EFFECT OF OPTICAL DEFOCUS CHARACTERISTICS IN THE LIVING ENVIRONMENT AND INTERACTION WITH PERIPHERAL REFRACTIVE ERROR ON MYOPIA PROGRESSION

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Effect of Optical Defocus Characteristics in the Living Environment and Interaction with Peripheral Refractive Error on Myopia Progression

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Certificate of originality

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Abstract

Introduction

Myopia prevalence has been soaring in recent decades, reaching extremely high levels worldwide. This increased the cases of pathological myopia, which causes irreversible visual impairments and socioeconomic burdens. Myopia was once thought to be a genetic disease, because of its apparent hereditary characteristics. However, genetics have been found to only weakly contribute to myopia development. In contrast, numerous factors have been identified to be associated with myopia, such as education, activity pattern, and living environment. The consensus is that myopia development is multi-factorial.

In Southeast Asia, including Hong Kong, the prevalence of myopia is amongst the highest globally. The city is characterised by an intense education modality, a dense population, and small living space. Education attainment has long been associated with refractive error. In Hong Kong, near work tasks are the mainstream of schoolwork, for which children have to spend hours studying. However, the contribution of the amount of near work is controversial, possibly due to the lack of comprehensive quantification of the near work environment other than one-dimensional working distance. Furthermore, the urban environment was found to be associated with myopia in places such as Australia and China. People in Southeast Asian regions generally live in small flats, with Hong Kong ranked amongst the most crowded in terms of living space per capita.

Understanding the mechanisms of myopia development is the key to providing adequate control of its progression. Animal experiments have shown that the eye itself is able to respond to visually driven signals to compensate for the defocus blur induced by the optical lens. Negative (or hyperopic) defocus falls behind the retina and drives the eye to become

myopic, while positive (or myopic) defocus falls in front of the retina, inducing hyperopia. This response occurs not only when the defocus is in the central retina, but also in the peripheral retina. However, the role of peripheral refractive error in control of myopia progression has been controversial in clinical studies. Epidemiology studies have revealed independence of myopia progression from peripheral refraction, whilst clinical trials of optical devices inducing peripheral myopic defocus successfully retarded myopia progression in children.

Objectives

In this thesis, Chinese schoolchildren in Hong Kong, who are prone to developing myopia, were targeted. Study I aimed to evaluate the association between living environment, mostly in terms of housing, and refractive error. Study II aimed to investigate the relationship between on-axis refractive status and peripheral refraction other than peripheral spherical equivalent refraction. Finally, Study III aimed to evaluate the effect of environmental scene defocus at home, mainly the child's reading desk, on myopia progression, and its interaction with peripheral refraction.

Study I

Methods

A total of 1,075 (age: 10.0 ± 1.0 years, 54.5% boys) subjects were recruited by random-cluster sampling according to the population density of the Hong Kong political districts. A self-reporting questionnaire was used to collect information on demographics, living environment, and near work related parameters. The data were analysed to assess the association with axial length and non-cycloplegic refractive error using univariate and multivariate analyses.

Results

Population density of the residential district and home size were found to be associated with axial length and non-cycloplegic refractive error, but not the type of housing. Children living in high population density districts had 0.22 mm longer axial length and 0.49 D more myopic refractive error than those living in low population density districts; while children living in small homes had 0.23 mm longer axial length and 0.47 D more myopic refractive error than those living in large homes. The effect of near work posture reached statistical significance, but was not conclusive. However, other factors including near working distance, resting frequency, and participation in extra-curricular activities were independent of the axial length and refractive error in this study.

Study II

Methods

The same subjects in Study I also participated in Study II, excluding those with small pupil sizes, who were unable to perform peripheral refraction, reducing the sample size to 1,052. Peripheral refraction was measured at ±10° vertically and horizontally. A further ±20° horizontally was measured in a 603-subject subset. The relative peripheral refractions, including spherical equivalent refraction (M), J_0, J_{45}, and radiality, which was defined as the absolute difference between P(90) and P(180), were compared between groups of different axial-length-to-corneal-radius-of-curvature (AL/CR) ratios. Multiple correlation analysis was used to assess the relationship between AL/CR and each peripheral refraction vector. Orientation bias was defined as the clearer meridian of the peripheral astigmatism in sphero-cylindrical form, which was compared among AL/CR groups.

Results

The results showed that M was more hyperopic with increased AL/CR both horizontally and vertically. In contrast, the magnitude of J_0 and J_{45} became smaller with increased AL/CR along horizontal and vertical visual fields, respectively. Radiality, which represented the quality of focus of the radial component of the retinal image, decreased with increasing AL/CR along the horizontal field. In multiple correlation analyses, M ($r = 0.50$) and radiality ($r = 0.35$) demonstrated a moderate, while J_0 ($r = 0.20$) and J_{45} ($r = 0.12$) demonstrated a weak correlation with on-axis AL/CR. Regarding orientation bias, radially oriented bias was over-represented in the low AL/CR group, but under-represented in the high AL/CR group. In contrast, tangentially oriented bias was under-represented in the low AL/CR group, but over-represented in the high AL/CR group.

Study III

Methods

Fifty subjects (age: 9.3 ± 1.2 years, 44% boys) were recruited from the Optometry Clinic of The Hong Kong Polytechnic University, and their homes visited. Demographics, parental myopia, activity pattern, and home size were obtained in a parental interview. Kinect was used to measure the three-dimensional distances of the child's reading desk from their eyes, in order to use these measurements to construct a scene defocus profile. The home scene parameters were calculated as dioptric volume (DV) and standard deviation of the scene defocus (SD_D), which represented the total amount of net defocus in the scene and the dispersion of the scene defocus, respectively. On-axis and peripheral refractions were measured at baseline, and myopia progression was measured one year later (ΔM). Peripheral refraction was measured ±30° horizontally, and the M, J_0, P(90), and P(180) values were fitted in quadratic regressions and analysed. The correlation between ΔM and home scene parameters was calculated. Stepwise multiple linear regression was also used to assess the relationship between ΔM and home scene parameters along with other co-variates. The correlation between ΔM and peripheral refraction was calculated. Following this, the partial correlation between ΔM and peripheral refraction, controlled for the home scene parameters, was also calculated. Multiple linear regression was also used to assess the relationship between ΔM and peripheral refraction, adding home scene parameters as co-variates.

Results

The findings revealed that faster myopia progression was associated with a more dispersed scene defocus profile ($\rho = -0.42$) and a more hyperopic scene defocus at the para-central field (B = -0.18). The results did not show that any quadrants of the scene, or a non-linear spatial summation between myopic and hyperopic scene defocus, had a better correlation with ΔM. In contrast, it was determined that peripheral refraction was independent of the ΔM after controlling for baseline M. However, after adding home scene parameters as co-variates, peripheral refraction was again associated with ΔM (M: $\rho = -0.30$; J_0: $\rho = -0.49$; P(180): $\rho = -0.35$). Finally, children living in a small home had 0.41 D and 0.49 D faster myopia progression than those living in medium and large homes, respectively.

Conclusions

Myopia development is complex and multi-factorial. Among the environmental factors, the living environment, specifically the home size, and the near working scene at home were associated with myopia progression. In contrast, despite the controversy in the myopia literature, the results showed a significant effect of peripheral refractive error in myopia development, but only when it was controlled for the home scene parameters. Therefore, it may be speculated that there is an interaction between external and internal factors, in terms of the scene defocus stimulation and peripheral refractive error, respectively. When the external factors were strong, the eye would depend on the external stimulation and emmetropise accordingly. However, when the external factors were weak, the eye would rely on the central and peripheral refractive profile internally. As home size is a difficult factor to modify, indoor scene modification can be further studied to assess the myopia control effect.

Publications arising from the thesis

1. Choi KY, Yu WY, Lam CHI, Li ZC, Chin MP, Lakshmanan Y, Wong FSY, Do CW, Lee PH, Chan HHL. (2017). Childhood exposure to constricted living space: a possible environmental threat for myopia development. Ophthalmic and Physiological Optics 37:568-575.
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Conference presentations

1. Choi KY, Yu WY, Lam CHI, Li ZC, Chin MP, Lakshmanan Y, Wong FSY, Do CW, Lee PH, Chan HHL. (2017). Living environment and myopia prevalence in Hong Kong schoolchildren. In: ARVO-Asia 2017, Brisbane, Queensland, Australia.
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3. Choi KY, Chan HHL, Mok AYT. (2019). Defocus characteristics of home-working scene of Hong Kong schoolchildren and association with their refractive error change. In: 17th International Myopia Conference, Tokyo, Japan

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'Commit your work to the LORD, and your plans will succeed.' Proverbs 16:3

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List of abbreviations

α - Axis of sphero-cylindrical form refractive error

ρ - Spearman's correlation coefficient

χ^2 - Statistical value of Chi-square test

2M - Twice myopic defocus potency

a_M - The first coefficient of quadratic regression of peripheral spherical equivalent refraction

a_{J0} - The first coefficient of quadratic regression of J_0 component of peripheral astigmatism

$a_{P(90)}$ - The first coefficient of quadratic regression of P(90) component of peripheral refractive error

$a_{P(180)}$ - The first coefficient of quadratic regression of P(180) component of peripheral refractive error

AL - Axial length

ANOVA - Analysis of variance

B - Coefficient of multiple linear regression

C - Cylindrical error

COMET - Correction Of Myopia Evaluation Trial

CR - Corneal radius of curvature

CREAM - Consortium for Refractive Error and Myopia

C.S.D. - Hong Kong Census and Statistical Department

df - Degrees of freedom

DIMS - Defocus Incorporated Multiple Segments

DV - Dioptric volume

FDM - Form-deprivation myopia

GEWIS - Gene-Environmental-Wide Interaction Study

GWAS - Genome-Wide Association Study

H.K.H.A. - Hong Kong Housing Authority

H.K.P.T.U. - Hong Kong Professional Teachers' Union

IR - Infra-red

J_0 - J_0 component of the vector form refractive error

J_{45} - J_{45} component of the vector form refractive error

M - Spherical equivalent refraction

OA - Outdoor activities

OLSM - Orinda Longitudinal Study of Myopia

p - Statistical significance level

PAL - Progressive additional lens

PISA - Program In Secondary Assessment

PRE - Peripheral refractive error

r - Pearson's correlation coefficient

R^2 - Coefficient of determination

RESC - Refractive Error Study in Children

RPRE - Relative peripheral refractive error

S - Spherical error

SAVE - Sydney Adolescent Vascular and Eye study

SCORM - Singapore Cohort study Of Risk factors for Myopia

SD - Standard deviation

SD_D - Standard deviation of the scene defocus

SEM - Standard error of mean

SMS - Sydney Myopic Study

S.o.C.O. - Society for Community Organisation

SPSS - Statistical Package for the Social Sciences

t - Independent t value

tDV - Dioptric volume after normality transformation

tSD_D - Standard deviation of the scene defocus after normality transformation

T_{desk} - Daily time spent in front of desk

T_{OA} - Weekly time spent outdoors

VIF - Variance inflation factor

W.H.O. - World Health Organisation

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Chapter 1. Introduction

Uncorrected refractive error is the most common cause of visual disturbance worldwide, causing millions of people to suffer from loss of vision (Bourne et al., 2013). It is estimated that about 120 million people could have improved vision simply by correcting their refractive errors (W.H.O., 2018). The most common types of refractive error are myopia (near-sightedness), hyperopia (far-sightedness), and astigmatism. Optics of a myopic eye focus the image in front of the retina, requiring a diverging lens (negatively powered) to correct the eyesight, while the image of a hyperopic eye focuses behind the retina, requiring a converging lens (positively powered) for correction. Astigmatism is caused by unequal optical power between the meridians of the eye and requires a cylindrical lens for correction. Refractive error is represented in minus-cylinder form in this thesis: Spherical error (S) / Cylindrical error (C) x Axis (α), where C is in negative value. For calculation purposes, the refractive error is transformed into vector forms (Thibos et al., 1997):

Spherical equivalent refraction (M) = $S + \frac{C}{2}$

J_0 component of astigmatism (J_0) = $-\frac{C}{2}\ cos2\alpha$

J_{45} component of astigmatism (J_{45}) = $-\frac{C}{2}\ sin2\alpha$

1.1 Myopia prevalence and projection

1.1.1 From the past to the future

Of the various types of refractive error, myopia is of the most concern because of its high prevalence and its association with various ocular complications (Verkicharla et al., 2015). The global myopic population had reached 1.95 billion in 2010, constituting 28.3% of the population. It is estimated to continue to climb, reaching 2.62 billion by the end of 2020 (34% of the population). In 2050, it is estimated that approximately half of the global population will suffer from myopia, i.e. 4.76 billion myopes (Holden et al., 2016). Prevalence of sight-threatening high myopia (often defined as $M \leq -6$ D) is also increasing (Holden et al., 2016; Morgan et al., 2018) and is estimated to affect 10% of the global population in 2050 (Holden et al., 2016). Myopia was not such a common condition until fairly recently. Taking East Asian regions (Taiwan, Singapore, Hong Kong, and South Korea) as examples, the myopia prevalence in the twenty-year-old population was approximately 30% in the 1950's. Since then, the prevalence has soared, reaching 50% in the early 1980's and 80% - 90% in the 2000's.

1.1.2 Prevalence across age groups and worldwide

Myopia prevalence is low in infants and pre-school toddlers (0.4% - 6.1%) (Low et al., 2010; Borchert et al., 2011; Lan et al., 2013; Wen et al., 2013; Chua et al., 2015). However, it increases with age, with school-myopia reaching 12.8% - 52.2% for children aged between 6 and 12 years (Rose et al., 2008b; He et al., 2009; Lam et al., 2012; O'Donoghue et al., 2015; Ma et al., 2016), and 20% - 90% for adolescents aged between 13 and 18 years (Morgan et al., 2012; Pan et al., 2012; Williams et al., 2015; Wu et al., 2015). The myopia prevalence peaks at approximately 35.1% - 85.0% in younger working adults (Rahi et al., 2011; Pan et al., 2015; Williams et al., 2015; Varma et al., 2017; Joseph et al., 2018), but declines towards old age (12% - 29.0%), when refractive errors mostly tend to become hyperopic (Wensor et al., 1999; Edwards and Lam, 2004; Saw et al., 2008; Rahi et al., 2011; Pan et al., 2015; Han et al., 2017; Xu et al., 2017; Wang et al., 2019). Compared with other regions, myopia prevalence is alarmingly high in East Asian countries (Morgan et al., 2012; Pan et al., 2015; Holden et al., 2016; Rudnicka et al., 2016; Wong and Saw, 2016; Morgan et al., 2018). Table 1.1 (adapted from Holden et al., 2016) lists the worldwide prevalence of myopia. The African countries have the lowest prevalence (8.4% - 12.1%). European countries (29.0% - 36.7%) report a relatively higher prevalence, which is similar to American (27.7% - 42.1%) and Middle Eastern countries (24.3% - 30.5%). The highest myopia prevalence was observed in developed East Asian countries (39.3% - 48.8%). Within the East Asian region, Hong Kong has one of the highest rates of myopia (Lam et al., 2012; Pan et al., 2015; Rudnicka et al., 2016; Choy et al., 2020; Grzybowski et al., 2020; Yam et al., 2020).

Table 1.1 Estimated prevalence of myopia for 21 global regions in the year of 2020 (adapted from Holden et al., 2016)

Region	Prevalence (%)	Region	Prevalence (%)
Central Latin America	34.2	Central Africa	9.8
Andean Latin America	28.1	East Africa	8.4
South Latin America	32.4	Southern Africa	12.1
Tropical Latin America	27.7	West Africa	9.6
North America	42.1	North Africa and Middle East	30.5
Caribbean	29.0	Australasia	36.0
Central Europe	34.6	Asia Pacific	53.4
Eastern Europe	32.2	Central Asia	24.3
Western Europe	36.7	East Asia	51.6
Oceania	9.1	South Asia	28.6
		Southeast Asia	46.1

1.2 Adverse effects of myopia and high myopia

1.2.1 Myopia associated ocular pathology

Management of myopia currently requires optical correction, either by spectacle lenses, contact lenses, refractive surgery, or orthokeratology. However, myopia is much more than merely an optical inconvenience. Myopia is largely attributable to an excessive axial elongation of the eyeball (Grosvenor and Scott, 1994; Park et al., 2010; Meng et al., 2011; He et al., 2015b), i.e. axial myopia, and the subsequent thinning of the posterior ocular structure can cause various degenerations in the eye (Jonas and Xu, 2014; Tideman et al., 2016). Myopia, especially high myopia, is associated with various ocular diseases, including glaucoma (Wong et al., 2003; Xu et al., 2007; Marcus et al., 2011), retinal detachment (Beijing Rhegmatogenous Retinal Detachment Study, 2003; Lewis, 2003; Polkinghorne and Craig, 2004; Mitry et al., 2010), cataract (Praveen et al., 2008; Pan et al., 2013; Kanthan et al., 2014), and myopic macular degeneration (Wong et al., 2014; Fricke et al., 2018; Wong et al., 2018). Some of these diseases can cause irreversible visual impairment (Saw et al., 2005; Verkicharla et al., 2015; Tideman et al., 2016). Pathological myopia is a common cause of vision loss, comprising up to 30% of the low vision and blind population (Yamada et al., 2010). More alarmingly, 11.1% of low vision children had pathological myopia as their main cause of visual impairment (Shah et al., 2011). Projection of European data suggests that the prevalence of uncorrectable visual impairment will increase seven- to thirteen-fold by 2055 in high-risk areas (Tideman et al., 2016).

1.2.2 Economic loss due to myopia and its complications

In addition to the permanent vision loss due to pathological myopia, the correctable myopia also brings an economic burden (Wang et al., 2014; Wong et al., 2014; Modjtahedi et al., 2018; W.H.O., 2018; Naidoo et al., 2019). The loss of global gross domestic product from uncorrected refractive errors (including hyperopia and astigmatism) was estimated to be USD202 billion annually in 2007 (Fricke et al., 2012). A more recent estimation in 2015 indicated the loss of global potential productivity by myopia alone had climbed to USD244 billion and that from myopic macular degeneration was USD6 billion (Naidoo et al., 2019). This demonstrated that myopes increased their health expenditure to correct and improve their vision (I.A.P.B., 2017), and to reduce the risk of developing pathological complications, such as myopic macular degeneration (Fricke et al., 2018). In Southeast Asian regions, the productivity loss resulting from visual impairment by pathological myopia was particularly severe, at 1.35%, 1.30%, and 1.27% of the gross domestic product for Southeast, South, and East Asian regions respectively (Naidoo et al., 2019). These figures were two-fold greater than those of other global regions. Productivity losses peaked in young adults aged between 25 and 29 years (Naidoo et al., 2019), in whom myopia prevalence, the spectacle coverage, the severity of visual impairment, and the labour force participation rate were considered.

1.2.3 Individual difficulties with visual impairment caused by myopia

In addition to economic costs, visual impairment also impinges on functional (Cavézian et al., 2013; Christ et al., 2014), psychological (Wang et al., 2014; Harris and Lord, 2016), and occupational (Shaw et al., 2007; Harrabi et al., 2014; Ma et al., 2014) aspects of individuals. A multi-ethnic study (Wang et al., 2014) reported that visual impairment was associated with decreased quality of life (QoL), especially with respect to mobility, usual activities, and anxiety or depression. Their results also suggested the drop in QoL associated with visual impairment was greater than that from obesity, hypertension, diabetes, or hyperlipidaemia, which was similar to the findings of studies in the US (Sullivan and Ghushchyan, 2006) and the UK (Sullivan et al., 2011). Vision loss adversely affects activities of daily living, such as bathing, dressing, and toileting, which increases the risk for mortality (Christ et al., 2014). Visual impairment affects children's visual attention (Cavézian et al., 2013) and is associated with psychiatric disturbance (Harris and Lord, 2016). Poorer academic performance in children is also associated with the poor optometry services, e.g. spectacle coverage in China (Ma et al., 2014). Poorer educational outcome together with visual impairment may hinder youth from obtaining proper employment. A study revealed generally low employment rates among blind and low vision youths, even if their education level was similar to that of the healthy population (Shaw et al., 2007).

1.3 Nature and Nurture

Until recently, refractive error was regarded as highly hereditary. Familial and ethnical studies supported the concept of genetic involvement in refractive error. However, with the ability to conduct more refined studies, it has been determined that genetics only contributes a relatively small portion to refractive error development. Rather, it was found environmental factors play a major role, especially since the economic changes in recent decades, which have led to urbanisation and better education. Several environmental risk factors associated with the prevalence, incidence, and progression of myopia have been identified. The debate of whether refractive error development originates from nature or nurture subsided as it became understood that the process is complex and multifactorial.

1.3.1 Evidence of heredity in myopia

The role of heredity in myopia was observed more than seventy years ago (Duke-Elder, 1943). Familial studies, including monozygotic twin studies, sibling pair studies, and parent-offspring pair studies, suggested that myopia heritability varied from as low as 10% to as high as 98% (Wojciechowski et al., 2005; Dirani et al., 2006; Klein et al., 2009; Guggenheim et al., 2013; Kim et al., 2013). This high variance may be due to the differences in study design and analytic methods, as well as the susceptibility to environmental factors. A recent report suggested the heritability of myopia is between 60% and 80% (Tedja et al., 2019). Epidemiology studies have indicated that ethnicity is a predictive factor for myopia, with Asians being more prone to myopia than Caucasians and Africans (Kleinstein et al., 2003; Hyman et al., 2005; Saw et al., 2006; Ip et al., 2008a). In addition, parental myopia was frequently associated with myopia in their offspring (Mutti et al., 2002; Jones et al., 2007; Kurtz et al., 2007; Lam et al., 2008; Liao et al., 2019) after the correction for other confounding factors, such as socioeconomic status and activity patterns. The association between parental and offspring myopia was particularly strong during the early childhood years. In addition to clinical epidemiology, the emergence of genome-wide association studies (GWAS) enabled easier detection of various common genetic variants associated with myopia. Before GWAS, linkage studies only discovered up to 50 loci and genes (Wojciechowski, 2011), which were non-repeatable in later replication studies. However, since the introduction of GWAS, consortia, including the Consortium for Refractive Error and Myopia (CREAM), have published meta-analyses and the number of genetic loci identified reached over 200 over a few years (Verhoeven et al., 2013). However, the common variants identified could only account for approximately 8% of the phenotypic variance (Kiefer et al., 2013; Verhoeven et al., 2013). Therefore, genetic research shifted focus to the interaction between environmental factors and the human genome, i.e. genome-environment wide interaction study (GEWIS) (Fan et al., 2016). Further technological advances could improve the understanding of myopia development and progression.

1.3.2 Impact of environmental factors

The recent rapid increase in prevalence of myopia over recent decades (Holden et al., 2016) cannot be completely accounted for by either heredity or ethnicity. It is now suggested that genetic factors predispose increased susceptibility to environmental effects, making children more prone to develop myopia if exposed to environmental risks. Associations have been established between increased myopia prevalence and various environmental factors, including near work, time spent outdoors, culture and education, and urbanisation, which will be discussed in coming sections.

1.3.2.1 Myopia and near work

For many years, researchers have noted an association between refractive error and near work, which has been considered as fundamental evidence of environmental risk for myopia development. Cross-sectional epidemiology studies revealed myopic children were likely to spend more time reading and studying (Mutti et al., 2002; Saxena et al., 2015). Vice versa, children with greater reading exposure were more likely to become myopic (Saw et al., 2002a; Saw et al., 2002b). As well as reading time, close reading distance was also associated with myopia (Ip et al., 2008c; Li et al., 2015a). A longitudinal study conducted over 5 years (French et al., 2013) reported that extensive near work was associated with myopia incidence. Less near work activity may contribute to myopia stabilisation by age 15 (Scheiman et al., 2014). In a recent four-year longitudinal study, although the daily reading time was not associated with the myopia incidence, attendance at cramming schools for over two hours a day increased the risk of myopia development (Ku et al., 2019). Faster axial elongation was also significantly associated with the number of books read in a week and the total reading time reported in a three-year longitudinal study, but reading distance was not significantly associated (Tideman et al., 2019).

In contrast, some studies did not demonstrate the effect of near work on myopia, with progression not significantly differing in children having various intensities of near work (Saw et al., 2000). Near work tasks, including school homework, leisure reading, and handheld console games, correlated poorly with refractive error in the children (Ip et al., 2008c). The amount of near work could not predict myopia incidence, in which baseline near work undertaken by future-myopes did not differ from that of participants who remained emmetropic (Jones-Jordan et al., 2011). Concerning the controversial role of near work in myopia, Huang and co-workers (Huang et al., 2015) performed a systematic review and meta-analysis, which reported that near work was associated with myopia prevalence, but not the risk of developing myopia.

The emergence and penetration of electronic devices has made device screen time more important for studies investigating near work, as electronic devices are now heavily infiltrating daily life in gaming, social media, and digital entertainment (Dirani et al., 2019). Myopic children are more likely to spend more than two hours per day watching television / video, using computers, and playing mobile games (Saxena et al., 2015). These digital screen activities were also reported to be significant risk factors for myopia progression (Saxena et al., 2017). However, a later study did not find any association between computer / internet / video games and either prevalence or incidence of myopia (Ku et al., 2019). With advances in technology, quantifying the amount of near work needs to be more sophisticated, rather than merely recording the distance, duration, or types of near tasks.

1.3.2.2 Myopia and outdoor activities

Despite the controversy of the effect of near work on myopia development, researchers have reached a consensus that outdoor activities (OA) is protective against myopia development (Sherwin et al., 2012; Xiong et al., 2017; Deng and Pang, 2019). A representative study, the Sydney Myopia Study (SMS), demonstrated an association between high levels of OA and lower myopia prevalence, as well as a more hyperopic M (Rose et al., 2008a). They also reported that, regardless of the amount of near work, the amount of OA was always negatively associated with the odds ratio of having myopia. An analogous study, the Singapore Cohort study Of Risk factors for Myopia (SCORM) (Dirani et al., 2009) conducted in Asian children, who have a significantly higher myopia prevalence, yielded similar results. A follow-up of SMS, the Sydney Adolescent Vascular and Eye (SAVE) study, reported that the lack of OA was associated with myopia incidence over 5 - 6 years (French et al., 2013). The Orinda Longitudinal Study of Myopia (OLSM) also reported more sports and outdoor hours were associated with a lower myopia prevalence (Mutti et al., 2002), as well as a lower myopia incidence over 5 years (Jones et al., 2007). Notably, the OLSM did not separate OA from sports activities. Although hours spent in sports were associated with total OA time, later studies suggested sports alone could not provide protective effect against myopia (Rose et al., 2008a; Guggenheim et al., 2012).

The negative association between OA and myopia prevalence and incidence was demonstrated in observational studies. Hence, later clinical trials shifted the focus to the protective effect of treating children with OA. In Taiwan, two nearby schools were recruited, in which one implemented a recess-outside-classroom program for the students with emptied classrooms during recess, while the second school served as a control without any intervention (Wu et al., 2013). After twelve months, the students in the intervention school had both significantly lower myopia incidence in non-myopic children and slower myopic progression than those in the control school. The same research group later extended the study to a multi-area, cluster-randomized controlled trial with a larger sample size of approximately 600 children (Wu et al., 2018). In this trial, the intervention group was also encouraged to participate more in OA via various campaigns, such as educational promotions, family events, and rewarding programs. The results indicated a protective effect of OA against myopia, with an odds ratio of myopia incidence in the intervention group of 0.46 compared with control group. Another three-year randomised clinical trial, which included approximately 2,000 children in 6 intervention and 6 control schools, was conducted in China (He et al., 2015a). In this study, one extra forty-minute OA class was added to the schedule every school day in the intervention schools. The myopia incidence was lower and myopia progression rate was slower in the intervention schools. However, an OA promotional campaign might not always have high compliance unless incentives are given (Ngo et al., 2014), as teachers and parents may prefer more study time for the children.

There are several theories suggesting the mechanism of OA preventing myopia development. The most widely accepted was the light intensity of the outdoor environment (Ngo et al., 2013). In clinical observational studies, Read and co-workers measured light exposure using a wrist-worn actigraphy device in emmetropes and myopes (Read et al., 2014). Their findings showed that emmetropes had significantly higher light exposure than age-matched myopes over 2 weeks within the school term. Furthermore, in another clinical trial carried out in China, elevated light intensity, achieved by improving the lighting system in classrooms, also lowered myopia incidence and the myopia progression rate over one year (Hua et al., 2015). In the OA promotion campaign in Taiwan mentioned earlier (Wu et al., 2018), collar light meters were used to measure light exposure for 7 days. The results suggested, rather than high light intensity (up to 10,000 lux), more time spent in even a relatively dimmer outdoor environment (1,000 to 3,000 lux, e.g. hallways with big windows, under tree shades) was also sufficient to be protective against myopia. The light intensity measured using a child-sized mannequin head light meter was comparable to that measured using light metres on children's collars (Lanca et al., 2019). Even with sunlight protective equipment, e.g. sunglasses and hats, the outdoor light intensity, which was eleven- to forty-three-fold greater than indoor lighting, was adequate for myopia protection. Hence, a glass classroom was designed and built for students to increase their light exposure during school time (Zhou et al., 2017). The light intensity was significantly increased and both teachers and students gave positive feedback of the glass classroom over a traditional classroom. However, neither refractive nor biometric data was measured in the study.

Other theories regarding the mechanism of OA protection concerned the properties of the outdoor visual stimuli, including 1) spatial details (Schmid and Wildsoet, 1997a; Hess et al., 2006; Chin, 2018) - myopisation was inhibited by high spatial frequency stimuli, which are abundant in outdoor natural environments, and 2) peripheral defocus (Charman, 2011; Flitcroft, 2012) - the distribution uniformity is more favourable for emmetropisation in an outdoor environment, while the distribution is more dispersed in an indoor environment. The peripheral decoding of defocus will be discussed in Section 1.4.4.2.

1.3.2.3 Myopia and education

It is widely believed that the increase in myopia is associated with education, as myopia onset usually occurs during school age (Morgan and Rose, 2005; Pan et al., 2012). Many studies have reported increased myopia prevalence to be associated with higher education levels. The earliest discovery published over a century ago (Cohn, 1886), observed that the frequency of myopia increased with intellectual achievement in Northern Europe. Later studies reported similar findings, showing that intelligence test scores and educational levels were independently associated with higher myopia prevalence (Rosner and Belkin, 1987) and amount of myopia (Teasdale et al., 1988) in young adults and children (Saw et al., 2004). Intelligence was later suggested to share common genetic factors with inherited myopia (Williams et al., 2017).

In addition to duration of education exposure, academic performance has been associated with myopia, as children with better nation-wide examination scores had a 250% higher chance of having myopia (Mutti et al., 2002; Saw et al., 2007) in both Western and Eastern countries. Comparison of academic performance between countries in international assessments, such as the results from the Program in Secondary Assessment (PISA), found higher achievement was associated with national myopia prevalence (Morgan and Rose, 2013). Eastern Asian regions, including Hong Kong, Japan, and Singapore, where the myopia prevalence is extremely high, ranked in the top quartile of the PISA performance. However, some other top-ranked-quartile countries, e.g. Australia and Finland, had relatively low myopia prevalence. The reason for the different myopia prevalence was suggested to be the participation in after-class tutorials and cramming schools, which are popular in East Asian countries. This hypothesis was later supported by a four-year longitudinal study in China (Ku et al., 2019), where the attendance at cramming school for over 2 hours per day increased the odds ratio of myopia incidence.

The Eastern and Western education modalities, such as Singaporean versus Australian, differ significantly, e.g. participation in after-class tutorials. This difference in modality was suggested to contribute to the higher myopia prevalence of Singapore over Australia (Rose et al., 2008b). Even within the same city, education modalities could be associated with myopia prevalence. In Hong Kong, students in international schools had significantly lower myopia prevalence than those in local-styled schools (Lam et al., 2004). Whereas in Sydney, students in academically selective schools had a higher odds ratio of having myopia than those in comprehensive schools (Ip et al., 2008c). However, an intense education modality and the higher academic performances were associated with longer time spent in studying and less time in OA (Ip et al., 2008c), which are the risk factors for myopia (Ip et al., 2008c; Rose et al., 2008a).

However, educational factors cannot completely explain the difference in myopia prevalence among ethnicities and birth cohorts. After adjustment for educational level, military conscripts with Chinese ethnicity still had a significantly higher prevalence of myopia in Singapore (Wu et al., 2001) compared with Malays and Indians. Similarly, Chinese students in the international schools in Hong Kong (Lam et al., 2004) also had a higher myopia prevalence compared with Caucasians and mixed-race Chinese. In Europe, more recent birth cohorts had higher myopia prevalence than older cohorts even if the educational levels were similar (Williams et al., 2015). These findings suggest the effect of cultural difference on myopia prevalence across ethnicities and generations.

1.3.2.4 Myopia and living environment

In addition to vision-related activities, the living environment may be associated with myopia prevalence. Children and adolescents spend most after-school time at home, doing homework and studying unless they have to attend cramming schools or tutorial classes. Common leisure activities are also most likely to take place at home (e.g. watching television, playing computer games, and leisure reading) or in the neighbourhood (e.g. going out for a walk, window shopping, and playing sports). Hence, the living environment could be an important contributor to children’s refractive development.

Urbanicity, which is the degree of how urban an area is, is also associated with myopia prevalence. The Refractive Error Study in Children (RESC) is a multi-national study, which unified the sampling and measurement protocol for ease of comparison of childhood refractive error among countries (Negrel et al., 2000). Interestingly, the study reported a consistently higher myopia prevalence in more urbanised regions (Maul et al., 2000; Pokharel et al., 2000; Zhao et al., 2000; Dandona et al., 2002; Murthy et al., 2002; Naidoo et al., 2003; He et al., 2004; He et al., 2007). Even within a country, a higher myopia prevalence was reported in urbanised regions in India [New Delhi vs. Mahabubnagar (Dandona et al., 2002; Murthy et al., 2002)] and China [Guangzhou vs. Shunyi vs. Yangxi (Zhao et al., 2000; He et al., 2004; He et al., 2007)], which was independent of age, gender, and parental myopia (He et al., 2009). In Australia, the SMS reported the amount and prevalence of myopia in the greater Sydney region (Ip et al., 2008b). The region was divided into 14 areas according to the statistical bureau, then classified into 5 levels based on the population density from region 1 (outer suburban) to region 5 (inner city). There was an increasing trend of myopia prevalence, as well as a myopic shift in refractive error, from low to high population densities in the outer suburban area to the inner city. China is rapidly urbanising, with millions migrating from the countryside to cities. With increasing population densities and socioeconomic status, the urbanised area within a town was also reported to impose a higher risk of myopia compared with the rural area (Zhang et al., 2010). In Barcelona, researchers investigated the effect of green space exposure on spectacle usage in children (Dadvand et al., 2017), inferring myopia prevalence, in the city. Green space near the children’s home, schools, and commuting routes were characterised using satellite data. The results showed that increased exposure to green space was associated with a lower percentage of spectacle usage, as well as the spectacle need incidence over three years.

In addition to the surrounding environment, the effect of housing is a controversial issue regarding its association with myopia prevalence. A study in Singapore classified the type of housing based on the number of rooms in government apartments and private housing and reported that it did not appear to affect either the prevalence or the amount of myopia (Saw et al., 2000). In contrast, the SMS reported that children living in smaller, confined housing types, such as apartments (26.3%) and terraced houses (21.4%), had a higher risk of having myopia than those living in stand-alone and separate houses (11.3%) (Ip et al., 2008b). In China, the height of the building was reported to be associated with myopia, with higher odds for the children to have myopia in taller buildings (Wu et al., 2016). Children living in a rental home were also reported to be at higher risk of myopia than those living in a private property (Tideman et al., 2018). Rather than being an independent factor, the housing type and home size were often regarded as an indicator of socioeconomic status, in which higher parental education and household income was reported to be associated with a higher myopia prevalence (Saw et al., 2000; French et al., 2013; O'Donoghue et al., 2015).

1.4 Emmetropisation

Emmetropisation is a visually guided process, in which the eye modulates its refractive components to achieve emmetropia (i.e. vision free from refractive errors). To date, the mechanism of emmetropisation is not fully understood. However, several factors have been reported to be influential on emmetropisation, in terms of the endpoint shift and the rate of change in refractive status. Also, in recent studies, it was suggested that the emmetropisation endpoint may not necessarily be zero dioptre, but mild hyperopia, in both children and adults (Morgan et al., 2010; Rose et al., 2016). Better understanding the mechanism(s) of emmetropisation, whether it can be retarded, or even reversed, may help in developing interventions to quell the soaring trend of myopia.

1.4.1 Effect of visual form deprivation on emmetropisation

Early studies reported that human eyes would fail to emmetropise if the vision was disrupted due to congenital diseases (Rabin et al., 1981), such as retro-lental fibrosis, blepharoptosis, or an extensive persistent pupillary membrane, which degraded the retinal image quality. The affected eyes had greater myopic refractive error and longer axial length (AL). However, the outcomes in humans were less predictable than those reported in animal studies (von Noorden and Lewis, 1987).

Like humans, several animal models exhibit myopic change when their form vision is interrupted. This myopisation is called form-deprivation myopia (FDM) and is a common type of myopia-inducing method employed in animal studies. Lid-sutured macaque monkey eyes developed myopia and ocular enlargement (Wiesel and Raviola, 1977). However, such developments would only occur in monkeys raised in an illuminated environment, but not in a dark environment (Raviola and Wiesel, 1978), indicating that visual input is essential in eye growth. Myopisation caused by lid-suture also occurs in tree shrews (Sherman et al., 1977), kittens (Kirby et al., 1982; Yinon et al., 1984), chicks (Yinon et al., 1980), common marmosets (Troilo and Judge, 1993), mice (Tejedor and de la Villa, 2003), and fish (Shen et al., 2005). As well as lid-suture, opaque diffusers could also deprive form vision and cause myopia in chicks (Wallman et al., 1978), mice (Tkatchenko et al., 2010), guinea pigs (Howlett and McFadden, 2006), tree shrews (Siegwart Jr and Norton, 1998), marmosets (Troilo et al., 2000), and monkeys (Smith and Hung, 2000). These studies using opaque diffusers mimicked a compromised ocular media, e.g. corneal opacification (Wiesel and Raviola, 1979), and caused FDM. The response to the form-deprivation was reported to be a graded phenomenon, which depended on the retinal image clarity (Smith and Hung, 2000). The more the image was blurred (reduced contrast), the greater the FDM resulting.

After ceasing the treatment, i.e. removing the lid-suture or the opaque diffuser, the refractive error of the animal would gradually return to baseline, close to emmetropia (Wallman and Adams, 1987; Qiao-Grider et al., 2004; Shen and Sivak, 2007; Zhou et al., 2007). The plasticity of development of FDM and its recovery decreased with the age of the animals (Siegwart Jr and Norton, 1998; Troilo et al., 2000; Troilo and Nickla, 2005; Norton et al., 2010).

1.4.2 Lens-induced emmetropisation, its origin, and role of choroid

Emmetropisation can also be interrupted by rearing animals with ophthalmic lenses. The eye differentiates, then becomes hyperopic under a positive defocus lenses, while becoming myopic under a negative defocus lens, i.e. lens-induced hyperopia and lens-induced myopia. Later, the changes in the eyeball make the resultant retinal image less blurred under the lens worn during development. Although the emmetropisation is interrupted by the imposed defocus causing ametropia, one could consider that the eye is emmetropising, compensating for the imposed refractive error. This phenomenon has been observed in various species of animals, including but not limited to chicks (Schaeffel et al., 1988; Schaeffel et al., 1990; Irving et al., 1991; Troilo and Wallman, 1991; Park et al., 2003), mice (Tkatchenko et al., 2010), cats (Smith et al., 1980; Nathan et al., 1984), guinea pigs (Howlett and McFadden, 2009; Lu et al., 2009), tree shrews (Norton et al., 2010; Siegwart Jr and Norton, 2010), marmosets (Whatham and Judge, 2001), and monkeys (Hung et al., 1995; Smith and Hung, 1999). This compensatory response is also a graded phenomenon, in which the eye compensates according to the magnitude of the induced lens power. However, the response was relatively less accurate and less predictable in higher vertebrates and primates (Troilo et al., 2019). Also, the threshold of defocus detection was different among species (Schmid and Wildsoet, 1997c; Smith and Hung, 1999), in which chicks were able to compensate for a larger amount of defocus than primates.

Like FDM, the plasticity of the compensatory response towards lens-induced refractive error decreases with age in different species, including chicks, tree shrews, marmosets, monkeys, and fishes (Irving et al., 2015). This characteristic is coherent to human myopia stabilisation occurring around age of 15 years (COMET, 2013; Scheiman et al., 2014). In addition to age, recovery from lens-induced ametropia would also be inhibited by optical correction (McBrien et al., 1999; Wildsoet and Schmid, 2000); i.e. the eye would cease emmetropising when the retinal image is clear despite the ametropia without the lenses.

Despite most visual signal / perceptual processing being located in the cortical level, lens-induced compensatory refractive changes and form-deprivation myopisation are believed to originate at retinal level. Chick eyes turned myopic under form-deprivation even if the optic nerve was sectioned (Troilo et al., 1987), despite the time course of response being changed by the nerve section. In primates, some species of monkeys showed FDM after cutting the optic nerve (Raviola and Wiesel, 1990). Lid-sutured tree shrews demonstrated FDM, even in the presence of tetrodotoxin blocking action potential (Norton et al., 1994). With respect to lens-induced ametropia, chick eyes were able to detect positive and negative defocus to become hyperopic and myopic respectively after either or both optic nerve and ciliary nerve section (Schmid and Wildsoet, 1996). However, the accuracy of the lens compensation was poorer compared with those with intact innervation. In addition, refractive recovery was inhibited by optical correction in chick eyes with optic nerve section (Wildsoet and Schmid, 2000). The results of lens-induced ametropia with ciliary nerve section suggested that accommodation is not essential for the eye to detect defocus (Schmid and Wildsoet, 1996; Wildsoet, 2003).

Although the exact mechanism remains unknown, many believe that choroidal change precedes emmetropisation (Zhu et al., 2005; Wang et al., 2016; Lau et al., 2019). In animal models, the choroid becomes thickened in response to a positive lens, while thinned in response to a negative lens (Wallman et al., 1995). Unlike the retina, the choroid is rich in vascular tissue and can change its thickness to a great extent. It has been suggested that changes in choroidal thickness were to alter the plane of the superficial retina, such that the retinal image would be more focused (Wallman et al., 1995). In humans, choroidal thickness is highly correlated with the degree of myopia (Read et al., 2013; Wei et al., 2013; Jin et al., 2016), whereby the higher the myopia, the thinner the choroid. The human choroid also exhibits the ability to vary its thickness under defocus. In a human study, children were asked to watch a movie under full correction in one eye, while experiencing defocus in the other eye for two hours, followed by two hours full correction for both eyes (Wang et al., 2016). Measurements showed rapid and reversible thickening and thinning under positive and negative defocus, respectively. Thickening of the choroid was also observed in children with myopia control interventions such as atropine treatment (Zhang et al., 2016) and orthokeratology (Li et al., 2017b; Lau et al., 2019).

The real world, however, is rarely fixed like an experimental setting, in which the treated eye is always under the exposure of a single defocus. Instead, the eye always experiences simultaneous positive and negative defocus of various magnitudes with different spatial extents (Tse et al., 2007; Flitcroft, 2012). To simulate a simultaneous defocus condition, researchers applied special ophthalmic lenses with concentric rings of alternative powers to chicks (Tse et al., 2007; Woods et al., 2013), guinea pigs (McFadden et al., 2014), marmosets (Benavente-Perez et al., 2012), and rhesus monkeys (Arumugam et al., 2014). Under the competing defocus, the eye tended to emmetropise to a point between the two powers, but closer to the less myopic power. The emmetropisation endpoint depended not only on the magnitudes of the two constituent powers, but also the area ratio of the two powers on the lens (Tse et al., 2007), indicating that spatial integration of defocus could modulate emmetropisation.

1.4.3 Other factors affecting emmetropisation

1.4.3.1 Astigmatism

Astigmatism is another major refractive error, affecting approximately 40% of the teenage population (Kee, 2013) and requiring correction by cylindrical lenses. Astigmatism mainly originates from corneal and lenticular toricity, in which the curvatures are different along meridians. The prevalence of astigmatism is significantly correlated with myopia, but only to a moderate extent (Guggenheim and Farbrother, 2004).

Fewer studies have investigated astigmatism than myopia. Only two animal models chicks (Irving et al., 1995; Schmid and Wildsoet, 1997b; Thibos et al., 2002; McLean and Wallman, 2003) and monkeys (Kee et al., 2004) have been used in astigmatism studies. Emmetropisation also includes astigmatic error, by which the eye is able to compensate for the imposed cylindrical power. However, the endpoint of astigmatic emmetropisation is less predictable than imposed spherical power. Most studies found that the eye under the imposed plano-cylindrical lenses tended to emmetropise towards the circle of least confusion (Irving et al., 1995; Thibos et al., 2002). In contrast, when the eyes were treated with cross-cylindrical lenses, there was a bimodal shift so that the eyes emmetropised towards either one of the two astigmatic foci (mainly the more hyperopic one) (McLean and Wallman, 2003; Kee et al., 2004).

Astigmatism in human eye showed a controversy in myopia development. In a clinic-based population, the prevalence of astigmatism increased from 17.8% in childhood, reaching the highest at 38.1% in 21 to 30 years age group, then dipped towards to older age (Leung et al., 2012). Magnitude of stigmatism was reported to increase over time in childhood in some studies (Gwiazda et al., 2000; Fan et al., 2004b), but decrease or no change in some others (Goss and Shewey, 1990; Chan et al., 2018). The relationship between astigmatism and juvenile myopia progression was also controversial. Chan et al. suggested an independency of astigmatism on spherical refractive error change (Chan et al., 2018), but Fan et al. and Gwiazda et al. suggested astigmatism in childhood may predispose subsequent myopia progression (Gwiazda et al., 2000; Fan et al., 2004b). In addition, peripheral astigmatism was suggested to be a cue for the peripheral retina to detect the direction of a defocus (Howland, 2010), which will be discussed in Section 1.4.4.

1.4.3.2 Lighting intensity and chromatic aberration

In animal studies, high ambient light exposure was protective against FDM and negative lens-induced myopia in chicks (Ashby et al., 2009; Ashby and Schaeffel, 2010), guinea pigs (Zhang and Qu, 2019), tree shrews (Siegwart Jr et al., 2012), and monkeys (Smith et al., 2012; Smith et al., 2013b) under simultaneous defocus (Zheng et al., 2018). The protective effect of the ambient light increased with the intensity, gradually from 500 lux to 15,000 lux, and finally 30,000 lux (Ashby et al., 2009). Another study demonstrated the same trend from 500 lux to 10,000 lux, then 20,000 lux, but a plateau was reported between 20,000 lux and 40,000 lux (Zheng et al., 2018).

As discussed in Section 1.3.2.2, OA could protect children from myopia, in which the effect was believed due to the exposure to a bright light intensity (Ngo et al., 2013). Interestingly, the effect of night-time lighting (or dim ambient light) in myopia development is controversial. Quinn and co-workers reported an association between night-time lighting during infancy and myopia prevalence (Quinn et al., 1999), while subsequent studies counter-reported there was no such association (Gwiazda et al., 2000b; Zadnik et al., 2000). In chick studies, dim light levels were reported to be myopiagenic (Feldkaemper et al., 1999; Cohen et al., 2011). In contrast, lid-sutured monkeys (Raviola and Wiesel, 1978) and kittens (Yinon et al., 1984) raised in whole-time complete darkness did not develop FDM. However, after exposure to a light-dark cycle, tree shrews developed axial elongation and myopia after eleven-day complete darkness. This may imply that the circadian rhythm, which is regulated by dopamine (Chakraborty et al., 2018), can be altered by light exposure. Dopamine signalling was also found to co-exist in light-dark oscillations of ocular parameters, (Stone et al., 1995) as well as experimental myopia models (Stone et al., 1989).

As well as its intensity, the chromaticity of the outdoor lighting differs from that of indoors, which was also believed to influence visually guided emmetropisation. In lower vertebrates, fish (Kröger and Wagner, 1996), chicks (Seidemann and Schaeffel, 2002), mice (Strickland et al., 2020), and guinea pigs (Qian et al., 2013) showed slower axial eye growth or a hyperopic shift when exposed to short-wavelength light when compared with long-wavelength light. In contrast, higher vertebrates such as monkeys (Smith et al., 2015; Hung et al., 2018) and tree shrews (Gawne et al., 2017) showed an opposite response, in which long-wavelength light inhibited axial eye growth or caused a hyperopic shift.

1.4.3.3 Spatial and temporal frequency of the visual stimulus

It has also been suggested that the efficacy of emmetropisation depended on the spatial frequency of the visual stimulus, in which mid to high spatial frequencies were shown to be effective in preventing FDM (Schmid and Wildsoet, 1997a), and was critical in compensational eye growth to myopic defocus (Diether and Wildsoet, 2005). These mid to high spatial frequency constituents were found to be richer in natural scenes and were reported to promote a more accurate emmetropisation in chicks (Hess et al., 2006), while in contrast, the spatial frequency content of urban and indoor environments may be a potential risk factor for myopia epidemic, especially in developed countries (Flitcroft et al., 2020). In a more recent chick study, higher spatial frequency was found to minimise myopisation induced by negative lenses, when compared with lower spatial frequency stimuli (Chin, 2018). This effect was also found to be a graded response, in that myopisation was more rapid when the constituent of low spatial frequency increased. In a human study, positive defocus increased, while negative defocus decreased, the retinal responses measured by multifocal electroretinography under low spatial frequency stimulus, but not high spatial frequency stimulus (Chin et al., 2015). This indicates that spatial frequency composition can influence the human retina responding to different optical defocus.

Time exposure and temporal integration to the visual stimulus could also modulate the emmetropisation response. For form-deprivation, brief periods of unrestricted vision could counterbalance the effect and reduce FDM in chicks (Napper et al., 1995) and monkeys (Smith et al., 2002). Not only clear unrestricted vision, but also intermittent bright light exposure demonstrated an inhibitory effect on FDM (Lan et al., 2014). This non-linear temporal integration was also demonstrated in lens-induced myopia in chicks (Schmid and Wildsoet, 1996; Winawer and Wallman, 2002; Winawer et al., 2005), tree shrews (Shaikh et al., 1999), guinea pigs (Leotta et al., 2013), and monkeys (Kee et al., 2007), even after ciliary nerve section (Schmid and Wildsoet, 1996). Brief periods, as short as 15 minutes, to interrupt continuous lens or diffuser wear could prevent the eye from axial elongation (Kee et al., 2007), in which the interruption was more effective in the earlier phase of the lens or diffuser rearing period (Benavente-Perez et al., 2019). When alternating myopic and hyperopic defocus were presented, myopic defocus dominated over hyperopic defocus even if the hyperopic defocus was presented for five times longer (Winawer and Wallman, 2002; Zhu et al., 2003). In clinical studies, temporal integration was significantly associated with myopia development in children (Xiong et al., 2017; Huang et al., 2020). Short episodes of time spent outdoors or discontinuation of near work, which are to break the continuous myopiagenic stimulation, were reported to be protective against myopia progression.

1.4.4 The locality of emmetropisation, central, and peripheral refraction

1.4.4.1 Regional eye growth in animal studies

Emmetropisation often refers to the on-axis refractive power, leading to a clear retinal image for distant objects. However, studies have found that not only the central, but also the peripheral retina could respond to visual stimuli to modulate eye growth. For instance, pigeon eyes, as well as other birds, would have emmetropia in the upper visual field, but became progressively more myopic in the lower visual field (Fitzke et al., 1985; Hodos and Erichsen, 1990). Such localised eyeball growth is also observed in other species, such as reptiles (Vietnamese Leaf turtle) (Henze et al., 2004), amphibians (frogs) (Schaeffel et al., 1994), and mammals (horse) (Harman et al., 1999) (guinea pig) (Zeng et al., 2013). The localised myopic change can be demonstrated in experimental settings, and not only along the vertical axis. Wallman and co-workers reported that chick eyes would regionally enlarge on the horizontal hemi-field according to the location of the form-deprivation (Wallman et al., 1987), while the other half would remain unchanged resulting in an asymmetric eyeball shape. Other species, such as guinea pigs (McFadden, 2002; Zeng and McFadden, 2010) and monkeys (Smith et al., 2009a) also showed similar characteristics following partial occlusion or hemi-retinal deprivation. In addition to FDM, the peripheral retina of various animal eyes have also been observed to respond to defocus induced by optical lenses and emmetropise locally, including chicks (Miles and Wallman, 1990), guinea pigs (Zeng et al., 2013), and monkeys (Smith et al., 2010; Smith et al., 2013c).

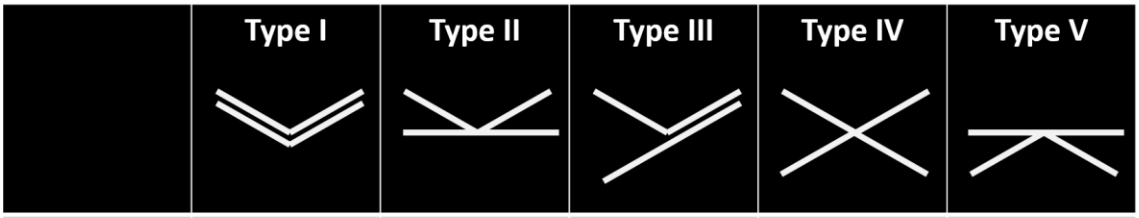
In addition, peripheral retinal defocus could modify axial eye growth and refractive error. With the use of a central plano zone, myopic and hyperopic peripheral defocus was demonstrated in chicks (Liu and Wildsoet, 2011), guinea pigs (Bowrey et al., 2017), and marmosets (Benavente-Pérez et al., 2014) to accelerate or inhibit myopia progression, respectively. The role of the peripheral retina was further suggested to be critical because emmetropisation could still take place even if the fovea was compromised. Following foveal laser ablation, monkeys were deprived from peripheral vision using diffusers with central 4 mm and 8 mm clear apertures (Smith et al., 2005). Monkeys with the 4 mm aperture became significantly more myopic than those with 8 mm aperture. In a later study, monkeys, both with and without foveal laser ablation, showed an axial myopic shift after being exposed to a "peripheral negative lens" with a central 6 mm clear aperture (Smith et al., 2009b). The characteristics of the peripheral retina, its role in myopia control strategies, and the implementation in myopia control devices, are discussed in Section 1.4.5 below.

1.4.4.2 Peripheral refraction in humans

Although peripheral refraction was first reported to be related to axial refractive error and acquired myopia in 1971 (Hoogerheide et al., 1971), only in the last two decades has it been widely reported in epidemiology studies and applied in the design of myopia control strategies. Instead of studying the absolute value of peripheral refractive error (PRE), researchers reported the importance of relative peripheral refractive error (RPRE), which is defined as the vectoral difference between absolute PRE and the axial refractive error (Thibos et al., 1997). Various studies reported that myopic eyes are more prolate-shaped and peripherally hyperopic (Mutti et al., 2000; Seidemann et al., 2002; Atchison et al., 2006; Mutti et al., 2007; Mutti et al., 2011; Sng et al., 2011; Lee and Cho, 2013). It was suggested that relative peripheral hyperopia was associated with on-axis myopia progression (Smith et al., 2013a), as the peripheral retina could recognise hyperopic defocus for the eye to emmetropise accordingly. The experimental results in animal models were promising as described in Section 1.4.4.1. However, epidemiology studies determined that baseline peripheral hyperopia was not predictive for subsequent myopia progression in school-aged children (Mutti et al., 2011; Atchison et al., 2015). The effects of peripheral hyperopia still remain controversial.

The role of the peripheral retina in myopia development may be more than the amount of peripheral hyperopia. It has been suggested that the peripheral retina can distinguish the sign of defocus by comparing the shells of peripheral astigmatism (Howland, 2010; Charman, 2011; Atchison and Rosén, 2016). When the off-axis light rays pass through an optical lens, it would create oblique astigmatism, which can be analogised as the astigmatism in the peripheral refraction, i.e. peripheral astigmatism. Two shells of tangentially and radially oriented lines would be formed onto two focal planes of different image distances, respectively. In the early 1930s, peripheral refraction was measured by a modified refractometer (Ferree et al., 1931; Ferree and Rand, 1933) and it was concluded to be related to axial refractive error and ocular shape. These findings were revisited and summarised into five types of skiagrams (Figure 1.1, adapted from Rempt et al., 1971). The characteristics of peripheral astigmatism were suggested to provide cues for the eye to emmetropise accordingly (Howland, 2010; Charman, 2011; Atchison and Rosén, 2016).

Another proposal for the role of the peripheral retina in modulating emmetropisation is the effect of distribution of the defocus profile in the peripheral visual field (Flitcroft, 2012). It is widely accepted that increased OA lowers the risk and progression of myopia (Xiong et al., 2017). Although the beneficial effects are usually attributed to the light intensity, others have suggested that the difference between outdoor and indoor defocus profile may also contribute to myopia development (Tse et al., 2007; Flitcroft, 2012; García et al., 2018; Garcia et al., 2019). In an outdoor environment, objects are usually far away, creating a generally low-magnitude and more even vergence to the eye. In contrast, objects are usually closer to eye indoors, resulting in the peripheral visual field experiencing a widely varied vergence across the retina (Sprague et al., 2016; García et al., 2018), although a weakness of such theory was the incompatibility of experimental results in local control of axial elongation.



	Type I	Type II	Type III	Type IV	Type V
P(90)	Hyperopic	Hyperopic	Hyperopic	Hyperopic	Emmetropic
P(180)	Hyperopic	Emmetropic	Asymmetric	Myopic	Myopic

Figure 1.1 Types of skiagram of peripheral refraction (adapted from Rempt et al., 1971). On-axis refractive error approximately increased from left to right (from myopic to hyperopic)

1.4.5 Clinical implications and optical myopia control interventions

To tackle the increasing prevalence of myopia, clinicians have been strongly promoting the concept of myopia control. In addition to the effects of OA, as mentioned in previous sections, active interventions on high-risk children can be implemented to prevent rapid myopia progression. One approach is pharmaceutical intervention using atropine (Chua et al., 2006; Chia et al., 2012; Yam et al., 2019), pirenzepine (Siatkowski et al., 2004; Tan et al., 2005; Siatkowski et al., 2008), or 7-methylxanthine (Trier et al., 2008). However, this section will focus on optical strategies, arising from the optical interventions which modulated emmetropisation in animal experiments.

1.4.5.1 Under-correction and lag of accommodation

The eye can modulate its optical (e.g. crystalline lens, corneal power) and structural (e.g. eyeball size) components to correctly focus the image on the retina. Specifically, a positive lens creates myopic defocus, whereas a negative lens creates hyperopic defocus, which inhibits or promotes axial elongation, respectively, and hence modulates myopia progression (Wallman and Winawer, 2004). Therefore, theoretically, under-correcting myopia, so that the focal point would fall in front of the retina, could inhibit the rate of myopia progression. To investigate this, 18 children were fitted with mono-vision correction on their non-dominant eye (Phillips, 2005). It was found that the under-corrected eye had significantly slower myopia progression. In a larger sample of Chinese children, myopia progression over one year was found to be weakly negatively correlated with the amount of under-correction (Li et al., 2015c). The same study group also compared children without spectacles versus full spectacle correction (Sun et al., 2017). They claimed children with full correction had faster myopia progression over 2 years after adjusting for baseline refractive error, parental myopia, age, and other factors. However, a randomised controlled clinical trial involving young children with under-correction revealed a contrary result, in which the under-corrected group progressed faster than the control group (Chung et al., 2002). Similar results were reported in other studies (Adler and Millodot, 2006; Vasudevan et al., 2014). It was suggested that the different effects of under-correction among studies was related to the variation in the amount of under-correction (Sun et al., 2017), i.e. 0.50 D (Adler and Millodot, 2006), 0.75 D (Chung et al., 2002), and 1.31 D (Sun et al., 2017). As a result, under-correction for young myopes to control myopia progression remains controversial and may be a non-ethical approach in myopia control for practitioners.

Another aspect of emmetropisation is the lag of accommodation. When viewing near objects, the eye accommodates to increase the power of the crystalline lens and focuses the image on the retina. However, a mismatch between accommodation and the near demand creates either a lead or a lag of accommodation, imposing a myopic and hyperopic defocus on the retina, respectively. Myopes were reported to have a greater lag of accommodation than both emmetropes and hyperopes (McBrien and Millodot, 1986). The difference in lag of accommodation was proposed as a reason for the differential myopia progression rate (Gwiazda et al., 1993), despite a later study reporting that baseline lag of accommodation did not predict subsequent myopia progression (Mutti et al., 2006). Nevertheless, progressive additional lenses (PAL) (Shih et al., 2001; Edwards et al., 2002; Gwiazda et al., 2003) and bifocal lenses (Cheng et al., 2010; Cheng et al., 2014) have been suggested for myopia control. However, a study in Hong Kong revealed no significant difference between single vision lenses and PAL in controlling myopia progression over 2 years (Edwards et al., 2002). In the Correction of Myopia Evaluation Trial (COMET), the PAL produced a statistically significant, but small control effect of 0.20 D over single vision lenses over 3 years (Gwiazda et al., 2003). The study reported a more prominent control effect by PAL of 0.64 D over 3 years in children with high lag of accommodation and near esophoria (Gwiazda et al., 2004). Another spectacle means for myopia control are bifocal lenses. In a three-year randomised clinical control trial, executive bifocals reduced myopia progression by 0.81 D on average when compared with single vision lenses (Cheng et al., 2014). Furthermore, three prism-dioptre base-in executive bifocals had an even higher efficacy, reducing myopia progression by 1.05 D compared with single vision lenses. The limited efficacy of PAL and the cosmetic concern of bifocals have led to the increase in popularity of other myopia control strategies described in the following sections.

1.4.5.2 Peripheral defocus and competing defocus

Similar to on-axis defocus, manipulating peripheral defocus can also modulate axial eye growth. Special spectacle lenses have been designed to reduce peripheral hyperopic defocus to retard myopia progression (Sankaridurg et al., 2010; Hasebe et al., 2014; Lam et al., 2019). The efficacy of three spectacle lenses with special designs, in which increasing positive power was added surrounding the central clear aperture, has been reported (Sankaridurg et al., 2010). The differences between these designs were whether the power was added in a rotationally symmetrical pattern and the size of the central clear zone. However, all three lens designs showed no significant difference with the control single vision lenses on either peripheral hyperopia or myopia progression. In contrast, another lens design was the positive power with either +1.0 D or +1.5 D in the superior and inferior portions of the lens (Hasebe et al., 2014). While +1.0 D did not show any significant difference compared with the single vision lens, +1.5 D retarded progression a mean of 0.27 D over the two-year trial, which is similar to the efficacy of the conventional PAL. Despite the ineffectiveness of the previous ramp additional power designs, a randomised clinical trial, conducted to test the efficacy of a new lens design with positive defocus incorporated in multiple segments (DIMS), showed a 0.44 D retardation over a two-year period (Lam et al., 2019).

In addition to spectacle lenses, contact lenses based on the peripheral defocus theory were also used in clinical trials, resulting in approximately 20% to 70% retardation of myopia progression (Li et al., 2017a). The lenses are mainly divided into concentric (Anstice and Phillips, 2011; Lam et al., 2014) or aspheric designs (Sankaridurg et al., 2011; Walline et al., 2013; Pauné et al., 2015), of which some were multifocal contact lenses originally designed for presbyopes. The effect was similar for the two designs, but other factors, including lens wear compliance and wearing time, need to be considered for result interpretation. Daily wearing time was found to be associated with myopia progression, whereby the efficacy of myopia control increased from 28% in those subjects wearing their lenses for 4 hours per day to 60% in those wearing lenses for 8 hours (Lam et al., 2014).

Corneal reshaping by orthokeratology has become a popular means to control myopia progression for children in the last two decades. An orthokeratology lens is a rigid gas permeable lens, which has a flat central base curve and steep peripheral curves (termed reverse geometry). Children wear the orthokeratology lens overnight to reshape the cornea by flattening the central cornea, thereby correcting the myopia. It was originally designed to reduce refractive error in adults (Coon, 1982). The first randomised controlled clinical trial for myopia control was performed in 2012 (Cho and Cheung, 2012), after quasi-experimental studies using self or historical controls (Cho et al., 2005; Kakita et al., 2011). The reported efficacy in the randomised clinical trial was 43% over 2 years, which is within the range of 32% to 50% reported by other quasi-experimental and historical control studies. Most researchers attributed the success of orthokeratology to the mechanism of peripheral myopic defocus (Smith et al., 2013a), which is created by the steepening of the para-central cornea. Other explanations include changes in corneal biomechanics (Wan et al., 2018) and higher-order aberrations (Lau et al., 2018).

1.5 Review of measurement techniques for myopia study

1.5.1 Refractive error measurement

Clinically, automated refractive error measurement is usually confirmed by subjective refraction, which incorporates the patients’ responses, ensuring the maximum suitability and comfort in case an optical prescription is needed. In contrast, refractive error measurements in research studies require objectivity to avoid any subjective bias. Hence, objective refraction measurements, such as retinoscopy, aberrometry, and autorefraction, are usually performed in these studies.

1.5.1.1 On-axis refractive error

Most common autorefraction systems consist of an infra-red (IR) light source and a Badal lens system. The advantage of using IR radiation is the invisibility to the human eye, which does not interfere with subjective comfort or trigger pupillary or accommodative response. The Badal lens system aims to vary the optical vergence without changing the retinal image size, hence determining the refractive status of the eye.

"Virtual fogging" autorefractors, in which the fixation target locates inside the autorefractor at optical infinity, is widely used in clinical applications. In contrast, research studies more commonly adopt an "open-field" type autorefractor, e.g. Autoref R-1 (Canon Inc., Japan) (Matsumura et al., 1983; McBrien and Millodot, 1985), which allows a binocular free-space view at variable fixation distances. Modern models of open-field autorefractors including SRW-5000 (Shin-Nippon, Japan), NVision K5001 (Shin-Nippon, Japan), WR-5100K (Grand Seiko, Japan), and WAM-5500 (Grand Seiko, Japan), have shown good and reliable repeatability and reproducibility (Chat and Edwards, 2001; Davies et al., 2003; Sheppard and Davies, 2010; Mallen et al., 2015). Another advantage of using an open-field autorefractor is the ease of measuring PRE, which will be discussed in Section 2.1.2.

However, despite the implementation of various techniques, accommodation control is still insufficient, especially in children (Morgan et al., 2015). Non-cycloplegic autorefraction may over-estimate the prevalence and amount of myopia (Zhao et al., 2004; Choong et al., 2006; Fotedar et al., 2007). However, under certain circumstances, where cycloplegia is not feasible, e.g. avoidance of altering astigmatism (Asharlous et al., 2016) or low compliance of the subject, non-cycloplegic refraction is still a valid method for providing information regarding a child's general refractive error development (Williams et al., 2008). To better interpret childhood refractive status in non-cycloplegic studies, other methods to minimise the effect of accommodation, such as fogging lenses (Queirós et al., 2008) and axial-length-to-corneal-radius-of-curvature (AL/CR) (Section 2.2.3) analysis can be applied.

1.5.1.2 Peripheral refractive error

The eye does not refract the same at different locations across the whole visual field. Thus, PREs are quite different from the on-axis refractive error. Since the peripheral retinal input has been suggested to modulate axial refractive error (Smith et al., 2005; Smith et al., 2009b), evaluation of PRE is believed to allow further understanding of the process of emmetropisation. As discussed in Section 1.4.4.2, PRE is usually presented as absolute PRE (the measured value at certain eccentricity) and RPRE (the difference between absolute PRE and axial refractive error). For ease of calculation, the refractive error is usually transformed from sphero-cylindrical form into vector form, i.e. M, J_0, and J_{45} (Thibos et al., 1997).

The measurement of PRE can be performed using an aberrometer or open-field autorefractor (Atchison, 2003). Among various models of open-field autorefractor, the NVision K5001 has been reported to give good intra- and inter-visit PRE repeatability in myopic children (Lee and Cho, 2012), in which the mean vectoral differences were less than 0.05 D across the visual field. For other models, the SRW-5000 and WAM-5500, the test-retest vectoral differences were 0.17 D and 0.10 D at 35° and 40° eccentricities, respectively (Atchison et al., 2005; Moore and Berntsen, 2014). In addition, a large magnitude of duction may cause changes of ocular shape, which would subsequently affect the values of PRE. However, within a period of 2.5 min and ±30° of eccentric fixation, the measured PRE would not have any significant difference when compared with those obtained in the primary straight-ahead position of the eye (Radhakrishnan and Charman, 2008). Table 1.2 summarises the reliability measures for different models of the open-field autorefractor.

Table 1.2 Reliability of open-field autorefractor models

	On-axis refraction		Peripheral refraction
	±0.50 D	±0.25 D	Test-retest difference
SRW-5000	97%	74%	0.17 D
	(Mallen et al., 2015)		(Atchison et al., 2005)
NVision K5001	96%	78%	0.05 D
	(Davies et al., 2003)		(Lee and Cho, 2012)
WAM-5500	91%	73%	0.10 D
	(Sheppard and Davies, 2010)		(Moore and Berntsen, 2014)

1.5.2 Ocular biometry

During emmetropisation, the eye modulates its physical parameters to alter its refractive state. Thus, ocular biometry could provide a secondary perspective to monitor refractive development, especially in children. There are many ocular biometry parameters, including AL, anterior chamber depth, keratometry, and posterior ocular shape. Two representative parameters, corresponding to axial and refractive myopia, AL and keratometry, respectively, were the focus of this study.

1.5.2.1 Axial length

AL is defined as the distance along the visual axis between the corneal apex to the posterior ocular surface. In children, the contribution of AL to the refraction of the eye increases with age (Ip et al., 2007), increasing from 24% in children at age of 6 years to 49% at 12 years. Common measurement techniques include ultrasound A-scan and IR partial coherence interferometry. Depending on the type of measurement, there is a slight difference in the reflection of various non-ionizing radiation from the posterior ocular surface. For example, ultrasound reflects on the anterior retinal surface, while IR reflects on the retinal pigment epithelium.

As traditional ultrasound A-scan requires an applanation technique with local anaesthetics or water-immersion measurement, non-contact partial coherence interferometry (Drexler et al., 1998) is currently more commonly used for monitoring childhood refractive development. Although the two techniques showed good agreement in adults (Haigis et al., 2000), partial coherence interferometry achieved better repeatability than ultrasound A-scan in children (Carkeet et al., 2004). The most widely used partial coherence interferometer is IOLMaster (Carl Zeiss, Germany) (Santodomingo-Rubido et al., 2002). The repeatability of IOLMaster AL measurement in children was approximately ± 0.05 mm (Carkeet et al., 2004; Chan et al., 2006). As a one-millimetre change in AL accounts for approximately 1.0 D refractive shift (Ip et al., 2007; He et al., 2015b), 0.05 mm error is negligible.

1.5.2.2 Keratometry

Occasionally, a long AL does not represent high myopia and vice versa. This would be due to the corneal curvature, which balances the weighting of the AL on refractive error. The cornea is indeed aspherical, thus the curvature varies along the corneal eccentricity. The keratometry value is the power of the best-fit sphere over the central cornea. Commonly, the keratometry reading is in the form of either power (in dioptre) or corneal radius of curvature (CR, in mm) along the flattest and steepest meridian.

Measurement of the CR differs among devices, being calculated from the first Purkinje image over different sizes of the central cornea. RK-F1 (Canon Inc., Japan), Javal-Schiötz keratometer, and IOLMaster measure the diameter of the central cornea at 3.2 mm, 3.4 mm, and 2.3 mm respectively (Santodomingo-Rubido et al., 2002; Huynh et al., 2006; Elbaz et al., 2007). Although the CR measured by IOLMaster was slightly, but significantly steeper than by other devices (Santodomingo-Rubido et al., 2002; Huynh et al., 2006; Elbaz et al., 2007), it showed good repeatability for CR, especially in children, making it good for monitoring development.

1.6 Knowledge Gaps and Aims of Investigation

1.6.1 Constricted living environment as a risk factor for myopia development

Myopia prevalence is soaring world-wide, especially in the East and Southeast Asia. In addition to Eastern-Western cultural differences, the living environment could be another risk factor in Asian countries. An urban environment was found to be a risk factor for myopia prevalence in Sydney, Australia. Hong Kong is a highly urbanised city and living space is one of the most constricted in the world, while the myopia prevalence is one of the highest. Many Hong Kong children live and grow up in small flats and densely populated areas as in some other East Asian cities. Hence, a study to establish relationship between this constricted living environment and myopia is warranted.

1.6.2 Risk factors of peripheral optics other than peripheral hyperopia

It has been suggested that the peripheral retina is involved in modulating eye growth. However, despite the promising results of optical myopia control devices, the initial PRE was not predictive of myopia development in epidemiology studies. Thus, M in the peripheral field may not be the sole factor regulating the peripheral retinal input. Other than M, the amount of astigmatism is also considerable in the development of off-axis refractive error and as a major orientation dependent blur in the periphery. While most studies demonstrating the relationship between peripheral astigmatism and on-axis refractive error focused on J_0 and J_{45} components, a study, hence, investigating the specific pattern of this orientation-selected blur in Chinese schoolchildren, who are prone to myopia development, is warranted.

1.6.3 Relationship between defocus profile of the near work scene at home and myopia development, and its interaction with peripheral refraction

In a home environment, there may be certain characteristics, which favour myopia progression. Children in Hong Kong spend many hours tackling their schoolwork at home. Hence, the near work scene may be crucial, as the defocus from the scene is stimulating the children for hours every day. Most studies that have quantified near work have focused on time and one-dimensional working distance and largely ignored the unique characteristics of the visual scene.

However, optical stimulation of retinal signalling depends on the resultant retinal defocus affected by internal and external factors, which are the PRE and the visual environment, respectively. Various studies have extensively investigated PRE, but most failed to establish the relationship between PRE and on-axis refractive development. A possible explanation for such results may be the lack of the input from the external environment.

Hence, a study using objective measurements to investigate the three-dimensional spatial characteristics of the near work scene at home, and the relationship with myopia progression is warranted. In addition, investigation of the relationship between PRE and on-axis myopia progression, including, but not limited to, peripheral hyperopia and controlling of external environmental factors, such as home environment, is warranted.

Chapter 2 General Methodology

2.1 Methodology for Study I and Study II

2.1.1 Subjects

Subjects were recruited via local primary schools using cluster sampling between June 2015 and February 2016. The eighteen political districts in Hong Kong were divided into three clusters according the district population density (C.S.D., 2012). High population density referred to more than 30,000 persons per km^2, low population density referred to less than 10,000 persons per km^2, and medium population density was between these levels. Four primary schools were randomly selected from each cluster and invited to participate in the study (twelve schools in total). Eight schools finally agreed to participate. Two were from the low density cluster, three from the medium density cluster, and three from the high density cluster. Table 2.1 lists the sample sizes and exclusion criteria for subject recruitment. Written consent and verbal assent were collected from the parents / guardians and the subjects, respectively. All procedures followed the tenets of the Declaration of Helsinki and were approved by The Hong Kong Polytechnic University Human Subjects Ethics Subcommittee. Subjects who failed in vision tests were referred to seek help from an optometrist or an ophthalmologist.

Table 2.1 Sample size and exclusion criteria for Study I and Study II

		n
	Total invited	1235
	Participated	1173
	Final sample size in Study I	1075
	Final sample size in Study II	1052
	Exclusion criteria	Excluded
Age (Study I and Study II)	Below age of 7 and above 12 years	19
Residency (Study I)	Non-Hong Kong residents	15
Ocular health (Study II)	Strabismus (n = 12) Subnormal visual acuity (worse than LogMAR 0.0 equivalent, n = 5) Corneal opacity (n = 2)	19
Myopia control (Study I and Study II)	Received myopia control intervention Orthokeratology (n = 4) Bifocal lens (n = 25) PAL (n = 23) Atropine (n = 12)	64
Small pupil (Study II)	Unable to perform peripheral refraction under natural pupil	38

2.1.2 Data collection

2.1.2.1 Central (on-axis) and peripheral refractive error

In order to obtain accurate and reliable results for both central (on-axis) and peripheral refraction, an open-field autorefractor (NVision K5001, Shin-Nippon, Japan) was chosen for the current study. A total of five measurements within ±1.00 D variation were performed for the central and each peripheral location, as in previous studies (Atchison et al., 2006; Chen et al., 2010; Lee and Cho, 2012; Moore and Berntsen, 2014; Mutti et al., 2019). Following this, the “Representative Value” displayed by the instrument was extracted and recorded (Tang et al., 2014).

As the data collection was performed in the schools on normal school days, a cycloplegic agent was not applied to cause minimal disruption to the children’s learning. A distant fixation target of a Maltese cross of 2.4° angular size, was placed 6 m away from the eye to control for proximal accommodation. In addition to the one for on-axis refraction, four more Maltese crosses were placed at ±10° along the horizontal and vertical visual fields to measure peripheral refraction. Peripheral refraction at ±20° along the horizontal field was also measured in a 603-subject subset. These subjects did not significantly differ from the whole group: age 10.1 ± 0.9 years vs. 10.0 ± 1.1 years ($p = 0.83$); on-axis M (-1.37 ± 1.99 D vs. -1.32 ± 1.73 D, $p = 0.28$); J_0 (0.23 ± 0.37 D vs. 0.26 ± 0.38 D, $p = 0.15$); and J_{45} (0.01 ± 0.21 D vs. -0.01 ± 0.18 D, $p = 0.08$). Subjects were asked to keep their head stationary on the head rest and turn their eyes to fixate on the distant peripheral target during peripheral refraction measurement (Radhakrishnan and Charman, 2008). The peripheral refraction measurements in each direction (i.e. superior, inferior, nasal, and temporal) were completed within 2 minutes.

Refractive errors were decomposed into the spherical equivalent refraction (M), J_0, and J_{45} astigmatic components, and P(90) and P(180) using the following formulae (Thibos et al., 1997).

$$M = S + \frac{C}{2}$$

$$J_0 = -\frac{C}{2} \times \cos\alpha$$

$$J_{45} = -\frac{C}{2} \times \sin\alpha$$

$$P(90) = M - J_0$$

$$P(180) = M + J_0$$

where S is the spherical error, C is the cylindrical error, and α is the axis of negative cylinder convention. RPRE was calculated by subtracting the central refraction from the peripheral refraction. Only the data from right eye was analysed. Although accommodation was not pharmacologically controlled by a cycloplegic agent, it has been reported to minimally affect RPRE (Calver et al., 2007; Davies and Mallen, 2009), because of the consistent accommodative control during on-axis and peripheral measurements. Hence, RPRE would remain stable as it was the outcome of subtraction between the on-axis and peripheral measurements.

2.1.2.2 Ocular biometry

The IOLMaster (Carl Zeiss Meditec, Germany) was chosen for ocular biometry in the current study, because it showed good repeatability in validation studies and can measure AL and CR at the same time. Another advantage is the ease of measurement, enabling more rapid flow for a large sample of young subjects in a limited time. As in previous studies, five measurements of AL (with signal-to-noise ratio > 2.0) and three measurements of CR (discrepancy < ±0.1 D) were adopted in this study and the average value was extracted and recorded (Chan et al., 2006; Huynh et al., 2006; Elbaz et al., 2007).

As cycloplegia was not performed in Study I and Study II, the prevalence and amount of myopia may be over-estimated (Zhao et al., 2004; Fotedar et al., 2007; Morgan et al., 2015). In view of this, AL and AL/CR were used to represent the central refractive status to support results of non-cycloplegic autorefraction (Grosvenor and Scott, 1994), as these measurements are independent of accommodative status and strongly correlated with M (He et al., 2015b). In this study, M was strongly correlated with AL (Pearson's $r = -0.74$, $p < 0.001$) and AL/CR (Pearson's $r = 0.87$, $p < 0.001$).

Details of further data processing, questionnaires, and statistics are in the method session of Study I and Study II.

2.2 Methodology for Study III

2.2.1 Subjects

Fifty-nine subjects aged from 7 to 12 years were recruited from the client population of The Hong Kong Polytechnic University Optometry Clinic between Dec 2016 and Oct 2017. Their clinical records were reviewed for inclusion criteria (Table 2.2). Six subjects were excluded, of whom one had started orthokeratology, one had a major home renovation, and four were lost to follow-up during the study period. An additional three subjects were excluded because of their home environment, which will be discussed in Section 2.2.2.2. Written consent and assent were obtained from the parents / guardians and the subjects, respectively. All procedures followed the tenets of Declaration of Helsinki and the study was approved by The Hong Kong Polytechnic University Human Subjects Ethics Subcommittee.

Table 2.2 Sample size and inclusion criteria for Study III

	n
Participated in baseline	59
Came back to follow-up	55
Included in analysis	50
	Inclusion criteria
Age	7 - 12 years
Visual acuity	At least LogMAR 0.0 or equivalent
Ocular health	Clear ocular media
	No strabismus
Myopia control	No myopia control intervention
	(e.g. orthokeratology, progressive addition lenses)

2.2.2 Data collection and processing

2.2.2.1 Central (on-axis) and peripheral refractive error

Eye examinations were performed in the Optometry Research Clinic of the university, and the subjects were asked to follow-up after one year. An open-field autorefractor (NVision K5001, Shin-Nippon, Japan) was again chosen for measuring both central (on-axis) and PREs. Two drops of 1% cyclopentolate were instilled, each five-minute apart, and the cycloplegic autorefraction measured at least 30 minutes after the second instillation when no pupillary reflex was observed. Subjects were asked to fixate on the central and peripheral targets placed 3 m away from the eye. A total of five measurements within ±1.00 D variation were performed for central and each peripheral location, before the "Representative Value" displayed by the instrument was extracted and recorded, as mentioned above. AL was also measured, and axial elongation after a year (ΔAL) was noted as a secondary outcome in Study III. On-axis and horizontal peripheral refraction up to 30° on each side were measured at 10° intervals, seven positions in total. Subjects were asked to keep their head stationary on the head rest and turn their eyes to fixate on the distant peripheral target, as in Study II. The peripheral refraction measurements in each direction (i.e. superior, inferior, nasal, and temporal) were completed within 2 minutes.

Refractive errors were decomposed into M, J_0, P(90), and P(180) using the following formulae (Thibos et al., 1997).

$$M = S + \frac{C}{2} \qquad P(90) = M - J_0$$

$$J_0 = -\frac{C}{2} \times \cos \alpha \qquad P(180) = M + J_0$$

where S is the spherical error, C is the cylindrical error, and α is the axis of the negative cylinder convention. J_{45} was not analysed in the current study because of its small magnitude compared to the other vector components. RPRE was calculated by subtracting the central refraction from the peripheral refraction. Only the data from right eye was analysed.

RPRE at each peripheral position was obtained by subtracting the central value from the peripheral values. RPRE along the horizontal visual field was fitted with a quadratic equation: $RPRE = a(Eccentricity - b)^2 + c$, then the first coefficients (including a_M, a_{J0}, $a_{P(90)}$, and $a_{P(180)}$) were obtained (Atchison et al., 2006). Demonstration of good and poor quadratic fits was shown in Appendix. Positive and negative a_M represented relative hyperopia and myopia respectively, while positive and negative a_{J0} represented relative with-the-rule and against-the-rule astigmatism, respectively. Magnitude of $a_{P(90)}$ and $a_{P(180)}$ represented the blurriness of radial and tangential orientation of the image on the peripheral visual field, respectively.

2.2.2.2 Home visit and visual scene measurement

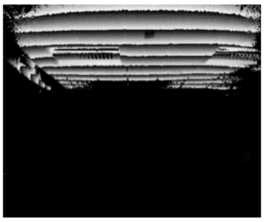
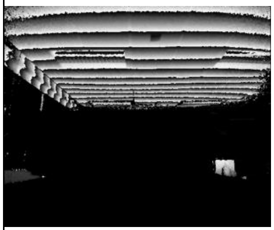
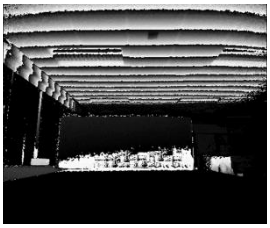
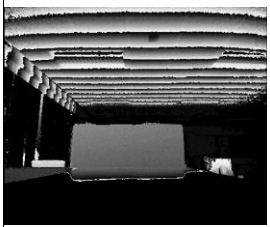
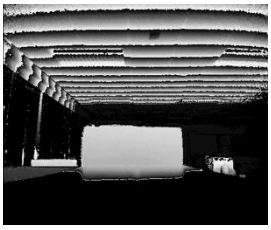
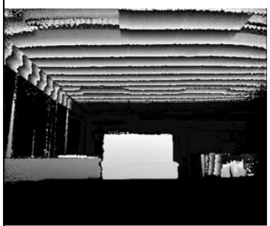
The home of each subject was visited to investigate their home environment before the baseline eye examination. Parents / guardians were interviewed to provide information, including daily time spent in front of the desk (T_{desk}) and weekly time spent outdoors (T_{OA}) by the subject, home size, and parental myopia. The near work scene was captured using the Kinect IR camera for Windows v2 (Microsoft Inc., US) to construct a three-dimensional spatial map. The Kinect measures the time of flight of near IR radiation to calculate the distance between the device and the measured objects. Its specifications are listed in Table 2.3. This model is more advanced in accuracy and precision than its older version Kinect v1 (Gonzalez-Jorge et al., 2015). Prior to the study, an accuracy validation of the one-dimensional working distance measured by the Kinect v2 was conducted . A rectangular box was placed at different distances from the Kinect (from 300 mm to 1000 mm, manually measured to the centre of the box). Then, the infra-red depth images, consisting of 512 x 424 pixels, were captured in five separate trials by directing the Kinect to focus on the centre of the box, mimicking the line of sight of the subject aligned to the centre of the box. Below 500 mm, the area of the rectangular box displayed zero values, indicating the Kinect's inability to capture at such short distances. For the distances above 500 mm, the Kinect showed sufficient accuracy and precision over different trials, as shown in Table 2.4. Outside of the targeted box, far-distant objects within the environment (most probably over 4.5 m away, e.g., the wall on the other side of the room) also displayed zero values, which exceeded the upper limit of the Kinect measurement. Only the one-dimensional working distance (by averaging the central 16 pixels) was validated, the eccentric objects in the environment were not taken into account.

Table 2.3 Specifications of Kinect for Windows v2 depth sensor

	Specifications
Resolution	512 x 424 pixel
Frame rate	30 fps
Light source	827 - 850 nm
Depth technology	Time of flight
Field of view (depth)	70 x 60°
Operative measuring range	0.5 - 4.5 m

The near work environment of the subjects, mainly their reading desk, was captured using the Kinect, because Hong Kong schoolchildren typically spend several hours after-school to study and complete their homework (H.K.P.T.U., 2015, 2018). Subjects were asked to perform near work sitting in front of the reading desk in their usual working posture, which was confirmed by their parents / guardians. The subjects were also asked to present the desk in its usual format, with their own book in place. Because of the characteristics of Kinect's operative range, the device was set 50 cm behind the position of the subject's eye. The Kinect was positioned to directly point at the visual target (e.g. the subject's exercise book) and was aligned with the subject's line of sight on a monopod to maintain stability. The scene was then captured for at least 5 s at an acquisition rate of 1 Hz, i.e. at least five depth images, with the subject absent from the measuring field. The depth maps were superimposed to obtain the average values, which were used for analysis.

Table 2.4 Validation of the accuracy of Kinect at different distances (average of the central 16 pixels)

Object distance (Kinect image)	Measurement by Kinect		Object distance (Kinect image)	Measurement by Kinect	
300 mm	Trial 1	0 mm	400 mm	Trial 1	0 mm
	Trial 2	0 mm		Trial 2	0 mm
	Trial 3	0 mm		Trial 3	0 mm
	Trial 4	0 mm		Trial 4	0 mm
	Trial 5	0 mm		Trial 5	0 mm
500 mm	Trial 1	500 mm	600 mm	Trial 1	598 mm
	Trial 2	0 mm		Trial 2	601 mm
	Trial 3	0 mm		Trial 3	600 mm
	Trial 4	501 mm		Trial 4	599 mm
	Trial 5	0 mm	Wilcoxon Z = 4.50 p = 0.41	Trial 5	600 mm
700 mm	Trial 1	701 mm	1,000 mm	Trial 1	999 mm
	Trial 2	701 mm		Trial 2	998 mm
	Trial 3	699 mm		Trial 3	999 mm
	Trial 4	699 mm		Trial 4	1,003 mm
Wilcoxon Z = 9.00 p = 0.66	Trial 5	699 mm	Wilcoxon Z = 6.50 p = 0.79	Trial 5	1,002 mm

Zeros indicate error (black in IR image), which cannot be measured by the Kinect. Every black-white interval in the IR image indicates 250 mm distance.

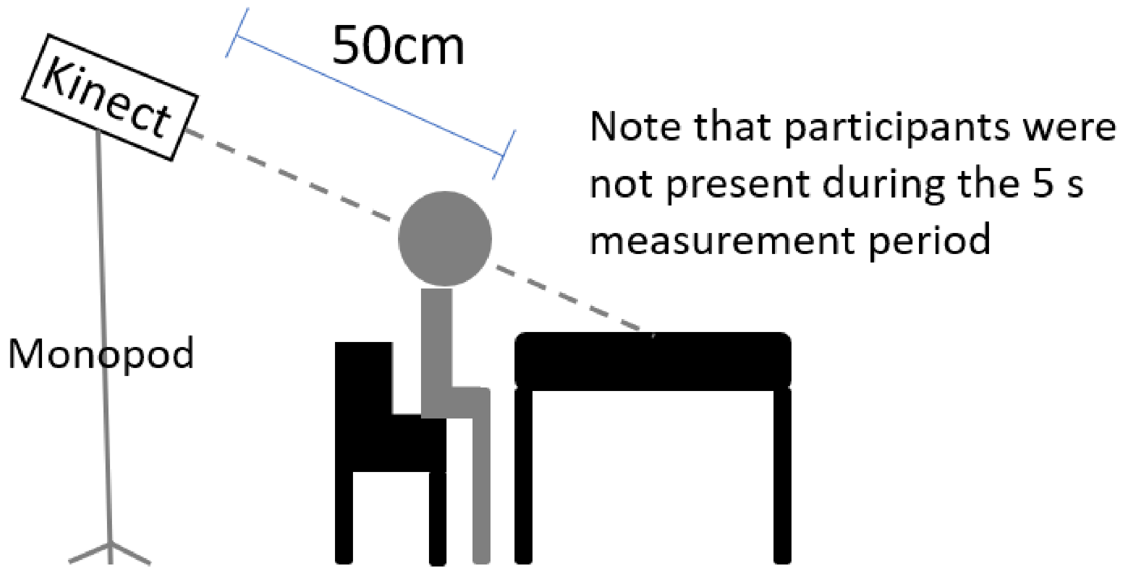


Figure 2.1 Schematic diagram of the measurement setup

As the Kinect was positioned behind the subject, the depth map was corrected by the actual viewing distance measured using a metric tape. The depth values were inversed to dioptric distances, and the central visual target was calibrated to zero. Therefore, objects further away than the visual target would create myopic scene defocus, while those closer would create hyperopic scene defocus. Because of the operative measuring range (maximum up to 4.5 m), if the measured scene contained a window, that area would be regarded as zero vergence (i.e. infinity distant with respect to the visual target). As mentioned in Section 2.2.1, three subjects were excluded because their desks were covered by a glass surface, which created specular reflection and prevented further processing of the defocus map, e.g. the approximate integration. A limitation of the method in this study was that the home scene parameters were obtained only at a single baseline time point. A subject with major home renovation was excluded, but minor movement of objects over the research period of other subjects were ignored in the data acquisition. Another limitation was the lack of eye tracking information, which overlooked the temporal interruption caused by eye movements and postural changes.

To represent the overall near work visual scene, two parameters were created: the dioptric volume (DV) and the standard deviation of defocus (SD_D). DV was defined as the approximate double integrals computed by the *trapz* function in Matlab (R2016b, MathWorks, US) over the central ±30° field of view, i.e. dioptres x degree^2, or D°°. As the measurement was taken with the Kinect placed 50 cm behind the subject, the angular distance between neighbouring pixels was more complicated than simply dividing 70° by 512 pixels along the horizontal direction, or dividing 60° by 424 pixels along the vertical direction. Instead, the angular distance between pixels was calculated by trigonometry based on the central working distance of each individual subject, separately along the horizontal and vertical directions, using Matlab. For instance, assuming the actual angular distance between neighbouring pixels along the horizontal direction for a subject with 40 cm to be θ, and metric distance to be *X* (which is unnecessary for calculation but for the ease of demonstration):

$$\tan 70° = \frac{X}{40cm + 50cm}, X = 90 \tan 70°$$

$$\tan \boldsymbol{\theta} = \frac{X}{40cm}, \boldsymbol{\theta} = \tan^{-1} \frac{90 \tan 70°}{40cm}$$

Central ±30° field was selected since this could accommodate various working distances of all subjects within the operating angle of the Kinect. In simple terms, DV represented the total amount of net defocus over the near work scene with respect to the visual target. SD_D was the standard deviation of the defocus values over the scene, which represented the dispersion of the defocus profile. Figure 2.2 summarises the data processing procedures.

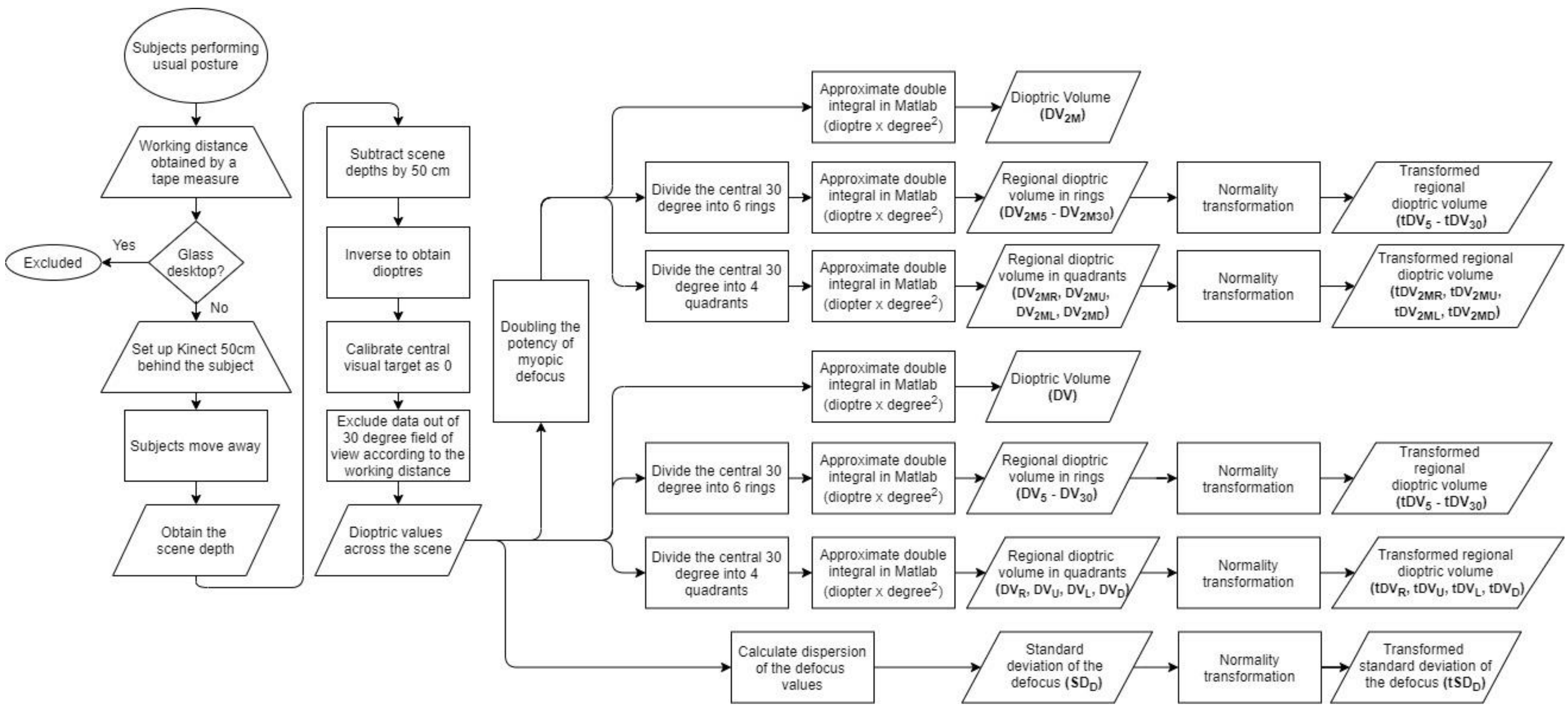


Figure 2.2 Flow chart for scene defocus data acquisition and processing

A linear relationship between myopic and hyperopic defocus was assumed during the calculation of DV, in which the myopic scene defocus was equally potent as the hyperopic defocus. The DV was calculated again with a non-linear assumption, in which the myopic scene defocus was twice as potent as the hyperopic defocus (DV_{2M}), based on the findings from previous studies on chicks (Tse et al., 2007; Tse and To, 2011). To assess the regional effects of DV, the measured area was divided into six rings of 5°-intervals (DV_5, DV_{10}, DV_{15}, DV_{20}, DV_{25}, and DV_{30}) and four quadrants (DV_R, DV_U, DV_L, and DV_D), respectively (Figure 2.3). The regional DVs were transformed to achieve normality using percentile ranking followed by inverse-normal transformation into normally distributed Z-scores (Templeton, 2011) when appropriate, i.e. tDV_5, tDV_{10}, tDV_{15}, tDV_{20}, tDV_{25}, tDV_{30}, tDV_R, tDV_U, tDV_L, and tDV_D. As for the Kinect was placed 50 cm behind the subject, the scene data extraction was demonstrated in the Appendix.

Subjects were sequenced by their home sizes and were divided into three groups: Small home (n = 16, Range: 297 - 500 ft^2 / 27.6 - 46.5 m^2), Medium home (n = 17, Range: 503 - 602 ft^2 / 46.7 - 55.9 m^2), and Large home (n = 17, Range: 614 - 1400 ft^2 / 57.0 - 130.1 m^2). It is worth noting that the definition of home size was different from Study I, which was based on the common sizes of Hong Kong dwellings. T_{desk} was divided into two groups [Low (< 2 hours / day) and High (≥ 2 hours / day)] (H.K.P.T.U., 2015), as well as T_{OA} [Low (< 2 hours / week) and High (≥ 2 hours / week) by median].

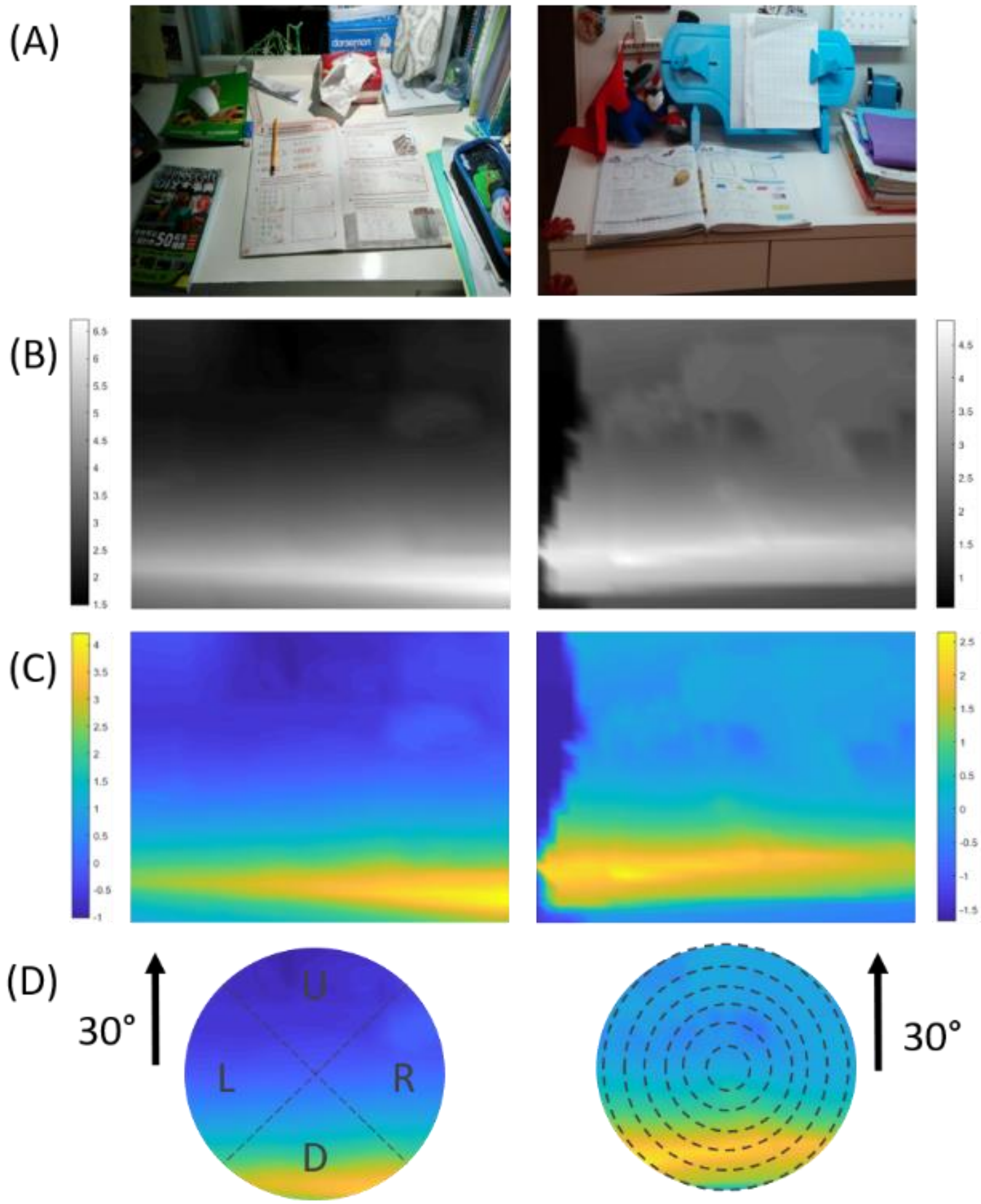


Figure 2.3 Scene demonstration. (A) Coloured picture. (B) Dioptric map of the inversed metric distance. (C) Scene defocus map after calibration with respect to central visual target. (D) Central ±30° field of view of field was divided into six rings and four quadrants. Colour scale in dioptres, in which positive and negative values indicate hyperopic and myopic scene defocus, respectively

Chapter 3. Study I: External factor - Living environment

(Part of Study I has been published in Ophthalmic and Physiological Optics, 2017;37:568-575)

3.1 Introduction

Myopia, or short sightedness, the most common refractive error, can be regarded as a type of ocular disorder. It is a global health concern not only because of costs for optical corrections to obtain clear distant vision, but also the medical burden of high myopes, who are predisposed to various ocular diseases such as cataract, glaucoma, macular degeneration, and retinal detachment (Verkicharla et al., 2015), which can cause severe or irreversible vision loss. As vision is crucial to our daily life, vision loss can adversely affect the quality of life (Christ et al., 2014). Alarmingly, an increasing number of children are becoming myopic at an early age (Holden et al., 2016) due to the failure of emmetropisation, which is a visually guided process for the eye to modify itself to obtain an optimum relationship between the AL and other ocular components, such as the cornea and crystalline lens, so that infantile refractive errors are corrected.

East Asian countries generally have a significantly higher myopia prevalence compared with elsewhere in the world (Pan et al., 2012). In this region, Hong Kong has an extraordinarily high prevalence of myopia (Fan et al., 2004a; Lam et al., 2004; Choy et al., 2020; Yam et al., 2020). Studies have shown that myopia is more prevalent in Asian than white European and African populations (Ip et al., 2008a; Twelker et al., 2009). Other than genetic differences, these findings were found to be associated with the culture and lifestyle of East Asians, who tend to spend little time in OA and engage in a near-work-predominant education system (Ip et al., 2008c). In addition, the crowded living environment of East Asian cities may also be associated with this high prevalence of myopia.

Previous studies have revealed that an urban environment is related to a higher prevalence of myopia in children compared with sub-urban and rural environments (He et al., 2009; Uzma et al., 2009). The Sydney Myopia Study (SMS) suggested that the urbanicity of the living region was associated with childhood myopia (Ip et al., 2008b), in that children living in a place with a denser population were reported to have a higher prevalence of myopia. Other studies attributed the association to the lack of OA (Rose et al., 2008a; Rose et al., 2008b) and the excess of near work (Mutti et al., 2002; Saw et al., 2002b; Ip et al., 2008c) for children living in an urban area. The SMS also reported that flat-styled rather than house-styled living in an urban area had an association with myopia prevalence. A recent study also suggested that the taller the building that the children lived in, the greater the chance that myopia would be observed (Wu et al., 2016).

In 2004, Fan and co-workers conducted a population-based study on myopia prevalence in Hong Kong, which included 7,560 schoolchildren, of whom 37% were myopic (Fan et al., 2004a). They recruited one school from each of the 18 political districts in Hong Kong. However, among the 18 political districts, half had a population density lower than 10,000 persons per km^2, while only a few of them had a population density higher than 30,000 persons per km^2 (C.S.D., 2012). Their samples may have been skewed towards the less populated areas and thus they may have underestimated the actual myopia prevalence of Hong Kong according to SMS (Ip et al., 2008b).

Hong Kong is one of the most densely populated cities in East Asia. The housing problem in Hong Kong has been intensely discussed, as the land supply is limited while the population is increasing (C.S.D., 2012). In 2015, 44.6% of the Hong Kong population lived in public housing (H.K.H.A, 2019), and the internal floor area per person was only 13.3 m^2. With hundreds of thousands of people queuing for public housing, it was reported that around 171,000 people in Hong Kong live in substandard sub-divided flats (S.o.C.O., 2013). Some children even live with their whole family in flats with a total area of around 9 m^2 (S.o.C.O., 2013).

In East Asian cities, people generally live in relatively small flats in highly populated areas and the prevalence of myopia is high. However, the association between refractive error and size of living space has not been established. In the current study, the association between this crowded living environment and refractive error in primary school children was investigated.

3.2 Methods

3.2.1 Subjects

Subject recruitment and sampling methods were previously described in Section 2.1.1 and the same subjects were involved.

3.2 Data collection

Eye examination procedures were as described previously in Section 2.1.2.

A self-reporting parental questionnaire was used to collect information and the items are listed in Table 3.1. Full content (in Traditional Chinese) is attached in the Appendix. To increase the readability and parents' understanding of the questionnaire, ten laymen were invited to comment on the questionnaire. Comments were received and the questionnaire was amended accordingly. The population density of each subject's residential district was determined according to the government survey (C.S.D., 2012) and defined as low (less than 10,000 persons per km^2), medium (10,000 to 30,000 persons per km^2), or high population density (more than 30,000 persons per km^2). Some responses of similar outcomes were grouped to avoid extreme sample size in each category, as listed in Table 3.2 Parental myopia was interpreted as the number of myopic parents, i.e. 0, 1, or 2. According to the common understanding of types of housing in Hong Kong, a flat is a set of rooms forming an individual residence; a studio has only one main room and an independent washroom; a rooftop shack house is built (illegally) on top a building with thin metal plates; a sub-divided flat lacks an independent washroom; a house is a stand-alone residential building; a duplex flat is on two floors, frequently the highest of a building.

Table 3.1 Items in the self-reporting parental questionnaire

Ocular history	Use of spectacles and contact lenses
	Use of myopia control strategies
	Experience of eye checking
	Issues identified in eye checking
Near work habits	Posture
	Resting frequency
	Working distance
Extra-curricular activities	Participation
Activity pattern	Weekly outdoor activities
	Weekly television and computer use
	Daily near work
	Daily mobile phone and handheld console
Living environment	Residential district
	Type of housing
	Home size
Parental history	Occupations
	Education level
	Refractive error

Table 3.2 Grouping of responses from the questionnaire

	Items in the questionnaire	%	Grouped response for analysis	%
Home size	Less than 100 ft^2	5.3	Less than 300 ft^2	28.4
	101 to 300 ft^2	23.1		
	301 to 600 ft^2	49.9	300 to 600 ft^2	49.9
	601 to 1000 ft^2	11.7	More than 600 ft^2	14.2
	More than 1000 ft^2	2.5		
	Missing	7.5	Missing	7.5
Housing type	Flat	84.9	Flat	84.9
	Studio	3.5	Studio / roof-top shack / sub-divided flat	5.6
	Rooftop shack	0.5		
	Sub-divided flat	1.6		
	House	2.2	House / duplex	2.5
	Duplex	0.3		
	Missing	7.0	Missing	7.0
Paternal RE	No spectacle correction	57.7	Non-myopic father	64.4
	Greater than +6.00 D	0.3		
	+3.00 to +5.75 D	3.0		
	+1.00 to +2.75 D	3.4		
	-1.00 to -2.75 D	15.3	Myopic father	29.6
	-3.00 to -5.75 D	10.0		
	Less than -6.00 D	4.3		
	Missing	6.0	Missing	6.0
Maternal RE	No spectacle correction	60.3	Non-myopic mother	65.0
	Greater than +6.00 D	0.2		
	+3.00 to +5.75 D	1.6		
	+1.00 to +2.75 D	2.9		
	-1.00 to -2.75 D	15.3	Myopic mother	30.2
	-3.00 to -5.75 D	11.1		
	Less than -6.00 D	3.8		
	Missing	4.8	Missing	4.8

3.3 Statistical analysis

Data analysis was performed using SPSS (Version 22, IBM Inc, Amonk, NY, US). AL was the primary outcome and non-cycloplegic M was the secondary outcome to assess the characteristics and trends between groups. Sub-categories of each parameter were compared using one-way analysis of variance (ANOVA) with Bonferroni post-hoc test or independent t-test, and parameters of the living environment were plotted against AL and M. Parameters that generated a significance level of $p < 0.10$ in univariate analyses were entered in a multiple linear regression to assess the impact on AL and M, respectively. Missing data were treated using ten-time multiple imputation (Rubin, 2004). Multicollinearity statistics, i.e. variance inflation factor (VIF), were reported. As data from right and left eyes were strongly correlated (AL: $r = 0.96$; M: $r = 0.92$), only right eye data were analysed. Significance level was set as $p < 0.05$.

3.3 Results

3.3.1 Descriptive characteristics of the sample

The subjects had a mean AL of 23.78 ± 1.04 mm and M of -1.21 ± 1.80 D. Table 3.3 shows the demographics and living environment of the participants, and the p values in Table 3.3 were from a univariate analysis of each variable. The age of the children did not significantly differ across all categories of population density ($F_{2,1072} = 2.82$, $p = 0.06$), home size ($F_{2,1072} = 2.10$, $p = 0.12$), and type of housing ($F_{3,1071} = 1.60$, $p = 0.19$).

Table 3.3 Axial length and spherical equivalent refraction by variables

	n (%)	AL ± SD (mm)	p value	M ± SD (D)	p value
All	1075 (100)	23.78 ± 1.04		-1.21 ± 1.80	
Gender					
Boys	586 (54.5)	24.02 ± 1.00	**< 0.001**	-1.20 ± 1.80	0.94
Girls	489 (45.5)	23.49 ± 1.02		-1.21 ± 1.80	
Age					
Lower third	358 (33.3)	23.53 ± 0.93	**< 0.001**	-0.90 ± 1.64	**< 0.001**
Middle third	358 (33.3)	23.80 ± 1.06		-1.34 ± 1.85	
Upper third	359 (33.3)	24.02 ± 1.07		-1.41 ± 1.87	
Parental myopia					
Neither parent is myopic	507 (47.2)	23.71 ± 1.02	**< 0.001**	-1.00 ± 1.59	**< 0.001**
One parent is myopic	336 (31.3)	23.83 ± 1.07		-1.37 ± 1.94	
Both parents are myopic	152 (14.1)	24.09 ± 1.11		-1.86 ± 2.01	
Parental education level					
Primary school or below	58 (5.4)	24.06 ± 1.07	0.11	-1.53 ± 2.12	0.51
Junior secondary school	375 (34.9)	23.78 ± 1.05		-1.22 ± 1.76	
Senior secondary school	422 (39.3)	23.72 ± 1.02		-1.17 ± 1.80	
Tertiary education	163 (15.2)	23.83 ± 1.08		-1.12 ± 1.65	
Population density of the residential district					
< 10k persons per km^2	209 (19.4)	23.56 ± 0.93	**< 0.01**	-0.89 ± 1.64	**< 0.001**
10k - 30k persons per km^2	236 (22.0)	23.74 ± 1.07		-1.01 ± 1.60	
> 30k persons per km^2	418 (38.9)	23.87 ± 1.09		-1.46 ± 2.01	
Home size					
< 300 ft^2 (< 27.87 m^2)	305 (28.4)	23.85 ± 1.07	**0.04**	-1.35 ± 1.88	**0.02**
300 - 600 ft^2 (27.87 - 55.74 m^2)	536 (49.9)	23.80 ± 1.10		-1.01 ± 1.60	
> 600 ft^2(> 55.74 m^2)	152 (14.1)	23.59 ± 0.88		-0.82 ± 1.38	

Type of housing					
Flat	913 (84.9)	23.77 ± 1.05	0.16	-1.22 ± 1.81	0.10
Studio / rooftop shack / sub-divided flat	60 (5.5)	23.97 ± 1.15		-1.39 ± 1.77	
House / duplex	29 (2.4)	23.52 ± 0.94		-0.50 ± 1.65	
Weekly outdoor activities					
Not at all	98 (9.1)	24.03 ± 1.06	**0.03**	-1.48 ± 1.84	0.10
Less than 1 hour	216 (20.1)	23.86 ± 1.04		-1.43 ± 1.87	
1 - 2 hours	350 (32.6)	23.72 ± 1.02		-1.16 ± 1.68	
3 or more hours	329 (30.6)	23.73 ± 1.08		-1.10 ± 1.90	
Weekly television and computer use					
Not at all	35 (3.3)	23.79 ± 1.00	0.85	-1.48 ± 1.72	0.57
Less than 1 hour	144 (13.4)	23.85 ± 1.03		-1.32 ± 1.70	
1 - 2 hours	409 (38.0)	23.78 ± 1.07		-1.14 ± 1.75	
3 or more hours	386 (35.9)	23.76 ± 1.04		-1.25 ± 1.92	
Daily near work					
Not at all	8 (0.7)	23.07 ± 0.68	0.24	-1.09 ± 1.38	0.69
Less than 1 hour	79 (7.3)	23.73 ± 0.81		-1.04 ± 1.47	
1 - 2 hours	488 (45.4)	23.81 ± 1.03		-1.21 ± 1.79	
3 or more hours	407 (37.9)	23.77 ± 1.10		-1.29 ± 1.91	
Daily mobile phone and handheld console					
Not at all	90	23.89 ± 1.05	0.06	-1.22 ± 1.61	**< 0.01**
Less than 1 hour	300	23.67 ± 1.09		-0.91 ± 1.67	
1 - 2 hours	344	23.77 ± 1.01		-1.40 ± 1.76	
3 or more hours	226	23.91 ± 1.06		-1.41 ± 2.11	
Near work posture					
Upright	225 (20.9)	23.65 ± 1.08	**< 0.01**	-0.98 ± 1.79	**0.03**
Tilted head	332 (30.9)	23.71 ± 1.02		-1.20 ± 1.78	
No specific posture	461 (42.9)	23.92 ± 1.05		-1.38 ± 1.85	

Near work distance					
≤ 10 cm	141 (13.1)	23.78 ± 1.06	0.78	-1.32 ± 1.86	0.15
> 10 cm and ≤ 20 cm	390 (36.3)	23.83 ± 1.01		-1.40 ± 1.97	
> 20 cm and ≤ 30 cm	321 (29.9)	23.76 ± 1.08		-1.06 ± 1.70	
> 30 cm and ≤ 40 cm	112 (10.4)	23.87 ± 1.02		-1.08 ± 1.55	
> 40 cm	30 (2.8)	23.69 ± 0.84		-1.09 ± 1.53	
Resting frequency during near work					
4 times / hour	241 (22.4)	23.68 ± 1.05	0.06	-1.10 ±1.85	0.10
2 times / hour	396 (36.8)	23.73 ± 0.97		-1.09 ± 1.64	
1 time / hour	159 (14.8)	23.85 ± 1.16		-1.36 ± 1.94	
< 1 time / hour	128 (11.9)	23.92 ± 1.04		-1.33 ± 1.68	
No rest	104 (9.7)	23.95 ± 1.09		-1.57 ± 2.16	
Participation in extra-curricular classes					
Tuition	617 (57.4)	23.81 ± 1.01	0.46	-1.16 ± 1.72	0.31
Static activities	362 (33.7)	23.74 ± 1.05	0.30	-1.20 ± 1.85	0.85
Dynamic activities	469 (43.6)	23.77 ± 1.08	0.65	-1.18 ± 1.74	0.64

p indicates the significance level of univariate analysis between groups

3.3.2 Living environment - between-group comparison

AL and M were plotted across different groups of each variable individually. For AL, significant difference was observed in population density of the residential district ($F_{2,1072}$ = 6.15, $p < 0.01$, Figure 3.1) and home size ($F_{2,1072}$ = 4.64, $p = 0.01$, Figure 3.2). However, the difference in association of AL in type of housing was not significant ($F_{2,1072}$ = 1.83, $p = 0.16$, Figure 3.3). AL increased as population density of the residential districts increased, but significant difference could only be observed in districts with low population density when compared with those with high population density ($p < 0.01$). There was also a decreasing trend of AL with home size. A significant difference was observed between those living in a large and medium homes ($p = 0.04$), and those living in a small home ($p = 0.01$). For M, we also observed significant difference in population density of the residential district ($F_{2,1072}$ = 7.88, $p < 0.001$, Figure 3.1) and home size ($F_{2,1072}$ = 4.87, $p = 0.01$, Figure 3.2). However, the difference in association of M in type of housing was again insignificant ($F_{2,1072}$ = 2.31, $p = 0.10$, Figure 3.3). M was more myopic as population density of the residential districts increased. Significant difference could be observed between residents of districts with low population density compared with those with high population density ($p = 0.001$) and districts with medium population density when compared with those with high population density ($p = 0.01$). M was less myopic as home size increased. A significant difference was observed between those living in a large-sized homes and those living in a small-sized home ($p = 0.01$), and between those living in a large-sized home and those living in a medium-sized home ($p = 0.02$).

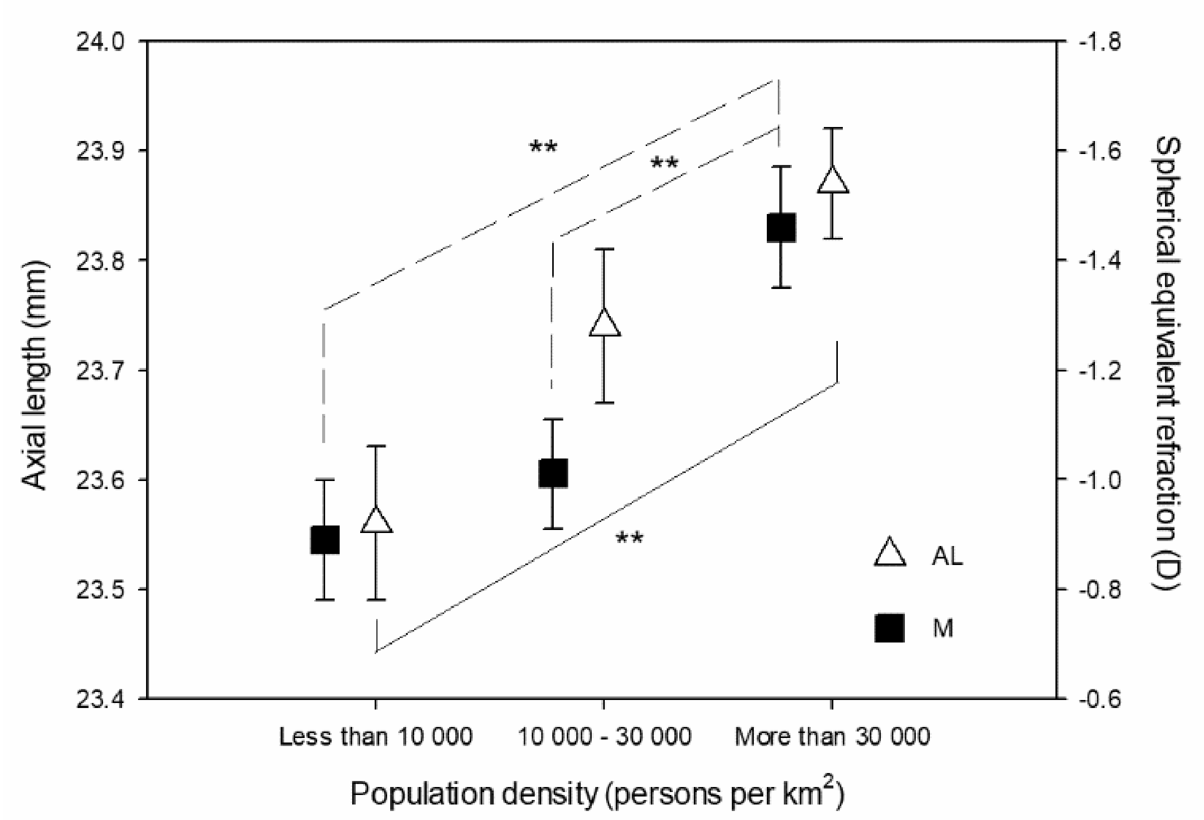


Figure 3.1 Association of population density of the residential district with axial length (AL) and spherical equivalent refraction (M). The triangles and squares represent the mean (± standard error of mean) of AL and M, respectively. **p < 0.01

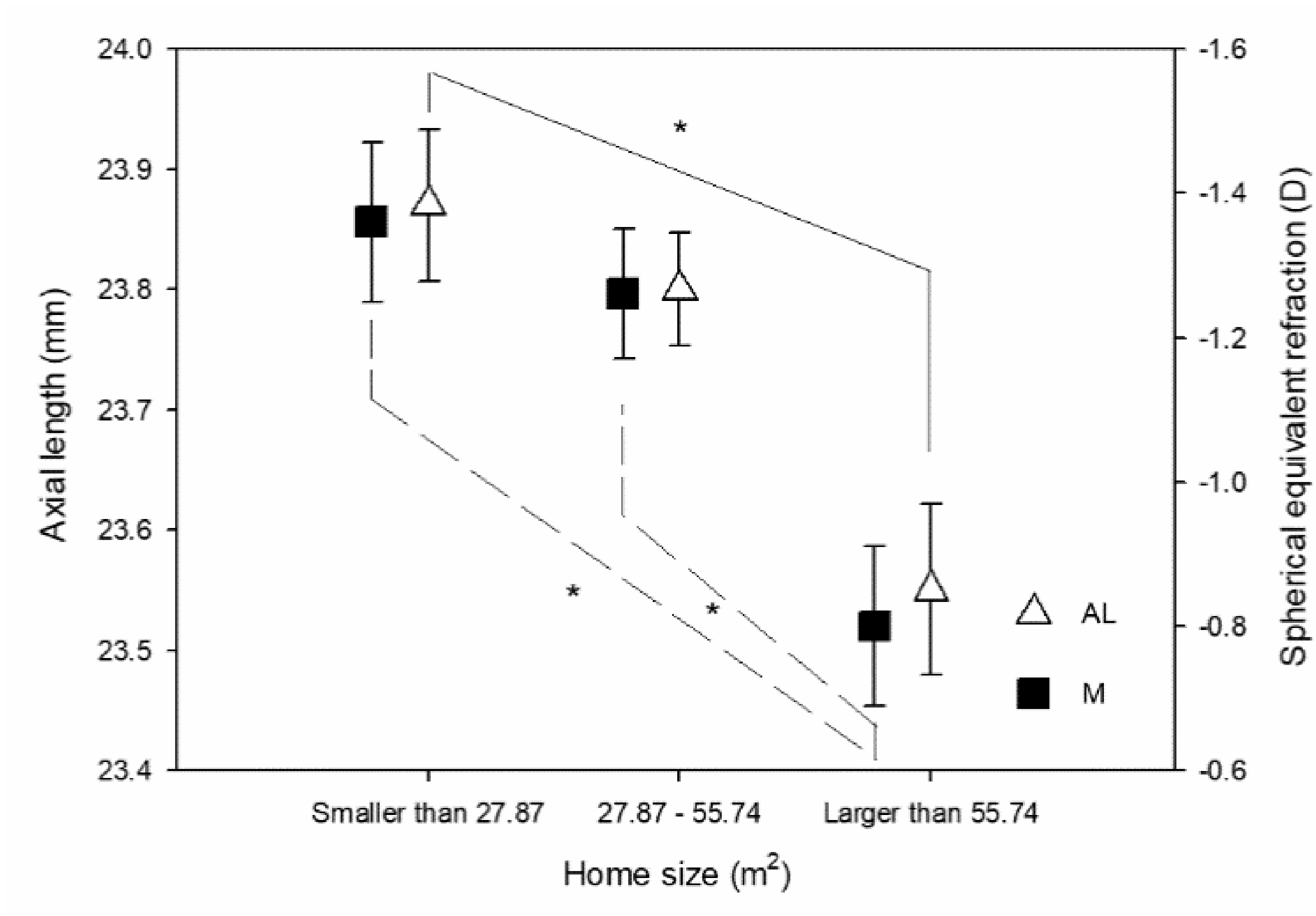


Figure 3.2 Association of home size with axial length (AL) and spherical equivalent refraction (M). The triangles and squares represent the mean (± standard error of mean) of AL and M, respectively. *p < 0.05

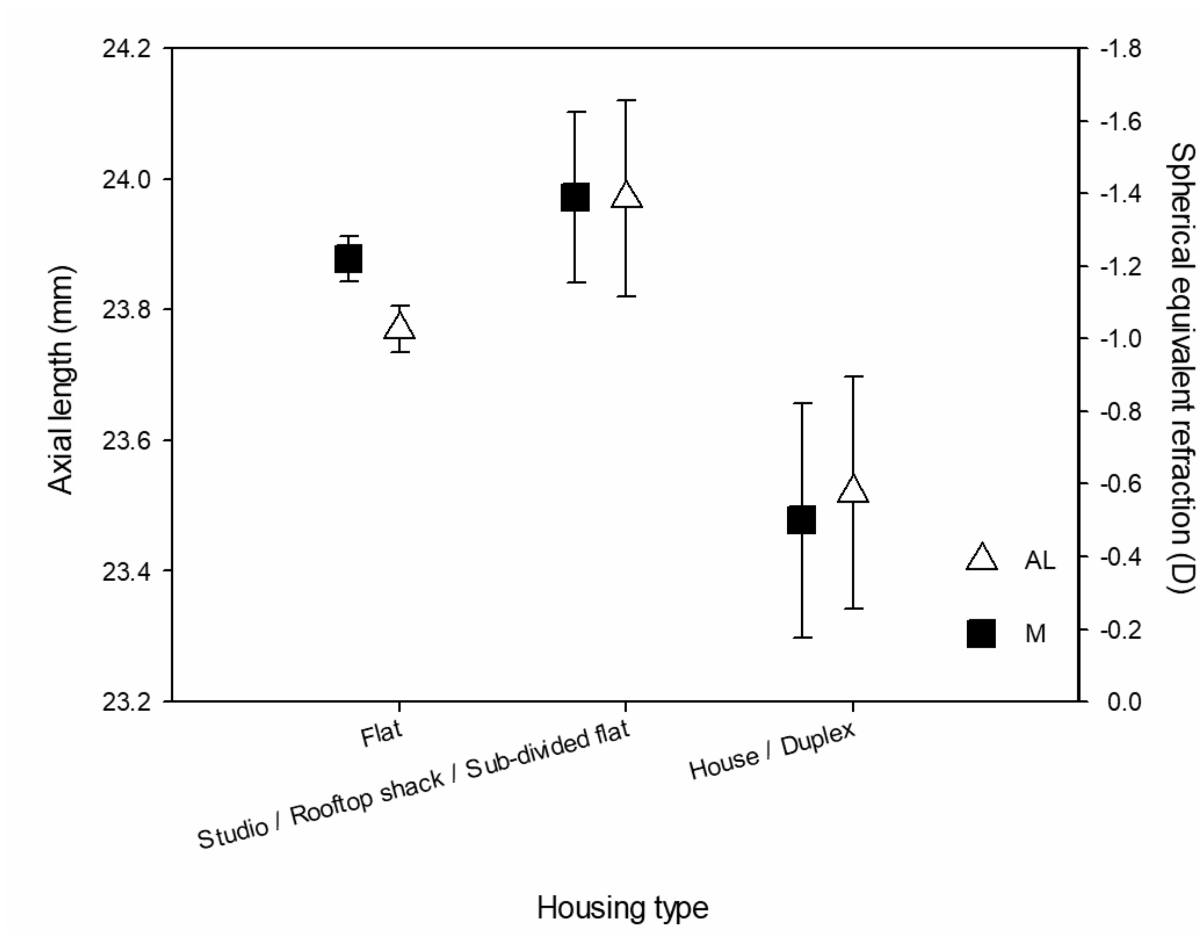


Figure 3.3 Association of housing type with axial length (AL) and spherical equivalent refraction (M). The triangles and squares represent the mean (± standard error of mean) of AL and M, respectively

3.3.3 Living environment - multivariate analysis

The multiple linear regression models were overall significant (AL: $F_{22,1052} = 6.25$, $p < 0.001$; M: $F_{26,1048} = 3.52$, $p < 0.001$) and the adjusted R^2 were 0.13 and 0.07, respectively. Table 3.4 summarises the effect of individual variables, and the p values from a multivariate analysis of all variables, adjusted for other co-variates. The B value (regression coefficient) for living in a district of high population density was 0.22 (95% CI 0.05 to 0.38), indicating that children living in districts with high population density were predicted to have a 0.22 mm longer eye compared with those living in districts with low population density. However, the B value for medium population density was not significant ($p = 0.49$). The home size recorded a B value of 0.23 (95% CI 0.03 to 0.43) when comparing a large-sized and a small-sized home, predicting a 0.23 mm longer eye for those living in a small-sized home, but the medium-sized home was not significant when compared to a large-sized home ($p = 0.07$). Furthermore, type of housing did not significantly contribute to the model (studio / rooftop shack / sub-divided flat: $p = 0.38$; house / duplex: $p = 0.79$, when compared with flat).

In the M model, only population density of the residential district and home size showed significant contributions. The B value for living in a district of high population density was -0.49 (95% CI -0.80 to -0.19), indicating that the M of children living in districts with high population density were predicted to be 0.49 D more myopic, or less hyperopic, compared with those living in districts with low population density. However, the B value for medium population density was not significant ($p = 0.98$). The home size recorded a B value of -0.47 (95% CI -0.84 to -0.01) when comparing a large-sized and a small-sized home, predicting the M for those living in a small-sized home were 0.47 D less, but the B value for medium-sized home was not significant (p = 0.05). Furthermore, type of housing did not significantly contribute to the model (studio / rooftop shack / sub-divided flat: p = 0.49; house / duplex: p = 0.50, when compared with flat). The non-cycloplegic M was similar to and supported the AL results.

Table 3.4 Statistical results for multivariate analysis of axial length (AL) and spherical equivalent refraction (M)

	Raw B value	95% CI	p value	VIF
Axial length model (Power > 99.9%)				
Gender				
Girls	-0.49	-0.61 to -0.37	< **0.001**	1.02
(ref Boys)				
Age	0.19	0.12 to 0.25	< **0.001**	1.04
Parental myopia				
One myopic parent	0.13	-0.01 to 0.26	0.07	1.13
Two myopic parents	0.40	0.22 to 0.59	< **0.001**	1.14
(ref No myopic parent)				
Population density of the residential district				
Medium population density	0.07	-0.12 to 0.26	0.49	1.66
High population density	0.22	0.05 to 0.38	**0.01**	1.67
(ref Low population density)				
Home size				
Small home size	0.23	0.03 to 0.43	**0.02**	2.21
Medium home size	0.16	-0.02 to 0.34	0.07	2.22
(ref Large home size)				

Housing type				
Studio / rooftop shack / sub-divided flat	0.12	-0.14 to 0.38	0.38	1.13
House / duplex	-0.05	-0.38 to 0.29	0.79	1.17
(ref Flat)				
Weekly outdoor activities				
Less than 1 hour	-0.09	-0.30 to 0.12	0.40	1.41
1 - 2 hours	-0.17	-0.37 to 0.03	**0.03**	1.58
3 or more hours	-0.19	-0.39 to 0.01	0.06	1.59
(ref Not at all)				
Daily mobile phone and handheld console				
Less than 1 hour	-0.04	-0.24 to 0.16	0.70	1.98
1 - 2 hours	-0.01	-0.21 to 0.20	0.97	2.01
3 or more hours	0.03	-0.18 to 0.24	0.77	1.90
(ref Not at all)				
Near work posture				
Upright	-0.22	-0.38 to -0.06	**0.01**	1.17
Tilted head	-0.20	-0.34 to -0.05	**0.01**	1.15
(ref No specific posture)				
Resting frequency during near work				
2 times / hour	0.02	-0.13 to 0.17	0.80	1.60
1 time / hour	0.08	-0.11 to 0.27	0.42	1.38
< 1 time / hour	0.14	-0.07 to 0.35	0.19	1.34
No rest	0.14	-0.08 to 0.35	0.21	1.28
(ref 4 times / hour)				

	Raw B value	95% CI	p value	VIF
Spherical equivalent refraction model (Power > 99.9%)				
Gender				
Girls	0.01	-0.20 to 0.23	0.90	1.02
(ref Boys)				
Age	-0.22	-0.33 to -0.11	< **0.001**	1.05
Parental myopia				
One myopic parent	-0.33	-0.58 to -0.08	**0.01**	1.15
Two myopic parents	-0.90	-1.23 to -0.58	< **0.001**	1.14
(ref No myopic parent)				
Population density of the residential district				
Medium population density	-0.01	-0.32 to 0.31	0.98	1.67
High population density	-0.49	-0.80 to -0.19	**0.002**	1.72
(ref Low population density)				
Home size				
Small home size	-0.47	-0.84 to -0.10	**0.01**	2.21
Medium home size	-0.32	-0.64 to 0.00	0.05	2.22
(ref Large home size)				
Housing type				
Studio / rooftop shack / sub-divided flat	-0.17	-0.64 to 0.31	0.49	1.16
House / duplex	0.21	-0.39 to 0.80	0.50	1.09
(ref Flat)				
Weekly outdoor activities				
Less than 1 hour	0.09	-0.27 to 0.46	0.65	1.41
1 - 2 hours	0.32	-0.03 to 0.67	0.07	1.58
3 or more hours	0.38	0.02 to 0.74	**0.04**	1.59
(ref Not at all)				

Daily mobile phone and handheld console				
Less than 1 hour	0.19	-0.18 to 0.55	0.32	1.98
1 - 2 hours	-0.14	-0.50 to 0.21	0.43	2.01
3 or more hours	-0.12	-0.53 to 0.29	0.57	1.90
(ref Not at all)				
Near work posture				
Upright	0.35	0.07 to 0.64	**0.01**	1.15
Tilted head	0.26	0.02 to 0.50	**0.04**	1.12
(ref No specific posture)				
Resting frequency during near work				
2 times / hour	0.03	-0.24 to 0.30	0.84	1.59
1 time / hour	-0.20	-0.54 to 0.15	0.26	1.38
< 1 time / hour	-0.11	-0.48 to 0.27	0.58	1.32
No rest	-0.19	-0.58 to 0.20	0.34	1.32
(ref 4 times / hour)				

VIF: variance inflation factor

3.3.4 Other co-variates

With respect to other co-variates, girls had a significantly shorter AL than boys, but M was similar between genders. In addition, AL increased, while M decreased with age ($p < 0.001$). The AL for subjects with one myopic parent did not differ from those with no myopic parent ($p = 0.07$), but M was significantly more myopic ($p = 0.01$). Subjects with two myopic parents had longer AL and more myopic M than those with one myopic parent and no myopic parent ($p < 0.001$). Parental education level had no effect on AL ($p = 0.11$) or M ($p = 0.51$). Weekly OA was associated with AL ($p = 0.03$), but not M ($p = 0.10$). Weekly OA of 1 - 2 hours and 3 hours or more were associated with a shorter AL (p = 0.03) and less myopic M (p = 0.04) in multivariate analyses, respectively when compared with no OA at all. Daily near work and weekly television and computer use were independent of AL or M. Daily mobile and handheld console usage was independent of AL (p = 0.06), but was associated with M (p < 0.01). Subjects with no specific near work posture had significantly longer AL (p < 0.01) and more myopic M (p = 0.03) than those with upright posture and tilted head. Near working distance, resting frequency, and participation in extra-curricular activities did not have a significant effect on AL or M.

3.4 Discussion

The results of this study provide further support for an association between living environment and childhood refractive error. One of the major findings is that children living in districts of higher population density have a greater risk of having a longer eye and a more negative non-cycloplegic M. Other research studies have shown supporting results (Ip et al., 2008b; He et al., 2009; Uzma et al., 2009). The Refractive Error Study in Children (RESC) (Negrel et al., 2000) provided a standardised protocol to measure the prevalence of refractive error in school-aged children worldwide (Maul et al., 2000; Pokharel et al., 2000; Murthy et al., 2002; Naidoo et al., 2003; He et al., 2009), enabling easy comparison, as all the sampling and measurement protocols were the same. The RESC group found that studies conducted in urban areas reported higher myopia prevalence than those in rural areas (He et al., 2004; He et al., 2007; He et al., 2009). In addition to RESC, the SMS (Ojaimi et al., 2005) investigated many modifiable risk factors, such as volume of near work (Ip et al., 2008c), time spent in OA (Rose et al., 2008a), and urbanicity of the residence (Ip et al., 2008b). For the living environment, Ip and co-workers found that children living in the inner city were more likely to have myopia than those living in outer suburban areas. In Hong Kong, the results were similar. The 18 political districts in Hong Kong were grouped into three clusters according to their population densities (C.S.D., 2012) and it was observed that a higher population density was associated with the risk of having a longer eye (Figure 3.1). Similar trends were also observed in both Sydney and Hong Kong, even with different city planning and ranges of population density, thus the effect of urbanicity should not be overlooked in considering factors associated with childhood refractive error.

The second major observation of our study was the association of the home size with childhood refractive error. Children living in a home smaller than 300 ft^2 (27.87 m^2) had a significantly longer eye compared to those living in a home larger than 600 ft^2 (55.74 m^2). Although myopia prevalence was thought to increase with socioeconomic status, which can partially be reflected by larger home size and high parental education level, in our sample the small home size showed a stronger association with longer AL and more negative M than higher parental education level (AL: $F_{3,1071} = 2.02$, $p = 0.11$; M: $F_{3,1071} = 0.77$, $p = 0.51$). One possible reason may be the constricted environment at home creating peripheral hyperopic defocus from the surroundings. Numerous studies have shown that peripheral hyperopic defocus accelerates, while peripheral myopic defocus retards, myopia progression (Wallman et al., 1987; Smith et al., 2009b). In different visual environments, objects nearby produce various amount of defocus to the eye with regards to the plane of focus (Tse et al., 2007; Flitcroft, 2012). Generally, an indoor environment creates more peripheral hyperopic defocus than an outdoor environment

(Flitcroft, 2012). This condition may also apply to a constricted area in an indoor setting versus an open area, thus children in a smaller home would be exposed to stronger peripheral hyperopic defocus compared with those in a larger home.

The type of housing may be another factor associated with myopia prevalence. A recent nationwide population-based study in China evaluated the impact of living environment on myopia in school-aged children (Wu et al., 2016). From their sizable sample, myopia was associated with the type of housing, in terms of the height of residential buildings. Higher myopia prevalence was observed in children living in taller buildings, which is independent of the residential region, age, gender, and ethnicity. In the SMS, myopia was more frequently observed in children living in apartments and terraced houses than those living in stand-alone or separate houses (Ip et al., 2008b). They suggested it was related to the nature of housing type, among which terraced houses and apartments are smaller and more confined. However, studies in Singapore did not show such a relationship (Saw et al., 2000, 2001). Our study showed that home size was associated with AL and refractive error rather than the type of housing. One possible reason for the lack of significance may be the low variation of housing type in Hong Kong, as the majority of people live in a flat. This could be a possible explanation for the high prevalence of myopia in Asian children living in urban areas as most live in flats, but this could not be determined in this study.

The housing issue has been a complicated problem in Hong Kong. In 2018, the average living space per person in public housing was 13.3 m^2 (H.K.H.A, 2019). Furthermore, according to a survey in 2009, Hong Kong had the lowest average residential floor space per person among 14 countries worldwide (Wilson, 2009). When compared to Australia, Hong Kong has only one-fifth of the average residential floor space per person. For the average new home size built in 2009, Hong Kong again had the smallest area (Wilson, 2009), which was less than one fourth of those in Australia, Canada, and the US. Our findings suggested that the small living space in Hong Kong is associated with a longer eye and a more minus refractive error. It is possible that small home size and dense population may be two additional factors associated with the high prevalence of myopia in East-Asian countries (Ho, 2015).

This study was strong in several aspects. The participation rate (95%) was high because this research project was also a community service project, which did not further filter subjects within the sampled groups. The sampling method was modified to recruit a proportional number of subjects from districts of different population densities, so that the sample would reflect the characteristics of the population. The questionnaire was designed to be as simple and straightforward as possible so that parents could easily provide valid data. Also, the questionnaire covered many items other than living environment to control as covariates, which were reported to be significantly associated with refractive error, including OA, near work, and parental factors.

However, the study was not without limitations. A cycloplegic agent was not instilled to avoid interrupting students' study, because the data were collected on normal school days. This may affect the accuracy of the auto-refraction as the subjects may accommodate, resulting in a more myopic M (Fotedar et al., 2007). However, the M results were strongly correlated with the AL measurements (M vs. AL: $r = -0.74$, $p < 0.001$), and hence could still identify the risk factors in the regression model, despite AL would generate a gender difference being independent of the refraction. In addition, the data collection process adopted a self-reporting questionnaire instead of an interview, which may hinder the data reliability to some extent. It was attempted to maximise the readability and ensure parents could understand the questionnaire without further explanation.

In conclusion, there was an association between childhood refractive error and living environment, in terms of the size of home and the population density of the residential area. It was speculated that small homes and densely populated residential areas are risk factors associated with the high prevalence of myopia. This study covered external factors, such as the living environment, that were associated with refractive error. However, further studies investigating the effect of internal factors on refractive error development, such as peripheral refraction, are warranted, as are studies on the effect of the living environment on longitudinal changes of refractive error.

Chapter 4. Study II - Internal factor - Peripheral refraction and optical orientation bias

(Part of Study II had been presented in ARVO Annual Meeting 2018, Honolulu, Hawaii, US)

4.1 Introduction

The contribution of PRE to myopia development has attracted considerable attention. An early cross-sectional study reported an association between on-axis myopia and relative peripheral hyperopia, which was confirmed by subsequent studies (Hoogerheide et al., 1971; Atchison et al., 2006; Mutti et al., 2011). These studies raised the question of whether emmetropisation, a vision-dependent eye growth process, utilises visual inputs from the central, peripheral, or entire retina. Emerging evidence from animal studies indicates that the peripheral retina, as well as the fovea, plays a critical role in eye growth. For example, the peripheral retina was shown to be able to compensate for localised blurred signals by modulating regional eye growth (Wallman et al., 1987; Smith et al., 2013c). In addition, it has been observed that even after ablating the fovea by laser photocoagulation, the eye could still detect imposed optical defocus and grow towards the focal plane (Smith et al., 2009b). In clinical trials, several optical interventions showed promising effects for myopia control by inducing myopic defocus to bring the focal plane in front of the central and peripheral retina (Cho and Cheung, 2012; Lam et al., 2014; Lam et al., 2019). Despite the convincing evidence from animal studies and clinical trials, the results from longitudinal studies have still failed to establish a solid relationship between the baseline relative peripheral spherical equivalent refraction (RPRE-M) and the subsequent rate of myopia progression in children (Mutti et al., 2011; Lee and Cho, 2013; Atchison et al., 2015). Some argued the magnitude of RPRE-M was too small to be resolved by the retina (Smith et al., 2013a). In contrast, relative peripheral astigmatism was found to be negatively correlated with on-axis myopia (Atchison et al., 2006). Although a longitudinal study also found a smaller magnitude of baseline J_0 in children who became myopic in subsequent follow-up (Sng et al., 2011), the results could not be replicated in a later study (Lee and Cho, 2013). Whether the astigmatic error, which constitutes a major part of the PRE of human eyes (Mutti et al., 2007; Mutti et al., 2011; Sng et al., 2011; Atchison et al., 2015), would be a contributing factor to the development of central refractive error in children warrants further investigation (Charman, 2011; Atchison and Rosén, 2016).

The peripheral retina of animal models contains neurons that are reported to be orientation sensitive (Sasaki et al., 2006). As confirmed by psychophysical and functional imaging experiments, the peripheral visual field of the human eye is more sensitive to radially orientated stimuli, i.e. along the direction pointing to the fovea, than tangential and oblique orientations. Howland proposed that the two perpendicular focal planes (tangential and sagittal) created by peripheral astigmatism could provide a cue for the retina to differentiate the direction of defocus (Howland, 2010). By comparing the output signal strength of the orientation-tuned neurons, the retina may be able to direct eye growth towards the focal plane. Existing data from clinical studies and animal experiments have demonstrated supportive evidence that uncorrected or lens-induced astigmatism, which changes the pattern of astigmatism across the entire visual field, could disrupt the normal eye growth process (Gwiazda et al., 2000a; Kee et al., 2004). However, most recent studies on peripheral refraction have focused on analysing astigmatic components (J_0 and J_{45}) or sagittal and tangential defocus, with few studies reporting whether the orientation-dependent blur matched with the functional radial bias, especially in children (Ferree et al., 1931; Ferree and Rand, 1933; Rempt et al., 1971; Mathur and Atchison, 2013).

Peripheral astigmatism is a major orientation-related component of PRE. The magnitude can be over 10 D at 60° eccentricity of the visual field (Millodot, 1981; Gustafsson et al., 2001; Mathur and Atchison, 2013), and astigmatic orientation can significantly affect vision (Zheleznyak et al., 2016). However, limited studies have reported the peripheral optical orientation bias along vertical and horizontal visual fields, especially in children who are prone to myopia development. Therefore, in addition to determining the peripheral M, J_0, and J_{45} components, this study aimed to report the optical orientation bias of PRE along the vertical and horizontal visual fields in Chinese schoolchildren with various AL/CR ratios. This study provides support to the role of peripheral orientation-dependent blur on childhood refractive status and may provide new insights into ocular development in children.

4.2 Methods

4.2.1 Subjects

Subject recruitment and sampling methods were previously described in Section 2.1.1 and the same subjects were involved.

4.2.2 Data collection

Eye examination procedures were as described previously in Section 2.1.2.

4.2.3 Data processing and statistical analysis

To assess the orientation dependent blur in the periphery, the radiality was defined as the difference between P(90) and P(180) magnitudes, i.e. $Radiality$: $|M + J_0| - |M - J_0|$ for the horizontal field; $|M - J_0| - |M + J_0|$ for the vertical field, which represents how well-focused is the radial component of the retinal image. Multiple correlation analysis was applied to assess the relationship between on-axis AL/CR and each element of RPRE-M, -J_0, -J_{45}, and radiality (Huberty, 2003). The analysis was performed with RPRE of vertical and horizontal fields at ±10° to utilise the whole sample (N = 1053), and then repeated with RPRE along the horizontal field at ±20° to utilise the whole eccentricity range.

Subjects were divided into three refractive groups based on their AL/CR ratio: Low (< 3.047, n = 527), Moderate (3.047 to 3.202, n = 365), and High (≥ 3.202, n = 160), which corresponded to M values of > -1.00 D, ≤ -1.00 D to > -3.00 D, and ≤ -3.00 D, respectively, in the regression formula: $M = 36.36 - 12.26 \times AL/CR$ (Figure 4.1). One-way ANOVA with Bonferroni correction was performed for RPRE-M, -J_0, -J_{45}, and radiality, to investigate the effect of refractive groups on the RPRE.

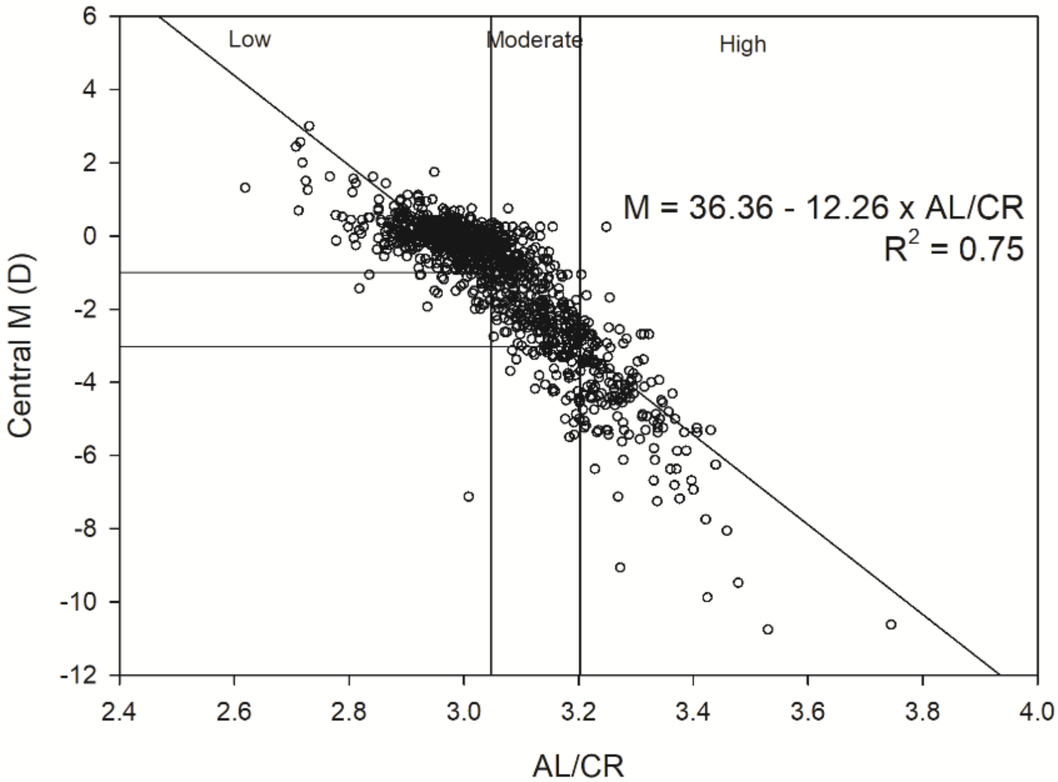


Figure 4.1 Correlation between spherical equivalent refraction (M) and axial-length-to-corneal-radius-of-curvature (AL/CR)

To further demonstrate the pattern of peripheral astigmatic blur across refractive groups, the vector forms of RPRE were converted back to the sphero-cylindrical form ($S + C \times \alpha$). The orientation bias was defined as the principal meridian (α or $\alpha \pm 90°$) that had the least magnitude, i.e. the clearer meridian. A flow chart demonstrating the process of calculation for the orientation bias was shown in Figure 4.2. The orientation bias was classified into four groups (Figure 4.3): radial (horizontal field: 180° ± 30°, vertical field: 90° ± 30°), tangential (horizontal field: 90° ± 30°, vertical field: and 180° ± 30°), oblique (45° ± 15° and 135° ± 15°), and iso-focal groups. The subject was classified as iso-focal if the circle of least confusion fell onto the retina (RPRE-M = 0).

The distribution of orientation bias of each visual field angle was evaluated by a four-by-three χ^2-test (four orientation groups and three refractive groups). Hochberg's method was used to control Type II error in post-hoc tests (Hochberg, 1988; Chen et al., 2017). Statistical analysis was performed using SPSS.

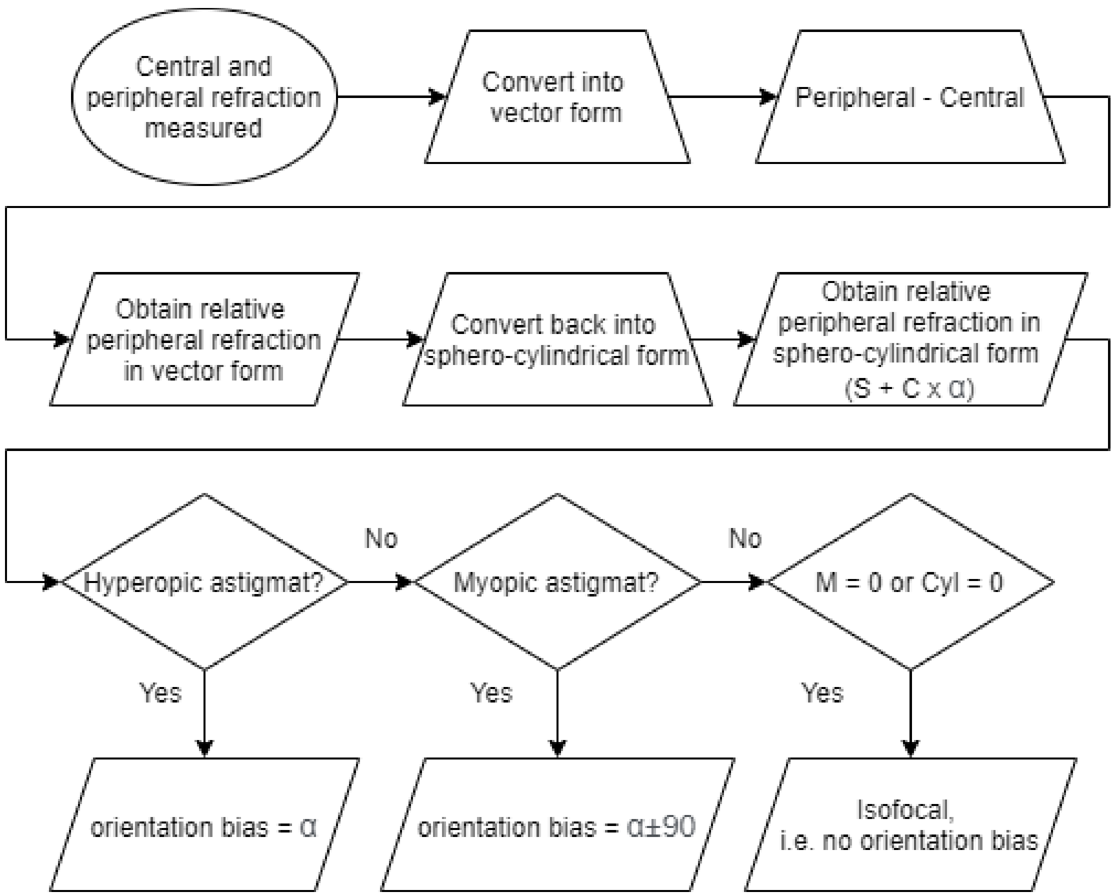


Figure 4.2 Flow chart for orientation bias calculations

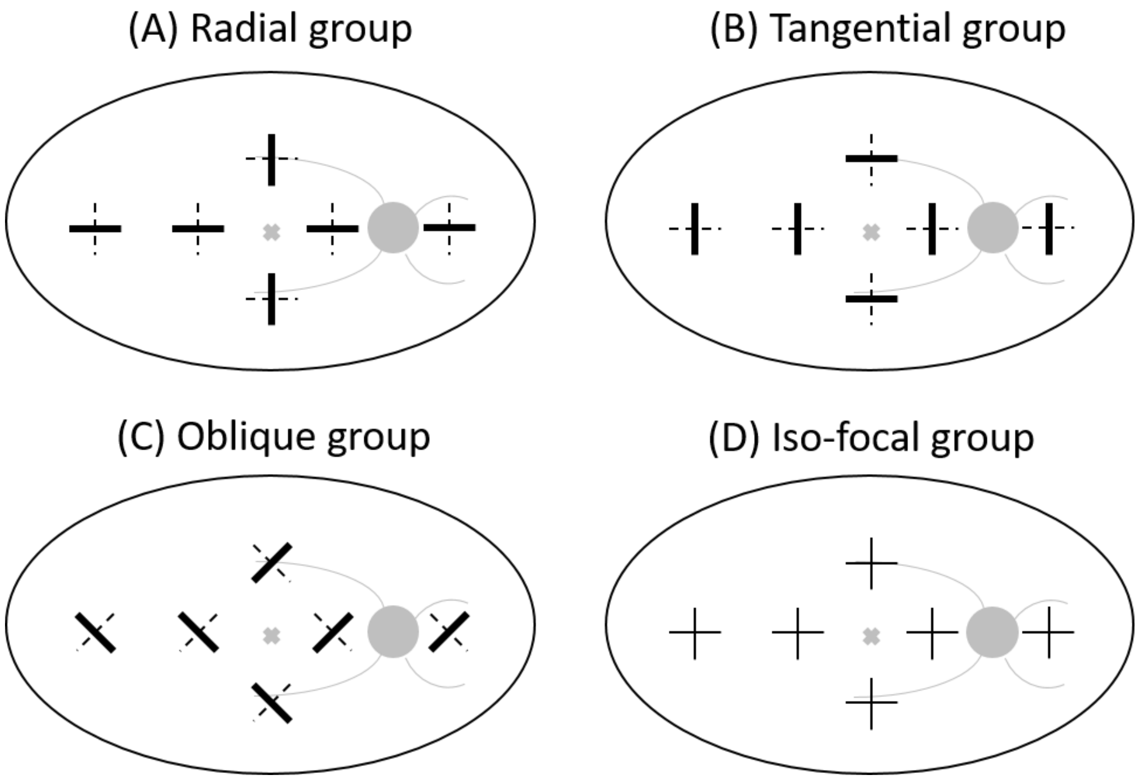


Figure 4.3 Schematic diagrams illustrating the four orientation biases: (A) radial, (B) tangential, (C) oblique, and (D) iso-focal. The thick solid line represents the clearer meridian, while the dashed line represents the blurrier meridian. The iso-focal group has equal clarity of the two principle meridians

4.3 Results

4.3.1 Demographics, on-axis refraction, and ocular biometry

Demographic information, refractive error, and ocular biometry of the subjects are shown in Table 4.1. There was no gender difference in AL/CR (Boys 3.07 ± 0.13 vs. Girls 3.06 ± 0.13, $t = 1.71$, $p = 0.09$). In general, children in the High AL/CR group were older, more myopic, and had greater on-axis astigmatism than those in Moderate and Low AL/CR groups.

Table 4.1 Demographic information and ocular parameters for the refractive groups

	All	Low AL/CR	Moderate AL/CR	High AL/CR	Statistical significance
Gender					
Male	576	272	206	98	
Female	476	255	159	62	
Age (year)	10.0 ± 1.1	9.8 ± 1.1	10.1 ± 1.1	10.3 ± 1.2	* +
Ocular biometry					
AL/CR ratio	3.06 ± 0.13	2.96 ± 0.06	3.12 ± 0.04	3.28 ± 0.08	* # +
Central refractive error					
M (D)	-1.30 ± 1.86	-0.07 ± 0.69	-1.69 ± 1.19	-4.44 ± 1.63	* # +
Cylindrical error (D)	-0.70 ± 0.68	-0.55 ± 0.51	-0.68 ± 0.63	-1.22 ± 0.95	* # +
J_0 (D)	0.24 ± 0.37	0.16 ± 0.30	0.24 ± 0.35	0.51 ± 0.50	* # +
J_{45} (D)	0.00 ± 0.19	-0.01 ± 0.16	-0.01 ± 0.18	0.06 ± 0.29	# +

Data are presented as mean ± SD. *, #, and + indicate significant difference by Bonferroni post-hoc test in Low vs. Moderate, Moderate vs. High, and Low vs. High AL/CR groups, respectively.

4.3.2 Relative peripheral refractive errors and on-axis AL/CR

The results of multiple correlation analysis are listed in Table 4.2. For ±10° horizontal and vertical field eccentricity, the correlations between on-axis AL/CR and RPRE are weak. With respect to the ±10° and ±20° horizontal eccentricity, the correlation between on-axis AL/CR and RPRE-J_{45} was insignificant, and that of RPRE-J_0 was weak. For both RPRE-M and radiality, the correlation with on-axis AL/CR was moderate. The results (mean ± SEM) of RPRE-M, -J_0, -J_{45}, and radiality across the horizontal and vertical eccentricity among refractive groups are shown in Figure 4.4.

Table 4.2 The relationship between on-axis axial-length-to-corneal-radius-of-curvature (AL/CR) and relative peripheral refractive error (RPRE) by multiple correlation analysis

	F	df	p	Pearson's r	Adjusted R^2
±10° horizontally and vertically (n = 1052) (All powers > 90.8%)					
RPRE-M	22.35	4, 1047	< **0.001**	0.28	0.08
RPRE-J_0	5.15	4, 1047	< **0.001**	0.14	0.02
RPRE-J_{45}	8.00	4, 1047	< **0.001**	0.17	0.03
RPRE-radiality	14.75	4, 1047	< **0.001**	0.23	0.05
±10° and ±20° horizontally (n = 603) (Power for J_{45} = 76%, power for others > 84%)					
RPRE-M	49.29	4, 598	< **0.001**	0.50	0.24
RPRE-J_0	6.10	4, 598	< **0.001**	0.20	0.03
RPRE-J_{45}	2.12	4, 598	0.08	0.12	0.01
RPRE-radiality	20.26	4, 598	< **0.001**	0.35	0.11

$Radiality$: $|M + J_0| - |M - J_0|$ for horizontal field; $|M - J_0| - |M + J_0|$ for vertical field.

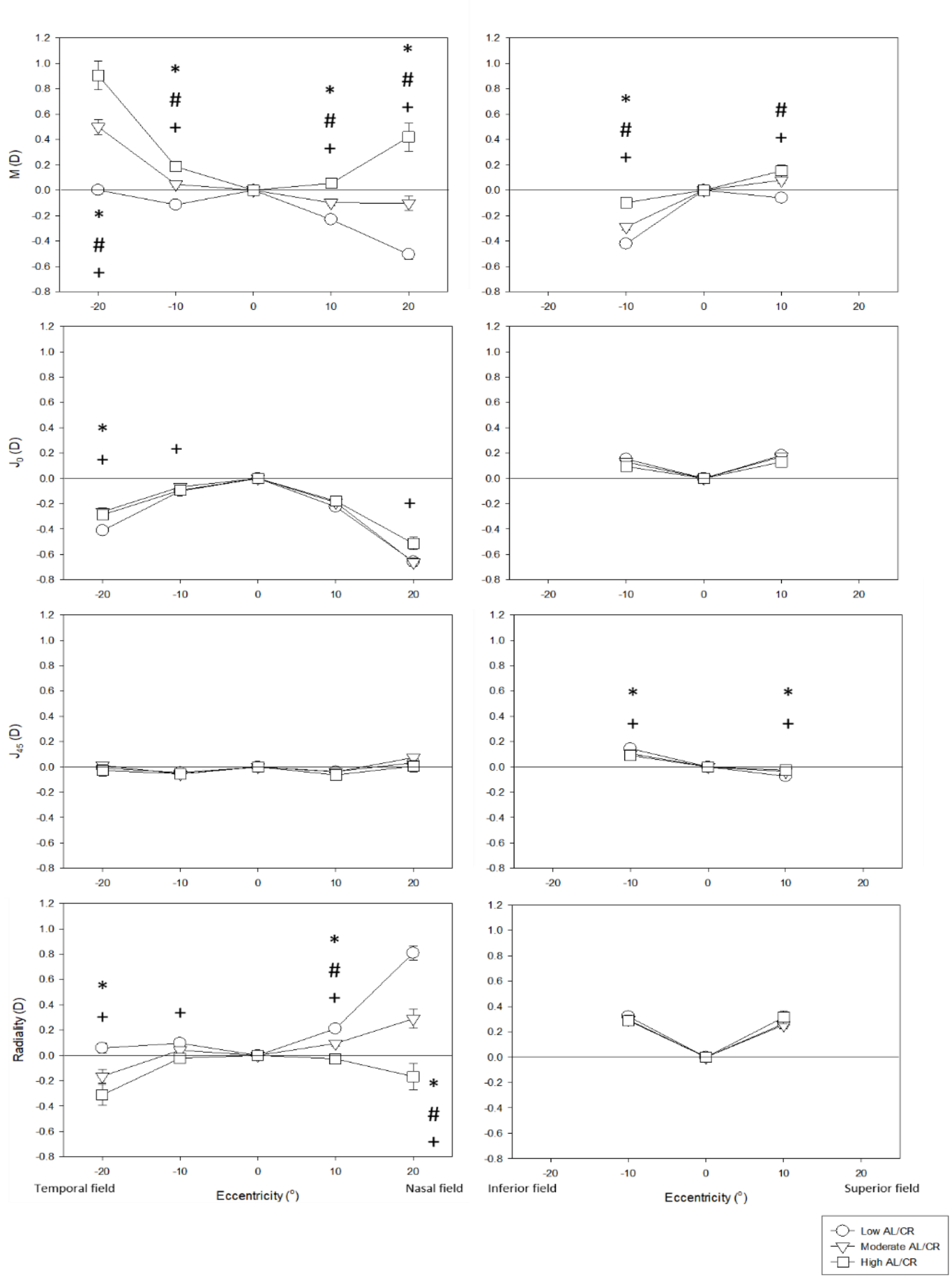


Figure 4.4 Relative peripheral refractive error (RPRE) in the three refractive groups. *, #, and + indicate significant difference calculated by Bonferroni post-hoc test in Low vs. Moderate, Moderate vs. High, and Low vs. High axial-length-to-corneal-radius-of-curvature (AL/CR) groups, respectively. The error bars (some obscured) represent the standard error of mean (SEM)

4.3.3 Proportion of orientation bias among refractive groups

Table 4.3 shows the proportion of orientation bias among refractive groups and the χ^2 statistics with post-hoc comparisons. In general, orientation bias along the vertical visual field did not differ among refractive groups. In contrast, orientation bias was significantly different among refractive groups along the horizontal eccentricity, except at Temporal 10°. In the Low AL/CR group, radial bias was over-represented, while tangential bias was under-represented. In contrast in the High AL/CR group, radial bias was under-represented, while tangential bias was over-represented.

Table 4.3 Proportion of orientation bias in different axial-length-to-corneal-radius-of-curvature (AL/CR) groups at different field eccentricity

	Proportion of orientation bias in each AL/CR group (%)			
	Radial	Tangential	Oblique	Iso-focal
Inferior 10°	$\chi^2 = 4.08$, $p = 0.67$			
Low	57.3	12.5	27.1	3.0
Moderate	58.1	14.5	23.8	3.6
High	51.3	16.3	28.8	3.8
Superior 10°	$\chi^2 = 3.78$, $p = 0.71$			
Low	51.8	25.8	19.7	2.7
Moderate	55.1	23.0	17.8	4.1
High	55.0	22.5	18.1	4.4
Temporal 10°	$\chi^2 = 11.31$, $p = 0.08$			
Low	38.1	26.0	30.0	5.9
Moderate	37.5	31.0	28.8	2.7
High	31.9	33.1	32.5	2.5
Nasal 10°	$\chi^2 = 29.43$, $p < 0.001$			
Low	54.1*	24.1#	17.8	4.0
Moderate	42.7	31.8	21.4	4.1
High	31.9#	37.5*	26.9	3.8
Temporal 20°	$\chi^2 = 24.47$, $p < 0.001$			
Low	45.0*	35.0#	17.5	2.4
Moderate	31.0	47.0	20.0	2.0
High	18.1#	52.8	25.0	4.2
Nasal 20°	$\chi^2 = 89.06$, $p < 0.001$			
Low	76.7*	16.9#	3.9#	2.4
Moderate	45.5#	44.5*	7.0	3.0
High	32.4#	46.5*	18.3*	2.8

* and # indicate over- and under-representation of orientation bias in AL/CR group, respectively

4.4 Discussion

This study characterised the pattern of relative peripheral refraction in a population of Chinese schoolchildren. The results showed a significant relationship between on-axis AL/CR ratio and peripheral refraction, in which both radiality and RPRE-M demonstrated a moderate correlation with on-axis AL/CR, while RPRE-J_0 and -J_{45} were weakly correlated. Furthermore, children with a higher AL/CR ratio had a lower magnitude of RPRE-J_0 and -J_{45} along the horizontal and vertical visual fields, respectively. The orientation bias was associated with on-axis AL/CR, in which the radial orientation was clearer, especially in the Low AL/CR group. In contrast, tangential orientation was clearer in the High AL/CR group along the horizontal eccentricity.

Peripheral astigmatism was found to increase in magnitude with the eccentricity. The averaged relative peripheral cylindrical error was 0.63 D at 10° eccentricity, rising to 1.33 D at 20° eccentricity along the horizontal field. The BLINK study for myopic children also reported an increase in peripheral astigmatism with retinal eccentricity (Mutti et al., 2019), in which the astigmatic error was less than 1 D at 20° eccentricity, increasing to more than 3 D at 40° eccentricity. For the RPRE-J_0 and -J_{45}, the results of the current study were -0.15 D and -0.05 D at 10° eccentricity, and -0.49 D and 0.02 D at 20° eccentricity. The PREP study for young children (mean age 7.2 years) found the central absolute J_0 to be 0.35 D, while approximately 0.17 D at peripheral absolute J_0 at 15° eccentricity, making the RPRE-J_0 -0.18 D (Sng et al., 2011). Similarly, the central absolute J_{45} was -0.04 D, while the peripheral absolute J_{45} at 15° eccentricity was approximately 0.03 D, making the RPRE-J_{45} 0.07 D. A recent study measuring peripheral refractions in non-myopic and myopic adults using a wavefront aberrometer demonstrated similar results (Shen et al., 2018). Despite the limited sample size in each of the refractive group ($N \leq 10$), all the RPRE-M, -J_0, and -J_{45} displayed similar trends along both the horizontal and vertical visual fields, as well as the difference among refractive groups.

A further aim of this study was to characterise the orientation-dependent blur in children with different AL/CR values. Figure 4.5 summarises the mode value of orientation bias (i.e. the clear meridian) across the visual fields in each AL/CR group. In the Low AL/CR group, the relative peripheral astigmatism created less blur to the radial orientation. However, the orientation bias tended to shift to tangential along the horizontal visual fields of the higher AL/CR groups. It can further be illustrated by the P(90) and P(180) vector components along the horizontal visual field (Figure 4.6). For the Low AL/CR group, the magnitude of P(90) was smaller, indicating that the horizontal component was clearer. However, in the High AL/CR group, the magnitude of P(180) became smaller, indicating the vertical component was clearer along the horizontal visual field. Rempt and co-workers suggested five types of skiagrams representing the peripheral orientation blur of different on-axis refractive error (Rempt et al., 1971), which was supported by Mathur and Atchison (Mathur and Atchison, 2013). Although measurements in the current study were limited to ±20°, while those in previous studies were extended to ±60° or more, and autorefraction was employed, while the previous studies used retinoscopy or aberrometry, the findings in a large sample of Chinese children supported previous results. The High AL/CR group in our sample exhibited similar characteristics to the type I and type II skiagrams, while the Moderate AL/CR group shared the characteristics of type III, and the Low AL/CR group was similar to type IV and type V skiagrams. Furthermore, although there are asymmetries between nasal and temporal fields as presented in Figures 4.4 and 4.6, the asymmetric appearance of RPRE did not appear to be different across AL/CR groups.

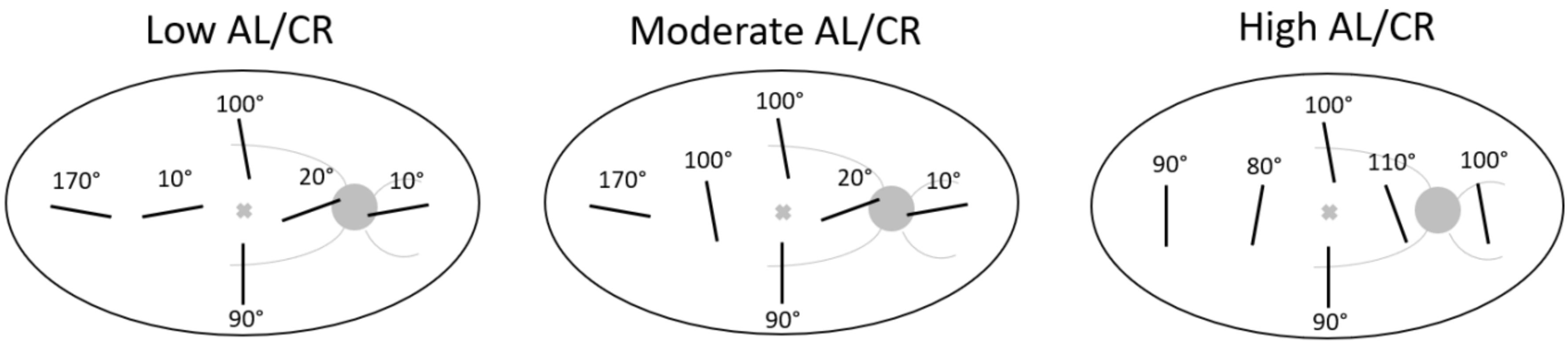


Figure 4.5 Schematic diagram summarising the orientation bias across visual fields in the Low, Moderate, and High axial-length-to-corneal-radius-of-curvature (AL/CR) groups. The black lines represent the mode value (bin size: 10°) of the orientation bias in each visual field angle

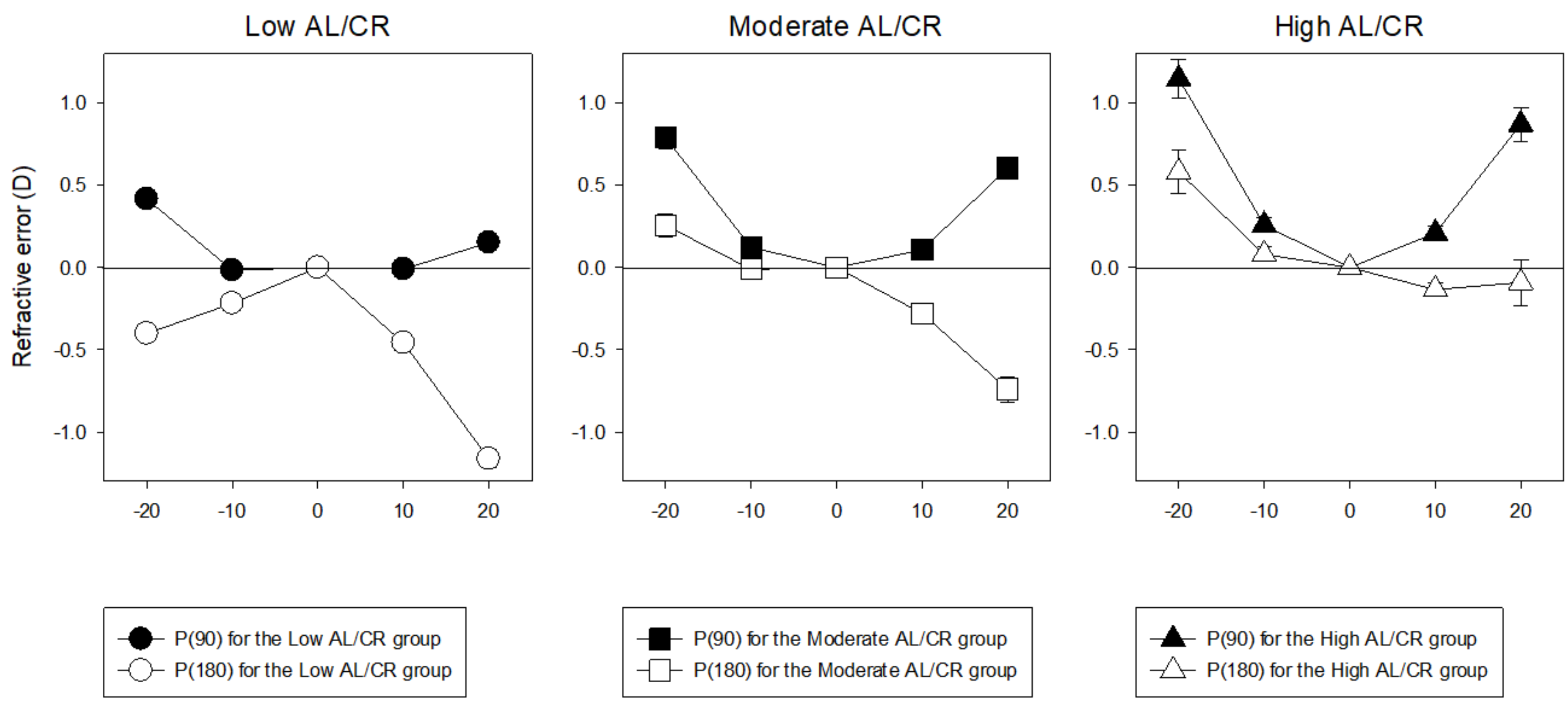


Figure 4.6 The P(90) and P(180) of the Low (●), Moderate (■), and High (▲) axial-length-to-corneal-radius-of-curvature (AL/CR) groups across the horizontal visual field. The error bars (some obscured) represent the standard error of mean (SEM)

In the current study, the orientation selective blurs were associated with on-axis refractive error. Such relationship may be proposed to be a cue for the eye to distinguish the direction of defocus, in order to emmetropise. On the other hand, higher-order aberration along the visual axis, particularly spherical aberration, was proposed to be an alternative cue (Kisilak et al., 2006; Lau et al., 2019). In natural developing chicks, the reduction rate of spherical aberration was slower than M, but overall achieving a better optical quality of retinal images. However, among defocus lens-rearing chicks, the spherical aberration rapidly changed initially, then followed a similar exponential drop as in that of natural developing chicks (although remained higher). The difference of spherical aberration change between natural and defocus-induced animals may indicate a fine-tune in structural-optical characteristics, and was suggested to be a cue to detect the sign of defocus, hence emmetropisation (Wilson et al., 2002; Thibos et al., 2013).

This study adopted a random-cluster sampling with relatively large sample size. It provides representative data of the peripheral refractive profile of Chinese schoolchildren in Hong Kong, where myopia has reached a very high prevalence (Lam et al., 2012; Choy et al., 2020). Although accommodation was not pharmacologically controlled by a cycloplegic agent, it has been shown to have limited effect on the measurement of the RPRE, the primary outcome of this study (Calver et al., 2007; Davies and Mallen, 2009). The fixation targets were placed 6 m away from the eye, creating a minimal 0.17 D accommodative stimulus. The strong correlation between the AL/CR ratio and central M (Figure 4.1), which was consistent with previous epidemiological studies performed under cycloplegic conditions (Ip et al., 2007; He et al., 2015b), suggested adequate control of accommodation when performing peripheral refraction in this study. The refractive status based on the AL/CR ratio, a biometric parameter that is suggested to be independent of the accommodative status, (Grosvenor and Scott, 1994; He et al., 2015b), was also categorised and used as primary outcome. To conclude, this study revealed that Chinese schoolchildren with various AL/CR ratios exhibited different patterns of peripheral astigmatic blur. These results provide a foundation for further studies aiming to investigate the contribution of PRE to the development of the eyes, as previous researchers have proposed that the retina might decode the direction of defocus by comparing the radial and tangential optical input of peripheral visual fields (Howland, 2010; Charman, 2011; Flitcroft, 2012; Atchison and Rosén, 2016). For instance, a positive defocus, which brings the peripheral astigmatic foci forward, would emphasise the radial component of the retinal image, and increase the retinal signal output as demonstrated in a human electrophysiology study (Ho et al., 2012). In comparison, the peripheral astigmatic pattern in the Low AL/CR group emphasises the radial component, which coheres with the functional bias of peripheral vision for radial orientation reported previously (Sasaki et al., 2006). This optical-functional coherence may consequentially increase the retinal signal output for positive defocus (vice versa for the negative defocus) (Ho et al., 2012).

It is possible that the coupling of peripheral astigmatism with the functional orientation bias, at least in the Low AL/CR group, may maximise the response of the visual system. In contrast, the orientation pattern of peripheral astigmatism in the higher AL/CR groups gradually slanted to the tangential orientation. Further study is needed to understand whether and how the orientation-dependent optical blur, together with external factors, such as the environmental defocus, contributes to the development and progression of myopia.

Chapter 5. Study III - Mixed factor - Home scene defocus profile, peripheral refraction, and myopia progression

(Part of Study III had been published in Ophthalmic and Physiological Optics, 2020;doi: 10.1111/opo/12698)

5.1 Introduction

Over the past decades, the prevalence of myopia has escalated in developed countries (Holden et al., 2016). This rapid increase has been linked to environmental effects, which are critical for refractive error development (Morgan et al., 2012). In East and Southeast Asian countries, the high prevalence of myopia has been attributed to the intense levels of near work during school-age. Studies have quantified near work in terms of working distance (Ip et al., 2008c; Li et al., 2015a), time span (Mutti et al., 2002; Saxena et al., 2015), type of near work (Saw et al., 2000; Ip et al., 2008c), and weighted near work (i.e. dioptre hour) (Saw et al., 2002a; Saw et al., 2002b). However, the relationship between near work and myopia still remains controversial (Huang et al., 2015).

The effect of peripheral refraction on myopia progression has also received considerable attention. Peripheral hyperopia and myopia have been associated with on-axis myopia and hyperopia, respectively (Atchison et al., 2006; Sng et al., 2011; Li et al., 2015b). Animal experiments have shown that axial eye growth is not limited to the central retina, but can also be regulated by the peripheral retina (Miles and Wallman, 1990; Smith et al., 2009b; Zeng et al., 2013), in which peripheral hyperopic and myopic defocus causes on-axis myopic and hyperopic shifts respectively. Hence, optical aids, which manipulate both central and peripheral refraction, can successfully retard myopia progression (Cho and Cheung, 2012; Lam et al., 2014; Lam et al., 2019). Although most studies have focused on spherical equivalent refraction, some have suggested that peripheral astigmatism might be a cue for the retina to decode emmetropisation signals (Howland, 2010; Charman, 2011; Atchison and Rosén, 2016). However, epidemiology studies have shown that baseline peripheral hyperopia was not able to predict subsequent myopia progression in children (Mutti et al., 2011; Atchison et al., 2015). To date, the effect of peripheral refraction on myopia development is still debatable (Smith et al., 2013a).

Human eyes are constantly exposed simultaneously to myopic and hyperopic defocus from the environment (Tse and To, 2011). Based on the simultaneous defocus concept, Flitcroft simulated human visual scenes using customised computer software (Flitcroft, 2012). In this simulation, outdoor scenes have a more evenly distributed dioptric profile, while indoor scenes (e.g. within an office) have a relatively uneven dioptric profile. The distribution of the defocus is even more varied when indoor object distances are closer. The uneven distribution of peripheral defocus from the indoor environment has been suggested as a risk factor for children, especially those who spent less time outdoors, to have a higher incidence and prevalence of myopia (Charman, 2011; Flitcroft, 2012). Childhood myopia is strongly associated with environmental factors (Morgan and Rose, 2005), in which the living environment plays a crucial role (Ip et al., 2008b; He et al., 2009; Wu et al., 2016). In Study I, it was found that the small home size in Hong Kong was associated with more myopia and longer AL. The reason for this increased risk was suggested to be the peripheral hyperopic defocus due to the close surroundings in small homes. However, it is still unknown whether certain home environment characteristics other than home size, could contribute to children's refractive development.

In Hong Kong and elsewhere in East Asia, children spend many hours at home to complete their heavy load of schoolwork (H.K.P.T.U., 2018). It is important to understand how the homeworking environment, especially the reading desk for near tasks, affects their refractive errors. Myopia studies investigating near tasks have focused mainly on the type of visual task, while the details of the visual scene, for example, the dioptric profile, received little attention. With the emergence of depth sensing technology (Khoshelham and Elberink, 2012; Gonzalez-Jorge et al., 2015), it is possible to obtain more information (e.g. depths across the visual field) from a scene with a handy device (Sprague et al., 2016; García et al., 2018). Additionally, peripheral refraction was found to be associated with the on-axis AL/CR in children in Study II, in terms of M, J_0, and the radiality along the horizontal visual field. The current study aimed to quantify the amount of relative scene defocus in the near work environment and investigate the relationship between these environments and juvenile refractive development. It also aimed to evaluate the interactive effect of peripheral refraction and scene profile in a home environment on myopia progression in children. The results may provide a new area for myopia control regimens in terms of manipulating the PRE and the home environment set-up for children.

5.2 Methods

5.2.1 Subjects

The subject recruitment was as described in Section 2.2 and involved the same subjects.

5.2.2 Data collection and processing

The data collection was as described in Section 2.2.

5.2.3 Statistical analysis

The home scene parameters were analysed using univariate, then multivariate analysis to investigate the relationship with myopia progression. The DV, SD_D, and regional DVs were individually correlated with ΔM using Spearman's test. The transformed regional DVs were then entered into four multiple linear regression models: equally potent and ring analysis; equally potent and quadrant analysis; myopic defocus twice potent and ring analysis; myopic defocus twice potent and quadrant analysis, along with other confounding factors, including age, baseline M, time spent in front of desk (T_{desk}), time spent outdoors (T_{OA}), working distance, parental myopia, home size, and transformed SD_D (tSD_D) to predict myopia progression over one year. Furthermore, the stepwise removal method was used to condense the number of independent variables catering for the small sample size, in which the insignificant variable with the highest p value was removed from the model stepwise until the p values of all remaining variables were below 0.05. The myopia progression was also compared using an independent t test or one-way ANOVA for each confounding variable.

The relationship between peripheral refraction, myopia progression, and home scene parameters was evaluated. Baseline a_M, a_{J0}, $a_{P(90)}$, and $a_{P(180)}$ were partially correlated with ΔM using Spearman's test controlled for the baseline M. DV and SD_D were also added as co-variates to evaluate Spearman's correlation between peripheral refractions and ΔM. Then, DV was further replaced by DV_H (DV_R+DV_L) and DV_V (DV_U+DV_D) individually to assess if the regional effect of horizontal and vertical visual fields, respectively, would be enhanced or diminished by matching the horizontal RPRE. To refine the results, the analysis was repeated with exclusion of subjects with insignificant fit in the quadratic regressions, i.e. only fitted subjects with regression $p < 0.05$. Four multiple linear regression models were used to analyse the effect of the four coefficients of RPRE, respectively, and home scene parameters on myopia progression after normality transformation (Templeton, 2011), which was performed on all subjects because of the sample size limitation. The significance level was set as $p < 0.05$.

5.3 Results

5.3.1 Descriptive statistics of on-axis and peripheral refraction, activity pattern, and home scene parameters

The subjects (n = 50, 22 boys) in the study were aged 9.3 ± 1.2 years (Mean ± SD) and had a baseline M of -1.51 ± 2.02 D. The ΔM was -0.56 ± 0.45 D over 1 year, which was independent of the baseline M (Pearson's r = 0.21, p = 0.14). The median T_{desk} was 2 hours / day (IQR 1.0 - 3.0 hours / day, Range 0.5 - 5.0 hours / day), with an average working distance of 29.7 ± 6.0 cm, while the median T_{OA} was 2 hours / week (IQR 1.0 - 4.5 hours / week, Range 1.0 - 20.0 hours / week). The raw infra-red images captured by the Kinect, representing different characteristics, were included in the Appendix. With respect to the home scene parameters, the median DV and DV_{2M} over the central 30° were 1.16 D°° (IQR 0.46 - 3.82 D°°, Range -0.48 - 8.43 D°°) and 0.86 D°° (IQR 0.27 to 3.56 D°°, Range -1.36 to 8.24 D°°), respectively, while the median SD_D over the central 30° was 0.49 D°° (IQR 0.31 - 0.69 D°°, Range 0.08 - 2.29 D°°). Plots of RPRE-M, J_0, P(90), and P(180) of the subjects are shown in Figure 5.1. Myopia progression was similar for both significantly fitted and non-fitted subjects (excluded in the repeated analysis) in the quadratic regression, which are listed in Table 5.1.

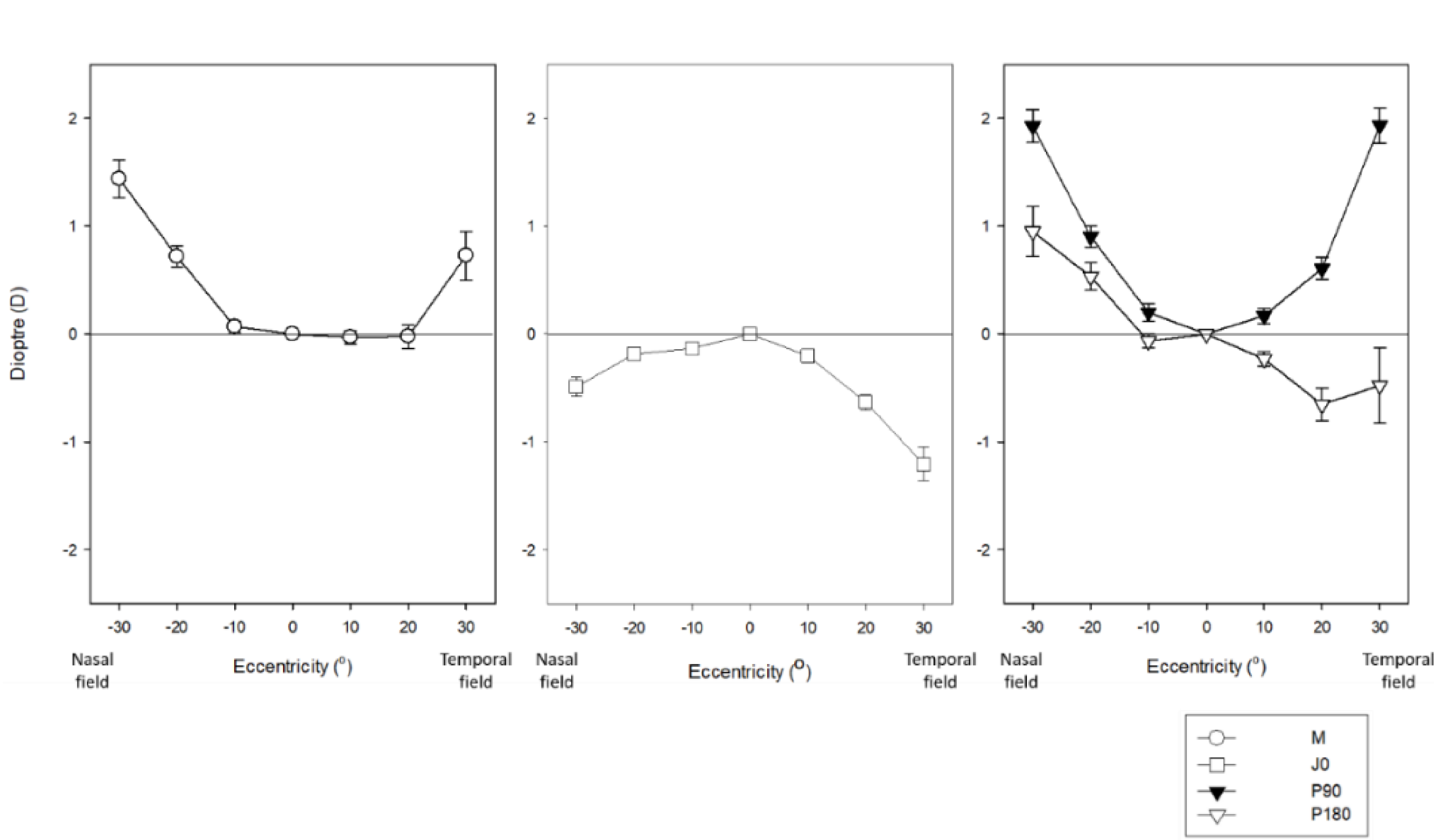


Figure 5.1 Relative peripheral refractive errors ± standard error of mean (RPRE ± SEM) in terms of M, J_0, P(90), and P(180) across eccentricity from nasal 30° to temporal 30° visual field

Table 5.1 Myopia progression (ΔM) in children's peripheral refraction significantly fitted and not fitted with quadratic regression

		n	ΔM (Mean ± SD)	Independent t	p	Minimum R^2
a_M	Fitted	37	-0.54 ± 0.46	0.17	0.86	0.79
	Non-fitted	13	-0.57 ± 0.45			
a_{J0}	Fitted	27	-0.65 ± 0.51	-1.30	0.20	0.78
	Non-fitted	23	-0.49 ± 0.39			
$a_{P(90)}$	Fitted	41	-0.59 ± 0.44	0.73	0.47	0.80
	Non-fitted	9	-0.46 ± 0.48			
$a_{P(180)}$	Fitted	30	-0.53 ± 0.40	-0.61	0.55	0.78
	Non-fitted	20	-0.61 ± 0.52			

5.3.2 Analysis of home scene parameters on myopia progression

The working distance of the subjects was not related to the ΔM (Pearson's r = 0.21, p = 0.15) or the home size (Kruskal-Wallis test $\chi^2_{2,50}$ = 0.82, p = 0.66), but was negatively correlated with DV (ρ = -0.60, p < 0.001) and SD_D (ρ = -0.67, p < 0.001) respectively. Thus, the shorter the working distance, the more positive and dispersed the overall scene defocus. For the partial correlation controlling for the baseline M, DV (ρ = -0.25, p = 0.08) and DV_{2M} (ρ = -0.21, p = 0.16) were not related to ΔM, while SD_D was negatively correlated to ΔM (ρ = -0.42, p < 0.01), i.e. subjects with faster myopia progression had a more dispersed baseline scene defocus. As a secondary outcome, partial correlation tests between ΔAL, controlled for the baseline AL, and SD_D, DV, DV_{2M} also showed similar results ($SD_{D:}$ ρ = 0.36, p = 0.01; DV: ρ = 0.26, p = 0.08; DV_{2M}: ρ = 0.22, p = 0.12).

Among the regional defocus parameters, DV_{20} was significantly correlated with ΔM ($\rho = -0.32$, $p = 0.02$), but not quadrants DV nor DV_{2M}. Table 5.2 shows the statistical results of the correlations of regional DV. Multiple regression analyses revealed that only age, baseline M, and tDV_{20} were significantly associated with ΔM in the regression models. Supplementary tables 2 - 5 list the detailed statistical analyses of individual variables, which are included in the Appendix. The results from the stepwise regression models showed that older children and those having a more hyperopic baseline M had significantly slower myopia progression. In contrast, more hyperopic para-central defocus at 15°- 20° (i.e. tDV_{20} and tDV_{2M20}) and at left quadrant (i.e. tDV_L and tDV_{2ML}) from the scene, were associated with faster myopia progression. The coefficients and statistics of the significant variables are listed in Table 5.3.

Table 5.2 Correlation between regional defocus and refractive change over one year

	DV_5	DV_{10}	DV_{15}	**DV_{20}**	DV_{25}	DV_{30}
Spearman's ρ	-0.12	-0.12	-0.23	**-0.32**	-0.13	0.04
p value	0.42	0.40	0.11	**0.02***	0.37	0.78

	DV_R	DV_U	DV_L	DV_D
Spearman's ρ	-0.18	0.27	-0.22	-0.18
p value	0.21	0.06	0.12	0.22

	DV_{2M5}	DV_{2M10}	DV_{2M15}	DV_{2M20}	DV_{2M25}	DV_{2M30}
Spearman's ρ	-0.15	-0.08	-0.23	-0.22	-0.07	0.11
p value	0.30	0.56	0.12	0.12	0.63	0.47

	DV_{2MR}	DV_{2MU}	DV_{2ML}	DV_{2MD}
Spearman's ρ	-0.16	0.26	-0.19	-0.15
p value	0.27	0.06	0.20	0.31

DV: dioptric volume

R: Right; U: Up; L: Left; D: Down

2M indicates twice myopic defocus potency

* asterisks indicate a significant correlation between myopia progression and the regional DV

Table 5.3 Stepwise multiple regression of refractive change over one year

	Raw B value	95% CI	Standardised B	p	VIF
Ring analysis: Adjusted R^2 = 0.32, $F_{3,50}$ = 8.63, p < 0.001, Power = 89.8%					
Age	0.12	0.03 to 0.29	0.31	**0.01**	1.02
Baseline M	0.05	0.01 to 0.11	0.24	**0.05**	1.01
tDV_{20}	-0.18	-0.28 to -0.08	-0.43	**0.001**	1.03
Quadrant analysis: Adjusted R^2 = 0.18, $F_{3,50}$ = 4.58, p = 0.01, Power = 73.1%					
One myopic parent	-0.38	-0.68 to -0.07	-0.34	**0.02**	1.10
tDV_U	0.14	0.02 to 0.26	0.31	**0.03**	1.10
tDV_L	-0.17	-0.28 to -0.05	-0.40	**0.01**	1.11
2M ring analysis: Adjusted R^2 = 0.31, $F_{3,50}$ = 8.18, p < 0.001, Power = 87.9%					
Age	0.12	0.03 to 0.21	0.32	**0.01**	1.02
Baseline M	0.06	0.01 to 0.12	0.28	**0.03**	1.04
tDV_{2M20}	-0.18	-0.28 to -0.07	-0.42	**0.001**	1.05
2M quadrant analysis: Adjusted R^2 = 0.16, $F_{4,50}$ = 4.09, p = 0.01, Power = 65.4%					
Medium home size	0.26	0.01 to 0.51	0.28	**0.04**	1.04
High T_{OA}	0.27	0.04 to 0.50	0.31	**0.02**	1.04
tDV_{2ML}	-0.28	-0.58 to -0.00	-0.26	**0.05**	1.05
tSD_D	-0.13	-0.25 to 0.02	-0.31	**0.02**	1.08

tDV: transformed dioptric volume

tSD_D: transformed standard deviation of the defocus

R: Right; U: Up; L: Left; D: Down

2M indicates twice myopic defocus potency

5.3.3 Analysis of peripheral refraction on myopia progression controlled of home scene parameters

The RPRE was significantly associated with myopia progression. The a_M was significantly correlated with ΔM. In contrast, a_{J0} was significantly correlated with ΔM for all subjects, but was independent of ΔM for fitted subjects. $a_{P(90)}$ was independent of ΔM, while $a_{P(180)}$ was significantly correlated with ΔM. Figure 5.2 shows the scatter plots for coefficients against myopia progression.

However, after controlling for baseline M, RPRE was generally not associated with myopia progression. In partial correlation controlled with baseline M, the correlation between ΔM and a_M became insignificant, as well as a_{J0}. $a_{P(90)}$ was independent of ΔM after controlled of baseline M, but $a_{P(180)}$ was still significantly correlated with ΔM, although the correlation coefficient dropped.

After controlling for baseline M and home scene parameters, RPRE was once again associated with myopia progression. The home scene parameters (DV and SD_D) were then added as co-variates in the partial correlation analysis. After controlling for baseline M, DV, and SD_D, a_M was then significantly correlated with ΔM. a_{J0} was independent of ΔM for all, but was significantly correlated with ΔM for fitted subjects. $a_{P(90)}$ was independent of ΔM after controlling for baseline M, DV, and SD_D. However, $a_{P(180)}$ was significantly correlated with ΔM.

With respect to the regional analysis, DV_H and DV_V were applied to replace DV as a co-variate individually. a_M was significantly correlated with ΔM after controlling for DV_H, but independent of ΔM when controlling for DV_V. In contrast, a_{J0} was independent of ΔM for all subjects, but was significantly correlated with ΔM for fitted subjects when controlling for DV_H. When controlling for DV_V, a_{J0} was independent of ΔM. As for $a_{P(90)}$, it was independent of ΔM when controlling for DV_H and DV_V, respectively. However, $a_{P(180)}$ was significantly correlated with ΔM when controlling for DV_H and DV_V, respectively. By matching the horizontal scene (DV_H), or mismatching the vertical scene (DV_V) with horizontal RPRE, the relationship between RPRE and ΔM did not appear to be affected. The correlation statistics are listed in Table 5.4, while Table 5.5 shows the results of multiple linear regression analyses. Regression models for a_M, a_{J0}, and $a_{P(180)}$ showed the peripheral refraction was a significant factor in predicting myopia progression, while for $a_{P(90)}$, it was insignificant.

Table 5.4 Correlation statistics of myopia progression and peripheral refraction, with and without control of home scene parameters

	All subjects		Fitted subjects	
	Spearman's ρ	p	Spearman's ρ	p
Simple correlation				
a_M	**-0.34**	**0.02***	**-0.41**	**0.01***
a_{J0}	**-0.29**	**0.05***	-0.30	0.13
$a_{P(90)}$	-0.17	0.24	-0.17	0.28
$a_{P(180)}$	**-0.37**	**0.01***	**-0.48**	**0.01***
Partial correlation controlled with baseline M				
a_M	-0.25	0.08	-0.32	0.06
a_{J0}	-0.27	0.06	-0.28	0.16
$a_{P(90)}$	-0.02	0.90	0.02	0.88
$a_{P(180)}$	**-0.31**	**0.03***	**-0.43**	**0.02***
Partial correlation controlled with baseline M, DV, and SD_D				
a_M	**-0.30**	**0.04***	**-0.36**	**0.04***
a_{J0}	-0.28	0.05	**-0.49**	**0.01***
$a_{P(90)}$	-0.06	0.71	-0.00	0.99
$a_{P(180)}$	**-0.35**	**0.02***	**-0.51**	**0.01***
Partial correlation controlled with baseline M, DV_H, and SD_D				
a_M	**-0.29**	**0.05***	**-0.34**	**0.05***
a_{J0}	-0.28	0.06	**-0.49**	**0.02***
$a_{P(90)}$	-0.06	0.68	0.00	0.98
$a_{P(180)}$	**-0.35**	**0.02***	**-0.49**	**0.01***
Partial correlation controlled with baseline M, DV_V, and SD_D				
a_M	**-0.26**	**0.08***	-0.33	0.06
a_{J0}	-0.28	0.05	-0.29	0.15
$a_{P(90)}$	-0.07	0.67	-0.01	0.94
$a_{P(180)}$	**-0.33**	**0.02***	**-0.45**	**0.02***

* asterisks indicate a significant correlation

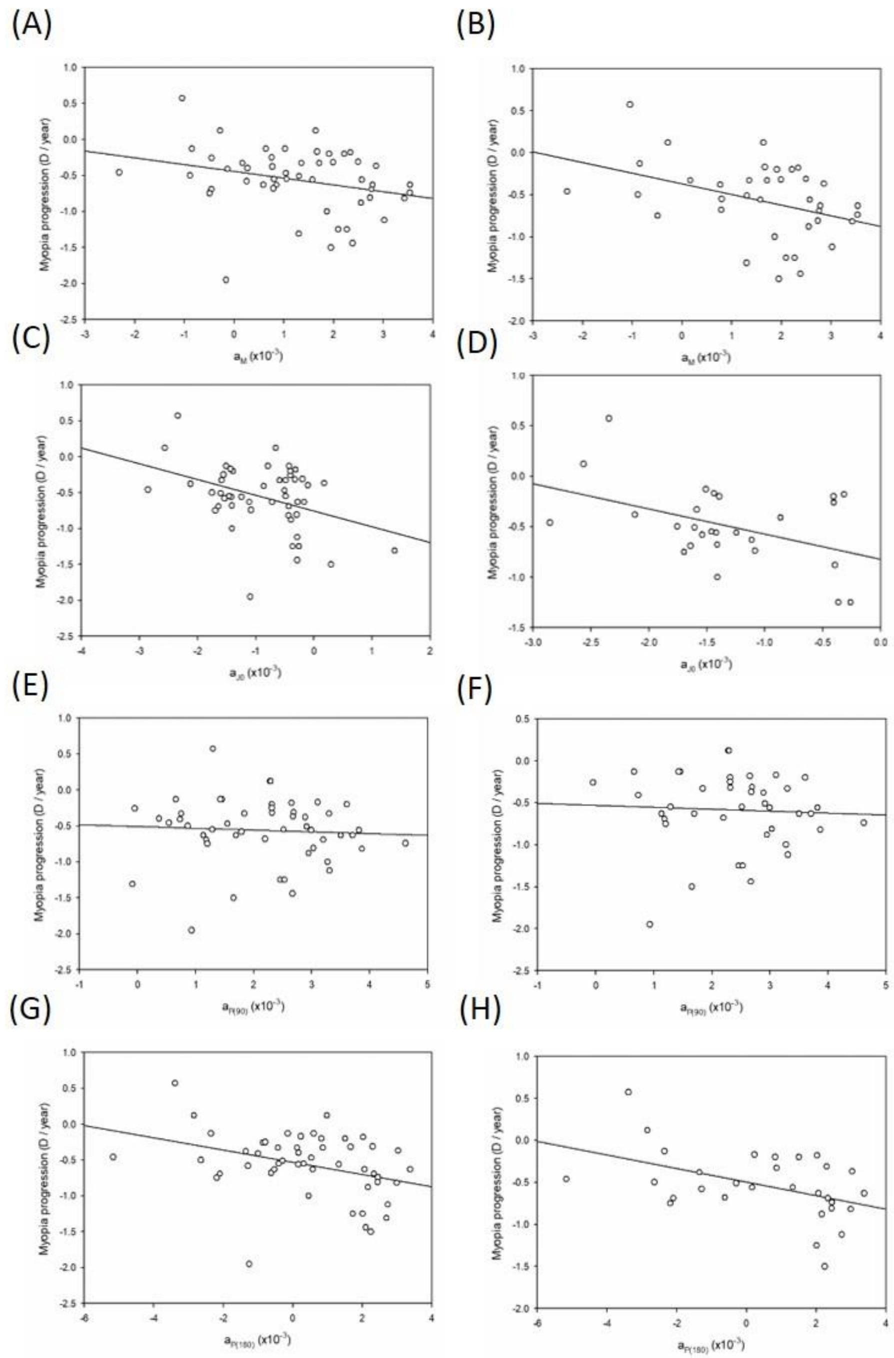


Figure 5.2 Relationship between the fitted first coefficient of relative peripheral refractive error (RPRE) and myopia progression (∆M). Left column: All subjects; Right column: Fitted subjects. First row: a_M; Second row: a_{J0}; Third row: $a_{P(90)}$; Fourth row: $a_{P(180)}$

Table 5.5 Multiple linear regression in the prediction of myopia progression (∆M)

		Raw B	95% CI	Standardised B	p	VIF
a_M	Adjusted R^2 = 0.13, $F_{4,50}$ = 2.85, p = 0.04, Power = 73.1%					
	Baseline M	0.03	-0.04 to 0.10	0.14	0.36	1.25
	Transformed SD_D	-0.10	-0.26 to 0.06	-0.24	0.21	1.98
	Transformed DV	-0.05	-0.21 to 0.11	-0.12	0.52	1.99
	Transformed a_M	**-0.14**	**-0.27 to -0.01**	**-0.30**	**0.04***	**1.27**
a_{J0}	Adjusted R^2 = 0.20, $F_{4,50}$ = 4.08, p = 0.01, Power = 79.6%					
	Baseline M	0.06	-0.00 to 0.11	0.25	0.07	1.03
	Transformed SD_D	-0.08	-0.23 to 0.07	-0.20	0.28	1.98
	Transformed DV	-0.04	-0.19 to 0.12	-0.08	0.65	1.98
	Transformed a_{J0}	**-0.16**	**-0.27 to -0.05**	**-0.37**	**0.01***	**1.01**
$a_{P(90)}$	Adjusted R^2 = 0.05, $F_{4,50}$ = 1.68, p = 0.17, Power = 59.4%					
	Baseline M	0.06	-0.02 to 0.13	0.25	0.14	1.40
	Transformed SD_D	-0.10	-0.26 to 0.07	-0.23	0.25	1.99
	Transformed DV	-0.04	-0.21 to 0.13	-0.09	0.64	2.00
	Transformed $a_{P(90)}$	-0.01	-0.16 to 0.13	-0.03	0.86	1.51
$a_{P(180)}$	Adjusted R^2 = 0.15, $F_{4,50}$ = 3.10, p = 0.02, Power = 71.0%					
	Baseline M	0.04	-0.02 to 0.10	0.18	0.20	1.11
	Transformed SD_D	-0.09	-0.25 to 0.07	-0.22	0.24	1.98
	Transformed DV	-0.05	-0.21 to 0.11	-0.11	0.54	1.98
	Transformed $a_{P(180)}$	**-0.13**	**-0.25 to -0.01**	**-0.31**	**0.03***	**1.09**

* asterisks indicate a significant predictor in the regression model

5.3.4 Analysis of other co-variates on myopia progression

The univariate analyses are listed in Table 5.6. Home size was associated with ΔM (One-way ANOVA, $F_{2,50} = 7.01$, $p = 0.002$), but not with DV (Kruskal-Wallis test, $\chi^2_{2,50} = 0.40$, $p = 0.82$), DV_{2M} (Kruskal-Wallis test, $\chi^2_{2,50} = 0.44$, $p = 0.80$), or SD_D (Kruskal-Wallis test, $\chi^2_{2,50} = 3.81$, $p = 0.15$). In post-hoc tests, children living in a Small-sized home had greater myopia progression than those in a Medium- (Bonferroni post-hoc test, $p = 0.02$) and Large-sized home (Bonferroni post-hoc test, $p = 0.003$). No significant association was found between Medium- and Large-sized homes (Bonferroni post-hoc test, $p > 0.99$). Parental myopia was not significantly associated with ΔM (One-way ANOVA, $F_{2,50} = 2.44$, $p = 0.10$). There was no significant difference for ΔM between the Low and High groups (Independent $t = 0.78$, $p = 0.44$) in terms of T_{desk}, and T_{desk} was also independent of home size ($\chi^2_{2,50} = 3.21$, $p = 0.20$). With respect to T_{OA}, the Low group progressed significantly faster than the High group (Independent $t = -2.13$, $p = 0.04$), but neither the correlation between T_{OA} and scene defocus (DV: $\rho = -0.24$, $p = 0.10$; SD_D: $\rho = -0.15$, $p = 0.30$) nor the correlation between T_{desk} and scene defocus (DV: $\rho = 0.13$, $p = 0.36$; SD_D: $\rho = 0.15$, $p = 0.29$) reached significance.

Table 5.6 Univariate analysis of co-variates on myopia progression (ΔM) over one year

	n	ΔM (Mean ± SD)	Achieved power
Total	50	-0.56 ± 0.45 D	
Home size			0.91
Small home	16	-0.87 ± 0.52 D†‡	
Medium home	17	-0.46 ± 0.32 D†	
Large home	17	-0.38 ± 0.35 D‡	
Parental myopia			0.53
No myopic parent	6	-0.23 ± 0.43 D	
One myopic parent	21	-0.67 ± 0.52 D	
Two myopic parents	23	-0.55 ± 0.35 D	
Time spent in front of desk (T_{desk})			0.14
Low (< 2.0 hours / day)	21	-0.50 ± 0.47 D	
High (≥ 2.0 hours / day)	29	-0.61 ± 0.43 D	
Time spent outdoors (T_{OA})			0.54
Low (< 2.0 hours / week)	24	-0.70 ± 0.47 D§	
High (≥ 2.0 hours / week)	26	-0.44 ± 0.40 D§	

†‡ indicate significant difference in Bonferroni post-hoc test

§ indicates significant difference in independent t-test

5.4 Discussion

The current study revealed an association between children's homeworking environment and their subsequent refractive development. Specifically, the defocus profile from the scene, in terms of the dispersion of defocus distribution and para-central regional defocus, were associated with the myopic change in refractive error in a year. In contrast, peripheral refraction alone could not predict subsequent myopia progression in children after controlling for the baseline refraction. However, after controlling for the home scene parameters, baseline RPRE, in terms of a_M and a_{J0}, was significantly correlated with subsequent myopia progression. Furthermore, myopia progression was significantly correlated with the more myopic image shell, i.e. $a_{P(180)}$, but independent of the more hyperopic image shell, i.e. $a_{P(90)}$. Additional to the cross-sectional relationship between home size and refractive error as reported in Study I, a small home size is believed to be a risk factor for faster myopic change.

Although findings for adverse effects of near work on childhood refractive development are controversial (Huang et al., 2015), a novel quantification of a near work environment was devised in the current study. Garcia and co-workers described their measurements to capture the defocus map using the Kinect v1 and an eye tracker by overlapping the acquired frames from both devices over five minutes (García et al., 2018). Unlike the scene of computer working desk in their study, the "in-focus" area of a child's writing / reading desk did not show a maximum (Figure 5.3), because the desk surface was inclined with respect to the eyes. Instead, most of the area of view incorporated a range of negative defocus. However, the calculated DVs, which is the total amount of net defocus within the central 30° field, for most subjects were positive, because the magnitude of the positive defocus was generally greater than that of negative defocus. Such spatial summation effect (area versus magnitude of defocus) will be further discussed in Section 6.2.3. Figure 5.3 shows the representative distributions (quartiles) regarding DV and SD_D, which is the dispersion of scene defocus value within the central 30°.

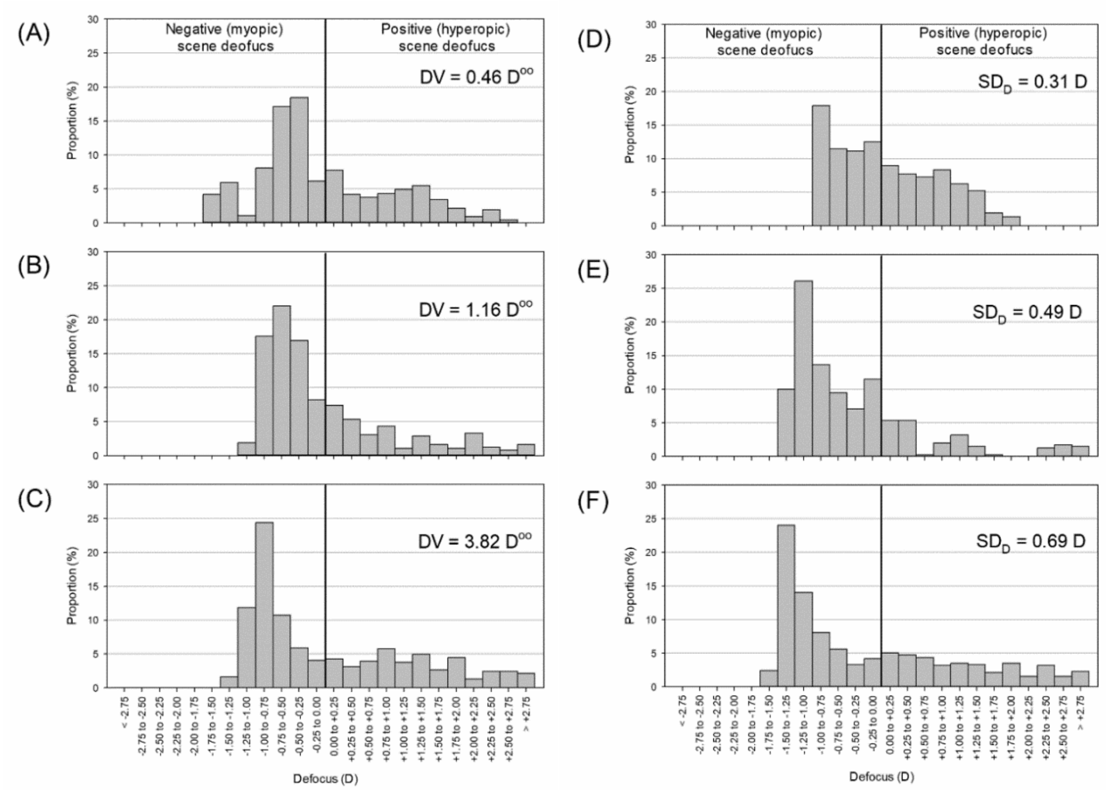


Figure 5.3 Scene defocus distribution of central 30° from representative subjects - Subject A: The 1st quartile of dioptric volume (DV); Subject B: The 2nd quartile of DV; Subject C: The 3rd quartile of DV; Subject D: The 1st quartile of standard deviation of the scene defocus (SD_D); Subject E: The 2nd quartile of SD_D; Subject F: The 3rd quartile of SD_D

These findings suggest a moderate correlation between peripheral defocus dispersion and myopia progression. Unlike an outdoor scene, in which peripheral defocus distribution is more uniform, an indoor scene consists of a more varied defocus profile, creating a rapid change in peripheral retinal defocus when the fixation is changed. Such rapid change has been suggested to cause a failure in emmetropisation as the temporal integration of the retinal signals is interrupted (Charman, 2011; Flitcroft, 2012). This non-linear temporal integration was also demonstrated in studies performed in both guinea pigs and monkeys (Leotta et al., 2013; Benavente-Perez et al., 2019). With respect to spatial integration, myopic defocus demonstrated approximately twice the potency of hyperopic defocus when simultaneously presented in chick eyes (Tse and To, 2011). In the current study, this doubled myopic potency assumption (i.e. 2M) could not better explain the relationship between scene defocus and myopic progression, which may be due to the difference in species as the myopic potency appears to be less prominent in mammals (McFadden et al., 2014). In addition, as in Study I, a smaller home was associated with more myopic refractive error. It is likely that a smaller home would create more surrounding hyperopic defocus, as the constricted environment would block the view of distant objects and / or have more close objects.

In contrast, although the total amount of net defocus within the central 30° field (i.e. DV and DV_{2M}) was not associated with refractive error development, the amount of net defocus across 15°- 20° eccentricity had a modest, but significant correlation with the change in refractive error as well as the multiple linear regression analysis controlled for other co-variates. Unfortunately, it was not possible to match the scene defocus with the subjects' fixation to generate the retinal defocus map as illustrated by Garcia and co-workers (Garcia et al., 2019). However, the para-central retina has been reported to have higher defocus sensitivity in human electrophysiological studies (Ho et al., 2012; Chin et al., 2015). If the scene eccentricity is matched with the retinal eccentricity, the positions of closely surrounding objects near the central visual target is likely to manipulate the peripheral retinal signal in control of the emmetropisation process. However, quadrant analysis did not show any conclusive association with myopia progression. Among the four quadrants, the left quadrant was significantly associated with DV in multivariate analyses, but not univariate analyses. A possible explanation could be the writing habit due to the dominance of right laterality, but further study is necessary to determine if this is the case. In the correlation analysis between myopia progression and peripheral refraction controlled for the home scene parameters, DV_H also showed a more prominent effect over DV_V. This might be explained by the matching between the external and internal defocus, in which the scene defocus along the horizontal meridian synergised with the horizontal peripheral refraction.

PRE imposes a blur signal on the peripheral retina. Individual analysis of RPRE in each location in the visual field may overlook the characteristics of the overall peripheral refractive profile of the eye. For peripheral M, J_0, P(90), and P(180), the magnitude of these components increases with visual field eccentricity (Ferree et al., 1931; Rempt et al., 1971), which mostly regress as a parabola (Atchison et al., 2006). Table 5.1 shows most of the subjects were able to be fitted in a quadratic regression with an R^2 close to 0.8. However, whether RPRE significantly fitted in a quadratic regression or not, was not associated with their myopia progression. In the repeated analyses for all and fitted subjects, the results also followed the same trend except for a_{J0}.

As mentioned in Study II, peripheral astigmatism has been suggested to be a cue for peripheral retinal decoding, as baseline M was not a predictor of subsequent myopia progression in epidemiology studies (Mutti et al., 2011; Atchison et al., 2015). Howland suggested that the imbalance of two focal shells created by peripheral astigmatism might generate a signal for axial elongation (Howland, 2010). The sagittal shell tends to create radial focal lines posteriorly, while the tangential shell creates perpendicular focal lines more anteriorly along the field eccentricity. The results showed that the myopia progression was associated with P(180), but not P(90), if the scene profile was taken into account. It was previously suggested that the retina emmetropises towards the more myopic image shell rather than the circle of least confusion (Kee et al., 2004). In the current study, the peripheral J_0 was significantly associated with myopia progression after adjusting for the external factor due to the home scene stimulus. In contrast, the fitted subjects (Fitted subjects $\rho = -0.49$) had a better correlation coefficient with myopia progression than those non-fitted ones (All subjects $\rho = -0.28$). The baseline on-axis cylindrical error was significantly lower in fitted subjects than non-fitted ones (Fitted: -0.60 ± 0.44 D vs. Non-fitted: -0.98 ± 0.71 D, $t = -2.27$, $p = 0.03$). While the quadratic fitness of a_{J0} was not as good as a_M (27 vs. 37 out of 50), whether other patterns of peripheral astigmatism in these on-axis astigmats play a role in modulating myopia progression warrants further investigations.

The scene defocus profile was the external stimulus from the environment, in which objects closer than the fixation plane create hyperopic scene defocus, while those farther away create myopic scene defocus. As a more dispersed defocus profile is associated with faster myopia progression, it is possible that the resultant defocus on retina does not only depend on the scene defocus, but also the peripheral refraction of the eye. Figure 5.4 shows the interaction between scene defocus dispersion (SD_D) and a_M on myopia progression. When the subjects were equally divided into two groups according to their SD_D, the a_M in subjects with lower SD_D had better correlation with ΔM ($\rho = -0.50$, $p = 0.01$) than those with higher SD_D ($\rho = -0.23$, $p = 0.28$). Thus, peripheral refractive influence was shown to be more effective in manipulating refractive changes if the scene defocus effect was less. In other words, peripheral myopia appeared to be a protective factor against myopia progression when scene defocus profile was less dispersed or more uniform. However, if the defocus profile was dispersed, the effect of peripheral refraction on myopia progression was minimal. It is possible that if RPRE is small, the retinal-signal-driven refractive development depends less on the internal factor due to the PRE, and hence the external factor created by surrounding visual stimuli plays a more important role. Combining Study I and Study II, there was a significant relationship between RPRE and the constricted living environment, in which high population density and small home size were associated with a more hyperopic RPRE-M, -P(180), and a less magnitude of RPRE-J_0. These results also provide evidence of the interaction between internal RPRE and external defocus profile.

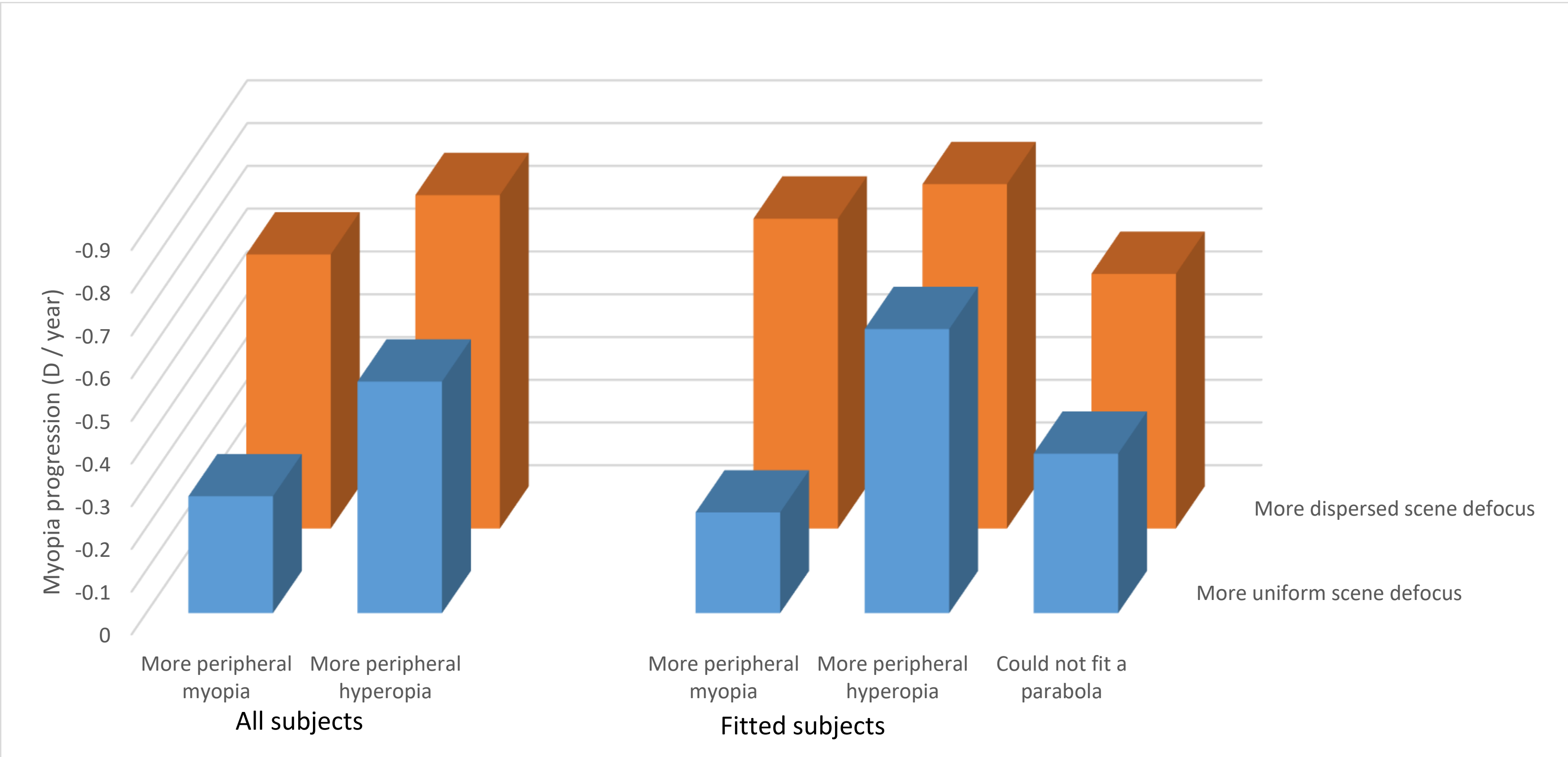


Figure 5.4 Myopia progression versus scene defocus profile and peripheral refraction. Columns on the left represent all subjects, while columns on the right represent subjects with relative peripheral spherical equivalent refraction (RPRE-M) significantly fitted in a quadratic regression. Front row represents the first half of subjects with more uniform scene defocus, while the rear row represents the second half of subjects with more dispersed scene defocus

To our knowledge, the current study is the first to investigate home environmental defocus profile and its relationship with PRE in relation to juvenile myopia development. However, there are several limitations preventing a comprehensive interpretation of the results. Firstly, the defocus profile measurement was performed at a single time point instead of longitudinally incorporating observation of changes in the environment, meaning that only the subsequent refractive change throughout the year with the baseline environmental defocus could be determined. Secondly, the DV was calculated as a net defocus over the three-dimensional space, assuming that positive and negative defocus would equally cancel each other out. Thirdly, as the subjects were required to move away during the measurement, such a move would ignore the defocus created by the subjects' own body parts, e.g. arms placed on the desk. Finally, although most analyses reached statistical significance, the post-hoc power for some analyses remained low, which may indicate a larger sample size is needed to reduce the type II error. In future studies, smartphones with a duo-, or even trio-camera could be used to gather longitudinal data at a larger scale. In addition, eye trackers could have been incorporated into the measurement to map the environmental defocus onto the retinal defocus (Garcia et al., 2019), as well as to investigate the defocus temporal integration (Leung et al., 2011; Leotta et al., 2013; Benavente-Perez et al., 2019), to evaluate myopia development.

Chapter 6. Outcomes, Discussion, and Future Studies

6.1 Outcomes

6.1.1 Living environment and refractive error

Hong Kong is a densely populated city, in which the living space per capita is one of the lowest in the world. Meanwhile, the prevalence of myopia in the city is among the highest worldwide. In Study I, higher population density was found to be associated with more myopic refractive error and longer AL in schoolchildren. Not only was the study in agreement with previously published reports performed at country (He et al., 2009) and city levels (Ip et al., 2008b), the association between refractive error and population density was significant at a district level in a small city like Hong Kong.

Other than population density, home size was found to be another significant factor associated with childhood refractive error. The residential area in Hong Kong is very limited to cater for the high population in the city (C.S.D., 2012). Hence, people in Hong Kong generally live in a small home (H.K.H.A, 2019), in which many Hong Kong children spend their childhood. The findings indicate that a small home size was associated with more myopic refractive error and longer AL, which could be a risk factor for myopia progression. As the vast majority of homes in Hong Kong are flat-styled dwellings, the type of housing was not a significant contributing factor in our study.

6.1.2 Peripheral refraction, orientation bias, and on-axis refractive status

Peripheral retinal input has been found to play a role in on-axis refractive error development. Although the analyses of RPRE-M, -J_0, and -J_{45} are common as suggested by Thibos and co-workers (Thibos et al., 1997) for the ease of calculation and comparison, these parameters may not completely reflect the pattern of PRE, especially for peripheral astigmatism, which was suggested to be a cue for peripheral defocus decoding. While human vision is orientation-selective in psychophysical experiments (Sasaki et al., 2006), the optical orientation selectivity over the peripheral visual field was investigated and its relationship with on-axis refractive error was revealed.

The PRE was measured in children over the horizontal and vertical visual fields. In Study II, the radiality was calculated by the difference of absolute magnitude of P(90) and P(180), while optical orientation bias was calculated based on the peripheral astigmatic meridian to reveal the clearer orientation on the peripheral retina. RPRE-M became more hyperopic, while RPRE-J_0 and the radiality decreased in magnitude, with increasing AL/CR along horizontal field. As for vertical field, the RPRE-M was more hyperopic and the magnitude of RPRE-J_{45} was smaller with increasing AL/CR. For low AL/CR children, radial orientation (high radiality) was more focused on both horizontal and vertical visual fields. However, with respect to high AL/CR children, tangential orientation (low radiality) was more focused on horizontal visual field, but radial orientation remained more focused on vertical visual field.

6.1.3 Home environment, peripheral refraction, and refractive development

Emmetropisation is a retinal signal-driven response, which depends on not only the central, but also the peripheral retina. The resultant stimulation to the retina is a composite of internal and external factors, which are the PRE and the environmental influence, respectively.

In Study III, near work scenes were novelistically captured with a Kinect IR depth camera, which provides additional quantification for near work other than one-dimensional working distance and the time spent, as it is able to measure a scene defocus profile of near work environment with respect to the child's visual experience. In particular, the scene defocus profile was quantified as DV and SD_D, which were the total amount of defocus and the dispersion of defocus over the scene, respectively.

Regarding the RPRE, instead of taking individual location in the visual field, the analysis was modified to represent the overall characteristics of the RPRE. While most peripheral refractive profiles along the horizontal visual field can be significantly fitted with a quadratic regression, the first coefficients of the quadratic equations (i.e. a_M, a_{J0}, $a_{P(90)}$, and $a_{P(180)}$) were calculated to represent the pattern of the RPRE as the internal factor.

In a home environment, schoolchildren usually spend much of their time doing their heavy load of homework in front of their desk. Despite the T_{desk} being independent of their refractive development, the SD_D and regional DV of the near work scene were identified as risk factors for myopia progression in schoolchildren. For SD_D, a more dispersed defocus profile was associated with faster myopia progression. Furthermore, a more hyperopic DV at the paracentral at 15° - 20° circular field eccentricity was associated with faster myopia progression. However, the results of regional quadrant analysis were not conclusive. Although linear and non-linear myopic-hyperopic spatial integration were also investigated, the results from the current study did not suggest any integration having a predominant effect of myopic scene defocus as observed in animal studies.

a_M, a_{J0}, and $a_{P(180)}$ were significantly correlated with myopia progression in univariate regression analysis. However, after controlling for the baseline M, the relationship between RPRE and myopia progression became insignificant, except for $a_{P(180)}$. While the internal factor alone was insufficient to predict myopia progression, when the external factor (i.e. environmental influence), DV and SD_D, were added as co-variates to control for the correlation, a_M and a_{J0} were again significantly correlated with myopia progression. Peripheral astigmatism was previously suggested as a cue for the peripheral retina to decode the emmetropisation signal. In the analyses, $a_{P(90)}$ and $a_{P(180)}$ represented the defocus of sagittal and tangential orientation along the horizontal visual field respectively. The results further suggested, taking the scene characteristics into account, myopia progression was associated with $a_{P(180)}$, which was the more myopic image shell, rather than $a_{P(90)}$.

6.2 Discussion

6.2.1 The paradox of peripheral refraction

Regarding the risk factors for refractive error development, attention has been focused on PRE since the 1970's, when peripheral hyperopia was first linked to increased risk of on-axis myopia (Hoogerheide et al., 1971; Rempt et al., 1971). In addition, animal experiments provided supportive evidence that the peripheral retina, rather than the central retina alone, could modulate axial eye growth and emmetropisation (Wallman et al., 1987; Smith et al., 2005; Smith et al., 2009b). In contrast, the failure of applying baseline peripheral hyperopia in prediction of myopia progression in various epidemiology studies has created the paradox of whether peripheral refraction is indeed a significant factor in emmetropisation process. In Study II, a cross-sectional relationship was established between PRE and on-axis refractive status, especially the orientation selective blurs. However, whether the difference in PRE precedes, or is a consequence following myopia progression remains unclear. Results from Study III suggested an alternative overall representation of PRE may demonstrate a better association with on-axis myopia progression. In addition, as mentioned in Study III, a possible reason for such failure could be that the resultant defocus on the retina does not solely depend on the PRE, but also external factors, which will be discussed in Section 6.2.3.

Many previous studies focused on peripheral myopia and hyperopia, while peripheral astigmatism also imposes a significant blur on the peripheral visual field (Millodot, 1981; Gustafsson et al., 2001; Mathur and Atchison, 2013). It was suggested to be a cue for signal decoding because of the two focal shells of different orientations created over the peripheral visual field, which the retina may use to compare the differential blur (Howland, 2010; Charman, 2011; Atchison and Rosén, 2016). In fact, human vision experiences an oblique effect, which is more sensitive to orthogonal stimuli (Appelle, 1972). The retina was found to be orientation-selective in animal model (Levick and Thibos, 1982), in that it generated a stronger signal when stimulated by a radially oriented stimulus. In Study II, the radiality (how well-focused is the radial component of the retinal image) decreased with increasing on-axis AL/CR, whereas in Study III, while myopia progression was associated with RPRE-a_{J0}, it was also associated with RPRE-$a_{P(180)}$, but not RPRE-$a_{P(90)}$. P(180) represented the blurriness of tangential orientation along the horizontal visual field, which was the more myopic image shell. This finding was in agreement with previous reports and suggests that the retina would emmetropise towards the more myopic meridian when imposed with astigmatic defocus (Kee et al., 2004). In addition to sphero-cylindrical error, peripheral refraction is also affected by other higher-order aberrations, such as spherical aberration, which has been associated with myopia development in animal (Kisilak et al., 2006) and clinical studies (Lau et al., 2018).

Another paradox for peripheral refraction is wear of spectacle lens. In the fore-mentioned epidemiology studies (Zadnik et al., 1993; Atchison et al., 2015), peripheral refraction was measured with naked eye. For myopes and astigmats who require spectacle correction, the peripheral optics becomes more hyperopic and less astigmatic (Tabernero et al., 2009; Lin et al., 2010), although the change in peripheral astigmatism did not reach significance. Pantoscopic tilting would further aggravate the peripheral hyperopic shift and reduction of peripheral astigmatism (Bakaraju et al., 2008) as demonstrated in myopic eye models. Some novel spectacles have been designed to reduce peripheral hyperopia, or even enhance peripheral myopia (Tabernero et al., 2009; Sankaridurg et al., 2010; Hasebe et al., 2014), but their efficacies remain questionable. While the novel spectacles had a clear central aperture, eye movements would alter the peripheral myopic stimuli vigorously over the visual field, which may affect the temporal integration of the defocus stimuli. The eye movement may also simulate the effect of tilting as mentioned before, which may dilute the effect of peripheral myopic defocus.

In contrast, contact lenses as an optical strategy more successfully retarded myopia progression (Sankaridurg et al., 2011; Cho and Cheung, 2012; Walline et al., 2013; Lam et al., 2014). Unlike spectacle lenses, single vision contact lenses created myopic shift, as well as an increased J_0 component on the temporal retina (Backhouse et al., 2012; Moore et al., 2017). Multifocal contact lenses were also found to increase peripheral myopic defocus (Sankaridurg et al., 2011; Berntsen and Kramer, 2013) to a greater extent. Presuming a good fitting, the relative movement of the contact lenses over the eye would be much less than that of spectacle lenses, hence the manipulation (e.g. enhancement of myopic defocus and astigmatism) of the optical stimuli over peripheral retina would be more stable instead of changing rapidly. With respect to orthokeratology, the peripheral refraction becomes more myopic and J_0 astigmatic (Charman et al., 2006; Kang and Swarbrick, 2011), especially in higher degrees of on-axis myopia (González-Méijome et al., 2016). The optical manipulation is even more stable as it is imprinted on the cornea. This increased efficacy of myopia control by contact lenses over spectacle lenses may indicate the temporal integration effect of defocus. This was further indirectly supported by Lam and co-workers (Lam et al., 2014), who reported that the myopia control effect was positively correlated with wearing time, from 25% retardation in the whole sample to 60% retardation in those who wore the lenses over eight hours daily.

Although the treatment efficacy appeared to depend on the generated magnitude of peripheral myopia, some researchers have suggested that the input from the peripheral retina may not be a major constituent for emmetropisation signalling (Smith et al., 2013a). While the fore-mentioned optical strategies generate myopic defocus over the peripheral retina, they produce simultaneous myopic defocus over the central retina. This simultaneous defocus is more pronounced with a larger pupil diameter, reducing the depth of focus, which was associated with better myopia control in orthokeratology patients (Chen et al., 2012). Regardless of the mechanism, optical manipulation remains an effective myopia control strategy to address soaring rates of myopia. Study III indicated that other than peripheral refraction, objects within the para-central visual field may also impose risk for myopia progression when their positions create hyperopic scene defocus or increase the dispersion of the defocus profile.

6.2.2 Eastern-Western cultural difference - Refractive error, dwelling, and education

Eastern and Western countries differ greatly in myopia prevalence (Holden et al., 2016). As the heredity of myopia is limited (Tedja et al., 2019), ethnicity is unlikely to be the main cause for such great discrepancy. Instead, cultural differences may be important in causing variation in environmental stimulus and be the reason for the higher prevalence of myopia in Eastern than Western countries. Most myopia develops during the school-age, hence the childhood activities and the relevant environments, e.g. indoors vs. outdoors, would be crucial for the later refractive error development.

The living environment was found to be associated with refractive error in Study I, which may also be a reason for such Eastern-Western discrepancy. Although the population density appeared to be an independent factor in multivariate analysis and the VIF was within acceptable range, there was an association between population density and home size ($\chi^2 = 50.90$, $p < 0.001$). The proportion of large sized homes was greater in low population density districts (Table 6.1). In Eastern countries with high population density, people in the cities usually live in a small flat-styled dwelling, while the proportion of stand-alone houses is greater in Western countries. Hence, the living space per capita was up to several times smaller in Eastern regions, such as Hong Kong, than Western countries (Wilson, 2009). Figure 6.1 shows the floor area per capita in different parts of the world, and the myopia prevalence reported in that place. Although other parameters, such as methodology and time of the study, were not controlled, and outliers existed, a negative correlation can be generally observed. This relationship was supported by Study I and Study III which also indicated that a small home was associated with more myopic refractive error and myopia progression in children, respectively. Although socioeconomic status, which is partially reflected by home size, was reported to be positively correlated with the degree of myopia, one possible confounding factor for such reverse trend could be the affordability of myopia control intervention. In terms of visual stimuli, it can be affected by the living space per capita or home size in many ways. In a small home, furniture and sundries can only be placed in a crowded way and the room for daily activities is limited (Figure 6.2). Children may have to remain in the same location to do their homework and other activities. From our findings, children living in a small home tended to spend more time in front of their desk ($\chi^2 = 8.84$, $p = 0.01$). However, in extreme cases, a very small home may be a predisposition for children to go outdoors more. This may explain the extremely low floor area per capita in Bangladesh combined with a relatively low myopia prevalence, as shown in Figure 6.1.

Table 6.1 Distribution of home size on population density of district

		Home size (%)			
		Small	Mid	Large	Total
Population density	Low	60 (30.5)	82 (41.6)	55 (27.9)	197 (100)
	Moderate	91 (40.6)	107 (47.8)	26 (11.6)	224 (100)
	High	103 (25.4)	256 (63.2)	46 (11.4)	405 (100)

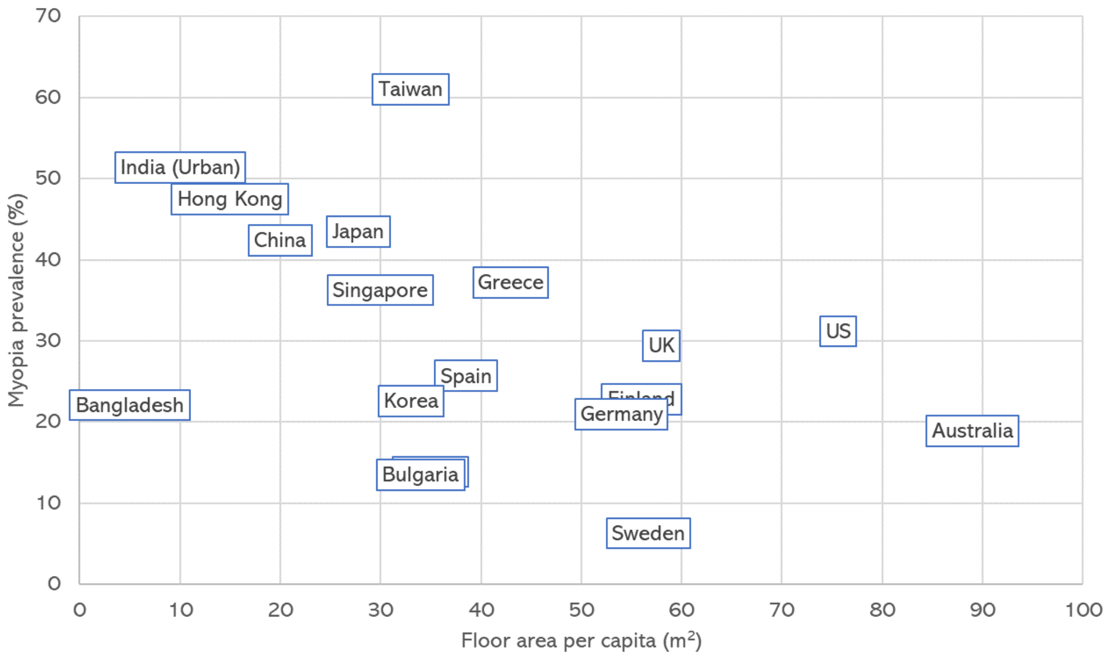


Figure 6.1 Myopia prevalence and floor space per capita worldwide. Myopia prevalence of countries was extracted from Supplementary information of Holden et al., 2016

Figure 6.2 Crowded living environment of a sub-divided flat in Hong Kong.

Source: http://photoblog.hk/wordpress/wp-content/uploads/2012/11/soco-2-low.jpg

As mentioned in Section 1.3.2.3, education modalities and attitudes in Eastern and Western culture differ significantly, with Eastern schools and parents tending to arrange more written schoolwork and after-school work. As reported in Study III, two-thirds of the children spent at least two hours daily in front of their homeworking desk, regardless of the schooling time (usually about 7 hours / day), during which the children may spend even more time performing near tasks. Although T_{desk} was not a significant factor for myopia progression (Less time spent: -0.50 ± 0.47 D vs. More time spent: -0.61 ± 0.43 D, $t = 0.78$, $p = 0.44$), it may still increase children's exposure to risky environment, such as a more dispersed defocus profile, which is related to myopia progression. In Study III, for the 25 children having SD_D over the median, the T_{desk} was significantly correlated with their myopia progression ($\rho = -0.41$, $p = 0.04$), while those below the median had poor correlation ($\rho = 0.04$, $p = 0.84$), indicating a possible temporal integration effect under a myopiagenic environment (Figure 6.3). In addition, the AL and M of the children who rested frequently during near work tended to be shorter and less myopic, respectively, when compared with those who performed near work for a longer time without resting, despite not reaching statistical significance (Figure 6.4). However, due to the uneven distribution of the sample size, in which "less frequently rested" subjects were less in number, the achieved statistical power was low that it could be a false negative finding. By re-grouping the "less frequently rested" subjects (1 time/hour, < 1 time/hour, and No rest) into "1 time/hour or less", univariate analysis revealed a significant difference (One-way ANOVA AL: $F = 4.29$, $p = 0.01$; M: $F = 3.34$, $p = 0.04$). In the Western education modality, children have relatively more OA compared to the Eastern. The T_{OA} in the US was reported to be approximately 9 hours / week (Jones et al., 2007; Jones-Jordan et al., 2011), while that of Australia was about 14 hours / week (Rose et al., 2008b). In contrast, Eastern children spent less time outdoors. T_{OA} was reported as 7 hours / week in urban Beijing (Guo et al., 2013) and 3 hours / week in Singapore (Rose et al., 2008b). In the current study, the children had even less T_{OA} of only 2 hours / week. The protective effect of OA against myopia is now well established (French et al., 2013; Wu et al., 2013; He et al., 2015a; Wu et al., 2018). The lack of OA in Eastern education modality could be a reason for higher myopia prevalence in the region. In contrast, T_{OA} were not associated with T_{desk} (correlation of hours: $\rho = -0.02$, $p = 0.87$; Grouping distribution: $\chi^2 = 0.38$, $p = 0.54$), indicating near tasks were not a substitute for OA, which was supported by previous findings (Jones et al., 2007; Dirani et al., 2009; Jones-Jordan et al., 2011). In the current study, SD_D remained significantly correlated with myopia progression in children with low T_{OA} ($\rho = -0.44$, $p = 0.03$), while independent of myopia progression in those with high T_{OA} ($\rho = -0.23$, $p = 0.27$). This may imply that, despite Eastern education modality focusing on near tasks, such as reading and writing, OA, and frequent resting should be encouraged for the sake of the children's physical and psychological health, as well as refractive error development (He et al., 2015a; Wu et al., 2018). In Study I, although 3 or more hours weekly OA was significantly associated with less myopic M, 1 - 2 hours weekly OA was also significantly associated with shorter AL. The lack of cycloplegia and age effect together may be the confounding factors to produce such odd findings.

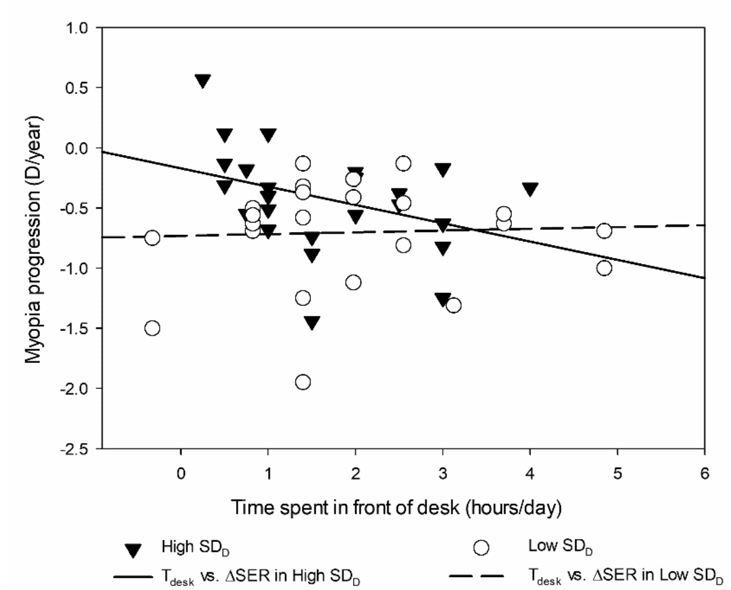


Figure 6.3 Association of near work time (T_{desk}) and myopia progression under strong and weak stimulation of defocus profile

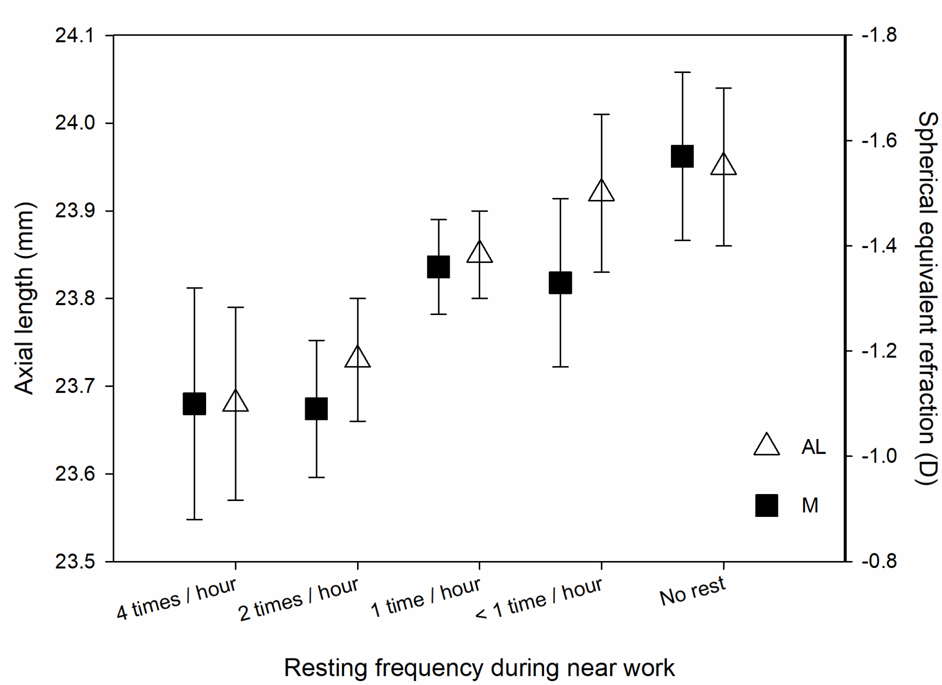


Figure 6.4 Association of resting frequency during near work with axial length (AL) and spherical equivalent refraction (M). The triangles and squares represent the mean ± standard error of mean (SEM) of AL and M, respectively

6.2.3 Defocus profile - Spatial integration

In Study III, the defocus profile of a homeworking scene of the children was created and found to be associated with the refractive error development. Two parameters were selected to represent the characteristics of the defocus profile: DV and SD_D. These parameters appeared to be superior to one-dimensional working distance and the time spent in near work quantification in relation to myopia monitoring. Certainly, condensing the whole defocus profile into one or two parameters could overlook some information from the profile. For example, as shown in Figure 6.5, defocus profiles may look different individually, but the parameters calculated would be the same. In Study III, rather than solely calculating the DV over the whole scene, it was sub-divided based on ring shaped (DV_5 to DV_{30}) and quadrant shaped (DV_R, DV_U, DV_L, and DV_D) divisions to access the regional effect, which spatial information DV and SD_D alone would not provide. DV magnitude was calculated based on two assumptions: firstly that the myopic and hyperopic defocus cancel each other out; and secondly that the myopic defocus was twice as potent as hyperopic defocus as shown in animal studies (Tse et al., 2007; Tse and To, 2011). The results of these studies indicate that the relationship between myopia progression and scene defocus appeared to be stronger assuming a linear spatial summation, which was not in agreement with findings of animal studies (Tse and To, 2011; Arumugam et al., 2014; McFadden et al., 2014), suggesting a greater potency of myopic defocus. The reason is uncertain, but may be related to the different visual demands and habits of human from the animals, i.e. behaviour could affect physiology.

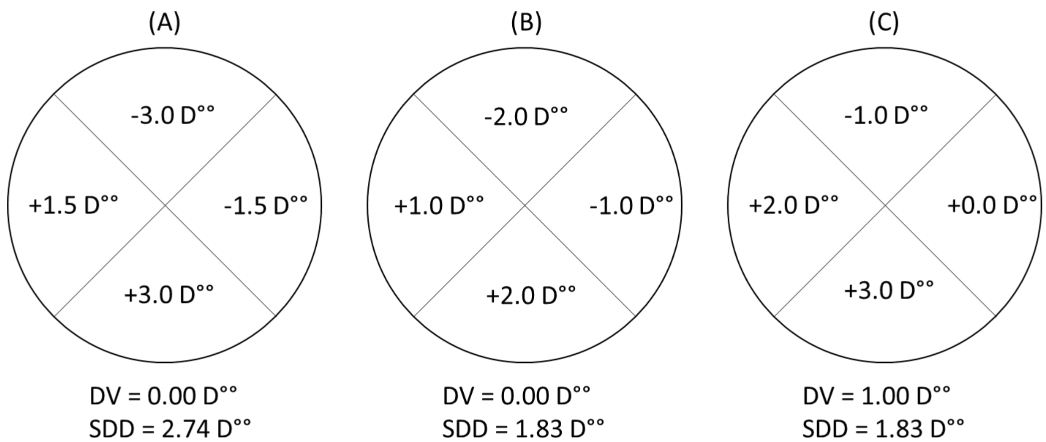


Figure 6.5 Limitations of dioptric volume (DV) and standard deviation of the scene defocus (SD_D). Scene (A) and (B) generate the same DV, while Scene (B) and (C) generate the same SD_D

While the external scene defocus depends simply on the distance of the environmental objects, generating either myopic or hyperopic scene defocus, optics of the eye would create other types of aberration, such as peripheral astigmatism as shown in Study II. This has been reported to degrade the retinal image in different ways at different locations because of the rotational asymmetry of the visual optics (Charman and Atchison, 2009). These second-order and higher-order aberrations may become useful visual stimuli for the retina to detect defocus (Ho et al., 2012; Chin et al., 2015), especially peripheral astigmatism, which is a predominant orientation-selective refractive error (Gustafsson et al., 2001; Mathur and Atchison, 2013). Whether peripheral myopic defocus increases, and hyperopic defocus decreases electrophysiological response is controversial (Ho et al., 2012; Turnbull et al., 2020). Theoretically, simply myopic or hyperopic defocus would not alter the retinal illuminance, which would not cause any luminance-related changes in electrophysiological response. In contrast, lens-induced ametropia creates peripheral astigmatism, in which the two image shells were proposed as a cue for the retina to detect sign and magnitude of defocus. Orientation-selective ganglion cells are evident in animal peripheral retinas (Levick and Thibos, 1982) and give a maximal response when the orientation of stimulus was in-line pointing to the centralis. Hence, the peripheral retina may generate a greater response when radial orientation was better focused, which could not be demonstrated by the Jackson Cross-Cylinder lens as it creates two image shells equidistant from the retina.

In addition, the effect of accommodation was not explicitly investigated in Study III. Presumably, the magnitude of accommodation lag would be greater in myopes (McBrien and Millodot, 1986), leading to a hyperopic shift from the scene defocus to the actual defocus that the retina is exposed to. Although the RPRE was shown to be unchanged during accommodation process (Calver et al., 2007; Davies and Mallen, 2009), the measurements in the previous studies limited on horizontal eccentricity and the changes along other directions of the paracentral visual field were unclear. Non-cycloplegic open-field auto-refractions at near distances (20 cm, 33 cm, 40 cm, and 50 cm) were preliminarily measured in Study III. The incorporation of the accommodative stimulus/response slope as a covariate in the partial correlation tests did not show an improved relationship between home scene parameters (SD_D and DV) and ΔM (SD_D: $\rho = -0.41$, $p < 0.01$; DV: $\rho = -0.26$, $p = 0.08$). However, the relationship between home scene parameters and ΔAL became significant after controlling for the accommodation

(SD_D: $\rho = 0.40$, $p < 0.01$; DV: $\rho = 0.32$, $p = 0.03$). The interactive effect of accommodation and scene defocus profile on myopia development needs further studies.

6.2.4 Limitations on interpretation of results

Despite the significance and insights generated from the outcomes of the current thesis, there are a few limitations which constrain further interpretation of the results. The lack of cycloplegia would overestimate the myopic refraction in children (Morgan et al., 2015), especially the hyperopes. From Figure 4.1, plotting the relationship between AL/CR and non-cycloplegic refraction, there was a downward bend on the top-left and bottom-right parts of the figure, possibly indicating an underestimation of hyperopic refraction in Low AL/CR children. To compensate this methodological weakness, AL and AL/CR were used to represent the central refractive status, instead of the non-cycloplegic auto-refraction in Study I and Study II, respectively. However, being an important outcome, the peripheral refractions in Study II could be over-estimated towards the myopia direction. From Figures 4.4, 4.6 (non-cycloplegic data in Study II), and 5.1 (cycloplegic data in Study III), children of similar age displayed comparable magnitudes of RPRE-M, -P(90), and -P(180), which implied the subtraction between central and peripheral to obtain RPRE may have eliminated the effect of non-cycloplegia.

The analytic methods applied in the current thesis, both cross-sectional and longitudinal studies, were mainly correlational, instead of causal analyses. In particular, the differences in RPRE between AL/CR groups in Study II may not precede but follow the existence of myopia and its progression. In addition, the significant predictors identified in Study I may also be confounded by the complex interaction between socio-economic status and living habits, despite of the use of multivariate regression analysis. To further improve the interpretation, more hypothesis-driven sequential statistical testing could be applied in epidemiology studies like Study I, allowing a more sophisticated understanding of the interaction between variables. For example, it was unexpected that parental education was independent of refractive error in children, unlike consistent results from Singapore (Saw et al., 2002a) and China (Guo et al., 2013). The interaction between living environment and other variables, including parental socio-economic status, and refractive error in children, could be further investigated in the future. Furthermore, in Study I, the parental questionnaire included items of multiple choices. However, some choices were rare that the sample distribution for such variable would be uneven, which would generate high possibility of type II error. The statistical powers of each variable were listed in Supplementary Table 1. Re-grouping of the choices, e.g., resting frequency in Study I as mentioned in Section 6.2.2, to obtain a more even distribution of sample size in each choice may improve the significance of such variables with limited achieved power.

6.2.5 Summary

The current series of studies investigated the effect of living environment on refractive error and its progression, especially home environment and near work scene. The daily visual environment imposes stimulation at various magnitudes and patterns of defocus profile, which were shown to be associated with myopia progression and, hence, may affect the emmetropisation process (Study III). This myopiagenic stimulus may be more abundant in constricted environments, such as a densely populated regions and a small home (Study I). In contrast, peripheral refraction was found to be associated with the on-axis refractive error (Study II), which may be a modulator between the external scenic stimulation and the myopia progression (Study III). It may be speculated that this spatial integration due to internal and external factors on the resultant retinal defocus, acting together with temporal integration (e.g. effect visual habit and eye movement), may contribute to childhood refractive error development.

6.3 Future studies and directions

6.3.1 Opportunities from the great digital era

The current era has hugely increased exposure to digital devices, and hence the device screen time of children, which may be associated with the development of myopia (Lanca and Saw, 2020). In contrast, the increasing use of smart devices also enables the collection of new data in different ways. For instance, duo- or even trio-camera systems have been installed in recent models of smartphones, which are capable of acquiring spatial depth information. In place of time-consuming home visits by researchers, subjects can upload the data of their home scene profile after simply taking a depth picture of their home environment. In Study III, one of the limitations is the relatively small sample size. In the future, data collection can be simplified by custom-written applications on development platforms, e.g. Project Tango and ARCore (Google Inc., US), such that the study scale can increase enormously to suitable sample sizes.

The use of depth sensors can also be improved in future studies. In Study III, Kinect v2 was applied to acquire depth information. In the analysis, the defocus map was captured with respect to the subject's viewpoint. With increased complexity of the processing algorithm, KinectFusion can be applied to the data acquisition (Izadi et al., 2011; Newcombe et al., 2011), which is a technique enabling instantaneous reconstruction of augmented reality space of an indoor scene with respect to the movement of the Kinect sensor measuring the scene at different angles. Measurements can be taken with and without the presence of the subject, such that the defocus calculation can be based on the relative position of the subject to the visual target, as in Study I in which the postural effect was found to be significant, but could not be interpreted. However, Kinect v2 was discontinued in 2017. It was replaced by the Azure Kinect (Microsoft Inc., US), which incorporates the use of cloud computing and artificial intelligence for computer vision, which may provide new information about other myopiagenic risk factors that have not yet been investigated.

6.3.2 Spatial and temporal integration of resultant retinal defocus

The results from Study III indicated that myopia progression had a similar relationship with either linear or non-linear myopic-hyperopic defocus interaction, which differed from other species, as it was suggested in animal studies that myopic defocus outweighed hyperopic defocus, although it was less prominent in mammals (Tse and To, 2011; Arumugam et al., 2014; McFadden et al., 2014). Other than the myopic-hyperopic defocus interaction, retinal input from different regions could be investigated. Although the foveal region was suggested as unnecessary for defocus compensational eye growth (Smith et al., 2009b), the central retina was reported to contribute to emmetropisation (Wang et al., 2015) as well as peripheral retina. Together with animal studies, human electroretinography studies have suggested the para-central retina was more sensitive to defocus changes than other retinal regions (Ho et al., 2012; Chin et al., 2015). Also, regional changes in choroidal thickness were observed under hemi-field myopic defocus (Hoseini-Yazdi et al., 2019), suggesting a local defocus sensitivity existed in the human retina. In Study I, association between the self-reporting near work posture and refractive error was observed, which could not be interpreted comprehensively. In Study III, the defocus at the para-central ring at 15 - 20° ring and left quadrant in the scene had stronger correlation with on-axis myopia progression. Whether certain locations in the retina correspond to the visual scene more is important, and the weighting ratio of the regional input signal strength in controlling emmetropisation warrants further studies.

Another limitation in Study III was the lack of eye tracking information. With information on eye movements during near work, the external stimuli (i.e. scene defocus) and internal optical factors (i.e. on-axis refractive error and PRE) could be integrated to obtain a more accurate resultant defocus profile on the retina. Other than spatial summation, temporal integration of the defocus can also be investigated. From animal studies, brief interruption by short periods of clear vision of the long-term imposed defocus could effectively retard axial elongation (Kee et al., 2007; Benavente-Perez et al., 2019). Small and wearable sensors, which can continuously acquire three-dimensional data, could be developed to provide a more comprehensive measurement than previously reported devices (Leung et al., 2011; Williams et al., 2019; Wen et al., 2020) with only one-dimensional working distances. Instead of a fixed visual scene, the wearable device could provide information of the temporal integration in the continuously changing visual environment, which could be investigated by the rate of change of defocus on the retina.

6.3.3 Clinical trial of a myopia-unfavourable near work scene

Evidence of interaction of the environment and myopia have been demonstrated by examining the effects of the living environment and visual habits. Regrettably, the environmental situation in Hong Kong is typified by crowded and limited living space and intensive near work, which are seemingly unfavourable for refractive error control in children, resulting in the prevalence of childhood myopia being among the highest in the world (Lam et al., 2012; Choy et al., 2020; Yam et al., 2020). Similar situations also apply to other regions of Southeast Asia. However, certain government policies have been implemented in some regions after the success of clinical trials of OA (Wu et al., 2013; He et al., 2015a), resulting in recent reverses in the long-increasing trend of myopia prevalence (Wu et al., 2020). Findings of the current studies suggest that home environment, particularly home size and the near work scene, together with PRE, are related to myopia progression. Despite housing, as a whole, which is difficult to modify in clinical trials, the near work scene may be a modifiable factor at home, and even in schools. If clinical trials can provide further supportive evidence for the effect of modifying the near work environment on myopia control, this novel concept of visual hygiene in myopia control can be implemented and may provide a synergic effect in the control of myopia with other current treatments, e.g. orthokeratology and atropine treatment as well as the effects of increased OA. Ideally, Hong Kong would replicate the success of reversing the increasing trend of myopia prevalence.

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Appendices

A. Supplementary tables

Supplementary table 1. Power analysis for results of Study I

Axial length

Independent variable	p value	Effect size	Achieved power
Gender	< 0.001	0.52	> 0.99
Age	< 0.001	0.19	> 0.99
Parental myopia	< 0.001	0.12	0.94
Parental education level	0.11	0.08	0.51
Population density of the residential district	< 0.01	0.12	0.88
Home size	*0.04*	*0.08*	*0.60*
Type of housing	0.16	0.06	0.38
Weekly outdoor activities	*0.03*	*0.09*	*0.69*
Weekly television and computer use	0.85	0.03	0.10
Daily near work	0.24	0.07	0.39
Daily mobile phone and mobile console	0.06	0.09	0.64
Near work posture	< 0.01	0.11	0.91
Near work distance	0.78	0.04	0.15
Resting frequency	0.06	0.09	0.65
Participation of extra-curricular classes	> 0.30	0.03	0.14

Spherical equivalent refraction

Independent variable	p value	Effect size	Achieved power
Gender	0.94	< 0.01	0.05
Age	< 0.001	0.13	0.97
Parental myopia	< 0.001	0.17	> 0.99
Parental education level	0.51	0.05	0.23
Population density of the residential district	< 0.001	0.14	0.97
Home size	0.02	0.12	0.92
Type of housing	0.10	0.08	0.62
Weekly outdoor activities	0.10	0.09	0.60
Weekly television and computer use	0.57	0.05	0.21
Daily near work	0.69	0.04	0.16
Daily mobile phone and mobile console	< 0.01	0.13	0.94
Near work posture	*0.03*	*0.09*	*0.69*
Near work distance	0.15	0.09	0.64
Resting frequency	0.10	0.07	0.41
Participation of extra-curricular classes	> 0.31	0.01	0.06

Italic items indicate an insufficient power to detect a true significance.

Supplementary table 2. Multiple regression with all variables on refractive change over 1 year by ring analysis.

Adjusted $R^2 = 0.38$, $F_{16,50} = 2.88$, $p = 0.01$

	Raw B value	95% CI	Standardised B value	p value	VIF
Age	**0.23***	**0.01 to 0.44**	**0.54**	**0.04**	**1.62**
Baseline M	**0.09***	**0.02 to 0.16**	**0.40**	**0.01**	**1.86**
Working distance	0.01	-0.02 to 0.04	0.13	0.52	3.01
Time in front of desk	-0.11	-0.24 to 0.01	-0.28	0.08	1.95
Parental myopia (ref no myopic parent)					
One myopic parent	-0.19	-0.52 to 0.13	-0.18	0.23	1.62
Two myopic parents	-0.23	-0.51 to 0.05	-0.26	0.10	1.85
Home size (ref Small)					
Medium	0.15	-0.14 to 0.44	0.16	0.30	1.82
Large	0.23	-0.07 to 0.52	0.24	0.13	1.93
Time spent outdoors	0.23	-0.03 to 0.49	0.26	0.08	1.59
tDV_5	0.03	-0.08 to 0.14	0.09	0.53	5.13
tDV_{10}	-0.10	-0.35 to 0.14	-0.25	0.39	6.66
tDV_{15}	0.03	-0.24 to 0.29	0.06	0.84	7.75
tDV_{20}	**-0.19***	**-0.37 to -0.00**	**-0.46**	**0.05**	**3.98**
tDV_{25}	0.03	-0.21 to 0.28	0.08	0.78	6.80
tDV_{30}	0.08	-0.09 to 0.26	0.21	0.34	3.71
tSD_D	-0.10	-0.32 to 0.13	-0.23	0.39	5.32

tDV: transformed dioptric volume

tSD_D: transformed standard deviation of scene defocus

* indicated significance of $p < 0.05$

Supplementary table 3. Multiple regression with all variables on refractive change over 1 year by quadrant analysis.

Adjusted $R^2 = 0.20$, $F_{14,50} = 1.86$, $p = 0.07$					
	Raw B value	95% CI	Standardised B value	p value	VIF
Age	0.03	-0.10 to 0.16	0.09	0.63	1.80
Baseline M	0.06	-0.02 to 0.13	0.25	0.13	1.52
Working distance	0.00	-0.03 to 0.03	0.03	0.91	2.64
Time in front of desk	-0.13	-0.40 to 0.14	-0.14	0.34	1.34
Parental myopia (ref no myopic parent)					
One myopic parent	-0.33	-0.68 to 0.03	-0.30	0.07	1.50
Two myopic parents	0.11	-0.18 to 0.39	0.12	0.44	1.50
Home size (ref Small)					
Medium	0.26	-0.05 to 0.57	0.28	0.10	1.58
Large	-0.01	-0.30 to 0.29	-0.01	0.96	1.47
Time spent outdoors	0.24	-0.04 to 0.51	0.27	0.09	1.39
tDV_R	0.07	-0.21 to 0.36	0.17	0.61	6.84
tDV_U	0.10	-0.05 to 0.24	0.22	0.18	1.52
tDV_L	-0.12	-0.38 to 0.14	-0.29	0.35	5.60
tDV_D	0.04	-0.19 to 0.27	0.10	0.72	4.53
tSD_D	-0.11	-0.40 to 0.17	-0.27	0.42	6.57

tDV: transformed dioptric volume

tSD_D: transformed standard deviation of scene defocus

R: Right; U: Up; L: Left; D: Down

* indicated significance of $p < 0.05$

Supplementary table 4. Multiple regression with all variables with doubled myopic defocus potency on refractive change over 1 year by ring analysis.

Adjusted $R^2 = 0.35$, $F_{16,50} = 2.67$, $p = 0.01$					
	Raw B value	95% CI	Standardised B value	p value	VIF
Age	**0.27***	**0.03 to 0.51**	**0.63**	**0.03**	**1.50**
Baseline M	**0.08***	**0.01 to 0.15**	**0.37**	**0.03**	**1.82**
Working distance	0.02	-0.02 to 0.05	0.23	0.30	3.56
Time in front of desk	-0.09	-0.34 to 0.16	-0.10	0.45	1.40
Parental myopia (ref no myopic parent)					
One myopic parent	-0.21	-0.55 to 0.13	-0.19	0.23	1.72
Two myopic parents	0.12	-0.14 to 0.38	0.13	0.36	1.54
Home size (ref Small)					
Medium	0.16	-0.14 to 0.46	0.17	0.29	1.89
Large	-0.10	-0.41 to 0.21	-0.11	0.51	1.98
Time spent outdoors	0.21	-0.03 to 0.46	0.24	0.09	1.40
tDV_{2M5}	0.06	-0.04 to 0.17	0.17	0.23	5.96
tDV_{2M10}	0.06	-0.15 to 0.27	0.14	0.56	4.57
tDV_{2M15}	-0.02	-0.26 to 0.22	-0.04	0.88	5.94
tDV_{2M20}	-0.20	-0.40 to 0.01	-0.47	0.06	4.36
tDV_{2M25}	-0.01	-0.23 to 0.22	-0.01	0.96	5.34
tDV_{2M30}	0.10	-0.07 to 0.28	0.24	0.25	3.22
tSD_D	-0.20	-0.47 to 0.07	-0.47	0.14	7.23

tDV: transformed dioptric volume

tSD_D: transformed standard deviation of scene defocus

2M indicates 2x myopic defocus potency

* indicated significance of $p < 0.05$

Supplementary table 5. Multiple regression with all variables with doubled myopic defocus potency on refractive change over 1 year by quadrant analysis.

Adjusted R^2 = 0.19, $F_{14,50}$ = 1.79, p = 0.08					
	Raw B value	95% CI	Standardised B value	p value	VIF
Age	0.05	-0.09 to 0.18	0.12	0.49	1.84
Baseline M	0.05	-0.02 to 0.12	0.23	0.15	1.53
Working distance	0.00	-0.03 to 0.04	0.05	0.81	2.63
Time in front of desk	-0.13	-0.40 to 0.14	-0.14	0.34	1.28
Parental myopia (ref no myopic parent)					
One myopic parent	-0.31	-0.67 to 0.05	-0.28	0.08	1.50
Two myopic parents	0.09	-0.19 to 0.38	0.11	0.51	1.50
Home size (ref Small)					
Medium	0.26	-0.05 to 0.57	0.28	0.10	1.59
Large	0.01	-0.29 to 0.30	0.01	0.97	1.47
Time spent outdoors	0.26	-0.01 to 0.53	0.29	0.06	1.35
tDV_{2MR}	0.12	-0.14 to 0.39	0.29	0.36	5.79
tDV_{2MU}	0.07	-0.07 to 0.21	0.16	0.34	1.63
tDV_{2ML}	-0.06	-0.30 to 0.18	-0.15	0.61	4.85
tDV_{2MD}	0.01	-0.02 to 0.22	0.02	0.92	3.64
tSD_D	-0.17	-0.43 to 0.10	-0.39	0.21	5.55

tDV: transformed dioptric volume

tSD_D: transformed standard deviation of scene defocus

R: Right; U: Up; L: Left; D: Down

2M indicates 2x myopic defocus potency

* indicated significance of p < 0.05

B. Parental questionnaire in Study I

有關近視與生活環境及習慣問卷調查

1. **關於你的小孩** 內部填寫 Subj ID ________

   姓名: ______________________ 性別: __________

   出生日期: ________年____月_____日 年齡: __________

   身高: ______厘米 體重: _______公斤

   就讀學校: ________________________________學校地區: ____________

   家長聯絡電話: ____________________

2. **關於眼鏡**

   a. 你的小孩平常有戴眼鏡或隱形眼鏡嗎?

   ☐沒有**(跳到 2d.)** ☐眼鏡

   ☐隱形眼鏡 ☐都有配戴

   b. 他/她何時會戴眼鏡?

   ☐經常 (除睡覺, 洗澡外)

   ☐大部份時間 (日間只有少於 4 小時沒戴)

   ☐部份時間 (日間約有 4-6 小時沒戴)

   ☐少部份時間 (日間只戴少於 4 小時)

   c. 你知道這眼鏡是甚麼度數嗎? (不計散光)

   ☐**遠**視 600 度或以上 ☐300-575 度**遠**視

   ☐100-275 度**遠**視 ☐少於 100 度**遠**視或**近**視

   ☐100-275 度**近**視 ☐300-575 度**近**視

   ☐**近**視 600 度或以上 ☐不知道

   d. 他/她曾用以下控制近視的方法嗎? (可選多於一項)

   ☐雙光眼鏡 ☐漸進眼鏡

   ☐多焦軟性隱形眼鏡 ☐角膜矯形術 (Ortho-K)

   ☐阿托品眼藥水(Atropine) ☐以上皆沒有

   ☐其他(請指明) ____

3. **關於眼科病歷**

a. 你的小孩曾驗過眼嗎?

☐從來沒有**(跳到 4a.)** ☐曾與眼科視光師/眼科醫生進行全面眼科檢查

☐在學童保健中驗過 ☐在眼鏡店驗過度數

b. 他/她曾有否被診斷有眼睛問題?

☐沒有

☐不知道

☐度數問題(如遠視，近視或散光)

☐雙眼協調問題(如斜視, 弱視等)

☐眼睛疾病(如白內障, 青光眼等)

4. **關於日常近距離書寫習慣**

a. 以下哪一項最能形容你小孩日常的工作坐姿?

☐腰板直，雙眼直視書本 ☐側頭看書或寫字

☐以上皆非

b. 他/她做近距離工作時會隔多久休息一次?

☐從不休息 ☐約十五分鐘休息一次

☐約三十分鐘休息一次 ☐約一小時休息一次

☐多於一小時才休息一次

c. 你的小孩在看書/寫字時, 眼睛大約距離書本或紙張多遠?

☐約少於 10 厘米(約 4 吋)

☐約少於 20 厘米(約 8 吋)

☐約少於 30 厘米(約 12 吋)

☐約少於 40 厘米(約 16 吋)

☐大於 40 厘米(約 16 吋)

5. **關於課外活動**

a. 你的小孩有參與以下的課外活動嗎?(可選多於一項)

☐補習班 每星期_______小時

☐靜態 如樂器班/書法/畫班 每星期_______小時

☐動態 如球類/游泳/跳舞/體操/武術 每星期_______小時

☐並沒有參加任何

6. 關於日常活動

a. 請選擇你小孩平均所花於以下項目的時數

		平均時數 (請打剔)			
		並沒有	少於 1 小時	1-2 小時	3 小時或以上
i	**每週**在室外活動 (如於公園遊玩或其他休閒活動)				
iii	**每週**看電視或玩電腦遊戲				
vi	**每天**做家課, 休閒看書, 畫畫				
viii	**每天**用手提電話或手提遊戲機				

7. 關於居住地點

a. 你的小孩現居於哪裡?

地區: ___________ **(請根據十八區分區填寫)**

b. 請選擇最適當描述他/她的家的項目

☐單位 (如屋邨/私人樓) ☐套房

☐單棟村屋 ☐複式單位

☐天台屋 ☐劏房

c. 他/她家有多大面積?

☐少於 100 平方尺 ☐101-300 平方尺

☐301-600 平方尺 ☐601-1000 平方尺

☐大於 1000 平方尺

8. 關於父母及其他家庭成員

a. 請列明父親職業

____

b. 父親的教育程度是?

☐小學程度 ☐初中程度
☐高中程度 ☐大專程度或以上

c. 父親的眼鏡度數是? (不計散光和老花)

☐**遠**視 600 度或以上 ☐300-575 度**遠**視
☐100-275 度**遠**視
☐100-275 度**近**視 ☐300-575 度**近**視
☐**近**視 600 度或以上
☐不需要配戴眼鏡 ☐不知道

d. 請列明母親職業

____

e. 母親的教育程度是?

☐小學程度 ☐初中程度
☐高中程度 ☐大專程度或以上

f. 母親的眼鏡度數是? (不計散光和老花)

☐**遠**視 600 度或以上 ☐300-575 度**遠**視
☐100-275 度**遠**視
☐100-275 度**近**視 ☐300-575 度**近**視
☐**近**視 600 度或以上
☐不需要配戴眼鏡 ☐不知道

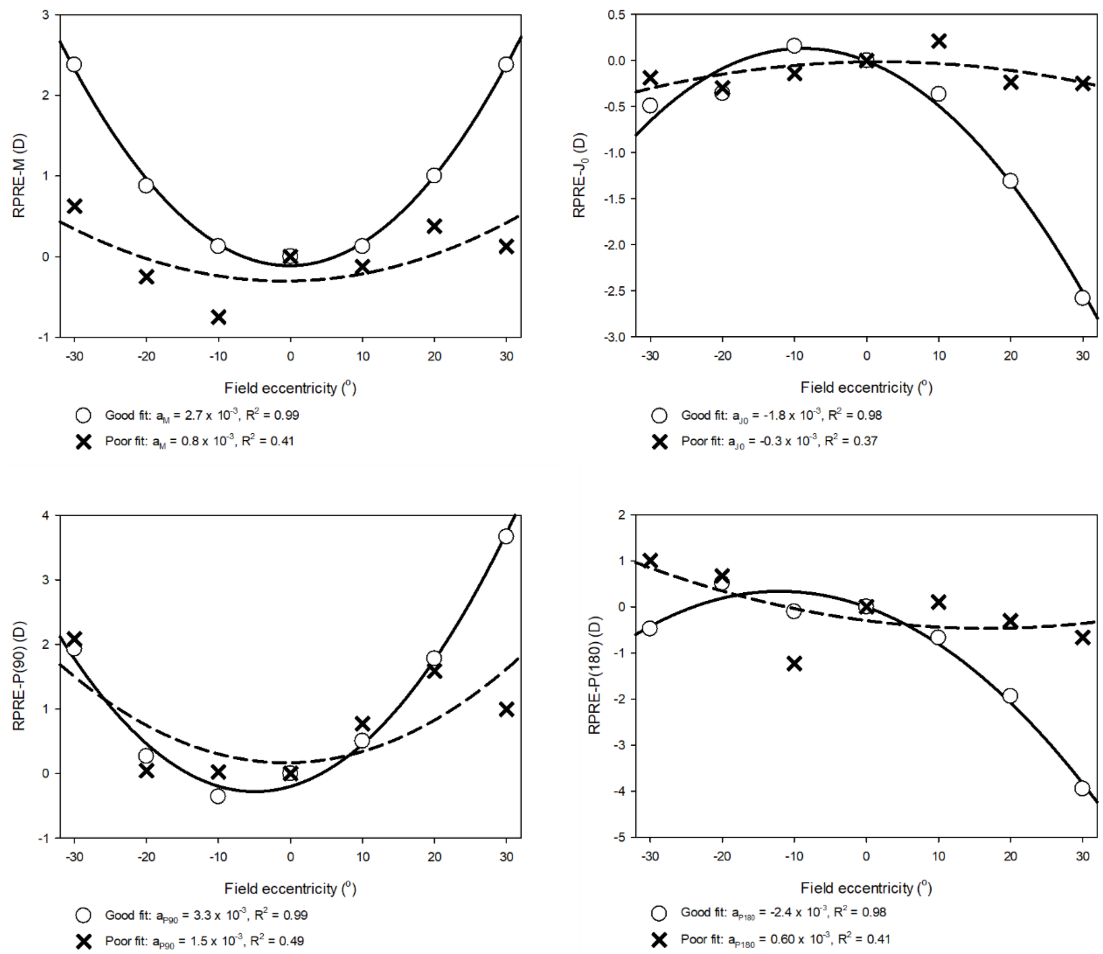
～～ （：多謝你花時間完成問卷：） ～～

資料保密

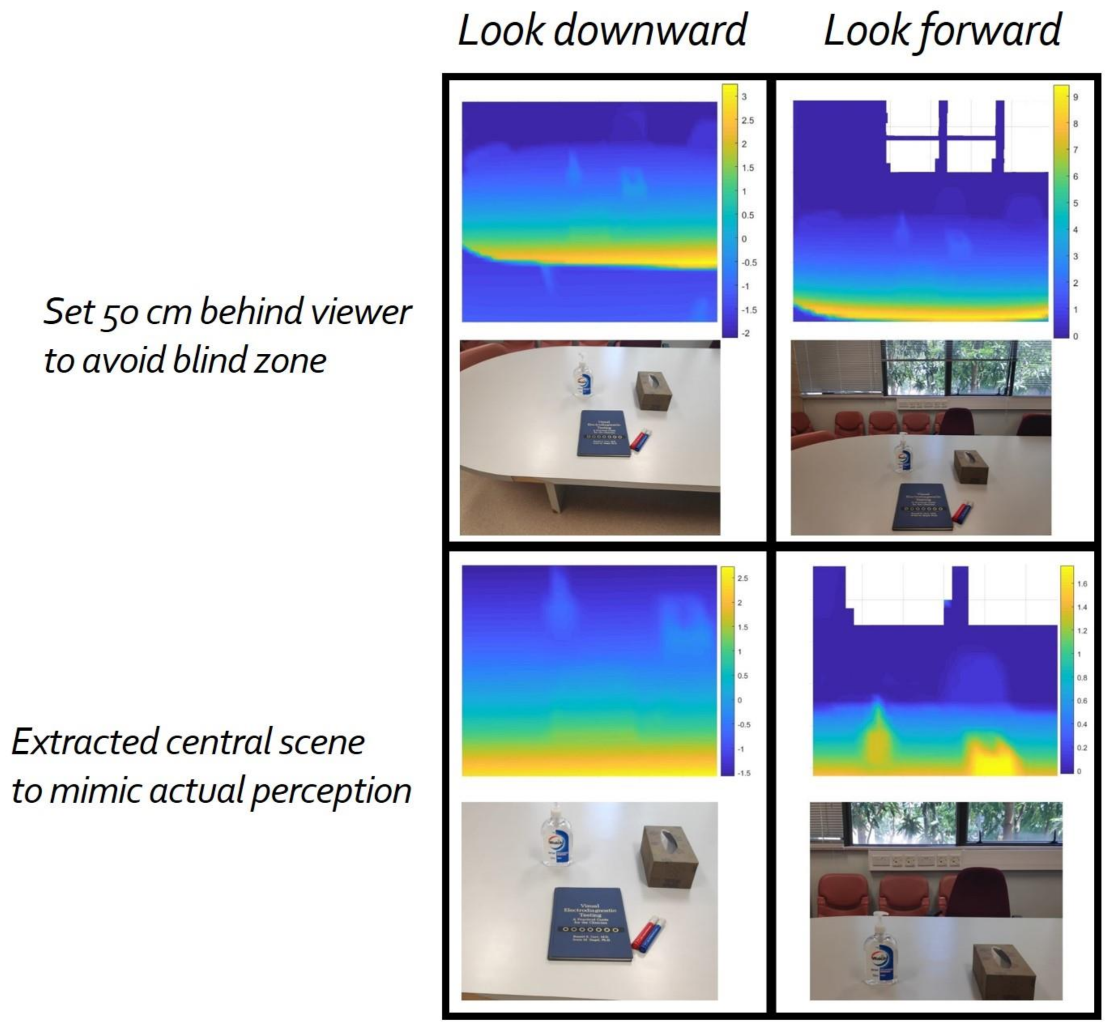
本計劃所收集的資料只供本研究計劃人員讀取及絕對保密，而所得研究結果將可能發表或刊憲，但參加者的個人資料不會被披露。本計劃所收集的資料會於本計劃完結後七年後銷毀。

此研究計劃已獲得香港理工大學眼科視光學院道德委員會批准。若閣下對今次研究有任何投訴，可親身或以書面向本委員會主席提出。

C. Quadratic fit demonstration in Study III

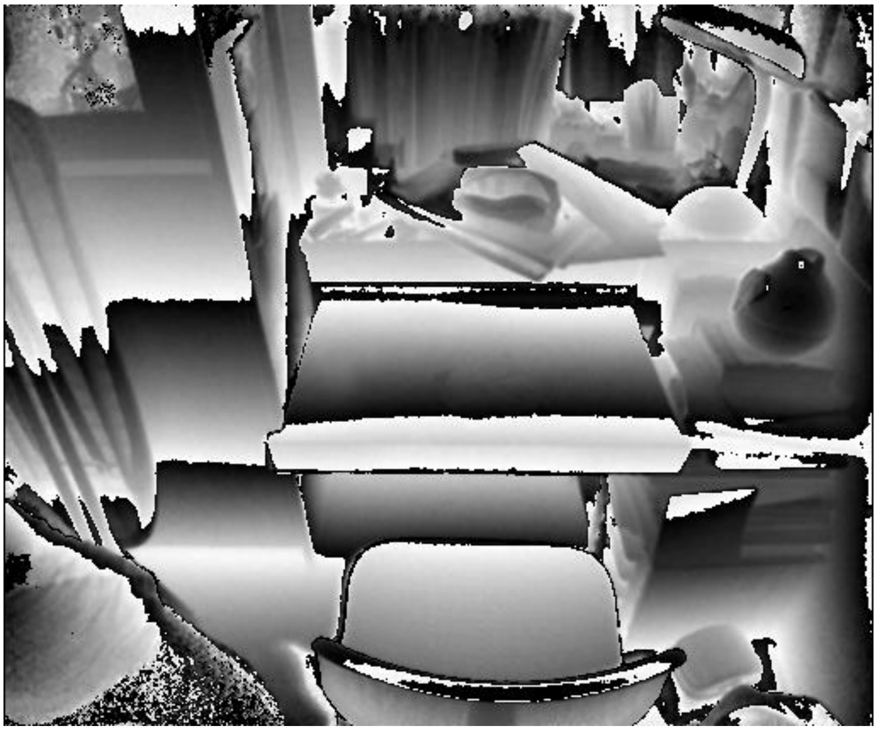


D. Demonstration of Kinect aligned with and 50 cm behind the viewer

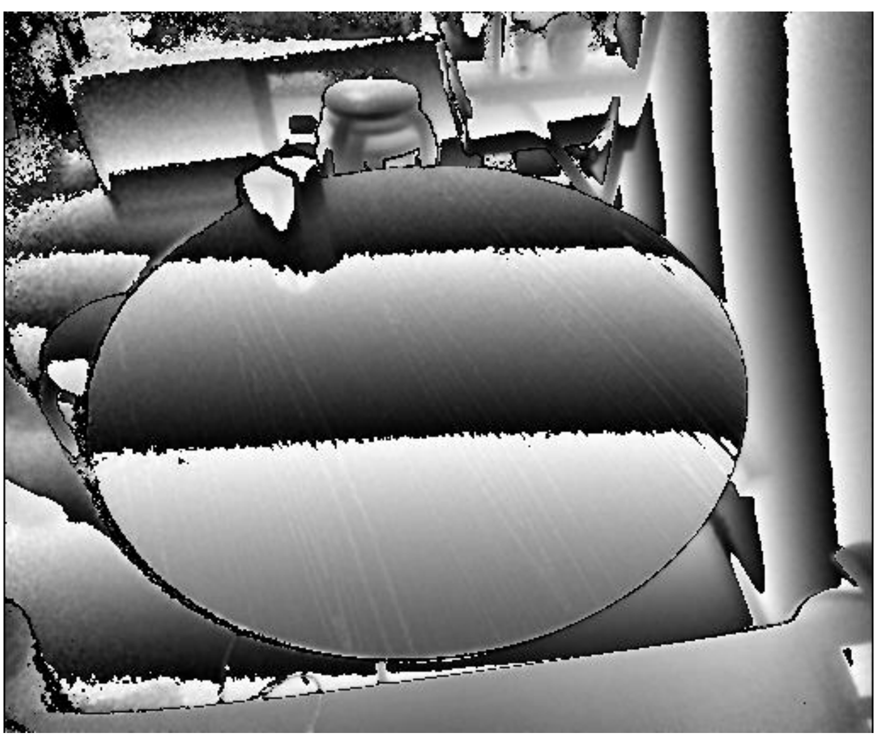


E. Representative raw Kinect images

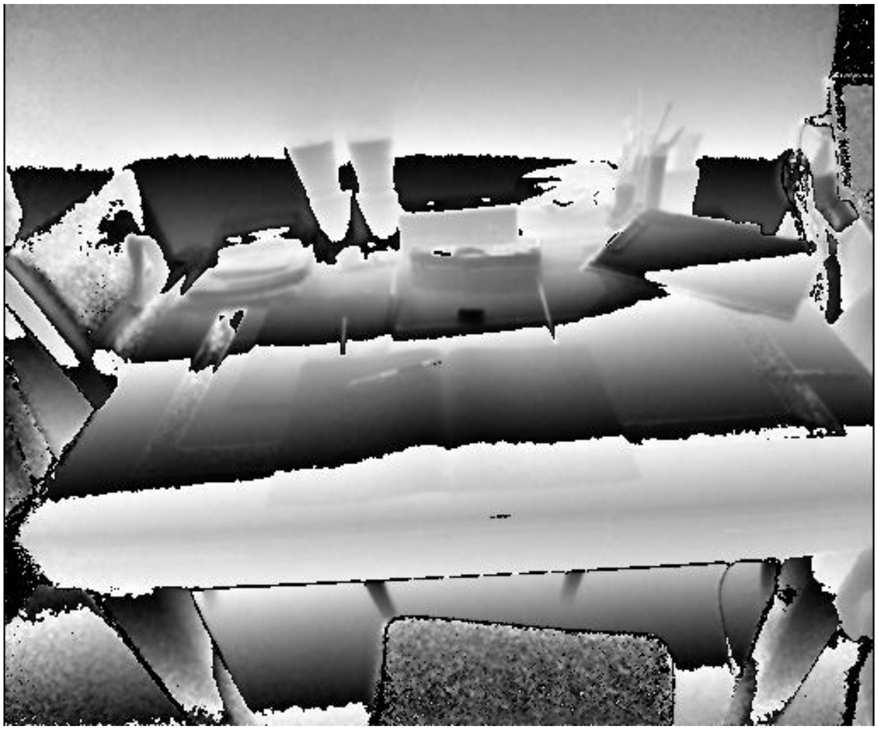
Regular desk – working distance: 30 cm



Dining table – working distance: 22 cm

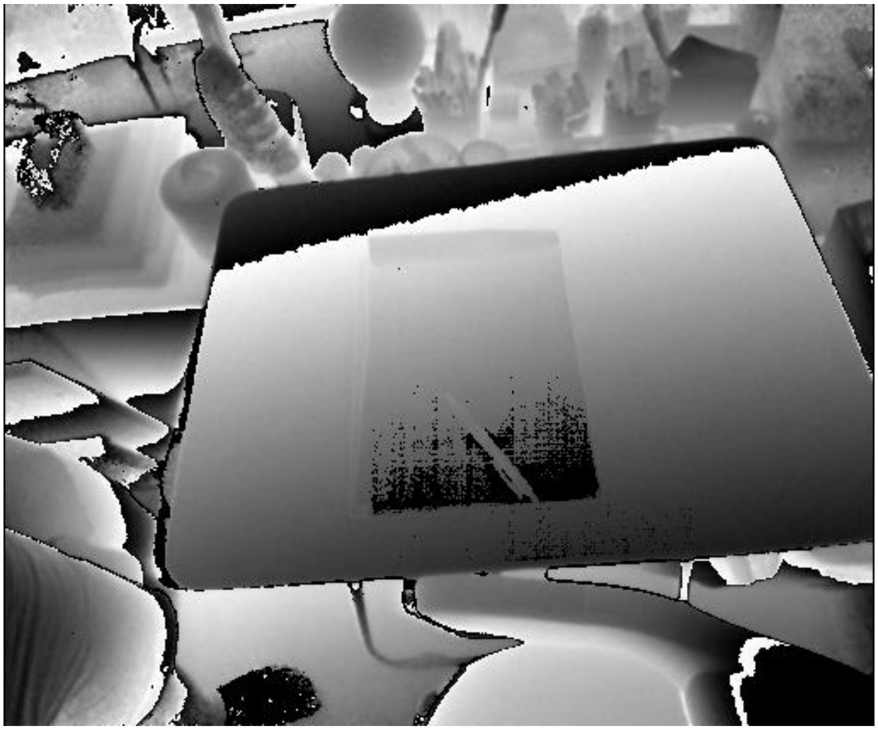


Head tilt to the right – working distance: 35 cm



Head tilt to the left – working distance: 30 cm

Close working distance – working distance: 13 cm



Far working distance – working distance: 41 cm

Window in the scene – working distance: 37 cm

Window in the scene – working distance: 25 cm