# THE ROLE OF RELATIVE PERIPHERAL REFRACTION IN MYOPIA CONTROL USING MYOPIC DEFOCUS

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# The Role of Relative Peripheral Refraction in Myopia Control Using Myopic Defocus

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# CERTIFICATE OF ORIGINALITY

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# Abstract

**PhD thesis title**

The role of relative peripheral refraction in myopia control using myopic defocus

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The prevalence of myopia has increased substantially worldwide in the last two decades, especially in Asia. High myopia increases the risk of ocular pathologies, which could cause visual impairment and subsequent deterioration of quality of daily life. Myopia control is now targeting children at a young age in an attempt to reduce the risk of high myopia and preferably delay the onset or slow the myopia progression.

The Defocus Incorporated Multiple Segments (DIMS) spectacle lens is a custom-made plastic spectacle lens. It includes a central optical zone (9.4 mm in diameter) for correcting distance refractive error and annular multi-focal zones with a relatively positive power (+3.50 D) and with multiple segments extending to the periphery (33 mm in diameter). This design simultaneously introduces myopic defocus and provides a clear vision for the wearer at all viewing distances. In a 2-year double-masked randomised controlled trial (RCT), children wearing the DIMS lens showed significantly slowed myopia progression and axial elongation by around 50 to 60%.

Most studies reported myopia control efficacy as changes in refractive error and axial length (AL), with few describing the retinal shape changes. It has been suggested that retinal shape might be a determinant for developing myopia through biomechanical factors, and relative peripheral refraction (RPR) has been used to indirectly describe the retinal shape. However, few studies have reported changes of RPR after myopia control

using myopic defocus in humans.

**Objectives of the study**

There are three objectives:

1. To determine and describe the RPR among Hong Kong Chinse children who participated in the RCT.
2. To compare changes in RPR associated with myopia progression in myopic children wearing DIMS lenses and SV spectacle lenses over 2 years.
3. To compare changes in RPR associated with myopia progression in myopic children wearing DIMS lenses for the third year and children wearing SV lenses in the first 2 years who then switched to wear DIMS lenses for one year.

**Methods**

In the first 2 years, a double-masked randomised clinical trial (RCT) was conducted between August 2014 and July 2017. The children were allocated randomly to wear either the DIMS lens (treatment group) or SV spectacle lens (control group). After completion of the RCT, participated children were offered a continuation of follow-up for 1 year. In the third year, the children who were in the DIMS group continued to wear the DIMS lenses (DIMS group), and those who were in the SV group were switched to wear the DIMS lenses (Control-to-DIMS group). We have also acquired a historical control group by searching clinical records from 2017 to 2019 of the Optometry Clinic in the Hong Kong Polytechnic University.

A standardised eye examination was performed every 6 months over the 3-year study.

Cycloplegic central and peripheral refraction across the horizontal retinal eccentricities were measured five times by using a Shin-Nippon NVision-K 5001 autorefractor (Ajinomoto Trading Inc., Tokyo, Japan) with the Maltese cross-target placed at the straight-ahead position (centre) and 10°, 20°, and 30° at nasal (10N, 20N, 30N) and temporal (10T, 20T, 30T) retinal eccentricity. AL was measured five times using the IOL Master 500 (Carl Zeiss, Oberkochen, Germany) and then averaged.

The primary outcome included the changes in central spherical equivalent refraction (SER), and secondary outcomes included changes in AL, peripheral refraction, and relative peripheral refraction and comparison between the treatment and the control groups on these parameters.

## Results

### Demography

Among 550 subjects recruited and assessed, 183 fulfilled inclusion and exclusion criteria and were also willing to participate in the RCT. They were randomised those 93 children were assigned to DIMS group, and 90 children were assigned to the SV group. There was no statistically significant difference in the baseline ocular parameters between the DIMS and SV groups ($p>0.05$). The mean age of the children were around 10 years old, and their mean SER were around −2.93±1.04D in the DIMS group and −2.70±0.98D in the SV group.

### Myopia progression and axial length changes in the 2-year RCT

One hundred sixty subjects completed the first 2-year measurements, with 79 subjects in DIMS group and 81 subjects in the SV group. Myopia progression was -0.38±0.06 D

and -0.93±0.06 D in the DIMS and SV groups, and the axial elongation was 0.21±0.02 mm and 0.53±0.03 mm in DIMS and SV groups, respectively. Over 2 years, DIMS showed significantly less myopia progression (−0.55±0.09 D, $p<0.0001$) and less axial elongation (0.32±0.04 mm, $p<0.0001$) than the SV group.

**Changes in RPR associated with myopia progression in myopic children wearing DIMS lenses and SV spectacle lenses over 2 years.**

At baseline, the two groups presented no significant differences in peripheral refraction along the horizontal retina. Over the 2 years, the DIMS group showed myopic shifts in all retinal eccentricities, with a similar amount of myopic shifts between nasal and temporal retina. SV group had asymmetrical peripheral myopic shifts between the nasal and temporal retina, with more myopic shifts at 10T (-0.32±0.62 D, $p\leq0.0001$), at 20T (-0.69±0.95 D, $p\leq0.0001$) and 30T (-0.85±1.52 D, $p\leq0.0001$). There was no significant difference in peripheral $J_0$ nor peripheral $J_{45}$ between the two groups after 2 years.

No significant changes in RPR were noted in the DIMS group, while significant hyperopic shifts in RPR were found at the nasal retina (10N: 0.27 ± 0.45 D; 20N: 0.75 ± 0.72 D; 30N: 0.98 ± 0.76 D, all $p<0.0001$) in the SV group.

**The RPR among Hong Kong Chinse children who participated in the RCT and its influences on myopia control.**

For children who completed the 2-year RCT, the mean central SER was -2.87 ± 0.97 D, and the mean age was 10.1 ±1.5 years. The two groups were combined for analysis as no significant difference in baseline peripheral refraction and RPR between DIMS and SV group. Hyperopic RPR was observed at most eccentricities across the horizontal

retina, and it increased with more peripheral eccentricity. A broad range of hyperopic RPR was present at 30N, which ranged from 0 to 6 D. Compared to the RPR in the temporal retina, there was more hyperopic RPR at 10N (paired t-test, mean difference:0.17±0.63 D, p=0.001), 20N (mean difference: 0.65±1.21 D, p<0.0001) and 30N (mean difference: 0.84±1.68 D, p<0.0001). However, only a weak correlation between RPR and central SER was found in the baseline cross-sectional observation.

Both relative $J_0$ and relative $J_{45}$ increased in magnitude with increasing eccentricity, and the magnitude of relative $J_{45}$ was less than relative $J_0$. An asymmetrical profile was also found in relative $J_0$, with more negative of relative $J_0$ at the 10T (paired t-test: mean difference: -0.28±0.36 D, p<0.0001), 20T (mean difference: -0.74±0.74 D, p<0.0001) and 30T (mean difference: -1.08±0.91 D, p<0.0001) compared with the corresponding eccentricity in the nasal retina. There was no significant difference in relative $J_{45}$ between the nasal and temporal retina.

In the DIMS group, baseline RPR in the nasal retina were positively associated with myopia progression (multiple linear regression,10N: r=0.36, p=0.001; 20N: r=0.35, p=0.001) and negatively associated with axial elongation (10N: r=-0.34, p=0.001; 20N: r=-0.29, p=0.006). In the SV group, baseline RPR at 10N (r=0.37, p=0.001) and 20N (r=0.36, p=0.001) and 30N (r=0.35, p=0.002) were positively associated with myopia progression but no statistically significant relationship between RPR axial elongation after Bonferroni correction (p>0.008).

Subjects were subdivided into two subgroups according to baseline RPR: myopic RPR

(10N,20N) and hyperopic RPR (10N,20N) group. Myopia progression and axial elongation were further compared between myopic RPR and hyperopic RPR group within the SV and DIMS group.

In the SV group, there was no statistically significant difference in myopia progression (mean difference: -0.26±0.14 D, p=0.06) and axial elongation (mean difference:0.04±0.05 mm, p=0.48) between myopic RPR (n=27) and hyperopic RPR (n=54) at 10N. Also, no significant difference in myopia progression (mean difference: -0.25±0.20 D, p=0.19) and axial elongation (mean difference: 0.08±0.08 mm, p=0.27) between myopic RPR (n=11) and hyperopic RPR (n=70) at 20N.

However, in the DIMS group, myopic RPR at 10N subgroup (n=27) showed statistically significant more myopia progression (mean difference: -0.36±0.14 D, p=0.009) and axial elongation (mean difference: 0.16±0.05 mm, p=0.001) than hyperopic PRR at 10N subgroup (n=52). And myopic RPR at 20N subgroup (n=12) showed statistically significant more myopia progression (mean difference: -0.40±0.16 D, p=0.01) and axial elongation (mean difference: 0.15±0.07 mm, p=0.02) than hyperopic PRR at 20N subgroup (n=67).

**Myopia progression and axial length changes in the third year**

Among the 160 children who completed the 2-year RCT study, 128 children participated in the extended 1-year post-trial follow-up study, and 120 children completed the third-year visits. Children in the DIMS group (n=65) continually showed good myopia control effects. On average, the annual changes in myopia progression

were -0.18 D, and this progression rate was almost linear over the 3 years. For the children who were in the original control group, the myopia control effect was significantly different over 3 years. In the first 2 years, the myopia progression rate ranged from -0.38 D to -0.49 D. After switching to DIMS lens, the annual myopia progression was reduced to only -0.05 D for the third year.

The annual axial elongation in the DIMS group was around 0.10 mm per year. A mean axial elongation of 0.08 mm in the third year was found in the Control-to-DIMS group (n=55), while it was 0.20 mm and 0.29 mm per year in the first and second years.

**The RPR changes in myopic children wearing DIMS lenses for the third year and children wearing SV wearers in the first 2 years who then switched to wear DIMS lenses.**

In the third year, DIMS group (n=65) showed myopic shifts in all the peripheral eccentricities and increased proportionally with the central myopia progression; therefore, it maintained a relatively constant RPR. When comparing the changes in RPR between the first 2 years and the third year, Control-to-DIMS (n=55) group showed a significant decrease in hyperopic RPR in the third year at nasal retina compared to the changes in RPR in the first 2 years ($p<0.05$, paired t-test). No significant difference in RPR changes between the nasal retina and temporal retina was found in the third year in the Control-to-DIMS group.

In the Control-to-DIMS group, the RPR at 24-month was statistical significantly associated with myopia progression (multiple linear regression, 10N: r=0.40, p=0.004; 20N: r=0.48, p=0.001; 30N: r=0.43, p=0.001) after adjusting for the initial central SER

at 24-month, age and sex. For the DIMS group, the baseline RPR was associated with the 3-year myopia progression (10N: r=0.38, p=0.002; 20N: r=0.35, p=0.007).

**Conclusion**

DIMS lenses showed myopia control effects in retarding myopia progression and slowing down the changes in axial length in myopic children. As a spectacle lens, it has the advantage of being non-invasive and easily accepted by young children. No adverse effects were reported in the visual functions after wearing the lens for 2 years

Over 2 years, myopia control using myopic defocus in the mid-periphery impacted the changes in peripheral refraction and slowed central myopia progression by somehow altering the overall retinal shape. In addition, the asymmetrical changes in RPR in traditional spectacle lenses may infer a faster myopia progression.

The determination in RPR among Hong Kong Chinse children who participated in the DIMS study suggested that among typical Chinese young myopes, there were asymmetrical hyperopic RPR at the horizontal retina, and the hyperopic RPR increased with increasing retinal eccentricities.

DIMS lens was more effective in myopia control for children having hyperopic RPR but less effective in children with myopic RPR at the periphery. This could be related to the too much of myopic defocus that may not benefit the myopia retardation. Customised myopic defocus to fit individual subjects may optimise the myopia control effect.

This study suggested that the myopia control effects of DIMS lenses was influenced by initial RPR. Initial RPR could be used as an indicator for the ordering lens and avoiding over-induce myopic defocus. RPR could be an important parameter to predict the changes in retinal shapes after myopia control. The mechanism of the signal detection and decoding of defocus required further investigation.

# List of publications and conference presentations

**Publications:**

Zhang, H.Y., Lam, C.S.Y., Tang, W.C., Leung, M., To, C.H., 2020. Defocus Incorporated Multiple Segments Spectacle Lenses Changed the Relative Peripheral Refraction: A 2-Year Randomized Clinical Trial. *Invest Ophthalmol Vis Sci* 61, 53.

Lam, C.S., Tang, W.C., Lee, P.H., Zhang, H.Y., Qi, H., Hasegawa, K., To, C.H., 2021. Myopia control effect of defocus incorporated multiple segments (DIMS) spectacle lens in Chinese children: results of a 3-year follow-up study. *Br J Ophthalmol, bjophthalmol*-2020-317664.

**Conferences:**

Zhang, H.Y., Lam, C.S.Y., Tang, W.C., Lee, R.P.K., To, C.H., Peripheral refraction in myopic children. *16th International Myopia Conference*, 2017, Birmingham

Zhang, H.Y., Lam, C.S.Y., Tang, W.C., To, C.H., Impact of Defocus Incorporated Multiple Segments (DIMS) spectacle lenses on relative peripheral refraction (RPR): a 2-year randomized clinical trial. *ARVO Annual Meeting*, 2019, Vancouver

Zhang, H.Y., Lam, C.S.Y., Tang, W.C., Leung, M., Visual performance of a Modified Defocus Incorporated Soft Contact (M-DISC) lens in young myopes. *17th International Myopia Conference*, 2019, Tokyo

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*ZHANG HAN YU*

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# List of Abbreviations

| | |
|---|---|
| 10N | 10˚ of nasal retina |
| 10T | 10˚ of temporal retina |
| 20N | 20˚ of nasal retina |
| 20T | 20˚ of temporal retina |
| 30N | 30˚ of nasal retina |
| 30T | 30˚ of temporal retina |
| AL | Axial length |
| ANOVA | Analysis of variance |
| ATR | Against-the-rule |
| CARE | Cumulative absolute reduction in axial elongation |
| CHASE | Child Heart and Health Study in England |
| CLEERE | Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error |
| COMET | Correction of Myopia Evaluation Trial |
| CONSORT | Consolidated Standards of Reporting Trials |
| DIMS | Defocus Incorporated Multiple Segments |
| DISC | Defocus Incorporated Soft Contact |
| DOF | Depth of focus |
| GEE | Generalized Estimation Equation |
| FDM | Form deprivation myopia |
| ITT | Intend-to-treated |

| | |
|---|---|
| IMI | International Myopia Institute |
| IOP | Intraocular pressure |
| LIM | Lens induced myopia |
| MRI | Magnetic resonance imaging |
| PALs | Progressive additional lenses |
| OK | Orthokeratology |
| OLSM | Orinda Longitudinal Study of myopia |
| RCT | Randomised controlled trial |
| RPR | Relative peripheral refraction |
| SD | Standard deviation |
| SEM | Standard error of the mean |
| SER | Spherical equivalent refraction |
| SV | Single vision |
| VA | Visual acuity |
| WHO | World health organization |
| WTR | With-the-rule |

## Chapter One: Myopia

Myopia, also known as nearsightedness, is a type of refractive error. As described by the World Health Organization's (WHO) International Classification of Disease (ICD-10), myopia is determined as parallel lights entering the eye and focusing in front of the retina when accommodation is relaxed, resulting from an overly curved cornea or overlong eyeball. People having uncorrected myopia will have blur vision at distance, and the level of blur is associated with the degree of myopia.

The cut-off value for myopia definition varies from -0.25 D to -1D, as reported in previous studies. Generally, the gold standard for measurement of refractive error is cycloplegic refraction (Morgan et al., 2015), especially for children. Incidentally, the measurement of myopia for children is often complicated by the existence of pseudo-myopia resulting from stress accommodation, and many findings of child myopia may have been overstated as a result. The latest definition from the International Myopia Institute (IMI) suggested that the threshold for myopia should be -0.50 D (Flitcroft et al., 2019) and advocated a standardized definition that will ease comparison among studies and unify clinicians approaches in explaining myopia to patients.

In the last twenty years, the prevalence of myopia has dramatically increased worldwide, especially in East Asia (Lam et al., 2012; Pan et al., 2012; McCullough et al., 2016). Myopia has shown a trend of affecting ever younger ages, which is a serious matter as the younger age of myopia onset allows higher myopia to develop over a

longer period of time before the eye reaches maturity (Hu et al., 2020). Myopia has now become a worldwide concern and has been suggested to significantly increase the burden of society in both economic and public health terms in the next decade (Lim et al., 2009; Zheng et al., 2013; Dolgin, 2015).

This chapter provides an overview of the current understanding of myopia, including its prevalence, possible risk factors, classification, and current myopia control methods.

## 1.1. Myopia prevalence

Numerous studies have reported that the prevalence of myopia varies among different ethnicities, geographical areas, and ages.

### 1.1.1. Ethnic differences

It has been well documented that Asian children show the highest prevalence of myopia globally compared with other ethnicities (Lam et al., 2004; Pan et al., 2012; Rudnicka et al., 2016). In Hong Kong international schools, the prevalence of myopia was found highest in Chinese students (82.8%) and lowest in Caucasian students (40.5%) aged from 13 to 15-year-old (Lam et al., 2004). In the United Kingdom, a study in 2016 also reported that myopia prevalence was more than doubled over the last 50 years among young adults, and children are becoming myopic at a younger age (McCullough, O'Donoghue, Saunders, 2016). The Aston Eye Study reported that myopia prevalence was higher in South Asian children (36.8%) compared to white European children (18.6%) aged 12 to 13 years (Logan et al., 2011), which echoed the results from the Child Heart and Health Study in England (CHASE) project (Rudnicka et al., 2010).

The Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error (CLEERE) study investigated the different ethnicities among different geographical areas in the United States (US) and suggested that Asian children had the highest myopia prevalence (18.5%) compared to Hispanics (13.2%), African Americans (6.6%) and Caucasians (4.4%) (Kleinstein et al., 2003). However, children with different ethnicities in the CLEERE study were recruited from different geographical areas of the US. Thus, environmental factors could not be separated.

### 1.1.2. Geographical differences

Previous authors have reported that the prevalence of myopia is positively associated with the urbanisation degree (Morgan and Rose, 2005; Sapkota et al., 2008; Morris et al., 2020).

In urban India, the prevalence of myopia was 10.8% in 15-year-old children (Dandona et al., 2002) and was 6.7% in 15-year-olds in rural India (Murthy et al., 2002). In urban Nepal, the prevalence of myopia among children aged 10 to 15 years old was 10.9% to 27.3% (Sapkota et al., 2008), but it was less than 3% in rural Nepal among children aged 5 to 15 years old (Pokharel et al., 2000). In urban China, the prevalence of myopia among 15-year-old children was 78.4% (He et al., 2004), while it decreased to 43.0% 15 -year-old children in rural areas of Southern China (He et al., 2007).

The cities with similar urbanisation degrees showed a similar myopia prevalence. The prevalence of myopia was 45% for 8-year-olds in Hong Kong (Lam et al., 2012), and

the prevalence was 34.7% for 8-year-olds in Singapore (Saw et al., 2002b).

The prevalence of myopia was lower in Caucasians. Only 2% to 20% of children aged 6 to 15-year-old were myopes in Poland (Czepita et al., 2007a; Czepita et al., 2007b). Only 2% to 15% of children aged 6 to 12 were myopes in Australia (Junghans and Crewther, 2003; 2005).

Children in Africa showed the lowest prevalence of myopia, where around less than 10% of teenagers were myopes (Mehari and Yimer, 2013; Atowa et al., 2017).

We summarise the prevalence of myopia in the adolescent population, referring to reports of the past 20 years in Figure 1-1. Higher rates of adolescent myopes were concentrated in East Asia compared to other regions in the world. Africa has reported the lowest prevalence of myopia.

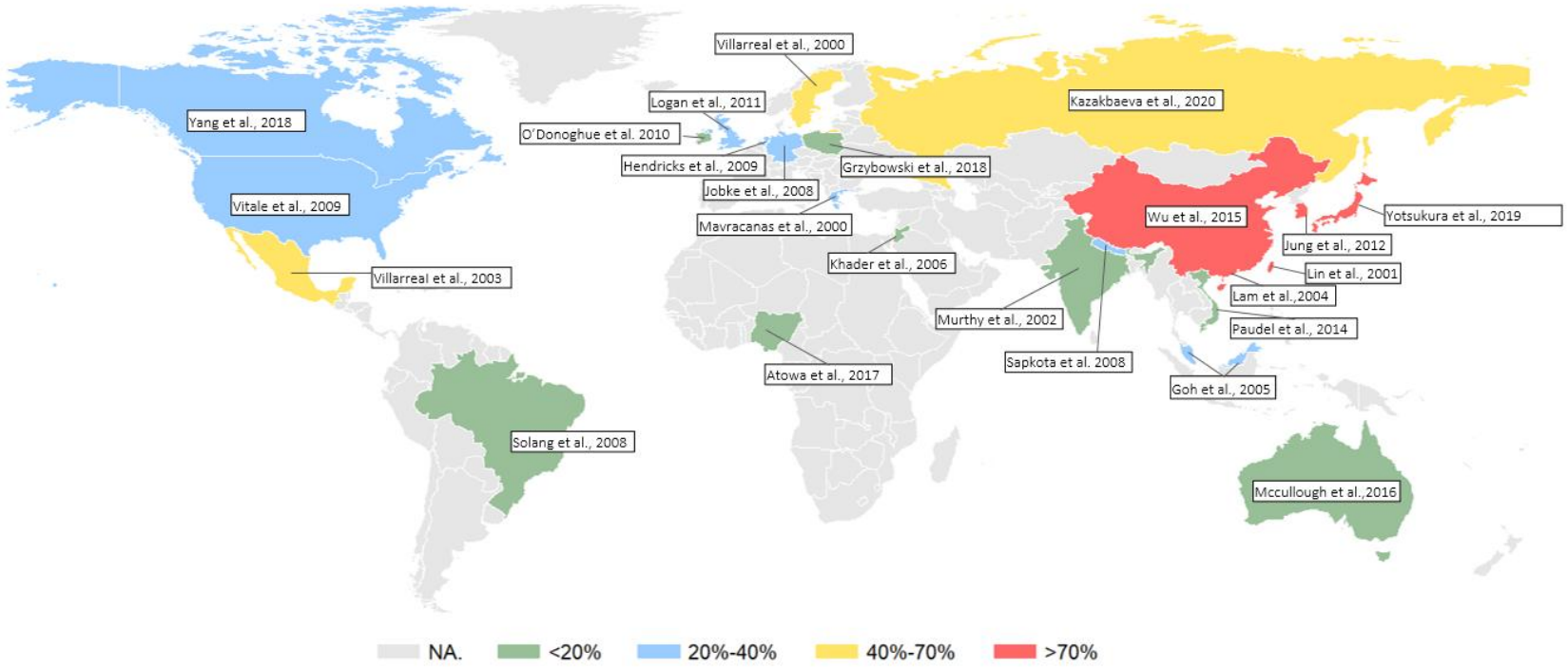



Figure 1- 1. The reported prevalence of myopia in the adolescent population in the recent 20 years.

### 1.1.3. Age difference

In addition, it has been reported that the prevalence of myopia increased with age up to the early twenties (Theophanous et al., 2018).

The prevalence of myopia was 4.7% in 5- year- old children and increased to 10.8% in 15-year-olds in India (Dandona et al., 2002). In China, the prevalence of myopia was 5.7% in 5-year-old children and increased dramatically to 78.4% in 15-year-old children (He et al., 2004). In Hong Kong, it has been reported by a cross-sectional study that the prevalence of myopia was 18.3% in 6-year-old children and rose dramatically to 45% for 8-year-olds and reached saturated levels to around 60% for 10-year-olds (Lam et al., 2012). The prevalence of myopia was 20% in children in 7-year-old and increased to 81% in 15-year-old children for Taiwanese (Lin et al., 2001). In Singapore, the prevalence of myopia was 29%, 34.7% and 53.1% in 7-year-olds, 8-year-olds and 9-year-old children, respectively (Saw et al., 2002b).

The Aston Eye Study reported that only 9.4 % of 7- year-olds were myopes and 29.4 % for 12-year-olds in the UK (Logan et al., 2011). The Orinda Longitudinal Study of myopia (OLSM) reported that the prevalence of myopia was 4.5% in 7-year-old children and increased to 28% for 12-year-olds in the United States (Zadnik, 1997).

### 1.1.4. Summary

A meta-analysis by Rudnicka et al., (Rudnicka et al., 2016) through searching the database from MEDLINE, EMBASE and web of Science covering a period from 1950 to February 2015 to estimate the prevalence of myopia by age, ethnicity and sex,

and examine trends over time. They analysed 143 published articles from 42 countries and over 370-thousand subjects aged from 1 to 18 years old and have included nearly 75-thousand myopia cases.

Their findings (Rudnicka et al., 2016) summarized the prevalence of myopia worldwide as:

a) The odds ratio of myopia in urban children was 2.6 times that of children in rural environments.
b) The increase in the prevalence of myopia with age varies with ethnicity.
c) East Asians showed the highest prevalence of myopia at 15 years old; Singaporean-Chinese was the top among East Asian, the prevalence of myopia was 86%. Their criteria of East Asians included Chinese, Japanese, Mongolian, Taiwanese, and Chinese children in Hong Kong and Singapore.
d) The Africa population had the lowest prevalence, with 5.5% at 15 years.
e) In the past decades, myopia prevalence was small in Caucasians, while it has increased by 23% among East Asians.

### 1.2. Aetiology of myopia

The prevalence of myopia is diverse according to different geographical areas and ethnic groups, so the aetiology of myopia is widely studied to identify the causal elements, resulting in such diversity. It is documented that both genetic and environmental factors influence myopia development and is dubbed the nature versus nurture argument when describing the mechanisms of myopia development (Mutti et

al., 1996; Wu and Edwards, 1999).

### 1.2.1. Genetics

Heritability studies indicated that genetic factors account for between 50% to 94% of population variance (Hammond et al., 2001; Dirani et al., 2008; Zhu et al., 2008; Schache et al., 2009).

Family studies reported that parental myopia could raise the risk of early-onset myopia (Kurtz et al., 2007; Jones-Jordan et al., 2010; Jiang et al., 2020). In addition, genetic linkage studies have mapped myopia loci and high myopia loci based on genetic conditions (Zhu et al., 2008; Abbott et al., 2012; Li et al., 2015a; Meguro et al., 2020). Some of these results contradict each other (Li and Zhang, 2017), and a direct causal connection between a certain gene and myopia has yet to be detected.

### 1.2.2. Environmental factor

Genetic factors influence eye growth, but environmental factors such as outdoor activities, near-work, education also contributed to myopia development (Morgan and Rose, 2013; Goldschmidt and Jacobsen, 2014; Enthoven et al., 2019).

#### 1.2.2.1. Outdoor activities

In the last few years, several reports support the theory that fewer outdoor activities are associated with more myopia development (Xiong et al., 2017). A Singapore cross-sectional study investigated the time of outdoor activities in youths aged 11-20 years using questionnaires and reported that a significantly negative association

between myopia and outdoor activity after adjusting for other confounders such as age, sex, ethnicities and near-work (Dirani et al., 2009). They reported that for each hour increase in outdoor activity per day, there were 0.17 D of hyperopic shifts and 0.06 mm reduction in axial length (Dirani et al., 2009). A 4-year longitudinal study in China conducted a questionnaire in primary school children aged from 5-8 years reported that more extended axial elongation was associated with less time spent outdoors (Guo et al., 2017). However, in this study, near-work time was not adjusted; fewer outdoor activities might be due to more intensive near-work.

The mechanism of fewer outdoor activities leading to more myopia has not been explained well; it may be related to the amount of dopamine release. Dopamine is suggested to inhibit axial elongation and myopia development (Smith et al., 2013a; Karouta and Ashby, 2014). Children with fewer outdoor activities were observed with lower Vitamin D level, which could impact dopamine release (Guggenheim et al., 2014; Cuellar-Partida et al., 2017).

#### 1.2.2.2. Near-work

Myopia has been observed with a higher prevalence in occupations requiring near-work (Adams and McBrien, 1992; McBrien and Adams, 1997), and near-work has been considered as a risk factor for myopia development in some studies (Goss, 2000; Saw et al., 2002a; Pan et al., 2012). However, others pointed out that the impacts of near-work on myopia might be negligible (Mutti et al., 2002; Jones et al., 2007).

A significant association between near reading exposure and myopia onset was reported in a Singapore study; they found that reading more books per week associated with higher myopia and earlier onset of myopia in Asian children, after many related factors were adjusted, such as ethnicities, parental myopia, and school type (Saw et al., 2002a). However, there was no significant relationship between reading time with the magnitude of myopia (Saw et al., 2002a). Ip et al. (Ip et al., 2008) suggested that myopia was not significantly associated with near-work time after adjusting for sex, ethnicities, parental myopia and outdoor activities. Nevertheless, the close reading distance (< 30 cm) and continuous reading (> 30 minutes) influenced myopia significantly.

#### 1.2.2.3. Education

The prevalence and severity of myopia are associated with higher levels of educational attainment (Rose et al., 2008b; Pan et al., 2012; Morgan and Rose, 2013; Verhoeven et al., 2013; Mountjoy et al., 2018).

It has been hypothesised that the higher the educational level attained meant that more near-work must have been performed, so high myopia could be ascribed to near-work, but the relationship between near-work and myopia was inconsistent in many reports (Ip et al., 2008; Huang et al., 2015), as illustrated above. Also, it was assumed that the predominant use of black text and white paper impacted the balance of stimulation of ON and OFF visual pathways (Aleman et al., 2018). ON pathways have been reported could restrict axial elongation in animal studies (Boelen et al., 1998; McCarthy et al.,

2007), but the high contrast between black and white dramatically overstimulated OFF pathways (Aleman et al., 2018); this is still inconclusive.

Although the exact mechanism of linking education and myopia is still under study, pieces of evidence suggest that education plays a dominant risk factor in myopia. The prevalence of myopia was higher in children in orthodox Jewish schools (81.3%); these schools conducted an intensive near reading education system compared with children in general Jewish schools (27.4%) (Zylbermann et al., 1993). A survey for myopia prevalence in Hong Kong Chinese schoolchildren showed that the prevalence of myopia at the local schools (85 to 88%) was higher than international schools (60 to 66%) (Lam et al., 2004). They also indicated that the local schools adopted a much more competitive and intensive curriculum when compared with other global regions (Lam et al., 2004). Asian schoolchildren who have the highest prevalence of myopia in the world spent much time on their homework, and after-school tutoring for achieving higher scores compared with western countries (Quek et al., 2004; Tsai et al., 2016), the prevalence of myopia has been associated with academic scores (Saw et al., 2007; Sun et al., 2012).

#### 1.2.2.4. Digital screen time

Digital devices have become widespread in recent years, and the prevalence of myopia also increased in recent years regardless of ethnicities. However, there were no clear findings to support that increased screen time would lead to more myopia onset or progression (Lanca and Saw, 2020). The significant association between

digital screen time and myopia prevalence was noted in both cross-sectional (Qian et al., 2016) and longitudinal studies (Jones-Jordan et al., 2011); while some other studies reported contradictory results (Jones et al., 2007; Chua et al., 2015).

Digital screen time might not act as a major role in myopia development or progression because the prevalence of myopia was already high before the boom of digital devices (Morgan et al., 2018). Also, the increase in digital screen time is also associated with other factors such as more intensive near-work and less outdoor activities (Rose et al., 2008a).

### 1.2.3. Evidence of interaction between genetic and environmental factors

Besides the individual gene or environmental factors, it has been suggested that gene could act differently among different environments, which is investigated by Gene-environmental (GxE) interactions studies. Primarily, the association between gene and education has been studied, some single nucleotide polymorphisms (SNPs) was related with lower education level (Wojciechowski et al., 2010) and some genes (DNAH9, GJD2, and ZMAT4) were linked with higher education level (Fan et al., 2014). By analysing the interaction between near-work, outdoor activities to 39 SNPs from Genome-wide association (GWS) studies, a weak association between near-work and gene interaction (Verhoeven et al., 2013; Fan et al., 2016) was identified. Up to now, these types of studies are still rare and more robust results are warranted.

The above risk factors showed an association with myopia, but few suggested a consistent causal relationship with myopia. Compared to the genetic factor, the

environment plays a more important role in myopia (Morgan et al., 2020). Among the environmental factors, the roles of near-work and digital screen time are still equivocal because of the inconsistent findings. Currently, most of these behavioural investigation studies used questionnaires, and subjects were asked to recall their memories to provide the average time of their near-work and screen time. Hence the data contained biases from subjects, and accuracy is questionable. With the development of wearable techniques, objective and real-time measurements for near-work related data could provide more valid information. Education and outdoor activities act as paramount factors which lead to myopia. Strong and consistent strands of evidence have documented that the higher the education level and lack of outdoor activities lead to high myopia, although the underlying mechanisms need to be identified.

### 1.3. Myopia classification and its significance to ocular health

For a long time, myopia has been classified by a comprehensive system, noting details including presumed aetiology, age at onset, progression pattern, amount of myopia, and structural complications (Flitcroft et al., 2019). (Table 1-1)

Table 1-1. Descriptive terms used to describe various subtypes of myopia. (Adapted from *Flitcroft et al., Invest Ophthalmol Vis Sci, 2019*)

| Basis of Classification | Associated Descriptive Terms for Different Types of Myopia |
|---|---|
| Presumed aetiology | Axial, benign, component, correlational, curvature, index, lenticular, physiologic, physiological, refractive, school, simple, syndromic |
| Age at onset | Childhood, congenital, acquired, juvenile onset, youth onset, school, adult, early adult onset, late adult onset |
| Progression pattern | Permanently progressive, progressive, progressive high, progressive high degenerative, stationary, temporarily progressive |
| Amount of myopia | Low, medium, intermediate, moderate, high, pathologic, pathological, physiologic, physiological, severe, simple |
| Structural complications | Degenerative, degenerative high, malignant, pathologic, pathological, pernicious, progressive, progressive high, progressive high degenerative |

Through this system, myopia can be described by its presumed aetiology, such as axial myopia, which is due to excessive axial elongation, and secondary myopia, which may have occurred as a result of disease (keratoconus, microspherophakia etc.) or external reasons (e.g., drug-induced myopia) etc. (Wolffsohn et al., 2019).

The IMI guidance proposed thresholds for different levels of myopia (SER ≤-0.50D), low myopia (-6.00 D<SER≤ -0.50D), and high myopia (SER≤ -6.00D) (Flitcroft et al., 2019). Also, WHO suggested the threshold for high myopia was -5.00 D in 2015 (Holden et al., 2016).

The definition of myopia and high myopia thresholds is useful for myopia diagnosis. However, it only acts as a reference and could not be used directly to estimate the severity of myopia. Some studies found that pathological changes in the retina were found in even low (Flitcroft, 2012) and moderate myopia and not only in high myopes (Vongphanit et al., 2002; Flitcroft, 2012). The classification according to structure complications could also be proposed as pernicious, progressive or malignant myopia. These are similar terms, and they can be grouped under pathological myopia.

### 1.3.1. Myopia and related ocular health

Myopia is a multifactorial condition, which cannot be classified simply into one category. The most important is to differentiate physiological myopia from pathological myopia. Therefore, we will focus on the comparison between standard physiological and pathological myopia in this section.

When fully corrected, physiological myopes have normal visual acuity. Usually, physiological myopia does not keep increasing throughout one's life. Myopia progression is fast during the puberty period and becomes slower and stable at the adult period (Sankaridurg et al., 2014). The typical physiological myopia may have retinal changes, for instance, lattice degeneration or myopic crescent, but these are not vision-threatening. However, high myopia with excessive axial length (over 26.5mm) and bigger eye size (Xu et al., 2010) is associated with retinal detachment, myopic macular degeneration, cataract and glaucoma, which impact the quality of life and increase risks of visual impairment (Saw et al., 2005; Cheng, 2012; Cheng et al.,

2013). It has been projected that 25% of high myopia develop pathological myopia (Wong et al., 2018).

Pathological myopia is the presence of "myopic maculopathy atrophy equal to or more serious than diffuse chorioretinal atrophy, with or without the presence of posterior staphylomas" (Ohno-Matsui et al., 2016). As one of the risk factors leading to irreversible visual impairment worldwide, pathological myopia results in complications including diffuse chorioretinal atrophy, patchy chorioretinal atrophy, lacquer cracks, and myopic choroidal neovascularisation (myopic CNV) (Neelam et al., 2012; Ohno-Matsui et al., 2016).

A study that reviewed and analysed 145 papers on the global prevalence of myopia projected that 49.8% of the global population suffer from myopia and 9.8 % of the global population suffer from high myopia (Holden et al., 2016). Normal physiological myopia will develop to high myopia or even pathological myopia if there is no appropriate intervention. WHO has reported that under-corrected myopia is the most common cause for leading to vision impairment. Therefore, it is important to formulate public health policies and study interventions to prevent myopia onset or to retard myopia progression. Some theories for myopia control have been investigated with animal studies. We will focus on the mechanisms of myopia control using optical and pharmacologic methods in the next section.

## 1.4. Understanding of myopia through emmetropisation and animal research

At birth, human usually present hyperopia (Mutti et al., 2005), but the infantile hyperopia could be resolved through a self-regulated process called emmetropisation in the early stage of childhood (Ehrlich et al., 1997). Emmetropisation is also widely displayed in animals, and scientists have used this mechanism as a myopia model for investigating myopia. The following section will interpret the mechanisms of emmetropisation, the myopia model and theories for myopia control.

The process of optical components coordinating with each other to reach error-free status (emmetropia) is termed emmetropisation. It has been identified to both passive and active mechanisms (Wildsoet, 1997; Brown et al., 1999; Mutti et al., 2005). The passive emmetropisation results from the coordination in the changes of optical components such as the lens power and the corneal power (Wallman and Adams, 1987). The eye growth is deemed to be driven by feedback from visual input, which adjusts to minimise refractive errors (Troilo, 1992; Wildsoet, 1997; Wallman and Winawer, 2004), and this process is identified as being a process of active emmetropisation. These visual regulation mechanisms for emmetropisation have been documented in various animal studies (Irving et al., 1992; Smith and Hung, 1999; Troilo et al., 2019). Not only do the central visual input guided the eye growth, but the peripheral signals also contribute to the emmetropisation of the eye, and this will be elaborated in Chapter 2.

### 1.4.1. Form deprivation myopia (FDM) model

There have also been studies using animal models to explore the mechanism of emmetropisation as well as myopia development. Animals with surgical eyelid closure by serendipity reported axial elongation (Hubel and Wiesel, 1977), which led to the development of the myopia model in animal studies (Wiesel and Raviola, 1977; Raviola and Wiesel, 1985). The use of eyelid suture encourages changes of corneal power in these closed eyes, which lead to transient hyperopia before myopia (von Noorden and Crawford, 1978; Smith et al., 1987). Other methods such as imposing translucent goggles or occluders have replaced the traditional eyelid closure and induced axial elongation and myopia progression in chicks (Seko et al., 1996), tree shrews (Norton and Rada, 1995), primates (Troilo and Judge, 1993; Smith and Hung, 2000), and guinea pigs (Howlett and McFadden, 2006; Lu et al., 2006). Form deprivation was proposed as an open-loop condition without an endpoint (Morgan et al., 2013), which prevents normal ocular growth (Schaeffel and Howland, 1991). The FDM demonstrates a graded phenomenon in which myopia progression was associated with image degeneration (Smith and Hung, 2000; Bowrey et al., 2015). In addition, the magnitude of myopia by form deprivation varied over a wide range, depending on the species, ocular size and environmental factors (Troilo et al., 2019).

### 1.4.2. Lens induced myopia (LIM) model

Myopia is induced by imposing a negative lens (hyperopic defocus) in the central fovea, while the placement of a positive lens (myopic defocus) led to hyperopia. These have been well documented in animal studies of chicks (Schaeffel et al., 1988),

guinea pigs (Howlett and McFadden, 2009), tree shrews (Metlapally and McBrien, 2008) and primates (Hung et al., 1995; Smith, 1998). When wearing a negative lens in the emmetropic eye, the parallel lights focus behind the retina and hyperopic defocus will be induced. It leads to axial elongation in order to detect the focus and reestablish emmetropia. When the hyperopic defocus is naturalised, axial elongation will stop. When wearing a positive lens in the emmetropic eye, myopic defocus in front of the retina will be induced and result in the retardation of myopia progression to compensate for the myopic defocus (Troilo et al., 2019). Therefore, LIM has been described as a close-loop condition (Morgan et al., 2013).

## 1.5. Myopia control based on animal research

### 1.5.1. Pharmacological pathway on myopia treatment

Pharmacological approaches form myopia treatment include Dopamine agonists (Feldkaemper and Schaeffel, 2013) and cholinergic (muscarinic) antagonists (McBrien et al., 2013); these are the two types of drugs that have been widely investigated.

The prevention effects of dopamine agonists on myopia have been observed in various animals, with inconsistent results. Using dopamine agonists to slow down myopia development has been successfully demonstrated in chicks (Nickla et al., 2010), guinea pigs (Lin et al., 2009) and mice (Tingting et al., 2015; Yan et al., 2015). However, the role of dopamine might be different in FDM, and LIM models as dopamine resulted in contradictory results in the two models, which have also been inferred in other findings (Dong et al., 2011; Nickla and Totonelly, 2011).

Significant and consistent effects of myopia retardation in FDM and LIM models by cholinergic agonists have been reported. Atropine as a non-selective muscarinic receptor (mAchR) antagonist has been widely implemented in chicks (Schmid and Wildsoet, 2004), tree shrews (McBrien et al., 2009) and mice (Jiang et al., 2018) to slow down myopia progression. Previously, people believed the mechanism of atropine downregulated eye growth due to accommodation. However, chick eyes, in which nicotinic receptors rather than mAchR receptors mediate the ciliary muscle, react with atropine. Therefore, it has been hypothesised that atropine may work in the retinal amacrine cells (Fischer et al., 1998) and scleral cells (Lind et al., 1998) rather than the accommodation system.

### 1.5.2. Myopia control utilising optical theories

#### 1.5.2.1. Accommodation

As the association between near work and myopia was observed, people have started to investigate if accommodation is related to myopia progression. Surgically disruption in the ciliary nerves to the chicks (Wildsoet and Wallman, 1995; Schmid and Wildsoet, 1996), and in the ciliary ganglion or superior cervical ganglion to the monkeys (Raviola and Wiesel, 1985), did not prevent FDM or LIM. Therefore, accommodation is not essential in the visual regulation of eye growth.

#### 1.5.2.2. Myopic defocus

Eye growth is driven by visual regulation in a bidirectional manner (Diether and Schaeffel, 1997), which has been demonstrated in avian, mammalian and primate (Zhu et al., 2013) animals. The range of adequate defocus power to manipulate

refractive error varies between different animals, such as between −10 and +20 D in chicks (Irving et al., 1992), −4 to +4 D in guinea pigs (Howlett and McFadden, 2009), and −30 to +5 D in mice (Tkatchenko et al., 2010; Jiang et al., 2018). The dosage of defocus beyond the effective range showed fewer compensation effects (Troilo et al., 2019).

The changes in choroidal thickness provided evidence for myopia control utilising myopic defocus. The decrease in the choroidal thickness is associated with myopia development, while the increase in thickness is associated with myopia reduction (Nickla and Wallman, 2010). The initial myopic defocus input result in the rapid thickening in choroid was first reported by Wildsoet and Wallman (Wildsoet and Wallman, 1995). Afterwards, various animal experiments consistently showed similar findings (Hung et al., 2000; Howlett and McFadden, 2009; Hammond et al., 2013).

### 1.5.3. Relevance to human research

Undoubtedly, the differences between the human eyes and the various animals cannot be ignored (Troilo et al., 2019). Rhesus macaque monkeys and marmosets are the most similar primates to humans, with similar inner retinal blood supply (Morcos and Chan-Ling, 2000) and accommodation system (Ostrin and Glasser, 2010), but their scarcity means that they cannot be widely used in myopia research (Tardif et al., 2003). Tree shrews, guinea pigs, and mice are different to humans in that they do not have a fovea, but the area centralis or visual streak provide them with visual acuity (Troilo et al., 2019). They have relatively larger crystalline lenses than primates, and

the accommodation system is weaker than humans (Troilo et al., 2019). Chicks grow fast and have a flexible accommodation system (Ostrin et al., 2011), which means that they can be widely used in research.

Although findings from animal research cannot be totally applied to humans, they nevertheless provide insights into myopia prevention research. Some theories, such as myopia control utilising myopic defocus or using atropine, have achieved significant myopia retardation (Kang, 2018; Walline et al., 2020a). These findings have opened new directions of myopia control in human eyes in the last decade.

## Chapter Two: Myopia management

Traditionally, myopia is treated by prescribing SV lenses to correct the refractive error. This approach has not considered that myopia progression will continue in most cases in young children who have just been prescribed with single vision lenses only. The fact that even low myopia would develop to high myopia or even pathological myopia if no appropriate management is given for the young children. Therefore, myopia should be managed in a holistic manner. It should not only the myopic error be corrected, but there should be strategies to slow the progression or even halt the development and progression so that myopia and the eye growth will not reach the level of high or pathological myopia. The new guidelines (Gifford et al., 2019) suggested that clinicians should aim to prevent or retard myopia progression and eyeball elongation to reduce the risks of pathological myopia and vision impairment. Currently, numerous clinical methods are designed for controlling myopia progression. In general, they are grouped under optical or pharmacological intervention. Clinical trials adopting the randomised double-masked approach are regarded to be the gold standards for effectiveness evaluation. The effectiveness percentage is calculated based on the change in ocular refraction, usually was represented as differences in spherical equivalent refraction (SER) between the control group and the treatment group over the change in the control group and multiply by 100%. This has the advantage of an objective evaluation based on a matched group from the population. However, recently, there has also been a

suggestion to use the absolute change in SER and axial length, which provides more information on the actual myopia progression in the treatment group for comparison with other studies (Cheng et al., 2019).

## 2.1. Optical interventions

Optical interventions with minimal side effects have been widely used for myopia retardation, containing spectacle lenses and contact lenses.

### 2.1.1. Spectacle lenses

#### 2.1.1.1. Under-correction of myopia

It has been a controversial method that if under-correction of spectacles could slow down myopia progression. A meta-analysis suggested that under-correction showed even greater of -0.15 D (95% CI, -0.29 to 0.00) myopia progression per year as well as more than 0.05 mm (95% CI, 0.00 to 0.11) axial elongation per year compared with full-correction (Prousali et al., 2019). Under-correction of myopia indeed increased the myopia progression.

Oppositely, two reports which investigated myopic children from Anyang Childhood Eye Study suggested that under-correction or un-correction might not accelerate myopia progression (Li et al., 2015c; Sun et al., 2017). Unexpectedly, they indicated significant retardation in myopia progression with under-correction (Li et al., 2015c) and a statistically significant decrease in myopia progression in uncorrected myopic children (Sun et al., 2017). However, there was a significant difference in some of the baseline parameters. Furthermore, the long period of blurred vision due to the under-

correction or un-correction may change the behaviour, such as the unwillingness of outdoor activities, which could emerge other risk factors for myopia acceleration (Wildsoet et al., 2019).

#### 2.1.1.2. Progressive additional lenses (PALs)

Although PALs have been suggested for myopia control, most studies reported that the myopia retardation by PALs was clinically insignificant (Edwards et al., 2002; Hasebe et al., 2008; Yang et al., 2009). A meta-analysis suggested that PALs showed less of -0.14 D (95% CI, -0.26 to 0.02) myopia progression and 0.04 mm (95% CI, 0.01 to 0.09) axial elongation compared to SV spectacle lenses per year (Huang et al., 2016).

#### 2.1.1.3. Bifocal and multifocal spectacle lenses

The earlier studies reported that bifocal or multifocal spectacle lenses showed barely satisfactory myopia control effects with less of -0.16 D (95% CI, -0.32 to -0.01) myopia progression and less of 0.06 mm (95% CI 0.00 to 0.12) axial elongation of compared to SV lenses per year (Huang et al., 2016).

The bifocal lenses were then modified and combined with prismatic lenses, and prismatic bifocal lenses showed better myopia retardation in myopes with a low lag of accommodation (Cheng et al., 2014). Compared to SV lenses, children wearing prismatic bifocal lenses had less of -0.25 D (95% CI, -0.54 to 0.03) myopia progression and 0.08 mm (95% CI, 0.00 to 0.16) axial elongation (Huang et al., 2016).

Multifocal spectacle lenses also have been designed for myopia control. Sankaridurg et al. (Sankaridurg et al., 2010) tested three types of spectacle lenses designed to reduce peripheral hyperopic defocus and maintain a clear central vision simultaneously. However, no significant myopia control effects were found (Sankaridurg et al., 2010).

#### 2.1.1.4. Constant myopic defocus incorporated spectacle lenses

Defocus Incorporated Multiple Segments (DIMS) spectacle lenses designed with a central optical zone for distance clear vision and surrounded with multi-segment of constant myopic defocus (+3.50 D) (Lam et al., 2020a). Such a design could induce myopic defocus and provide clear central vision simultaneously. Over 2 years, DIMS retarded myopia progression of -0.44±0.09 D and slowed down the axial elongation of 0.34±0.04 mm compared to SV lenses (Lam et al., 2020a).

### 2.1.2. Contact lenses

#### 2.1.2.1. Orthokeratology (OK) contact lenses

It has been suggested by a meta-analysis study that wearing OK lenses slowed down the axial elongation 0.27 mm over 2 years, equivalent to 45% of myopia control effects (Sun et al., 2015). Also, the long-term effect of myopia control effects in OK lenses has been reported that children showed axial elongation was 0.99 ± 0.47 mm and 1.41 ± 0.68 mm in the OK lenses and control groups, respectively over 5 years (Hiraoka et al., 2012).

Although OK lenses showed long-lasting effects in slowing down myopia progression, the concerns of safety would not be ignored (Liu and Xie, 2016). The

potential complications such as corneal staining (Cho et al., 2005; Cho and Cheung, 2012; Charm and Cho, 2013), microbial keratitis (Watt and Swarbrick, 2007; Santodomingo-Rubido et al., 2012a; Zimmerman et al., 2016) have been reported in previous studies, and the specific education for parents and children should be enhanced.

#### 2.1.2.2. Bifocal, multifocal and myopic defocus incorporated soft contact lens

In recent decades, extensive research has studied myopia control with bifocal and multifocal soft contact lenses. Soft contact lenses are more convenient for myopic children for daily life and sporting activities compared with spectacle lenses (Walline et al., 2007).

Previous meta-analysis study reported a favourable effect of bifocal or concentric contact lenses in retarding myopia progression of -0.31 D (95% CI, -0.57 to -0.05) and slowing axial elongation of 0.12 mm (95% CI, 0.07 to 0.18) per year (Li et al., 2017). With peripheral add power, the multifocal lenses also had significant myopia retardation, with less of -0.22 D (95%CI, -0.31 to -0.14) in myopia progression and less of 0.10 mm (95% CI, 0.07 to 0.13) in axial elongation per year (Li et al., 2017). Generally, using bifocal or multifocal contact lenses had a 37% retardation in myopia progression and 47% in the decrease of axial elongation (Li et al., 2017). In a 3-year clinical trial, Walline et al. (Walline et al., 2020b) reported that a high add power (+2.50D) multifocal contact lenses slowed down 0.46 D of myopia progression and 0.23 mm of axial elongation compared to SV contact lenses; as well as retarded 0.30

D of myopia progression and 0.16 mm of axial elongation compared to medium add power (+1.50D) multifocal contact lenses.

However, most of the bifocal or multifocal contact lenses were spherical lenses, and toric lenses for myopes with higher astigmatism are still not available.

### 2.2. Pharmacological interventions

Regarding the pharmacological approaches, atropine has been used widely and showed an adequate and stable treatment to slow myopia progression, for example, the ATOM1, ATOM2 and ATOM3 studies (Chua et al., 2006; Chia et al., 2012). A meta-analysis based on different race evaluated the myopia control effects among low-dose (0.01%), moderate-dose (>0.01% to <0.5%) and high-dose (0.5% and 1%) and indicated no significant difference in refraction changes among different dosage (Gong et al., 2017). They reported myopia progression reduction was -0.50 D (95%CI, -0.76 to -0.24) for low-dose, -0.57 D (95%CI, -0.71 to -0.43) for moderate-dose and -0.62 D (95%CI, -0.79 to -0.45) for high-dose per year compared to placebo (Gong et al., 2017). Although there was a racial variation in sensitivity to atropine, it relates to the amount of pigmentation (ocular melanin) in the human iris (Koneru et al., 1986). No significant difference in myopia control efficacy using 0.01% and 1% atropine was reported between Asian and Caucasian (Gong et al., 2017).
Referring to the side effects, such as blurred vision in near-work, photophobia, and high dropouts in high-dose atropine occurred in high-dose atropine (Yen et al., 1989; Chua et al., 2006). Compared to high-dose, 0.01% atropine was the most effective in

retarding myopia progression with fewer visual side effects as well as had the least myopia rebound after ceasing atropine treatment (Chia et al., 2016).

Although atropine showed the most remarkable effects in myopia retardation compared to the optical methods, the side effects of higher dosage of atropine such as loss of accommodation (Chua et al., 2006) and rebound effects after cessation of treatment (Tong et al., 2009) made atropine less adoption for myopia control. Although the lower dosage of atropine had fewer side effects and could maintain satisfactory myopia control effects, the potential allergies to atropine (Chua et al., 2006), premature presbyopia and retinal phototoxicity in long-term use are still concerned (Wu et al., 2018b).

### 2.3. Combination of pharmacological and optical interventions

Both the pharmacological and optical interventions have shortcomings, such as the myopia control effects by OK lenses were less than atropine generally, and higher dosage of atropine have rebound effects and adverse effects. Inspired by combination therapy in other diseases, Kinoshita et al.(Kinoshita et al., 2018) proposed a combination treatment in myopia through using OK lenses and a low dosage of atropine (0.01%) to reduce the adverse effects and increase the effects by individual treatment. They reported a significantly more effective in myopia control by combination therapy than OK lenses alone over 1 year (Kinoshita et al., 2018). Also, it has been reported well tolerance and addictive effects of the combination of OK lenses and 0.01% atropine; the combined treatment slowed eye growth by 0.09 mm

compared to OK lenses monotherapy over 1 year (Tan et al., 2020). However, more studies on large sample size and long-term are warranted.

### 2.4. Time Outdoors

Besides either optical or pharmacological interventions, spending time outdoor have shown effects on inhibiting myopia onset (Dirani et al., 2009; French et al., 2013; Wu et al., 2013; Xiong et al., 2017) and slowing down myopia progression (Wu et al., 2013; Wu et al., 2018a). The mechanism behind time outdoors is unclear yet, the possible pathway for might be higher illuminance, Vitamin D, chromatic spectrum of light, and reduced peripheral defocus from outdoor activities (Mutti and Marks, 2011; Guggenheim et al., 2014; Lingham et al., 2020).

A meta-analysis based on Asian studies pointed out the protective effects of more time outdoors myopia onset (relative risk 0.66, 95% CI, 0.49 to 0.89), while rare effects on myopia retardation, of which reduction of myopia progression was -0.13 D (95% CI, -0.18 to -0.08) and slowing of axial elongation was 0.03 mm (95% CI, 0.00 to 0.05) per year (Deng and Pang, 2019).

Without a doubt, a long time of direct exposure to sunlight also sparked concerns to cataract or skin cancer. Read et al. (Read et al., 2014) indicated that light exposure of over 1000 lux could already have a significant effect on myopia control. Therefore, enough outdoor time even under the shade of the tree and without the direct exposure of bright sunlight could be sufficient for myopia slowing.

It is worth mentioning that it might be difficult to encourage schoolchildren to spend more outdoor time in the schools under higher pressure of study, the good cooperation among education system, school and parents will be needed.

## 2.5. Mechanism of myopia control

A number of studies have been conducted to investigate the mechanism behind myopia control, while the full-understand of the mechanism of myopia control interventions has not been worked out yet.

### 2.5.1. Alteration of accommodation

During near work, eyes will accommodate and convergence for focusing the object clearly. The persistently near work may lead to excessive accommodation, and myopes have been observed to be associated with excessive accommodation (lead of accommodation) more than emmetropes (Hinkley et al., 2014). It has been speculated that excessive accommodation could promote myopia progression while relaxing accommodation would retard myopia progression (Sankaridurg and Holden, 2014; Leo, 2017).

In recent decades, more evidence supported that most of the myopic children showed insufficient accommodation with the lag of accommodation (Nakatsuka et al., 2003). Although previous studies have obtained paradoxical results, some reports suggested no significant association between lag of accommodation and myopia onset (Lan et al., 2008; Berntsen et al., 2011), while some authors suggested there was a significant association (Allen and O'Leary, 2006). Some interventions based on reducing

accommodative demand at near work or decreasing lag of accommodation have been proposed for myopia control, such as under-correction (Adler and Millodot, 2006), PALs (Leung and Brown, 1999; Gwiazda et al., 2003; Cheng et al., 2011) and bifocal or multifocal spectacle lenses (Berntsen et al., 2010). As the alteration of accommodation could influence the defocus in near-work, therefore, the rationale of some myopia control devices could also be based on defocus.

### 2.5.2. Myopic defocus

It has been supported by animal studies that myopic defocus could slow down or stop myopia progression (Wildsoet, 1997). Imposing the myopic defocus in the foveal retina in animals such as tree shrews (Metlapally and McBrien, 2008), chicks (Schmid and Wildsoet, 1996), marmoset (McFadden et al., 2004) or infant monkeys (Smith and Hung, 1999). Nevertheless, under-correction in myopes, which induces fovea myopic defocus, showed opposite results with animal studies that enhanced myopia progression (Prousali et al., 2019).

With the increasing interest in the investigation of peripheral vision, people found that peripheral myopic defocus appeared to inhibit myopia progression in animal studies (Morgan and Ambadeniya, 2006), while peripheral hyperopic defocus was found to induce myopia progression (Smith et al., 2009b).

During near work, a large lag of accommodation could result in hyperopic defocus. Therefore, some interventions base on reducing the peripheral hyperopic defocus or inducing peripheral myopic defocus have been designed for myopia control, such as PALs (Cheng et al., 2011; Berntsen et al., 2012), bifocal and multifocal spectacle

lenses (Cheng et al., 2014), DIMS lens (Lam et al., 2020a), bifocal and multifocal soft contact lenses (Walline et al., 2013; Lam et al., 2014), OK lenses have been studied for myopia control (Queiros et al., 2018).

Related to myopic defocus, there have also been suggestions that higher-order aberrations such as positive spherical aberration could results in a similar effect as myopic defocus and, therefore, could also benefit for myopia retardation when applied to soft contact lens (Paune et al., 2016) or OK lens wear (Mathur et al., 2009a; Hiraoka et al., 2015). Likewise, corneal reshaping has been proposed to introduce myopic defocus during the OK lens wear, which causes the redistribution of corneal epithelial cells (Choo et al., 2008).

### 2.5.3. Pharmacological mechanisms

In addition, atropine was initially used as relaxing accommodation to control myopia regression, while the later investigations indicated the mechanism might work in non-accommodation pathways (McBrien et al., 2013). The potential pathway may be through regulating the retinal and scleral muscarinic receptors, atropine could influence the scleral matrix and then control myopia progression (Wu et al., 2018b). Although Pirenzepine as the M1 muscarinic receptor antagonist and Timolol as a non-selective beta-blocker also were studied for myopia control, the less myopia control effects and side effects lead to them have not been widely used yet.

Although the other potential mechanisms for myopia retardation have been investigated (Vagge et al., 2018), none of them could stop myopia progression or

myopia onset. Future studies in mechanisms are warranted.

### 2.6. Efficacy of treatments and limitations

Among the above myopia control interventions, the acknowledged most effective approach is atropine, but the side effects of longitudinal using and rebound effects should be alerted (Huang et al., 2016; Prousali et al., 2019). Regarding the optical treatment, PALs and under-correction have shown the least myopia retardation. The myopia control effects are similar among OK lenses (slowing in axial length: 0.14 mm/year, myopia control effects: 45%), bifocal and multifocal contact lenses (reduction in myopia progression: -0.23 D to -0.31 D/year, slowing in axial length: 0.10 to 0.12 mm/year, myopia control effects: 50%) and recent DIMS lenses (reduction in myopia progression: -0.22 D/year, slowing in axial length: 0.17 mm/year, myopia control effects: 52%) (Huang et al., 2016; Prousali et al., 2019; Tang et al., 2020). The combination of OK lenses and low dosage of atropine showed additive effects on myopia control than monotherapy, but the long-term effects need to be investigated.

### 2.7. Standards and main outcomes in myopia control effects monitoring

The gold standard for measuring the myopia progression is using refractive error and axial length (Wolffsohn et al., 2019). Although refractive error could be measured directly and quickly, the changes in corneal curvature may result in changes in refractive error. Therefore, corneal curvature or corneal power are usually measured

for data interpretation (Walline et al., 2011). Also, the strong accommodation in children leads to the overestimation in myopia; therefore, most studies used cycloplegic refractive error as their primary outcome (Wolffsohn et al., 2019). Several studies established the high correlation between refractive error and axial length, as the myopia development was observed with excessive eyeball elongation (Atchison et al., 2004; Olsen et al., 2007). As we have elaborated in Chapter 1, eye stretching increased the risks of retinal degeneration and ocular diseases. Even moderate myopia could have vision-threatening conditions resulting from excessive axial elongation (Flitcroft, 2012). So axial length is an essential parameter for monitoring not only the refractive status but also health status.

The current clinical trials for myopia control have adopted the use of cycloplegic ocular refraction and mainly in spherical equivalent refraction (SER) and axial length measurement as the standards of measurement. And the changes in these parameters as the primary outcomes of the control effect.

## 2.8. Insights for future myopia management

For a long time, research into myopia concentrated on refractive or binocular function changes along the optical axis, while some recent exploratory studies suggested that eye biometry parameters and complex interactions between eye and environment, as well as peripheral refraction, are also associated with myopia progression. Referring to the biometry changes in the eye, it has been reported that changes in choroidal thickness is associated with myopia development (Bulut et al., 2016). And the

interaction with the environment could impact the optical defocus entering the eye, such as near reading may induce hyperopic defocus, while outdoor activities will produce more myopic defocus (Flitcroft, 2012). All these could interact with myopia control interventions and impact the myopia control effects. It has also been suggested that peripheral refraction is essential in emmetropisation in primates. When combined with optical defocus, the peripheral retina profile will have a summative effect and alter myopia progression (Smith et al., 2005). Therefore, these new parameters are worthwhile to study for a better understanding of myopia progression and myopia prevention. But for measuring choroidal thickness, comprehensive software to detect thickness is needed (Giannakaki-Zimmermann et al., 2019; He et al., 2021), and for detecting the real world's three dimensional defocus, a wearable device to track the visual habits is required (Williams et al., 2019). At the start of this study, none of these techniques has been studied well and validated, while measurement of peripheral refraction was possible and convenient for the clinicians. Based on the ample evidence from animal research and current myopic defocus clinical trials, further understanding of the change of peripheral refraction will provide insight into the mechanism of myopia control using myopic defocus. The following chapter provides the background of peripheral refraction measurement, retinal shape and its relationship with myopia progression.

## Chapter Three: Peripheral refraction

### 3.1. Retinal shape

Peripheral refractive error is peripheral parallel light entering the eye reflected through the optical components and leads to the focal point in the peripheral retina region. Figure 3-1 shows the different focal points at the peripheral retina, depending on the shape of the eye. Take an emmetropic eye as an example, the peripheral light would converge to a focal point that could 1: coincide on the normal spherical retina, or 2: in front of the flatter retina leading to myopia in the periphery, or 3: behind the steeper retina, resulting in the hyperopia in the periphery (Verkicharla et al., 2012).

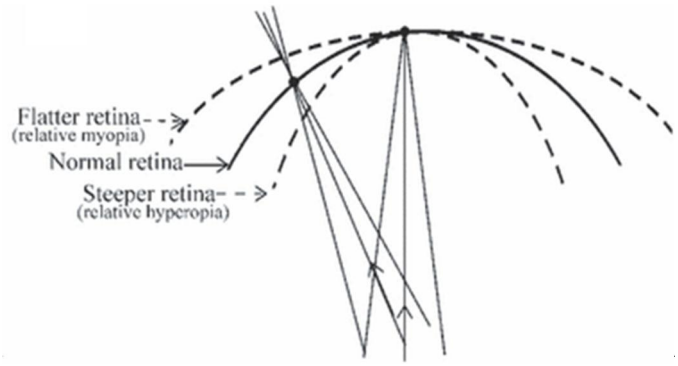



Figure 3-1. Retinal shape and their relation to peripheral refraction. (Adapted from *Verkicharla et al., Ophthalmic Physiol Opt, 2012*).

Relative peripheral refraction (RPR) is used to indicate the difference between peripheral refraction and central refraction. In general, the myopic eyes tend to show less myopia in the periphery, thus present hyperopic RPR; while hyperopic eyes tend to show less hyperopia in the periphery, thus show myopia RPR (Figure 3-2).

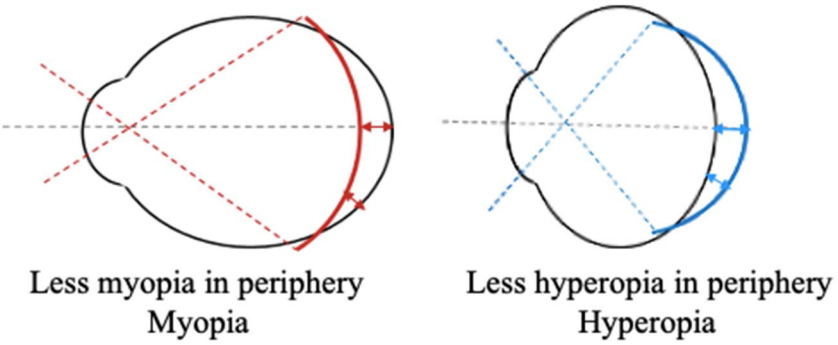



Figure 3-2. Schematic diagram of the eye shape of the myopic and hyperopic eye.

The variation in retinal shapes could be a result of different patterns of retinal stretching. It has been modelled as global, equatorial, posterior polar and axial expansion (Strang et al., 1998; Verkicharla et al., 2012) as in Figure 3-3. Using Magnetic Resonance Imaging (MRI) technique, it has been observed that most of the myopes tend to present axial elongation (Atchison et al., 2004)

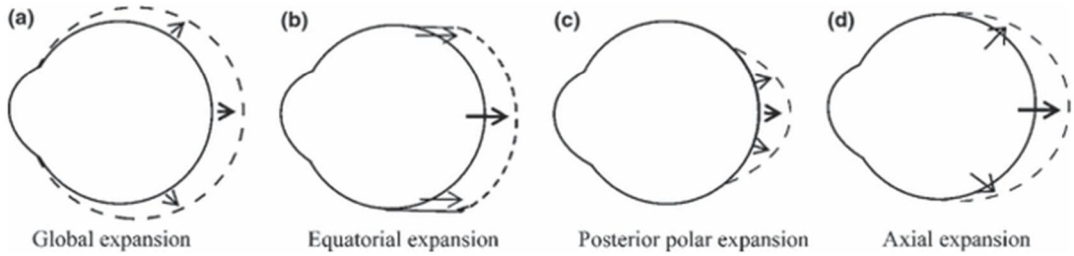



Figure 3- 3. Models of retinal stretching in myopia. (Adapted from: *Verkicharla, et al., Ophthalmic Physiol Opt, 2012*).

### 3.2. Peripheral refraction

Peripheral refraction has been described in ametropes in cross-sectional studies (Ferree et al., 1931; Millodot, 1981; Seidemann et al., 2002; Chen et al., 2010; Kang et al., 2010; Sng et al., 2011a).

In a study among 250 Singaporean Chinese children aged 6.9 ±3.0 years, hyperopic RPR was presented in myopic children. In contrast, hyperopic and emmetropic children showed myopic RPR (Sng et al., 2011a). Children in the moderate and high myopia group (more than -3.00 D) had hyperopic RPR at all eccentricities, and low myopic children (-2.99 D to -0.50 D) showed myopic RPR at 15˚of visual field (Sng et al., 2011a).

In the OLSM study, children aged 5 to 14 years with different ethnicities were recruited, and emmetropic and hyperopic children had myopic RPR at 30˚ of the nasal visual field. In contrast, myopic children (mean central SER 2.84±2.09 D) had hyperopic RPR (0.80±1.29 D) at 30˚ of the nasal visual field (Mutti et al., 2000). They also reported that hyperopic RPR was associated with myopic ocular component characteristics, including deeper anterior chamber and vitreous chambers, flatter crystalline lenses and steeper cornea, although only 30˚ of the nasal visual field was measured in that study.

Different peripheral refraction patterns have also been reported in different ethnicities. Kang et al. (Kang et al., 2010) found that East Asian children had a significantly higher relative hyperopia in the periphery than Caucasian children with the same

degree of myopia.

In terms of astigmatism, it is traditionally calculated into two components: $J_{45}$ and $J_0$. The $J_{45}$ stands for oblique astigmatism (45 ˚ -135 ˚), while $J_0$ stands for with or against rule astigmatism (90˚-180 ˚). Peripheral astigmatism $J_{45}$ and $J_0$ showed passive increasing in magnitude with the increase of eccentricities compared to central astigmatism (Seidemann et al., 2002; Atchison et al., 2005b; Atchison et al., 2006; Calver et al., 2007; Kang et al., 2010). Children have been reported to exhibit a considerable variation of cylindrical power range, and the magnitude of cylindrical power has been reported to increase with the eccentricities reaching as high as around 9D at 30T (Atchison et al., 2006; Lee and Cho, 2013).

### 3.3. Evidence of peripheral vision in regulating eye growth

Early chick study provided evidence that peripheral vision could impact the local eye shape; for example, hemiretinal deprivation-induced regional alterations in eye shape and myopia development (Wallman et al., 1987).

Peripheral retina was suggested to play an essential role in eye growth and emmetropisation as there are more retinal neurons in the periphery compared to the central fovea (Wallman and Winawer, 2004). By peripheral form deprivation and allowing unrestricted central vision, Smith and the colleagues (Smith et al., 2005) reported a significant increase in axial length in infant monkeys, which indicated the central vision might not be essential in emmetropisation. With the ablation of the central fovea while leaving the unrestricted vision, the treated monkeys showed a

similar course of emmetropisation compared to normal untreated monkeys. Furthermore, peripheral form deprivation in central ablation, these monkeys developed myopia, suggesting that peripheral vision could regulate the visual development in an isolated way (Smith et al., 2007). In their later study, both monkeys with peripheral hyperopic defocus but unrestricted central vison and foveal ablation showed axial myopia development, which suggested the peripheral area might have a considerable effect on emmetropisation and even myopia development (Smith et al., 2009b).

The interaction of peripheral vision and central vision has also been studied. Two-zone concentric lenses with central design (either +5D or -5D in the centre and surrounded with plano lens in the periphery) and peripheral design (plano lens in the centre and surrounded with either +5D or -5D in the periphery), +5 D SV lenses, -5D SV lenses and plano lenses were imposed into chick eyes (Liu and Wildsoet, 2011). The greater changes in refractive errors and eye growth were found in chicks reared with peripheral design lenses compared to central design lenses. And +5 D peripheral design lenses showed a greater effect on eye growth than +5 D SV lenses. This result suggested that peripheral defocus could influence central eye growth and may be used for myopia control.

In summary, peripheral hyperopic defocus could lead to eye growth; on the other hand, peripheral myopic defocus could retard myopia progression.

### 3.4. Peripheral refraction and myopia development in human

The earliest concept that peripheral refraction could lead to human myopia development was arisen by Hoogerheide (Hoogerheide et al., 1971) measured refraction along 120° of the horizontal visual field in young hyperopes and emmetropes who were undertaking pilot training. They found 65% of emmetropes and hyperopes who developed myopia afterwards displayed hyperopic RPR. However, Rosén et al. (Rosén et al., 2012) argued that it was unclear that if the peripheral refraction measurement was conducted before the Hoogerheide's study or after the myopia development, it has been believed that the hyperopic RPR was observed after myopia onset rather than a factor which leads to myopia development. Mutti et al. (Mutti et al., 2007) found that more hyperopic RPR within 2 to 4 years before myopia onset may be one of the factors that leads to the onset of myopia; however, RPR was stable from the year of onset to 5 years following myopia onset.

After that, many longitudinal studies have been conducted, but most of them revealed that baseline RPR could not predict myopia onset or progression (Mutti et al., 2011; Sng et al., 2011b; Lee and Cho, 2013; Atchison et al., 2015; Hartwig et al., 2016). Mutti and his colleagues (Mutti et al., 2011) investigated children from different ethnicities, including Asians, African-Americans, and Caucasians. They reported a weak influence of RPR on the risk of myopia onset and development or axial elongation. Sng et al. (Sng et al., 2011b) monitored changes in central and peripheral refraction in Singapore Chinese children over 1 year and found that peripheral

refraction did not lead to myopia onset or influence myopia progression. The controversial results led to the conclusion that RPR is more likely to be a consequence rather than a cause of myopia progression.

During the eyeball elongation process, AL increases to a more considerable extent than the equatorial diameter; then, the myopic eye shows a relatively more prolate ocular shape (Mutti et al., 2000; Atchison et al., 2005a). Peripheral refraction would appear less myopic than the central refraction, leading to a more hyperopic RPR (Figure 3-2). At the same time, animal studies suggested that the eyes elongated with the synthesis of new posterior scleral tissue, which may be an important factor causing the relatively prolate eye shape of myopes (Logan et al., 2004).

Although the relationship between RPR and myopia onset or myopia progression could not be established, numerous animal studies suggested that peripheral visual input by form deprivation and lens induction could also guide eye growth (Smith et al., 2005; Smith et al., 2007; Smith et al., 2009a; Smith et al., 2009b) (see Section 3.3.).

In an ideal situation, parallel light from both the on-axis and periphery entering the eye will be reflected through the optical system and form an image shell along the retina. However, it has been speculated that the image shell through a spectacle lens might not match the retinal shape and lead to different effects. Lin et al. suggested that traditional spectacle correction for myopia could result in hyperopic defocus in the peripheral retina, which is a trigger for myopia development (Lin et al., 2010)

(Figure 3-4 A.). Smith et al. (Smith, 2011) pointed out that if inducing the focal point in the periphery to match the retinal shape or inducing myopic defocus in the periphery, the myopia control effects would be achieved (Figure 3-4 B.).

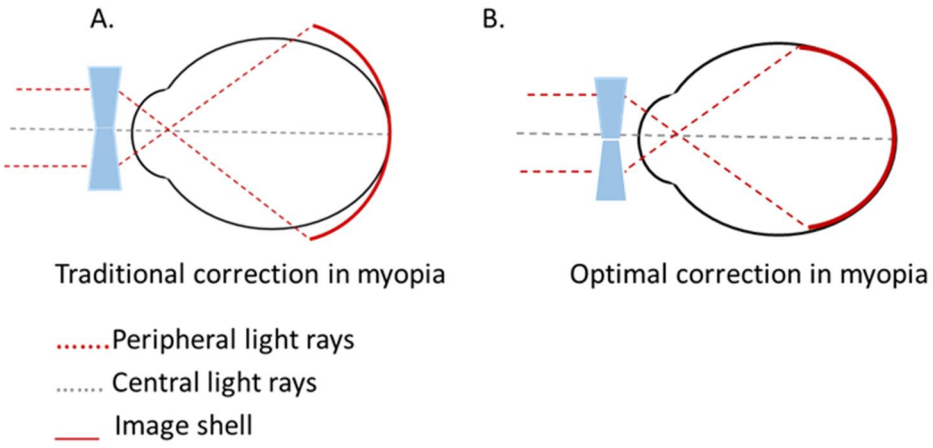



Figure 3-4. A: Schematic diagram of image shell by traditional myopia correction using spectacle lenses. B. Schematic diagram of optimal optical myopia correction.

### 3.5. Current research gap

There is a big concern on the increasing prevalence of myopia globally and the sight-threatening risks of high and pathological myopia. The current methods of myopia control have shown positive results; however, the optimal effectiveness was not achieved yet. Both animal and human studies pointed out that myopic defocus could be used to slow myopia progression, and a number of these treatments have a direct influence on the peripheral retina (Morgan and Ambadeniya, 2006).

Several studies suggested that retinal shape might be a determinant for the development of myopia through biomechanical factors, such as the thinning of the sclera and localised ectasia of the posterior sclera during myopia development (McBrien and Gentle, 2003; Rada et al., 2006).

A variety of retinal shape has been observed in the human eye, resulting in myopes displaying mainly hyperopic RPR, while emmetropes and hyperopes display myopic RPR generally (Mutti et al., 2000; Sng et al., 2011a). However, previous studies could not shed light on RPR and myopia onset or myopia progression (Hoogerheide et al., 1971; Mutti et al., 2007; Mutti et al., 2011; Sng et al., 2011b; Lee and Cho, 2013; Radhakrishnan et al., 2013)

Using traditional spectacle lenses to correct myopia, on-axis light will focus on the fovea, while off-axis light will lead to peripheral hyperopic defocus (Tabernero et al., 2009; Lin et al., 2010); this has been hypothesised to be a possible trigger for myopia progression. Animal studies inferred that peripheral visual input could play a key role in driving eye growth (see Section 3.3.).

The efficacy of myopia control applying myopic defocus was varied among subjects ranged from 25% to 60% (see Section 2.6.), which may be due to the difference in ages, parental myopia or the wearing time etc. Besides these factors, it is also not known whether the initial RPR could influence myopia control effects when using myopic defocus as the treatment method. Theoretically, the subjects with less hyperopic RPR (or with myopic RPR) would experience more myopic defocus than the subjects with higher hyperopic RPR when wearing myopic defocus lenses. We hypothesised that initial RPR (when start to wear myopic defocus lenses) could influence the effects of myopia retardation.

In addition, the majority of previous studies investigating myopic defocus have reported myopia control effects as changes in ocular refraction and axial length, with

few reporting the changes in retinal shape. Significant correlations between peripheral eye length and peripheral refraction have been found (Verkicharla et al., 2016; Mutti et al., 2019). Therefore, peripheral refraction or RPR, which clinicians can easily measure and monitor, has been used to indirectly describe the retinal shape (Stone and Flitcroft, 2004; Verkicharla et al., 2012). To date, few studies have reported changes in RPR after myopia control using myopic defocus in humans. The current study aims to investigate the changes in peripheral refraction and RPR and how the eye shape changed or expanded during myopia control.

## Chapter Four: Study introduction

Based on the findings from the animal studies, it is noted by competing defocus; the resultant refractive error can be manipulated to the desired end point, for example, emmetropia (Tse et al., 2007). However, in the animal studies, there was not really a focus for seeing clearly through high plus and high minus lenses. This is strong evidence that eye growth may not require clear vision at all.

In the human eye, it has been hypothesised that the natural process of emmetropisation is regulated by the equilibrium between the hyperopic and myopic defocus. Incidences of refractive errors may be caused by the disruption of the equilibrium, for instance, insufficient ambient myopic defocus leads to myopia and excessive ambient hyperopic defocus results in hyperopia (Lam et al., 2014). Several clinical trials have supported this hypothesis. By using constant under-correction in one eye to introduce myopic defocus during binocular viewing, myopia progression in the eye with constant myopic defocus was significantly reduced compared to the distance corrected eye (Phillips, 2005). Using the concentric Fresnel multifocal lens, diffractive multifocal lens, and their derivatives, significant myopia retardation has been achieved, such as the DISC and the MiSight contact lens (Lam et al., 2014; Chamberlain et al., 2019). Both DISC and MiSight contact lenses were designed with simultaneous vision bifocal power and applied concentric alternating distance correction, and myopic defocus zones covered the pupil area and thus provided the simultaneous vision for all distances and myopic defocus. The myopic defocus zone

was not for vision but constantly induce blur images in front of the retina. Such design could shift the defocus equilibrium of the eye and hence influence eye growth in a direction towards emmetropia or less myopia.

A alternative solution is to apply myopic defocus to the spectacle lens that the lens provides the same optical myopic defocus stimulation as the DISC lens, while without the inherent disadvantages of contact lens wearing.

### 4.1. The design and principle of the DIMS lens

The DIMS lens applies the principle of simultaneous vision, it provides myopic defocus and corrects refractive error simultaneously, it gives clear vision at all distances. Figure 4-1 is a schematic diagram of the DIMS lens. The lens comprises a central correction zone surrounded by multiple island-shape segments of constant myopic defocus (+3.50D) at the mid-periphery, which can simultaneously provide clear central vision and peripheral myopic defocus (Lam et al., 2020a). The total area between the two powers zones were about 50:50 ratio.

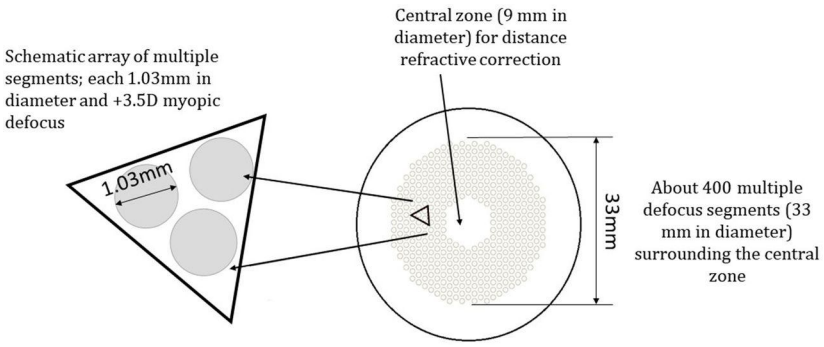



Figure 4- 1. The design of the DIMS spectacle lenses. (Adapted from *Lam et al. Br J Ophthalmol, 2020*).

A 2-year double-masked randomised clinical trial (RCT) to evaluate the efficacy of myopia control with the DIMS lens was conducted from 2014 to 2017. The trial protocol was the same as the DISC lens (Lam et al., 2014). The treatment group wore the DIMS lens while the control group wore the single vision lens. The primary outcome of the trial was the cycloplegic refraction measured by an open-field autorefractor. And the secondary outcome was the axial length change. The trial aimed to determine the myopia control efficacy of defocus incorporated multiple segments (DIMS) spectacle lenses in myopic children. The changes in central SER and axial length (AL) in children wearing the DIMS lenses and those wearing single vision (SV) spectacle lenses were compared.

This thesis was part of the RCT with focus on the investigation of the role of peripheral refraction and RPR and myopia control. The peripheral refraction changes and their relationship with other parameters, including sex, age, age of onset of myopia and myopia progression were also evaluated.

### 4.2. Study objectives

The objectives are:

1. To determine and describe the RPR among Hong Kong Chinse children who participated in the RCT.
2. To compare changes in RPR associated with myopia progression in myopic children wearing DIMS lenses and SV spectacle lenses over 2 years.

3. To compare changes in RPR associated with myopia progression in myopic children wearing DIMS lenses for the third year and children wearing SV wearers in the first 2 years who then switched to wear DIMS lenses.

## 4.3. Hypothesis

1. We hypothesised that baseline RPR pattern could influence myopia control effects.
2. We hypothesised that myopia control by myopic defocus could lead to a different change in peripheral refraction and RPR.

## 4.4. Methodology

### 4.4.1. Study design

There were two experimental strategies in this clinical trial. It was a double-masked RCT in the first 2 years; the children were randomly assigned to wear either the DIMS lens (DIMS group) or SV spectacle lens (SV group). Both the participated children (including their parents) and the masked investigators were masked from grouping and lens design. Masked investigators were responsible for conducting the eye examination and data collection and were not allowed to see or handle the lenses throughout the study. The unmasked investigators were responsible for grouping, lenses dispense, measuring visual performance etc. The masking procedures followed the 'Consolidated Standards of Reporting Trials' (CONSORT) requirements for a double-masked trial.

After completion of the 2-year RCT, both groups of children were asked to continue

for a further year. In the third year, the children who had worn DIMS lenses continued to wear DIMS lenses (DIMS group) and those who had worn SV lenses switched to wear DIMS lenses (Control-to-DIMS group). The children originally in the control group switched to wear DIMS lenses in the third year, so they could not be used as the 'control group' to assess myopia control efficacy. Therefore, a separate historical control group was obtained by recalling 2017-2019 clinical records from the Optometry Clinic of the Hong Kong Polytechnic University. The criteria for subject selection followed the inclusion and exclusion criteria in the original RCT. They were healthy Chinese myopic children who taken eye examinations in the clinic with at least 12-month follow-up data. They had not received any myopia interventions and were matched for age (between 10 and 15 years) and SER ranges (-1.00 to -5.50D) with the DIMS subjects at the end of the 2-year RCT. Annual myopia progression and AL changes in this history control group were calculated and then compared with the third-year changes in the DIMS and Control-to-DIMS groups.

### 4.4.2. Subject recruitment

The project recruitment was conducted and promoted through placing posters, public media and the study website from August 2014 and July 2015. Initial contact was made by telephone. The researcher explained the necessary information of the clinical trial and checked the study eligibility if relevant by asking questions such as the age of the child, history of the recent eye exam, spectacle prescription, etc. The potential participants who met the eligibility criteria from the phone screening were invited to

have an eligibility examination. Subject recruitment criteria and exclusion criteria were:

1. Age at enrolment: 8–13 years
2. Central SER: −1.00 to −5.00 D
3. Astigmatism: 1.50 D or less
4. Anisometropia: 1.25 D or less
5. Free of ocular and systemic abnormalities which might affect the visual function or refractive development
6. No prior use of any drugs or optical devices for myopia control

Exclusion Criteria:

1. any ocular and systemic abnormalities might affect visual functions or refractive development
2. prior treatment of myopic control, e.g. OK lenses, PALs, bifocal lenses, drugs (e.g. atropine), etc.

The pre-baseline screening tests included: autorefraction, cover tests, non-contact intraocular pressure (IOP), subjective refraction, best-corrected visual acuity (VA) and external ocular health exam. All the eye examinations and data collection were performed at The Hong Kong Polytechnic University Optometry Clinic. The study was approved by Human Subject Ethics Sub-committee of The Hong Kong Polytechnic University and adhered to the tenets of the Declaration of Helsinki. All

participates and their parents or guardians received the information sheet and signed the informed consent prior to study commencement.

### 4.4.3. Sample size calculation

G Power calculation was conducted to estimate the sample size; 90% power was used to detect 0.50 D difference (with 0.70 D of SD) (Lam et al., 2014) in myopia progression between two groups with a significance alpha level of 0.01 (Independent t-test, 2-tailed). We estimated the minimum sample size in each group was 59; after adjusting a 15% for loss to follow-up visits, 70 subjects were needed in each group.

### 4.4.4. Materials and methods

Both central and peripheral refractive error was measured by Shin-Nippon NVision-K 5001 autorefractor (Ajinomoto Trading Inc., Tokyo, Japan), which has been used widely for measuring peripheral refraction up to 80˚ degree across the horizontal retina.

The open-field autorefractor, with the unrestricted view and better control of accommodation, as subjects could fix the real target at a distance, has been one of the most popular methods to measure both central and peripheral refraction (Mutti et al., 2000; Mutti et al., 2007; Lee and Cho, 2012; Verkicharla et al., 2016; Jaisankar et al., 2019). The Shin-Nippon NVision K5001 and Shin-Nippon SRW5000 showed high repeatability and have been used widely in research, which could measure the peripheral refraction up to 40° horizontal retina and up to 15° in the vertical field (Fedtke et al., 2009; Zhao and Fang, 2020).

Axial length was tested by the IOL master 500 (Zeiss, German). It has been considered as a golden standard in axial length measurement as its high repeatability, high accuracy and non-invasive for studies with children.

### 4.4.5. Follow-up examinations

A standardised eye examination without and with cycloplegia was performed on eligible subjects every 6 months over the 3-year trial period from August 2014 to July 2018 (Table 4-1). The timeline of measurements conducted in each visit over 3 years lists in Table 4-2.

Table 4- 1. The measurements conducted at baseline, 6-, 12-, 18-, 24-, 30- and 36-month.

| Without cycloplegia |
| --- |
| - Determination of dominant eye |
| - Subjective and objective refraction |
| - Best corrected visual acuity |
| - Corneal curvature/ topography |
| - Binocular vision tests: phoria tests, stereopsis |
| - Accommodative tests: amplitude of accommodation, lag of accommodation with 3D stimulus |
| - Pupil diameters under different illumination, during distance and near viewing |
| - Non-contact IOP |
| - Subfoveal choroidal thickness (SFCT) by Spectral Domain Optical Coherence Tomography (SD-OCT) |
| With cycloplegia |
| - Subjective refraction (as reference for the prescription of contact lenses) |
| - Objective refraction: measured by using Shin-Nippon NVision-K 5001 (open-field) autorefractor. Five measurements are obtained for each eye and the average of SER of was used for statistical analysis. |
| - AL measurement: measured by IOL Master (Carl Zeiss). Five measurements were taken and averaged. |
| - Peripheral refraction: measured by using a Shin-Nippon NVision-K 5001 autorefractor at center, 10, 20 and 30 degrees at the nasal and temporal retina across the horizontal meridian. |
| - Dilated fundus examination |

Table 4- 2. The timeline of measurements conducted in each visit over 3 years

| Procedures/ measurements | *Screening | Baseline | 2 week | 1M | 3M | 6M | 12M | 18M | 24M | 30M | 36M |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Consent form signed | | x | | | | | | | | | |
| History-initial | x | x | | | | | | | | | |
| History-Update | | | x | x | x | x | x | x | x | x | x |
| Non-cycloplegic autorefraction | x | x | | | | x | x | x | x | x | x |
| Habitual spec VA | x | x | | | | x | x | x | x | x | x |
| Subjective refraction | x | x | | | | x | x | x | x | x | x |
| Best-corrected VA | x | x | | | | x | x | x | x | x | x |
| Cover test (distance, near) | x | | | | | | | | | | |
| Phoria (distance and near) | | x | | | | x | x | x | x | x | x |
| Lag of accommodation | | x | | | | x | x | x | x | x | x |
| Amplitude of accommodation | | x | | | | x | x | x | x | x | x |
| Stereopsis | | x | | | | x | x | x | x | x | x |
| Pupil size | | x | | | | x | x | x | x | x | x |
| Keratometry | | x | | | | x | x | x | x | x | x |
| Slit-lamp exam, external ocular health check | x | x | | | | x | x | x | x | x | x |
| IOP measurement | x | x | | | | x | x | x | x | x | x |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Choroidal thickness measurement | | x | x | x | x | x | x | x | x | x | x |
| Eye drops: Anesthetic, Cycloplegics | | x | | | | x | x | x | x | x | x |
| Cycloplegic subjective refraction | | x | | | | x | x | x | x | x | x |
| Cycloplegic autorefraction | | x | | | | x | x | x | x | x | x |
| Axial length measurement | | x | | | | x | x | x | x | x | x |
| Peripheral refraction | | x | | | | x | x | x | x | x | x |
| Dilated fundus exam | | x | | | | x | x | x | x | x | x |
| VA with habitual spectacle | | | x | x | x | x | x | x | x | x | x |
| Questionnaire of visual habits and spectacle lens performance | | | | | | | | | x | | x |

Corneal power was measured by Shin-Nippon NVision-K 5001 autorefractor (Ajinomoto Trading Inc., Tokyo, Japan) without cycloplegia (Davies et al., 2003). One drop of proparacaine 0.4%, followed by 1–2 drops of cyclopentolate HCL 1%, were used to induce cycloplegia. Shin-Nippon NVision-K 5001 autorefractor was used to measure the central and peripheral refraction across the horizontal retinal by using a with the Maltese cross-target placed at the straight-ahead position (centre) and 10°, 20°, and 30° at nasal (10N, 20N, 30N) and temporal (10T, 20T, 30T) retinal eccentricity. During measurement, subjects were asked to fixate on Maltese cross-targets placed at 10°, 20°, and 30° angles of the nasal (10N, 20N, 30N) and temporal (10T, 20T, 30T) retina while keeping their head facing towards the central target (Radhakrishnan and Charman, 2008) (Figure 4-2). Only the right eye was measured peripheral refraction, and the right gaze was considered as the temporal retina, and the left gaze was considered as the nasal retina.

Peripheral refraction was measured in the right eye because the ocular biometry between the two eyes was highly correlated (Lam et al., 2012; Lam et al., 2020b). In this group of children, the correlation coefficient between the right and left eye was 0.91 for the central SER, 0.97 for axial length, 0.94 for the steep corneal curvature and 0.97 for flat corneal curvature (Lam et al., 2020b). AL was measured five times by using the IOL Master (Carl Zeiss, Oberkochen, Germany) and then averaged. Spherocylindrical peripheral refraction measurements regarding spherical power (S), cylindrical power (C) and axis (θ) were converted into a power vector by a conventional formula for analysis. (Thibos et al., 1997)

$M = S + C/2$

$J_0 = -(C/2) \cos(2\theta)$

$J_{45} = -(C/2) \sin(2\theta)$

Positive $J_0$ represents with- the- rule astigmatism, while negative results represent against- the- rule astigmatism. The $J_{45}$ stands for oblique astigmatism. RPR is calculated as central refraction subtracted from peripheral refraction.

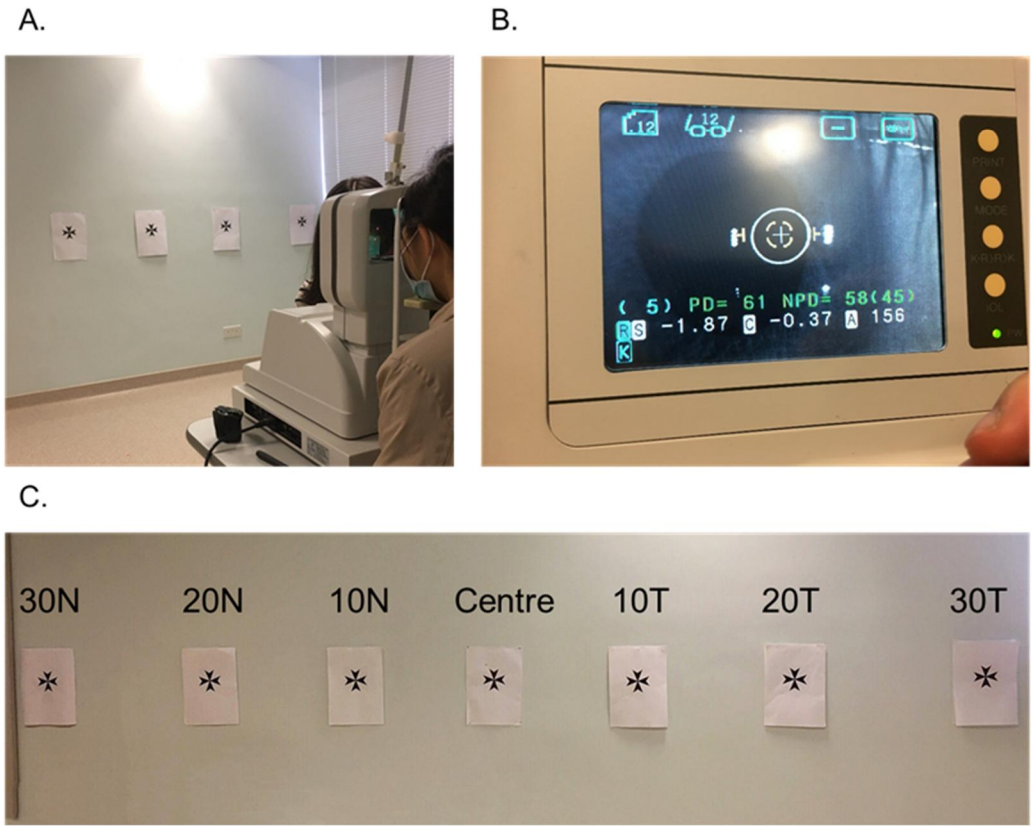



Figure 4- 2. The setting of peripheral refraction measurement.
A. Subjects sit at a 3m distance away from the Maltese cross-target. B. the screen in Shin-Nippon NVision-K 5001 autorefractor when measuring peripheral refraction. C. Maltese cross-target placed at the straight-ahead position (centre) and 10°, 20°, and 30° at nasal (10N, 20N, 30N) and temporal (10T, 20T, 30T) retinal eccentricity.

### 4.4.6. Visual performance with spectacle lens

The final prescription of spectacles was determined by cycloplegic subjective refraction conducted by the masked optometrist. The lens were upgraded if the SER of the prescription changed by 0.50 D or more (or habitual aided Log MAR VA worsen than 0.2).

Visual performance measurement, frame adjustment was conducted by unmasked investigators. Visual performance with spectacle lenses included visual acuity at distance and near under high and low contrast was tested at the lens dispense visit. The measurements are as follows:

a. Objective visual assessment: distance and near visual acuity in low and high contrast

b. Binocular vision tests: horizontal phoria at distance and near, stereoacuity (minute of arc), amplitude of accommodation (D), lag of accommodation

c. Patient-reported measures of lens performance using questionnaires.

### 4.4.7. Statistical analysis

All statistical analyses were performed using IBM SPSS v.16.0 (IBM Corporation, Armonk NY, USA). The right eye was used for data analyses, and all data were normally distributed (Kolmogorov-Smirnov $p>0.05$).

Repeated Measures Analysis of Variance (RM-ANOVA) was used to assess the effects of the treatment of two groups on myopia progression, changes in AL, changes of

peripheral refraction, and RPR over time. Independent t-tests were used to compare differences in RPR between the two groups. Paired t-test was used to compare the difference within the group.

Multiple linear regression (with myopia progression and axial elongation as the dependent variable) were run to detect the relationship of (1) baseline RPR with either myopic shifts and axial elongation, (2) changes in RPR with either myopic shifts and axial elongation, adjusting for sex and age. In the third year, the association of the initial RPR (when start to wear DIMS) with myopia progression and axial elongation was conducted by multiple linear regression after adjusting for age, sex, and initial myopia.

A p-value of less than 0.05 was considered statistically significant; Bonferroni adjustment (adjusted significance level was set to 0.008) was applied when analysing the parameters related to peripheral retinal eccentricities to avoid type I error because we measured six retinal eccentricities in the right eye of each subject.

## Chapter Five: Results of the study

The RCT conducted to investigate the efficacy of the DIMS lens on myopia control was completed in July 2017. A further follow-up year was conducted for the same group of subjects who participated in the RCT, and the third-year study was completed in July 2018. The main findings related to the myopic control effect were published in 2020 (Lam et al., 2020b). The results on the changes in the relative peripheral refraction have been partly published in a separate article (Zhang et al., 2020). The findings related to the myopia progression and control effect for the third year were also published in another article (Lam et al., 2021).

This chapter covers the results mainly related to the peripheral refraction of the subjects from baseline throughout the 2 years of the RCT, and the third-year extended follow-up study and the changes. The association of peripheral refraction and RPR with other ocular parameters would be studied and discussed. Whenever necessary, there could be duplication of data from the published manuscripts. The results will be divided into sections covering the baseline demography, the 2- year changes for the treatment and control groups, and a separate section on the third-year study in which the control subjects were switched to wear the treatment lens while the DIMS group continued to wear the DIMS lens.

## 5.1. Baseline demography

Figure 5-1 illustrates the flow chart of subject recruitment, enrolment, and withdrawal. Among 550 subjects recruited and assessed, 183 fulfilled inclusion and exclusion criteria and were also willing to participate in the RCT. They were randomized those 93 children were allocated to DIMS group, and 90 children were allocated to the SV group. There was no statistically significant difference in the baseline ocular parameters between the DIMS and SV groups ($p>0.05$) (Table 5-1); and this included age, sex, initial baseline SER, axial length, corneal powers, near phoria, the amplitude of accommodation, accommodative lag and myopia in their parents. The mean age of the children was around 10 years old, and their mean SER was around −2.93±1.04D in the DIMS group and −2.70±0.98D in the SV group.

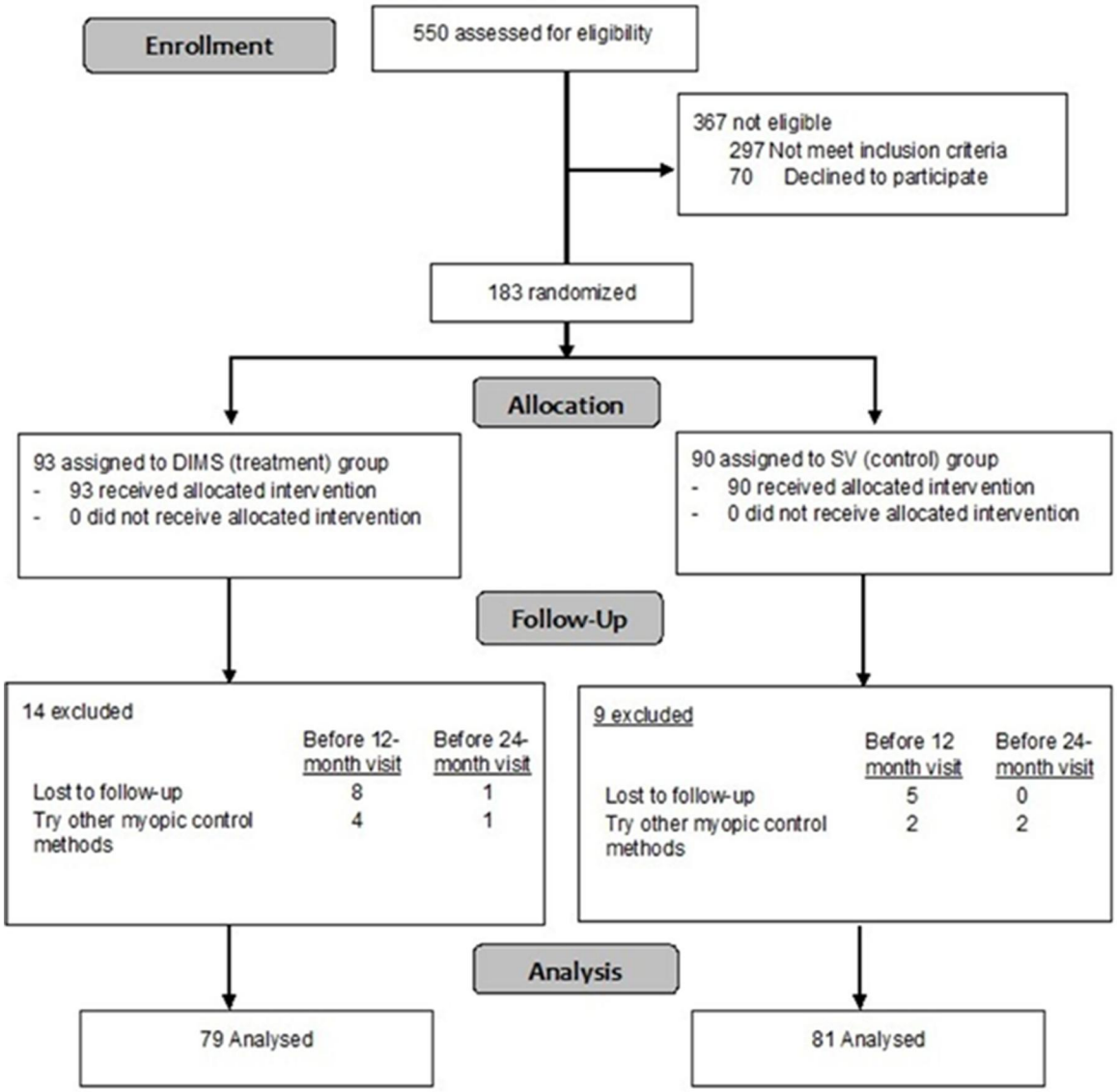



Figure 5- 1. A flow chart of the research design. (Adapted from: *Lam et al., Br J Ophthalmol, 2020*)

Table 5- 1. Baseline characteristics of all recruited subjects and completed 2-year study subjects in DIMS and SV group. (Adapted from *Lam et al., Br J Ophthalmol, 2020*)

| Baseline demographic data, mean (SD) | Mean (SD) | | | |
|---|---|---|---|---|
| | All | | Completed | |
| | DIMS (n=93) | SV (n=90) | DIMS (n=79) | SV (n=81) |
| Age at enrolment (years) | 10.19±1.46 | 10.01±1.44 | 10.20±1.47 | 10.00±1.45 |
| Gender | | | | |
| Male, % (n) | 59.1 (55) | 55.6 (50) | 58.2 (46) | 54.3 (44) |
| Female, % (n) | 40.9 (38) | 44.4 (40) | 41.8 (33) | 45.7 (37) |
| Cycloplegic autorefraction in SER (D) | −2.93±1.04 | −2.70±0.98 | −2.97±0.97 | −2.76±0.96 |
| Axial length (mm) | 24.85±1.59 | 24.72±1.30 | 24.70±0.82 | 24.60±0.83 |
| Corneal power at steep meridian (D) | 44.46±1.67 | 44.39±1.69 | 44.5±1.61 | 44.5±1.65 |
| Corneal power at flat meridian (D) | 43.14±1.41 | 43.09±1.45 | 43.2±1.41 | 43.2±1.44 |
| Near phoria, Δ | −1.96±3.93 | −0.98±3.53 | −2.16±4.07 | −0.15±3.28 |
| Accommodation lag 30cm (D) | 0.97±0.49 | 1.06±0.40 | 0.98±0.42 | 1.04±0.35 |
| Myopic parents, n | | | | |
| 0 | 3(3.2%) | 6 (6.7%) | 2(2.5%) | 5(6.2%) |
| 1 | 22(23.7%) | 23(25.6%) | 18(22.8%) | 20(24.7%) |
| 2 | 68(73.1%) | 61(67.7%) | 59(74.7%) | 56(69.1%) |

## 5.2. Baseline peripheral refraction

The peripheral refraction displayed a gradual decrease of myopia from the near periphery to mid-periphery in DIMS group. Peripheral M was -3.00±1.02 D, -2.71±1.23 D and -1.60±1.58 D at 10T, 20T and 30T respectively, and -2.81±0.99 D at 10N, -2.10±1.22 D at 20N and -1.07 ±1.33 D at 30N. The SV group showed a similar trend of decreasing in myopic refractive error it was -2.78±0.98 D at 10T, -2.68±1.23 D at 20T and -2.09±1.74 D at 30T and -2.62±0.93 D at 10N, -1.99±1.06 D at 20N and

-0.93±1.28 D at 30N at the nasal retina.

At the baseline, the DIMS and SV group showed no significant differences in peripheral refraction M across the horizontal retina (independent t-test, $p>0.05$). Therefore, we combined and analysed the baseline peripheral refraction together to determine and describe the RPR among Hong Kong Chinse children who participated in the RCT.

Figure 5-2 shows the profile of peripheral M, peripheral astigmatism $J_0$ and $J_{45}$ across the horizontal retinal eccentricities. These myopic children were observed less myopia at the periphery, more myopic peripheral $J_0$, and more hyperopic peripheral $J_{45}$ than at the centre. Both the magnitude of astigmatism $J_0$ and $J_{45}$ increased from the centre to the periphery.

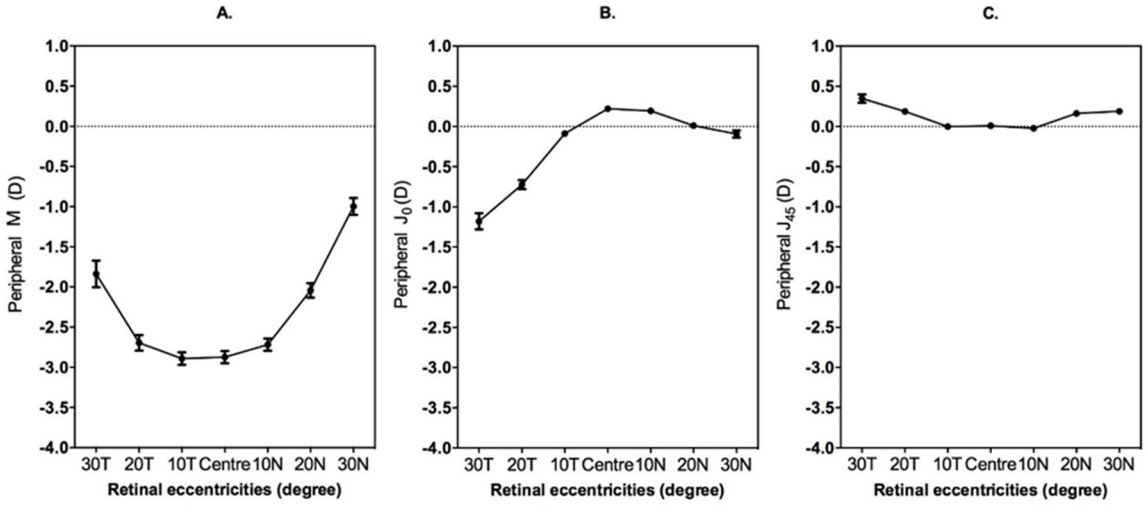



Figure 5- 2. The profile of peripheral refraction (M, $J_0$, $J_{45}$) across the horizontal retina of all children (n=160). Error bars denote the standard error of the mean (SEM). Zero horizontal lines have been shown as a dashed line.

Asymmetrical peripheral (M, $J_0$, $J_{45}$) was observed in the horizontal retina. Peripheral M decreased with the increasing of eccentricities, it was –2.89±1.00 D, -2.70±1.23 D, and -1.84±1.67 D at 10T, 20T and 30T respectively as well as -2.72±0.96 D，-2.04±1.12 D and -1.00±1.30 D at 10N, 20N and 30N respectively. Peripheral M showed significantly less myopia at the nasal retina (mean difference at 10N: 0.15±0.40 D, $p<0.0001$; 20N: 0.83±0.81, $p<0.0001$; 30N: 1.87±1.17 D, $p<0.0001$) and 30T (mean difference 1.03±1.60 D, $p<0.0001$) compared to centre SER.

Peripheral $J_0$ was significantly more myopia at the temporal (mean difference at 10T: -0.31±0.26 D, $p<0.0001$; 20T: -0.95±0.67, $p<0.0001$; 30T: -1.40±1.02 D, $p<0.0001$) and nasal retina (mean difference at 20N: -0.21±0.39, $p<0.0001$; 30N: -0.32±0.53 D, $p<0.0001$) except the 10N retina ($p=0.18$). Conversely, peripheral $J_{45}$ showed significantly more hyperopia at 20T (mean difference: 0.18±0.37 D, $p<0.0001$) and

30T (mean difference: 0.34±0.52 D, p<0.0001) as well as at 20N (mean difference: 0.16±0.40 D, p<0.0001) and 30N (mean difference: 0.18±0.38 D, p<0.0001) compared with central $J_{45}$. The magnitude in peripheral $J_{45}$ was less than peripheral astigmatism $J_0$. Children showed a broad range of cylindrical power across the horizontal retina, with some children showing up to 6 D of astigmatism at 30T (Table 5-2).

Table 5- 2. Mean and SD of peripheral refraction (M, $J_0$, $J_{45}$) at different eccentricities in all subjects.

| Retinal eccentricities (degree) | | | | | |
|---|---|---|---|---|---|
| 30T | 20T | 10T | 10N | 20N | 30N |
| *Mean (SD) of peripheral M* | | | | | |
| -1.84(1.67) | -2.70(1.23) | -2.89(1.00) | -2.72(0.96) | -2.04(1.14) | -1.00(1.30) |
| *Mean (SD) of peripheral $J_0$* | | | | | |
| -0.09(0.35) | -0.72(0.72) | -1.14(0.95) | 0.19(0.30) | 0.01(0.42) | -0.09(0.55) |
| *Mean (SD) of peripheral $J_{45}$* | | | | | |
| 0.01(0.23) | 0.19(0.38) | 0.35(0.53) | -0.02(0.20) | 0.16(0.37) | 0.19(0.36) |

### 5.2.1. The association between peripheral refraction and ocular parameters

A higher myopic central SER was associated with a more myopic peripheral M at all eccentricities (p< 0.008). However, there was no significant association between peripheral refraction with age, sex, corneal power, and AL after Bonferroni correction (Table 5-3).

Table 5- 3. Multiple linear regressions between peripheral M and central SER as well as ocular parameters with peripheral M as the dependent variable.

| Variables in the Equation | 10T | | | | 20T | | | | 30T | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Regression coefficient | 95% CI for B | | | Regression coefficient | 95% CI for B | | | Regression coefficient | 95% CI for B | | |
| | B | Lower Bound | Upper Bound | *P* † | B | Lower Bound | Upper Bound | *P*† | B | Lower Bound | Upper Bound | *P*† |
| Central SER (D) | 0.96 | 0.87 | 1.05 | <0.0001* | 0.89 | 0.70 | 1.09 | <0.0001* | 0.66 | 0.25 | 1.07 | 0.002* |
| Age (years) | -0.04 | -0.09 | 0.00 | 0.07 | -0.03 | -0.13 | 0.07 | 0.58 | -0.05 | -0.29 | 0.20 | 0.70 |
| Gender (Female) | 0.17 | 0.02 | 0.31 | 0.03 | 0.31 | -0.02 | 0.63 | 0.07 | 0.41 | -0.27 | 1.10 | 0.23 |
| Corneal power (D) | 0.07 | 0.01 | 0.13 | 0.03 | 0.12 | -0.03 | 0.26 | 0.11 | 0.35 | 0.04 | 0.67 | 0.03 |
| AL (mm) | 0.05 | -0.10 | 0.20 | 0.48 | 0.10 | -0.24 | 0.43 | 0.57 | 0.29 | -0.46 | 1.04 | 0.45 |
| Variables in the Equation | 10N | | | | 20N | | | | 30N | | | |
| | Regression coefficient | 95% CI for B | | | Regression coefficient | 95% CI for B | | | Regression coefficient | 95% CI for B | | |
| | B | Lower Bound | Upper Bound | *P*† | B | Lower Bound | Upper Bound | *P*† | B | Lower Bound | Upper Bound | *P*† |
| Central SER (D) | 0.89 | 0.81 | 0.98 | <0.0001* | 0.87 | 0.70 | 1.04 | <0.0001* | 0.73 | 0.48 | 0.98 | <0.0001* |
| Age (years) | 0.04 | 0.00 | 0.09 | 0.05 | 0.08 | -0.01 | 0.17 | 0.09 | 0.12 | -0.02 | 0.25 | 0.09 |
| Gender (Female) | -0.10 | -0.24 | 0.03 | 0.14 | -0.22 | -0.51 | 0.06 | 0.13 | -0.20 | -0.61 | 0.22 | 0.35 |
| Corneal power (D) | -0.01 | -0.07 | 0.05 | 0.71 | 0.00 | -0.12 | 0.13 | 0.99 | 0.09 | -0.09 | 0.27 | 0.32 |
| AL (mm) | -0.05 | -0.19 | 0.09 | 0.50 | 0.04 | -0.25 | 0.34 | 0.77 | 0.12 | -0.31 | 0.54 | 0.59 |

†Significance was considered as less than 0.008 after Bonferroni correction. *p<0.008

### 5.2.2. Baseline relative peripheral refraction

Hyperopic RPR M was observed at most eccentricities across the horizontal retina except at 10T in DIMS and SV group. Hyperopic RPR M increased with more peripheral eccentricity in both nasal and temporal retina. The PRR was -0.03±0.47 D (in the DIMS group) and -0.01± 0.35 D (in the SV group) at 10T and increased to 1.39±1.49 D (DIMS) and 0.66± 1.64 D (SV) at 30T. Similarly, in the temporal retina, it was 0.16±0.41 D (DIMS) and 0.15± 0.38 D (SV) at 10N and grew to 1.89± 1.20 D and 1.84± 1.15 D at 30N in the DIMS and SV group, respectively. As there was no statistically significant difference in RPR between DIMS and SV group ($p>0.008$) after the Bonferroni correction, the RPR profile was analysed for all subjects together at the baseline.

A broad range of hyperopic RPR M was present at 30N, which ranged from 0 to 6 D. Asymmetry in RPR M between the temporal and nasal parts of the retina was found (Figure 5-3A), with more hyperopic RPR M at 10N (paired t-test, mean difference: 0.17±0.63 D, $p=0.001$), 20N (mean difference: 0.65±1.21 D, $p<0.0001$) and 30N (mean difference: 0.84±1.68 D, $p<0.0001$) (Table 5-4).

Both relative $J_0$ and relative $J_{45}$ increased in magnitude with increasing eccentricity, and the magnitude of relative $J_{45}$ was less than relative $J_0$ (Figure 5-3 B and C). An asymmetrical profile was also found in relative $J_0$, with more negative of relative $J_0$ at the 10T (mean difference: -0.28±0.36 D, $p<0.0001$), 20T (mean difference: -0.74±0.74 D, $p<0.0001$), and 30T (mean difference: -1.08±0.91 D, $p<0.0001$) compared with the

corresponding eccentricity in the nasal retina. However, no statistically significant difference in relative $J_{45}$ between the nasal and temporal retina was noted (paired t-test, the corresponding mean difference at 10° was 0.02±0.30 D, p=0.34; 20° was 0.02±0.56 D, p=0.59; 30° was 0.13±0.75 D, p=0.09).

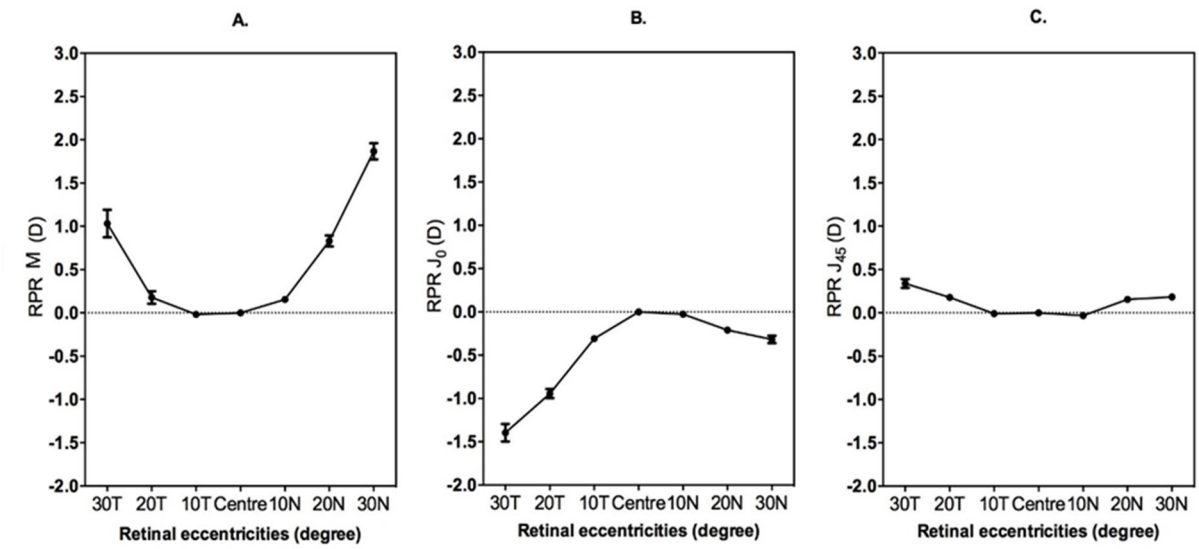



Figure 5- 3. The profile of RPR (M, $J_0$, $J_{45}$) across the horizontal retina of all children (n=160). Error bars denote SEM. Dashed lines represent zero for M, $J_0$ and $J_{45}$.

Table 5- 4. Mean and SD of RPR (M, $J_0$, $J_{45}$) at different eccentricities in all subjects.

| Retinal eccentricities (degree) | | | | | |
|---|---|---|---|---|---|
| 30T | 20T | 10T | 10N | 20N | 30N |
| *Mean (SD) of RPR M* | | | | | |
| 1.03(1.60) | 0.18(0.92) | -0.03(0.38) | 0.15(0.39) | 0.83(0.81) | 1.87(1.81) |
| *Mean (SD) of relative $J_0$* | | | | | |
| -1.40(1.02) | -0.95(0.67) | -0.31(0.26) | -0.01(0.22) | -0.21(0.39) | -0.32(0.53) |
| *Mean (SD) of relative $J_{45}$* | | | | | |
| 0.34(0.52) | 0.18(0.37) | -0.01(0.20) | -0.03(0.21) | 0.16(0.40) | 0.18(0.38) |

There was no significant association between central SER, age, sex, corneal power, axial length and RPR M, with RPR M as the dependent variable ($p>0.008$). (Table 5-5)

Table 5- 5. Multiple linear regressions between RPR M and central SER as well as ocular parameters with RPR M as the dependent variable.

| Variables in the Equation | 10T | | | | 20T | | | | 30T | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Regression coefficient | 95% CI for B | | | Regression coefficient | 95% CI for B | | | Regression coefficient | 95% CI for B | | |
| | B | Lower Bound | Upper Bound | *P* † | B | Lower Bound | Upper Bound | *P*† | B | Lower Bound | Upper Bound | *P*† |
| Central SER (D) | -0.09 | -0.13 | 0.05 | 0.38 | -0.11 | -0.30 | 0.09 | 0.27 | -0.19 | -0.75 | 0.07 | 0.10 |
| Age (years) | -0.15 | -0.09 | 0.00 | 0.07 | -0.05 | -0.13 | 0.07 | 0.58 | -0.04 | -0.29 | 0.20 | 0.70 |
| Gender (Female) | 0.20 | 0.02 | 0.31 | 0.03 | 0.17 | -0.02 | 0.63 | 0.07 | 0.13 | -0.27 | 1.10 | 0.23 |
| Corneal power (D) | 0.25 | 0.01 | 0.13 | 0.03 | 0.19 | -0.03 | 0.26 | 0.11 | 0.32 | 0.04 | 0.67 | 0.03 |
| AL (mm) | 0.11 | -0.10 | 0.20 | 0.48 | 0.09 | -0.24 | 0.43 | 0.57 | 0.14 | -0.46 | 1.04 | 0.45 |
| Variables in the Equation | 10N | | | | 20N | | | | 30N | | | |
| | Regression coefficient | 95% CI for B | | | Regression coefficient | 95% CI for B | | | Regression coefficient | 95% CI for B | | |
| | B | Lower Bound | Upper Bound | *P*† | B | Lower Bound | Upper Bound | *P*† | B | Lower Bound | Upper Bound | *P*† |
| Central SER (D) | -0.26 | -0.19 | -0.02 | 0.01 | -0.16 | -0.31 | 0.04 | 0.13 | -0.22 | -0.52 | -0.02 | 0.03 |
| Age (years) | 0.16 | 0.00 | 0.09 | 0.05 | 0.14 | -0.01 | 0.17 | 0.09 | 0.14 | -0.02 | 0.25 | 0.09 |
| Gender (Female) | -0.13 | -0.24 | 0.03 | 0.14 | -0.14 | -0.51 | 0.06 | 0.13 | -0.08 | -0.61 | 0.22 | 0.35 |
| Corneal power (D) | -0.04 | -0.07 | 0.05 | 0.71 | 0.00 | -0.12 | 0.13 | 0.99 | 0.12 | -0.09 | 0.27 | 0.32 |
| AL (mm) | -0.10 | -0.19 | 0.09 | 0.50 | 0.04 | -0.25 | 0.34 | 0.77 | 0.08 | -0.31 | 0.54 | 0.59 |

†Significance was considered as less than 0.008 after Bonferroni correction. *p<0.008

### 5.2.2.1. Relationship between RPR and age

Age was significantly correlated with RPR at 10N (Pearson correlation, $R^2$ =0.13, p=0.001), 20N ($R^2$ =0.10, p=0.004) and 30N ($R^2$ =0.10, p=0.006) in the DIMS group, but not in the SV group (p>0.05).

In the DIMS group, RPR at 10N in 8-year-old children was statistically significantly more myopic than in 11-year-old groups (mean difference: -0.65±0.16 D, p=0.002). RPR at 10N in 9-year-old children also showed a more myopic RPR than in 11-year-old groups (mean difference: -0.43±0.13, p= 0.03), but it did not reach a statistically significant level after applying the Bonferroni correction (p>0.008). The RPR profile among each age group is shown in Figure 5-4.

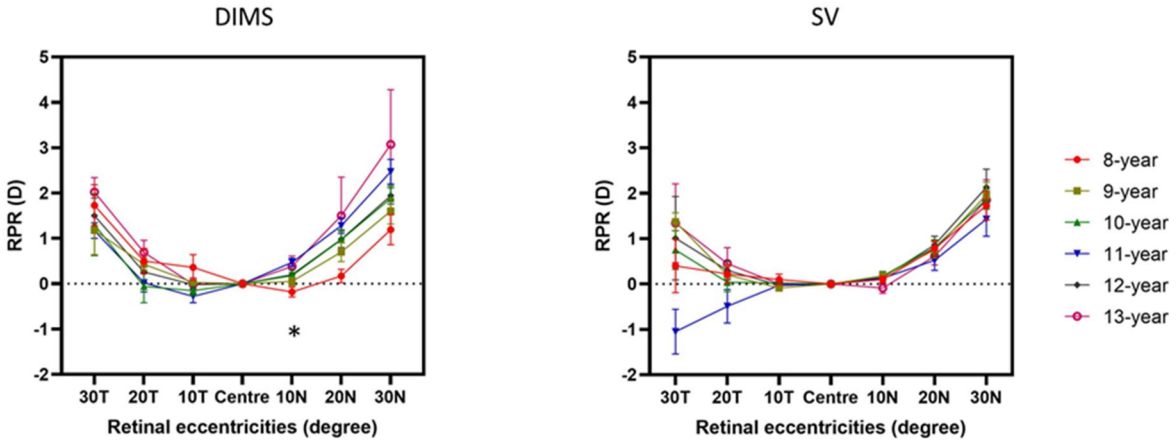



Figure 5- 4. RPR among each age sub-group in the DIMS and SV group respectively. * Indicated the significant difference in RPR among age-subgroups after Bonferroni correction (ANOVA, p<0.008). Error bars denote SEM. Zero horizontal lines have been shown as a dashed line.

## 5.3. 2-year RCT results

### 5.3.1. Subjects

One hundred and sixty children completed the first 2-year RCT study, with 79 children in the DIMS group and 81 children in the SV group. 15% of the children in the DIMS group withdrew the study, which was slightly higher than the SV group (10%). The main reasons for withdrawal from the trial were related to a long time to wait for the lenses, refusal to undergo cycloplegia, or not willing to attend follow-ups, while some others preferred to try other myopic control methods. The number of drop-out subjects at the different follow-ups and reasons was shown in Table 5-6 and Table 5-7.

Table 5- 6. The number of the drop-outs at different stages of the study. (Adapted from: *Lam, et al. Br J Ophthalmol, 2020*)

| After the visit of | DIMS | SV | Total |
|---|---|---|---|
| Baseline data collection | 9 | 5 | 14 |
| 6-month follow up | 3 | 2 | 5 |
| 12-month follow up | 0 | 0 | 0 |
| 18-month follow up | 2 | 2 | 4 |
| Total no. of dropouts | 14 | 9 | 23 |

Table 5- 7. Reasons for drop-outs. (Adapted from: *Lam, et al., Br J Ophthalmol, 2020*)

| Main reasons | DIMS | SV | Total |
|---|---|---|---|
| Long time to wait for delivery of lenses | 5 | 0 | 5 |
| Refuse to undergo cycloplegia | 2 | 2 | 4 |
| Try other myopic control methods | 5 | 4 | 9 |
| Not willing or unable to attend follow-up | 2 | 3 | 5 |
| Total | 14 | 9 | 23 |

### 5.3.2. Compliance and visual performance

Both groups showed good compliance and well accepted with the spectacle lenses, and no statistically significant difference in lens-wearing time was found (DIMS: 15.5±2.6 hours/day; SV: 15.3±2.1 hours/day).

For the visual performance, both groups showed a statistically significant enhancement in the best-corrected distance high-contrast VA ($p < 0.001$) and stereoacuity scores ($p < 0.001$) were observed after 2 years (Lam et al., 2020b). In addition, the monocular and binocular amplitude of accommodation and accommodative lag were significantly reduced after wearing DIMS or SV lenses ($p < 0.01$). However, the DIMS and the SV group did not show significant differences in the changes of visual function after 2 years ($p > 0.05$) (Lam et al., 2020b).

### 5.3.3. Changes in SER and axial length

**All enrolled subjects**

The intend-to-treated (ITT) method was conducted to analyse the subject who lost to follow-up. Missing data were addressed by the Generalized Estimation Equation (GEE). In the GEE function, time was set as the intra-subject factor, and the inter-subject factor was group (DIMS or SV). The interactions between time and group were used to determine the treatment effect of the myopia progression and changes in AL after adjusting for the covariates including age, sex, baseline refractive error, phoria, accommodative lag, number of myopic parents, and time of near-work and outdoor activities (Lam et al., 2020a).

Time, group, and age were found to be significantly associated with the magnitude of myopia progression ($p<0.05$). The myopia progressions were −0.41±0.06 D and −0.85±0.08 D in the DIMS and SV group, respectively, after adjusting covaries, which the corresponding controlling in myopia progression by DIMS lenses was 52% (mean difference −0.44±0.09 D, $p<0.0001$) (Lam et al., 2020a).

After model adjustment, the axial elongation was 0.21±0.02 mm in the DIMS group and 0.55±0.02 mm in the SV group, which the corresponding retardation in axial elongation by DIMS lens was 62% (mean difference 0.34±0.03 mm, $p<0.0001$) (Lam et al., 2020a) (Table 5-8).

Table 5- 8. Changes in SER and axial length in DIMS and SV group for all enrolled subjects over 2 years. (Adapted from *Lam et al., Br J Ophthalmol, 2020*)

| | DIMS (n=93) | SV (n=90) | Mean difference (SE) |
|---|---|---|---|
| Time/visit | SER changes in dioptres (D), mean (SE) | | |
| 6 months | −0.15±0.05 | −0.32±0.04 | −0.17±0.04* |
| 12 months | −0.08±0.06 | −0.18±0.06 | −0.10±0.07* |
| 18 months | −0.10±0.05 | −0.17±0.05 | −0.07±0.07* |
| 24 months | −0.08±0.06 | −0.18±0.06 | −0.09±0.07* |
| Total | −0.41±0.06 | −0.85±0.08 | −0.44±0.09* |
| Time/visit | Changes in AL (mm), mean (SE) | | |
| 6 months | 0.05±0.01 | 0.21±0.02 | 0.16±0.02* |
| 12 months | 0.06±0.02 | 0.12±0.02 | 0.06±0.03* |
| 18 months | 0.04±0.01 | 0.11±0.02 | 0.07±0.03* |
| 24 months | 0.06±0.02 | 0.11±0.02 | 0.05±0.04* |
| Total | 0.21±0.02 | 0.55±0.02 | 0.34±0.04* |

**Completed subjects**

Myopia progression over 2 years was -0.38±0.06 D and -0.93±0.06 D in the DIMS and SV groups, and the axial elongation was 0.21±0.02 mm and 0.53±0.03 mm in DIMS and SV groups, respectively (Table 5-9). Over 2 years, DIMS showed significantly less myopia progression (−0.55±0.09 D, $p<0.0001$) and less axial elongation (0.32±0.04 mm, $p<0.0001$) than the SV group, the corresponding myopia control effects were 59% in myopia retardation and 60% in less axial elongation.

Table 5- 9. Cumulative changes in SER and axial length in DIMS and SV group over 2 years. (Adapted from *Lam et al., Br J Ophthalmol, 2020*)

| | DIMS (n=79) | SV (n=81) | Mean difference (SE) |
|---|---|---|---|
| Time/visit | SER changes in dioptres (D), mean (SE) | | |
| 6 months | −0.13±0.03 | −0.37±0.04 | −0.24±0.05* |
| 12 months | −0.17±0.05 | −0.55±0.04 | −0.38±0.07* |
| 18 months | −0.31±0.06 | −0.72±0.05 | −0.42±0.08* |
| 24 months | −0.38±0.06 | −0.93±0.06 | −0.55±0.09* |
| Time/visit | Changes in AL (mm), mean (SE) | | |
| 6 months | 0.03±0.01 | 0.20±0.01 | 0.16±0.02* |
| 12 months | 0.11±0.02 | 0.32±0.02 | 0.21±0.02* |
| 18 months | 0.15±0.02 | 0.43±0.02 | 0.27±0.03* |
| 24 months | 0.21±0.02 | 0.53±0.03 | 0.32±0.04* |

### 5.3.4. Correlation between myopia progression and age

Statistically significant correlation between age and myopia progression was found in the DIMS group (Pearson correlation, $R^2$=0.22, p<0.001). Myopia progression was slightly slower in older children while faster in younger children in the DIMS group (Figure 5-5). In SV group, there was no statistically significant correlation between age and myopia progression ($R^2$=0.04, p>0.05).

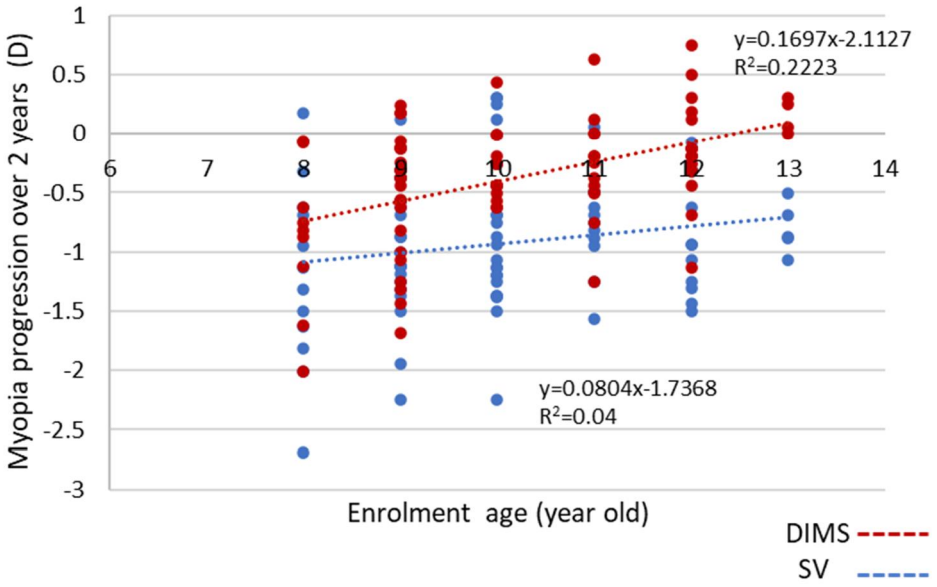



Figure 5- 5. Correlation between myopia progression (SER) and age of the subjects at enrolment in the DIMS and SV groups. (Adapted from *Lam et al., Br J Ophthalmol, 2020*)

## 5.4.Changes in peripheral refraction in the DIMS and SV group in the first 2 years

Table 5-10 and Figure 5-6 depict the results of peripheral M in the DIMS and SV groups at 6-month intervals. At baseline, there were no significant differences in peripheral M across the horizontal retina between the two groups (independent t-test, $p>0.05$). After 2 years, both groups have shown a steady increase in myopic shift centrally and peripherally, but the patterns of the change were contrasting.

DIMS group presented myopic shifts in peripheral M at all the horizontal retinal eccentricities, with a range from -0.34 D to -0.60 D (paired t-test, $p<0.0001$). They displayed a symmetrical pattern of myopic shifts between the nasal and temporal retina (Figure 5-6). In terms of the difference between the nasal and temporal retina, no

significant difference between the corresponding eccentricities was observed, with the mean difference at 20° was 0.04±0.71 D (p=0.65) and at 30° was 0.23±1.71 D (p=0.37) and not clinically significant at 10° was 0.17±0.49 D (p=0.003).

The SV group showed significant myopic shifts at the temporal retina, with a larger range from -0.59 D to -0.91 D (p<0.0001) over 2 years, and presented an asymmetrical pattern of myopic shifts between the nasal and temporal retina (Figure 5-6). Compared to the nasal retina, the temporal retina had significantly more myopic shifts at 10T (mean difference: -0.32±0.62 D, p<0.0001), at 20T (mean difference: -0.69±0.95 D, p<0.0001), and at 30T (mean difference: -0.85±1.52 D, p=0.001) compared to the nasal retina.

In fact, a more uniform myopic shift at all eccentricities was displayed in the DIMS group, while an asymmetrical myopic shift was presented in the SV group. In terms of the difference in changes of peripheral M between two groups, DIMS group had significantly more myopic shifts at 30N (mean difference -0.70±0.18 D, p<0.0001) and 20N (mean difference -0.38±0.14 D, p = 0.006) but significantly less myopic shifts at 10T (mean difference 0.57±0.12 D, p<0.0001) compared with the SV group over 2 years.

Table 5- 10. Mean and SD of peripheral M in the DIMS and SV groups over the first 2 years.

| Group | 10T | 20T | 30T | 10N | 20N | 30N |
|---|---|---|---|---|---|---|
| *Baseline* | | | | | | |
| DIMS | -3.00(1.02) | -2.71(1.23) | -1.60(1.58) | -2.81(0.99) | -2.10(1.22) | -1.07(1.33) |
| SV | -2.78(0.98) | -2.68(1.23) | -2.09(1.74) | -2.62(0.93) | -1.99(1.06) | -0.93(1.28) |
| *P*† | 0.16 | 0.86 | 0.14 | 0.21 | 0.55 | 0.49 |
| *6-Month* | | | | | | |
| DIMS | -3.16(0.99) | -2.81(1.15) | -1.91(1.24) | -2.94(1.26) | -2.21(1.29) | -1.30(1.41) |
| SV | -3.16(1.01) | -2.99(1.16) | -2.16(1.56) | -2.95(1.01) | -1.87(1.19) | -0.79(1.38) |
| *P*† | 0.98 | 0.32 | 0.40 | 0.96 | 0.08 | 0.02 |
| *12-Month* | | | | | | |
| DIMS | -3.19(0.98) | -2.98(1.05) | -1.81(1.15) | -3.09(1.15) | -2.29(1.38) | -1.28(1.50) |
| SV | -3.37(1.07) | -3.10(1.09) | -2.11(1.66) | -3.03(1.12) | -1.97(1.27) | -0.76(1.39) |
| *P*† | 0.26 | 0.85 | 0.32 | 0.74 | 0.12 | 0.003* |
| *18-Month* | | | | | | |
| DIMS | -3.28(1.02) | -3.15(1.12) | -2.27(1.16) | -3.20(1.13) | -2.40(1.24) | -1.47(1.54) |
| SV | -3.62(1.11) | -3.46(1.16) | -2.47(1.63) | -3.18(1.16) | -2.00(1.28) | -0.70(1.53) |
| *P*† | 0.05 | 0.08 | 0.45 | 0.94 | 0.05 | 0.003* |
| *24-Month* | | | | | | |
| DIMS | -3.34(1.10) | -3.14(1.20) | -2.19(1.35) | -3.32(1.26) | -2.57(1.41) | -1.73(1.68) |
| SV | -3.69(1.20) | -3.50(1.16) | -2.74(1.56) | -3.21(1.37) | -2.08(1.43) | -0.79(1.60) |
| *P*† | 0.06 | 0.06 | 0.03 | 0.59 | 0.03 | <0.0001* |

†The p-value was considered as significant if < 0.008 after Bonferroni adjustment. *p<0.008 indicates the significant difference between DIMS and SV group.

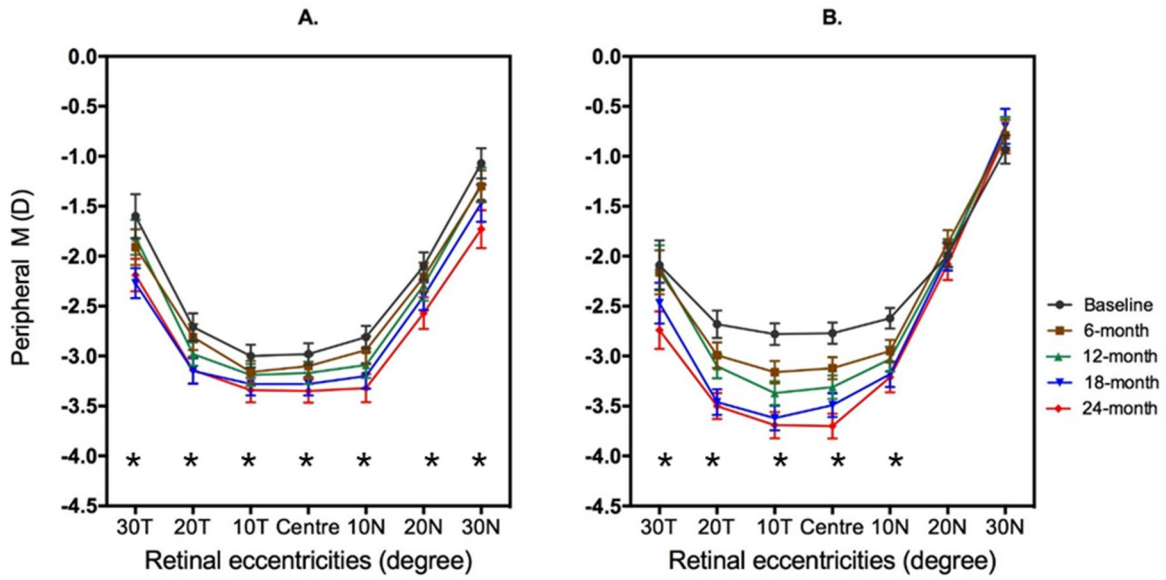



Figure 5- 6. Peripheral M in the first 2 years.
A: Peripheral refraction changes across the horizontal retina over the first 2 years in the DIMS group. B: Peripheral refraction changes across the horizontal retina over the first 2 years in the SV group. Error bars denote the standard error of the mean (SEM). The significance of the p-value was considered as less than 0.008 after the Bonferroni adjustment. *p<0.008 indicates the significant difference between baseline and 24-month within the group (paired t-test).

There were no statistically significant differences in peripheral $J_0$ and $J_{45}$ between the two groups at baseline (at all eccentricities, $p>0.05$). After 2 years, peripheral $J_0$ presented significant positive shifts at 10T (mean difference: 0.25 ± 0.33 D, $p<0.0001$), 20T (mean difference: 0.25 ± 0.47 D ($p<0.0001$) in the DIMS group. And in the SV group, significant positive shifts were observed at 10T (mean difference: 0.29 ± 0.28 D, $p<0.0001$), 20T (mean difference: 0.54 ± 0.50 D, $p<0.0001$), 10N (mean difference: 0.10±0.35 D, $p=0.01$), 20N (mean difference: 0.17 ± 0.38 D, $p<0.0001$) and 30N (mean difference: 0.16 ± 0.47 D, $p=0.004$). No significant difference in peripheral $J_0$ between the two groups was observed after 2 years.

No changes in peripheral $J_{45}$ within the DISM and SV group were found at all eccentricities after Bonferroni correction ($p>0.008$). After 2 years, there was no significant difference in peripheral $J_{45}$ between the two groups ($p>0.008$) (Figure 5-7).

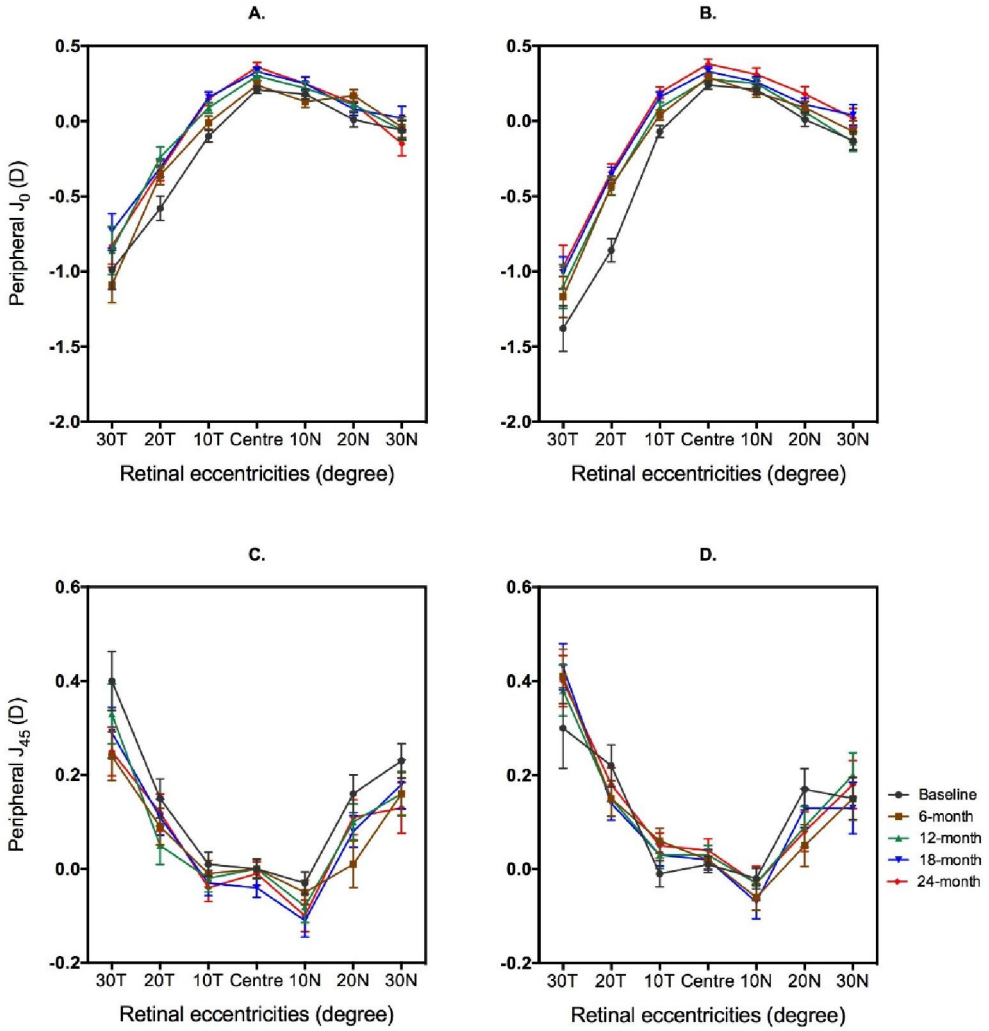



Figure 5- 7. Peripheral $J_0$ and $J_{45}$ in the first 2 years.
A: Peripheral $J_0$ changes across the horizontal retina over 2 years in the DIMS group. B: Peripheral $J_0$ changes across the horizontal retina over the first 2 years in the SV group. C: Peripheral $J_{45}$ changes across the horizontal retina over the first 2 years in the DIMS group. D: Peripheral $J_{45}$ changes across the horizontal retina over 2 years in the SV group. Error bars denote SEM.

### 5.4.1. Changes in relative peripheral refraction in DIMS and SV group

Table 5-11 and Figure 5-8 describe the RPR M in DIMS and SV group over 2 years. At

baseline, no statistically significant difference in RPR M between the DIMS and SV groups was found after Bonferroni correction ($p>0.008$).

After 2 years, the myopic shifts in all the peripheral refractions increased proportionally with the central refraction and therefore maintained a relatively constant RPR M in the DIMS group. Despite a significant decrease of hyperopic RPR M at 10N (mean difference -0.13 ± 0.43 D, $p<0.0001$) in the DIMS group, all the changes were regarded to be clinically negligible.

In the SV group, there were significant hyperopic shifts in RPR at the nasal retina, with mean changes of 0.27 ± 0.45 D, 0.75 ± 0.72 D and 0.98 ± 0.76 D at 10N, 20N and 30N ($p<0.0001$), but no significant changes have shown in the temporal retina. The RPR presented a skewed pattern.

The comparison of the two groups revealed that the SV group had significantly greater hyperopic RPR M at 10N (mean difference 0.46±0.11 D, $p<0.0001$), 20N (mean difference 0.82±0.16 D, $p<0.0001$), and 30N (mean difference 1.25±0.23 D, $p<0.0001$) but not in the temporal retina when compared with the DIMS group.

Table 5- 11. Mean (SD) of RPR M in the DIMS and SV group over the first 2 years.

| Group | 10T | 20T | 30T | 10N | 20N | 30N |
|---|---|---|---|---|---|---|
| *Baseline* | | | | | | |
| DIMS | -0.03(0.47) | 0.26(0.91) | 1.39 (1.49) | 0.16(0.41) | 0.88(0.89) | 1.89(1.20) |
| SV | -0.01(0.35) | 0.09(0.93) | 0.66 (1.64) | 0.15(0.38) | 0.78(0.72) | 1.84(1.15) |
| *P*† | 0.77 | 0.25 | 0.02 | 0.84 | 0.46 | 0.80 |
| *6-Month* | | | | | | |
| DIMS | -0.05(0.41) | 0.29(0.75) | 1.15 (0.97) | 0.16(0.82) | 0.89(0.94) | 1.80(1.07) |
| SV | -0.04(0.34) | 0.13(0.72) | 0.97 (1.40) | 0.18(0.44) | 1.25(0.86) | 2.33(1.19) |
| *P*† | 0.77 | 0.17 | 0.46 | 0.90 | 0.01 | 0.003* |
| *12-Month* | | | | | | |
| DIMS | -0.01(0.42) | 0.19(0.70) | 1.21(1.05) | 0.08(0.46) | 0.88(0.87) | 1.90(1.18) |
| SV | -0.06(0.34) | 0.21(0.67) | 1.15(1.45) | 0.28(0.60) | 1.35(0.92) | 2.55(1.26) |
| *P*† | 0.44 | 0.86 | 0.81 | 0.02 | 0.001* | 0.001* |
| *18-Month* | | | | | | |
| DIMS | 0.00(0.45) | 0.14(0.80) | 1.05(0.99) | 0.09(0.78) | 0.88(1.00) | 1.84(1.35) |
| SV | -0.13(0.35) | 0.03(0.70) | 0.96(1.23) | 0.31(0.55) | 1.48(0.90) | 2.70(1.31) |
| *P*† | 0.04 | 0.34 | 0.67 | 0.04 | <0.0001* | <0.0001* |
| *24-Month* | | | | | | |
| DIMS | 0.01(0.47) | 0.21(0.78) | 1.15(1.31) | 0.03(0.56) | 0.80(0.89) | 1.63(1.42) |
| SV | 0.01(0.68) | 0.20(0.80) | 1.00(1.39) | 0.49(0.86) | 1.62(1.10) | 2.88(1.42) |
| *P*† | 0.98 | 0.97 | 0.52 | <0.0001* | <0.0001* | <0.0001* |

†The p-value was considered as significant if < 0.008 after Bonferroni adjustment. *p<0.008 indicates the significant difference between DIMS and SV group.

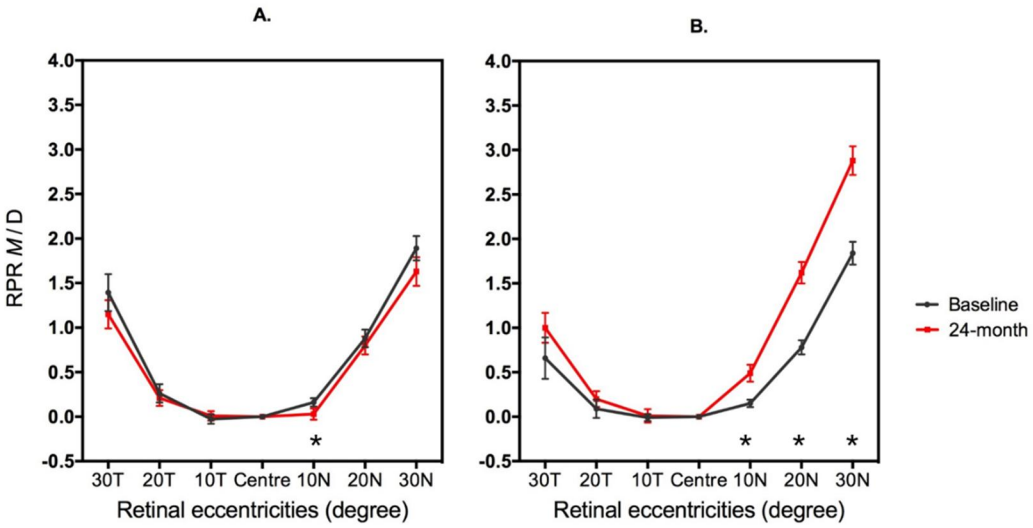



Figure 5- 8. RPR in the first 2 years.
A: Relative peripheral refraction changes across horizontal retina over the first 2 years in the DIMS group. B: Relative peripheral refraction changes across horizontal retina over the first 2 years in the SV group. Error bars indicate SEM. The significance of the p-value was considered as less than 0.008 after the Bonferroni adjustment. *p<0.008 indicates the significant difference between baseline and 24-month within the group (paired t-test).

### 5.4.2. Relationship between RPR and myopia progression

In the SV group, there was no statistically significant association between baseline RPR M with either myopic progression or the axial elongation in the first year after adjusting for sex, age and initial refractive error or AL after Bonferroni correction (multiple linear regression, p>0.008)

In the DIMS group, baseline RPR M at 10N (r=0.45, p<0.0001) and 20N (r=0.34, p=0.003) was found to be associated with myopia progression after adjusting for age, sex, initial refractive error (Figure 5-9) and axial elongation (10N, r=-0.34, P=0.003; 20N, r=-0.29, p=0.01) (Figure 5-10) after adjusting for age, sex and initial AL in the first year. Although the relationship between RPR at 20N and axial elongation did not

reach to a significant level after the Bonferroni correction.

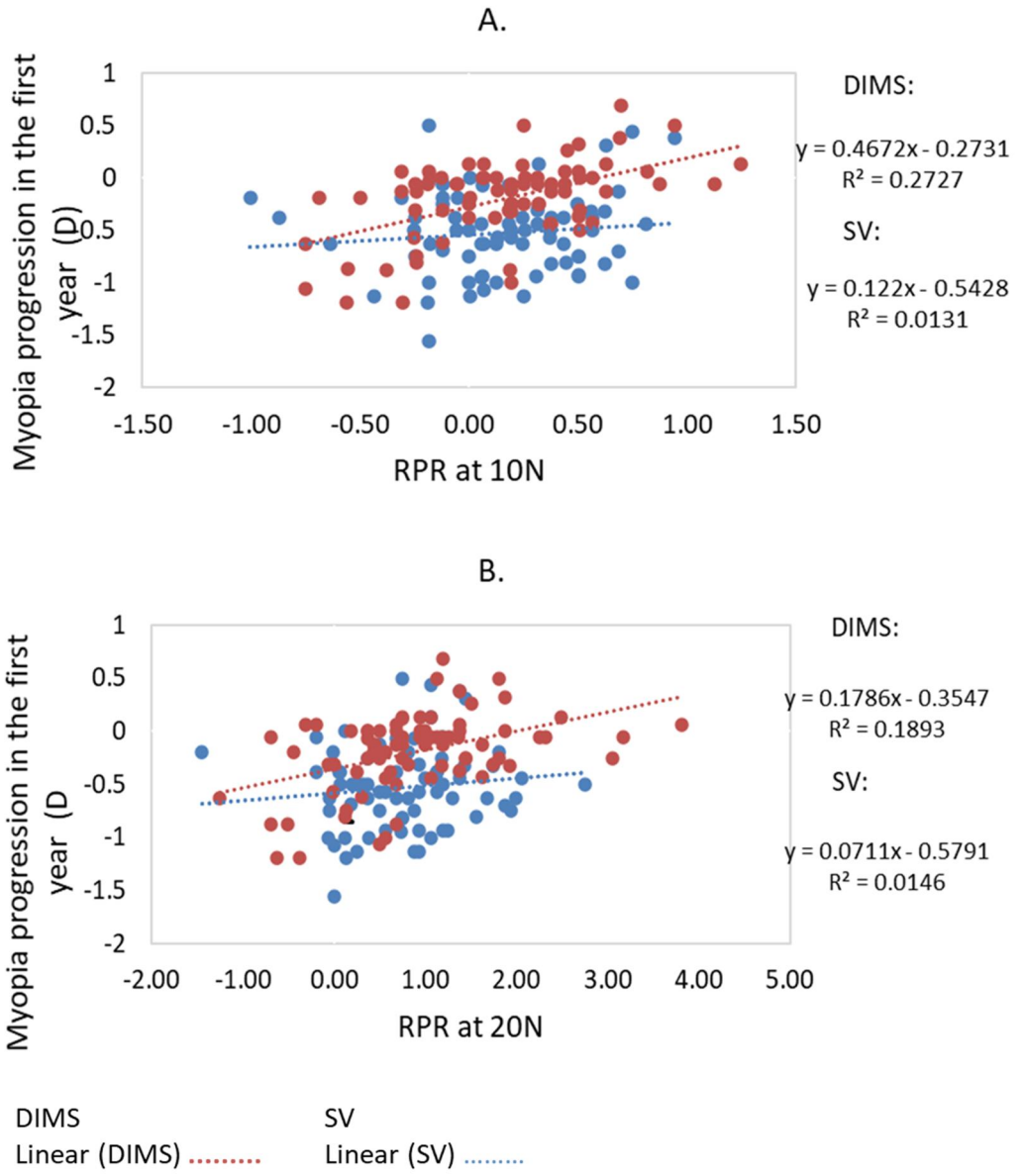



Figure 5- 9. Myopia progression in the first year and RPR at baseline.
A: Correlation between baseline RPR at 10N and myopia progression in DIMS and SV group in the first year; B: Correlation between baseline RPR at 20N and myopia progression in DIMS and SV group in the first year. Red is the DIMS group and blue is the SV group.

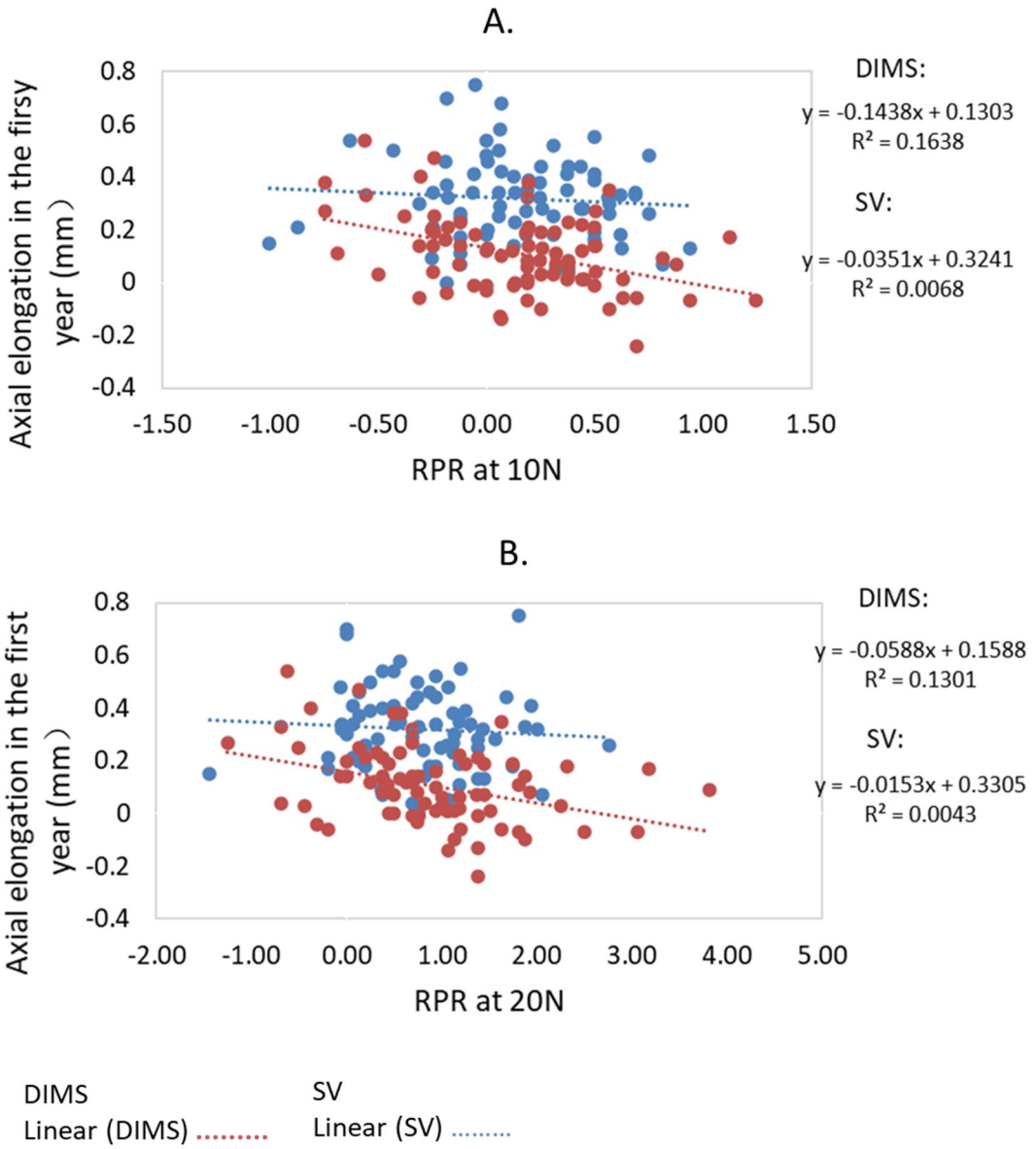



Figure 5- 10. Axial elongation in the first year and RPR at baseline.

A: Correlation between baseline RPR at 10N and axial elongation in DIMS and SV group in the first year; B: Correlation between baseline RPR at 20N and axial elongation in DIMS and SV group in the first year. Red is the DIMS group and blue is the SV group.

Over 2 years, in the SV group, baseline RPR M at 10N (r=0.37, p=0.001) and 20N (r=0.36, p=0.001) and 30N (r=0.35, p=0.002) were positively associated with myopia progression after adjusting for co-factors but there was no statistically significant relationship between RPR M and axial elongation after Bonferroni correction (p>0.008). In the DIMS group, baseline RPR M at 10N (r=0.36, p=0.001) and 20N (r=0.35, p=0.001) positively associated with myopia progression (Figure 5-11) as well as negatively associated with axial elongation (10N, r=-0.35, P=0.001; 20N, r=-0.30, p=0.004) (Figure 5-12) in the first 2 years after adjusting co-factors. Less hyperopic RPR (or more myopic RPR) at baseline was associated with more myopia progression and axial elongation over 2 years. According to the formula in Figure 5-11, DIMS wearers with baseline hyperopic RPR larger than 0.80 D at 10N and larger than 2.34 D at 20N showed no myopia progression or even hyperopic shifts in the first 2 years.

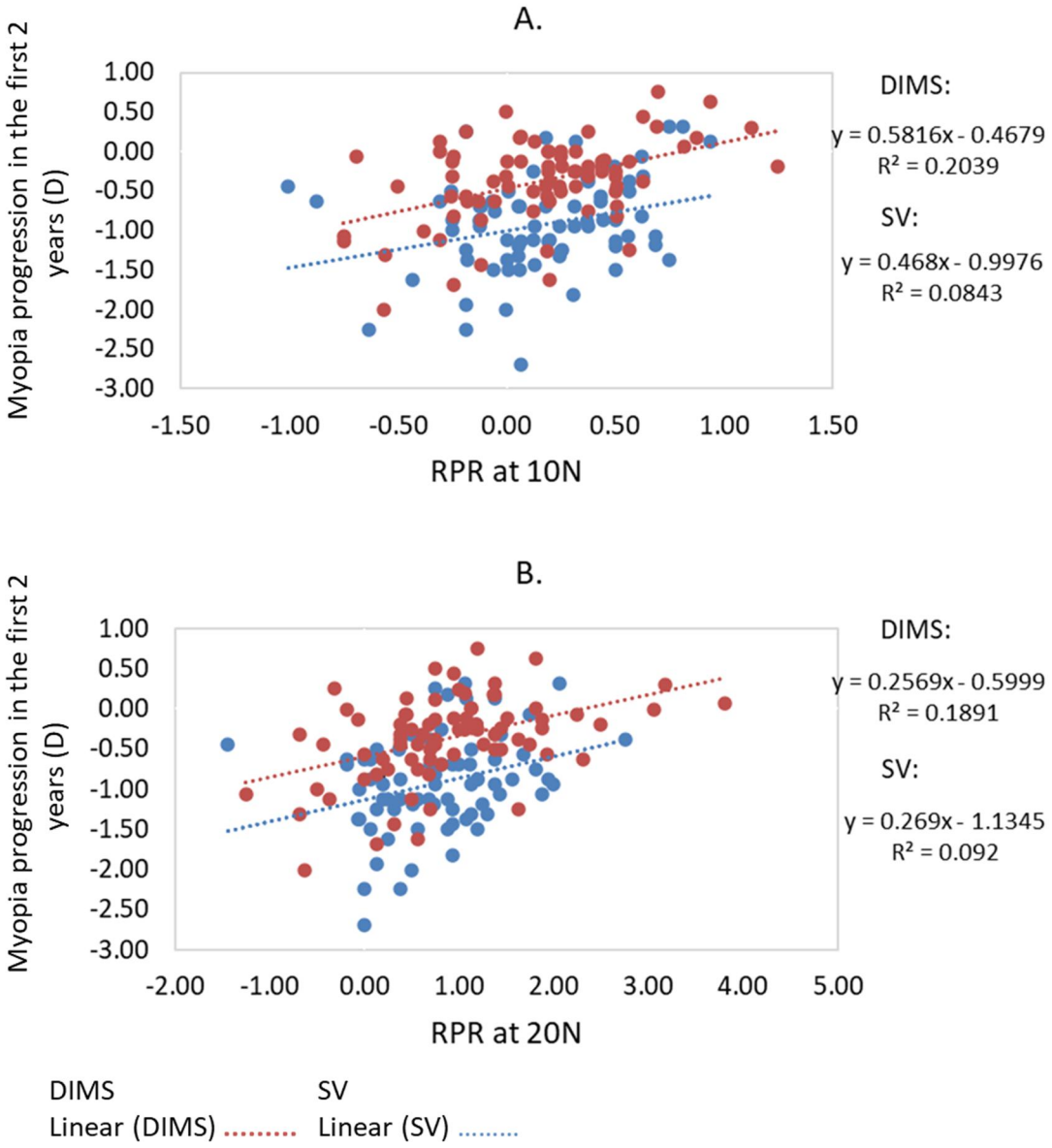



Figure 5- 11. Myopia progression in the first 2 years and RPR at baseline.

A: Correlation between baseline RPR at 10N and myopia progression in DIMS and SV group over 2 years; B: Correlation between baseline RPR at 20N and myopia progression in DIMS and SV group over 2 years. Red is the DIMS group and blue is the SV group.

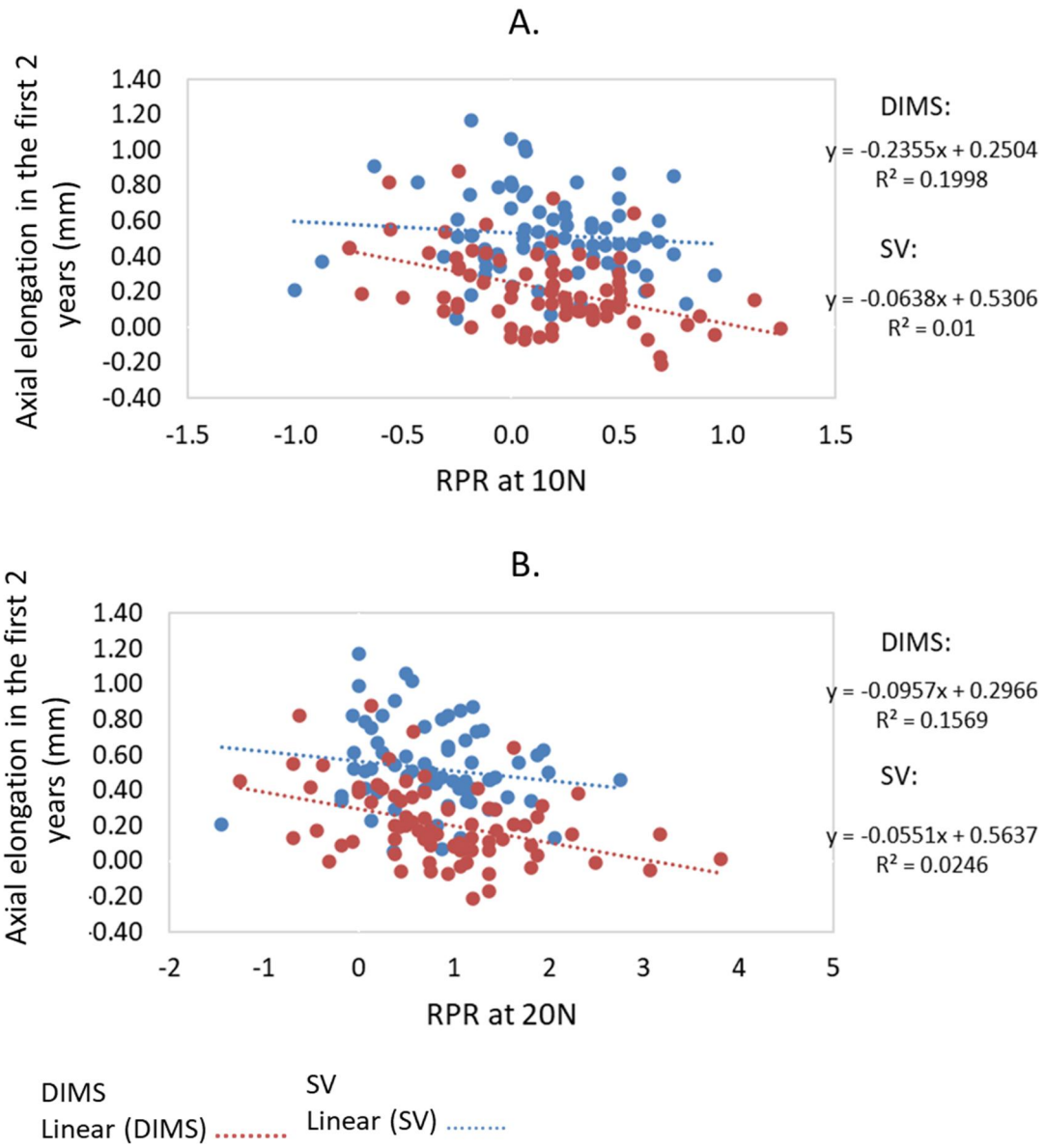



Figure 5- 12. Axial elongation in the first 2 years and RPR at the baseline.
A: Correlation between baseline RPR at 10N and axial elongation in DIMS and SV group over 2 years; B: Correlation between baseline RPR at 20N and axial elongation in DIMS and SV group over 2 years. Red is the DIMS group and blue is the SV group.

### 5.4.3. Comparison between myopic RPR and hyperopic RPR subgroups

Subjects were subdivided into two subgroups according to baseline RPR: myopic RPR (10N, 20N) and hyperopic RPR (10N, 20N) group. Myopia progression and axial

elongation were further compared between myopic RPR and hyperopic RPR group within the SV and DIMS group.

In the SV group, there was no statistically significant difference in myopia progression (mean difference: -0.26±0.14 D, p=0.06) and axial elongation (mean difference:0.04±0.05 mm, p=0.48) between myopic RPR (n=27) and hyperopic RPR (n=54) groups at 10N. Also, no significant difference in myopia progression (mean difference: -0.25±0.20 D, p=0.19) and axial elongation (mean difference: 0.08±0.08 mm, p=0.27) between myopic RPR (n=11) and hyperopic RPR (n=70) groups at 20N.

However, in the DIMS group, myopic RPR at 10N subgroup (n=27) showed statistically significant more myopia progression (mean difference: -0.36±0.14 D, p=0.009) and axial elongation (mean difference: 0.16±0.05 mm, p=0.001) than the hyperopic PRR at 10N subgroup (n=52). And myopic RPR at 20N subgroup (n=12) showed statistically significant more myopia progression (mean difference: -0.40±0.16 D, p=0.01) and axial elongation (mean difference: 0.15±0.07 mm, p=0.02) than the hyperopic PRR at 20N subgroup (n=67).

### 5.5. The third-year results

#### 5.5.1. Subject profile

Table 5-12 illustrates the number of subjects recruited and those lost to follow-up in the third year. One hundred and sixty Chinese children completed the 2-year RCT, and 128 were eligible to participate in the extended 1-year post-trial follow-up study. There was

no statistically significant difference in the age, sex, baseline myopia or AL, myopia progression or axial elongation in the previous 2-year trial between the subjects who joined and did not join the third year ($p>0.05$) (Table 5-13). After 3 years, 120 subjects completed the third-year follow-up visits, with 65 subjects in the DIMS group and 55 subjects in the Control- to-DIMS group. There was no significant difference in age at the age at enrolment, sex proportion between DIMS and Control-to-DIMS when starting the third-year follow-up ($p>0.05$).

Table 5- 12. Subjects numbers in the third year.

| No. of subjects | DIMS | Control- to-DIMS | Total |
|---|---|---|---|
| Enrolled subjects | 68 | 60 | 128 |
| Drop-out | 3 | 5 | 8 |
| Completed | 65 | 55 | 120 |

Table 5- 13. Demographic data between the subjects joined and the subject did not join the third year.

| DIMS group | joined study (n=65) | did not join study (n= 14) | p-value (t-test /chi-square test) |
|---|---|---|---|
| Age at enrolment (years) | 10.15 ± 1.52 | 10.43 ± 1.22 | 0.521 |
| Sex | | | |
| Male, % (n) | 57% (37) | 64% (9) | 0.612 |
| Female, % (n) | 43% (28) | 36% (5) | |
| Baseline SER (D) | -2.98 ± 0.96 | -2.93 ± 1.05 | 0.863 |
| Baseline AL (mm) | 24.68 ± 0.82 | 24.81 ± 0.84 | 0.594 |
| Myopia progression (D) in previous 2 years | -0.34 ± 0.52 | -0.55 ± 0.54 | 0.177 |
| Axial elongation (mm) in previous 2 years | 0.20 ± 0.21 | 0.27 ± 0.23 | 0.270 |
| Control to DIMS group | joined study (n=55) | did not join study (n= 26) | p-value (t-test /chi-square test) |
| Age at enrolment (years) | 10.24 ± 1.42 | 9.83 ± 1.35 | 0.089 |
| Sex | | | |
| Male, % (n) | 47% (26) | 62% (16) | 0.261 |
| Female, % (n) | 53% (28) | 38% (10) | |
| Baseline SER (D) | -2.73 ± 0.99 | -2.86 ± 0.91 | 0.573 |
| Baseline AL (mm) | 24.57 ± 0.88 | 24.73 ± 0.73 | 0.423 |
| Myopia progression (D) in previous 2 years | -0.87 ± 0.59 | -1.01 ± 0.62 | 0.330 |
| Axial elongation (mm) in previous 2 years | 0.49 ± 0.24 | 0.59 ± 0.23 | 0.080 |

### 5.5.2. Changes in SER and axial length

Table 5-14 showed the changes in SER and axial length in the DIMS and the Control-to-DIMS group over 3 years.

Children in the DIMS group continually showed good myopia control effects. On average, the annual changes in myopia progression were -0.18 D and this progression rate was almost linear over the 3 years, which implied that the myopia control effect was sustained at around 50 to 60% (Figure 5-13 A). For the children who were in the original control group, the myopia control effect was significantly different over 3 years. In the first 2 years, the myopia progression rate ranged from -0.38D to -0.49D. After switching to DIMS lens, the annual myopia progression was reduced to only -0.05D for the third year (Figure 5-13 B).

The annual axial elongation in the DIMS group was steady and consistent over 3 years; it was around 0.10 mm per year (Figure 5-13 C). In addition, in the Control-to-DIMS group, the third-year axial elongation was 0.08 mm, while it was ranged from 0.20 mm to 0.29 mm per year in the first 2 years. Children once switched to wear DIMS lenses benefited from myopia control significantly (Figure 5-13 D).

Table 5- 14. Cumulative changes in SER and axial length in the DIMS and Control-to-DIMS groups over 3 years.

| | Mean ± SD | | | |
|---|---|---|---|---|
| | DIMS (n=65) | Control-to- DIMS (n=55) | DIMS (n=65) | Control-to-DIMS (n=55) |
| Time (months) | SER (D) | | Changes in SER (D) | |
| Baseline | -2.98 ± 0.96 | -2.73 ± 0.99 | - | - |
| 6 months | -3.10 ± 0.97 | -3.07 ± 1.02 | -0.12 ± 0.30 | -0.34 ± 0.33 |
| 12 months | -3.16 ± 0.97 | -3.22 ± 1.08 | -0.18 ± 0.37 | -0.49 ± 0.40 |
| 18 months | -3.23 ± 0.96 | -3.41 ± 1.09 | -0.25 ± 0.50 | -0.68 ± 0.52 |
| 24 months | -3.32 ± 1.00 | -3.61 ± 1.15 | -0.34 ± 0.52 | -0.87 ± 0.59 |
| 30 months | -3.39 ± 1.01 | -3.73 ± 1.23 | -0.41 ± 0.58 | -1.00 ± 0.67 |
| 36 months | -3.50 ± 1.08 | -3.65 ± 1.34 | -0.52 ± 0.69 | -0.92 ± 0.81 |
| Time (months) | AL (mm) | | Changes in AL (mm) | |
| Baseline | 24.68 ± 0.82 | 24.57 ± 0.88 | - | - |
| 6 months | 24.72 ± 0.81 | 24.75 ± 0.89 | 0.04 ± 0.10 | 0.18 ± 0.09 |
| 12 months | 24.78 ± 0.81 | 24.86 ± 0.91 | 0.10 ± 0.14 | 0.29 ± 0.14 |
| 18 months | 24.81 ± 0.81 | 24.97 ± 0.93 | 0.13 ± 0.18 | 0.40 ± 0.18 |
| 24 months | 24.88 ± 0.80 | 25.06 ± 0.96 | 0.20 ± 0.21 | 0.49 ± 0.24 |
| 30 months | 24.93 ± 0.79 | 25.12 ± 0.99 | 0.25 ± 0.24 | 0.55 ± 0.27 |
| 36 months | 24.99 ± 0.80 | 25.14 ± 1.01 | 0.31 ± 0.26 | 0.57 ± 0.33 |

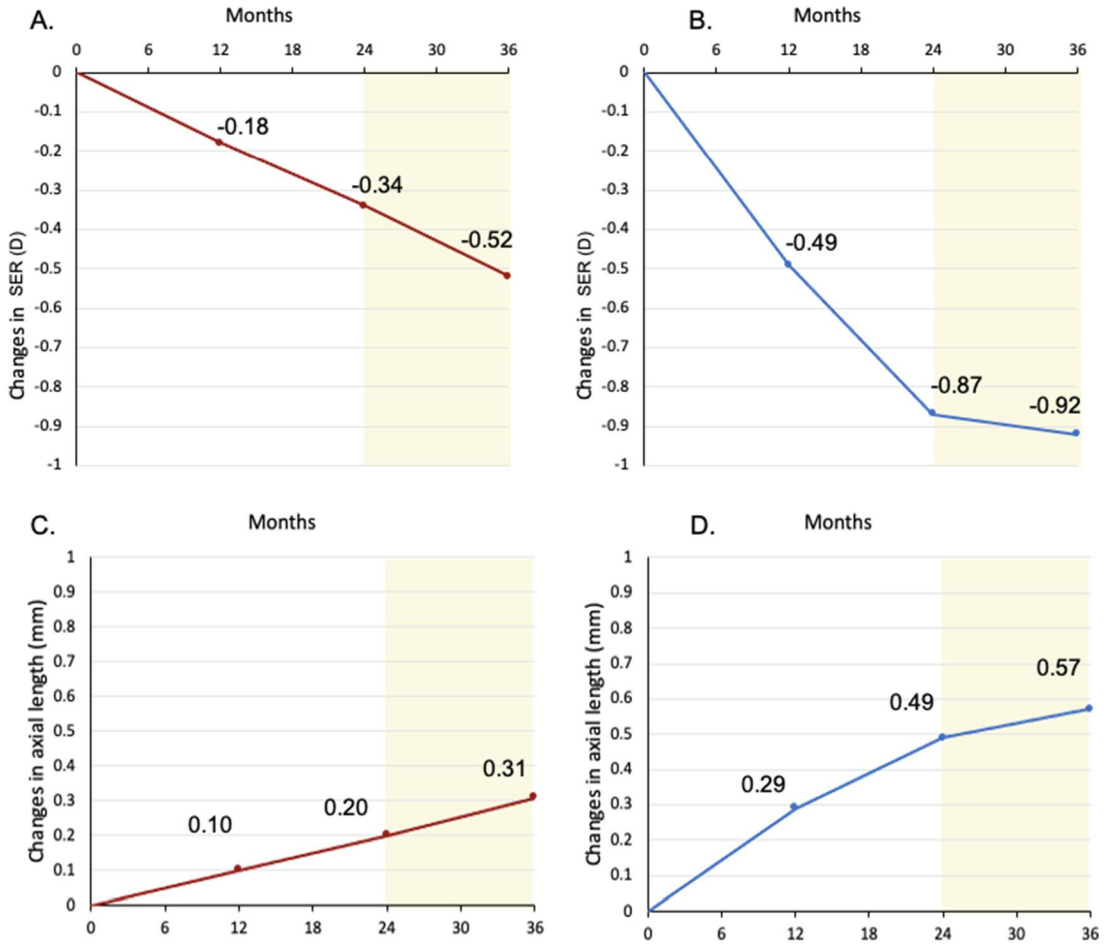



Figure 5- 13. A. Cumulative changes in SER from baseline to 36-month in the DIMS group. B. Cumulative changes in SER from baseline to 36-month in the Control-to-DIMS group. C. Cumulative changes in axial length from baseline to 36-month in the DIMS group. D. Cumulative changes in axial length from baseline to 36-month in the Control-to-DIMS group.

#### 5.5.2.1. Correlation between myopia progression and age

In the DIMS group, myopia progression and axial elongation over 3 years were significantly correlated with age ($R^2$= 0.22, p=0.001 & $R^2$= 0.39, p=0.001), but no statistically significant correlation was found in the third year. The trend lines (Figure 5-14) indicated that myopia progression rate in older children in the DIMS group (10 years old or above) was slower than the younger ones (8-9 years old).

For the Control-to-DIMS group, the younger children (8-9 years old) showed more myopia progression in the first two years than the other groups of older children (10 to 13 years), however, no significant correlation was found with age. Also, no correlation was found between age and the third-year changes in the Control-to-DIMS group ($p>0.05$)

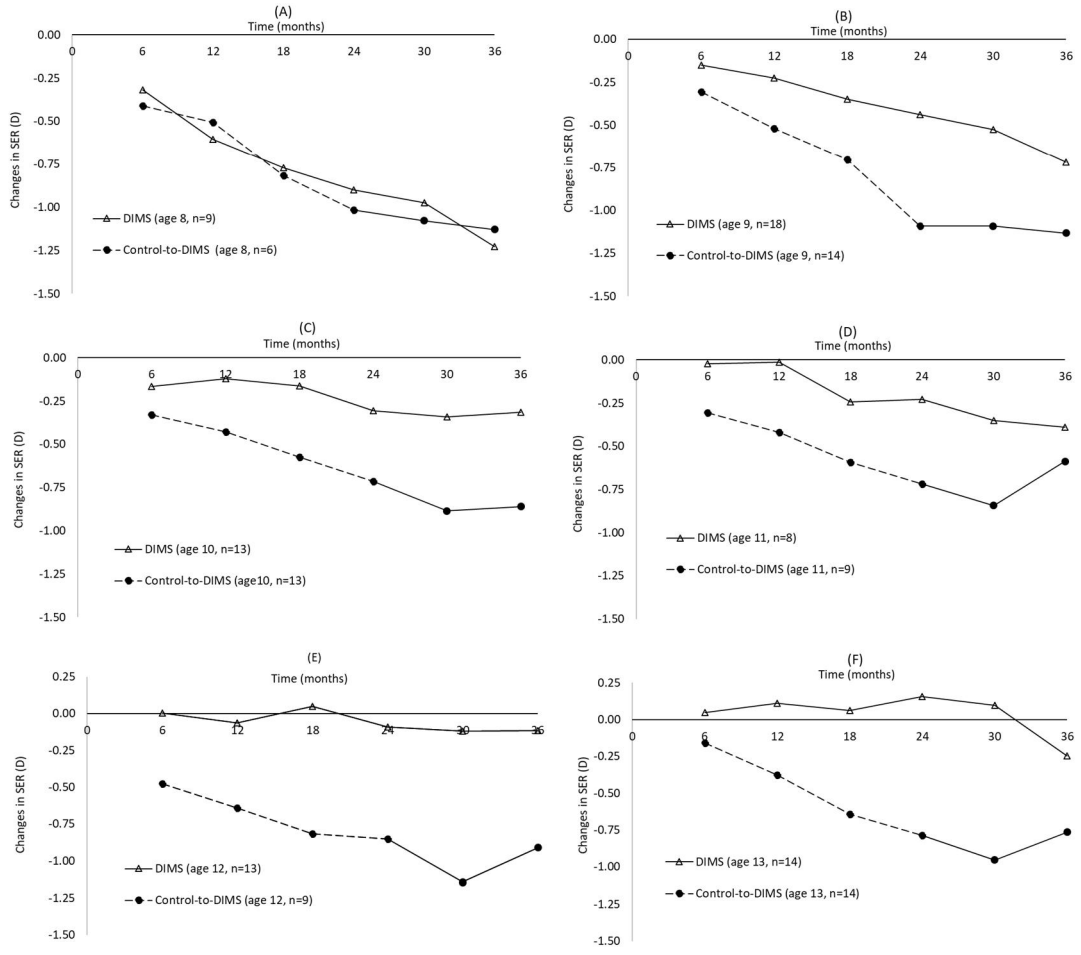



Figure 5- 14. Mean changes in SER throughout 3 years in different age groups of the DIMS and the Control-to-DIMS subjects.

#### 5.5.2.2. Comparison of the historical control group with the DIMS group and with the Control-to-DIMS group

The baseline of the historical control group (n =76, 39 males and 37 females) corresponding to the 24-month of DIMS and Control-to-DIMS group. There was no significant difference in demography characteristics among baseline historical control group, 24-month DIMS, and 24-month Control-to-DIMS group (Table 5-15), except the SER at baseline in the historical group, was significantly less than Control-to-DIMS at 24-moth ($p<0.003$)

Table 5- 15. Baseline data comparison among the historical control group with and the DIMS group and with the Control-to-DIMS group.

| | DIMS (n=65) | Historical control group (n= 76) | p-value (t-test /chi-square test) |
|---|---|---|---|
| Age | 12.14 ± 1.52 | 12.19 ± 0.71 | 0.856 |
| Sex | | | |
| Male, % (n) | 57% (37) | 51% (39) | 0.506 |
| Female, % (n) | 43% (28) | 49% (37) | |
| Baseline SER (D) | -3.32 ± 1.00 | -2.93 ± 1.33 | 0.054 |
| Baseline AL (mm) | 24.88 ± 0.88 | 24.77 ± 0.91 | 0.469 |
| | Control-to-DIMS (n=55) | Historical control group (n= 76) | p-value (t-test /chi-square test) |
| Age | 12.24 ± 1.47 | 12.19 ± 0.71 | 0.793 |
| Sex | | | |
| Male, % (n) | 47% (26) | 51% (39) | 0.722 |
| Female, % (n) | 53% (28) | 49% (37) | |
| Baseline SER (D) | -3.61 ± 1.15 | -2.93 ± 1.33 | 0.003* |
| Baseline AL (mm) | 25.06 ± 0.96 | 24.77 ± 0.91 | 0.081 |

The 1-year changes in SER and AL were on average-0.35 ±0.40 D and 0.18 ±0.14mm in the historical group. In the third year, DIMS group showed significantly less myopia progression (mean difference = -0.18± 0.42 D, p=0.012) than the historical control group. Axial elongation in the DIMS group was also less than in the historical control group (mean differences= 0.08 ± 0.15 mm, p=0.001).

After adjusting the covariates, age, sex, baseline SER, axial length by multiple linear regression, myopia progression of children in the Control-to-DIMS group were statistically significantly slower than the historical control group (mean differences = -0.30± 0.42 D, p<0.001). Similarly, less axial elongation (mean differences = 0.12 ± 0.16 mm, p<0.001) was noted in the Control-to-DIMS group after correcting the confounding factors.

### 5.6. Peripheral refraction and RPR in the third year

Subjects who joined and did not join the third year showed no statistically significant difference in peripheral (M, $J_0$, $J_{45}$) (Table 5-16, 5-17, 5-18) and RPR (Table 5-19) at 24-month.

Table 5- 16. Peripheral M between the subjects joined, and the subjects did not join the third year.

| DIMS group | joined study (n=65) | did not join study (n= 14) | p-value |
|---|---|---|---|
| 10T | -3.30±1.06 | -3.53±1.31 | 0.55 |
| 20T | -3.13±1.20 | -3.20±1.20 | 0.86 |
| 30T | -2.19±1.40 | -2.18±1.09 | 0.99 |
| 10N | -3.30±1.19 | -3.42±1.58 | 0.80 |
| 20N | -2.47±1.32 | -3.04±1.74 | 0.26 |
| 30N | -1.65±1.64 | -2.11±1.87 | 0.41 |
| Control-to-DIMS group | joined study (n=55) | did not join study (n= 26) | p-value |
| 10T | -3.52±1.23 | -4.05±1.10 | 0.05 |
| 20T | -3.32±1.11 | -3.89±1.20 | 0.05 |
| 30T | -2.59±1.47 | -3.06±1.75 | 0.28 |
| 10N | -3.10±1.42 | -3.45±1.26 | 0.26 |
| 20N | -1.96±1.43 | -2.32±1.44 | 0.31 |
| 30N | -0.64±1.54 | -1.14±1.72 | 0.24 |

Table 5- 17. Peripheral $J_0$ between the subjects joined and the subjects did not join the third year.

| DIMS group | joined study (n=65) | did not join study (n= 14) | p-value |
|---|---|---|---|
| 10T | 0.13±0.41 | 0.26±0.26 | 0.14 |
| 20T | -0.36±0.62 | -0.16±0.38 | 0.12 |
| 30T | -0.85±1.08 | -0.73±0.53 | 0.73 |
| 10N | 0.25±0.40 | 0.30±0.20 | 0.46 |
| 20N | 0.13±0.48 | 0.07±0.31 | 0.53 |
| 30N | -0.14±0.74 | -0.18±0.45 | 0.82 |
| Control-to-DIMS group | joined study (n=55) | did not join study (n= 26) | p-value |
| 10T | 0.17±0.34 | 0.23±0.35 | 0.44 |
| 20T | -0.38±0.49 | -0.28±0.50 | 0.42 |
| 30T | -1.05±1.21 | -0.80±1.20 | 0.42 |
| 10N | 0.31±0.40 | 0.31±0.34 | 0.97 |
| 20N | 0.21±0.46 | 0.13±0.38 | 0.41 |
| 30N | 0.03±0.60 | -0.03±0.47 | 0.64 |

Table 5- 18. Peripheral $J_{45}$ between the subjects joined and the subjects did not join the third year.

| DIMS group | joined study (n=65) | did not join study (n= 14) | p-value |
|---|---|---|---|
| 10T | -0.03±0.25 | -0.08±0.30 | 0.54 |
| 20T | 0.12±0.34 | 0.09±0.39 | 0.80 |
| 30T | 0.26±0.45 | 0.23±0.34 | 0.84 |
| 10N | -0.09±0.30 | -0.15±0.25 | 0.42 |
| 20N | 0.12±0.35 | 0.08±0.25 | 0.65 |
| 30N | 0.13±0.50 | 0.14±0.41 | 0.97 |
| Control-to-DIMS group | joined study (n=55) | did not join study (n= 26) | p-value |
| 10T | 0.03±0.2 | 0.09±0.24 | 0.25 |
| 20T | 0.17±0.31 | 0.22±0.34 | 0.52 |
| 30T | 0.33±0.43 | 0.56±0.46 | 0.05 |
| 10N | -0.03±0.34 | -0.05±0.33 | 0.75 |
| 20N | 0.11±0.36 | 0.02±0.43 | 0.36 |
| 30N | 0.21±0.43 | 0.11±0.47 | 0.38 |

Table 5- 19. RPR between the subjects joined and the subjects did not join the third year.

| DIMS group | joined study (n=65) | did not join study (n= 14) | p-value |
|---|---|---|---|
| 10T | 0.02±0.45 | -0.04±0.53 | 0.67 |
| 20T | 0.19±0.80 | 0.29±0.68 | 0.65 |
| 30T | 1.15±1.32 | 1.19±1.29 | 0.91 |
| 10N | 0.02±0.54 | 0.06±0.66 | 0.83 |
| 20N | 0.88±0.88 | 0.44±0.90 | 0.11 |
| 30N | 1.69±1.44 | 1.38±1.31 | 0.44 |
| Control-to-DIMS group | joined study (n=55) | did not join study (n= 26) | p-value |
| 10T | 0.10±0.74 | -0.18±0.48 | 0.05 |
| 20T | 0.31±0.82 | -0.01±0.71 | 0.08 |
| 30T | 1.10±1.44 | 0.80±1.29 | 0.40 |
| 10N | 0.52±0.94 | 0.43±0.64 | 0.61 |
| 20N | 1.65±1.15 | 1.56±1.03 | 0.71 |
| 30N | 2.94±1.41 | 2.75±1.46 | 0.60 |

For the subjects who completed all 3-year clinical trial, two groups presented different pattern of myopic shifts in the peripheral retina in the first 2 years. DIMS group had myopic shifts in all eccentricities with the magnitude from -0.30 D to -0.70D, without clinical difference between nasal and temporal retina. However, children who wore SV lenses showed asymmetrical changes in peripheral refraction. There were more myopic shifts at the temporal retina than the nasal retina, with the mean difference at 10º was -0.29±0.59 D ($p=0.001$), at 20º, was -0.74±0.99 D ($p<0.0001$) and at 30º was 0.88±1.40 D ($p=0.001$) (Figure 5-16 left).

In the third year, DIMS group kept stable in peripheral M. Only 30T increased myopia with the magnitude of -0.33±0.96 D (paired t-test, $p=0.02$), while it did not reach a statistically significant level after Bonferroni correction ($p>0.008$). And no changes in peripheral M at other retinal eccentricities. There was no significant difference in myopic shifts between the nasal and temporal retina ($p>0.05$) (Figure 5-15).

Children who wore SV lenses in the first 2 years started to present symmetrical myopic shifts in the peripheral retina after wearing DIMS for 1 year. When comparing the magnitude of changes in peripheral M between nasal and temporal, no significant difference in myopic shifts between the nasal and temporal retina was found ($p>0.05$) (Figure 5-16 right). Myopic shifts were noted at 10T, 20T and 30N, with the changes of -0.27±0.80 D ($p=0.02$), -0.43±0.84 D ($p<0.0001$), and -0.36±1.10 D ($p=0.02$) respectively, while only the changes in 20T reached significant level after Bonferroni

correction (p<0.008) (Figure 5-16).

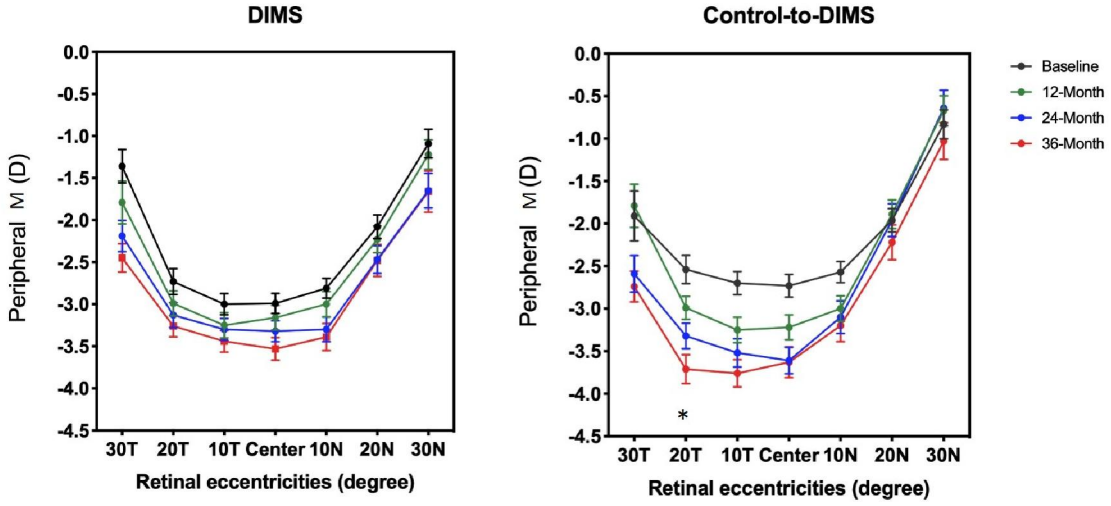



Figure 5- 15. Peripheral M in the third in DIMS and Control-to-DIMS group. *p<0.008 indicates the significant difference between 24-month and 36-month within the group (paired t-test).

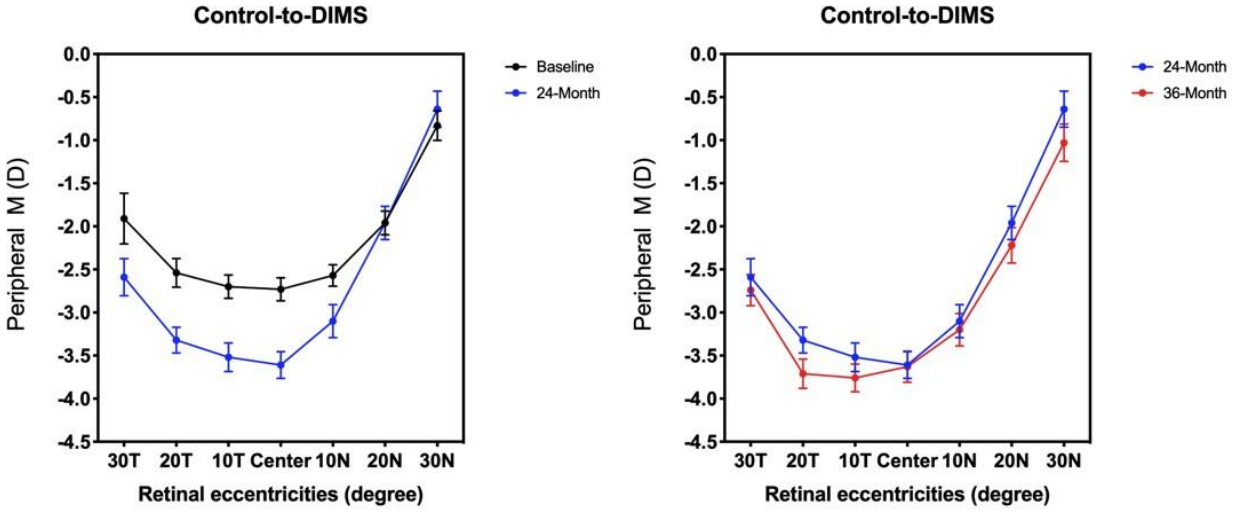



Figure 5- 16. Peripheral M in the first 2 years (left) and in the third year (right) in the Control-to-DIMS group.

In the first 2 years, DIMS group had significantly positive shifts in peripheral $J_0$ at 10T (mean difference: 0.23±0.33 D, p<0.0001) and 20T (mean difference:0.23±0.46 D, p<0.0001), while children wore SV lenses showed significantly positive shifts at almost all eccentricities, with the changes of 0.22±0.29 D (p<0.0001) at 10T, 0.49±0.53 D (p<0.0001) at 20T, 0.11±0.36 D (p=0.03) at 10N, 0.23±0.35 D (p<0.0001) at 20N and

0.14±0.49 D (p=0.04) at 30N. However, there was no significant difference in peripheral $J_0$ between the two groups after 2 years. And no significant changes in peripheral $J_{45}$ were found in either DIMS or Control to DIMS group over 2 years.

In the third year, DIMS group showed significant positive shifts in peripheral $J_0$ at 20T with the changes of 0.23±0.51 D (p=0.001), whereas the Control-to-DIMS group showed no significant changes in peripheral $J_0$ after Bonferroni correction. Besides, both groups had no significant changes in $J_{45}$ after the Bonferroni correction. (Figure 5-17)

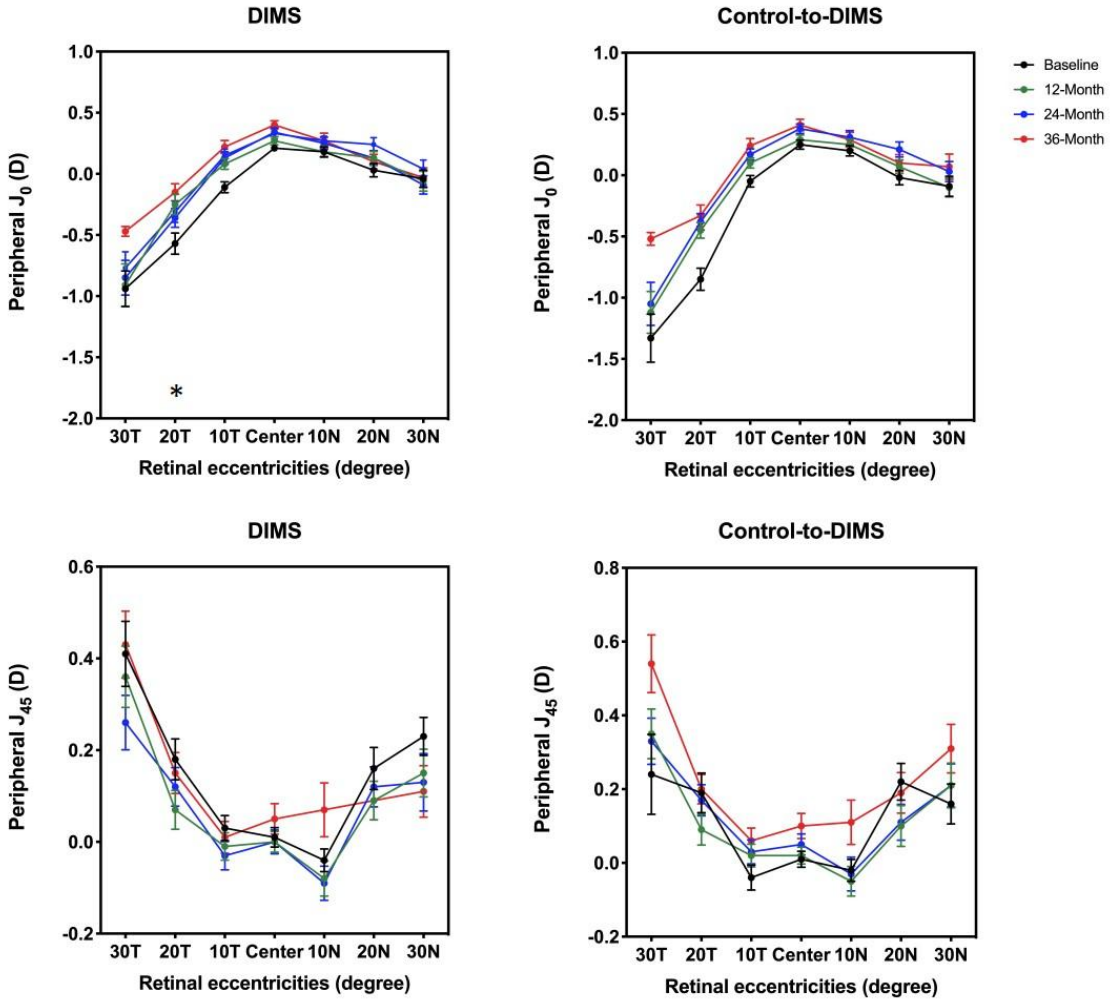



Figure 5- 17. Peripheral $J_0$ and $J_{45}$ in the third in DIMS and Control-to-DIMS group. The significance of the p-value was considered as less than 0.008 after the Bonferroni adjustment. *p<0.008 indicates the significant changes between 24-month and 36-month within the group.

### 5.6.1. Changes in RPR in DIMS and Control-to-DIMS group

For the subjects who completed all 3-year clinical trial over 2 years, the DIMS group showed stability in RPR without statistically significant changes in RPR at almost all retinal eccentricities (p>0.05). The only statistically significant changes in RPR were found at 10N (mean difference: 0.15±0.43 D, p=0.005), while it was not clinically significant. However, children who wore SV lenses showed asymmetrical changes in

RPR, with the statistically significant increase in hyperopic RPR at 10N (mean difference: 0.22±0.51 D, p=0.03), 20N (mean difference: 0.88±1.06 D, p<0.0001) and 30N (mean difference: 1.07±1.09, p<0.0001) (Figure 5-19 left). When the comparison between two groups, DIMS showed less hyperopic RPR at the nasal retina (mean difference at 10N:0.35±0.10, p<0.0001; 20N:0.78±0.19, p<0.0001; 30N:1.25±0.26, p<0.0001) compared to children who wore SV lenses.

In the third year, the RPR was found to be stable in the DIMS group. There were no statistically significant changes at almost all retinal eccentricities (p>0.05). Although the changes at 20N were 0.21±0.59 D, (p=0.005), it did not reach to a clinically significant level (Figure 5-18). Control-to-DIMS group showed decrease in hyperopic RPR at 10T (mean difference: -0.09±0.39, p=0.11), 20T (mean difference: -0.30±0.67, p=0.002) and 30T (mean difference: -0.18±1.12, p=0.29), 10N (mean difference: 0.05±0.54 D, p=0.48), 20N (mean difference: -0.25±1.10, p=0.11) and 30N (mean difference: -0.32±1.16, p=0.06) compared to 24-month, although only 20T reached statistically significant level after Bonferroni correction (p>0.008) (Figure 5-19 right).

In the third year, the changes of RPR in the Control-to-DIMS group showed a significantly more decrease in hyperopic RPR at 20N (mean difference: -1.14±1.93, p<0.0001) and 30N (mean difference: -1.07±1.17, p<0.001) compared to the first 2 years. There was no statistically significant difference in RPR changes between the

nasal retina and temporal retina in the third year (Figure 5-19 right).

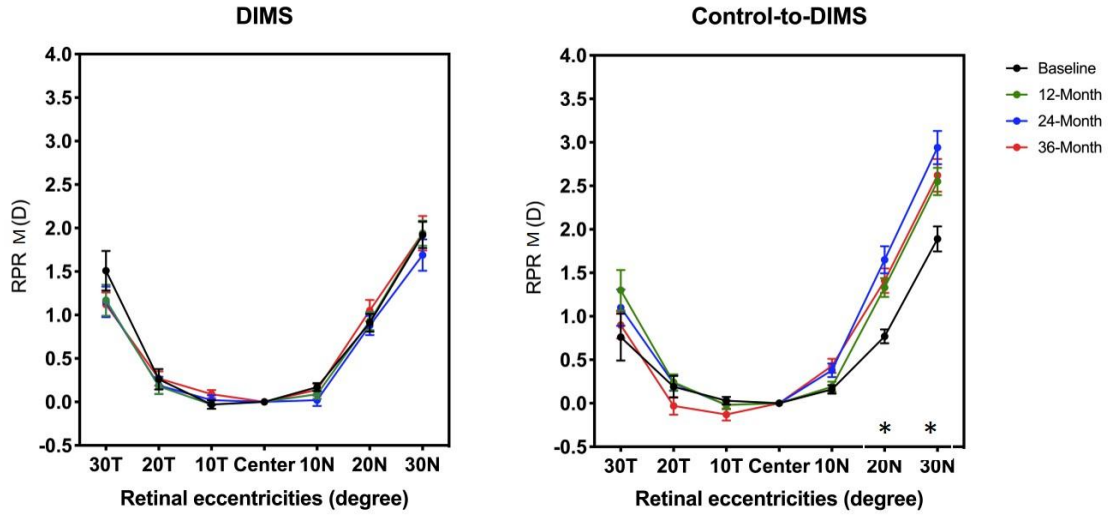



Figure 5- 18. Relative peripheral refraction in the third year.
The significance of the p-value was considered as less than 0.008 after the Bonferroni adjustment. * p<0.008 indicates the significant changes between 24-month and 36-month within the group.

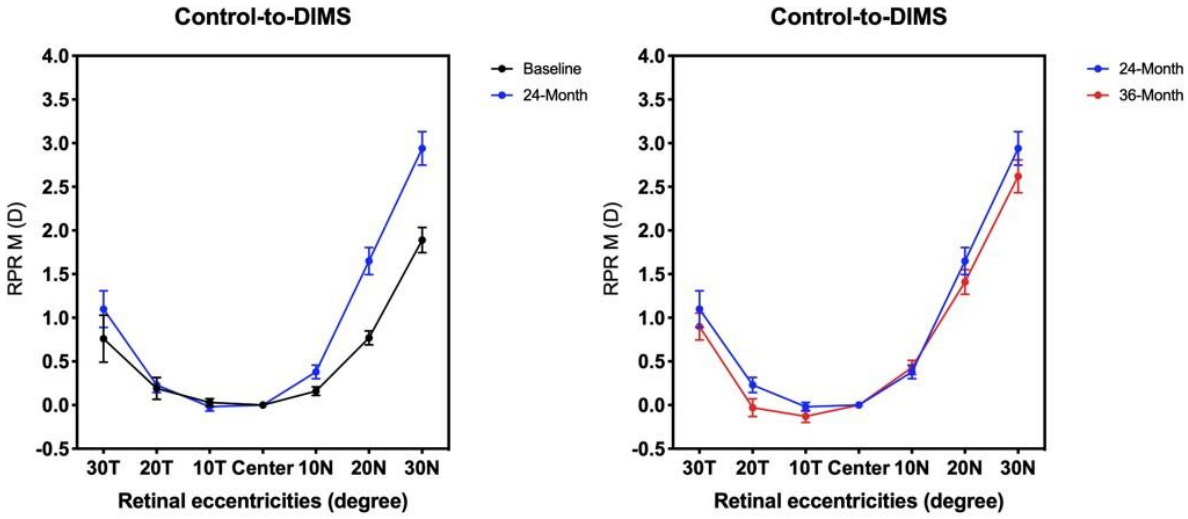



Figure 5- 19. RPR in the first 2 years (left) and in the third year (right) in the Control-to-DIMS group.

### 5.6.2. Relationship between initial RPR and myopia retardation

In the third year, Control-to-DIMS group showed a significant association between 24-month RPR (10N: r=0.40, p=0.004; 20N: r=0.48, p=0.001; 30N: r=0.43, p=0.001) and

myopia progression, as well as the axial elongation (10N: r=-0.31, p=0.02; 20N: r=-046, p=0.0130; 30N: r=-0.42, p=0.01) after adjusting for the initial SER at 24-month, age and sex (Figure 5-20, 5-21).

However, only the relationship between RPR at the nasal retina and myopia progression reached a statistically significant level ($p<0.0008$) after Bonferroni correction. According to the equations in Figure 5-20, if the RPR was greater than 0.31 D, 1.50 D and 2.85 D at 10N, 20N and 30N, respectively, these subjects did not show any myopia progression.

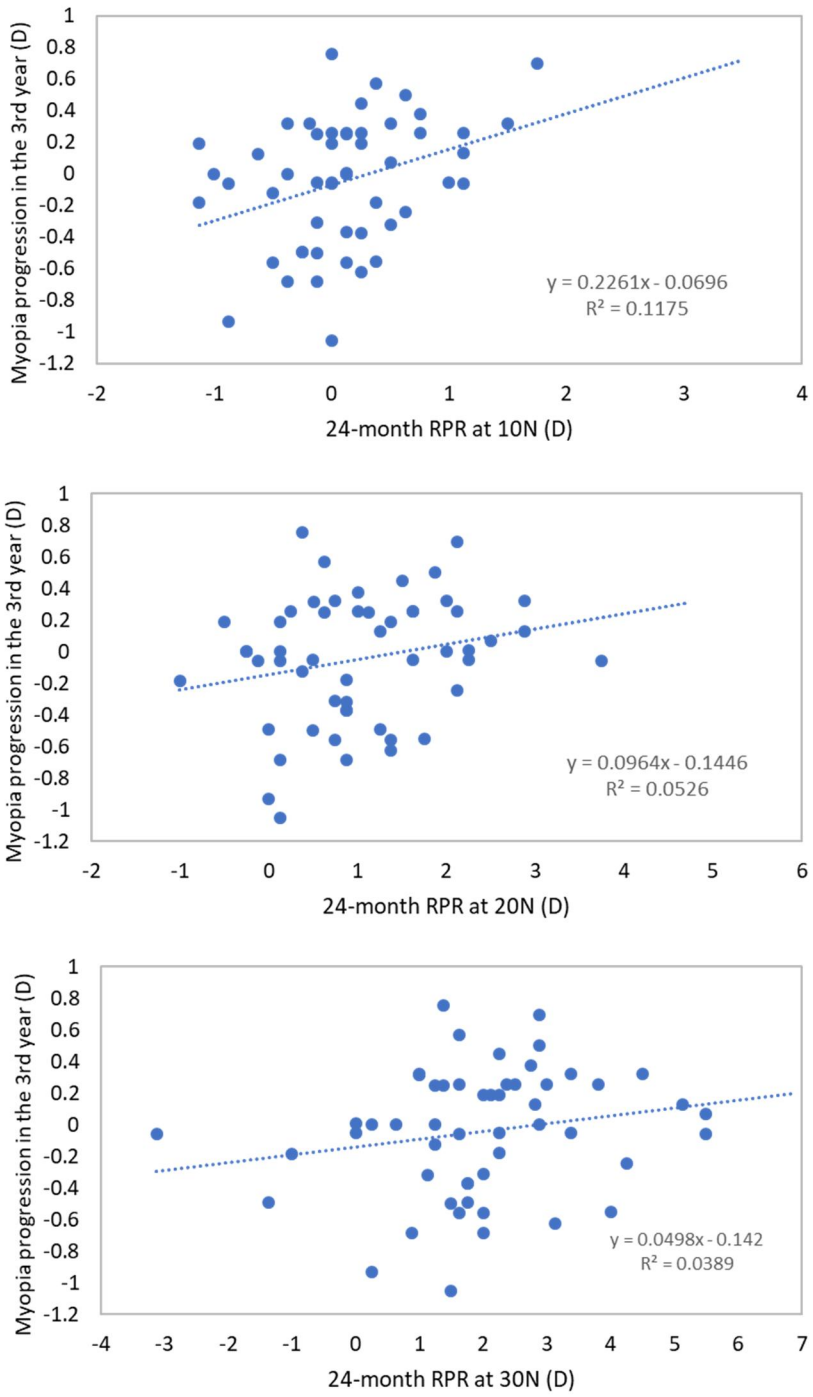



Figure 5- 20. Correlation between 24-month RPR at 10N, 20N and 30N with myopia progression in the third year after switched to wear DIMS lens in the Control-to-DIMS group.

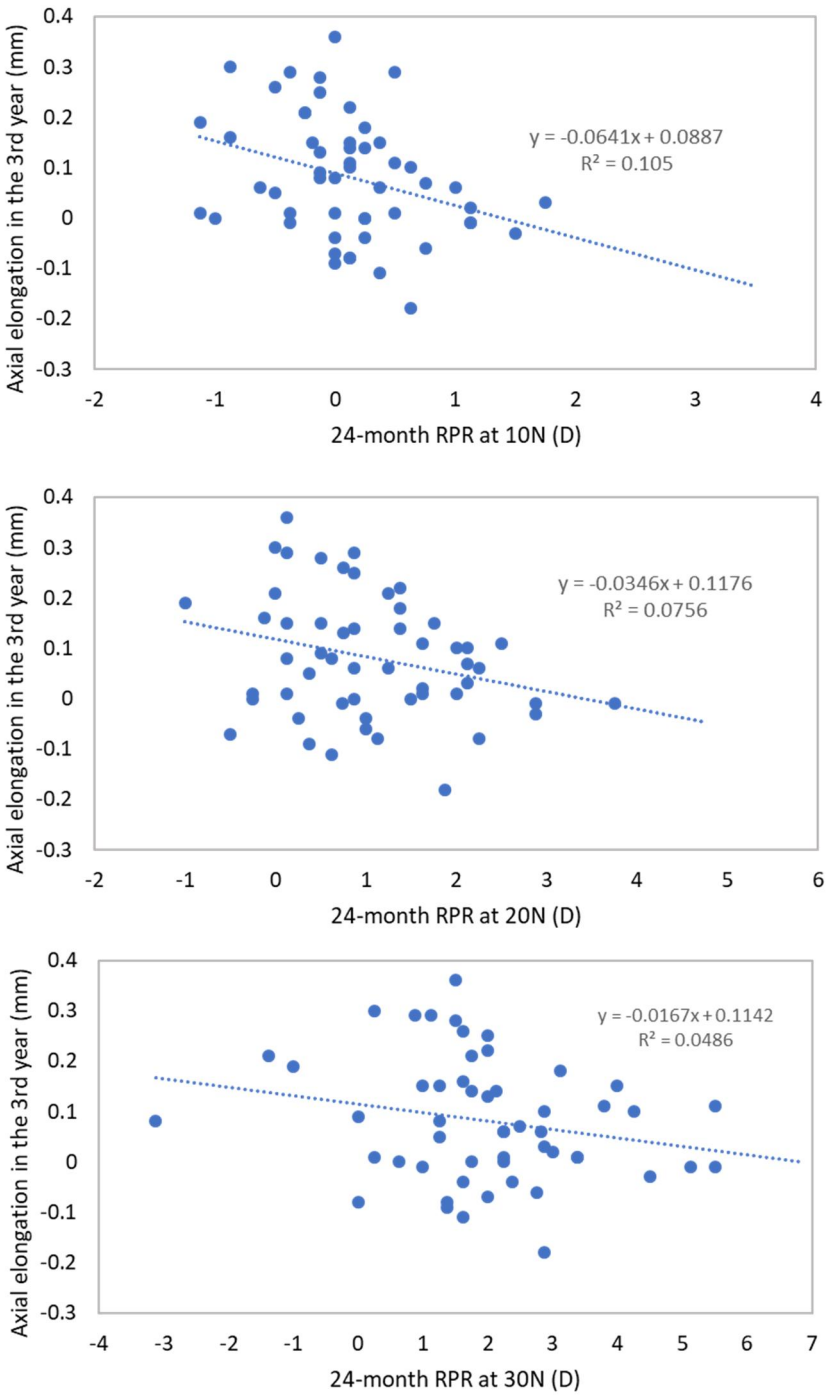



Figure 5- 21.Correlation between 24-month RPR at 10N, 20N and 30N with the axial elongation in the third year after switched to wear DIMS lens in the Control-to-DIMS group.

For the children in the DIMS group who completed 3-year study, the baseline RPR could even predict 3-year myopia progression (10N: r=0.38, p=0.002; 20N: r=0.35, p=0.007), and 3-year axial elongation (10N; r=-0.23, p=0.04; 20N: r=-0.23, p=0.04) while the influence in axial elongation did not reach a significant level Bonferroni correction (Figure 5-22). This may imply that a higher hyperopic RPR at baseline could benefit with better myopia control from wearing DIMS lenses. According to the equations in Figure 5-22, children with RPR greater than 0.74 D at 10N or greater than 2.17 D at 20N showed no myopia progression.

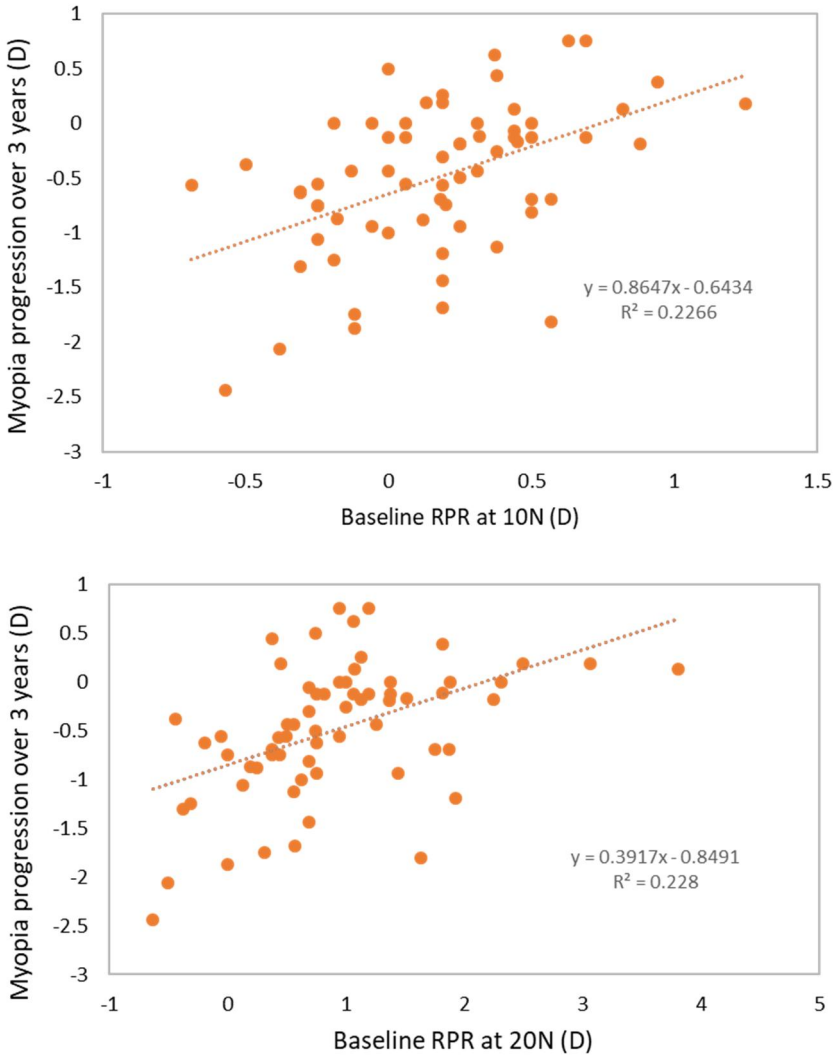



Figure 5- 22. Correlation between baseline RPR at 10N and 20N with myopia progression over 3 years in DIMS group.

### 5.6.3. Comparison between myopic RPR and hyperopic RPR subgroups

Subjects were subdivided into two subgroups according to their initial RPR (when tart to wear the DIMS lenses): myopic RPR (10N, 20N) and hyperopic RPR (10N, 20N) group. Myopia progression and axial elongation were further compared between myopic RPR and hyperopic RPR group within the Control-to-DIMS and DIMS group.

In the third year, in the Control-to-DIMS group, there was statistically more myopia progression (mean difference: -0.26±0.13 D, p=0.04) in the myopic RPR at 10N children (n=15) compared to hyperopic RPR at 10N children (n=36), while no statistically difference in the third year axial elongation (mean difference: 0.06±0.04 D, p=0.11). Also, no statistically significant difference in myopia progression (mean difference: -0.50±0.53 mm, p=0.51) and axial elongation (mean difference: 0.11±0.17 mm, p=0.65) between myopic RPR (n=2) and hyperopic RPR (n=51) groups at 20N.

Over 3 years, in the DIMS group, myopic RPR at 10N subgroup (n=32) showed statistically significant more myopia progression (mean difference: -0.62±0.18 D, p=0.002) and axial elongation (mean difference: 0.16±0.17 mm, p=0.03) than the hyperopic PRR at 10N subgroup (n=30). And myopic RPR at 20N subgroup (n=10) showed statistically significant more myopia progression (mean difference: -0.85±0.26 D, p=0.008) and axial elongation (mean difference: 0.21±0.09 mm, p=0.03) than the hyperopic PRR at 20N subgroup (n=50).

### 5.7. Summary of 3-year results on RPR

One hundred and eighty-three subjects were recruited, with 93 children allocated to DIMS group and 90 children allocated in the SV group. One hundred and sixty children completed the first 2-year RCT study. After 2 years, the DIMS group (n=79) showed significant retardation of myopia progression of −0.55±0.09 D ($p<0.0001$) (59%) and slowing of axial elongation by 0.32±0.04 m ($p<0.0001$) (60%) compared to SV group (n=81).

As there was no significant difference in baseline peripheral refraction between DIMS and SV group, we described the RPR profile of all 160 subjects together to determine the characteristic of the RPR among myopic children in this age group. Hyperopic RPR was observed at most eccentricities across the horizontal retina, and it increased with the increase in eccentricity. A broad range of hyperopic RPR was present at 30N, which ranged from 0 to 6 D. More hyperopic RPR at nasal retina than temporal retina was observed, with the mean difference of 0.17±0.63 D ($p=0.001$), 0.65±1.21 D ($p<0.0001$) and 0.84±1.68 D ($p<0.0001$) at 10˚, 20˚ and 30˚ of the retina, respectively. In the DIMS group, initial RPR in the nasal retina were positively associated with myopia progression (10N: $r=0.36$, $p=0.001$; 20N: $r=0.35$, $p=0.001$) and negatively associated with axial elongation (10N: $r=-0.34$, $p=0.001$; 20N: $r=-0.29$, $p=0.006$). However, no significant association between baseline RPR and myopia progression was found in the SV group.

The comparison of changes in RPR indicated a different pattern of eyeball expansion between the DIMS and the SV group. Over the first 2 years, the DIMS group showed myopic shifts in all retinal eccentricities, with a similar amount of myopic shifts between nasal and temporal retina. SV group showed asymmetrical peripheral myopic shifts between the nasal and temporal retina, with more myopic shifts at 10T (-0.32±0.62 D, $p \leq 0.0001$), at 20T (-0.69±0.95 D, $p \leq 0.0001$) and 30T (-0.85±1.52 D, $p \leq 0.0001$). There was no significant difference in peripheral $J_0$ nor peripheral $J_{45}$ between the two groups after 2 years nor over the first 2 years. No significant changes in RPR were noted in the DIMS group, which indicated uniform eye growth. In contrast, significant hyperopic shifts in RPR were found at the nasal retina (10N: 0.27 ± 0.45 D; 20N: 0.75 ± 0.72 D; 30N: 0.98 ± 0.76 D, all $p<0.0001$) in the SV group, which reflected a skewed eye growth pattern.

In the third year, 65 subjects in the DIMS group and 55 subjects in the Control- to-DIMS group completed the post-1-year follow-up. There were no significant differences in myopia progression and axial elongation between the Control-to-DIMS group and the DIMS group in the third year. DIMS group showed no significant changes in peripheral refraction at the majority of retinal eccentricities. Thus RPR was stable. However, Control-to-DIMS presented symmetrical myopic shifts in the peripheral retina in the third year, which was different from previous 2 years. Control-to-DIMS showed a reduction in hyperopic RPR. For the children in the DIMS group who completed the 3-year study, the baseline RPR could even impact 3-year myopia

progression (10N: r=0.38, p=0.002; 20N: r=0.35, p=0.007). That means a higher hyperopic RPR at baseline could benefit more from myopia control by wearing DIMS lenses. In the third year, Control-to-DIMS group showed a significant association between 24-month (the time start to wear DIMS lenses) RPR (10N: r=0.40, p=0.004; 20N: r=0.48, p=0.001; 30N: r=0.43, p=0.001) and myopia progression.

# Chapter Six: Discussion and conclusion

## 6.1. The DIMS lens

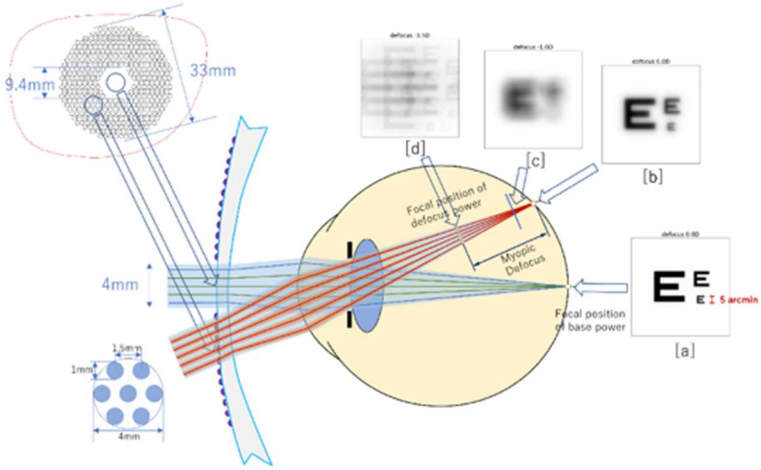
In the design of the DIMS lens as a myopia control spectacle lens, the principle of simultaneous vision was applied; that is, the lens provides myopic defocus and corrects refractive error simultaneously. It gives clear vision at all distances. At the mid-periphery of the DIMS lens, there are around 400 with 1 mm in diameters lenslets of +3.50D, surrounding the central zone of 9.4 mm in diameter. This central zone is for distance correction (Figure 6-1). The total area between the two powers zones is about a 50:50 ratio. The purpose of this ratio was to ensure that distance vision will not be degraded too much while myopic defocus can have a sufficient effect on slowing myopia progression.

This design is different from the PALs and bifocal type of spectacle lenses, although both lens types provide a hyperopic addition to the refractive correction. The multiple segments in the DIMS lens are not for seeing clearly; in fact, they form a constant blur overlapping with the clear vision. The degree of blur depends on the viewing direction and also the distance of the viewing target.

The optical and imaging properties of DIMS lens have been measured by high-resolution aberrometry objectively. Jaskulski et al. (Jaskulski et al., 2020) reported that the images produced by the multiple segments region were blurry. Therefore, myopes could not use the add power to focus the near targets. Such design could lead myopes to

keep looking through the central optical zone, and the myopic defocus through the multiple segments could be formed in the peripheral retina. The importance of the peripheral retina in eye growth has been explained in Chapter 3.

It has been tested by real light tracing that viewing an object through the lens's central region leads to a clear image without ghosting. Observing a target through the lens's peripheral region produces a ghosting image, which is influenced by the relative refractive error at the retina (Figure 6-1 [c], [d]) (Lam et al., 2020b). The image quality in the peripheral retina would be affected by the peripheral myopic defocus while fixating straight ahead. When the eye moves away from the central zone and looks through the peripheral parts of the lens, both the central and peripheral retina will perceive the myopic defocus from the multiple segments. Figure 6-1 shows the different peripheral regions of the retina while viewing targets from various distances without accommodation.




Blue rays represent ray traces from the central (carrier) part of the lens and forming a clear image on retina [a] and the red rays show ray traces from the peripheral part of the lens, which contains the lenslets, forming an image that is simultaneously refracted by both the base part and lenslets [b]. If the target is at near and the eye does not accommodate, the image [c] or [d] will be formed on retina. The smallest Snellen chart in each image in the figure has the size of 5 arcmin which indicates VA 0.0 logMAR (20/20). Other two charts indicate VA +0.30 logMAR (20/40) and +0.50 logMAR (20/80), respectively. All images were generated using real ray tracing and wave optics calculations. Viewing an object through the central part of the lens produces a clear image with no ghosting. Viewing a target through the peripheral part of the lens leads to ghosting depending on the relative refractive error at the retina as described in [c] or [d].

Figure 6- 1. Basic structure and design of the DIMS lens. (Adapted from *Lam et al., Transl Vis Sci Technol, 2020.*)

### 6.1.1. Visual functions performance and changes

Several visual functions have been tested at baseline and the end of the 2-year RCT. These included high and low contrast visual acuity at both distance and near. At baseline, no statistically significant difference in these visual functions was found between the DIMS and SV lens wearers.

After 2 years, DIMS lens wearers had slightly better stereopsis than the SV group, but this difference did not reach to a clinically significant level (Lam et al., 2020b).

Children in DIMS groups had statistically significant improvements in high contrast VA with nearly one line of letters after 2 years. A similar significant increase in high contrast VA (almost one line of letters) was also observed in children in the SV group. The potential reason for the improvement in high contrast VA could be that the subjects get to familiar with the data collection process (Lam et al., 2020b). However, we did not observe significant improvements in distance low contrast VA, near high contrast VA, or low contrast VA in either group of children. The order of VA measurements was from distance high contrast VA and then undertaking other VA tests. Children may be tired and bored during the whole VA tests, which limited the increases in VA in both DIMS and SV group (Lam et al., 2020b).

Children in either DIMS or SV group showed a reduction in amplitude of accommodation and lag of accommodative after 2 years, which might be because of the increase in age (Castagno et al., 2017). Overall, the binocular functions in DIMS and SV group were similar after 2 years.

In addition, Lu et al. (Lu et al., 2020) reported good tolerance and acceptance of DIMS lenses in Chinese children. Similar to our current findings, they did not observe a significant difference in central VA between DIMS and SV wearers. However, they found a significant mid-peripheral blurred vision reported only once or twice per day. After being notified of the myopia control efficacy by DIMS, 90% of children would like to wear the DIMS lenses and not be bothered by the slight blur at mid-periphery.

In summary, the DIMS lens is a first-of-its-kind spectacle lens that is specially designed for myopia control. The blur peripheral vision from the lenslets is not for seeing but projects constant myopic defocus in the peripheral retina. There may be comprised in vision quality as only around 50% of the light is contributed for vision correction. The slight drop in visual acuities is clinically negligible. There was no adverse effect on any of the visual functions.

### 6.2. Subjects and study design

The myopia control efficacy of the DIMS lenses was studied for a period of 3 years. The first 2-year study was a double-masked RCT, and subjects were randomly allocated to wear DIMS or SV lenses. Children who completed the 2-year RCT study were invited to join the third-year follow-up, and all children were assigned with DIMS lenses (see **Section 6.6**.). The design of the study followed the consolidated standards of reporting trials (CONSORT) statement.

Follow-up of participants after randomised trials allows monitoring the participants' condition over time after the intervention. There could be several important reasons to conduct follow-ups after trials, such as further evaluating the endpoint, reviewing new developments, consider any wash-out effect, or fulfilling a research promise. It is the case to fulfil a research promise for the DIMS lens trial that at the start of the trial, participants were informed that if the treatment were found effective, the control group of children would be offered the treatment lens. Post-trial follow-up further informs or

defines the effect of an intervention long-term and ascertains the safety profile and outcomes.

At the start, 183 Chinese myopes were recruited. Among that, 93 children aged 10.19±1.46 years were allocated to DIMS group, 90 children aged 10.01±1.44 years were assigned to the SV group (Table 5-1). After 2 years, 79 children in DIMS group and 81 children in the SV group completed the RCT study (Table 5-1). The drop-out ratio was 15% and 10% in DIMS and SV group, respectively. The general reasons for drop-out were a long time to wait for delivery of lenses, refuse to undergo cycloplegia, try other myopic control methods, not willing or unable to attend follow-up.

Compared to other studies, this study showed good compliance and less drop-out rate. In an RCT study, which investigated the myopia control efficacy using Defocus Incorporated Soft Contact (DISC) contact lenses, a high drop-out rate (42%) was reported (Lam et al., 2014). It has been found that the lack of motivation to wear contact lenses in the first year was the major cause (Lam et al., 2014). In the OK lens studies, the drop-out rate was from 6% to 30% (Walline et al., 2009; Cho and Cheung, 2012; Santodomingo-Rubido et al., 2012b), and the causes could be ascribed to ocular health, unsatisfactory myopia reduction, or poor lens fitting. The spectacle lens is more convenient and easily adapted by young children. It is worthy to note that maintaining a lower drop-out ratio is essential for a clinical trial to attain a representative outcome, and the intervention could be well accepted.

### 6.3. Myopia control efficacy of the DIMS lens – 2-year RCT

The main findings of the 2-year RCT have been reported in 2020 (Lam et al., 2020a). After model adjustment of factors related to myopia progression, adopting GEE for handling missing data, myopia progression was -0.41D in the DIMS group versus -0.85D in the SV group for all enrolled subjects. (Table 5-8). A similar trend has shown in the AL changes over the 2 years. The DIMS lens wears had a slower myopia progression by 52% and a less axial elongation by 62%. The DIMS lens showed better myopia control efficacy than other methods such as PALs, bifocal or multifocal spectacle lenses, and multifocal contact lenses (see Chapter 2) and are comparable to OK lenses and atropine methods.

Most studies suggested that the myopia retardation by PALs is clinically insignificant (Hasebe et al., 2008; Yang et al., 2009). In Edwards et al. 's study (Edwards et al., 2002), the myopia progression by PALs and traditional spectacles for 2 years were evaluated; the results showed that although wearing PALs could retard myopia progression and slow axial elongation statistically significant, but it was not clinically significant. Likewise, only a small and statistically significant effect was found in the first year in the Correction of Myopia Evaluation Trial (COMET) study (Gwiazda et al., 2003) and a Japanese study (Hasebe et al., 2014).

Multifocal soft contact lenses, which are designed to counterbalance the relative peripheral hyperopic defocus, have also been promoted for myopia control. In Walline's study, children aged from 8 to 11 years old were recruited into a 2-year study

to investigate the efficacy of CooperVision Proclear Multifocal lenses (centre D design) (Walline et al., 2013). The lenses had a distance correction optical zone in the centre and surrounded with an aspheric zone of progressive additional power up to +2.00 D. After 2 years, children with Proclear Multifocal lenses showed a 0.52 D (50%) retardation in the myopia progression and a 0.12 mm (29%) decrease in axial elongation compared to a historical SV contact lenses group (Walline et al., 2013). Similarly, Lam et al. (Lam et al., 2014) reported statistically significant myopia retardation of slower myopia progression by -0.20 D (25%) compared to the SV group over 2 years. And the myopia control efficacy was up to 60% (less myopia progression of -0.54 D) for those children who worn the lenses for more than 7 hours per day. Aller et al. (Aller et al., 2016) investigated 8- to 18-year children with esophoria who wore distance centre concentric soft contact lenses (Visakon Acuvue Bifocal) compared to SV lenses (Vistakon Acuvue 2). Children who wore concentric multifocal soft contact lenses showed less of -0.57 D (72%) myopia progression and less of 0.19mm (80%) axial elongation than the SV wearers over 2 years. They reported one of the most significant myopia control efficacies compared to other studies but only for children with eso fixation disparity at near (Aller et al., 2016).

The myopia control efficacy in OK lenses was comparable with DIMS lenses. A 2-year RCT study reported significant retardation in axial elongation by 0.27 mm (43%) in low and moderate myopes than the control group (Cho and Cheung, 2012). Charm et al. (Charm and Cho, 2013) reported the partial reduction of OK lenses (target reduction of 4.00 D) in high myopes slowed down by 0.32 mm (63%) axial elongation compared to

the control group over 2 years. The traditional OK lenses were spherical design which fitted children with less astigmatism, and the toric lenses have been designed for high astigmatism with the development of the instrument. Myopia Control Using Toric Orthokeratology project investigated the efficacy of a new designed toric OK lens in myopic children with low to moderate myopia and -1.25 to -3.50 D with-the-rule (WTR) astigmatism(Chen et al., 2013). After 2 years, children with toric OK lenses showed 0.33 mm (52%) less axial elongation than children with SV spectacle lenses.

Low dose 0.01% atropine was one of the most effective methods in retarding myopia progression, while less side efficacy and less myopia rebound after ceasing atropine treatment (Chia et al., 2016). Also, recent studies indicated that the combination of OK lenses and atropine had better myopia control efficacy than monotherapy, but long-term studies were needed (Kinoshita et al., 2018).

Each myopia control method has its strengths and weakness, and we have illustrated in **Chapter 2**. Nevertheless, the DIMS lens showed substantial myopia retardation compared to other optical or pharmacological methods regarding the myopia control efficacy in refractive error or axial length. There is potential in adopting the DIMS lens technology to further investigate the different myopic defocus powers or combinations with other therapies to assess the myopia control efficacy.

Changes related to the refractive error and axial length, and other visual parameters have been described, discussed, and published (Lam et al. 2020a &b). We have emphasised that this thesis investigates the role of relative peripheral refraction on

myopia control with the DIMS lens. The following sections cover the peripheral refraction and RPR changes and examine its general profile, association with other parameters such as age, sex, and myopia at baseline and progression, as well as its influence when DIMS lens is used for treatment. It is hoped that understanding these consistent phenomena will provide more information on how myopic defocus interacts with the retinal shape and understanding of myopia control mechanisms with the DIMS lens.

### 6.4. Peripheral refraction in the 2-year RCT

The main findings of the 2-year RCT peripheral refraction changes have been reported in 2020 (Zhang et al., 2020). At baseline, there was no significant difference in peripheral refraction between the DIMS and SV groups, while they showed a quite different pattern of peripheral myopic shifts over the 2-year RCT.

In the SV group, myopic shifts were observed in the temporal retina at every 6-month follow-up visit (range from -0.07 D to -0.37 D) (Figure 5-6). Over 2 years, significant myopic shifts in the temporal retina and 10N were found, with the range of -0.60 to -0.90 D (Figure 5-6). However, no myopic shifts were observed in most nasal retina. Such asymmetry increased during the progression of myopia and was echoed with previous authors (Atchison et al., 2005b; Lee and Cho, 2013). Some studies suggested that this asymmetry can be explained by a combination of several factors, consisting of angle alpha (difference in angle between the optical axis and visual axis) (Calver et al., 2007; Charman and Atchison, 2009), asymmetries in vitreous chamber depth (Smith et

al., 2013b) and corneal curvature (Atchison et al., 2006). The increased asymmetrical peripheral profile has also been presumed as a result of different rates of eyeball expansion along the axial and equatorial regions during myopia progression and especially in eyes with rapid myopia progression (Lee and Cho, 2013).

In contrast, children in the DIMS group displayed myopic shifts at all peripheral retinal eccentricities at every 6-month follow-up visit (range from -0.03 D to -0.30 D) (Figure 5-6). Over 2 years, statistically significant myopic shifts were found in all peripheral retina eccentricities, with the range of -0.30 to -0.60 D. Thus, children using DIMS lenses had uniform myopic shift manner along the horizontal retina.

Referring to peripheral astigmatism, there was no significant difference in peripheral $J_0$ between DIMS and SV group at baseline (Figure 5-7). They presented positive $J_0$ at the centre, while negative $J_0$ at the periphery, indicating the myopic children showed WTR astigmatism in the centre while showing against-the-rule (ATR) astigmatism in the periphery. We found that the magnitude of peripheral astigmatism exhibited a considerable variation (reaching as high as around 9.00 D at 30T) (Figure 5-7), which was also observed by other authors (Atchison et al., 2006; Lee and Cho, 2013). Over 2 years, both groups showed similar positive shifts in peripheral $J_0$, with less than 0.50 D shifts in $J_{0,}$ inferring a reduction in peripheral ATR astigmatism. No significant difference in peripheral $J_0$ was shown between the DIMS and SV groups after 2 years. Peripheral $J_{45}$ maintained stability in both groups, without significant changes within

each group over 2 years. Therefore, myopia control using myopic defocus might not influence peripheral astigmatism.

In conclusion, DIMS wearers had less myopia progression compared to SV wearers, and myopic shifts were observed in all peripheral retinal eccentricities. However, SV wearers showed peripheral myopic shifts at only the temporal retina and 10N. It could be assumed that eye growth was relatively slower and uniform in DIMS group children. In comparison, the eye growth was relatively faster in the axial expansion than in the equatorial region in the SV group children.

### 6.5. RPR in the 2-year RCT

The main findings of the 2-year RCT RPR changes have been reported in 2020 (Zhang et al., 2020). Over 2 years, changes in RPR were also different between the DIMS and SV groups.

In the SV group, the statistically significant increase in hyperopic RPR at the nasal retina (ranging from around 0.27 D to 0.98 D) (Table 5-11) was found over 2 years, which presented an asymmetrical pattern of RPR profile at 24-month. In contrast, RPR was just a slightly statistical change in the DIMS group, but it was not clinically significant; therefore, the RPR profile kept stable in the DIMS group over 2 years.

To the best of our knowledge, this is the first human study to report the changes in RPR after myopia control using myopic defocus. Among animal studies, contradictory findings have been reported from a guinea pig study (Bowrey et al., 2017); there was a

significant increase in hyperopic RPR after superimposing myopic defocus in the periphery. It was suggested that there might be an area of the retina that can decode signs of defocus and result in local retinal area changes; such an ability to decode depends on the area or threshold of the defocus, which may be different in humans compared with other animals (Bowrey et al., 2017).

RPR has been suggested to indirectly describe the retinal shape (Stone and Flitcroft, 2004; Verkicharla et al., 2012). A higher hyperopic RPR suggested a less curved image shell compared to the retinal shape (Shen et al., 2010), and when corneal curvature and AL are constant, a higher hyperopic RPR indicated a steeper retinal shape (Verkicharla et al., 2012). This suggested that the image shell with a reduced curve compared to the retinal shape of the SV group indicated a steeper retinal shape, while there was a flatter retinal shape in the DIMS group.

### 6.5.1. Asymmetry in RPR

With respect to the asymmetrical changes in peripheral refraction of the SV group, the mechanism of the inhibited peripheral expansion in the SV group remained unclear, and several potential mechanisms have been discussed in a previous study by Mutti et al. (Mutti et al., 2007). They considered that insufficient lens material might prevent the eye from stretching equatorially as the eye grows (Mutti et al., 2000; Mutti et al., 2007). In this study, retardation of myopia progression and axial elongation in the DIMS group may be elucidated as switching back to coordinated eye growth. On the other hand, the faster increase in axial elongation than the equatorial region in the SV

group may express non-coordinated eye growth. It has been suggested that equatorial restriction of the growing eye has the potential to accelerate axial elongation (Mutti et al., 1998).

Pan et al. (Pan, 2019) suggested that the signalling of ON-OFF retinal ganglion cells (RGCs) in the mouse retina could be altered by the defocused image and displayed different responses to various power of defocus image (Banerjee et al., 2020). It could be possible that the RGCs signal might be changed due to the defocus stimulation in the DIMS lens, producing the uniform and symmetrical pattern of peripheral refraction changes. However, further work to relate to the human eye is also needed.

### 6.5.2. RPR in Chinese myopic children

As the different pattern in RPR changes was observed between the two groups, we further evaluate the baseline RPR to determine if the RPR may be associated with myopia control efficacy using myopic defocus.

At the start of the study, hyperopic RPR was observed in myopic children, and the magnitude of hyperopic RPR increased with increasing eccentricities in both DIMS and SV groups; it was around 0 at the near periphery and increased to around 1.80 D to the mid-periphery. As no significant difference in RPR between DIMS and SV group showed at baseline, we described and analysed the RPR profile of both groups together for a bigger sample population. For all children who completed the 2-year RCT study, the baseline RPR was -0.03±0.38 D at 10T and 1.03±1.60 D at 30T. Similarly, in the nasal retina, it was 0.15±0.39 D at 10N and 1.87± 1.81 D at 30N. Hyperopic RPR was

found in both temporal and nasal sides. The high standard deviation of RPR inferred a broad range of RPR among these children; we found that some children had hyperopic RPR of 6 D.

Previous studies also suggested that myopic children generally showed hyperopic RPR (Mutti et al., 2000; Atchison et al., 2004; Atchison et al., 2006; Chen et al., 2010; Kang et al., 2010; Sng et al., 2011a; Li et al., 2015b). In a study among 250 Singaporean Chinese children aged from 40 to 190 months, myopic children presented hyperopic RPR, while hyperopic and emmetropic children showed myopic RPR (Sng et al., 2011a). Children in the moderate and high myopia group had hyperopic RPR at all eccentricities, and low myopic children showed myopic RPR at 15˚ of the visual field. They separated these children into two age groups, younger than 72 months and older than 72 months. We compared the RPR profile between our current children (age from 8 to 13 years, mean myopia was -2.87 D) and their older than 72 months group (6 years to 15.83 years, mean myopia was -2.50 D). Similar to our current findings, they presented an increasing trend of hyperopic RPR with eccentricities, but the magnitude of hyperopic RPR was less than our study. They reported RPR was only 0.50 D to 1.00 D at mid-periphery, while our study showed the RPR ranged from 1.00 D to around 2.00 D at mid-periphery. They showed less hyperopic RPR might because they investigated children from different refractive statuses, and the mean value of RPR might be reduced by the myopic RPR from emmetropes and hyperopes. As they did not separate the RPR of myopes into a different group, we could not make a further comparison.

In the OLSM study, 822 children aged 5 to 14 years and with different ethnicities (Caucasians, Asian-American, African-American, and Hispanic) were recruited (Mutti et al., 2000). Emmetropic and hyperopic children had myopic RPR while myopic children (mean myopia: -2.84±2.09 D) had hyperopic RPR (0.80±1.29 D) (Mutti et al., 2000). However, only the 30˚ of the nasal visual field (corresponding to 30 T retinal eccentricity) was measured in that study; the RPR across the horizontal retina was not described (Mutti et al., 2000). When compared to Mutti's result, a similar hyperopic RPR (1.03± 1.60 D) at 30T of retinal eccentricity was noticed in our current results.

Another Chinese study investigating children aged 8 to 12 years old reported that children with moderate myopia (mean: -4.09 ± 0.81 D) showed less than 1 D of hyperopic RPR at the 30º retina area (Chen et al., 2010); their study suggested that children with higher myopia presented a higher hyperopic RPR than those with lower myopia. However, the opposite was observed in our current study. We found the children in our study of similar age as in their study showed higher RPR even though our group of children had less myopia than theirs.

Our findings also indicated that the RPR profile in myopic children was asymmetric with more hyperopic RPR at the nasal retina than the temporal retina; such asymmetry was also reported by previous studies (Lee and Cho, 2013) and our study (Zhang et al., 2020). In addition, the reason for the asymmetrical profile may be angle alpha (Calver et al., 2007; Charman and Atchison, 2009), asymmetries in eyeball structure (Smith et al., 2013b) (see **Section 6.4.**)

Our findings also suggested that there was no significant association between PRR with either age or sex ($p>0.05$) (Table 5-5), which was consistent with other studies (Atchison et al., 2005b; Mutti et al., 2011).

Summarising the results from our and other studies, myopic children showed different RPR compared to emmetropic or hyperopic children. Ethnic differences and degree of myopia were also found to show varying magnitudes of RPR. There was obvious asymmetry in RPR between the nasal and temporal retina.

### 6.5.3. RPR and myopia control efficacy in the 2 years RCT

We tested the relationship between RPR and myopia progression in the SV group by multiple linear regression, and there was statistically significant but weak relationship between baseline RPR with myopia progression ($p<0.008$) and no statistically significant relationship with axial elongation over 2 years ($p>0.008$) after Bonferroni correction (Figure 5-11& 5-12). Baseline RPR at nasal retina only influenced less than 10% of myopia progression variation among the SV wearers ($R^2 <0.10$). These findings were in agreement with previous studies (Mutti et al., 2011; Sng et al., 2011b; Lee and Cho, 2013; Radhakrishnan et al., 2013; Atchison et al., 2015). Mutti et al. (Mutti et al., 2011) investigated the changes in peripheral refraction at 30° of nasal visual field, and they pointed out that peripheral refraction exerted a weak influence on predicting myopia onset or progression. Atchison (Atchison et al., 2015) investigated emmetropic, hyperopic and myopic children, and found that although myopes with myopic RPR at baseline were associated with more myopia progression, emmetropes with myopic RPR at baseline still remained emmetropic after the study (Sng et al., 2011b; Atchison et al.,

2015). They suggested that myopia development was associated with the changes from myopic RPR in emmetropes and hyperopes to hyperopic RPR in myopes during eyeball stretching. RPR may not be a trigger of myopia progression (Hoogerheide et al., 1971; Mutti et al., 2007) but a consequence of myopia as the eyeball becomes more prolate during axial elongation (Atchison et al., 2006).

We further divided subjects according to their RPR at baseline into myopic RPR and hyperopic RPR subgroup. Since there were no statistically significantly relationships between RPR at temporal retina with either myopia progression or axial elongation, and RPR at 30N only had less than 5 subjects with myopic RPR, we subdivided all children according to their RPR at 10N and 20N. In the SV group, no statistically significant difference in myopia progression and axial elongation between myopic RPR and hyperopic RPR at 10N and 20N subgroups were observed. Such findings reinforced the weak influence of baseline RPR in normal myopia development.

In the DIMS group, a significant positive association between baseline RPR and myopia progression and a negative relationship between baseline RPR and axial elongation was noted (Figure 5-11& 5-12). The more myopic RPR at baseline, the more myopia progression was found in DIMS group. Children with myopic RPR were found not to have the same myopia control efficacy as those with hyperopic RPR. Theoretically, the initial RPR profile superimposing with myopic defocus (+3.50 D) from DIMS lenses will have different residual defocus perceived by the retina. For the hyperopic RPR at mid-periphery children, the defocus power will counterbalance initial

hyperopic RPR, therefore, less than 3.50 D myopic defocus will be perceived by the retina. But for a myopic RPR children, the existed myopic RPR combined with 3.50 D myopic defocus will lead to more myopic defocus perceived by the retina.

Berntsen et al. (Berntsen et al., 2013) studied whether peripheral defocus was associated with myopia progression. They pointed out that although peripheral myopic defocus was associated with less myopia progression, higher peripheral myopic defocus did not slow myopia progression as well when compared with that lower peripheral myopic defocus. A study with guinea pigs found that when imposing +4 D peripheral myopic defocus lenses, the myopia progression and axial elongation were actually enhanced (Bowrey et al., 2017). They suggested the retinal area was able to decode whether it was a clear or blur signal. If the defocus was above the threshold of signal detection, the decoding function will fail and might lead to myopia progression (Bowrey et al., 2017), similar to lens deprivation in animal studies. The depth of focus (DOF), which could represent the threshold of blur detection, has been investigated in a human study. It has been reported that DOF increased with the eccentricities (Wang and Ciuffreda, 2004), and DOF could reach as high as ±6 D in the mid-periphery (Wang et al., 1997). However, more repeatable studies are needed to confirm the suggestion. If the dosage of peripheral myopic defocus is adequate to counterbalance the existing hyperopic RPR, myopia control efficacy can be achieved. For those having myopic RPR, when receiving a dosage of peripheral myopic defocus, the overall higher amount of myopic defocus will be beyond the threshold of signal detection, then

myopia control would be less effective and may have ended up with more myopia progression.

Therefore, myopic RPR children may receive the too much of myopic defocus and showed less myopia control effects. Therefore, magnitude and direction of RPR may partially explain why myopia control efficacy varied among children.

Referring to the 8- and 9-year-old children, they showed faster myopia progression and unsatisfactory myopia control effects in the DIMS group in the first 2 years (Figure 5-5). However, in the SV group, no statistically significant relationship between age and myopia progression. In addition, the unsatisfactory myopia control effects by DIMS lenses in 8-and 9-year-old group, were irrelevant to lag of accommodation, initial myopia or parental myopia (Lam et al., 2020a) but because of the baseline RPR profile. In the DIMS, baseline RPR were different among the ages. The younger age children had myopic RPR or small amount of hyperopic RPR, while older age group had higher hyperopic RPR (Figure 5-4). Therefore, the unsatisfactory myopia control effects the younger children may because they receive too much of myopic defocus.

As indicated from the equation in Figure 5-11, $R^2$ in the DIMS group was around 0.15 to 0.20. Therefore, baseline RPR could only explain 15% to 20% myopia progression and axial elongation in the first 2 years. It is worth noting that other factors could also influence myopia control efficacy.

Notably, such a relationship between RPR and myopia control efficacy was only found within 20° of the nasal retina in the DIMS group. There have been suggestions that the

nasal retina is more sensitive to defocus signals to slow eye growth (Faria-Ribeiro et al., 2013; Smith et al., 2013b), and there was a study that reported that the influences of myopic defocus on refractive progression was reduced with eccentricity (Smith et al., 2020). In Smith et al. study (Smith et al., 2020), rhesus monkeys in the experimental group were imposed with concentric lenses designed with plano power in the centre and surrounded by alternating with annular +3 D and plano power. The control group was reared with +3 D SV lenses. The only difference in the experimental lenses was the central diameter, which was 2mm, 4mm, 6mm and 8mm, such design leads to the light passing through simultaneous myopic defocus beyond 11°, 16°, 19°, and 23° of retina respectively (Smith et al., 2020). At the end of the study, 8 mm central diameter lenses that received myopic defocus beyond 20° of the retina showed the least hyperopic shifts than the control and other experimental lenses. The magnitude of hyperopic shifts actually varied with the eccentricity of add power (defocus). Thus, their findings inferred that imposing myopic defocus in the near periphery rather than far periphery could benefit myopia control. Mapping the peripheral retinal profile or at least the nasal retina to customise the demanded defocus and avoid producing a strong peripheral myopic defocus is vital for optimising myopia control efficacy.

Although the mechanism of how the retina reacts to defocus is still under study, one theory is that image quality might be an indicator for the retina to detect blur, leading to regulating eye growth (Sun et al., 2015). Garcia et al. (Garcia et al., 2019) reported a decay of image quality caused by multifocal contact lenses in young myopes and a significant difference in image quality between hyperopic RPR myopes and myopic

RPR myopes wearing multifocal contact lenses. Defocus could lead to the degradation of image quality in the retina, and eye growth modulated to compensate for this blur. If the image quality is inferior to the threshold, the retina will fail to adjust. Thus, unsatisfactory myopia retardation would occur.

Myopic children in the current study showed a large range of RPR from negative to even 6 D at the mid-periphery. If there are varying degrees of RPR, the resultant myopic defocus dosage will be dependent on the RPR at different eccentricities. To counterbalance the higher hyperopic RPR or large myopic RPR in the mid-periphery, varying the power of the DIMS lenslets to avoid producing a strong peripheral myopic defocus might produce better myopia control.

### 6.6. The third-year follow up

#### 6.6.1. Subjects

One hundred and twenty-eight Chinese myopic children who completed the 2-year double-masked RCT study of DIMS lenses agreed to join the third-year study. In the third year, the children who had worn DIMS lenses continued to wear DIMS lenses (DIMS group), and those who had worn SV lenses switched to wear DIMS lenses (Control-to-DIMS group). After completing the third-year follow-up, there were 65 children in the DIMS group and 55 children in the Control-to-DIMS group (Table 5-12). In the third year, the drop-out rate was 4% in the DIMS group and 8% in the Control-to-DIMS group. Since the third year was no longer an RCT study, we obtained a historical control group by consulting the 2017-2019 clinical records of the

Optometry Clinic in the Hong Kong Polytechnic University. The selection criteria have followed the criteria of inclusion and exclusion in the original 2-year RCT, except for the criteria for the range of spherical equivalent power.

### 6.6.2. Myopia control efficacy

Children wearing DIMS lenses over 3 years showed less myopia progression and axial elongation compared to the original control group in the first 2 years and the historical control group in the third year. The main findings of the third-year follow-up visits have been published and reported (Lam et al., 2021).

Among the 65 subjects who participated in the third year, the DIMS group showed less of -0.53 D myopia progression and less of 0.29 mm axial elongation than the original SV group in the 2-years RCT (Table 5-14). The mean myopia progression and AL change in the historical control group aged from 10 to 15 years were -0.35 D and 0.18 mm per year. After switching to wear DIMS lenses in the third year, the Control-to-DIMS group showed significant retardation in myopia progression and axial elongation. Compared to the historical control group, the myopia progression was slowed down by 88% and axial elongation was reduced by 56% in the Control-to-DIMS group. These findings indicated that myopia control efficacy was accomplished even if the children started to wear DIMS lenses at an older age. Compared with the historical control group, DIMS group controlled the myopia progression by -0.18 D and axial elongation by 0.08 mm in the third year. Over 3 years, myopia progression was retarded by -0.68 D, and axial elongation was decreased by 0.37 mm in the DIMS

group; this is the cumulative absolute reduction in axial elongation (CARE) (Brennan et al., 2020).

Previously, clinical reports provided the annual treatment efficacy, but it may be decreased over time. Some myopia control interventions showed significant myopia retardation in the first year, while effects diminish over time (Edwards et al., 2002; Hiraoka et al., 2012). The cumulative data provided the treatment efficacy in a given period. The absolute reduction in axial elongation could provide the constant changes in treatment. For example, the 0.15 mm reduction in axial length would be a slight relative reduction in a faster myopia progression group but a high relative reduction in a slow myopia progression group. Thus, the absolute changes provided the constant and independent parameter for clinicians to estimate the treatment efficacy (Brennan et al., 2020). Also, the axial length is more accurate than the refractive error, and it is the only accurate way to estimate the myopia retardation by using OK lenses or atropine (see **Section 2.6.**) Therefore, CARE is the preferred efficacy metric for myopia control efficacy in a given time (Brennan et al., 2020). Figure 6-2 provides the representative CARE values for different treatments. The maximum CARE was reported in the OK study, that the axial elongation was reduced 0.44 mm by wearing OK lenses for 7 years (Santodomingo-Rubido et al., 2017). Our 2-year myopia control efficacy was preceded only by 7-year OK lens and a 2-year 1% atropine study.

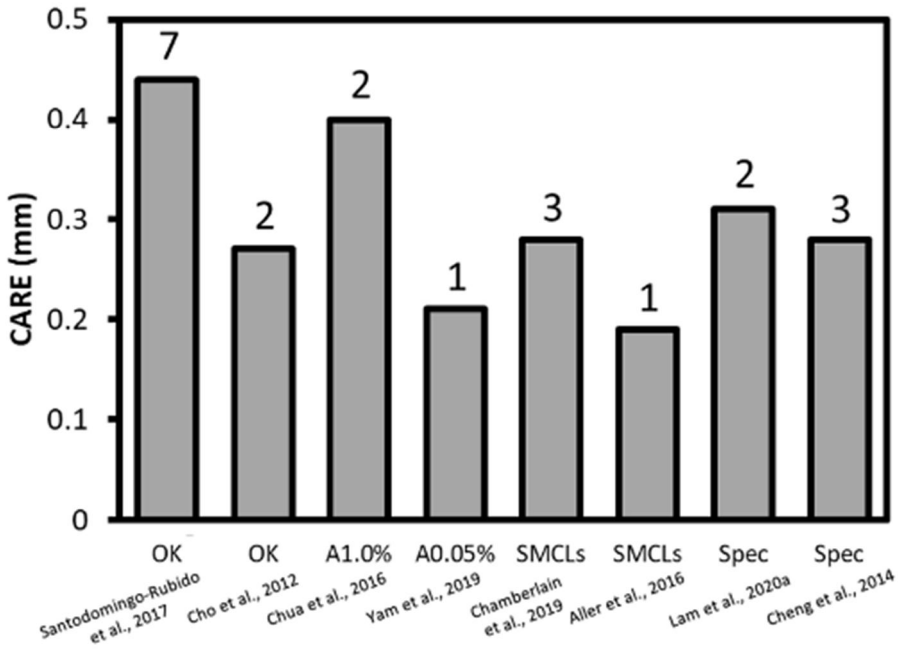



Figure 6- 2. Representative CARE values for different treatments. Years of follow-up are indicated above each bar. OK: orthokeratology, A1.0% : 1.0 % atropine drops, A0.05 %: 0.05 %atropine drops, SMCLs: soft multifocal contact lenses, Spec: spectacles. (Adapted from: *Brennan et al., Prog Retin Eye Res, 2020*)

The retardation of myopia progression by DIMS lenses is comparable to the results from other 3-year studies using bifocals and multifocal soft contact lenses. In a 3-year study, myopic children were allocated to wear SV lenses, +1.50 D bifocals, and +1.50 D bifocals with 3Δ base-in prism lenses (Cheng et al., 2014). They reported that and children with prismatic bifocal lenses showed the highest myopia retardation by reducing -1.05 D of myopia progression and 0.28 mm of axial elongation compared with SV lenses (Cheng et al., 2014). Chamberlain et al (Chamberlain et al., 2019) reported a significantly less myopia progression by -0.73 D, and less axial elongation by 0.32 mm in children who wore MiSight lenses (Cooper Vision, Inc., Pleasanton, CA) compared to children who wore SV contact lenses over 3 years. Walline et al.

(Walline et al., 2020b) reported that children wearing high add power (+2.50D) multifocal contact lenses had slower of -0.46 D myopia progression and less of 0.23 mm axial elongation compared to SV lens wearers over 3 years.

Therefore, the DIMS lenses showed a better myopia control efficacy in CARE than other interventions.

### 6.6.3. Relative peripheral refraction

The third-year results illustrated the changes in retinal shape in the group wearing the DIMS lenses and the SV group after switched from SV lenses to DIMS lenses, through the measurement of the peripheral refraction and RPR. We found there were no statistically significant changes in RPR at most retinal eccentricities ($p>0.05$), except at 20N (0.21±0.59 D, $p=0.005$), but it did not reach the clinically significant level (Figure 5-18). Therefore, the retinal shape still maintained a stable and symmetrical pattern. However, the Control-to-DIMS group showed a significant decrease in hyperopic RPR compared to 24-month (the time they start to wear DIMS), a direction towards myopic RPR (flatter retinal shape). In addition, the Control-to-DIMS group showed a symmetrical pattern of myopic shifts between the nasal and temporal retina, which was similar to the DIMS group.

It has been suggested (Mutti et al., 1998), that equatorial restriction of the growing eye has the potential to accentuate axial elongation while a uniform eye growth may benefit the myopia retardation. Therefore, the third-year follow-up study supported our assumption in the 2-year RCT study (Zhang et al., 2020), in which the mechanism of

DIMS may be through the constant myopic defocus influenced the retinal shape to grow into a uniform pattern.

The summation of myopic defocus and RPR showed a significant relationship with myopia progression. We found that DIMS wearers with higher hyperopic RPR (>0.74 D at 10N, and > 2.17 D at 20N) may achieve better myopia retardation over 3 years, and the RPR profile associated with over 20% of myopia control efficacy (Figure 5-22). Such a relationship was also noted in the Control-to-DIMS group. The hyperopic RPR in the nasal retina (within 20°) was correlated with less myopia progression. Nevertheless, the influence of initial RPR (RPR in the 24-month, the first time for Control-to-DIMS to wear DIMS lenses) could only be associated with 10% myopia progression, and this impact was reduced with the increase of retinal eccentricities.

Why there was a robust association between initial RPR and myopia progression in DIMS wearers in the first year as well as over 3 years? On the other hand, this association became weaker, although it was statistically significant when it comes to children in the Control-to-DIMS group who switched to wear DIMS lenses in the third year. We further divided these children according to their initial RPR into myopic RPR an hyperopic RPR at 10N and 20N. In the DIMS group, baseline myopic RPR at either 10N or 20N subgroup did lead to statistically significant more myopia progression (around -0.62 D to -0.85 D) and more axial elongation (from 0.16 mm to 0.21mm) over 3 years. However, in the Control-to-DIMS group, 24-month myopic RPR at 10N subgroup showed a small statistically more myopia progression than hyperopic RPR at

10N children, but not in axial elongation. The reason may because of the small numbers in myopic RPR children in 24-month. Over 2 years, hyperopic RPR showed a significant increase in the nasal retina compared to the baseline of the study in the SV group, with mean of RPR was 0.49±0.86 D and 1.62±1.10 D and 2.88±1.42 D at 10N, 20N, and 30N, respectively. Compared to the baseline RPR profile in the DIMS group, Control-to-DIMS children would be expected to receive less myopic defocus, and avoided the too much of myopic defocus when they started to wear DIMS lenses. In the third year, we reported better myopia control efficacy in the Control-to-DIMS group than the DIMS group. This finding echoed our hypothesis that too much of myopic defocus would not guarantee better myopia control efficacy, and there would be a threshold of blur detecting in the retina to guide eye growth from visual input. As the RPR profile was not changed over 3 years in the DIMS group, children in the DIMS group who were regarded to have 'too much' or 'appropriate dosage' of myopic defocus at baseline would keep this state continuously for 3 years. For the 8-and 9-year-old children, they kept the myopic RPR or small amount of hyperopic RPR over 3 years, so they received too much myopic defocus, leading to an unsatisfactory myopia control over 3 years (Figure 5-14).

However, children in the Control-to-DIMS have higher hyperopic RPR at 24-month (0.49±0.86 D and 1.62±1.10 D and 2.88±1.42 D at 10N, 20N and 30N). Combing with induced +3.50 D myopic defocus, the resultant myopic defocus results in good myopia control when they started to wear DIMS lenses, and then achieve better myopia retardation compared to DIMS group in the third year.

### 6.7. The role of relative peripheral refraction in myopia control

Eye growth could be guided by visual input from both the central and periphery (Smith et al., 2005; Wang et al., 2015). Imposing positive power (myopic defocus) leads to hyperopia, while negative power (hyperopic defocus) produces myopia. Myopic defocus played a more dominant role in eye growth than hyperopic defocus. Animal studies demonstrated that short periods of myopic defocus could block the axial elongation produced by hyperopic defocus, when imposing the myopic and hyperopic defocus separately (Zhu et al., 2013), successively (Zhu et al., 2003) or simultaneously (Tse et al., 2007). We hypothesised that the natural process of human emmetropisation is coordinated by the competition between the hyperopic and myopic defocus (Lam et al., 2014). The refractive errors occurred due to the disruption of the equilibrium; in other words, insufficient ambient myopic defocus may cause myopia, and excessive ambient hyperopic defocus may lead to hyperopia.

Traditional spectacle lens leads to hyperopic defocus in the periphery of myopes, which has been pointed out by the previous author (Lin et al., 2010). Children with higher RPR would experience more peripheral hyperopic defocus, which is the trigger for myopia progression (Smith et al., 2009b). Superimposing myopic defocus (add positive power) in the peripheral retina to counterbalance the existing hyperopic RPR or accommodative lag showed significant effects in myopia retardation. (see Section 3.3) The RPR profile would influence the actual myopic defocus receiving in the retina (the

magnitude of myopic defocus after counteracting the RPR). Therefore, we inquired into the relationship between baseline RPR and myopia progression in DIMS wearers.

The current study described the RPR profile in myopic schoolchildren from 8 to 13 years old and reported the role of RPR in myopia control. The initial RPR could impact the myopia control efficacy; it has been speculated that hyperopic RPR children would receive less myopic defocus, and myopic RRR children would experience more myopic defocus. However, more myopic defocus would not assure better myopic control efficacy. Therefore, RPR could be a parameter for lens ordering and avoid the too much of myopic defocus.

The DIMS lens provides a myopic defocus of +3.5D, at the mid-periphery where there was hyperopic RPR, the resultant myopic defocus will be expected to be less. As shown in Figure 5-11, the regression line crossed at the point of no myopia progression in the first 2 years if children with initial hyperopic RPR greater than 0.80 D at 10N and greater than 2.34 D at 20N in the DIMS group. If RPR is less than this amount at 10N and 20N respectively, myopia continue to increase but still at a slower rate comparing to the SV group. Furthermore, the regression line crossed the point of no myopia progression over the whole 3 years for the children with RPR greater than 0.74 D at 10N or greater than 2.17 D in the DIMS group (Figure 5-19).

One of the limitations was that we could not figure out if myopes fulfil the criteria of RPR at all eccentricities or just one position could stop myopia progression. Although this range was only calculated from the formula and could not be used unconditionally

for selecting optimised DIMS wearers, it could actually point out a direction that myopes with higher hyperopic RPR than myopic RPR in the mid-periphery may benefit more from wearing DIMS lenses. As the influence of initial RPR on myopia control efficacy was noted in the near fovea area (within 20º degree), the myopic defocus near the central distance optical zone is crucial. Initial RPR in the Control-to DIMS group (24-month) was around 0.30 D to 0.90 D higher than that in the DIMS group (baseline). Therefore, children in the Control-to-DIMS group, rather than children in DIMS group, were assumed to experience a suitable dosage of myopic defocus after the summation of their initial RPR and myopic defocus (+3.50 D) at 24-month.

We hypothesised that there would a better myopia control efficacy in DIMS group if the current dosage of myopic defocus decreased by 0.30 D to 0.90 D (reaching 2.50 D to 3 D approximately). To further improve the myopia control efficacy, the different dosage of myopic defocus, such as +1.50 D and +2.50 D, could be employed in the DIMS lenses.

In addition, RPR could be used to describe the retinal shape after the myopic control treatment. Few studies have studied the changes in peripheral refraction or RPR when in myopia control. This is the first study that proved myopia control using myopic defocus with simultaneous clear vision leads to changes in the mid-peripheral refraction and RPR. Our current description of retinal shape by RPR in the two groups may only be part of the wider picture; further study on investigating the retinal or eye shape needs to be conducted using imaging examination such as MRI and B-ultrasonography.

More work on understanding the mechanism of RPR changes in myopia control utilising myopic defocus is required.

The changes in RPR indirectly reflected the eyeball expansion process. The uniform PRR revealed the proportional changes in peripheral refraction and myopic shifts, which means an overall uniform and slow eye growth after wearing DIMS. In contrast, the asymmetrical hyperopic shifts in RPR reflected the faster growth in on-axis axial length than the peripheral retina. This local and non-coordinated eyeball expansion could also be a trigger for myopia progression.

The PRR plays an important role in myopia control using myopic defocus. Therefore, accurate and standardised measurements are needed.

### 6.7.1. Instruments of peripheral refraction measurements

Numerous techniques have been used to measure the peripheral refraction in subjective and objective approaches such as retinoscopy, aberrometer, photorefraction, autorefractor (Fedtke et al., 2009; Zhao and Fang, 2020).

The earliest subjective peripheral refraction measurement was reported in 1971 (Ronchi, 1971), which correcting oblique astigmatism to test the perception of the point-like peripheral target. In the general process, subjects have to concentrate on the peripheral target while adding trial lenses like the foveal subjective refraction (Millodot and Lamont, 1974; Thibos et al., 1996). It is a difficult process that needs patience and concentration, especially for the large angle of the visual field (Lundström et al., 2005), and the results can be impacted by peripheral aberration and other neural factors.

Peripheral refraction and peripheral refraction patterns were measured by retinoscopy in 1971 for the first time (Hoogerheide et al., 1971; Rempt et al., 1971). A larger eccentricity up to 80° has been tested by Leibowitz (Leibowitz et al., 1972), while Millodot (Millodot and Lamont, 1974) reported that the peripheral refraction over 50° was unreliable. With the increase of peripheral angle, the pupil tended to a more elliptical shape to the examiner and lead to more aberrations, which raise the difficulty to measure accurately (Fedtke et al., 2009). However, it has been pointed out that the small angle of off-axis retinoscopy could induce errors in objective measurement (Tay et al., 2011).

Photorefraction can estimate the refractive error easily, which is used widely in screening. The rationale of this measurement is to project the light into the eye by flash photography and then examine the reflected image in the fundus. Nevertheless, photorefraction showed less accuracy compared to retinoscopy, and it was limited to the large eccentricity of gaze and large astigmatism (Choi et al., 2000). Photorefraction was not promoted in peripheral refraction measurement for research (Lundström et al., 2005; Lundstrom et al., 2007).

Aberrometer worked as an instrument to measure the wavefront passes through the optical system. The values of wavefront aberration are presented in the form of Zernike coefficients, and it could be transformed into the spherocyclindrical refractive prescription. Hartmann-Shack technique (Atchison and Scott, 2002; Atchison et al., 2003; Lundström et al., 2005) and the complete ophthalmic analysis system (COAS)

(Ma et al., 2005; Shen and Thibos, 2011; Shen et al., 2018) have been the most well know types of aberrometers to test peripheral wavefront aberration. However, in the traditional Hartmann-Shack technique, subjects had to fix at a series of targets, which is time-consuming and tiring. In the recent decade, Scanning Aberrometer (Wei and Thibos, 2010; Polans et al., 2015), Eye Mapper (Fedtke et al., 2014; Fedtke et al., 2017; Fedtke et al., 2020), which is modified based on Hartmann-Shack aberrometer have been proposed and promoted in peripheral refraction study.

Besides, the open-filed autorefractor has been one of the most popular methods to measure both central and peripheral refraction (Mutti et al., 2000; Mutti et al., 2007; Lee and Cho, 2012; Verkicharla et al., 2016; Jaisankar et al., 2019). The Shin-Nippon NVision K5001 and Shin-Nippon SRW5000 showed high repeatability and have been used widely in research, which could measure the peripheral refraction up to 40° horizontal retina and up to 15° in the vertical field (Fedtke et al., 2009; Zhao and Fang, 2020). And the open-filed autorefractor has been widely used by clinicians for testing peripheral refraction. Only horizontal peripheral refraction was measured in our current project, as previous studies found no significant association between myopia and peripheral refraction across the vertical meridian when we were setting up the project (Atchison et al., 2006; Chen et al., 2010).

### 6.7.2. Standardised measurement methods

Generally, subjects were asked to turn their eyes or turn their heads to align the measurement axis with the desired visual field location, and the targets were at the

steps of 5 ˚ or 10 ˚(Wolffsohn et al., 2019). However, a large angle of eye rotation will influence muscular and eyelid pressure on the eyeball, which may cause optical changes (Seidemann et al., 2002), although previous authors did not report a significant difference between eye rotation and head-turn methods (Radhakrishnan and Charman, 2008; Mathur et al., 2009b).

If measuring peripheral refraction with a contact lens, the eye rotation would induce soft contact lens movements by more than 0.5 mm (El-Nimri and Walline, 2017), leading the errors in the measure. The latest IMI report recommended that head-turn should be used instead of eye-turn (Wolffsohn et al., 2019).

### 6.8. Limitations

There are some limitations in this study. We did not measure the peripheral eye length; measuring peripheral eye length could determine the actual peripheral eye growth situation and could be interpreted to a more direct retinal shape (Koumbo Mekountchou et al., 2020). It is worth noting that the broad standard deviations of the mean RPR values indicated that the actual retinal shape might be variable (Stone and Flitcroft, 2004; Sng et al., 2011a).

Another limitation was that the study was no longer an RCT study in the third year as the original control group changed to accept DIMS treatment. Thus, we could only use historical clinical data as a matched control group. A further RCT study over 3 years is warranted.

## 6.9. Summary of major findings

To our best knowledge, this is the first study that demonstrated the role of peripheral refraction on myopia control using myopic defocus simultaneously compared with traditional SV spectacle lenses.

The determination of RPR in Chinese myopic children who participated in the RCT study suggested that Chinese myopic schoolchildren displayed asymmetrical hyperopic RPR at the horizontal retina. The hyperopic RPR increased with increasing retinal eccentricities. There was a considerable variation of RPR shown in myopic children. DIMS lens was more effective in myopia control for children having hyperopic RPR at the periphery but less effective in children with myopic RPR at the periphery, which may partially explain why myopia control efficacy was varied among children. Customised myopic defocus, based on the RPR, may better fit the individual subject and optimise myopia control efficacy.

The comparison of changes in RPR after wearing DIMS and SV lenses over 2 years indicated a different eyeball expansion between myopia control treatment and normal myopia development. Myopia control using myopic defocus in the mid-periphery impacted peripheral refraction changes and slowed central myopia progression by altering the overall retinal shape. The asymmetrical and non-coordinated eye growth may infer a faster myopia progression. Further studies to elucidate the mechanism of this intervention are warranted.

The third-year results supported our hypothesis in the first 2 years, which the mechanism of myopia control using DIMS may through influencing the retinal shape into a uniform pattern.

Therefore, this study provided the insights that RPR plays an essential role in myopia control using myopic defocus. Initial RPR could be used to order myopia control lens and could be an important parameter to depict the changes in retinal shapes after myopia control.

# Chapter Seven: Conclusions

In recent decades, myopia prevalence increased dramatically worldwide, especially in Asia. Myopia has shown a tendency to impact younger ages, which is a serious matter as the younger myopia onset leads longer period of myopia development before the eye reaches maturity. Now, myopia control has been targeted at young children to reduce the risk of high myopia. Some theories for myopia control have been investigated with animal studies.

According to the findings in animal studies, it has been known that eye growth could be manipulated by the feedback from visual input at both the central and peripheral retina. In addition, animal studies pointed out that peripheral myopic defocus could inhibit myopia progression, while peripheral hyperopic defocus could cause myopia progression. We hypothesised that the natural process of human emmetropisation is modulated by the competition between the hyperopic defocus and myopic defocus. The refractive errors occurred due to the disruption of the equilibrium; in other words, insufficient surrounding myopic defocus may lead to myopia, while excessive surrounding hyperopic defocus may result in hyperopia. Based on this theory, myopia control interventions using myopic defocus have shown significant achievements. The DIMS lenses were designed to slow down myopia progression.

Most previous myopia control studies focused on investigating changes in refractive error, while the changes in retinal shape were rarely reported. The retinal shape has been indicated as an important factor in influencing eye growth and reflecting the

patterns of retinal stretching. For clinicians, the easy and convenient approach to indirectly depict retinal shape was by measuring peripheral refraction and RPR. So far, few studies have reported changes in RPR after myopia control using myopic defocus in humans. The investigation of peripheral refraction changes and RPR may provide more information about how the eye expansion in myopia control.

Previous meta-analysis studies reported that the efficacy of myopia control applying myopic defocus varied among subjects ranging from 25% to 60% (Tang et al., 2020). Moreover, the optimal dosage of myopic defocus to stop myopia progression has not been determined. In theory, the actual dosage of myopic defocus received would be influenced by RPR profile of myopes. For instance, children with less hyperopic RPR (or with myopic RPR) would experience more myopic defocus than the subjects with higher hyperopic RPR when wearing constant myopic defocus lenses. Therefore, it is worthy of study if the initial RPR could influence myopia control effects when using myopic defocus as the method.

The data we analysed in this thesis were from a 3-year clinical trial for testing the myopia control efficacy by DIMS lenses. There were two strategies in this 3-year clinical trial: the first 2-year study was an RCT and double-masked clinical trial, subjects were assigned to either DIMS or SV group randomly; children who completed the 2-year RCT study were invited to join the third-year follow-up visits, and all children were assigned with DIMS lenses. This thesis focused on investigating the relative peripheral refraction changes and their relationship with other important

parameters, including myopia progression, sex, and age. Consistent with previous authors, no statistically significant relationship between age, sex, and relative peripheral refraction was found.

The annual changes in myopia progression were on average -0.18 D, and this progression rate was almost linear over the 3 years. For children who were in the SV group, the myopia progression rate was -0.38 D and -0.49 D in the first 2 years, and it reduced to only -0.05 D in the third year after switching to DIMS lens. The annual axial elongation in the DIMS group was steady and consistent over 3 years, with around 0.10 mm each year. For children who were in the SV group, the axial elongation ranged from 0.20 mm to 0.29 mm per year in the first 2 years, and it reduced to 0.08 mm per year after wearing DIMS lenses. Over 3 years, myopia progression was retarded by on average -0.68D, and axial elongation was reduced by 0.37 mm; this is the CARE.

Comparing changes in RPR associated with myopia progression in myopic children wearing DIMS lenses and SV spectacle lenses, a different eyeball expansion pattern was observed between the myopia control treatment group and the group with normal myopic eye growth. In the first 2 years, myopic shifts at all the peripheral eccentricities (range from -0.30 D to -0.60 D) increased proportionately with the central myopia progression; thus DIMS group kept a relatively constant RPR profile. SV group showed asymmetrical peripheral myopic shifts, with myopic shifts at the temporal retina in the magnitude of -0.60 D to -0.90 D. Over 2 years, the SV group presented a skewed pattern and more hyperopia in RPR than DIMS group, which may indicate non-

coordinated eye growth and a steeper retinal shape in SV group. In the third year, children in DIMS group still showed changes in peripheral refraction proportionally with the central refraction, so they kept constant in the RPR profile (flatter retinal shape). After wearing DIMS lenses, children in the original SV group showed symmetrical changes in peripheral refraction at both temporal and nasal retina and reduction in hyperopic RPR (steep retina became flattered). Therefore, the 3-year results indicated the constant myopic defocus influenced the retinal shape to grow into a uniform pattern, which is the proposed mechanism of DIMS lenses to retard myopia progression.

The investigation in the baseline RPR profile suggested that hyperopic RPR was observed at most eccentricities across the horizontal retina, and it increased with more peripheral eccentricity. A broad range of hyperopic RPR was present at 30N, which ranged from 0 to 6 D. For the DIMS wearers, baseline RPR in the nasal retina were positively associated with myopia progression and negatively associated with axial elongation. However, in the SV group, baseline RPR could not associate with myopia progression. It could be speculated that DIMS wearers with myopic RPR at baseline received more myopic defocus than DIMS wearers; thus, it inferred that myopic defocus could be used as a signal for controlling myopia progression, more myopic defocus would not guarantee better myopia control effects. There might be a threshold of blur detection in the human retina; if the dosage of myopic defocus is adequate to counterbalance the existing hyperopic RPR, myopia control effects can be achieved. While too much myopic defocus will be beyond the signal detection threshold, myopia

control would be less effective or end up with more myopia progression. Thus, the appropriate dosage of myopic defocus rather than an too much of myopic defocus is required. The accurate RPR profile could provide an important parameter for lens design and lens orders in the future. Based on the regression line, we found myopes with hyperopic RPR larger than 2 D in the mid-periphery may benefit more from wearing DIMS lenses, yet this range was only calculated from the formula and could not be used unconditionally. To further improve the myopia control efficacy, the different dosage of myopic defocus, such as +1.50 D and +2.50 D, could be employed in the DIMS lenses.

All sum up, the 3-year study provided insights regarding the role of RPR in myopia control using myopic defocus. Initial RPR profile would impact the myopia control; thus, accurately measuring RPR could provide the parameter for lens design to avoid too much myopic defocus. In addition, the changes in RPR after myopia control treatment may provide information for the investigation of eye growth during myopia control. Measuring peripheral refraction or RPR is easy and convenient for clinicians to handle.

**Summary**

1. DIMS lens is safe, convenient, and non-invasive, which is well accepted for myopic children.
2. Children in the DIMS group continually showed good myopia control effects. The annual changes in myopia progression almost linear over the 3 years, with an

average rate of -0.18 D per year. For the children who were in the SV group, the myopia control effect was significantly different over 3 years. Myopia progression was reduced to only -0.05 D in the third year after wearing DIMS lenses, while it was -0.38D and -0.49 D per year when wearing SV lenses. The annual axial elongation in the DIMS group was steady and consistent over 3 years, with around 0.10 mm each year. The axial elongation was 0.20 mm to 0.29 mm per year for SV lens wearers in the first 2 years, while it reduced to 0.08 mm per year after wearing DIMS lenses. Children once switched to wear DIMS lenses benefited from myopia control significantly.

3. The observation in RPR among Hong Kong Chinse children who participated in the current project suggested that asymmetrical hyperopic RPR displayed at the horizontal retina, and the hyperopic RPR increased with increasing retinal eccentricities. A broad range of hyperopic RPR was noted at 30N, which was up to 6 D.
4. Over 2 years, different patterns of RPR changes were shown in the DIMS and SV group. The DIMS group showed a steady pattern in RPR over 3 years, which suggested a coordinated eye growth in the equatorial and axial direction. The asymmetrical changes in RPR of the SV group inferred asymmetrical and non-coordinated eye growth. In the third year, after switching to wear DIMS lenses, children who wore SV lenses in the first 2 years tended to show a coordinate eye growth in the periphery and centre. In addition, the DIMS group showed less hyperopic RPR than the SV group, which suggested a flatter retinal shape in the

DIMS group. In the third year, the hyperopic RPR was reduced after altering to wear DIMS lenses in the Control-to-DIMS group; that is, the retinal shape became flatter. Therefore, the difference in RPR changes corresponded to a different pattern in eyeball expansion between myopia control treatment and normal myopia development. Myopia control using myopic defocus in the mid-periphery impacted peripheral refraction changes and slowed central myopia progression by altering the overall retinal shape.

5. A weak association between PRR and myopia progression was observed in the control group, suggesting that RPR may be the consequence rather than a trigger of normal myopia progression. However, in DIMS wearers, we observed a significantly positive association between baseline RPR and myopia progression, which suggested that DIMS lens is more effective in myopia control for children with hyperopic RPR but less effective in children with myopic RPR. Furthermore, myopia control effect of DIMS spectacle lens is influenced by initial relative peripheral refraction. In other words, children who have myopic RPR superimposing with myopic defocus would receive more myopic defocus than children with hyperopic RPR. Children with hyperopic RPR larger than 2 D in the mid-periphery may benefit more from wearing DIMS lenses. For an optimal myopia control efficacy, further modification of DIMS lenses may point to different dosage myopic defocus (such as, +1.50 D and +2.50 D) for the children with myopic RPR or less hyperopic RPR. Customised myopic defocus based on the RPR profile may better fit individual subjects and optimise myopia control efficacy.

6. Therefore, this project suggested that RPR plays an essential role in myopia control using myopic defocus. Initial RPR could be used as an indicator for the ordering lens and avoiding too much myopic defocus; as well as could be an important parameter to predict the changes in retinal shapes after myopia control. Further mechanism investigation is required.
7. For the limitation, the peripheral eye length was not measured; measuring peripheral eye length could determine the actual peripheral eye growth situation and could be interpreted to a more direct retinal shape. In addition, the wide range of the standard deviations relative to the mean RPR values could indicate that the actual retinal shape may be variable. Further studies using MRI or other imaging examination to describe the retinal shape after wearing DIMS lenses are needed.

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