	(<0.001)		(<0.001)	(<0.001)	(<0.001)
IH	0.70¶	0.74¶	0.86¶	N/A	0.62¶	0.20	0.67¶
(23)	(<0.001)	(<0.001)	(<0.001)		(0.001)	(0.35)	(<0.001)
IE	0.37	0.80¶	0.83¶	N/A	0.56	0.46	0.36
(16)	(0.34)	(<0.001)	(<0.001)		(0.12)	(0.24)	(0.18)
IM	0.82¶	0.94¶	0.91¶	N/A	0.62¶	0.43	0.44
(19)	(<0.001)	(<0.001)	(<0.001)		(0.005)	(0.07)	(0.06)
(B) Changes in Subj-M							
ALL	-0.71¶	-0.76¶	-0.80¶	-0.80¶	-0.64¶	-0.36¶	-0.46¶
(58)	(<0.001)	(<0.001)	(<0.001)	(<0.001)	(<0.001)	(<0.001)	(<0.001)
IH	-0.33	-0.31	-0.65¶	-0.53	-0.23	002	-0.34
(23)	(0.52)	(0.45)	(0.007)	(0.06)	(0.60)	(0.92)	(0.55)
IE	-0.50	-0.77¶	-0.66¶	-0.61	-0.60	-0.39	-0.41
(16)	(0.14)	(<0.001)	(0.03)	(0.052)	(0.05)	(0.14)	(0.24)
IM	-0.75¶	-0.81¶	-0.67¶	-0.82¶	-0.73¶	-0.43	-0.43
(19)	(<0.001)	(<0.001)	(0.002)	(<0.001)	(<0.001)	(0.07)	(0.07)

IH (Initially hyperopic): SER ≥ 0.50D; IE (Initially emmetropic): -0.50D < SER < 0.50D; IM (Initially myopic); SER ≤ -0.50D

N: nasal; T: temporal; C: central

¶ significant correlations were found

(C) Changes in RPEL, changes in Subj-M and axial elongation

Table 8.14 summarizes the correlations between changes in RPEL and axial elongation or changes in Subj-M.

Table 8.14. Correlations (p value) between changes in relative peripheral eyeball length and (A) changes in axial length and (B) changes in M vector of cycloplegic subjective refraction (Subj-M)

Groups	Field angles					
(N)	**N30**	**N20**	**N10**	**T10**	**T20**	**T30**
(A) Axial elongation						
ALL	-0.57	-0.35	-0.14	-0.21	-0.46	-0.75
(58)	(<0.001) ¶	(0.021) ¶	(0.28)	(0.24)	(<0.001) ¶	(<0.001) ¶
IH	-0.63¶	-0.16	0.02	0.04	-0.30	-0.50
(23)	(0.006)	(0.47)	(0.93)	(0.85)	(0.17)	(0.065)
IE	-0.79¶	-0.74¶	-0.55	-0.23	-0.42	-0.81¶
(16)	(<0.001)	(0.004)	(0.09)	(0.39)	(0.22)	(<0.001)
IM	-0.40	-0.34	-0.26	-0.26	-0.47	-0.60¶
(19)	(0.09)	(0.16)	(0.28)	(0.29)	(0.05)	(0.006)
(B) Changes in Subj-M						
ALL	0.34	0.17	-0.08	0.05	0.36	0.58
(58)	(0.032) ¶	(0.19)	(0.55)	(0.69)	(0.025) ¶	(<0.001) ¶
IH	0.39	0.20	-0.39	0.12	0.29	0.29
(23)	(0.06)	(0.37)	(0.07)	(0.59)	(0.18)	(0.18)
IE	0.29	0.13	0.09	-0.17	0.15	0.38
(16)	(0.27)	(0.63)	(0.74)	(0.53)	(0.59)	(0.14)
IM	0.20	0.18	0.37	-0.06	0.30	0.43
(19)	(0.42)	(0.46)	(0.12)	(0.80)	(0.21)	(0.07)

IH (Initially hyperopic): SER ≥ 0.50D; IE (Initially emmetropic): -0.50D < SER < 0.50D; IM (Initially myopic); SER ≤ -0.50D

N – nasal field; T – temporal field;

¶ significant correlations found

Considering all subjects, changes in RPEL correlated significantly with axial elongation from N20 – N30 and from T20 – T30. The changes in RPEL only correlated significantly with changes in Subj-M at N30, T20 and T30.

In the IH group, changes in RPEL were significantly correlated with axial elongation at N30 only. In the IE group, significant correlations between

changes in RPEL and axial elongation were found at N20 - N30 and at T30. In the IM group, significance between changes in RPEL and axial elongation was found at T30 only. RPEL changes were, however, not significantly correlated with changes in Subj-M in any individual group.

8.3.10 Subgroup analysis on peripheral refraction and peripheral eye length

(A) IE-FAST vs IE-SLOW

The IE-FAST and the IE-SLOW subgroups had six and nine subjects, respectively. Table 8.15 and Figures 8.7 summarize the baseline and 12-month changes in Subj-M, AL, RPR-M and RPEL in each subgroup. Age, baseline Subj-M and baseline AL did not differ significantly between the two subgroups (age: $p = 0.38$; baseline Subj-M: $p = 0.06$; baseline AL: $p = 0.47$), while changes in Subj-M and axial elongation in 12 months were significantly greater in the IE-FAST than in the IE-SLOW subgroups (changes in Subj-M: $p < 0.001$; axial elongation: $p = 0.02$).

There were no significant differences in baseline RPR-M ($0.05 < p < 0.55$) or in baseline RPEL ($0.01 < p < 0.32$, Bonferroni-adjusted $\alpha = 0.008$) between the two subgroups at any angle. Changes in RPR-M ($0.03 < p < 0.69$, Bonferroni-adjusted $\alpha = 0.008$) or changes in RPEL ($0.19 < p < 0.95$) in 12 months did not differ significantly between the two subgroups. An increase in asymmetry was observed.

Table 8.15. Summary of sub-group analyses

	Sub-group comparisons and p values								
	IE-Fast	**IE-Slow**	**p**	**IM-Fast**	**IM-Slow**	**p**	**IH-Slow**	**IE-Slow**	**p**
Subject number	6	9	/	11	8	/	17	8	/
Age (years)	7.85 (0.66)	8.15 (0.62)	0.38	7.83 (0.83)	7.92 (0.81)	0.83	7.65 (0.98)	7.92 (0.81)	0.17
Baseline Subj-M (D)	-0.32 (0.07)	-0.14 (0.23)	0.06	-1.77 (1.00)	-1.81 (0.22)	0.90	1.00 (0.46)	-1.81 (0.22)	< 0.001 §
Baseline RPR-M (D)	Figure 8.7		0.05 – 0.55	Figure 8.8		0.15 – 0.70	Figure 8.9		0.03 – 0.55
Baseline AL (mm)	22.87 (0.87)	23.17 (0.53)	0.47	24.12 (0.89)	24.30 (0.67)	0.65	22.96 (0.86)	24.30 (0.67)	0.51
Baseline RPEL (mm)	Figure 8.7		0.01 – 0.32	Figure 8.8		0.15 - 0.80	Figure 8.9		0.01 – 0.78
12-month changes in Subj-M (D	-1.36 (0.23)	-0.58 (0.27)	< 0.001§	-1.39 (0.27)	-0.77 (0.28)	< 0.001 §	-0.36 (0.24)	-0.77 (0.28)	0.04 §
12-month changes in RPR-M (D)	Figure 8.7		0.03 – 0.69	Figure 8.8		0.09 – 0.89	Figure 8.9		0.15 – 0.97
12-month axial elongation (mm)	0.55 (0.24)	0.33 (0.09)	0.02 §	0.68 (0.16)	0.42 (0.13)	0.001 §	0.26 (0.13)	0.42 (0.13)	0.13
12-month changes in RPEL (mm)	Figure 8.7		0.19 – 0.95	Figure 8.8		0.14 – 0.87	Figure 8.9		0.004 at T30 ¶ 0.02 – 0.91 for others

IH: Initially Hyperopic; IE: Initially Emmetropic; IM: Initially Myopic; Fast: myopic progression > 1D in 1 year; Slow: myopic progression ≤ 1D in 1 year
Subj-M: M vector of subjective refraction; RPR-M: M vector of relative peripheral refraction; AL: axial length; RPEL: relative peripheral eye length.
§: significant difference found at $\alpha = 0.05$; ¶: significant difference found after Bonferroni corrections, $\alpha = 0.008$

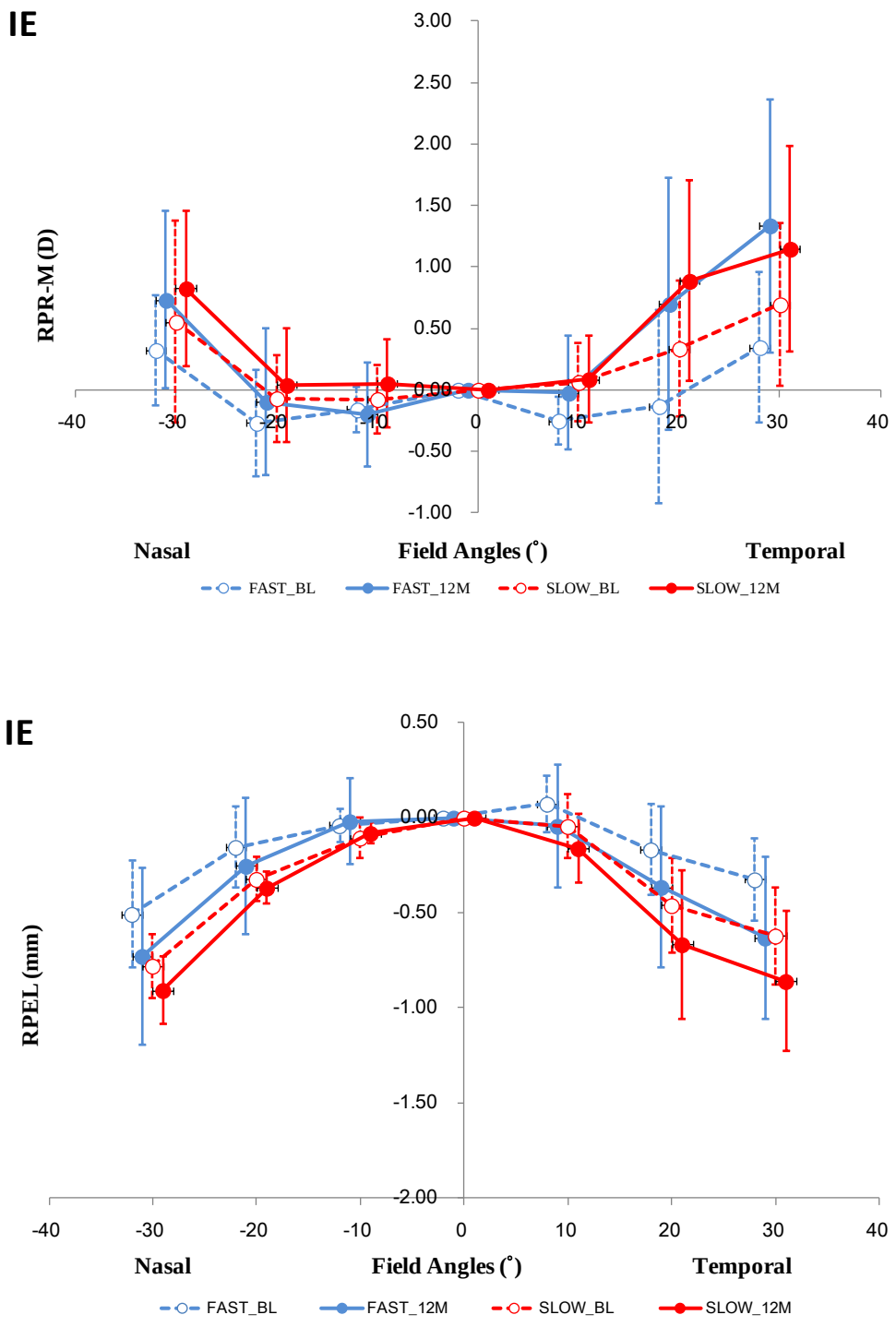
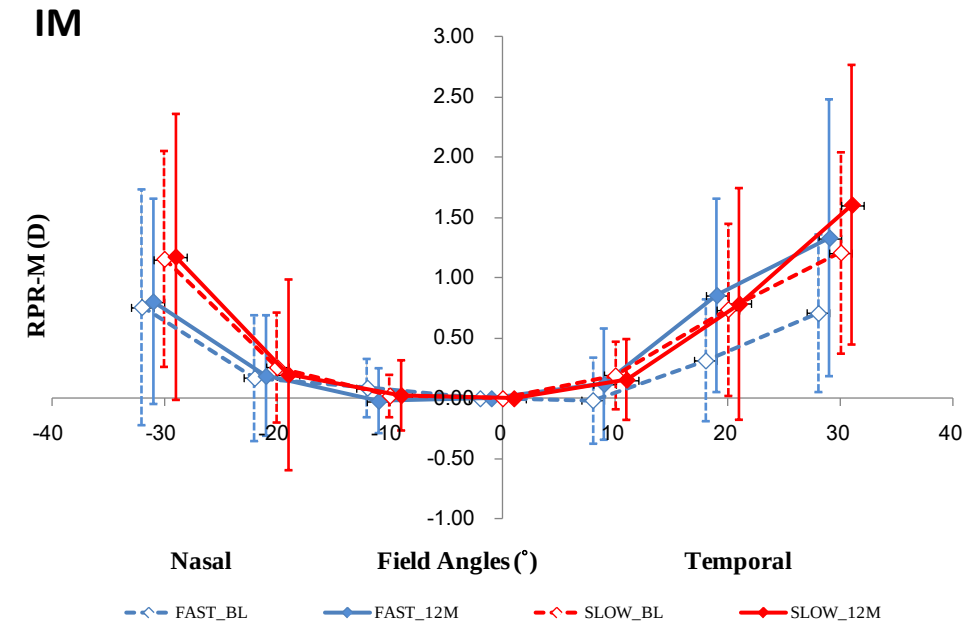


Figure 8.7. M vector of relative peripheral refraction (RPR-M) and relative peripheral eye length (RPEL) at baseline (BL) and at 12-month (12M) visits in the IE-FAST (N = 6) and IE-SLOW (N = 9) subgroups. N = nasal; T = temporal, C = central. Error bar = 1SD.

(B) IM-FAST vs IM-SLOW



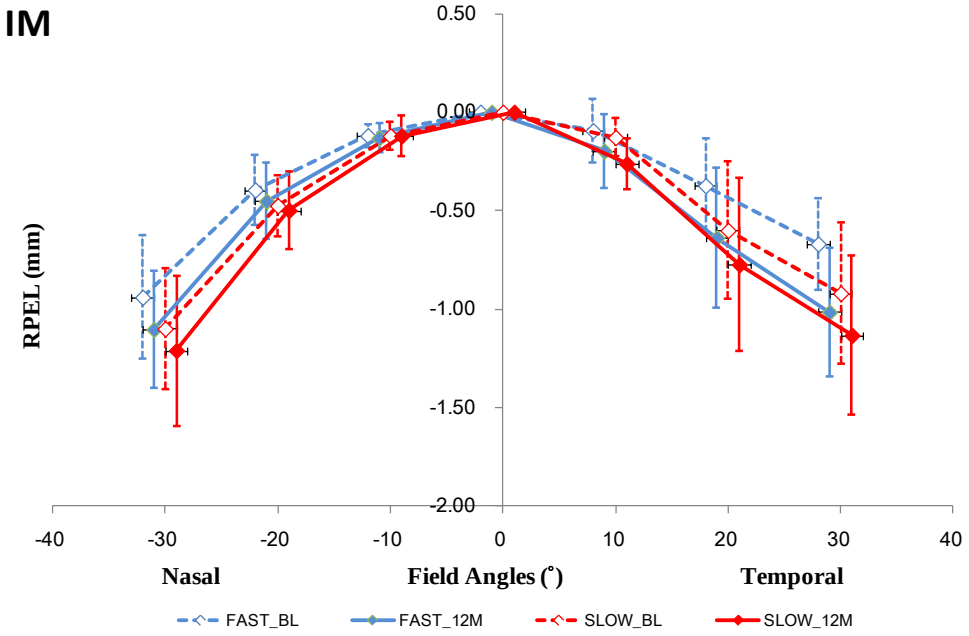


Figure 8.8. M vector of relative peripheral refraction (RPR-M) and relative peripheral eye length (RPEL) at baseline (BL) and at 12-month (12M) visit of the IM-FAST (N = 11) and IM-SLOW (N = 8) subgroups. N = nasal; T = temporal, C = central. Error bar = 1SD.

There were 11 and eight subjects in the IM-FAST and IM-SLOW subgroups, respectively. Table 8.15 and Figure 8.8 summarize the baseline and 12-month changes in Subj-M, AL, RPR-M and RPEL in each subgroup. There were no significant differences between the subgroups in age ($p = 0.83$), initial Subj-M ($p = 0.90$) or baseline AL ($p = 0.65$). The annual myopic progression and axial elongation in the IM-FAST group was significantly greater than that in the IM-SLOW group (change in Subj-M: $p < 0.001$; axial elongation: $p = 0.001$).

There were no significant differences in baseline RPR-M ($0.15 < p < 0.70$), changes in RPR-M ($0.09 < p < 0.89$), baseline RPEL ($0.15 < p < 0.80$) or changes in RPEL ($0.14 < p < 0.87$) between the two subgroups. Changes in RPR-M and RPEL were not significantly different across the tested field in the IM-SLOW subgroup (changes in RPR-M: $p = 0.37$; changes in RPEL: $p = 0.18$) while significant differences in RPR-M changes and RPEL changes across the tested field were found in the IM-FAST subgroup (changes in RPR-M: $p = 0.001$; changes in RPEL: $p = 0.04$). In the IM-FAST subgroup, the RPR-M did not change at the nasal field, whereas it became increasingly more hyperopic and more prolate in shape with eccentricity at the temporal field. Moreover, the RPR-M profiles of both groups had become more asymmetrical (the temporal field being steeper than the nasal field) at the end of the study period.

(C) IH-SLOW vs IE-SLOW

There were 17 subjects in in the IH-SLOW subgroup. Table 8.15 and Figure 8.9 summarize the baseline and 12-month changes in Subj-M, AL, RPR-M and RPEL in the IH-SLOW and the IE-SLOW subgroups.

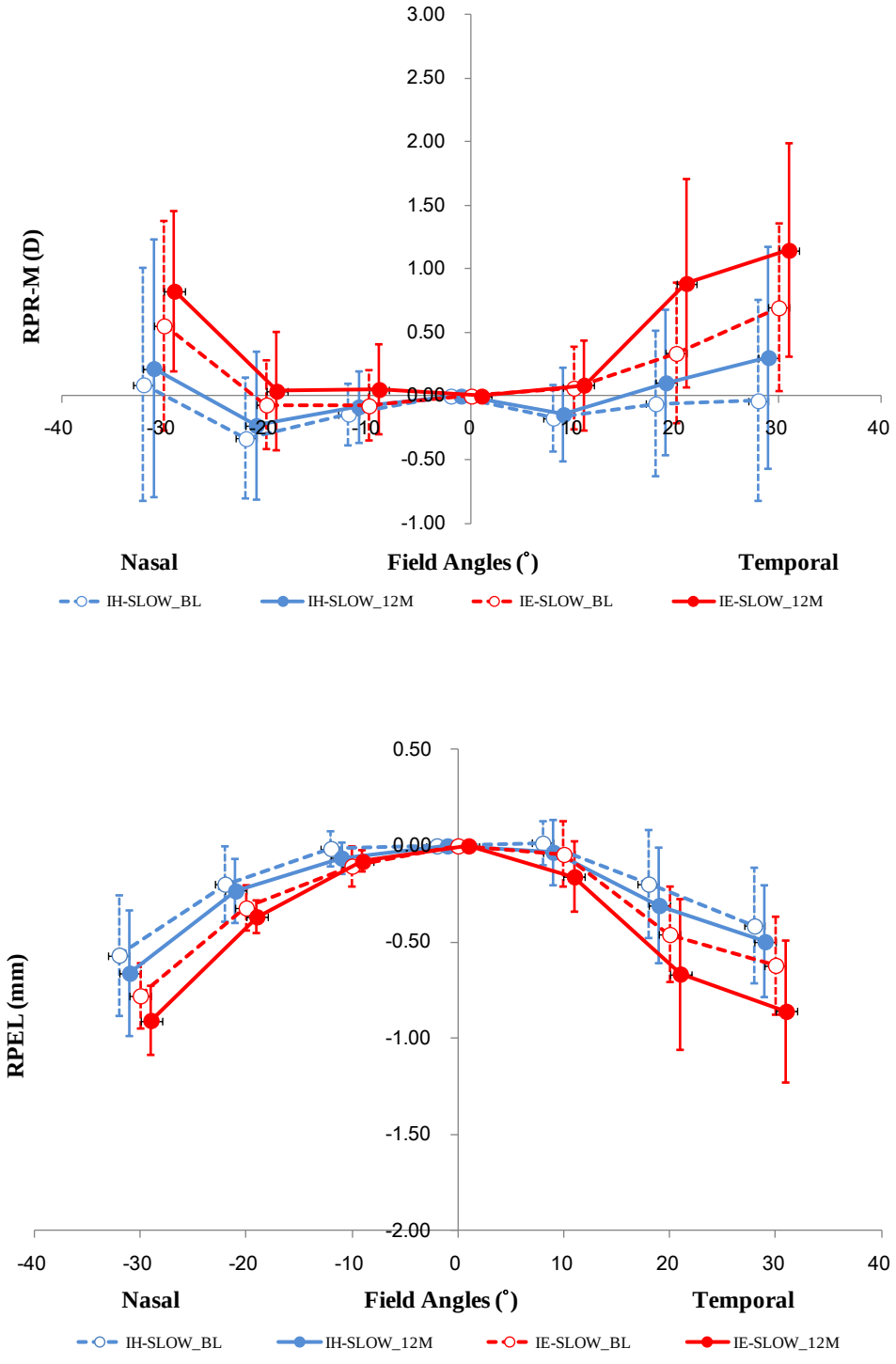


Figure 8.9 M vector of relative peripheral refraction (RPR-M) and relative peripheral eye length (RPEL) at baseline (BL) and at 12-month (12M) visit of the IE-SLOW (n = 9) and IH-SLOW (N = 17) subgroups. N = nasal; T = temporal, C = central.

Compared to the IE-SLOW subgroup, the baseline Subj-M of the IH-SLOW subgroup was significantly more hyperopic ($p < 0.001$) and the IH-SLOW subgroup had significantly smaller central myopic shift at 12 months ($p = 0.04$). However, the two subgroups did not differ from each other significantly in age ($p = 0.17$), baseline AL ($p = 0.51$) or axial elongation ($p = 0.13$) during the study period.

Baseline RPR-M and RPEL did not differ significantly at any angle between the IH-SLOW and the IE-SLOW subgroups (RPR: $0.18 < p < 0.55$; RPEL: $0.06 < p < 0.78$, with Bonferroni corrections). Except for changes in RPEL at T30 ($p = 0.004$), changes in RPR-M and RPEL did not differ significantly between the two subgroups (changes in RPR-M: $0.15 < p < 0.97$; changes in RPEL: $0.12 < p < 0.91$, with Bonferroni corrections).

Post-hoc power analyses of t-tests in the sub-group analyses (baseline RPR) are summarized in Table 8.16. The highest power achieved by the sub-group analyses was 0.63.

Table 8.16. Power analysis of t-tests in the sub-group analyses on baseline RPR

Groups	**Field angles**					
(N)	**N30**	**N20**	**N10**	**T10**	**T20**	**T30**
IE-FAST vs IE-SLOW	0.53	0.42	0.25	0.23	0.55	0.61
IM-FAST vs IM-SLOW	0.18	0.17	0.05	0.09	0.34	0.39
IH-SLOW vs IE-SLOW	0.49	0.42	0.69	0.13	0.63	0.39

8.3.11 Correlations between central myopic shift and peripheral refraction in the fast and slow progression groups

No significant correlation was found between changes in Subj-M and baseline RPR-M in any subgroup ($p > 0.06$, with Bonferroni corrections). There was no significant correlation between changes in Subj-M and changes in RPR-M in either the fast-progressing ($p > 0.18$, with Bonferroni corrections) or the slow-progressing ($p > 0.28$) groups.

8.3.12 Correlations between central myopic shift and peripheral eye length in the fast and slow progression groups

There was no significant correlation between changes in Subj-M and baseline RPEL ($0.33 < p < 0.97$) and between axial elongation and baseline RPEL ($0.09 < p < 0.88$) in the overall fast-progressing subjects [change in Subj-M ± SD = -1.34 ± 0.24 D]. However, in the overall slow-progressing subjects [changes in Subj-M = -0.51 ± 0.30 D], there were significant correlations between changes in Subj-M at 12 months and baseline RPEL at T10 and T30 only ($p < 0.003$). A significant correlation between baseline RPEL and axial elongation was found at T10 only in the slow-progressing subjects ($p = 0.006$).

The 12-month changes in RPEL did not show a significant correlation with changes in Subj-M in the fast-progressing ($0.06 < p < 0.96$) subjects. In the slow-progressing subjects, significant correlation was found at T30 only ($p = 0.007$). A significant correlation between axial elongation and changes in RPEL was found at N10 to N30 and T30 in the fast-progressing subjects ($p < 0.0119$) and at T30 ($p < 0.001$) in the slow-progressing subjects.

8.4 Discussion

The results of the current study agree with previous reports that hyperopic eyes have different optical profiles from myopic eyes (Millodot, 1981; Seidemann *et al.*, 2002; Atchison *et al.*, 2004; Calver *et al.*, 2007). In general, hyperopic eyes tend to have relative peripheral myopia whereas myopic eyes tend to show relative peripheral hyperopia. The optical shell of emmetropic eyes, however, was found to be mixed in the current study – the more central field (from N20 to T10) was relatively hyperopic while the field beyond was relatively myopic. Results from previous studies on the PR pattern for emmetropic eyes were not consistent (Chen *et al.*, 2009; Ehsaei *et al.*, 2011b). Tabernero et al. (2011) have illustrated different PR patterns observed in emmetropic eyes. Our results also demonstrated individual variations among the emmetropes, ascribing symmetrical and asymmetrical patterns or profiles with relative peripheral hyperopia in one hemi-field and relative peripheral myopia in the other.

The variations in the observed peripheral defocus in emmetropic eyes may reflect the transient status of the eye, which previously has relative peripheral myopia, before acquiring the typical peripheral profile (being relatively hyperopic in the periphery) of a myopic eye. The RPR-M at the more central field at baseline was indeed very close to zero in the IE group, and with myopic progression during the study period, it assumed a profile which was similar to the IM group. It provides further support for the transitional shape changes when an eye remains emmetropic. Mutti and colleagues (2007) found that relative peripheral hyperopia would develop one to two years in advance of the development of central myopia. They

measured PR at 30° in the nasal field only. From our results, the IE group had baseline relative peripheral hyperopia at both N30 and T30. In the current study, we measured PR at more field angles covering the central 60° field but our results were unable to provide further longitudinal information on this issue as none of the subjects in the hyperopic group developed myopia by the end of the study period.

PEL was shorter than AL in all ametropias, giving a negative value for RPEL. This indicated that their shapes, regardless their ametropias, were prolate along the axial plane. Where they differed was only in the extent of their prolateness. Myopic eyes were the most prolate while hyperopic eyes were the least prolate in shape. This agrees with the results from previous reports (Ehsaei *et al.*, 2012; Faria-Ribeiro *et al.*, 2012) (see Section 2.3.2).

The current study reports that a central myopic shift and axial elongation were greatest in the IM group and smallest in the IH group. However, we did not find any significant correlation between changes in Subj-M and baseline RPR-M or between changes in Subj-M and baseline RPEL in any refractive group and in all subjects. Although the IM group showed relative peripheral hyperopia and the most prolate eye shape while the IH group showed relative peripheral myopia and the least prolate eye shape at baseline, we were unable to conclude whether relative peripheral hyperopia or a steeper retina could induce a central myopic shift.

In fact, the observation from the subgroup analyses did not support this hypothesis. According to the PR hypothesis, it is expected that the subgroup with larger relative peripheral hyperopia or a steeper retina at baseline will demonstrate a faster central myopic shift during the study period. On the contrary, in our study, there were no significant differences in baseline

RPR-M and baseline RPEL between the fast and the slow progressing subjects in both the IE and IM groups, but the central myopic progression rates were significantly different between the IM-FAST and the IM-SLOW and between the IE-FAST and the IE-SLOW subgroups. Similar observations were obtained in the IH-SLOW and IE-SLOW subgroup comparisons. The IH-SLOW and the IE-SLOW subgroups did not have a significant difference in RPR-M and RPEL at baseline, but the IH-SLOW subjects showed a significantly slower central myopic shift.

Schmid (2011) found a weak but significant correlation between RPEL and central myopic shift, and suggested that the shape of the posterior pole may be a factor influencing active eye growth (see Section 2.3.2). Subjects in Schmid's study were near-emmetropes and their myopic shift over the study period was small. In our study, we also found some significant correlations (at T10 and T30) between baseline RPEL and a central myopic shift in the slow-progressing subjects only. However, similar observation was not found in the fast-progressing subjects. Inspection from individual subgroups indicated that significant correlations were found at T30 in the IE-SLOW subgroup only, but not in the other subgroups. The current study included subjects with different ametropias, included both fast- and slow-progressing eyes and monitored their myopia and RPEL at a more regular time-intervals than those in Schmid's study (2011). However, we were unable to find further evidence, in particular from the fast-progressing groups, to support the hypothesis that eye shape can influence the visually-driven eye growth in humans.

Post-hoc analyses of statistical power were performed for the correlations between baseline RPR and myopic shift in all subjects and in individual

groups. The power of the correlation analyses were high when considering all subjects as well as in individual groups (IH and IM groups). The relatively weaker power found in the IE groups is possibly a result of the subject numbers. Similar explanation may apply in small statistical power found in the sub-group analyses.

We were unable to conclude that relative peripheral hyperopia or steeper retinal contour (or eye shape) predisposes the eye to myopic progression. Our study was unable to find evidence to support the feedback mechanism model which hypothesizes relative hyperopia as a causative factor in the development of myopia in humans.

Our analyses on correlations showed an association between myopic progression and changes in PR and PEL in the nasal field, whereas there was no association between myopic progression and changes in RPR or RPEL. This indicates that although axial myopia is accompanied by changes in the peripheral optics and biometry, they may be localized to a half field. Moreover, these changes may not be present in all ametropias. These may partially explain why an increase in asymmetry in some ametropias but not in others.

Changes in RPR reflect either a lead or a lag in the change in PR with respect to the CR change. Our results showed that the rates of changes in PR-M and CR-M were not the same, but tended to decrease with field angles, resulting in a greater increase in RPR-M at the more peripheral angles, particularly in the temporal field. The changes were statistically significant at T30 in all groups. Consider the repeatability of measurements reported in Chapter 6, the changes found in the current study reflected a real change for the IE and IM groups.

Similarly, changes in RPEL reflect a discrepancy of peripheral eye elongation from the axial elongation. Elongation of the peripheral eye lagged behind axial elongation during the study period. The eyeball became more prolate in shape by the end of the study. Considering the repeatability of RPEL measurements reported in Chapter 7, only the changes at N30 and T30 in both IE and IM groups reflected real changes.

The current study did not find consistent results on correlations between changes in Subj-M, axial elongation, changes in RPR-M and changes in RPEL across the horizontal field in all refractive groups. This indicates that changes in the optical profiles and the eye shapes were unable to predict the progression of myopia.

Subj-M was statistically different from the CR-M measured by auto-refraction in the current study. A possible explanation is that the depth of focus was greater in subjective refraction than in objective refractive methods (Yao *et al.*, 2010). In other words, the detection of blur may be less sensitive in subjective refraction. In addition, the current study measured Subj-M and PR-M after cycloplegia. It has been demonstrated that subjective refraction might differ from objective measurements with large pupils (Martin *et al.*, 2011). It has also been shown that subjective refraction was affected by pupil size, spherical aberration and level of apodisation (Bradley *et al.*, 2014).

At baseline, the shape of the optical shell was symmetrical in all groups. It became more asymmetrical after 12 months in the IE and IM groups. Both groups demonstrated a significant myopic shift in CR-M compared to the IH group ($F_{2,55} = 20.81$, $p < 0.001$). We observed that relative peripheral hyperopia increased more markedly in the temporal field in both IE and IM

groups at the 12-month visit, while that on the nasal field was comparatively stable (i.e. almost parallel changes with CR-M changes). This indicated a smaller increase in peripheral myopia in the temporal field than in the nasal field during eye growth. From the subgroup analysis on the IM group, the optical shell of the IM-FAST subgroup became increasingly asymmetric at the end of the 12-month period while the asymmetry of the IM-SLOW subgroup showed less change. The change in RPEL in the two subgroups being different in extent and between the nasal and the temporal fields explained the observations of the ocular asymmetry. Previously, the dimensional changes of the myopic eyes have been shown to be different in vertical, horizontal and equatorial directions (Atchison *et al.*, 2004). The development of axial myopia is likely to initiate a series of changes which resulted in asymmetrical PR changes between the nasal and temporal fields, and faster myopic progression may enhance the asymmetry in the PR profile. Previous studies proposed that the angle alpha (or angle lambda) (Calver *et al.*, 2007; Berntsen *et al.*, 2008) and corneal asymmetry (Atchison *et al.*, 2006) as explanations for the skewness of the peripheral profiles in emmetropes and myopes. Our results suggested that the different rates of ocular dimensional changes during myopic progression and faster myopic progression in some eyes might contribute to the increased asymmetry in the peripheral profile in myopes.

The human orbital volume increases rapidly from birth to adolescence with a corresponding increase in axial length (Chau *et al.*, 2004). In adults, the lateral pole of the eyeball is closer to the lateral wall of the orbital socket, indicating a smaller orbital volume laterally (Detorakis *et al.*, 2010). Whether this is a result of eye growth leaving a smaller cavity by the

temporal boundary of the socket is not clear, as there is no similar information in children. We speculate that the anatomical characteristics of the orbital socket may put different constraints on the expansion of the globe in different directions, resulting in an asymmetrical expansion of the eyeball. Our RPEL results are indicative of a slower expansion of the eyeball in the temporal field (nasal retina or medial orbit). However, this will require further investigation.

Recent research has focused on the cellular mechanism of eye growth in choroid and the RPE layer (Nickla and Wallman, 2010). It has been found that the choroid responds to hyperopic defocus by thinning in order to pull the retina backward to match the shell of focus. Conversely, it thickens to bring the retina forward to match the shell. The choroid is also comparatively thinner in high myopes than in moderate or low myopes. The clinical measurement of choroidal thickness has been challenged by a number of technical constraints: the diurnal variation in choroidal thickness, the precise definition of the choroidal boundary on the images captured and the control of factors affecting the molecular activities which will influence the plexus spontaneously.(Ikuno and Tano, 2009; Agawa *et al.*, 2011) Evaluation of *in vivo* choroidal changes with myopic progression, if measured accurately, would give a better insight and support to the observations in PR studies.

The current report investigated the association of baseline and changes in RPR and RPEL with CR changes in different refractive groups. Mean myopic shift was the slowest in the hyperopic group which generally had relative peripheral myopia and less prolate eye shape. The fastest mean myopic shift was found in the myopic group which generally had relative

peripheral hyperopia and more prolate eye shape. However, our results did not show that RPR or RPEL characteristics determine the rate of myopic progression.. However, PR and PEL were measured along the horizontal field only. Our analysis was limited to the horizontal field, without considering the PR along the vertical field and PEL in the sagittal plane. We defined emmetropia by -0.50 D < SER < 0.50 D in subjective refraction while other reports may have a different definition of emmetropia (Millodot, 1981; Seidemann *et al.*, 2002). The present protocol measured uncorrected distance PR under cycloplegia, with the assumption that the optical defocus of an eye when it is performing close work is the same as that when it is viewing at distance. Moreover, we have not taken into consideration the possible influence, although small, of spectacle lenses (Calver *et al.*, 2007; Bakaraju *et al.*, 2008; Lin *et al.*, 2010) on PR.

Finally, there is a need to confirm our findings with a larger sample size and longer study period

8.5 Conclusions

Results from the current study showed that the baseline RPR and RPEL were different in hyperopic, emmetropic and myopic eyes. Hyperopic eyes tended to have relative peripheral myopia while myopic eyes tended to have relative peripheral hyperopia. The myopic progression was also different by ametropias – myopic eyes progressed most rapidly while hyperopic eyes progressed least rapidly. However, the baseline RPR and RPEL or the changes in RPR and RPEL did not correlate with the central myopic shift in any refractive groups. The subgroup analyses did not show any difference in

baseline or changes in RPR and RPEL between the fast-progressing and the slow-progressing subgroups. The current study did not provide further evidence to support the PR hypothesis for myopia development in humans.

Chapter Nine

Changes in Peripheral Refraction and Peripheral Eye Length in Ortho-k-treated Eyes

9.1 Introduction

The myopic control effect of ortho-k has been reported in a number of studies (Cho *et al.*, 2005; Walline *et al.*, 2009; Kakita *et al.*, 2011; Cho and Cheung, 2012; Santodomingo-Rubido *et al.*, 2012) (Section 1.4.2). Some of these earlier studies were methodologically weak. However, later studies were more robust. Cho and Cheung (2012) have also confirmed the effectiveness of ortho-k in retarding myopic progression in Hong Kong Chinese children in a recent single-masked randomized clinical trial. However, little is known about the mechanism by which ortho-k slowed myopic progression. Previous studies have shown that RPR was significantly changed in ortho-k lens wear (Charman *et al.*, 2006; Queirós *et al.*, 2010a; Kang and Swarbrick, 2011) (Section 2.5.1). Before ortho-k treatment, myopic eyes showed relative peripheral hyperopia. After the treatment, the ortho-k-treated eyes demonstrated relative peripheral myopia. The dramatic field curvature changes observed in the ortho-k-treated eyes, together with slower axial elongation observed in them, are in favour of the PR hypothesis that relative peripheral hyperopia was responsible for the visually-driven eye growth. Researchers, therefore, hypothesized that ortho-k might exert a myopic control effect through the manipulation of PR (Charman *et al.*, 2006; Smith *et al.*, 2013).

Of the results reported by different ortho-k studies in children, ortho-k-treated eyes demonstrated about 36% - 66% slower in axial elongation compared to those who wore single vision spectacles or contact lenses (Section 1.4.2). Although variability among different study protocols probably contributed to the variations in outcomes, there were also

variations in myopic control effect among individuals in the same study. How and why the myopic control effect varies has yet to be studied more vigorously.

This chapter reports an experiment designed to investigate how field curvature and retinal contour was affected by ortho-k lens wear. Changes in RPR and RPEL with time were also compared with those in myopic control subjects from the previous longitudinal study in spectacle-wearing eyes (Chapter 8) and whether changes in RPR and RPEL would affect the rate of myopic progression in ortho-k treated eyes were also investigated.

9.2 Methods

Children satisfying the inclusion criteria shown in Table 5.2 were recruited. These subjects had also participated in the repeatability studies on PR and PEL measurements in ortho-k-treated eyes (Chapters 6 and 7, respectively). They were fitted with a pair of ortho-k lenses which were worn during sleep for at least eight hours every night. Detailed fitting procedures and the treatment protocol can be found in Section 5.3.

Each subject had to attend data collection visits once before (Pre-OK) and three times after ortho-k treatment. The three post-ortho-k visits were arranged after ortho-k treatment had stabilized. Stabilization was achieved when the well-centered lenses which provided full myopia reduction without compromise on corneal health was confirmed. Stabilization was defined as a bull's eye topographical response with no significant topographical change between two consecutive visits and maximum myopic reduction without any compromise on corneal health (Section 5.3.2). The

three post-ortho-k treatment visits were the post-treatment stabilized visit (OK-S), 6-month visit (OK-6M) and 12-month visit (OK-12M) after OK-S. At each data-collection visit, subjective refraction, VA using LogMAR charts, corneal topography, external ocular health, and non-contact tonometry (Section 5.2) were performed before the instillation of cycloplegic drugs. After cycloplegia, subjective refraction was performed again, followed by PR and PEL measurements, corneal topography and internal ocular health evaluation. Detailed examination procedures and information on cycloplegia can be found in Section 5.2.

Treatment of data and statistical analyses were similar to those employed in the longitudinal study in RPR and RPEL in the spectacle-wearing eyes (Chapter 8) and the same terminologies and short forms are adopted in this Chapter. As the subject number was below 30, all variables were tested for normal distribution using Shapiro-Wilk tests. The statistical results of the normality tests are summarized in Appendix II. Only a few variables were not normally distributed, therefore parametric tests were used for all analyses:

Differences between in PR and PEL characteristics at the Pre-OK and OK-S visits

Paired t-tests were used to compare the pre- and post-treatment PR and PEL characteristics of the ortho-k-treated eyes.

Time effects on PR and PEL characteristics

The effect of time on PR and PEL characteristics during the ortho-k treatment period (from the OK-S visit to the OK-12M visit) in the

ortho-k-treated eyes were analyzed using repeated measure (RM)-ANOVA

Associations between parameters

Pearson coefficients (r) were used to show the associations between the tested parameters. The following pairs of association were reported:

(a) axial elongation – PR at the OK-S visit

(b) axial elongation – RPR at the OK-S visit

Subgroup analyses

Sub-group analyses were performed according to the progression of myopia. Since changes in the residual refraction in the ortho-k-treated eyes did not reflect the true myopic progression, the ortho-k-treated subjects were divided into fast- and slow-progressing groups based on their axial elongation at OK-12M visit. In Chapter 8, we defined fast-progressing group in the spectacle-wearing eyes by more than 1.00 D in central myopic shift at 12 months. One diopter change is equivalent to 0.34 mm in axial elongation. Therefore, we defined the fast-progressing group in the ortho-k-treated eye as those with axial elongations of more than 0.34 mm during the period between the OK-S and OK-12M visits. Slow-progressing eyes were those whose axial elongations were 0.34 mm or less at the OK-12M visit.

Comparisons between the ortho-k-treated eyes and the spectacle-wearing myopic eyes

The spectacle-wearing eyes of the IM group in the previous experiment reported in Chapter 8 were recruited as controls. In the rest of this chapter,

"the controls" refers the IM group in Chapter 8. PR and PEL characteristics at baseline visits of the controls were compared against those at the OK-S visits of the ortho-k-treated eyes, using t-tests.

Where applicable, a Bonferroni correction was employed to adjust the critical values and the adjusted critical value (α) was specified where appropriate. All statistical tests were performed with PASW Statistics 18, unless otherwise specified.

9.3 Results

Twenty-eight ortho-k-treated subjects (age = 8.30 ± 0.90 years) completed the 12-month longitudinal study on PR and PEL. Table 9.1 summarizes the Subj-M, Subj-J_0, Subj-J_{45} and AL at different visits before and after ortho-k treatment.

Subj-M was significantly reduced by ortho-k treatment ($p < 0.001$) while Subj-J_0 and Subj-J_{45} were not ($0.14 < p < 0.19$). Post-treatment Subj-M at different times (i.e. OK-S, OK-6M and OK-12M visits) were not significantly different ($p = 0.11$), whereas AL increased significantly with time ($p < 0.001$). Axial length changed significantly in both of the first six months (i.e. OK-6M - OK-S) and the second six months (i.e. OK-12M - OK-6M) of the study period ($p < 0.001$).

Table 9.1. Subjective refraction ± SD and axial elongation ± SD of orthokeratology-treated subjects at pre-orthokeratology (pre-ortho-k) and post-orthokeratology (post-ortho-k) visits

Subjective refraction and biometric parameters	Pre-orthokeratology visits	Post-orthokeratology visits		
	Pre-OK	**OK-S**	**OK-6M**	**OK-12M**
Subj-M (D)	-2.71 ± 1.04	-0.45 ± 0.43	-0.63 ± 0.53	-0.69 ± 0.70
Subj-J_0 (D)	0.16 ± 0.03	0.13 ± 0.03	0.± 0.04	0.22 ± 0.05
Subj-J_{45} (D)	0.01 ± 0.01	0.03 ± 0.02	0.03 ± 0.10	0.04 ± 0.02
AL (mm)	24.42 ± 0.65	24.52 ± 0.66	24.68 ± 0.6	24.83 ± 0.69
Change in AL from previous visit (mm)	N/A	N/A	0.16 ± 0.10)	0.15 ± 0.1

Subj-M, -J_0 and -J_{45}: M, J_0 and J_{45} vectors of subjective refraction; AL: axial length; Pre-OK: pre-orthokeratology visit; OK-S: stabilized orthokeratology treatment; OK-6M: six-month after OK-S; OK-12M: 12-month after OK-S).

9.3.1 Twelve-month changes in peripheral refraction and peripheral eye length in ortho-k-treated eyes

(A) Changes in PR

Figure 9.1 shows the PR-M, PR-J_0 and PR-J_{45} of the ortho-k-treated eyes at the OK-S, OK-6M and OK-12M visits.

During the 12-month ortho-k treatment period, PR-M, -J_0 and -J_{45} (Figure 9.1) did not change significantly ($0.06 < p < 0.98$, with Bonferroni corrections) except at T30 for PR-M ($p < 0.001$) and T10 for PR-J_0 ($p = 0.003$).

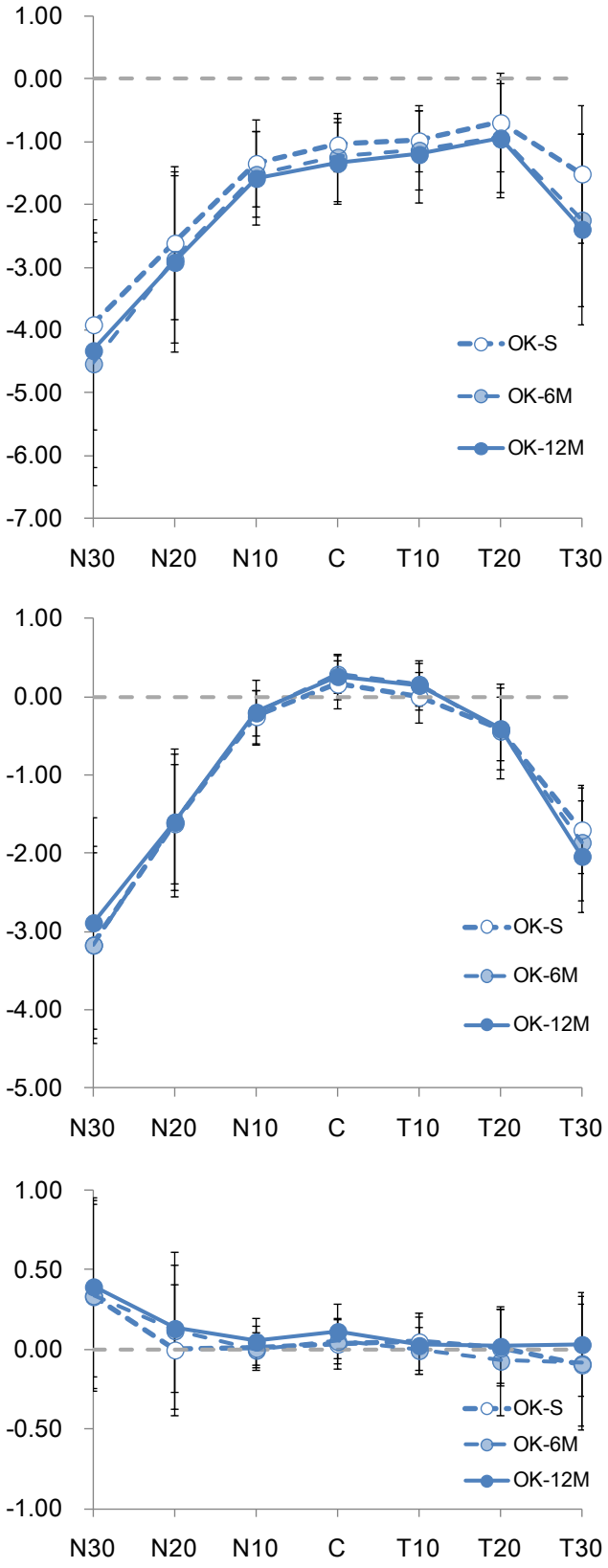


Figure 9.1. M, J_0 and J_{45} vectors of peripheral refraction (PR-M, PR-J_0 and PR-J_{45}, respectively) of the orthokeratology-treated eyes at post-treatment stabilized visit (OK-S), post-treatment 6-month visit (OK-6M) and post-treatment 12-month visit (OK-12M). N: nasal; T: temporal; C: central. Error bar = 1SD.

(B) Changes in RPR

Figure 9.2 shows the RPR-M of the ortho-k-treated eyes at the OK-S, OK-6M and OK-12M visits. Since PR-J_{45} did not change significantly, results of the statistical analyses for RPR-J_{45} were not reported.

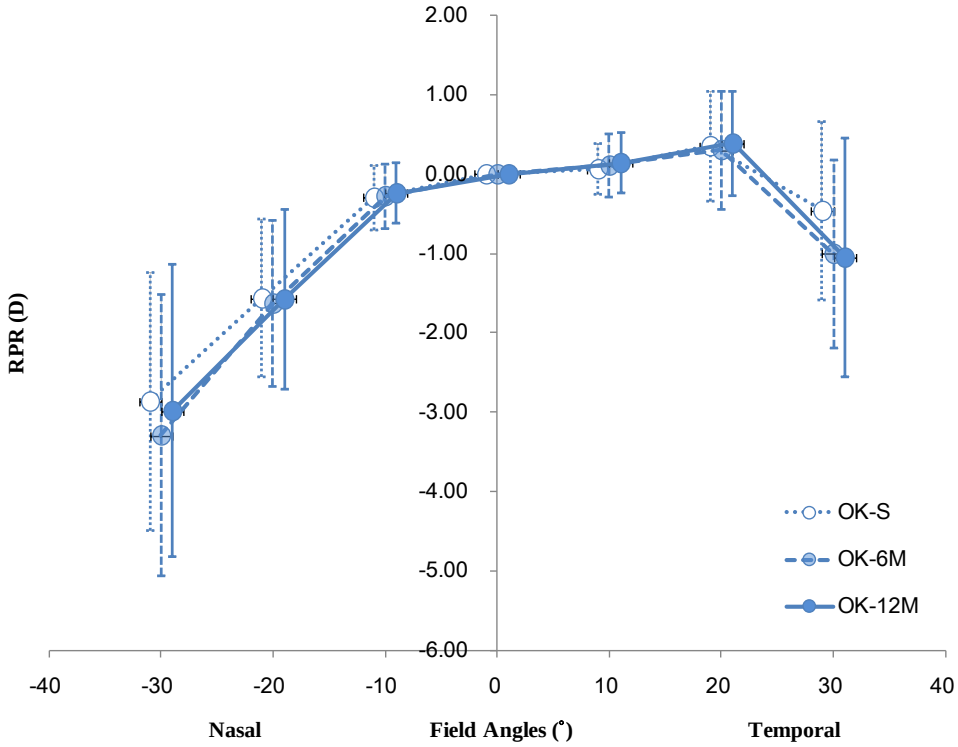
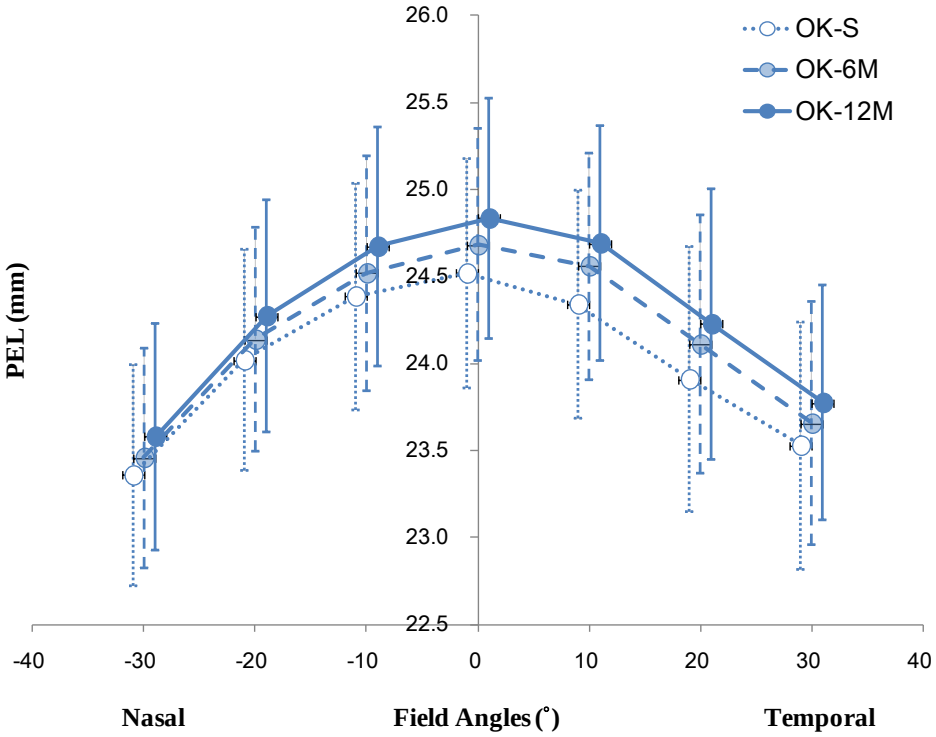


Figure 9.2. M vectors of relative peripheral refraction (RPR-M and RPR-J_0, respectively) at post-treatment stabilized visit (OK-S), post-treatment 6-month visit (OK-6M) and post-treatment 12-month visit (OK-12M). N: nasal; T: temporal; C: central. Error bar = 1SD.

There were no significant changes in RPR-M and RPR-J_0 during the lens-wearing period ($0.12 < p < 0.94$ with Bonferroni corrections), except at T30 for RPR-J_0 ($p = 0.003$).



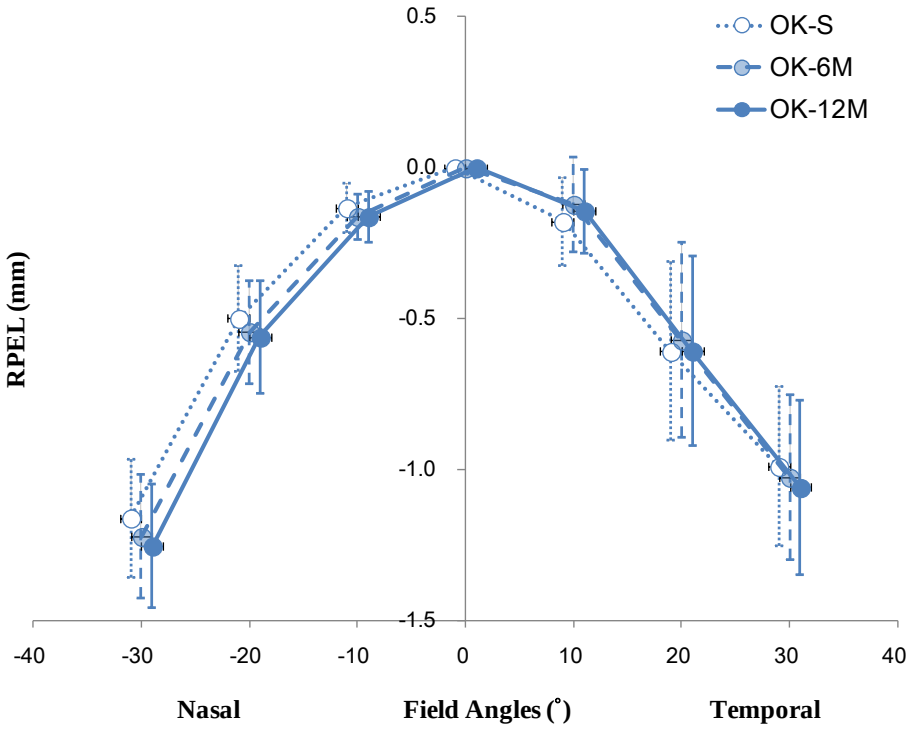


Figure 9.3. Peripheral eye length [PEL] and relative peripheral eye length (RPEL) in orthokeratology-treated eyes at at post-treatment stabilized visit (OK-S), post-treatment 6-month visit (OK-6M) and post-treatment 12-month visit (OK-12M). N: nasal; T: temporal; C: central.

(C) Changes in PEL

Figure 9.3 shows the changes in PEL and RPEL of the ortho-k-treated eyes at the OK-S, OK-6M and OK-12M visits. PEL changed significantly at all angles ($p < 0.001$).

(D) Changes in RPEL

RPEL showed significant changes at N20 and N30 only ($p \leq 0.001$) during this period.

9.3.2 Association between axial elongation, peripheral refraction and peripheral eye lengths at the post-treatment stabilized visit

(A) Axial elongation and PR at the ortho-k-stabilized visit

Table 9.2 summarizes the Pearson coefficients (p-values) between axial elongation and PR at the OK-S visit.

Table 9.2. Pearson coefficients (p-values*) between axial elongation and peripheral refraction after the stabilization of orthokeratology treatment

	Field angles						
	N30	**N20**	**N10**	**C**	**T10**	**T20**	**T30**
PR-M	-0.02	0.14	0.10	-0.01	-0.10	-0.01	-.04
	(0.91)	(0.47)	(0.62)	(0.97)	(0.62)	(0.96)	(0.85)
PR-J_0	-0.10	0.14	-0.00	-0.12	-0.09	0.15	0.05
	(0.60)	(0.49)	(0.99)	(0.54)	(0.64)	(0.46)	(0.79)

PR-M: M vector of peripheral refraction

PR-J_0: J_0 vector of peripheral refraction

N: nasal; T: temporal; C: central

*No significant correlation found

Since PR-J_{45} and RPR-J_{45} did not change significantly with ortho-k treatment, they were not included in the statistically analyses for correlations.

Axial elongation was not significantly correlated with PR-M or PR-J_0 at the OK-S visit ($0.46 < p < 0.99$).

(B) Axial elongation and RPR at the post-treatment stabilized visit

Table 9.3 summarizes those between axial elongation and RPR at the OK-S visit. No correlation was found between axial elongation and RPR-M and RPR-J_0 at OK-S ($0.20 < p < 0.97$)

Table 9.3 Pearson coefficients (p-values*) between axial elongation and relative peripheral refraction after the stabilization of orthokeratology treatment

	Field angles					
	N30	**N20**	**N10**	**T10**	**T20**	**T30**
RPR-M	-0.02	0.18	0.18	-0.14	-0.01	0.04
	(0.91)	(0.36)	(0.37)	(0.48)	(0.97)	(0.84)
RPR-J_0	-0.07	0.20	0.13	0.04	0.25	0.12
	(0.74)	(0.31)	(0.51)	(0.84)	(0.20)	(0.56)

RPR-M: M vector of relative peripheral refraction

RPR-J_0: J_0 vector of relative peripheral refraction

N: nasal; T: temporal

*No significant correlation found

9.3.3 Peripheral refraction and peripheral eye length in the fast-progressing and slow-progressing orthokeratology-treated eyes

There were 13 and 15 subjects in the fast-progressing and slow-progressing groups, respectively. Table 9.4 summarizes the age, subjective refraction and AL of the two progressing groups at each visit. Subj-M, Subj-J_{45} and AL did not differ significantly between the two progression groups ($0.20 < p < 0.40$)

before or during the ortho-k treatment period. Although the difference in Subj-J_0 (mean difference was less than 0.25 D) was statistically significant between the two groups ($p < 0.049$), it was not clinically significant.

Table 9.4. Age, subjective refraction ± SD and axial length ± SD of the fast-progressing and slow-progressing orthokeratology-treated groups.

Visit	Measurement	Fast-progressing group	Slow-progressing group	p-values (t-tests)
Pre-OK	**Age at Pre-OK / years**	8.00 ± 0.88	8.63 (0.80)	0.06
	Subj-M / D	-3.16 ± 0.62	-3.48 ± 0.75	0.20
	AL (mm)	24.27 ± 0.70	24.56 ± 0.58	0.33
OK-S	**Subj-M (D)**	-0.58 ± 0.32	-0.34 ± 0.48	0.14
OK-6M	**Subj-M (D)**	-0.77 ± 0.30	-0.51 ± 0.66	0.23
OK-12M	**Subj-M (D)**	-0.93 ± 0.45	-0.48 ± 0.83	0.11
	Axial elongation (mm) (OK-12M – OK-S)	0.47 ± 0.15	0.18 ± 0.09	< 0.001*

Subj-M, -J_0 and -J_{45}: M, J_0 and J_{45} vectors of subjective refraction AL: axial length

Pre-OK: pre-orthokeratology visit; OK-S: stabilized orthokeratology treatment; OK-6M: six-month after OK-S; OK-12M: 12-month after OK-S;

Fast-progressing group: axial elongation at OK-12M > 0.34 mm; slow-progressing group: axial elongation at OK-12M ≤0.34 mm.

***significant difference found between the two groups**

There was no significant difference between the groups for post-treatment PR-M, PR-J_0, RPR-M or RPR-J_0 at any angle ($0.14 < p < 0.94$). Figure 9.4 shows the RPR-M of the ortho-k-treated eyes at the Pre-OK and OK-S visit.

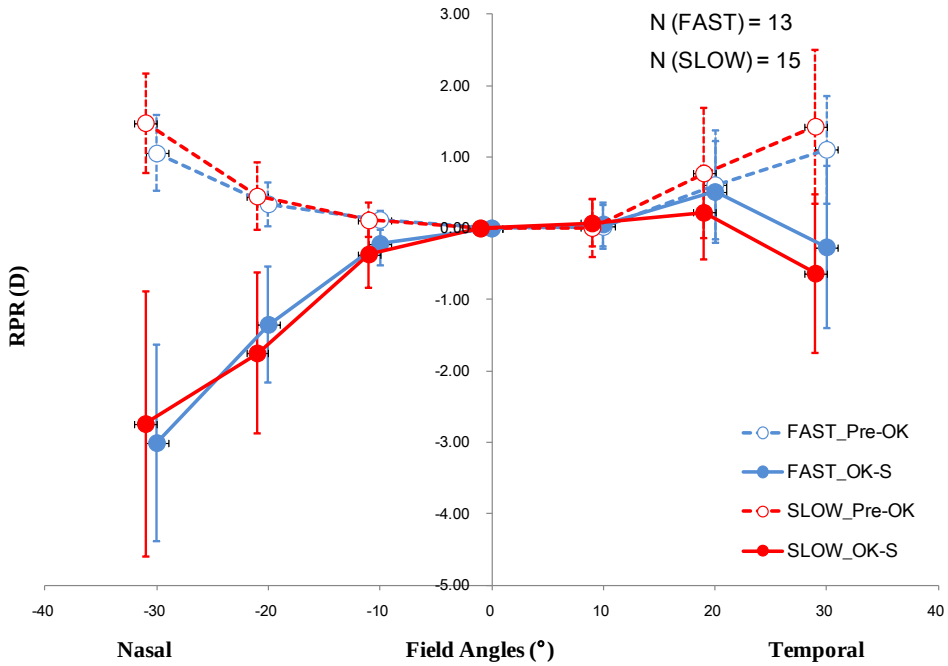


Figure 9.4. M vector of relative peripheral refraction (RPR-M) at the Pre-OK and post-treatment stabilized visit in the fast-progressing (axial elongation at 12 months after OK-S > 0.34 mm) and slow-progressing (axial elongation at 12 months after OK-S ≤0.34 mm) orthokeratology-treated eyes. N: nasal; T: temporal.

Figure 9.5 shows the PEL and RPEL of the ortho-k-treated eyes at the OK-S visit. PEL and RPEL at the OK-S visit did not differ significantly between the two groups at any angle ($0.14 < p < 0.91$).

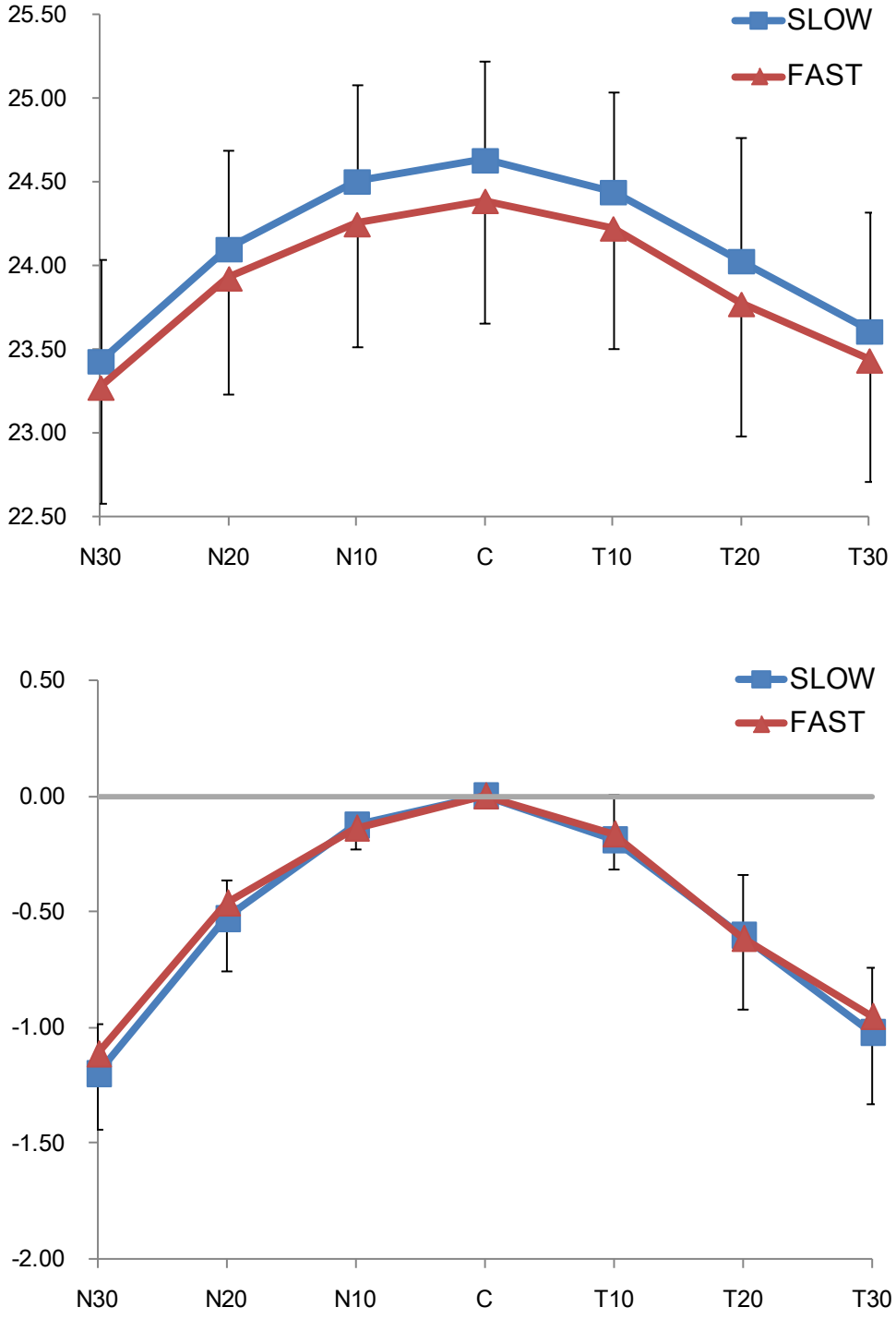


Figure 9.5. Peripheral eye length (PEL) and relative peripheral eye length (RPEL) at the post-treatment stabilized visit in the fast-progressing (FAST; axial elongation at 12 months after OK-S > 0.34 mm) and slow-progressing (SLOW; axial elongation at 12 months after OK-S ≤0.34 mm) orthokeratology-treated eyes. N: nasal; T: temporal; C: central. Error bar = 1SD.

9.3.4 Peripheral refraction and peripheral eye length characteristics between the orthokeratology-treated and control eyes

Table 9.5. Subjective refraction ± SD, axial length ± SD at baseline or pre-treatment visits (A) and axial elongation ± SD in spectacle-wearing and ortho-k-treated subjects (B)

	Visit	Ortho-k-treated subjects	Visits	Control subjects	p-values (t-tests)
Age / years	**OK-S**	8.49 ± 0.88	**BL**	7.87 ± 0.80	0.02
Subj-M / D	**Pre-OK**	-3.33 ± 0.70	**BL**	-1.79 ± 0.75	< 0.001*
Subj-J_0 / D		0.19 ± 0.20		0.12 ± 0.16	0.23
Subj-J_{45} / D		0.01 ± 0.09		0.01 ± 0.07	0.82
AL / mm	**Pre-OK**	24.42 ± 0.65	**BL**	24.20 ± 0.79	0.29
	OK-S	24.51 ± 0.66		24.20 ± 0.79	0.14
Axial elongation / mm	**OK-12M – OK-S**	0.32 ± 0.19	**12M - BL**	0.57 ± 0.20	< 0.001*

Subj-M, -J_0 and -J_{45}: M, J_0 and J_{45} vectors of subjective refraction AL: axial length.

Control subjects: Initially Myopic subjects in Chapter 8

Pre-OK: pre-orthokeratology visit; OK-S: stabilized orthokeratology treatment; OK-12M: 12-month after OK-S;BL: baseline visit of control subjects; 12M: 12-month visits of the control subjects

***significant difference between the ortho-k-treated and control subjects**

Table 9.5 compares the pre-treatment subjective refraction and AL of ortho-k-treated subjects with the baseline subjective refraction and AL of the control subjects (the IM group in Chapter 8).

There was a significant difference between the initial Subj-M in the controls and the pre-treatment Subj-M in the ortho-k-treated subjects ($p < 0.001$).

The pre-treatment AL in the ortho-k-treated subjects and the initial AL in the spectacle-wearing subjects, however, did not differ significantly ($p = 0.29$).

The axial elongation in the spectacle-wearing eyes over the 12-month study

period was significantly faster ($p < 0.001$) than that in the ortho-k-treated eyes during the 12-month ortho-k treatment period.

(A) Comparison between PR and PEL at the post-treatment stabilized visit in the ortho-k-treated eyes and baseline PR and PEL in the control eyes

RPR-M and RPR-J_0 were significantly different between treatment groups at all nasal field angles and at T30 ($p < 0.007$), but RPR-J_{45} was not different between groups ($0.24 < p < 0.94$, with Bonferroni corrections). AL and PEL did not differ between groups at any angles ($0.13 < p < 0.64$). Moreover, RPEL did not differ significantly between groups at any angle ($0.08 < p < -0.57$, with Bonferroni corrections)

(B) Twelve-month changes in PR in the ortho-k-treated and control eyes

PR-M in control eyes became significantly more myopia at all angles at 12-month visit ($p < 0.001$), while PR-M in the ortho-k-treated eyes has not changed significantly since the OK-S visit, except for T30 ($p < 0.001$). The between-group difference in the 12-month changes in PR-M was significant between the two groups from N20 to T20 ($p < 0.01$). However, a significant between-group difference in 12-month changes in RPR-M was found at T30 only ($p < 0.001$).

(C) Twelve-month changes in PEL in ortho-k-treated and spectacle-wearing eyes

Both groups showed significant increase in PEL at all angles ($p < 0.001$).

Significant between-group differences in PEL was observed in the nasal field from 10° to 30° ($p < 0.001$), while no significant between-group difference was found in the temporal field ($0.14 < p < 0.70$). For RPEL, a significant between-group difference was observed at T20 and T30 only ($0.003 < p < 0.005$).

9.4 Discussion

Our results are consistent with previous reports (Charman *et al.*, 2006; Queirós *et al.*, 2010a; Kang and Swarbrick, 2011) that ortho-k lens wear had induced a significant reduction in relative peripheral hyperopia and was also able to convert it into relative peripheral myopia in ortho-k treated eyes. A greater amount of induced changes in RPR-M towards the peripheral field were observed in our study. It is likely due to the pre-treatment myopia being higher in our subjects and therefore a greater change in corneal profile was produced by ortho-k treatment.

During the 12-month ortho-k treatment period, PR of the ortho-k-treated eyes did not change significantly. Results from Chapter 8 have demonstrated that the control subjects (i.e. IM groups in Chapter 8) had significant increase in myopia across the tested horizontal field (Figure 8.1). However, the field curvature in both groups was maintained throughout a period of 12 months.

During the lens wearing period, AL and PEL increased with time. Compared to the control eyes, ortho-k-treated eyes had a slower increase in PEL which were also found to be steadier across the horizontal field. This indicates that ortho-k lens wear did not stop eye elongation or expansion, but slowed

down the rate. The reason why the ortho-k-treated eyes continue to elongate while PR-M did not change significantly was unclear. Further investigation will be needed to study the interactions between corneal profiles changes, retinal contour changes and other contributing factors in peripheral refraction during the course of ortho-k treatment.

In the control eyes, the elongation of PEL in the temporal field lagged behind AL and those in the nasal field, resulting in significant changes in RPEL in the temporal field. This was associated with a significant increase in RPR-M in the same eccentricities. Our previous results in spectacle-wearing eyes have suggested that myopic progression might cause an increase in asymmetry in field curvatures (see Chapter 8). Results from the current experiment that ortho-k-treated eyes (showing less myopic progression compared to the controls) did not show much change in the symmetry of eye shapes further supports this view.

However, our results did not indicate that axial elongation was affected by PR or RPR at the OK-S visit. Comparison between the fast-progressing and the slow-progressing ortho-k-treated eyes did not find any relationship between RPR or RPEL and the rate of myopic progression. Although animal studies have shown that relative peripheral hyperopia could induce a central myopic shift in primates (Chapter 2), this phenomenon has yet to be confirmed in human eyes.

Asymmetry in optical shell was observed at the post-ortho-k baseline visit. The skewness of the optical shell was caused by an asymmetrical reduction in both PR-M and PR-J_0 between the temporal and nasal fields, while the contribution from PEL elongation was negligible. We suspect that it resulted from the treatment zone centre being deviated from pupil centre as a result

of angle lambda and lens decentration. The increase in asymmetry between the temporal and the nasal field is thought to have contributed to the difference in RPR-M in the nasal field between the ortho-k-treated and control eyes.

The baseline central refraction was different between the ortho-k-treated eyes and the control eyes. This may have resulted from the non-randomized study design in which subjects who opted for ortho-k treatment were more likely myopic initially.

The current study assessed only the horizontal field curvature and retinal profile. Any changes in the vertical field were not detected. However, the use of the Shin-Nippon instrument would limit the extent of the vertical field to be assessed, unless modification of the fixation method was to be made.

9.5 Conclusions

The current study demonstrated that ortho-k-treated eyes had significantly different RPR from the control eyes. However, there was no evidence to show that relative peripheral myopia prevented myopic progression.

Chapter Ten

Changes in Peripheral Refraction and Peripheral Eye Length Before and After Ortho-k Treatment in an Ortho-k-treated Subgroup – a Pilot Study

10.1 Introduction

From the longitudinal study on spectacle-wearing eyes (Chapter 8), the shape of the emmetropic and the myopic eyes, determined by field curvatures and retinal contour, remained unchanged in the nasal field, but showed an increase in relative hyperopia which was associated with a greater lag of PEL elongation relative to axial elongation. From the longitudinal study on ortho-k-treated eyes (Chapter 9), relative hyperopia was significantly reduced and even converted into relative myopia with ortho-k lens wear. The change in field curvatures and retinal contour during the 12-month of lens wear period was not significant, indicating a consistent increase in PEL cross the central field such that the shape of the shell of defocus was maintained. These two experiments, however, did not show that RPR was related to myopic progression, and there was no correlation found between baseline RPR or RPEL and myopic progression in all refractive groups of the spectacle-wearing eyes, nor was there a correlation between the post-ortho-k axial elongation and the amount post-ortho-k RPR or RPEL. We did not even find a significant association between the amount of RPR changes with the myopic control effect. A direct comparison between the ortho-k-treated myopic eyes and the spectacle-wearing myopic eyes suffered from a major limitation that the baseline refractive error was not similar between the treatment and the control subjects. This might introduce a difference in the rate of myopic progression between the two groups at the beginning of the 12-month study period. Using self-controls might be able to reduce such limiting factors. In this experiment, we re-analyzed and compared the pre-ok and post-ok changes in RPR and RPEL in six ortho-k

subjects who had PR and PEL measurements for at least six months before the commencement of ortho-k treatment.

10.2 Methods

The PR and PEL characteristics of a six-month period before ortho-k treatment (spectacle-wearing phase) in six ortho-k-treated subjects from the experiment reported in Chapter 9 were retrieved retrospectively. These variables were compared against those obtained over a six-month period after the OK-S visit (ortho-k phase). Treatment of data follows the same procedures as previously described in Chapter 5. The changes in RPR and RPEL during these two phases were relatively constant.

10.3 Results

Axial elongation was 0.29 ± 0.08) mm during the spectacle-wearing phase (six months) and was 0.16 ± 0.04) mm during the ortho-k phase (six months). Axial elongation during the spectacle-wearing phase was significantly faster ($p = 0.04$).

Figure 10.1 shows the RPR changes during the two study phases. Ortho-k treatment significantly reduced relative peripheral hyperopia in the nasal field and at T30 in ortho-k-treated eyes ($p < 0.006$). The induced changes in RPR in the nasal field also increased with eccentricity. However, RPEL before ortho-k treatment and those after stabilization of the ortho-k treatment did not differ significantly at any angle ($0.17 < p < 0.63$). Changes in RPR-M during both of the spectacle-wearing phase and the

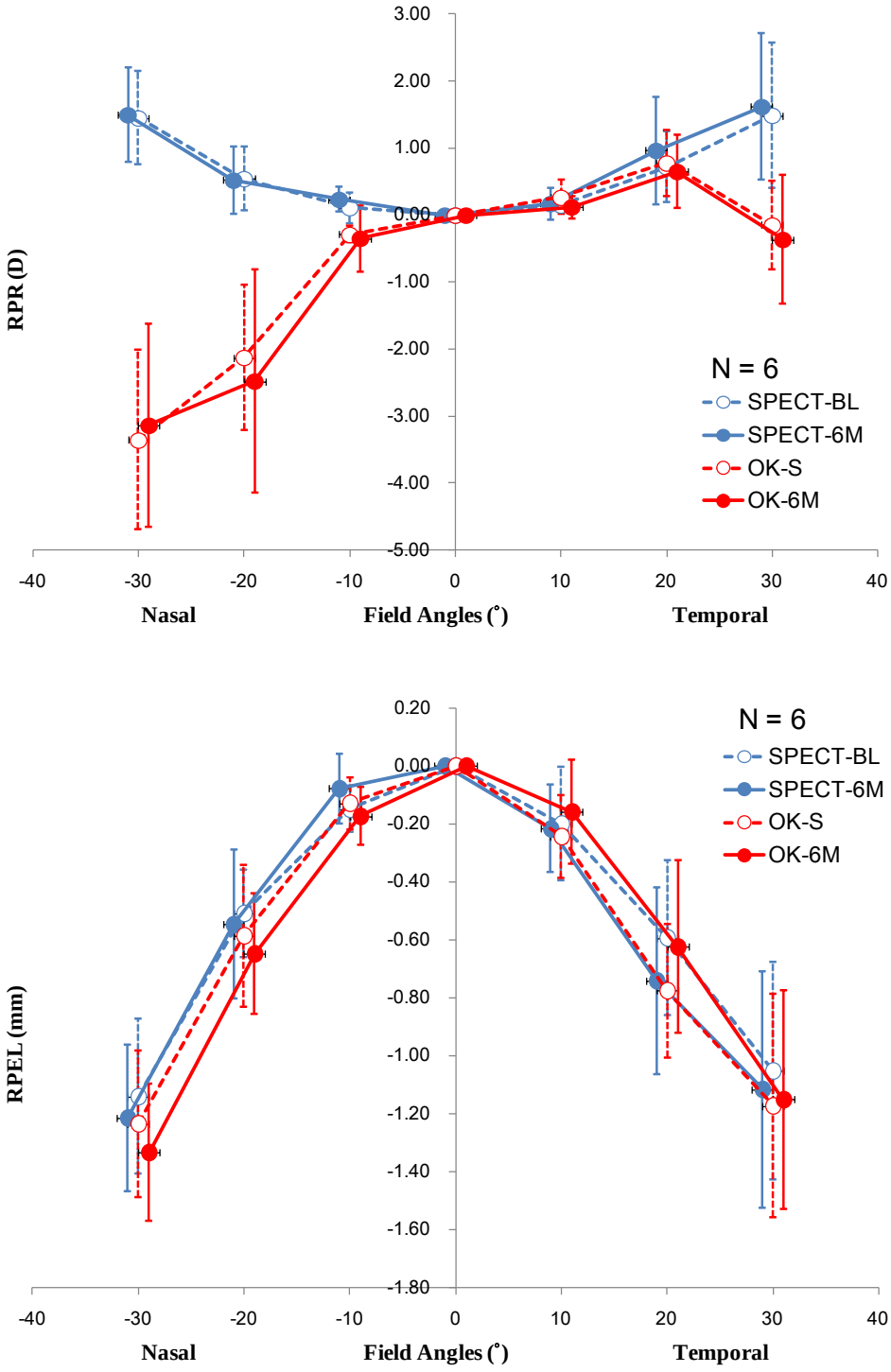


Figure 10.1. M vector of relative peripheral refraction (RPR-M) and relative peripheral eye length (RPEL) during the spectacle-wearing phase and the orthokeratology-phase in six orthokeratology-treated subjects. N: nasal; T: temporal; C: central; Spectacle-wearing (BL): baseline visit of the spectacle-wearing phase; Spectacle-wearing (6M): six months after Spectacle-wearing (BL); OK-S: post-treatment stabilized visit; OK-6M: six months after OK-S visit.. Error bar = 1SD.

ortho-k phase were insignificant at all angles ($0.11 < p < 0.96$).
Changes in RPEL were not significant in either phase ($0.12 < p < 0.52$, with Bonferroni corrections).

10.4 Discussion

Re-analysis of the changes in RPR and RPEL with time during the spectacle-wearing and ortho-k-wearing phases did not show significant differences between phases on the same subject. The field curvature and the shape of the retinal contour remained the same shape over time, in spite of axial elongation and myopic progression. The eye seemed to grow in all direction (along the horizontal field) at more or less the same pace in this subgroup. The eye became more myopic at all field angles, the increase in myopia was found to be greater during the spectacle- wearing phase than in the ortho-k phase at all angles. This indicated that axial elongation or expansion of the eye along the horizontal meridian did not cause significant changes at both phases. Our results from the longitudinal study on spectacle-wearing eyes have shown that the changes in RPR during eye growth were significant in the temporal field. However, we did not observe such changes in the spectacle-wearing phase of the ortho-k-treated subjects and this may be due to the small sample size in the current analysis.

10.5 Conclusion

Changes in RPR and RPEL were not significantly different between spectacle-wearing and ortho-k phases for selected myopic subjects. Results

from this self-control study, *albeit* small sample, on ortho-k subjects further suggested that relative hyperopia may not be a causative factor in myopic progression, or that relative peripheral myopia may not prevent against myopic progression.

Chapter Eleven

Summary and Conclusions

The prevalence of myopia in children, particularly in Asian countries, is high. High myopia, whose prevalence has been shown to increase in some places, has also become a concern. In order to minimize the ocular complications associated with high myopia, such as glaucoma, macular degeneration and retinal detachment, many resources have been invested to investigate the cause of myopia and the means for preventing it from developing or controlling its progression.

It is well accepted that ocular growth is guided by an active feedback, visually driven mechanism named emmetropization. The eye grows in response to the optical signals received by the retina. The direction of growth aims to match the focused image onto the retina. Emmetropization was focused on-axis initially. However, it was found inadequate in explaining continual eye growth after emmetropia has been achieved in some eyes. This has expanded the emmetropization theory to include the visual activities in the peripheral retina.

Results from animal studies suggested that peripheral hyperopic defocus was responsible for the visually driven ocular growth. Human studies have also shown different ametropias assumed different eye shapes. Regardless of whether the eye shape is defined by the peripheral refractive errors or sometimes by off-axial eye lengths, myopic eyes demonstrate different optical and biometrical characteristics from non-myopic eyes. The onset of myopia was also found to be associated with the development of relative peripheral hyperopia. This has led researchers to postulate that RPR is associated with myopic development in human eyes.

PR investigations on eyes undertaking ortho-k for myopic control have demonstrated that this corneal reshaping procedure was able to convert

relative peripheral hyperopia in myopic eyes into relative peripheral myopia. Effective slowing of eyeball elongation with ortho-k has led researchers to further postulate that ortho-k treatment was able to arrest myopic progression by altering the field curvatures of the myopic eyes.
However, some clinical trials did not find significant associations between myopic progression and RPR. These studies suggested that RPR might not be a predisposing factor for myopic development. In addition, there were variations in myopic control effect in eyes undertaking ortho-k. How the effectiveness of ortho-k in myopic control differed and whether these variations were related to the extent of the alteration on PR were unclear.

Results from the current study

The current study set out to investigate the characteristics of field curvatures, as represented by RPR, and retinal contour, as represented by RPEL, in eyes with different ametropias as well as in eyes undergoing ortho-k for myopic control. The tested hypotheses were:

1. There were no differences in PR or PEL between eyes with fast and slow myopic progression.
2. There were no differences in changes of PR or PEL between eyes with different ametropias.
3. There were no differences in changes in PR or PEL between eyes with fast and slow myopic progression.
4. There were no difference in PR or PEL between ortho-k-treated and spectacle-wearing eyes.
5. There were no differences in PR or PEL between ortho-k-treated

eyes showing fast and slow myopic progression during the treatment period.

Variability of PR measurements was larger beyond the central 20-degree field in both spectacle-wearing and ortho-k-treated eyes. PR measurements were more repeatable in the spectacle-wearing eyes than in the ortho-k-treated eyes. Repeatability of PEL measurements were comparable to the AL measurements and demonstrated good repeatability, which was not affected by ortho-k treatment.

Results from the current study have shown that RPR and RPEL pattern were different along the horizontal meridian among different ametropias. Myopic eyes assumed more prolate retinal contours with relative peripheral hyperopia, whereas hyperopic eyes had the least prolate retinal contour among all refraction groups and they had either relative myopia or their peripheral refractive errors were similar to the central refraction.

The absolute PR and PEL at peripheral fields changed significantly in all ametropias. This was mainly due to the expansion of the posterior pole during the course of eye growth in all ametropias. However, the 12-month changes in field curvatures and retinal contour in association with central refractive changes varied among ametropic groups. Significant changes in RPR and RPEL were found at T30 with eye growth, and these were observed in all groups. RPR changes were observed in the emmetropic groups at N20 and T20, but no significant associated change in RPEL was found. In myopes, RPR did not change significantly at other angles, but significant changes in RPEL were observed in the temporal field. Association between RPR and RPEL was significant at individual field angle and the presence of significant association was not consistent among

groups. These results indicated that changes in RPR were not necessarily accompanied by changes in RPEL, or vice versa.

There were no significant correlation between baseline RPR, RPEL and central refractive changes, nor there was correlation between changes in RPR and RPEL with central refractive changes in any group.

In the sub-group analysis on myopic subjects, the IM-FAST and IM-SLOW sub-groups did not show a significant difference in baseline RPR and RPEL or in changes of RPR and RPEL over 12 months. Mean RPR of the IM-SLOW sub-group indicated a more relative hyperopia than the IM-FAST sub-group, but the former, on the contrary, progressed less rapidly.

An increase in asymmetry in RPR and RPEL in emmetropic and myopic eyes was observed. Both refractive groups had faster myopic progression, compared to the hyperopic group, which did not show a significant increase in asymmetry during the 12-month period. It is postulated that asymmetry was the result of asymmetrical elongation of the posterior pole. As such, RPR would be more likely to be a result of eye growth rather than a cause for myopic progression.

Our results from the longitudinal study on spectacle-wearing eyes did not provide evidence to support that RPR or PEL and changes in RPR or RPEL were predictive of central refractive changes.

Ortho-k lens wear was able to reduce relative peripheral hyperopia and even to convert it into relative peripheral myopia in centrally myopic eyes. However, the post-ortho-k field of curvature did not change significantly during the 12-month ortho-k lens wear period. Significant change in RPEL over 12 months was found at N30 only.

Axial elongation of ortho-k treated subjects did not show significant

correlation with post-ortho-k RPR. Sub-group analysis on the more rapidly progressing and the slower progressing ortho-k treated eyes revealed no difference post-ortho-k baseline RPR or RPEL, or in the amount of ortho-k-induced changes in RPR.

Comparing the PR and PEL characteristics of the ortho-k-treated eyes and the control eyes, the post-ortho-k baseline RPR of the ortho-k-treated eyes was significantly more myopic than the control eyes at baseline, while AL and RPEL did not show a significant between-group difference. The annual axial elongation in the spectacle-wearing eyes was significantly faster than that in the ortho-k-treated eyes. The ortho-k-treated eyes demonstrated significant increase in PEL but no significant changes in PR over a 12-month lens wearing period, while the control eyes showed significant changes in both.

The longitudinal study on ortho-k-treated eyes confirmed that RPR was abruptly changed in myopic eyes by ortho-k lens wear. However, it did not show any associations between the post-ortho-k RPR, the amount of RPR changes induced in the field curvatures and axial elongation. Field curvature remained stable during the lens wear period, while retinal contour changed significantly in the peripheral nasal field. This indicated that eye growth in the ortho-k-treated eyes was relatively stable across the horizontal field. Apart from the RPR pattern, ortho-k-treated eyes and spectacle-wearing eyes did not differ in retinal contour or changes in both parameters at most field angles. The significant between-group difference in 12-month changes in RPEL at peripheral field angles may be a result of the different rates in eye growth.

We further investigated a sub-group of the ortho-k-treated subjects who had

provided previous PR and PEL data before ortho-k treatment to look for differences in different treatment phases. Again, similar results as in the comparison between the ortho-k-treated eyes and the control eyes were obtained.

In conclusion, the current study did not find any evidence for relative peripheral hyperopia as a causative factor for myopic progression, or that relative peripheral myopia was protective against myopic progression. Future studies are necessary to confirm if RPR is merely a result of eye growth or indeed is a factor in some sort of feedback mechanism. The current study did not provide further evidence to support the PR hypothesis in ortho-k treatment for myopic control. Further investigation on the mechanisms of myopic control with ortho-k is also warranted.

Limitations of the current study

The current study has a few limitations which include sample size, experimental design, and time:

a) The current study investigates the horizontal field only, sparing the vertical or the oblique field. During eye growth, the globe should grow in all directions. The vertical or other meridians do not necessarily grow in the same way as the horizontal meridian does. Research in myopia progression will be limited if we only consider changes in the horizontal meridian.

b) The sample size of the current study was relatively small, particularly for the ortho-k-treated eyes with self controls. With a larger sample size, we will be able to have a larger subject number for each subgroup. The

current study required all subjects to attend data-collection visits every six months. In each visit, cycloplegia was performed. Moreover, the duration for each data-collection visit was long. Therefore, many of the children screened decided not enroll into the study eventually.

In addition, the current study required the subjects fixated the peripheral targets with eye turn while keeping their head steadily against the head rest of the instrument. This requires the subject to be highly cooperative and concentrated during the data collection. These have put further constraints during subject selection. The current study was further limited by the resource and manpower to satisfy the large number of visits and long chair time during the data collection visits.

c) the baseline refractive errors were different between the ortho-k-treated and the controls. It was because the two longitudinal experiments did not start at the same time. The experiment with the spectacle-wearing eyes commenced first while the experiment with the ortho-k-treated subjects commenced about one year later. This partially explains why age of the subjects in the ortho-k-treated and control eyes was different.

Moreover, parents were concerned about safety with the ortho-k treatment and contact lens handling in children. Therefore, parents were more willing to enroll their children into ortho-k-treatment when their children were older, or when the myopia of their children had changed significantly to moderately myopic.

The pilot study with six ortho-k-treated eyes as self controls suffered also from the small subject number. Since data was retrieved retrospectively, this experiment was therefore under more constraints than the other two experiments.

It is desirable to recruit subjects with similar age and refractive errors at enrollment as these factors may predispose an eye into higher risks of myopic progression. Samples for different treatments should have similar age, myopia and myopic progression rate initially in order to minimize bias.

d) The current study did not employ randomization during the recruitment of subjects for the ortho-k treatment as there were other constraints (as mentioned above) which had discouraged many of the screened subjects from participating in our research. In view of the potential effect on the progress of subject recruitment and the time constraints of the PhD project, we decided to opt for a non-randomized design. Randomization is, however, advantageous in minimizing subject bias due to differences in age, gender and initial myopia.

e) The age of subjects in the current study was limited to six to nine years for the spectacle-wearing eyes. This range was selected because of the high risks of school myopia development during this period. However, the critical age for myopic development in human eyes is still unclear. Results from the current study are, therefore, unable to confirm the changes in PR and PEL during the critical period of ocular growth. Unlike other PR studies in primates, the observation or manipulation of PR were performed during the critical period. Therefore, results from the current study, as well as in other studies, may not be comparable to those found in the animal studies.

f) We have employed the Bonferroni corrections in our statistical analyses. The use of Bonferroni adjustment was justified as we made six to seven multiple comparisons each time for the PR and PEL

analyses. With Bonferroni corrections, we were able to minimize the risk for false positives. However, at the same time, this has increased the risk of introducing false negatives (Type II errors).

Future work

As mentioned above, our results suggested that RPR is more likely to be a resultant of eye growth rather than a cause for myopic progression but with the limitations of this study, we were unable to draw any firm conclusion. With more time and resources, and modification on the study protocol including subject recruitment and randomization, larger sample with reduced bias from age, refractive errors and initial myopic progression rate at enrollment can be recruited.

The current study did not investigate the PR and PEL during the critical period for myopic development in human eyes. It is desirable to recruit subjects with younger ages in future to investigate how PR and PEL change during the early years of life. With the expansion on the age range towards younger years of life, it is necessary to develop measurement methods with higher accuracy and reproducibility as these subjects will be less cooperative and have shorter period of concentration.

The reason why changes in PEL in the ortho-k-treated eyes were not accompanied by changes in PR was unclear. We would need further investigations on other factors such as the corneal topographical data which might alter the PR characteristics during the course of ortho-k-treatment. Moreover, it is desirable to compare the changes in PR and PEL with and without ortho-k-treatment in the self-control subjects. In future investigation,

the subject number should be largely increase and randomization on the sequence of treatment phases should be incorporated. It will need two groups of subjects with one group participating in the spectacle-wearing phase first and followed by the ortho-k phase, while the other group participating in the ortho-k-phase first and followed by the spectacle-wearing phase. Investigation on the effect of the duration of the treatment phases on the myopic control effect, PR and PEL changes should also be undertaken.

Appendix I

Statistics on Normality Tests for Chapter 8

Table AI. 1. Kolmogorov-Smirnov tests stastics (p-values) on cycloplegic subjective refraction in spectacle-wearing eyes at different visits

Subjective Rx at Different Visits	**Subj-M**	**Subj- J_0**	**Subj- J_{45}**
BL	0.07	<0.001¶	<0.001¶
6M	0.19	0.003¶	<0.001¶
12M	0.20	<0.001¶	<0.001¶

Subj-M: M vector of subjective refraction
Subj- J_0: J_0 vector of subjective refraction
Subj-J_{45}: J_{45} vector of subjective refraction
BL: baseline visit
6M: 6-month visit
12M: 12-month visit
¶ Non-normal distribution after Bonferroni correction

Table AI.2. Kolmogorov-Smirnov tests statistics (p-values) on PR in spectacle-wearing eyes at different visits

Visit	Field Angles	PR-M	PR-J_0	PR-J_{45}
BL	N30	0.17	0.20	0.01¶
	N20	0.20	0.20	0.20
	N10	0.20	0.04	0.04
	C	0.20	0.20	0.20
	T10	0.20	0.07	<0.001¶
	T20	0.20	0.20	0.20
	T30	0.07	0.20	0.20
6M	N30	0.03	0.20	<0.001¶
	N20	0.20	0.20	0.05
	N10	0.19	0.20	0.004¶
	C	0.20	0.20	0.20
	T10	0.20	0.20	0.20
	T20	0.20	0.20	0.20
	T30	0.03	0.20	0.20
12M	N30	0.01¶	0.20	0.20
	N20	0.20	0.20	0.20
	N10	0.20	0.02	0.20
	C	0.20	0.20	0.20
	T10	0.20	0.20	0.20
	T20	0.20	0.10	0.20
	T30	0.001¶	0.20	0.20

PR-M: M vector of peripheral refraction
PR-J_0: J_0 vector of peripheral refraction
PR-J_{45}: J_{45} vector of peripheral refraction
BL: baseline visit
6M: 6-month visit
12M: 12-month visit
N: nasal; T: temporal; C: central
¶ Non-normal distribution after Bonferroni correction

Table AI.3. Kolmogorov-Smirnov tests statistics (p-values) on RPR in spectacle-wearing eyes at different visits

Visit	Field Angles	**RPR-M**	**RPR-J_0**	**RPR- J_{45}**
BL	N30	0.20	0.20	0.20
	N20	0.20	0.20	0.20
	N10	0.08	0.09	0.18
	T10	0.09	0.20	0.20
	T20	0.20	0.20	0.20
	T30	0.20	0.20	0.20
6M	N30	0.20	0.19	0.01¶
	N20	0.20	0.20	0.20
	N10	0.08	0.07	0.20
	T10	0.20	0.20	0.01¶
	T20	0.07	0.20	0.20
	T30	0.016¶	0.20	0.20
12M	N30	0.20	0.20	0.20
	N20	0.17	0.20	0.20
	N10	0.09	0.20	0.20
	T10	0.20	0.20	0.20
	T20	0.20	0.20	0.20
	T30	0.001¶	0.20	0.20

RPR-M: M vector of relative peripheral refraction
RPR-J0: J0 vector of relative peripheral refraction
RPR-J_{45}: J_{45} vector of relative peripheral refraction
BL: baseline visit
6M: 6-month visit
12M: 12-month visit
N: nasal; T: temporal; C: central
¶ Non-normal distribution after Bonferroni correction

Table AI. 4. Kolmogorov-Smirnov tests statistics (p-values) on PEL and RPEL in spectacle-wearing eyes at different visits

Visit	Field Angles	**PEL**	**RPEL**
BL	N30	0.20	0.20
	N20	0.20	0.20
	N10	0.20	0.20
	C	0.20	-----
	T10	0.20	0.06
	T20	0.20	0.013¶
	T30	0.20	0.20
6M	N30	0.20	0.20
	N20	0.20	0.20
	N10	0.20	0.20
	C	0.20	-----
	T10	0.20	0.16
	T20	0.20	<0.001¶
	T30	0.20	0.16
12M	N30	0.20	0.20
	N20	0.20	0.20
	N10	0.20	0.008¶
	C	0.20	-----
	T10	0.20	0.20
	T20	0.20	0.006¶
	T30	0.20	0.20

PEL: peripheral eye length
RPEL: relative peripheral eye length
BL: baseline visit
6M: 6-month visit
12M: 12-month visit
N: nasal; T: temporal; C: central
¶ Non-normal distribution

Appendix II

Statistics on Normality Tests for Chapter 9

Table AII.1Shapiro-Wilk tests statistics (p-values) on cycloplegic subjective refraction in orthokeratology-treated eyes at different visits

	Subjective refraction		
Visits	Subj-M	Subj-J0	Subj-J_{45}
Pre-OK	0.46	0.04	0.02
OK-S	0.01¶	0.03	0.23
OK-6M	0.82	0.26	0.03
OK-12M	0.47	0.35	0.03

¶ Non-normal distribution after Bonferroni correction

Subj-M: M vector of subjective refraction

Subj-J0: J0 vector of subjective refraction

Subj-J_{45}: J_{45} vector of subjective refraction

Pre-OK: before orthokeratology treatment

OK-S: after stabilization of orthokeratology treatment

OK-6M: six month after stabilization of orthokeratology treatment

OK-12M: 12 months after stabilization of orthokeratology treatment

Table AII.2Shapiro-Wilk tests statistics (p-values) on peripheral refraction in orthokeratology-treated eyes at different visits

Visit	Field Angles	PR-M	PR-J0	PR-J_{45}
Pre-OK	N30	0.07	0.99	0.35
	N20	0.42	0.95	0.28
	N10	0.44	0.11	0.02
	C	0.20	0.54	0.29
	T10	0.76	0.67	0.03
	T20	0.40	0.43	0.30
	T30	0.65	0.76	0.71
OK-S	N30	0.45	0.94	0.26
	N20	0.36	0.03	0.13
	N10	< 0.001¶	0.55	0.15
	C	0.03	0.53	0.42
	T10	0.46	0.16	0.21
	T20	0.02	0.64	0.34
	T30	1.00	0.04	0.42
OK-6M	N30	0.48	0.80	0.84
	N20	0.57	0.01¶	0.23
	N10	0.87	0.48	0.23
	C	0.03	0.50	0.96
	T10	0.13	0.56	0.35
	T20	0.02	0.12	0.21
	T30	0.14	0.85	0.04
OK-12M	N30	0.40	0.66	0.28
	N20	0.02	0.03	0.33
	N10	0.04	0.37	0.06
	C	0.59	0.90	0.82
	T10	0.19	0.83	0.21
	T20	0.09	0.04	0.47
	T30	0.05	0.28	0.87

¶ Non-normal distribution after Bonferroni correction
PR-M: M vector of peripheral refraction
PR-J0: J0 vector of peripheral refraction
PR-J_{45}: J_{45} vector of peripheral refraction
Pre-OK: before orthokeratology treatment
OK-S: after stabilization of orthokeratology treatment
OK-6M: six month after stabilization of orthokeratology treatment
OK-12M: 12 months after stabilization of orthokeratology treatment
N: nasal; T: temporal; C: central

Table AII.3 Shapiro-Wilk tests statistics (p-values) on relative peripheral refraction in orthokeratology-treated eyes at different visits

Visit	Field Angles	**RPR-M**	**RPR-J0**	**RPR-J_{45}**
Pre-OK	N30	0.48	0.45	0.71
	N20	0.49	0.22	0.09
	N10	0.80	0.26	0.57
	T10	0.13	0.31	0.38
	T20	0.02	0.61	0.62
	T30	0.07	0.19	0.61
OK-S	N30	0.84	0.93	0.71
	N20	0.63	0.32	0.21
	N10	0.22	0.08	0.10
	T10	0.54	0.61	0.19
	T20	0.21	0.75	0.54
	T30	0.72	0.57	0.07
OK-6M	N30	0.10	0.32	0.93
	N20	0.06	0.02	0.17
	N10	0.01¶	0.34	0.47
	T10	0.001¶	0.79	0.43
	T20	0.67	0.88	0.93
	T30	0.39	0.09	0.05
OK-12M	N30	0.80	0.88	0.07
	N20	< 0.001¶	0.01¶	0.33
	N10	0.01¶	0.49	0.09
	T10	0.65	0.22	0.78
	T20	0.27	0.47	0.44
	T30	0.03	0.13	0.51

¶ Non-normal distribution after Bonferroni correction

RPR-M: M vector of relative peripheral refraction

RPR-J0: J0 vector of relative peripheral refraction

RPR-J_{45}: J_{45} vector of relative peripheral refraction

Pre-OK: before orthokeratology treatment

OK-S: after stabilization of orthokeratology treatment

OK-6M: six month after stabilization of orthokeratology treatment

OK-12M: 12 months after stabilization of orthokeratology treatment

N: nasal; T: temporal; C: central

Table AII.4 Shapiro-Wilk tests statistics (p-values) on PEL and RPEL in orthokeratology-treated eyes at different visits

Visit	Field Angles	**PEL**	**RPEL**
Pre-OK	N30	0.86	0.06
	N20	0.77	0.10
	N10	0.74	0.45
	C	0.50	-----
	T10	0.88	0.57
	T20	0.67	0.003¶
	T30	0.99	0.01¶
OK-S	N30	0.67	0.51
	N20	0.57	0.15
	N10	0.41	0.23
	C	0.20	-----
	T10	0.92	0.34
	T20	0.37	0.14
	T30	0.72	0.01¶
OK-6M	N30	0.72	0.92
	N20	0.39	0.51
	N10	0.39	0.06
	C	0.27	-----
	T10	0.22	0.30
	T20	0.66	0.34
	T30	0.78	0.76
OK-12M	N30	0.43	0.60
	N20	0.22	0.32
	N10	0.13	0.04¶
	C	0.08	-----
	T10	0.13	0.68
	T20	0.30	0.34
	T30	0.30	0.98

¶ Non-normal distribution

PEL: peripheral eye length

RPEL: relative peripheral eye length

Pre-OK: before orthokeratology treatment

OK-S: after stabilization of orthokeratology treatment

OK-6M: six month after stabilization of orthokeratology treatment

OK-12M: 12 months after stabilization of orthokeratology treatment

N: nasal; T: temporal; C: central

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