

Preventing the epidemic of myopia in China

**- An integrated epidemiological and
biological approach**

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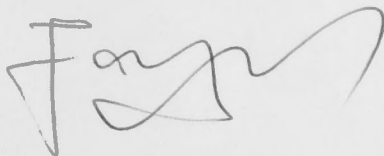
Statement of Authorship

This thesis contains no material that has been extracted in whole or in part from a thesis by which I have qualified for or been awarded another degree or diploma.

Work presented herein is the original work of the author, except where otherwise acknowledged. The Guangzhou Outdoor Activity Longitudinal Study (CHAPTER 7) was designed primarily by the author in consultation with colleagues at the Department of Preventive Ophthalmology of the Zhongshan Ophthalmic Center, Sun Yat-Sen University, Guangzhou, China. During the course of my PhD studies, I was involved in collection of data for the Guangzhou Twin Eye Study and the Guangzhou Outdoor Activity Longitudinal Study.

This thesis has not been submitted for the award of any degree or diploma in any other tertiary institute. Parts of the thesis have been published or are currently under review. Specifically, the contents of CHAPTER 3 have been published in Optometry and Vision Science (Optom Vis Sci 2012; 89:884-891), and the contents of CHAPTER 4 are currently under review for that journal. The contents of CHAPTER 8 have been accepted for publication in Ophthalmology (2012, Epub, May 9).

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Abstract

Myopia is the most common refractive error. It is generally accepted that there is an epidemic of myopia in urban areas of East Asia, as more than 80% of the children who complete secondary school are shorted-sight, with around 20% highly myopic.

Importantly, this problem is not unique to East Asia, and prevalence of myopia is increasing in other parts of the world. The high prevalence of myopia imposes costs for both optical correction and visual impairment. Furthermore, the high prevalence of severe myopia increases the risk of uncorrectable visual impairment and even blindness. Myopia has emerged as major health issue in the world, and been included as one of the priority areas of Vision 2020.

The key findings of this thesis are:

1. The prevalence of myopia has increased progressively from 20-30% to over 80% over the past 100 years in East Asia, and it is plausible that a secular shift in life-style has taken place, resulting in more intensive education and less time spent outside by most children;
2. Environmental influences played an important role during the process, as in Guangzhou, most children now become myopic, and some become highly myopic, irrespective of the refractive status of their parents. There is an additional risk of myopia in children with myopic parents, and an increased risk of developing more severe myopia for those who had severe myopic parents. Exposure to the environment in younger generations did not simply shift the population mean of the refraction;

3. Increased rates of progression in a myopic direction and increased rates of axial elongation occur prior to the onset of clinical myopia. It might therefore be possible to initiate myopia prevention before the onset of myopia. Once a myopic refraction is established, the rates of axial elongation and myopic progression are reduced. The rapid slowing of axial elongation after the onset may suggest that myopic defocus is able to inhibit myopic progression to some extent.

4. The first two years of follow up of the Guangzhou Outdoor Activity Longitudinal Study showed promising results, with a consistent pattern of reduced axial elongation and myopia development in children with outdoor intervention, although greater exposure is needed to obtain clinically significant effects.

Table of Contents

Statement of Authorship.....	ii
Acknowledgements	iii
Abstract	v
Table of Contents.....	vii
List of Figures	x
List of Tables.....	xii
Abbreviations List.....	xiii
CHAPTER 1 General Introduction.....	1
1.1 General overview	1
1.2 Definition and classification of myopia	3
1.3 Biological basis of myopia.....	6
1.4 Epidemiology of Myopia and implications for public health	9
1.4.1 Epidemiology of myopia.....	9
1.4.2 Implication on public health.....	10
1.5 Aetiology of myopia.....	11
1.5.1 Genetic determination of myopia	11
1.5.2 Environmental influence on myopia	16
1.6 Interventions on myopia progression	22
1.7 Study aims	23
CHAPTER 2 Increase in the prevalence of reduced visual acuity in Guangzhou over the past 20 years	26
2.1 Introduction.....	26
2.2 Methods.....	28
2.2.1 Study population.....	28
2.2.2 Examinations	28
2.3 Results	30
2.4 Discussion.....	40
CHAPTER 3 The impact of parental myopia and other familial factors on childhood myopia in Guangzhou	49
3.1 Introduction.....	49
3.2 Method.....	51
3.2.1 Study population.....	51
3.2.2 Examinations	51
3.2.3 Questionnaires and validation test.....	52
3.2.4 Statistical analysis	53
3.3 Results	54
3.3.1 Validation test for questionnaire	54
3.3.2 Parental characteristics	56
3.3.3 Impact of parental myopia on myopia in the children	63
3.3.4 Impact of parental education level.....	66
3.3.5 Impact of family income and parental occupation.....	69
3.3.6 Logistic regression analysis	69
3.4 Discussion.....	75

CHAPTER 4 The impact of severity of parental myopia on childhood myopia 82

4.1 Introduction.....82

4.2 Methods.....83

 4.2.1 Study sample and examinations..... 83

 4.2.3 Statistical analysis 84

4.2 Results85

4.4 Discussion.....99

CHAPTER 5 Relationships between parental myopia and myopia in children in the Guangzhou Twin Eye Study106

5.1 Introduction.....106

5.2 Methods.....107

 5.2.1 Study population.....107

 5.2.2 Examinations107

 5.2.3 Statistical analysis108

5.3 Results109

 5.3.1 Prevalence of myopia in two generations.....109

 5.3.2 Impact of parental myopia on myopia in children112

 5.3.3 Impact of severity of parental myopia in children’s myopia114

 5.3.4 Relationship between rank order in the distribution of refractive error in parents and children121

5.4 Discussion.....126

CHAPTER 6 Reconstructing the secular change of myopia in Guangzhou129

6.1 Introduction.....129

6.2 Data sources and their limitations for estimating the prevalence of myopia131

 6.2.1 Guangzhou RESC132

 6.2.2 The Guangzhou Twin Eye Study.....132

 6.2.3 Liwan Eye Study133

 6.2.4 School-based Visual Acuity Surveillance in Guangzhou133

 6.2.5 Comparison data sets.....134

6.3 Results135

6.4 Discussion.....142

6.5 Implications for the future147

CHAPTER 7149

Guangzhou Outdoor Activity Longitudinal (GOAL) Study149

7.1 Introduction.....149

7.2 Study design.....151

 7.2.1 Study site151

 7.2.2 Sample selection.....151

 7.2.3 Sample size calculation152

 7.2.4 School matching procedure.....153

 7.2.5 Recruitment and informed consent.....154

 7.2.6 Intervention157

 7.2.7 Quality control and validation test.....158

 7.2.8 Study visits.....158

 7.2.9 Related information collection163

 7.2.10 Data entry and analysis164

7.3 Baseline data166

7.4 One-year follow up data.....178

7.5 Two-year follow up data.....188

7.6 Discussion.....189

CHAPTER 8 Annual change rates of refraction and other ocular components before and after the onset of myopia195

8.1 Introduction.....	195
8.2 Methods.....	198
8.2.1 Participants	198
8.2.2 Eye Examinations	198
8.2.3 Statistical analysis	199
8.3 Results	202
8.4 Discussion.....	215
CHAPTER 9 Conclusions.....	220
REFERENCES	226
APPENDIX	240
Appendix 1 Family information questionnaire	240
Appendix 2 Myopia risk factor questionnaire	242
Appendix 3 Children's learning behaviour questionnaire	245

Figure 1.10 Distribution of family monthly income in NPM, OPM and TPM groups	30
Figure 2.1 Distribution of myopia in parents in terms of year of birth.....	41
Figure 2.3 Percentage of parents with tertiary education in terms of year of birth.....	42
Figure 3.1 Distribution of myopia in children in NPM, OPM and TPM groups.....	54
Figure 3.10 Refractive errors in children in NPM, OPM and TPM groups	55
Figure 3.11 Prevalence of myopia in children by parental education levels.....	57
Figure 3.12 Refractive errors in children by parental education levels.....	58
Figure 4.1 Percentage of children in each category of myopia severity (low, mild, moderate, high) by the severity of parental myopia.....	61
Figure 4.2 Mean and SD of SFR in the children in terms of the severity of myopia in the parents.....	62
Figure 4.3 Percentage of parents in each category of myopia severity (low, mild, moderate, high) by the severity of myopia in the children.....	64
Figure 4.4 Percentage of high myopia children as a function of age.....	66
Figure 5.1 Prevalence of myopia in children in NPM, OPM and TPM groups.....	113
Figure 5.2 Percentage of children in each category of myopia severity (low, mild, moderate, high) by the severity of parental myopia.....	116
Figure 5.3 Percentage of parents in each category of myopia severity (low, mild, moderate, high) by the severity of myopia in the children.....	117
Figure 5.4 Percentage of children in each category of myopia severity (low, mild, moderate, high) by the severity of parental myopia.....	119
Figure 5.5 Percentage of parents in each category of myopia severity (low, mild, moderate, high) by the severity of myopia in the children.....	120
Figure 5.6 Distribution of refractive error in the parents.....	122
Figure 5.7 Distribution of refractive error in 16-18 years children.....	123
Figure 5.8 Correlation of mean value of refractive error between parents and children.....	125
Figure 6.1 Secular change in the prevalence of myopia in Singapore.....	136
Figure 6.2 Comparison of myopia prevalence in Hong Kong, Singapore, Taiwan and Hong Kong.....	138
Figure 6.3 Graduation rate in Cambridge.....	140
Figure 7.1 Flow chart of study procedures.....	156
Figure 7.2 Flow chart of examination procedures.....	162
Figure 7.3 Distribution of refractive error in participating children with myopia.....	171
Figure 7.4 Distribution of axial length in participating children.....	173
Figure 7.5 Distribution of corneal curvatures in participating children.....	174
Figure 7.6 Distribution of AL/CR ratio in participating children.....	174
Figure 7.7 Distribution of height in participating children.....	175

List of Figures

Figure 1.1 Hyperopic and myopic defocus	8
Figure 2.1 Percentage of students with normal vision by school grade.....	33
Figure 2.2 Percentage of students with severely reduced VA by school grade	35
Figure 2.3 Visual Acuity Categories in Grade 1	36
Figure 2.4 Visual Acuity Categories in Grade 12	37
Figure 2.5 Comparison of the prevalence predicted from moderately and severely reduced VA for 2002 with myopia prevalence from other studies	39
Figure 3.1A Distribution of parental highest education level in NPM, OPM and TPM group	60
Figure 3.1B Distribution of family monthly income in NPM, OPM and TPM groups ..	60
Figure 3.2 Prevalence of myopia in parents in terms of year of birth.....	61
Figure 3.3 Percentage of parents with tertiary education in terms of year of birth.....	62
Figure 3.4A Prevalence of myopia in children in NPM, OPM and TPM groups	64
Figure 3.4B Refractive errors in children in NPM, OPM and TPM groups	65
Figure 3.5A Prevalence of myopia in children by parental education levels.....	67
Figure 3.5B Refractive errors in children by parental education levels.....	68
Figure 4.1 Percentage of children in each category of myopia severity (non, mild, moderate, high) by the severity of parental myopia.....	91
Figure 4.2 Mean and SD of SER in the children in terms of the severity of myopia in the parents	92
Figure 4.3 Percentage of parents in each category of myopia severity (non, mild, moderate, high) by the severity of myopia in the children	94
Figure 4.4 Prevalence of high myopia children as a function of age	96
Figure 5.1 Prevalence of myopia in children in NPM, OPM and TPM groups.....	113
Figure 5.2 Percentage of children in each category of myopia severity (non, mild, moderate, high) by the severity of parental myopia.....	116
Figure 5.3 Percentage of parents in each category of myopia severity (non, mild, moderate, high) by the severity of myopia in the children	117
Figure 5.4 Percentage of children in each category of myopia severity (non, mild, moderate, high) by the severity of parental myopia.....	119
Figure 5.5 Percentage of parents in each category of myopia severity (non, mild, moderate, high) by the severity of myopia in the children	120
Figure 5.6 Distribution of refractive error in the parents	122
Figure 5.7 Distribution of refractive error in 15-18 years children.....	123
Figure 5.8 Correlation of rank order in refractive error between parents and children	125
Figure 6.1 Secular change in the prevalence of myopia in Guangzhou	136
Figure 6.2 Comparison of myopia prevalence in Guangzhou, Singapore, Taiwan and Hong Kong.....	138
Figure 6.3 Graduation rate in Guangzhou	140
Figure 7.1 Flow chart of study procedure	156
Figure 7.2 Flow chart of examination procedures	162
Figure 7.3 Distribution of refractive error in participating children with cycloplegia..	171
Figure 7.4 Distribution of axial length in participating children	172
Figure 7.5 Distribution of corneal curvature in participating children	173
Figure 7.6 Distribution of AL/CR ratio in participating children	174
Figure 7.7 Distribution of height in participating children	175

Figure 7.8 Distribution of weight in participating children	176
Figure 7.9 Distribution of BMI in participating children.....	177
Figure 7.10 Distribution of refractive error in participating children with cycloplegia (one-year follow-up visit)	181
Figure 7.11 Distribution of axial length in participating children (one-year follow-up visit).....	182
Figure 7.12 Distribution of corneal curvature in participating children (one-year follow- up visit).....	183
Figure 7.13 Distribution of AL/CR ratio in participating children (one-year follow-up visit).....	184
Figure 7.14 Distribution of height in participating children (one-year follow-up visit)	185
Figure 7.15 Distribution of weight in participating children (one-year follow-up visit)	186
Figure 7.16 Distribution of BMI in participating children (one-year follow-up visit) .	187
Figure 8.1 The numbers of children as a function of age of onset of myopia	203
Figure 8.2 Annual change in spherical equivalent refraction relative to the first detection of myopia	204
Figure 8.3 Annual change in axial length relative to the to the first detection of myopia	206
Figure 8.4A Annual change in spherical equivalent refraction in younger and older children relative to the first detection of myopia	207
Figure 8.4B Annual change in axial length in younger and older children relative to the first detection of myopia	208
Figure 8.5 Annual change in axial length/corneal radius ratio (AL/CR) ratio relative to the first detection of myopia	211
Figure 8.6 Annual change in anterior chamber depth relative to the first detection of myopia.....	212
Figure 8.7 Annual change in corneal curvature relative to the first detection of myopia	213
Figure 8.8 Annual change in lens power relative to the first detection of myopia	214

List of Tables

Table 1.1 Heritability from twin studies	14
Table 2.1 Enrolment Number and Gender Ratio in examined schools, 1988-2007	31
Table 2.2 Enrolment rates in Guangzhou city	42
Table 3.1 Participants' responses to the validity question, categorized by non-cycloplegic refraction	55
Table 3.2 Prevalence of myopia in parent	57
Table 3.3 Logistic regression Model for potential risk factors of children's myopia	71
Table 3.4 Logistic regression model for potential risk factors for children's myopia in 12-15 year-olds	72
Table 3.5 Near work activities in children in NPM, OPM and TPM groups	74
Table 3.6 Major studies on the relative risk associated with parental myopia	79
Table 4.1 Responses to validity questionnaire, classified by three categories	86
Table 4.2 Myopia categories in children and parents	89
Table 4.3 Near work activities in children from NPM, OPMiM, OPMoM and OPHM families	98
Table 4.4 Prevalence of high myopia in young and old adults	102
Table 5.1 Prevalence of myopia in children and parents	110
Table 5.2 SER mean, median, 25% and 75% percentiles	111
Table 7.1 Baseline characteristics by study group	167
Table 7.2 Baseline mean Spherical Equivalent Refraction (SER) by school	169
Table 7.3 Baseline mean axial length (AL) by school	170
Table 7.4 Changes of SER in control and intervention group	179
Table 7.5 Changes of axial length in control and intervention group	180
Table 8.1 Definition of examination year relative to the first detection of myopia	201
Table 8.2 Ratio of annual change in spherical equivalent refraction (SER) and axial length (AL) relative to the first detection of myopia	209

Abbreviations List

ACD: Anterior chamber depth

AL: Axial length

AL/CR: Axial length/corneal radius of curvature ratio

CLEER: Collaborative Longitudinal Evaluation of the Ethnicity and Refractive Error

CR: Corneal radius of curvature

CTNND2: cadherin-associated protein, neural plakophilin-related arm-repeat protein

D: Diopter

ECM: Extracellular Matrix

GDP: Gross domestic product

GSHCI: Guangzhou Students' Health Care Institute

No.: Number

PISA: Programme for International Student Assessment

RESC: Refractive Error Study in Children

SCORM: Singapore Cohort study of the Risk factors for Myopia

SER: Spherical Equivalent Refraction

SD: Standard deviation

SMS: Sydney Myopia Study

VA: Visual acuity

WHO: World Health Organization

CHAPTER 1 General Introduction

1.1 General overview

Myopia (short-sightedness) is a refractive error that is caused by excessive elongation of the eye during development, causing a mismatch between the optical power of the eye and its axial length. This mismatch causes the focal plane of distant objects to fall in front of the photoreceptor layer of the retina, rather than on the fovea, causing images to be blurred (Duke-elder, 1978).

Myopia is among the most common refractive errors and the prevalence of myopia is reaching epidemic proportions in many parts of the world. A comprehensive review of the literature has shown that in urban East Asia, 80-90% of school-leavers are now myopic, while around 20% have high myopia (Morgan and Rose, 2005). The high prevalence of myopia in young people imposes a high demand for optical correction, and causes considerable visual impairment through under-correction (Dandona and Dandona, 2001, Resnikoff et al., 2008). Furthermore, for those who are highly myopic, there is a higher risk of myopic chorio-retinal degenerations and pathologies (Saw et al., 2005), which can lead to higher levels of visual impairment and legal blindness later in life.

The high prevalence of myopia and its public health and clinical consequences make prevention of myopia a top priority. The recent and rapid emergence of the high prevalence of myopia suggests that social or environmental changes have been critical in the process, and understanding the causes of the current pandemic is important if preventive measures are to be put in place. The first part of this thesis first looks at the

secular change in the prevalence of myopia over the past century in Guangzhou, China. Comparison of the myopia between generations will enable us to understand the recent epidemic of myopia. The second part of this thesis reports on the methodology and follow-up results of an ongoing clinical trial on myopia prevention, the Guangzhou Outdoor Activity Longitudinal (GOAL) Study. The third part looks at biometric and refractive changes around the onset of myopia.

1.2 Definition and classification of myopia

The word “myopia” comes from the Greek word “myopos” which relates to the squinting that is frequently resorted to by myopes to improve their vision. Squinting effectively narrows the pupil, and this improves vision, but only for the duration of the squinting.

Myopia is now defined as a state in which the optical system of the unaccommodated eye bring parallel light rays from distant objects to focus in front of the photoreceptor layer of the retina, instead of on the foveal photoreceptors. In clinical and epidemiological practice, cycloplegic agents such as cyclopentolate and atropine are used to paralyze the ciliary muscle, resulting in a loss of accommodation, and thus permitting measurement of myopia without the complications of uncontrolled accommodation.

Myopia is measured by the spherical power in diopters (D) of the diverging lens needed to focus light onto the retina. Since eyes are also frequently astigmatic, refractive status is often expressed as the spherical equivalent refraction (SER), which is, sphere plus half negative cylinder (Curtin, 1985, Curtin, 1988). The most commonly applied definition of myopia in epidemiology studies is an SER of at least -0.5D, but other cut-offs such as -0.75D and 1.0D have been frequently used (Luo et al., 2006).

Myopia can be classified by degree/severity: low or mild myopia (myopia of -3.0 D or less), medium or moderate myopia (myopia between -3.0 and -6.0 D) and high or severe myopia (myopia of -6.0 or more).

Myopia can also be classified by the age of onset: congenital myopia (present at birth and persisting through infancy), youth-onset or juvenile-onset myopia (occurs prior to age 20, particularly in the school-age years), and adult-onset myopia, which includes early adult onset myopia (occurs between 20 and 40 years) and late adult onset myopia (occurs after 40 years)(Grosvenor, 1987).

Another common classification refers to simple or pathological myopia, with classification depending on whether there are pathological changes associated with and to some extent dependent on the refractive error. The distinctions between the different types of myopia are rarely clear-cut, and overlap considerably. For example congenital or early-onset myopia is commonly associated with continued myopic progression, leading to high or severe myopia, and in turn leading to the emergence of myopic pathology.

For many clearly inherited syndromes with identified underlying genetic defects, such as Marfan(Dietz et al., 1991) and Weill-Marchesani(Faivre et al., 2003), myopia is only one of a complex of symptoms. Most of these syndromes are characterized by congenital or early onset high myopia, in association with a range of other abnormalities. There are also a number of inherited non-syndromic high myopias in which myopia is the major symptom. However, specific genes associated with these conditions have not been identified. Collectively, these syndromes and inherited non-syndromic high myopia only account for a small proportion of myopia in the population. Most myopia appears during childhood, particular during the school years.

The main focus of the thesis will be on youth-onset or school myopia. Classical school myopia occurs in the primary school or early secondary school years (8-14 years), and

1.3 Biological basis of myopia

It is generally accepted that most species, including humans, are born with hyperopic refractive errors (long-sightedness), where the eye is too short for the optical power of the cornea and crystalline lens. Over the first or two years after birth, the normally-distributed, predominantly hyperopic, neonatal refractive errors are rapidly reduced towards emmetropia (Gwiazda J, 1993, Mayer et al., 2001, Mutti et al., 2005), through a vision-dependent process known as emmetropisation (Wildsoet, 1997). This process produces spherical equivalent refraction in the low hyperopic range, roughly between +0.5 and +2.0D (Morgan et al., 2010), where normal vision can be achieved through accommodation.

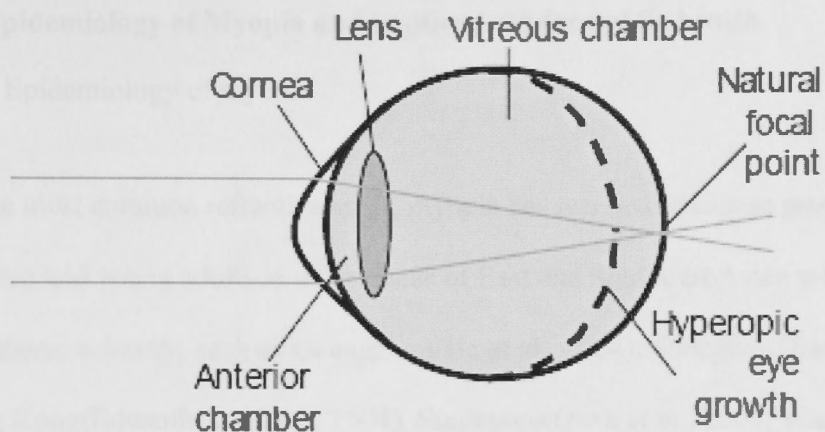
The process of emmetropisation involves matching axial length to corneal power, so that the distribution of refraction changes from a normal to a highly kurtotic distribution, at mean refraction values which are slightly hyperopic (Mayer et al., 2001, Mutti et al., 2005). While data is not available on younger children, a markedly kurtotic ratio of axial length (AL) and corneal radius of curvature (CR) is also seen in 5-6 year-olds, whereas all other biometric contributors to refractive status retain their normally distributed neonatal status (Ojaimi et al., 2005a). Reductions in lens power over this period have also been documented (Mutti et al., 2005). At this stage in development, the prevalence of myopia is generally low, and mean SER is mildly hyperopic, and in some circumstances, this distribution can be maintained into adult life (Sorsby et al., 1960, Attebo et al., 1999, Shufelt et al., 2005).

Corneal power stabilizes during development after the age of 3. Subsequent refractive development then appears to involve continued axial elongation, combined with reductions in lens power (Sorsby et al., 1961, Zadnik et al., 2003, Twelker et al., 2009).

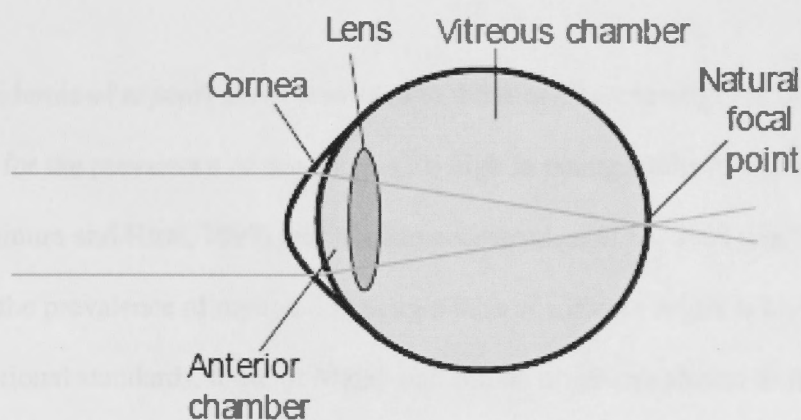
Axial length is highly correlated with SER, whereas lens power is not highly correlated with refraction, as though changes in lens power are a general developmental phenomenon(Mutti et al., 2012). An important consequence of the axial elongation is that the axial length can become too long for the optical power of the eye, and parallel light rays converge in front of the photoreceptors. Thus, myopia is largely due to excessive axial elongation (Figure 1.1).



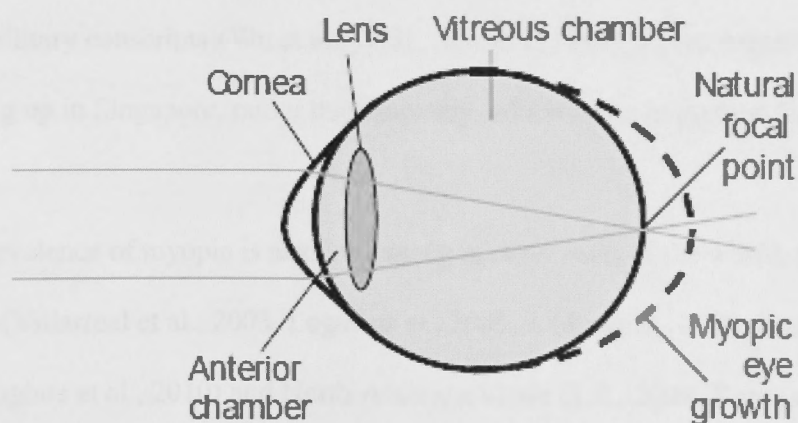
Figure 1.1 Hyperopic and myopic defocus



A Hyperopic defocus



B Emmetropic defocus



C Myopic defocus

Figure 1.1 Hyperopic and myopic defocus

1.4 Epidemiology of Myopia and implications for public health

1.4.1 Epidemiology of myopia

As the most common refractive error, myopia has reached epidemic proportions in children and young adults in urban areas of East and Southeast Asian with populations of Chinese ancestry, such as Guangzhou(He et al., 2004), Shanghai(Qian et al., 2009) , Hong Kong(Edwards and Lam, 2004), Singapore(Quek et al., 2004, Wu et al., 2001)and Taiwan(Lin et al., 2004). In these areas, more than 80% of school-leavers are now myopic, and approaching 20% have severe myopia.

The epidemic of myopia is not restricted to those of Chinese origin in these parts of the world, for the prevalence of myopia is also high in young adults of Japanese (Matsumura and Hirai, 1999) and Korean ancestry(Lee et al., 2011). In Singapore, where the prevalence of myopia in young adults of Chinese origin is high by international standards, those of Malay and Indian origin are almost as myopic as those of Chinese origin (Chinese: 82.2%, Malays: 65.0%, Indians: 68.7% for 1996-1997 male military conscripts; Chinese: 85.9%, Malays: 70.7%, Indians: 74.5% for 2009-2010 male military conscripts)(Wu et al., 2001, Saw et al., 2011). This suggests that it is growing up in Singapore, rather than ancestry, which is the important factor.

The prevalence of myopia is also increasing in other parts of the world, and in parts of Europe(Villarreal et al., 2003, Logan et al., 2005, Jobke et al., 2008, Plainis et al., 2009, O'Donoghue et al., 2010) and North America(Vitale et al., 2008, Kempen et al., 2004), the prevalence of myopia may now be as high as 40-60% in young adults. More detailed information is needed from these areas. Internationally, the prevalence of myopia seems likely to increase as more countries develop economically, since urbanisation and

intensive education have been implicated in the increasing prevalence of myopia(Rose et al., 2001).

1.4.2 Implication on public health

The high prevalence of myopia imposes both high costs for optical correction(Javitt and Chiang, 1994), and visual impairment where refractive error is not corrected or under-corrected. Under-correction is very common in both rural(He et al., 2007) and urban areas of China(He et al., 2004, He et al., 2009b), and internationally, analyses by the WHO have shown that uncorrected or under-corrected refractive error is a major cause of visual Impairment(Resnikoff et al., 2004, Resnikoff et al., 2008).

Furthermore, even when corrected, the high prevalence of severe or high myopia increases the risk of uncorrectable visual impairment and even blindness later in life(Saw et al., 2005). Most of the pathological consequences of high myopia are associated with excessive and progressive elongation of the eye and pathological changes in the fundus(Goldschmidt, 1988, Tokoro, 1988). The excessively elongated eye leads to various chorio-retinal pathologies, probably due to the stretching of the ocular tissues. It is evident that myopes have an increased risk of developing retinal detachment(Arevalo, 2000), choroidal neovascularisation(Avila et al., 1984, Hotchkiss and Fine, 1981), and glaucoma(Mitchell et al., 1999). For these reasons, myopia has been included as one of the priority areas of Vision 2020(Pararajasegaram, 1999, Pizzarello et al., 2004).

1.5 Aetiology of myopia

Since it was first realized that highly educated people are more likely to become myopic than less educated people, there has been a long-standing debate over whether myopia is inherited, or environmentally determined. An important issue is that human myopia is aetiologically heterogeneous, and different forms of myopia may well be different. It is now generally agreed that there are major genetic contributions to high myopia, although these may be reduced in younger cohorts given the increasing prevalence of acquired high myopia. In contrast, it is increasingly clear that school myopia is multifactorial, possibly involving a large number of genes of small effect, and major environmental effects. Both genetic inheritance and environmental influence are involved in the aetiology of myopia, while the environmental influences play important roles in the international and ethnic differences of myopia(Morgan and Rose, 2005, Wojciechowski, 2011).

1.5.1 Genetic determination of myopia

Evidence for a significant role for genetic inheritance comes in the first instance from familial studies. Many familial studies have reported the within-family correlations in myopia, - there is, for example, an increased risk of myopia for a child if it has one myopic parent and a further increased risk if there are two myopic parents(see, for example, (Zadnik, 1997, Saw et al., 2001a, Mutti et al., 2002, Mutti and Zadnik, 1995). In addition, there is an increased risk of myopia in one sibling if other siblings are myopic(see, for example, (Guggenheim et al., 2007, Sorsby et al., 1966, Wojciechowski et al., 2005, Guggenheim et al., 2000).

Other work has shown that children with myopic parents tend to have longer eyes than those without myopic parents(Zadnik et al., 1994), even before the onset of myopia.

This is often quoted as evidence of genetic determination, as longer eyes are associated with myopia, although this would also be true if myopigenic family environments were the cause of myopia, since myopia results from excessive axial elongation.

However, because of the matching of AL and CR that takes place, there is no absolute association between longer eyes and myopia. A simple example is that the males tend to have longer eyes than women, but, if anything, women tend to be more myopic than men, or no systematic gender difference in refractive error is reported(Wong et al., 2000, Wong et al., 2001, Wong et al., 2003).

Genetic evidence also comes from the estimates of heritability derived from parent-offspring and sibling correlations, and from twin studies(Guggenheim et al., 2000).

Heritability is the proportion of the phenotypic variance attributable to genetic effects, in a defined population and a defined environment. High heritability suggests that there is a significant genetic contribution to the variance, and little environmental impact.

The heritability estimated from inter-sibling correlations is generally higher and more consistent than that from parent-offspring correlations(Rose et al., 2002, Guggenheim et al., 2000). However, it should be noted that the strength of sibling association is dependent on the age difference, - the greater the gap in age between siblings, the lower the correlation in refractive error(1996b).

Although the family clustering in myopia studies is often assumed to be a genetic effect, the evidence is clearly ambiguous, because within-family correlations confound shared environments with shared genes. Siblings tend to share the same environment, and

correlations between siblings are more consistent. Conversely, there are major differences in the environments in which parents and their children grow up, and the parent-offspring correlations tend to be lower. Further, where the prevalence of myopia is relatively stable and environmental changes are small, within-family correlations are high. But when the prevalence of myopia has changed rapidly, which is generally associated with major changes in the social environment from the parental generation to that of the children, parent-offspring correlations are reduced, sometimes to trivial levels, consistent with strong environmental effects(Nakajima, 1968d, Nakajima, 1968b, Young et al., 1969, Young and Leary, 1972, Keller, 1973, Hegmann et al., 1974, Alsbirk, 1979, Johnson et al., 1979, Guggenheim et al., 2000, Morgan and Rose, 2005). However, correlations between siblings are still high, since siblings are experiencing the same environmental change.

Heritability is most conclusively estimated from studies on refractive error in monozygotic and dizygotic twins (Table 1.1). Twin studies have been described as the “the perfect natural experiment to separate familial resemblance from genetic influence”(Martin et al., 1997), but this statement needs to be qualified in view of the assumptions needed for calculating heritability(Hopper, 1992). Estimates of heritability are generally high, except in two studies. One of them was carried out on a population in which the prevalence of myopia was rapidly changing under environmental influence(Lin and Chen, 1987), and the another one contained an unusually high component of myopia attributable to form-deprivation due to congenital cataract(Angi et al., 1993).

Reference	Heritability*
Sorsby 1962	0.87
Nakajima 1968	0.83
Nakajima 1968	0.73
Kimura 1965	0.80
Hu 1981	0.61
Lin and Chen 1987	0.25
Teikari 1991	0.58
Angi 1993	0.11
Hammond 2001	0.84-0.86
Lyhne 2001	0.89-0.94
Chen 2007	0.50
Klein 2009	0.58
Dirani 2006	0.75-0.88
Lopes 2009	0.77

* Data are derived from Guggenheim, with the addition of more recent references

Table 1.1 Heritability from twin studies

Twin studies depend critically on the assumption that the correlation of environments for dizygotic and monozygotic twin pairs is complete, or at least the same. This assumption is rarely tested, and if monozygotic twin pairs share more similar post-natal environments than the dizygotic twin pairs, their excess similarity cannot be attributed to their genetic identity. Even if rigorous testing validates the assumption on which the high heritability values have been calculated in twin studies, these values cannot be extrapolated to the general population. This being said, twin studies tend to underestimate the importance of environmental factors, because the range of environmental variation between twins within pairs is likely to be much more limited than the range of variations between individuals and families present in society as a whole. Nevertheless, the high correlation and heritability values calculated on refractive error in twin studies are consistent with the idea that there may be a genetic contribution to refractive error, which can be seen when environmental variation is low.

Several recent reviewers have extensively covered genetic analysis in human myopia(Wojciechowski, 2011, Young, 2009, Hornbeak and Young, 2009, Baird et al., 2010), and I will not review this area in detail. For the syndromic high myopias, a common feature is the involvement of genes involve in scleral extracellular matrix (ECM). For the non-syndromic high myopias (MYP1-MYP17), a large number of chromosomal locations, but few specific genes have been identified. The one exception appears to be MYP16, where mutations in CTNND (cadherin-associated protein) have been identified and replicated(Li et al., 2011b). While there are many problems with replication, Wojciechowski(Wojciechowski, 2011) has shown that many of the mutations reported form a coherent nexus of linked structural and metabolic constituents of the ECM.

At present, the very low number of defined genotypic contributions to variation in refractive error in the school myopia range account for only a small proportion of the variation(Hysi et al., 2010, Solouki et al., 2010). Thus school myopia is faced with a mismatch between the high heritability defined in twin studies and defined, associated allelic variations – a common problem in complex disease genetics now known as missing heritability(Manolio et al., 2009). Further research in this area will continue, but with existing knowledge, the contribution that genetic analysis can make to the prediction of susceptibility to school myopia appears to be limited.

1.5.2 Environmental influence on myopia

1.5.2.1 Evidence for environmental factors

There is considerable evidence of the importance of environmental factors. Evidence for a significant role for environmental effects firstly comes from the rapid change of myopia prevalence in East and Southeast Asia. In Taiwan, 6 nationwide surveys of ocular refraction from 1983 to 2006 reported a continuous increase in the prevalence of myopia in school-aged children over the past 20 years. The prevalence of myopia ($SER \leq -0.25D$) in school-leavers (15 year-olds) increased from 64% to more than 80%, and the prevalence of high myopia ($SER \leq -6.0D$) in 18 year-old children increased from 11% to more than 20%. Besides the significant increase in the prevalence of myopia and high myopia, the data also showed a decrease in the age of onset, and the systematic shift in mean refractive error values, with broader distributions of refractive errors in recent cohorts. Data from Singapore showed that in the 1960s, only 20-30% of male school leavers (17-19 years old) were myopic(Tay et al., 1992), while the prevalence of myopia rapidly increased, and reached around 80% in more recent birth cohorts. The initial evidence was based on visual acuity data rather than refraction(Au Eong et al., 1993b, Au Eong et al., 1993a, Tay et al., 1992), but more recent data have measured

non-cycloplegic refraction. The assumption that the majority of cases of low visual acuity were due to myopia is very plausible, since, at least in children, children with significant hyperopia often have normal visual acuity (Leone et al., 2010).

Wu and Edwards (Wu and Edwards, 1999) reported the prevalence of myopia over three generations in Hong Kong and China. While the estimates were often based on an unvalidated questionnaire, there appears to have been a progressive increase in the prevalence of myopia across generations, - the prevalence of myopia in the 3rd generation (grand children) was more than five times higher than that in the 1st generation (grand parents) and there was a declining risk associated with parental myopia. Similar trends can also be seen in mainland China, Japan and other parts of East Asia, and there is also considerable evidence that the prevalence of myopia in populations of European origin has been increasing in the past decades (Vitale et al., 2008, Vitale et al., 2009). The speed of these changes suggests a role for environmental exposures, since gene pools in human population do not change so rapidly.

1.5.2.2 Excessive accommodation theory

Evidence for the environmental impacts on myopia also comes from studies of the influence of education, urbanization, and more specifically near-work on the prevalence of myopia (Saw et al., 1996, Saw et al., 2000). The correlation between myopia prevalence and education was noticed as long ago as in 1813 (Ware, 1813), and numerous studies have demonstrated that increased education and increased myopia go hand in hand (see, for example, (Curtin, 1985, Morgan and Rose, 2005). Based on the strong association between myopia and education, it was postulated that more education exposed children to increased duration and intensity of near-work, and that myopia results from excessive accommodation associated with near-work. The fact that

increased eye growth and myopia can be induced in experimental animals by fitting them with minus lenses is also consistent with this idea(Irving et al., 1991, Irving et al., 1992, Irving et al., 1995, Schaeffel et al., 1988, Schmid and Wildsoet, 1996, Wildsoet and Wallman, 1995). The successful use of atropine eye drops for blocking accommodation at least myopic progression further appears to give strong support to this idea(Bedrossian, 1985).

Despite this, in recent years, the importance of excessive accommodation has been questioned. Studies using detailed time-based or accommodation-weighted measures of near work have not revealed strong association between near work and myopia, particularly when the effects of other potential risk factors are considered(Saw et al., 2002a, Mutti et al., 2002, Mutti and Zadnik, 2009a, Ip et al., 2008c). Attempts to reduce the demand for accommodation using optical techniques have not been particularly successful in preventing myopia. Initial approaches to prevention were made by reducing accommodative demand with reading glasses, bifocals or most recently, progressive addition lenses. At best, these trials have achieved statistically significant, but clinically insignificant gains, except for the small group of near esophores, where significant gains were achieved(Saw et al., 2002c, Gwiazda, 2009, Li et al., 2011a). In addition, studies on experimental myopia in animals have also questioned the importance of accommodation. In these studies, it has been shown that atropine blocks axial elongation and the development of myopia, even in species such as chicken where accommodation is mediated by nicotinic rather than muscarinic receptors, and hence is not blocked by atropine(McBrien et al., 1993b). Eye growth regulation and the inhibitory effects of atropine have also been demonstrated in animals with little or no accommodative capacity(McBrien et al., 1993a), and in experimental animals where control of accommodation has been blocked by section of the ciliary nerve or

destruction of the Edinger-Westphal nucleus(Troilo, 1990, Wildsoet, 2003). Most strikingly, form-deprivation or exposure to lens-induced defocus of only part of the visual field, leads to regional changes in eye growth(Wallman et al., 1987), which are difficult to explain in terms of a global process such as accommodation. These results show that accommodation per se is not really a critical factor.

1.5.2.3 Balance of myopia and hyperopic defocus

This suggests that other possibilities rather than successive accommodation need to be considered. Experimental work on animals has replaced the emphasis on excessive accommodation with a different explanatory framework - namely that the retina is able to generate growth control signals in response to image defocus: a STOP signal evoked by myopic defocus and a GROW signal evoked by hyperopic defocus, although the detailed mechanisms are currently unclear(Wallman and Winawer, 2004). Thus, the link between education and myopia would not be explained by the excessive need for accommodation, but rather by the hyperopic defocus induced by accommodative lag when large amounts of near work are performed.

Despite uncertainties about the mechanisms, the experimental evidence is strong - fitting negative lenses over eyes leads to hyperopic defocus, and even when the animal can clear the defocus by accommodating, leads to increased axial elongation. This probably reflects a mechanism for clearing neonatal hyperopia. In contrast, fitting a positive lens over eyes leads to myopic defocus, and decreased eye growth(Schmid and Wildsoet, 1996). The impact of imposed myopic defocus is much more powerful than that of imposed hyperopic defocus, and quite brief periods of imposed myopic defocus can over-rule much longer exposures to hyperopic defocus(Wildsoet and Wallman,

1995, Wallman et al., 1995), which may be of critical importance for myopia prevention.

The observation that imposed myopic defocus blocks the development of myopia is, of course, paradoxical, because taken literally, this would mean that myopia should be a self-limiting condition, and myopia should be impossible. Two possible resolutions of this paradox are that the strength of the inhibitory growth signal generated by myopic defocus declines in older children, requiring longer or stronger exposures to produce effective inhibition of growth. Alternatively, it is possible that the defocus-detecting systems habituate to the slowly changing habitual level of defocus in a developing myope, and thus more defocus is required to inhibit eye growth, which does not happen naturally. Tse and To have reported that as the proportion of retinal receiving myopic defocus increased, the degree of myopic eye growth was reduced in chicks, while more work on these possibilities is required(Tse and To, 2011).

1.5.2.4 Time spent outdoors

Very recent work has brought forward a powerful factor that prevents the development of myopia - time spent outdoors(Jones et al., 2007, Rose et al., 2008a). Children who spend a lot of time outside are much less likely to become myopic than those who do not. The effect is robust, since it has now been reported in children of European(Jones et al., 2007, Rose et al., 2008a, Rose et al., 2008b) and Chinese origin(Dirani et al., 2009a, Wu et al., 2010) in several different environments, and powerful, since it is able to reduce markedly the impact of high amounts of near-work(Rose et al., 2008a) and of parental myopia(Jones et al., 2007). The protective effect appears to come from the total time spent outdoors, rather than sporting activities per se(Rose et al., 2008a). The hypothesis that the protective effect was due to the typically higher light intensities

outside during daylight hours, possibly acting via increased release of the retinal transmitter dopamine which is known to be able to inhibit eye growth in some circumstances(Rose et al., 2008a) has now been supported by laboratory studies in which the development of experimental myopia in chickens(Ashby and Schaeffel, 2010) and primates(Smith et al., 2011) is blocked by exposure to bright light.

Results from the Sydney Myopia Study suggest that children who combine high amounts of near-work with little time outdoors are the most at risk of myopia, while those who combine little near-work with lots of time outside are at low risk(Rose et al., 2008a). However, all children who spent higher amounts of time outside were protected from the development of myopia. In the global analysis, time outdoors appeared to be a strong factor, while there was little overall impact of near-work. Recently the idea that near-work is of any importance has been challenged(Mutti and Zadnik, 2009a), but there has to be a factor that mediates the impact of education on the biology of the eye, and near-work, via induced defocus, remains a viable candidate. One possibility, that the effects of education are due to reduction in time spent outdoors seems unlikely, since this would require a clear negative correlation between time outdoors and hours of near-work, whereas the actual correlation is weak(Rose et al., 2008a).

1.6 Interventions on myopia progression

Although various interventions have been evaluated in previous studies, there has been no convincing or widely accepted method of preventing myopia to date. As mentioned above, attempts to manipulate accommodation have not been particularly successful(Saw et al., 2002c, Gwiazda, 2009, Li et al., 2011a). Several studies demonstrated that the rate of myopia progression is lower in children given atropine eye drops, but its wide utilization is restricted by the side effects such as photophobia(Tong et al., 2009, Chua et al., 2006) and possible long term adverse events including light induced retinal damage and cataract formation(Kao et al., 1988). However, recent studies showed that low concentration atropine eye drop might be safe and effective for slowing myopia progression in children, with minimal impact on visual function(Chia et al., 2011, Wu et al., 2011).

More definitive work needs to be carried out in this area. Most of the results published have limited validity. Some of the early intervention trials did not have a control group for comparison. Many clinical trials did not include randomization(Goss and Grosvenor, 1990, Hosaka, 1988), thus allowing for selection bias by the investigators and participants. Furthermore, the treatment groups were not comparable with regard to measured confounding factors. The sample size and length of follow-up were often insufficient(Hosaka, 1988). In addition, large numbers of dropouts were common(Grosvenor et al., 1987), and a difference in myopia progression among subjects lost to follow-up may have led to biased conclusions.

1.7 Study aims

This thesis consists of three parts. PART 1 is a retrospective analysis of the development of the epidemic of myopia. The aims for this part are:

1. Use unaided visual acuity data from a representative sample of school-aged children in Guangzhou over the past 20 years to reveal the secular change of the prevalence of myopia and its severity, interpreting the data in the context of other information, particular the changes in education system on the increasing prevalence of myopia in urban Chinese populations and to use anthropometric data such as height, weight from this population to analyze the relationship between childhood myopia and obesity;
2. Use refractive error data in children and information from parents from Guangzhou Refractive Error Study in Children (RESC) study to assess the relationship between myopia in parents and myopia their children, as well as the effect of other familial demographic factors on childhood myopia;
3. Further treat myopic refractive errors as quantitative variables by using corresponding data from the Guangzhou Twin Study to analyze the correlation of refractive errors between two generations, to determine the extent to which the parental myopia affects on myopia in the next generation;
4. Use the unique set of data, including above studies plus Liwan Eye Study in Guangzhou to reconstruct the pattern of secular change in the prevalence of myopia over the past century, and to explore the cause of the recent explosion of myopia.

PART 2 of this thesis is the Guangzhou Outdoor Activity Longitudinal (GOAL) Study, which is an on-going large-scale controlled randomized trial on myopia prevention. The purpose of the study is to assess whether outdoor activities are effective in preventing the development and progression of juvenile-onset myopia in Chinese children.

Specifically, this study aims:

1. To determine if increased engagement in outdoor activities reduces the development and progression of myopia in Chinese school children;
2. To identify the risk factors associated with the development and progression of juvenile-onset myopia;
3. To characterize the interaction between refractive error and education.

PART 3 of this thesis is a preliminary exploration of the mechanisms of myopia development. This part examines the annual changes in refraction and ocular components around the onset of myopia in Chinese children.

CHAPTER 3 focuses on the prevalence of myopia and visual acuity in Guangzhou over the past 20 years.

1.1 Introduction

The prevalence of myopia in up to 9% of the population is now well documented with around 10% of children developing myopia by school entry in most, and as much as 30% of those highly myopic (Waid, 2017; Fong et al., 2004; Leung et al., 2004). The prevalence of myopia is expected to rise further post-2020 – 1.2% for 15-year-olds

in a scenario where near display use is high (Waid et al., 2017). In Guangzhou, previous (Ho et al., 1997) studies have shown a prevalence of 10% in Guangzhou (15% for 15-year-olds).

PART 1

SECULAR CHANGE IN

MYOPIA/VISUAL ACUITY IN

GUANGZHOU

generations, using a novel design (Waid et al., 2017). In this study, we investigate the secular change in myopia across the generations, and a declining risk associated with parental myopia in addition, population-based survey of children in Guangzhou, China. In a recent study (Waid et al., 2017), we found that the prevalence of myopia in Guangzhou has increased from 10% in 1997 to 15% in 2017. In the parent cohort of myopia, a decrease in the age of onset and an increase in the prevalence of high myopia. Similar trends are seen in Hong Kong (Ho and Lam, 1994; Lam et al., 1994), Japan (Miyamoto and Hara, 1999) and Singapore (Tong et al., 1992; Au-Yang et al., 1993a; Waid et al., 2017). Collectively, these data demonstrate that the prevalence of myopia has increased substantially in East Asia over the past few decades. The spread of myopia is now a major public health concern, which may change more rapidly than other genetic diseases (Khan, 2005).

CHAPTER 2 Increase in the prevalence of reduced visual acuity in Guangzhou over the past 20 years

2.1 Introduction

The prevalence of myopia in cities in East Asia is now very high in children, with around 80% of students completing secondary school now myopic, and as much as 20% of them highly myopic(Wu et al., 2001, He et al., 2004, Lin et al., 2004). The prevalence of myopia is somewhat lower in more rural areas – 38.8% for 15 year-olds in a semi-rural area near Beijing, 53.9% for 17-year-olds in a rural area in Guangdong province(He et al., 2007) and even lower in Yongchuan District in Chongqing (27.1% for 15-year-olds)(Pi et al., 2010).

The prevalence of myopia in East Asia was lower in the past. Wu and Edwards(Wu and Edwards, 1999) reported the prevalence of myopia in China and Hong Kong over three generations, using noncycloplegic autorefraction for the children and questionnaire data for the parents and grand-parents. There was a progressive increase in the prevalence of myopia across the generations, and a declining risk associated with parental myopia. In addition, population-based surveys of children from Taiwan using cycloplegic autorefraction(Lin et al., 2004, Shih et al., 2009) demonstrated three trends – an increase in the prevalence of myopia, a decrease in the age of onset, and an increasing prevalence of high myopia. Similar trends are seen in Hong Kong(Goh and Lam, 1994, Lam et al., 1994), Japan(Matsumura and Hirai, 1999) and Singapore(Tay et al., 1992, Au Eong et al., 1993b, Wu et al., 2001). Collectively, these data demonstrate that the prevalence of myopia has increased substantially in East Asia over the past few decades. The speed of change suggests a role for environmental exposures, which can change more rapidly than gene pools(Morgan and Rose, 2005).

Most of this data was derived from cross-sectional studies. The only longitudinal data-set based on cycloplegic refractions that covers a significant period comes from Taiwan(Lin et al., 2004). Using a series of cross-sectional studies, it demonstrates a marked increase in the prevalence and severity of myopia over the past 20 years, with a tendency towards earlier onset of myopia and a markedly increasing prevalence of high myopia by the end of schooling. These studies also demonstrated marked differences in the prevalence of myopia between urban and rural areas.

Unfortunately, longitudinal data based on cycloplegic autorefractions is rarely available. When such data is not available, it has been suggested that an increasing prevalence of bilateral low visual acuity (VA) in school-aged children, combined with normal near VA and increasing with age, could be used as an indicator of the prevalence of myopia(Peckham et al., 1977a), and in fact the earliest evidence of an increasing prevalence of myopia from Singapore was based on VA measurements(Au Eong et al., 1993a, Au Eong et al., 1993b, Tay et al., 1992). The use of VA measurements as an index of the prevalence of myopia has been validated on cohorts of children with both VA and cycloplegic refractions from Singapore(Tong et al., 2002) and Sydney(Leone et al., 2009). In this chapter, we document the changes in unaided VA in school children in Guangzhou over the past 20 years, interpreting the data in the context of other information on the increasing prevalence of myopia in urban Chinese populations in East Asia.

2.2 Methods

2.2.1 Study population

The Guangzhou Students' Health Care Institute (GSHCI) of the Guangzhou Department of Education has performed annual medical health check-ups, including visual acuity measurements, for students in a large sample of public schools in Guangzhou city for almost 20 years. Before 1997, examinations were conducted in 4 districts of Guangzhou (Dongshan District, Yuexiu District, Haizhu District, Liwan District) with 5 primary schools and 5 secondary schools, which integrate junior high school and senior high school, in each district. From 1997 on, another 13 primary schools and 14 secondary schools in another 5 districts (Tianhe District, Baiyun District, Huangpu District, Fangcun District and Luogang District) were added.

2.2.2 Examinations

VA examinations were carried out by a clinical team from GSHCI comprising 5-6 experienced nurses and general practitioners, applying a uniform protocol.

Examinations were conducted in temporary stations set up in each school, generally during the weekdays while classes were in session.

Unaided VA was measured with a retro-illuminated logarithm of the minimum angle of resolution (LogMAR) chart, with tumbling-E optotypes (Precision Vision, La Salle, IL). Illumination of the examination rooms was controlled to around 500 Lux. The right eye was tested first, then the left eye, each time occluding the fellow eye. The child was asked to indicate the direction of the E optotype either by pointing with his/her hand or by calling the direction, and the child was observed closely to detect squinting to produce a pinhole effect while reading the optotypes. Measurements began at a distance

of 5 meters with the fourth line from the bottom (1.0). The orientation of each optotype had to be identified within 5 seconds. If the orientation of at least six of the eight optotypes was correctly identified, the child was then tested by dropping down to the next line. If three or less optotypes were missed, the testing continued to the line below and finally to the line at the bottom. If the child did not recognize the orientation of at least six of the eight optotypes, the line immediately above the failed line was tested, until successful detection of orientation was achieved. The lowest line read successfully was assigned as the VA for the eye undergoing testing. If the top line at 5 meters was unable to be read, the child was advanced to 2.5 or 1 meter with progression down the chart as described above. Presenting VA and best-corrected VA were not measured. I was given access to the de-identified data through Professor Mingguang He at the Department of Preventive Ophthalmology at Zhongshan Ophthalmic Center, Guangzhou.

Vision categories were defined using the unaided VA measurements. Normal VA was defined as VA equal to or better than 6/6. Mildly reduced VA was defined as VA better than 6/9 and worse than 6/6; moderately reduced as VA equal to or worse than 6/9 and better than 6/18, and severely reduced VA was defined as equal to or worse than 6/18. These categories should not be confused with World Health Organization(1993) or the United States definitions of visual impairment(Congdon et al., 2004). Our category of moderately and severely reduced unaided VA includes the WHO categories of moderate and severe visual impairment and blindness, but is broader. Our categories of mildly and moderately reduced VA would not be regarded as visual impairment under the WHO definitions.

2.3 Results

The total number of schools and students examined is shown in Table 2.1. The increase in schools enrolled in 1997 led to a natural increase in the number of students examined. In the schools examined, the number of students enrolled in Grade 1 decreased from 2,268 in 1988 to 1,768 in 1996. After the increase in numbers of schools examined, enrolments went from 4,207 in 1997 to 5,067 in 2007. There was some increase in enrolments in Grade 12 from 1988 to 1996, and after the 1997 increase in number of schools enrolled, there was a continuing increase in the number of students enrolled in Grade 12, particularly from 2004 on. In 2007, the last year for which data were available, the Grade 1 sample covered almost 5% of the total Grade 1 enrolment in primary schools in Guangzhou, while the Grade 12 sample encompassed almost 15% of the enrolment at that level. The significant increase in percentage of students enrolled in Grade 12 would have contributed to the increase in student numbers at this level.

There was also a consistent trend in the gender ratio in Grade 12. In 1988, 53.5% students staying to the end of senior high schools were boys, significantly more than girls. This figure decreased to 48.3% in 2007, with the switchover in 1999. The shift from a predominance of boys to a predominance of girls is seen in the overall enrolment data through all grades (data not shown).

Year	Number of primary Schools	Secondary School No.	Grade 1 Students No.	Grade 12 Students No.	% of Males	% of Females
1988	20	20	2268	4110	53.45	46.55
1989	20	20	1560	2806	58.41	41.59
1990	20	20	1754	5042	54.56	45.35
1991	20	20	1664	4481	55.39	44.61
1992	20	20	1877	5118	54.04	45.96
1993	20	20	2061	2511	57.54	42.45
1994	20	20	1701	5028	56.86	43.14
1995	20	20	1607	4492	55.72	44.28
1996	20	20	1768	4710	56.32	43.67
1997	34	33	4207	2455	52.05	47.95
1998	34	33	4467	4918	50.63	49.37
1999	34	33	6141	5983	49.12	50.81
2000	34	33	6356	5163	48.05	51.95
2001	34	33	4167	9200	47.15	52.85
2002	34	33	4237	7328	46.98	53.02
2003	34	33	4805	8877	44.98	55.02
2004	34	33	4655	10258	46.34	53.66
2005	34	33	5223	10496	46.28	53.72
2006	34	33	5010	12928	48.35	51.65
2007*	34	33	5067	15458	48.25	51.75

*: Total enrolment number in Guangzhou city was 119,184 for Grade 1, 141,982 for Grade 12 in 2007
(Data derived from Guangzhou Yearbook, 2007)

Table 2.1 Enrolment Number and Gender Ratio in examined schools, 1988-2007

The percentage of students with normal VA for each Grade for 3 selected years (1988, 1998 and 2007) is shown in Figure 2.1. The proportion of students with normal VA decreased with increasing school grade. In 1988, the proportion of students with unaided normal VA decreased from 85.1%(95% CI, 83.5%-86.5%) in primary school Grade 1 to 76.4%(95% CI, 74.4%-78.3%) in the last year of primary school, then dropped to 52.4%(95% CI, 51.2%-53.7%) in the first year of junior high school (Grade 7) and further declined to 33.4%(95% CI, 32.0%-34.97%) in Grade 12 (school leavers). Similar patterns were seen in 1998 and 2007, but there was a clear trend for the percentage of students with normal VA to drop over that period at both the Grade 1 (1988, 85.1 %(95% CI, 83.5%-86.5%); 1998, 78.4%(95%CI, 77.2%-79.6%); 2007, 62.2%(95% CI, 60.9%-63.5%)) and Grade 12 (1988, 33.4%(95% CI, 32.0%-34.9%); 1998, 15.2%(95% CI, 14.2%-16.2%); 2007, 13.2%(95% CI, 12.7%-13.85%); (Chi squared test for tendency $P < 0.0001$ at both grade levels)).

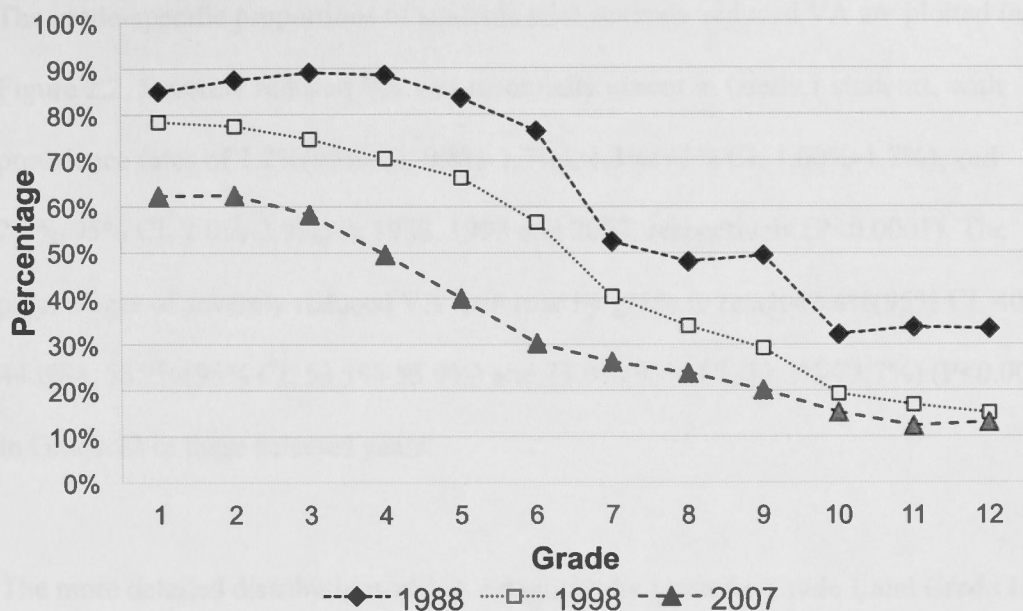


Figure 2.1 Percentage of students with normal vision by school grade

The grade-specific proportions of students with severely reduced VA are plotted in Figure 2.2. Severely reduced VA was essentially absent in Grade 1 students, with prevalence rates of 1.2%(95% CI, 0.8%-1.7%), 1.3%(95% CI, 1.00%-1.7%), and 2.5%(95% CI, 2.0%-2.9%) in 1988, 1998 and 2007, respectively ($P<0.0001$). The percentages of severely reduced VA then rose by grade to reach 42.4%(95% CI, 40.9%-44.0%), 58.2%(95% CI, 53.1%-55.9%) and 73.0%(95% CI, 72.3%-73.7%) ($P<0.0001$) in Grade 12 in these selected years.

The more detailed distributions of VA categories by years for Grade 1 and Grade 12 are shown in Figures 2.3 and 2.4. A very simple pattern is seen in the data from young students (Figure 2.3), where the population had predominantly normal VA for all years, but with a decline in more recent cohorts. There was little severely reduced VA in any year, but the percentages of mildly reduced VA increased from 8.7%(95% CI, 7.6%-10.0%) in 1988 to 22.4%(95% CI, 21.7%-23.6%) in 2007, with an increase in the proportion of moderately reduced VA over the same period. A very different pattern was seen in the Grade 12 (Figure 2.4). At this level, the proportion of severely reduced VA was relatively high at 42.4%(95% CI, 40.9%-44.0%) in 1988, then increased steadily to 58.2%(95% CI, 56.8%-59.6%) in 1998, reaching a maximum just above 70%(95% CI, 72.3%-73.7%) in 2007. Severely reduced unaided VA was the predominant state of Grade 12 students from around 1996. In contrast to the situation in Grade 1, there was some decrease in the proportion of mildly reduced VA over the 20-year period. From 2003 on, there was little change in prevalence. Girls consistently showed lower proportions of normal VA and higher proportions of moderately and severely reduced VA than boys ($P<0.05$ for each year).

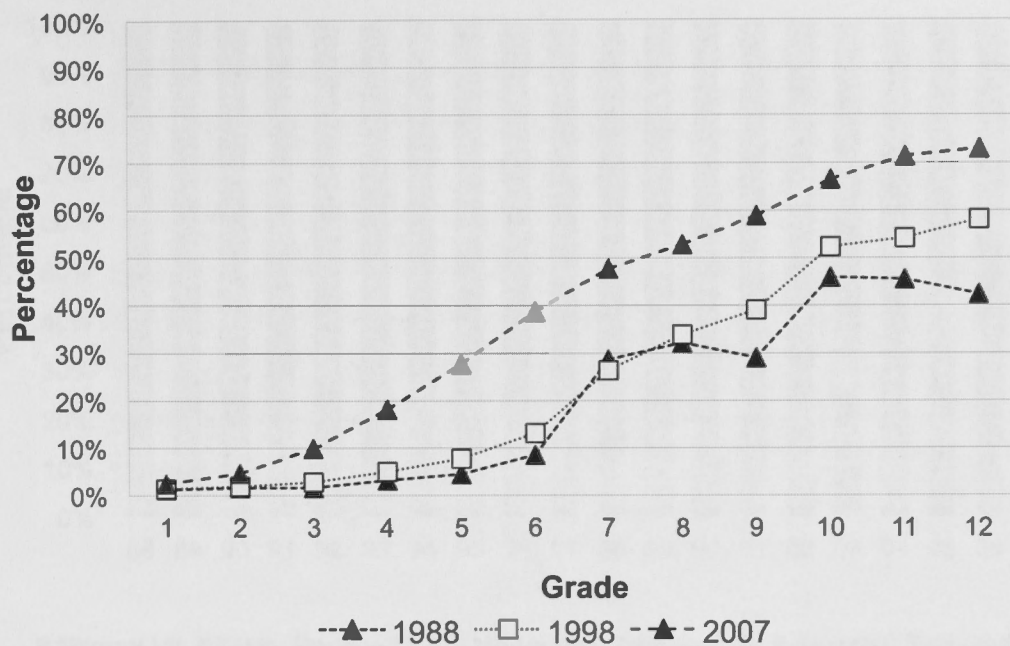


Figure 2.2 Percentage of students with severely reduced VA by school grade

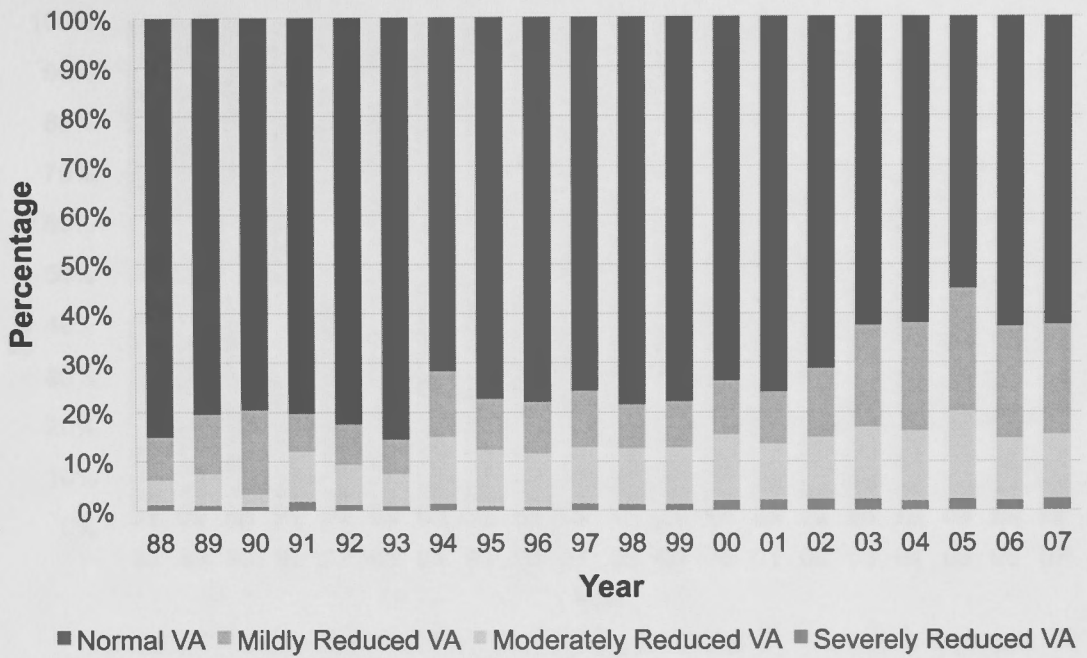


Figure 2.3 Visual Acuity Categories in Grade 1

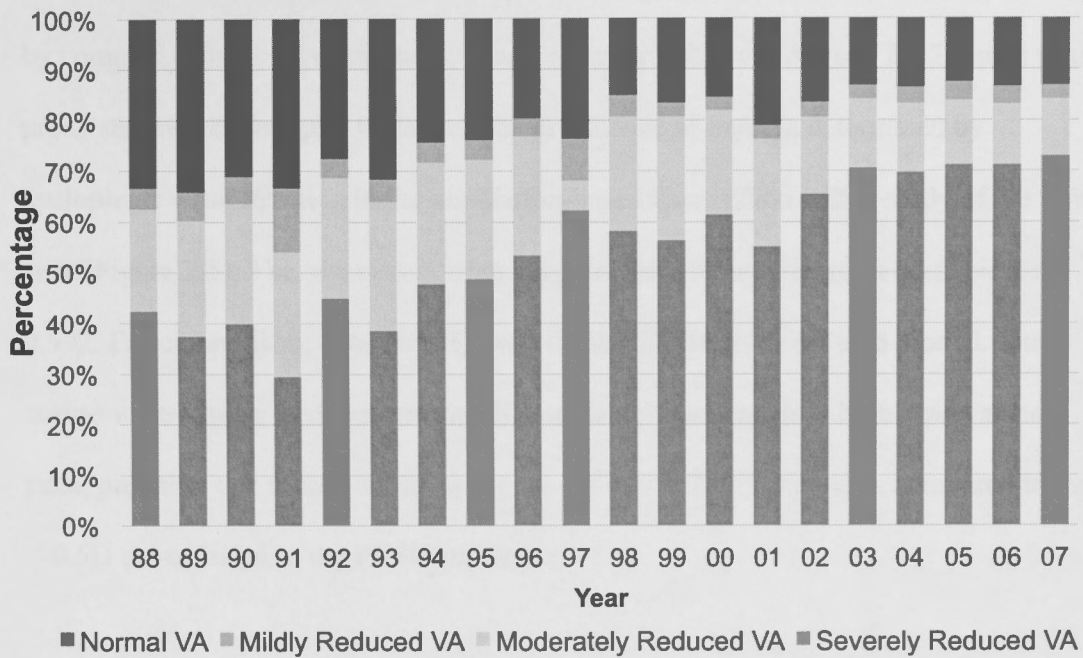


Figure 2.4 Visual Acuity Categories in Grade 12

How well the VA acuity data corresponded to the prevalence of myopia was assessed by comparing the level of moderately and severely reduced VA from 2002 (taken as the proxy measure of myopia) to data on the prevalence of myopia determined by cycloplegic autorefraction in the population-based Guangzhou RESC study of the same year (Figure 2.5). The two curves were very similar with a correlation coefficient of 0.992. For comparison, data from Taiwan for the 2000 survey are also plotted. The curves were similar in slope, but the Taiwan data showed slightly higher prevalence rates, probably due to the less stringent cut-off of $<-0.25\text{D}$ for myopia compared to the $\leq -0.5\text{D}$ cut-off used in the RESC studies.

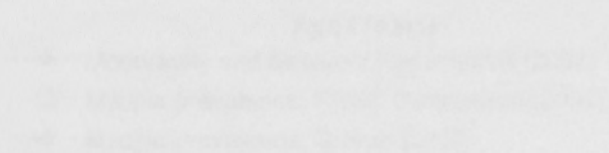


Figure 2.5 Comparison of VA data from the Guangzhou RESC study and Taiwan data. The Guangzhou RESC data are shown as a solid line and the Taiwan data as a dashed line. The correlation coefficient for the Guangzhou RESC data is 0.992.

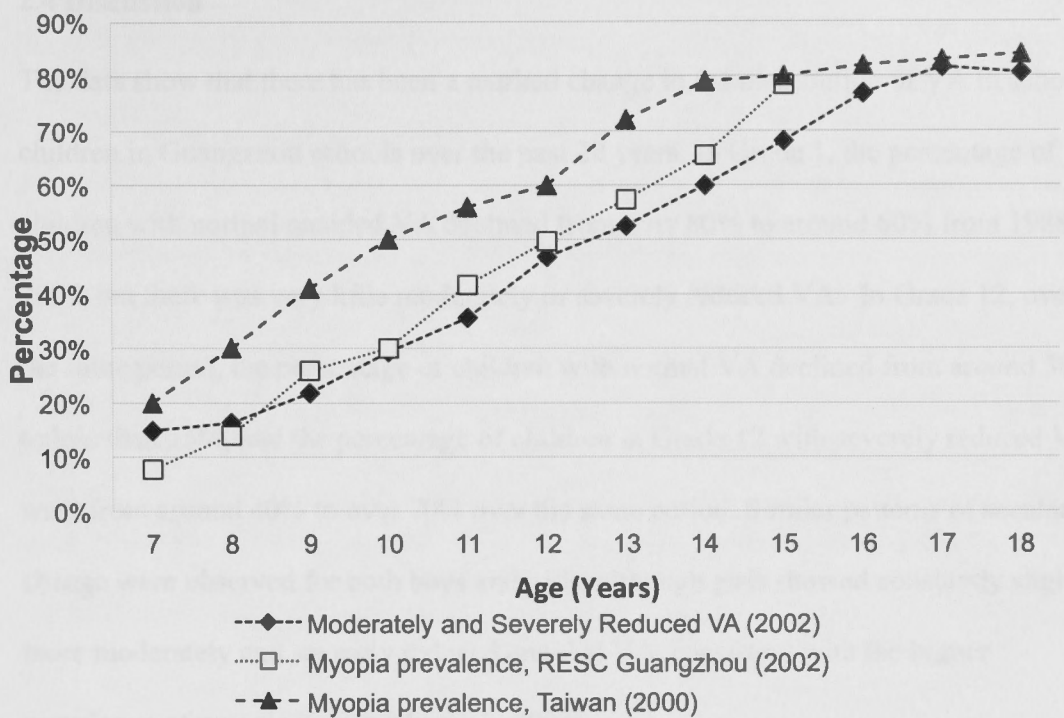


Figure 2.5 Comparison of the prevalence predicted from moderately and severely reduced VA for 2002 with myopia prevalence from other studies

2.4 Discussion

The data show that there has been a marked change in the distribution of VA in school children in Guangzhou schools over the past 20 years. In Grade 1, the percentage of children with normal unaided VA declined from over 80% to around 60% from 1988 to 2007, but there was very little moderately or severely reduced VA. In Grade 12, over the same period, the percentage of children with normal VA declined from around 30% to less than 15%, and the percentage of children in Grade 12 with severely reduced VA went from around 40% to over 70% over the same period. Similar patterns of secular change were observed for both boys and girls, although girls showed constantly slightly more moderately and severely reduced unaided VA, consistent with the higher prevalence of myopia in girls(He et al., 2004).

On the basis of the high correlation between the VA measurements from Guangzhou and the population-based data on the prevalence of myopia from the Guangzhou RESC study(He et al., 2004), and the validation of reduced VA as a predictor for myopia in the Singapore SCORM and Sydney Myopia studies(Tong et al., 2002, Leone et al., 2009), we suggest that the changes in VA over this 20 year period are largely due to an increasing prevalence of myopia. The characteristics of earlier onset, greater severity at the end of school, and current stabilization have previously been described in Taiwan for myopia(Lin et al., 2004).

The data analyzed in this chapter were derived from a series of annual large-scale, cross-sectional, school-based screening studies of children enrolled in Grade 1 through to Grade 12 in primary, junior high and senior high schools in Guangzhou. Participation in the school health survey in Guangzhou was compulsory, so participation was high. The schools were selected to give a representative sample of school students, although

strict statistical randomization was not applied. School-based samples can give population-representative results when enrolment rates are high, as they have been in Guangzhou over this period, although rare disorders which could lead to exclusion from mainstream schooling might be missed. However, myopia, which is a very common condition in Guangzhou should be quite reliably estimated.

The high enrolment rates in Grade 1 from 1988, and Grade 7 from 1998 rule out major selection bias (Table 2.2). The increased retention rate in senior high school to Grade 12 may mean that the Grade 12 students in the earlier years were more highly selected for high educational achievement, and hence that the population prevalence of myopia might be overestimated in those earlier years. Gender is also a possible confounder, given the increase in the percentage of female students completing high school, but the gender differences are slight. Because the data compare large representative samples of students, comparison between years provides a valid estimate of secular changes, although it should be noted that the use of de-identified data from a series of cross-sectional studies means that we cannot follow changes in individual students.

The pattern seen in the enrolment data of increasing retention to Grade 12, and a shift towards a predominance of girls can be seen in the educational enrolment data of most advanced western countries(http://stats.uis.unesco.org/unesco/ReportFolders/ReportFolders.aspx?IF_ActivePath=P,50&IF_Language=eng). The over 95% retention rate to the end of Grade 12 in 2007 in Guangzhou schools is high by international standards, and surpasses that seen in countries like the United States, the United Kingdom, Canada, Australia and many western European countries, although overall school retention rates to Grade 12 in China as a whole are somewhat lower.

Enrolment rates	Primary school Grade 1	Junior High school Grade 1	Senior High school Grade 1
1988*	99.12%	92.36%	71.63%
1998*	99.99%	99.92%	89.89%
2007*	99.99%	99.99%	95.32%

* Data derived from Guangzhou Yearbook, 1988, 1998, 2007

Table 2.2 Enrolment rates in Guangzhou city

Within one year, the increasing prevalence of reduced VA with grade in the cross-sectional data is probably due to an effect of years of education, since a secular increase in the prevalence of myopia, or other causes of reduced VA, would, on their own, lead to a cross-sectional decline in prevalence with age. A rise in the prevalence of myopia with age and years of schooling has been reported in many studies, but the RESC data from Nepal illustrate that the rise in the prevalence of myopia with age is not inevitable(Pokharel et al., 2000), as does recent data on the low prevalence of myopia in Laos (Casson, personal communication). The lack of increase in myopia with age in these studies in comparison to major effect observed in Guangzhou is likely to be associated with the low educational standards and low schooling intensity in both Nepal and Laos, where less than 50% of children attend secondary school, compared to the high completion rate for secondary schools in Guangzhou. The difference is unlikely to be due to ethnic differences, since children of South Asian origin, who comprise the predominant ethnic group in Nepal, become much more myopic if they grow up in Singapore and Malaysia(Saw et al., 2006), while children from Laos are part of the East Asian genetic cluster.

The comparison of children at the same age and level of schooling, over different years, provides clear evidence of a secular increase in reduced unaided VA over the period from 1988 to 2007. This picture is reinforced by the more detailed evidence of an increasing prevalence of moderately and severely reduced VA, seen most clearly in the Grade 12 data. The fact that the prevalence of moderately and severely reduced unaided VA has not changed since 2003 suggests that situation has stabilized, but at a very high level of reduced VA. The high prevalence of severely reduced unaided VA emphasizes the need for correction of these refractive errors, where they are refractive in origin. Previous studies in Guangzhou suggest that around 90% of reduced unaided VA in

school-aged children is refractive in origin(He et al., 2004). In Guangzhou, around one third of children requiring correction do not have glasses, and around one third of those who do are significantly undercorrected. In rural areas, as much as two thirds of the children needing correction do not have glasses(He et al., 2009b, Zhao et al., 2000, He et al., 2004, Li et al., 2008).

At the Grade 1 level, there was little increase in the prevalence of severely reduced VA, but the prevalence of moderately and mildly reduced VA increased until 2003, after which it stabilized. This may reflect increasing early educational pressures, with parents, particularly in major cities, attaching great importance to an early start to education for their children, imposing higher study loads and reducing the amount of time their children spend outside, which is known to promote the development of myopia(Rose et al., 2008a, Jones et al., 2007, Rose et al., 2008b, Dirani et al., 2009b). The early onset of myopia in Taiwan(Lin et al., 2004), Singapore(Saw et al., 2002d) and Hong Kong(Fan et al., 2004) may reflect similar changes in the patterns of activity of children. In Guangzhou, most children have one or two years of formal, learning-oriented preschool prior to starting school at the age of 5 years, and from the early years of primary school have around 2 hours of homework each day, with additional work to complete on weekends.

The idea that the reductions in unaided VA are primarily due to the development of myopia is supported by several papers from the RESC series, which have shown that reduced VA in children is primarily due to refractive error, and predominantly myopia(He et al., 2004, He et al., 2007, Zhao et al., 2000, Goh et al., 2005, Pokharel et al., 2000, Dandona et al., 2002, Maul et al., 2000, Murthy et al., 2002, Naidoo et al., 2003). The impact of hyperopia on visual acuity is limited, because of the high

accommodative powers of children, and astigmatism only appears to significantly reduce VA for cylinder powers of more than 1 to 1.5 D (Leone et al., 2009). This level of astigmatism is relatively rare, and the prevalence of astigmatism does not appear to increase markedly with age during childhood (Huynh et al., 2007, Huynh et al., 2006). The prevalence of other conditions causing reduced unaided VA (e.g. retinal disorders, cataract, glaucoma) is low in young children (Robaei et al., 2005), and would not be expected to contribute to the prevalence of unaided VA to a significant extent. In fact, the Singapore SCORM study found that 0.28 or worse unaided LogMAR VA was a good predictor of myopia ≤ -0.5 D in children, with a sensitivity and specificity of 72% and 98 % respectively (Tong et al., 2002), in a sample with a high prevalence of myopia, and little hyperopia. The Sydney Myopia Study reported that unaided VA of less than 45 LogMAR letters ($<6/9.5$) had a higher sensitivity and specificity for the prediction of myopia of ≤ -1 D with high sensitivity (97%) and specificity (97%) (Leone et al., 2009) in a population-based sample from which non-refractive causes of reduced VA had been excluded. These analyses suggest that, where data on cycloplegic refractions are not available, measurements of unaided VA may give a picture of changes in the prevalence of myopia, which will enable interpretation of existing databases on visual acuity. It should be noted that the changes in the prevalence of moderately and severely reduced VA in Guangzhou show very similar features to those seen in Taiwan for myopia measured by cycloplegic refraction, with an increasingly early onset and a high prevalence in the later school years, and stabilisation over the past few years (Lin et al., 1999, Lin et al., 2001, Lin et al., 2004, Lin et al., 1988, Holden et al., 1988). The strong correlation between the prevalence of reduced VA and myopia means that in countries where the prevalence of myopia is low or has not been systematically studied, monitoring VA may provide a simple and cost-effective means of detecting the emergence of an epidemic of myopia in those countries as they develop economically.

The increasing prevalence of reduced VA and probably myopia in Guangzhou are probably largely due to environmental changes in Guangzhou. However, it is possible that a change in the genetic background of the children in Guangzhou, such as the selective migration of myopic parents to a city at the forefront of economic development in China, who might pass their myopia to their children, has contributed to the increase, particularly since the Guangzhou population rose from 3,490,927 in 1988 to 6,367,621 in 2007(Guangzhou Yearbook, 1988 and 2007). However, the relative risk of myopia in the children associated with parental myopia in Guangzhou is quite low at only 1.3, and most children in Guangzhou become myopic irrespective of the refractive status of their parents (see CHAPTER 3). We therefore conclude that the most plausible explanation of the secular changes in VA is the changing visual environment of children in Guangzhou.

The environmental factors involved have not been precisely identified. Guangzhou has undergone dramatic changes over the past 60 years, in terms of social, economic and educational development. Changes in education are a prime candidate, given the association between education achievement and myopia(Morgan and Rose, 2005). The oldest cohort in our data was born around 1970, and therefore was not enrolled in the school system until the formal end of the Cultural Revolution in 1976. After the reintroduction of uniform national university entry examinations (Gao Kao) in 1977, the Chinese government instituted a nine-year compulsory education policy in 1986, and, in 1999, institutions of higher learning began to enroll many more students, and the admission rate for those taking the university entrance examinations nationwide increased from 30% to nearly 50%. Consequently, more students may have stayed in

senior high schools, with aspirations for tertiary education, as appears to be reflected in the retention rates to Grade 12 and the increasing enrolment numbers seen in Table 2.2.

Other factors have also changed over the period in which this data was collected. The degree of urbanization has increased in Guangzhou, with an increase in population density from 776 persons per square kilometer in 1988 to 1351 in 2007 (data from Guangzhou Yearbook 1988 and 2007), probably reflecting a move towards living in larger blocks of apartments. Higher myopia associated with apartment dwelling has been reported in the Sydney Myopia Study (Ip et al., 2008b). In Singapore, the prevalence of myopia is higher in children who live in larger apartments, possibly due to higher parental education, occupation and income. Access to, and use of outdoor spaces for children to play also be important, given the substantial protective effect from the development of myopia of greater time spent outdoors (Rose et al., 2008b, Rose et al., 2008a, Dirani et al., 2009b, Jones et al., 2007). Unfortunately, there are few, if any collections of data on time spent outdoors, and it is not clear how it could be evaluated retrospectively. Other factors, such as nutrition and diet have almost certainly changed over the last 20 years as well, but are difficult to document retrospectively. Estimating the role of the complexity of factors involved in the emergence of high prevalence rates for reduced VA and myopia therefore will probably require well-designed studies to be carried out in countries that are currently in the process of transition from low to high prevalence rates for myopia.

In summary, this chapter has provided detailed evidence on the reductions in unaided VA that have occurred in school children from Guangzhou over the past 20 years. The level of reduction increases with years of schooling completed, and in the past few years has reached a plateau, but at a very high level of reduction of VA. This poses a challenge to provide accurate correction for all children as they progress through schooling. This reduction appears to parallel the emergence of myopia in school children, and thus simple monitoring of VA appears to provide a simple and probably cost-effective means of surveillance that could be used throughout the region.

CHAPTER 3 The impact of parental myopia and other familial factors on childhood myopia in Guangzhou

3.1 Introduction

There has been a long-standing debate over the role of nature (genetic variation) and nurture (environmental variation) in the aetiology of myopia, which began with early observations of the link between myopia, education and occupation(Curtin, 1985, Mutti et al., 1996, Saw et al., 1996, Morgan and Rose, 2005). One consideration is that myopia often shows strong familial clustering, in terms of the correlations between myopia in parents and their off-spring, and between siblings(Sorsby et al., 1966, Keller, 1973, Hegmann et al., 1974, Ashton, 1985, Lee et al., 2001, Klein et al., 2005, Wojciechowski et al., 2005, Fotouhi et al., 2007).

It is often claimed that familial clustering suggests a substantial genetic contribution to the determination of refractive error, and particularly myopia, but this evidence is clearly ambiguous because families share environments as well as genes. As discussed by Guggenheim et al.(Guggenheim et al., 2000) and Morgan and Rose(Morgan and Rose, 2005), sibling correlations tend to remain high, even when there have been rapid changes in the prevalence of myopia(Young et al., 1969, Alsbirk, 1979), although data from the Framingham Offspring Eye Study(1996a) have shown that greater difference in age between the siblings significantly reduces the correlation. Guggenheim et al.(Guggenheim et al., 2007) found that, in the Singapore SCORM study, the correlations between siblings in measures of environmental risk factors (e.g., using computer, reading, watching TV, playing video game, outdoor activity etc.) were often slightly higher than in myopia itself, emphasising the potential for environmental explanations. In contrast to the stability of sibling correlations, when the prevalence of

myopia has changed rapidly, which is generally associated with major changes in the social environment from one generation to the next, parent-offspring correlations are reduced, sometimes to trivial levels, consistent with strong environmental effects(Nakajima, 1968a, Nakajima, 1968c, Young et al., 1969, Young and Leary, 1972, Keller, 1973, Hegmann et al., 1974, Alsbirk, 1979, Johnson et al., 1979, Guggenheim et al., 2000, Morgan and Rose, 2005).

Another way of looking at the relationship between myopia in parents and their children is to see if there is increased risk of the development of myopia in children whose parents are myopic. Several studies have shown that this is the case(Gwiazda J, 1993, Pacella et al., 1999, Mutti et al., 2002, Saw et al., 2001a, Ip et al., 2007c). This issue has been examined in a unique study of myopia over three generations in Hong Kong and China(Wu and Edwards, 1999), which documented an increasing prevalence of myopia over the three generations, with a decline in the odds ratio for risk associated with parental myopia through the generations. We have now examined this issue using data from the Guangzhou Refractive Error Study in Children (Guangzhou RESC) where the parental refractive statuses were collected by questionnaire.

3.2 Method

3.2.1 Study population

The Guangzhou RESC survey carried out in 2002 used the standard RESC protocol, with randomized cluster sampling to provide a representative, population-based sample of children combined with high examination participation rates and the use of cycloplegic refraction to determine spherical equivalent refraction (SER)(Negrel et al., 2000, He et al., 2004). In brief, 5330 children aged 5-15 years living in Liwan District, Guangzhou were enumerated (based on the Guangzhou 2000 Census) using cluster sampling followed by door-to-door verification. 4364 children were examined, 86.4% of those enumerated. Informed consent for each child examined was obtained from a parent or other responsible adult. The research followed the tenets of the Declaration of Helsinki. The ethics committees of both the Zhongshan Ophthalmic Center and the Liwan District Bureau of Education and Bureau of Health approved the implementation of the study.

3.2.2 Examinations

Cycloplegia was induced with two drops of 1% cyclopentolate administered 5 minutes apart to each eye, with a third drop administered after 20 minutes. Cycloplegia was considered complete if the pupil dilated to 6mm or greater, and a light reflex was absent after a further 15 minutes. Refractions were measured using a streak retinoscope (Welch-Allyn, Skaneateles, NY) and a handheld auto-refractor (ARK-30; Nidek Corp.) after cycloplegia. For this paper, only auto-refraction data from right eyes with complete cycloplegia were analysed. Myopia was defined as a spherical equivalent refractive error of at least -0.50 D.

3.2.3 Questionnaires and validation test

After enumeration to identify eligible children, for children attending schools, the project ophthalmologist visited the schools three days before the eye examinations to distribute parent questionnaires, which were completed by the parents and returned before the examination. For children not yet enrolled in school, parent questionnaires were completed by the parents in temporary community examination stations. The investigators were available to answer queries. The questionnaires investigated children's near work activities, living habits, parental refractive status and family socio-economic background. In general, questions were posed with multiple-choice answers. However, parental occupation was posed as an open-ended question.

Parental refractive status was determined with a question for each parent: "Is the child's father (or mother) myopic?" (YES/NO/NOT SURE). A validation test was conducted to examine whether this simple question is valid to examine parents' refractive status.

Father/mother's education level was based on the highest level of schooling achieved in categories of no formal schooling, primary, junior high, senior high and university. Because of the low numbers in the less educated categories, education levels were grouped as primary or less, secondary and tertiary for analysis.

Family monthly income categories were less than or equal to 2,000 RMB, 2,000 RMB to 5,000 RMB, 5,000 to 10,000 RMB, and more than 10,000 RMB, then grouped as less than or equal to 2,000RMB and more than 2,000 RMB for analysis, because of very low numbers in the higher income groups. Average family monthly income was 2,100RMB in Guangzhou in 2002 (Guangzhou Yearbook 2002).

From responses to an open-ended question, parental occupations were classified into three categories: Category A: Unemployed/Home duties/Farming; Category B: Blue collar/ Physical labour/ Manual worker; Category C: White collar/ Administrative worker/Officer/ Professional.

3.2.4 Statistical analysis

After being reviewed for accuracy and completeness, clinical examination forms and questionnaires were transferred to Zhongshan Ophthalmic Center for data entry and cleaning. Measurement data ranges, frequency distributions, and consistency among related measurements were checked with data cleaning programs. The Chi-square test was used to compare proportions (prevalence) between different groups. Given the large sample size, ANOVA was used to compare the mean SER across different groups. Relative risk (RR) was calculated for each factor relative to the condition without the risk factor, as the prevalence with the factor divided by the prevalence without that factor. In addition, to give a common basis for comparison of the risks associated with the factors examined, relative risk was calculated relative to the sample mean (RR_{mean}). The associations between myopia and child's age, gender, parental myopic status, parental education level, income and occupation were explored by univariate and multivariate logistic regressions. Statistical analyses were performed with SPSS, 16.0 (SPSS Inc., Chicago, IL). All statistical tests were two-sided, and $P < 0.05$ was considered statistically significant.

3.3 Results

3.3.1 Validation test for questionnaire

In order to examine whether the simple question (Is the child's father (or) mother myopic?) is valid to estimate parents' refractive status, a sample of 98 consecutive subjects drawn from the parents of children participating for the first time in the Guangzhou Twin Study (n=49) and who visited the Zhongshan Ophthalmic Center Optometry Clinic (n=49) during the validation period, were asked to answer the same question, before undergoing non-cycloplegic auto-refraction. In The response to the question and the results of non-cycloplegic refraction are shown in Table 3.1. The question yielded both high sensitivity (0.77) and specificity (0.84) for the detection of myopia, with a positive predictive value of 0.98 and a negative predictive value of 0.79, and a kappa coefficient for overall agreement between questionnaire and auto-refraction data of 0.77 (95%CI, 0.64, 0.90).

Are you myopic?	Non-cycloplegic refraction (right eye)		Total
	Myopia($\leq -0.5D$)	Non-myopia	
Yes	44	1	45
No	9	34	43
I don't know	4	6	10
Total	57	41	98

After excluding the uncertain responses, the validation gave a sensitivity of 0.83 and a specificity of 0.79, with a positive predictive value (0.98) and negative predictive value (0.79). The kappa coefficient for detecting myopia was 0.77 (95%CI, 0.64-0.90).

Table 3.1 Participants’ responses to the validity question, categorized by non-cycloplegic refraction

3.3.2 Parental characteristics

From a total of 4364 children with cycloplegic refractions, the parents of 3618 (82.9%) children responded to the parental myopia question. The children without information on parental myopia were not significantly different to the children analysed in terms of age (10.6 ± 2.9 years vs. 10.7 ± 12.3 years, $p > 0.05$), gender (boys: 51.5% vs. 52.3%, $p > 0.05$) or refractive error (-2.5 ± 1.9 D vs. -2.4 ± 1.7 D, $p > 0.05$).

A detailed break-down of parental myopia is shown in Table 3.2. Overall, just under 20% of the parents were identified as myopic, with a slightly higher prevalence of myopia in mothers than in fathers. Less than 2% of the sample was unsure of the answer to this question, and these parents and their children were excluded from this analysis. The prevalence of myopia in the parents (19.8%, 95%CI, 19.2%-20.3%) was considerably less than that measured in the total sample of children (38.1%, 95% CI, 36.5%-39.7%) or the prevalence in children aged 15 years (78.4%, 95% CI, 73.9%-82.6%).

	Parents ^a			Children ^b		
	Fathers	Mothers	Total	Boys	Girls	15-year-olds
Myopia	17.1%	22.4%	19.8%	30.3%	37.0%	78.4%
No myopia	81.0%	76.0%	78.5%	69.7%	63.0%	21.6%
Not sure	1.9%	1.6%	1.7%			

a Parents' myopia was determined by questionnaire
b Children's myopia was determined by cycloplegic autorefraction

Table 3.2 Prevalence of myopia in parents

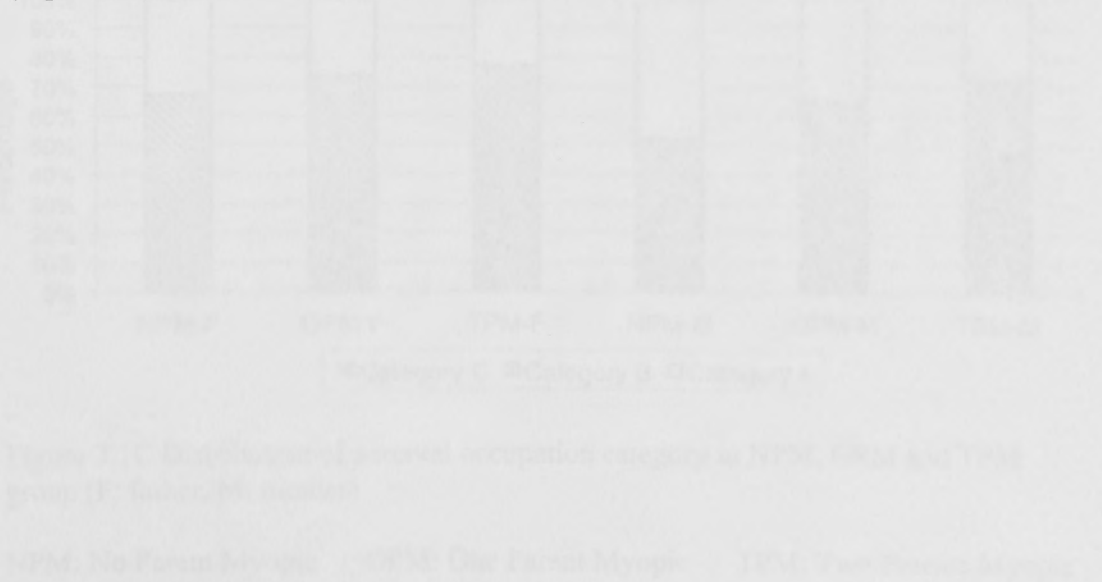
Preliminary analysis of individual parental characteristics showed, as expected, that myopic parents were more likely to have post-secondary education (27.6% in myopic parents vs. 8.4% in non-myopic parents), to work in white collar and professional occupations (38.4% in myopic parents vs. 21.8% in non-myopic parents), and to be members of families with higher incomes (54.2% in myopic parents vs. 37.1% in non-myopic parents). Children were classified into three family categories – no parent myopic (NPM) – 66.2% (2395), one parent myopic (OPM) – 28.1% (1016), and two parents myopic (TPM) – 5.7% (207). Compared to what would be expected from random mating, - no myopic parents of 64.3%, and two myopic parents of 3.0% - there was a slight excess of no myopic parents and two myopic parents, suggesting that there was only very slight assortative mating.

Families defined on the basis of parental myopia were then analysed in terms of the highest parental education level (Figure 3.1A). In NPM families, the highest parental educational level was overwhelmingly secondary or less (89.9%), while in TPM families, just under 50% of the parents were in this education category, while just over 50% had some level of tertiary education. Families categorised by myopic parents also differed in income (Figure 3.1B). More than 60% of NPM families were lower income families, whereas in TPM families, only around 40% fell into the lower income category. Parental occupation categories in NPM, OPM and TPM groups are shown in Figure 3.1C. As can be seen, from the NPM to TPM families, there was a decrease from 32.7% to 22.7% in the percentage of fathers who were unemployed, engaged in home duties, or worked in farming and an increase from 22.2% to 47.5% in the percentage of those with white collar and professional occupations. A similar picture was seen for mothers' occupation categories, with slightly more mothers than fathers falling into Category A occupations in all three groups. Distributions between families were

significantly different for each characteristic (Chi-squared test, $p<0.001$). Thus, analysis in terms of parental myopia is potentially confounded by parental education, income and occupation.

The age range of the children examined in this study was 5 to 15, a span of 10 years. Parental ages were not collected in this study, but assuming an average age at child-birth age of 25 in Guangzhou, the parents of children would have been born from 1962 to 1972. All groups of parents were predominantly not myopic, but the proportion of parents myopic nearly doubled from 17.2% for the parents of 15 year-old children, born in 1987 to 32.1% for the parents of the 5 year-old children born in 1997 ($P<0.001$) (Figure 3.2).

A similar, but somewhat larger change was also seen in the data on highest parental education levels. The proportion of parents with no formal education or primary schooling only was very small for all age groups (less than 10%), but an increasing proportion of the parents had completed tertiary education, from just above 10% for the parents of the 15 year-olds to around 30% in parents of the 5 year-olds ($P<0.001$) (Figure 3.3).



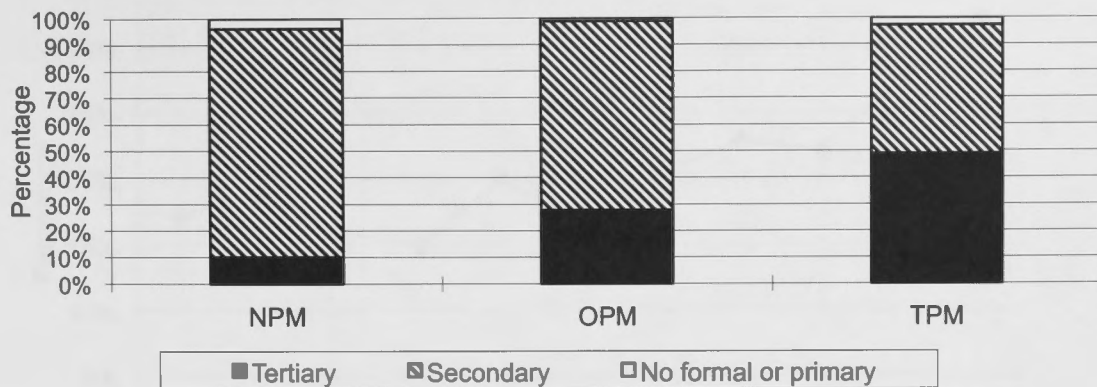


Figure 3.1A Distribution of parental highest education level in NPM, OPM and TPM group

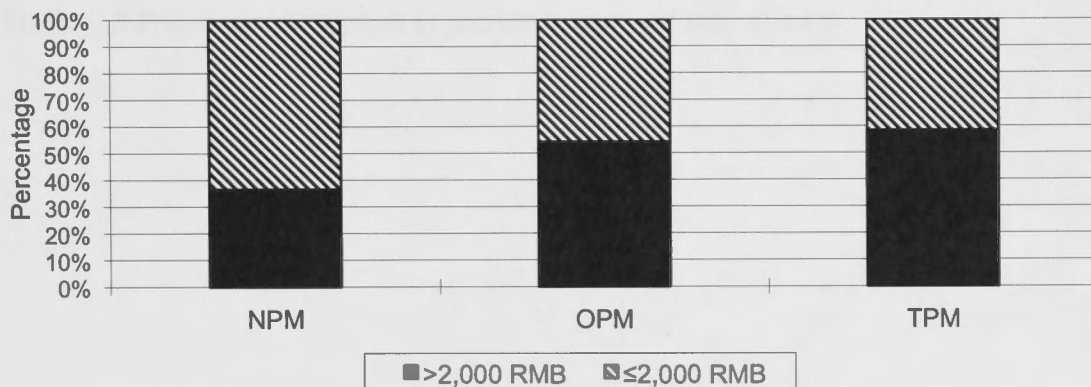


Figure 3.1B Distribution of family monthly income in NPM, OPM and TPM groups

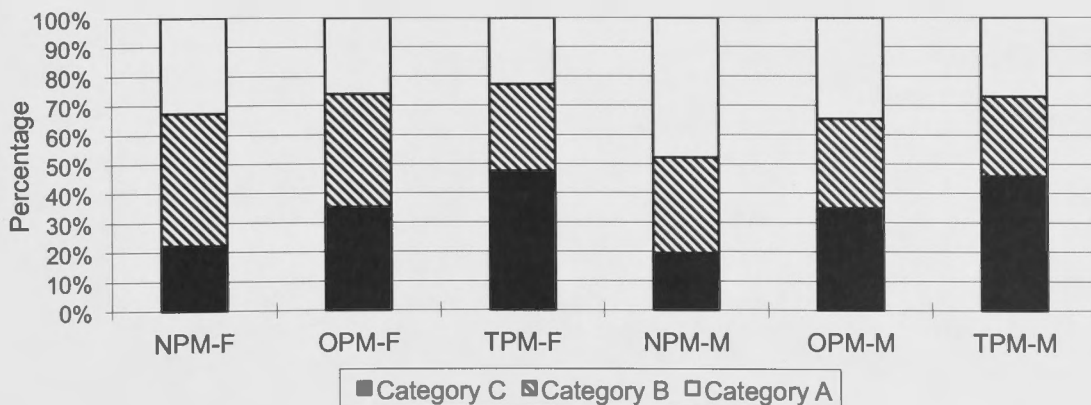


Figure 3.1C Distribution of parental occupation category in NPM, OPM and TPM group (F: father, M: mother)

NPM: No Parent Myopic OPM: One Parent Myopic TPM: Two Parents Myopic

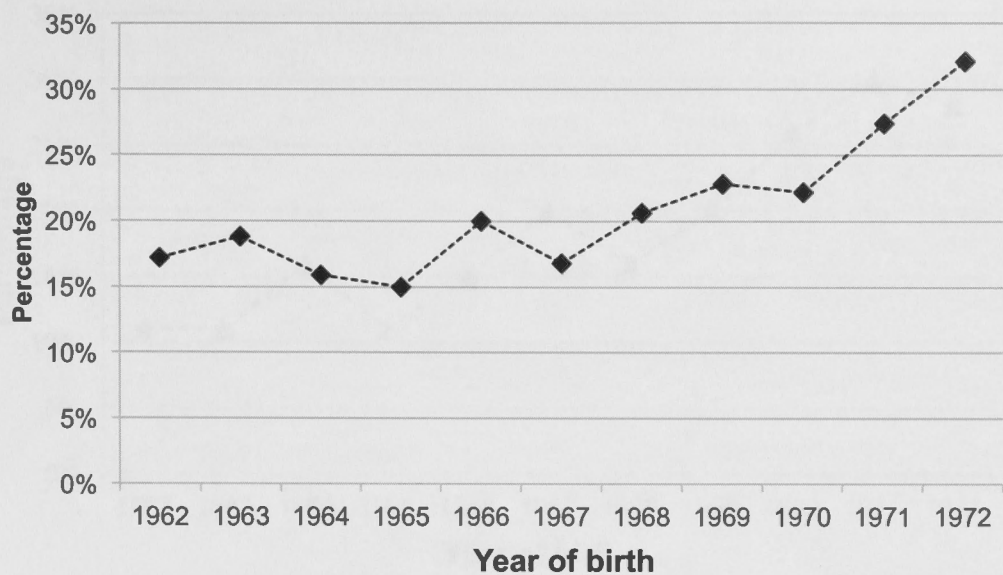


Figure 3.2 Prevalence of myopia in parents in terms of year of birth

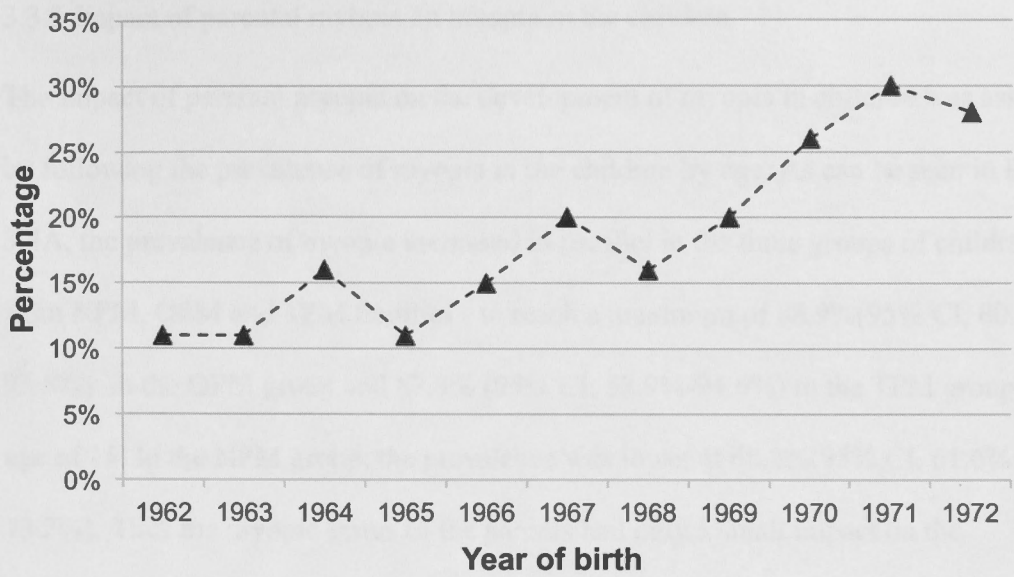


Figure 3.3 Percentage of parents with tertiary education in terms of year of birth

3.3.3 Impact of parental myopia on myopia in the children

The impact of parental myopia on the development of myopia in children was assessed by following the prevalence of myopia in the children by age. As can be seen in Figure 3.4A, the prevalence of myopia increased in parallel in the three groups of children – from NPM, OPM and TPM families - to reach a maximum of 88.9%(95% CI, 80.4%-93.8%) in the OPM group and 83.3% (95% CI, 58.9%-94.6%) in the TPM group at the age of 15. In the NPM group, the prevalence was lower at 68.2%(95% CI, 61.6%-73.7%). Thus the myopic status of the parents had only a small impact on the development of myopia in the children, with the relative risk (RR) of myopia compared to the NPM at the age of 15 for the OPM group of 1.30, and for the TPM group 1.21, and the relative risk compared to the population mean (RR_{mean}) for the OPM group of 1.13, and for the TPM group 1.06. The age-related increase in the prevalence of myopia by age 15 in all groups was much greater than the difference made by parental myopia.

The impact of parental myopia can also be seen in mean SER (Figure 3.4B). The mean SER first became myopic at the age of 9 in the TPM group, between 10 and 11 in the OPM group, and between 12 and 13 in the NPM group, and by the age of 15, the mean SER values for the OPM and TPM groups were close to -3D, compared to close to -1.5D in the NPM group.

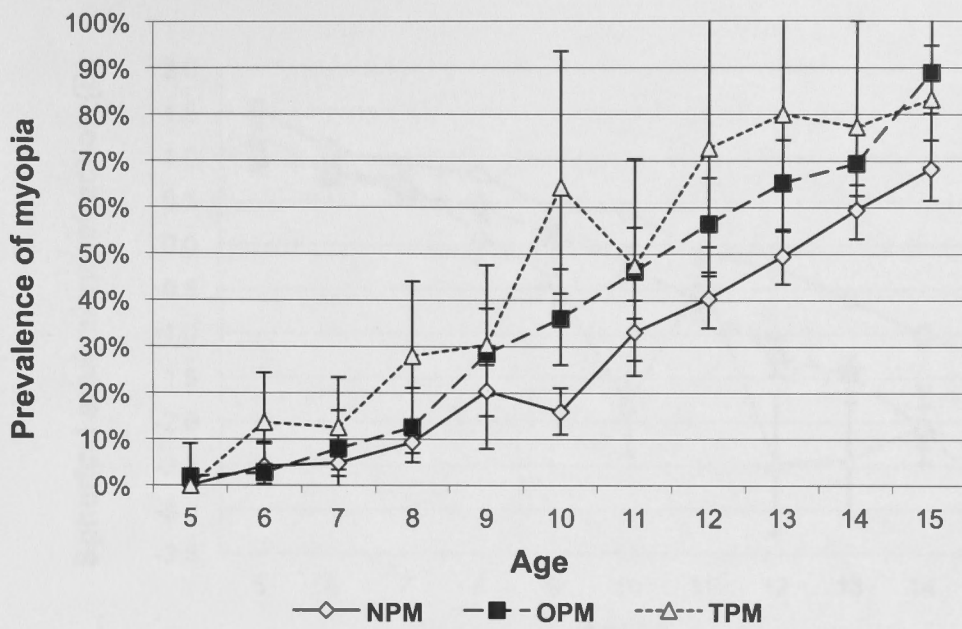


Figure 3.4A Prevalence of myopia in children in NPM, OPM and TPM groups (Error bars represent 95% confident intervals)

NPM: No Parent Myopic OPM: One Parent Myopic TPM: Two Parents Myopic

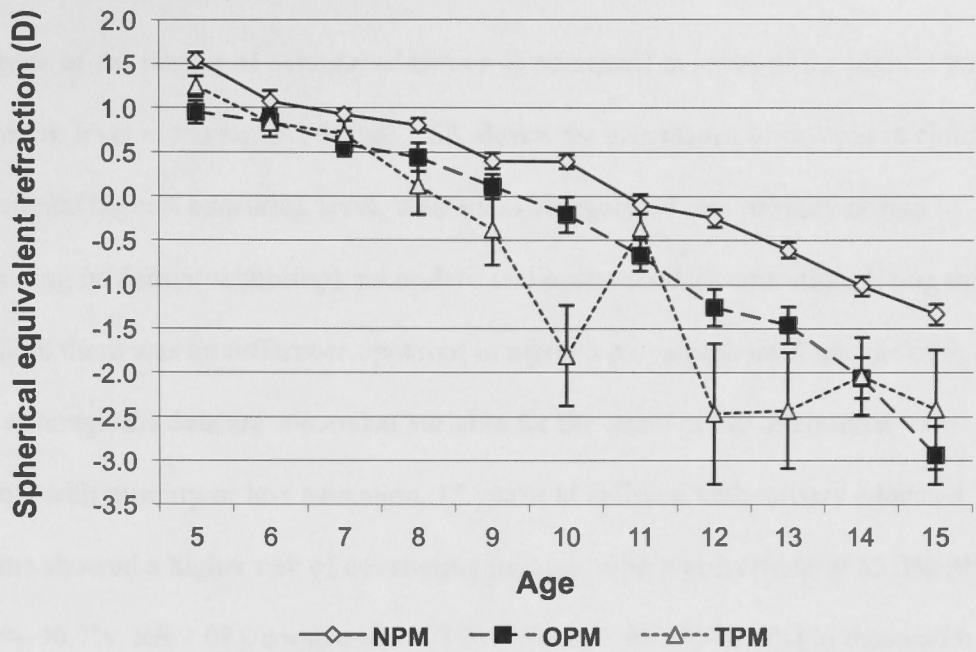


Figure 3.4B Refractive errors in children in NPM, OPM and TPM groups
(Error bars represent standard errors)

NPM: No Parent Myopic OPM: One Parent Myopic TPM: Two Parents Myopic

3.3.4 Impact of parental education level

Analysis of the impact of parental education is presented in terms of the highest parental education level in the family. Figure 3.5A shows the prevalence of myopia in children by parental highest education level, which was categorized into primary or less (including no formal schooling), secondary and postsecondary education. Using this division, there was no difference apparent in myopia prevalence until the age of 9. After this, although the data are somewhat variable for the small group of children with parents with primary or less education, 15 year-old children with tertiary educated parents showed a higher risk of developing myopia, with a prevalence of 85.3% (95%CI, 77.3%-90.7%, RR 1.08), compared to 73.3% (95%CI, 66.2%-79.6%) in those with secondary-educated parents (RR 0.93), and 60.0% (95%CI, 46.4%-71.9%, RR 0.73) in those with parents with only primary school education. Analyses were also carried out for father's or mother's highest education level with essentially similar results.

Figure 3.5B illustrates the refractive error of children in these groups in terms of highest parental education level. In younger children, the increase in SER with age was similar in all groups, but after the age of 9-10 years, the gaps between groups became greater, with mean SER generally more myopic in the children of parents with secondary and tertiary education. The mean SER of children with tertiary educated parents became myopic at the age of 9 and reached nearly -2.5D at the age of 15, while the children of less educated parents progressed more slowly towards myopia.

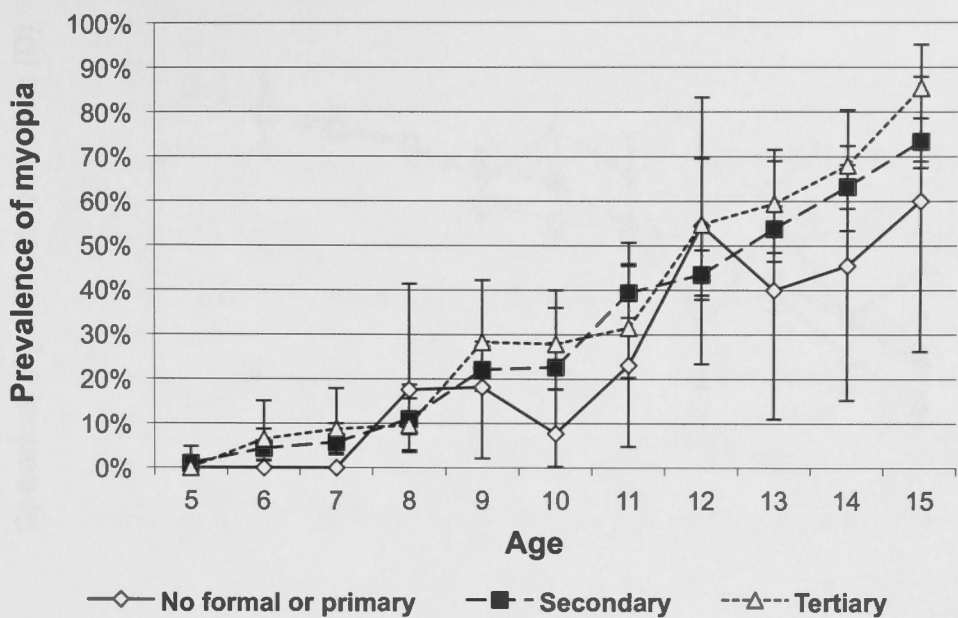


Figure 3.5A Prevalence of myopia in children by parental education levels
(Error bars represent 95% confident intervals)

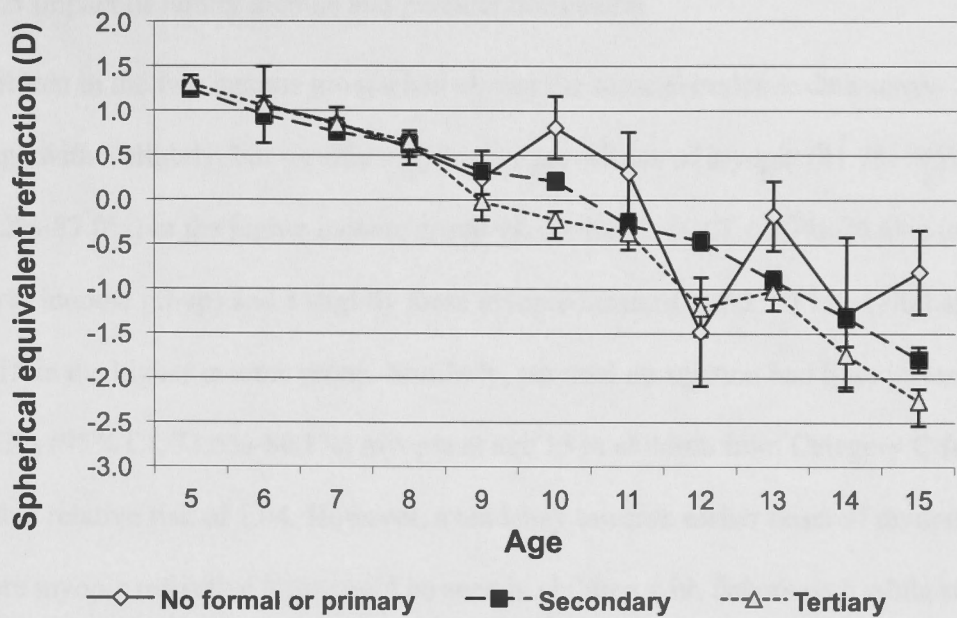


Figure 3.5B Refractive errors in children by parental education levels
(Error bars represent standard errors)

3.3.5 Impact of family income and parental occupation

Children in the two income groups had almost the same prevalence data across the age range with a slightly, but significantly higher prevalence of myopia (81.7% (95% CI, 75.2%-87.0%) in the higher income group vs. 69.9% (95% CI, 62.7%-76.6%) in the lower income group) and a slightly more myopic mean SER (-2.2D vs. -1.6D) at the age of 15 in the higher income group. Similarly, parental occupation had little impact with 81.3% (95% CI, 73.5%-88.1%) myopia at age 15 in children from Category C families, with a relative risk of 1.04. However, a tendency towards earlier onset of myopia and more myopic refractive error could be seen in children with fathers with white collar and professional occupations.

3.3.6 Logistic regression analysis

Table 3.3 shows the results of univariate and multivariate logistic regression. In univariate logistic regression, childhood myopia was associated with age, female gender, number of myopic parents, and secondary educated parents. In multivariate logistic regression, age, gender, number of myopic parents was significantly associated with myopia in the children. Parental education, family income and fathers' occupation were not significant in the final model.

In order to further assess the relative importance of number of myopic parents and highest parental education, two restricted models were used (Table 3.4). In model 1, where female gender, older age and highest parental education were considered as potential factors, highest parental education had the smallest OR and entered the equation at the last step. In model 2 which used the number of myopic parents instead

of highest parental education as one of the covariates, the results were quite similar to the overall model.

	1.27 (1.18-1.37)	<.001	1.42 (1.36-1.49)	<.001
Female	1.27 (1.18-1.37)	<.001	1.42 (1.36-1.49)	<.001
Female ²	1.27 (1.17-1.39)	<.001	1.37 (1.30-1.45)	<.001
Female ³	1.34 (1.13-1.59)	<.001	1.52 (1.37-1.69)	<.001
Nonhighly educated parent ^a	1.34 (1.09-1.60)	<.001	Not in final model	NS
Female ^a × nonhighly educated parent ^a	1.25 (0.79-1.92)	>.05	Not in final model	NS
Female ^a × nonhighly educated parent ^a ²	0.92 (0.56-1.49)	>.05	Not in final model	NS
Female ^a × nonhighly educated parent ^a ³	1.26 (0.78-1.75)	>.05	Not in final model	NS
Female ^a × nonhighly educated parent ^a ⁴	1.21 (0.74-1.77)	>.05	Not in final model	NS

NS = not significant.

NS = not significant.

^aFemale and nonhighly educated parent were entered as dummy variables in the regression model where 1 = female or nonhighly educated parent.

²Quadratic, ³cubic, ⁴quartic polynomial functions were tested.

⁵Quadratic, cubic, and quartic polynomial functions were tested for the interaction term.

⁶Quadratic, cubic, and quartic polynomial functions were tested for the interaction term.

⁷Quadratic, cubic, and quartic polynomial functions were tested for the interaction term.

Table 2.3 Log odds regression model for emotional distress (child self-report)

Potential risk factors	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	P	OR (95% CI)	P
Older age ^a	7.59 (6.43-8.95)	<.001	8.90 (7.40-10.70)	<.001
Female	1.37 (1.19-1.57)	<.001	1.42 (1.20-1.67)	<.001
OPM	1.37 (1.17-1.60)	<.001	1.77 (1.48-2.13)	<.001
TPM	1.54 (1.15-2.06)	0.04	2.53 (1.78-3.60)	<.001
Secondary educated parents ^b	1.54 (1.00-2.36)	0.05	Not in final model	NS
Tertiary educated parents ^b	1.21 (0.77-1.90)	0.41	Not in final model	NS
Family income>2,000 RMB ^c	0.92 (0.56-1.00)	0.24	Not in final model	NS
Father's occupation category B ^d	1.06 (0.90-1.25)	0.50	Not in final model	NS
Father's occupation category C ^d	1.01 (0.84-1.22)	0.91	Not in final model	NS

Abbreviations:

OR: Odds ratio

NS: not significant in multivariate logistic regression model when a stepwise method is used

^a 11-15 year-olds, 7-10 year-olds as reference category

^b Children with no formal or primary educated parents as reference category

^c Children with family income equal or less than 2,000 RMB as reference category

^d Children with Category A father's occupation as reference category

Table 3.3 Logistic regression Model for potential risk factors of children's myopia

Covariates	Overall Model		Split Model 1		Split Model 2	
	OR (95%CI)	P	OR (95% CI)	P	OR (95% CI)	P
Older age	2.12 (1.71-2.62)	<0.001	2.17(1.76-2.67)	<0.001	2.10(1.70-2.59)	<0.001
Female	1.71 (1.39-2.12)*	<0.001	1.70(1.38-2.10)	<0.001	1.73(1.40-2.13)*	<0.001
OPM	2.02 (1.57-2.59)	<0.001			1.96(1.53-2.52)	<0.001
TPM	3.14 (1.69-5.81)	<0.001			3.21(1.74-5.93)	<0.001
Secondary educated parents	Not in the model	NS	1.28(0.68-2.40)*	0.445		
Tertiary educated parents	Not in the model	NS	1.89(0.95-3.76)*	0.072		
-2 Log likelihood	1984		2022		2010	

Older age: 14-15 year-olds
 * Entered in the equation on the last step when stepwise (wald) method used

Table 3.4 Logistic regression model for potential risk factors for children’s myopia in 12-15 year-olds

The associations between parental myopia and education and myopia in the children could potentially be explained in terms of environmental variables - that is different behaviors encouraged by more myopic or better educated parents. As shown in Table 3.5, children from NPM, OPM and TPM families showed significant differences in reported activity patterns. Of the statistically significant effects, children from TPM families reported that they were less likely to read and write for more than 2 hours per day, and were less likely to read or write for more than 2 hours without a break. They were also less likely to watch television for more than an hour a day. Similar results (not shown) were obtained in relation to parental education groups. In multivariate logistic regression that included interactions between near-work (time spend on reading and writing) and parental characteristics (number of myopic parents, highest education level, occupation), the results showed that none of the interactions was significant in the final model.

Activity	Category	NPM	OPM	TPM	P
Read and write per weekday	≤2 hours	68.9%	66.2%	71.8%	0.034
	>2 hours	31.1%	33.8%	28.2%	
Watch TV per weekday	≤1 hours	52.8%	58.9%	66.5%	<0.001
	>1 hours	47.2%	41.1%	34.5%	
Read books per week	≤1 book	61.3%	60.2%	57.0%	0.491
	>1 books	38.9%	39.8%	43.0%	
Read or write more than 2 hours without any break	Never or occasionally	79.4%	77.7%	88.8%	0.001
	Most of time or everyday	20.6%	22.3%	11.2%	
Age can read	≤4 years old	65.9%	67.2%	70.5%	0.341
	>4 years old	34.1%	32.8%	29.5%	

Table 3.5 Near work activities in children in NPM, OPM and TPM groups

3.4 Discussion

A critical question for this analysis is the validity of the questionnaire for determining parents' refractive status. The results of the validation study suggest that the simple question used in the Guangzhou RESC can be used to estimate the prevalence of myopia in adults of parental age, with high sensitivity and specificity. The kappa coefficient showed substantial agreement between the questionnaire responses and non-cycloplegic refractions.

Two factors should be considered in assessing the validity of the questionnaire responses. Firstly, the parents recruited for the validation study were either participating in another refractive error study, or had brought their children to an optometry clinic for assessment, and thus may have been more aware of issues concerning refractive error than the general population. While this raises issues concerning the application of this questionnaire to a naïve sample from the general population, the parents in the Guangzhou RESC study had given informed consent to the participation of their children in a study of refractive error which involved cycloplegia, after information about the significance of myopia, and, thus, were also likely to be better informed than the general population. It should also be noted that the validation was performed based on non-cycloplegic autorefractions for the parents. Since non-cycloplegic refractions over-estimate the prevalence of myopia in adults at least until the age of 50 years(Fotouhi et al., 2010), it is likely that some of the responses reporting no myopia, classified as incorrect in this validation, may actually have been correct. Overall, these results show that the questionnaire responses have substantial validity.

A previous analyses of the use of questionnaires for estimating parental myopia suggested that simple direct questions of this kind we have used were not valid(Walline

et al., 1996). The greater accuracy of the simple question in this study may be due to a high awareness of myopia among Chinese parents in urban areas, and because the parents enrolling their children in an eye study or seeking clinical assessment were more aware about eye problems or myopia. Either way, the use of the questionnaire in the current analysis appears likely to be valid.

Our results show that many children in Guangzhou are likely to become myopic, irrespective of whether their parents are myopic. Nevertheless, children with myopic parents are more likely to become myopic than children without myopic parents, with a relative risk slightly greater than 1.00 (1.2 - 1.3). There was little difference between having one parent myopic and two parents myopic, either in terms of the prevalence of myopia or the mean SER of the children.

Parental education also had significant effects, although they were slightly weaker than those of parental myopia. Parental income and occupation had much weaker associations, and multivariate logistic regression showed that, after inclusion of parental myopia in the models, other parental characteristics did not exert significant effects. The effect of parental myopia could not be explained in terms of higher levels of near-work for children with myopic parents.

These data show that all groups of children, from NPM, OPM and TPM families, become substantially myopic in Guangzhou. In particular, the proportion of children without myopic parents who were myopic by the age of 15 was 68.0%. We suggest that this "baseline" level of myopia is associated with environmental pressures, including increased educational pressures and urbanisation. Having myopic parents increases the risk of myopia over this baseline level by 20-30%.

The impact of parental myopia has often been assumed to be genetic, although it is clear that families share environments as well as genes. As an alternative, it has been suggested that myopic parents, who are generally better educated, create myopigenic environments characterised by higher educational pressures, and perhaps by less time spent outdoors. While we found significant associations between time spent reading or writing and times spent reading or writing without a break and myopic parents, the children with myopic parents spent less time reading or reading without a break - the reverse of the associations between near-work activities and myopia that have generally been reported (Saw et al., 2002a, Mutti et al., 2002, Ip et al., 2008c). This further weakens the case that higher near-work hours are a significant risk factor for myopia (Mutti and Zadnik, 2009b), and suggests that the effect of parental myopia cannot be explained in these terms. Similar results were obtained in relation to parental education.

The Guangzhou RESC study was carried out before time spent outdoors was shown to be negatively associated with myopia (Rose et al., 2008a, Rose et al., 2008b, Jones et al., 2007), and data on this parameter was not collected. Analysis of differences in the amount of time spent outdoors is required, given the strong protective effects of time spent outdoors, before it can plausibly be concluded that the effects of parental myopia are genetic.

The impact of parental myopia on myopia in children has been reported in several studies, and has often been quantified in terms of odds ratios. However, as noted by Wu and Edwards (Wu and Edwards, 1999), relative risk is the important consideration. Odds ratios give a reasonable approximation to relative risk only for low prevalence conditions. For myopia, with generally moderate to high prevalence, odds ratios

systematically overestimate the deviation from a relative risk of 1, sometimes markedly so.

The results of other major studies on the relative risk associated with parental myopia are summarised in Table 3.6. While all the studies support the idea that having myopic parents increases the risk of myopia, there is no consistent relationship between childhood myopia and number of myopic parents.

Table 3.6 Major studies on the relative risk associated with parental myopia

Study	Relative risk
Wong et al. (1987)	1.5
Wong et al. (1990)	1.5
Wong et al. (1991)	1.5
Wong et al. (1992)	1.5
Wong et al. (1993)	1.5
Wong et al. (1994)	1.5
Wong et al. (1995)	1.5
Wong et al. (1996)	1.5
Wong et al. (1997)	1.5
Wong et al. (1998)	1.5
Wong et al. (1999)	1.5
Wong et al. (2000)	1.5
Wong et al. (2001)	1.5
Wong et al. (2002)	1.5
Wong et al. (2003)	1.5
Wong et al. (2004)	1.5
Wong et al. (2005)	1.5
Wong et al. (2006)	1.5
Wong et al. (2007)	1.5
Wong et al. (2008)	1.5
Wong et al. (2009)	1.5
Wong et al. (2010)	1.5
Wong et al. (2011)	1.5
Wong et al. (2012)	1.5
Wong et al. (2013)	1.5
Wong et al. (2014)	1.5
Wong et al. (2015)	1.5
Wong et al. (2016)	1.5
Wong et al. (2017)	1.5
Wong et al. (2018)	1.5
Wong et al. (2019)	1.5
Wong et al. (2020)	1.5
Wong et al. (2021)	1.5
Wong et al. (2022)	1.5
Wong et al. (2023)	1.5
Wong et al. (2024)	1.5
Wong et al. (2025)	1.5

Study	%Myopia Total	%Myopia NPM	%Myopia OPM	%Myopia TPM	Age	%Myopia Parents
Guangzhou RESC ^a	78.4	68.2	88.9	83.3	15	19.2
SCORM –Chinese ^b	n/a	22.5	37.7	51.3	7-9	n/a
SCORM – non-Chinese ^b	n/a	16.9	19.4	36.8	7-9	n/a
Wu and Edwards ^c	59.1	54.5	69.8	69.6	17	20.8
SMS –East Asian ^d	39.5	28.2	48.6	77.3	12	30.9
SMS –European ^d	4.6	3.0	6.0	17.2	12	21.8
Orinda ^e	18.5	6.3	18.2	32.9	14	48.5
Boston ^f	46.6	30.0	30.0	57.0	15	60.0

Abbreviation:

n/a: not available

NPM: No Parent Myopic

OPM: One Parent Myopic

TPM: Two Parents Myopic

RESC: Refractive Error Study in Children

SCORM: Singapore Cohort study Of the Risk factors for Myopia

SMS: Sydney Myopia Study

^a data from this paper

^b data from Saw et al. (2002)(Saw et al., 2002a), children's myopia was defined as cycloplegic refraction $\leq$ -0.5D, parents' myopia was defined by question "whether wearing spectacles or contact lenses for nearsightedness".

^c data from Wu and Edwards (1999)(Wu and Edwards, 1999), children's myopia was defined as non-cycloplegic refraction $\leq$ -1.0D, parents' myopia was defined by a questionnaire asking about their refractive status.

^d data from Ip et al. (2007)(Ip et al., 2007c), children's myopia was defined as cycloplegic refraction $\leq$ -0.5D, parents' myopia was defined by questionnaire asking the age at first use and the purpose of use, and partially validated against spectacle prescriptions(Ip et al., 2007a).

^e data from Mutti et al (2002)(Mutti et al., 2002), children's myopia was defined as cycloplegic refraction $\leq$ -0.75D, parents' myopia was defined by questionnaire asking whether glasses were worn, for what purpose, and at what age they were first prescribed.

^f data from Gwiazda et al. (1993)(Gwiazda J, 1993) and Pacella et al. (1999)(Pacella et al., 1999), children's myopia was defined with non-cycloplegic retinoscopy, parents' myopia was defined by asking about whether they wore glasses, for what purpose, and at what age they began wearing them.

Table 3.6 Major studies on the relative risk associated with parental myopia

Another obvious feature of the data in Table 3.6 is that, where data are available, children of East Asian origin are more myopia than their parents, whereas in populations of European origin, the children were consistently less myopic than their parents. However, it should be noted that the definitions for myopia in children and their parents in these studies were different, since one was based on cycloplegic refraction and the other on questionnaire Allowance needs to be made for the ages at which the children were examined, often prior to the full development of myopia, and it is therefore possible that there will be continuing development of myopia in the children of European origin after the age at which they were studied. But, in the case of both the Orinda(Mutti et al., 2002) and Sydney Myopia Study(Ip et al., 2008a) studies, there would need to be considerable development of myopia throughout the high schools years for the children to develop a similar or higher prevalence of myopia to their parents. Considerable later-onset myopia in populations of European and more broadly Caucasian origin(Hashemi et al., 2004, Cumberland et al., 2007) has been reported, and thus this possibility cannot be dismissed. A simple explanation of the pattern observed is that East Asian populations are more likely to take advantage of increased educational opportunities for cultural reasons, and combine higher engagement in study with less engagement in outdoor activities.

One strength of these analyses is that the sample we used was population-based, with a high participation rate, and with statistical randomization. These characteristics are shared with the Sydney Myopia Study(Ojaimi et al., 2005b). Other studies did not share all these characteristics. Another strength of this study was the measurement of cycloplegic refraction, as was also the case for the Sydney Myopia Study, the Orinda Study and the Singapore study. However the lack of cycloplegia in the other studies may have resulted in overestimation of the prevalence of myopia(Hashemi et al., 2004).

A limitation of this study was the diversity of ages at which myopia was measured in the children, often before the full development of myopia. For this reason, the data have sometimes been analyzed for 11-15 year-old children, or sometimes just for 15 year-olds. Another limitation was that myopia in the parents was self-reported in questionnaire responses, as were other parental characteristics. Another significant limitation was in the collection of data on activity patterns in the children, since data was only collected by questionnaire on near-work factors, not on time spent outdoors. Other factors such as maternal age(Rahi et al., 2011) and birth order(Peckham et al., 1977b, Rudnicka et al., 2008) that have been reported to be associated with myopia have not been considered.

Nevertheless, these results show that many children in Guangzhou become myopic without myopic parents, with an additional risk of myopia in those with myopic parents. This additional risk could not be explained in terms of increased engagement in near work activities by the children with myopic parents. This suggests that additional genetic risk may be involved, although further analysis of the role of time spent outdoors is required.

CHAPTER 4 The impact of severity of parental myopia on childhood myopia

4.1 Introduction

The relative importance of genetic and environment influences on the variation in refractive errors has been examined in a population-based sample of school-aged children in Guangzhou, China (See CHAPTER 3). There was a higher prevalence of myopia and a significant increased risk of myopia in children with myopic parents, with a relative risk of 1.2-1.3, which could not be explained by a myopigenic environment hypothesis involving higher levels of near work performed by the children of myopic parents. Despite the somewhat higher risk of myopia in the children associated with having myopic parents, most children in Guangzhou became myopic, irrespective of whether their parents were myopic, including a majority of those who did not have myopic parents by self-report.

Another way in which genetic influences might manifest themselves is through family similarities in the severity of myopia in parents and children, as appears to be the case in many forms of high myopia(Young, 2009). In the Guangzhou RESC study, all parents who reported myopia were also asked to classify the severity of their myopia into three bands based on their refraction - mild, moderate and high. Here we examine the impact of the self-reported severity of parental myopia on myopia in the children.

4.2 Methods

4.2.1 Study sample and examinations

For details on study population and examination procedures, refer to the previous chapter (CHAPTER 3).

4.2.2 Questionnaires and validation test

Parental refractive status was determined with a question for each parent: “A. Is the child’s father (mother) myopic?” (YES/NO/NOT SURE) and “B. If yes, how severe is the myopia” (Less than 3.0 Dioptres myopia/3.0 Dioptres to 6.0 Dioptres myopia/More than 6.0 Dioptres myopia). Parental myopia severity was categorised into NO (answers NO in A), MILD (answers “YES” in A and “Less than 3.0 Dioptres myopia” in B), MODERATE (answers “YES” in A and “3.0 Dioptres to 6.0 Dioptres myopia” in B), and HIGH (answers “YES” in A and “More than 6.0 Dioptres myopia” in B) myopia. In order to examine the validity of this approach for estimating parents refractive status, 98 subjects derived from the parents of children who were participating for the first time in the Guangzhou Twin Study (n= 49), or parents of children presenting at the optometry clinic of the Zhongshan Ophthalmic Center (n= 49) were asked to fill out the same questionnaire about their refractive status. Then, noncycloplegic refraction was performed to identify the objective refractive status of the parents.

Myopia in the children was determined by cycloplegic autorefraction, as previously described. Myopia was defined as a spherical equivalent refractive error (SER) of at least -0.5D (for details, see CHAPTER 3). In children, myopia severity was also categorised into the same three groups as for their parents (MILD ($\leq -0.5\text{D}$ to $> -3.0\text{D}$), MODERATE ($\leq -3.0\text{D}$ to $> -6.0\text{D}$), and HIGH ($\leq -6.0\text{D}$) myopia).

4.2.3 Statistical analysis

For details on statistical analysis, refer to the previous chapter (CHAPTER 3).

4.2 Results

The validity of the questionnaire on severity of parental myopia assessed by questionnaire was compared to parental refraction determined by non-cycloplegic autorefraction. As shown in Table 4.1, the agreement between questionnaire and refraction was substantial for any myopia (kappa coefficient 0.77), complete for high myopia (kappa coefficient 1.00), and substantial for the moderate (kappa coefficient 0.78), mild (kappa coefficient 0.62) and no myopia (kappa coefficient 0.75) categories (Landis and Koch, 1977).

How severe is the myopia?	Non-cycloplegic refraction (right eye)			No myopia
	HIGH myopia	MODERATE myopia	MILD myopia	
More than 6D myopia	6	0	0	0
3D to 6D myopia	0	11	1	0
Less than 3D myopia	0	3	22	1
No myopia	0	0	10	34
I don't know	0	1	3	6
Total	6	15	36	41

Kappa coefficient for no myopia 0.75 (0.62-0.89); Kappa coefficient for any myopia 0.77 (0.64-0.90); Kappa coefficient for high myopia 1.00 (1.0-1.0); Kappa coefficient for moderate myopia 0.78(0.63-0.93); Kappa coefficient for mild myopia 0.62 (0.45-0.80)

Table 4.1 Responses to validity questionnaire, classified by three categories

In order to minimise the impact of age differences, information on 1567 children 12-15 years was primarily used for this analysis. Because of the relatively low numbers of parents reporting mild, moderate and high myopia, there were few families with combinations of mildly, moderately and highly myopic parents (in total 63 children, 4.0%). For this reason, analysis was restricted to children/families where one parent reported no myopia, while the other parent reported no, mild, moderate or high myopia (1504 children, 96.0%). Given the one-child policy in China, 95% children in our study came from a family with only one child. More than one child from the same family would be very rare, and thus would have little impact on the analysis.

The proportions of children in the four parental myopia severity groups were: No Parent Myopic (NPM), 74.1%; One Parent Mildly Myopic (OPMiM), 16.0%; One Parent Moderately Myopic (OPMoM), 7.8% and One Parent Highly Myopic (OPHM), 2.1%. The children in the four groups were not significantly different in terms of age and gender (the mean age for NPM, OPMiM, OPMoM and OPHM groups were 13.39 ± 1.05 , 13.47 ± 1.09 , 13.47 ± 1.02 , and 13.67 ± 1.05 years, $P=0.85$; the percentages of boys for NPM, OPMiM, OPMoM and OPHM groups were 51.5%, 51.5%, 53.0% and 49.4%, $P=0.93$).

Table 4.2 shows the detailed break-down of myopia categories in the two generations. There was a marked increase in the prevalence of overall myopia and more severe forms of myopia from the parents' to the children's generation. Based on cycloplegic refraction, the prevalence of myopia was 57.7% in children 12-15 years old. Restricting analysis to the 15-year-olds to give a better estimate of the prevalence of myopia as adults, 74.3% of the children were myopic based on cycloplegia refraction. In contrast, in the parents' generation, just 14.2% of fathers and 18.8% of mothers reported myopia,

with slightly more mothers than fathers with mild and moderate myopia, and slightly more fathers with high myopia (Chi-square test for the prevalence of myopia between the two generations, $P<0.001$; for the prevalence of myopia between fathers and mothers, $P=0.11$). The prevalence of high myopia in 15-year-olds was higher than that in the total sample of parents (3.9% vs. 1.4%, $P<0.001$).

	12-15 year-olds *	15 year-olds*	Fathers**	Mothers**	Parents in total
No myopia	42.3%	25.7%	85.8%	81.2%	83.6%
Myopia	57.7%	74.3%	14.2%	18.8%	16.4%
Mild myopia	40.7%	48.2%	8.9%	11.9%	10.4%
Moderate myopia	14.5%	22.4%	3.4%	5.7%	4.6%
High myopia	2.5%	3.9%	1.8%	1.1%	1.4%

* Myopia categories are defined based on cycloplegic refraction.

** Myopia categories based on questionnaire responses

Table 4.2 Myopia categories in children and parents

The impact of parental myopia on children's myopia is shown in Figure 4.1. There was a progressive increase in the prevalence of myopia with increasing severity of myopia in the myopic parent (P for trend <0.001). There was also a progressive increase in the prevalence of high myopia in the children with increasing severity of myopia in the parents. Having one parent highly myopic resulted in an increased relative risk of myopia of 1.53 (81.6% for OPHM vs. 53.5% for NPM, $P<0.001$). For high myopia, children with one parent highly myopic were 11.1-fold more likely to develop high myopia than children without myopic parents (16.1% for OPHM vs. 1.4% for NPM, $P<0.001$).

The impact of the severity of parental myopia on the development of myopia in children can also be seen in mean SER (Figure 4.2). There was a progressive increase in the mean SER with increasing severity of parental myopia (ANOVA $P<0.001$), and the mean SER was more myopic in the children in the OPHM group (-3.05 ± 3.24 D), compared to that in children in NPM group (-0.93 ± 1.80 D, t -test $P<0.001$). The standard deviations were significantly different for the four groups of children Barlett's test, $P<0.001$).

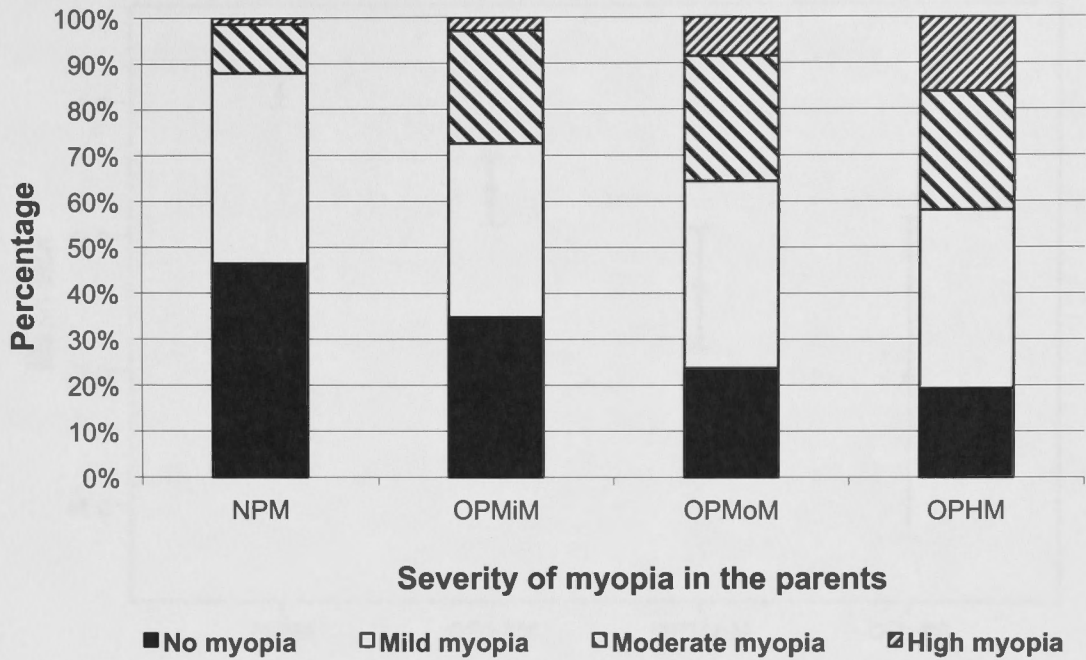


Figure 4.1 Percentage of children in each category of myopia severity (non, mild, moderate, high) by the severity of parental myopia

NPM: No Parent Myopic
 OPMiM: One Parent Mildly Myopic
 OPMoM: One Parent Moderately Myopic
 OPHM: One Parent Highly Myopic

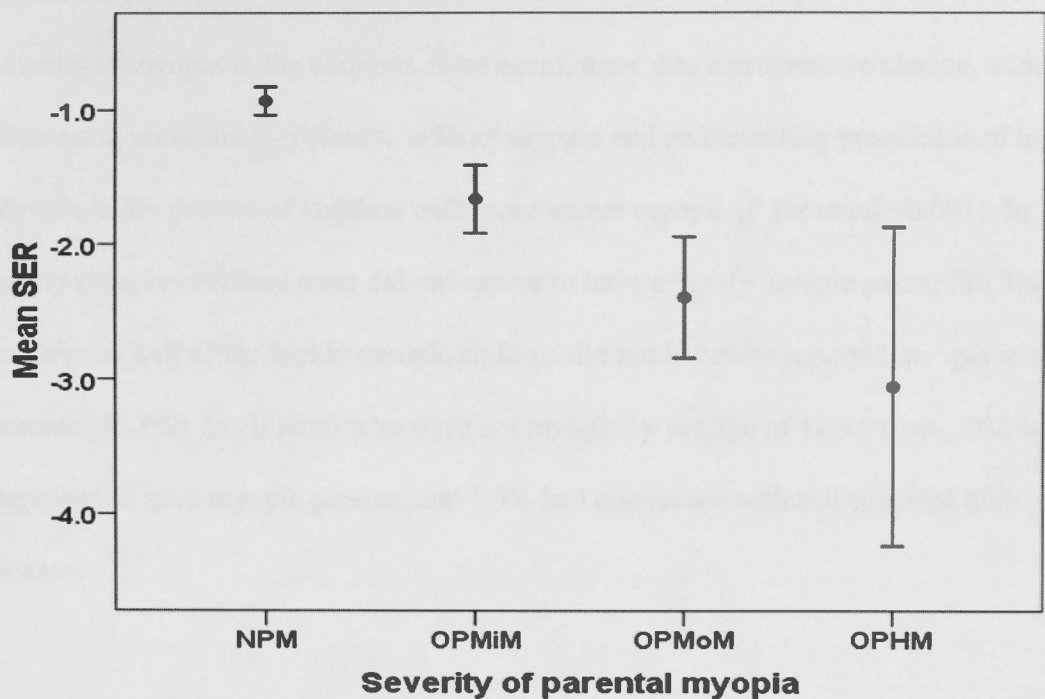


Figure 4.2 Mean and SD of SER in the children in terms of the severity of myopia in the parents

NPM: No Parent Myopic
OPMiM: One Parent Mildly Myopic
OPMoM: One Parent Moderately Myopic
OPHM: One Parent Highly Myopic

Figure 4.3 shows the distribution of the severity of parental myopia in terms of the severity of myopia in the children. Here again, there was a progressive change, with a decreasing prevalence of parents without myopia and an increasing prevalence of high myopia in the parents of children with more severe myopia (P for trend <0.001). In highly myopic children, most did not appear to have a highly myopic parent (86.8%), and almost half of the highly myopic children did not have any reported myopia in their parents (45.3%). In children who were not myopic by the age of 12-15 years, 26.7% appeared to have myopic parents, and 1.5% had one parent with self-reported high myopia.

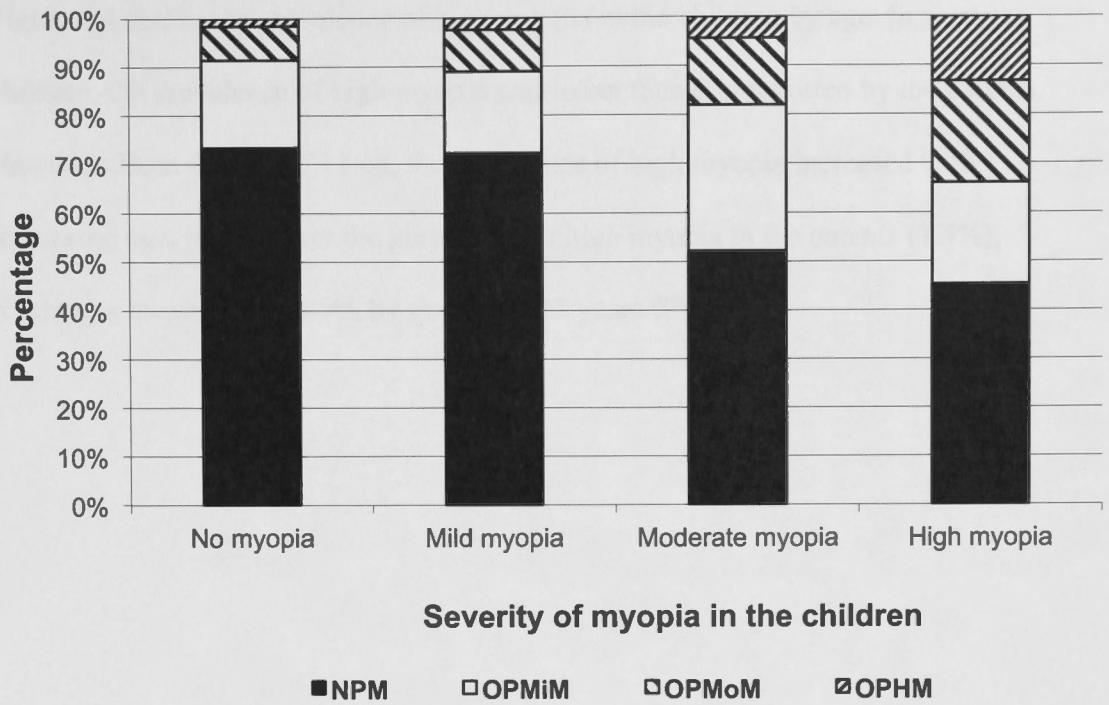


Figure 4.3 Percentage of parents in each category of myopia severity (non, mild, moderate, high) by the severity of myopia in the children

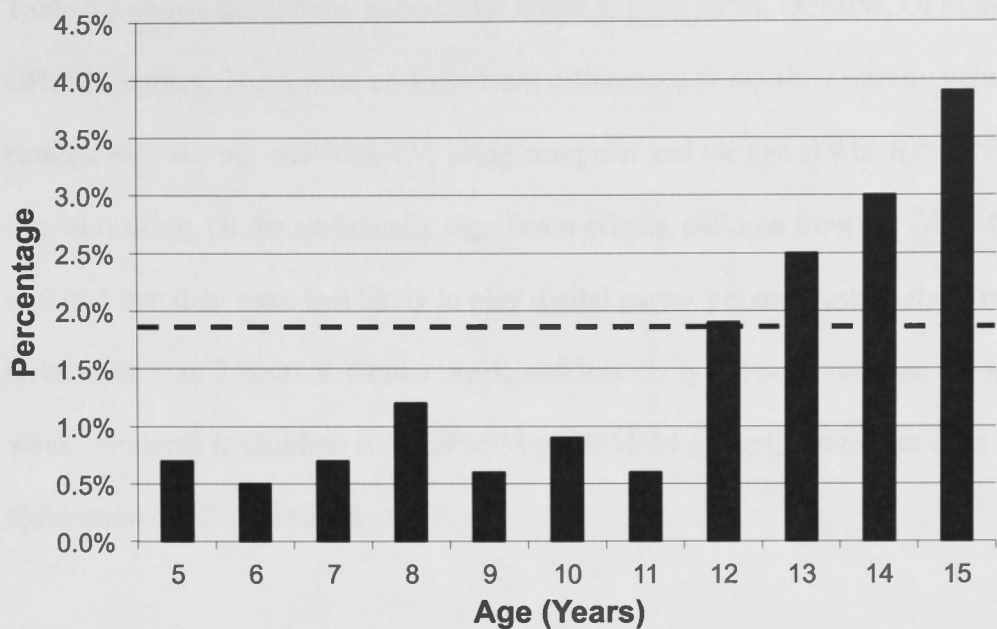
NPM: No Parent Myopic
 OPMoM: One Parent Moderately Myopic
 OPMiM: One Parent Mildly Myopic
 OPHM: One Parent Highly Myopic

Figure 4.4 shows the prevalence of high myopia in the children by age. In younger children, the prevalence of high myopia was lower than that reported by the parents. However, from the age of 12 on, the prevalence of high myopia increased with increasing age, to well over the prevalence of high myopia in the parents (1.4%), reaching a maximum of 3.9% by the age of 15 years ($P<0.001$).



Figure 4.4 Prevalence of high myopia in children by age.

Figure 4.4 shows the prevalence of high myopia in the children by age. In younger children, the prevalence of high myopia was lower than that reported by the parents. However, from the age of 12 on, the prevalence of high myopia increased with increasing age, to well over the prevalence of high myopia in the parents (1.4%), reaching a maximum of 3.9% by the age of 15 years ($P<0.001$).



Dashed line represents the prevalence of myopia in parents

Figure 4.4 Prevalence of high myopia children as a function of age

Table 4.3 shows the activity patterns for children from NPM, OPMiM, OPMoM and OHPM families. There were no significant differences in reported activity patterns in reading and writing, watching TV, using computer and the age at which the children started reading. Of the statistically significant effects, children from the OPHM group reported that they were less likely to play digital games per day, less likely to read or write more than 2 hours without a break, and less likely to read more than 1 book per week compared to children from OPMiM or OPMoM groups, sometimes even less than children from NPM families.

Activity	Category	NPM	OPMiM	OPMoM	OPHM	P
Number		1114	241	117	32	
Read and write per weekday	≤2 hours	64.1%	58.8%	58.3%	58.1%	0.300
	>2 hours	35.9%	41.2%	41.7%	41.9%	
Watch TV per weekday	≤1 hour	54.1%	59.0%	56.5%	58.1%	0.559
	>1 hours	45.9%	41.0%	43.5%	41.9%	
Play digital game per weekday	0 hour	78.8%	84.5%	89.6%	87.1%	0.010
	≥1 hours	21.2%	15.5%	10.4%	12.9%	
Use computer per weekday	0 hour	71.3%	72.4%	79.1%	83.9%	0.150
	≥1 hours	28.7%	27.6%	20.9%	16.1%	
Read books per week	≤1 book	59.5%	48.1%	55.3%	58.1%	0.015
	>1 books	40.5%	51.9%	44.7%	41.9%	
Read or write more than 2 hours without any break	Never or occasionally	75.0%	65.3%	73.0%	80.7%	0.016
	Most of time or everyday	25.0%	34.7%	27.0%	19.3%	
Age started reading	≤4 years old	64.4%	70.7%	59.7%	54.8%	0.092
	>4 years old	35.6%	29.3%	40.4%	45.2%	

Table 4.3 Near work activities in children from NPM, OPMiM, OPMoM and OPHM families

4.4 Discussion

The validity of the results in this chapter depends on how accurately the severity of parental myopia can be estimated by questionnaire. Table 4.1 shows that the agreement between questionnaire response and non-cycloplegic refraction measurements is substantial for all categories. Most misclassification occurred for the mild and no myopic categories, where some of those with mild myopia may not be aware of their mildly reduced visual acuity. This is certainly the case for children in Guangzhou, where uncorrected myopia is largely confined to children with less severe myopia, or with unilateral myopia. In contrast, children with severe visual impairment without correction which is refractive in origin were in fact completely corrected(He et al., 2004).

As discussed in CHAPTER 3, the parents concerned had either been exposed to information about refractive errors as part of the eye study recruitment process, or were sufficiently concerned about their child's refractive status to seek professional assessment. Thus the results obtained may not apply to a totally naive general population, but in the context of an eye study, where parents were required to give informed consent after recruitment, during which information on refractive errors was provided, the high validity seems likely to be applicable. In future studies, a validated series of indirect questions about the use of glasses and age at first dispensing could be used(Walline et al., 1996, Ip et al., 2007a), but ideally, parental myopia should be directly measured.

Misclassification is primarily an issue in relation to the distinction between no myopia and mild myopia in the parents. Roughly 25% of the parents who reported no myopia were found to have myopic refractions, but since noncycloplegic refractions were

measured, this could be an overestimate of the level of misclassification (Fotouhi et al., 2010). In order to examine how misclassifications would affect the study findings, we conducted qualitative sensitivity analysis. In detail, if 25% of the non-myopic parents in fact had mild myopia, this would reduce the prevalence of no-myopia in the parents to around 60%, and the prevalence of myopia in the parents would then rise to around 40% (Table 4.2), which was still much lower than in the older children. Therefore, the conclusion that the prevalence of myopia was higher in the children would still be valid. There might be some impact of misclassification on the results shown in Table 4.3. However, in order to analyse this, we would have to assume a relationship between questionnaire responses in the misclassified parents that would be purely speculative. For Figure 4.1, as the percentage of high myopic parents is probably quite accurate, so the conclusion that children from families with one parent highly myopic covered the range from no myopia to high myopia is appropriate. Given that the major misclassification would be of non-myopic parents, some of whom might be mildly myopic, the conclusion that non-myopic parents could have mildly, moderately and highly myopic children is also appropriate. Misclassification would have little impact on Figure 4.2. For Figure 4.3, the conclusions that parents with high myopia could have non-myopic children and that children with high myopia were more likely to have highly myopic parents are still appropriate. This suggests that all of our results are quite robust and the conclusions derived from them appropriate, assuming the level of misclassification reported.

Our analysis shows that more severe parental myopia carries an increased risk of myopia developing in children. There was a progressive increase (a dose-response effect) in the prevalence of myopia in the children with increasing severity of self-reported myopia in the parents, with a 1.5-fold increased risk of developing myopia by

the age of 12-15 with self-reported high myopia in one parent. High myopia in one parent carried an 11.5-fold increased risk of high myopia in the children. However, most highly myopic children in Guangzhou did not have parents with self-reported high myopia, and over 40% of highly myopic children had no reported myopia in their parents. The prevalence of high myopia in the children was below that in the parents up to the age of 11, but after that there was an increase in the prevalence of myopia with increasing age to over that reported by the parents. Overall these results are consistent with genetic contributions to the determination of severity of myopia in the children, but also suggest that environmental factors contribute to the development of more severe myopia in children, including high myopia in children. The prevalence of high myopia in young and old adults from current analysis and other major studies on Chinese populations were summarized in Table 4.4. Although the myopia definitions for the two generations in these studies were different, it is clear that the prevalence of high myopia in young generation was much higher than in the older generation.

Study site	Older adults	Age	Young adults	Age
Guangzhou ^a	4.9%	40-43 years	9.7%	15-18 years
Guangzhou ^b	1.4%	40 years	3.9%	15 years
Taiwan ^c	2.3%	>65 years	21%	18 years
Singapore ^d	6.9%	>40 years	14.8%	16-25 years

^a Data from Guangzhou Twin Eye Study (CHAPTER 5), high myopia in old adults was defined as non-cycloplegic refraction $\leq$ -6.0D, high myopia in young adults was defined as cycloplegic refraction $\leq$ -6.0D, old adults' age was estimated assuming an average age at child-birth of 25 in Guangzhou.

^b Data from Guangzhou RESC study (CHAPTER 4), high myopia in old adults was defined by question "are you myopic" and "how severe is the myopia", high myopia in young adults was defined as cycloplegic refraction $\leq$ -6.0D, old adults' age was estimated assuming an average age at child-birth of 25 in Guangzhou.

^c Data from Cheng et al(Cheng et al., 2003) and Lin et al(Lin et al., 2004), high myopia in old adults was defined as non-cycloplegic refraction $\leq$ -6.0D, high myopia in young adults was defined as cycloplegic refraction $\leq$ -6.0D.

^d Data from Wong et al(Wong et al., 2000) and Wu et al(Wu et al., 2001), high myopia in old adults was defined as non-cycloplegic refraction $\leq$ -5.0D, high myopia in young adults was defined as cycloplegic refraction $\leq$ -6.0D.

Table 4.4 Prevalence of high myopia in young and old adults

Several studies have investigated the impact of self-reported parental myopic status on childhood myopia, and most of them reported that having myopic parents is an important risk factor for having myopia in children, with an increased risk of myopia if one or both parents are myopic (Mutti et al., 2002, Saw et al., 2002a, Wu and Edwards, 1999, Ip et al., 2007c). In contrast, the impact of the severity of parental myopia on children's myopia has been rarely studied, because of the lack of quantitative data on the parents. Our results can, however, be compared to those from a study from Taiwan (Liang et al., 2004) which was carried out on a selected sample of adult probands. They found that probands with one highly myopic parent were 1.63-fold more likely to be highly myopic than those without myopic parents, and 1.78-fold more likely for those who had two highly myopic parents. The much lower relative risk associated with having highly myopic parents than in our study may be because the Taiwanese sample was highly enriched in highly myopic probands (44.1%), which inevitably reduces the relative risk, but the odds ratios were high at 5.47 for one highly myopic parent and 6.03 for two highly myopic parents. The results of this study are very similar to those we have obtained with a population-based sample, in that 44% of probands who had high myopia had no reported myopia in their parents, suggesting that the environmental factors which have led to the increased prevalence of myopia in Taiwan and Guangzhou can also lead to the development of high myopia.

Another significant effect of the severity of parental myopia is on the onset of childhood myopia. Liang et al. (Liang et al., 2004) found that probands with highly myopic parents were more likely to have an early onset of myopia with an odds ratio of 2.61. In our study, we found that a small portion of children had been highly myopic from the age of 5, and that there was a marked increase in the prevalence of high myopia from the age of 12. If we assume that most children start with about +2D, then they will need to

change by around 8D to reach the cut-off of -6D for high myopia. This means that to reach this threshold by the age of 11, children need to be progressing at about 0.7D per year, which is quite a high rate. The environmentally driven component of this increase could be called acquired high myopia. The pattern of the appearance of high myopia by age in our results is very similar to that in Taiwan(Lin et al., 2004, Shih et al., 2009), where the prevalence of high myopia is low before the age of 11 years, then increases continuously with increasing age. Lin et al. also concluded that most of the high myopia in young adults in Taiwan developed from low myopia, rather than as early onset congenital high myopia(Lin et al., 2004).

One possible explanation of the impact of parental myopia is that myopic parents create myopigenic environments for their children, with an emphasis on near work.

We did not find a systematic association between near work activity patterns in the children and the severity of parental myopia. The associations that were found were not consistent with a myopigenic environment hypothesis. This strengthens the idea that the effect of more severe parental myopia may be genetic, although the amount of time spent outdoors also needs to be examined in future studies. Despite this uncertainty, it is clear that environmental factors in Guangzhou affect a significant proportion of highly myopic children, since most did not have highly myopic parents, and nearly half did not report any myopia in their parents. In addition, the late onset of much of the high myopia in the children is consistent with a progressive impact of environmental factors.

In our analysis, the prevalence of myopia and high myopia in 15-year-olds is somewhat lower than the prevalence in their peers in Singapore and Taiwan(Lin et al., 2004, Shih et al., 2009, Quek et al., 2004), but continuing myopic progression would be expected in the 15 year-old children in Guangzhou.

The strengths of this analysis are that the Guangzhou RESC was a population-based sample with a high participation rate, which used statistical randomization and measured cycloplegic refraction. In addition, detailed questionnaires on the severity of parental myopia gave more detailed resolution of parental myopia, enabling analysis of the impact of parental myopia on that in their children.

Nevertheless, these are two important limitations. The first is that estimates of parental myopia, including the severity of parental myopia, are based on self-report, but validation of the questionnaire suggested that it was substantial, and sensitivity analysis indicated that our major conclusions are robust to the level of misclassification detected. Another limitation is that myopia in children in the Guangzhou RESC was measured at ages between 5 and 15 - prior to the age at which maximum development of myopia is reached. Although most of the analysis was therefore restricted to children aged 12 and 15, and in some cases to 15 to minimize this problem, the proportion of high myopia as a percentage of total myopia was less in 15 year-old children (5.2%) than in their parents (8.5%). However, as more mild and moderate myopes progress to high myopia, this proportion will increase, as will the absolute prevalence of high myopia.

Despite these limitations, these results suggest that there is an impact of the severity of parental myopia on the severity of myopia in the children, and in particular for a markedly increased risk of high myopia associated with high myopia in one parent. At the same time, exposure to the myopigenic environment of Guangzhou has led to an increase in the prevalence of high myopia in the younger generation in children without a family background of high myopia, or even any myopia, just as such exposure has increased the overall prevalence of myopia in children in Guangzhou.

CHAPTER 5 Relationships between parental myopia and myopia in children in the Guangzhou Twin Eye Study

5.1 Introduction

As discussed in previous chapters, refractive error shows high heritability in twin studies, but environmental exposures such as intensive education and reduced time outdoors have combined to produce marked changes in the population distribution of refractive error, particularly in East Asia. For example, in the Guangzhou RESC, where parental myopia was determined by questionnaire, the prevalence of myopia was significantly higher in the children's generation than in the parents' generation (see CHAPTER 3 and 4). One way this can occur is if the environmental exposures shift the population mean, but the position within the distribution of refractive errors would be inherited from parents to their children. Previous studies have not been able to analyse this possibility, because quantitative data on parental refractions was not available. We have now examined this issue using data on children and their parents from a population-based sample of twins from Guangzhou, where non-cycloplegic refraction data on the parents have been collected.

5.2 Methods

5.2.1 Study population

The study population were drawn from the Guangzhou Twin Registry(He et al., 2006). In brief, twins born in Guangzhou between 1987 and 2000 were identified by using the official Household Registry of Guangzhou, followed by door-to-door verification. Twins aged 7 to 15 years (on July 1, 2006) living in two districts adjacent to the Zhongshan Ophthalmic Center, where the examination station was set up, were recruited and examined annually. The biological parents of these twin children were also invited to participate. The response rate for the baseline study in 2006 was 82.3%.

The Guangzhou Twin Eye study was conducted in accordance with the tenets of the World Medical Association's Declaration of Helsinki. Ethics approval was obtained from the Sun Yat-sen University Ethics Review Board and the Ethics Committee of Zhongshan Ophthalmic Center. Written informed consent was obtained for all participants from either parents or guardians of the participating children. Participating children and their parents were requested to attend annual follow-up examinations in the summer or winter school holidays from 2006 on. Annual examinations took place approximately one year apart.

5.2.2 Examinations

Children's refractive errors were determined by cycloplegic autorefraction. Cycloplegia was induced with two drops of 1% cyclopentolate administered 5 minutes apart to each eye, with a third drop administered after 20 minutes. Cycloplegia was considered complete if the pupil dilated to 6mm or greater, and a light reflex was absent after a further 20 minutes. Refractions and keratometry were measured using an

autorefractor (KR8800, Topcon Corp, Tokyo, Japan) after cycloplegia. Parental refractive status was determined by autorefraction without cycloplegia.

5.2.3 Statistical analysis

Children's refractive error data were derived from the 4th year (2009) phenotypic collection. Parents' data were derived from the first study year (2006). Given that twin heritability studies are consistent with additive genetic effects (Hill et al., 2008), the mean refractive error of both parents was calculated to represent the parental refraction for each child. However, analyses were also carried out for the most myopic and least myopic parent.

Refractive error data on right eyes of the children were used for data analysis, given the generally high correlation between measurements from left and right eyes (data not shown, $P=0.97$). Myopia was defined as a spherical equivalent refractive error (SER) of at least $-0.5D$. Myopia severity was categorised into three groups, - MILD ($\leq -0.5D$ to $> -3.0D$), MODERATE ($\leq -3.0D$ to $> -6.0D$), and HIGH ($\leq -6.0D$) myopia.

The Chi-square test was used to compare proportions (prevalence) among different groups. Spearman correlation analysis was used to assess the association of the rank orders between parents and children. Statistical analysis was performed using STATA 11.0 (Stata Statistical Software, Release 11.0, Stata Corp., College Station, TX). All statistical tests were two-sided, and $P < 0.05$ was considered statistically significant.

5.3 Results

5.3.1 Prevalence of myopia in two generations

A total of 792 children aged 10-18 years with both parents' data were included in analysis. The children without information on parental myopia were not significantly different to the children analysed in terms gender or refractive error ($P=0.79$ for gender, $P=0.88$ for refractive error).

Table 5.1 shows a detailed break-down of the prevalence of myopia in children and parents. Overall, the prevalence of myopia and severe forms of myopia was significantly higher in the children's generation. In the parents, about 40% were myopic, with a slightly higher prevalence of myopia in mothers than in fathers (41.8% vs. 38.8%, $P=0.79$). The prevalence of high myopia and moderate myopia was also higher in mothers ($p<0.001$). In the children's generation, the prevalence of myopia was markedly higher at 64.8%. Restricting the analysis to the 15-18 year-olds, the prevalence of myopia in the children was 72.6%. The prevalence of high myopia was twice as high in 15-18 year-old children as in their parents (9.7% vs. 4.9%, $P<0.001$). Table 5.2 shows the mean value, median, 25% and 75% percentiles of the spherical equivalent (SER) in the two generations. Similar to the prevalence data, the mean SER was more myopic in mothers than in fathers, and it was significantly more myopic in the children's generation ($P<0.001$).

	10-14 year-olds	15-18 year-olds	Children in total	Fathers	Mothers	Parents in total
No myopia	41.4%	27.4%	35.2%	61.2%	58.2%	59.7%
Myopia*	58.6%	72.6%	64.8%	38.8%	41.8%	40.3%
Mild myopia	37.8%	32.5%	35.4%	25.4%	24.0%	24.7%
Moderate myopia	18.8%	34.7%	24.3%	9.1%	12.2%	10.7%
High myopia	2.0%	9.7%	5.1%	4.3%	5.6%	4.9%

*Mild myopia ($\leq -0.5D$ to $> -3.0D$), Moderate myopia ($\leq -3.0D$ to $> -6.0D$), High myopia ($\leq -6.0D$)

Table 5.1 Prevalence of myopia in children and parents

SER (D)	10-14 year-olds	15-18 year-olds	Children in total	Fathers	Mothers	Parents in total
Mean±SD	-1.28±2.03	-2.47±2.58	-1.70±2.39	-0.89±2.41	-1.27±2.81	-1.08±2.62
Median	-0.9375	-2.44	-1.5	-0.1275	-0.25	-0.25
25% percentile	-1.75	-4.125	-3.25	-1.2475	-1.81	-1.5
75% percentile	0.375	-0.5	0.1875	0.375	0.185	0.25

Table 5.2 SER mean, median, 25% and 75% percentiles

5.3.2 Impact of parental myopia on myopia in children

Based on parental refractive status, children were classified into three family categories – no parents myopic (NPM) – 37.4% (296), one parent myopic (OPM) – 44.7% (345), and two parents myopic (TPM) – 17.9% (142).

The impact of parental myopia on the development myopia in children was assessed by following the prevalence of myopia in children by age. As shown in Figure 5.1, the prevalence of myopia increased in all three groups of children, at the age of 18, the prevalence of myopia was 95.5% in the OPM group and 83.8% in the TPM group. In the NPM group, the prevalence was lower at 68.0%. Thus, the relative risk (RR) of myopia compared to the NPM group at the age of 18 was 1.30 for the OPM and TPM groups, and the relative risk compared to the population mean was 1.13 for the OPM and TPM groups. And there was also a slight tendency for children from TPM and OPM groups to show an increased prevalence of myopia at earlier ages.

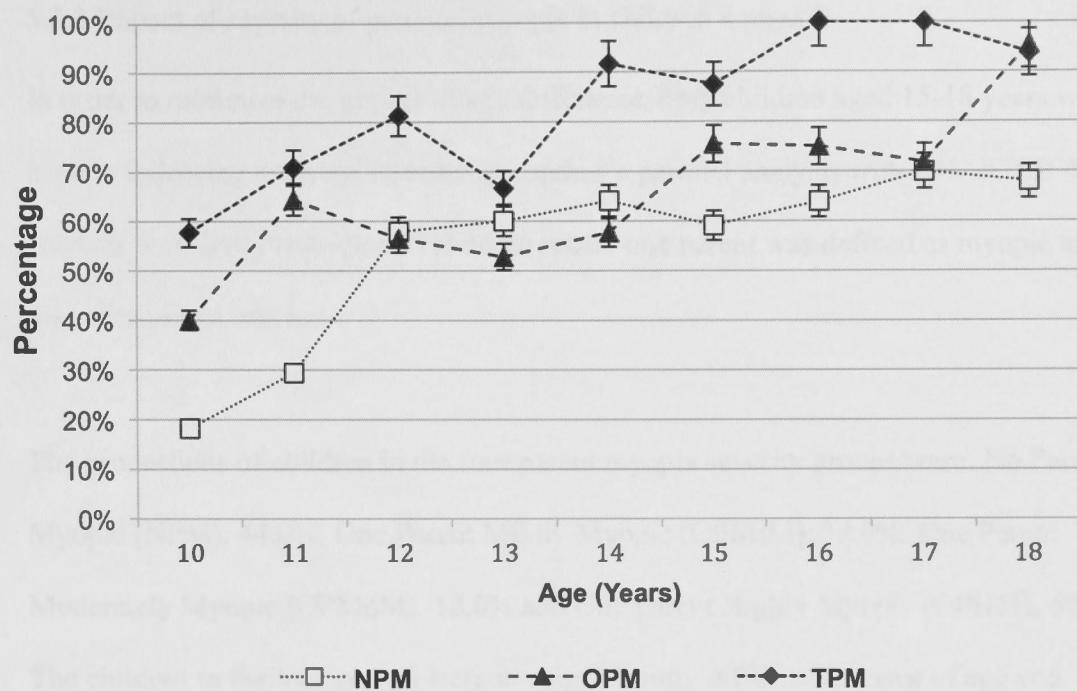


Figure 5.1 Prevalence of myopia in children in NPM, OPM and TPM groups

NPM: No Parent Myopic OPM: One Parent Myopic TPM: Two Parents Myopic

5.3.3 Impact of severity of parental myopia in children's myopia

In order to minimize the impact of age difference, only children aged 15-18 years were used in following analysis. In order to conduct a parallel analysis with CHAPTER 4, analysis was firstly restricted to children where one parent was defined as myopic and the other parent was not.

The proportions of children in the four parent myopia severity groups were: No Parent Myopic (NPM), 44.0%; One Parent Mildly Myopic (OPMiM), 38.0%; One Parent Moderately Myopic (OPMoM), 12.0% and One Parent Highly Myopic (OPHM), 6.0%. The children in the four groups were not significantly different in terms of age and gender (the mean age for NPM, OPMiM, OPMoM and OPHM groups were 16.6 ± 1.08 , 16.1 ± 1.08 , 16.1 ± 0.97 , and 16.7 ± 1.36 years, $P=0.82$; the percentages of boys for NPM, OPMiM, OPMoM and OPHM groups were 50.7%, 51.1%, 51.0% and 50.2%, $P=0.96$).

The impact of parental myopia on children's myopia is shown in Figure 5.2. There was a progressive increase in the prevalence of myopia with increasing severity of myopia in the myopic parent from the NPM to OPMoM groups (P for trend <0.001), while the proportion of children with myopia was slightly lower in the OPHM group than in the OPMoM groups (78.57% vs. 85.71%, $P<0.001$), this may be due to small sample size in the OPHM group (14 children). Having one parent highly myopic yielded an increased relative risk of myopia of 1.16 (78.57% for OPHM vs. 67.96% for NPM, $P<0.001$). For high myopia, there was no child without myopic parents developing high myopia, and more than 20% children with one parent moderately (OPMoM) or highly myopia (OPHM) developing myopia by the age of 15-18 years. The impact of the severity of parental myopia on the development of myopia in children can also be seen in mean

SER. There was a progressive increase in the mean SER with increasing severity of parental myopia, except for children with one parent highly myopic – -1.31 ± 2.20 for NPM, -2.54 ± 2.11 for OPMiM, -3.74 ± 2.61 for OPMoM, -3.72 ± 2.80 for OPHM groups, (ANOVA $P < 0.001$).

Figure 5.3 shows the distribution of the severity of parental myopia in terms of severity of myopia in the children. There was an increasing proportion of myopia in the parents of children with more severe myopia ($P < 0.001$). Most of the highly myopic children did not have a highly myopic parent (78.6%), while none of them had non-myopic parents. In children who were not myopic, 45.0% had myopic parents, and 5.0% had one highly myopic parent.

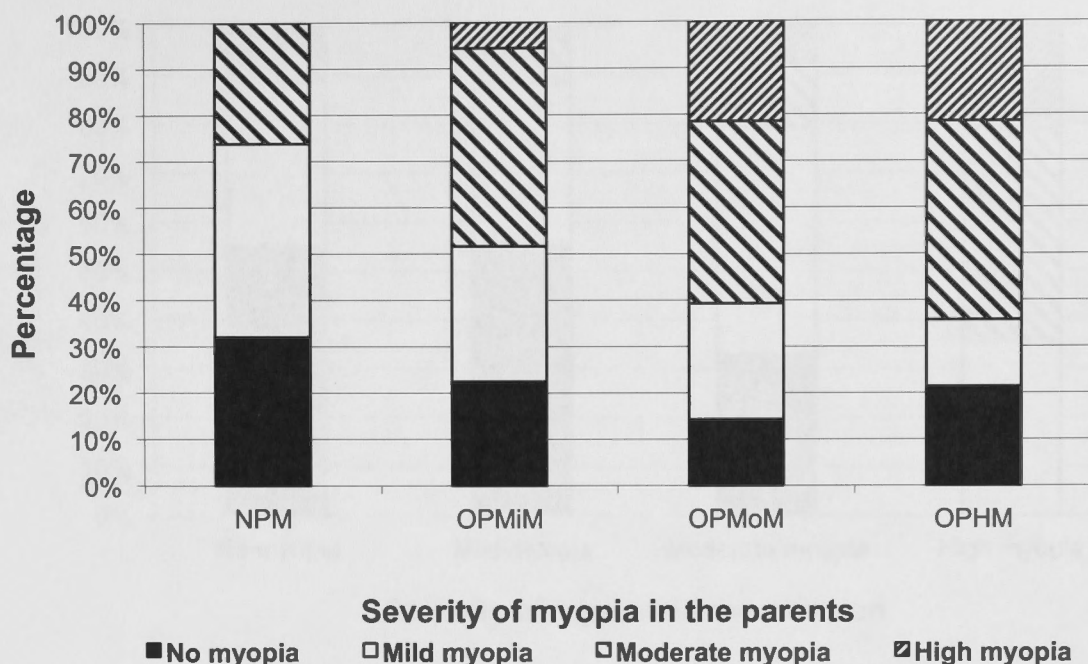


Figure 5.2 Percentage of children in each category of myopia severity (non, mild, moderate, high) by the severity of parental myopia

NPM: No Parent Myopic

OPMoM: One Parent Moderately Myopic

OPMiM: One Parent Mildly Myopic

OPHM: One Parent Highly Myopic

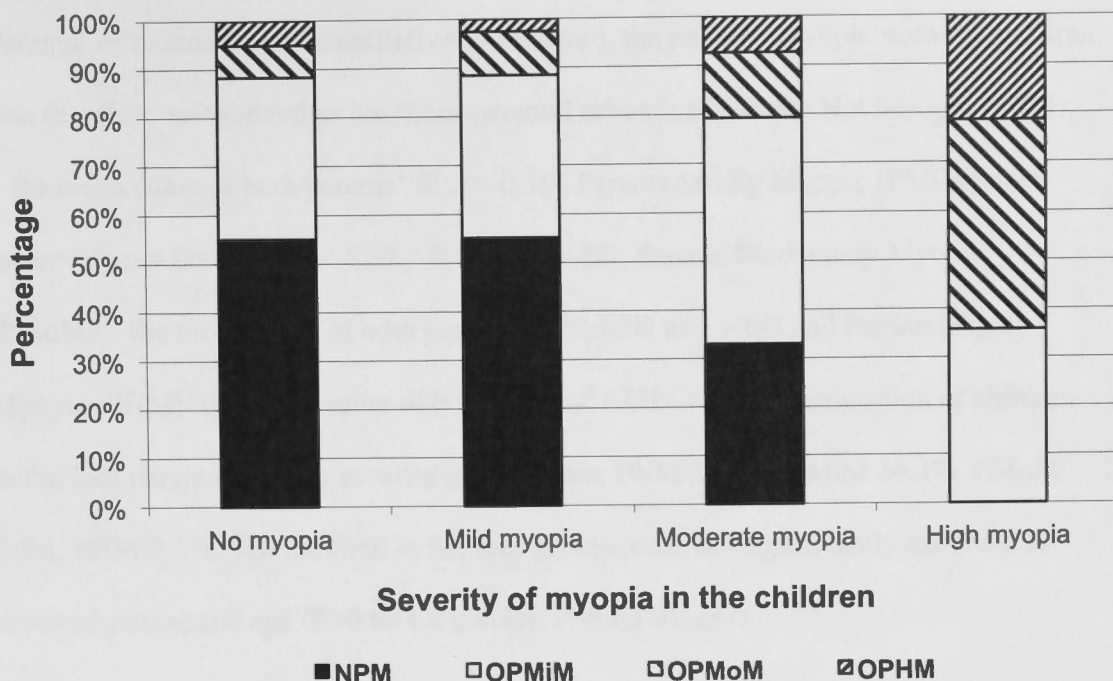


Figure 5.3 Percentage of parents in each category of myopia severity (non, mild, moderate, high) by the severity of myopia in the children

NPM: No Parent Myopic

OPMiM: One Parent Mildly Myopic

OPMoM: One Parent Moderately Myopic

OPHM: One Parent Highly Myopic

Parents' refractions were quantitatively measured, the parental myopia status of children was therefore categorized as the mean parental refraction: Parents Not Myopic (PNM), – the mean value of both parents' SER > -0.5D, Parents Mildly Myopic (PMiM)- the mean value of both parents' SER ≤ -0.5D and > -3D, Parents Moderately Myopic (PMoM) – the mean value of both parents' SER ≤ -3D and > -6D and Parents Highly Myopic (PHM)- the mean value of both parents' SER ≤ -6D. The proportion of children in the four parental myopia severity groups were: PNM 56.0%, PMiM 34.3%, PMoM 7.5%, PHM 2.2%. The children in the four groups were not significantly different in terms of gender and age (P=0.68 for gender; P=0.63 for age).

Using this family grouping, Figure 5.4 shows the impact of the severity of parental myopia on children's myopia. There was an increase in the prevalence of myopia with increasing severity of myopia in parents ($p < 0.001$). In children with moderately myopic parents and highly myopic parents, all were myopic. There was also a significant increase in the prevalence of high myopia in the children with increasing severity of myopia in the parents. In children with highly myopic parents, half of them were highly myopic, in contrast, in children without myopia parents, only 1.3% were highly myopic.

The distribution of the severity of parental myopia in terms of the severity of myopia in the children is shown in Figure 5.5. There was a progressively increasing prevalence of high myopia in the parents with more severe myopia in the children ($p < 0.001$), whereas the proportion of non-myopic parents was high at 67.8% in non-myopic children, and significantly dropped to 4.5% in highly myopic children. In highly myopic children, most of them did not have highly myopic parents (86.4%), and more than half of the highly myopic children had mildly myopic parents or non-myopic parents.

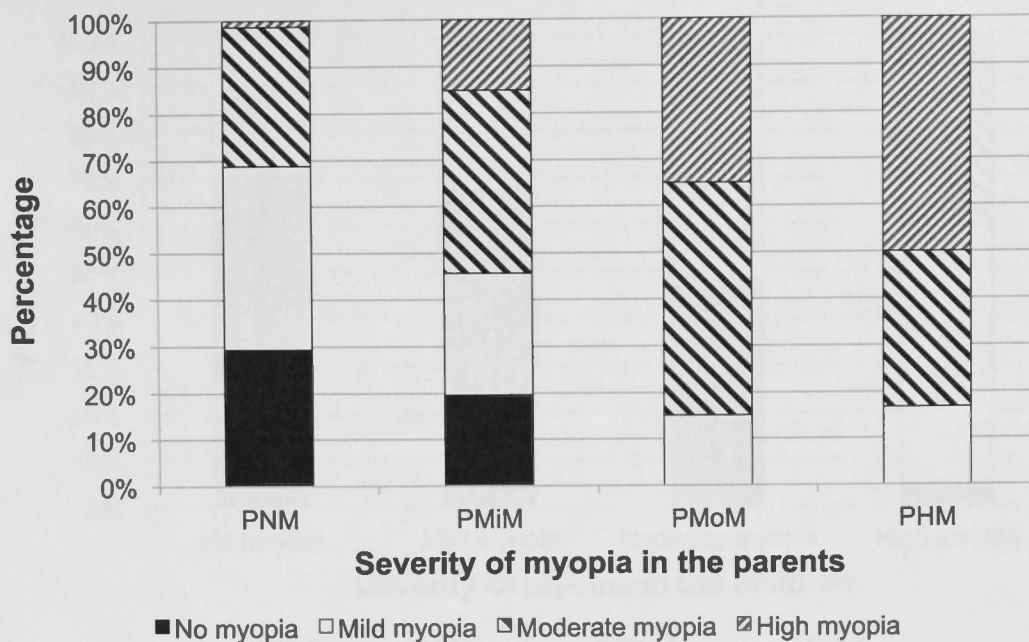


Figure 5.4 Percentage of children in each category of myopia severity (non, mild, moderate, high) by the severity of parental myopia

NPM: No Parent Myopic

OPMoM: One Parent Moderately Myopic

OPMiM: One Parent Mildly Myopic

OPHM: One Parent Highly Myopic

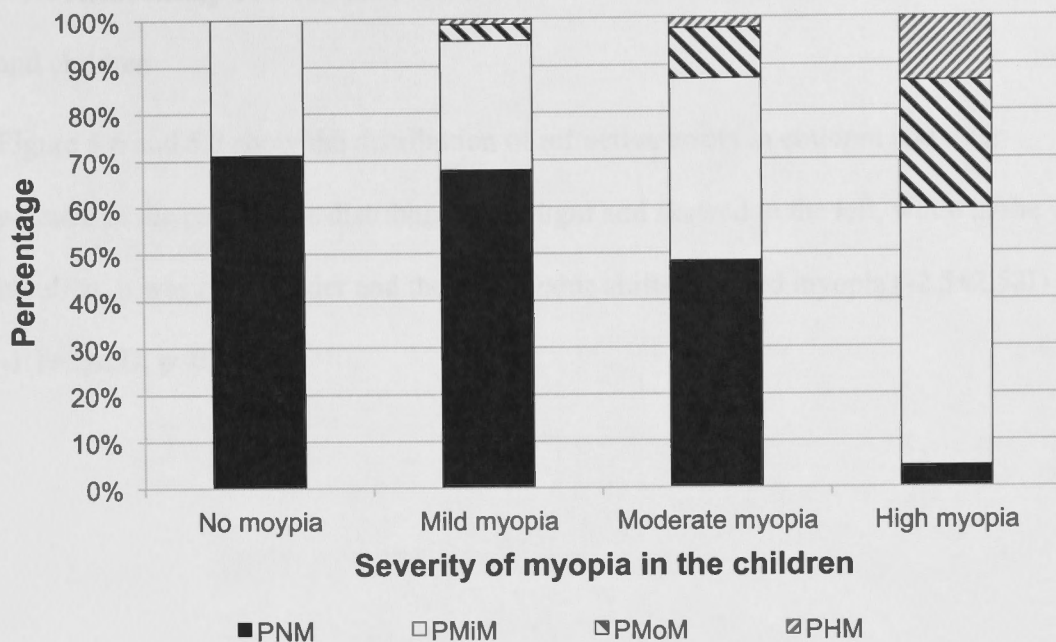


Figure 5.5 Percentage of parents in each category of myopia severity (non, mild, moderate, high) by the severity of myopia in the children

NPM: No Parent Myopic

OPMoM: One Parent Moderately Myopic

OPMiM: One Parent Mildly Myopic

OPHM: One Parent Highly Myopic

5.3.4 Relationship between rank order in the distribution of refractive error in parents and children

Figure 5.6 and 5.7 show the distribution of refractive errors in children and their parents. In the parents the distribution was tight and skewed to the left, while in the children, it was much wider and the mean value shifted toward myopia ($-2.5\pm2.58D$ vs. $-1.1\pm2.62D$, $p<0.001$).



Figure 5.6 Distribution of refractive error in the parents

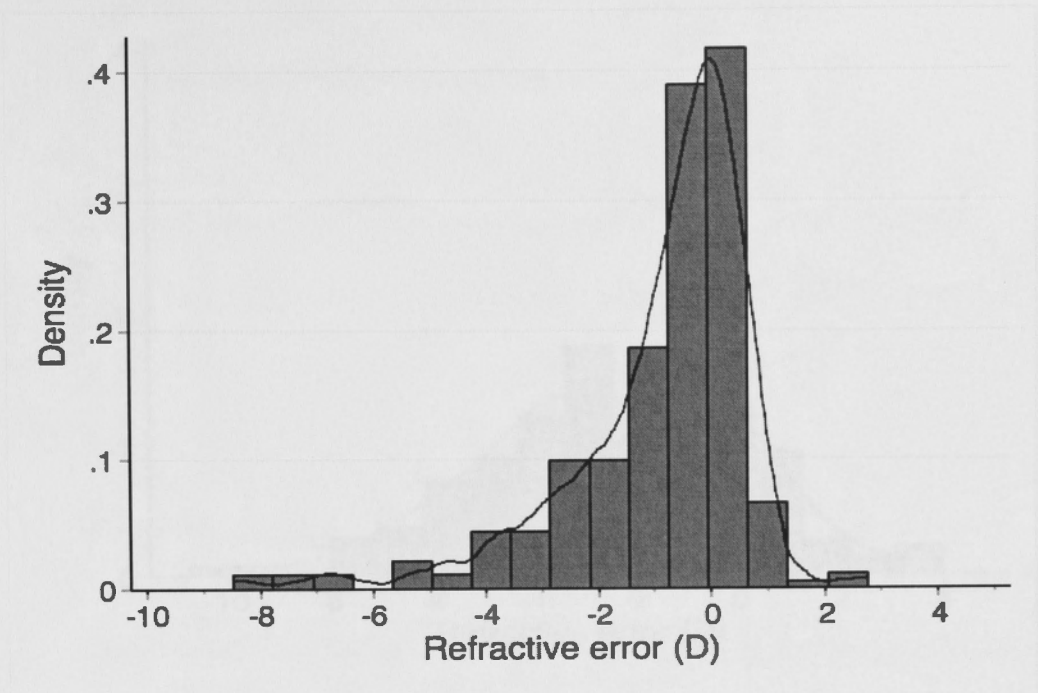


Figure 5.6 Distribution of refractive error in the parents

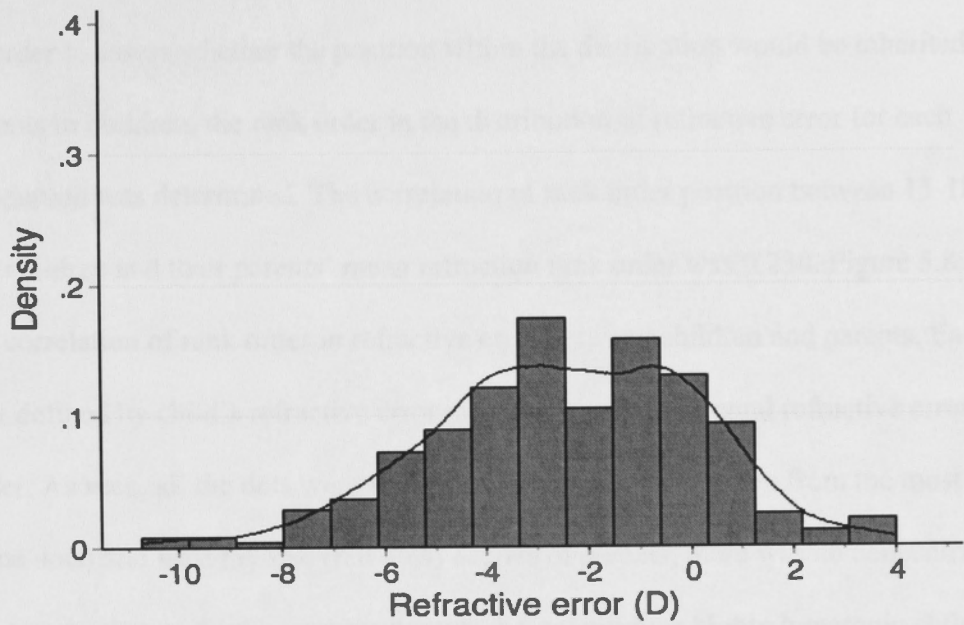
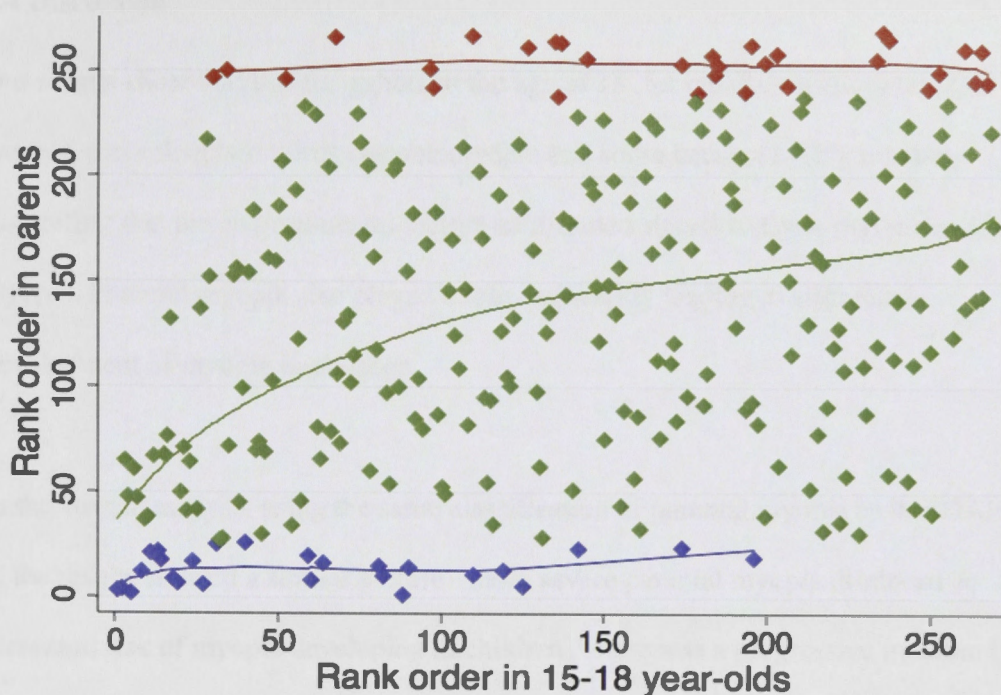


Figure 5.7 Distribution of refractive error in 15-18 years children

In order to assess whether the position within the distribution would be inherited from parents to children, the rank order in the distribution of refractive error for each generation was determined. The correlation of rank order position between 15-18 year-old children and their parents' mean refraction rank order was 0.230. Figure 5.8 shows the correlation of rank order in refractive error between children and parents. Each dot was defined by child's refractive error rank order and its parental refractive error rank order. As seen, all the dots were widely scattered. As for children from the most myopic (blue dots) and least myopic (red dots) deciles of parents, there was no concentration in the two extremes - highly myopic parents did not produce highly hyperopic children and highly hyperopic parents did not produce highly myopia children. The correlations of rank orders position between children and the most myopic and least myopic parent were also assessed. If the most myopic parents' refractive error was used to represent parental refraction, the correlation between 15-18 years children and their parents' rank order was 0.396 (compared to the correlation using parents' mean, $P=0.06$), and if the least myopic parents' refractive error was used, the correlation was 0.254 (compared to the correlation using parents' mean, $P=0.77$).



Blue dots represent children with the most myopic decile of parents ($\leq -3.00D$), blue line represents the Lowess curve for children with the most myopic decile of parents;
 Red dots represent children with the least myopic decile parents ($\geq 0.53D$); red line represents the Lowess curve for children with the least myopic decile parents;
 Green lines shows the Lowess curve for all children

Figure 5.8 Correlation of rank order in refractive error between parents and children

5.4 Discussion

Our results show that in Guangzhou, at the age of 18, for children without myopic parents, more than two thirds became myopic and some became highly myopic, suggesting that the environmental factors contributed significantly to myopia and high myopia. Parental myopia also played a role, apparently leading to additional development of myopia in children.

In the current analysis using the same classification of parental myopia as in CHAPTER 4, the results showed a similar picture - more severe parental myopia produced an increased risk of myopia developing in children. There was a progressive increase in the prevalence of myopia and the prevalence of high myopia in the children with increasing severity of parental myopia. However, there was no apparent dose-response relationship between the severity of myopia in children and the severity in the parents.

In the analysis using the mean SER of both parents' refraction to represent parental refractive status, the results showed that only a small proportion of children with non-myopic parents had high myopia (1.3%), which was similar to the result obtained in CHAPTER 4 (1.4%). In contrast to the results in CHAPTER 4, the current analysis showed that moderately and highly myopic parents never had non-myopic children, and that 50% of highly myopic parents had highly myopic children. This proportion was significantly higher than that in CHAPTER 4 (16.1%). It should be noted that, comparing with the Guangzhou RESC, the Guangzhou Twin Eye Study was conducted 7 years later (2009 vs. 2002), and the age range in the current analysis was also 3 years older (15-18 years vs. 12-15 years). The prevalence of high myopia in the Guangzhou Twin Eye Study was markedly higher (9.7% vs. 2.5%). The higher prevalence of high myopia in the more severe parental myopia group in the current analysis may be due to

greater environmental impacts which have pushed more children towards more severe myopia.

As with the Guangzhou RESC, most highly myopic children did not have highly myopic parents, however, only 5% of them did not have any myopic parents, compared to 45.3% in the Guangzhou RESC. This may be because that the prevalence of myopia in parents in the current analysis was much higher than the prevalence of self-reported myopia in the Guangzhou RESC (40.3% vs. 16.4%, $P < 0.001$), and because more children have reached the cut-off for high myopia due to environmental exposures.

The results also show that the position in the distribution of refractive errors did not appear to be transmitted from parents to children. This was true whether we used mean parental SER, or the most myopic or least myopic parental refraction. Therefore, it rules out the possibility that the environmental exposures shift only the population mean, but do not change the distribution.

This can also be seen quite clearly in the actual distributions of refraction in the two generations. The distribution for the parents is only mildly skewed towards myopic refractions, whereas that of the children is markedly skewed towards myopia. It is clear that a simple shift in the distribution has not taken place. There are two possible explanations of the change in shape of the distributions of SER between generations. It is possible that there are significant differences in environmental exposures between children, which act on similarly susceptible genomes. Alternatively, there may be gene-environment interactions, in which some genomic backgrounds are more susceptible to the environmental changes. In other words, the differences in genomes cause children to respond differently to the same environmental exposure, so some children have a fairly

low risk of developing myopia, while others are much more vulnerable to environmental exposures. At this stage, these explanations are not mutually exclusive, and further work needs to be done to distinguish between differential exposures and gene-environment interactions.

In summary, the results presented in this chapter rule out the simple hypothesis that the change in environmental conditions simply shifts the population mean, whereas genetic factors determine place in the distribution. However, an impact of parental myopia and severity of parental myopia on the refractive status of the children can still be seen.

CHAPTER 6 Reconstructing the secular change of myopia in Guangzhou

6.1 Introduction

The epidemic of myopia in urban areas of East Asia and its public health impact have been discussed in previous chapters. While it is clear that the prevalence of myopia is high, there has been some debate about whether the prevalence of myopia has always been high in East Asia. This has been largely based on the report of Rasmussen that the prevalence of myopia was over 60% in China in the 1930s(Rasmussen, 1936).

However, this appears to be based on a mis-reading of the original report, for in fact Rasmussen reported on the percentage of optical prescriptions which were for myopia, which is a quite different matter. Unfortunately, this mis-interpretation was reproduced in Curtin's classic book, *The Myopias*, and has thus been widely disseminated. The origins of the epidemic in East Asia are also relatively obscure, and most of the limited data available is methodologically flawed.

Despite these limitations, it is important to understand something of the origins of the secular increase which has taken place. At present, there are no well-validated optical or pharmaceutical methods for preventing or the development of myopia or limiting its progression over the long-term, although there are a number of approaches currently being studied(Gwiazda, 2009). In principle, it would be preferable to use public health interventions which address the cause of the problem, rather than approaches which treat the symptoms. The recent and rapid emergence of the high prevalence of myopia suggests that social or environmental changes have been critical in the process, and understanding the causes of the current pandemic is important if preventive measures are to be put in place.

Unfortunately, while there has been much speculation on the critical factors, evidence on when the prevalence of myopia increased to the current levels is limited, largely because population-based studies using the gold standard for measuring refraction, cycloplegic retinoscopy or autorefraction, have generally not been carried out in the past. Some data using other techniques for estimating the prevalence of myopia, such as measuring refraction without cycloplegia exist, and there is other relevant data based on estimating the prevalence of myopia by questionnaire, or from measurements of reduced visual acuity, which are problematic, but which may, in context, provide useful insights.

There is a unique set of data using a variety of these techniques available on myopia and visual acuity in Guangzhou, which we have used to reconstruct the pattern of secular change in the prevalence of myopia over the past 100 years. Comparison of the changes seen in Guangzhou to those in Singapore, Taiwan and Hong Kong is then used to throw additional light on the causes of the recent explosion of myopia.

6.2 Data sources and their limitations for estimating the prevalence of myopia

The prevalence of myopia changes throughout the life-course of a birth cohort - increasing during childhood, reaching a plateau in young adults, possibly declining after that due to hyperopic shifts during middle age, before increasing again due to cataract-associated myopic shifts in the elderly. Ideally, for examination of secular change, the prevalence of myopia should be estimated at a standard developmental stage, preferably when it reaches a plateau in young adults, using cycloplegic refraction. The life-course changes mean that estimates of prevalence from children are likely to under-estimate the prevalence of myopia in young adults from a given birth cohort. Similarly, since there are hyperopic shifts in refraction in adult life, data based on older participants may also under-estimate the peak prevalence of myopia, except in the oldest samples, in which cataract-associated myopic shifts may complicate the analysis (Morgan et al., 2010).

The extensive data on the prevalence of myopia and unaided visual acuity now available from Guangzhou, in southern China, is derived from four studies: the Guangzhou Refractive Error Study in Children (Guangzhou RESC, see CHAPTER 3 and 4) (He et al., 2004); the Guangzhou Twin Eye Study (Guangzhou TES, see CHAPTER 5) (He et al., 2006); the Liwan Eye Study (He et al., 2009a); and the results of visual acuity surveillance in school children over the past 20 years by the Guangzhou Ministry of Education (see CHAPTER 2). We have attempted to estimate the prevalence of myopia in Guangzhou for people born in different birth years, to time more precisely the emergence of the epidemic of myopia, and to enable more critical analysis of the factors that might be involved..

6.2.1 Guangzhou RESC

The Guangzhou RESC is a population-based study of the prevalence of myopia in the Liwan District of Guangzhou in children aged from 5 to 15 years using cycloplegia, carried out in 2002. This study gave two relevant estimates of the prevalence of myopia in Guangzhou. The first is the prevalence of myopia in the oldest children examined in the study, 15 year-olds, using cycloplegic autorefraction, with myopia defined as a spherical equivalent refractive error (SER) of at least 0.5 Diopter (D). This figure will slightly underestimate of the prevalence of myopia in young adults, because progression of myopia continues after the age of 15.

In addition, in this study, a parental questionnaire was administered. All parents were asked the following question: “Are you myopic? (Yes/ No/ I don’t know)”. In a validation study, the specificity (77%) and sensitivity (84%) of the questionnaire were high, but it is likely that a questionnaire of this kind will underestimate the prevalence of myopia, since some parents with low myopia may not be aware of their condition. Parental age was not collected, but the mean age of child-birth in Guangzhou was used to estimate the year of birth of the parents.

6.2.2 The Guangzhou Twin Eye Study

The Guangzhou Twin Eye Study is an on-going population-based study of twins drawn from twin registers in Guangzhou. The twins were initially enrolled at ages from 7-15 years, and received annual eye examinations from 2006 on, including annual cycloplegic refractions. That the data on twins could be treated as representative of the population was validated by comparing the results from the Guangzhou Twin Eye Study with those from the Guangzhou RESC. The data on the oldest children available were used to estimate the prevalence of myopia, and as with the data from the Guangzhou

RESC may underestimate the true prevalence of myopia in the cohort, because of continuing progression. Non-cycloplegic refractions were performed on the parents, which may give a slight overestimate of the prevalence of myopia due to the lack of cycloplegia,(Fotouhi et al., 2010). In contrast, hyperopic shifts in refraction in adults may tend to underestimate the actual prevalence.

6.2.3 Liwan Eye Study

This is a population-based study of adults over the age of 50 in the Liwan District of Guangzhou, carried out in 2002-3. Autorefractometry was performed on all participants using a handheld autorefractor (ARK-30; Nidek Corp., Gamagori, Japan) without administration of cycloplegic eye drops. Myopia was defined as the spherical equivalent refractive error of at least 0.5 D. These measurements in older people may deviate from the prevalence of myopia as young adults due to the lack of cycloplegia, which will tend to lead to overestimation of myopia, the possibility of hyperopic shifts reducing the prevalence of myopia, and the possibility of cataract-associated myopic shifts in the oldest participants leading to an over-estimate of the prevalence in the subjects as young adults.

6.2.4 School-based Visual Acuity Surveillance in Guangzhou

The Bureau of Students' Health from the Guangzhou Ministry of Education has measured visual acuity (VA) each year from 1988 on in all students from a large, representative sample of schools, using a LogMAR tumbling E chart. VA is reported as Snellen categories: normal ($VA \geq 6/6$), mildly reduced ($6/9 < VA < 6/6$), moderately reduced ($6/18 < VA \leq 6/9$) and severely reduced VA ($VA \leq 6/18$), and the prevalence of myopia was defined as the sum of the prevalence of moderately and severely reduced

VA. A cut-off for the prediction of myopia was defined in 12 year-olds from the Sydney Myopia Study as $VA \leq 6/9$ with high specificity and sensitivity. A similar cut-off was defined from analysis of the Guangzhou RESC data, and the results were cross-validated by comparison of the measured prevalence of myopia using cycloplegic refraction measurements from the Guangzhou RESC with the predicted prevalence of myopia from the visual acuity data from Guangzhou schools for the same year (2002). This gave a correlation between measured and predicted prevalence of myopia of 0.993. The results on Grade 12 students were used to estimate the prevalence of myopia, which is likely to slightly underestimate the prevalence of myopia in young adults due to continuing progression beyond the school years.

6.2.5 Comparison data sets

For comparative purposes, the following papers were used as sources of data on the prevalence of myopia in Singapore (Chew et al., 1988, Wong et al., 2000, Au Eong et al., 1993a, Wu et al., 2001), Hong Kong (Lam et al., 1994, Goh and Lam, 1994) and Taiwan (Cheng et al., 2003, Lin et al., 2004). As with the data from Guangzhou, the data is based on a variety of techniques for estimating the prevalence of myopia, and is subject to the same limitations.

6.3 Results

Using the estimates of the prevalence of myopia in Guangzhou obtained as outlined above, it has been possible to reconstruct the changes in prevalence in Guangzhou over the past 100 years (Figure 6.1). Despite the potential errors in the estimates, the data show a quite consistent picture, with a significant increase in the prevalence of myopia from around 30% for people born prior to 1970 to over 80% in today's young adults. In one part of the curve, there are two estimates of the prevalence of myopia as young adults for those born between 1966 and 1972 from two different methods. As can be seen, the two estimates change roughly in parallel, with measurements based on noncycloplegic autorefraction slightly higher than those derived by questionnaire, consistent with expectations from the strengths and weaknesses of the two techniques.

It has been suggested that the prevalence of myopia may have declined slightly in those whose education was disrupted during the Cultural Revolution. While the data are not inconsistent with this possibility, the accuracy of the estimates is not sufficient for confident conclusions. However, it is clear that for birth cohorts from roughly the end of the Cultural Revolution, the prevalence of myopia has gradually increased in Guangzhou to reach a high plateau level in recent years.

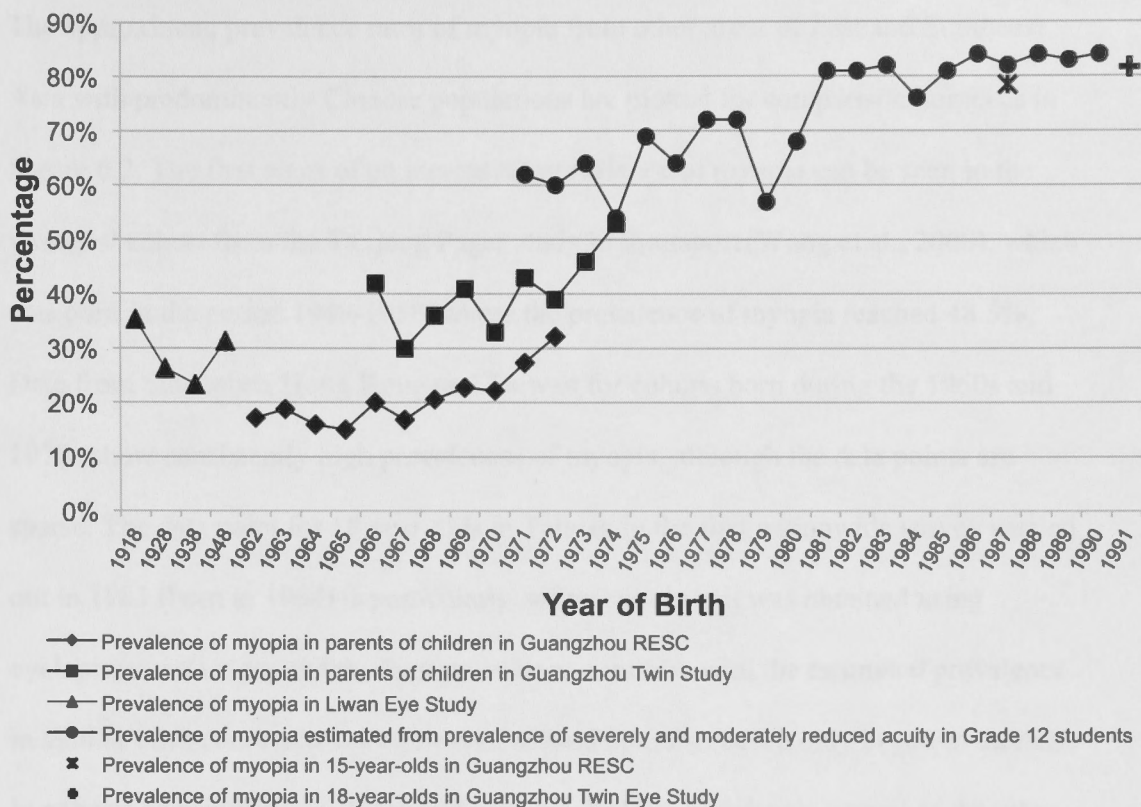


Figure 6.1 Secular change in the prevalence of myopia in Guangzhou

The approximate prevalence rates of myopia from other areas of East and Southeast Asia with predominantly Chinese populations are plotted for comparison purposes in Figure 6.2. The first signs of an increasing prevalence of myopia can be seen in the youngest cohort from the Tanjong Pagar study in Singapore(Wong et al., 2000), which was born in the period 1949-1958, where the prevalence of myopia reached 48.5%. Data from Singapore, Hong Kong and Taiwan for cohorts born during the 1960s and 1970s show consistently high prevalences of myopia, although the data points are sparse. The data point for 18 year-olds in Taiwan in the first nationwide survey carried out in 1983 (born in 1964) is particularly definitive, since it was obtained using cycloplegic refraction, and the high prevalence contrasts with the estimated prevalence in similar birth cohorts in Guangzhou of around 20-30%, which only began to increase in cohorts born in the late 1970s, and only reached the high levels typical of the other sites for cohorts born well after 1975-6.

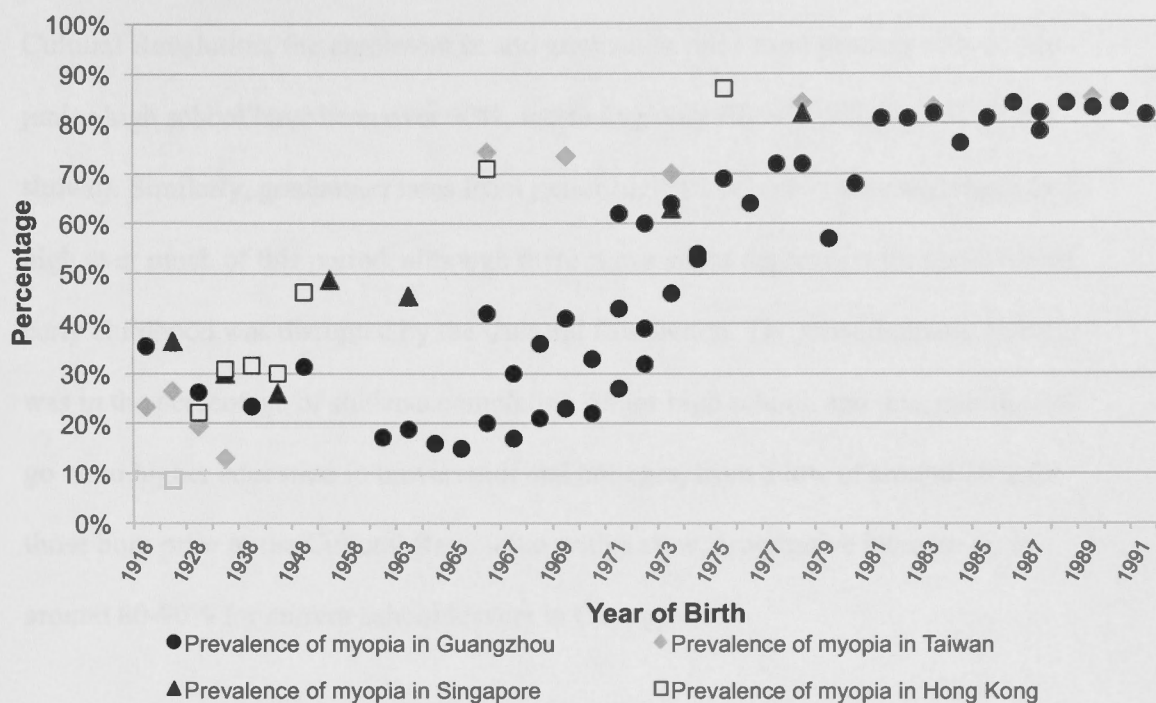
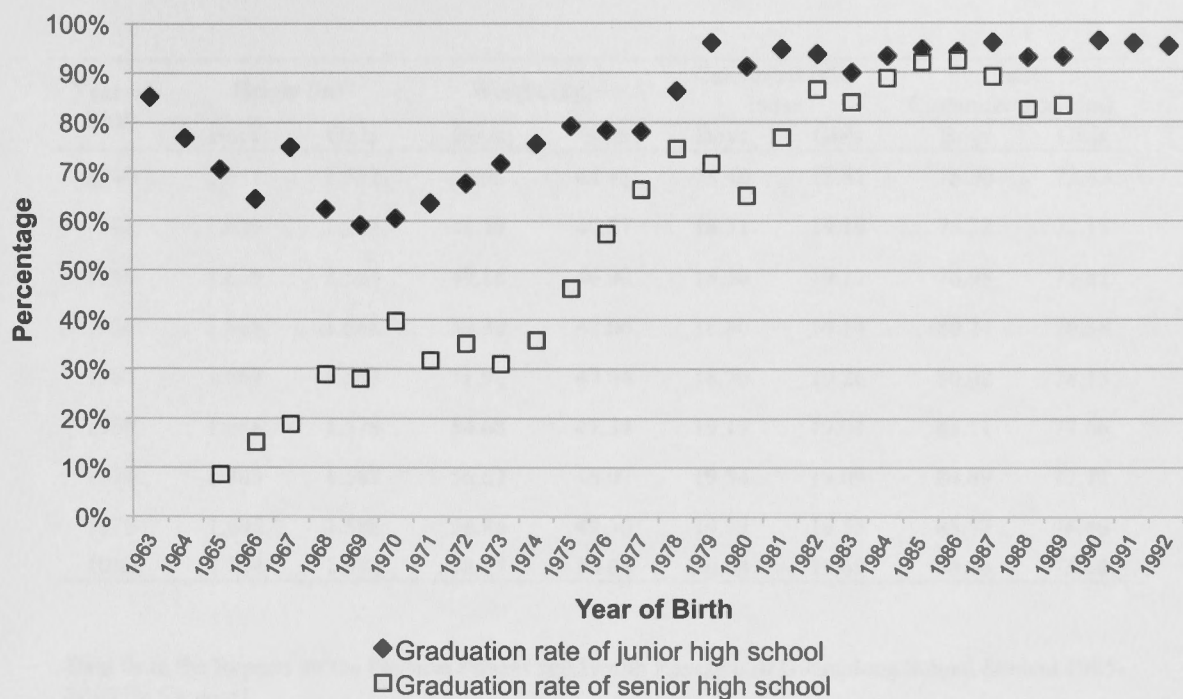


Figure 6.2 Comparison of myopia prevalence in Guangzhou, Singapore, Taiwan and Hong Kong

Data on changes in education in Guangzhou are given in Figure 6.2. From the end of the Cultural Revolution, the enrolment in and graduation rates from primary school into junior high school have been over 90%, increasing only slightly with time (data not shown). Similarly, graduation rates from junior high school into senior high have been high over much of this period, although there was a slight depression for those whose early childhood was disrupted by the Cultural Revolution. The most dramatic change was in the percentage of students completing senior high school, and thus qualified to go on to higher education in universities and colleges, from a low of around 10% for those born prior to the Cultural Revolution with a slow, progressive increase up to around 80-90% for current school leavers in Guangzhou.

Data on changes in height, weight, body mass index (BMI) and chest circumference in Guangzhou are shown in Table 6.1. Height, weight and chest circumference at age 17 have increased progressively and substantially from those born in 1940 to those born in 1983, for both boys and girls. However, over this period, there has been only a minor increase in mean BMI.



Graduation rate is calculated by expressing the number of students entering the next higher education level as a percentage of the total number of students enrolled in the current education level. The data therefore show that most students progress from junior high school to senior high school, and an increasing percentage has progressed from senior high school to further education in universities and colleges. Data from Guangzhou Yearbook

Figure 6.3 Graduation rate in Guangzhou

Year of Birth	Height (m)		Weight (kg)		Calculated BMI Index		Chest Circumference (cm)	
	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls
1940	1.631	1.532	48.95	44.15	18.40	18.81	78.30	73.82
1943	1.629	1.529	48.59	44.87	18.31	19.19	74.32	72.18
1946	1.639	1.564	49.16	46.90	18.30	19.17	76.98	75.81
1956	1.668	1.568	52.30	47.06	18.80	19.14	80.24	76.38
1962	1.667	1.563	51.96	47.04	18.70	19.26	80.02	78.15
1968	1.688	1.578	54.68	47.34	19.19	19.01	83.11	77.66
1974	1.703	1.587	56.67	48.07	19.54	19.09	84.89	77.72
1978	1.695	1.588	56.86	49.30	19.79	19.55	85.57	76.46
1983	1.714	1.594	58.75	50.04	20.00	19.69	84.08	75.69

Data from the Reports on the Physical Fitness and Health Research of Guangdong School Student 1985-2000 [in Chinese]

Table 6.1 Physical parameters of 17-year-olds in Guangzhou

6.4 Discussion

The methodological limitations of this reconstruction of the secular changes in prevalence of myopia in Guangzhou have already been discussed. A note of caution is also required because Guangzhou, a geographically limited site, is probably not representative of China as a whole, and because the population of Guangzhou has changed over time.

Despite these reasons for caution, the picture that emerges from these data is quite consistent. The prevalence of myopia in young adults in the four sites appears to have increased markedly. The prevalence of myopia in those born in the early years of last century was close to or under 30% in all sites, and remained at roughly that level until after the Second World War. But in all sites, the prevalence of myopia is now around 80-90% in young adults. There is, however, a striking difference between Guangzhou and the other sites in that the prevalence of myopia was already high in Taiwan, Hong Kong and Singapore in cohorts born in the 1960s, and probably somewhat earlier. The prevalence of myopia was much lower in Guangzhou for cohorts born in the early 1960s, and apparently only began to increase markedly in the early to mid 1970s. From then, there were progressive increases in the prevalence of myopia until high levels were reached for birth cohorts from the 1990s on.

These changes took place over a turbulent historical period for all sites. Taiwan was ceded to Japan in 1885, and only became part of China again at the end of the Second World War. During the Second World War, the other three sites were occupied by Japan. At all sites, living standards, including standards of health provision, were very low, even before the privations of the war period. After the Second World War, a process of rapid economic development began in Taiwan, Hong Kong and Singapore, which led to them being labeled the Asian Tigers (Kim, 1999). In contrast to these sites,

economic development in China was significantly delayed by the civil war which led to the founding of the Peoples Republic of China in 1949, and the tumultuous periods of the Great Leap Forward and the Cultural Revolution, which only finally came to a formal end in 1974.

After the end of the Cultural Revolution, the prevalence of myopia in Guangzhou gradually increased to reach levels in 1980 birth cohorts already reached at the other locations twenty years earlier. There is thus a good temporal parallel between economic development and the changes in prevalence of myopia. However, it is not simply a matter of GDP per capita, since GDP per capita in China, and even specifically in Guangzhou, is still well below that of the other sites – In 2009, the GDP per capita was 11,695 U.S. dollars in Guangzhou, compared to 29,825 U.S. dollars in Hong Kong, 19,074 U.S. dollars in Korea, 37,293 U.S. dollars in Singapore and 16,391 in Taiwan(Guangzhou Statistical Bureau , <http://data.gzstats.gov.cn/gzStat1/chaxun/njsj.jsp>; International Monetary Found database, <http://www.imf.org/external/pubs/ft/weo/2010/01/weodata/index.aspx>), yet the prevalence of myopia is now quite similar.

The degree of urbanisation has also increased markedly in Guangzhou, and the population density has increased over the period that myopia has increased, from 796 persons per square kilometer in 1970 to 1351 in 2007(Guangzhou Statistical Bureau, <http://data.gzstats.gov.cn/gzStat1/chaxun/njsj.jsp>). However, increasing population density is probably not the critical factor, since recent evidence from China suggests that the prevalence of myopia is now high across a range of sites with quite different population densities, even though there is a statistically significant increase in the prevalence of myopia with increasing population density(Zhang et al., 2010). This

suggests that other factors are associated with the bulk of the increase in prevalence of myopia in China. There is also some evidence of associations between myopia and the lived environment from both Sydney (Ip et al., 2008b), where children living in apartments are more myopic than those living in houses, and in Singapore (Saw et al., 2002d), where children living in smaller apartments are more myopic than those living in larger apartments. These data do not fit easily with an explanation in terms of restricted living space, and are highly confounded by educational and socio-economic differences and ethnicity. The lower prevalences of myopia in Shunyi (Zhao et al., 2000), Yangxi (He et al., 2007) and Yongchuan District (Pi et al., 2010) are consistent with an impact of lived environment, but may also be confounded by education.

Changes in diet are also a possibility. Cordain et al. (Cordain et al., 2002) put forward a biochemically plausible theory on how diet, specifically the consumption of high glycaemic load foods, and development of myopia might be linked. Height, weight and other indicators of stature such as chest circumference have increased significantly in Guangzhou since the Second World War and the Cultural Revolution, but there has been little change in BMI, as shown in Table 6.1. In addition, the evidence on associations between myopia and height, weight or BMI is mixed and inconsistent (Saw et al., 2002b, Ojaimi et al., 2005a, Low et al., 2010), and evidence from China has not associated myopia with body stature (Sharma et al., 2010). Overall, the evidence available gives little support to the idea that changes in diet which lead to increased height, weight or BMI inevitably lead to the development of myopia. While diet in Singapore children has been shown to affect axial length, no significant effects on refraction were observed (Lim et al., 2010), which is perhaps not surprising if emmetropisation is designed to provide all people, irrespective of their stature, with normal vision.

In contrast, there is a great deal of evidence supporting a link between myopia and education, based on associations between myopia and years of education, school grades and educational streams(Morgan and Rose, 2005). These associations have been reported from Singapore(Saw et al., 2007), and from other sites in China(Xu et al., 2005, Li et al., 2009, Liang et al., 2008, Pi et al., 2010). Singapore, Hong Kong, Taiwan and Guangzhou have developed highly intensive and highly competitive mass education systems, which deliver high educational outcomes by international standards(PISA 2009, http://www.oecd.org/document/61/0,3746,en_32252351_32235731_46567613_1_1_1_1,00). But, whereas highly competitive education rapidly became a feature of economic development in Singapore, Hong Kong and Taiwan, the development of education in China was massively disrupted by the Cultural Revolution, during which schools were barely functional and universities closed. School curriculums were frequently abandoned, and the plan to eradicate illiteracy fell behind schedule. Even earlier, the national university entrance examination, known as Gao Kao, was abolished, and political/social considerations were of major importance in access to higher education. But, after the end of the Cultural Revolution, the national university entrance examination was re-established. In subsequent years, 9 years of education was made compulsory. From Figure 6.3, it is clear that there have been marked increases in participation in schooling in Guangzhou. Now preschool (3-5 years), primary school (6-12 years) and junior high school (13-15 years) are close to universal, and an increasing percentage of children complete senior high school, and enroll in colleges or universities. This situation has emerged progressively from the end of the Cultural Revolution, and the slow but constant increase in senior high school graduation rates is quite similar to that in the prevalence of myopia. In Chongqing(Pi et al., 2010), the

prevalence of myopia in academically challenging schools is similar to that in Guangzhou, but in normal schools it is very much low. School completion rates by girls are higher than for boys. In Singapore, the rank order of prevalence of myopia for the major ethnic groups, Chinese>Indians>Malays, coincides with the rank order of educational outcomes(Saw et al., 2006).

More recently, another powerful, but protective environmental factor, the amount of time that children spend outside or on sports has been identified, since children who spend more time outside have a lower prevalence of myopia, irrespective of their performance of near work(Rose et al., 2008a, Rose et al., 2008b, Dirani et al., 2009a). The critical parameter appears to be spending time outside rather than physical activity per se(Rose et al., 2008a). Evidence of a protective effect of increased time spent outdoors has also been reported from Singapore(Dirani et al., 2009a) and Taiwan(Wu et al., 2010), and appears to account for the much higher prevalence of myopia in children of Chinese ancestry in Singapore as compared to ethnically matched children growing up in Sydney(Rose et al., 2008b), although no association has been reported from one Chinese site(Low et al., 2010). Again, in Singapore, the rank order of time spent outdoors of the major ethnic groups is the reverse of that seen for educational outcomes and the prevalence of myopia(Dirani et al., 2009a).

It is therefore plausible that a secular shift in life-style has taken place, resulting in less time spent outside by most children, leading to a shift in the population distribution of refractive error. Unfortunately, data on physical activity and time spent outdoors in the past has not been collected, and estimating the amount of time spent outdoors retrospectively may not be feasible.

6.5 Implications for the future

If reductions in the amount of time children spend outside in an educationally intensive social environment are the critical factors in the emergence of a pandemic of myopia, then prevention of myopia by increasing the amount of time spent outside by children could provide a method of prevention. In contrast, it is probably not feasible, let alone desirable, to reverse the trend towards urbanisation, greater availability of food and intensive education. Epidemiological estimates of the association of time spent outdoors with myopia suggest that the differences in time spent outdoors between children who become myopic and those who do not are relatively small (estimates range from a little as 1-2 hours per week to 1-2 hours per day), and could be achieved by public health programs. Reduced time outdoors may not be an inevitable concomitant of urbanisation and mass education, even if these factors encourage such trends. We have therefore begun a randomized trial in Guangzhou schools of a program to increase the amount of time that children spend outside by at least one hour per day through changes to the school day and education programs aimed at parents (see CHAPTER 8). Given that children who spend more time outside may also be more physically active, it may also be that a strategy developed to prevent myopia may also lead to reductions in overweight and obesity.

2.1 Introduction

As discussed in previous chapters, myopia has reached epidemic proportions in children and young adults in urban areas of East and South Asia, along with populations of Chinese ancestry. The rise of this epidemic is a consequence of a complex interplay of a number of factors, including changes in lifestyle, environmental factors, and genetic factors (Muller, 2007).

PART 2

PREVENTION OF MYOPIA IN CHILDREN

Myopia has been particularly prevalent in East and South Asia since the 1970s. In a 2006 review, Morgan et al. (2006) estimated that the prevalence of myopia in children and young adults in urban areas of East and South Asia was between 10% and 20%. The prevalence of myopia in children and young adults in urban areas of East and South Asia was between 10% and 20%.

Recent work has broadly focused on two potential factors in the development of myopia: (1) the environment and (2) the genetics. The protective effect appears to be due to both environmental factors and genetic factors (Morgan et al., 2006). The original hypothesis that the prevalence of myopia is due to the high light intensity outside, possibly acting via retinal stimulation of the visual system (Morgan et al., 2006a) has now been supported by observational studies (Morgan et al., 2006b). The protective effect of light appears to be mediated by the retinal stimulation of the visual system (Morgan et al., 2006b). The protective effect of light appears to be mediated by the retinal stimulation of the visual system (Morgan et al., 2006b).

Guangzhou Outdoor Activity Longitudinal (GOAL) Study

7.1 Introduction

As discussed in previous chapters, myopia has reached epidemic proportions in children and young adults in urban areas of East and Southeast Asia with populations of Chinese ancestry. The size of the myopia problem in China has been recognized by a recent resolution of the State Council (No.7 document of central government, May 2007 [in Chinese]), which requires schools to adopt strategies to limit the development of myopia. At present, there is no widely used optical or pharmaceutical method of preventing myopia or limiting its progression, although various interventions have been, or are being trialed (see CHAPTER 1). Attempts to manipulate accommodation have not been particularly successful (Saw et al., 2002c, Gwiazda, 2009, Li et al., 2011a). Recent studies showed that low concentration atropine eye drop might be safe and effective for slowing myopia progression in children, with minimal impact on visual function (Chia et al., 2011, Wu et al., 2011), although further validation is required.

Recent work has brought forward a powerful factor that prevents the development of myopia - time spent outdoors (Rose et al., 2008a, Jones et al., 2007). The protective effect appears to be due to total time outdoors, rather than sports per se (Rose et al., 2008a). The original hypothesis that the protective effect was due to the higher light intensities outside, possibly acting via increased release of the retinal transmitter dopamine, which is known to be able to reduce eye growth in some circumstances (Rose et al., 2008a) has now been supported by laboratory studies (Iuvone et al., 1991, McCarthy et al., 2007). The protective effect of bright light has been replicated in

animal experiments using UV-free light(Ashby and Schaeffel, 2010, Ashby et al., 2009).

The cross-sectional relationship between more time outdoors and decreased in myopia prevalence is strong, and it has also been shown that children who became myopic had fewer outdoor/sports activity hours than the emmetropes even before the onset of myopia on(Jones-Jordan et al., 2011). However, there is no longitudinal evidence showing that increased outdoor activity can cause a decreased incidence of myopia. The cause-effect relationship needs to be evaluated via an interventional clinical trial. Based on previous epidemiological studies and animal experiments, the Guangzhou Outdoor Activity Longitudinal (GOAL) Study has been designed to evaluate the effect of outdoor activities on children. The purpose of the GOAL study is to assess whether an intervention aimed at increasing time outdoors is effective in preventing the development and progression of juvenile-onset myopia in Chinese children. In this paper, we will report the design, methodology and baseline data of the GOAL study, and interim data on outcomes.

7.2 Study design

7.2.1 Study site

Guangzhou, the capital city of Guangdong province, is the economic, cultural, and academic centre of south China. According to a population census in 2008, it has a population of 10.18 million (Guangzhou Bureau of Statistics. Statistical Annual Report 2009 [in Chinese]). Residents are of Han Chinese ethnicity, and cover a wide socioeconomic spectrum. The Guangzhou metropolitan region has been chosen for the survey because extensive background data on the prevalence of myopia are available, which reveal that myopia is of extremely high prevalence among those completing high school.

7.2.2 Sample selection

In China, children normally start their formal primary school education at the age of 6 to 7. Before that, attending kindergarten or preschool is voluntary, but the enrolment rate is high in the city of Guangzhou. Given the high school attendance rates for school-aged children in Guangzhou (100% in 2007, Guangzhou Bureau of Statistics. Statistical Annual Report 2008 [in Chinese]), school-based populations represent the general population of Guangzhou children, except for rare conditions which might lead to schooling in special schools, and we therefore drew our study samples directly from school children. Considering the period during which myopia develops and progresses significantly, we chose to establish baseline data on children in primary school Grade 1 (aged 6 to 7 years), with follow-up to at least Grade 4. This cohort also provides a high retention rate, as younger students in primary schools are not very likely to change schools.

The Guangzhou Students' Health Care Institute takes the responsibility of performing annual medical health check up (including visual acuity test) for students in 30 public primary schools in Guangzhou city (evenly located in each district) over the past 20 years. Participating schools were selected from these schools.

7.2.3 Sample size calculation

Clinical trials normally involve randomisation of individuals to control and intervention arms. Preliminary power calculations suggested that randomisation of individuals would be logistically complex for recruitment and examination, and prohibitively expensive. The alternative of randomisation by classes within schools was considered, but required larger numbers. However this alternative was rejected primarily because, if the intervention gave promising results, it would be almost impossible to prevent strong demand from parents for extension of the intervention to the control arm. In addition, it is difficult, if not impossible, to promote time outdoors to only some parents in a school context. We therefore decided that randomisation by schools was the only practical alternative.

We enrolled 6 schools in each arm, with a total of approximately 1,500 students, based on the following considerations:

1. The cluster size is approximately 120, being the average number of students of Grade 1 in each school;
2. The background incidence rate is around 10% per year from Grade 1 to 4(He et al., 2004);
3. For statistical purposes, we set the required reduction in the incidence of myopia at 50%, compared to control group, since minor effects are not particularly helpful in a public health context;

4. The intra-class correlation coefficient (ratio of between cluster variance to between and within cluster variance, ICC) was assumed to be 0.01 and the precise matching of schools on the basis of visual acuity data permitted use of a low estimate of the inflation factor (IF) of 0.01 associated with randomisation by schools, rather than by individuals and classes;
5. Participation rate of 90%;
6. Loss-to-follow up of no more than 5% per year.

7.2.4 School matching procedure

Among 30 schools, 29 schools had complete visual acuity data over the past 20 years. We stratified them into 6 strata, based on similarity of visual acuity from Grade 1 to Grade 6. In each stratum, 2 schools were randomly selected and allocated to intervention group or control group. As such, schools in the intervention group were matched closely to schools in the control group. The detail school matching procedure was as follows (Figure 7.1):

1. The twenty-nine schools with visual acuity data (conducted by the Guangzhou Students' Health Care Institute) were allocated a number from #1 to #29. For each school, the proportion of students with normal vision (visual acuity $\geq 20/25$) in their right eyes was calculated by grade (grade 1 to grade 6). Out of the 29 schools, 4 with a percentage of normal vision students less than 80% in grade 1 were eliminated from the school matching procedure: #7, #17, #20, and #24.
2. Twenty-five line graphs were drawn to illustrate the percentage of children with normal vision from grade 1 to 6 for each school. These graphs were printed out on transparencies and matched by eye. Schools with the most similar trends of change from grade 1 to 6 were grouped with 6 groups created. 3 schools were eliminated as they could not be grouped: #4, #6 and #29.

3. Six groups of schools were then defined in descending order of the percentage of normal vision in grade 1 and assigned from stratum 1 to 6. Each stratum from 1 to 4 was allocated 4 schools while strata 5 and 6 were allocated 3 schools each. At random, 2 schools were selected from each stratum, and randomised in intervention group or control group.
4. Validation test. Chi-square test was applied to verify whether the schools in one stratum were well matched in terms of the percentage of students with normal vision in each grade. If any two of the schools had differed significantly from each other (Chi-square test $P \leq 0.05$), a third school would then be selected from the same stratum and the validation test applied again, until two matching schools were identified. In practice, all schools in each stratum were matched using this criterion.

7.2.5 Recruitment and informed consent

When the school selection and randomization completed, the Guangzhou Education Bureau administratively designated 6 schools as the intervention group and awarded them the title of “Myopia Prevention Trial Model School”. The Guangzhou Education Bureau and the Guangzhou Students’ Health Institute assisted the study team from Zhongshan Ophthalmic Center to conduct information sessions for principals and head teachers of Grade 1 in the intervention schools. In the sessions, we explained the study rationale, procedure, and teachers’ duty in detail, to obtain better cooperation.

Before data collection, all 12 participating schools held the parent seminars in each participating class (i.e., all classes in Grade 1). In the seminars, parents/guardians were informed on the proposed baseline eye examinations, including the effects of the papillary dilation and cycloplegia, and were asked to sign an informed consent form. Study investigators answered queries raised by parents and made further attempts to

recruit if the parents initially refused to give consent. In addition, parents of children in the intervention schools were told about the positive effect of outdoor activities on myopia. A flow chart summarizing study procedure is shown in Figure 7.1.

Approval for the study of human subjects was obtained from the Ethics Committee of the Zhongshan Ophthalmic Center and Guangzhou Education Bureau. The work was conducted in accordance with the tenets of the World Medical Association’s Declaration of Helsinki. The study has been registered on the Clinic Trial Protocol Registration system (ClinicalTrial.gov ID: NCT00848900).

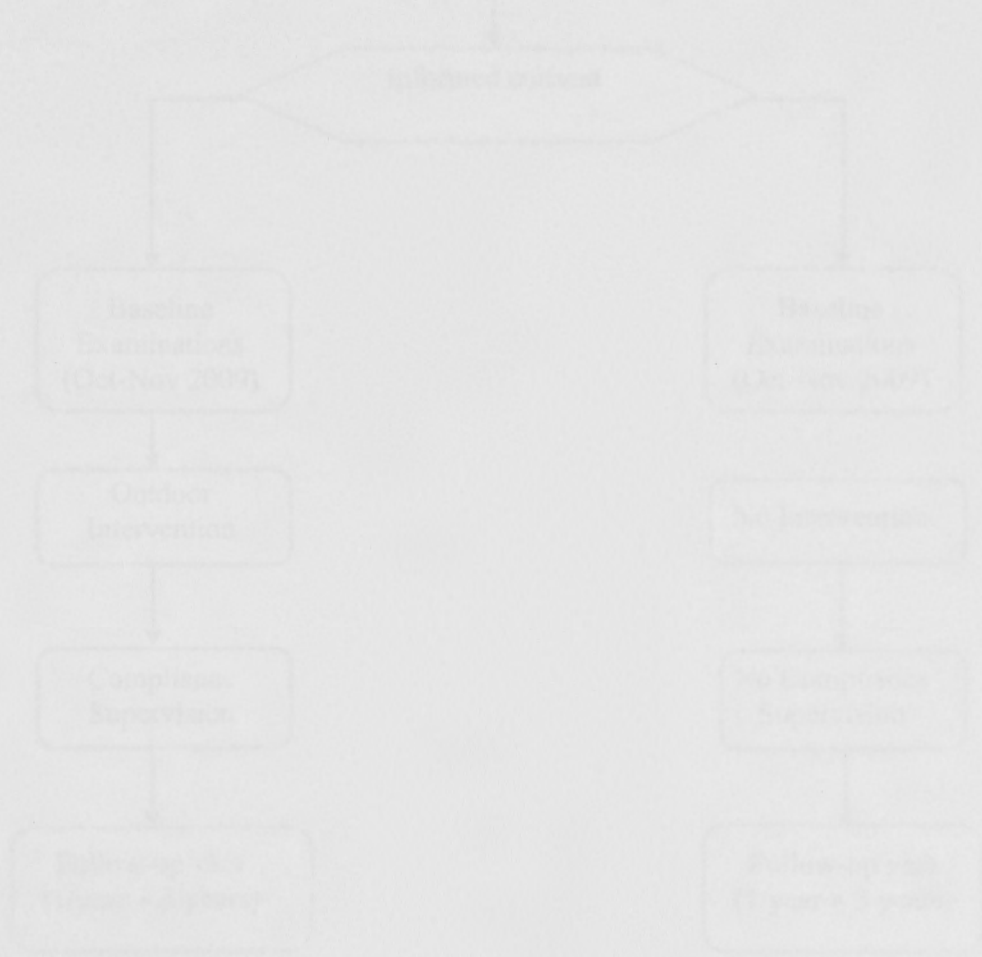


Figure 7.1 Flow chart of study procedure

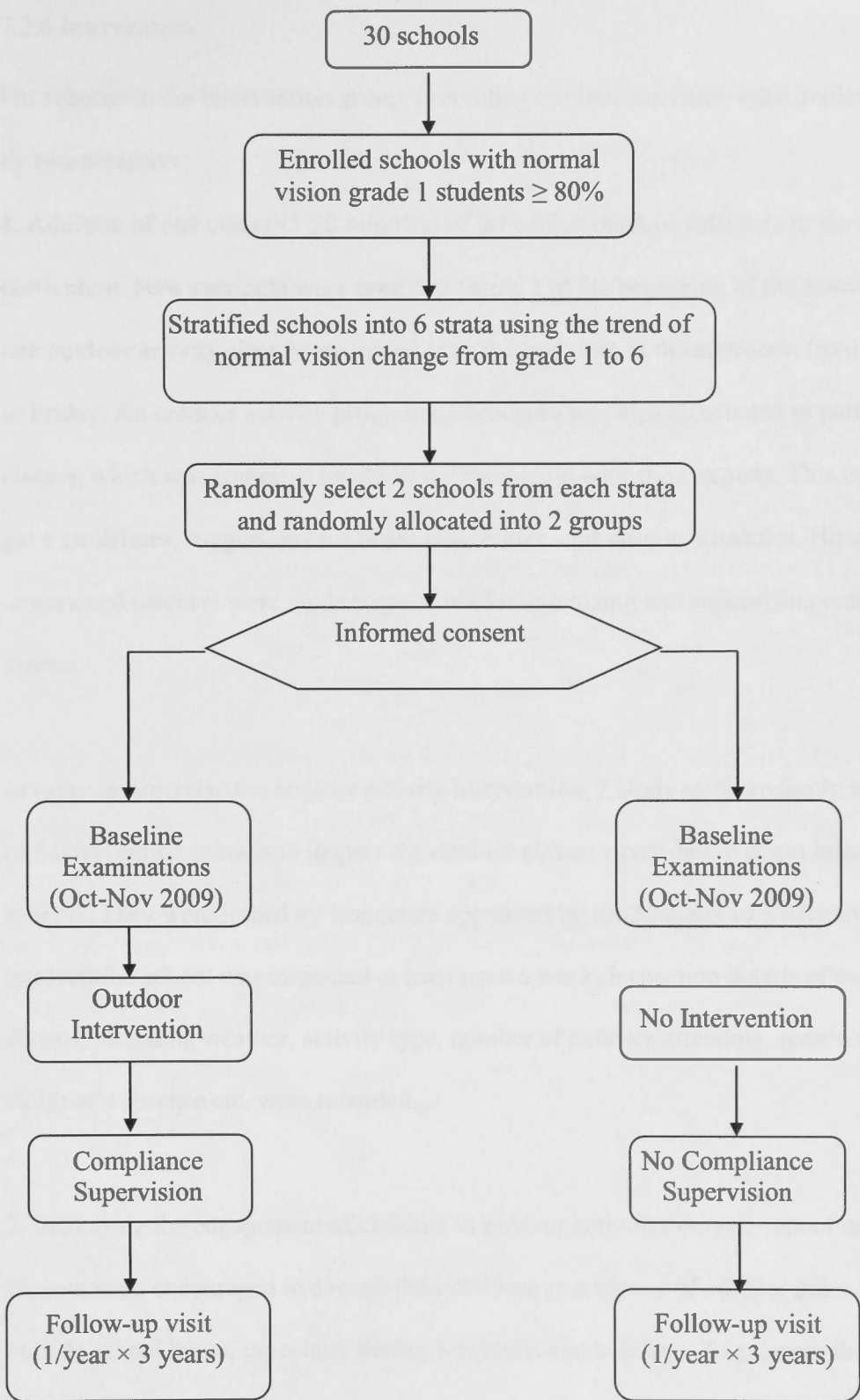


Figure 7.1 Flow chart of study procedure

7.2.6 Intervention

For schools in the intervention group, promoting outdoor activities were implemented by two measures:

1. Addition of one class (45-50 minutes) of scheduled outdoor activities to the school curriculum. New curricula were issued to Grade 1 at the beginning of the semester, with one outdoor activity class being added after the last class in the afternoon from Monday to Friday. An outdoor activity programme brochure was also distributed to participating classes, which was compiled by study staff and child education experts. This brochure gave guidelines, suggestions for outdoor activities, and sample schedules. Head teachers or assigned teachers were made responsible for organizing and supervising outdoor classes.

In order to supervise the outdoor activity intervention, 2 study staff randomly went to 2 of 6 intervention schools to inspect the outdoor classes every day, without informing schools. They were joined by inspectors appointed by the Ministry of Education. Each intervention school was inspected at least once a week. Inspection details of each classes, including weather, activity type, number of children attending, reason for children's absence etc. were recorded.

2. Increasing the engagement of children in outdoor activities outside school hours.

Parents were encouraged to engage their children in a variety of outdoor pursuits outside school hours, especially during weekends and holidays. To promote this engagement, several measures were implemented, such as providing children with gear (e.g., school bags, umbrellas, water bottles, caps etc.) with special printed outdoor logos, periodical newsletters to parents, and a diary competition where children recorded their weekend outdoor activities.

This intervention was negotiated with participating schools and GSHI, and the Ministry of Education. The intervention is in many ways minimal, but was the maximum that could be achieved, and which could be sustained for the proposed intervention period.

Children in control schools continued with their normal patterns of activity.

7.2.7 Quality control and validation test

In order to evaluate whether the children in the intervention group increased the amount of time spent outdoors, skin colour measurement was applied as the validation test. In detail, a piece of upper inner arm skin was chosen as reference skin for each child, given the minimal sun exposure of this part of the skin, and the dorsal part of lower forearm was chosen as exposure skin, for determining the amount of sun exposure (UV radiation). A chromameter was used to measure the colour of reference skin and exposure skin (Konica Minolta Chromameter CM-2600D, Konica Minolta, Japan), and the colour differences between two pieces of skin were calculated. If children in intervention group spend more time outdoors than children in control group, the difference between reference skin and exposure skin should be more significant in intervention group. Skin colour measurements were performed in baseline examination and each follow up examination. This validation approach has proven to be difficult to apply in practice.

7.2.8 Study visits

Baseline visits were conducted from October to November, 2009. Follow-up visits were to be conducted at the end of the first, second and third intervention year. The design and protocols of examinations in our study was based on the Guangzhou Twin Eye

Study(He et al., 2006) and RESC series study(Negrel et al., 2000). Wherever possible, non-contact technology (IOLMaster, autorefraction etc.) was applied.

The examinations were carried out by one clinical team comprising 6 ophthalmic nurses, 2 optometrists and 1 ophthalmologist. In the baseline examinations, firstly, children's **anthropometry**, including weight, height, and skin colour were measured using standard protocols. Eye examinations then began with **distance visual acuity tests** at 4 m using an ETDRS chart (Precision Vision, Villa Park, Illinois, USA) with standard illumination. If the orientation of at least four of five optotypes was identified, the child was then tested by dropping down to the 4th line (20/100). If at least four optotypes were identified correctly, the 7th line (20/50) was tested, continuing to the 10th (20/25) line and finally the 11th line (20/20). If at any level, the child failed to identify four optotypes, the line immediately above the line was tested. If the top line (20/200) could not be identified, the child was advanced to a distance of 1 meter from the chart, and tested from the top line again. The lowest line identified successfully was recorded as the visual acuity for the testing eye. The right eye was tested first, followed by the left eye, each time occluding the fellow eye. In children who were wearing glasses, **lens power** was measured with an autolensometer (LM-970, Nidek Corp., Tokyo, Japan). **Cover-uncover tests** were used to identify any tropia. The child was required to fixate a torch at 0.5m with both eyes open, then the right eye was covered to detect any movement of the left eye. After a short uncover time, the left eye was covered and right eye was checked. If the uncovered eye moved outward, esotropia was assigned, if it moved inward, extropia was assigned, while if there were no significant eye movements. Then the 4m cover test was performed with the same procedure. The corneal light reflex was assessed to quantify the degree of tropia, and categorized as less than 15 degrees (a reflex within the pupillary margin), 16-30 degrees (a reflex at mid-

iris), and greater than 30 degrees (a reflex at limbus). **Cycloplegia** was induced with three drops of 1% cyclopentolate administered at 0, 5th, 20th minute to each eye, respectively. The light reflex and pupil dilation were checked after an additional 15 minutes. Dilation and light reflex status were recorded and full cycloplegia was assumed if the pupil dilated to 6 mm or greater and the light reflex was absent. During the waiting time for the pupil dilation, **ocular biometry**, including axial length, anterior chamber depth and corneal curvature were measured by non-contact partial-coherence laser interferometry (IOL Master, Carl Zeiss Meditec, Oberkochen, Germany). Three measures were taken for the right eyes only. The axial length and anterior chamber depth measurement was based on the mean of three values if the desired precision (i.e., <0.1 mm) was achieved. The procedure was performed on children after the third eye drop was administrated. **Autorefraction** was performed with an autorefractor (KR-8800, Topcon, Tokyo, Japan) by an experienced optometrist. Three measurements were taken on the right eye first, followed by the left eye. The reliability of each measure was indicated by an automatic numeric assessment provided by the autorefractor. A mean value of three measurements were printed out and recorded in the examination form.

Subjective refraction was performed on children with uncorrected visual acuity 20/40 or worse, using autorefractive values as a starting reference. After refraction, the **anterior segment**, including eyelid, conjunctiva, cornea, iris and pupil was examined and **direct ophthalmoscopic examinations**, including lens, vitreous and fundus, were performed by the team ophthalmologist. Specific abnormalities were recorded in detail. Finally, all eyes were categorized as no visual impairment (uncorrected visual acuity $>20/40$) and visual impairment (uncorrected visual acuity $\leq 20/40$). For eyes in the visual impairment category, a principal cause of reduced vision was designated by the team

ophthalmologist using a seven-item list (refractive error, amblyopia, corneal opacity due to trachoma, other corneal opacity, cataract, retinal disorder, other causes).

When all examinations were completed, reading glasses were provided to children with cycloplegia free of charge to minimise difficulties with nearwork associated with cycloplegia. The reading glasses were collected by head teachers after three days. For children with an uncorrected visual acuity of 20/40 or worse in the better eye which improved with refractive correction, prescription glasses were also given free of charge. The flow chart of baseline examination procedures is shown in Figure 7.2. Examinations for follow up visits will be the same as for the baseline visit.

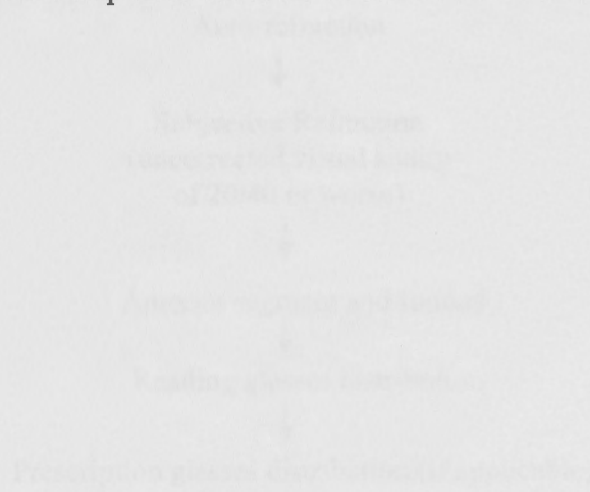


Figure 7.2 Flowchart of examination procedures

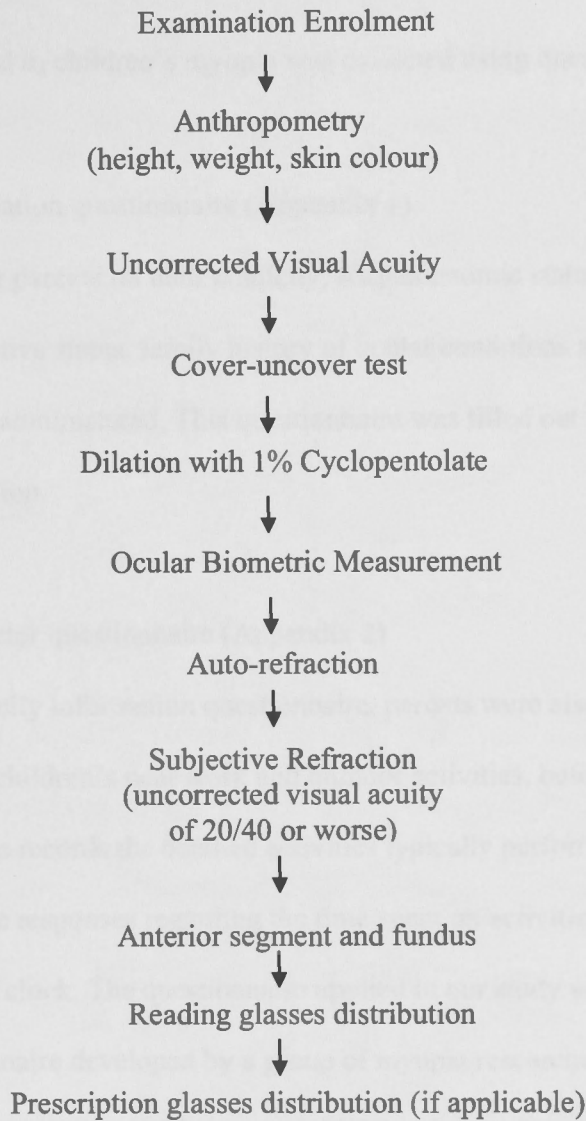


Figure 7.2 Flow chart of examination procedures

7.2.9 Related information collection

Information related to children's myopia was collected using questionnaires and standard tests.

1. Family information questionnaire (Appendix 1)

Questionnaires for parents on their ethnicity, socioeconomic status, education level, occupation, refractive status, family history of ocular conditions and other related information were administered. This questionnaire was filled out by parents before the baseline examination.

2. Myopia risk factor questionnaire (Appendix 2)

Together with family information questionnaire, parents were also asked to complete a questionnaire on children's near work and outdoor activities, before the baseline visit. This questionnaire records the detailed activities typically performed on weekdays and weekends, and the responses regarding the time spent on activities were validated against a 24-hour clock. The questionnaire applied in our study was based on the standard questionnaire developed by a group of myopia researchers convened by the World Health Organization in Singapore, which has been adopted in several on-going WHO-sponsored studies on myopia in children (He et al., 2004, He et al., 2007, Rose et al., 2008b).

3. Children's learning behaviour questionnaire (Appendix 3)

Children's learning behaviour including examination ranks, performance in class, homework accomplishment etc. were reported by the head teacher of each class. This questionnaire will be administered annually.

4. Children's academic performance

A series of standardized exams (including Chinese, Mathematics, English, etc.) were organized by the Guangzhou Education Bureau every academic year, for collecting information on academic achievement for all participating students.

5. Children's physical and fitness performance

The Guangzhou Students' Health Care Institute collects data on physical health parameters every year. The test protocol and standard for evaluation were uniform in all participating schools.

7.2.10 Data entry and analysis

Examination forms and questionnaires were reviewed for accuracy and completeness before computer data entry at the Zhongshan Ophthalmic Center. Measurement data ranges, frequency distribution, and consistency among related measurements were checked with data cleaning programs. Statistical analyses were performed with Stata (Statistical Software, Stata Corp., College Station, TX).

The definitions for myopia, hyperopia, and astigmatism were in accordance with the RESC studies (Negrel et al, 2000). Briefly, myopia was defined as a spherical equivalent refractive error (SER, sphere + $\frac{1}{2}$ cylinder) of at least -0.50 diopters (D), hyperopia was defined as 2.00 D or greater, and astigmatism was defined as a cylinder of 0.75 D or greater.

In this study, there are three major outcomes for evaluating the development of myopia - changes in mean spherical equivalent refraction and axial length, and in the prevalence of myopia. The progressions of refractive error and axial length will be compared between two groups using standard parametric tests (t-test), while changes in the

prevalence of myopia will be compared using Chi-square tests. The refractive error data of right eyes were used for analysis, and data of left eyes were used only if right eye data was not available. In addition, multivariate analysis, including linear correlation and linear regression models, will be applied to analyse the associations of risk factors with the progression of refractive error and axial length.

7.3 Baseline data

Grade 1 in 12 primary schools were enrolled, with a total of 18 classes and 1955 children. Baseline examinations began in October 2009 and were completed in November 2009. For intervention schools, the outdoor intervention began immediately after baseline examinations. On the day of baseline examinations, 66 children did not attend school, and 10 children were uncooperative and could not complete examinations, so baseline data were collected from a total of 1879 children. For all the children examined, the overall baseline visual acuity was good, with 1693 (90.1%) children having uncorrected acuity of 20/32 or better in both eyes, while 186 children had visual acuity 20/40 or worse in one or both eyes, of whom 149 (80.1%) attained acuity 20/32 or better in at least one eye with subjective refractive correction. Only 27 children had uncorrectable low visual acuity in both eyes.

Baseline characteristics for children with complete examination data are summarized in Table 7.1. As shown, there was no significant difference for gender proportion, height and weight between the intervention group and control group, but children in the intervention group were slightly older than those in the control group (6.62 ± 0.37 years vs. 6.54 ± 0.40 years, $p < 0.001$). There was also no significant difference for the percentage of children with better visual acuity (20/30 or better) and worse visual acuity (20/63 or worse) between two groups. The percentage of parents agreeing to cycloplegia was significantly higher for the intervention group. This may be because that the parents of intervention schools had been given more information about myopia during the parents seminars. The prevalence of myopia was low in both intervention and control groups, and the difference between two groups was not significant.

Characteristic	Intervention group (n=938)	Control group (n=941)	P	Total (n=1879)
Gender				
Boy	492 (52.45%)	517 (54.94%)	0.290	1009 (53.70%)
Age	6.62±0.37	6.54±0.40	<0.001	6.59±0.34
Height	120.2±5.3 cm	120.5±5.0 cm	0.207	120.4±5.1cm
Weight	22.5±4.5 kg	22.6±5.2 kg	0.859	22.5±4.3 kg
Agreement to cycloplegia	889 (94.78%)	754 (80.13%)	<0.001	1643 (87.44%)
Visual Acuity in both eyes				
20/32 or better	833 (88.80%)	860 (91.39%)	0.688	1693 (90.10%)
20/63 or worse	8 (0.86%)	12 (1.28%)	0.501	20 (1.06%)
Prevalence of myopia	1.9%	2.1%	0.860	2.0%

Table 7.1 Baseline characteristics by study group

The mean SER and axial length in intervention and control schools by stratum are shown in Table 7.2 and 7.3. Overall, for all children with cycloplegia, there was no statistically significant difference for SER and axial length between the two groups ($p=0.474$). The mean axial length was also similar between two groups ($p=0.065$), as was the prevalence of myopia. Comparing the schools in each stratum, there were no statistically significant differences in mean SER, axial length and prevalence of myopia.

The distributions of cycloplegic autorefraction, axial length, corneal curvature and AL/CR ratio in right eyes for all participating children are presented in Figures 7.3 to 7.6. The distribution of refractive error at baseline was tight with substantial kurtosis (kurtosis value: 72.8). The distribution of AL/CR had a similar shape to that of refractive error. The distributions of axial length and corneal curvature were wider and tended to be normally distributed. Overall, a majority of Grade 1 children were emmetropic. In children with cycloplegic refraction, 83.4% of them had a refractive error between -0.5D to 2D, and 14.6% had a hyperopic refractive error, while only 2.0% of them had myopic refractive error. The mean value of cycloplegic SER for all children was 1.27 ± 0.91 D. The distributions of height, weight and BMI index for all participating children were shown from Figure 7.7 to 7.9. The distribution of height was normal, while the distributions of both weight and BMI were skewed to the right.

School Stratum	Mean SER (D)*		P value
	Control	Intervention	
1	1.31±0.89	1.27±0.86	0.666
2	1.23±0.77	1.37±0.76	0.055
3	1.25±1.05	1.35±0.72	0.348
4	1.15±0.58	1.33±0.85	0.059
5	1.29±0.82	1.23±0.81	0.595
6	1.19±0.64	1.18±1.42	0.951
Overall	1.26±0.84	1.29±0.97	0.474

* For children with cycloplegia

Table 7.2 Baseline mean Spherical Equivalent Refraction (SER) by school

School Stratum	Mean AL (mm)		P value
	Control	Intervention	
1	22.64±0.71	22.62±0.79	0.798
2	22.68±0.65	22.58±0.67	0.107
3	22.68±0.78	22.58±0.68	0.243
4	22.65±0.65	22.59±0.71	0.501
5	22.74±0.73	22.55±0.66	0.051
6	22.65±0.71	22.63±0.76	0.837
Overall	22.67±0.70	22.61±0.71	0.065

Table 7.3 Baseline mean axial length (AL) by school

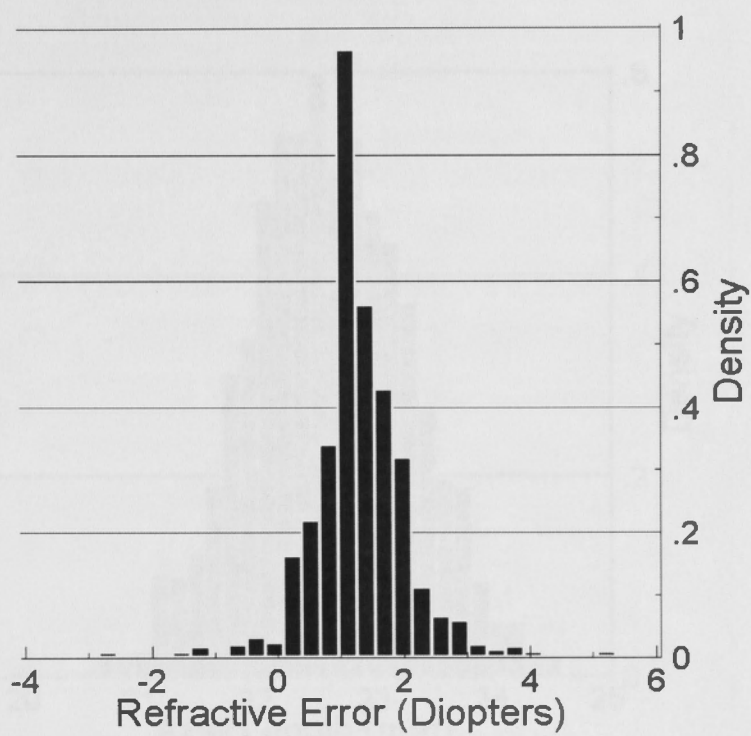


Figure 7.3 Distribution of refractive error in participating children with cycloplegia

Figure 7.4 Distribution of axial length in participating children

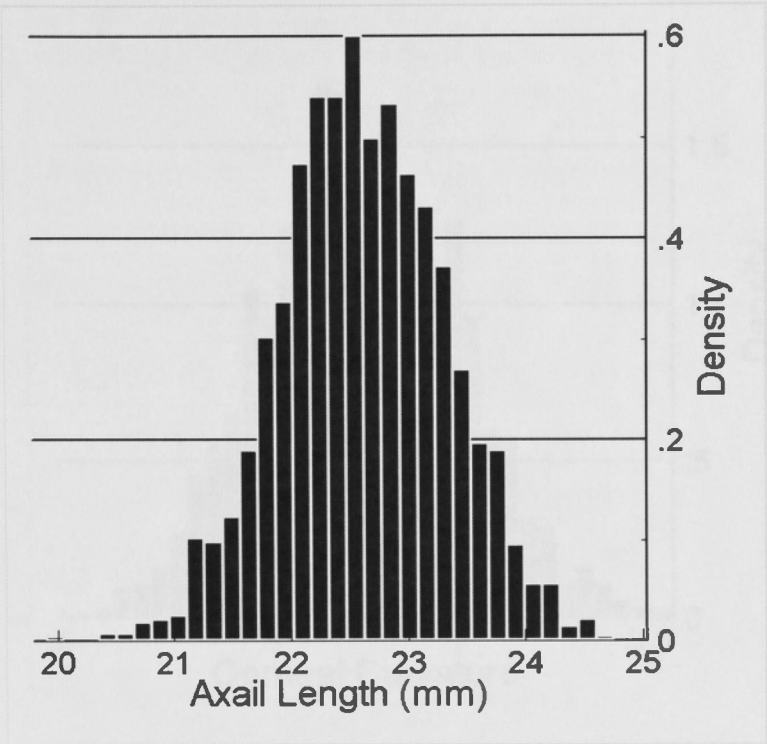


Figure 7.4 Distribution of axial length in participating children

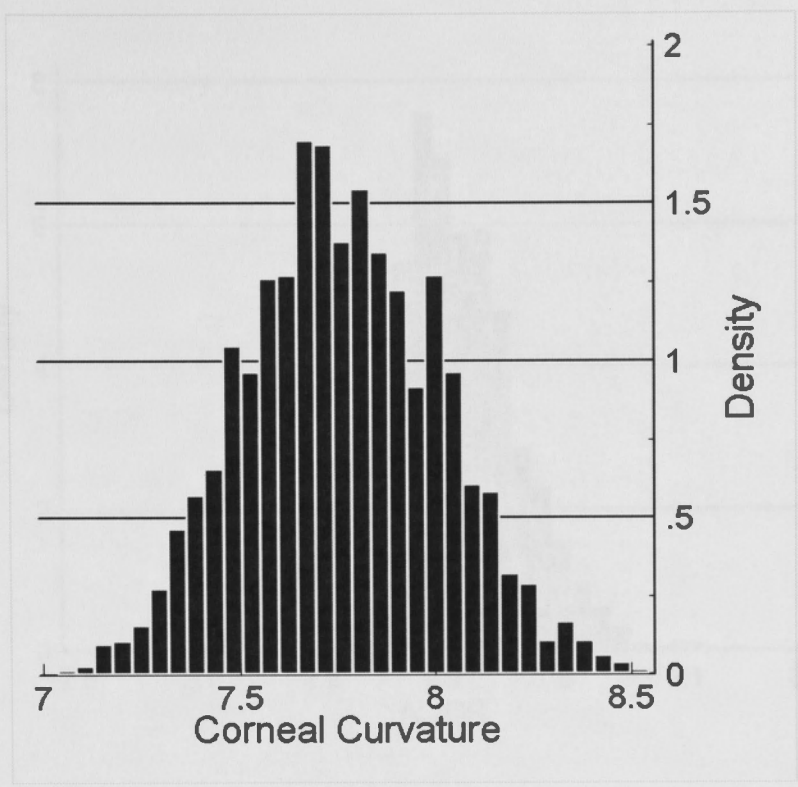


Figure 7.5 Distribution of corneal curvature in participating children

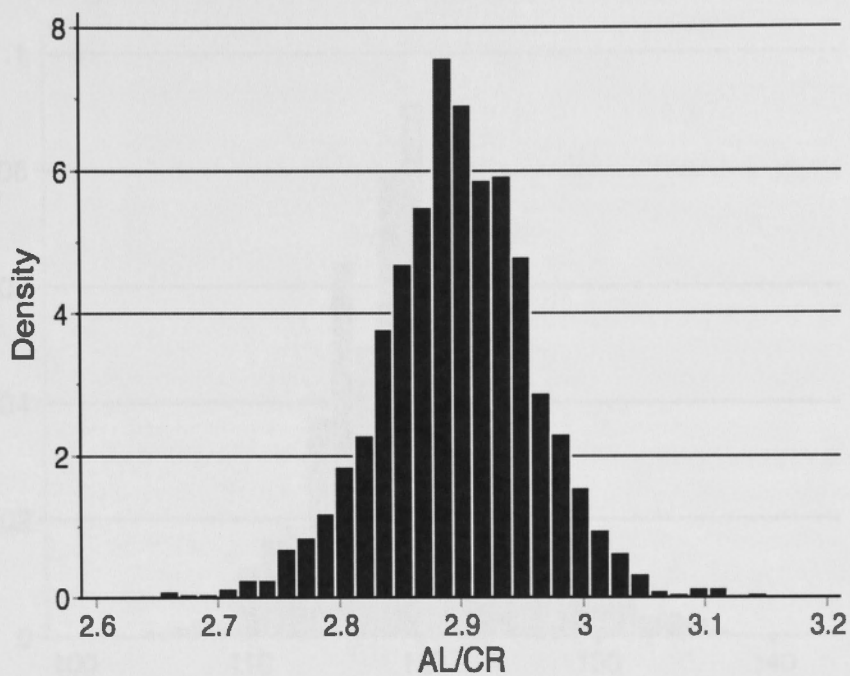


Figure 7.6 Distribution of AL/CR ratio in participating children

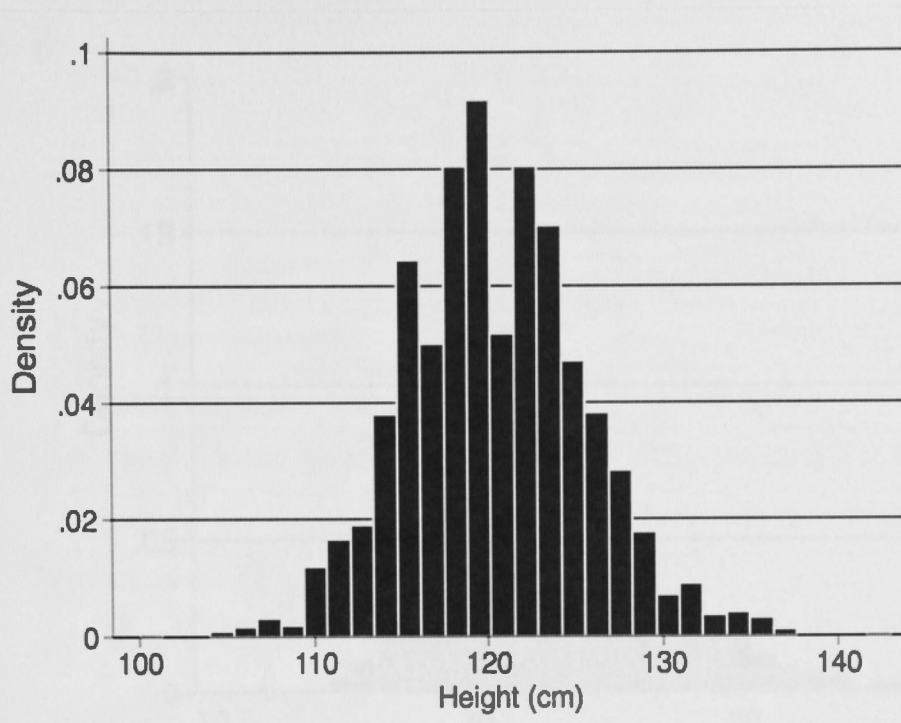


Figure 7.7 Distribution of height in participating children

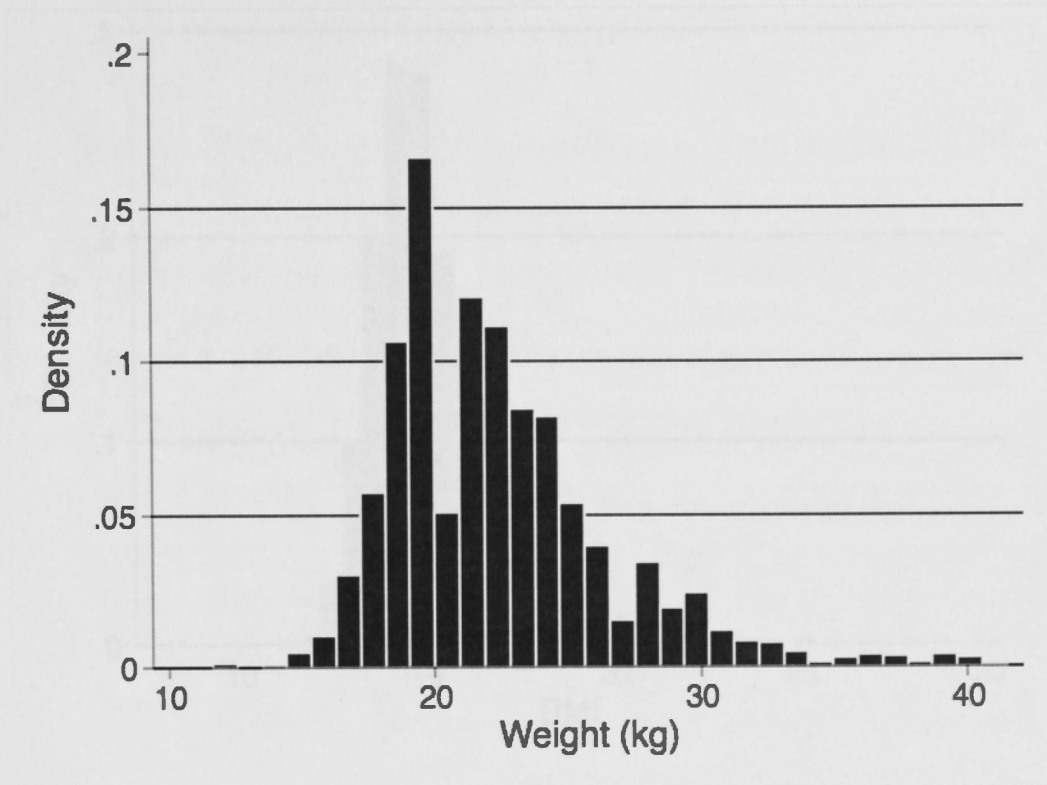


Figure 7.8 Distribution of weight in participating children

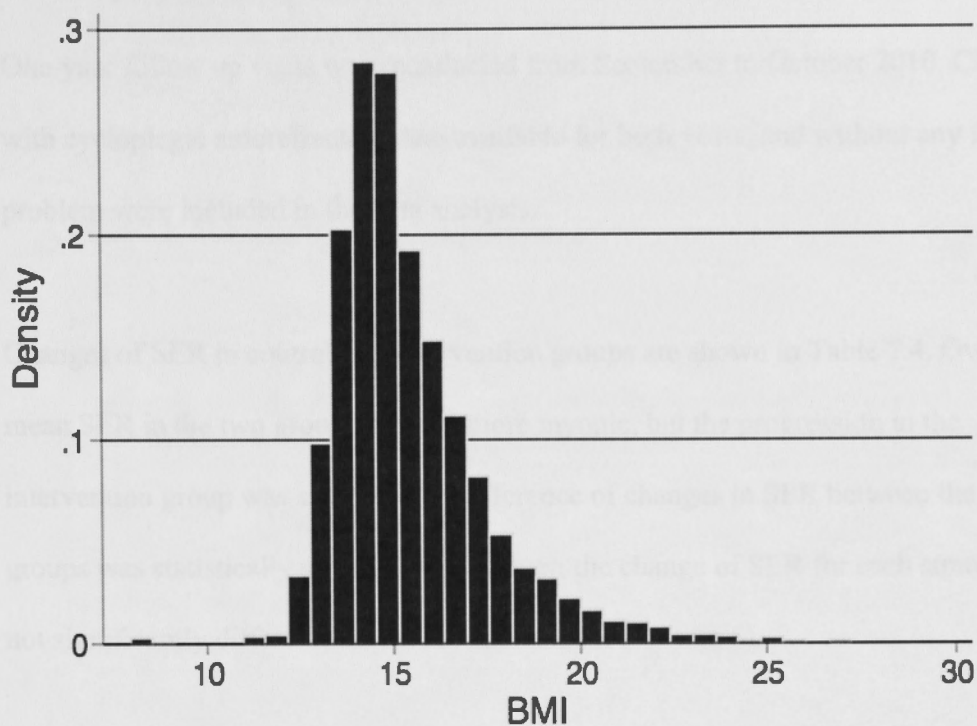


Figure 7.9 Distribution of BMI in participating children

7.4 One-year follow up data

One-year follow up visits were conducted from September to October 2010. Children with cycloplegic autorefraction data available for both years, and without any fundus problem were included in the data analysis.

Changes of SER in control and intervention groups are shown in Table 7.4. Overall, the mean SER in the two groups became more myopic, but the progression in the intervention group was smaller. The difference of changes in SER between the two groups was statistically significant. However, the change of SER for each stratum was not significantly different, except for one stratum (stratum 6).

Table 7.5 shows the changes of AL in the two groups. Again, the axial length elongated more slowly in the intervention group, and the difference was statistically significant between the two groups. However, within each stratum, the difference was not significant.

The distribution of SER, axial length, corneal curvature and AL/CR ratio in right eyes for children participating in one-year follow up visit are shown in Figure 7.10 to 7.13. Comparing with the baseline data, the distribution of SER became wider and shifted toward myopia (kurtosis value: 6.79). The distributions of axial length, corneal curvature and AL/CR ratio were also broader than in the baseline, but still tended to be normally distributed. The distributions of height, weight and BMI index for all participating children are shown from Figure 7.13 to 7.16. The distributions of height and weight shifted to the right, compared to the baseline data, and the distribution of BMI became wider and was still skewed to the right.

School Stratum	Change of SER (D)		P value
	Control	Intervention	
1	-0.397±0.54	-0.387±0.46	0.438
2	-0.372±0.45	-0.341±0.43	0.265
3	-0.241±0.35	-0.166±0.36	0.054
4	-0.206±0.34	-0.181±0.39	0.356
5	-0.325±0.43	-0.225±0.44	0.081
6	-0.401±0.54	-0.172±0.38	<0.001
Overall	-0.337±0.46	-0.248±0.42	<0.001

Table 7.4 Changes of SER in control and intervention group

School Stratum	Change of AL (mm)		P value
	Control	Intervention	
1	0.36±0.22	0.34±0.19	0.229
2	0.35±0.21	0.32±0.19	0.137
3	0.29±0.37	0.24±0.14	0.054
4	0.30±0.13	0.27±0.14	0.085
5	0.30±0.17	0.29±0.19	0.387
6	0.33±0.21	0.28±0.20	0.048
Overall	0.33±0.24	0.29±0.18	<0.001

Table 7.5 Changes of axial length in control and intervention group

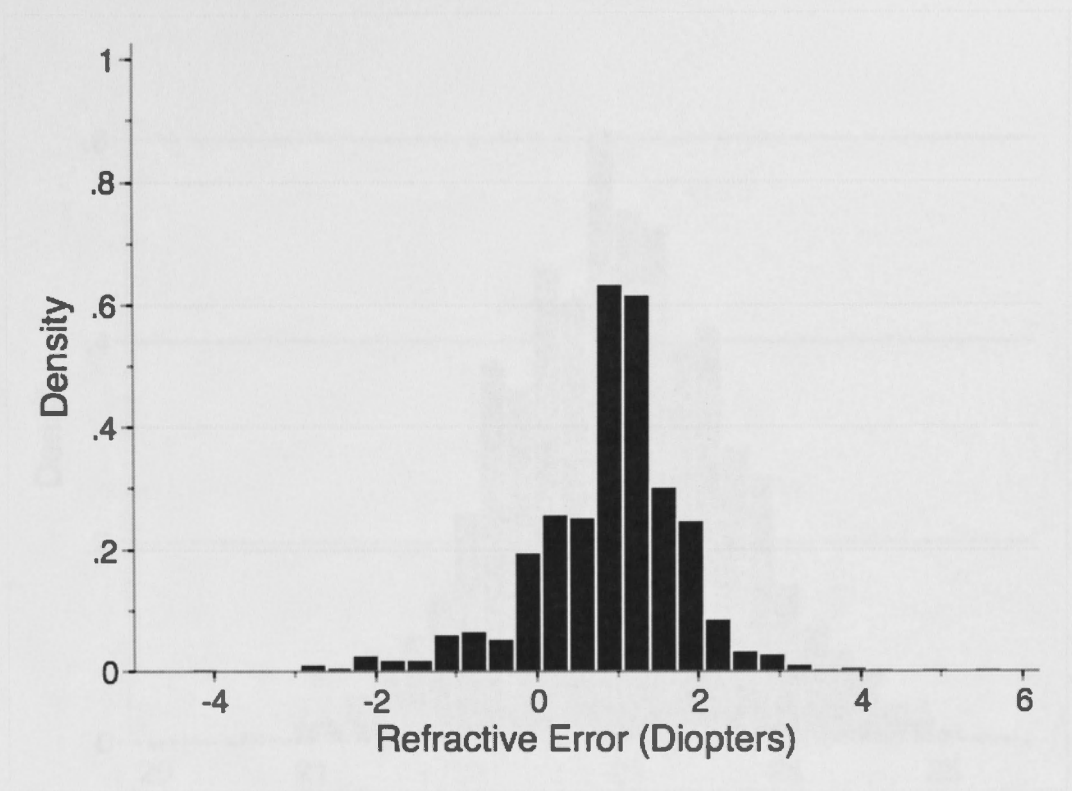


Figure 7.10 Distribution of refractive error in participating children with cycloplegia (one-year follow-up visit)

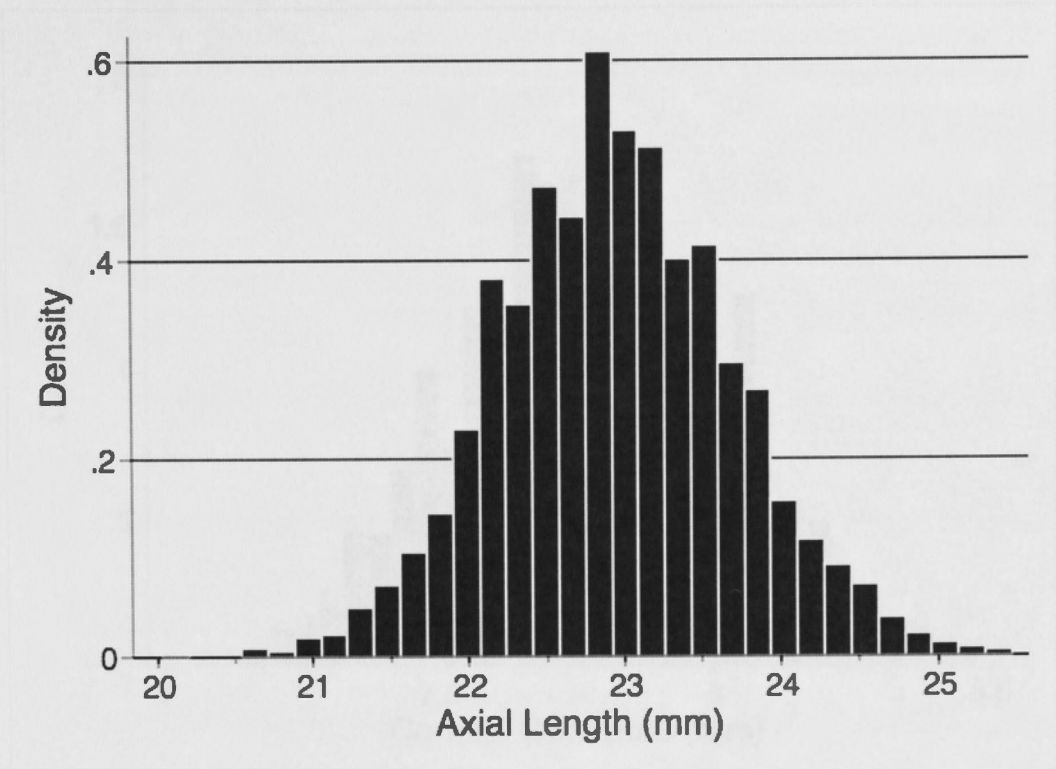


Figure 7.11 Distribution of axial length in participating children (one-year follow-up visit)

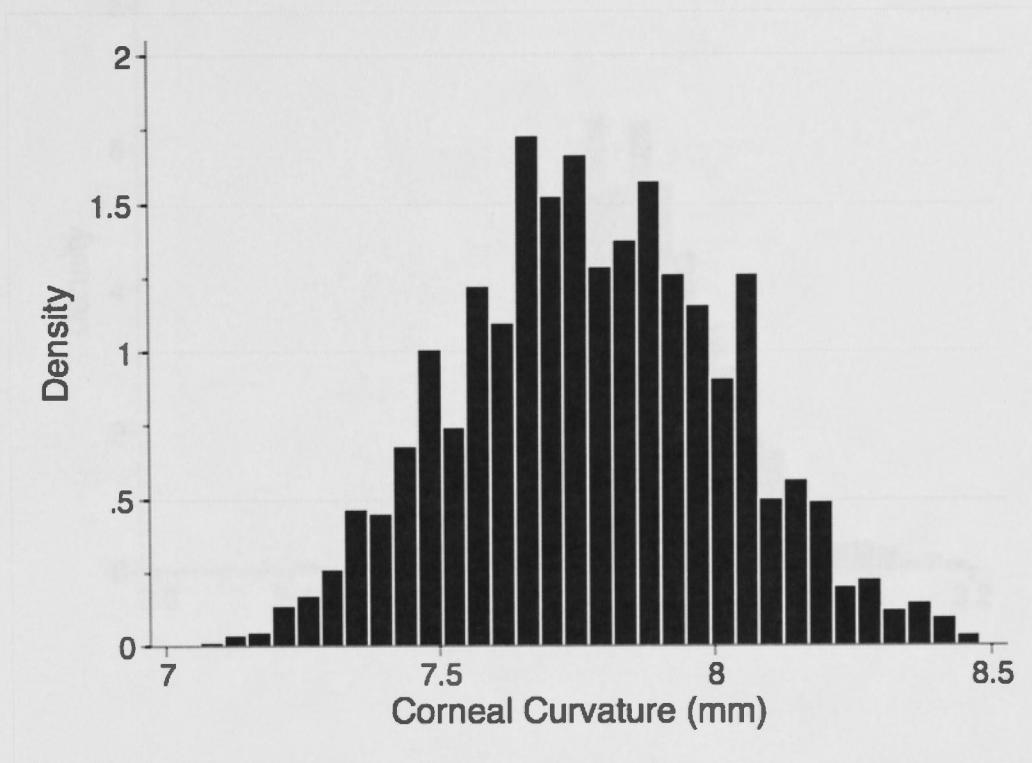


Figure 7.12 Distribution of corneal curvature in participating children (one-year follow-up visit)

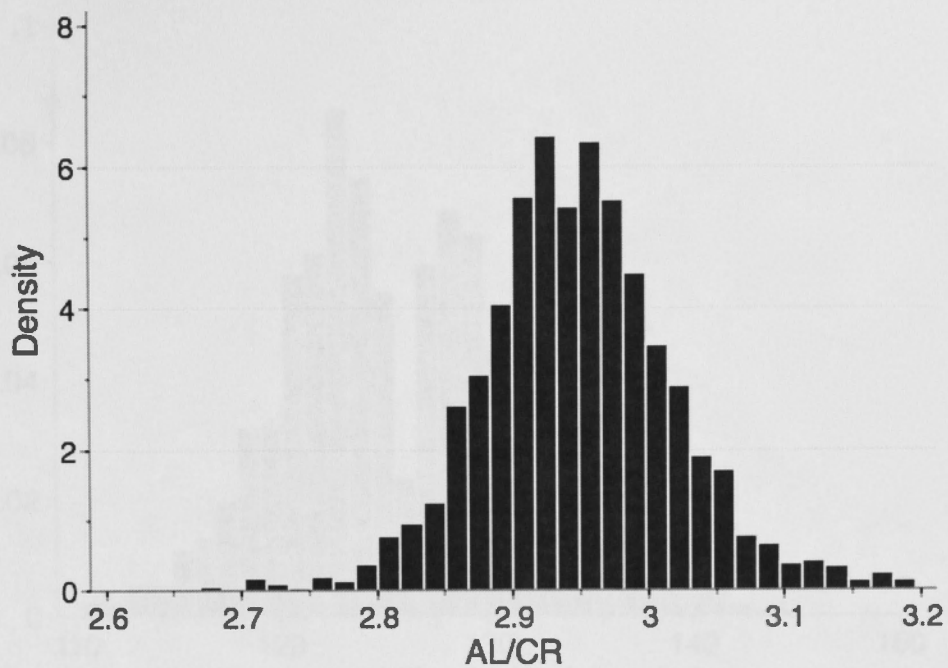


Figure 7.13 Distribution of AL/CR ratio in participating children (one-year follow-up visit)

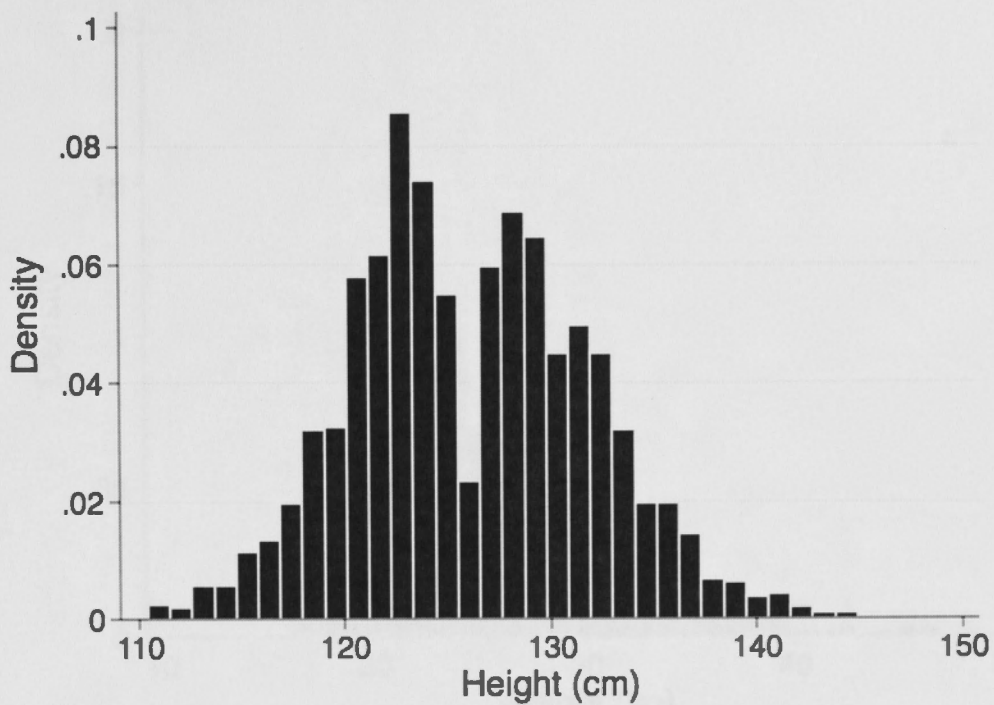


Figure 7.14 Distribution of height in participating children (one-year follow-up visit)

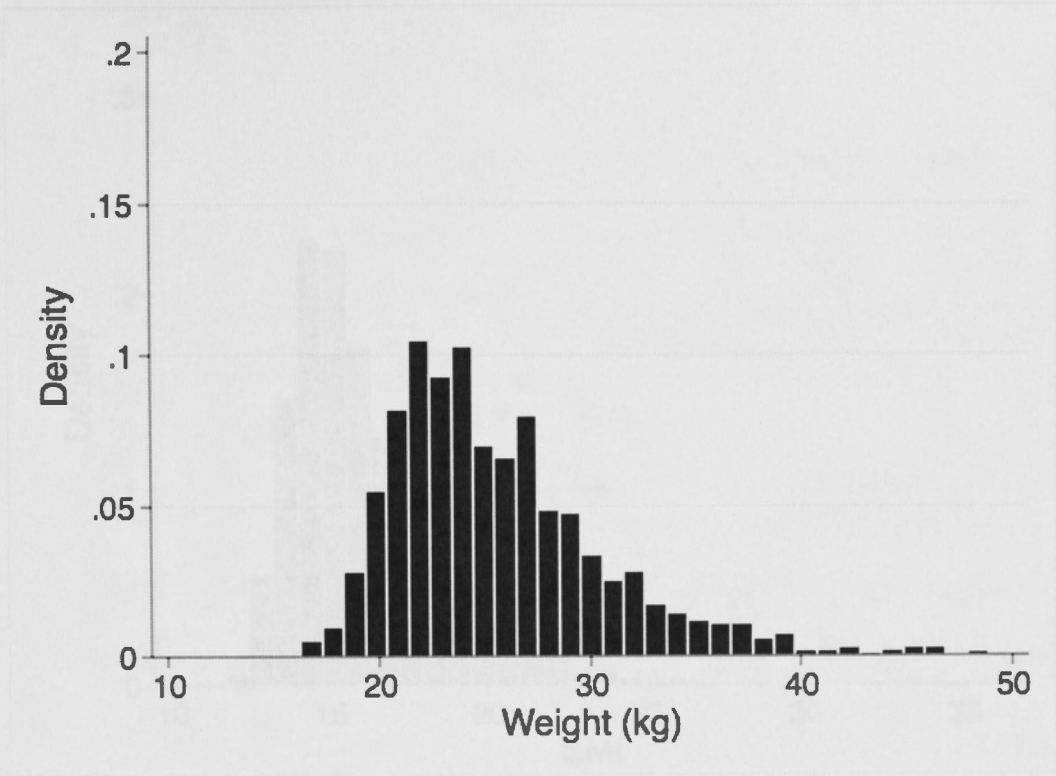


Figure 7.15 Distribution of weight in participating children (one-year follow-up visit)

1.2.1 one-year follow-up data

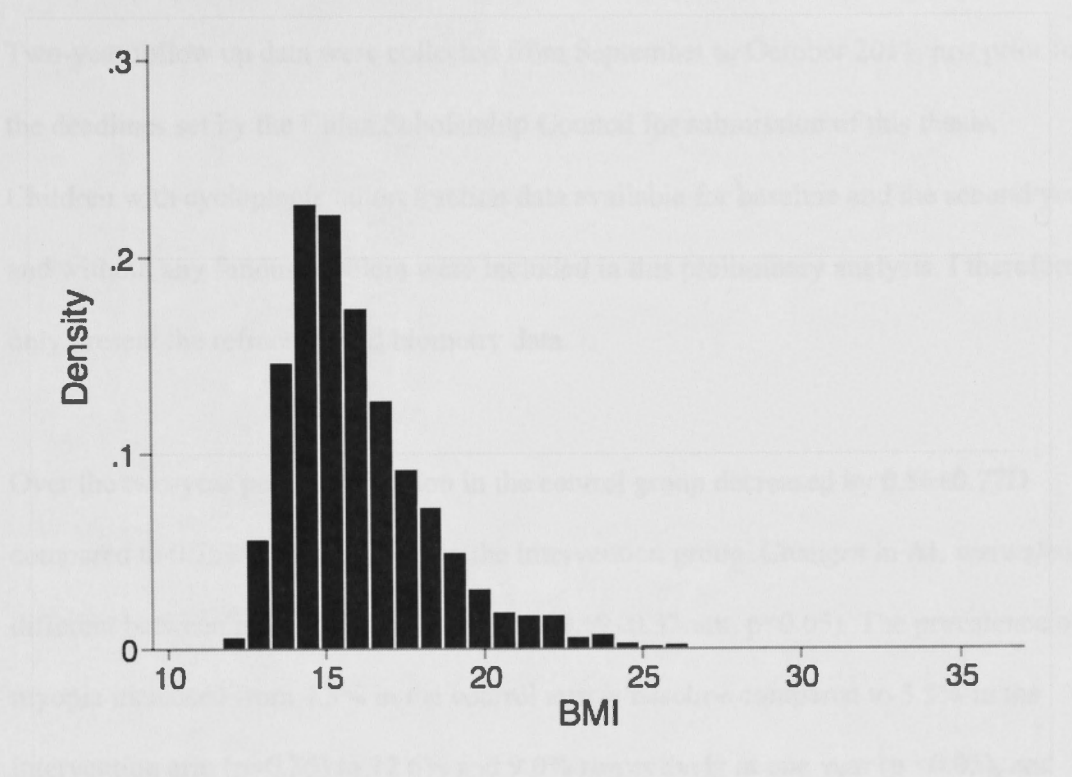


Figure 7.16 Distribution of BMI in participating children (one-year follow-up visit)

7.5 Two-year follow up data

Two-year follow up data were collected from September to October 2011, just prior to the deadlines set by the China Scholarship Council for submission of this thesis.

Children with cycloplegic autorefraction data available for baseline and the second year and without any fundus problem were included in this preliminary analysis. I therefore only present the refraction and biometry data.

Over the two-year period, refraction in the control group decreased by $0.86\pm0.77D$ compared to $0.75\pm0.69D$ ($p<0.01$) in the intervention group. Changes in AL were also different between groups ($0.61\pm0.35mm$ vs. $0.59\pm0.33mm$, $p<0.05$). The prevalence of myopia increased from 4.3% in the control arm at baseline compared to 3.5% in the intervention arm ($p=0.35$) to 12.6% and 9.0% respectively at one year ($p<0.05$), and 25.2% and 20.7% ($p<0.05$).

7.6 Discussion

The GOAL study is a large-scale, school-based, longitudinal clinical trial to evaluate the effect of outdoor activities for preventing the development and progression of myopia in Chinese children. Given the high prevalence of myopia and its heavy burden on public health, it is of increasing importance to identify effective treatments that prevent myopia development and slow its progression. At the same time, priority must be given to identify a treatment which is inexpensive and can be easily applied on a large scale.

Since the protective effect of time spent outdoors was realised, it has been proposed that increasing children's engagement in outdoor activities could be a public health measure (Rose et al., 2008a, Gwiazda, 2009). A well designed, longitudinal trial is needed to investigate whether the increase of time spent outdoors during daylight hours is actually able to reduce the myopia development and progression. A very small longitudinal trial on myopic children has reported that children with an outdoor activity intervention (near- and middle-vision activities <30 hours per week and outdoor activities >14-15 hours per week) had significantly lower myopia progression ($0.38 \pm 0.15D$) compared to that in the control group (0.52 ± 0.19 ; $P < 0.01$) (Yi and Li, 2011).

Although this study was designed based on what appears to be robust evidence, there are several issues that need to be addressed. The first one is the amount of time spent outdoors. There is some evidence to indicate the total hours required outdoors to prevent myopia. Jones et al reported that for children with two myopic parents, having more than 14 hours of outdoor activities per week (about 2 hours per day) reduced the chance of becoming myopia to the same level as children with one or no myopic parent, neutralizing the impact of parental myopia (Jones et al., 2007). SMS found that Chinese

children in Sydney had 10 hours more outdoor activities per week (about 1.4 hours per day) and a refraction about 1 dioptre more hyperopic than Chinese children in Singapore(Rose et al., 2008b). Based on the studies above, it is assumed that 1-2 hours spent outdoors per day should be effective to make a considerable difference. A recent meta-analysis of the available data has suggested that one hour per day of additional time outdoors might produce a 10-20% reduction in progression.

However, an important component of our study is that the outdoor activity intervention is practical and must be sustainable for 3 years. Through discussions with the Education Bureau of Guangzhou and participating schools, we were able to reach agreement on adding one class of outdoor activities (about 50 minutes) every afternoon in Grade 1 children. It was agreed that this could be continued in all participating schools until the children had completed Grade 3. Agreement could not be reached on a greater amount, given that many schools in Guangzhou hold extra tutorial classes or special interest classes after school. Clearly this is at the lower limit of what appears to be required. It should be noted that in the second year of the intervention, there was considerable pressure from some parents to abandon the intervention, given that homework pressures on the children were increasing.

The second issue would be compliance with the outdoor intervention. In contrast to many intervention studies, where compliance is directly monitored by investigators, compliance with outdoor intervention largely relies on the schools, teachers and parents. This method is complex and may create problems. It is likely that outdoor intervention during school days can be implemented effectively, because of teacher supervision and study staff inspections. However, outdoor activities during weekends and holidays are unsupervised, and compliance is therefore problematic. Asking children to keep outdoor

activity diaries in weekends may be helpful, however, parents may limit children's outdoor time for various reasons (e.g., safety issues, insufficient outdoor space, lack of transportation, tutorial classes).

The third issue is the concern that whether increasing outdoor activities compromises children's academic outcomes. One of the most important priorities for parents in China is their child's educational achievements, which requires a high level of near work on reading and writing. There has been a long-standing belief that more time spent outdoors will decrease the time spent on near work and compromise children's education. However, in the epidemiological studies that have been reported, there is not a negative correlation between time spent outdoors and hours of near work, but rather a weak, but positive correlation (Jones-Jordan et al., 2011, Dirani et al., 2009a, Rose et al., 2008a, Rose et al., 2008b).

Furthermore, the protective effect of outdoor activities is able to neutralise the effect of high levels of near work (Rose et al., 2008a). The example of Australia shows that it is possible to obtain high education outcomes and low myopia prevalence if the right balance is reached. Australia ranks in the top 10 of education outcomes in the world (PISA 2009, <http://www.oecd.org/dataoecd/54/12/46643496.pdf>) while having a very low myopia prevalence (Ojaimi et al., 2005a, Ip et al., 2008c), along with parts of China, Japan, Singapore and Korea, which have very much higher levels of myopia. Even in children of Chinese origin, the prevalence of myopia is lower than in East Asia (Ip et al., 2008a) and follow-up data from the Sydney Myopia Study indicates that the prevalence at age 17 is about half that seen in Guangzhou (Rose, personal communication). One of the key explanations for this may be that Australian children of all ethnic backgrounds

spend a large amount of time outdoors, exposing them to high levels of ambient light which protects them from myopia in a quite natural way.

In this study, full individual randomization and masking were not applied. We divided schools into different strata, in terms of the prevalence and progression of low visual acuity (as a surrogate measure myopia, which is the major cause of low VA in children in Guangzhou)(He et al., 2004).

One- and two-year follow up results showed promising results, with a consistent pattern of less axial elongation and development of myopia in the intervention group, which suggests that the intervention is having some effect. However, the differences between two groups reached statistical significance, but not clinical significance. This may be because, at this stage, the changes in SER, AL and prevalence of myopia were small. Alternatively, the small difference could be due to weak implementation in the intervention group, which largely relies on the schools, teachers and parents, and compliance may create problems.

However, we believe that the small effect size may be primarily due to the low level of increased time outdoors achieved in this study. These data may therefore provide “proof-of-principle” evidence for the effectiveness of the intervention, but suggest that greater exposures will be required to obtain clinically significant effects.

To our knowledge, the GOAL study is the first longitudinal study to examine the protective effect of outdoor activities on a large-scale population basis. The study sample is representative of the population which becomes myopic, all measurements are non-invasive and reproducible, and outdoor activity intervention implementation is

supervised during the whole study period. Because of above methodological strengths, we should be able to obtain reliable results on whether myopia incidence and progression slow in intervention group. The one year results and the interim two year results suggest that the intervention is working, but that the intervention effects, while statistically significant, are very small. The intervention will be continued for the programmed third year, but the results already lay down a challenge – if the principle of the intervention is working, how can time outdoors be increased much further in way which is compatible with the emphasis on education in Chinese society. One possibility is to combine educational activities with bright light exposures. Another is to make use of the extended midday break in Chinese schools, most of which is spend indoors and sleeping. Perhaps some of this time could be used for time outdoors. But these are possibilities which will need to be carefully negotiated with school authorities and parents.

PART 3

PRELIMINARY EXPLORATION

OF THE MECHANISM OF

MYOPIA

before and after the onset of myopia

8.1 Introduction

The epidemic of myopia and its impact on public health have been discussed in detail in previous chapters (see CHAPTER 1). We now have a clearer, although far from perfect, picture of the aetiology of myopia from comparative epidemiological studies. But the changes in eye growth which lead to a departure from the normal process of refractive development are still rather obscure.

The early stages of refractive development are reasonably well understood. Over the first year or two of life, normal early refractive development involves reductions in neonatal refractive errors, which are generally hyperopic in nature (Gwiazda J, 1993, Mayer et al., 2001, Mutti et al., 2009), through a process which has come to be known as emmetropisation, even though it generally produces spherical equivalent refractions in the mildly hyperopic range (Morgan et al., 2010) – a state in which normal visual acuity can be obtained through accommodation. This process involves matching of the axial length of the eye to the corneal power, which produces a highly kurtotic distribution of refraction centred around 1-2D of hyperopia by the age of 2 years (Mayer et al., 2001), and a markedly kurtotic ratio of axial length/corneal radius ratio (AL/CR) by the age of 6 years (Ojaimi et al., 2005a). At this stage in development, the prevalence of myopia is generally low, and in some circumstances, the low prevalence of myopia and this kurtotic distribution of refractive error can be maintained into adult life (Sorsby et al., 1960). But in populations in which the prevalence of myopia becomes high, many eyes are clearly going beyond this point.

To understand why myopia develops, it is important to understand both the normal process of eye development, and the abnormal process which leads to myopia. The major biometric correlation of refraction is axial length (Ip et al., 2007b, Shufelt et al., 2005), and even more strongly the ratio of the axial length to the corneal radius of curvature (AL/CR ratio) of the eye. Myopia appears when the axial length becomes too long for the optical power, leading to the image of distant objects being focused in front of the retinal photoreceptors. Corneal power is essentially stable during development after the age of 3 years, while lens power decreases significantly over the period in which myopia develops in children (Sorsby et al., 1961, Zadnik et al., 2003, Twelker et al., 2009), but is not highly correlated with refraction. Thus, the development of myopia appears to be largely due to excessive axial elongation.

Only a few studies have documented in detail the changes in refractive error and ocular components which take place around the onset of myopia. Thorn and colleagues (Thorn et al., 2005) described a very rapid onset of high rates of change in refractive error, typical of the rates of myopic progression in myopes, but starting prior to the appearance of clinical levels of myopia. The CLEERE study found that the rate of change in refraction and axial elongation accelerated before the onset of myopia (Mutti et al., 2007), and this finding has been confirmed in the SCORM study (Wong et al., 2010). Both these studies reported a deceleration of the rate of progression after the onset of myopia.

In the current analysis, we examine rates of change in refractive errors and ocular components (axial length, AL/CR ratio, anterior chamber depth, corneal curvature, and lens power) before and after the onset of myopia in a large sample of Chinese children, using longitudinal data from a large cohort of twins enrolled in the Guangzhou Twin

Eye Study. Previous studies have shown that the twins provide a representative sample of children in terms of ocular development(Sanfilippo et al., 2011, Hur et al., 2009).

1.1.1 Participants

Participants in this study were drawn from the Chinese Twin Birth Registry, which has been described in detail previously (Wang et al., 2007). In brief, twins born in Guangdong between 1987 and 2006 were identified by using the official Household Registry of Guangdong, and followed by doctors from birth. Twins aged 7 to 16 years (on July 1, 2007) living in two districts adjacent to the Zhongshan Ophthalmic Center, where the examination station was set up, were recruited, and the study included the biological parents of the twins were also invited to participate. The response rate for the baseline study in 2006 was 82.3%.

This study was conducted in accordance with the tenets of the World Medical Association's Declaration of Helsinki. Ethical approval was obtained from the Tsinghua University Ethical Review Board and the Ethics Committee of Zhongshan Ophthalmic Center. Written informed consent was obtained for all participants from either parents or guardians of the participating children. For ongoing children and adolescents, written informed consent was obtained from the participants themselves. All participants were requested to attend annual follow-up examinations at the ophthalmic center, school holidays from 2007 on. Annual examinations took place every 12 months, and were free of charge.

1.1.2 Eye Examination

Axial length and anterior chamber depth were measured by non-invasive optical coherence tomography (OCT) (IOLMaster 700, Carl Zeiss Meditec, Germany) in a dark room before pupil dilation. The mean of 5 measurements was used as the axial length. Measurements were taken with the subject in a supine position. ACO

8.2 Methods

8.2.1 Participants

Participants in this study were drawn from the Guangzhou Twin Registry, which has been described in detail elsewhere (He et al., 2006). In brief, twins born in Guangzhou between 1987 and 2000 were identified by using the official Household Registry of Guangzhou, and followed by door-to-door verification. Twins aged 7 to 15 years (on July 1, 2006) living in two districts adjacent to the Zhongshan Ophthalmic Center, where the examination station was set up, were recruited, and examined annually. The biological parents of the twins were also invited to participate. The response rate for the baseline study in 2006 was 82.3%.

This study was conducted in accordance with the tenets of the World Medical Association's Declaration of Helsinki. Ethics approval was obtained from the Sun Yat-sen University Ethics Review Board and the Ethics Committee of Zhongshan Ophthalmic Center. Written informed consent was obtained for all participants from either parents or guardians of the participating children. Participating children and their parents were requested to attend annual follow-up examinations in the summer or winter school holidays from 2006 on. Annual examinations took place close to one year apart.

8.2.2 Eye Examinations

Axial length and anterior chamber depth (ACD) were measured by non-invasive partial-coherence laser interferometry (IOLMaster, Carl Zeiss Meditec, Oberkochen, Germany), in a dark room before pupil dilation. The mean of 5 measurements was used as the axial length. Measurements with error messages were deleted and repeated. ACD

was measured as the distance between the anterior lens surface and corneal epithelium illumination, and thus included the thickness of the cornea.

Cycloplegia was induced with two drops of 1% cyclopentolate administered 5 minutes apart to each eye, with a third drop administered after 20 minutes. Cycloplegia was considered complete if the pupil dilated to 6mm or greater, and a light reflex was absent after a further 20 minutes. Refractions and keratometry were measured using an autorefractor (KR8800, Topcon Corp, Tokyo, Japan) after cycloplegia.

8.2.3 Statistical analysis

Annual examination data from 2006 to 2010 on right eyes only were used for data analysis, given the generally high correlation between measurements from left and right eyes each year (data not shown). Only participants with a complete set of annual data from 2006 to 2010 were included in the analysis. Myopia was defined as a spherical equivalent (SER) refractive error of at least -0.5 D, and changes prior to and after the first examination in which this criterion was reached were examined. Thorn et al (Thorn et al., 2005) have shown that the most rapid changes and acceleration of the rates of change in fraction occur 1-2 years before the criterion for clinical myopia is attained. For SER and axial length, we have also examined annual rates of change relative to the criterion refraction of 0D and +0.5D. The AL/CR ratio was calculated by dividing the axial length (mm) by the corneal radius of curvature (mm). Lens power was calculated from the refraction and biometric measurements, using the formula of Bennett and Rabbetts (Bennett and Rabbetts, 1984).

Children who were not myopic on at least one examination and were myopic on at least one subsequent examination from 2006 to 2010 were included in the analysis. The

examination years in relation to the onset myopia are shown in Table 8.1. Specifically, the first year before the first detection of myopia was defined as -1, the second year before onset was -2, and so on to -4. Likewise, the first year after myopia was detected was defined as 1, the second year was defined as 2, and the third year as 3.

The annual changes are shown as mean values and standard errors. Differences between examination years were assessed with ANOVA, and the subsequent post-hoc pair-wise comparison was assessed using the Scheffe method. A p value of ≤ 0.05 was considered as statistically significant. Statistical analysis was performed using STATA 11.0 (Stata Statistical Software, Release 11.0, Stata Corp., College Station, TX).

2006	2007	2008	2009	2010
-1	detection	1	2	3
-2	-1	detection	1	2
-3	-2	-1	detection	1
-4	-3	-2	-1	detection

Numbers of children in each year relative to the first detection of myopia: -4(26); -3(56); -2(107); -1(165); Detection(165); 1(139); 2(109); 3(58)

Table 8.1 Definition of examination year relative to the first detection of myopia

8.3 Results

Of 2567 children enrolled in the Guangzhou Twin Eye study from 2006 to 2010, 607 had all data for each of the 5 examinations. Among them, 273 were myopic in 2006 and 169 had not met the myopia criterion in 2010. The remaining 165 children who became myopic between 2006 and 2010 were included in data analysis. The numbers of children as a function of age of onset of myopia are presented in Figure 8.1.

The annual changes of spherical equivalent refraction (SER) relative to the examination in which myopia was first detected are shown in Figure 8.2. The points represent the change over a period of one year relative to the time at which myopia was first detected. Using -0.5D as the criterion for myopia, the annual change in SER formed a characteristic shape, with the rate of change increasing slowly from that seen 4 years prior to the first detection of myopia (-0.25D) to two years prior to myopia onset (-0.4D). In the year prior to the first detection of myopia, the rate of progression was much higher at -0.92D ($p<0.001$). After myopia was first detected, the rates of progression declined to -0.71D in the following year, then kept decelerating (-0.65D in the second year after detection and -0.34D in the following year ($p<0.001$)). Very similar results were obtained relative to the first detection of a refraction of 0D or $+0.5\text{D}$.

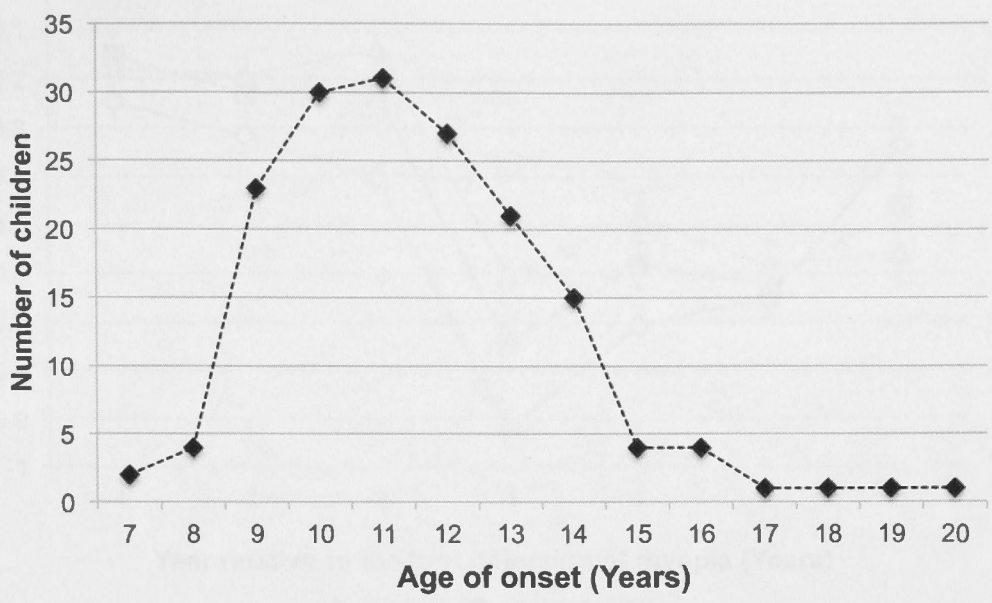


Figure 8.1 The numbers of children as a function of age of onset of myopia

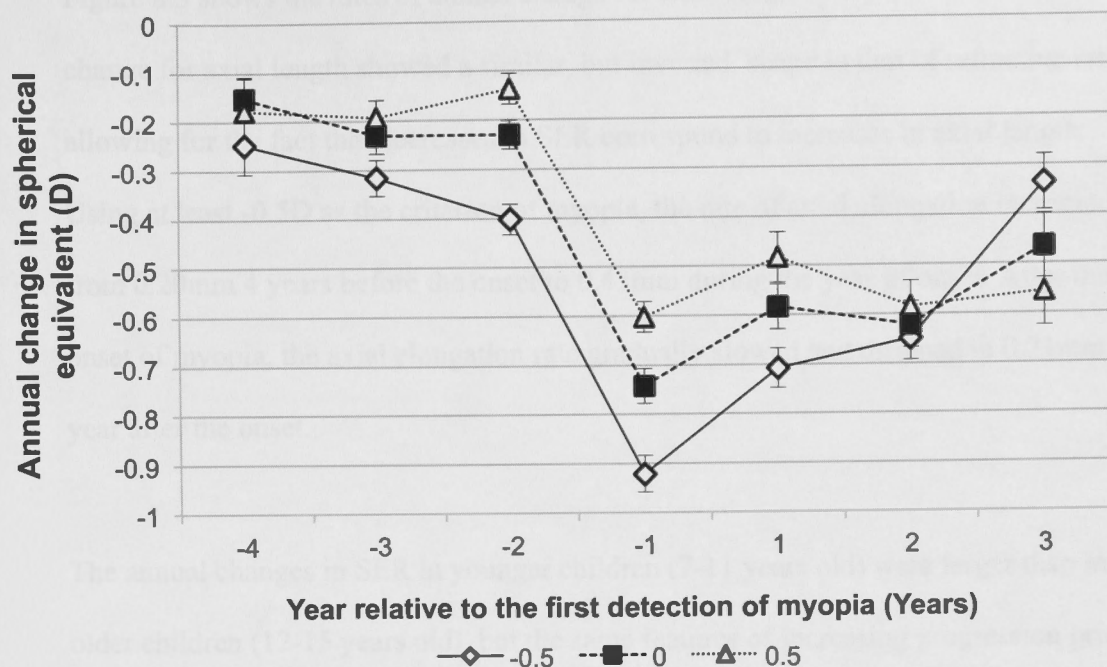


Figure 8.2 Annual change in spherical equivalent refraction relative to the first detection of myopia

Figure 8.3 shows the rates of annual change for axial length (AL). The trend of annual change for axial length showed a similar, but inverted, shape to that of refractive error, allowing for the fact that decreases in SER correspond to increases in axial length. Using at least -0.5D as the criterion of myopia, the rate of axial elongation increased from 0.20mm 4 years before the onset to 0.43mm during the year of onset. After the onset of myopia, the axial elongation rate gradually slowed and dropped to 0.21mm 3 year after the onset.

The annual changes in SER in younger children (7-11 years old) were larger than in older children (12-15 years old), but the same features of increasing progression prior the first detection of myopia and decreasing progression in the years after are seen (Figure 8.4A). As shown in Figure 8.4B, the rates of annual changes for AL were also smaller in younger children.

Table 8.2 shows the ratio of annual change in SER and AL relative to the time of first detection of myopia. The ratio of the annual changes in SER and AL increased quite abruptly in the year prior to the first detection of myopia. The largest ratio occurred during the year prior to the first detection of myopia (-2.16), and remained high from then on, although it dropped to -1.60 during the 3rd year after the first detection of myopia.

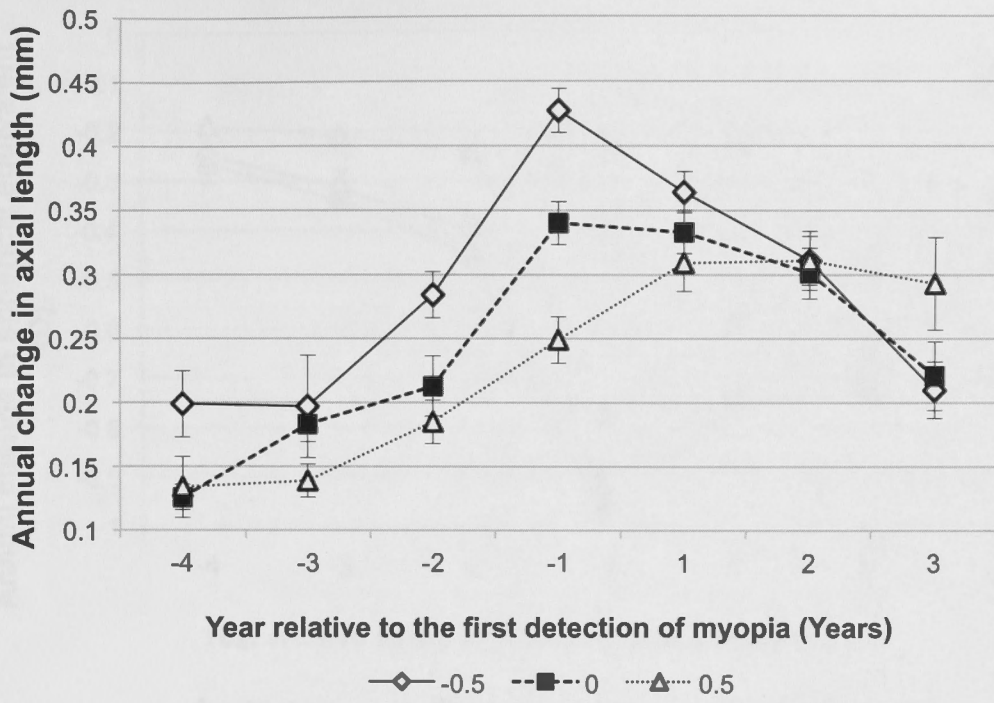


Figure 8.3 Annual change in axial length relative to the to the first detection of myopia

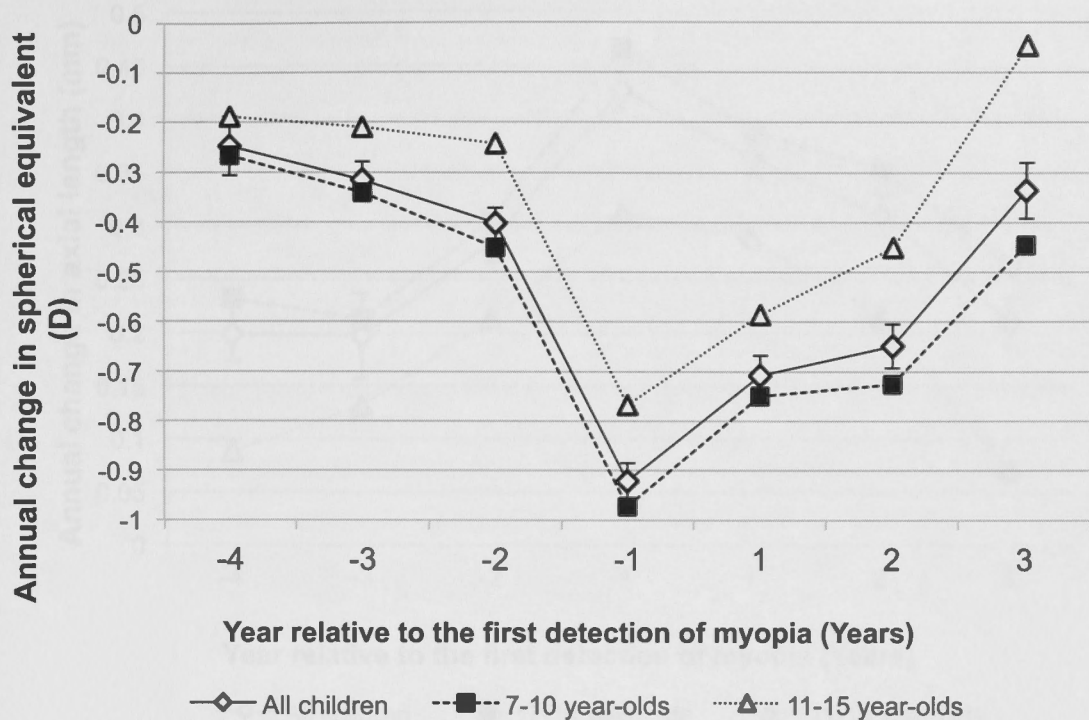


Figure 8.4A Annual change in spherical equivalent refraction in younger and older children relative to the first detection of myopia

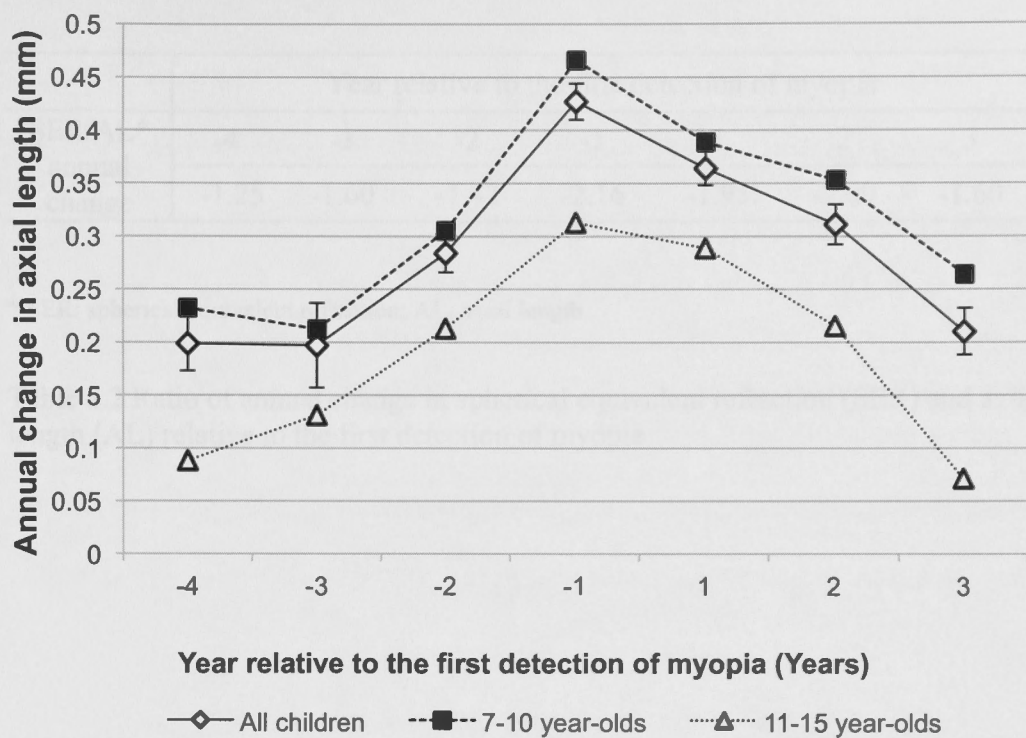


Figure 8.4B Annual change in axial length in younger and older children relative to the first detection of myopia

SER/AL* annual change	Year relative to the first detection of myopia						
	-4	-3	-2	-1	1	2	3
	-1.25	-1.60	-1.42	-2.16	-1.95	-2.09	-1.60

* SER: spherical equivalent refraction; AL: axial length

Table 8.2 Ratio of annual change in spherical equivalent refraction (SER) and axial length (AL) relative to the first detection of myopia

(Figure 8.5). The rates of annual change were 3.25 (0.55 to 5.95) mm from 4 years before the first detection of myopia to the first year after the first detection of myopia, but decreased in the second and third years to 0.55–0.74 mm each year ($p=0.001$). The annual change rates for corneal curvature were very small over the period analysed, amounting at most to 0.1 mm, or a change in corneal power of around 0.5D (Figure 8.7).

The rates of annual progression for the calculated lens power did not show significant change around the onset of myopia (Figure 8.8). From 4 years prior to the first detection of myopia, the annual change of lens power fluctuated around -0.2D annually, and there was no statistically significant difference over all years ($p=0.07$).

The AL/CR ratio showed a pattern of annual change similar to that of axial length (Figure 8.5). Using -0.5D as the criterion for myopia, the largest rate of annual change was in the year before the first detection of myopia (0.05mm), which was significantly different to that in the second year prior to first detection ($p<0.001$) and two years after first detection ($p<0.001$)

The rates of annual change for anterior chamber depth showed a different pattern (Figure 8.6). The rates of annual change were high (0.08 to 0.12mm) from 4 years before the first detection of myopia to the first year after the first detection of myopia, but dropped in the second and third years to 0.02-0.04mm each year ($p<0.001$). The annual change rates for corneal curvature were very small over the period analysed, amounting in total to 0.1mm, or a change in corneal power of around 0.5D (Figure 8.7).

The rates of annual progression for the calculated lens power did not show significant change around the onset of myopia (Figure 8.8). From 3 years prior to the first detection of myopia, the annual change of lens power fluctuated around -0.2D annually, and there was no statistically significant difference over all years ($p=0.07$).

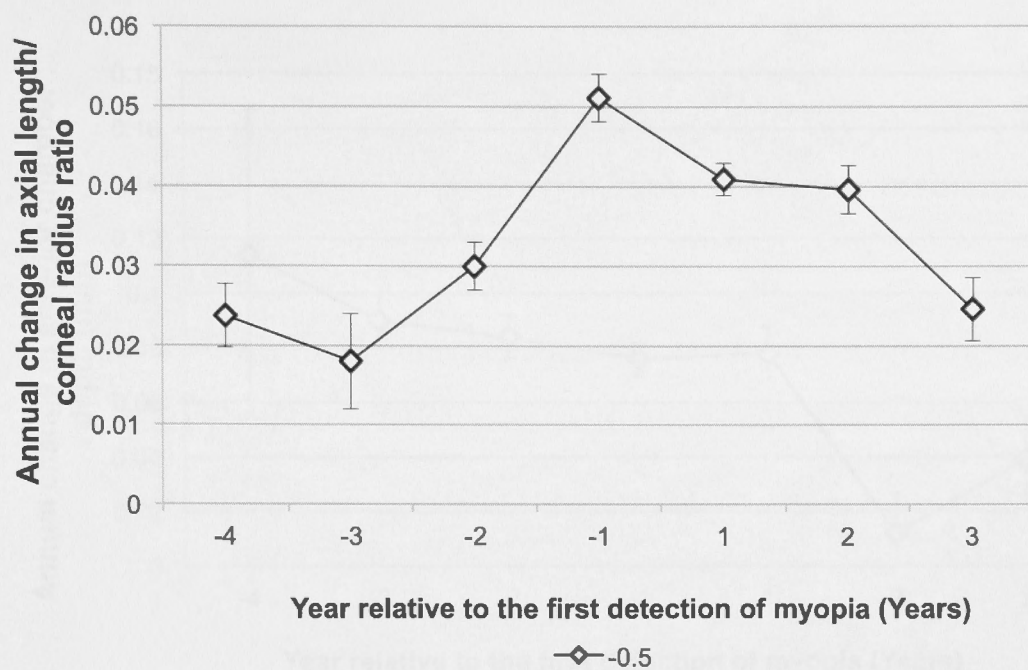


Figure 8.5 Annual change in axial length/corneal radius ratio (AL/CR) ratio relative to the first detection of myopia

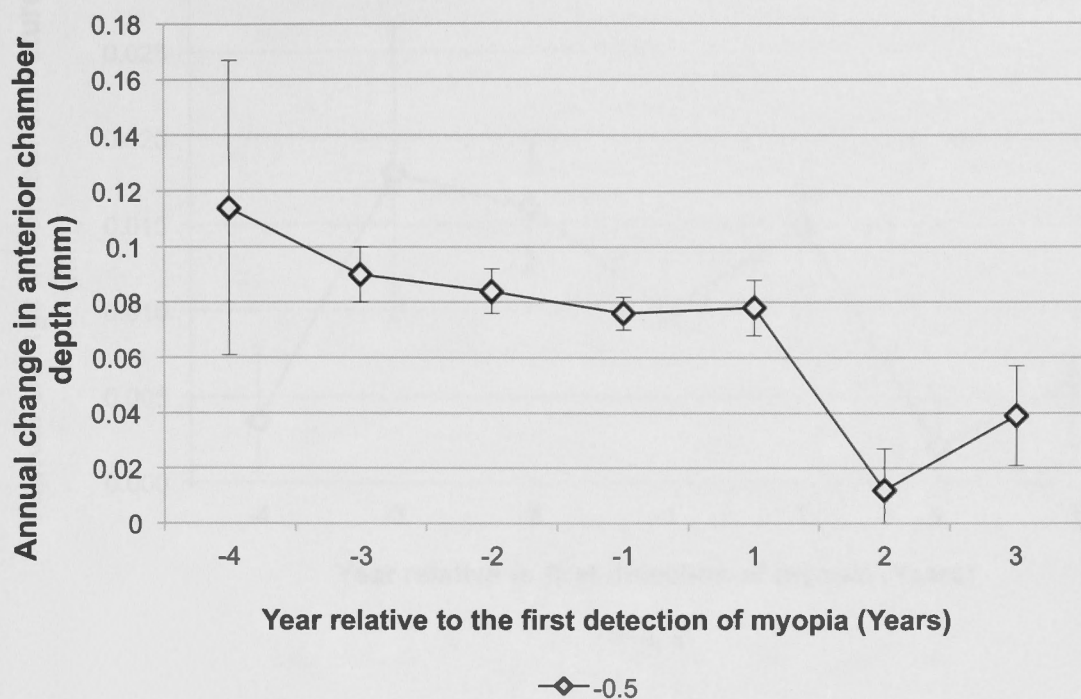


Figure 8.6 Annual change in anterior chamber depth relative to the first detection of myopia

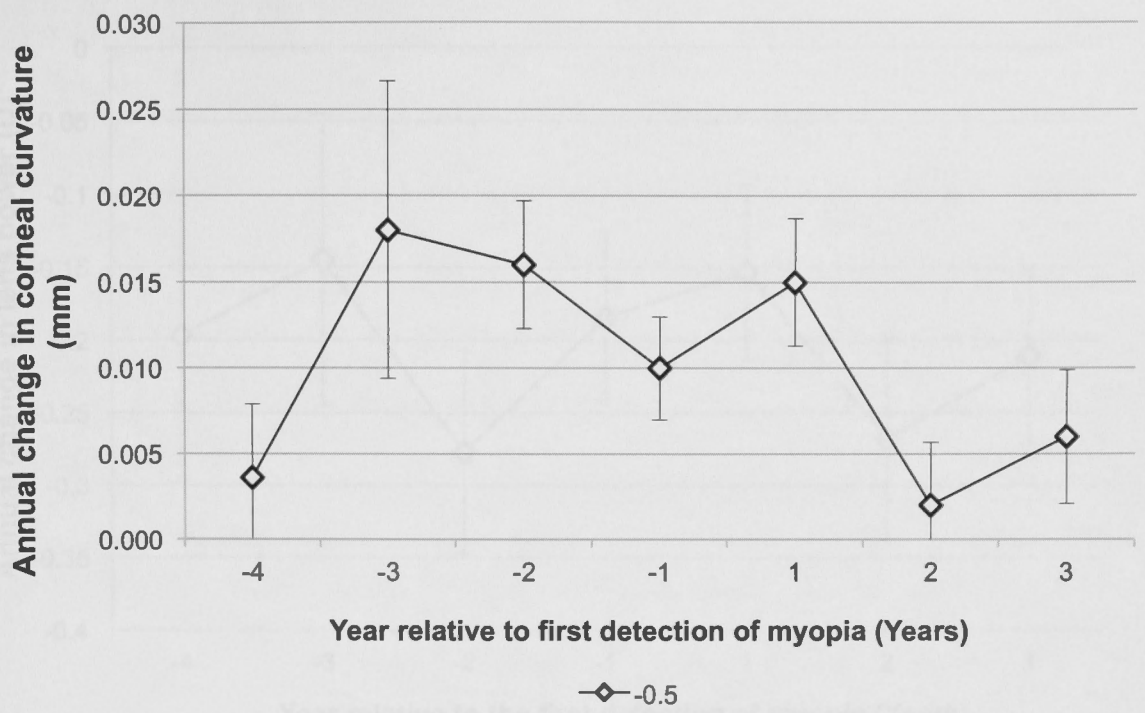


Figure 8.7 Annual change in corneal curvature relative to the first detection of myopia

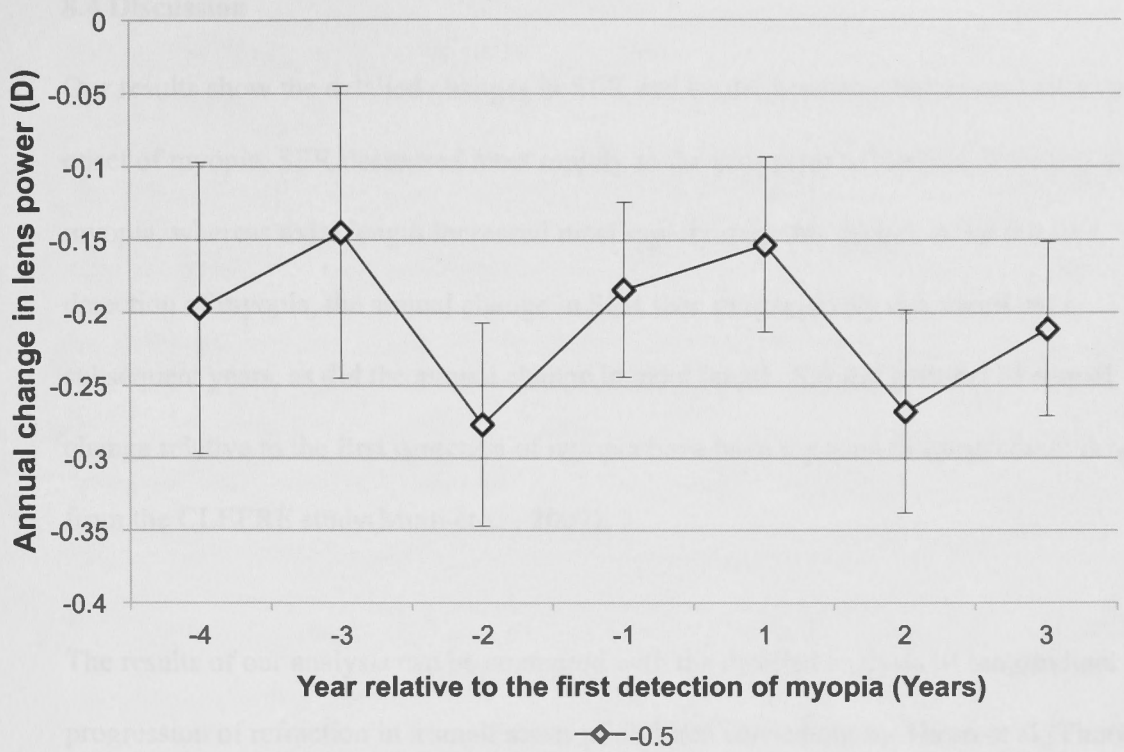


Figure 8.8 Annual change in lens power relative to the first detection of myopia

8.4 Discussion

Our results show the detailed changes in SER and ocular biometry before and after the onset of myopia. SER decreased most rapidly in the year prior to the first detection of myopia, whereas axial length increased most rapidly over this period. After the first detection of myopia, the annual change in SER then progressively decreased over subsequent years, as did the annual change in axial length. Similar patterns of annual change relative to the first detection of myopia have been reported in longitudinal data from the CLEERE study (Mutti et al., 2007).

The results of our analysis can be compared with the detailed analysis of longitudinal progression of refraction in a small series of children carried out by Thorn et al. (Thorn et al., 2005). Their analysis showed that myopisation onset, defined by the peak acceleration of the rate of progression, starts a year prior to the achievement of a myopia criterion of 0.5D, and it usually starts before spherical equivalent refraction reaches zero. Our results are quite consistent with this analysis, since, using an SER criterion of zero or +0.5D, there was still a higher rate of annual change in refraction and axial length in the year prior to first detection of that criterion refraction, consistent with the hypothesis that the critical events leading to the development of myopia occur well before the appearance of clinical myopia. Thorn et al. (Thorn et al., 2005) further noted that the time to achieve 50% acceleration was reached as much as 2 years prior to the attainment of the -0.5D criterion.

These clear patterns of increased axial elongation and increased progression of SER in a myopic direction leading up to the first detection of myopia, followed by slowed axial elongation and progression after the first appearance of myopia pose two obvious

questions - why does axial elongation accelerate prior to the onset of myopia, and why does it slow once a myopic refraction has been established.

One interpretation of these results is that the patterns of change reflect a genetically determined increase in axial elongation, which pushes SER values from moderate hyperopia or emmetropia into the myopic range. There have been repeated suggestions that there is genetic contribution to refraction (Mutti et al., 2002, Zadnik et al., 1994, Saw et al., 2001b, Wu and Edwards, 1999, Sorsby and Young, 1970). However, as extensively discussed in Morgan and Rose (Morgan and Rose, 2005), the evidence for genetic contributions to myopia is largely based on the results of heritability analysis in twin studies (Hammond et al., 2001, Lyhne et al., 2001, Dirani et al., 2006), which are not necessarily generalizable to the population as a whole (Vitart et al., 2010). In fact, attempts to define the genetic loci involved, other than in clearly familial high myopia, have met with only limited success, with only a few loci of small effect so far characterised (Baird et al., 2010, Hysi et al., 2010, Solouki et al., 2010). In the population examined, children in Guangzhou, having myopic parents, a possible surrogate measure of genetic susceptibility, increased the relative risk of myopia only by around 30% (Xiang et al., 2010). This suggests that most of the development of myopia in Guangzhou, and presumably other East Asian cities with high prevalences of myopia, results from environmental exposures at those sites, rather than under-lying genetic influences.

An alternative possibility is therefore that the acceleration of axial elongation and associated changes in refraction are driven by changing environmental exposures. Specifically, we suggest that the rate of axial elongation is determined primarily by the balance between educational pressures towards high rates of axial elongation, and time

spent outdoors(Jones et al., 2007, Rose et al., 2008a), which appears to slow the rate of axial elongation and myopic progression though light-stimulated release of retinal dopamine in the brighter light exposures typical of outdoors during day-light hours(Ashby et al., 2009, Ashby and Schaeffel, 2010). We hypothesise that children who are adopting activity patterns which emphasise study activities while reducing the amount of time spent outdoors will show increased rates of axial elongation and rapidly become myopic. Little longitudinal evidence on patterns of activity relative to the onset of myopia is available, but, in partial support of this hypothesis, the CLEERE study has shown that children who become myopic tend to spend less time outside than children who do not become myopic in the years prior to the onset of myopia(Jones-Jordan et al., 2011).

The other question posed is why the rate of axial elongation and myopic progression decreases after the first detection of myopia. Experiments on animal models have shown that eye growth responds to lenses fitted to the eyes. Imposed positive lenses (myopia defocus) slow eye growth while imposed hyperopic defocus with negative lenses accelerate eye growth(Morgan and Megaw, 2004). It is a plausible hypothesis that the reduction in the rate of axial elongation and myopic progression once a myopic refraction has been established is due to a reduced rate of axial elongation caused by exposure to myopic defocus. An alternative explanation is that the reductions after myopia onset simply represent an age-related reduction in the rate of axial elongation and progression. This seems unlikely, because the rate of decrease in progression with age in the overall population is much less abrupt and much smaller in magnitude than seen in the children who have become myopic. For the overall sample, the age-weighted average decrease in SER in the year after myopia is first detected is 0.02D (a 4% decrease), and -0.01mm for AL (a 5% decrease), whereas the average change in annual

change after first detection of myopia in the children who are becoming myopic is 0.21D for SER (23% decrease), and -0.06mm for AL (15% decrease). The analysis of Thorn et al (Thorn et al., 2005) also shows a significant gap between the onset of myopia and marked slowing in progression.

We found there was systematic change in the ratio of annual change in SER and axial length, from relatively low before the appearance of myopia to relatively high a year before the first detection of myopia. Given the overall stability of corneal power over these ages, and the fact that lens power changes are decreasing developmentally over this period, it seemed possible that a reduction in rate of loss of lens power, leading to a reduced ability of decreasing lens power to neutralise the impact of axial elongation, could account for this change. However an analysis of changes in lens power in relation to the first detection of myopia did not support this idea. This issue requires further analysis.

Our results have some potential clinical implications. The first is that if children were monitored annually for changes in axial length and corneal curvature which can be done without cycloplegia, increasing rates of axial elongation might indicate the future development of myopia a year or two prior to onset, enabling preventive intervention, such as the use of atropine eye drops (Chua et al., 2006, Chia et al., 2011). The evidence that natural STOP signals may slow axial elongation and myopic progression somewhat in children of this age also lends plausibility to the idea that imposed myopic defocus may be a useful tool for the prevention of myopia.

One feature of study is that the participants were derived from a population of twins, which raises the issue of whether they are representative of the general population in

terms of refractive development. However, in the Guangzhou Twin Eye Study, there is no difference between twins and non-twin children, in terms of refractive status and axial length in a comparison of data from the Guangzhou RESC(He et al., 2004) and results from the Guangzhou Twin Eye Study(He et al., 2006). Furthermore, an extensive analysis of twin and non-twin sibling data has shown only limited difference in ophthalmic phenotypes between the two groups, supporting the idea that the basic ophthalmic phenotype and the pattern of refractive development in twins are similar to those in singletons(Sanfilippo et al., 2011).

In summary, our results show that increased rates of progression in a myopic direction and increased rates of axial elongation occur prior to the onset of myopia, using a criterion of $-0.5D$. They further suggest that these increases occur prior to $0.0D$ and even $+0.5D$. We hypothesise that these changes are associated with changes in the behaviour of children, involving increased study and decreased time outdoors. These changes prior to the onset of clinical myopia suggest that with appropriate monitoring, it may be possible to initiate myopia prevention prior to the onset of myopia – thus preventing incident myopia rather than simply controlling progression. Our results also suggest that once a myopic refraction is established, the rate of axial elongation and myopic progression is reduced, which lends support to the idea that myopic progression could be reduced by imposed myopic defocus.

CHAPTER 9 Conclusions

Myopia has emerged as a major health issue in East Asia, because of its high prevalence in children and young adults in urban areas (80% in school-leavers), and because of the sight-threatening pathologies associated with high myopia (Saw et al., 2005), which now affects 20% of those completing secondary schooling (Wu et al., 2001, He et al., 2004, Lin et al., 2004). Similar changes are occurring in other parts of the world, but are so far less severe (Rose et al., 2001, Vitale et al., 2009). The higher prevalence of myopia in East Asian cities appears to be associated with increasing educational pressures, combined with life-style changes which have reduced the time children spend outdoors.

An analysis of unaided visual acuity data of school-aged children in Guangzhou over the past 20 years demonstrated a major secular change in the prevalence of reduced visual acuity, and by implication the prevalence of myopia and its severity. The results showed that the loss of visual acuity increased with increased number of years of schooling completed, and that this pattern of loss has become more severe over time. In the past few years, the level of reduced visual acuity has reached a plateau, though with a very high level of reduction of visual acuity. This reduction appeared parallel to the emergence of myopia in school children, and thus monitoring of visual acuity, without the need for cycloplegic refractions, should provide a simple and potentially cost-effective means of surveillance.

Using refractive error data from children and parental information collected with questionnaires from the Guangzhou Refractive Error Study in Children (RECS), relationship between myopia in parents and their children was examined. The results showed that the prevalence of myopia and high myopia was significantly higher in the children's generation than in the parents' generation. Most of the children in Guangzhou

become myopic and some became highly myopic, irrespective of the refractive status of their parents. This suggested that the environmental effects have led to an increase in the prevalence of myopia and high myopia in the younger generation. The increased prevalence of high myopia is of particular importance, because these levels of severity of myopia are associated with a markedly increased risk of sight-threatening pathological complications, such as retinal detachment, choroidal neovascularisation, and glaucoma (Saw et al., 2005). There was an additional risk of myopia in children with myopic parents, and also an impact of the severity of parental myopia on the severity of myopia in the children. This additional risk could not be explained in terms of increased engagement in near-work activities by the children with myopic parents, suggesting that additional genetic risk might be involved. However, data were only collected by questionnaire on children's near-work activities, not on time spent outdoors. Myopia in the parents was self-reported in questionnaire responses, rather than quantitatively measured.

Using corresponding data from the Guangzhou Twin Eye study, the correlation of refractive errors between two generations was further analysed. An impact of parental myopia and severity of parental myopia on the refractive status of the children was still seen. Because of the quantitative measurement of parental refractions, the results in this chapter could be shown to rule out the simple hypothesis that the change in environmental conditions only shifts the population mean, whereas genetic factors determine place in the distribution.

The unique sets of data from Guangzhou were then used to reconstruct the pattern of secular change in the prevalence of myopia over that past 100 years. The results showed that the prevalence of myopia in young adults was around 20-30% for the cohorts born

prior 1970s, but then increased progressively to reach over 80% from 1980s onwards. Of three possible factors – urbanisation, diet, and education, it was concluded that increased education, probably coupled with decreased time spent outdoors by children is the key to the change. In contrast, in three other East Asian sites, Singapore, Taiwan and Hong Kong, while the data are much more limited, it appears that the prevalence of myopia was higher from much earlier, with the changes in myopia reflecting the relative pace of economic development and expansion of the education system in these locations.

These analyses strongly favoured environmental explanations of the dramatic increases in prevalence that have taken place in East Asia. In the context of the continuing debate over nature and nurture that has surrounded myopia and refractive error, this explanation has now been increasingly accepted (Wojciechowski, 2011). However this does not entirely resolve the issue because it can be argued that Chinese are genetically more susceptible to developing myopia.

One of the most influential papers in this respect is that of Rasmussen (Rasmussen, 1936), who reported that the prevalence of myopia was over 60% in China 70-80 years ago. However, Rasmussen did not actually measure refractions, or report the prevalence of myopia. Rather, he reported a clinical measure, the percentage of spectacle prescriptions which were for myopia, which does not, in any population, equate to the prevalence of myopia in the population.

Wu and Edwards (Wu and Edwards, 1999) documented an increasing prevalence of myopia in China over three generations, but the sample size was small, and the refractions were not cycloplegic. More recently, by reconstructing the pattern of secular

change in the prevalence of myopia in Guangzhou, we have found that the prevalence of myopia has least tripled over the past 100 years (see CHAPTER 6). The significantly lower prevalence of myopia reported for older people in epidemiological surveys in China(Li et al., 2009, He et al., 2009a, Xu et al., 2005, Liang et al., 2009) is also consistent with the idea that there has been a marked increase in the prevalence of myopia over the past decades, although longitudinal hyperopic shifts with age, which are known to occur, can also contribute to this.

The idea that people of Chinese origin are inevitably myopic does not fit with the sometimes marked differences recently reported in the prevalence of myopia between urban and rural areas in China(Pi et al., 2010, He et al., 2009b, He et al., 2007, He et al., 2004). It also does not fit with the lower prevalence of myopia reported in children of Chinese origin growing up in Malaysia(Saw et al., 2006), and the even lower prevalence reported in children of Chinese origin growing up in Sydney, Australia(Rose et al., 2008b). Moreover, the propensity to develop myopia does not appear to be restricted to people of Chinese origin, but is found in other East countries such as Japan. In Singapore, children of South Asian (Indian) origin, who are closer in genetic origin to Europeans than to Chinese(Rosenberg et al., 2002) are almost as myopic as their peers of Chinese origin(Saw et al., 2006), although Indian children in India have a low prevalence of myopia(Murthy et al., 2002). There is also considerable evidence that the prevalence of myopia is increasing in Europe and North America as well, suggesting that most ethnic groups may be susceptible to developing myopia under particular environmental conditions.

It should also be noted that there is considerable evidence for a role for genetic factors in the aetiology of myopia. The main evidence comes from heritability studies in twins,

where the calculated heritability values are high, and in other studies of family associations. The evidence is stronger for high myopia than for school myopia, but the field is complicated by difficulties in replicating associations. In principle, this could be attributed, at least in part, to ethnic differences. One possibility is that the genetic factors are more important within population groups than between population groups(Wojciechowski, 2011). More work in this area is clearly needed, since, at present there appears to be only one well-replicated polymorphism associated with school myopia(Solouki et al., 2010), which accounts for only a small proportion of the variation.

The variability in the prevalence of myopia, including in people of Chinese ethnicity, across different environments highlights the importance of environmental exposures, which implies that myopia can be reduced if the right environmental conditions can be achieved.

Based on previous epidemiological studies, the Guangzhou Outdoor Activity Longitudinal (GOAL) Study evaluated the effect of outdoor activities for preventing the development and progression of myopia in Chinese children. The one- and two-year follow-up have showed promising results, with a consistent pattern of less axial elongation and development of myopia in the intervention group, suggesting that the intervention was having some effect. However, the differences between the two groups reached statistical significance, but not clinical significance. These data provides “proof-of-principle” evidence for the effectiveness of the outdoor intervention, but suggests that greater exposure will be required to obtain clinically significant effects. One possibility is to combine educational activities with bright light exposures. Another

is to make use of the extended midday break in Chinese schools, most of which is spent indoors and sleeping. Perhaps some of this time could be used for time outdoors.

The last chapter was a preliminary exploration of the mechanisms of myopia development. By analysing the 5-year longitudinal data of the Guangzhou Twin Eye Study, the results showed that there were increased rates of progression in a myopic direction and increased rates of axial elongation prior to the onset of myopia; once a myopic refraction was established, the rate of axial elongation and myopic progression was reduced. The changes prior to the onset of clinical myopia may be due to changes in the behaviour of children, which involved increased study and decreased time outdoors. This suggested that with appropriate monitoring, it might be possible to initiate myopia prevention prior to the onset of myopia. In contrast, the rapid slowing of axial elongation after the onset of myopia may represent an inhibitory effect of myopic defocus on eye growth.

This thesis provided the evidence that the exposure to the myopigenic environment in big cities - such as Guangzhou has led to an increase in the overall prevalence of myopia in the younger generation, and an increase in the severity of myopia. From a prevention perspective, it is possible to use non-invasive interventions to prevent myopia incident and myopic progression. Health behaviour programs aiming to increase time outdoors may be able to prevent myopia incident and slow its progression. The evidence that myopic progression appears before the onset of clinical myopia may help prevent myopia incident, while the evidence for a reduction after onset of myopia support the idea that myopic progression could be reduced by imposed myopic defocus.

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Guangzhou Outdoor Activity Longitudinal Study
Family Questionnaire (Parents completed)

Family information

Child's Name: _____ School: _____ Grade: _____ Class: _____

GOAL ID

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Contact Number: _____ E-mail: _____

Name	Relationship with child *	Ethnicity 1: Han 2: Muslim 3: Zhuang 4: Yao 5: Other, please specify	D.O.B. (YY/MM/DD)	Educational background 0: No formal education 1: < Primary school 2: Primary school 3: Secondary school 4: Tertiary education 5:>Tertiary education	Occupation 0: Unemployed 1: Blue collar 2. White collar	Any ocular disease? 0: No 1: Yes If yes, please specify	Wearing glasses? 0: No 1: Yes	If yes	
								1: Distance 2: Near 3: Both 9: Not sure	Age of the first wearing?
	Child								
	Mother								
	Father								
	Paternal grandfather								
	Paternal grandmother								
	Maternal grandfather								
	Maternal grandmother								
	Sister(s)								
	Brother(s)								

* Half-sibling should be indicated whether he/she comes from mother's side or father's side.

Signature: _____ Relationship with child : _____

Date: ____/____/____

Appendix 2

Myopia risk factor questionnaire

The Guangzhou Outdoor Activity Longitudinal Study

Myopia Risk Factor Questionnaire

School: _____ Class: _____ Child's name: _____

GOAL ID

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Date of birth: ____/____/____ Gender: _____

Please read the instructions carefully before complete this questionnaire

Part 1 Weekdays (Activities from Monday to Friday)

☐ ☐ ☐ Before school			
Activity	Yes or No	If yes	
		Time	From ____ to ____
1 ☐ When does your child get up from bed?	Yes	____	N/A
2 ☐ Does your child spend anytime outdoors (jogging, reading etc) before school?	☐ Yes ☐ No	____ Minutes	From ____:____ to ____:____
3 ☐ How long does it take for your child to get to school?	Yes	____ Minutes	From ____:____ to ____:____
☐ ☐ ☐ In school			
4 ☐ Does your child spend the break between classes indoors or outdoors (Please ask your child if you don't know)?	☐ Stay indoors ☐ Go outdoors		
☐ ☐ ☐ After school			
5 ☐ Does your child spend anytime outdoors before it gets dark (exercising, playing, walking etc)?	☐ Yes ☐ No	____ Minutes	From ____:____ to ____:____ ☐ From ____:____ to ____:____
6 ☐ Does your child read or write after school (including doing homework)?	☐ Yes ☐ No	____ Minutes	From ____:____ to ____:____ ☐ From ____:____ to ____:____
7 ☐ Does your child watch TV after school?	☐ Yes ☐ No	____ Minutes	From ____:____ to ____:____ ☐ From ____:____ to ____:____
8 ☐ Does your child play computer game after school?	☐ Yes ☐ No	____ Minutes	From ____:____ to ____:____ ☐ From ____:____ to ____:____
9 ☐ When does your child go to sleep?	Yes	____	N/A

Part 2 Weekends (Activities on the most relaxing day during the weekend)

Activity	Yes or No	If yes	
		Time	Form ____ to ____
1 When does your child get up from bed?	Yes	__	N/A
2 Does your child have any indoor extracurricular class (English, music etc)?	☐ Yes ☐ No	__ Minutes	From __: __ to __: __ ☐ From __: __ to __: __ ☐
3 Does your children have any outdoor extracurricular class (football, basketball etc)?	☐ Yes ☐ No	__ Minutes	From __: __ to __: __ ☐ From __: __ to __: __ ☐
4 Besides extracurricular classes, does your child read or write during the day (including doing homework)?	☐ Yes ☐ No	__ Minutes	From __: __ to __: __ ☐ From __: __ to __: __ ☐
5 Does your child watch TV?	☐ Yes ☐ No	__ Minutes	From __: __ to __: __ ☐ From __: __ to __: __ ☐
6 Does your child play computer?	☐ Yes ☐ No	__ Minutes	From __: __ to __: __ ☐ From __: __ to __: __ ☐
7 Besides outdoor extracurricular classes, does your child spend anytime outdoors (exercising, playing, walking etc)?	☐ Yes ☐ No	__ Minutes	From __: __ to __: __ ☐ From __: __ to __: __ ☐
8 When does you children go to sleep?	Yes	__	N/A

Signature _____ Contact number _____

Relationship with child _____ Date ____/____/____

Children's learning behaviour questionnaire

Guangzhou Outdoor Activity Longitudinal Study
Children's Learning Behavior Questionnaire (Head teacher completed)

School:

Grade:

Class:

[illegible]

