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EPIDEMIOLOGY OF MYOPIA IN A UNITED KINGDOM URBAN CHILD POPULATION

PARTH SHAH

Doctor of Philosophy

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SUMMARY

The significant increase in prevalence of child myopia over recent decades has initiated a global surge of research into its epidemiological characteristics and ocular biometric corollaries. Such knowledge is a prerequisite to the implementation of therapeutic protocols aimed at ameliorating the onset and progression of the condition. However little contemporary data exists regarding the distribution and prevalence of child myopia in the United Kingdom (UK), particularly alongside biometric measures. The classic work by Sorsby *et al.,* (1961) remains the most recent and comprehensive study to examine refractive and biometric outcomes in a UK child cohort.

The Aston Eye Study (AES) was instigated in October 2005 to determine the distribution of refractive error and associated ocular biometry in a sample of UK urban school children. Quantifying the variation in data as a function of age and ethnicity was a primary aim of the investigation, together with the identification of myopiagenic risk factors through analysis of responses to detailed questionnaires. The AES is the first study to compare outcome measures separately in White, South Asian and Black children. Children were selected from two age groups (Year 2 children aged 6/7 years, Year 8 children aged 12/13 years of age) using random cluster sampling of schools in Birmingham, West Midlands UK. Protocols were designed to facilitate comparison of findings with published epidemiological studies. The thesis gives an account of the rationale for AES, the methodology employed, the approach taken in analysing cross-sectional data from the first two years of the study and the significance of the data in terms of understanding further the natural history of myopia.

To date, the AES has examined 598 children (302 Year 2, 296 Year 8). Using open-field cycloplegic autorefraction, the overall prevalence of myopia (≤-0.50D SER in either eye) determined was 19.6%, with a higher prevalence in older (29.4%) compared to younger (9.9%) children ($p<0.001$). Using multiple logistic regression models, the risk of myopia was higher in Year 8 South Asian compared to White children (Odds Ratio [OR] 2.97, 95%CI:1.58-5.59) and higher in children attending grammar schools relative to comprehensive schools (OR 1.84 95%CI 1.28-2.64). In addition, the prevalence of uncorrected ametropia was found to be high (Year 8:12.84%, Year 2:15.23%), which will be of concern to bodies responsible for the implementation of school vision screening strategies.

Biometric data using non-contact partial coherence interferometry revealed a contributory effect of axial length (AL) and central corneal radius (CR) on myopic refraction, resulting in a strong coefficient of determination of the AL/CR ratio on refractive error (Year 8: $r^2= 0.69$, Year 2: $r^2= 0.57$, $p<0.001$). Ocular biometric measures did not vary significantly as a function of ethnicity, suggesting a greater miscorrelation of components in susceptible ethnic groups to account for their higher myopia prevalence. Measures of height and weight did not vary significantly by refractive group. Corneal radius was found to be steeper in myopes in both age groups, but was found to flatten with increasing axial length. Due to the inextricable link between myopia and axial elongation, the paradoxical finding of the cornea demands further longitudinal investigation, particularly in relation to myopia onset.

Questionnaire analysis revealed a history of myopia in parents and siblings to be significantly associated with myopia in Year 8 children, with a dose-dependent rise in the odds ratio of myopia evident with increasing number of myopic parents. By classifying socioeconomic status (SES) using Index of Multiple Deprivation values, it was found that Year 8 children from moderately deprived backgrounds were more at risk of myopia compared with children located at both extremities of the deprivation spectrum (OR relative to most deprived 1.84, 95%CI:1.39-2.44). However, the main effect of SES weakened following multivariate analysis, with South Asian ethnicity (OR 2.54, 95%CI:1.30-4.97) and grammar schooling (OR 2.42 95%CI:1.49-3.30) remaining associated with Year 8 myopia after adjustment.

The thesis provides key data on the epidemiology of myopia in UK children. Based on current findings, a cohort effect of increasing myopia prevalence is evident in older UK urban children, as AES Year 8 findings using the same myopia definition as Sorsby *et al.,* (1961) highlight a greater proportion of children with the condition. It is anticipated that continuance of this study, through cross-sectional and longitudinal follow-up, will complement current findings and provide data of considerable significance to vision scientists, practitioners and public health authorities alike.

Key Words: Myopia, Epidemiology, Refractive error, Ocular biometry, Prevalence

To the people who make my world: Dad, Mum, Mira and Binit.

My joy exists in yours. Thank you for your unconditional love through the years.

This thesis is dedicated to you.

कर्मण्येवाधिकारस्ते मा फलेषु कदाचन ।
मा कर्मफलहेतुर्भूर् मा ते संगोऽस्त्वकर्मणि ॥ ४७ ॥

"You have the right to perform your duty but not to its results. Do not remain motivated by the results of your actions nor refrain from performing what is yours to do"

The Bhagavad Gita, 2:47

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The grant provided by the Central LOC fund to support the Aston Eye Study is gratefully acknowledged. Thank you to all who contributed to the Aston Eye Study – Head teachers, teachers, parents and most importantly, the children who partook in the study. A warm thank you to all helpers who assisted in data collection.

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Finally, a person without whom the last 3 years would have been impossible. A mere thank you will never justify the unconditional love provided by my best friend, who experienced every emotion that I did and has always been the source of my inspiration. Mira – you travelled this journey with me every step of the way and you enabled me to experience the good times and endure the bad. You are as much a part of this thesis as I am. Thank you.

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CHAPTER 1

A REVIEW OF MYOPIA

1.1 INTRODUCTION

The following chapter reviews the literature on myopia, with particular focus on the areas of prevalence, animal models, aetiology and treatment. It serves to highlight the vast magnitude of research undertaken on the subject and provide an overview of a rapidly expanding field.

1.1.1 Definition of myopia

Myopia refers to one aspect of the continuum that is the refractive error spectrum. Commonly known as 'short-sightedness', it is an ocular condition in which parallel light rays from a distant object come to focus not at the retina as expected in an emmetrope, but at a point anterior to the retinal plane in an unaccommodating eye (Figure 1.1.1). The further the focal point of light from the retinal surface, the greater the degree of myopia.

Physiologically, the majority of ametropia is caused by a breakdown in correlation between the eye's axial length and refractive power (Feree and Rand, 1933; Sorsby *et al.,* 1957), the co-ordinated growth of which give rise to an emmetropic eye (Sorsby and Leary, 1970; Edwards, 1998).
However, higher refractive errors are thought to be the product of an anomalous ocular component, predominantly an excessively long or short axial length, which results in myopia or hyperopia respectively (Sorsby *et al.,* 1961).

The prevalence of myopia in children is thought to be rising globally, with studies highlighting a prevalence level approaching epidemic proportions, particularly in East Asia (Grosvenor, 2003; Saw, 2003). These countries include Taiwan (>80% children aged 16-18; Lin *et al.,* 1999), Hong Kong (82% children aged 13-15; Lam *et al.,* 2004), China (>80% females aged 15; He *et al.,* 2004) and Singapore (82% military conscripts; Wu *et al.,* 2001). However, the claim of an epidemic has been disputed based on the veracity of data from this region (Park and Congdon, 2004).
An increase in the exposure of children worldwide to environmental factors such as near work (Richler and Bear, 1980; Zadnik and Mutti, 1987; Zadnik and Mutti, 1998; Saw *et al.,* 2002) and urbanisation (Zadnik and Mutti, 1998; Garner *et al.,* 1999; Rose *et al.,* 2001; Morgan and Rose, 2005) has been postulated to account for the increased prevalence of myopia (Section 1.4.2).

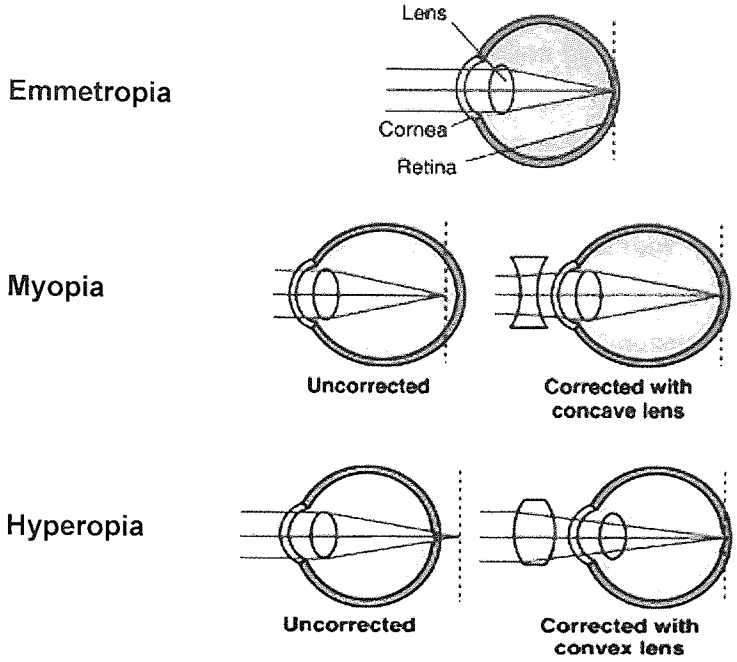


Figure 1.1.1 The emmetropic and ametropic eye. Note the focal planes in relation to the retina in each type of refractive anomaly. Reproduced with permission from The Merck Manual of Medical Information - Second Home Edition, p.1287, edited by Mark H. Beers. Copyright 2003 by Merck & Co., Inc.,Whitehouse Station, NJ. http://www.merck.com/media/mmhe2/ figures/fg226_1.gif. Accessed 07/02/2007.

1.1.2 History of myopia research

Myopia was first identified as a visual defect by the ancient Greeks and Romans (Goldschmidt, 1968; Schaeffel and Howland, 1995). However, it was not until the 17th Century that the physicist Kepler proposed a link between myopia and excessive near work (cited by Wold, 1949). During the 19th Century Donders pursued this theory with research into refractive errors, accommodation and near work (Grosvenor, 1987). Though Donders held the view that myopia occurred as a result of prolonged near work, he further recognised that some people were genetically predisposed to the condition.

A large study carried out in 1867 by Cohn (cited by Goldschmidt, 1968) investigated refractive error in a large sample of schoolchildren (n= 10,000). He concluded that the prevalence of myopia increased with age and level of schooling as children moved from primary to secondary grammar school, instigating the notion that an excessive use of the eyes was the cause of myopia onset and progression (i.e. the 'use-abuse' theory of myopia).

The 20th Century saw an increasing interest in structural correlates and the pathophysiology of refractive error. Much work was conducted on the distribution and relationship between ocular components such as axial length (AL), anterior chamber depth (ACD), corneal radius of curvature (CR) and more recently, crystalline lens characteristics (power, thickness and curvature).

Preliminary work by Steiger in 1913 led to the hypothesis that ocular components are freely associated and independent of each other in growth (cited by van Alphen, 1961). Consequently refraction must follow a Gaussian (i.e. normal) distribution by the free association of these individual components; myopia was merely a tail of the normal curve.

However, this theory was later refuted by studies (Sorsby *et. al.,* 1957) showing that although individual ocular components vary normally in children (Figure 1.1.2) and adults, the distribution of refractive error in humans follows a leptokurtotic distribution (Sorsby, 1932; Ojaimi *et al.,* 2005a), with a greater frequency of refractions congregating around the mean than expected in a normal distribution. These leptokurtotic distributions contradicted the Gaussian range of refraction postulated by Steiger.

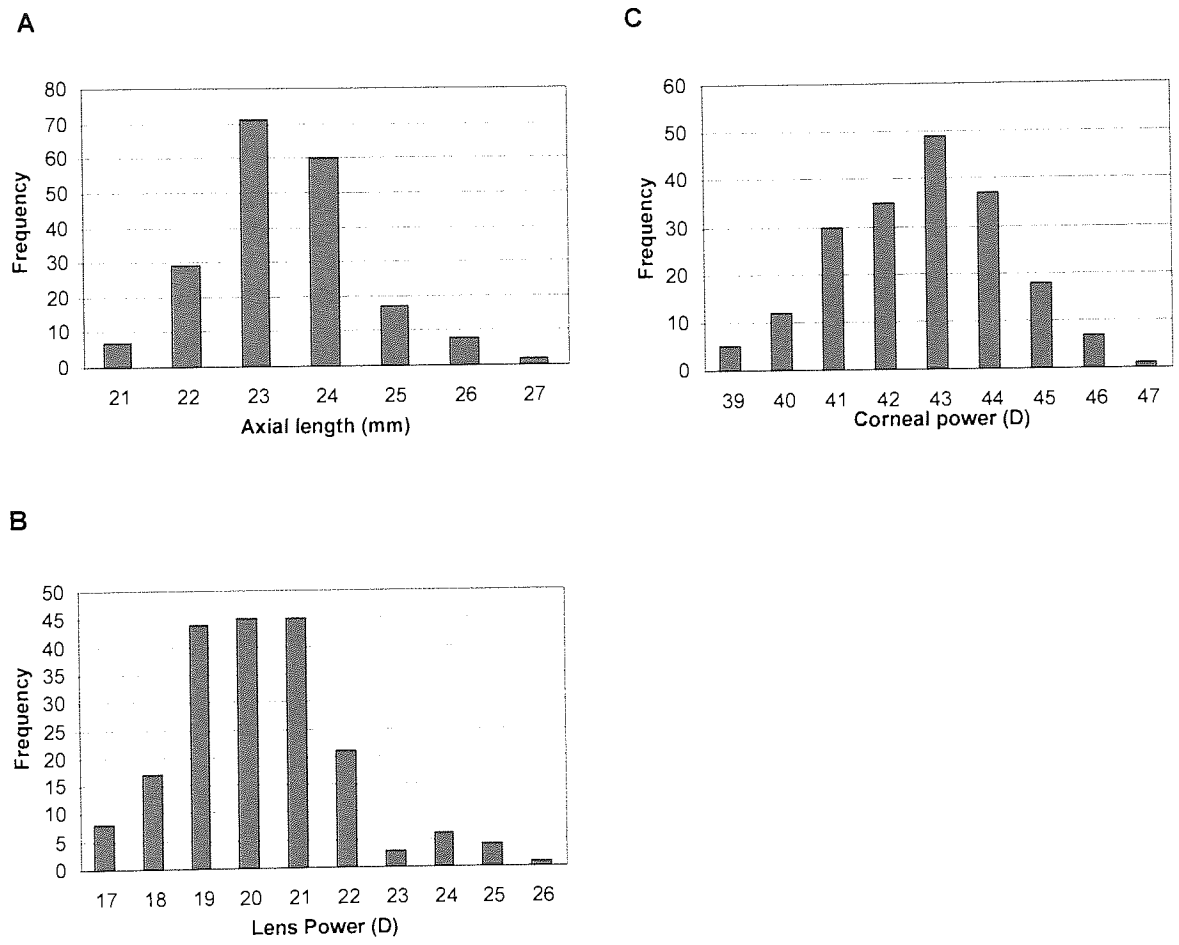


Figure 1.1.2 Data redrawn from results of Sorsby *et al.,* (1957) highlighting the Gaussian distributions of ocular components. N= 194 eyes. A: Axial length; B: Lens Power; C: Corneal Power

The leptokurtotic distribution of refractive error lent credence to the theory of emmetropisation (i.e. the process of refractive error towards emmetropia) postulated by Straub in 1918 (cited by Goldschmidt, 1968). Straub suggested that during infancy the eye perpetually attempts to regulate its size based on defocused images it receives, by regulating the growth rate of one or more of its ocular components (Brown *et al.,* 1999) such that the level of defocus is minimised and the image falls onto the retinal plane resulting in emmetropia.

1.1.3 Human Emmetropisation

Data are equivocal as to whether human neonates are born myopic (Goldschmidt, 1969; Mohindra and Held, 1980; Gwaizda *et al.,* 1993) or hyperopic (Slataper, 1950, Hirsch and Weymouth, 1991, Mayer *et al.,* 2001; Mutti *et al.,* 2005), a result perhaps dependent upon the methodology used to measure infant refraction, although it has been stated that emmetropia itself is rarely found in the newborn infant (Cook and Glasscock, 1951). Some studies have suggested that a normal distribution of refractive error at birth exists (Mohindra and Held, 1980; Robinson, 1999; Mutti *et al.,* 2005).

Irrespective of neonatal refractive error, the majority of eyes subsequently follow rapid progression towards emmetropia (Figure 1.1.3), with full emmetropisation achieved by the ages of 6 - 8 years (Edwards, 1991; Gwaizda *et al.,* 1993; Robinson, 1999; Mayer *et al.,* 2001). The theory of emmetropisation is supported by findings that children with higher levels of hyperopia have a greater rate of refractive change towards emmetropia in an attempt to ameliorate blur (Hirsch, 1962; Mutti *et al.,* 2005).

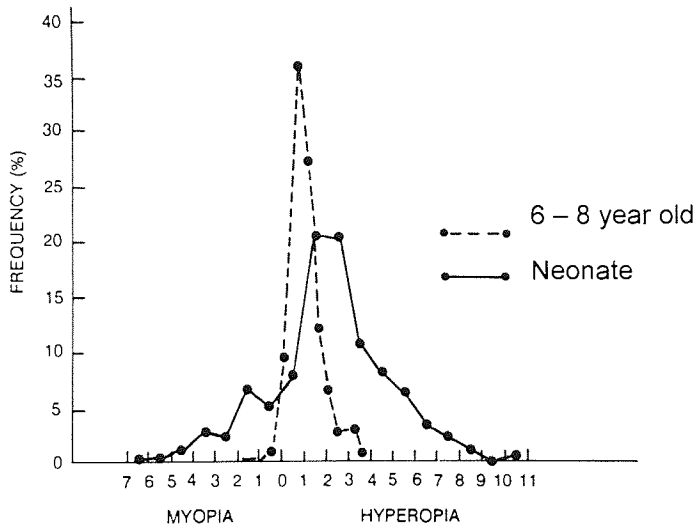


Figure 1.1.3 The effect of emmetropisation on refractive distribution from birth to the age of 6 - 8 years. Figure reproduced from Refractive Anomalies, Research and Clinical Applications, Hirsch and Weymouth, Prevalence of Refractive Errors, Page 22, Copyright Elsevier (1991).

Emmetropia in the majority of children is achieved by the growth of ocular components (Sorsby *et al.*, 1957) in a co-ordinated manner such to modify refractive error towards a state where distance light achieves focus at the retinal plane (Figures 1.1.4 – 1.1.5).

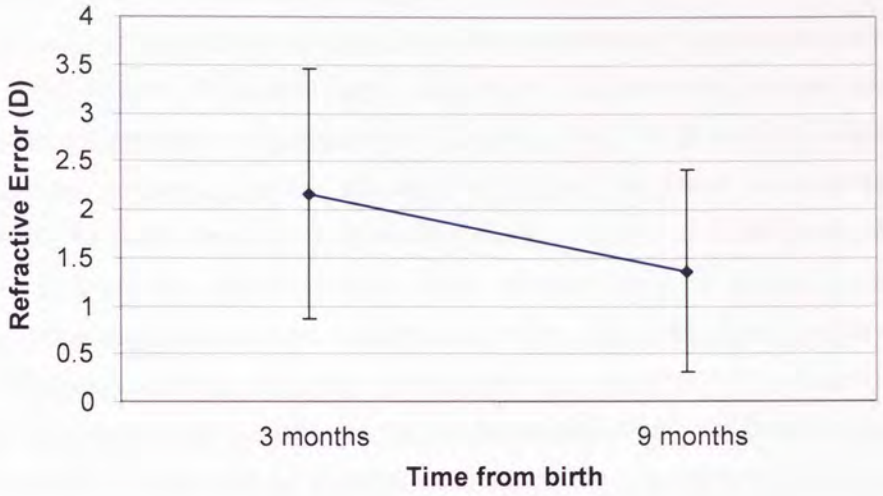
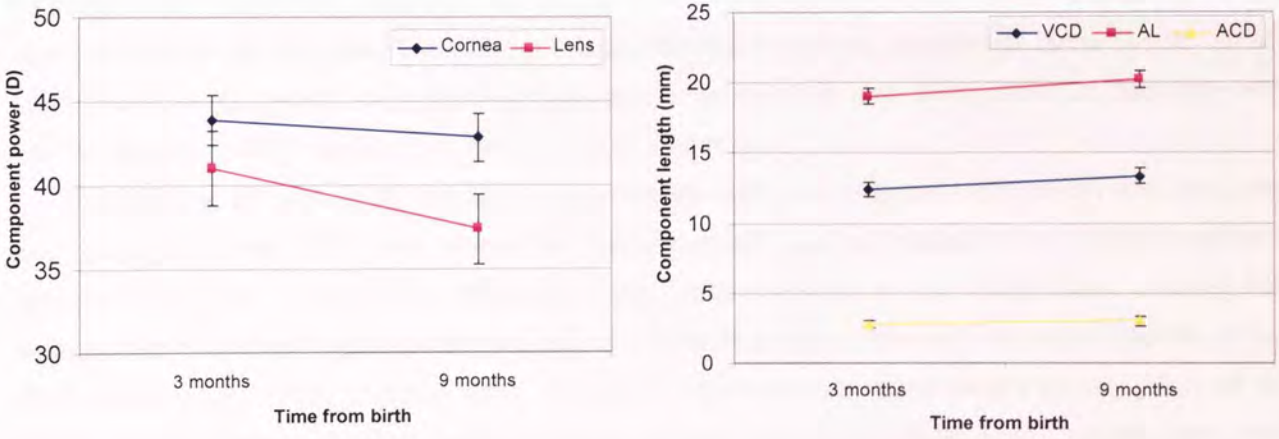


Figure 1.1.4 The progression of mean refractive error (± standard error bars) from the ages of 3 to 9 months. From results of Mutti *et al.*, (2005)



A Refractive **B Axial**

Figure 1.1.5 The change in ocular components (± standard error bars) as a function of age from birth. AL: Axial length, ACD: Anterior chamber depth, VCD: vitreous chamber depth. Based on results from Mutti *et al.*, 2005

On attaining an emmetropic state, eye growth does not become static but instead has been shown to continue growth between the ages of 6 – 14 years (Jones *et al.*, 2005) as a dynamic equilibrium regulated by feedback.

1.1.3.1 The role of Axial Length during Emmetropisation

Sorsby and Leary (1970) concluded that during childhood, eye growth consists of a rapid infantile growth phase wherein the majority of axial growth occurs by the age of 2 years, followed by a slower growth phase until the age of 13 years. Adults AL values by the age of 13 years were also found by Larsen (1971). The effect of AL growth is countered by a compensatory change in corneal and/or lenticular power, such that ocular refraction progresses towards emmetropia.

It is the growth of the axial length, specifically the vitreous chamber depth (VCD), that is the primary structural correlate driving myopia (Gernet, 1980; McBrien and Adams, 1997). Recent significant work by Jones *et al.,* (2005) showing the longitudinal growth of ocular components between the ages of 6 – 14 years demonstrated an increase in the rate of axial growth in myopes after the age of 10 years, whilst the growth rates in other refractive groups slowed. In addition, it has been recently reported that ocular growth accelerates in the year preceding myopia onset (Mutti *et al.,* 2007) and immediately decelerates once the condition has manifest. Thus it appears that myopia is not a result of monotonic axial growth into the negative refractive error domain, but is likely to be a multi-stage process characterised by intermittent changes of ocular growth rate in susceptible children.

1.1.3.2 The role of the Crystalline Lens during Emmetropisation

Though the crystalline lens continues to grow throughout life, child studies have shown a sagittal thinning of the lens during emmetropisation (Larsen, 1971a; Brown *et al.,* 1999), explained by the observation that as the eyeball expands, it stretches the lens in an equatorial plane (Mutti *et al.,* 1998; Brown *et al.,* 1999). The refractive index within the lens has also been shown to decrease with age (Mutti *et al.,* 1998), leading to a further loss of lens power.

It is thought that the lens is the primary compensative component to axial elongation and becomes less powerful (Gernet, 1981) and thinner with age to maintain a sharp image on the retina via either a passive (Mutti *et al.,* 2005) or an active feedback system (Garner *et al.,* 1992). Lens thinning has been shown in children to offset normal ocular elongation up to the age of 9 -10 years (Zadnik *et al.,* 2004; Jones *et al.,* 2005) and has been found to temporally follow axial length growth (Mutti *et al.,* 2005) as a compensatory adjustment of the eye. Myopia appears to initiate once compensatory lens flattening can no longer offset AL growth (Garner *et al.,*1992; Jones *et al.,* 2005).

1.1.3.3 The role of the Cornea during Emmetropisation

Initial work postulated that the cornea flattens rapidly by 7D over the first 2 years of life, acting as the principal offset to axial elongation (Hirsch and Weymouth, 1991). However, recent evidence has suggested that although the cornea flattens during infancy, it does so at a lower rate than the lens (Figure 1.1.5 A; Mutti *et al.,* 2005) hence the cornea does not appear to contribute as extensively to create and maintain an emmetropic state as the crystalline lens (Grosvenor, 1989; Mutti *et al.,* 1998; Brown *et al.,* 1999).

By the age of 2-3 years, the cornea is said to have reached adult curvature levels (van Alphen, 1961), with little change after this time during childhood (Sorsby *et al.,* 1961; Garner *et al.,* 1990). However, it has been shown longitudinally that the cornea does flatten until late teenage years (Friedman *et al.,* 1996), although at a radically slower rate than during the first 2 years of life (Mutti *et al.,* 2000a).

Corneae of myopes have been found to be more powerful and steeper than those of emmetropes (Goss *et al.,* 1997; Jones *et al.,* 2005). In contrast, other work has found corneae in myopes to similar to that of emmetropes in curvature (Garner *et al.,* 1990). As yet, data remain equivocal as to the role of the cornea in the genesis of refractive error.

1.1.3.4 The role of Anterior Chamber Depth during Emmetropisation

Ultrasonographic ACD measures by Larsen (1971b) complemented earlier work by Sorsby *et al.,* (1961) in determining the changes of ACD with growth. Larsen showed rapid infantile growth of the ACD up to the age of 18 months, followed by 2 progressively slower growth phases until the age of 13 years when values were comparable to an adult. Other studies have shown a progressive deepening of the ACD with age (Zadnik *et al.,* 1993; Zadnik *et al.,* 2003) although it is not known how much of the increase can be attributed to a thinning of the lens with age (Zadnik *et al.,* 1993) instead of an actual increase in ACD depth.

The ACD has been found to be deeper in myopes (Larsen, 1971b; Jones *et al.,* 2005) and shows an increased rate of growth compared to other refractive groups (Jones *et al.,* 2005).

1.1.4 Classification of myopia

The myriad of myopia classification is diverse. An important observation by Sorsby and Leary (1970) and Morgan and Rose (2005) is that myopia is not simply a generic condition, but can be further categorised based on severity, age of onset, risk of pathology and causative optical structures.

1.1.4.1 Severity

Many authors have attempted to classify myopia by its severity. Three subgroups have been identified with essentially arbitrary categorisations, namely *mild, moderate* and *high* myopia. One conventional system categorises mild myopia as a spherical equivalent refraction (sphere + ½ cylinder) from 0D to -3.00D, moderate myopia from -3.00D to -6.00D and high myopia greater than -6.00D (Curtin, 1985; Gilmartin, 2004). It has been suggested that high myopia should not be thought of as simply an extreme in the refractive error spectrum, but rather as a separate condition with its own aetiology and prognosis (Goldschmidt, 1981; Young *et al.,* 2007).

1.1.4.2 Age of onset

Early onset - This form of myopia has an age of onset from very early infancy until the age of 6 years (Grosvenor, 1987). It tends to progress rapidly in degree during early life and carries with it the risk of ocular pathology commonly associated with high myopia (Tokoro, 1988; Frederick, 2002; Logan *et al.,* 2004). These cases of high myopia are usually thought to be genetically inherited (Goldschmidt, 1968; Morgan and Rose, 2005) with a number secondary to systemic diseases such as Marfans syndrome, homocystinuria and Down's syndrome (Logan *et al.,* 2004).

However, it has been argued that although a considerable proportion of high myopia may be congenital, this does not confirm a direct genetic link (Grosvenor, 1987). Premature infants including those of low birth weight (Robinson, 1999) may be at risk of myopia secondary to either refractive changes in the eye (e.g. relatively steep corneae) or to ocular pathology as a consequence of their premature birth (e.g. retinopathy of prematurity) and not due to a hereditary trait *per se* (Varughese *et al.,* 2005).

School myopia – The greatest incidence of *youth onset, juvenile onset* or *school* myopia occurs in children with an age of onset from 7 years of age to late teenage years (Slataper, 1950; Grosvenor, 1987; Saw *et al.,* 1996). The nomenclature *school myopia* refers to the time of onset (i.e. when a child is at school) and is not necessarily of aetiological significance. School myopia is characterised by a gradual increase in refractive error through teenage years and an eventual stabilisation in late teenage years/early twenties at a level of myopia below -4D (Gilmartin, 2004).

It is the swift rise in global prevalence within this class that has led authors to purport an environmental aetiology for school myopia (Saw, 2003), as the rise in prevalence has occurred too rapidly to be accounted for by a change in the gene pool of a region.

Adult onset - Myopia developing after the age of 20 years is defined as *adult onset* and may be further sub-classified into *early adult-onset* developing between late teenage years until an age of approximately 40 years, and *late adult-onset* commencing after the age of 40. Myopia onset in this group occurs at an age when ocular growth is effectively complete hence has been attributed to sustained environmental exposure to myopiagenic risk factors (Gilmartin, 2004). Myopia onset in very elderly people can be attributed to age-related lenticular changes and subsequent myopic shift (Wensor *et al.,* 1999).

1.1.4.3 Risk of pathology

A straightforward classification devised by Duke-Elder and Abrams (1970) sub-divides myopia into two categories: *simple* and *degenerative*.

Degenerative (or malignant) myopia typically begins early in life and progresses to high levels. By definition, it is associated with ocular complications secondary to myopia e.g. chorioretinal changes and posterior staphyloma.

Simple myopia includes the remaining cases of myopia, which are moderate both in magnitude and risk of complications relative to its fellow group.

Curtin (1985) modified the classification of Duke-Elder and Abrams. He rejected the nomenclature *degenerative/malignant* myopia, instead replacing it with *pathological* to avoid neoplastic concerns that may have arisen if patients were told their myopia was malignant. The additional two categories to simple myopia proposed by Curtin were *physiological* and *intermediate* myopia. *Physiological* myopia results from a miscorrelation between the axial length of the eye and the refracting power of the lens/cornea although all components are within the normal ranges found in emmetropes by Sorsby *et al.* (1957).

Intermediate myopia describes the overlap between physiological and pathological myopia. Here, the posterior segment of the globe expands and exceeds the normal range of ocular growth in the absence of subsequent pathological changes, although the eye is at increased risk of secondary complications than in physiological myopia (Curtin, 1979). Intermediate myopia therefore represents a transition between the relatively normal eye of physiological myopia and an eye that is potentially at high risk from pathological changes.

1.1.4.4 Correlation versus Component ametropia

The terms *correlation* and *component* ametropia were presented by Sorsby *et al.* in works published in 1957 and 1961. The research group studied various ocular components and concluded that refractive errors within ± 4.00DS (later amended to include hyperopes to +6.00DS, Sorsby *et al.*, 1962) were a result of an imperfect correlation between axial and refractive components. Each component was distributed normally, supporting the theory of Straub (1918), but it was the breakdown in the correlating mechanism between these structures that caused the ametropia. Sorsby and colleagues termed this *correlation ametropia*.

Component ametropia refers to refractions outside the - 4.00DS to +6.00DS range caused by one or more of the ocular components, invariably axial length, being of an abnormal size i.e. outside that expected from a normal distribution of emmetropic ocular components (Sorsby *et al.*, 1957; Sorsby *et al.*, 1962). It is estimated that only 3% of the population have one or more ocular components outside the normal ranges evident in emmetropes (Sorby *et al.*, 1962).

1.2 MYOPIA PREVALENCE WORLDWIDE

1.2.1 Methodological disparities

A plethora of evidence exists regarding myopia prevalence worldwide, however direct comparisons between studies are confounded by variations in methodology, such as:

- method of refraction (e.g. autorefraction *vs.* retinoscopy)
- sampling strategy (random cluster sampling *vs.* convenience sampling)
- age of sample
- use of cycloplegia
- type and dosage of drug (e.g. cyclopentolate *vs.* tropicamide)

A further variation between studies is the criterion utilised to define refractive error (Negrel *et al.,* 2000; Logan and Gilmartin, 2004; Park and Congdon, 2004). The effect of variations in this criteria is well illustrated by a study on the prevalence of myopia in teenage high school students in Singapore (Quek *et al.,* 2004). The prevalence in this study was compared based on three definitions of myopia: a spherical equivalent refraction (SER) of ≤-0.50D (-0.50D or more myopic), ≤-0.75D and ≤-1.00D. The SER is defined as the sum of the spherical component of the refraction plus half the cylindrical power.

Using an SER of ≤-0.50D, the prevalence of myopia in the total population (n= 946) was 73.9%. However, using a definition of SER ≤-0.75D, the prevalence dropped to 63.4%; with a more conservative boundary of SER ≤-1.00D, the proportion of myopes dropped to 56.1%. Modification of the myopia criterion by -0.50D SER reduced the proportion of myopes by 17.8%, illustrating the significance of refractive error criteria in estimating prevalence levels and that they should be considered when interpreting data (Park and Congdon, 2004). Calls for an international consensus on myopia definition have been made (Luo *et al.,* 2006) based upon a level at which functional impairment occurs, thereby preventing deployment of arbitrary classifications that preclude comparisons between studies.

To account for the above variations, the Refractive Error Study in Children (RESC) was introduced early this century. The RESC are a corpus of cross-sectional refractive error studies adherent to a uniform methodology (Negrel *et al.,* 2000) and conducted in parts of the world where refractive error studies are required due to either their paucity (e.g. Chile, South Africa) or necessity (e.g. China). These studies have proved an invaluable resource to the World Health Organisation (WHO) in its *Vision 2020* strategy to determine the contribution of uncorrected refractive error to global avoidable blindness prevalence (Holden and Resnikoff, 2002; Ellwein, 2002).

The RESC has investigated cross-sectional samples of children from the general population aged principally between 5-15 years. Door-to-door enumeration of children has been used to recruit subjects, thereby providing true population-based estimates of prevalence (Negrel *et al.*, 2000) as not all children would be attending school in regions where the RESC was carried out, such as India (Dandona *et al.*, 2002; Murthy *et al.*, 2002). Many non-RESC studies have sampled children from schools (Laatikainen and Erkkilä, 1980; Garner *et al.*, 1999; Lam *et al.*, 1999; Lin *et al.*, 1999; Zhang *et al.*, 2000; Zadnik *et al.*, 2003; Lam *et al.*, 2004; Ojaimi *et al.*, 2005; Saw *et al.*, 2005).
RESC refractive measurements were taken using either cycloplegic autorefraction or cycloplegic retinoscopy. Myopia was defined as SER ≤–0.50D and hyperopia as SER ≥+2.00D in the worst eye. Table 1.2.1 and Figure 1.2.1 summarise the findings to date.

Many epidemiological studies of myopia have shown country-specific prevalence rates. For example, the prevalence of myopia (SER ≤–0.75D) in Indians aged between 16-25 years resident in Singapore (68.7%, Wu *et al.*, 2001) has been shown to be notably greater than that recorded on a cohort of a similar age (16-29 years) in India (8.4%, Dandona *et al.*, 2002), indicating a country-specific environmental influence. However, this does not preclude intrinsic variation in ethnic susceptibility, as illustrated by the higher prevalence of myopia in Chinese children compared to other ethnic groups, in studies conducted both in and out of China (Kleinstein *et al.*, 2003; Lam *et al.*, 2004; *Goh et al., 2005*; *Cheng et al., 2007*).

Figure 1.2.1 Global child myopia prevalence determined by the RESC studies. M: Male, F: Female

Country	Reference	Region	N	Myopia Prevalence [M=Male, F=Female]
Chile	Maul *et al.* (2000)	LaFlorida, Santiago (suburban)	5303	5 years: 3.4% 15 years: M=19.4%, F= 14.7%
Nepal	Pokharel *et al.* (2000)	Jhapa District, Mechi Zone (rural)	5067	5 years: M~ 0.8%, F~ 0% 15 years: M~ 2.8%, F~ 0.5% (Results estimated from graph)
China	Zhao *et al.* (2000)	Shunyi District (semi-rural)	5884	5 years: M< 2%, F~ 0% 15 years: M= 36.7%, F= 55%
China	He *et al.* (2004)	Guangzhou (urban)	4364	5 years: 5.7% M & F 15 years: M= 73.4%, F= 83.2%
India	Dandona *et al.* (2002)	Mahabubnagar, Andhra Pradesh (rural)	4074 (ages 7-15)	7 years: 2.80% M & F 15 years: 6.72% M % F (cycloplegic retinoscopy)
India	Murthy *et al.* (2002)	Trilokpuri, New Delhi (urban)	6447	5 years: 4.68% M & F 15 years: 10.80% M & F (cycloplegic retinoscopy)
South Africa	Naidoo *et al.* (2003)	Durban, (metropolitan)	4890	5 years: 3.2% M & F 15 years: 9.6% M & F
Malaysia	Goh *et al.* (2005)	Gombak Dist. Kuala Lumpur (urban)	4364 (ages 7-15)	7 years: 10.0% M & F 15 years: 32.5% M & F

Table 1.2.1 A summary of the studies to date using the Refractive Error Study on Children (RESC) protocol (Negrel et al. 2000). Myopia prevalence determined with cycloplegic autorefraction unless otherwise stated. M: Male, F: Female

1.2.2 Asia

The focus of myopia in East Asian countries, namely Singapore, Taiwan and China, has attracted considerable attention in recent years due to the high numbers of myopic children in the population. Myopia prevalence is not just purported to be mounting, but its onset is appearing earlier in children (Lin *et al.,* 2004; Morgan and Rose, 2005).

1.2.2.1 China

A large study in China by Rasmussen in the early half of last century (1936) found a myopia prevalence between 42% and 65%, similar to current values (Zhao *et al.,* 2000; He *et al.,* 2004) suggesting that the Chinese predisposition to myopia may be longstanding. However, Rasmussen's estimates were based on a retrospective analysis of previous sight tests conducted using very basic equipment in a hospital setting. No mention of the ages of the children in each sector, methodology (including the use of cycloplegia) or criteria for defining myopia was given. Therefore it is likely that a selection bias existed in the cohort and the myopia prevalence was overestimated.

Current prevalence estimates of school myopia in cities such as Hong Kong (Lam *et al.,* 1999; Fan *et al.,* 2004; Lam *et al.*, 2004) and Guangzhou (He *et al.,* 2004) have been found to be high, attributed in part to urbanisation of the region as well as the high intensity and academic rigour of the schooling system (Lam and Goh, 1991; Park and Congdon, 2004; Edwards and Lam, 2004). Chinese students are brought up in a very congested and competitive environment (Fan *et al.,* 2004) where an ethos exists to excel academically from a very young age. This culture of education is very different to that experienced by children in Western parts of the world such as Europe or the USA (Edwards, 1999; Lam *et al.*, 2004).

Studies conducted in rural areas of the country have detected lower myopia prevalence levels in children compared to urban regions. A direct comparison can be drawn between a study in urban Guangzhou (He *et al.,* 2004) and the semi-rural population of the Shunyi District (Zhao *et al.,* 2000) as both adhered to the RESC protocol (Negrel *et al.,* 2000) outlined previously. In 5 year olds, myopia was virtually absent (~0%) in the Shunyi district though a prevalence of 5.7% existed in Guangzhou. Fifteen year-old children in the Shunyi District demonstrated a prevalence of 36.7% males and 55% females whereas in Guangzhou, the levels were 73.4% and 83.2% respectively.

A recent study in the rural Yangxi County found a lower prevalence than that in both Guangzhou and La Shunyi district (He *et al.,* 2007). Here, the myopia prevalence in 15 year olds was 34.1% and 50.9% in males and females respectively although there may have been a slight bias in that the sampling frame was different in this study compared to the previous two (i.e. school-based *vs.* population-based respectively). Nevertheless, the results of these 3 studies in China lead to the conclusion that urbanised areas are associated with a higher prevalence of myopia.

A separate study examining the urban-rural divide investigated the distribution of refractive error in children aged 6 to 7 years in three schools of varying demographic profiles (Zhang *et al.*, 2000). Two schools (one urban, one rural) were selected from Xiamen, a port on the southeast coast of China alongside a third school from Singapore. These locations were chosen as the children measured were predominantly of a similar genetic stock (i.e. South Chinese), thereby minimising confounding effects of genetic variation on environmental disparities. The results of Zhang and colleagues support the theory of urban myopiagenesis, with Singapore children having the highest prevalence of myopia (12.3%), followed by children from Xiamen city (9.1%) and lastly from Xiamen countryside (3.9%). Axial length measures were related to the respective myopia prevalence within each area. Children in Singapore had on average longer axial lengths than children in Xiamen city who in turn had longer axial lengths than children in Xiamen countryside ($p<0.001$). Unexpectedly, the anterior chamber depth contributed predominantly to a change in axial length and not the vitreous chamber depth as has commonly been implicated (Lam and Goh, 1991; Zadnik *et al.*, 1993; Saw *et al.*, 2005 [human], Wildsoet, 1997 [animal]). However, the greater contribution to AL by the ACD may have been an artefact caused by thinning of the lens (Zhang *et al.*, 2000).

Vitreous chamber depth (VCD) was the main structural correlate of myopia in a two-year longitudinal study (Lam *et al.*, 1999) of myopia progression among Hong Kong schoolchildren (aged 6–17 years). Myopia prevalence increased from 52.1% to 63.3% over the two years with an associated increase in VCD. Children who were myopic at the beginning of the study (n= 74) were found to undergo a greater myopic shift compared to children who began emmetropic/hyperopic (n=68, $p<0.001$). There were no significant age or gender differences between the two groups to confound findings. Lam *et al.* (1999) further concluded that myopia began earlier, had a higher prevalence and progressed faster in Chinese children compared to Caucasians participating in the study. This notion of an effect of ethnic variation on myopia prevalence in China is supported by further research conducted in Hong Kong (Table 1.2.2, Lam *et al.*, 2004).

	Gender	Ethnicity	n	Myopia prevalence (%)
Lam and Goh, (1991)				
14-15 years of age	Male	Chinese	57	60
	Female	Chinese	45	52.6
Lam *et al.* (2004)				
Local School 13-15 years of age	Male	Chinese	156	84.6
	Female	Chinese	133	90.2
International School 13-15 years of age	Male	All	393	60.3
	Female	All	396	63.6
International School 13-15 years of age	All	Chinese	348	82.8
	All	Caucasian	321	40.5

Table 1.2.2 Results of studies conducted on Hong Kong school children

A significant difference in the proportion of myopes was determined by Lam *et al.,* (2004) by comparing Chinese students in international schools to their Caucasian colleagues (82.8% *vs.* 40.5% respectively,$p<0.001$). Overall myopia prevalence between Chinese students of local and international schools were not found to differ ($p= 0.12$). These results suggest a genetic influence on myopia development, as Chinese students were susceptible to myopia irrespective of the type of they school they attended (i.e. local *vs.* international).

Myopia in Chinese students between the two studies in Table 1.2.2 shows an apparent increase in prevalence from below 60% to above 80%. However, direct comparison is precluded by methodological differences between studies. For example, Lam and Goh (1991) performed non-cycloplegic autorefraction on their subjects (n=102) whilst Lam *et al.* (2004) used a basic non-cycloplegic subjective method to determine the degree of myopia in their subjects (n= 1,078).

Myopia in Chinese adults has not been investigated as extensively as in children. Two studies published in 1994 examined the prevalence of refractive errors and associated biometry in adults. The first study found that myopia prevalence was similar in young adults aged 19-39 years (71.5% myopia ≤-0.50D SER) compared to that found in younger teenagers (Goh and Lam, 1994). The second study examined adults over the age of 40 years and found a dramatic decrease in myopia prevalence to 29% (Lam *et al.,* 1994) compared to the younger cohort studied by Goh and Lam. In addition, a positive association was demonstrated between age and hyperopia (prevalence at age 40-44: 2%; age 65+: 66%), with a concurrent reduction in axial length. The authors postulated a cohort effect to explain the decrease in myopia prevalence in older persons, and cited a more competitive schooling system for younger children compared to previous years.

A cohort effect refers to an actual effect across generations. If the prevalence of a particular condition, such as myopia changes with time, it can be said that a true effect is occurring i.e. more

people are becoming myopic compared to previous years. The alternate outcome, a longitudinal effect, occurs when the level of a condition varies with time in an individual. Hence if a sample of adults is found to contain more myopes compared to children in the same cross-sectional study, it may be deduced either that the prevalence of myopia has decreased in the child population (cohort effect) or that individuals generally become more myopic with age, and that the children measured will also become more myopic with time (longitudinal effect). The ambiguity in determining whether an effect is cohort or longitudinal is a significant limitation of cross-sectional studies i.e. temporal variations cannot be confirmed from results.

A more recent population-based survey in Beijing on adults 40-90 years of age examined the epidemiology of refractive error in 4,319 subjects (Xu *et al.,* 2005). Overall myopia prevalence (<-0.50D SER) with cycloplegic autorefraction was found to be 22.9%, with myopia significantly associated with younger age, urban region, education and nuclear cataract. The authors concluded by stating that although the myopia prevalence was higher than that found in adult studies in Australia, it was comparative to North American studies and lower than Singaporean investigations.

1.2.1.2 Singapore

Singapore is the epitome of East Asian urbanisation. It has a high prevalence of myopia comparable to those of neighbouring urban regions Hong Kong and Taiwan (Saw, 2003). The myopia prevalence level in Singapore is currently a public health issue due to the economical and medical ramifications of the condition (Seet *et al.,* 2001). There have been calls for an increase in public awareness about the necessity of regular visits to eye care providers (Ho *et al.* 2006). The Singapore National Myopia Register was initiated in 2001 (Lim, 2006) to track children with high myopia, its progression and the outcomes of interventional strategies.

Early studies to determine myopia prevalence were carried out in Singapore between 1987-1992 on male military conscripts aged 17-19 years (cited by Morgan and Rose, 2005), although the veracity of the data can be questioned as the classification of myopia was based on uncorrected vision <6/18 and not objective refraction. Vision can be reduced due to high levels of uncorrected hyperopia, amblyopia, astigmatism and pathological causes, all in the absence of a myopic eye. It is also possible that false negatives (i.e. true myopes not classified as myopic) eluded detection by squinting their eyes to see clearly via a pinhole effect. Therefore using vision as a basis for refractive classification is likely to lead to considerable inaccuracies.

A more recent study on male military conscripts (n = 15,095) aged between 17 – 19 years (Wu *et al.*, 2001) measured refraction objectively (non-cycloplegic autorefraction) and compared myopia prevalence in Singapore as a function of ethnicity (i.e. Chinese, Indians and Malays) and educational background. All participants were educated in Singapore. Chinese conscripts had a greater prevalence of myopia (82%) compared to Indians (69%) and Malay (65%) conscripts, even after adjustment for educational attainment. Educational attainment itself was also correlated with myopia, with conscripts who had been to high school having a higher prevalence of myopia than those who had not.

Singapore-Chinese students showed the highest myopia prevalence (77.1%) in a school-based study (n= 946) on teenagers aged 15-19 years using non-cycloplegic autorefraction (Quek *et al.*, 2004). Malays and Indians were the next largest ethnic groups with lower myopia levels of 69.4% (Malay) and 65.8% (Indian). Myopia was also associated with educational level (Ho *et al.*, 2006) in a dose-dependent manner. Children taught through the *Express* stream (i.e. most academically advanced) had a greater risk of myopia than those in the *Normal Academic* and *Normal Technical* streams (age and gender adjusted Odds Ratios (OR): *Express* 3.03, *Normal Academic* 1.68 and *Normal Technical* 1.00 [referent], $p < 0.01$).

Increased levels of near work were associated with a higher myopia prevalence in similar aged schoolchildren (aged 7-9 years, n = 1,005) across two Singapore schools (Saw *et al.*, 2002) as part of the Singapore Cohort Study of the Risk Factors for Myopia (SCORM). This prospective cohort study sought to investigate both the incidence and prevalence of myopia by examining children with and without the condition for a period of 3 years on a longitudinal (Saw *et al.*, 2005) basis.
Results from the initial baseline cross-sectional study (Saw *et al.*, 2002) showed that children who read more than two books a week were at a greater risk of 'higher' (≤-3.00D SER) myopia compared to those who did not read as avidly (OR 3.15, 95%CI: 1.96-5.04). However, results from the longitudinal study over the 3 year period found that non-myopic children (at baseline) who read a high number of books per week were not at greater risk of becoming myopic than those children who did not read as many books (Saw *et al.*, 2006), therefore near work was not associated with myopia. Non-verbal IQ was shown to contribute more to the variance of refraction than books read per week (Saw *et al.*, 2004), highlighting a role for intelligence in myopia onset. The SCORM study highlights the importance of longitudinal work in ascertaining the causal nature of risk factors, which may be inferred artificially through cross-sectional investigations.

Refractive data on adult Singaporeans is sparse, but it can be seen that adults in Singapore, in a similar vein to children, are more susceptible to myopia than their Western counterparts. Research conducted by Wong *et al.* (2000) on a population based sample of Singapore Chinese adults aged 40-79 years (n= 1,113) derived a myopia (<-0.50D SER) prevalence of 38.7%, with a relatively large prevalence (10%) of high myopia (<-5.00D SER), raising a concern of secondary pathological risks in these patients. These figures were greater than those found in adult studies in the West although the socio-demographic risk factors that increased the odds for myopia, such as education and income levels, are similar to those found in Western studies and postulate a higher intrinsic susceptibility to environmental influences than Western populations.

1.2.1.3 India

Myopia prevalence in India has not reached the levels detected in East Asian countries such as China and Taiwan. It is not yet conclusive whether this disparity is due to a genetic predisposition of myopia within Chinese peoples or a particular environmental factor (e.g. educational system) lower in intensity within India (Murthy *et al.*, 2002).

An early study comparing refractive error of middle-class Indian children in Africa to traditionally upper-caste Indian children resident in India revealed similar distributions (McLaren, 1961), with a highly leptopkurtotic peak (86% children between 0.00D and +2.00D SER). Measured using cycloplegic retinoscopy, the prevalence of myopia (taken as any negative SER) was 11% in the African-Indian cohort (*n*= 359).

More recently, two distinct regions in India have been investigated adherent to RESC protocol (Negrel *et al.*, 2000), to determine the effect of urbanisation on child refractive error distribution. A rural study was conducted in Mahabubnagar, a district in the state of Andhra Pradesh (Dandona *et al.*, 2002). Overall myopia prevalence was 4.1% (n= 4,074) and was most strongly associated with father's schooling level (OR 1.48, $p<0.05$). An urban study was carried out in New Delhi, a populous city where 6,447 children were examined (Murthy *et al.*, 2002). The myopia prevalence was found to be higher than in the rural location (7.4%) and once more, strongly associated with level of father's schooling (age 11-13 years, OR 1.69, $p<0.05$). The authors of both RESC studies above propounded father's schooling as an adequate surrogate for socioeconomic status and that an emphasis on schooling would be higher in children from educated families, leading to an increased exposure to myopiagenic risk factors.

Additional work suggesting an environmental aetiology of myopia was conducted in Nepal (Garner *et al.*, 1999). Tibetan and Sherpa children, both sharing common genetic backgrounds were invited to participate in the study (n=825), the Tibetan children attending Westernised schools with more rigorous schooling standards than those of the poorly resourced Sherpa children. Results showed Tibetan children to have a higher prevalence of myopia (≤-0.50D SER) of 21.7% compared to 2.9%

within the Sherpa children. Although methodology between cohorts differed (Tibetan children were measured using cycloplegic autorefraction and Sherpa children by non-cycloplegic retinoscopy), the use of cycloplegia in the Sherpa sample would have served only to reduce the proportion of pseudomyopes, thereby increasing the difference between cohorts. Differences in schooling have been suggested to account for the disparity but others such as altitude, dietary differences and urbanisation warrant further investigation.

Myopia in Indian adults (n= 2,321) has been shown to increase with age in people over 40 years (Dandona *et al.,* 2002a). However, a relatively high prevalence of myopia within the study by Dandona and colleagues was linked to the presence of nuclear cataract in older subjects.

1.2.1.4 Malaysia

The most recent study conducted adhering to the RESC protocol (Goh *et al.,* 2005) compared the three principal ethnic groups in Malaysia (Chinese, Malays and Indians). As expected, children of Chinese ethnicity proved to be the most susceptible to myopia onset (Table 1.2.1) followed by Malay and Indian children (prevalence levels aged 15 years of 65.4%, 30.7% and 16.1% respectively).
The Malay results by Goh *et al.* are similar to that of a study conducted by Garner *et al.* (1990) with a myopia prevalence of 25.6% in Malay children aged 15-16 years. Melanesian children were also involved in the Garner study and were found to have a much lower myopia prevalence of 4.3%. Considering both Malays and Melanesian children are thought to undergo similar amounts of schoolwork (Garner *et al.,* 1990), these results lend support to a role played by genetics in the aetiology of myopia.

1.2.1.5 Taiwan

A high prevalence of myopia has been detected in this country, where children are mainly of Chinese descent. Periodic large scale cross-sectional surveys have been carried out over the course of the past 25 years, determining a upward trend in myopia progression (Lin *et al.,* 2004). The results suggest an increase in the prevalence of myopia over time (a cohort effect) in comparison to an intrinsic age-related decrease in an individual's degree of myopic error (Mutti and Zadnik, 2000). Table 1.2.3 provides an indication of the change in myopia prevalence found from the studies.

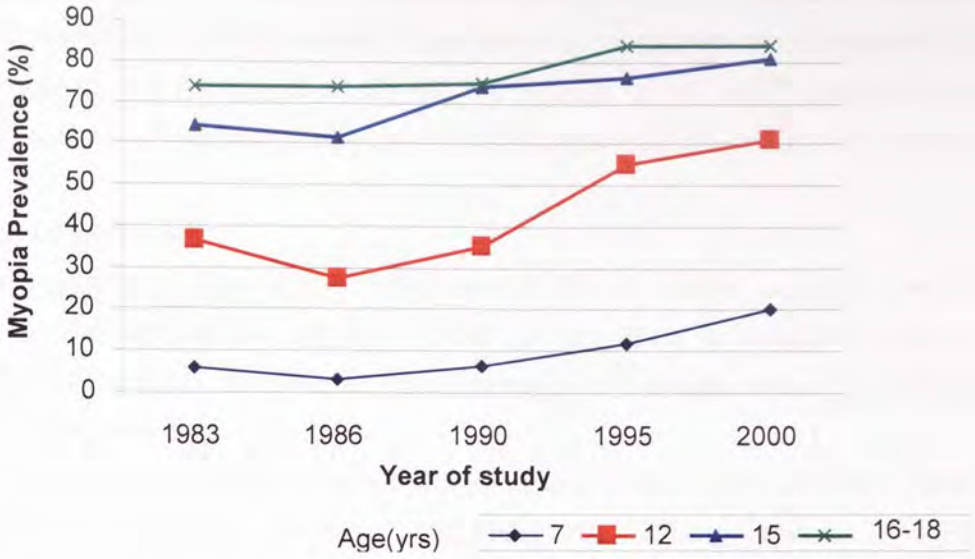


Figure 1.2.2 Myopia prevalence by age group with time in Taiwan (Lin *et al.*, 1988; Lin *et al.*, 1999; Lin *et al.*, 2004). Prevalence estimates are provided in Table 1.2.2

	YEAR OF STUDY				
Age (yrs)	**1983**	**1986**	**1990**	**1995**	**2000**
7	5.8%	3%	6.6%	12%	20%
12	36.7%	27.5%	35.2%	55%	61%
15	64.2%	61.6%	74%	76%	81%
16-18 (High school)	~74%	~74%	75%	~84%	~84%

Table 1.2.3 The change in myopia prevalence with age and year of study in Taiwan (from Lin *et al.*, 1988; Lin *et al.*, 1999; Lin *et al.*, 2004). ~70% = an estimated prevalence from graphs

Of note from earlier studies conducted by Lin and co-workers is that the criterion for myopia was not made explicit (Lin *et al.*, 1988; Lin *et al.*, 1988a). A latter review of the Taiwan myopia studies (Lin *et al.* 2004) defined myopia as an SER of <-0.25D; this criterion is assumed to apply to all previous work by the Taiwanese group.

It can be seen from Table 1.2.3 that an increase in prevalence occurred both with time and with age. An especially large increase is apparent between the ages of 7 and 12, corresponding to the greatest period of school myopia incidence. The prevalence levels appear to plateau in older children, as many will have undergone myopia onset. A striking observation from these studies is not just the high numbers of myopes in Taiwan, but also the increasingly high prevalence in younger children as a result of an earlier myopia onset (Lin *et al.*, 1999). An earlier age of onset would imply a longer period of time for myopia to develop while the eye grows (Lin *et al.*, 2004) and presents a concern with respect to the risks of pathology associated with high myopia (Curtin, 1985; Tano, 2002). A

National Myopia Prevention Programme (NMPP) initiated in 1999 for 5 years to address this issue did show some positive results in decelerating the growth rate of myopia prevalence in children as measured in 2005 (Lai *et al.*, 2006). The strategy of the NMPP primarily revolved around reducing the amount of near work (reading, VDU use) performed by very young children.

1.2.1.6 Indonesia

Indonesia is a developing country where little is known regarding refractive error distribution. Provincial Indonesians are of a similar genetic stock to Singapore Malays (Saw *et al.*, 2002b) although subject to different environmental influences, including differences in urbanisation, schooling and diet.

A refractive error study on adults 21 years and older in Sumatra (n= 1,403) determined a myopia prevalence of 48.1% (myopia ≤-0.50D SER) and 26.1% (myopia ≤-1.00D SER). The myopia levels here were found to be somewhere between the lower rates of white populations in the West and the higher levels of more urbanised countries in East Asia (Saw *et al.*, 2002b), although the use of non-cycloplegic autorefraction may have artificially overestimated myopia prevalence.

1.2.1.7 Mongolia

Although this nation lies on an Asian continent where myopia awareness is expanding, relatively little is known about the state of its ocular health. Mongolia is not as industrialised as its metropolitan neighbours Hong Kong and Taiwan, however it retains literacy rates above 95% in adults. A recent study on rural Mongolian children (n= 1,057) aged between 7-17 years using non-cycloplegic retinoscopy and subjective methods derived a myopia prevalence of 5.8% (myopia ≤-0.50D SER), which was lower compared to other reported Asian populations (Morgan *et al.*, 2006). The lower urbanisation of the area (i.e. less rigorous schooling, less industrialisation) was thought to account for this. A study on urban dwelling Mongolian children will assist in determining the sensitivity of Mongolians to increased exposure of myopiagenic factors as well as providing the relevant Mongolian authorities with vital information on the refractive status of children within its borders (Morgan *et al.*, 2006).

Adult Mongolians (n= 1,617 aged 40 years and over) have been found to have a lower myopia prevalence than similarly aged Chinese Singaporeans (Wickremasinghe *et al.*, 2004). Using non-cycloplegic autorefraction, the prevalence of myopia in Mongolian adults was determined to be 17.2% (95%CI: 15.9-18.5). The authors concluded that the genetic similarity between East Asian populations lent support to environmental factors (e.g. nutrition, educational demands, near visual demands) causing the disparity in results between countries (Wickremasinghe *et al.*, 2004).

1.2.2 Australia

Low numbers of myopic children in Australia were reported by Junghans *et al.* (2002) from a cohort of 2,697 children aged between 3 and 12 years of age. The prevalence of myopic spherical component ≤-0.50D (differs from SER in that the astigmatic component of the refraction is disregarded) was on average 5.3% across the age range with only 1.1% children having a spherical component ≤-2.00D. The exclusion of many astigmatic children whose cylindrical powers would have rendered them myopic may account in part for the low myopic numbers.

The most recent epidemiological survey in Australia- the Sydney Myopia Study (SMS), defined myopia as ≤-0.50D SER based on the RESC protocol (Ojaimi *et al.,* 2005). Established as a 3-year follow up refractive and biometric study, the SMS examined children aged 6 and 12 years of age with specific regard to myopia. Further ocular measures taken included Optical Coherence Tomography, which analyses retinal and nerve fibre layer thickness and Wavefront Aberrometry, which investigates spherical and higher order aberrations within the eye. In addition, the SMS examined the relationship between myopia and potential risk factors by means of detailed questionnaire analysis.
Results on the younger cohort (Ojaimi *et al.,* 2005a) aged 6 years (n= 1,724 eyes refracted) determined an overall myopia prevalence of 1.43% (95%CI: 0.94-2.18%) with a mildly hyperopic population (mean SER: +1.26 ± 0.03D). The prevalence of hyperopia (≥+0.50D SER) was very high at 91% (95%CI: 88.8-93.3%), largely due to the liberal criterion of hyperopia applied.
Ocular biometric measures (axial length, anterior chamber depth, corneal radius) were found to range normally, although the refractive error distribution showed a leptokurtotic peak around emmetropia. Mean axial length:corneal radius (AL/CR) ratio was 2.9, below the threshold of 3.0 postulated as a myopiagenic risk factor (Grosvenor and Scott, 1994). The distribution of AL/CR ratio was also shown to be leptokurtotic, indicating a strong relationship between the AL/CR ratio and refractive error.
A correlation was derived between parameters at birth (birth weight, height and head circumference) and ocular component size (AL and CR) in the 6 year old cohort (n= 1,765) although no correlation was determined for refraction (Ojaimi *et al.,* 2005c). Therefore, though congenital parameters may predetermine the size and shape of the eye, they seem to have a minimal effect on refraction, supporting a dual control (visual and non-visual) hypothesis of eye growth (van Alphen, 1961).
Examining the role of ethnicity in the Sydney study, 6 year old Caucasian children (n=1,109) were shown to have a significantly lower myopia prevalence compared to 'Other ethnicities' combined (n= 615) with a myopia prevalence of 0.73% versus 2.73% respectively ($p< 0.001$). Almost half (48.4%) of the ethnic cohort consisted of East Asians, however the results were not broken down further by individual ethnic group.

The 12 year old (n= 2,353, 11-14 years of age) results as expected showed a greater prevalence of myopia compared to the younger age group (Robaei *et al.*, 2006). Mean SER for the 12 year old cohort was +0.48 ± 1.34D, lower than that found in the 6 year olds (Ojiami *et al.*, 2005a). The prevalence of myopia in this cohort (Ip *et al.*, 2007) was 11.9% overall (95%CI: 6.6-17.2%) and hyperopia ≥+2.00D SER was 3.5% (95%CI: 2.8-4.1%). Girls were more myopic (14.1%) than boys (9.7%) which was attributed to factors other than variations in biometry by gender.

Due to the greater number of ethnic participants in the older age cohort, differences in myopia prevalence as a function of ethnic group was feasible (Figure 1.2.3), compared to the 6 year old data where only 'White' and 'Other Ethnicity' categories were devised.

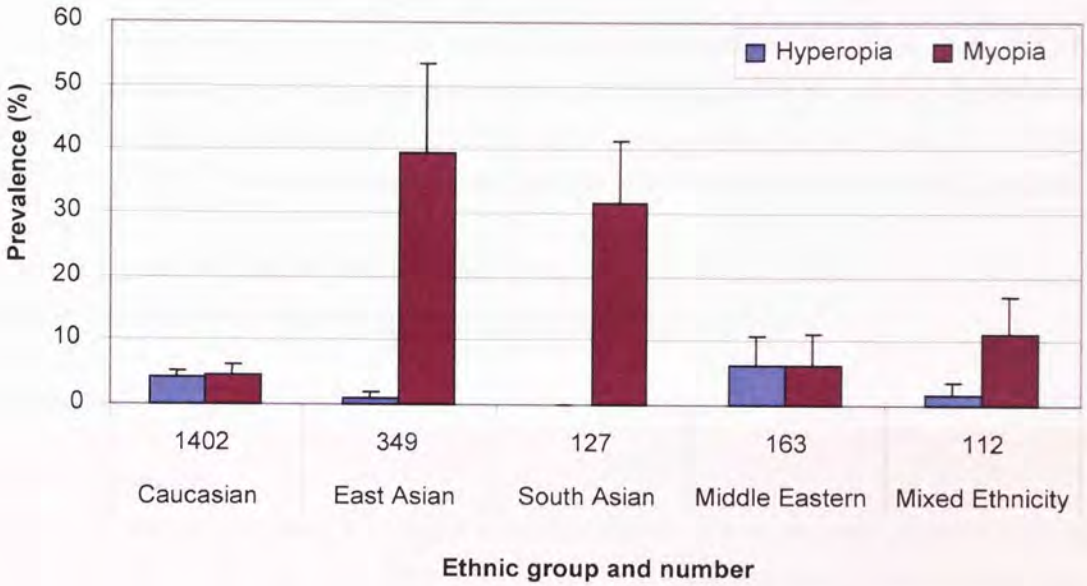


Figure 1.2.3 Differences in prevalence of ametropia by ethnic group in the 12 year old cohort of the Sydney Myopia Study (after Ip *et al.*, 2007). Error bars refer to the upper end of the 95% confidence interval. The numbers above each ethnic group represent the sample size of that group

East Asians, as expected, also had the longest mean axial length measurement (mean ± SD= 23.86 ± 0.75mm, $p<0.001$) and the most negative mean SER (-0.69D, $p<0.001$), reinforcing their greater myopic tendency. The mean AL for the entire 12 year old cohort was 23.38 ± 0.85mm. Based on questionnaire responses for 12 year olds, East Asian children spent a significantly lower proportion of their time on outdoor activities, instead focusing more on near work compared to their Caucasian counterparts (Rose *et al.*, 2006).

Overall, level of outdoor activity remained the only significant variable associated with myopia (OR 0.78, 95%CI: 0.63-0.96) after adjustment for variables such as parental myopia, gender and ethnicity, whilst the adjusted OR for near work did not remain significant (Rose *et al.*, 2006). The effect of environmental variables on myopiagenesis is discussed further in Section 1.4.

Refractive data on an adult Australian population is provided by two studies: the Blue Mountains Eye Study (BMES) and the Visual Impairment Project (VIP).

Australia adult studies	n	Age range (yrs)	Myopia prevalence (%)
BMES	3174	46-97	15.5 (95%CI: 12.4 -18.6)
VIP	4744	40-98	17 (95%CI: 15.8 -18.0)

Table 1.2.4 Results from studies carried out on adult Australians. BMES = Blue Mountains Eye Study (Attebo *et al.*, 1999); VIP = Visual Impairment Project (Wensor *et al.*, 1999)

Both studies established a link between myopia and educational level. They also show similar overall prevalence estimates with an age-related decrease, although the VIP study discovered that after the age of 80 the level of myopia rose again in the population, similar to that found in Chinese adults (Wong *et al.*, 2000). This was attributed to an increase in lenticular opacities causing a myopic shift in the individual.

In summary, there are relatively low numbers of myopes in Australia, reflecting why the awareness of myopia in this country is not at the same level as that found in East Asia.

1.2.3 Europe

1.2.3.1 Scandinavia

Studies in Scandinavian countries suggest that the prevalence of myopia has remained relatively stable in the region for over 100 years (see Table 1.4.2; Goldschmidt, 1968; Morgan and Rose, 2005). Other research however, has discovered a higher prevalence of myopia than would be expected from a predominantly Caucasian population. In Sweden, 1,045 children between the ages of 12-13 years underwent cycloplegic refraction from which it was determined that 49.7% were myopic (≤-0.50D SER) in at least one eye and 39% were bilaterally myopic (Villareal *et al.*, 2000). These rates are analogous to those found in East Asia (Fan *et al.*, 2004) and show a rise of over double the number of myopes in comparison to a similar study carried out in Finland 20 years earlier (21.8% myopia in children aged 14-15 years; Laatikainen and Erkkilä, 1980). Both Scandinavian studies used cycloplegic retinoscopy and the same criterion for myopia thus although inherent methodological differences may have existed, the results are somewhat comparable and serve to show a rise in the number of myopic children in the Scandinavian region. A possible explanation for this may be the recent migration of populations from Asian gene pools to parts of Scandinavia (Morgan and Rose, 2005).

In Denmark, myopia prevalence appears to have decreased over time. Based on 3 cross-sectional studies conducted in 1882, 1964 and 2004, Jacobsen *et al.* (2007) evaluated the prevalence of myopia in male conscripts (aged 18 years) and found that it had decreased (8.3% in 1882, myopia <-2.00D sphere; 9.2% in 1964, myopia<-1.50D sphere; 7.7% in 2004, myopia<-1.50D SER, p= 0.013). In addition, the prevalence of high myopia showed a concurrent decline. A tentative explanation for this observation is that in recent times, school children may be postponing intensive studying until after military service, suggesting that a study conducted on the general population post-conscription would reveal a myopic surge as conscripts become involved in intense periods of studying (Jacobsen *et al.,* 2007). Overall, even though methodological disparities did exist between the three cross-sectional studies, the prevalence of myopia in Denmark - an industrialised developed nation - in young male adults appears to have been stable at the very least.

1.2.3.2 Poland

A recently published study (Czepita *et al.,* 2007) on the prevalence of ametropia in a cohort of Caucasian Polish school children (n= 4,422, 6-18 years of age) found a 13.3% myopia prevalence (588 children) with cycloplegic retinoscopy using a myopia cut-off ≤-0.50D SER. An increase in myopia levels with age was noted though the overall figures are considerably lower than that determined in Sweden by Villareal *et al.,* (2000) on fellow Caucasian children.

1.2.3.3 United Kingdom

The classic study by Sorsby *et al.* (1961) remains the most recent comprehensive study conducted on both refractive status and ocular biometry in children from the United Kingdom (UK). Considering the significant demographic and technological advances that have occurred in the UK since (Section 2.1), the data collated is not representative of the current population.

Children aged between 3 and 15 years (n= 1,432; 671 males) were invited to participate in the initial cross-sectional study by Sorsby *et al.* (1961) conducted in South London. However, the response rate of participants to invitations was limited at between 30-40%. Combining this finding with the urban bias introduced from the London-based cohort led Sorsby and co-workers to state that their sample could not be representative of the general UK child population. Nevertheless, the primary aim of this study was not to determine ametropia prevalence levels, but to derive biometric correlates of refraction and establish how ocular components vary with age. A photographic method was employed to measure ACD, lens thickness and radii. AL was computed based on refractive index assumptions and corneal radius (CR) was measured using a Haag-Streit keratometer. The protocol involved the use of an anti-muscarinic drug, 0.05% hyoscine hydrobromide, to initiate cycloplegia in subjects. Results from the cross-sectional study revealed a reduction in refractive error with age, a tendency for refractions to congregate at emmetropia and a co-ordination between the refractive and axial components of the eye to achieve this end-point.

A follow up study was conducted 2-6 years later (Sorsby *et al.*, 1961) on 386 of the initial children examined. Of these children, at the time of initial examination (i.e. the cross-sectional study), 24 were classified myopic (6.2%) with a negative refraction in the vertical meridian ≤-1.00D, 88 (22.8%) were emmetropic (0.0D to -0.9D) and 274 (71.0%) were hyperopic (Table 1.2.5).

Refractive Group	Children < 10 years of age	Children ≥ 10 years of age	Total (%)
Myopia (≤-1.00D)	10 *(4.1)*	14 *(10.0)*	**24 *(6.2)***
Emmetropia	45 *(18.3)*	43 *(30.7)*	**88 *(22.8)***
Hyperopia (≥+1.00D)	191 *(77.6)*	83 *(59.3)*	**274 *(71)***
Total	**246 *(100)***	**140 *(100)***	**386 *(100)***

Table 1.2.5 Refractive results (n= 386) taken at the initial examination as a function of age group. Percentage figures in parentheses. From Sorsby *et al.* (1961)

The high prevalence of hyperopes in children under the age of 10 years may have been caused by a high number of participants who had not fully emmetropised at the time of initial examination.
At the end of the follow-up period (2-6 years later), 39 of the initial 362 emmetropic/hyperopic children had become myopic resulting in a total of 63 myopes, or 16.3% of the total sample. However, this figure would have included the children at a much older age and not the initial range of 3-15 years due to the time period of the follow-up (2-6 years).

More recent longitudinal work by Pointer (2001) in the UK (n=60) calculated a myopia prevalence of 37.9% in children aged 13 years at the end of the 6 year study (myopia ≤-0.50D SER) from an initial prevalence of 5% (aged 7 years) based on non-cycloplegic refraction results. A strength of the study lay in its longitudinal nature; however two major limitations to the study were firstly the small sample size and secondly the bias introduced due to self-selection of subjects. As the patient base consisted of children attending Pointer's optometric practice, it is more likely that patients attending for an eye examination would be ametropic compared to the general public. Therefore these results derived by Pointer cannot be extrapolated to the general population.

Retrospective research by Logan *et al.* (2004a) further examined data from optometric practices in the West Midlands and reported on myopia progression as opposed to prevalence. Electronic data records from 61 optometric practices within the West Midlands region were analysed to provide non-cycloplegic refractive information on 7,376 myopic children aged between 5-15 years. The results showed a clear myopic shift in mean sphere from the ages of 9 through to 15 years (0.04D per annum) with a maximal shift between the ages of 12-13 years (0.09D per annum). These results supported those of the Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error (CLEERE) study conducted in the USA (Zadnik *et al.*, 2003) and led Logan and co-workers to suggest that the optimum age to commence therapeutic myopia treatment in UK children while also maintaining a high level of compliance was at the age of 9 years.

A recent study on an urban university population found no significant difference in myopia prevalence between similarly aged students (n= 373) of differing ethnic backgrounds (White: 50%, British Asian: 53.4%, p= 0.16). The finding that both sets of students had exposure to the same level of schooling in the UK appeared to predominate over any intrinsic ethnic disparities that may have existed (Logan *et al.*, 2005). However, contrasting findings by Guggenheim *et al.*, (2003) on university undergraduates (n= 122) determined a higher myopia prevalence in Asian children compared to Whites (White: 55%, Asian: 81%, p=0.005). A disparity between the aforementioned two studies however, is the categorisation of Asians. Logan *et al.* measured South Asians specifically whilst Guggenheim *et al.*, incorporated East and South Asians within their cohort, which may account for the discrepant findings.

The Avon Longitudinal Study of Parents and Children (ALSPAC), a longitudinal study into the medical history of 14,541 mothers and their children from birth onwards in Bristol began in 1991-1992 (www.alspac.bris.ac.uk, accessed 12/05/2005). Data on the refractive error of children (aged 7 years old) using non-cycloplegic autorefraction showed a myopia prevalence of 1.1% with a myopia criterion of <1.00D SER (n= 7,600, Barnes *et al.*, 2001) and 13.6% with a criterion of ≤-0.50D SER (n= 6,700, Williams *et al.*, 2005).

1.2.4 North America

1.2.4.1 United States of America

As part of the National Health and Nutrition Examination Survey (NHANES) conducted from 1971-1972 (n= 14,147) on persons aged 12-54 years, an estimation of refractive error prevalence was determined. A subject was crudely classified as myopic if their unaided vision was reduced and improved by the addition of a negative lens. The proportion of myopic eyes was found to be 25.0% and 24.3% for right and left eyes respectively (Sperduto *et al.*, 1983) with a significantly decreased risk for both Black and male subjects. In addition, an increased family income and educational level presented as risk factors.

Data on USA adult populations as a function of age have been comprehensively assessed in four large-scale studies, described in Table 1.2.

American adult studies	Reference	Myopia definition	n	Age Range	Ethnicity	Myopia Prevalence %
Beaver Dam Eye Study	Wang *et al.*, 1994	<-0.50D SER	4275	43-84	All	26.2
Framingham Offspring Eye Study	Framingham Eye Study Group, 1996	≤-1.00D SER	1585	23-78	All	35.0
Baltimore Eye Study	Katz *et al.*, 1997	<-0.50D SER	2200	40+	Black	19.4
Baltimore Eye Study	Katz *et al.*, 1997	<-0.50D SER	2659	40+	White	28.1
Los Angeles Eye Study	Tarczy-Hornoch *et al.*, 2006	≤-1.00D SER	5396	40+	Latino	16.8

Table 1.2.6 Myopia prevalence determined in large-scale adult American studies

Each of the four adult USA studies above used varying definitions of myopia and methodology, although all demonstrated an increase in hyperopia prevalence with age. The Los Angeles Eye Study suggested that these findings indicate an age-related hyperopic shift caused by a loss of accommodation in the individual which unmasks underlying hyperopia (Shufelt *et al.*, 2005). Nevertheless, the limitation of cross-sectional studies on the inference of temporal effects must be recognised. It is equivocal from the above studies on adults whether the overall reduction in myopia prevalence with age is due to an age related hyperopic shift in the individual (Mutti and Zadnik, 2000), a cohort effect, or a combination of the two (Wong *et al.*, 2000).
An attempt to retrospectively evaluate six studies conducted on adults aged 40 years and over in the USA, Western Europe and Australia (Kempen *et al.*, 2004) concluded that a similar prevalence of refractive errors exists between the USA and Western Europe. Though a conservative cut-off value for both hyperopia (SER ≥ +3.00D) and myopia (SER ≤ -1.00D) was employed, it was still found that a third of adults need some form of refractive correction in the USA and Western Europe as opposed to Australia where this figure dropped to approximately 1 in 5 adults. According to the authors, the disparity in estimates highlights the environmental/genetic differences existing between the regions.

In addition to adult estimates, many studies have investigated child refractive error in the USA. The Ojai Longitudinal study commenced in 1954 (Hirsch, 1955) and was a longitudinal study examining child refractive error twice a year using static non-cycloplegic retinoscopy, alongside that of height

and weight (Hirsch, 1964). The prevalence of myopia (≤-0.50D SER) found (n= 766 eyes) in subjects aged 13-14 years was 12.0% (Hirsch, 1964a).

The Orinda Longitudinal Study of Myopia (OLSM) aimed to be the first epidemiological study to measure all major ocular components (Zadnik *et al.*, 1993), replacing calculated substitutions for unmeasured parameters required in previous work (Sorsby *et al.*, 1961).
Based on initial cross-sectional findings, it was postulated that the component responsible for the maintenance of emmetropia during childhood was likely to be the crystalline lens, which became thinner and flatter with age (Zadnik *et al.*, 1993) to compensate for axial length growth. The overall baseline myopia prevalence in the Orinda cohort (n= 791, 6-14 years old) was determined to be 7.5% by cycloplegic (1% tropicamide) retinoscopy (Zadnik *et al.*, 1994).
The Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error (CLEERE) study began in 1997 when additional sites were added as an extension to the OLSM (Zadnik *et al.*, 2003). These were included to recruit specific ethnic groups, namely African-Americans (Black), Asians (South and East) and Hispanics and compare findings against the predominately Caucasian cohort in the original Orinda study. Children participating were aged between 5 and 17 years of which overall, 10.5% were found to be myopic (n = 2,583) at baseline (≤-0.50D in both meridia), showing a modest increase from that determined by the predominantly Caucasian OLSM cohort. An investigation into the CLEERE as a function of ethnicity supported the notion of differential ethnic susceptibilities to myopia (Figure 1.2.4). The prevalence of myopia in Asians was 19.8% with Caucasians presenting a significantly lower prevalence of 5.2% (Kleinstein *et al.*, 2003).

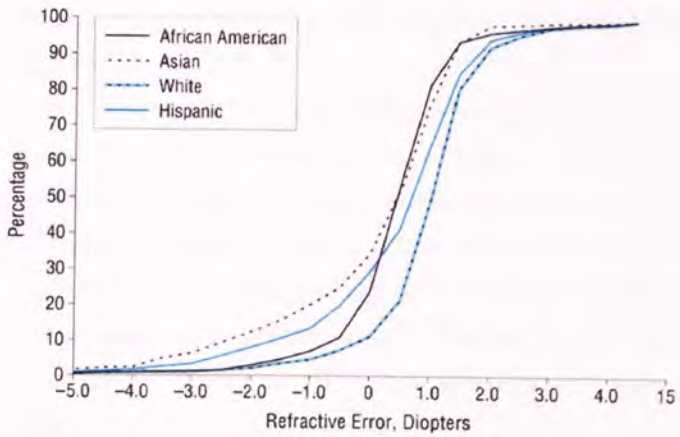


Figure 1.2.4 Cumulative frequency graph of spherical refractive errors for children from four ethnic groups in the CLEERE study. Reproduced with permission from Kleinstein *et al.*, (2003). *Arch Ophthal*; 141: 1121-7. Copyright © (2003), American Medical Association. All Rights reserved

It can be seen from Figure 1.2.4 that the line representing the Asian group ascends earlier than the other sub-cohorts, indicating a higher proportion of children with myopia in that particular ethnic group. The Asian cohort here stipulates children of both South and East Asian origin.

The CLEERE results support a genetic basis for refractive error with high Asian myopia levels persisting outside of the Asia and indicate that Asian people are susceptible to myopia irrespective of geographic location. However, it may also be a case of shared environments instead of genes. It is feasible that a transfer of cultural traditions and ethos within the Asian community is maintained abroad, creating a myopiagenic environment for children at home (e.g. strong work ethic, long periods of intense studying) with subsequent high numbers of myopes (Zadnik, 1997; Morgan and Rose, 2005).

A major limitation of the CLEERE study was the sampling of specific ethnicities from specific regions. Recruiting Hispanics from Houston, Blacks from Eutaw and Asians from Irvine in addition to Whites from Orinda introduced a confounding variable of geography, which precluded unequivocal conclusions regarding ethnic variations in refractive error. For example, it could not be differentiated whether a difference in myopia prevalence between Asians and Hispanics was a result of a differential demographical or geographical susceptibility.

1.2.4.2 Canada

A study on 6-year old Caucasian children (n= 10,616) in the New Brunswick area of Canada (Robinson *et al.,* 1999) determined myopia (defined as <-0.25D in the right eye horizontal meridian) in 6% of the population (95%CI: 5.5-6.5). Myopia was primarily associated with mother's early use of spectacles (OR 1.54, 95%CI: 1.16-2.05) and low birth weight (<2500g, OR 1.87, 95%CI: 1.13-3.10). The authors concluded that both hereditary and environmental factors were responsible for myopia in these children.

Studies on the Chinese population advocate that this ethnic group has a predisposition to myopia (Fan *et al.,* 2004). Retrospective analysis of optometric records on Chinese children in Canada (Cheng *et al.,* 2007) was performed to investigate whether a Western environment which was 'anti-myopiagenic' relative to that of China, would affect the prevalence of myopia in the cohort (n= 1468, 6-12 years of age). The majority of the children were second generation Chinese who were born in Canada and thus fully exposed to a Western system of education, but whose parents had migrated from China in recent decades and were likely to have retained cultural practices from their native country.

An adjusted myopia prevalence level (≤-0.50D SER) of 22.4% at the age of 6 years and 64.1% at 12 years was detected, similar to that found in the urban studies conducted in China and Hong Kong by Saw *et al.,* (2002) (age 7 = 27.6% myopia) and Fan *et al.,* (2004) (≥11 years of age = 53.1% myopia). The prevalence estimates for 6 year old children were higher than the Caucasian data derived by Robinson *et al.,* (1999), supporting a higher susceptibility of the Chinese to myopia.

The validity of this study however, can be questioned. The clinic bias introduced by examining optometric record cards was adjusted for through the incorporation of a 'bias factor' by Cheng *et al.,* (2007). However this corrective factor was based on the Caucasian study by Robinson *et al.* (1999) and presumed that the same factors affecting Caucasian children would apply to the Chinese. In addition there was no use of cycloplegia in the study. Although stated by the authors as not being significant in altering the detected myopia prevalence, it was nevertheless concluded that cycloplegic autorefraction was the method of choice for prospective studies.

1.2.4.3 Barbados

A predominantly Black (93%) adult population (n= 4,330, 40-84 years) partook in the evaluation of Black ethnicity on refractive error in the population-based Barbados Eye Study (BES). Non-cycloplegic autorefraction was performed to determine refractive error alongside other ocular characteristics (Wu *et al.,* 1999). The prevalence of myopia in this cohort (21.9%, 95%CI: 20.6-23.2) was comparable to the Baltimore Eye Study (Katz *et al.,*1997) although the authors of the BES noted a trend of increasing myopia prevalence with age from 60 years onwards. This was contrary to many other studies where myopia prevalence decreases with age, although some have found a prevalence surge in persons aged over 75 years accounted for by a lens-related myopic shift (Katz *et al.,* 1997, Wensor *et al.,* 1999). It seems as though an earlier age of onset of conditions such as cataract may explain the increase in myopia with age in this cohort (Wu *et al.,* 1999).

1.2.5 Further global research

1.2.5.1 Middle East

A database of refractive error prevalence and biometric correlates was gathered on a working age population of adults in Jordan (n= 1,093) aged between 17-40 years (Mallen *et al.,* 2005). A relatively high prevalence of myopia (53.7%) was determined and is comparable to cohorts from the West (Framingham Eye Study Group, 1996) although it is lower than the 71.5% found in East Asian adults (Goh and Lam, 1994). Axial length, more specifically vitreous chamber depth, was found to be the major biometric correlate of refractive error, which echoes the findings from other adult studies (Sorsby *et al.,* 1957; McBrien and Adams, 1997).

Children measured in Dezful County, Iran (Fotouhi *et al.,* 2006) were found to have a higher myopia prevalence than that found in the West. Based on RESC refractive error definitions, 33% of teenagers aged 14-18 years were deemed myopic, although the notable finding in this study was that of a 16.6% prevalence of hyperopia (≥+2.00D SER) in school children aged 7-15 years of age.

The prevalence of myopia in a young Israeli cohort is described in a highly-cited study by Zylbermann *et al.* (1993). Students from genetically similar backgrounds were measured (n= 870) for refractive error as a function of gender and type of schooling. It was found that males attending Orthodox Jewish schools, where study periods of sustained near work extend up to 16 hours a day, were at a significantly greater risk of developing myopia than other students, whose school day lasted on average 6 hours ($p<0.05$). Table 1.2.7 illustrates the differences in myopia prevalence.

Type of schooling	Orthodox	General
Male	81.3%	27.4%
Female	36.2%	31.7%

Table 1.2.7 Prevalence of myopia by school and gender, after Zylbermann et al. (1993)

Thus the effect of sustained reading demands appear to be the cause of the high levels of myopia detected, although a confounding effect could be the varying accommodative demands caused by a rocking motion adopted by Orthodox males while studying.

A recent review of a series of cross-sectional studies carried out in Israeli nationals aged between 16-22 years over 13 years (n= 991,929 in total) determined an increase in myopia prevalence from 20.3% in 1990 to 28.3% in 2002 (Dayan *et al.*, 2005). The greatest increase was noted in mild myopia (-0.50D to -3.00D spherical component), concurrent with a growing use of near visual technology such as computer games and the Internet. These parallel increases led the authors to suggest a causal link between the variables.

1.2.5.2 Brazil

A low myopia prevalence was detected from a refractive study conducted on inhabitants of the Brazilian Amazon rainforest (Thorn *et al.*, 2005). Indigenous residents in the Amazon have a distant Asian ancestry hence if myopia is determined genetically, their lineage may assume a high prevalence of the condition. In contrast, the majority of subjects were illiterate and living in rural villages, therefore if the current environmental theory surrounding myopia and near work is valid, this community would have been expected to show very low myopia levels.

Indeed this was shown to be the case (n= 486) with only 2.7% of eyes showing myopia of $\leq$-1.00D SER as measured by cycloplegic retinoscopy. Young, educated Brazilians demonstrated a higher prevalence of myopia (9.7% subjects) than the mean. The results, although using a more conservative estimate for myopia than in other studies, demonstrate the effect of literacy (near work) on myopia development, or possibly the protective effect of a lack of sustained near tasks on the maintenance of emmetropia.

1.2.5.3 Mexico

A cross-sectional investigation into children aged 12-13 years (Villarreal *et al.,* 2003) in a metropolitan area of the country (n= 1,035) using cycloplegic retinoscopy yielded a high prevalence of myopia in children (44% myopic in at least one eye). The majority of this myopia was of a low level and the criterion used to define the condition was identical to other studies (≤-0.50D SER). Environmental factors were held responsible for the high number of Mexican children who were myopic. Of greater concern than the prevalence derived was that over 70% of myopic children had no means of optical correction. Adding this to the low compliance of spectacle wear in Mexican children (Castanon-Holguin *et al.*, 2006) and the issue of child refractive error is one that appears to require urgent attention in this region of the world.

1.2.5.4 Arctic regions

The Arctic Zone provides a strong homogeneous population base from which to investigate the relative effects of environmental and genetic influences on refractive error. It was the seminal work by Young *et al.* (1969) on Eskimos in Alaska (n=197) that initially raised awareness of the rapid variation in myopia prevalence between generations. Using a myopia definition of ≤-0.25D SER measured by cycloplegic subjective refraction, myopia prevalence was 13.8% in an age group 26 years onwards but 43.4% in the age group 6-25 years. There was a high inter-sibling correlation of refraction but the parent-offspring correlation was low, diminishing a role for heredity.

The results were attributed to environmental influences, as the change in myopia prevalence between generations was too rapid to be accounted for by a change in the native gene pool. A change in lifestyle of the Eskimo population had occurred recently and natives had begun to adopt an American lifestyle. Schooling had become compulsory for children resulting in greater periods of reading. Dietary changes, specifically an increase in carbohydrate and salt intake in children, may also have been responsible for the change in refractive error prevalence (Johnson, 1988). However, the role of diet remains equivocal as it was declared that only adults received the 'Americanised' meal, whilst children (who had the greater prevalence of myopia) maintained their traditional diet of whale and caribou (Young *et al.,* 1969). The emphasis therefore turned to schooling and its primary surrogates (i.e. near work, intelligence, education, urbanisation) to account for the rapid shift in prevalence levels. This work was further supported by research on communities in the Canadian Artic region (Morgan *et al.,* 1975), where a sudden increase in myopia prevalence was noted in subjects under 30 years of age compared to adults above it, attributed to a change in the environment (schooling).

1.3 ANIMAL MODELS OF MYOPIA

Animal models play an important role in myopia research by enabling the anatomy and pathophysiology of myopia to be studied *in vivo*. Animal work further permits the elucidation of putative mechanisms utilised by the eye to regulate growth (Wallman and Winawer, 2004). Caution must be exercised however in the application of animal myopia models to humans (Zadnik and Mutti, 1995; Adler and Millodot, 2006):

i. Animals are subjected to specific experimental paradigms i.e. lid suturing. Many of these are too extreme to explain normal variations in refractive error.

ii. Discrepancies in experimental results have been demonstrated within a species i.e. disparate results between two groups of *Macaca* monkey (Raviola and Weisel, 1985). These findings increase the likelihood that differences exist between species, questioning the overall validity of animal studies to provide accurate models for human myopia (Edwards, 1996). However, it is argued that these within-species disparities may exist just as physiological variations exist amongst humans of different demographical backgrounds (Smith III, 1998).

iii. Protocols are generally imposed during animal infancy when the plasticity period is at its peak and which declines with age (Wallman and Adams, 1987). School myopia in humans develops most commonly between 7-12 years of age and experiments on adolescent animals of a similar age have often produced equivocal results (Raviola and Wiesel, 1978).

iv. Physiological variations between species raise doubts as to the relevance of findings for humans. Chicks, for example, have shown an ability to modulate choroidal thickness, a response not as yet determined in humans (Wildsoet and Wallman, 1995) though positive findings in other mammals i.e. monkeys (Hung *et al.*, 1998) have been demonstrated.

The following section summarises the prominent themes of animal research to myopia development.

1.3.1 Animal Species

Several animal species have been used as models of refractive error, including chicks (Wallman *et al.*, 1978; Wallman and Adams, 1987; Schaeffel *et al.*, 1988; Irving *et al.*, 1992), tree shrews (McBrien and Norton, 1992), guinea pigs (Howlett and McFadden, 2006) and monkeys (Wiesel and Raviola, 1977; Troilo *et al.*, 2000; Smith III *et al.*, 2002).

Chicks are the most commonly used animals; their eyes develop rapidly, they are readily accessible and are very sensitive to alterations in visual experience (Schaeffel and Howland, 1995). The relative independence of both eyes also prevents any form of binocular vision from confounding experimental results (Wildsoet, 1997).

Tree shrews are diurnal mammals and have been used as animal models due to a closer link with the higher primate visual system. They also share with chicks a capacity for rapid breeding and maturing (McBrien and Norton, 1992) which makes them economically feasible to study in large numbers.

Monkeys are well known for sharing many common characteristics with humans, justifying their deployment as animal models (Wildsoet, 1997). They share a very close evolutionary relationship to humans thus their data can be applied to humans with a high degree of confidence (Smith III and Hung, 1999). However, the high costs involved with monkey research, the greater length of experimental time required compared to more primitive species and the relatively low numbers involved in experiments are significant obstacles for vision scientists utilising monkey models.

1.3.2 Form Deprivation

Form deprivation myopia (FDM) is induced by a withdrawal of form vision in the neonatal emmetropising eye. Two seminal experiments by Weisel and Raviola (1977) and Wallman *et al.* (1978) on monkeys and chicks respectively involved depriving the animals of form vision at various stages of infancy. The two experiments produced complementary results. Both sets of animals developed myopia in restricted fields which was axial in nature and caused by an elongation of the posterior segment of the eye. The age of the animal and the duration of form deprivation greatly influenced the magnitude of the final error. Larger refractive errors were obtained in younger animals and those who were deprived of visual input for longer. Experiments performed on tree shrews have shown similar results to that of monkeys and chicks (McBrien and Norton, 1992). The major structural correlate of FDM has been shown to be an increase in the vitreous chamber depth (VCD) in all species (Wallman and Adams, 1987; Norton and Siegwart 1995; Troilo *et al.* 2000). Overall, FDM reveals that the final refractive state of the eye is not solely pre-determined and can be manipulated by altering the visual environment.

1.3.2.1 Recovery from FDM

When the obstructing apparatus initiating FDM is removed, chick eyes have shown recovery and their level of myopia has reduced, in many cases, back to emmetropia (Wallman and Adams, 1987; Troilo and Wallman, 1991). Equivocal results have been found to recovery from FDM in mammals (McBrien and Norton, 1992; McBrien *et al.*, 2000; Qiao-Grider *et al.*, 2004).

Biometrically, recovery from FDM is shown to be caused by a relative slowing in the rate of VCD growth compared to other ocular components which grow as normal (Wallman and Adams, 1987; McBrien *et al.*, 2000). A second mechanism, involving modulation of choroidal thickness to compensate for induced refractive error has been demonstrated primarily in avian eyes (Wallman *et al.*, 1995).

1.3.2.2 Mechanism of FDM

There have been natural cases in humans of axial myopia caused by pathological interference of neonatal emmetropisation (O'Leary and Millodot, 1979; Hoyt *et al.,* 1981) although both studies argued that deprivation myopia was induced as a direct thermal/mechanical result of lid ptosis, as opposed to an attenuation of form vision.

However, infant rhesus monkeys with lid suture reared in the dark do not develop FDM and instead, have been shown to be slightly hyperopic (Raviola and Wiesel, 1985). In addition, several experiments have successfully induced FDM by introducing diffusers in front of the eyes to block form vision without the need for lid suture (Wallman *et al.,* 1978; McBrien *et al.,* 2000; Qiao-Grider *et al.,* 2004). Therefore, it appears that it is a degradation of spatial vision and not a mechanical interference to the eye that results in FDM.

1.3.2.3 Local FDM changes

The site of visual growth regulation within the animal eye has been investigated by examining the effect of local form deprivation. Occluding half an eye has corresponded to FDM and a relative increase in VCD in the deprived hemi-retinal region only. The non-deprived area of retina does not show any relative change in refraction or morphology compared to its contralateral control eye (Wallman *et al.,* 1987; Troilo *et al.,* 1987). In addition, chicks with optic nerve section (ONS) have been shown to undergo hemi-retinal FDM in response to localised retinal deprivation (Troilo *et al.,* 1987; Troilo and Wallman, 1991). These findings purport local (retinal) control of eye growth whereby local changes in visual experience result in appropriate localised responses.

1.3.3 Lens Induced Defocus

Lens induced defocus experiments involve the use of positive and negative lenses to instigate compensatory changes in the refractive state of animals and their ocular components. Chicks shown negative lenses will respond with axial elongation and subsequent myopia; converse effects have been shown with positive lenses, with hyperopia development and regression of axial elongation (Schaeffel *et al.,* 1988; Irving *et al.,* 1992). Lens defocus responses have further been shown to exist in tree shrews (McBrien *et al.,* 1999) and infant monkeys (Smith III and Hung, 1999).

Negative lenses are thought to increase axial length by introducing a hyperopic defocus and extending the focal length of the image behind the eye. The active emmetropising eye grows in search of a clearer image, rendering the eye myopic once the lens is taken away. The opposite occurs when positive lenses are used - the myopic defocus imposed diminishes the growth of the eye relative to its contralateral eye and renders it hyperopic (Figure 1.3.1). An important caveat to note is that in many experiments, the eye does not develop an absolute refractive error, but a relative error compared to its contralateral eye (Diether and Schaeffel, 1997).

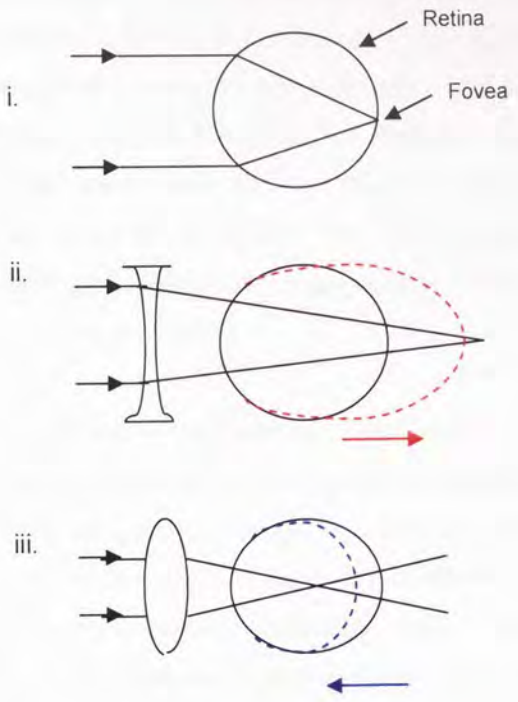


Figure 1.3.1 Lens induced defocus on a neonatal eye. i. Normal emmetropic eye receiving clear images at fovea. ii. Hyperopic defocus induced by negative lens (red dashed line) resulting in subsequent acceleration in AL growth (red arrow) and myopia iii. Myopic defocus induced by positive lens (blue dashed line) causing a decrease in AL growth (blue arrow) and hyperopia

1.3.3.1 Local lens induced changes

As with FDM, local areas of imposed lens defocus have resulted in local alterations to eye growth, with only the deprived region of retina responding to defocus (Diether and Schaeffel, 1997). To test the origin of the mechanism as with FDM (Troilo *et al.*, 1987), it was found that ONS did not prevent compensation for myopic defocus (using positive lenses) in chicks but did inhibit induced myopia in treatment with negative lenses. In addition, ONS eyes without treatment were found to be hyperopic (Wildsoet and Wallman, 1995). These studies support the hypothesis of local retinal control of eye growth, mediated by the retina, choroid and sclera (Wallman *et al.*, 1995; Wildsoet and Wallman, 1995) although do not preclude the involvement of a higher pathway as a fine-tuner of eye growth (Troilo and Wallman, 1991).

1.3.3.2 Myopic versus Hyperopic Defocus

A further observation by Diether and Schaeffel (1997) was that positive lenses caused a larger change in refraction than negative lenses (in respective directions). The authors hypothesised that the eye is disproportionately sensitive to the effect of myopic defocus compared to hyperopic defocus. Morgan (2003) effectively conveyed this effect with two types of signal that direct growth of the eye: a STOP signal evoked by myopic defocus and a GO signal evoked by hyperopic defocus or form deprivation. STOP signals are generated by brief periods of myopic defocus and are far more

powerful than GO signals (Zhu *et al.*, 2003), which are weaker and generated only by prolonged exposure to hyperopic defocus/form deprivation.

In addition to the imposition of STOP signals by positive lenses, the attenuation of GO signals has also been shown to have a powerful effect in inhibiting FDM and lens defocus in mammals, instigated through both the removal of negative lenses (Shaikh *et al.*, 1999) and through brief periods of unrestricted vision on form deprived chicks (McCarthy *et al.*, 2007) and monkeys (Smith III *et al.*, 2002; Kee *et al.*, 2007). The finding that myopia can be prevented with as little as 2 hours of interrupted vision a day supports the concept of differential potency of defocus in mammals (Wallman and Winawer, 2004).

1.3.3.3 Recovery from Lens Defocus

The blur imposed from an unobstructed field upon removal of lens defocus acts as a new stimulant for ocular growth, though in a direction opposite to that during compensation for lens defocus. The recovery process has been demonstrated with both positive and negative lens induced defocus, with the eyes becoming relatively more myopic and hyperopic in recovery respectively. The main structural correlate in recovery from lens induced defocus is the VCD, as in form deprivation myopia (Irving *et al.*, 1992; Smith III and Hung, 1999; McBrien *et al.*, 2000). However, the recovery of lens induced defocus does not seem to be mediated in the same way as the actual induction of refractive error (Irving *et al.*, 1992).

1.3.3.4 Susceptibility to Visual Manipulation

The age of onset of visual manipulation, through either form deprivation or lens induced defocus, has a bearing on the magnitude of response shown by the animal. Chicks have been shown to be highly sensitive to treatment soon after birth, with susceptibility to form deprivation declining rapidly from birth to 3 months (Wallman and Adams, 1987).

However, in mammals the window of sensitivity appears to commence some days after birth. It has been demonstrated that the peak susceptibility period for FDM in tree shrews begins between 15-45 days after eye opening (McBrien and Norton, 1992; Siegwart and Norton, 1998) and declines with age, corresponding to the end of the rapid infantile growth phase and the beginning of the juvenile slow growth phase in the eye.

Monkeys have been shown to be susceptible to visual manipulation at an age corresponding to a time of school myopia onset in human children (Smith III *et al.*, 1999; Troilo *et al.*, 2000). Monkeys are estimated to mature four times faster than humans and based on FDM induction in adolescent monkeys (equivalent to an approximate human age of between 15-20 years), it has been shown that monkeys are susceptible to environmental influences on ocular growth at an age when axial growth is thought to be essentially complete (Troilo and Nickla, 2005). These findings can be extrapolated as an aetiology for early adult-onset myopia in humans when axial growth is also thought to be

complete. Although the magnitude and speed of growth response has been shown to be slower in older animals (Troilo *et al.,* 2000), the fundamental finding that eye growth can be manipulated by visual input at an age when eye growth is thought to be complete has implications in terms of providing an aetiology for human myopia onset.

Nevertheless, caution is advised when extrapolating animal data to humans (Smith III *et al.,* 1999) as sustained form deprivation induced experimentally is a very strong stimulus and one rarely encountered by human children in normal visual environments.

Further work investigating the effect of lens defocus on adolescent/adult monkeys would be beneficial as it will determine the ability of the higher primate visual system to respond to blur at a stage when plasticity is thought to be minimal. The findings from such work will prove a significant step in devising a valid model of the human visual system at an age corresponding to juvenile myopia onset.

1.3.4 Mechanisms for Emmetropisation

1.3.4.1 Accommodation

Accommodation has long been implicated as the controlling mechanism for refraction by detecting changes in visual input and adjusting ocular growth accordingly (Donders, 1864; cited by Grosvenor, 1989). The advocacy for an accommodative effect on eye growth is primarily from human epidemiological surveys linking myopia to near work (Richler and Bear, 1980; Zylbermann *et al.,* 1993; Saw *et al.,* 1996; McBrien and Adams, 1997). Accommodation appears an intuitive aetiology considering its increased use during near work – the 'use-abuse theory' (Angle and Wissman, 1980). However, animal studies have questioned the role of accommodation in the control of eye growth for two main reasons:

i. Sectioning the optic nerve (ONS) or blocking its conduction with tetrodotoxin (a neurotransmitter) does not prevent form deprivation myopia (Trolio *et al.,* 1987). Positive spectacle lenses have also been compensated for by ONS eyes (Wildsoet and Wallman, 1995).

ii. Locally induced lens defocus (Section 1.3.3.1), if controlled by accommodation, would require locally differential accommodative responses by the retina in order to produce local changes (Diether and Schaeffel, 1997). The eye cannot accommodate differentially across the lens hence local changes in the retina argue against an accommodative mechanism in eye growth control.

In view of these findings, mechanisms of emmetropisation excluding a role for accommodation have been suggested. Troilo and Wallman (1991) propose two components to eye growth: a visually

guided mechanism responding to blur received on the retina via the adjustment of VCD and a second endogenous 'shape-related' mechanism that is responsible for maintaining a proportional relationship between ocular components within the eye. However, a question then arises as to how the visual system is able to detect the sign and magnitude of blur on the retina without the use of accommodation. A hypothesis involving temporal measures of image contrast by retinal image processors have been suggested to differentiate between hyperopic and myopic blur (Bartmann and Schaeffel, 1994; Wildsoet and Wallman, 1995) although a tested explanation to this query remains unidentified (Morgan, 2003).

A further complication surrounding the issue of emmetropisation is whether form deprivation and lens induced defocus share the same mechanism of action. The attenuation of image contrast in form deprivation has been shown to be comparable to levels of defocus induced by spectacle lenses (Bartmann and Schaeffel, 1994). However it is supposed that form deprivation is a very severe form of defocus rarely encountered in normal environments (Zadnik and Mutti, 1995) and it has been hypothesised that form deprivation and lens induced defocus operate via separate mechanisms (Schaeffel *et al.,* 1994; Choh *et al.,* 2006).

1.3.5 Scleral and Choroidal Modulations

1.3.5.1 The Sclera

The change in ocular length responsible for refractive error compensation and recovery has been principally attributed to a scleral mechanism controlling eye size and shape and moving the retinal plane to compensate for blur. The sclera in mammals is a dense fibrous connective tissue comprised of glycoproteins, collagen and proteoglycans (Rada *et al.,* 2006).

As the eye expands in myopia, the sclera must adjust to the expansion by either remodelling new tissue or redistributing that which it is comprised of (Wildsoet, 1998). FDM eyes in tree shrews have shown thinner posterior sclerae than control eyes (Kang and Norton, 1993; Phillips and McBrien, 1995). Evidence points to a remodelling of tissue (active loss/gain) rather than redistribution of existing tissue (McBrien *et al.,* 2000) predominantly at the posterior pole of the eye.

Scleral (ocular) rigidity is an additional variable to consider, as lower resistance to stretch in predisposed eyes may be the cause of ocular elongation and myopia (Wold, 1949). It may be that ocular rigidity is reduced in (pre)myopic eyes rendering them susceptible to elongation by myopiagenic forces (Mallen *et al.,* 2006). Scleral elasticity has been shown to be greater in FDM tree shrew eyes compared to controls (Phillips and McBrien, 1995).

A caveat applied to the study of the sclera from many animal and human eyes is that it is often difficult to establish cause and effect (Rada *et al.,* 2006) as to whether it is changes in the sclera that cause myopia or that myopia itself leads to biochemical variations in scleral tissue.

1.3.5.2 The Choroid

The choroid is the rich vascular layer in the eye providing the outer retina with oxygen (Figure 1.3.2). It lies between the sclera and the retinal pigment epithelial (RPE) layer of the retina and is comprised of the choriocapillaris and the main portion of the choroid (Wallman *et al.*, 1995).

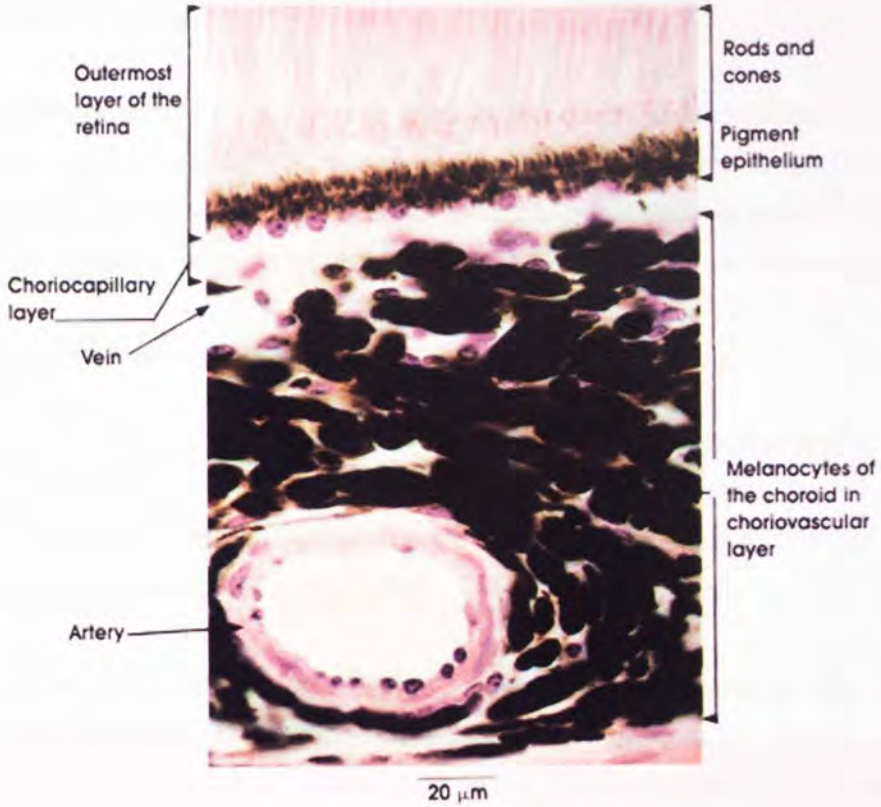


Figure 1.3.2 Cross-section through the choroidal layers of a Rhesus monkey http://www.anatomyatlases.org/MicroscopicAnatomy/Section02/Plate0225.shtml. Accessed 07/09/2005

It has been shown in chicks that the thickness of the choroid alters in response to myopic and hyperopic defocus. With myopic defocus (to both FDM recovery and positive lens defocus), the choroid thickens and effectively moves the retinal plane forwards towards the image plane to minimise blur. A thinning of the choroid in hyperopic defocus has an equal and opposite effect. Local myopic defocus has also produced local choroidal thickening (Wallman *et al.*, 1995), supporting the local control theory of eye growth.

The choroidal response mechanism to blur has been most dramatically demonstrated in the chick eye (Wallman *et al.*, 1995) although responses of lower magnitudes in tree shrews (Siegwart and Norton, 1998, Shaikh *et al.*, 1999), monkeys (Hung *et al.*, 1998) and most recently guinea pigs (Howlett and McFadden, 2006) have been detected.

The mechanism behind choroidal thickness modulation remains elusive. A separate area (the retina) may be in direct control of both choroid and sclera in parallel via a humoral system or it may be that the choroid mediates the sclera itself through feedback (Wallman *et al.,* 1995). The retinal pigment epithelium (RPE) layer is also thought to play a significant role in the relay of signals between retina, choroid (Figure 1.3.2) and perhaps the sclera through the secretion of neurotransmitters (Rymer and Wildsoet, 2005).

Although a mild form of choroidal modulation has been detected in monkeys (Hung *et al.,* 1998), no variation in choroidal thickness has been noted in humans. Further work to determine the *in vivo* scleral and choroidal response to defocus in humans will serve to demonstrate the validity of their modulation in animals as representations for human ocular responses.

1.3.6 Human Application of Blur Driven Growth

Animal models serve to show that manipulation of the visual environment can produce dramatic variations in ocular length and refractive error. However, many animal studies may be more applicable to human infants than to older children due to the age of the animals at the time of experimentation (Edwards, 1996).

It has been shown that myopic children have a greater lag of accommodation, a weaker accommodative response to near targets (Gwiazda *et al.,* 1993a) and a reduced accommodative facility (Pandian *et al.,* 2006), due to a putative reduction in blur sensitivity threshold (Rosenfield, 1999; Cufflin *et al.,* 2007). The lag created would initiate hyperopic defocus, which has been implicated in animal work as a stimulus for axial length growth and myopia onset (Gwiazda *et al.,* 1993a; Wildsoet, 1997).

However, an important consideration in relation to accommodative anomalies is whether they chronologically precede myopia onset or whether myopia itself leads to accommodative difficulties (Rosenfield, 1999). Clinical research by Gwiazda *et al.,* (2005) claimed that emmetropic children who became myopic during the course of their longitudinal study had higher accommodative convergence: accommodation (AC/A) ratios at least two years prior to their onset of myopia. The increased AC/A ratios were predominantly due to a reduced accommodative response to stimuli, as accommodative convergence only became significantly different between myopes and emmetropes at onset of myopia (two years into the study). Gwiazda and colleagues hypothesised that accommodative lag was either the direct cause of myopia onset by inducing hyperopic defocus in the eye or that it was simply a by-product of a structural change in the eye leading to myopia regardless of accommodation levels and therefore not part of a causative mechanism.

However, recent work on marmosets to determine the temporal nature of the relationship suggested that accommodative deficiencies are a result of myopia and not a cause (Troilo *et al.,* 2007), although the authors did concede that any hyperopic defocus induced, if not linked to myopia onset, may be involved with myopia progression. Human research in line with this finding also concluded that increased accommodative lag occurs after the onset of myopia in children and not precedent to it (Mutti *et al.,* 2004), refuting the role of lag as a predictor of future refractive status.

1.3.6.1 Peripheral refraction

Conventional refraction is measured at the plane of the posterior pole, however research is now increasingly being undertaken on the retinal periphery following studies that have determined relationships between eye shape and foveal refraction. Initial work on refractive error of the peripheral retina showed that with growing eccentricity from the fovea, astigmatism was a predominant outcome (Feree *et al.,* 1931; Feree and Rand, 1933). Following these studies, Hoogerheide *et al.* (1971) attempted to elucidate the relationship between peripheral and foveal refraction and found that myopes had a greater relative hyperopic peripheral refraction compared to non-myopes.

Recent work on infant monkeys has shown that form deprivation (FD) of the peripheral retina (n= 12) leads to a relative myopia in the deprived eye compared to control (n= 24) and that even after ablation of the fovea, recovery from FD occurs in all monkeys as the eyes grow back towards emmetropia (Smith *et al.,* 2005). As elimination of the fovea did not impede upon the recovery of the eye from FD, the authors were led to conclude that the peripheral retina plays a significant role in determining the refractive status of the eye, perhaps moreso than the fovea.

Emmetropes are believed to have a reasonably spherical eye (Stone and Flitcroft, 2004). In relation, myopes have been shown to have prolate shaped eyeballs (Figure 1.3.3) i.e. the peripheral retina is relatively hyperopic than that expected from a sphere (Hoogerheide *et al.,* 1971; Mutti *et al.* 2000a; Logan *et al.,* 2004b), possibly due to a mechanical restriction on equatorial expansion causing the formation of an elliptical eyeball (van Alphen, 1986; Mutti *et al.,* 1998). Hyperopes, by contrast have an oblate (or relatively myopic) periphery compared to emmetropes (Figure 1.3.3). Some studies have refuted this classification system however, after finding oblate eyes in myopes (Atchison *et al.* 2005), although there is thought to be a significant amount of overlap between the 3 refractive groups and their ocular shapes (Stone and Flitcroft, 2004) which may explain this anomalous finding. Differences have also been found within a myopic eye in that the horizontal peripheral contour has been found to be relatively hyperopic (prolate) whilst the vertical profile found to be relatively myopic (oblate), contradicting somewhat the hypothesis of peripheral hyperopic defocus driving axial elongation in myopia as the peripheral hyperopia appears to exist principally along one meridian only (Atchinson *et al.,* 2006).

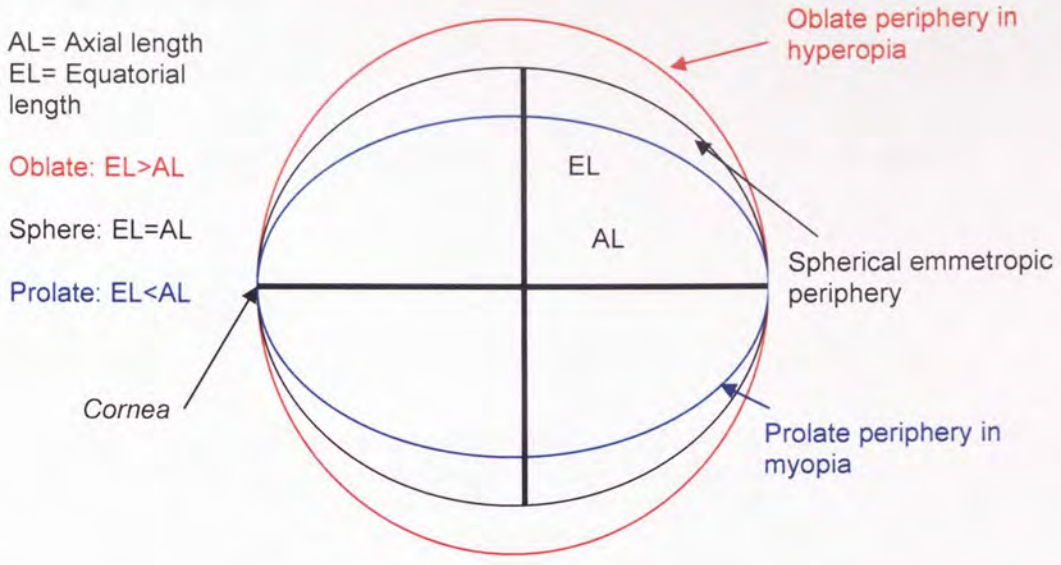


Figure 1.3.3 The definition of asphericity with refractive status

It has been hypothesised that as axial length (AL) increases, there is a concomitant increase in global expansion, analogous to the inflation of a balloon (van Alphen, 1961). In eyes that are myopic, AL increases at a greater rate than equatorial length (EL) giving rise to a prolate eccentricity (Atchison *et al.*, 2004).

Recent data derived retrospectively from American children (Mutti *et al.*, 2007) showed that pre-myopic children (children who were to become myopic but at the time were emmetropic) became relatively peripherally hyperopic two years prior to myopia onset. Thus it seems that the eye becomes relatively prolate prior the onset of myopia. However, once the child became myopic, although the AL continued growing linearly, the amount of relative peripheral hyperopia stabilised. This indicated that two years prior to myopia onset, the eye grew in a prolate manner (axial growth > equatorial growth), though once myopia commenced, the eye grew in a spherical manner (axial growth = equatorial growth). Had the eye continued to grow in an asymmetric manner, the degree of relative peripheral hyperopia would have persistently increased.

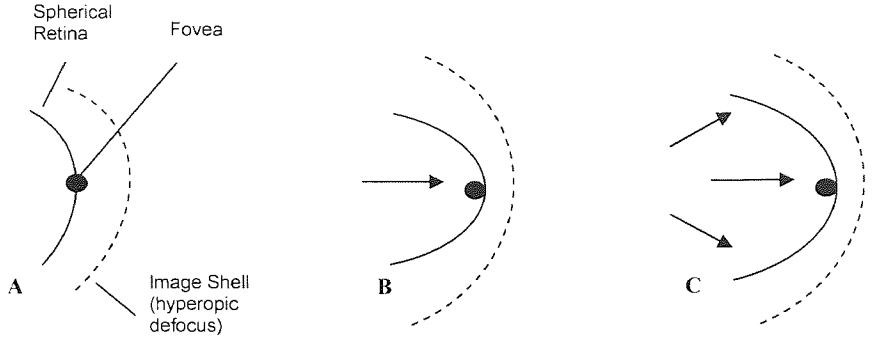
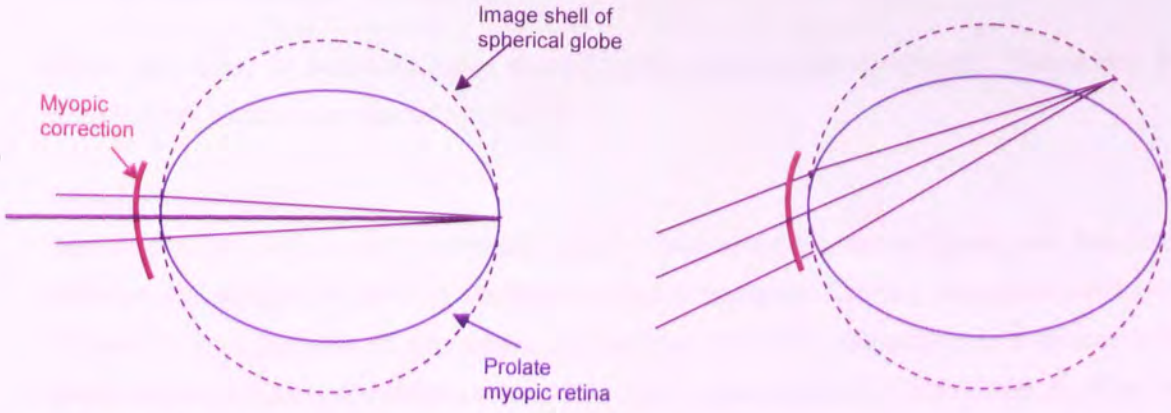


Figure 1.3.4 Putative differential potency to defocus of fovea *vs.* peripheral retina, as hypothesised by Mutti *et al.*, (2007). A. Lag of accommodation causing hyperopic defocus >2 years prior to myopia onset in a spherical eye. B. The more potent fovea grows towards the defocused image shell, inducing a prolate ocular shape. During this time, the eye becomes myopic. C. Negative feedback to the fovea as it grows closer towards the defocus results in a weakened growth signal. The foveal signal is equal to the highly defocused but less potent peripheral signal thus the eye grows approximately spherically

The stabilisation of peripheral hyperopia was accounted for tentatively by Mutti *et al.* to be a result of differential sensitivity between the fovea and the peripheral retina to defocus (Figure 1.3.4). Prior to myopia onset, the axial rate of growth was more rapid than the equatorial due an increased potency to hyperopic blur of the fovea relative to the periphery, causing the eye to assume a prolate shape. However, as the fovea grew nearer to the defocused image shell, the strength of the foveal growth signal diminished via negative feedback and matched that of the peripheral retina, which was less sensitive to defocus although it had a higher magnitude of defocus to overcome (Mutti *et al.*, 2007). The theory remains to be validated.

In myopes, although central refraction may be corrected, due to the shape of the peripheral retina, off-axis light falls behind the prolate retina giving rise to relative peripheral hyperopia. Light falling in front of an oblate hyperopic retina will lead to relative peripheral myopia. The relative peripheral defocus has been postulated to drive axial elongation/regression in the same manner that STOP and GO signals are thought to drive central defocus, as discussed in Section 1.3.3.2 (Figure 1.3.5). The relative peripheral hyperopic defocus in a myope due to its prolate periphery would be a stimulus for further ocular elongation by initiating a GO signal (Wallman and Winawer, 2004; Smith *et al.*, 2005). By correcting a myopic error, the relative peripheral hyperopic defocus is again reinstated (Figure 1.3.5) to drive forward axial elongation by GO signals (Atchison *et al.*, 2005), perhaps accounting for why myopes tend to progress into myopia at a greater rate than non-myopes (Lam *et al.*, 2004).



A. Corrected myopic eye with image falling at the fovea

B. Corrected myopic eye. Peripheral rays falling on spherical image shell behind retina causing relative peripheral hyperopia and stimulus to drive axial elongation

Figure 1.3.5 Peripheral refraction in a corrected myopic eye, after Atchison *et al.* 2005

Children from differing ethnic backgrounds have demonstrated variations in peripheral refraction prior to myopia onset, with more prolate eyes found in Asian children, who go on towards more myopic refractive errors (Mutti *et al.*, 2007). Therefore, future epidemiological work should incorporate peripheral ocular shape and refraction as an important variable.

1.4 MYOPIA RISK FACTORS: THE NATURE NURTURE DEBATE

It has long been debated whether myopia is under genetic or environmental control (Wold, 1949; Goldschmidt, 1968; Mutti *et al.*, 1996). Many authors suggest that some form of interaction exists between the variables (Wu *et al.*, 1999; Goldschmidt, 2003). One proposal is that myopia has a biphasic aetiology i.e. high myopia with a very young age of onset is inherited whereas school myopia is determined by environmental risk factors (Guggenheim *et al.*, 2000; Morgan and Rose, 2005). In low myopia a person's genes are responsible for the growth of ocular components although the subtle correlation between these components is influenced by the environment (Goldschmidt, 1968).

A second mode of interaction is thought to be due to a genetic susceptibility of individuals to environmental risk factors (Saw *et al.*, 1996; Mutti *et al.*, 2002). Many people are exposed to environmental risk factors (i.e. near work, intelligence) yet only a proportion of these will develop myopia. It may be that genes are responsible for this predisposition.

1.4.1 Genetic Influences on Myopia

Three core lines of evidence have established a genetic link to myopia. These are twin studies, genealogical studies and genetic mapping.

1.4.1.1 Twin Studies

Twin studies are very useful in investigating the relative importance of genes and the environment as confounding effects of genetic variation on environmental factors are minimised. Heritability is defined as the proportion of phenotypic (expressed) variation attributable to a genotype (Rose *et al.*, 2002). High heritability of refractive error has been demonstrated in many twin studies (Hammond *et al.*, 2001; Lyhne *et al.*, 2001; Dirani *et al.*, 2006).

Hammond and colleagues (2001) recorded heritability values at between 84-86% (n= 506 female adult twin pairs, age 50-79 years), with a greater concordance of refraction between monozygotic (MZ) twins compared to dizygotes (DZ), supporting a genetic effect on refraction. These concordance values were reiterated by Lyhne *et al.* (2001), who purported heritability to lie between 89-94% and by Dirani *et al.* (2006) with a heritability for refraction between 75-88%. Heritability values do make an important assumption that both MZ and DZ twins share intra-pair common environments (Lyhne *et al.*, 2001). If this assumption is violated it may confound results, as it may be that MZ twins share a more common environment compared to DZ twins, thereby accounting for their higher concordance in refraction.

The Genes in Myopia (GEM) study conducted on a predominantly Caucasian background in Australia (age range 18-88 years) and involving both MZ (n= 690) and DZ (n= 534) twins expanded on the twin study by Hammond *et al.* (2001) by taking ocular biometry measures alongside those of refractive error (Dirani *et al.*, 2006). In addition to the heritability values for refractive error (89-94%), higher heritability was demonstrated for axial length (>90%); suggesting that this ocular component, if genetically pre-determined, may provide the best predictor for the development of ametropia before its onset. MZ twins were also found to have a greater intra-pair correlation of refractive error than DZ twins (r= +0.82 *vs.* +0.36, $p<0.001$), in agreement with Hammond *et al.* (2001). In conclusion, Dirani *et al.*, (2006) stated that the majority of the variance in refractive error can be accounted for by a polygenic (i.e. many genes) effect.

High heritability (62%) has also been demonstrated between normal siblings in an elderly American population (Wojciechowski *et al.*, 2005). Heritability levels varied according to ethnicity (Blacks: 80%; Whites: 50%) although these differences were not significant (p= 0.32). The Framingham Offspring Eye Study (The Framingham Offspring Eye Study Group, 1996) determined a high risk of myopia between siblings (OR= 2.81, $p<0.001$; odds of developing myopia if a sibling has the condition compared to if sibling is not myopic). However, the OR decreased as the age difference between

siblings increased, leading to suggestions of an environmental influence as well as that of a common genetic background as similarly aged siblings were more likely to be exposed to the same environmental risk factors compared to those with larger age gaps

1.4.1.2 Genealogical Studies

Familial traits of myopia have been identified in several epidemiological investigations (Goss and Jackson, 1996; Zadnik, 1997; Konstantopoulos *et al.*, 2007). The results illustrated in Figure 1.4.1 and Table 1.4.1 examine the prevalence of myopia in children as a function of the number of myopic parents in a family. These findings support earlier work by Wold (1949), who found that for children with no myopic parents (n= 645) myopia prevalence was 35.7%, for those with one myopic parent (n= 628) the child myopia prevalence was 49.2% and for children with two myopic parents (n= 27), 74.1% were deemed myopic.

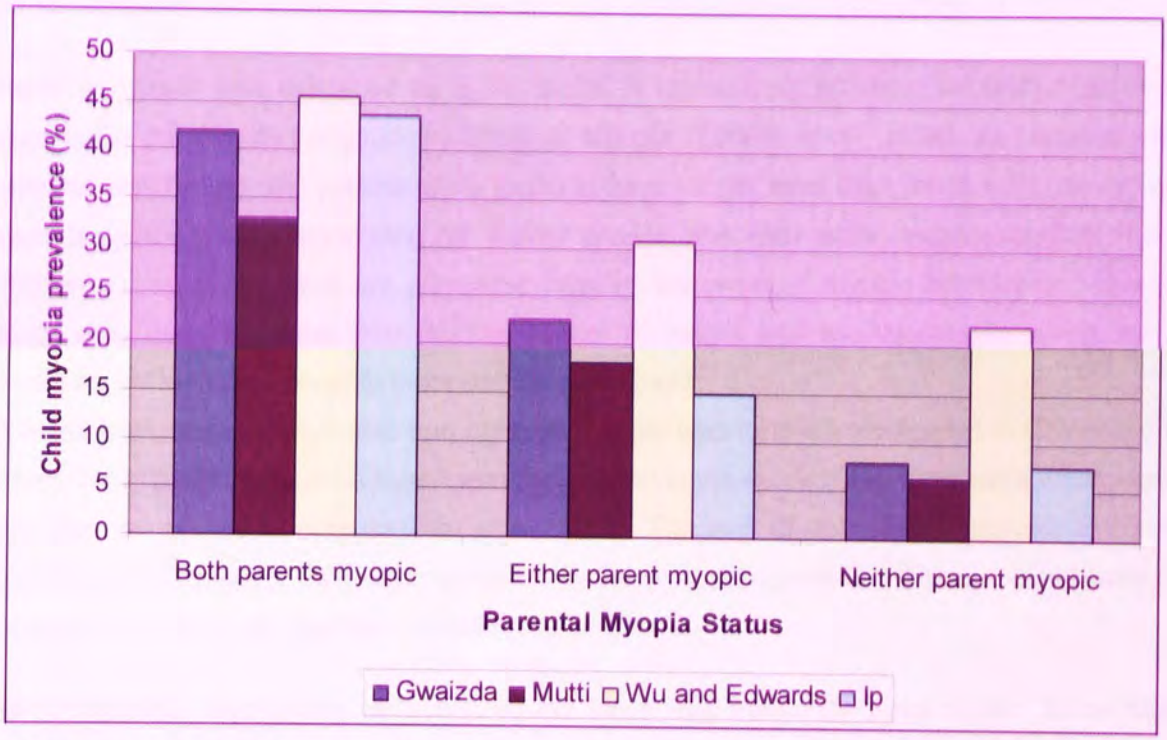


Figure 1.4.1 Child myopia prevalence as a function of parental myopia frequency. Series names refer to study from which data was obtained. Full references can be derived using the corresponding table below (Table 1.4.1)

Study	n	Age range (years)	Both parents myopic (%)	Either parent myopic (%)	Neither parent myopic (%)
Gwiazda *et al.* (1993)	72	9-16	42	22.5	8
Mutti *et al.* (2002)	366	13-14	32.9	18.2	6.3
Wu and Edwards (1999)	3,131	7-17	45.6	30.8	22.1
Ip *et al.* (2007a)	2,353	12-13	43.6	14.9	7.6

Table 1.4.1 Details of 4 studies examining the prevalence of child myopia as a function of the number of myopic parents in a family

The results of the above studies show very similar dose-dependent reductions in child myopia prevalence with a decrease in the number of myopic parents. Additional studies have examined parental myopia as a dichotomous variable (Yap *et al.*, 1993; Goss and Jackson, 1996); their results support parental influence on child refractive error and propound strong evidence for a familial effect on the aetiology of child myopia, whether through shared genes or environments.

Parental myopia was assessed as a risk factor in emmetropic children (n= 662) aged 6-14 years enrolled in the Orinda Longitudinal Study of Myopia (Zadnik *et al.*, 1994). At baseline measures, children with two myopic parents were found to have longer eyes than those with one or no myopic parents (p=0.01) after controlling for school grades and near work, suggesting that the eyes of children in myopic families are elongated prior to the onset of myopic symptoms. However, this study may have benefited from further control of height and socioeconomic status as potential confounders to the relationship proposed by the authors.

A relationship between eye size and parental myopia was further investigated in Chinese pre-school children (n= 514) although no significance was found in the relationship between a child's axial length and number of myopic parents (Fan *et al.*, 2005). The lack of association derived, in contrast with Zadnik and colleagues, may have been due to the younger age of the Chinese cohort and the small number of children who had two myopic parents (n= 45).

Within families, inter-sibling refraction concordance has frequently been shown to be higher than parent-offspring concordance (Morgan and Rose, 2005). Data based on the SCORM study in Singapore (159 sibling pairs) found a high sibling-sibling correlation for refractive error and for the two ocular components thought to be primarily responsible for refractive error: VCD and CR (Guggenheim *et al.*, 2007). Furthermore, the rate of change over 1 year of VCD and refractive error was highly correlated between siblings.

However, there also existed a high sibling-sibling correlation for level of environmental exposure, meaning that the siblings were exposed to a similar frequency and intensity of external risk factors (i.e. reading, computer use, outdoor activity). Thus it cannot be concluded from this study as to

whether the high sibling-sibling correlation is a result of genetic or environmental factors (Guggenheim *et al.*, 2007).

1.4.1.3 Genetic Mapping

The huge advances in the mapping of the human genome have undoubtedly aided researchers in their quest to find the gene(s) involved in myopia onset.

High myopia (≤-6.00D) shows a large pattern of inheritance (Morgan and Rose, 2005), either alone (non-syndromic) or associated with systemic conditions such as Marfan syndrome and homocystinuria (Curtin, 1985; Logan *et al.*, 2004). Several gene loci have been proposed to account for its non-syndromic inheritance including loci on chromosomes 18p, 12q and 17q (Young *et al.*, 1998; Young *et al.*, 1998a; Paluru *et al.*, 2003). However, these genes were postulated after examining a relatively low number of highly myopic families. To investigate whether these loci were responsible for high myopia in a larger number of families and a variant population base, the aforementioned loci were analysed in 51 UK families (Farbrother *et al.*, 2004). Chromosome 12q appeared responsible for approximately 25% of autosomal dominant high myopia whilst the other two loci (18p and 17q) were considerably lower in accounting for high myopia variance. The authors concluded by stating that either additional loci remain to be discovered or high myopia carries a complex mode of inheritance involving more than just genes (Farbrother *et al.*, 2004a). To date, 13 loci (MYP1 - MYP13) have been approved as loci for candidate high myopia genes (Young *et al.*, 2007).

Though a large quantity of research has been invested into the candidate loci of high myopia, attempts to link these loci to common school myopia (>-6.00D) have not been successful to date (Ibay *et al.*, 2004). The lack of success may be because refractive error, although measured on a continuous scale, has varying aetiologies separated by arbitrarily defined boundaries (Klein *et al.*, 2005). School myopia may be caused by a preponderance of environmental factors relative to high myopia which is predominantly genetic in origin.

In a study of UK fraternal twins (n= 221 DZ twin pairs), the PAX6 gene located on chromosome 11p13 was implicated in common myopia onset via the inheritance of a dysfunctional emmetropisation mechanism (Hammond *et al.*, 2004). Genetic mapping for common myopia has also been carried out in the United States on a group of 44 homogenous Ashkenazi Jewish families (n= 964). It was found that the strongest evidence for myopia susceptibility loci was on chromosomes 22q12, 8p23 and 3q26 (Stambolian *et al.*, 2004; Stambolian *et al.*, 2005). These findings reiterate the alternative chromosomes proposed by Hammond *et al.* (2004), alongside the PAX6 gene. Further work is recommended on the PAX6 gene alongside putative candidates to determine if repeated studies are able to verify associations between candidate gene loci and school myopia.

1.4.2 Environmental Influences on Myopia

A considerable corpus of epidemiological and animal work has lent support to the hypothesis that the environment of an individual has an impact on their propensity to become myopic (Mutti *et al.*, 1996; Morgan and Rose, 2005). Previous epidemiological studies also suggest that the increase in myopia prevalence measured within the studied region has occurred over too short a time period as to be accounted for by a change in the local gene pool (Young *et al.*, 1969; Morgan *et al.*, 1975; Saw, 2003).

1.4.2.1 Near Work

Near work has been associated with myopia as far back as Kepler in the 17th Century (Curtin, 1985). There are two hypotheses that link the variables:

i) excessive accommodation exerted at near leading to axial elongation and myopia - the 'use-abuse' theory (Angle and Wissman, 1980).

ii) near viewing inducing hyperopic blur (due to accommodative lag) in turn leading to ocular elongation and myopia (Rosenfield, 1998).

Sustained accommodative effort exerted during near work and the finding of an increased myopia prevalence in areas where near work levels are high (Richler and Bear, 1980; Zylbermann *et al.*, 1993; Edwards and Lam, 2004) have led to the association between near work and myopia (Mutti *et al.*, 2002). In addition, the dramatic increase in juvenile myopia prevalence in urbanised regions of East Asia has been attributed to the intense educational demands of the schooling system where children study for prolonged time periods with a relative lack of outdoor activities (Lin *et al.*, 2004; Saw *et al.*, 2005). Much time out of school is devoted to supplementary tuition classes and children are taught to use a computer from a young age (Zhang *et al.*, 2000).

Evidence of myopia in occupations requiring intense periods of near focusing is well established (Table 1.4.2; Goldschmidt, 1968; National Research Council, 1989; McBrien and Adams, 1997, Wensor *et al.*, 1999, Ting *et al.*, 2006). However, this may simply imply that jobs involving large amounts of near work are attractive to myopes (Wensor *et al.*, 1999) due to their superior reading ability compared to non myopes (Curtin, 1985) and not that the occupation itself is a causal factor.

Occupation Category	Tscherning (1882) % Myopia <-2.00D N=7523	Goldschmidt (1968) % Myopia <-1.50D N=3651
1. Undergraduates, Teachers	32.4	30.1
2. Clerks/Office workers	15.8	11.8
3. Skilled/'Cultured' professions (e.g. civil servant)	13.3	13.9
4. Skilled Manual fine work (e.g. electrician)	11.7	9.1
5. Skilled Manual heavy work (e.g. blacksmith)	5.2	4.3
6. Unskilled labourer (e.g. factory worker)	2.5	2.9
Overall mean	**8.3**	**9.2**

Table 1.4.2 The prevalence of myopia by occupational category. Categories were defined by Tscherning and duplicated by Goldschmidt. After Goldschmidt (1968). Occupation categories descend according to amount of near work involved in occupation

An attempt to quantify near work was devised by Mutti *et al.* (2002) and termed the 'dioptre-hour'. It is the magnitude of accommodation exerted weighted by the distance of the stimulus per unit time. Continuous reading would therefore constitute a greater value of dioptre-hours than the same time spent in front of a computer screen, due to their respective working distance from the viewer.

However the use of this measure to quantify near work has been bought into question due to the finding that the accommodative response of myopes is lower than that of emmetropes (Saw *et al.*, 2002), in addition to the confounding effect of cognitive task load, which has also been shown to affect accommodative levels (Rosenfield and Gilmartin, 1998; Davies *et al.*, 2005). Finally, parental recall bias may often produce inaccurate responses to questionnaires, in particular when recalling quantitatively precise measures such as amount of time spent reading (Saw *et al.*, 2002d). A more categorical measure devised by Saw and co-workers (2002) introduced the number of books read per week as a measure of near work although this measure too is limited (Saw *et al.*, 2002, Saw *et al.*, 2006). Recently two provisional measures of near work have been postulated. Saw *et al.* (2007) have proposed that cumulative measures of near work over a period of time (exam grades/performance) may be a more accurate reflection of the total amount of near work performed rather than questionnaire-based quantifications of the amount of reading undertaken. Alternatively, the experience sampling method (Rah *et al.*, 2006), which involves the dictation of a person's activities at regular episodes during a day, may prove a more encompassing measure of visual demand over a period of time.

Although near work has been implicated in myopia onset, some studies have refuted causality (Mutti *et al.*, 2002; Ip *et al.*, 2007a). In addition, most studies investigating near work and myopia are cross-sectional therefore a causal relationship can only be assumed (Rosenfield and Gilmartin, 1998; Gilmartin, 2004; Konstantopoulos *et al.*, 2007).

However, when measuring near work, asymmetries in visual signal strength should be taken into account. It is known from animal studies that myopic defocus has a greater potency to drive visual growth in the eye compared to hyperopic defocus (Shaikh *et al.*, 1999; Smith *et al.*, 2002). Therefore, when measuring the amount of reading a child undertakes, the frequency and duration of breaks from sustained near work should be taken into consideration, as the nature of these breaks may be as important protectively as the amount of near work carried out (Kee *et al*,. 2007). It may be necessary to assimilate the entire visual environment a child is exposed to over a period of time, in particular the ratio of hyperopic to myopic defocus a child is subjected to, in order to determine exactly how eye growth is manipulated by visual stimuli at varying distances.

Perhaps it is a lack of distance vision, as opposed to excessive near vision that plays a dominant role in myopia onset (Morgan and Rose, 2005, Tarczy-Harnoch *et al.*, 2006). Studies have demonstrated outdoor activities as a protective factor for myopia (Rose *et al.*, 2006; Cheng *et al.*, 2007), even after adjustment for potentially confounding variables such as near work and parental myopia (Rose *et al.*, 2006). Support is further provided by animal work showing the protective effects of short periods of relative myopic defocus at reducing myopia progression in monkeys undergoing sustained hyperopic defocus (Kee *et al.*, 2007). Levels of outdoor activity, alongside parental myopia, have been recently purported as strong non-ocular myopiagenic predictive factors in pre-myopic children (Jones *et al.*, 2007). A prospective longitudinal study on emmetropic children of a similar genetic stock is warranted to build on the study by Jones *et al.*, (2007), by developing robust measures of near work and outdoor activity unreliant upon questionnaires. These measures can be utilised further to determine associations between exposure to myopiagenic factors and the number of children developing myopia through the course of the cohort investigation.

1.4.2.2 Education

A myriad of research has identified a link between educational level and myopia prevalence across all ages (Sperduto *et al.*, 1983; Wang *et al.*, 1994; Katz *et al.*, 1997; Lynhe *et al.*, 2001; Wu *et al.*, 2001; Quek *et al.*, 2004, Tarczy-Harnoch *et al.*, 2006, Konstantopoulos *et al.*, 2007). High numbers of myopes have been found in students from highly academic degree courses such as law (Zadnik and Mutti, 1987) and medicine (Lin *et al.*, 1996; Woo *et al.*, 2004). Educational level/school performance may be taken as a surrogate for quantity of near work performed or level of intelligence either independently (Wu *et al.*, 2001, Konstantopoulos *et al.*, 2007) or as a hybrid of the two factors (Saw *et al.*, 2007). Even though several studies have highlighted an association with myopia, due to the potentially confounding effects of intelligence and near work and lack of temporal confirmation, causality remains elusive (Saw *et al.*, 1996; Saw *et al.*, 2007).

1.4.2.3 Intelligence

Intelligent children have been found to be more at risk of developing myopia (Rosner and Belkin, 1987; Quek *et al.*, 2004). It has also been found that the personality of an average myope may resemble that of a scientific/abstract thinker (van Alphen, 1961) with a psychological profile of introversion and reclusion (Lanyon and Giddings, 1974; Beedle and Young, 1976), which may result in a greater devotion to studying/occupation habits, increasing intelligence levels.

As expected, it is very difficult to disentangle the confounding effects of near work and intelligence. It appears logical to assume that increased near work is the cause of both intelligence and myopia independently, that is by reading more, a person simultaneously increases their intelligence and risk of myopia. However, an alternative hypothesis purports an inheritance of intelligence and myopia via nearby alleles or genes (Zadnik and Mutti, 1998). The causal link to near work is counterintuitive; intelligent children, determined genetically, would be more attracted to reading/near work through a genetic predisposition. Myopia would be associated with intelligence by the close proximity of the alleles to each other.

The notion of near work as a surrogate for IQ has been refuted by Saw *et al.* (2004), who found in their study that non-verbal IQ scores contributed more to refraction (n= 1,204; age range 10-12 years), even after controlling for near work. A European cohort reinforced an independent role for IQ by highlighting the association of IQ with myopia in Danish conscripts, even after controlling for number of years in education (Jacobsen *et al.*, 2007). Saw and colleagues (2004) tentatively suggest shared genes may be involved between eye growth (myopia) and cerebral development (IQ).

However, limiting intelligence to a measure of IQ scores may preclude further links between myopia and intelligence from being discovered. Adopting a more holistic measure of intelligence may reveal true associations that are otherwise masked by restricting intelligence to IQ scores.

1.4.2.4 Oculometric factors prior to myopia onset

Investigations on children prior to myopia onset to determine risk factors have yielded equivocal results:

Refraction – Longitudinal case-control analysis by Pacella *et al.*, (1999) has found that children who develop myopia have less hyperopic refractions at the age of 1 year compared to those who do not. In addition, neonates born myopic in the USA have a greater risk of regressing back to myopia later in life than infants who are born hyperopic (Gwiazda *et al.*, 1993). A further study examining the correlation between refractive state at 11 weeks of age with refraction at age 7-8 years in Chinese children (Edwards and Shing, 1999) concluded that initial SER at a very young age was not a good predictor of future risk to myopia. It was shown however that hyperopia >+2.50D SER (at age 11 weeks) protected against a child's risk of developing myopia later. A limitation of this study was that it

investigated children aged 7-8 years and not at a later age when the prevalence of school myopia is greater.

Low hyperopic refractions (≤+0.75D SER) at the age of 8 have been postulated as a risk factor for future myopia although the authors (Zadnik *et al.*, 1999) suggest that refractive status should be considered in conjunction with pre-myopic biometric measures to improve predictability. In support of these findings, recent evidence by Gwiazda *et al.* (2007) showed that children with a similar level of refractive error (≤+0.75D SER) at 5 years of age were twice as likely to develop myopia by 15 years of age as those with a refraction above this value (42.3% vs. 21% prevalence at 15 years of age).

Biometry - AL/CR ratios above 3.0 in young emmetropes have been postulated as a risk factor for myopia (Grosvenor, 1988; Goss and Jackson, 1995) and this ratio has shown a stronger correlation with refractive error compared to AL or CR alone (Kimura *et al.*, 2007). The rationale behind this theory (Grosvenor, 1988) is that emmetropic eyes in young children with high AL/CR ratios will invariably have a long AL (as CR does not vary much with age) which has been offset by a thinning of the crystalline lens to maintain a status of emmetropia. However, the lens can only thin finitely, thus if the AL continues to grow, it will become difficult for the lens to compensate for this elongation. Upon maximal thinning of the lens, myopia will result with further axial elongation. Emmetropic eyes with high AL/CR ratios have therefore been presented as a risk factor for myopia and highlight the findings by Sorsby and colleagues (1957) of correlation ametropia resulting from a misalignment of ocular components rather than the growth of an anomalous component *per se.*

Additional studies have postulated predictive factors identified in pre-myopic children aged 7-9 years old, including longer axial lengths and vitreous chamber depths and reduced lens thicknesses (Saw *et al.*, 2005). Increased corneal power was found in children who became myopic relative to children who remained emmetropic in a longitudinal case-control analysis by Goss and Jackson (1995).

Retrospective work on the ocular components of pre-myopic children (those who became myopic during the course of the study) compared to emmetropes (n= 374) found that pre-myopic children (n= 605) had less hyperopia, longer axial lengths and greater relative peripheral hyperopia compared to those children who remained emmetropic. However, these disparities were only evident between 2-4 years prior to myopia onset (Mutti *et al.*, 2007). A limitation of the study is that it was conducted as a function of time relative to myopia onset, not absolute age, therefore it lacks predictive value for thresholds that may enable classification of children at an early age into differential susceptibilities. Future work should build on this important study and derive predictive values as a function of absolute age.

Non-ocular factors - Recent published work from the Orinda Longitudinal Study (n= 514) determined low levels of outdoor activity/sports and a high number of myopic parents as strong 'non-ocular' predictive myopiagenic risk factors in young children (Jones *et al.*, 2007), supporting findings from the Sydney Myopia Study (Rose *et al.*, 2006). The level of near work did not remain significant in multivariate models. However, the authors did state that outdoor activity and reading are not mutually exclusive i.e. children with high levels of outdoor activity tend to be more active academically and may therefore read more. The finding of a lack of multivariate association with near work in this study may have been due to a limited measure of near work by the research group.

1.4.2.5 Urbanisation

The urban-rural disparity in myopia prevalence has been documented in many studies (Garner *et al.* 1999; Zhang *et al.*, 2000; Saw *et al.*, 2001), with a greater prevalence of myopia consistently found in built-up areas, leading to suggestions of an urban myopiagenic effect. The term urbanisation however, is vague. It may be a surrogate for linked variables, namely education or schooling congestion. However, it may also exist independently, referring to the 'closeness' within a city, the proximity of buildings to each other and the lack of true distance vision permissible, preventing complete relaxation of accommodation (Grosvenor, 2003).

The Refractive Error Study in Children (RESC, see Table 1.2.1) documented myopia prevalence in varying locations worldwide via consistent protocols (Negrel *et al.*, 2000). The urbanised city of New Delhi in India (Murthy *et al.*, 2002) was found to have a higher level of myopia prevalence than rural regions in both India (Dandona *et al.*, 2002) and neighbouring Nepal (Pokharel *et al.*, 2000). A similar trend was noted in China, when comparing the urban city of Guangzhou (He *et al.*, 2004) with the rural La Shunyi and Yangxi districts (Zhao *et al.*, 2000; He *et al.*, 2007).

A possible explanation for this disparity may be that urban children have a more intense level of schooling than rural populations, or that their accommodative system is exerted at both a greater intensity and frequency in a visual environment where tall buildings, small spaces and computer screens predominate. Rural children may spend more time outdoors and live in an environment where true distance vision is achievable, minimising defocus cues to central and peripheral retinae and acting protectively against the onset of myopia (Morgan and Rose, 2005).

A confounding effect of varying diets cannot be ruled out between urban and rural areas to account for disparities in myopia risk. City residents living busy lives may be dependent on a greater proportion of carbohydrate/refined foods which have been linked to refractive error (Section 1.4.2.8) compared to rural residents (Cordain *et al.*, 2002).

1.4.2.6 Night lighting

Chicks raised in prolonged periods of darkness have been found to become hyperopic (Troilo and Wallman, 1991). Therefore, it has been postulated that the light levels a human infant receives may influence his/her future refractive status.

Quinn and co-workers (1999) published a well-cited paper describing a dose-dependent association between the use of a night-light in the first 2 years of a child's life and myopia. Within their sample (n=479), children who slept with a room light on had a much higher myopia prevalence compared to those sleeping with just a night light, who in turn had a higher prevalence of myopia compared to children who slept in the dark (55% *vs.* 34% *vs.* 10% respectively, $p<0.001$). Although the limitations of their results were recognised (discussed by Appen and Mares-Perlman, 2000), Quinn *et al.* tentatively advised against the use of night-lights by parents until further work validated their findings. Their results were supported by Czepita *et al.* (2004) who found an association between child myopia and the use of a night light prior to the age of 2 years.

However, this association has been refuted by several authors who did not detect a relationship between the variables on both Asian (Saw *et al.*, 2001a; Saw *et al.*, 2002d) and Caucasian cohorts (Zadnik *et al.*, 2000; Gwiazda *et al.*, 2000; Guggenheim *et al.*, 2003; Konstantopoulos *et al.*, 2007).

A positive association was detected in two of the aforementioned studies between the use of a child night-light and parental myopia (Zadnik *et al.*, 2000; Gwiazda *et al.*, 2000), such that myopic parents were more likely to employ a night light for their child than non-myopic parents. It is accepted that myopic parents are at an increased risk of producing myopic children (Mutti *et al.*, 2002; Guggenheim *et al.*, 2003) therefore it seems plausible that parental myopia acts as an intermediary variable between night lighting and child myopia (Gwiazda *et al.*, 2000; Zadnik, 2001a). It may be speculated that myopic parents are more likely to use a night-light in their house, in relation to their poor vision, so they can see better if awoken at night. The relationship however may be more indirect, in that the higher socioeconomic status afforded to myopic parents (Appen and Mares-Perlman, 2000; Seet *et al.*, 2001) may account for the increased use of night-lights, as wealthier families tend to have more child-monitoring devices in place (Gwiazda *et al.*, 2000). Of interest would be to determine whether the parents using a night light are habituated into their use from their childhood (i.e. were they provided with a night light when they were younger?).

A prospective longitudinal cohort study comparing the prevalence of myopia in children raised with a night-light compared to those raised without may aid in determining whether light/dark cycles do play a role in ametropia (Saw *et al.*, 2002d).

1.4.2.7 Anthropometry

One of the first reports citing a strong correlation between a person's stature and ocular refraction was by Gardiner (1954), who examined height and weight through a case-control analysis between myopes and non-myopes. Myopes were found to be both taller and heavier. Sorsby *et al.,* (1961) however found no association between height, weight and refraction/ocular biometry.

In Singapore, it has been found that although taller adults (40 years and older) have longer axial lengths, the effect this has on refractive error is minimal (Wong *et al.,* 2001). Weight was also correlated positively with axial length, although paradoxically, refractive error became more hyperopic with increased weight. The authors were unable to account for this finding.

The Singapore SCORM study on children (n= 1,453 aged 7-9 years) supported the correlations derived by Wong and co-workers i.e. between height and axial length and between weight and hyperopia (Saw *et al.,* 2002c). Taller children were also found to be more at risk of myopia, a finding attributed to a cohort effect rise in myopia prevalence, as it was not determined in the adult study by Wong *et al.* (2001).

A Finnish cohort analysed by Teikari (1987) found a correlation between myopia and height in men but not in women. No correlation was derived between weight in either sex. These results disagree with those of a Danish study on male conscripts that found no link between myopia and height, weight or BMI (Jacobsen *et al.,* 2007). However, ocular biometry was not performed in either study hence potential correlations with ocular components were not determined.

The Sydney Myopia Study (Ojaimi *et al.,* 2005b) found similar correlations to the SCORM cohort with regards to height and axial length (n= 1,700 children aged 6 years) though not with weight and BMI. However, there were no significant associations between refractive error and height, weight and BMI, highlighting the ability of the eye to compensate for axial length changes such that refractive error remains unaltered.

Many authors investigating the role of anthropometry on the eye have postulated that there may not be a direct causal link between height and axial length but that a 3rd variable may act as an independent control. There has been a trend of an increase in height over recent decades (a cohort effect) in children living in developed countries (Whincup *et al.,* 1988), possibly linked to dietary changes and an improved lifestyle, both of which may concurrently cause ocular elongation. This area requires further longitudinal research to identify the causal relationship between height, ocular biometry and refractive error after controlling for potential confounders such as diet and socioeconomic status.

1.4.2.8 Diet

The substantial rise in child myopia prevalence within indigenous communities such as Eskimos was attributed by Young *et al.,* (1969) primarily to a change in culture, namely increased level of schooling and/or a change in diet. Traditional high protein and low carbohydrate intakes were replaced at this time by Westernised diets of highly refined cereals and sugars. It is thought that this increase in dietary carbohydrate intake (Cordain *et al.,* 2002; Fox, 2002) or a decreased intake of protein (Gardiner, 1956) may play a role in the pathogenesis of juvenile-onset myopia.

The hypothesis propounded by Cordain *et al.* concerns the high glycaemic load of carbohydrates. Glycaemic load is calculated as the product of a food's glycaemic index (an intrinsic value reflecting the effect of food on blood glucose levels) and its constitution (%) within a meal. The high glycaemic load offered by Western diets promotes the development of hyperinsulinaemia leading to a cascade of reactions that are thought to lead to tissue growth in the body. In the eye, scleral tissue growth may lead to an elongation of the eye and subsequent myopia (Cordain *et al.,* 2002).

In Vanuatu societies where the level of schooling is the same as in the West (8 hours per day), the level of myopia in children has been found to be very low (~2%), attributed to the low levels of refined carbohydrate in their diet (Fox, 2002). Corroborative evidence for this hypothesis is that a high glycaemic diet is also thought to increase stature (through tissue growth), reinforcing findings of increased stature in children of industrialized countries (Whincup *et al.,* 1988). It may be tentatively suggested that diet acts as a third variable indirectly associating myopia and stature.

Furthermore, it may transpire that it is not actually an increased carbohydrate load *per se* that is responsible for myopia onset, but that eating more carbohydrates results in the lower consumption of other food classes i.e. protein and fats, indirectly leading to myopia; a hypothesis which combines the work of Cordain *et al.* (2002) and Edwards *et al.,* (1996a). The latter research group performed a cohort study on pre-myopic children (n=92, aged 7 years at baseline) and compared the diets of those children who became myopic to those who remained emmetropic. Myopes tended to consume lower amounts of protein, fats, phosphorus, iron and vitamins B_1, B_2 and C, and did not demonstrate a difference in stature with emmetropes, even though their dietary intake was significantly lower. However, Edwards *et al.* (1996a) concluded by stating that a greater amount of research is required in this area using longitudinal cohort studies on a large sample size adjusted for near work measures to illustrate the relative contributions of diet and near work to myopia onset.

1.4.2.9 Gender

The role of gender in myopia remains equivocal. Many studies allege the prevalence of myopia to be higher in one sex than the other (Morgan *et al.,* 1975) although it may be that the prevalence is higher in a particular sex at varying periods throughout life (Hirsch and Weymouth, 1991).

During early childhood, the growth rates of ocular components remain parallel across the gender groups (Mutti *et al.*, 2005) and the prevalence of myopia in children aged 6 years has been found to be similar (Robinson, 1999; Zhao *et al.*, 2000). A difference in component size has been found post-emmetropisation in children and adults, with females showing on average steeper corneae and shorter axial lengths compared to males (Larsen, 1971; Lam *et al.*, 1994; Zadnik *et al.*, 2003; Wickremasinghe *et al.*, 2004; Ip *et al.*, 2007). A consistently higher prevalence level of myopia in females compared to males (Kleinstein *et al.*, 2003; He *et al.*, 2007) has also been determined in studies in addition to a faster rate of refractive progression (Hyman *et al.*, 2005), though others have refuted these findings (Lam *et al.*, 1999). It is not know precisely why females are at a greater risk of myopia. Hypotheses include the earlier onset of puberty and maturation in girls leading to subsequent ocular changes (Gardiner, 1954; Hirsch and Weymouth, 1991). A greater engagement in outdoor activities by boys may provide a protective myopiagenic effect over girls, or that conversely a greater level of near work undertaken by females may be responsible for their increased prevalence levels determined (Morgan *et al.*, 1975; Ip *et al.*, 2007).

In adults, the prevalence of myopia has been found to be higher in both males (Wu *et al.*, 1999) and in females (Wong *et al.*, 2000), with further studies stating a minimal difference between the sexes (Sperduto *et al.*, 1983). It appears that many extraneous factors (socioeconomic status, stature, education, near work, outdoor activity) encountered in observational studies may confound results on the effect of gender and refractive error. Rigorously designed prospective cohort studies on samples with identical exposure levels to myopiagenic risk factors would be required to determine the true effect, if any, of gender on refractive error.

1.5 THERAPEUTIC TREATMENT OF MYOPIA

Myopia is considered a relatively benign form of ametropia easily corrected with optical appliances such as spectacles and contact lenses. However, myopia also carries a social, pathological and economic burden.

Wearing spectacle lenses during teenage years when social interactions increase and self-consciousness is high can prove to be a hindrance to the social development of the child (Safir, 1979). It has been found that wearing spectacles may lead to an increased risk of victimisation/bullying in children (Horwood *et al.*, 2005). In addition, high myopia has been shown to impair the quality of life in adults compared to lower levels of myopia (Rose *et al.*, 2000). The increasing availability of contact lenses offer young myopes an alternative, although this can be limited to those able to afford them and whose parents and practitioner support their use of contact lenses, especially if required for frequent wear. A current investigation into the effect of contact

lenses and spectacles on a child's self-perception (Walline *et al.*, 2006a) will provide meaningful insight into the social connotations that refractive correction can impose.

The pathological risk of myopia is well known. Ocular elongation and subsequent myopia leaves the eye significantly more at risk of serious retinal pathology (Curtin, 1985), even though a myopic eye may be functionally corrected by an optical appliance (Zadnik, 2001; Morgan and Megaw, 2004).

Finally, the economic impact of myopia can be considered both individually and socially. Individually, the cost of corrective spectacles in higher myopes is often augmented by the cost of high index lenses and contact lenses, which can increase the initial outlay significantly. Alternatively, the relatively recent advent of laser correction may minimise long term expenditure against other optical appliances, but the initial high disbursement to undergo surgery emphasises the obstacles involved for myopes to attain adequate uncorrected vision.

Collectively, the economic burden of myopic correction was estimated to cost approximately $4.5 billion in 1990 (£2.75 billion) in the United States (Javitt and Chiang, 1994). However this figure was quoted conservatively, without taking into account the cost of medical inpatient care for secondary pathological changes attributable to myopia. A more recent evaluation of the cost of refractive correction through spectacles in the Unites States (both myopia and hyperopia) overlapped the assessment by Javitt and Chiang, with an estimated expenditure between $3.9 - $7.2 billion a year for distance refractive correction only (Vitale *et al.*, 2006).

No data for the full economic cost of myopia correction in the UK are available, although the total number of spectacles for which full vouchers (GOS 3) were issued by the General Ophthalmic Services (GOS) at the year-end March 2005 (in England and Wales alone) rested at 3,838,655. Of these vouchers, 1,057,056 were accounted for by children aged 0-15 years (data downloaded from www.dh.gov.uk/assetRoot/04/11/80/75/04118075.pdf, accessed 15/08/05). Considering the minimum voucher value (Voucher A) currently lies at £33.70 and assuming each voucher was prescribed in addition to a sight test (GOS 1 - £18.85), this would result in a minimum annual expenditure by the GOS of £55.5 million for children alone, without accounting for higher voucher values and repairs. These figures demonstrate that optical correction, in which myopia plays a major role, places a considerable financial burden on the public health system.

Thus it is evident that research into a therapy for myopia is crucial, in order to identify individuals at risk of future onset and implement prophylactic measures in these persons in addition to retarding progression in those people already myopic.

Myopia treatment has been approached from two main perspectives; optical and pharmacological. Both lines of study are discussed.

1.5.1 Optical Treatment of myopia

1.5.1.1 Bifocal/Progressive Addition Lenses

The rationale for optical methods of treatment is to ameliorate ocular blur initiated through inaccurate focusing of the eye. Larger lags of accommodation at near have been found in myopes (Gwiazda *et al.*, 1993a), leading to the theory that this lag is responsible for hyperopic defocus at the retina and subsequent axial growth, as demonstrated in animal studies (Smith III, 1998).

Studies have used bifocal lenses to minimise retinal blur by reducing the stimulus for accommodation at near and consequently, the accommodative lag produced (Gilmartin, 2004). Results to date on the use of these lenses have been equivocal, with some studies showing a positive effect of bifocal spectacles on the retardation of myopic progression (Goss, 1994; Fulk *et al.*, 2000) whilst others have shown no effect compared to single vision lenses (Saw *et al.*, 2002a). Increased benefit has been shown in myopes with near esophoria (Fulk *et al.*, 2000), which is especially useful as the rate of myopia progression has also been shown to be higher in this particular cohort (Goss, 1994).

A putative explanation behind the inconclusive results of bifocal trials is thought to be poor experimental design. A high quality prospective clinical trial should contain an adequate sample size, be randomised with both a treatment and control group, double-masked to both investigators and subjects and involve the use of cycloplegia (Saw *et al.*, 2002a). Furthermore, bifocals do not allow clear vision at all distances; the presence of a blurred image at intermediate distances (requiring some accommodation by children and subsequent lag creation) may itself be a catalyst for myopic growth (Leung and Brown, 1999). Finally, bifocal lenses are less cosmetically appealing to a child hence carry a greater risk of non-compliance.

Progressive addition lenses (PALs) overcome some of the complications mentioned above. They allow the wearer unrestricted access to visual space at any distance without initiating accommodation. PALs are also aesthetically acceptable to children and appear to look no different to a single vision pair of lenses.

A two year longitudinal study by Leung and Brown (1999) showed a positive effect of PALs on reducing myopic progression in Chinese school children (n= 68; 9-12 years) compared to single vision (SV) lens wearers ($p<0.001$). A dose-dependent effect was elicited though statistically insignificant; wearers of a +1.50D addition had mean myopia progression reduced by 38% of that attained by SV cohort and those wearing the +2.00D addition had their mean myopia progression reduced by 46% ($p= 0.51$). The rate of axial length growth correlated with mean refraction as expected within each group, suggesting that the effect of PALs was directly on axial length. Leung and Brown advocated the replication of their protocol in other ethnic cohorts prior to adopting PALs for clinical use.

However, several limitations existed with the study by Leung and Brown:

i. Sample size was small.
ii. Non-cycloplegic refractions conducted.
iii. No masking carried out leading to examiner bias.
iv. Sample was of Chinese ethnicity.
v. Study did not ascertain whether children were using the correct portion of the lens for their working distance.

A second study in Chinese children - the Hong Kong Progressive Lens Myopia Control Study (Edwards *et al.*, 2002) refuted the results of Leung and Brown (1999). No significant differences between PAL and SV groups in the rate of myopic progression ($p= 0.11$) and axial length ($p= 0.62$) were found over a period of 2 years ($n= 254$).

A study investigating the effect of PALs on children of varying ethnic backgrounds was carried out in the United States - the Correction Of Myopia Evaluation Trial (COMET). Lasting for 3 years, this multi-centre randomised trial on children ($n= 469$) aged between 6-11 years (Gwiazda *et al.*, 2002) fitted PALs (+2.00 add power) high on children to encourage use of the near portion for reading. This was important, as a factor which can confound both PAL and bifocal studies is children viewing all distances of free space through their distance portion.

The results of the COMET study showed a slight but statistically significant reduction in myopia progression over 3 years with PALs compared to SV lenses (mean reduction ± SE = 0.20 ± 0.08D, $p= 0.004$). However, this effect was not sufficient to warrant the application of PAL prescribing in clinical practice (Gwiazda *et al.*, 2003). The majority of the treatment effect (0.18D) occurred within the first year of the study, an indication of a potential temporal limitation of myopia treatment with spectacle lenses (Gwiazda *et al.*, 2003).

A greater treatment effect with PALs was noted in COMET subjects with larger accommodative lags, particularly in combination with near esophoria, shorter reading distances and a lower levels of baseline myopia (Gwiazda *et al.*, 2004). The differential findings by baseline lag measures lend credence to the hypothesis that it was the reduction in hyperopic defocus by the PAL and not a reduction in accommodation *per se* that was responsible for the retarded myopic progression in the treatment group (Guggenheim and To, 2005).

1.5.1.2 Undercorrection

The rationale behind the undercorrection of a myopic error is to use myopic blur at distance to reduce the rate of ocular elongation, as described by Morgan and Megaw (2004). In addition, undercorrection may reduce the accommodative lag experienced by myopes at near, depending on the level of undercorrection provided and the accommodative lag present in the individual.

Bilateral undercorrection on 94 children (age 9-14 years) performed by Chung *et al.* (2002) showed an increase in axial myopic progression in children instead of the anticipated decrease. This led the authors to purport that the eye could not differentiate between hyperopic and myopic blur and merely acted on any defocus by stimulating axial length growth. These findings were reinforced by Adler and Millodot (2006), who detected an increase in myopic progression in undercorrected subjectes which was not significantly different to progression rates in fully corrected myopes over an 18 month period. Adler and Millodot too refuted the use of undercorrection as a means of myopia treatment.

However, recent work on the undercorrection of one eye has shown that the eye is able to respond to myopic blur and reduce its rate of VCD growth (Phillips, 2005). Subjects (n= 13, 11 years of age) were provided with a monovision spectacle correction for on average 2½ years in the belief that the non-dominant eye, corrected for near, would perhaps reduce myopic progression in both eyes due to a lower level of accommodation exerted (with a subsequent reduction in accommodative lag at near) while reading compared to a fully corrected eye.

The results were unexpected; it was found that the dominant eye (corrected for distance) was being used to view all distances. This meant that the level of accommodation exerted by both eyes was dependent on the viewing distance of the dominant eye alone. The non-dominant eye by contrast experienced myopic blur continuously (Figure 1.5.1) and showed a 50% reduction in myopia progression (with concomitant VCD growth reduction) compared to the dominant fully corrected eye. However, these results must be taken with some caution as firstly the sample size was small but more crucially, a control group was not used as a comparison, thus the possibility of myopic acceleration in the dominant eye cannot not be ruled out (Phillips, 2005).

Clinical application of these results has been discussed by other authors. Guggenheim and To (2005) suggest that if monovision is a viable treatment for myopia progression, periodic reversal of monovision correction would subject both eyes to temporally separated periods of myopic blur, a hypothesis that is currently being trialled using soft contact lenses (SCLs) in the Dual-focus Inhibition of Myopia Evaluation (DIMENZ) trial in New Zealand (Anstice and Phillips, 2006). In the DIMENZ trial, myopic subjects wear a normal distance corrected SCL in one eye and a specially designed dual-focus contact lens in the other eye full time. The dual-focus lens has a distance corrected central zone and a peripheral zone imposing simultaneous myopic defocus, allegedly slowing down myopic progression in that eye. The lenses are swapped over after a period of 10 months.

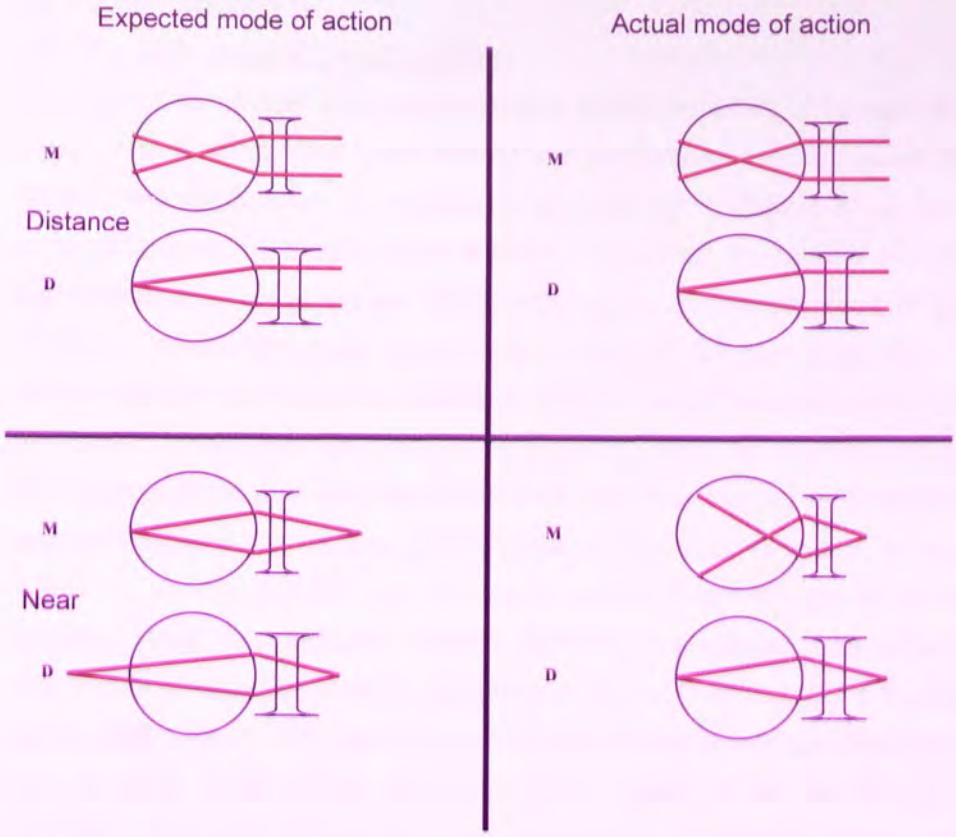


Figure 1.5.1. An illustration of how the expected mode of action differed from actual mode of action in reducing myopia progression (Phillips, 2005). Ray traces show whether eye would have been experiencing hyperopic defocus (ray falling behind eye), myopic defocus (ray falling in front of eye) or that ray was in focus. **D=** Dominant eye set for distance, **M=** Non-dominant (monovision) eye set for near. Lens in front of non-dominant eyes drawn smaller to emphasise undercorrection to the eye

It is postulated that if the eye maintains visual function through the distance refractive zones (even on accommodation), the dual-focus lens will impose continuous myopic defocus, theoretically retarding myopic progression in the eye with the dual-focus lens (Phillips, 2006), with the contralateral eye wearing a normal distance lens acting as a control.

Even if the dual-focus trial is found successful, further work is recommended to determine the amount of blur (i.e. dioptric difference between the eyes) required to retard progression as excessive blur may actually induce form deprivation myopia instead of reducing myopic refractive error. However, these findings in humans support animal work in suggesting that defocus plays an important role in eye growth, even when the plasticity of the eye to respond to visual manipulation is thought to be minimal.

1.5.1.3 Contact lenses

1.5.1.3.1 RGP and Soft Contact lenses

Although some studies have demonstrated a positive effect of contact lenses on the retardation of myopia, the majority have been fraught with limitations of experimental design and the influence of uncontrolled confounders on results (Kerns *et al.*, 1981; Walline *et al.*, 2001). Early positive findings involved polymethyl methacrylate (PMMA) lenses by Stone and Powell-Cullingford (1974), who demonstrated an approximate 1D retardation in myopia progression with PMMA lenses (n=80) compared to a control group of spectacle wearers (n=40) over a period of 4 years. Corneal flattening did not account for the entire slowdown in progression, thus prompting the authors to suggest that the contact lenses may have had some inhibitory effect on axial elongation of the eye, although AL was not measured directly in the study. This work was echoed by Grosvenor *et al.* (1989) using rigid gas permeable (RGP) lenses, who showed a significant reduction in myopia progression (-0.28 ± 0.60D *vs.* -0.80 ± 0.77D) over 3 years in a RGP treatment group (n= 60) compared to an age-matched group of spectacle wearers (n= 31) respectively. The slowdown in progression was matched by a reduction in axial elongation in the RGP cohort (0.1 ± 0.3mm *vs.* 0.6 ± 1.1mm growth respectively). Again, although the RGP lenses did cause corneal flattening, this flattening accounted for only 40% of the difference in myopia progression between the groups (RGP *vs.* spectacle wearers). Therefore Grosvenor and colleagues supported Stone and Powell-Cullingford by suggesting that hard lenses had a direct effect in inhibiting AL growth.

However, recent evidence for the RGP lens has pointed to the contrary. The Contact Lens and Myopia Progression (CLAMP) study (Walline *et al.*, 2001) was designed on the basis of many prior study limitations in the RGP arena. It was a rigorously designed 3 year prospective randomised controlled trial (n= 110), comparing the effects of RGPs *vs.* SCLs on myopia progression. The results showed a significant treatment effect (myopia progression over 3 years, RGP: -1.56 ± 0.95D *vs.* SCL: -2.19 ± 0.89D, $p<0.001$), attributed chiefly to a flattening of the cornea in RGP wearers and not an inhibition in axial length growth. The authors concluded by stating that "RGPs should not be prescribed for children solely to slow myopia progression" (Walline *et al.*, 2006).

SCLs have themselves shown to provide no therapeutic effect against myopia progression *per se* (Horner *et al.*, 1999). Low Dk lens wearers have even shown progression of myopia compared to high Dk lens wearers over a 9 month period (Harris *et al.*, 1975; Dumbleton *et al.*, 1999), although control groups were not employed in these studies to verify an actual lens effect. Despite the lack of direct success, SCL's have been employed as the vehicle for the current DIMENZ trial attempting to retard myopia progression (see Section 1.5.1.2).

1.5.3.1.2 Orthokeratology

The technique of orthokeratology (OK) has been practiced for several decades and involves flattening the myopic cornea with RGP lenses overnight to provide unaided clear vision during the day. However, OK appears to be a palliative remedy rather than a treatment for low levels of myopia (Polse *et al.*, 1983). OK involves reshaping the cornea directly, although on cessation of OK wear, myopia regresses and the cornea returns to its original shape, suggesting that the cornea is either highly elastic or possesses a memory mechanism of its original shape (Polse *et al.*, 1983).

The rate of ocular elongation over a period of 2 years in child OK wearers *vs.* spectacle wearers (n= 35, 7-12 years) has been shown to be slower (0.29 ± 0.27mm *vs.* 0.54 ± 0.27mm respectively, $p<0.001$) although these effects were variable between subjects. The authors suggested from these results that further work was required to determine the long term effects of OK on myopia progression, particularly on cessation of lens wear (Cho *et al.*, 2005).

In summary, further research into contact lenses and myopia treatment has to be explored using stringent and rigorously defined protocols, with a greater degree of success and repeatability before this method of myopia treatment can be advocated. Perhaps there are a specific sub group of myopes for whom contact lenses would be therapeutically beneficial (Kerns, 1981), although this group remains to be identified.

5.2 Pharmacological treatment

Research into the therapeutic use of antimuscarinic drugs for myopia progression is longstanding due to the purported link between accommodation (inhibited by non-selective antimuscarinics) and myopia. Atropine is a drug commonly employed, however serious systemic side effects are possible and an ingested dose of 10mg can be fatal in children (Eperjesi and Jones, 2005).

Dyer (1979) compared the effect of atropine sulphate 1% instilled in both eyes once daily (n= 86) for a period between 2-8 years on the progression of myopia compared to normal spectacle use. Two percent of children wearing spectacles showed no change or a reduction in myopia in contrast to 47% of atropine treated children who showed this effect. The author noted no serious side effects to the use of the eye drops and that accommodation and pupillary responses returned to normal once treatment had ceased.

A study by Bedrossian (1979) in the same year involved treating one eye with atropine 1% once daily and using the other eye as a control (n= 90). Periodic reversal of the atropine treated eye was undertaken annually for either 2 (n= 62) or 4 years (n= 28). It was found that each year, the treated eye remained static in refraction and in most cases, its myopia regressed slightly, whilst the control eye became more myopic. The long-term effect of the drug on refraction was examined in 24 people for an average period up to 55 months after cessation of treatment. The average post-treatment

myopic change was 0.06D/yr compared to a pre-treatment change of 0.91D/yr, showing that myopia retardation with atropine remained after cessation of treatment.

A more recent investigation by the Atropine in the Treatment Of Myopia (ATOM) study backed up earlier claims of atropine efficacy and relatively good short term safety profile. Over a period of 2 years, eyes subjected to a daily regime of atropine 1% progressed by a mean value of -0.25D compared to -1.20D in eyes given placebo eye drops (Chua *et al.*, 2003). The treatment effect was further supported by an unchanged axial length in treated eyes compared to a mean growth in placebo eyes of 0.38mm. A similar finding was noted in a small interventional pilot study using atropine 1% ointment (23 cases, 23 controls) conducted by Fan *et al.*, (2007). Over the period of 1 year, a retardation in myopia progression was found in the treatment group compared to the control (atropine *vs.* control group., mean refractive change: +0.06D versus -1.19D, p= 0.005 respectively), predominantly driven by changes in the axial length. However, a lack of placebo in controls, the provision of confounding progressive lenses for the atropine group and a lack of follow up on cessation in terms of both safety and efficacy limits the application of these results.

Atropine is an unselective antagonist of both M_3 (found on ciliary and sphincter muscle) and M_1 receptor cells in the eye (Tan *et al.*, 2005) hence prolonged therapeutic use would cause chronic dilation of the pupil and long term focusing difficulties (due to cycloplegia), although it has been shown that atropine does not reduce best corrected visual acuity (Fan *et al.*, 2007). A need for early presbyopic correction in myopic children using atropine would require both distance and reading correction. Invariably this would be with a multifocal lens with the undesired inconvenience associated with wearing reading spectacles at a young age. Weighing these complications in context of the relatively benign nature of most myopia, it appears as if atropine, for all its ability to retard myopia, may not be justified as the first line treatment choice in juvenile-onset myopes. However, for higher levels of myopia, in view of the ability of atropine to retard the principal structural corollary of myopia (i.e. axial length elongation), the risks of atropine use may be outweighed by the potential prophylactic benefits it would bring in minimising the risks of secondary pathology.

A pharmacological agent relatively selective for M_1 receptor sites has been trialled on humans in recent years with promising results (Siatkowski *et al.*, 2003; Tan *et al.*, 2005) following successful experiments on animal models (Leech *et al.*, 1995). Pirenzepine is not thought to carry any substantial toxic risks through histological examination of chick retinae (Leech *et al.*, 1995) although this was noted only after short-term use of the drug.

A study on children aged 8-12 years in the USA (n= 174) demonstrated a 50% reduction in myopia progression over one year (Siatkowski *et al.*, 2003). Pirenzepine 2% ophthalmic gel was also used to investigate its effects on East Asian children (n= 298) over one year (Tan *et al.*, 2005). This was a double-masked, placebo-controlled randomised parallel-group study, emphasising its rigorous experimental design (Khoo and Ng, 2006). A dose-dependent effect of the drug was shown, with a

mean increase in myopia of -0.47D after 12 months in a group taking pirenzepine twice daily, -0.70D in a group taking pirenzepine and placebo both once daily, and -0.84D in a third group taking a placebo drug twice daily. The difference between pirenzepine twice daily and placebo twice daily (0.37D, $p<0.001$) equated to a 44% reduction in myopia progression. Axial length differences were also significantly different between groups ($p=0.008$) and due to its selective pharmacological properties, cycloplegia and mydriasis induced was considerably less than with atropine. Additional adverse side effects were minimal and recovered on cessation of treatment.

The two human studies stated above establish the efficacy and safety profile of pirenzepine 2% gel. Further studies validating these measures and comparing the long-term efficacy and safety profile of pirenzepine with atropine over an extended period, particularly on cessation of treatment (Wong and Saw, 2004) are necessitated for the elucidation of pharmacological treatments of myopia.

CHAPTER 2

RATIONALE

2.1 INTRODUCTION

The high prevalence of myopia in children in East Asian countries such as China, Taiwan and Singapore is not only a cause of public health concern in the respective countries (Saw, 2003; Saw *et al.,* 2005), but has increased the global drive of myopia research into the prevalence, aetiology and therapeutic treatments of the condition.

However, there is a paucity of data in the United Kingdom (UK) regarding child refractive error distribution. It is over 40 years since a large-scale epidemiological study examined the distribution of child ametropia and associated biometric correlates in the UK (Sorsby *et al.,* 1961). In the intervening period most studies have been conducted either on specific populations e.g. microscopists (McBrien and Adams, 1997) and student undergraduates (Guggenheim *et al.,* 2003; Logan *et al.,* 2005), or on small sample sizes (Pointer *et al.,* 2001).

In addition, several demographical and technological changes have occurred since Sorsby and colleagues undertook their last study in South London. The most significant of these changes are:

1. Demographical variations in the population base
2. An increase in urbanised areas
3. Technological advances in measurement of ocular parameters

Demographical changes in recent years include a change in the ethnic composition of the UK. The ethnic composition of urban regions (i.e. cities) has altered considerably in recent decades, therefore data sampled from a predominantly White homogenous population by Sorsby *et al.,* (1961) is likely not to adequately represent the current demographical profile of these areas, including the city of Birmingham.

Currently, Whites make up 68.1% of the population of Birmingham based on 2004 projections of population estimates (National Statistics Office, 2001), compared to 1961 data when this proportion was over 95% (Table 2.1.1).

		Ethnic Group					
Year	Total	White	% White	Black	% Black	South Asian	% Asian
1961[¶]	1,097,000	1,055,000	**96.2%**	16,000	**1.5%**	10,000	**0.9%**
2004[§]	977,099	687,406	**70.4%**	59,835	**6.1%**	190,689	**19.5%**

[¶] Sutcliffe and Smith, 1974. Black: Black Caribbean only. South Asian: Indian and Pakistani only.
[§] 2004 Mid-Year Projected estimates based on Census data 2001.
Table S101 Sex and Age by Ethnic Group. Census output is Crown copyright and is reproduced with the permission of the Controller of HMSO and the Queen's Printer for Scotland.

Table 2.1.1 The population of Birmingham as a function of ethnic group. The table focuses primarily on the 3 major ethnic groups in the city and serves to illustrate the shift in population base since 1961

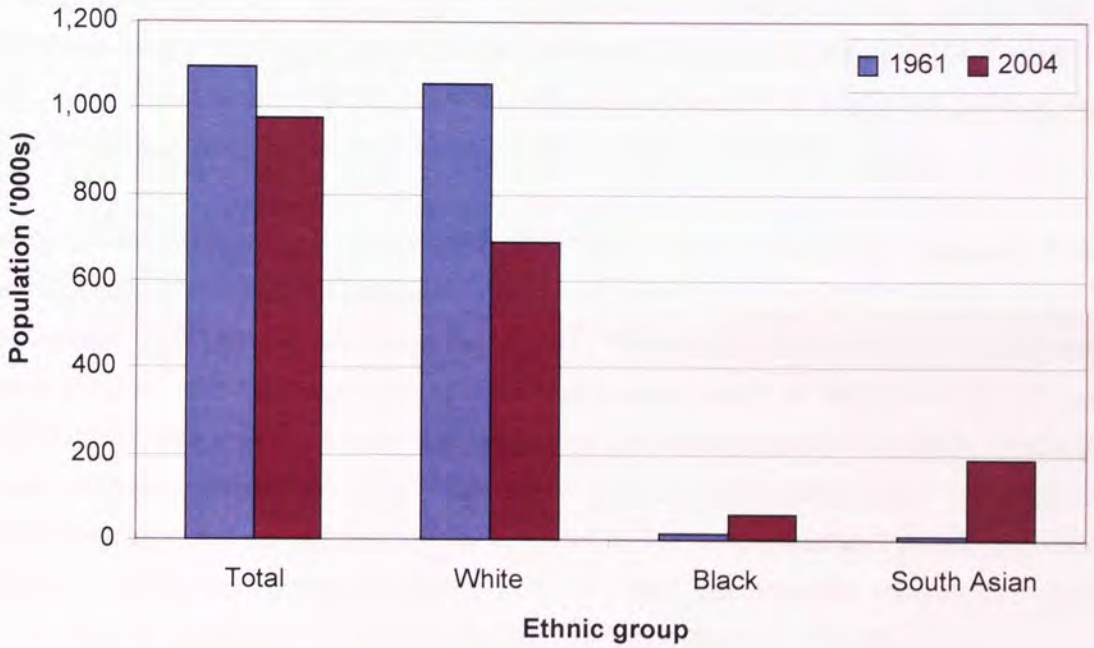


Figure 2.1.1 Changes in Birmingham demographics by ethnic group between 1961 and 2004. Sources are as in Table 2.1.1

Although direct comparison between data from the Census of 1961 with that of 2004 estimates is limited due to changes in boundary/ward structure and methods of analysis between the 2 surveys, Figure 2.1.1 does highlight strongly the substantial immigration of ethnic minorities into Birmingham over the past 5 decades. Furthermore, considering that the total population of Birmingham has remained relatively static since 1961 (Table 2.1), it can also be concluded that there has been a significant emigration of Whites out of Birmingham.

These statistics are a fair reflection of the demographical composition of many UK cities, with ethnic minorities congregating in cities to ensure employment, fill employment gaps in the market and foster a community with fellow minority members. Therefore, it can be seen that epidemiological data on refraction published in 1961 is not an accurate representation of UK cities today due to intrinsic ethnic variations in myopia susceptibility (Morgan and Rose, 2005) and the ethnic shift in the UK urban population.

The author is unaware of studies that have specifically examined the difference in prevalence between White, Black and South Asian children. Recent data from the Sydney Myopia Study (Ip *et al.*, 2007) determined a considerably higher myopia prevalence in South Asian 12 year olds (31.5%, 95%CI: 21.6-41.4) compared to European White children (4.6%, 95%CI: 3.1-6.1). Seven year old South Asian children also had a higher odds ratio (OR) for myopia compared to White children from the recent ALSPAC[1] study in Bristol (Williams *et al.*, 2005), though the increased risk was not found to be significant (OR 1.81, 95%CI: 0.86-3.80). However, none of the above studies stated a prevalence level of myopia in Black children. Additionally, data from the CLEERE[2] study (Kleinstein *et al.*, 2003) found similar myopia prevalence levels between White and Black children (4.4% *vs.* 6.6%, p= 0.69), though Asian children in this study were of East Asian origin.

Further to ethnic differences, the UK since 1961 has become increasingly urbanised. Recent reports state that over half the global population now live in cities (http://news.bbc.co.uk/go/pr/fr/-/1/hi/sci/tech/4561183.stm, accessed 13/08/2007). The size of Birmingham has also increased in the past 4 decades, with 1961 estimates of the city coverage resting at 206.98km² (51,147 acres, Sutcliffe and Smith, 1974) *vs.* current estimates at 267.80km² (National Statistics Office, 2001). The current population density for Birmingham based on 2001 Census data is 3,649 people per km². Comparing this to the current average for England (377.2 people per km²) provides a strong indication of the overcrowding instigated by an urbanised, populous city such as Birmingham. Urbanisation is purported to be a myopiagenic risk factor (Section 1.4.2.5).

A third change since the study by Sorsby and colleagues (1961) is that of measurement accuracy and technological advances. Axial length was not measured directly, but calculated by this UK-based research group over 40 years ago (see Appendix D by Bennett in Sorsby *et al.*, 1961). Calculation coalesces small measurement errors made on dependent components and can result in a large error in calculation (Ludlam *et al.*, 1965). However major progresses in technology over recent decades now enable direct non-contact measurements of both refractive error and biometry to occur to a high degree of accuracy and repeatability (Chapter 3).

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[1] Avon Longitudinal Study of Parents and Children
[2] Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error

2.2 THESIS AIMS AND OBJECTIVES

In view of the professed increase in child myopia prevalence globally and the variation in demographical profiles of cities in the UK since the report by Sorsby and colleagues (1961), it is clear that a current large scale epidemiological study of refractive error is warranted to derive determinants and distributions of refractive error in children.

This is the rationale behind the Aston Eye Study (AES) – a prospective population-based cross-sectional epidemiological study examining the distribution of ametropia in an urban child population, with particular focus on myopia and the effects of age and ethnicity. In addition, the AES will be the first study to examine the prevalence of ametropia and biometric correlates in White, South Asian and Black children specifically.

Protocols and definitions will be constructed to facilitate comparison of results with those of other child population-based studies i.e. the Sydney Myopia Study (Ojaimi *et al.,* 2005) and the Refractive Error Study in Children (Negrel *et al.,* 2000). The age groups targeted by the AES are children aged 6/7 years of age and 12/13 years of age. The rationale for enrolling 6/7 year old children (Year 2) is to provide pre-myopic data, as it is assumed that the majority of these children will be emmetropes/mild hyperopes. Children aged 12/13 years (Year 8) will provide a strong indication of the cross-sectional distribution of school myopia prevalence in UK urban children as it is thought that the majority of juvenile-onset myopia occurs by this age. As both cohorts (Year 2 and Year 8) will be present at the same respective school for a few years, the potential for longitudinal follow-up on both groups is also feasible.

Schools will be invited to participate using random cluster sampling methods (see Chapter 5) after consideration of age, ethnicity and socioeconomic status.

Measures of ocular biometry and anthropometry (height and weight) will be recorded in each participant to derive links between refraction and eye shape and to ascertain conclusions on the morphological changes in the eye contributing to a change in refraction. In addition, risk factors for myopia will be proposed based upon questionnaire responses from parents and their children. These responses will be analysed in multivariate models to determine the risk factors independently associated with myopia.

Notwithstanding the findings of the study, it is appreciated that the AES cohort will represent an urban sample. In order to extrapolate AES findings to represent the entire UK child cohort, a separate study is to be conducted by the University of Ulster, Northern Ireland, on a relatively homogenous population base. This study however does not form part of the thesis.

In recent years, although the benefits of child school vision screening have been emphasised (Logan and Gilmartin, 2004) and the number of children under the age of 11 years visiting an optometrist has been found to be disproportionately low compared to the overall population (Guggenheim and Farbrother, 2004), there has been a gradual attenuation of school vision screening in many areas, as reviewed by Snowdon and Stewart-Brown (1997).

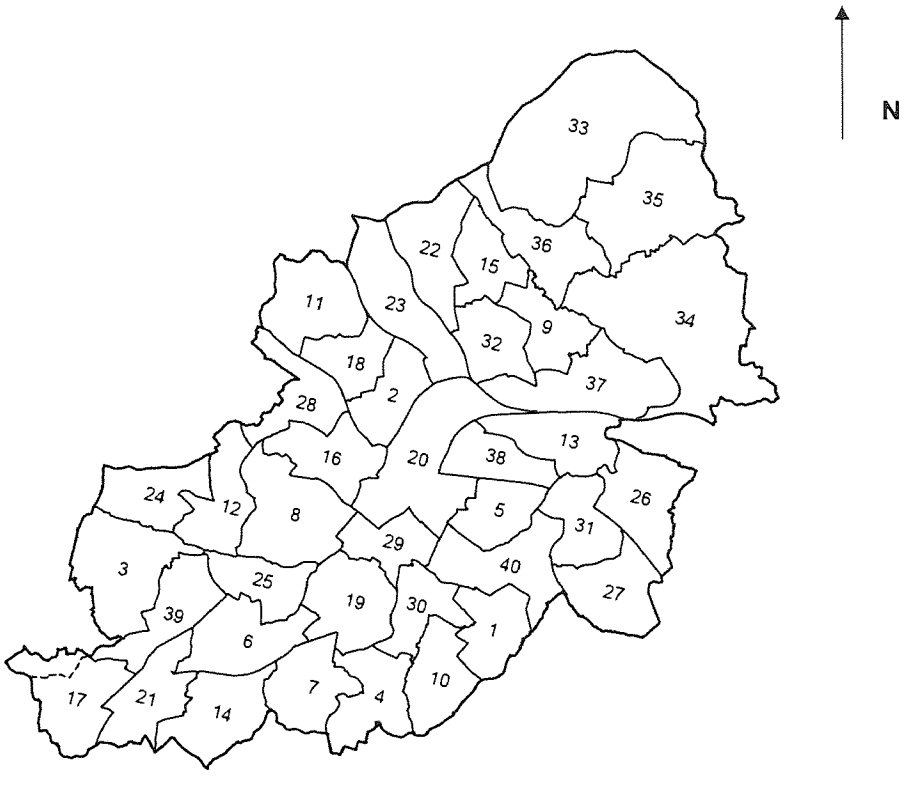
A report by Hall and Elliman (2003) states that although the benefits of screening pre-school children at a young age of 4-5 years are clear with regards to the detection and treatment of 'non-incapacitating' visual defects (i.e. amblyopia and refractive error), it does not appear to be justified to screen children thereafter during primary school (5 years of age and upwards). In addition, the need for screening children at an older (secondary school) age is equivocal and will only become clearer with further research (Hall and Elliman, 2003).

Therefore, there appears to be a dearth of evidence on which to base policy decisions regarding vision screening in the UK (Rahi and Dezateux, 1997). One of the aims of the present study thus is to evaluate the report by Hall and Elliman (2003) in light of findings and identify the proportion of children with uncorrected refractive error, many of whom will have undergone pre-school screening at a young age. If the number of uncorrected children detected is sufficiently high, a case may be argued to reintroduce screening at later ages to identify uncorrected ametropes. It should be recognised that AES data will provide an underestimation of the proportion of children with visual defects as protocols will identify only those children with refractive defects and significant oculomotor anomalies (large angle squint/latent deviations) and not those children with non-refractive visual defects.

Birmingham is the city in which the AES is to be conducted. Due to the city's disproportionately high ethnic mix compared to England (31.9% *vs.* 10.5% non-White residents respectively), an ethnically diverse sample is expected from which important information will be gained on the susceptibility of ethnic groups to refractive error within an urban environment.

2.3 BIRMINGHAM

Birmingham is a city of population 977,099, of which 14.8% (144,978) are aged 5-14 years. Divided into 40 wards (Figure 2.3.1), Birmingham covers an area of 267.8 km^2.



Key to Wards

1 Acock's Green	11 Handsworth Wood and West Handsworth	21 Northfield	31 Stechford
2 Aston	12 Harborne	22 Oscott	32 Stockland Green
3 Bartley Green	13 Hodge Hill	23 Perry Barr	33 Sutton Four Oaks
4 Billesley	14 King's Norton	24 Quinton	34 Sutton New Hall
5 Bordesley Green	15 Kingstanding	25 Selly Oak	35 Sutton Trinity
6 Bournville	16 Ladywood	26 Shard End	36 Sutton Vesey
7 Brandwood	17 Longbridge	27 Sheldon	37 Tyburn
8 Edgbaston	18 Lozells and East Handsworth	28 Soho	38 Washwood Heath
9 Erdington	19 Moseley and King's Heath	29 Sparkbrook	39 Weoley
10 Hall Green	20 Nechells	30 Springfield	40 Yardley

Figure 2.3.1 Birmingham and its wards. Reproduced with permission

A higher myopia prevalence within AES participants is hypothesised compared to estimates from the Sydney Myopia Study (Ojaimi *et al.*, 2005). It is predicted that children in Birmingham in general spend a greater amount of leisure time indoors on computers, video games and the Internet in relation to their Australian counterparts, which may contribute to the anticipated increase in myopia prevalence. Furthermore, the higher proportion of non-White subjects in the AES compared to the Sydney Study may augment the prevalence level. South Asians have shown a higher myopia prevalence than Whites (Ip *et al.*, 2007) and it is postulated that the higher proportion of ethnic participants will result in a higher UK prevalence estimate.

Recent work by the ALSPAC team in Bristol (n= 6,700) determined a myopia prevalence of 13.6% in 7 year old children (Williams *et al.*, 2005). However, due to the non-cycloplegic nature of their study (closed-field autorefraction potentially inducing proximal accommodative effects), which can overestimate myopia prevalence levels in children compared to cycloplegic autorefraction (Fotedar *et al.*, 2007), it is anticipated that AES Year 2 prevalence estimates will be lower than that determined by the ALSPAC team, notwithstanding a minor age difference between the cohorts.

In summary, potential therapies and strategies to minimise the impact of myopia are currently being devised and implemented, although it is vital that these therapies are targeted to children most susceptible to myopiagenesis. This requires a solid understanding of the aetiological processes and distribution of myopia in children. The AES aims to provide significant updated epidemiological data on the distribution of refractive error in children residing in a UK conurbation alongside biometric corollaries. It will be one of the first studies reporting refractive error and ocular biometry in White, South Asian and Black children specifically. In addition, potential myopic risk factors will be ascertained through the use of questionnaires.

CHAPTER 3

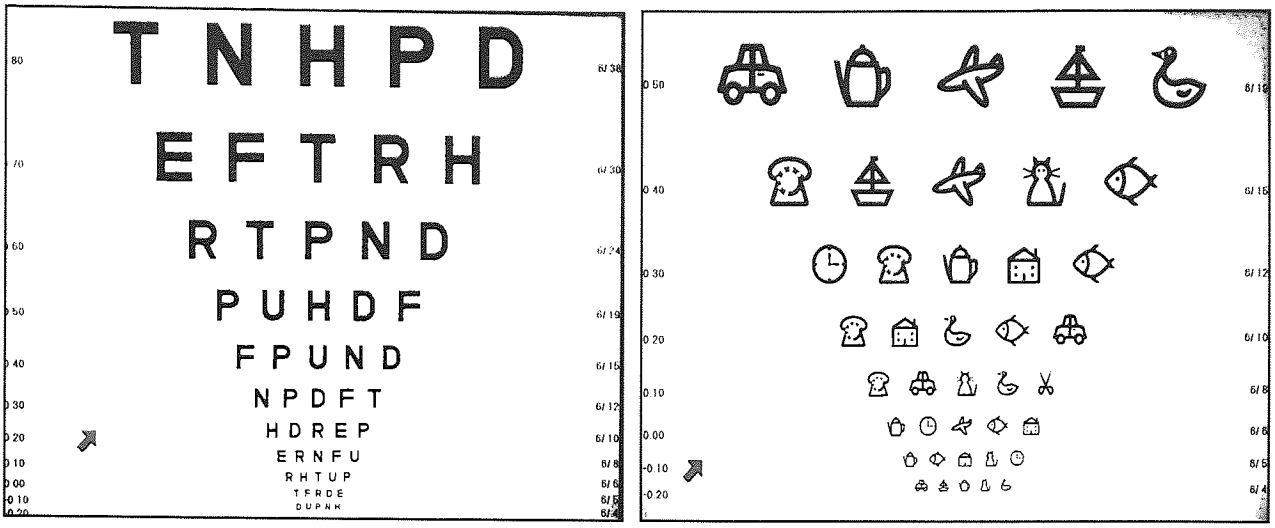
INSTRUMENTATION

3.1 INTRODUCTION

The following chapter details the instrumentation utilised in the AES and their operation. Complete methodological details are presented in Chapter 5.
In summary, vision, oculomotor balance, height, weight, refractive error and ocular biometry recordings were taken participating subjects aged 6/7 years (Year 2) and 12/13 years (Year 8) of age. Visual acuity was determined if the child presented with spectacles. Refraction and ocular biometry were conducted with the child under cycloplegia.

3.2 VISION/VISUAL ACUITY

Vision and visual acuity were measured using the portable Test Chart 2000 (Thompson Software Solutions, Herts) installed on a laptop and calibrated for a 3 metre working distance.
The Test Chart 2000 contains both Bailey-Lovie and Snellen charts with notation in conventional logMAR and Snellen form. The Bailey-Lovie chart with logMAR notation was employed for use in the AES (Figure 3.2.1A) as it has several advantages over the Snellen chart, namely a geometric progression in letter size. The chart also permits examination at varying distances, due to an equal number of optotypes per line (Bailey and Lovie, 1976). Using Bailey-Lovie optotypes throughout the study prevented a variation in optotype from confounding recordings. However the order of optotype presentation was changed frequently between children, minimising the effect of learning on the assessment. Pre-literate children were shown a picture test chart and asked to identify pictures presented (Figure 3.2.1B). There were 10 pre-literate children in Year 2 and one child in Year 8 for whom the picture chart was necessitated.
A disadvantage of the portable chart was that ambient room lighting levels were not controlled from one school to the next. The laptop was set to full screen intensity and aligned perpendicular to the line of sight of each child at the beginning of each session. However, though room lights were switched on and the test chart kept out of bright sunlight, ambient light levels could not be precisely controlled. The luminance of the test chart (measured in normal indoor lighting conditions) based on the average of 5 readings taken with a hand-held light meter was 116cd/m^2.



A. Bailey-Lovie chart **B. Picture chart**

Figure 3.2.1 The computerised test charts used in the AES.

3.3 REFRACTIVE ERROR

Refractive error was measured using objective infra-red autorefraction, which has been shown to be a much more reliable method of determining refractive status compared to retinoscopy and subjective refraction (Zadnik *et al.,* 1992). The Shin Nippon SRW-5000 (Shin Nippon, Japan) autorefractor was employed for use in the study under cycloplegic conditions.

3.3.1 Cycloplegia

Many large-scale eye studies conducted on children in recent years have used cycloplegia and a consensus exists proposing the control of accommodation as a pre-requisite to a valid research protocol (Zadnik *et al.,* 1992; Zhao *et al.,* 2004; Khoo and Ng, 2006; Fotedar *et al.,* 2007).

Although it may be disputed that cycloplegia leaves the eye in an unnatural state, paralysis of accommodation has been comprehensively shown to reduce variability in results and increase accuracy in refraction (Zadnik *et al.,* 1992; Zhao *et al.,* 2004). This is especially true when employing machines to measure refraction, as a poor/variable retinoscopy reflex or variable answers on subjective refraction may normally raise suspicion to a practitioner that a child may be a pseudomyope/latent hyperope; this is not picked up by an autorefractor. Recent work from the Sydney Myopia Study (Fotedar *et al.,* 2007) has advocated the use of cycloplegia with autorefraction to minimise the overestimation of myopia prevalence.

The type of cycloplegic drop used along with dosage administered varies between studies. Many studies have also incorporated the use of a corneal anaesthetic to minimise discomfort caused by cycloplegic drops. The Orinda Longitudinal Study of Myopia (OLSM) used 0.5% proparacaine (anaesthetic) followed by 2 drops of tropicamide HCl 1% 5 minutes apart, on a predominantly Caucasian sample (Zadnik *et al.,* 1993). The follow-on study to the OLSM, The Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error (CLEERE) incorporated the use of 0.5% proparacaine immediately followed by 1% tropicamide HCl and 1% cyclopentolate HCl (1 drop of each) at its three additional sites. However Orinda, which was the original OLSM site from which the majority of Caucasians for the CLEERE study were recruited, maintained its use of tropicamide alone. The use of cyclopentolate at the additional CLEERE sites was due to the concern of inadequate cycloplegia in darker-skinned children recruited (Zadnik *et al.,* 2003).
The Sydney Myopia Study administered 0.5% amethocaine HCl as a corneal anaesthetic prior to the instillation of 1 drop of cyclopentolate 1% and 5 minutes later, a drop of tropicamide 1% to induce cycloplegia in their cohort (Ojaimi *et al.*, 2005). Phenylephrine HCl 2.5% was also used in a small proportion of children who were slow to dilate, though primarily as a requirement of maximal mydriasis for fundus photography, as its effect on ciliary muscle is as yet equivocal (Gilmartin, 1998).

Cyclopentolate hydrochloride is an extensively used paediatric cycloplegic drug. It has a distinct advantage over its predecessor, atropine, in that cycloplegia occurs between 30-45mins after instillation (Siu *et al.,* 1998) and dissipates between 6 to 24 hours after instillation (Mutti *et al.,* 1994), whereas atropine requires repeated instillation for several days to produce adequate and deep cycloplegia. The level of residual accommodation at which cycloplegia can be considered sufficient for refractive purposes has been professed at less than 2.00D (Milder, 1961); this was the value adopted by the AES for determining adequate cycloplegia.
Cyclopentolate, atropine and tropicamide each act as non-selective muscarinic antagonists preventing the binding of acetylcholine in the eye, principally at the site of iris sphincter and ciliary smooth muscle, which results in mydriasis and cycloplegia respectively (Eperjesi and Jones, 2005). It has been shown to produce effective cycloplegia in children independent of iris colour, though a longer period of time is required in eyes with heavily pigmented irides to achieve sufficient cycloplegia compared to lighter irides (Lovasik, 1986; Chan and Edwards, 1994).

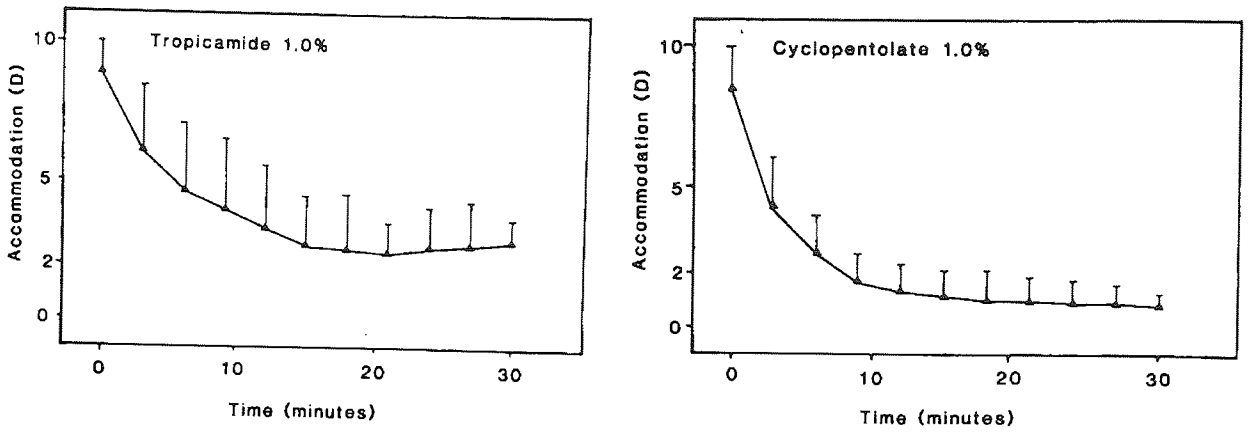


Figure 3.3.1 A comparison of the temporal nature and depth of cycloplegia on undergraduate students with 2 agents: Tropicamide 1% and Cyclopentolate 1%. One-tailed error bars represent one standard deviation from each mean. Modified with permission from Rosenfield and Linfield (1986)

The depth of cycloplegia achieved has been shown to be greater with cyclopentolate 1% compared to tropicamide 1% (Figure 3.3.1, Rosenfield and Linfield, 1986; Adams *et al.*, 1992, Egashira *et al.*, 1993) although it is suggested that the difference between the two types of eye drops is not significantly notable (Adams *et al.*, 1992; Mutti *et al.*, 1994).

The AES feasibility study (Chapter 4) incorporated a cycloplegic regime of 0.5% proxymetacaine prior to tropicamide HCl 1%, 1 drop of each agent in both eyes. However, the regime for cycloplegia for the main AES study was modified to 1 drop of proxymetacaine 0.5% followed by 1 drop of 1% cyclopentolate HCl in both eyes (Chapter 5).

3.3.2 Shin Nippon SRW-5000

The ideal autorefractor should be accurate, repeatable, practitioner-friendly and provide an open field-of-view for the subject to minimise the confounding effects of proximal accommodation. The Shin-Nippon SRW-5000 (Shin Nippon, Japan) is a binocular, infrared, open view autorefractor used in the AES and is reported to read refractive error measurements between ±22.00D sphere and ±10.00D cylinder in 0.125D steps. Cylinder axes are measurable to within 1° (Mallen *et al.*, 2001). An autorefractor has the evident advantage over subjective refraction in that it is an objective method and minimises intra-reading variation, more so in combination with cycloplegia (Khoo and Ng, 2006). The open-field nature of the Shin-Nippon (Figure 3.4.1B) has the distinct advantage of minimising proximal accommodative effects potentially induced in closed-field autorefractors, which may give rise to erroneously over-minused readings i.e. instrument myopia.

3.3.2.1 Mechanism of operation

The SRW-5000 calculates refractive error in two stages (Figure 3.3.2). Once the eye is aligned by the operator, the first stage consists of the machine imaging an infrared ring of light (λ= 850nm) onto the subject's retina and capturing its reflection onto a CCD[1] sensor by means of a semi-reflecting mirror. The ring target is brought into approximate focus on the retina by a moveable lens within the machine (Mallen *et al.*, 2001).

The second stage involves the digital processing and refinement of this image in multiple meridians to derive a sphero-cylindrical refraction (Mallen *et al.*, 2001). The size of the ring target imposes a minimum pupil diameter of 2.9mm, as in pupils below this size, the ring becomes fragmented and the SRW-5000 is unable to take a reading. An updated model, the Shin Nippon NVision-K 5001 (Shin Nippon, Japan) has replaced the ring target with three arcs of infrared light, enabling measures on pupil sizes ≥ 2.3mm (Davies *et al.*, 2003).

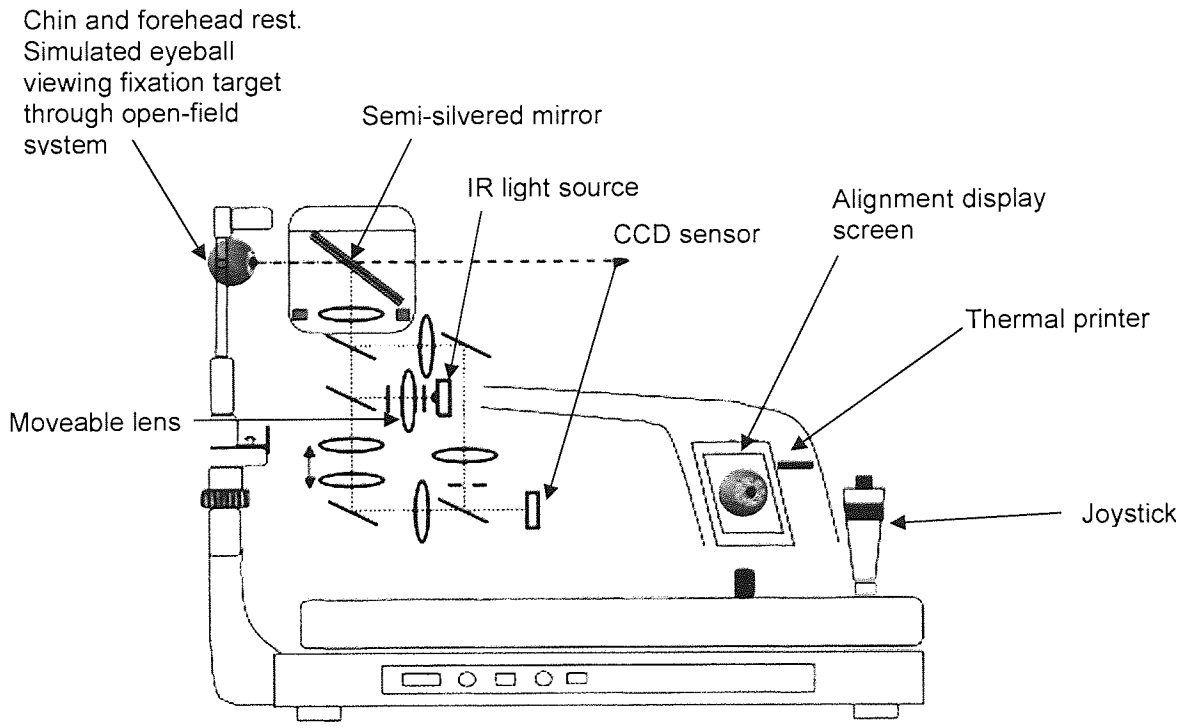


Figure 3.3.2 Schematic diagram of the Shin Nippon SRW-5000. Modified with permission from Mallen *et al.*, (2001)

The measurement procedure on the SRW-5000 involves the patient resting their chin on the instrument head rest and looking through the semi-reflecting mirror at a distance fixation target. With the benefit of a display screen for the investigator, the ring target is focussed through the pupil and the joystick button depressed to record a measurement. The patient experiences a transient red ring

[1] Charge-Coupled Device

flash of light during each measurement. Individual recordings are printed out after taking a series of measurements in both eyes.

The SRW-5000 has been clinically evaluated for accuracy and reliability in both adults (Mallen *et al.*, 2001) and children (Chat and Edwards, 2001). Accuracy defines how close a test result lies in comparison to an accepted 'gold standard', the reference in this case being subjective refraction. Reliability can be split into two categories; repeatability, which is a measure of agreement between values taken under identical conditions (i.e. at the same time and by the same examiner) and reproducibility, which is a measure of agreement between values taken at different times and by different examiners (Zadnik *et al.*, 1992, Chat and Edwards, 2001).

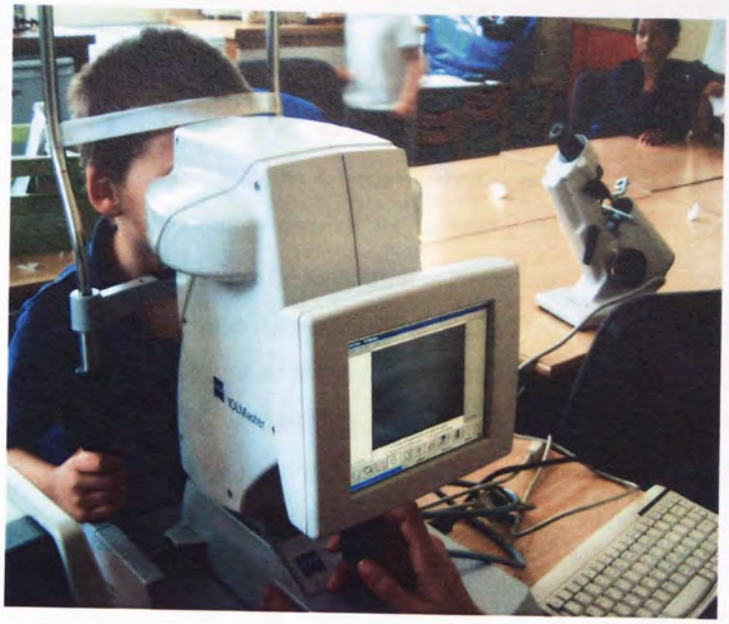
SRW-5000 measurements on adults (n=100) have established that it is an accurate and reliable autorefractor comparing well to both subjective refraction and other autorefractors (Mallen *et al.*, 2001). Furthermore, the device has been found to be both accurate and reliable on children aged between 4-8 years (n= 53), though the authors advocate that cycloplegia should be used for greatest accuracy (Chat and Edwards, 2001).

3.4 BIOMETRY

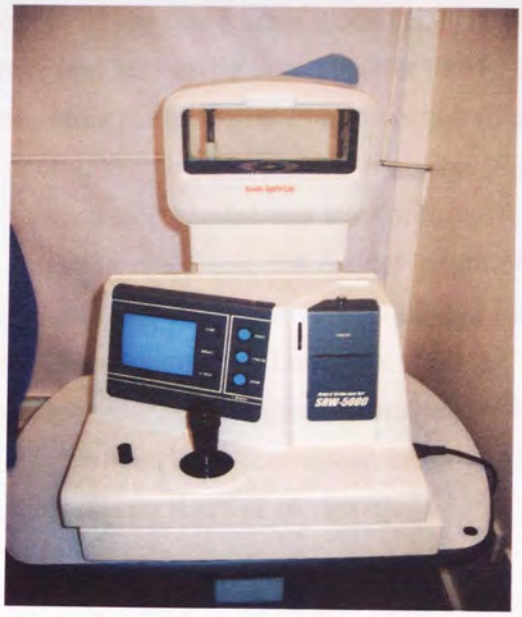
In addition to refractive error, ocular biometry measures recorded in the AES were axial length (AL), corneal radius of curvature (CR) and anterior chamber depth (ACD).

Over recent decades, AL and ACD have been assessed using A-scan ultrasound. However, based upon the principle of Partial Coherence Interferometry (PCI), a non-contact method of AL assessment has been devised. The *Zeiss* IOLMaster (Jena, GmbH), a commercially available device primarily intended to aid intraocular lens implant (IOL) calculations (Figure 3.4.1A) has been found to measure AL and ACD to a higher resolution (±0.01mm) compared to that determined by conventional ultrasound methods (±0.15mm), as reported by Santodomingo-Rubido *et al.* (2002). The IOLMaster also has the facility to measure corneal radius of curvature using image analysis methods (similar to a conventional keratometer), eliminating the requirement for a separate keratometric device.

Furthermore, the IOLMaster eradicates the necessity for corneal contact as required by A-scan ultrasound, making it considerably patient-friendly and more likely to be accepted by both children and parents (Sheng *et al.*, 2004).



A



B

Figure 3.4.1 A: The *Zeiss* IOLMaster during biometric measurement on a Year 2 child. B: The Shin Nippon SRW5000 with open-field viewing system

3.4.1 Mechanism of Axial Length measurement

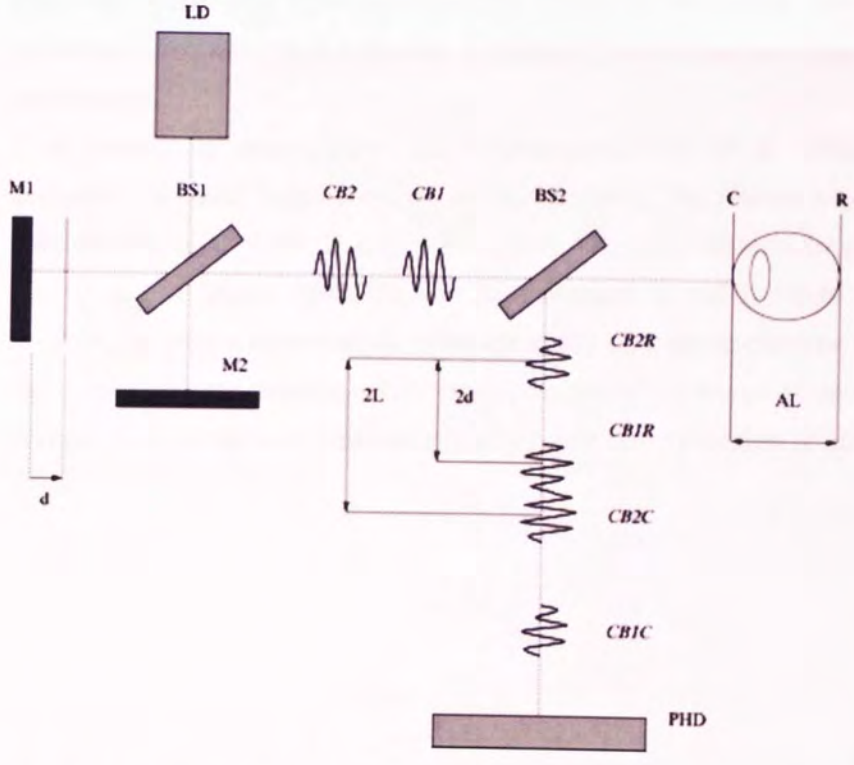


Figure 3.4.2 Operating mechanism of the IOLMaster for AL measurement. Reproduced with permission after Santodomingo-Rubido *et al.*, (2002)

An infrared laser beam (λ= 780μm) of short coherence length emitted by a laser diode (LD) is split up into 2 equal coaxial beams CB1 and CB2 via 2 mirrors (M1 and M2) and a beam splitter (BS1). Both beams enter the eye, where reflections take place at the retina (CBR 1 and 2) and cornea (CBC 1 and 2) to give rise to 4 beams that are recorded by a photodetector (PHD) in the machine (Figure 3.4.2). By moving one of the mirrors (M1) at constant speed and measuring interference fringes between reflected beams until a particular interference condition is fulfilled, the optical length of the eye is determined (Hitzenberger, 1991). This is then translated into a geometrical (axial) eye length by taking account of the eye's mean refractive index (1.3549), as reported by Lam *et al.* (2001).
The laser light emitted from the IOLMaster is reflected from the retinal pigment epithelium layer (RPE) as opposed to the internal limiting membrane (ILM) in ultrasound. A conversion factor has thus been incorporated into the IOLMaster to account for this discrepancy (Lam *et al.*, 2001).

The IOLMaster has been shown to be highly accurate in measuring axial length (Santodomingo-Rubido *et al.*, 2002) compared to ultrasound (mean difference: 0.02 ± 0.32mm, p=0.47). A study using the IOLMaster to calculate IOL power in patients (n= 51 eyes) undergoing phacoemulsification showed a significantly longer axial length (mean difference: 0.15mm, p<0.001) compared to that obtained by ultrasound (Rose and Moshegov, 2003), a finding in agreement with a study on children where IOLMaster readings on average were 0.14mm longer than ultrasound (Carkeet *et al.*, 2004). However Rose and Moshegov (2003) also determined a 35% improvement in postoperative refractive error with the IOLMaster, suggesting that ultrasound may have been underestimating true axial length.
With respect to repeatability, Santodomingo-Rubido *et al.* (2002) found very close agreement between repeated measures of all components. Repeated measures of CR showed a mean difference of 0.00 (95%CI: -0.04 – 0.04mm). The mean difference between repeated measures of AL was 0.00 ± 0.04mm (p=0.75) and with respect to ACD, mean difference was -0.01 ± 0.08mm (p=0.24). A recent examination of repeatability on myopic children echoed these findings (Kimura *et al.*, 2007), with repeatability of AL measures within ±0.05mm of each other (95% limits of agreement) compared to ultrasound repeatability which has been reported at ±0.35mm (Sheng *et al.*, 2004).

3.4.2 Mechanism of Corneal Radius measurement

The IOLMaster measures central corneal radius using image analysis methods (Figure 3.4.3). Six points of light (fixation light λ= 590μm) arranged in a 2.3mm diameter hexagonal pattern (Elbaz *et al.*, 2007) are imaged onto the mid-peripheral cornea and brought into focus. The imaged distance between three opposite pairs of light points is measured by the machine and analysed in relation to the actual physical separation of the points to determine the curvature in that meridian (IOLMaster manual, 2003). The three toroidal surface curvatures can then be used to derive the overall central radius of curvature in the two principal meridia (Burek, 1990). Corneal radius measures have been shown to agree well with conventional Javal-Schiotz keratometry (mean difference: 0.03mm, 95%CI: -0.13 – 0.01mm; Santodomingo-Rubido *et al.*, 2002)

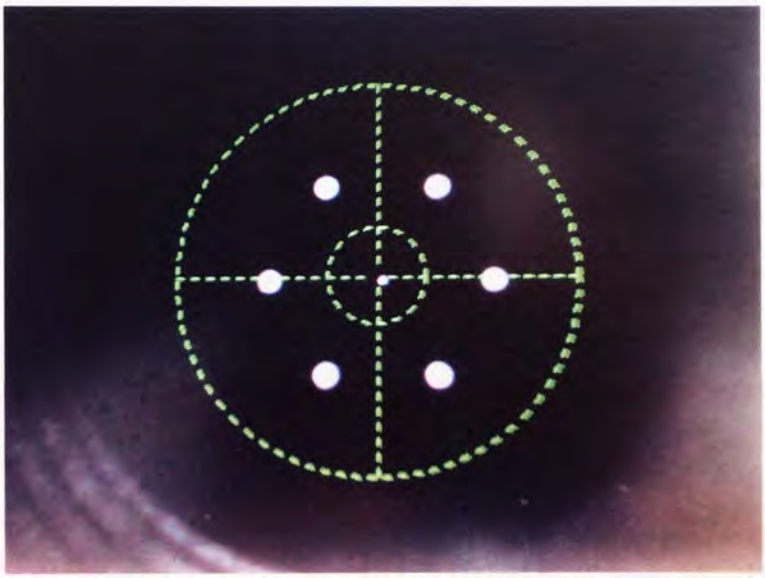


Figure 3.4.3 Set-up of IOLMaster on model eye. The centre of the green graticule target is aligned with the central light spot before a reading is taken

On depression of the joystick once the points are aligned with the graticule target, 5 short measurements of corneal radius are taken over a period of 0.5 seconds and their average displayed as the CR values along both principal meridians.

3.4.3 Mechanism of Anterior Chamber Depth measurement

The anterior chamber depth (ACD) is measured using a photographic technique by directing a 0.7mm width optic section beam through the anterior chamber at 38 degrees to the angle of fixation (*Zeiss* IOLMaster manual, 2003). The internal software of the machine measures the distance between the corneal vertex and the anterior lens section to calculate the depth of the anterior chamber (Santodomingo-Rubido *et al.*, 2002; Elbaz *et al.*, 2007). The correct position for

measurement is found by aligning the sections of cornea and lens within a box target (Figure 3.4.4). On depression of the joystick, 5 readings of the ACD are taken successively and reported alongside an average value. ACD measures have shown to be deeper than with A-scan ultrasound (mean difference: 0.15mm; 95%CI: -0.03mm - 0.34mm, $p<0.01$), possibly due to the temporal positioning of the illumination source (Lam *et al.*, 2001).

The use of cycloplegia in child ocular biometry has been advocated for optimal repeatability (Sheng *et al.*, 2004), in particular with ACD measures, which are sensitive to fluctuations in accommodation (*Zeiss* IOLMaster manual, 2003).

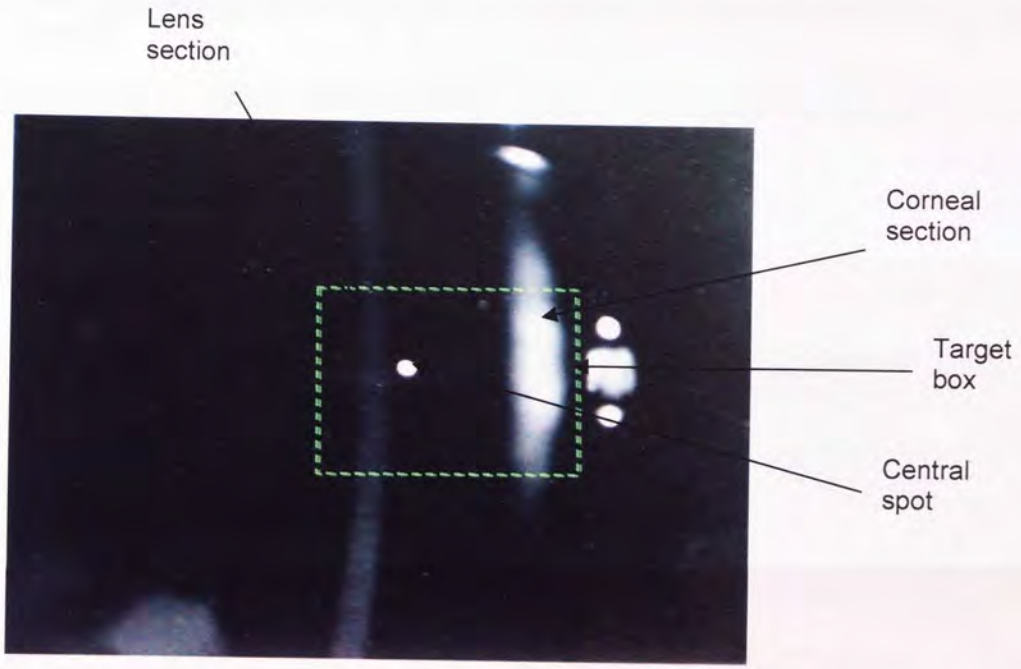


Figure 3.4.4 Set-up for measurement of the anterior chamber depth using the IOLMaster. The machine is aligned once the central spot is focused near to the lens section with both sections placed within the target box

Overall, the IOLMaster is a highly accurate, repeatable, practitioner and patient-friendly machine of particular benefit in child studies due to a lack of invasive corneal contact.

3.5 CALIBRATION

The City 2000 test chart screen was calibrated regularly by using a preset function to calibrate screen size. Calibration involved the physical measurement of letters on the computer screen and the insertion of this distance into the program. The letter size was then automatically adjusted for the working distance required (3 metres).

The Shin Nippon SRW-5000 was calibrated at periodic intervals using a standardised model eye (Figure 3.5.1). The eye was clipped on to the device and 5 readings taken on each side (left and right). The accepted tolerance for model eye data is detailed in Table 3.5.1.

Model eye sphere reading = -4.75D at a vertex distance of 12mm	
Sphere Tolerance	Cylindrical Tolerance
± 0.25D	± 0.25D

Table 3.5.1 Accepted tolerance level of Shin Nippon SRW 5000 model eye (Shin Nippon SRW-5000 manual)

All calibration readings taken on the Shin Nippon remained within tolerance and deemed the device valid for use in the AES.

Figure 3.5.1 Model eye set-up on the Shin Nippon

The IOLMaster was calibrated at regular intervals during the term of the AES. This was conducted using calibration apparatus which again consisted of a dummy eye set to predetermined standards within a set tolerance (Table 3.5.2 and Figure 3.5.2).

	Calibration value (mm)	**Tolerance (mm)**
Axial length	20.82	± 0.05
Corneal radius	7.18	± 0.03
Anterior chamber depth	3.22	± 0.10

Table 3.5.2 Calibration values of the IOLMaster and accepted tolerance limits

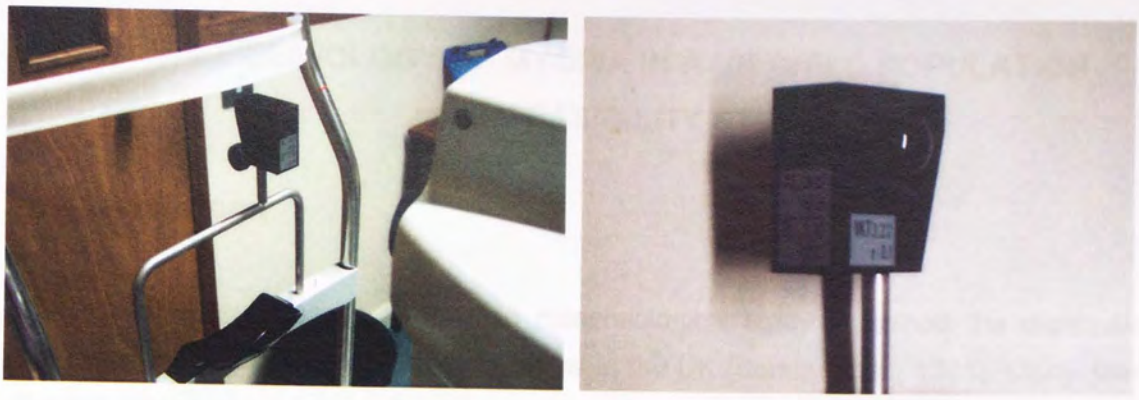


Figure 3.5.2 Calibration apparatus and set-up of the IOLMaster

The IOLMaster remained within the accepted limits of tolerance during each calibration and was thus deemed fit for use throughout the AES time period.

CHAPTER 4

EPIDEMIOLOGY OF MYOPIA IN A UK CHILD POPULATION - A FEASIBILITY STUDY

4.1 INTRODUCTION

It is over 40 years since a large-scale epidemiological study examined the distribution of child ametropia and associated biometric correlates in the UK (Sorsby *et al.*, 1961). Many demographical changes have occurred since Sorsby and colleagues undertook their study in South London. These include a greater level of technological advancement both in terms of visual demand (i.e. increasing use of VDU's, Dayan *et al.*, 2005) and measurement of ocular function now available (i.e. non-contact methods of ocular biometry).

Myopia prevalence has been shown to vary with ethnicity (Kleinstein, 2003) and it is clear from the ethnic composition of UK cities such as Birmingham (Section 2.1) that results derived over 40 years ago would be unrepresentative for the current population. Thus an updated epidemiological study of UK child refractive error is warranted to determine the prevalence levels of ametropia in the urban population and determine groups of children particularly susceptible to the condition.

4.2 FEASIBILITY STUDY

In view of the requirement of an updated epidemiological survey of UK child refractive error, the Aston Eye Study was instigated in October 2005 (Chapter 5). In order to determine whether the AES protocol was suitable, a feasibility study was undertaken in February 2005 at a primary school in the West Midlands.

The principal rationale behind the feasibility study was to confirm and validate the logistical procedures involved in the set-up of the main AES study. This included all procedures, from the initial contact with the head teacher, children and their parents, the handling of consent forms, the physical set-up of equipment as well as the management of young children and their responses to the procedures (particularly the instillation of cycloplegic drops).

All children aged between 5 and 6 years (Year 1) attending Perton First Primary school in Wolverhampton, West Midlands were invited to participate in the feasibility study. Approval for the feasibility study was obtained from the Aston University Ethics Committee (Appendix 1) and the study adhered to the tenets of the Declaration of Helsinki (http://www.wma.net/e/policy/pdf/17c.pdf, accessed 20/06/2005).

4.3 METHODOLOGY

The methodology of the feasibility study forms the basis of the main study (Chapter 5). The participating primary school - Perton First School - is located in Perton, a village in the county of Staffordshire. The area has a high ethnically homogenous population (95.8% White, National Office for Statistics, 2001) and is a region of low deprivation according to Index of Multiple Deprivation values constructed in the year 2000 (Perton Central = 6.17, see Section 5.1 for further explanation of values).

Once a meeting with the school Head teacher had occurred and agreement obtained to conduct the study at the school, consent forms were distributed to all Year 1 pupils (n= 60) detailing the study procedures. Written consent was obtained from the parent in advance and verbal assent gained from the child on the day of the study. In addition, an information sheet was distributed with the consent form detailing the protocol in a manner easily translatable by parents to their child. Of 60 consent forms distributed, 19 affirmative replies were received (31.1%).
On the day of the study, the study team were allocated a classroom. A schematic set-up of the classroom is displayed in Figure 4.4.1

4.4 CLINICAL PROTOCOL

A flowchart detailing the protocol of the feasibility study is displayed in Figure 4.4.2.

1. The initial stage of the assessment was to determine the child's vision and if wearing spectacles, presenting visual acuity. These measures were performed using a City 2000 computerised test chart (Thompson Software Solutions, Herts) calibrated for a 3 metre working distance (Section 3.2). Pre-literate children who could not classify letters were asked to identify pictures.

2. Assessments of basic oculomotor function were performed by means of a cover test, both at distance (using a letter target in the distance) and at near at 33cm (with the child fixating a target on a budgie stick). If the child was wearing spectacles, the cover test was repeated with correction on.

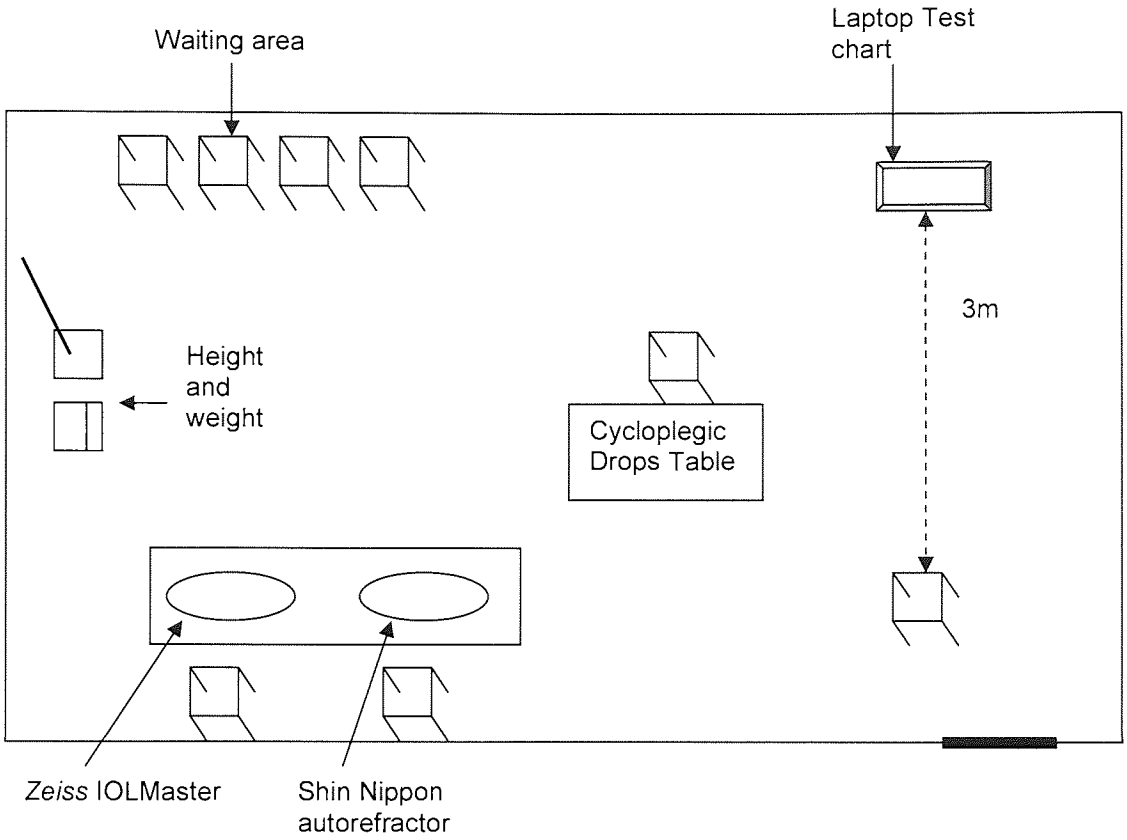


Figure 4.4.1 Diagram of feasibility set-up at Perton First primary school. Diagram not to scale.

3. The next stage was to ascertain the child's non-cycloplegic refractive error. This was measured using the Shin Nippon SRW-5000 infra-red autorefractor (Section 3.3.2). The child fixated through the open-field semi-silvered mirror at a coloured Maltese cross (Figure 5.5.5) located 3m away. Three concurrent readings from each eye were taken once stable fixation had occurred. The mean spherical equivalent refraction (SER= sphere + ½ cylinder) from each eye was further averaged across both eyes to provide a single measure of SER per individual
4. The fourth stage involved the measures of axial length (AL), corneal radius of curvature (CR) and anterior chamber depth (ACD) using the *Zeiss* IOLMaster (Jena, GmbH). Following entry of the child's details into the machine, the child was instructed to fixate a red light within the IOLMaster. This infra red source is the imaging beam and is of such a wavelength (λ= 780μm) as to be dimly visible to the human eye. On steady fixation, 3 measures of axial length were recorded and an average computed by the machine.

Measurements were considered valid if the SNR (signal:noise ratio) was greater than 2.0, in line with manufacturer recommendations (IOLMaster manual, 2003) and the protocol employed by Carkeet *et al.*, (2004).

5. Following axial length measurement, 3 measures of corneal curvature were taken in each eye using the IOLMaster. The child fixated the central yellow light and the 6 hexagonal imaged lights enabled bi-meridional orthogonal corneal radii to be simultaneously determined upon depression of the joystick.
6. The final biometric measure taken using the IOLMaster was the anterior chamber depth (ACD). Five simultaneous readings were provided per eye from one measure and averaged. For all biometric measures (AL, CR and ACD), as with refractive error, the mean value from each eye was further averaged to provide a single representative value per subject.
7. Cycloplegia was induced following ocular biometry. Prior to the instillation of any eye drops, amplitudes of accommodation were measured monocularly using an RAF rule, to enable the effect of cycloplegia to be monitored.

   One drop of the corneal anaesthetic proxymetacaine 0.5% was instilled in both eyes to diminish corneal sensation prior to the instillation 1-2 minutes later of 1 drop of tropicamide HCl 1% *Minims*® (Chauvin Pharmaceuticals, Surrey) in both eyes.

Tropicamide HCl was chosen as the cycloplegic agent of choice as it was felt the earlier dissipation of the drug would prevent prolonged cycloplegic and mydriatic effects. In addition, the risks of systemic side effects related to muscarinic antagonists are virtually eliminated with this choice of agent (Mutti *et al.*, 1994).

8. While cycloplegia was taking effect, height was measured using a standard height chart to the nearest cm. Weight was recorded using digital weighing scales (with shoes on) to the nearest 0.1kg.
9. After 25 minutes had elapsed, the child's accommodative amplitudes were re-measured monocularly. If they were >2D in either eye, the amplitudes were rechecked every 10 minutes until they had fallen to below 2D when the child was considered cyclopleged. There were no children in whom residual accommodation was found to be above 2D at the time of measurement.
10. Following cycloplegia, objective refractive error was determined using the Shin-Nippon autorefractor with 3 measures taken from both eyes. These values were averaged as described in procedure 3.

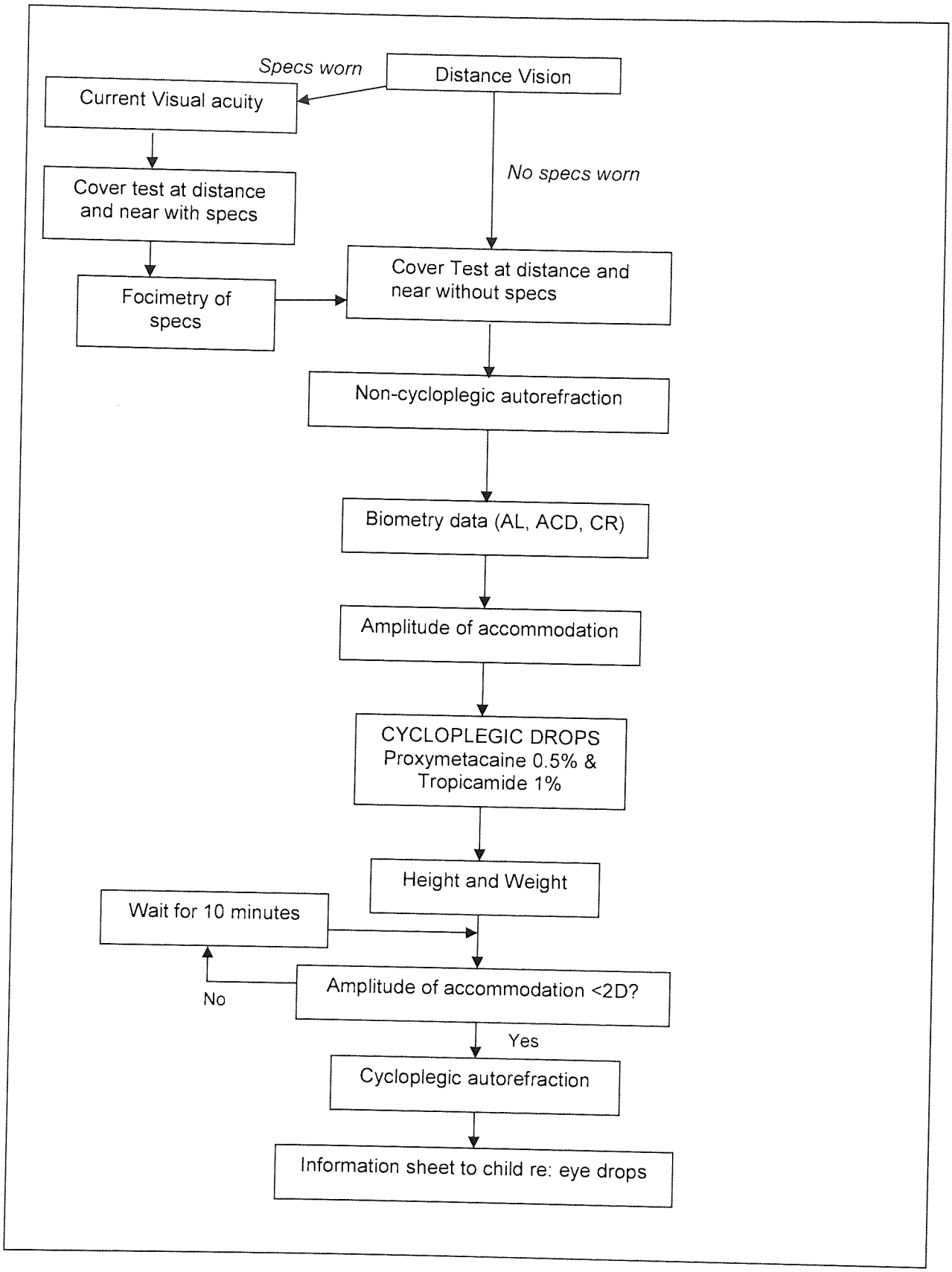


Figure 4.4.2 Flowchart of feasibility study protocol

On completion of recordings, the child was asked whether they were comfortable with their vision and reassured that any near vision difficulties they were experiencing were temporary. The child was handed an information sheet to give to their parent/guardian, reiterating the advice given to the child.

The definitions for refractive error were based upon those of the Refractive Error Study in Children (RESC) protocol (Negrel *et al.*, 2000). A child was considered myopic if the mean SER in either eye was ≤-0.50D. Hyperopia was classified if the mean SER was ≥+2.00D in either eye, as long as neither eye was myopic.

4.5 RESULTS

4.5.1 Data Analysis

Data was processed through a MS *Access* database with a 7/8 digit alphanumeric code utilised to preserve the anonymity of the subject. All subjects were coded using the prefix 'PER-' in reference to the school followed by a unique code related to the name of the child. Statistical and graphical analysis was conducted using MS *Excel*.

Of 19 children who gave assent to participate, cycloplegic refraction, height and weight were not measured in 3 children (the same 3 children for all procedures); 2 due to time constraints (PERSPS19 and PERCB17) and 1 through refusal of cycloplegia (PERET18). One of these children (PERCB17) had reduced visions in both eyes and a clinically significant non-cycloplegic hyperopic astigmatic refraction. A letter was sent to his parents recommending the child be seen for a full optometric eye examination.
AL and CR were not taken in 3 children (PERON9, PERET18 and PERSPS19) due to time constraints whilst several children could not be measured for ACD (n= 9) due to poor fixation and time constraints (see Appendix 1 for results table). All children with missing data were excluded from relevant comparisons.

The mean age (±SD) of participating children was 5.26 ± 0.45 years with 6 females (31.58%). A high degree of concordance was determined for cycloplegic refractive error between both eyes (r= +0.69, p= 0.003). The correlation between the eyes with non-cycloplegic autorefraction was considerably lower and not statistically significant (r= +0.38, p= 0.1).

4.5.2 Refractive error

The distributions of refractive error with and without the use of cycloplegia are shown in Figures 4.5.1 – 4.5.2. The median cycloplegic SER (10^{th} – 90^{th} percentile) for the cohort (n= 16) was +0.85D (+0.34 , +1.44D) and median non-cycloplegic SER (n=19) was +0.34D (+0.03D, +0.81D). The difference between calculated medians was statistically significant (Wilcoxon matched pairs rank test, z= -3.46, p<0.001) indicating that cycloplegic refraction manifested a half dioptre (+0.51D) latent hyperopia on average per child (Figure 4.5.3 and 4.5.4). The mean cycloplegic SER (±SD) was +0.86 ± 0.44D and mean non-cycloplegic SER was +0.39 ± 0.31D.

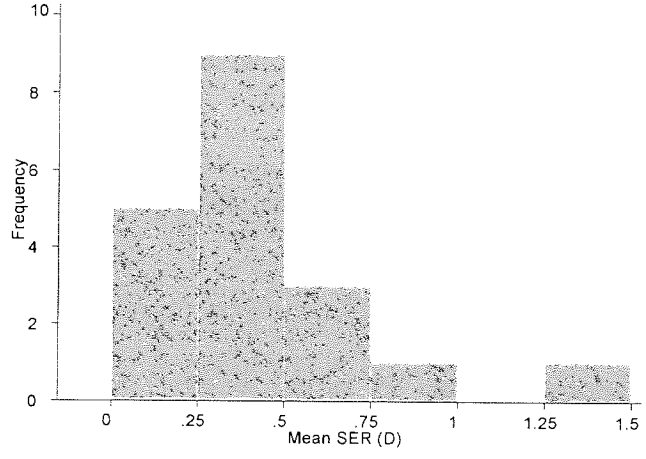


Figure 4.5.1 Distribution of non-cycloplegic SER. Skew= 1.27 p= 0.01, kurtosis= 4.80 p= 0.04.

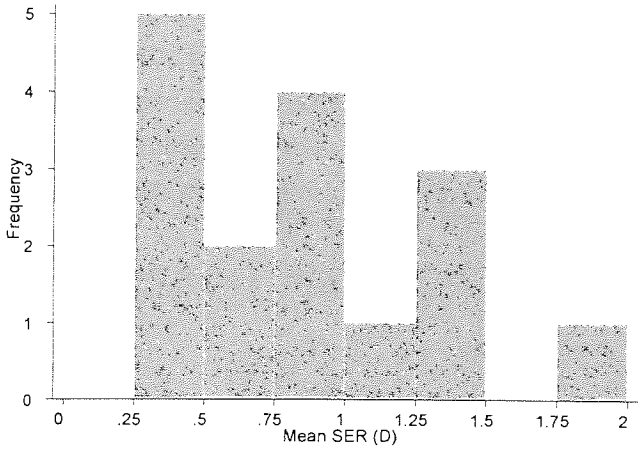


Figure 4.5.2 Distribution of cycloplegic SER. Skew= 0.52 p= 0.29, kurtosis = 2.39 p= 0.87.

To clarify the bias between the methods of refraction, a plot of the difference between cycloplegic *vs.* non-cycloplegic SER was plotted against the mean of the two methods (Figure 4.5.3), after Bland and Altman (1986).

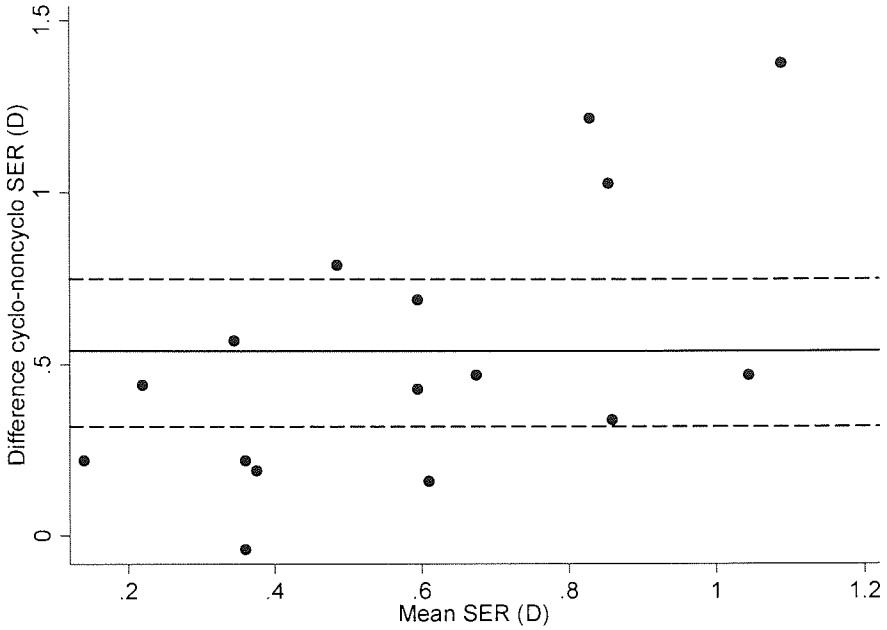


Figure 4.5.3 Difference against the mean for cycloplegic *vs.* non cycloplegic refractive error. Mean difference is displayed as central horizontal line. Dashed lines illustrate 95% confidence interval around the mean

Males (n=10) had a more negative median cycloplegic SER (10^{th} – 90^{th} percentile) compared to females (n= 6), although this difference was not statistically significant (+0.66D [+0.35D, +1.35D] *vs.* +1.20D [+0.34D, 1.44D] respectively; Mann-Whitney U test, z= -1.74, p= 0.08). The mean cycloplegic SER (±SD) was +0.73 ± 0.42D in males and +1.07 ± 0.41D in females.

As all but one child was White, an analysis of refractive error as a function of ethnicity is not feasible although this will be a central theme in the main AES study.

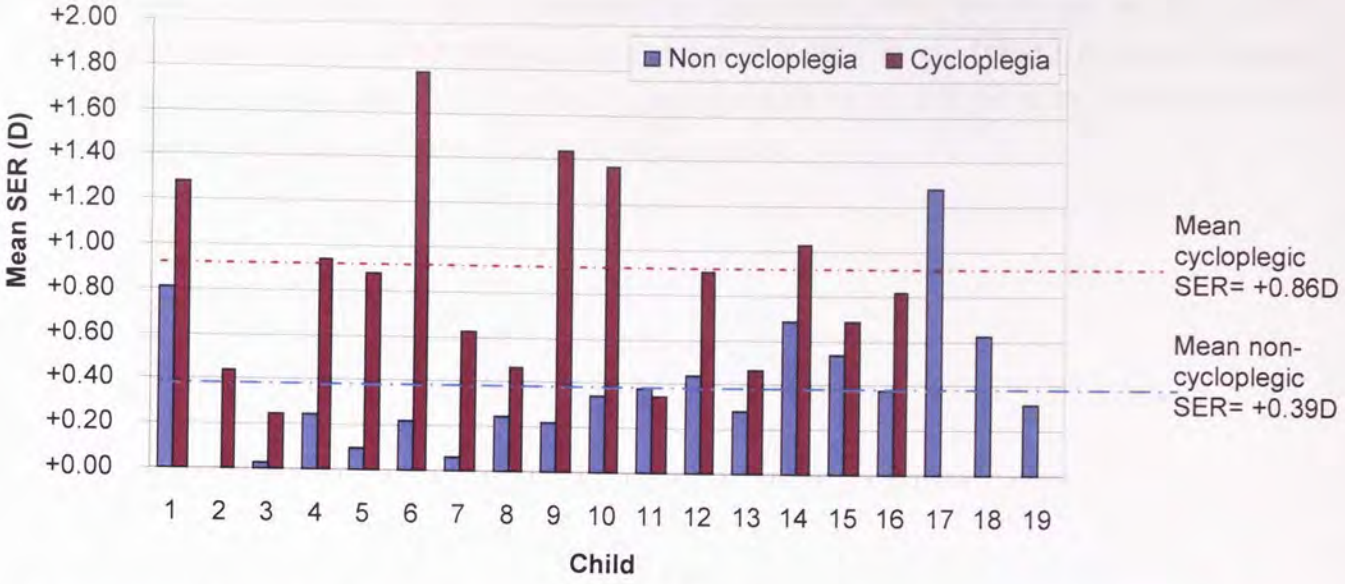


Figure 4.5.4 Mean SER as a function of cycloplegia obtained by autorefraction in each child. Missing cycloplegic data is represented by a blank space along the X axis in children 17-19. Mean values for each method are represented by dashed lines across the graph with corresponding legend on right hand side

Gender	Mean SER (D)	Mean AL(mm)	Mean CR (mm)	Mean ACD (mm)	Mean RE Vision (logMAR)	Mean LE Vision (logMAR)	Mean Height (m)	Mean Weight (kg)
Male	+0.73	22.49	7.75	3.07	0.18	0.19	1.18	22.7
SD	0.42	0.60	0.29	0.60	0.09	0.08	0.06	2.25
Female	+1.07	22.09	7.64	3.22	0.19	0.16	1.18	22.2
SD	0.41	0.43	0.15	0.14	0.05	0.10	0.05	5.10
Combined	**+0.86**	**22.35**	**7.72**	**3.12**	**0.19**	**0.18**	**1.18**	**22.5**
SD	**0.44**	**0.57**	**0.26**	**0.50**	**0.08**	**0.09**	**0.06**	**3.43**

Table 4.5.1 Mean recordings (±SD) as a function of gender. None of the comparisons by gender reached statistical significance using Mann Whitney U tests. Mean SER = cycloplegic SER

4.5.3 Biometry

The mean AL for the cohort was 22.35 ± 0.58mm, mean CR was 7.72 ± 0.26mm and the mean ACD was 3.12 ± 0.50mm (Table 4.5.1). Mean cycloplegic refractive error was not significantly correlated with either ocular component (Figures 4.5.5 - 4.5.7; AL: r= -0.20, p= 0.45; CR: r= 0.31, p= 0.27; ACD: r= 0.07, p= 0.85). However, after mutual adjustment using partial correlation coefficients, significant associations were derived (partial correlation coefficient AL adjusted for CR: r= -0.74, p= 0.002; CR adjusted for AL r= +0.76, p= 0.002). ACD was not included in partial measurements due to the low number of readings taken.

The AL/CR in emmetropes is a ratio that has been purported to be indicative in determining myopia (Grosvenor and Scott, 1994). The mean AL/CR ratio in this cohort was 2.90 ± 0.06, higher than that

of 6/7 year old Melanesian children examined by Grosvenor (1988) though not as high as the calculated values for UK children using the dataset of Sorsby *et al.*, (1961). A strong negative correlation was derived when plotting mean cycloplegic SER *vs.* AL/CR (r= -0.73, p= 0.002) with a strong coefficient of determination (r^2) at 0.50 (Figure 4.5.8).

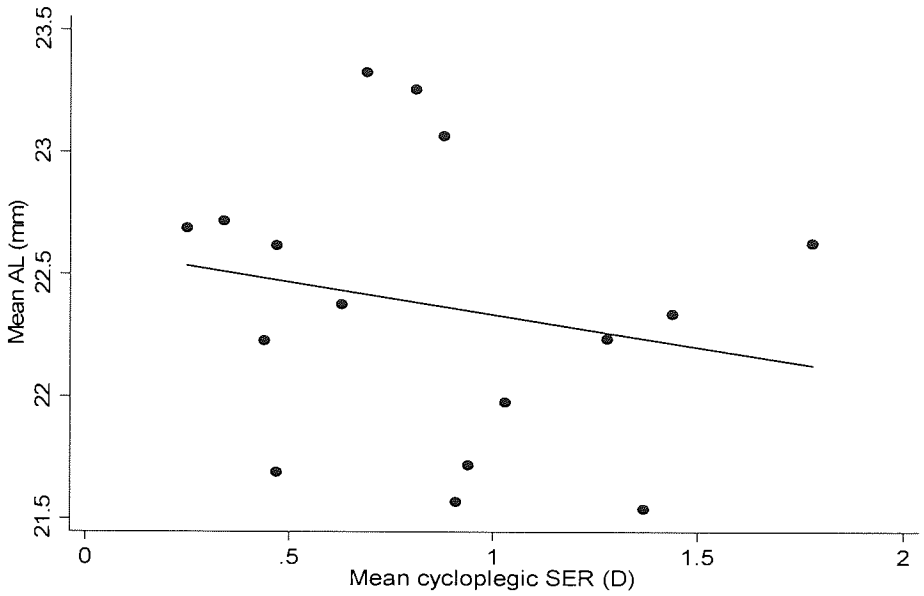


Figure 4.5.5 The association between mean axial length and mean cycloplegic refractive error (Spearman's r= -0.31, p= 0.25)

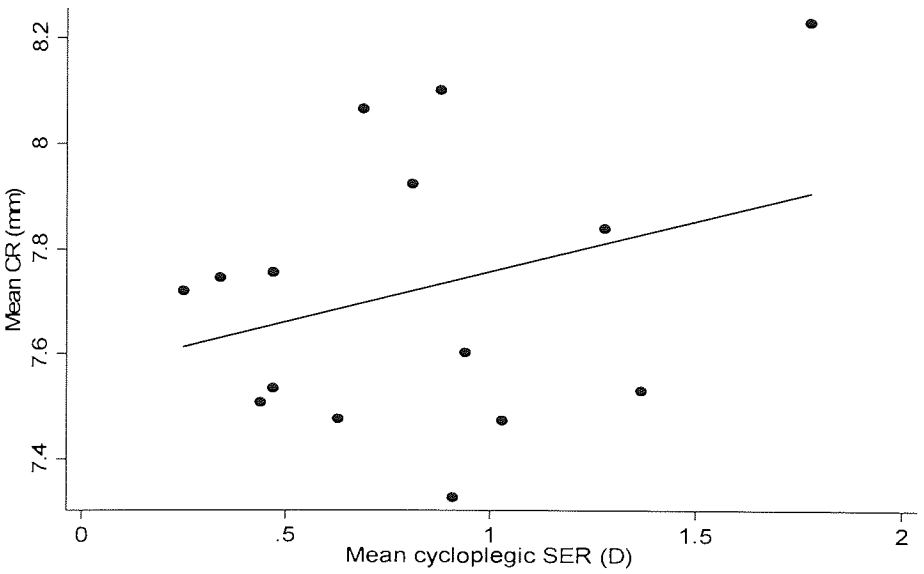


Figure 4.5.6 The association between mean corneal radius and mean cycloplegic refractive error (r= +0.11, p= 0.71)

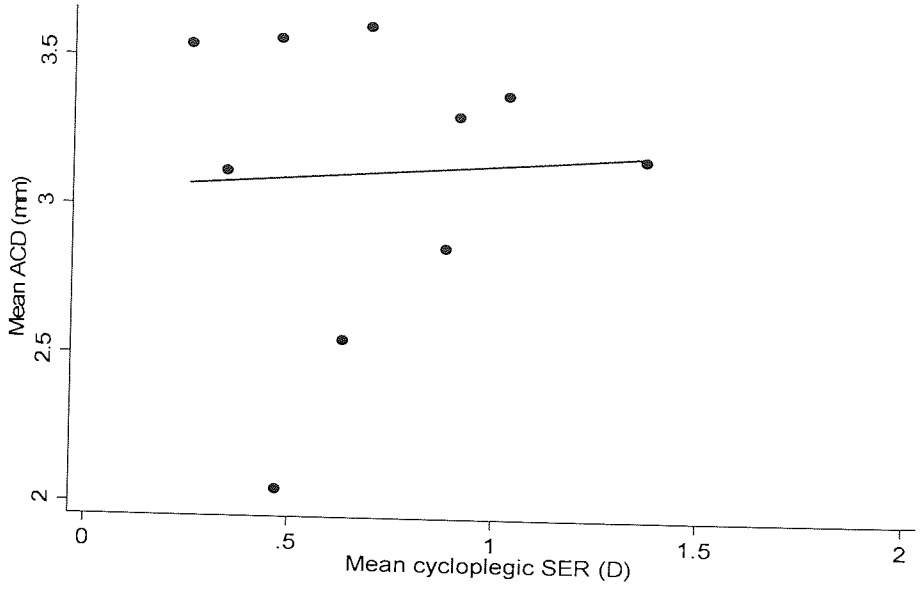


Figure 4.5.7 A scatterplot illustrating the relationship between mean ACD and mean cycloplegic refraction (r= +0.006, p= 0.99)

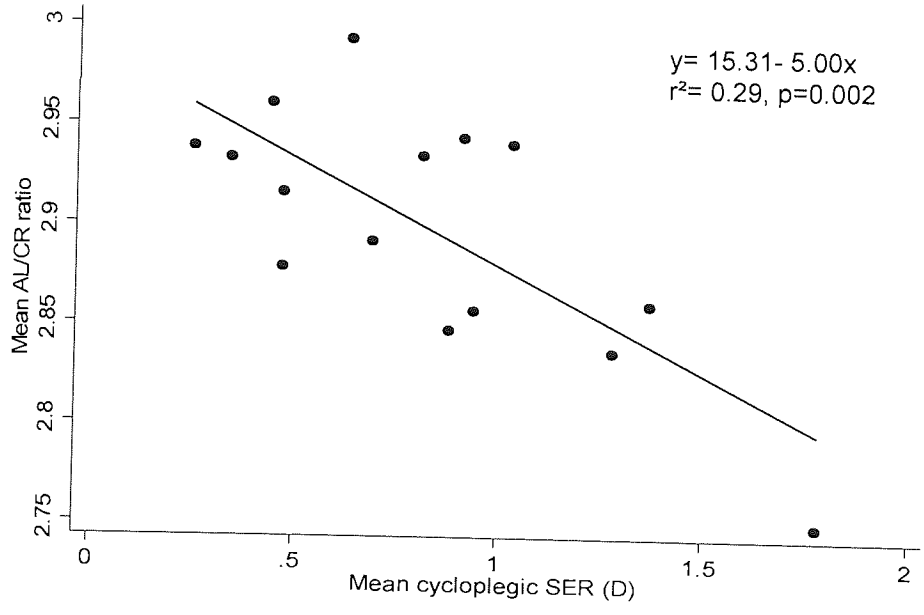


Figure 4.5.8 Linear regression of AL/CR ratio on mean cycloplegic refraction (r= -0.54, p= 0.04)

4.5.4 Anthropometry

The correlation between anthropometric measures of height and weight with mean cycloplegic refraction and ocular biometry is displayed in Table 4.5.2.

	Mean cycloplegic SER (D)	Mean AL (mm)	Mean CR (mm)	Mean ACD (mm)
Height	+0.47	+0.06	+0.18	-0.17
p value	*0.17*	*0.85*	*0.63*	*0.64*
Weight	+0.16	-0.02	-0.07	+0.04
p value	*0.56*	*0.95*	*0.84*	*0.92*

Table 4.5.2 Correlation values (r) between anthropometric variables and ocular measurements

There were no significant correlations between anthropometry and ocular components or cycloplegic refractive error.

4.5.5 Ametropia prevalence

None of the 19 children measured were found to be myopic with or without cycloplegia according to a criterion of SER ≤ -0.50D in either eye. There were also no hyperopes detected, using the criterion for hyperopia of SER ≥ +2.00D in either eye. Therefore all subjects that underwent cycloplegia (n=16), including a child who had been prescribed spectacles to wear (PERTH7), were found to be emmetropic in accordance with the AES refractive error criteria.

4.6 DISCUSSION

The feasibility study principally served to demonstrate that the devised protocols were operational and that the study process could be successfully implemented. A lower correlation between the mean SER in right *vs.* left eyes was determined for non-cycloplegic measures (r= +0.38, p= 0.1) compared to cycloplegic measures (r= +0.69, p= 0.003), suggesting that the actual concordance in refraction between the eyes may have been concealed by the effects of accommodation in eyes that were not cyclopleged.

4.6.1 Cycloplegic *versus* Non-cycloplegic refractive error

A significant difference between cycloplegic and non-cycloplegic refractive error was present in young children, with cycloplegic measures on average half a dioptre more positive than non-cycloplegic (median difference cycloplegic – non-cycloplegic= 0.51D). All participants were found to have more positive mean refractive errors with cycloplegia compared to without (Figure 4.5.3).

These findings support much literature that has shown considerable differences between cycloplegic and non-cycloplegic measures. A more positive refraction was shown post-cycloplegia compared to pre-cycloplegia in 4,973 children aged 7 - 18 years using autorefraction (mean difference = 1.23 ± 1.65D, Zhao *et al.,* 2004). Recent evidence from the Sydney Myopia Study 12 year old cohort (n= 2,233) has also shown a consistently more positive refraction after cycloplegia (Fotedar *et al.,* 2007) with a mean difference of +0.84D (95%CI: 0.81 – 0.87D). However, both the aforementioned studies used closed-field autorefraction in conjunction with a more severe cycloplegic procedure. Two drops of cyclopentolate 1% were instilled by Zhao *et al.,* (2004) and the Sydney Study administered 1 drop of cyclopentolate 1% followed by 1 drop of tropicamide 1%. The supplementary drop in addition to proximal residual effects on accommodation induced by closed-field autorefraction may account for the greater latent refraction elucidated by cycloplegia compared to the AES feasibility study.

4.6.2 Spectacle wear

One child (PERTH7) was found to be a spectacle wearer amongst the cohort examined and claimed they had been prescribed by his optometrist for occasional near work. He had not brought the spectacles with him on the day though his refractive error as measured with autorefraction was not clinically significant.

4.6.3 Biometry and refractive error

It was unexpected that a significant correlation was not obtained between any ocular component (AL, CR and ACD) alone and cycloplegic refraction, in particular considering axial length has inextricably been linked to ocular refraction in previous literature (Wildsoet, 1998). However this was likely to have occurred due to the small sample size. A significant association was derived once the effects of AL and CR were mutually adjusted.

Many recordings, in particular those of ACD, were not taken due to a lack of time, familiarity with equipment and poor child fixation. However, the strong correlation between refractive error and AL/CR ratio (Figure 4.5.8) supports previous work by Grosvenor and Scott (1994) in emphasising the importance of the AL/CR ratio as a correlate of refractive error. None of the children had an AL/CR ratio > 3.0, though one child did have ratios of 2.99 in both eyes. His refraction was unremarkable (mean SER= +0.81D).

4.6.4 Gender

The acceptance of null hypotheses against a difference between males and females (Table 4.1) highlights the ocular similarities between the sexes at a young age when emmetropisation is thought to be near completion (Mohindra and Held, 1980; Gwiazda *et al.*, 1993). The more positive refraction in females at the age of 5/6 years compared to males (+1.07D *vs.* +0.73D) may serve to lower their risk of future myopia onset (Zadnik *et al.*, 1999).

A shorter axial length and steeper corneal radius was also present in females, in support of other research (Zadnik *et al.*, 2003, Ojaimi *et al.*, 2005a). Nevertheless, the small sample sizes must render any conclusions tentative until further work on UK children is conducted.

4.6.5 Ametropia prevalence

The absence of myopes in this young group supports the low prevalence in a study on predominantly White children (Ojaimi *et al.*, 2005a) in a similarly aged cohort. The Sydney Myopia Study (n= 1765) measured children aged 6/7 years (this study involved younger children aged 5/6 years) and detected a very low myopia prevalence in Caucasians of 0.79%. Non-Caucasian children showed a significantly higher myopia prevalence of 2.73%. Only one child was Asian in this study. It is anticipated that future work examining children of varying ethnic backgrounds will provide greater insights into the effects of ethnicity on refractive error.

4.6.6 Anthropometry

None of the anthropometrical variables (height and weight) were significantly linked to refractive error or ocular components although a greater number of children will need to be measured to exclude any definite link.

4.6.7 Feasibility

The primary aim of this study was to determine the feasibility of the AES protocol, from initial contact with schools, distribution of letters and their collection to the execution of the study itself, data collation and post-study analysis.

Procedures carried out prior to the study were found to be straightforward (i.e. contacting the Headteacher, distribution of letters to parents, collection of letters). Preparation of administrative duties (e.g. creation of letters and self-addressed envelopes) did however consume a larger proportion of time than initially estimated.

On the day of the study, it was found that a 3 metre room in length was sufficient for measurement of vision using the electronic test chart. Equipment set-up took approximately 30 minutes to complete

before the first child was assessed. The cohort of children (n= 19) were seen over a period of 4 hours. Some of the measurements were not completed on all children, due to a lack of time or poor fixation by the child. Thus it was concluded that to complete the full range of tests including set-up time and cessation around school recreation break/lunch times, a full school day would be required (9.30am – 3pm) to measure 20-25 children.

4.6.8 Amended Protocol

The protocols for the AES study were modified on analysis of the feasibility study as follows:

1. As a result of the large administrative workload required to prepare letters to both schools, parents and sheets for the day of the study, it was felt necessary that a printer be purchased for sole use by the AES. In addition, a Royal Mail Freepost™ address was created to minimise wastage of stamps from non-respondents to letters.

2. The feasibility study involved 5/6 year olds (Year 1) but it was suggested that the involvement of children a year older would improve compliance with procedures i.e. steadier fixation on machines and greater proportion able to read letters on test chart instead of pictures. Therefore the AES proper will examine children from Year 2 (aged 6/7 years of age). The older cohort will remain at 12/13 years of age (Year 8).

3. One drop of cyclopentolate HCl 1% will be used in the main study due to its deeper and prolonged cycloplegic effect compared to tropicamide HCl 1% (Lovasik, 1986) and to facilitate comparison with child refractive error studies from other countries using the same cycloplegic agent (Negrel *et al.*, 2000; Ojaimi *et al.*, 2005).

4. Due to the necessity of cycloplegia to a valid research protocol (Zadnik *et al.*, 1992) and to minimise the number of recordings required, it was felt that non-cycloplegic refractive error should be excluded from the main study.

5. Ocular biometry will be measured, under identical conditions to that of refractive error i.e. under cycloplegia. In addition, research has shown that the variability of AL and ACD measurements is greater in the absence of cycloplegia (Sheng *et al.*, 2004), reiterating the necessity of cycloplegic biometry.

6. It was felt that removing one child from class at a time was an avoidable distraction for class teachers and required continuous interruption for AES investigators to accompany children

back to their classrooms. Therefore, it was decided that a group of approximately 5 children at a time would be tested. However, to occupy the children, educational activities and games would be required. These were created and included word searches, dot-to-dot puzzles and mazes for Year 2 children, whilst for Year 8 children, optical illusions, blind spot activities and a video introducing university life were assembled.

In summary, the successful response of the feasibility study provided encouragement to initiate the main body of the AES study. Modifications were made to the methodology to facilitate an efficient protocol, including the use of cycloplegia, the nature of the cycloplegic drug utilised and the order of tests conducted.

CHAPTER 5

METHODOLOGY

The following chapter details the methodology of the Aston Eye Study (AES), from the initial sampling stages of the study to its implementation. Full ethical approval for the AES was obtained from the Aston University Ethics Committee (Appendix 2) and all protocols adhered to the tenets of the Declaration of Helsinki.

5.1 SAMPLING STRATEGY

A stratified random cluster sampling strategy was devised for the AES based on schools in the Birmingham conurbation, in collaboration with epidemiologists from St. Georges, University of London (AR and CO[1]). Education is compulsory in the UK until the age of 16 years, therefore targeting schools to capture the child population prevented the need for enumeration and door-to-door recruitment. Enumeration has been necessary in countries such as India where many children do not attend a centre of education (Dandona *et al.,* 2002). AES target schools were stratified by age of pupils and deprivation index of ward (see Chapter 2 for Ward information). In addition, ethnic composition of schools was incorporated into sampling models.

Age

The AES target age groups were children aged 6/7 years (Year 2) and children aged 12/13 years (Year 8). In England, the education system is divided dichotomously into primary (5 -11 years of age) and secondary (11-16 years of age) schooling, conveniently splitting up the target age groups.

Deprivation Index

The Index of Multiple Deprivation (IMD) is a directory of deprivation indices produced by the Oxford University Social Disadvantage Research Centre. Values range between 1 and 100 to reflect the deprivation characteristics of a ward (www.birminghameconomy.org.uk, accessed 02/072007). The IMD takes into account seven general socioeconomic factors to determine an overall index value: Income, Education, Crime, Living Environment, Health and Disability, Employment and Barriers to Housing. Higher IMD values reflect areas of greater general deprivation.

Using data from January 2000 (National Statistics Office, 2001) based on IMD values of Birmingham (range: 8.18 - 75.96), tertiles of deprivation were created (1= high, 3= low) and a deprivation number

[1] AR: Dr Alicja Rudnicka CO: Dr Christopher Owen

assigned to each ward These values were used to stratify the sample ensuring an equal representation from schools within each deprivation category.

Ethnicity

The ethnic composition of children resident in Birmingham was acquired from Census data based on 2004 Ward information (National Statistics Office, 2001). The AES was principally concerned with detecting differences in outcomes between the 3 predominant ethnic groups in the city: Blacks (Black Caribbean, Black African, Black Other), Whites (White British, White Irish and White Other) and South Asians (Bangladeshi, Indian, Pakistani). Although East Asian children are reported to be highly susceptible to myopia (Saw, 2003; Cheng *et al.,* 2007), the potential sample size of East Asian children in Birmingham (i.e. Chinese, Taiwanese) was too low to justify their separate sampling, though data on these children was incidentally collected and analysed. Throughout the remaining chapter, South Asian children will be referred to as Asian for ease of discussion.

Refinement of target schools by ethnicity was conducted by determining the ethnic composition of schools in Birmingham. Information on ethnic breakdown by school in 2004 was kindly provided by Birmingham City Council on request. Schools were excluded from invitation when the proportion of a single ethnic group was >70% of the entire cohort. The rationale behind this criterion was to target a wide a range of ethnically diverse children from similar schooling backgrounds, minimising factors such as geographic location and inter-school quality of teaching from confounding the effect of ethnicity on outcome measures.

5.1.1 Sample size determination

It is of great importance prior to an epidemiological study to determine the required sample size (Woodward, 2005). An insufficient sample size may neglect a significant result due to a lack of power in the results. Thus a rigorous sampling methodology was required for the AES.

Based on previous literature of myopia prevalence in countries with a similar demographical profile to the UK, a myopia prevalence of 3% and 10% was hypothesised for Year 2 and Year 8 children respectively. Aiming for a precision (standard error) of 1% in the Year 2 cohort and 2% in the Year 8 group (1% would have resulted in an unreasonably high sample size), the required sample size per ethnic group (Black, White and Asian) was 291 in Year 2 and 225 in Year 8, giving a total sample size of 873 and 675 children respectively.

Significance

The significance of a result is complementary value to a Type 1 (α) error (Significance = $1 - \alpha$) and is symbolised by a p value. A p value refers to the probability that the obtained result occurred by

chance, thus the lower the p value, the more 'significant' the result (Florey, 1993). Conventional statistical significance is set at 0.95 (95%) hence a result with a p value <0.05 is deemed as being statistically significant, with a probability of <5% that the result occurred fortuitously and that the null hypothesis was incorrectly rejected.

Power

A type 2 (β) error is one in which the null hypothesis is false but is not rejected (Florey, 1993). The probability that a type 2 error will not occur and a true difference, if present will be detected is referred to as the power of a study. It is the complementary value to a Type 2 (β) error (Power = 1 - β). The β value in the AES was set to 0.1 (10%), reflecting a power of 0.9 (90%).

5.1.2 Design effect

Each school in the sampling design was considered a cluster. The AES sample size was inflated to account for the disparity between random cluster sampling and random individual sampling, a factor known as the design effect or *deff* (Woodward, 2005). Individuals within a cluster are more likely to share characteristics compared to that found in the general population. The *deff* is a measure of this and is dependent upon the intracluster correlation coefficient (ICC), a ratio of between-cluster variance to total variance (total variance = between-cluster + intra-cluster). Intuitively, if a high ICC is present, a common factor may exist within a cluster to account for its low variance in relation to the higher between-cluster variance. Therefore a greater sample size would be needed to offset this bias and minimise the impact of clusters.

ICC values for refractive error epidemiological studies were not known from previously published research, thus an assumed range of values (from 0.01 to 0.001) were tested by AR in order to obtain an ICC for the study. An ICC of 0.005 was derived through the examination of the number of clusters required and the number of individuals per cluster. From the assigned ICC value, the *deff* was calculated using the following formula (Woodward, 2005):

$$\text{Deff} = 1 + C(m - 1) \qquad \text{Equation 5.1}$$

Where C = ICC and m = number of individuals per cluster. Limiting the number of children to 60 per school resulted in a *deff* value of 1.295. Based on the *deff* value calculated, the sample size was further inflated by approximately 30%, resulting in a revised Year 2 figure of 1130 children and Year 8 figure of 874 children.

5.1.3 Minority groups

On extrapolation from Birmingham school ethnicity data, 15% of the AES cohort invited to participate would comprise of minority ethnic groups (e.g. mixed ethnicities, East Asian) which were not pertinent to the sampling design. Subsequently, both age groups were inflated by 15% to account for this factor, resulting in a revised sample size of 1300 Year 2 and 1005 Year 8 children.

5.1.4 Non-participation

A further inflation of the sample size was undertaken to account for the refusal of some invited schools and subjects from AES participation. Assuming a 75% participation rate of invited children, the figures were inflated using the formula of 1/participation rate:

1/0.75 = 1.33 (33%). Year 2: 1300 x 1.33 = **1727** Equation 5.2
Year 8: 1005 x 1.33 = **1337**

5.1.5 Final sample size

The final required sample size was rounded off to **1,700** Year 2 children and **1,300** Year 8 children (3,000 children in total).

5.2 RECRUITMENT

Having devised a sample size and a target list of schools in Birmingham, the primary stage in recruitment was to initiate contact with schools. Primary contact was conducted through an introductory letter to the Head teacher inviting the school to participate in the AES and explaining the rationale of the study. Based on the feasibility study (Chapter 4), it was felt that approaching Year 8 students (secondary schools) initially would enable AES investigators to become familiarised with protocols, facilitated by the greater co-operation of Year 8 children compared to younger subjects.
The initial letter to the school was followed up within 2-5 days by a telephone call to the Head teacher, to gauge the school's interest and to enable queries to be answered (Figure 5.2.1). This stage frequently impeded the smooth running of the study due to delays and difficulties in communicating with the Head teacher directly.
To minimise a loss of response due to postage costs and curtail administrative duties, a Royal Mail Freepost™ address was established by the AES team. All invitations to schools included an addressed envelope to encourage a swift response.

5.2.1 Information Packs

On agreement of participation by a school, an initial meeting was arranged to discuss the logistics of procedures and to meet with staff at the school premises. Information packs were also distributed at this time for the attention of parents/guardians of the relevant Year group (Year 2 or Year 8).

The contents of each information pack are outlined below (Appendix 4):

1. A letter to the parent/guardian, detailing the rational of the eye study and what would be involved.

2. An information sheet, written in a lay-person language such that it could be read by children with their parents. Upon reading the sheet, the child would have a sound understanding of the AES and would be well informed about whether he/she wished to participate. The parents of all children were encouraged to discuss this sheet with their child.

3. A consent form for the parent/guardian to sign to allow their child to participate in the study. This form was returned to the school in a provided envelope.

Schools were requested to provide a covering letter endorsing the study in addition to the information pack. The covering letter served to reassure parents that the school was aware of and had approved the AES. Frequently, the AES team organised a short presentation for Year 8 children through a school assembly format. The assembly provided a relatively informal opportunity to introduce the AES directly to children and inform them of its rationale, procedures and method of participation.
A 2-3 week deadline was negotiated with the majority of schools in which to have consent forms returned back to the AES team via the Freepost™ address. On receipt, consent forms were processed and a spreadsheet created containing the names of participating children. Based upon the number of affirmative responses received from a school, a date(s) was arranged with the school to attend and carry out the data collection.

5.2.2 Translation

The parent letter, information sheet and consent form were translated into Urdu and Somali at the request of several schools as according to Head teachers, these were the languages whose native speakers were least fluent in the English language. The translation was carried out by the Brasshouse Language Centre in Birmingham.

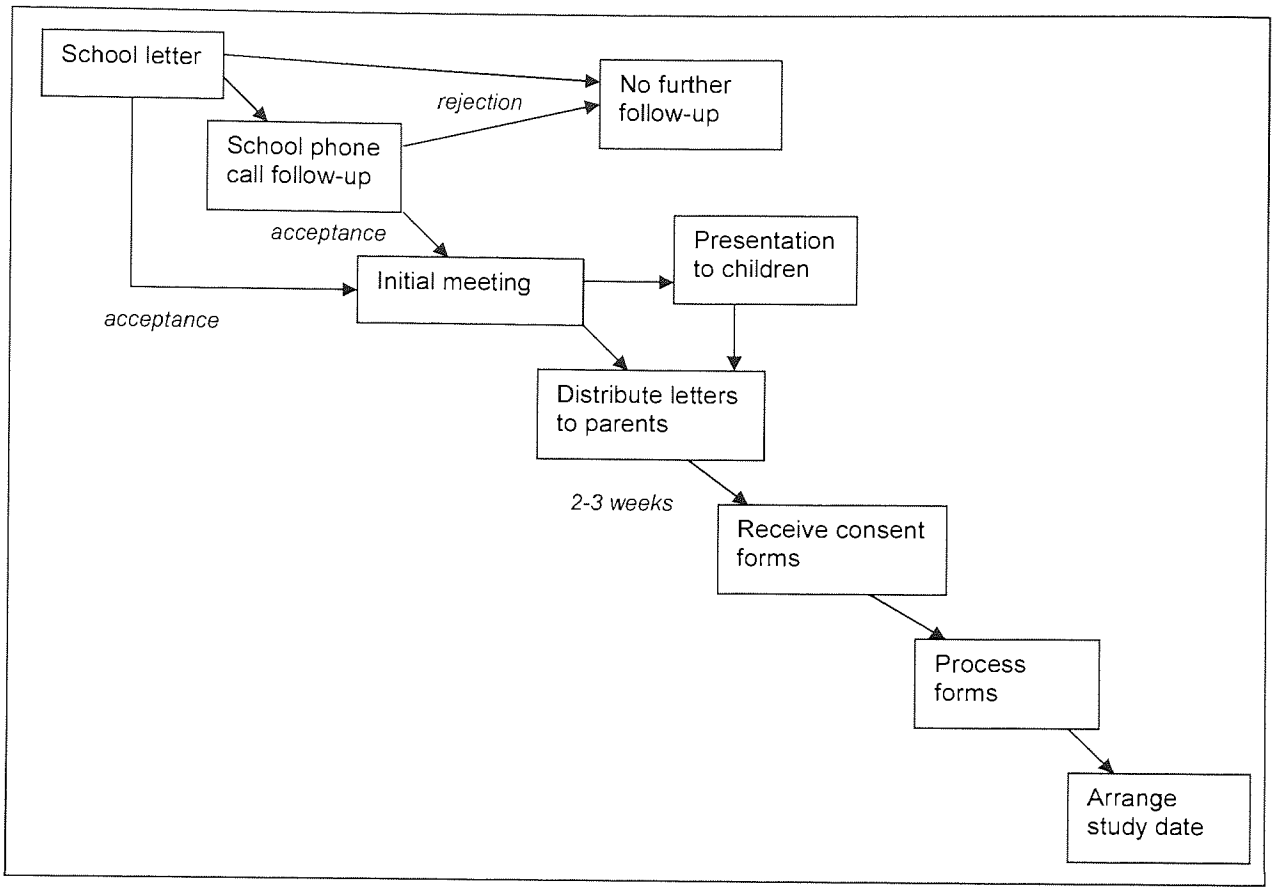


Figure 5.2.1 Flowchart illustrating logistical procedures of recruitment.

5.3 STUDY PERSONNEL

The principal co-ordinators of the AES comprised of 3 UK GOC registered optometrists (BG, NL and PS)[2] and 2 epidemiologists with optometric backgrounds (AR and CO)[3].

At least one of the principal co-ordinators was present at every school to lead data collection (PS). Additional members to facilitate data collection and perform educational activities with children were recruited as necessary. The 3 optometrists all have extensive experience of primary care practice and hold current Criminal Records Bureau (CRB) accreditation for working with children. All were familiar with the range of equipment employed in the study and safety aspects of protocols.

[2] BG: Professor Bernard Gilmartin NL: Dr Nicola Logan PS: Mr Parth Shah
[3] AR: Dr Alicja Rudnicka CO: Dr Christopher Owen

5.4 QUESTIONNAIRES

A key component of the AES was the use of questionnaires to elicit potential myopiagenic risk factors (Appendix 8). The format and content of the questionnaires was based on the CHASE Study (www.chasestudy.ac.uk, accessed 15/05/2007) an extension of the TenTowns child heart-health study conducted by a research team at St. George's University of London (Whincup *et al.*, 1992; Whincup *et al.*, 1996). In addition, various questions included were modified from the Sydney Myopia Study (Ojaimi *et al.*, 2005).

Two questionnaires were designed: one for completion by parent/guardians (of both age groups) and a child questionnaire for completion by Year 8 children only. The rationale of the child questionnaire was to gauge validity of the parental questionnaire by matching up responses, and to provide the AES team with information about the child in the absence of a returned parental questionnaire.
The parental questionnaire consisted of 91 items and requested detailed birth/medical/ocular history of the child, lifestyle questions (e.g. time spent on exercise, reading, diet and night lighting) and family history of spectacle use. Socio-demographic information of the family (including parental education, occupation and ethnicity) was also obtained.

The child questionnaire consisted of 64 items, with an additional 26 items requesting information to construct a psychological profile of the child. The child questionnaire was completed by Year 8 children at the time of the study and the parental questionnaire was distributed on completion of the study for all participating children to take home. Once the parent/guardian had completed the questionnaire, parents were instructed to post back the document to the AES team directly via the Freepost™ address.
Three to four weeks after a study, the school was advised to remind parents to return uncompleted questionnaires, normally through the issuance of a verbal reminder to pupils during school assemblies. In addition, questionnaire reminders were posted directly to parents (Appendix 8), as correspondence addresses had been requested from parents at the time of child consent. The reminders consisted of a letter, an A5 sized questionnaire (in the event of the original questionnaire being misplaced) and a Freepost™ reply envelope. Chapter 8 details the response rate of questionnaires returned.

5.5 CLINICAL PROTOCOL

5.5.1 Preparation

Prior to the study date, the required equipment was gathered (see Appendix 5: Equipment List), machines were checked and supplies (i.e. printer paper, cycloplegic drops, tissues) were replenished as required. The school was informed in advance of the children who were to participate in the AES.

5.5.2 Set-up and consent

The set-up of the equipment at the school invariably occurred on the morning of the study. The room size required a minimum length of 3 metres to ensure accurate testing on the City 2000 computerised test chart. A table set-up for the cycloplegic procedure was kept separate from waiting pupils to limit the risk of non-participation due to an apprehension in seeing eye-drops instilled in fellow pupil's eyes.
A sequence of testing for children was devised by AES investigators to minimise the time spent by a child outside his/her classroom. A group of 5 children were seen at a time and once cycloplegic drops had been instilled, the 5 children were taken back to their classrooms and a second set of 5 were taken out of class for vision measurement. On administration of drops in the second group of 5 children and returning them back to class, the initial 5 children were reassembled for post-cycloplegic procedures.

Children were initially introduced to study personnel and made to feel comfortable about the tests to follow. Though parental consent had been provided, signed consent was required from Year 8 children as they were considered capable of understanding the procedures involved. Verbal assent was required from Year 2 children and was documented by an investigator (Appendix 5). Children were permitted to withdraw from the study at any point during the examination.

The ethnicity of each Year 8 participant was self-reported (based on classifications used by the National Census 2001). Year 2 ethnicity was estimated by an investigator (PS) at the time of measurement by asking a child which, if any, other language(s) the child spoke at home, and where their parents originated from. Ethnic classifications from both age groups were confirmed via the parental questionnaire

5.5.3 Study procedures

AES study procedures are detailed chronologically below (Figure 5.5.6):

1. Vision/Visual Acuity: The initial stage of the assessment was to determine the child's vision and if wearing spectacles, presenting visual acuity (Section 3.2). This was performed using the Test Chart 2000 (Thompson Software Solutions, Herts) calibrated for a 3 metre working distance on a laptop computer (Figure 3.2.1). Monocular vision/visual acuity measures were taken from each eye in logMAR notation with the aid of monocular occluder spectacles (Figure 5.5.1). The screen intensity on the laptop was increased to full and the screen was set perpendicular to the line of sight of the viewer.

If the child was wearing spectacles, their power was determined using a manual focimeter (Topcon LM-6, Topcon, Japan). The focimeter was calibrated before each school visit by ensuring that a focused corona registered a zero dioptric value in the absence of a lens.

Figure 5.5.1 Monocular occluder spectacles

2. Oculomotor balance: Oculomotor function was assessed by means of a cover test at distance using a letter target on the test chart, and at near (33cm) while fixating a budgie stick target (Figure 5.5.2). If the child presented with spectacles, the cover test was repeated with the correction *in situ*. The amount of latent or manifest deviation was graded subjectively by the same observer (PS) to determine whether a deviation was present and its type.

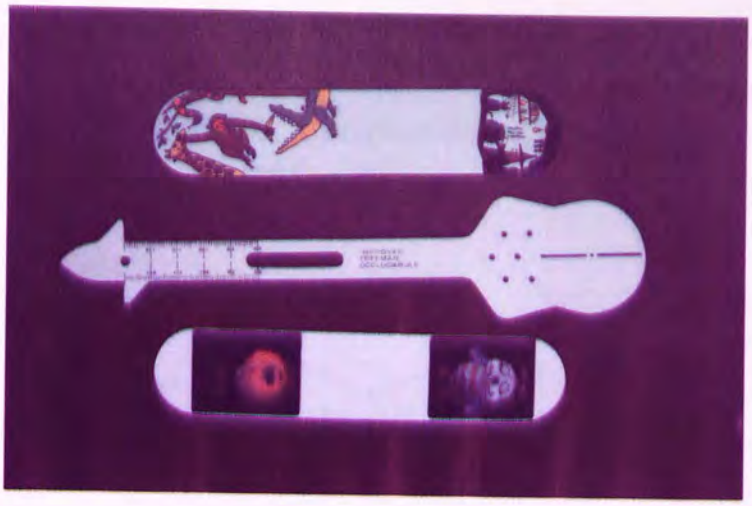


Figure 5.5.2 Cover and budgie sticks

3. Cycloplegia: The Aston Eye Study regime of cycloplegia involved the instillation of 1 drop of the corneal anaesthetic proxymetacaine 0.5% *Minims*® (Chauvin Pharmaceuticals, Surrey) followed 1 – 2 minutes later by 1 drop of 1% cyclopentolate HCl *Minims*® (Chauvin Pharmaceuticals, Surrey) in both eyes.

An anaesthetic eye drop was used for three reasons:

- To diminish the blink reflex and subsequent cyclopentolate washout ensuring greater absorption of the cycloplegic agent through the eye (Lovasik, 1986).
- To reduce time to full cycloplegia, as demonstrated in a Chinese cohort (Siu *et al.*, 1998) through increased drug absorption through the cornea.
- To minimise the stinging sensation from the application of cyclopentolate leading to better child co-operation (Shah *et al.*, 1997).

Proxymetacaine action is rapid, with anaesthesia occurring approximately 30 seconds after instillation and dissipating after approximately 25-30 minutes (Eperjesi and Jones, 2005). Though the effects of proxymetacaine were expected to have worn off by the end of the child's measurements, both child and parent/guardians were warned (verbally and through an information letter respectively) not to let the child vigorously rub his/her eyes for several hours following the eye study.

Tropicamide HCl 1% was used as the cycloplegic agent in the feasibility study. Residual accommodation with tropicamide has been shown to begin recovery towards normal levels after 35 minutes (Gettes and Belmont, 1961), whilst maximal effects with 1% cyclopentolate have shown to last for approximately two hours (Figure 5.5.3). If tropicamide is to be used as a cycloplegic, two drops have been recommended by Egashira *et al.* (1993), though the use of an additional drop may act as a deterrent to a child and their parents.

In view of these findings, it was felt that the longer window of maximal cycloplegia offered by cyclopentolate compared to tropicamide was vital to the accuracy of recordings (Gettes and Belmont, 1961; Lovasik, 1986). Cyclopentolate HCl 1% was therefore chosen as the cycloplegic agent of choice for the main AES study.

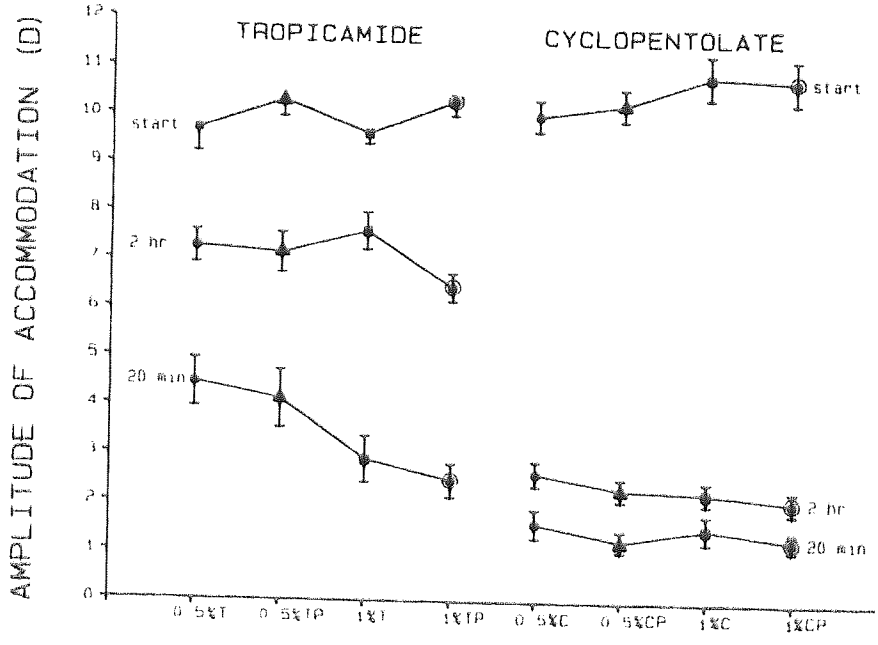


Figure 5.5.3 A comparison of Tropicamide *vs.* Cyclopentolate on the amplitudes of accommodation with time. X-axis represents varying regimes of cycloplegia. T: Tropicamide, C: Cyclopentolate, P: Proxymetacaine (proparacaine). Of relevance to the AES are the columns with circled data points, indicating a cycloplegic regime involving prior instillation of proxymetacaine. Modified with permission from Lovasik (1986). *Am J Optom Physio Optics* ; 63 (10): page 795

Use of cyclopentolate in the AES will facilitate comparison of AES results with those of other studies utilising the same agent (i.e. RESC: Negrel *et al.* 2000; Sydney Myopia Study: Ojaimi *et al.*, 2005). It is recognised that the dosage of cyclopentolate administered by these studies is larger than that of the AES. However, the essential requirement is that desired levels of residual accommodation (≤2D) are attained in children with a minimal invasion of ocular integrity (i.e. repeated use of drops). It has been shown that a single drop of cyclopentolate 1% is sufficient for cycloplegia in children (Bagheri *et al.*, 2007), with repeated instillation increasing the likelihood of adverse reactions.

Children of both age groups were very receptive to the eye drops. It was evident that the use of the anaesthetic proxymetacaine prevented the enhanced stinging effects of cyclopentolate compared to tropicamide. There is a longer recovery period from cycloplegia and mydriasis with cyclopentolate but this time period was highlighted to parents/guardians in information sheets prior to granting consent.

Accommodative amplitudes of the child were measured using an RAF rule approximately 25 minutes following drop administration. Children were measured with full distance refractive correction if present. Cycloplegia was affirmed if monocular amplitudes were ≤2D. Amplitudes were re-checked every 10 minutes if found to be >2D. After 40 minutes, if cycloplegia was not achieved, a second drop of cyclopentolate was instilled into both eyes. A second drop was necessitated in 6 Year 2 children and 2 Year 8 children. There were no children requiring a third cycle of cyclopentolate.

4. Height and Weight: The child's height was measured using a height chart (Leicester Height Measure, Seca Ltd, Birmingham) to the nearest 0.1cm. Weight was measured using digital weighing scales (Tanita Model 2000, Tanita Corporation, Japan) and was recorded to the nearest 0.1kg (Figure 5.5.4). The height chart is a portable device assembled by slotting individual components together on top of a base stand. The weighing scales were calibrated periodically by placing a known 5kg and 10kg weight onto the scales and ensuring the digital output read accurately.
Heavy coats and school blazers were removed prior to measurement. Year 8 height and weight was measured with shoes on. However, on advice from AES epidemiologists (AR and CO), it was felt that shoe (heel) size could introduce a confounding variable thus for Year 2 children, height and weight measures were conducted with shoes off.

Figure 5.5.4 Height stand and digital weighing scales

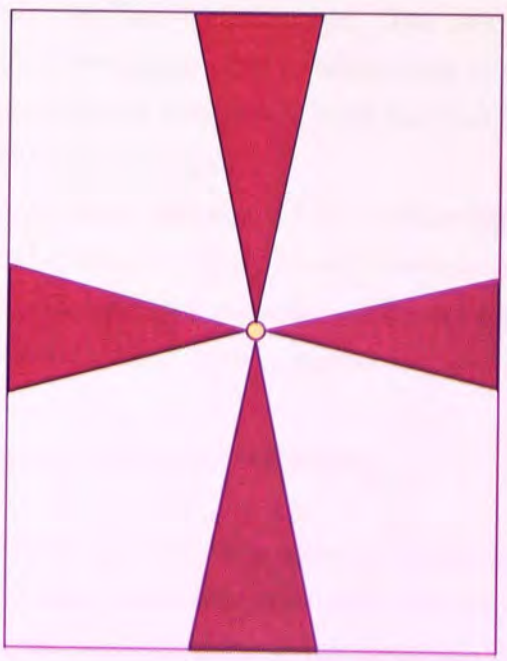


Figure 5.5.5 Maltese cross fixation target

5. Questionnaire and Activities: Children waiting for measurements participated in many informative activities set up by the AES team, following recommendations from the feasibility study. For Year 8 children, these ranged from optical illusions and eye activities (e.g. 'finding the blind spot'), to watching videos on university life (kindly provided by Aston University Schools Liason).
For Year 2 children, a worksheet consisting of dot-to-dot and basic wordsearch puzzles were distributed for the children to complete.
Within both cohorts, cyclopleged children experiencing focusing difficulties at near were provided with a temporary pair of +2.50DS ready readers to complete their activities/questionnaire.

6. Refractive Error: Cycloplegic refractive error was determined using the Shin-Nippon SRW-5000 (Shin Nippon, Japan) infra-red binocular open-field autorefractor (Section 3.3.2). The child was instructed to fixate a high contrast coloured (red) Maltese cross located a minimum of 3 metres away (Figure 5.5.5). Three measures of refraction were taken in both eyes and a printout obtained of readings. The Maltese cross was coloured red to attract the attention of young children.

7. Biometry: Ocular biometry was taken on the cyclopleged eye using the *Zeiss* IOLMaster (Jena, GmbH). On entry of the child's details into the machine, the child was instructed to fixate a red light within the IOLMaster. On steady fixation, 3 measures of axial length were recorded per eye. Measurements were considered valid if the SNR (signal:noise ratio) was greater than 2.0, as recommended by manufacturers (IOLMaster manual, 2003).
Following axial length, 3 measures of corneal radius were taken in each eye. The child fixated a yellow light and the investigator aligned the eye with a hexagonal array of light points imaged onto the cornea (Section 3.4.2). The joystick was depressed once a central light point was focused and a reading was taken, providing the corneal radii of both principal meridia.
The final biometric measure was the anterior chamber depth (Section 3.4.3). A secondary off-axis light source, analogous to a slit lamp optic section, was shone obliquely through the cornea and the distance measured between light reflected off the cornea and light reflecting off the crystalline lens section (i.e. the ACD). Five measures were simultaneously taken from one recording and averaged by the machine.
All biometric data were printed to provide a hard copy of the child's measurements.

8. Completion: On completion of measurements, children were asked whether they were comfortable with their vision and reassured that any near vision difficulties and glare experienced were temporary and would return to normal. Each child was handed a sheet containing advice for parent/guardians on the specific eye drops used (Appendix 5).

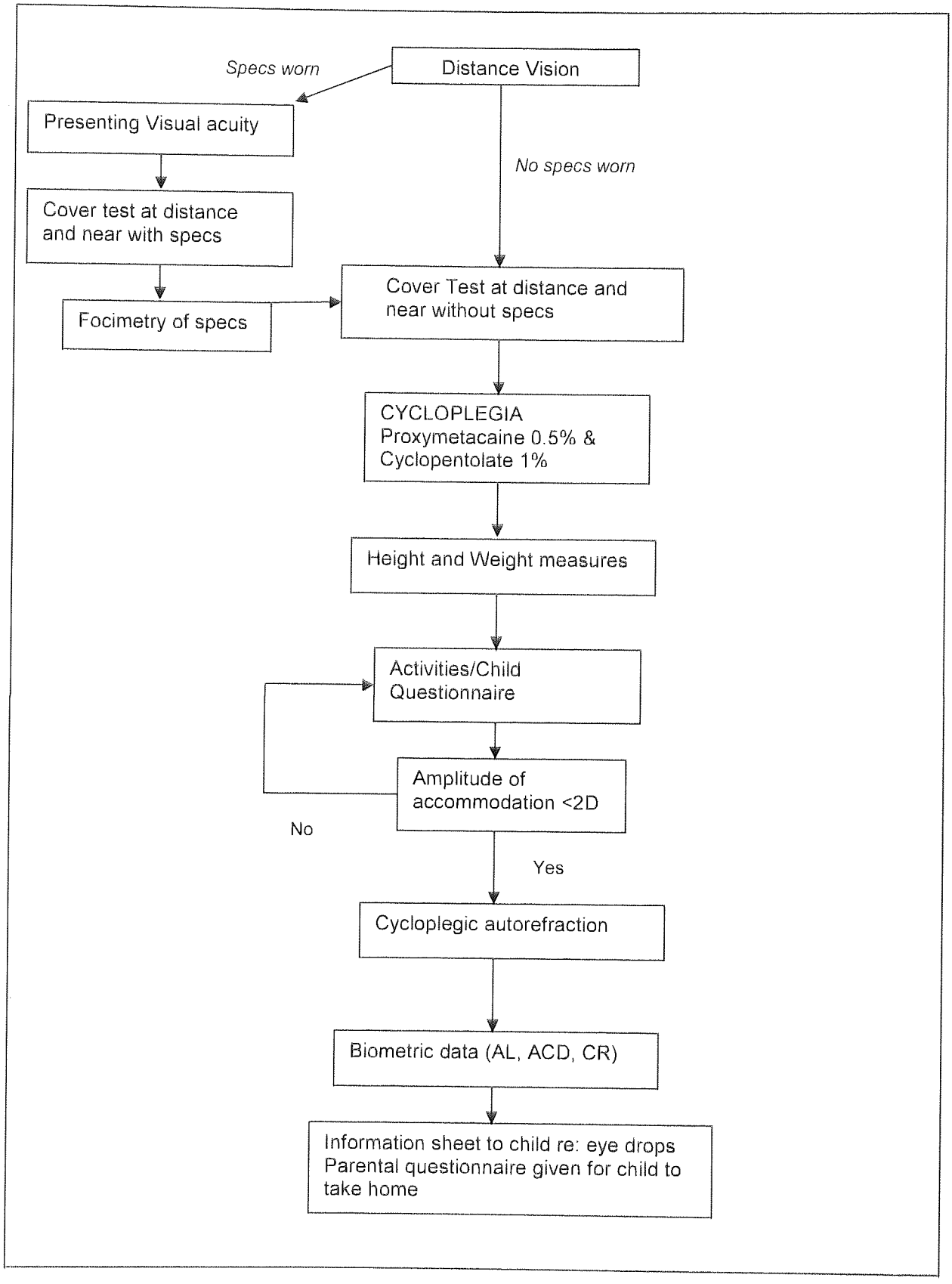


Figure 5.5.6 Flowchart of AES study protocol

In addition, the parental questionnaire was distributed for the attention of the parent/guardian. As a gesture of gratitude for participation, each child was given a named certificate of participation, a branded pen (Year 8) or pencil (Year 2).

5.5.3 Data Entry

Data collected from schools was processed electronically. Raw data was initially entered into a Microsoft *Access* database after converting the name of each child into a 4/5 digit alphanumeric code. The first two digits of the code identified the school of the child with the remaining digits based on the child's name. To render results and questionnaire data anonymous, only codes were listed alongside data and a separate confidential file was created to identify the name of the child from their code.

A statistical package was used (Stata Intercooled version 9, StataCorp, Texas) to enter measurements and analyse both recorded data and questionnaire responses. Coded data was eventually entered directly into the Stata database without the use of Access. Examples of completed recording sheets are provided for 6 children (3 from each age group) in Appendix 5. An example of entered Stata data is provided for 30 children from each age group in Appendix 6.

Measurement outcomes were analysed as a single average value of the respective mean values from both eyes. The approach to analysing data recorded from the two eyes of an individual has been reviewed in previous literature (Murdoch *et al.,* 1998), with authors recommending the use of data from both eyes to increase the precision and power of results (Ray and O'Day, 1985; Newcombe and Duff, 1987). Recent reviews of eye laterality (i.e. greater refractive error in one eye) have shown that ocular dominance can influence refractive growth, with dominant eyes, invariably the right eye in over 90% of cases (Mansour *et al.,* 2003) showing a more myopic refraction (Cheng *et al.,* 2004; Goldschmidt *et al.,* 2004).

The use of averaged data can lead to a loss of information created by pooling results together. However, this loss is thought to be less than that from single eye analysis, in particular if a high degree of correlation exists between eyes (Murdoch *et al.,* 1998). The level of correlation between right and left outcome measures in the AES was very high (Table 5.5.1), justifying the use of averaged data in the AES to ensure full inclusion of data without any loss in precision or power from single eye analysis.

Interocular Correlation	Year 2	Year 8
Mean refractive error (D)	+0.93	+0.92
Axial length (mm)	+0.97	+0.97
Corneal curvature (mm)	+0.95	+0.97
Anterior chamber depth (mm)	+0.80	+0.82

Table 5.5.1 Pearson correlation coefficients (r values) of right eye *vs.* left eye for each ocular measurement as a function of age group measured. All coefficients are statistically significant ($p<0.001$ in all measures)

5.5.4 Referral

After analysis of results, the parents/guardian of children who the AES team felt would benefit from a full eye examination were sent a letter via the school requesting that the child be seen by an optometrist for a full eye examination. The clinical referral criteria employed by the AES team is specified below:

- Uncorrected vision ≤ 0.2 logMAR (6/10) in either eye irrespective of refractive error measures
- Mean myopia SER ≤ -0.50D in either eye
- Mean hyperopia SER ≥ +2.00D in either eye
- Mean astigmatism ≤ -1.00DC in either eye
- Strabismus

A child presenting with strabismus was sent a referral letter stating that this was the finding (irrespective of spectacle wear) and for parents/guardian to seek optometric attention if they and their eye care practitioner were unaware of the strabismic eye.

In addition to referrals for uncorrected children, if a child presented with spectacles at the time of study with a corrected VA better than the referral criteria (0.2 logMAR each eye), a routine letter was sent requesting that the child's normal eye examination schedule be maintained. If the child had left his/her spectacles at home, a letter was sent stating that this was the case and that results were unable to determine the adequacy of the child's visual acuity with their spectacles *in situ*.

5.6 MODIFICATIONS OF PROTOCOL

The school response (SR) rate based upon the recruitment protocol outlined in Figure 5.2.1 transpired to be lower than anticipated. Of 22 secondary schools (Year 8 children) applied to between September 2005 – June 2006, 6 schools agreed to participate in the study (27.3%), 11 schools declined (50%) and 5 schools did not respond despite repeated efforts to contact them. The most frequent reason for non-participation was a lack of time and available space in the school to accommodate the eye study within a very busy curriculum. One school did raise a concern with the use of cycloplegia as their grounds for non-participation.

For primary/infant schools, 14 schools were targeted using the initial methodology between 2005 - 2006. Of these, 5 schools (35.7%) initially agreed to participate. However, 2 of these schools did not respond further to requests to arrange a meeting despite repeated attempts to contact them. A third school received no consent forms back from their parents, stating a general lack of interest from parents to all school events; this left 2 schools partaking in the study (14.3% of original number targeted). Of the remaining 9 schools, 6 schools did not wish to participate (42.9%) and 3 schools (21.4%) did not reply, again despite the best efforts of the AES team to initiate contact.

Once a school concurred to participation, the following stage was to obtain consent from parents/guardians. For participating Year 8 schools, affirmative parental response (PR) rates varied greatly (median PR: 31.2%, range: 4.8 - 76.7%). From the 2 primary schools taking part, the median PR rate was 17.0% (range: 13.0 – 21.1%).

With these low SR and PR response rates in mind, modifications were made to the AES protocol to encourage greater participation. The revisions were as follows:

1. The initial introduction of the Eye Study was performed by a senior member of the AES team (BG or NL) in place of the introductory letter. The Headteacher of a school was contacted directly by telephone and informed of the study. This promoted the profile of the study and enabled the correspondent to fully clarify the minimum imposition of the AES on the regular school day, which was more effectively conveyed through a telephone call. Following acceptance by the Headteacher, a letter was sent out to the school detailing study specifics (Appendix 3).
2. The introductory school letter to the Head teacher was shortened following consultation with a Head teacher (EI)[4] whose school had the highest PR rate of 77%. The minimised demands of the AES on the school timetable was further emphasised in the letter (Appendix 3).

[4] Miss Elspeth Insch, Head Teacher, King Edward VI Handsworth School

3. A greater frequency of communication was instigated with target schools. Upon invitation, schools were encouraged to reply back to the AES team, whether or not they wanted to participate in the study. The advantage of receiving back replies from all schools was a reduction in avoidable time spent chasing schools who had not replied.
4. The emphasis on cycloplegia was minimised in parental letters, to fully inform them of potential side-effects and risks yet minimise apprehension caused which would act as a deterrent. Anecdotally, almost all children who received the drops did not find the instillation process distressful.
5. Reminder parent letters were created and distributed to children as a follow-up to initial introductory packs (Appendix 4). This was an additional step introduced to bolster PR rates. The AES team were very interested in receiving responses from parents, regardless of whether consent was provided for the study. This was in order to determine whether low PR rates were as a result of refusal to the study itself (e.g. apprehension to cycloplegia) or possibly that the letters were not reaching parents at all. The use of a reminder letter, although open to the same systematic error, increased the probability of at least one of the 2 letters reaching a parent/guardian.
6. The parental and child questionnaires were modified in the quantity and order of questions asked (Appendix 8). The changes were to reduce the apparent size of the questionnaire without losing any necessary information required for analysis. Specific questions were omitted from the redesigned questionnaires after consultation with epidemiologists (AR and CO).
7. As an added safety feature, disposable sunglasses were introduced to all participating children from September 2006. This was to minimise glare and retinal exposure to UV radiation caused by pupil mydriasis.

Full ethical approval was obtained for revisions to the Eye Study by the Aston University Ethical Committee (Appendix 2).

5.6.1 Changes to SR and PR rates

The new protocol was implemented between September 2006 – June 2007. The majority of schools targeted using the revised protocol were primary schools (n= 47), with 14 having been targeted using the initial protocol. This contrasted to secondary schools which were predominantly targeted using the initial protocol (n= 22), with only 6 targeted using the new protocol. Therefore, strict comparison of the overall difference in SR and PR rates as a function of protocol would not be valid due to the confounding effects of type of school e.g. primary schools may have had a greater flexibility to

accommodate the AES accounting for an increased SR rates as opposed to the new methodology making an actual difference.

By analysing primary schools alone as a function of old *vs.* new protocol, the proportion of primary schools that took part in the AES (as a percentage of the number that were targeted) increased from 14.3% to 31.9% respectively (Figure 5.6.1). In addition, the number that did not reply diminished from 21.4% to 6.4%. However, the number of schools refusing to take part in the study also increased from 42.9% to 51.1%.

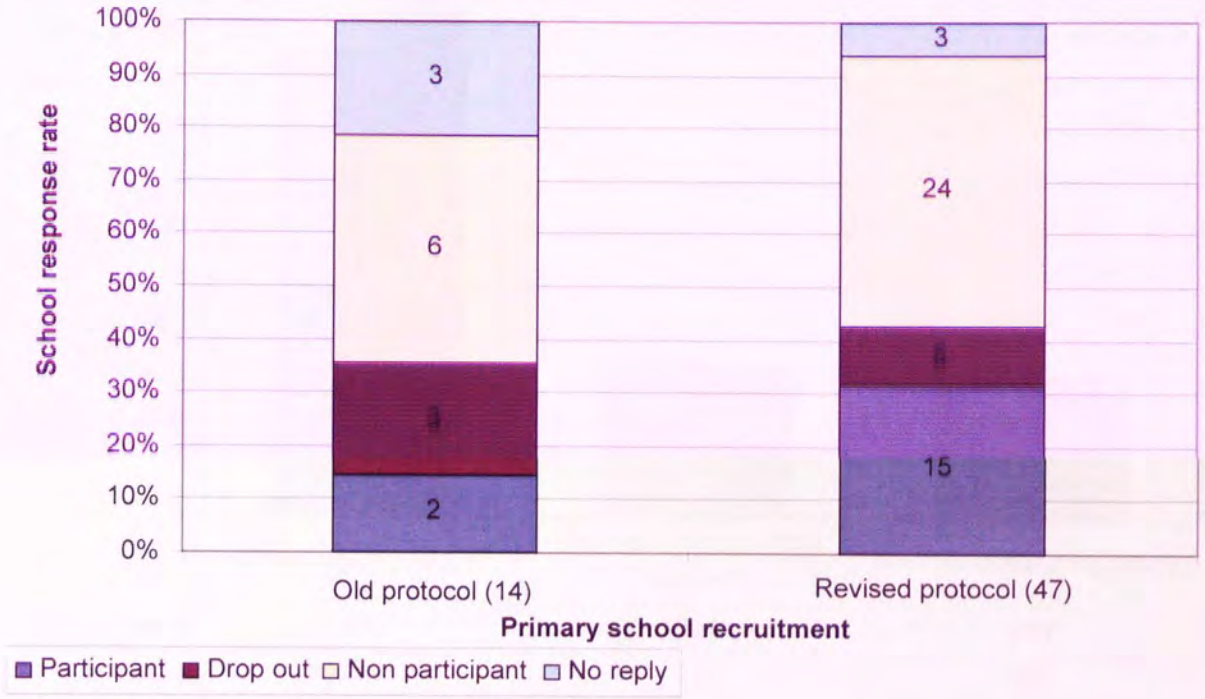


Figure 5.6.1 The impact on primary school recruitment of the old (n= 14) *vs.* the revised (n= 47) protocol. Participant School = a school which took part in the AES; Drop out = a school that initially agreed to take part but later dropped out; Non participant = schools that replied back negatively; No reply = schools from which a reply was not received. Numbers within bars refer to school frequency. Secondary schools have not been analysed due to a lack of secondary schools applied to using the revised methodology (n= 6)

It is apparent that the increase in primary schools both agreeing and refusing to take part in the study was a result of a drop in the number of schools that did not reply back at all.

With regard to secondary schools, 6 were applied to using the revised protocol, of which 1 school agreed to participate (16.7%), 4 replied back negatively (66.7%) and 1 school did not reply (16.7%) despite repeated attempts to follow-up the initial enquiry.

Examining the affirmative PR rate in primary schools as a function of new *vs.* old protocol, the median PR rate for the new protocol was found to be 29.2% (range: 13.3 – 60%), a considerable improvement from that using the old protocol (17.0%, 13.0 – 21.1%).

Despite the increased response rate on modification of the protocol, PR and SR rates fell significantly short of the 75% participation rates determined by the Sydney Myopia Study (Ojaimi *et al.*, 2005a) although they appear to be in line with participation rates from the Orinda Longitudinal Study of Myopia (Rah *et al.*, 2002).

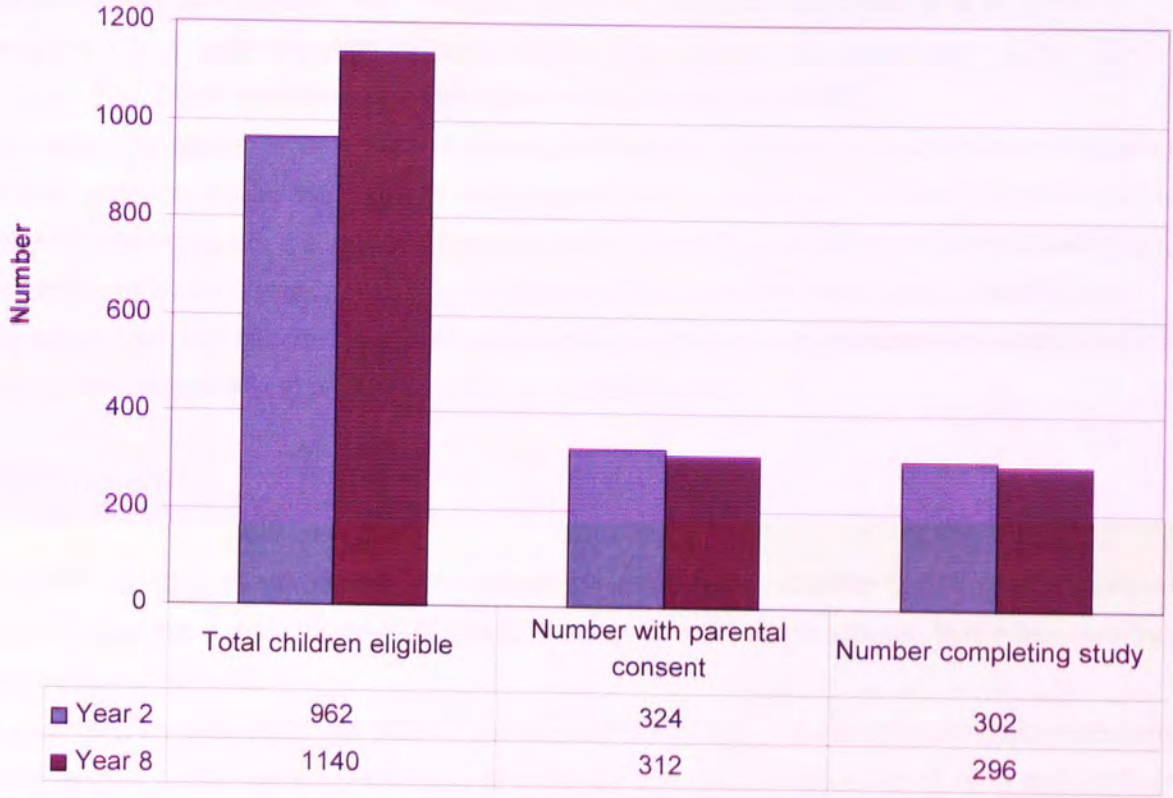


Figure 5.6.2 Illustration of the proportion of participants within each year group as a function of total number invited and thereafter given parental consent. Figures are an overall representation using both old and new protocols. It can be seen that the once a child obtained parental consent, a majority partook in the study

CHAPTER 6

THE PREVALENCE OF MYOPIA IN UK SCHOOL CHILDREN AND ITS VARIATION WITH AGE AND ETHNICITY

6.1 INTRODUCTION

Data on the distribution of refractive error in UK children is sparse and has been limited by sampling frame (McBrien and Adams, 1997; Pointer, 2001) and methodology (Williams *et al.*, 2005) in comparison to population-based epidemiological studies conducted abroad such as the RESC[1] (Negrel *et al.*, 2000) and the Sydney Myopia Study (Ojaimi *et al.*, 2005).
The Aston Eye Study (AES) is the first population-based cross-sectional study in over 40 years to assess comprehensively the status of child refractive error and ocular biometry in a UK cohort by age and ethnic background. It is also the first study to compare the prevalence of refractive error and biometric correlates across White, South Asian and Black children specifically. The AES is an ongoing project and the current chapter details the distribution and prevalence of refractive error as a function of demographical profile in the cohort studied to date.

6.2 METHODS

The AES set-up and methodology is systematically described in Chapter 5. Full ethical approval was obtained from the Aston University Ethics Committee and the study adhered to the tenets of the Declaration of Helsinki.
In summary, an initial target list of local primary and secondary schools in Birmingham was compiled using random cluster sampling methods stratified by age, deprivation index of ward and excluding schools with a predominance of a single ethnic group (>70%). The Head teachers of these schools were contacted and invited to participate in the study.
On agreement of participation by a school, an initial meeting was organised and parental consent forms distributed to all Year 2 or Year 8 children. Informed consent was obtained from the parents/guardians of participating children (Year 2 and Year 8). In addition, on the day of the study, signed consent was taken from participating Year 8 children with verbal assent taken from Year 2 children and documented by an investigator (Consent and Assent Sheets, Appendix 5).

Examination procedures are described in Section 5.5 and were performed by UK registered optometrists experienced in the techniques and protocol employed (BG, NL and PS).

[1] Refractive Error Study in Children

Initially the child's vision/visual acuity was measured monocularly using a computerised Bailey-Lovie test chart with logMAR notation (Test chart 2000, Thompson Software Solutions, Herts, UK). The oculomotor balance of the child was measured by means of a cover test at both distance (a target on the test chart) and near (target on a budgie stick at 33cm) with and without spectacles.
Following this, cycloplegia was induced in each participating child (0.5% proxymetacaine followed by 1% cyclopentolate HCl 1 drop of each drug separated by 1 - 2 minutes in both eyes). Height and weight measures were also recorded at this time.

Twenty five minutes after instillation of drops, the child's accommodative amplitude was measured using an RAF rule. Cycloplegia was considered full when monocular accommodative amplitudes measured less than 2D binocularly (when the N5 target on an RAF rule could not be read at its maximal distance away from the child's nose). If amplitudes were not <2D within 40 minutes, a further drop of cyclopentolate was added in both eyes to facilitate cycloplegia. A second drop was necessitated in 6 Year 2 children and 2 Year 8 children.
Once the child was deemed to be fully cyclopleged, refractive error was measured using an objective binocular open-field autorefractor (Shin-Nippon SRW-5000, Shin Nippon, Japan). Three sphero-cylindrical measures were taken in each eye with the child fixating a high contrast Maltese cross target at a distance of 3 metres away. Following autorefraction, ocular biometry measures were recorded using the *Zeiss* IOLMaster (Jena, GmbH), a device measuring axial length (AL), corneal radius of curvature (CR) and anterior chamber depth (ACD) using non-contact methods (Chapter 3).

6.3 DEFINITIONS

Myopia was defined as a mean spherical equivalent refraction (SER) ≤ -0.50D in at least one eye. Hyperopia was defined as a mean SER ≥ +2.00D SER in either/both eyes, as long as neither eye was myopic. Emmetropes were defined by a mean SER > -0.50D and a mean SER < +2.00D in both eyes. Astigmatism was defined by a cylindrical power ≤ -1.00DC in either eye although the relationship of astigmatism to SER is beyond the scope of this chapter.

Ethnicity was self-reported by Year 8 children and confirmed via replies from parental questionnaires. Year 2 ethnicity was estimated by the investigator at the time of measurement by asking a child what (other) language(s) they spoke at home and where their parents originated from. The responses were confirmed or otherwise by return of Year 2 parental questionnaires.
An analysis between presumed (examiner) ethnicity and confirmed ethnicity (through parental questionnaire reply) showed an excellent level of agreement (kappa= 0.93, $p<0.001$), confirming that the examiner's judgement in the absence of parental confirmation of the child's ethnic background

was a valid assumption and similar to the level of agreement determined by Jones *et al.* (2001) in the CLEERE[2] study.

6.4 SAMPLE CHARACTERISTICS

6.4.1 Response rates

With regards to secondary schools (Year 8), of 28 schools invited, 7 replied back and consented to participate (25%), 15 (53.6%) did not wish to take part and 6 (35.3%) did not reply back at all.
Of 61 primary schools (Year 2) invited to participate, 25 initially agreed to take part (41.0%) although of these, 8 (13.1%) schools later withdrew leaving 17 participant schools in total (27.9%). Thirty schools (49.2%) did not wish to take part whilst 6 failed to reply to invitations (9.9%).

Once a school agreed to take part, information letters and consent forms were distributed to the children. For the Year 8 cohort, 1,140 consent forms in total were distributed and for the Year 2 cohort, 962 consent forms were handed out. The median parental response (PR) rate, irrespective of whether consent was given, was significantly lower than expected although the large range illustrates the large variation in response rate between schools (Year 8 median PR rate: 28.9%, range: 4.8-76.7%. Year 2 median PR rate: 40%, range: 13.0-68.9%).
In total, 312 children (27.4% of total consent forms distributed) from Year 8 and 324 children from Year 2 (33.7% of total forms distributed) were given parental consent to take part in the study.

Once parental consent was provided, the response rate from enrolled children on the day of the study was excellent. The majority of children were present on the study day and partook in the measurements (Year 8 median child acceptance rate: 93.9%, range: 78.9-98.3%; Year 2 child acceptance: 93.3%, range: 60 -100%).
Of children in the Year 8 cohort, 16 did not take part on the day, principally due to absence on the study day (n= 14) or a fear of drops (n= 2).
From the Year 2 cohort, 22 children did not participate on the day of the study. The predominant factor for non-participation was once more absence from school on the study date (n= 17). Three children did not wish to undergo cycloplegia and 2 children were excluded by investigators, one child due to nystagmus secondary to albinism (and hence poor fixation) and the second child due to Down's syndrome. Due to poor communication skills in this child, it was felt that she should be excluded from measurements. By virtue of the above responses, the final numbers of participants in the AES were 296 Year 8 and 302 Year 2 children.

[2] Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error

6.4.2 Data Analysis

Data for the raw measurements were entered into a Microsoft (MS) *Access* database after coding each child with a unique 4/5 digit alphanumeric code. Only codes were listed alongside the data thus masking the identity of the child from investigators.
A statistical package was used (Stata Intercooled version 9, StataCorp, Texas) to enter in raw recordings and perform data analysis, with periodic use of MS *Excel* for table and graph creation. Examples of statistical output tables in Stata are displayed in Appendix 7. Refractive error and biometry measures are given as average values for both right and left eyes, except for the following children in whom only single eye measurements were possible, thus these have been taken as representative for overall recordings:
One child from Year 8 (KE3ER) was cyclopleged and measured in her left eye only as she was on a course of topical medication for an infection in her right eye. Of the Year 2 cohort, one child (BCUM) was measured in the right eye only due to left eye corneal warpage preventing objective measures of refractive error and biometry from being taken. A second child (BCUA) had very poor fixation and therefore measures of refraction could only be taken in his left eye. Both children were fully cyclopleged in both eyes.

6.4.3 Gender and Ethnicity

Of the 296 Year 8 participants, the mean age (± SD) was 13.12 ± 0.33 years (range 12.33 – 14.04 years) with 165 females (55.7%). The wide age range of the cohort was accounted for by a child (GBLF) who had just turned 14 years of age at the time of examination. All other pupils were within the desired age range (12-13 years).
Within the Year 2 cohort (n= 302), the mean age was 7.16 ± 0.33 years (range 6.20 – 7.86 years) with an approximately equal gender split of 148 females (49%) to 154 males (51%).
Tables 6.4.1 and 6.4.2 display the ethnic composition of Year 8 and Year 2 participants respectively. Ethnicity was categorised into 6 main groups based on the classification of ethnicity from the 2001 Census for England and Wales (National Statistics Office, 2001):

- White: White British, Irish and European and Other White.
- Asian: Asian Pakistani, Indian, Bangladeshi and Other South Asian.
- Black: Black African, Black Caribbean and Black Other.
- Mixed: Both parents from a combination of White, South Asian or Black.
- Chinese: Including other East Asian descent i.e. Taiwanese, Vietnamese.
- Other: any ethnicity not stated above.

In accordance with Census definitions and for the purposes of this thesis, the term 'Asian' will refer to people of South Asian descent. The term Chinese will be used for people of East Asian background.

Ethnic Group	n	Mean age ±SD (yrs)	Female (%)	Grammar (%)[3]
White	115	13.21 ± 0.31	59 (51.3)	90 (78.3)
Asian	114	13.01 ± 0.32	63 (55.3)	63 (55.3)
Black	40	13.11 ± 0.31	25 (62.5)	10 (25.0)
Chinese	5	13.19 ± 0.45	4 (80.0)	5 (100.0)
Mixed	15	13.20 ± 0.35	9 (60.0)	5 (33.3)
Other	7	13.21 ± 0.26	5 (71.43)	2 (28.57)
Total	**296**	**13.12 ± 0.33**	**165 (55.7)**	**175 (59.1)**

Table 6.4.1 Sample characteristics of the Year 8 cohort. Percentage values in parentheses

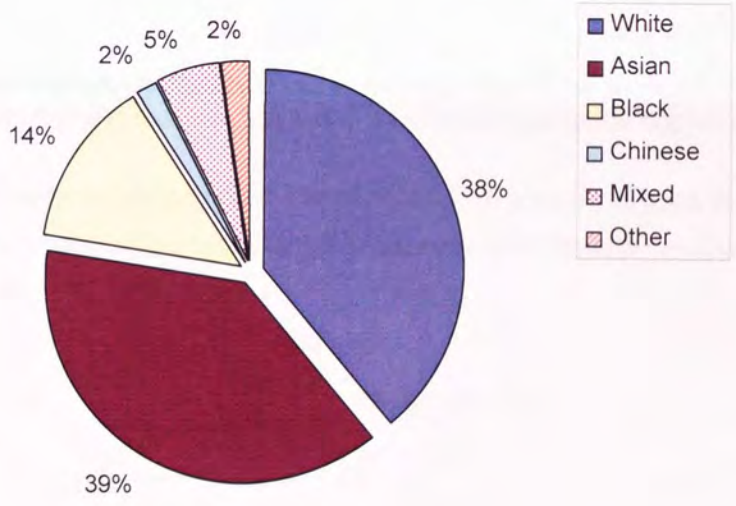


Figure 6.4.1 Composition of the Year 8 cohort as a function of ethnicity

[3] Children attending a grammar school

Comparing the ethnic composition of the AES Year 8 cohort with that of children aged 10 - 14 years of age in Birmingham schools (National Statistics Office, 2001), a comparative illustration is shown in Figure 6.4.2.

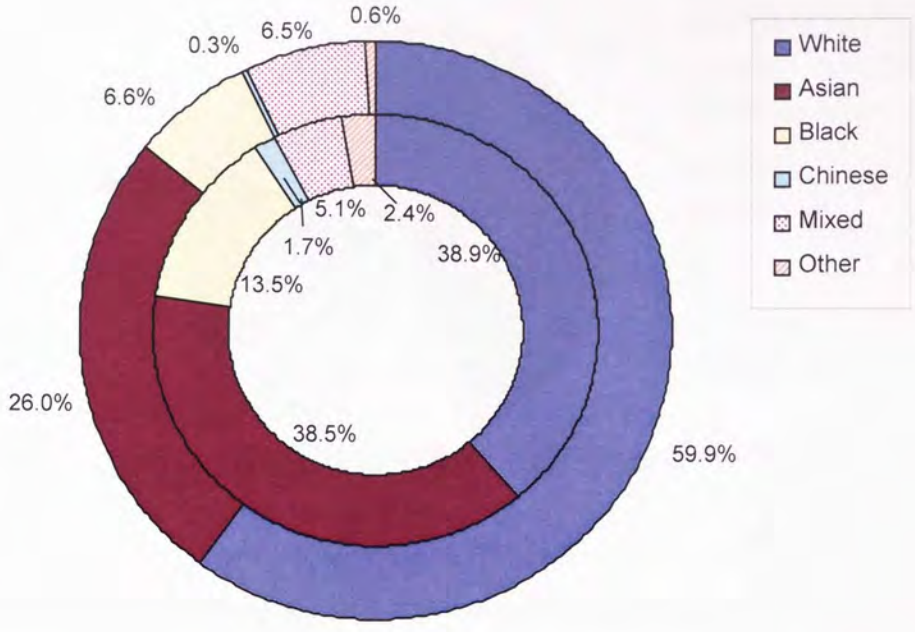


Figure 6.4.2 A comparison of the ethnic mix of the AES Year 8 cohort (inner ring) with the ethnic composition of Birmingham students aged 10 – 14 years of age (outer ring) in 2004

The Year 8 AES sample had a greater representation of minority groups in comparison to Birmingham as a whole, which has a larger proportion of White children than that seen by the AES (60.1% *vs.* 38.9%).

Ethnic Group	n	Mean age ±SD (yrs)	Female (%)
White	51	7.09 ± 0.34	24 (47.06)
Asian	193	7.17 ± 0.33	96 (49.74)
Black	36	7.23 ± 0.32	19 (52.78)
Chinese	2	6.98 ± 0.12	0 (0.00)
Mixed	15	7.09 ± 0.28	8 (53.33)
Other	5	7.25 ± 0.18	1 (20.00)
Total	**302**	**7.16 ± 0.33**	**148 (49)**

Table 6.4.2 Sample characteristics of the Year 2 cohort. Percentage values in parentheses

The Year 2 cohort was disproportionately represented by a high number of South Asian children in the cohort (Table 6.4.2 and Figure 6.4.3), constituting 64% of the total cohort size.

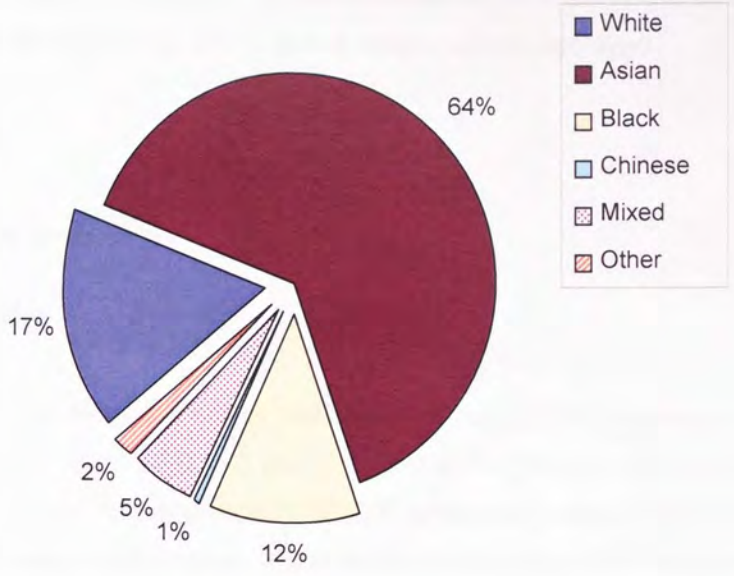


Figure 6.4.3 Composition of the Year 2 cohort as a function of ethnicity

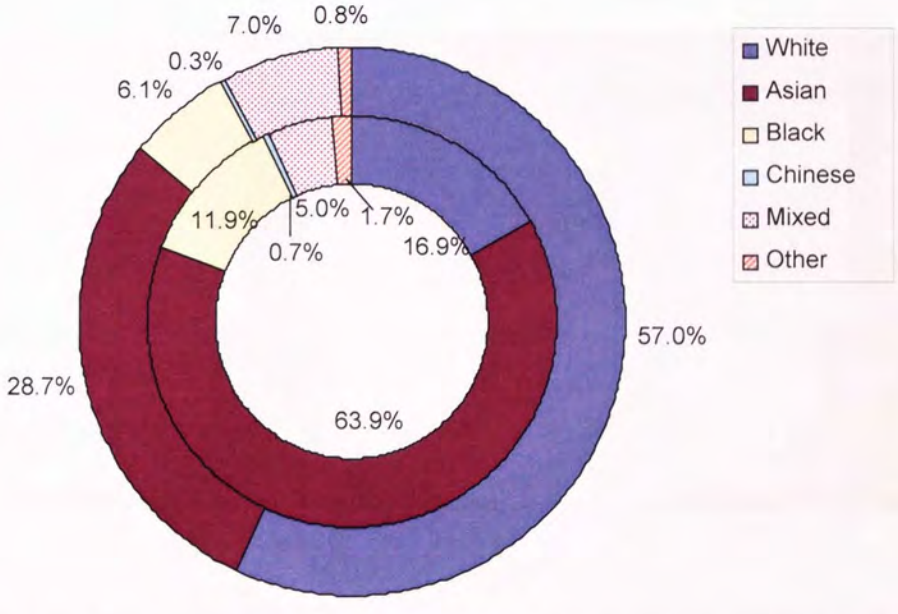


Figure 6.4.4 A comparison of the ethnic mix of the AES Year 2 cohort (inner ring) with the general ethnic composition of Birmingham students aged 5 – 7 years (outer ring) in 2004

In both Year 8 and Year 2 cohorts (Figures 6.4.1 - 6.4.4), it can be seen that the proportion of ethnic minority children in the AES is considerably greater than that derived from Census data for the population of Birmingham, with a concurrent reduction in the proportion of White participants. Comparison of AES outcomes will focus predominantly on differences between White, Asian and Black children, although other ethnic group results will be displayed.

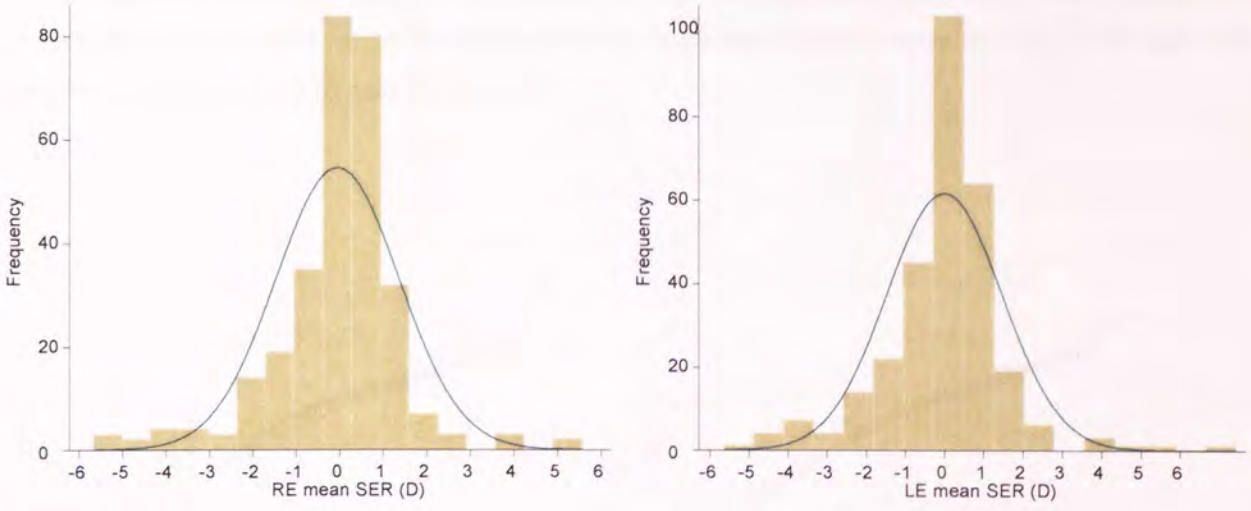
6.5 RESULTS

6.5.1 Refractive Error

6.5.1.1 Normality

Year 8

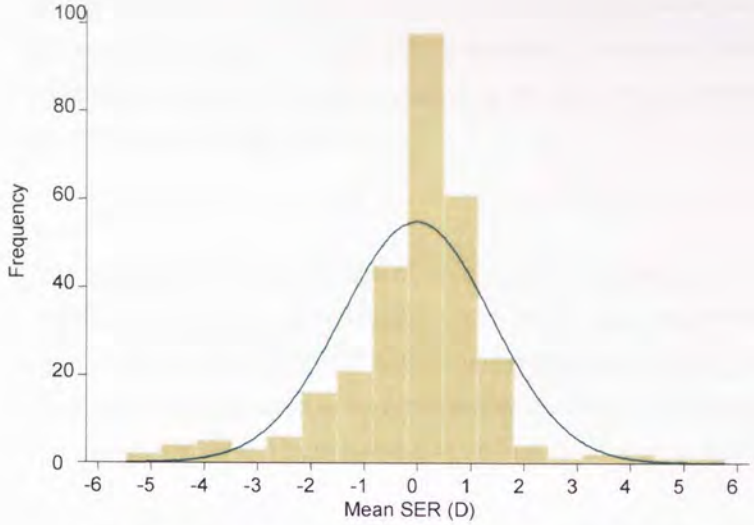
The mean spherical refractive error (mean SER) of the elder cohort as an average of both eyes was -0.02 ± 1.42D (mean SER ± SD = -0.05D ± 1.42 in 295 right eyes measured and +0.00D ± 1.47 in 296 left eyes). The median refractive error (10^{th}-90^{th} percentile) across both eyes was +0.23D (-1.76, +2.23D). There was a high degree of correlation of refractive error between both eyes (Pearson correlation coefficient between eyes; r= +0.92, p<0.001). Refractive error was distributed with a slight negative skew (Figure 6.5.1) in both eyes separately and overall as a combined average (Figure 6.5.2).



A Right Eye: Skew= -0.62 p<0.001, Kurtosis= 6.55 p<0.001

B Left Eye: Skew= -0.19 p= 0.17, Kurtosis= 7.03 p<0.001

Figure 6.5.1 A distribution showing the mean SER in Year 8 children. A normal density plot is superimposed by the continuous line



Skew= -0.54 p<0.001, Kurtosis= 6.27 p<0.001

Figure 6.5.2 Distribution of mean SER as an average of both eyes in Year 8 children

Distributions were assessed for normality (i.e. fit to a Gaussian distribution) to confirm the use of parametric analyses. Measures of skew and kurtosis are often sensitive in epidemiological studies to minor deviations from a perfect normal distribution, especially if the sample size is large (Woodward, 2005). Therefore, a better indicator of normality is a normal probability plot, where data measured is plotted against expected values if values were from a perfect normal distribution. For normality to be assumed, a straight line should be derived.

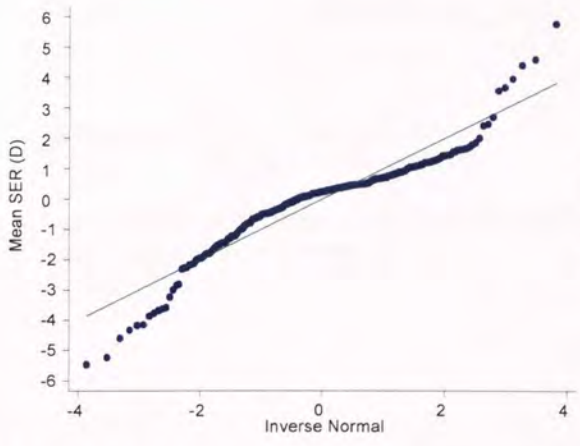


Figure 6.5.3. A normal plot of Year 8 mean SER showing deviation from normality

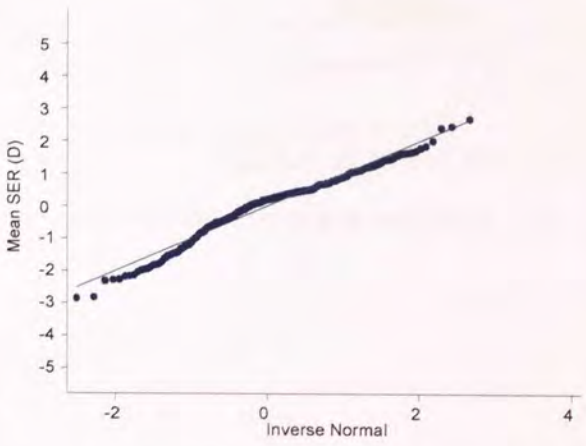


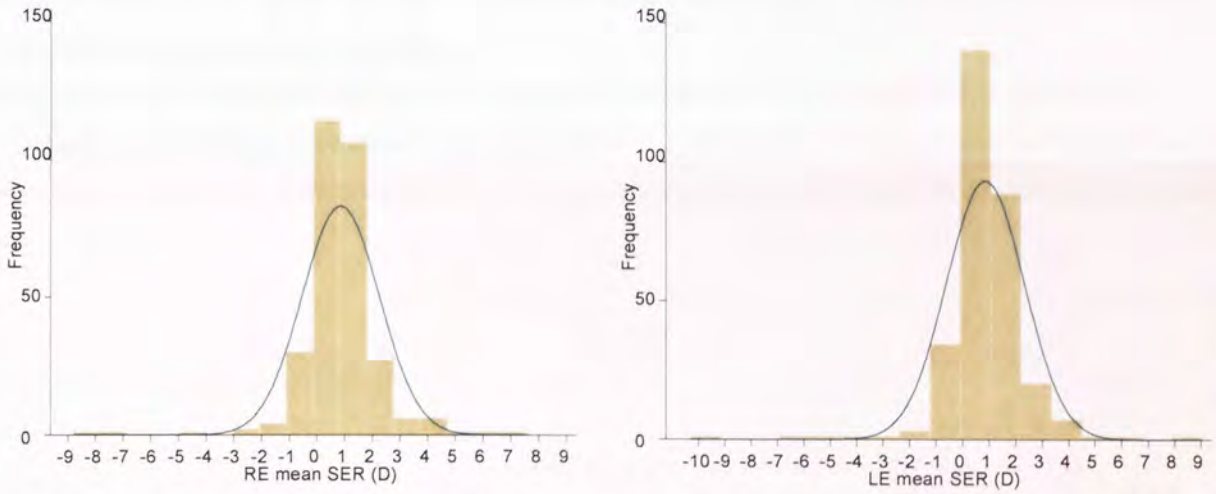
Figure 6.5.4 Year 8 normal plot after exclusion of outliers (> 2 SD from mean)

The principal areas of deviation in Figure 6.5.3 lie towards the extremes of refractive error where several outliers exist. If mean SER is curtailed to exclude these outliers (only mean SER values within 2 SD of the mean are included), a straight line is achieved (Figure 6.5.4). Nineteen children (6.42%) were classed as outliers.

Year 2

The mean SER as an average of both eyes in the younger cohort (mean SER ± SD) was +0.85 ± 1.40D (mean SER ± SD = +0.85D ± 1.40 in 301 right eyes measured and +0.86D ± 1.47 in 300 left eyes). The median SER (10^{th} – 90^{th} percentile) was +0.87D (-0.29, +2.07D). The mean refractive error between eyes was once more highly correlated (Pearson correlation coefficient r= +0.93, p<0.001) indicating a high degree of co-ordinated growth between eyes.

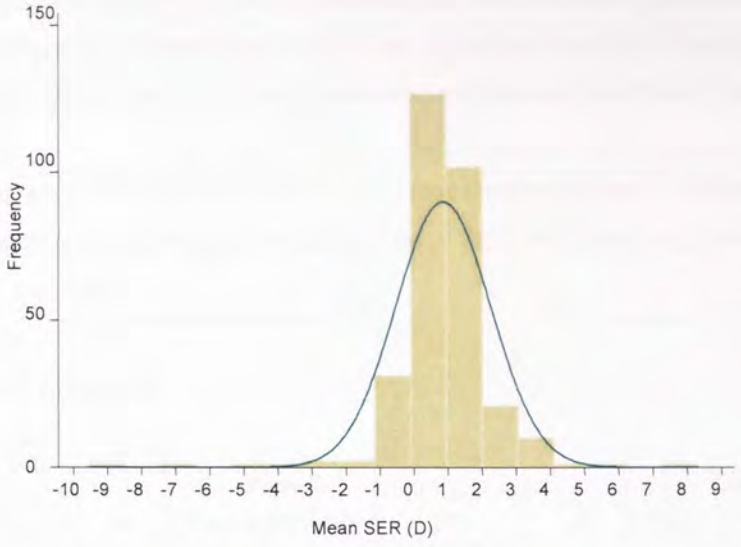
The distribution of refractive error in both eyes separately is shown in Figures 6.5.5 and as an average of both eyes in Figure 6.5.6.



A Right eye: Skew= -1.23, p<0.001
Kurtosis= 17.48, p<0.001

B Left eye: Skew= -1.34, p<0.001
Kurtosis= 20.26, p<0.001

Figure 6.5.5 A distribution showing the mean SER in Year 2 children. A normal density plot is superimposed by the continuous line



Skew= -1.35 p<0.001, Kurtosis= 19.24 p<0.001.

Figure 6.5.6 Distribution of mean SER across both eyes in Year 2 children

A more leptokurtotic distribution can be seen for Year 2 distributions compared to Year 8 children, with higher kurtosis values reported.

A normal plot of the mean SER in Year 2 showed deviation from a straight line (Figure 6.5.7). However, on exclusion of children with mean SER> 2 SD from the mean, a linear relationship was formed (Figure 6.5.8). Sixteen children (5.3%) were excluded on this basis to derive a straight normal plot.

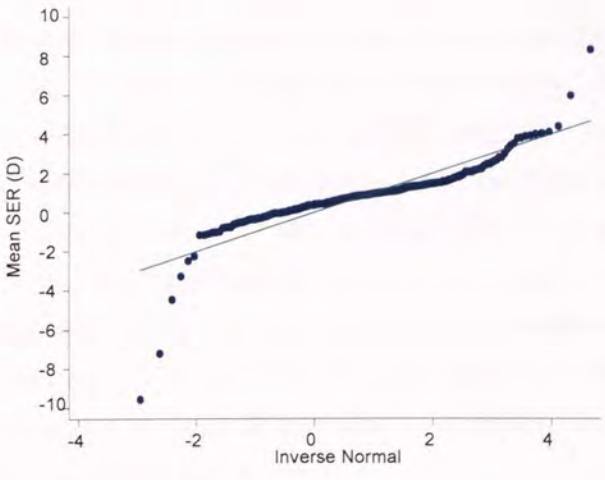


Figure 6.5.7. Normal plot of Year 2 Mean SER

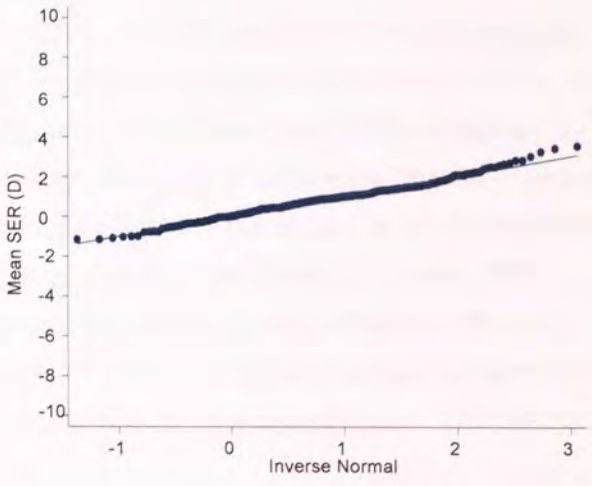


Figure 6.5.8 Year 2 normal plot after exclusion of outliers (>2 SD from mean)

Therefore although the complete data set within both age groups deviates from a Gaussian distribution at the extreme ends of the refractive spectrum, the large majority of refractive data can be classed as normal, enabling parametric methods of analysis to be used.

There was a significant difference in mean refractive error between age groups, with Year 8 children displaying a more myopic refractive error than the younger cohort (two-tailed independent t-test, t= 7.59, p=0.001).

6.5.1.2 Ethnicity

	Year 8			Year 2		
Ethnicity	**n**	**Mean SER (D)**	**SD**	**n**	**Mean SER (D)**	**SD**
White	115	+0.45	1.29	51	+1.31	1.08
Asian	114	-0.43	1.52	193	+0.74	1.57
Black	40	-0.10	0.99	36	+0.73	0.98
Mixed	15	+0.55	1.36	15	+1.05	0.83
Chinese	5	-1.81	1.09	2	+0.01	0.20
Other	7	-0.71	0.99	5	+1.17	0.49
Overall	**296**	**-0.02**	**1.42**	**302**	**+0.85**	**1.40**

Table 6.5.1 Mean refractive error across both eyes as a function of ethnic group in AES participants

Year 8

Examining mean SER by ethnic group (Table 6.5.1), a significant difference was found to exist between ethnic groups (one way between-groups ANOVA, F= 7.59, p<0.001). *Post-hoc* analysis using Scheffe's test determined a significantly lower mean SER in Asians compared to Whites (mean difference Whites – Asians: +0.87D, p<0.001). Blacks also had a lower mean SER compared to Whites although this was not found to be statistically significant (mean difference Whites – Blacks: +0.55D, p= 0.43). Scheffe's test has been employed throughout the thesis as it is a robust *post-hoc* measure conservative to Type 1 errors (Armstrong *et al.*, 2000). The difference in mean SER between Asians and Blacks also did not reach statistical significance (mean difference Blacks – Asians: +0.33D, p= 0.88). Chinese pupils, though low in number (n= 5) demonstrated a significant difference in mean SER compared to Whites (p= 0.04) with a strongly myopic mean SER for the 5 participants (Table 6.5.1).

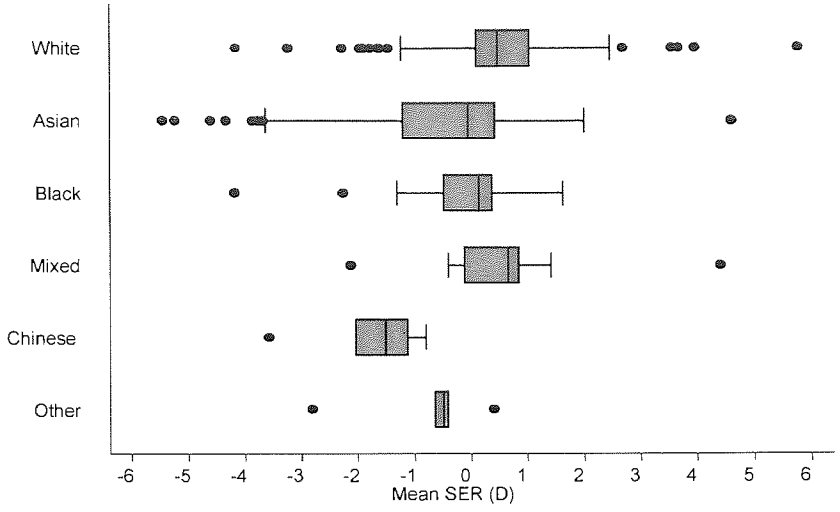


Figure 6.5.9 Box plot of Year 8 mean SER by ethnic group

The negative tail of Asian children (Figure 6.5.9) and myopic outliers indicate a negative skew contributing towards their relatively more myopic SER compared to White and Black children.

Year 2

Within the younger cohort, there were no significant differences in mean SER as a function of ethnicity (one way between-subjects ANOVA, F= 1.64, p= 0.15).

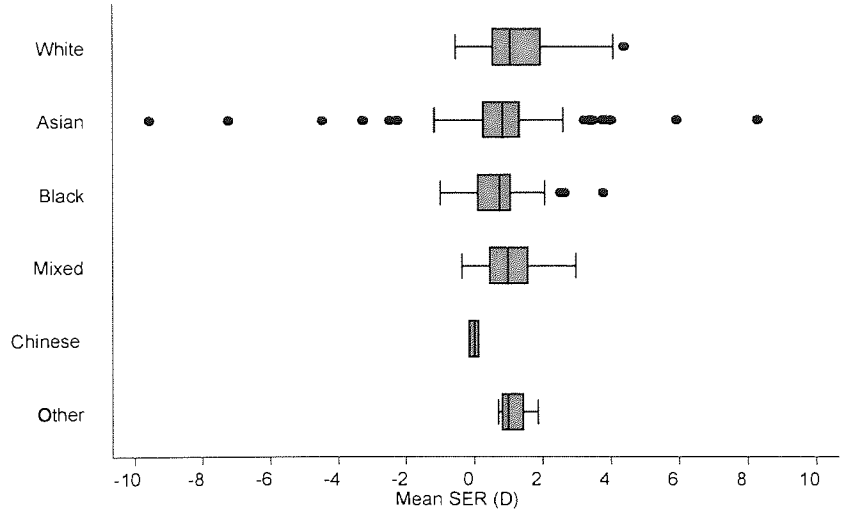


Figure 6.5.10 Box plot of Year 2 mean SER by ethnic group

Variation in refraction between ethnic groups was lower in this cohort than in Year 8 children (Table 6.5.1). In addition, the box widths in Figure 6.5.10 appear narrower relative to Year 8 (Figure 6.5.9), indicating a smaller variation of refractive error in younger children.

6.5.1.3 Gender

Year 8

Mean spherical equivalent refraction (Figure 6.5.11) was found to be more myopic in females compared to males (mean ± SD: -0.17 ± 1.15D *vs.*+0.17 ± 1.58D respectively, two-tailed independent t= 2.09, p= 0.037). However, female gender did not remain a significant main effect after the introduction of ethnicity, which did show statistically significant differences in mean SER (two factor between-subjects ANOVA overall model F= 5.63, p<0.001. Main effect ethnicity F= 7.57, p<0.001. Main effect gender F= 0.00, p= 0.97). A significant interaction effect was also determined (F= 3.72 p= 0.003) suggesting that the difference between male and female mean SER varied across ethnic groups, as illustrated in Figure 6.5.13 with Asian females in particular showing a considerably more negative refractive error relative to other ethnic and gender cohorts.

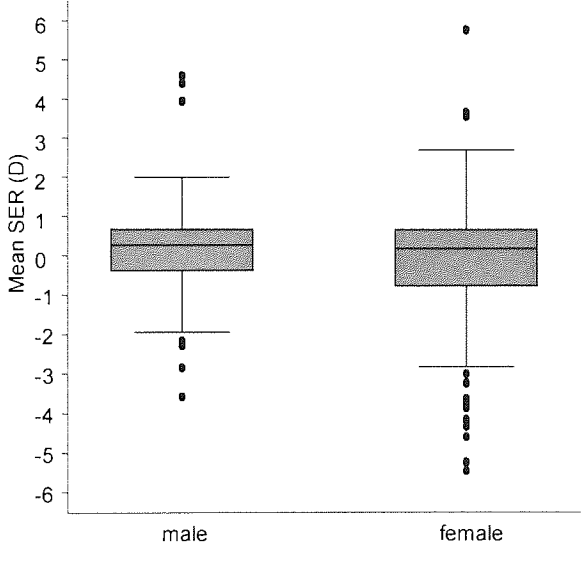


Figure 6.5.11 Year 8 distribution of mean SER by gender

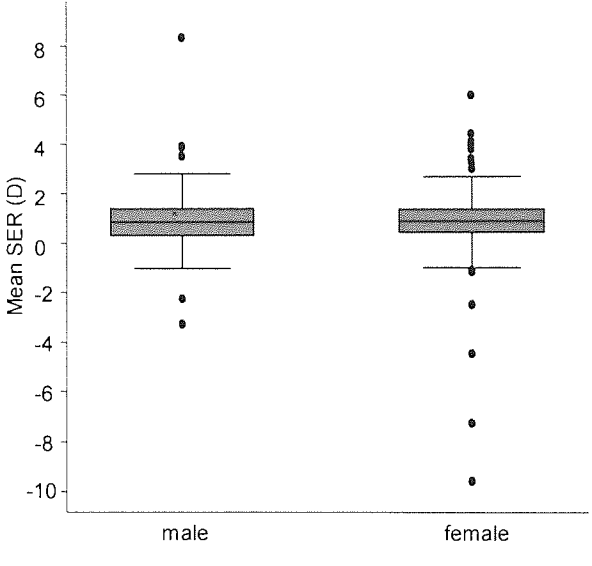


Figure 6.5.12 Year 2 distribution of mean SER by gender

Year 2

The variance of mean SER as a function of gender appeared in younger children to be greater in females compared to males (Figure 6.5.12) However, the mean difference in Year 2 refractive error was not found to be significant between the sexes (mean ± SD: males +0.89 ± 1.14D, females +0.82 ± 1.64D, two-tailed independent t= 0.44, p= 0.66).

Examining the effect of ethnicity and gender on mean SER, it can be seen that White children had a more positive mean refraction compared to Asians and Blacks (Figure 6.5.14). However, neither the main effects of ethnicity or gender were found to vary significantly with respect to mean SER (two factor between-subjects ANOVA overall model F= 0.88, p=0.55. Main effect ethnicity F=1.61, p=0.16. Main effect gender F=0.08, p=0.78). In addition a significant interaction effect was not found (F= 0.13, p= 0.97).

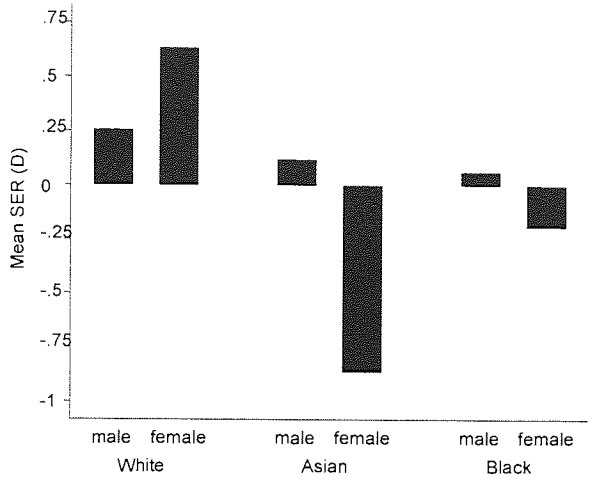


Figure 6.5.13 The effect of gender on mean SER in Year 8 within the 3 major ethnic groups

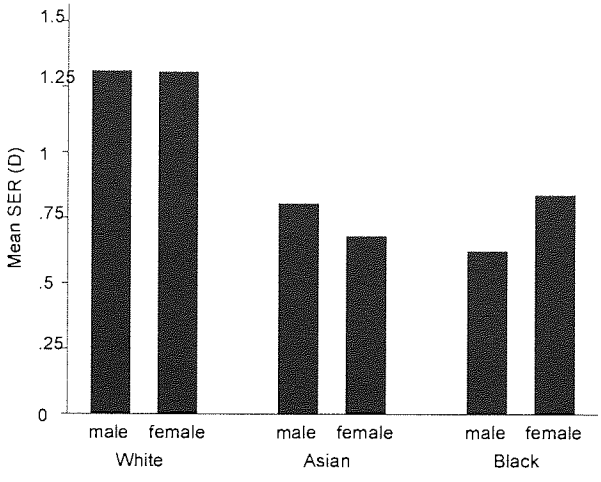


Figure 6.5.14 The effect of gender on mean SER in Year 2 within the 3 major ethnic groups

6.5.1.4 Grammar Schooling

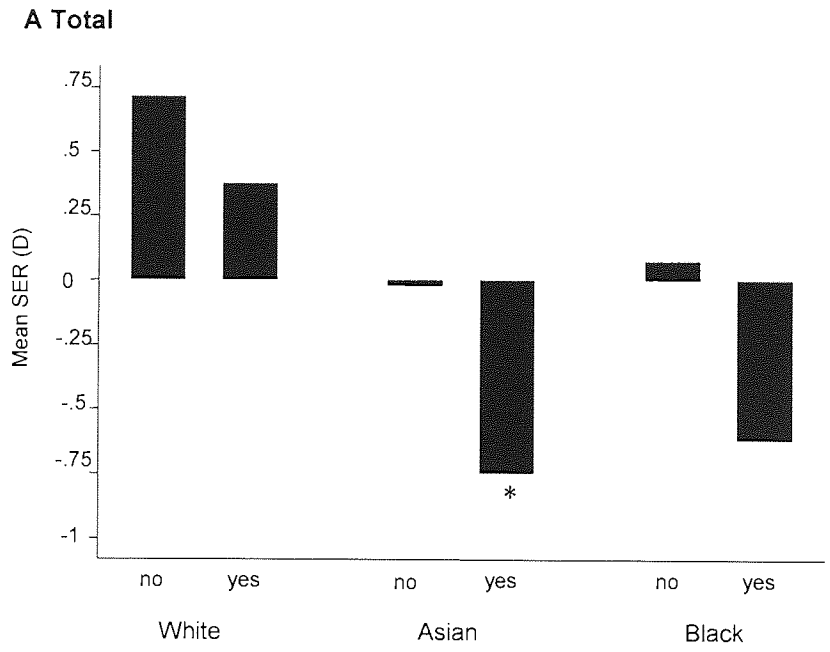
Within Year 8, children attending a grammar school (n= 175) were found to have a more negative mean SER than those attending state comprehensive schools (n= 121); this difference was found to be significant (mean SER ± SD: -0.16D ± 0.12 *vs.* +0.18D ± 0.11D respectively, one-tailed independent t = 2.03, p = 0.022). Even after incorporation of the main effect of ethnicity through a factor way between-subject ANOVA for the three primary ethnic groups (White, Asians and Blacks), grammar schooling remained a significant risk factor for a more myopic mean SER (overall model F= 7.31, p<0.001. Main effect ethnicity F=11.83, p<0.001. Main effect grammar schooling F= 7.91, p= 0.005. Interaction effect F= 0.52, p= 0.60; Figure 6.5.15).

	Comprehensive education				Grammar education			
Ethnicity	n	SER (D) Male	n	SER (D) Female	n	SER (D) Male	n	SER (D) Female
White	10	+0.27	15	+1.01	46	+0.25	44	+0.51
SD		0.99		1.51		1.14		1.38
Asian	38	+0.14	13	-0.49	13	+0.07	50	-0.96
SD		0.95		1.45		1.61		1.69
Black	15	+0.06	15	+0.09	0	-	10	-0.62
SD		0.66		0.71				1.55

Table 6.5.2 Mean SER (± SD) as a function of ethnic background, gender and grammar school attendance

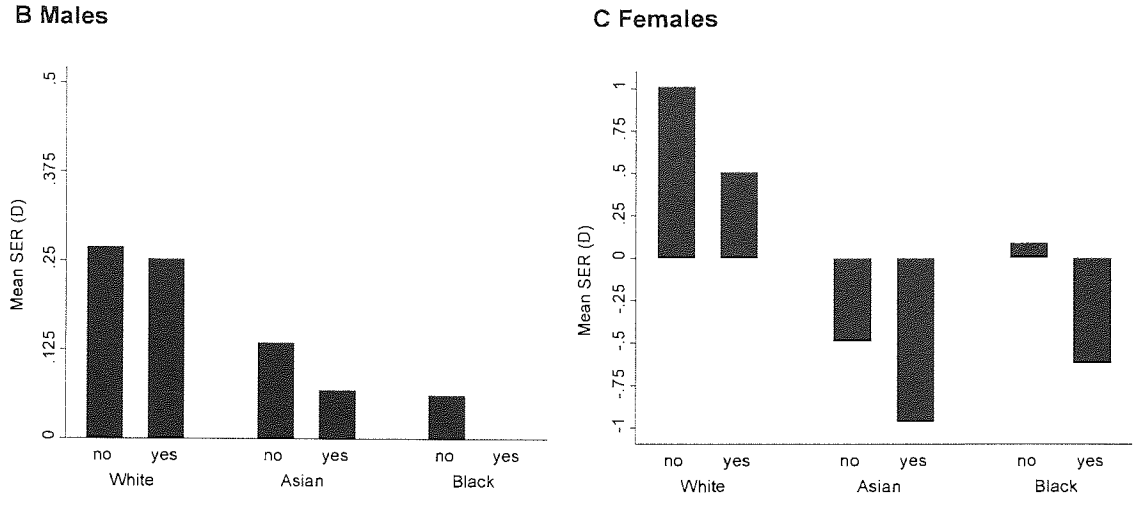
It can be seen in Figure 6.5.15 A-C, that the mean SER for each ethnic group was more myopic in grammar school children compared with non-grammar school children (Figure 6.5.15 A-C), though significant differences emerged only when data from both genders were combined (Figure 6.5.15A). None of the pairwise comparisons in graphs B & C as a function of schooling within each ethnic group were found to differ significantly.

Table 6.5.2 also serves to illustrate the effect of grammar school attendance on males and females of varying ethnic backgrounds.



*p=0.005

A cross-section of grammar school attendance by ethnic group



no: non-grammar (comprehensive) schooling yes: grammar schooling

Figure 6.5.15 The effect of grammar schooling on mean SER within the 3 major ethnic groups by gender

6.5.2 Prevalence of refractive error

The overall prevalence of myopia (≤ -0.50D SER either eye) across both age groups in the AES was 19.57% (95%CI: 16.38-22.75%) and the prevalence of hyperopia (≥+2.00D SER either eye) was 8.53% (95%CI: 6.28-10.77%).

Year 8

Myopia ≤ -0.50D SER in either eye was present in 87 of the 296 subjects tested, equating to a prevalence level of 29.39% (95%CI: 24.17-34.61%). Bilateral myopia was present in 63 of the 296 children (21.28%).

Changing the criterion of myopia definition to ≤ -1.00D SER as used by Sorsby *et al.*, (1961) modified the prevalence of myopia in either eye to 19.93% (95%CI: 15.35-24.51%).

The prevalence of hyperopia was 5.41% (95%CI: 2.81-8.00%), with 7 children (2.36%) bilaterally hyperopic. One hundred and ninety three subjects were emmetropic (65.2%). There were no subjects who were myopic in one eye and hyperopic in the other. The prevalence of astigmatism (mean cylinder ≤ -1.00DC in either eye) was 17.11% (95%CI: 13.51-22.30%).

Year 2

Myopia in either eye was present in 30 of the 302 Year 2 subjects tested, equating to a prevalence level of 9.93% (95%CI: 6.54-13.32%). Bilateral myopia was present in 17 children (5.63%). Using Sorsby *et al.*'s criterion (≤1.00D SER) lowered the prevalence to 4.30% (95%CI: 2.0-6.61%). The prevalence of hyperopia in either eye was 11.92% (36 children; 95%CI: 8.25-15.60%), with 8.94% bilaterally hyperopic (27 children). There were 236 emmetropes in this age group (78.15%). The prevalence of astigmatism was 18.21% (95%CI: 13.83-22.59%), a similar value to that derived from the elder age group ($\chi^2 = 0.001$, p=0.92), implying that astigmatic error does not change with age.

As expected, the prevalence of myopia was significantly different between age groups (Year 2 = 9.93% *vs.* Year 8 = 29.39%, $\chi^2 = 35.96$, p<0.001), with the prevalence of myopia almost 3 times greater in the elder cohort.

6.5.2.1 Ethnicity

Year 8

Examining the prevalence of ametropia by ethnic group (Table 6.5.3) in Whites, Blacks and Asians only, a significant difference in myopia prevalence between ethnic groups was found (χ^2= 9.91, p= 0.007), primarily accounted for by the difference between Whites and Asians (χ^2= 9.91, p= 0.002). The difference in myopia prevalence between Whites and Blacks (χ^2= 1.55, p= 0.21) and between Black and Asian cohorts (χ^2= 1.15, p= 0.29) was not significant.

		Myopia		Hyperopia	
Ethnic Group	**n**	**Prevalence %**	**95% CI**	**Prevalence %**	**95% CI**
White	115	18.3	11.1-25.4	10.4	4.8-16.1
Asian	114	36.8	27.9-45.8	2.6	0 -5.6
Black	40	27.5	13.0-42.0	0	0
Mixed	15	13.3	0 -32.8	6.7	0 -21.0
Chinese	5	100	1	0	0
Other	7	85.7	50.8-100	0	0
Total	**296**	**29.4**	**24.2-34.6**	**5.4**	**2.8-8.0**

Table 6.5.3 Year 8 prevalence of refractive error by ethnic group

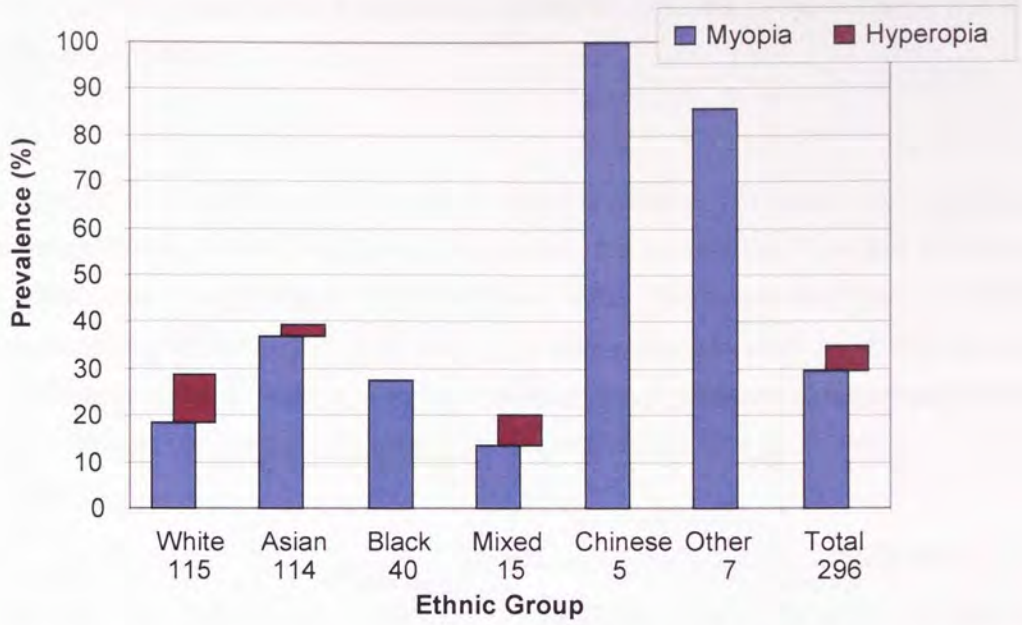


Figure 6.5.16 Prevalence of ametropia by ethnic group (%) in Year 8. Blue bars indicate myopia prevalence and red indicate hyperopia prevalence. Numbers below each ethnic group refer to sample size

Although a high proportion of Chinese children and those from 'Other' ethnic backgrounds (e.g. Middle Eastern) presented with myopia (Figure 6.5.16), these cannot be representative of their respective population base due to limited sample sizes.

Ethnic group	n	Myopia Prevalence (%)	Relative Risk ratio	95%CI
White	115	18.26	1 (referent)	1
Asian	114	36.84	**2.02**	**1.28-3.18***
Black	40	27.5	1.51	0.80-2.84
Mixed	15	13.33	0.73	0.19-2.81
Chinese	5	100	**5.48**	**3.72-8.06¶**
Other	7	85.71	**4.69**	**2.87-7.67¶**

*p=0.0016 ¶ p<0.001

Table 6.5.4 Year 8 risk ratios for myopia within each ethnic group relative to Whites. Significant risk ratios displayed in bold

The relative risk (RR) ratio is a measure of the relative effect an exposure variable (i.e. ethnicity) has on the risk of an outcome (i.e. myopia). A referent value of 1 is used to rank varying exposures (White ethnicity in this case); a value above 1 indicates that the exposure increases the risk of the

outcome whilst a value below 1 indicates a reduction in the risk of the outcome with exposure (Davies *et al.*, 1998).

Year 2

The prevalence of refractive error by ethnic group is displayed in Table 6.5.5 and Figure 6.5.17. Examining Whites, Asians and Black children only, the prevalence of myopia appears higher in Asian and Black children compared to Whites although these figures were not deemed statistically significant using Fisher's exact test (p= 0.44). Fisher's test was used as an alternative to χ^2 due to the low number of myopes in this age group. However, the prevalence of hyperopia was significantly higher in Whites compared to Asian and Black children (25.49% *vs.* 9.33% *vs.* 11.11% respectively, p= 0.01).

		Myopia		Hyperopia	
Ethnic Group	**n**	**Prevalence %**	**95% CI**	**Prevalence %**	**95% CI**
White	51	5.89	0 – 12.57	25.49	13.11-37.89
Asian	193	10.89	6.45-15.31	9.33	5.19-13.47
Black	36	13.89	2.02-25.76	11.11	0.33-21.90
Mixed	15	6.67	0 -20.97	6.67	0-20.97
Chinese	2	0	0	0	0
Other	5	0	0.13	0	0
Total	**302**	**9.93**	**6.54-13.33**	**11.92**	**8.25-15.60**

Table 6.5.5 Year 2 prevalence of refractive error by ethnic group

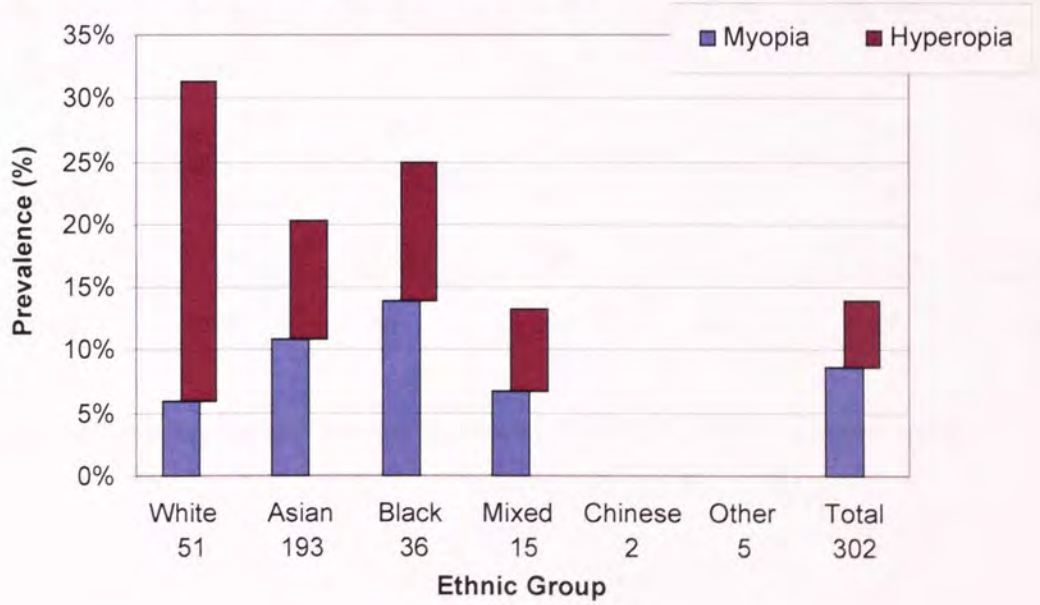


Figure 6.5.17 Prevalence of refractive error by ethnicity in the AES Year 2 cohort

Ethnic group	n	Myopia Prevalence (%)	Relative Risk ratio	95%CI
White	51	5.88	1 (referent)	1
Asian	193	10.88	1.85	0.54-5.96
Black	36	13.89	2.36	0.60-9.26
Mixed	15	6.67	1.13	0.13-10.11
Chinese	2	0	-	-
Other	5	0	-	-

Table 6.5.6 Year 2 risk ratios for myopia within each ethnic group relative to Whites

RR ratios for Year 2 myopia prevalence were derived with ethnic group as the exposure variable (relative to Whites as the reference group), and excluded Chinese and 'Other' children due to their limited sample size. The wide 95% confidence intervals around the risk ratios in Asians, Blacks and Mixed race children and their inclusion of unity (RR= 1) indicate either an actual lack of association between ethnicity and myopia in young children, or a lack of power due to sample size. The point estimates however do suggest an increase in the risk of myopia in Asians and Blacks.

6.5.2.2 Gender

	Year 2			Year 8		
Gender	**Non myope**	**Myope**	**Total**	**Non myope**	**Myope**	**Total**
Male	142	12	**154**	101	30	**131**
%	*92.21*	*7.79*	***100***	*77.10*	*22.90*	***100***
Female	130	18	**148**	108	57	**165**
%	*87.84*	*12.16*	***100***	*65.45*	*34.55*	***100***
Total	**272**	**30**	**302**	**209**	**87**	**296**

Table 6.5.7 The frequency of myopia as a function of gender within each age group

Year 8

The prevalence of myopia was found to be significantly higher in females than males (34.55% vs. 22.90%; χ^2= 4.77, p = 0.029) with a RR ratio of 1.51 (95%CI: 1.03-2.20) for female gender (Table 6.5.7). Females were therefore more likely to have a myopic refractive error and 1.5 times more likely to be myopic than males.

Year 2

Although the myopia prevalence in females was higher than males (12.16% *vs.* 7.79%), this difference was not statistically significant (χ^2= 1.61, p= 0.20).

6.5.2.3 Grammar schooling and Myopia prevalence

Education has been determined a risk factor for myopia in many studies (Wu *et al.,* 2001; Konstantopoulos *et al.,* 2007). It is thought that grammar schools provide a higher standard of education relative to comprehensive schools in the UK, therefore comparing the effects of grammar *vs.* non-grammar schools may indicate a role for education in myopia.

Grammar school children (Year 8 only) did show a greater prevalence of myopia compared to non-grammar school children (Table 6.5.8), however this difference did not reach statistical significance (32.57% vs. 24.79% respectively. χ^2= 2.09, p = 0.15).

Grammar School attendance	Non Myope	Myope	Total
No	91	30	**121**
%	*75.21*	*24.79*	*100.00*
Yes	118	57	**175**
%	*67.43*	*32.57*	*100.00*
Total	**209**	**87**	**296**
%	***70.61***	***29.39***	***100.00***

Table 6.5.8 Comparison of the myopia prevalence in children attending grammar school vs. children attending non-grammar schools

Examining the prevalence of ametropia (myopia and hyperopia), though grammar school children appear to have a higher prevalence of ametropia (Figure 6.5.18), this was not statistically significantly different from non grammar school children (χ^2= 4.55, p = 0.1). However, these results may have been confounded by other variables, namely gender and ethnicity. The following section controls for these two variables respectively using multiple logistic regression models.

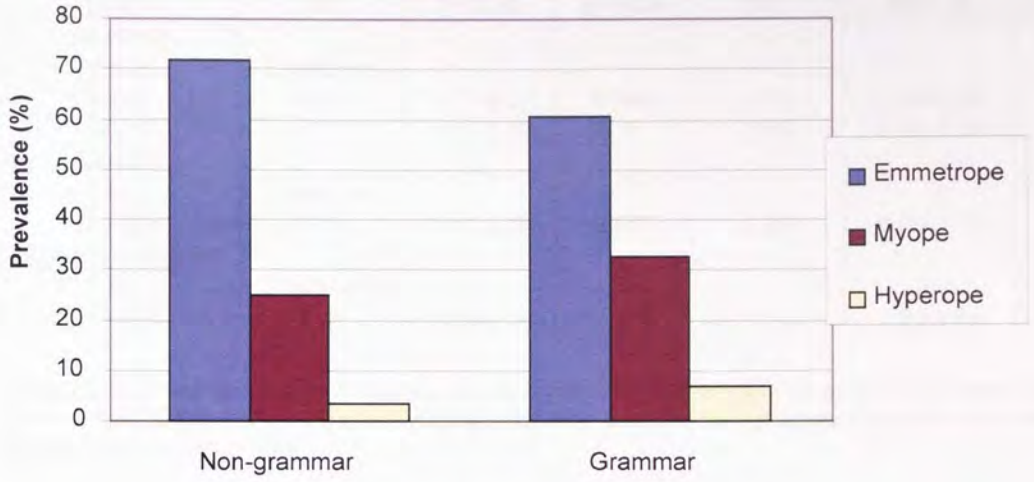


Figure 6.5.18 Comparison of refractive groups by educational background of child

6.5.2.4 Multiple logistic regression models

Logistic regression is used to determine the effect of a variable on a binary categorical outcome, in this case myopia (0= no, 1= yes). Univariate and multivariate logistic regression models are reported as odds ratios (OR) and 95% CI (confidence intervals), as conversion from OR to RR is highly complex and converted 95% CI values can be inaccurate (Woodward, 2005). Although odds ratios are less intuitive to describe than risk ratios (Davies *et al.,* 1998) there are no qualitative differences in interpreting ORs as RRs (i.e. if RR>1, OR will also be >1).

An OR > 1 indicates a positive association between the exposure and outcome and an OR < 1 a protective association (Kuper and Gilbert, 2005).

Year 8

The ORs for myopia as a function of ethnicity, gender and grammar schooling are reported below (Table 6.5.9) in univariate and multiple regression models, after mutual adjustment and adjustment for cluster sampling design.

Year 8	Univariate OR	95% CI	p value	Adjusted OR	95% CI	p value
Ethnicity						
White	1 (referent)	-	-	-	-	-
Asian	2.61	1.27-5.34	**0.009**	2.97	1.58-5.59	**0.001**
Black	1.7	0.75-3.87	0.21	2.26	0.90-5.69	0.083
Gender						
Male	1 (referent)	-	-	-	-	-
Female	1.78	1.17-2.70	**0.007**	1.36	0.85-2.17	0.21
Grammar School						
No	1 (referent)	-	-	-	-	-
Yes	1.47	0.95-2.26	0.085	1.84	1.28-2.64	**0.001**

Table 6.5.9 Univariate and multivariate logistic regression with myopia as an outcome measure in Year 8 children. OR: Odds Ratio. Adjusted ORs are mutually adjusted for variables shown as row headings. Significant p values in bold

It can be seen that Asian ethnicity remained a strong risk factor for myopia compared to White children, even after adjustment for gender and grammar schooling (adjusted OR 2.97, 95%CI:1.58-5.59). This suggests that female gender or grammar schooling did not confound the risk of myopia within this ethnic group. Thus there appears to be an exogenous factor within this ethnic group accounting for its increased risk to myopia.

With regards to gender, though females did appear to be at a greater risk of myopia compared to males (OR 1.78, 95%CI: 1.17-2.70) in univariate models, this ratio lost significance when other factors, namely grammar schooling, were introduced into the model. Grammar schooling effects were reversed, with a significant adjusted effect on myopia (OR 1.84, 95%CI: 1.28-2.64).

Year 2

The ORs for myopia as a function of ethnicity and gender are reported below (Table 6.5.10) in both univariate and multivariate analyses after mutual adjustment and adjustment for cluster sampling design:

Year 2	Univariate OR	95% CI	p value	Adjusted OR	95% CI	p value
Ethnicity						
White	1 (referent)	-	-	-	-	-
Asian	1.95	0.67-5.66	0.22	1.94	0.67-5.61	0.22
Black	2.58	0.68-9.76	0.16	2.53	0.67-9.54	0.17
Gender						
Male	1 (referent)	-	-	-	-	-
Female	1.64	0.75-3.56	0.21	1.48	0.69-3.15	0.31

Table 6.5.10 Univariate and multivariate logistic regression using myopia as an outcome measure in Year 2 children. OR: Odds Ratio. Adjusted ORs are respectively adjusted for ethnicity and gender

Neither ethnicity nor gender was found to be significantly associated with a risk of myopia.

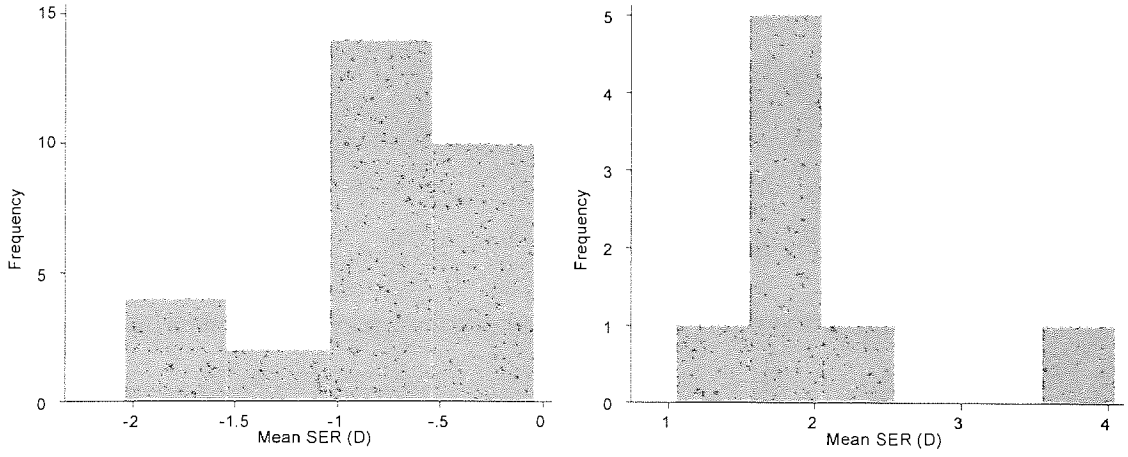
6.5.3 Uncorrected ametropia

	Year 8		Year 2	
	n	95%CI	n	95% CI
Total examined	**296**		**302**	
Uncorrected Myopia	30		21	
%	10.14	6.68 - 13.59	6.95	4.07 - 9.84
Uncorrected Hyperopia	8		25	
%	2.70	0.84 – 4.56	8.28	5.15 -11.40
Uncorrected Ametropia	38		46	
%	12.84	9.00 – 16.67	15.23	11.16 -19.31

Table 6.5.11 The frequency and prevalence of uncorrected visual defects in Year 2 and Year 8 children as determined by the AES, using predefined definitions of refractive error (Section 6.3)

Year 8

Using AES definitions of refractive error (Section 6.3), it was found that 30 children were uncorrected myopes i.e. did not have any form of refractive correction (Table 6.5.11), relating to an uncorrected prevalence of 10.14% (95%CI: 6.68 -13.59%). The mean SER of these uncorrected myopes was -0.83 ± 0.48D.



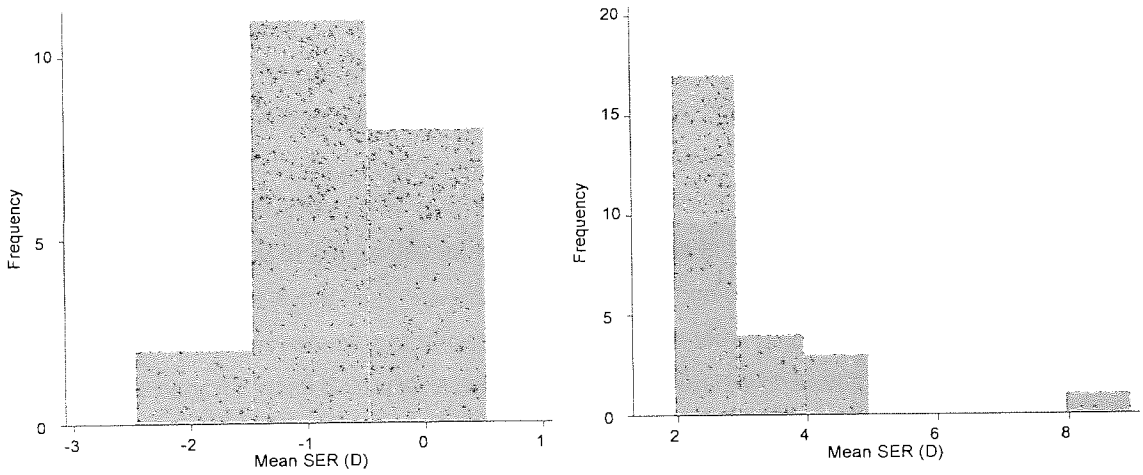
A Myopia **B Hyperopia**

Figure 6.5.19 Distribution of Year 8 uncorrected mean SER. A: uncorrected myopes, B: uncorrected hyperopes

Seven children were found to be uncorrected hyperopes, equating to a prevalence of 2.27% (95%CI: 0.63-4.12%). The overall mean SER of these 7 children was +2.05D (95%CI: +1.33 - +2.77D). There was only one child with uncorrected bilateral hyperopia (KE3LH1).
The overall prevalence of uncorrected ametropia (myopia and hyperopia) was 12.84% (95%CI: 9.0-16.67%) in all Year 8 children. It can be seen that the majority of uncorrected ametropia was low in magnitude (Figure 6.5.19).
The number of uncorrected children with astigmatism (≥1.00DC either eye) irrespective of associated SER value was 31 (10.47%, 95%CI: 6.96-13.98%).

Year 2

Examining Table 6.5.11, it can be seen that 21 uncorrected children from the total cohort of 302 seen were myopic in at least one eye. This equates to an uncorrected prevalence of 6.95% (95%CI: 4.07-9.84%). The mean SER of these children was -0.79 ± 0.59D.



A Myopia **B Hyperopia**

Figure 6.5.20 Distribution of Year 2 uncorrected mean SER. A: uncorrected myopes, B: uncorrected hyperopes

Twenty five children were deemed to be uncorrected hyperopes, equating to a prevalence of 8.28% (95%CI: 5.15 - 11.40%). The mean SER of these children was +2.91 ± 1.35D.

Overall, the uncorrected prevalence of ametropia was 15.23% (95%CI:11.16 - 19.31%) in the Year 2 AES cohort. There were 31 children with uncorrected astigmatism (≥1.00DC) in either eye (10.26%, 95%CI: 6.82-13.71%).

6.6 DISCUSSION

6.6.1 Refractive error

6.6.1.1 Refractive error distribution

The Aston Eye Study (AES) measured refractive error using cycloplegic autorefraction and examined the effects of ethnicity, gender and type of schooling on outcomes in a sample of UK urban school children.

The distributions of mean refractive error (mean SER) were found to be leptokurtotic and negatively skewed in both Year 2 and Year 8 children, although the distribution in Year 8 children was less peaked than in Year 2 (Figures 6.5.2 *vs.* 6.5.6). This difference is expected, as by the age of 6-7 years, many children are approaching the final stages of the emmetropisation process, therefore a leptokurtotic peak is likely. With increasing age and the onset of refractive error in susceptible individuals, the refractive error distribution deviates from emmetropia, causing a relative flattening of the distribution histogram.

Mean SER was more negative in Year 8 children compared to Year 2, a trend which has been demonstrated with age in the Sydney Myopia Study (mean SER ± SD age 6 years = +1.26 ± 1.24D, age 12 years = +0.48 ± 1.34D). However, a greater number of extreme outliers (i.e. high hyperopes and high myopes) were present in Year 2 compared to Year 8 children (Figures 6.5.9 *vs.* 6.5.10). A greater preponderance of congenital early-onset ametropia in the Year 2 cohort compared to Year 8, or perhaps a cohort effect of high myopia (i.e. the prevalence of high ametropia increasing) in younger children may account for the outliers. However, in view of the relatively small age gap between the cohorts (*circa* 6 years), a cohort effect between the groups appears unlikely.

6.6.1.2 Ethnicity and refractive error

The principal ethnic groups compared in the AES were White, Asian and Black children. The mean refractive error in Year 8 Asian children was more negative compared to Whites, with results between Whites and Asians very similar to that of the Sydney Myopia Study 12 year old cohort (Ip *et al.,* 2007). This ethnic difference persisted in the younger (Year 2) cohort although was not found to be statistically significant. Thus it may be inferred that Asian children become more myopic relative to White children with age, and is illustrated by comparing the mean SER within an ethnic group by age (mean difference Whites Year 2 - Year 8 = +0.058 ± 0.19D, two-tailed independent t= 0.31, p=0.86; mean difference Asians Year 2 - Year 8 = +0.65 ± 0.13D, two-tailed independent t= 4.83, p<0.001). Therefore, the refractive error of White children remained relatively stable between age groups compared to that of Asian children, which become significantly more myopic with age. However, it is recognised that temporal inferences would require longitudinal confirmation.

Black children did show a more negative mean SER compared to Whites, although their sample size may have precluded significant results.

6.6.1.3 Gender and refractive error

Examining refractive error by gender, Year 8 females were found to have a significantly more negative mean SER compared to males. However, this association was not present in ANOVA models for ethnicity and gender, with a significant interaction term and main effect of ethnicity. These findings imply that gender was associated with refractive error through ethnicity and that the proportion of total females that were Asian in the Year 8 cohort was larger than the proportion of Asians within the male cohort. The findings in Asian females were of particular interest and may point to a particularly susceptible group of individuals to myopiagenesis.

Females from the Year 2 cohort did have a more negative mean SER compared to males Year 2 children, though a statistically significant difference was not demonstrated. Due to similar ocular growth rates during the early emmetropisation process (Mutti *et al.*, 2005), a significant difference between the sexes may not be present at a young age.

6.6.1.4 Education and refractive error

Grammar schooling in Year 8 children remained significantly associated with a negative SER compared to comprehensive schooling, even after the incorporation of ethnicity into a two factor ANOVA model (Figure 6.5.15). Grammar schools in the UK are selective schools which generally achieve higher educational standards compared to comprehensive schools. Due to the association between myopia and education (Wu *et al.*, 2001; Quek *et al.*, 2004), it is suggested that grammar schools create a myopiagenic environment for children in terms of substantial amounts of near work undertaken by a greater number of children present with higher intelligence quotients, both of which are risk factors implicated in myopia (Saw *et al.*, 2002; Saw *et al.*, 2004).

6.6.2 Prevalence levels

6.6.2.1 Myopia prevalence

The prevalence of myopia followed similar qualitative patterns to that of mean SER. The difference in myopia prevalence between age groups implies an increase in the number of children becoming myopic with age ($p<0.001$), supporting previous UK work by Pointer (2001). The prevalence levels determined can be compared to studies conducted worldwide as similar methodologies and definitions of refractive error were employed (Ojaimi *et al.*, 2005; Negrel *et al.*, 2000). A selection of studies are displayed in Table 6.6.1 which have been selected based on the inclusion of subjects comparably aged to the AES cohorts.

Country	Location	Sampling frame	Myopia definition	Method	Sample size	Age (yrs)	Ethnicity	% Myopia prevalence (95%CI)	Reference
UK	Birmingham *urban*	SC	≤-0.50D SER	CA	302	6/7	All	**9.9** (6.5-13.3)	**Aston Eye Study**
					296	12/13	All	**29.8** (24.2-34.6)	
UK	Bristol, *metropolitan*	PB	≤-0.50D SER	NCA	6758	7	All	**13.6** (12.8-14.4)	Williams *et al.*, 2005
Sweden	Göteburg	SC	≤-0.50D SER	CR	1045	12-13	White	**49.7**	Villarreal, 2000
Australia	Sydney *metropolitan*	SC	≤-0.50D SER	CR	1724	6	All	**1.43** (0.94-2.18)	Ojaimi *et al.*, 2005a
					2340	12	All	**11.9** (6.6-17.2)	Ip *et al.*, 2007
USA	*Several*	SC	≤-0.50D both meridia	CA	2523	5-17	All	**10.5**	Kleinstein *et al.*, 2003
USA	Orinda, CA. *Urban*	SC	≤-0.50D both meridia	NCR	716	6	Caucasian	**4**[§]	Zadnik, 1997
						12	Caucasian	**20**[§]	
China	Guangzhou *Urban*	PB	≤-0.50D SER	CA	326	7	Chinese	**7.7** (4.7-10.8)	He *et al.*, 2004
					498	13	Chinese	**57.4** (52.1-62.6)	
Iran	Dezful County *Urban/rural*	SC	≤-0.50D SER	CA	366	7	Iranian	**2.5** (0.7-4.4)	Fotouhi *et al.*, 2006
					502	13	Iranian	**3.8** (2.2-5.3)	
Poland	Szczecin *Semi-urban/rural*	SC	≤-0.50D SER	CR	428	7	White	**3.97**	Czepita *et al.*, 2007
					288	13	White	**11.11**	
Taiwan	Nationwide *Urban &Rural*	PB	≤-0.50D SER	CA	924	7	Chinese	**20**	Lin *et al.*, 2004
					920	12	Chinese	**61**	
Malaysia	Gombak District,KL *Metropolitan*	PB	≤-0.50D SER	CA	590	7	All	**10** (6.8- 13.1)	Goh *et al.*, 2005
					431	13	All	**25.3** (19.5 - 31.1)	
India	Trilokpuri, N.Delhi *Urban*	PB	≤-0.50D SER	CR	544	7	Indian	**3.13** (1.17-5.08)	Murthy *et al.*,2002
					510	13	Indian	**10.6** (6.02-15.2)	

Table 6.6.1 Myopia prevalence in studies examining children of similar ages to the AES

[§] estimated from Figure 1 in reference

CA: cycloplegic autorefraction, NCA: non-cycloplegic autorefraction,
CR: cycloplegic retinoscopy, NCR: non-cycloplegic retinoscopy
PB: population-based enumeration, SC: school-based sampling

The AES used similar clinical protocols to the RESC corpus of research (Negrel *et al.,* 2000), although subject recruitment was carried out at schools and not through door-to-door enumeration. However, as full-time education is compulsory in the UK until the age of 16, it was felt that sampling children from schools would provide a suitable population-based estimate.

The Year 8 myopia prevalence in the AES (29.79%) was considerably higher than that determined in the Sydney Myopia Study (11.9%, Ip *et al.,* 2007) and showed very similar results to that derived using non-cycloplegic retinoscopy in 13 year old American children from the Orinda Longitudinal Study of Myopia (OLSM - 28% myopia prevalence estimated from graph for myopia ≤ -0.50D each principal meridia, Zadnik, 1997). However, the prevalence determined was considerably less than the 57.4% detected by autorefraction in urban China (He *et al.,* 2004).

In addition, the Year 2 myopia prevalence in the AES (9.93%) was higher than 6 year old subjects in the Sydney Study (1.43%, Ojaimi *et al.,* 2005a) and the 7 year old cohort in the OLSM (~5% graph estimation; Zadnik, 1997). However the AES Year 2 myopia prevalence was lower than that determined in a cross-sectional examination of 6,700 children aged 7 in the UK (13.6%, Williams *et al.,* 2005). The ALSPAC[2] team, though working with a large sample, did not employ the use of cycloplegia while conducting closed-field autorefraction, which may have contributed to an artificially high prevalence level. The lower myopia levels determined by the AES on a highly urban population base emphasises the importance of cycloplegia as a prerequisite for robust epidemiological results (Zadnik *et al.,* 1992; Fotedar *et al.,* 2007).

6.6.2.2 Myopia and ethnicity

To the authors knowledge, this is the first study to have reported the prevalence of myopia and ocular biometry in White, South Asian and Black children.

The relative risk (RR) ratio for myopia was found to be higher for Year 8 Asian (significant) and Black (insignificant) children compared to Whites (Figures 6.5.5 and 6.5.6), supporting the earlier findings of mean SER (Section 6.6.2). It appears therefore that ethnicity is a strong risk factor for myopia (Table 6.5.4). Asian children are over twice as likely to be myopic compared to their White peers during early teenage years.

In support of AES findings, work on undergraduates in the UK has found a higher myopia prevalence in Asian undergraduates relative to Whites (Guggenheim *et al.,* 2003). However this has been countered by Logan *et al.* (2005), who found no significant difference in prevalence between South Asian and White undergraduates. However, the Asian category in the study by Guggenheim and colleagues included both East and South Asians, which may account for the discrepancy. Therefore

[2] Avon Longitudinal Study of Parents and Children

the findings of an equivalent myopia prevalence between South Asian and White undergraduates by Logan *et al.* in combination with ethnically disparate AES Year 8 results lends itself to a suggestion of varying peaks of myopia incidence between the ethnic groups. It may be that the incidence of myopia peaks in Whites at an age older than Year 8, such that by undergraduate level, both ethnic groups contain a similar number of myopes. Confirmation of this hypothesis will naturally require longitudinal follow-up of children over time as a function of ethnic group.

Year 8 Black children appeared to be 1.5 times more likely to develop myopia compared to White children (RR = 1.5), however this risk cannot be extrapolated to the general urban Black population, as the 95%CI encompassed the referent value of 1, indicating an insignificant result. A greater number of Year 8 Black children are required to confirm this point estimate statistically.

The differential risk ratios between Whites, Asians and Blacks (Table 6.5.4) may reflect a selection bias in the study. It may be that the parents of myopic Asian and Black children were more willing to consent for their child to participate in the study compared to the parents of (Asian and Black) emmetropic children. White parents who gave consent, by contrast, may have done so irrespective of the refractive error of their child. This bias would have artificially increased the numbers of Black and Asian myopic children detected.

Year 8 Chinese children were all deemed myopic, however their limited sample prohibits extrapolation and comparison with fellow ethnic groups. It would be of great interest to conduct a longitudinal cohort study of Chinese *vs.* White *vs.* Asian pre-myopic children raised in a homogenous environment (i.e. from the same school) to determine whether Chinese susceptibility to myopia persists outside of East Asian countries.

Myopia prevalence did not vary significantly as a function of ethnicity in Year 2 children. However, relative risk point estimates were higher for myopia in Asian and Black children compared to Whites (Table 6.5.6), supporting work conducted in Bristol by the ALSPAC team on 7 year old children (Williams *et al.,* 2005). The ALSPAC study determined a non-significant higher risk in Asian children for myopia compared to Whites (adjusted OR 1.81, 95%CI: 0.86-3.60, p= 0.12), similar to unadjusted OR values for AES Year 2 children (OR 1.95, 95%CI: 0.67-5.66, p= 0.22).

The prevalence of hyperopia was found to vary significantly by ethnic group in this young cohort. A quarter of White children were found to be hyperopic in at least one eye (25.5%), higher than the proportion of 6 year old White hyperopes (15.7%) in the Sydney Myopia Study (Ip *et al.,* 2007c) using the same definition of hyperopia. However, the Sydney study determined significant ethnic variations in hyperopia prevalence with a lower prevalence in South Asians compared to Whites, which was similar in nature to the AES. Reanalysis of data with particular focus on hyperopia is required to expand on this finding.

6.6.2.3 Myopia and gender

The prevalence of myopia was found to be higher in females compared to males in both age groups, although the difference was found to be statistically significant in the older cohort only (p= 0.03). It may be that the younger age group (Year 2) represents the initial stages at which the incidence of female myopia increases relative to males, accounting for the higher prevalence noted, albeit without statistical support. The disparity in myopia incidence with gender may be a result of differential ages of pubertal onset and physiological maturation. Therefore, due to an accelerated myopia incidence in females from the ages of 6/7 years of age, the prevalence at the age of 12/13 years would manifest as significantly greater in females compared to males, supporting the AES findings.

6.6.2.4 Multivariate analysis

Asian ethnicity remained a significant risk factor in Year 8 multivariate models, suggesting that type of schooling (grammar *vs.* non-grammar) and gender are not surrogate factors for Asian ethnicity. It may be that genetic susceptibilities or extra-curricular cultural influences specific to Asian children are responsible for the differential prevalence levels.

The main gender effect determined for Year 8 children in Section 6.6.2.3 was negated when adjusting for the effects of ethnicity and grammar schooling (Table 6.5.9). It appeared that the female preponderance for myopia was a surrogate for Asian ethnicity as exclusion of ethnicity from the multivariate model rendered the effect of gender significant ($p<0.001$). Nevertheless, the female multivariate point estimate did remain above 1, suggesting an increased risk of myopia in females even after adjustment. Thus the lack of multivariate significance may indicate a lack of power preventing a significant effect from being displayed. Grammar schooling also persisted as a significant associate of child myopia in multivariate models ($p<0.001$), supporting a role for education in myopiagenesis.

Year 2 multivariate analyses did not show a significant effect of ethnicity or gender on the risk of myopia. However, OR point estimates for these variables were above 1, indicating an increased risk with female gender, Asian and Black ethnicity, which may indicate the early stages of differential demographic susceptibilities to myopia onset.

6.6.2.5 Uncorrected refractive status

A child was deemed an uncorrected ametrope after determining the presence of a clinically significant refractive error (using AES definitions) and a lack of optical correction.

The proportion of children aged 12/13 years of age who were uncorrected myopes was 10.14%. This suggests that on average, 1 in every 10 children will have a clinically significant myopic error in at least 1 eye although upon extrapolation, the true proportion of uncorrected child myopia in the urban population could range from 7 to 14% (based on the 95%CI). The proportion of uncorrected Year 8

hyperopes was lower, at 2.70%. For 6/7 year old children, the respective uncorrected myopia and hyperopia prevalence levels were 6.95% and 8.28%. Although much of the uncorrected ametropia was of a low dioptric value, the AES criterion was set to qualify for clinical significance.

The prevalence of uncorrected myopia in both Year 2 (6.95%) and Year 8 (10.14%) children can be considered high given the free and universal access to child eye care available in the UK through the General Ophthalmic Services.
It has been demonstrated that the rate of myopia progression in children already myopic is more rapid than in non-myopes (Lam *et al.*, 1999; Fan *et al.*, 2004), therefore it is likely that these uncorrected myopes will progress further with age.
An evaluation of uncorrected ametropia by quartiles of socioeconomic group (derived in Chapter 8) failed to reach significance with myopia in either age group (Year 2: χ^2= 2.13, p= 0.55; Year 8: χ^2= 1.50, p= 0.68). The prevalence of uncorrected ametropia also did not vary significantly by ethnicity (Year 2: χ^2= 3.17, p= 0.67; Year 8: χ^2= 1.02, p= 0.80). These findings indicate that a general lack of eye care awareness exists in UK urban populations and is not specific to particular demographical strata.

Therefore, the high levels of uncorrected ametropia in AES children alongside studies showing the greatest incidence (Mutti *et al.*, 1998; Cheng *et al.*, 2007) and progression (Logan *et al.*, 2004a) of school myopia to occur between the ages of 9-10 years of age support the reintroduction of a universal secondary school vision screening system at the age of 11 years in the UK. Vision screening conducted at the commencement of secondary education would be responsible for the identification of uncorrected refractive error and would be an adjunct to a pre-school screening system, as propounded by Logan and Gilmartin (2004).

6.6.3 Summary

The strengths of the AES lie in the robust sampling design of the study. In addition, the methodology is derived from well established protocols conducted globally (Negrel *et al.*, 2000; Ojaimi *et al.*, 2005) and provides comparable data on the prevalence of refractive error in an urban population. The use of cycloplegic autorefraction has been advocated in refractive error studies (Zadnik *et al.*, 1992) and was employed by the AES. All data were collated by registered UK optometrists.
Limitations of the study revolve around the low school response (SR) and parental response (PR) rates to invitations. The AES was also vulnerable to selection bias therefore the prevalence levels derived may be an overestimation of the ametropia prevalence in the general urban child population.

The disproportionately high Asian composition of the AES cohort in both age categories compared to Birmingham census data (Figures 6.4.2 and 6.4.4) can be accounted for by the exclusion of schools containing >70% of a single ethnic group. The exclusion criteria applied to White and Pakistani children, the 2 predominant ethnic groups in Birmingham (Section 5.1). Therefore access to White children for the study was only through schools with a considerable mix of difference ethnicities (i.e. <70% White children in a school).
However, as fellow South Asian children (i.e. Indian, Bangladeshi) were not part of the exclusion criteria, schools with >70% Pakistani were excluded but not those with >70% Asian. Therefore schools with 50% Pakistani, 25% Indian and 25% Bangladeshi, though a predominantly Asian school, were included in the sampling procedure. This may have accounted for the high numbers of Asian children in the AES. Nevertheless, the primary purpose of sampling was to enable the capture of sufficient numbers of the 3 main ethnic groups and not necessarily to provide a representative sample of the region. This was successfully achieved for White and Asian children, though the low numbers of Black children indicate that a greater number of children from this ethnic group would be required for future investigation.
Although the sample size studied to date is far from that required by sample size calculations (Section 5.1.5), continuance of the study will increase the cohort size and afford greater power to each ethnic group in analysis. Nevertheless the differences in outcomes between ethnic groups was found to be greater than that predicted by the sampling strategy, enabling a smaller sample of each ethnic group to provide statistically significant findings.

In conclusion, the AES has determined the prevalence of refractive error in urban schoolchildren aged 6/7 years and 12/13 years of age. Variations in ethnicity and type of schooling have been determined in the older cohort, with Asian ethnicity and grammar schooling acting as significant risk factors in multivariate models. Differences can be seen in younger children with regards to ethnicity and gender though these are not significant. However, this age may represent the initial stages of changes in susceptible children in response to myopiagenic risk factors.

The prevalence of uncorrected myopia in urban populations can be seen as a cause for concern, with almost 1 in 10 children aged 12 years and 1 in 14 children aged 6/7 years lacking any form of necessary optical correction for clear distance vision. These figures should be followed up and reviewed with particular reference to recommendations by Hall and Elliman (2003) to limit school vision screening strategies. At the very least, a greater parental awareness of the availability of child eye care in a primary care setting should be raised to minimise the impact of poor uncorrected vision on a child's education and development at school.

CHAPTER 7

OCULAR BIOMETRIC AND ANTHROPOMETRIC CORRELATES OF REFRACTIVE ERROR

7.1 INTRODUCTION

Knowledge of biometric corollaries of refractive error is well established (van Alphen, 1961). Refractive error and axial length (AL) have been shown to correlate strongly in many studies and AL is recognised as the primary ocular correlate of an ametropic refraction (Gernet, 1980; McBrien and Adams, 1997; Strang *et al.*, 1998). The crystalline lens has been found to be less powerful in myopes, with data by Garner *et al.*, (1992) and Jones *et al.*, (2005) supporting this finding. A deeper anterior chamber depth (ACD) has also been found in myopes by Jones *et al.*, (2005). Data is equivocal as to whether the cornea is steeper in myopes (Goss *et al.*, 1997) or stable across refractive groups (Garner *et al.*, 1992; McBrien and Adams, 1997).
Refractive error has been shown to correlate with height, with taller children being more at risk of myopia (Saw *et al.*, 2002c). Other studies have refuted this finding although positive correlations have been derived between height and axial length (Ojaimi *et al.*, 2005b). Weight has been linked to axial length in Singaporean adults though not to refractive error (Wong *et al.*, 2001).

The Aston Eye Study (AES) is a population-based epidemiological child study in the UK measuring ocular biometry alongside ocular refraction. Analysis of demographical factors with outcome measures will enable the relationship between a child's background and ocular parameters to be determined. In addition, by incorporating height and weight into recordings it is anticipated that further conclusions will be drawn into the role of body stature in eye size and subsequent refractive error.

7.2 METHODS

The AES set-up and protocol is comprehensively described in Chapter 5. Full ethical approval was obtained from the Aston University Ethical Committee and the study adhered to the tenets of the Declaration of Helsinki. Population sample characteristics are described in Section 6.4.

In summary, a sample list of local primary and secondary schools in Birmingham was created using random cluster sampling methods stratified by age and deprivation index (a measure of socioeconomic status). Schools were excluded from invitation if the proportion of a single ethnic

group exceeded 70%, to ensure schools with a sufficient mix of ethnic backgrounds were targeted. The remaining schools were contacted and invited to participate in the study.
An initial meeting was organised with affirmative schools and consent forms distributed at this time to all parents of respective children (Year 2 or Year 8). Written consent was required from all parent/guardians along with written consent from Year 8 children. Verbal assent was required from Year 2 children on the day of the study and was documented by an investigator (Appendix 5).

Examination procedures were performed by experienced registered optometrists familiar with the techniques and protocol employed (BG, NL and PS)[1]. Refractive and biometric measures were all conducted under cycloplegia (0.5% proxymetacaine followed by 1% cyclopentolate 1 drop of each drug in both eyes separated by 1-2 minutes). Amplitudes of accommodation were measured 25 minutes after drop administration. A child was considered fully cyclopleged when his/her accommodative amplitudes measured <2D monocularly. If cycloplegia was not complete within 40 minutes, a further drop of cyclopentolate was administered to both eyes and the accommodative amplitudes re-measured at periodic intervals until residual accommodative levels were suitable for measurement.

Ocular biometry was determined using the *Zeiss* IOLMaster (Jena, GmbH), a commercially available device which offers measurement of axial length (AL), corneal radius (CR) and anterior chamber depth (ACD) to a high resolution (±0.01mm) and with excellent accuracy and repeatability (Santodomingo-Rubido *et al.*, 2002). Due to its non-contact nature, it is a very patient-friendly device and of particular benefit in studies involving children (Chapter 3).
Three measures of AL and CR and 1 measure of ACD (a single measure providing 5 readings) were taken for each eye using the IOLMaster and the mean values for each component was calculated. An overall average of the two mean recordings from each eye was determined to provide a single value of AL, CR and ACD for each subject.

Refractive error was determined by using the Shin Nippon SRW-5000 (Shin Nippon, Japan) a binocular open-field autorefractor. Three measures of refraction were taken per subject per eye under cycloplegia and averaged to provide a spherical equivalent refraction (SER) measure per eye. These measures were further averaged across both eyes to provide a representative value of refractive error per subject (mean SER). The averaging of data across both eyes is based on reviews advocating the use of the method (Ray and O'Day, 1985; Newcombe and Duff, 1987) as single eye analysis may not adequately represent the refractive status of an individual due to a loss of information from the eye discounted from analysis (Murdoch *et al.*, 1998).

[1] BG: Professor Bernard Gilmartin NL: Dr Nicola Logan PS: Mr Parth Shah

Height and weight were measured using a standard height chart (Leicester Height Measure, Seca Ltd, Birmingham) and digital weighing scales (Tanita Model 2000, Tanita Corporation). Children were measured without heavy clothing (e.g. school blazers, jackets). Year 8 height was measured with shoes on though it was felt on epidemiological advice (AR and CO) that heel size would confound findings, therefore Year 2 height and weight were recorded without shoes.

7.3 DEFINITIONS

Myopia was defined as SER ≤-0.50D in at least one eye. Hyperopia was defined as mean SER ≥ +2.00D in either/both eyes, providing neither eye was myopic. Emmetropia was categorised by an SER >-0.50D (less myopia than -0.50D) and <+2.00D (less than 2 Dioptres).

Ethnicity was self-reported by Year 8 children (categories based on the classifications of the National Census 2001) and confirmed via parental questionnaire reply. Year 2 ethnicity was estimated by the investigator at the time of measurement by asking a child what (other) language(s) they spoke at home and where their parents originated from. This was confirmed by parental questionnaire responses and a statistical test employed to determine agreement between methods. An excellent level of agreement was derived between the investigator-reported classification and parental confirmation of child ethnicity (kappa = 0.93, $p<0.001$), similar to agreement values derived in the CLEERE study (Jones *et al.*, 2001).
For the purposes of this chapter, the term 'Asian' will refer to people of South Asian descent. The term Chinese will be used to describe people of East Asian background.

A statistical package was used (Stata Intercooled version 9, StataCorp, Texas) to enter in raw recordings and perform data analysis, with periodic use of MS *Excel* for table and graph creation. Examples of statistical output tables in Stata are displayed in Appendix 7.

7.4 RESULTS

7.4.1 Distribution of Ocular Components

Year 8

The mean AL (± SD) for the Year 8 cohort (n= 296) was 23.48 ± 0.86mm, mean CR was 7.77 ± 0.27mm and the mean ACD was 3.64 ± 0.28mm. Distributions of ocular components are shown below (Figures 7.4.1-7.4.3) with associated normal probability plots to ascertain normality as described in Section 6.5.1.1.

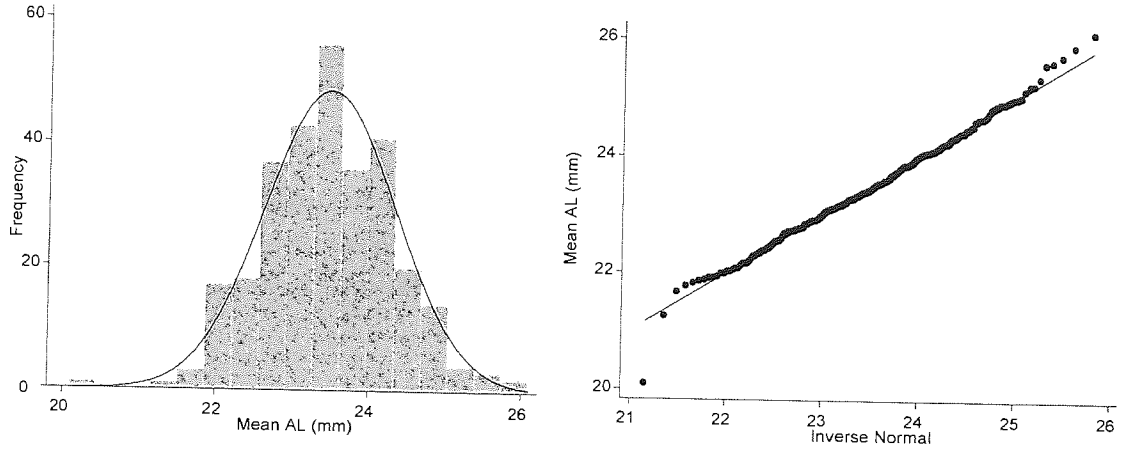


Figure 7.4.1 Mean AL distribution in Year 8 children and associated normal plot.
Skew= 0.28 p= 0.80, Kurtosis= 3.56 p= 0.07

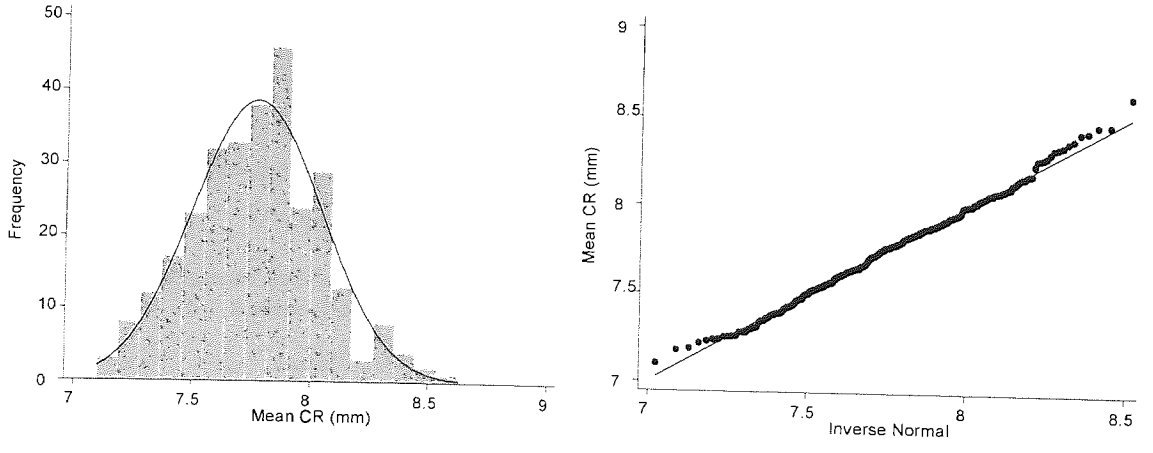


Figure 7.4.2 Mean CR distribution in Year 8 children and associated normal plot.
Skew= 0.14 p= 0.31, Kurtosis= 2.93 p= 0.96

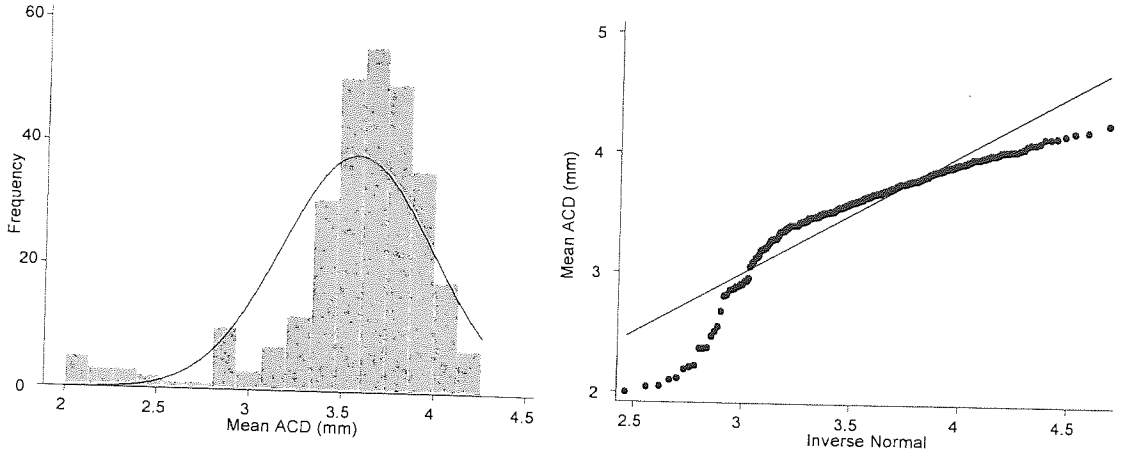


Figure 7.4.3 Mean ACD distribution in Year 8 children and associated normal plot.
Skew= -1.67 p<0.001, Kurtosis = 6.42 p<0.001

It is apparent that while AL and CR measures follow a normal curve, ACD measures are strongly skewed and show a significant departure from normality.
Excluding 15 children (5.1% of total) with mean ACD values > 2 SD from the mean enabled a return to an approximate Gaussian curve (Figure 7.4.4):

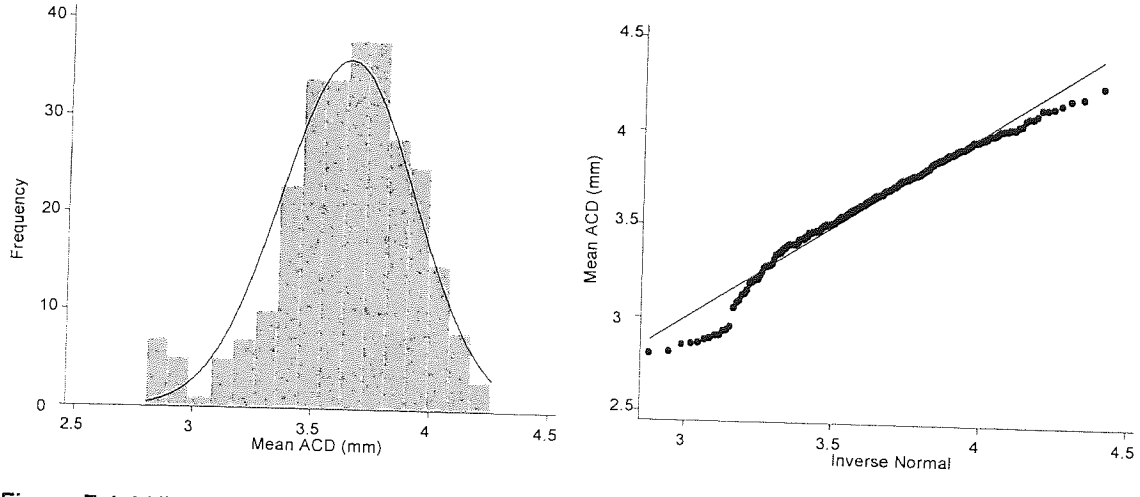


Figure 7.4.4 Histogram and normal plot of adjusted mean ACD excluding children with mean ACD >2 SD (n= 15). Skew= -0.64 p<0.001, Kurtosis= 3.52 p= 0.09

Year 2

The mean AL (±SD) for the younger cohort in the AES (n= 302) was 22.72 ± 0.77mm, mean CR was 7.78 ± 0.27mm and mean ACD was 3.50 ± 0.27mm. Distributions of AL, CR and ACD with associated normal plots to illustrate distributions are shown in Figures 7.4.5-7.4.7.

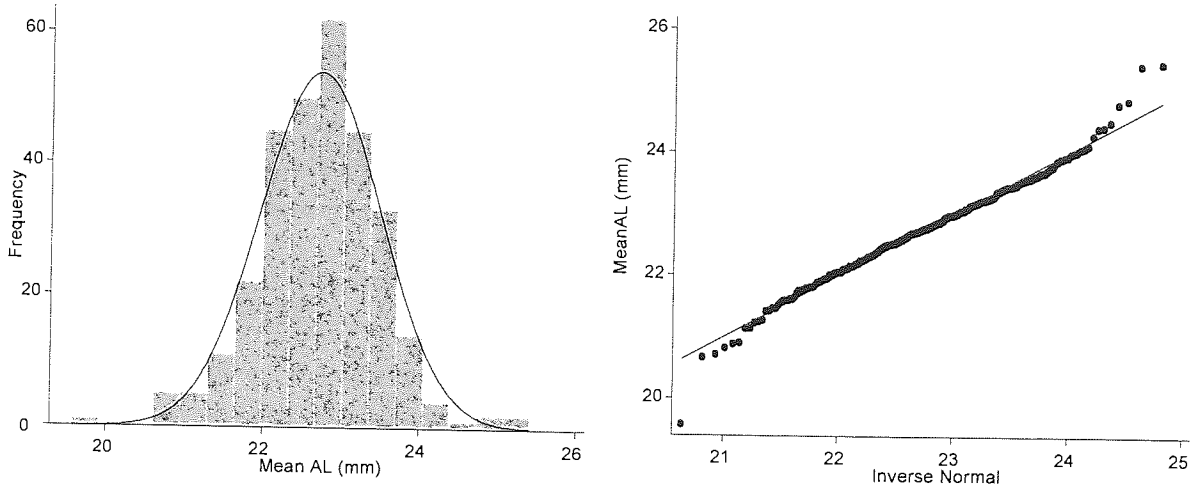


Figure 7.4.5 Mean AL distribution and normal plot in Year 2 children. Skew= -0.34 p= 0.81, Kurtosis= 4.37 p=0.001

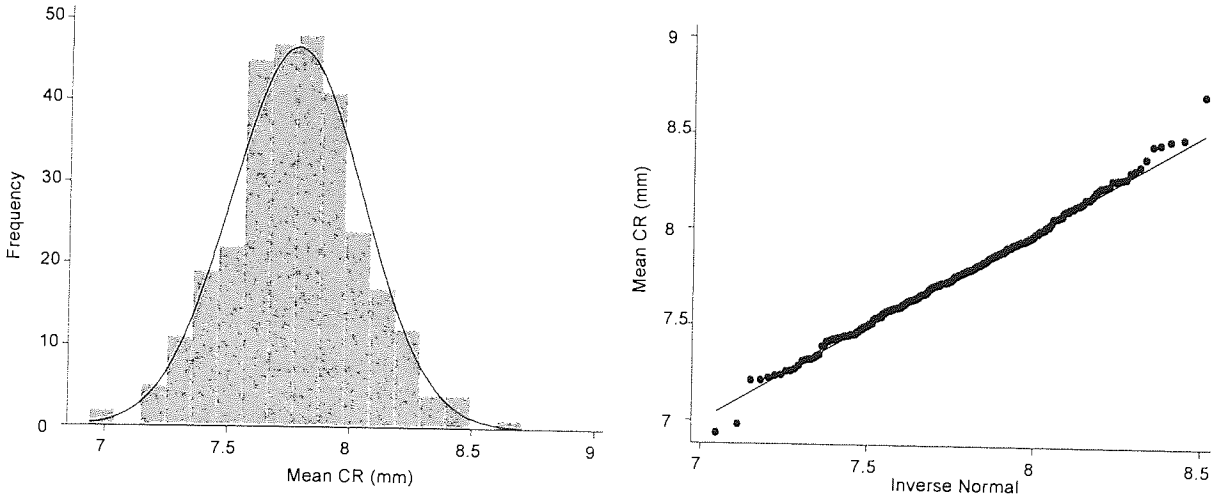


Figure 7.4.6 Mean CR distribution and normal plot in Year 2 children. Skew= 0.15 p= 0.26, Kurtosis= 3.4 p= 0.15

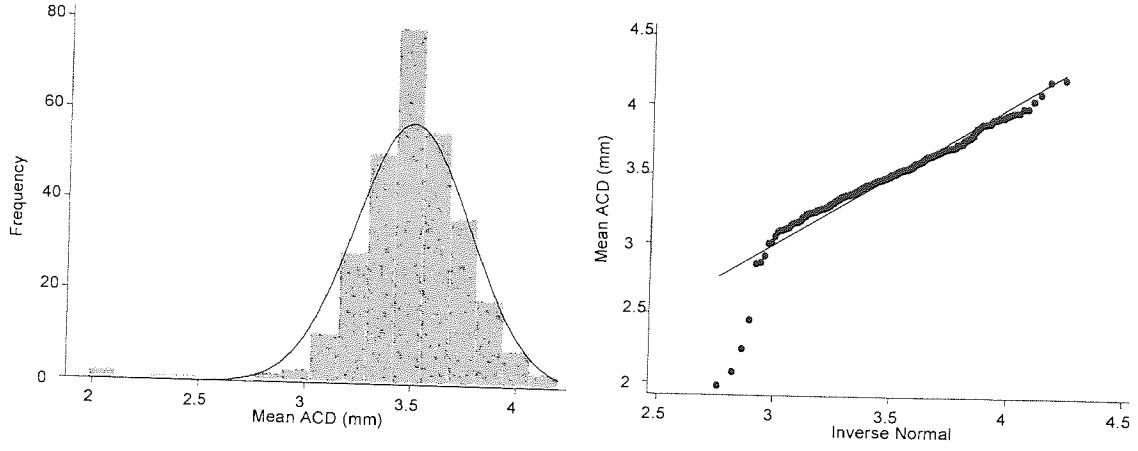


Figure 7.4.7 Mean ACD distribution and normal plot in Year 2 children. Skew= -1.39 p<0.001, Kurtosis= 9.57 p<0.001

Echoing Year 8 findings, the distribution of Mean ACD did not conform as well to a Gaussian distribution as AL and CR. This was due to a negative skew on the curve (Figure 7.4.7). Excluding values >3 SD (4 children, 1% of values) enabled a redrawn distribution (Figure 7.4.8) which conformed to normality.

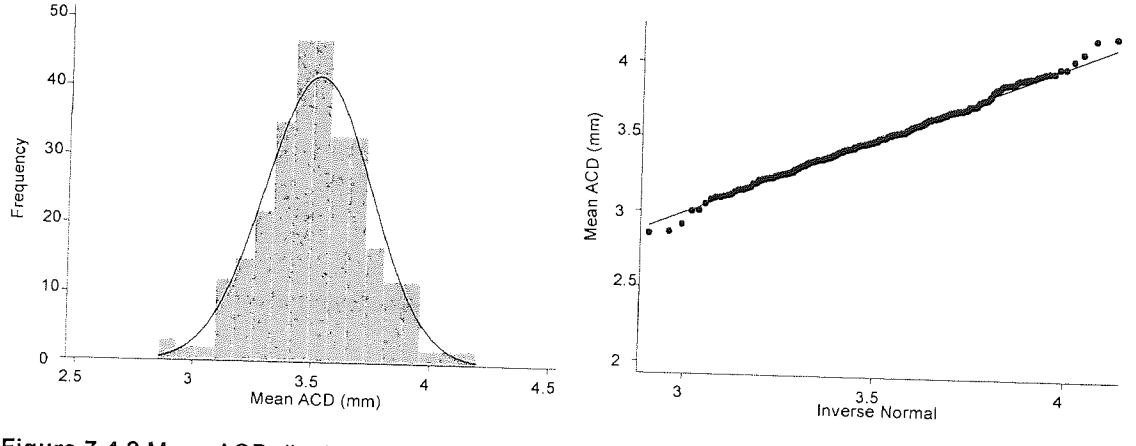


Figure 7.4.8 Mean ACD distribution and normal plot in Year 2 children after exclusion of outliers >3SD from the mean. Skew= 0.95 p= 0.49, Kurtosis= 3.27 p= 0.28

Based upon this distribution, normality is assumed for all ocular components for the use of parametric tests. Future analyses involving ACD will exclude outlier values >2SD and >3 SD from the mean for Year 8 and Year 2 children respectively.

Comparing the 3 ocular components as a function of age (Year 8 *vs.* Year 2), it was found that the mean AL was longer in older children (mean difference Year 8 – Year 2 = 0.76mm,

one-tailed t= 11.39, p<0.001), mean ACD was deeper in Year 8 children (mean difference= 0.096mm, one-tailed t= 4.11, p<0.001) but that the mean CR did not vary between cohorts (mean difference= 0.0082mm, two-tailed t= 0.37, p= 0.64).

7.4.2 Refractive Error and Biometry

Year 8

Mean AL correlated significantly with mean SER (Pearson's correlation coefficient r= -0.54, p<0.001) and accounted for 29% of the variation in SER (r^2= 0.29, Figure 7.4.9). The partial correlation coefficient for mean AL with mean SER was strengthened after controlling for CR and ACD (partial r= -0.85, p<0.001).

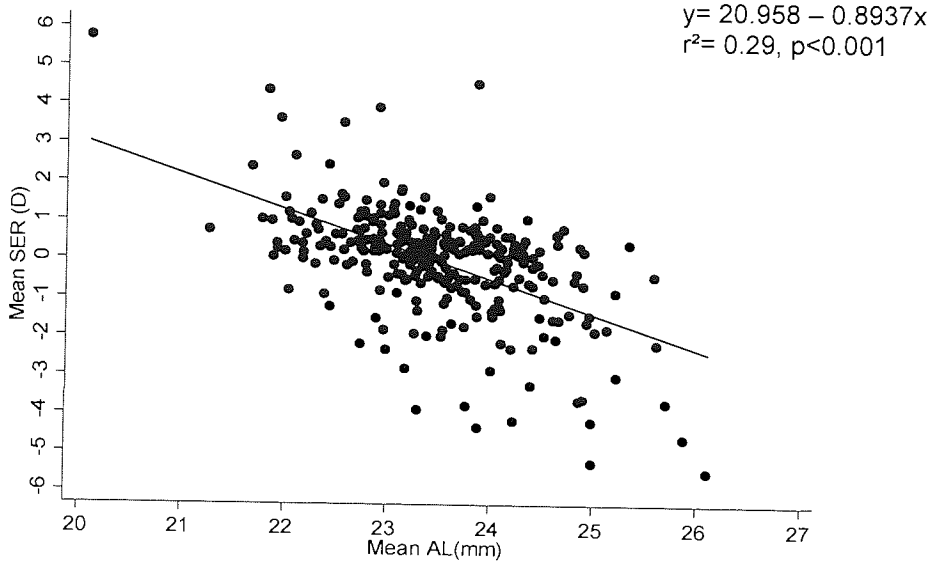


Figure 7.4.9 Year 8 linear regression of mean AL and mean SER (r= -0.54, p<0.001)

There was a positive correlation between mean CR and mean SER (r= +0.23, p< 0.001, Figure 7.4.10), increasing to a partial r= +0.81 (p< 0.001) after controlling for AL and ACD.

A weak negative correlation also existed between mean SER and mean ACD (r= -0.19, p= 0.002, Figure 7.4.11); this relationship strengthened after controlling for AL and CR although the direction of correlation switched from negative to positive (partial r= +0.35, p= <0.001).

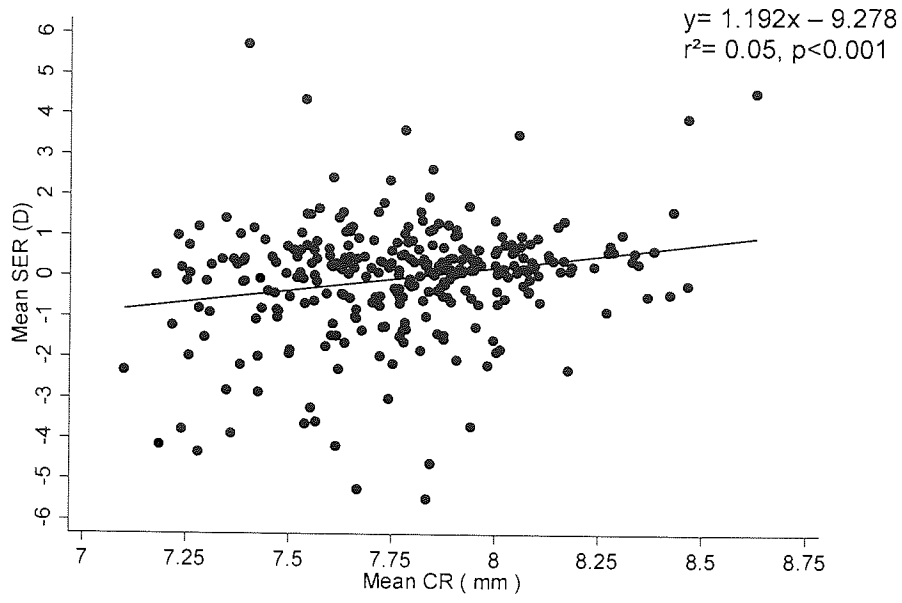


Figure 7.4.10 Year 8 linear regression of mean CR and mean SER (r= +0.23, p< 0.001)

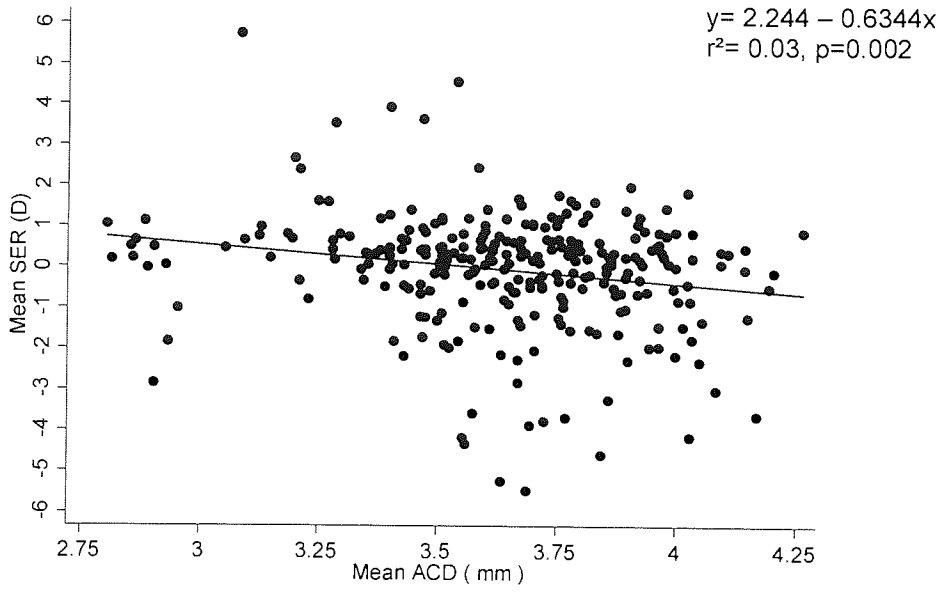


Figure 7.4.11 Year 8 linear regression of mean ACD and mean SER (r= -0.19, p=0.002)

To determine the relative contribution of each component to the overall refractive status of the eye, a multiple linear regression model was constructed (Table 7.4.1) with mean SER as the outcome variable and the 3 ocular components (AL, CR and ACD) as explanatory variables, adjusted for cluster design effects.

	Regression Coefficient	95% CI	t value	p value
Mean AL (mm)	-1.7850	-1.9829 - -1.5872	-22.07	<0.001
Mean CR (mm)	4.3274	3.8902 - 4.7647	24.22	<0.001
Mean ACD (mm)	1.0431	0.7382 - 1.3480	8.37	<0.001
Constant	4.4430	-0.6830 - 9.5690	2.12	0.078

Table 7.4.1 Year 8 multiple linear regression of ocular components on mean SER

The overall coefficient of determination of this model (R^2) was 0.76 and the model was significant (F= 280.99 p<0.001), indicating that 76% of the variability in SER is explained by AL, CR and ACD. Therefore an overall equation for the determination of refractive error from biometric components was calculated as:

SER = 4.4430 – 1.7850AL + 4.3274CR + 1.0431ACD

Year 2

A similar relationship was derived in younger children between AL and mean SER (Pearson r= -0.52, p<0.001), with 28% of the variation in mean SER accounted for by AL (r^2= 0.28, Figure 7.4.12). On controlling for CR and ACD, the partial correlation coefficient for mean AL with SER rose to -0.84 (p<0.001), similar to Year 8 values.

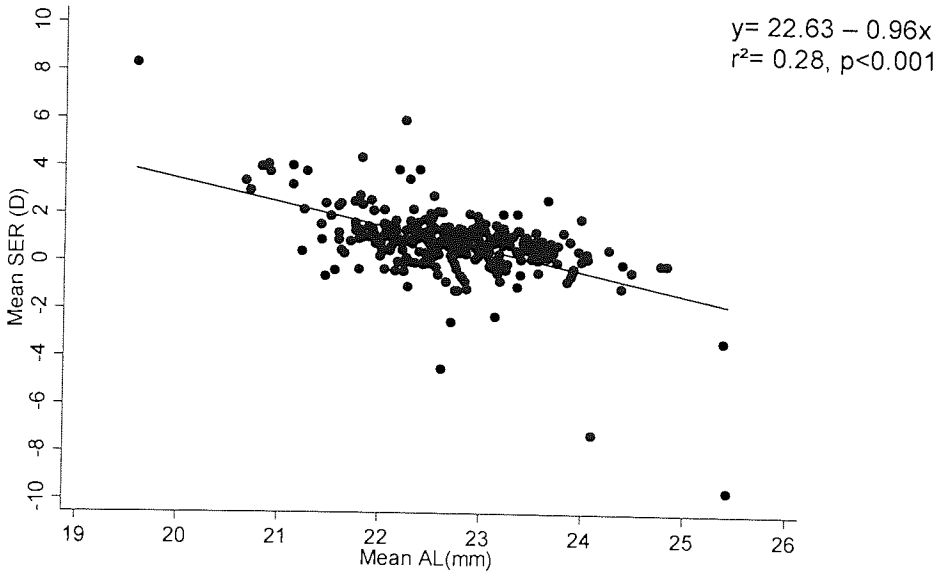


Figure 7.4.12 Year 2 linear regression of mean AL and mean SER (r= -0.52, p<0.001)

There was a positive correlation between mean CR and mean SER (r= +0.14, p=0.014, Figure 7.4.13) which appeared to be concealed by both the AL and ACD as adjustment for these factors considerably strengthened the relationship between mean SER and CR (partial r= +0.77, p<0.001).

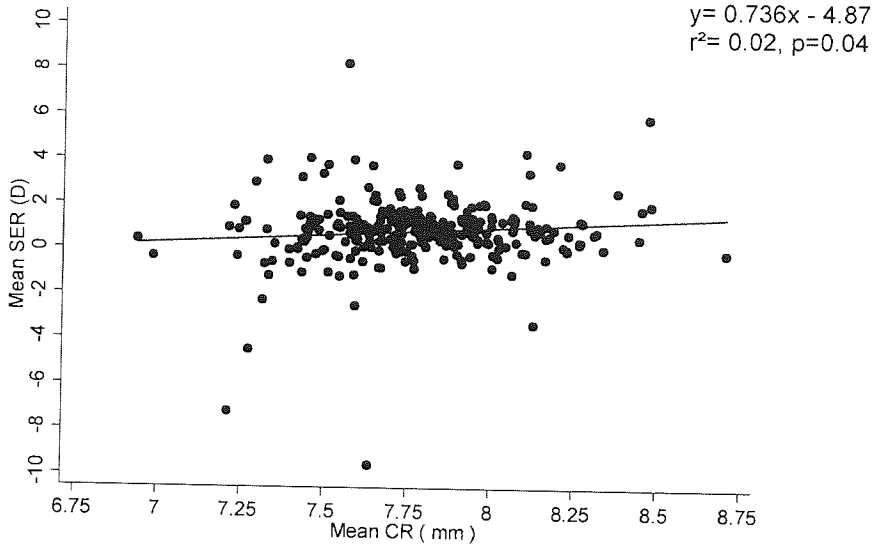


Figure 7.4.13 Year 2 linear regression of mean CR and mean SER (r= +0.14, p=0.014)

There did not appear to be a significant relationship between ACD and SER (r= -0.08, p=0.17, Figure 7.4.14). However, after adjusting for AL and CR, a significantly positive correlation was found as found in Year 8 children (partial r= +0.50, p<0.001), indicating that a negative refractive error was coupled with a shallower ACD.

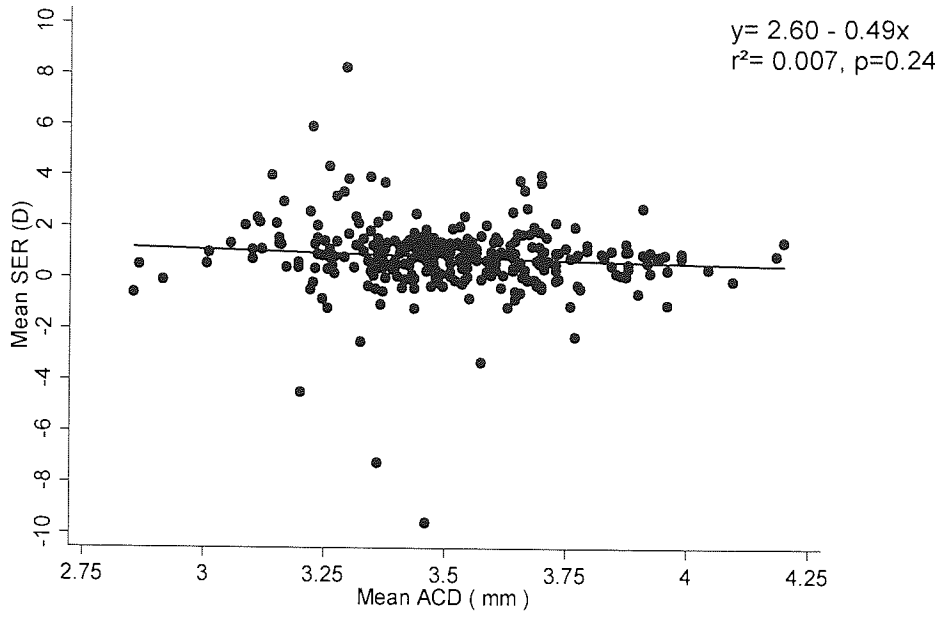


Figure 7.4.14 Year 2 linear regression of mean ACD and mean SER (r= -0.08, p= 0.17)

The relative contribution of each component to the overall refractive status of each Year 2 child was tested using a multiple linear regression model with mean SER as the outcome and AL, CR and ACD as explanatory variables (Table 7.4.2).

	Regression Coefficient	95%CI	t value	p value
Mean AL	-2.1788	-2.5923 - -1.7654	-11.17	<0.001
Mean CR	4.5759	3.4628 - 5.6889	8.71	<0.001
Mean ACD	2.2014	1.3435 - 3.0592	5.44	<0.001
Constant	7.0201	3.1293 - 10.911	3.82	0.001

Table 7.4.2 Year 2 multiple linear regression of ocular components on mean SER

The overall fit of the model was again strong (R^2= 0.71) and significant (F= 85.55 p<0.001), suggesting that 71% of the variability in SER was accounted for by AL, CR and ACD. Therefore the overall regression equation for the calculation of SER from ocular components in Year 2 children is:

SER= 7.0201 – 2.1788AL + 4.5759CR + 2.2014ACD

7.4.3 Biometry and Ethnicity

Year 8

Examining refractive components by ethnicity (Table 7.4.3), there were no differences in mean ocular component values as a function of ethnic group (one way between-subjects ANOVA with ethnic group as explanatory variable and ocular component as outcome variable. **AL**: F= 2.48 p= 0.09; **CR**: F= 1.04 p= 0.36; **ACD**: F= 0.80 p= 0.45), though on inspection Asians appeared to have a longer mean AL than Whites and Blacks.

Ethnic Group	Mean AL ± SD (mm)		Mean CR ± SD (mm)		Mean ACD ± SD (mm)	
	Year 8	Year 2	Year 8	Year 2	Year 8	Year 2
White	23.37±0.88	22.62±0.75	7.80±0.28	7.78±0.29	3.66±0.28	3.58±0.25
Black	23.36±0.85	22.68±0.76	7.75±0.28	7.77±0.28	3.59±0.22	3.49±0.21
Asian	23.61±0.85	22.75±0.77	7.75±0.27	7.78±0.26	3.63±0.32	3.50±0.22

Table 7.4.3 Mean biometric component size as a function of ethnicity and age group

Year 2

A one way analysis of variance was conducted on Year 2 children for each ocular component with ethnicity as the explanatory variable (Figure 7.4.3) and the ocular component as the outcome. Mean ACD was the only component to show a marginally significant difference across ethnic groups, with Scheffe's *post-hoc* analysis revealing that White children had, on average a deeper ACD than Asian children (one way ANOVA: **AL**: F= 0.60, p= 0.55; **CR**: F= 0.02, p= 0.98; **ACD**: F= 3.25, p= 0.04. Scheffe *post-hoc* Whites – Asians mean difference: +0.088mm, p=0.05).

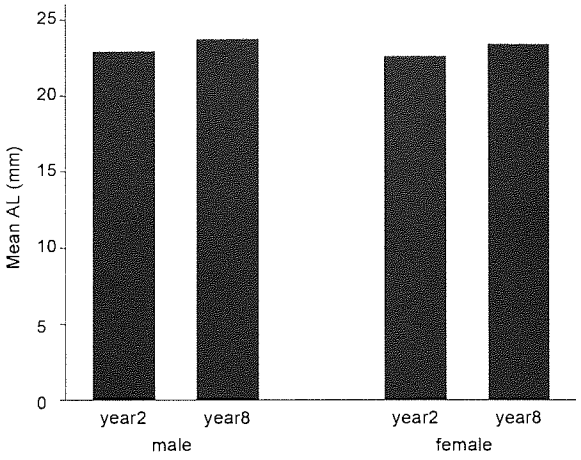
7.4.4 Biometry and Gender

Examining the effect of biometry by gender within each age group, a two factor between-groups ANOVA model was constructed for each ocular component with gender and age group as explanatory variables. Pairwise comparison significance values were determined using independent t-tests with a modified critical p value of 0.05/4= 0.0125 determined via a Bonferroni correction (Table 7.4.4 and Figure 7.4.15).

A

Two factor Anova, F= 58.98, p< 0.001
Age: F=146.71, p<0.001
Gender: F= 39.11, p<0.001

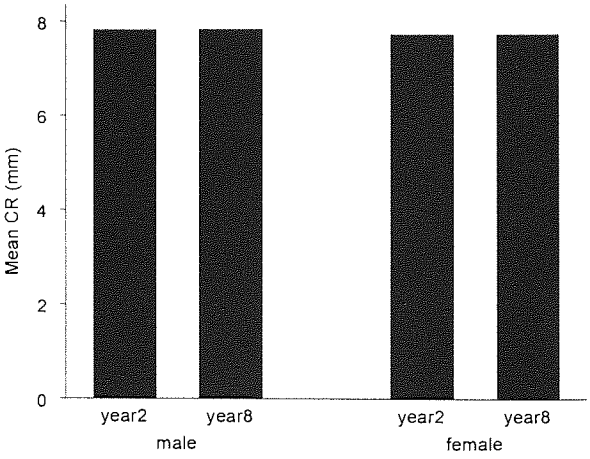
	Mean AL ±SD (mm)		
Gender	**Year 2**	**Year 8**	***one-tailed p value***
Male	22.92±0.74	23.70±0.77	***<0.001***
Female	22.51±0.74	23.30±0.88	***<0.001***
two-tailed p value	***<0.001***	***<0.001***	*IE= 0.90*



B

Two factor Anova, F= 9.80, p< 0.001
Age: F=0.00, p=0.99
Gender: F= 29.18, p<0.001

	Mean CR ±SD (mm)		
Gender	**Year 2**	**Year 8**	***one-tailed p value***
Male	7.83±0.27	7.84±0.28	*0.40*
Female	7.72±0.25	7.71±0.26	*0.61*
two-tailed p value	***<0.001***	***<0.001***	*IE= 0.71*



C

Two factor Anova, F= 12.74, p< 0.001
Age: F=20.78, p<0.001
Gender: F= 20.39, p<0.001

	Mean ACD ±SD (mm)		
Gender	**Year 2**	**Year 8**	***one-tailed p value***
Male	3.57±0.22	3.67±0.23	***<0.001***
Female	3.46±0.33	3.57±0.33	***<0.001***
two-tailed p value	***<0.001***	***0.004***	*IE= 0.99*

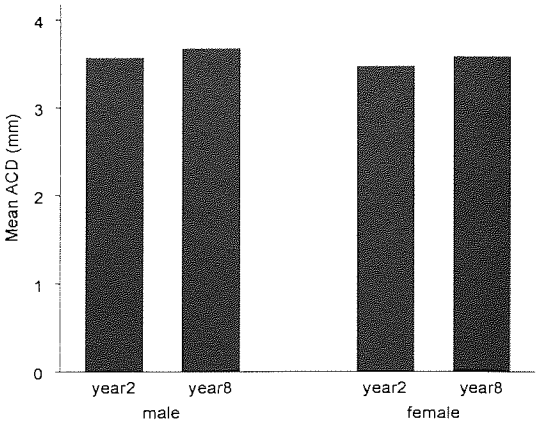


Table 7.4.4 and Figure 7.4.15 Mean biometric values as a function of age and gender tabulated and shown graphically. A: Axial length, B: Corneal radius, C: Anterior chamber depth. Pairwise comparison p values are shown in the boxes, with significant results (<0.0125) in bold. IE= interaction effect of gender and age

A significant difference was determined between males and females for all ocular components, with males having, on average, a longer AL, flatter CR and a deeper ACD. Within each gender, the differences as a function of age were also significant with the exception of CR, which was not affected by age in male or female subjects (Table 7.4.4B). A lack of interaction between age and gender suggests that both variables are independently associated with biometric components.

7.4.5 Anthropometry, Biometry and Refractive Error

Anthropometry is the physical measure of stature and body dimensions. The AES measured two anthropometric variables on subjects, height and weight, in order to derive relationships between measures of stature and ocular biometric parameters.

7.4.5.1 Assessment of Normality

Year 8

The distributions of height and weight are illustrated below with accompanying normal plots (Figures 7.4.16 -7.4.18). Height was measured in 284 children and weight in 282 children.

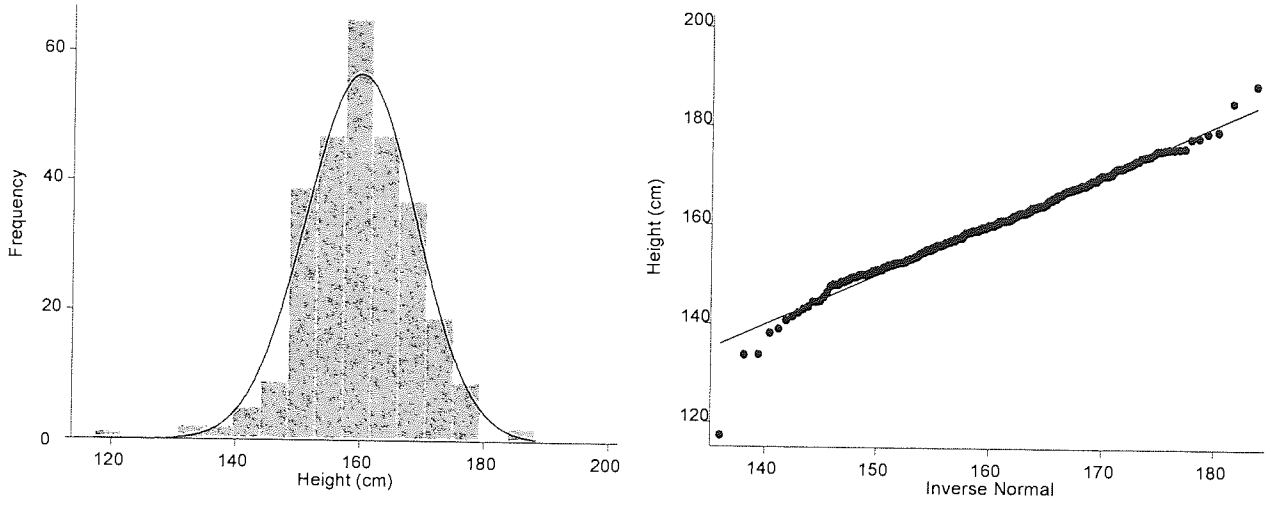


Figure 7.4.16 Year 8 height distribution with associated normal plot.
Skew= -0.35 p= 0.02, Kurtosis= 4.78 p<0.001

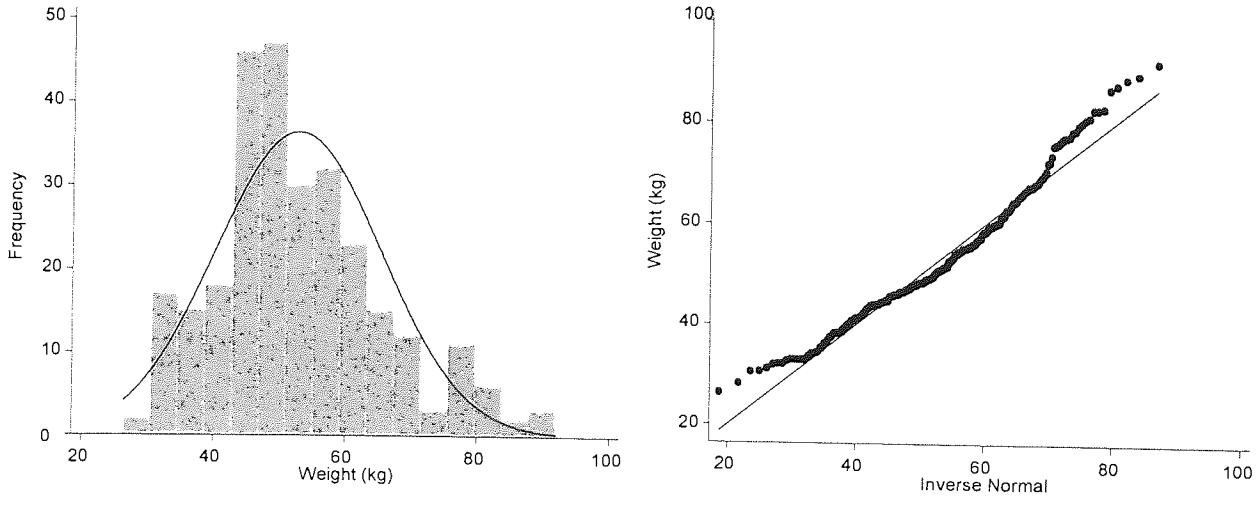


Figure 7.4.17 Year 8 weight distribution with associated normal plot.
Skew= 0.68 p<0.001, Kurtosis= 3.35 p=0.20

A normal distribution was not evident for weight therefore a log transformation was conducted on the distribution of weight to produce a normal distribution.

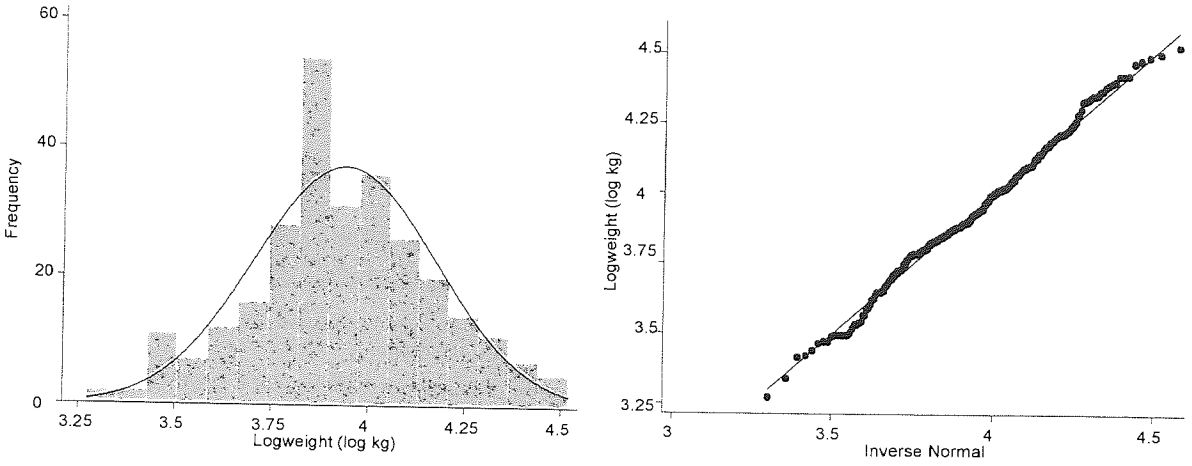


Figure 7.4.18 Natural log transformation on Year 8 weight distribution and associated normal plot.
Skew= 0.016 p= 0.91, Kurtosis= 2.92 p= 0.94

The natural log transformation adhered to a Gaussian distribution (Figure 7.4.18) and enabled parametric analysis on weight.

Year 2

The distributions for height and weight of Year 2 children are illustrated below (Figures 7.4.19-7.4.21). Height was measured in 299 children and weight in 298 children.

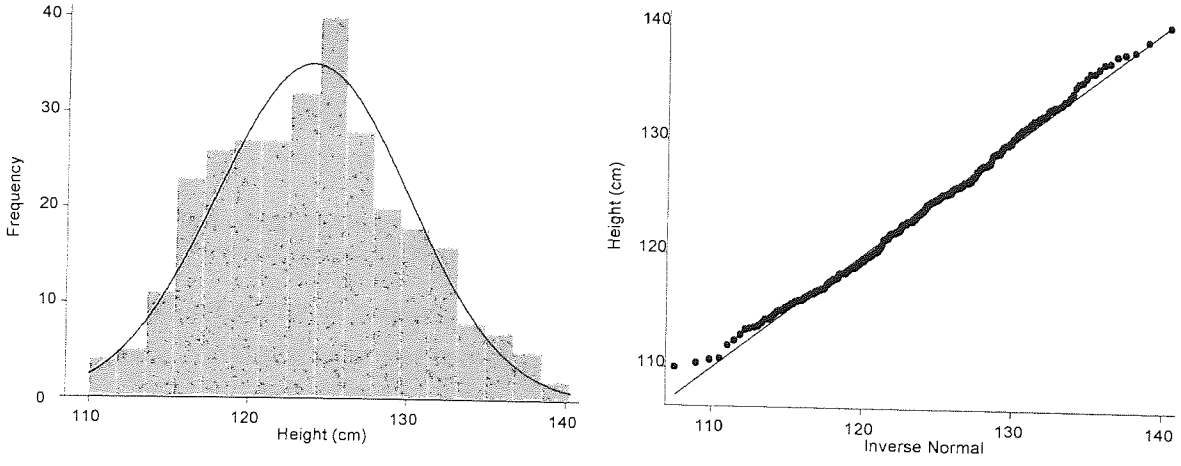


Figure 7.4.19 Year 2 height distribution with associated normal plot.
Skew= 0.19 p= 0.17, Kurtosis= 2.63 p= 0.14

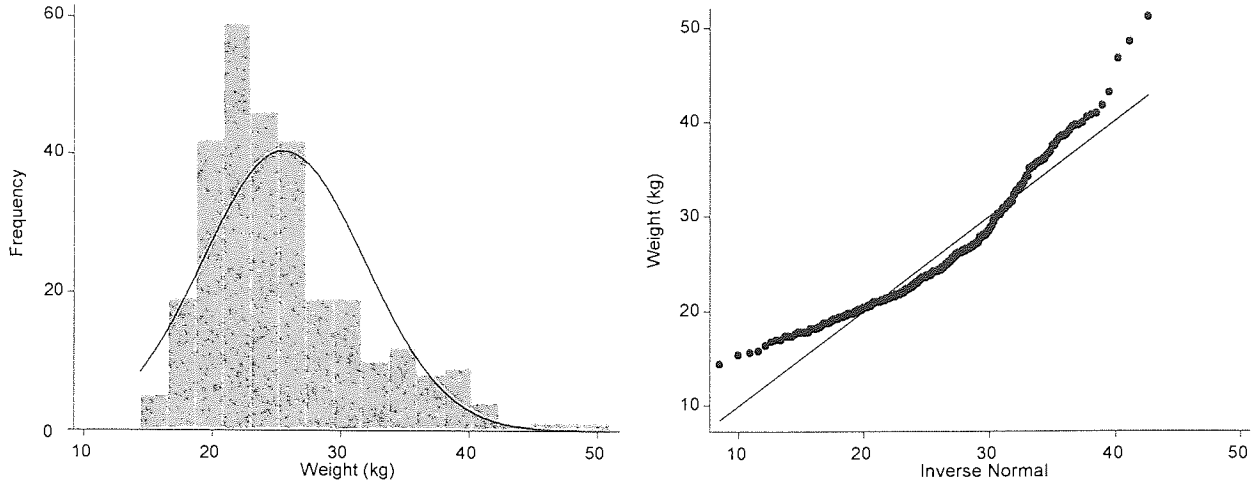


Figure 7.4.20 Year 2 weight distribution with associated normal plot.
Skew= 1.11 p< 0.001, Kurtosis= 4.17 p= 0.003

It is evident from the normal plot in Figure 7.4.20 that the distribution of weight was positively skewed. A reciprocal transformation (1/weight) was best suited to enable the distribution to satisfy normality (Figure 7.4.21).

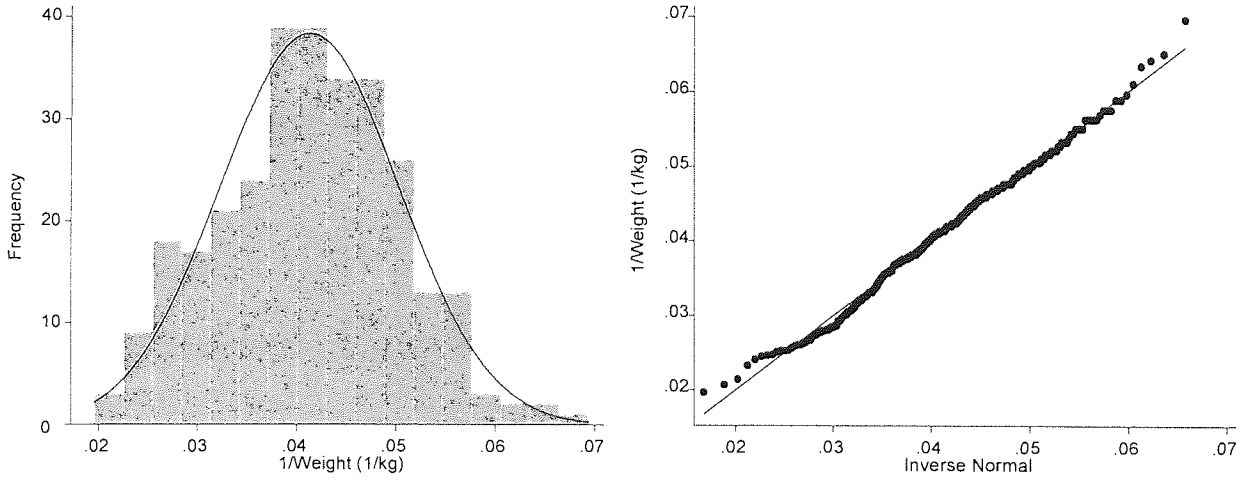


Figure 7.4.21 Reciprocal transformation on Year 2 weight distribution with associated normal plot.
Skew= 0.06 p= 0.71, Kurtosis= 2.74 p= 0.39

The reciprocal weight transformation satisfied the constraints of normality. As expected, Year 8 children were found to be taller and heavier on average compared to Year 2 children. (mean ± SD Year 8 *vs.* Year 2: Height= 159.88 ± 8.86cm *vs.* 123.94 ± 6.05cm respectively, one tailed t= -57.45 p<0.001. Weight [untransformed]: 52.74 ± 12.63kg *vs.* 25.56 ± 6.31kg respectively, Mann-Whitney U z= -20.07, p<0.001). All future analyses of weight in this chapter use transformed weight values.

7.4.5.2 Anthropometric and Biometric Correlations

Pearson cross-correlation coefficients examining the relationship between height, weight and ocular components are given in Table 7.4.5 for Year 8 and 7.4.6 for Year 2 children:

Year 8

r values	Mean SER	Mean AL	Mean CR	Mean ACD	Height	Log Weight
Mean SER	1					
p value						
Mean AL	**-0.54**	1				
p value	**<0.001**					
Mean CR	**+0.23**	**+0.56**	1			
p value	**<0.001**	**<0.001**				
Mean ACD	**-0.19**	**+0.28**	-0.002	1		
p value	**0.0015**	**<0.001**	0.98			
Height	-0.007	**+0.25**	**+0.23**	**+0.21**	1	
p value	0.91	**<0.001**	**<0.001**	**<0.001**		
Log Weight	+0.029	**+0.14**	**+0.17**	**+0.13**	**+0.66**	1
p value	0.62	**0.022**	**0.0038**	**0.03**	**<0.001**	

Table 7.4.5 Correlation coefficients of refractive, ocular and anthropometric parameters in Year 8 AES subjects. Significant coefficients are highlighted in bold with underlying p values

Year 2

r values	Mean SER	Mean AL	Mean CR	Mean ACD	Height	1/Weight
Mean SER	1					
p value						
Mean AL	**-0.53**	1				
p value	**<0.001**					
Mean CR	**+0.14**	**+0.61**	1			
p value	**0.014**	**<0.001**				
Mean ACD	-0.079	**+0.37**	+0.011	1		
p value	0.17	**<0.001**	0.85			
Height	-0.039	**+0.29**	**+0.28**	**+0.14**	1	
p value	0.50	**<0.001**	**<0.001**	**0.013**		
1/ Weight	+0.019	**-0.23**	**-0.24**	-0.11	**-0.72**	1
p value	0.75	**<0.001**	**<0.001**	0.059	**<0.001**	

Table 7.4.6 Correlation coefficients of refractive, ocular and anthropometric parameters in Year 2 AES subjects. Significant coefficients are highlighted in bold with associated p values

A high degree of correlation is present between many ocular and anthropometric variables. The strength of relationships between parameters was similar across both age groups, reinforcing the nature of the associations found and indicating temporally stable correlations, although longitudinal follow-up would be needed to confirm these findings.

A taller child, on the basis of the above findings, was likely to be heavier, have a longer eyeball, a flatter cornea and a deeper ACD. However, the correlation between refractive error and the anthropometrical variables failed to reach significance in both age groups.

Due to high inter-correlation levels, many variables may have become associated indirectly, giving the appearance of a direct relationship. This was illustrated through the measurement of partial correlation coefficients of height and weight (mutually adjusted) on AL, CR and ACD (Table 7.4.7).

Partial r values	AL		CR		ACD	
	Yr 2	Yr 8	Yr 2	Yr 8	Yr 2	Yr 8
Height	**+0.18**	**+0.22**	**+0.16**	**+0.16**	+0.087	**+0.14**
p value	***0.002***	***<0.001***	***0.005***	***0.006***	*0.14*	***0.03***
Trans Weight	-0.03	-0.04	-0.05	+0.024	-0.01	+0.04
p value	*0.59*	*0.49*	*0.38*	*0.69*	*0.8*	*0.50*

Table 7.4.7 Partial correlation coefficients (r) for height and 'trans' weight (transformed weight values: log [Year 8] and reciprocal [Year 2]) with ocular components after mutual adjustment. Significant coefficients highlighted in bold with underlying p values

On controlling for height (Table 7.4.7), weight did not remain significantly correlated to ocular components. Height however did remain correlated with all parameters after adjustment for weight, except ACD in Year 2 children. Therefore it can be assumed that height acted as a surrogate for weight and linked it indirectly to the ocular components.

7.4.5.3 Ethnicity and Anthropometry

It is of interest to investigate whether systematic differences are present between ethnic groups with regards to height and weight and how these may relate to ocular findings (see Section 7.4.3).

Within the Year 8 cohort, a comparison of mean height by ethnic group (Figure 7.4.22) revealed a trend for Asian children to be shorter than their White counterparts (mean height ± SD: Asians= 157.43 ± 8.22cm *vs.* Whites= 161.95 ± 9.04cm *vs.* Blacks= 160.94 ± 6.50cm. One way between-groups ANOVA, F= 3.32, p=0.006. Scheffe *post-hoc* analysis Asians *vs.* Whites p= 0.013).

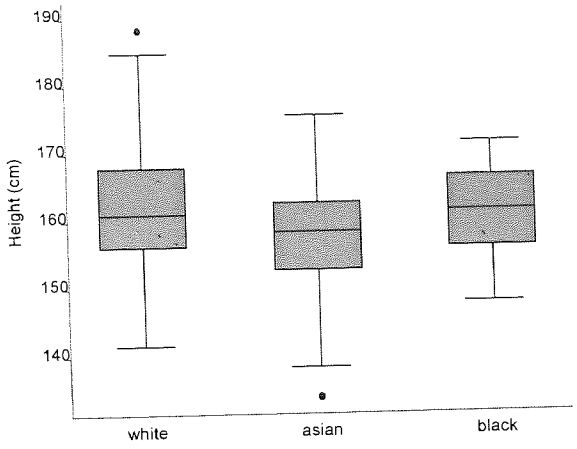


Figure 7.4.22 Year 8 box plot of height by ethnic group

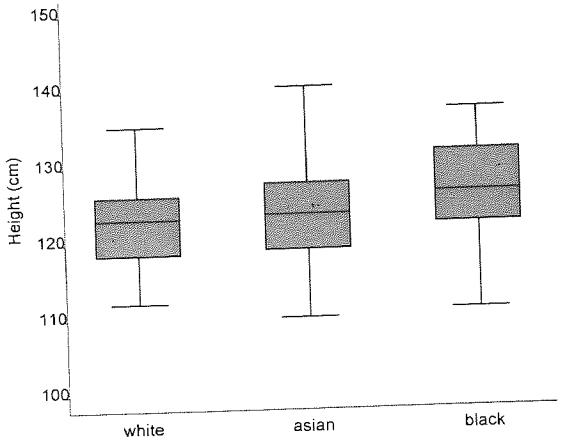


Figure 7.4.23 Year 2 box plot of height by ethnic group

Within the younger cohort (Figure 7.4.23), an upward trend in height was manifest across ethnic groups, with Black children (mean ± SD:126.63 ± 6.25cm) taller than Asian (123.63 ± 5.96cm), who in turn were taller than Whites (123.03 ± 5.65cm). A one way ANOVA rendered an overall significant result ($F=4.53$, $p= 0.012$), with Scheffe's *post-hoc* analyses revealing that Black children were significantly taller than Asians ($p=0.022$) and Whites ($p=0.022$). White and Asian children could not be differentiated by height ($p= 0.81$).

Examining weight as a function of ethnicity (Figures 7.4.24 - 7.4.25), Year 8 children Asians had a lower mean log weight compared to Whites (mean log weight [log kg]: Whites= 3.98 ± 0.23 *vs.* Asians= 3.87 ± 0.25 *vs.* Blacks= 3.95 ± 0.18. One way ANOVA, $F= 5.97$, $p=0.003$, Scheffe *post-hoc* Asians *vs.* White $p= 0.003$). Asian children were lighter than White children, in line with the finding of a lower height in these children. However, this difference was not significant in Year 2 children (mean reciprocal weight [kg^{-1}]:Whites= 0.040 ± 0.0072 *vs.* Asians= 0.042 ± 0.01 *vs.* Blacks= 0.039 ± 0.0075; $F= 2.41$, $p=0.09$).

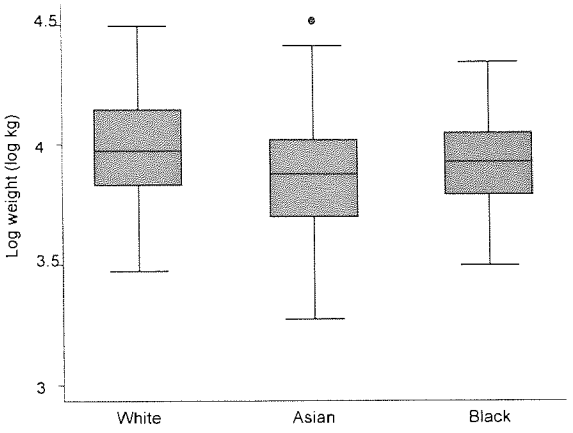


Figure 7.4.24 Year 8 box plot of weight by ethnic group

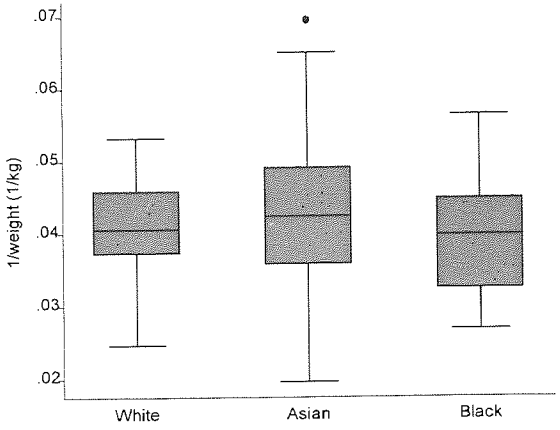


Figure 7.4.25 Year 2 box plot of weight by ethnic group

7.4.5.4 Gender and anthropometry

No difference was found in the mean height or mean transformed weight values in either Year 2 or Year 8 children by gender (Table 7.4.8, Figures 7.4.26 -7.4.29)

	Year 2				Year 8			
Mean values (±SD)	**Male**	**Female**	**t**	**p value**	**Male**	**Female**	**t**	**p value**
Height (cm)	124.42 ± 5.90	123.42 ± 6.17	1.48	0.14	160.63 ± 9.62	159.33 ± 8.24	1.23	0.22
Trans weight	0.042 ± 0.008	0.041 ± 0.01	1.15	0.25	3.93 ± 0.23	3.95 ± 0.24	-0.73	0.46

Table 7.4.8 A comparison of height and transformed weight values (Year 8= log values. Year 2= 1/weight) by gender within each age group using a two-tailed independent t test

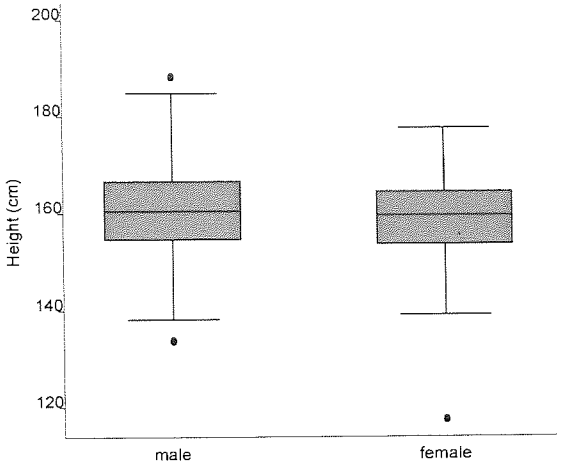


Figure 7.4.26 Year 8 plot of height by gender

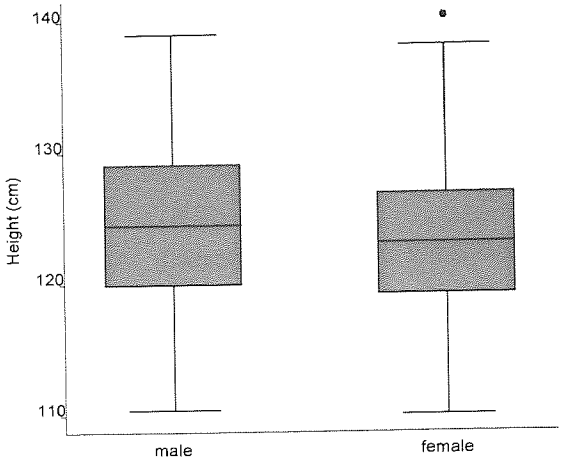


Figure 7.4.27 Year 2 plot of height by gender

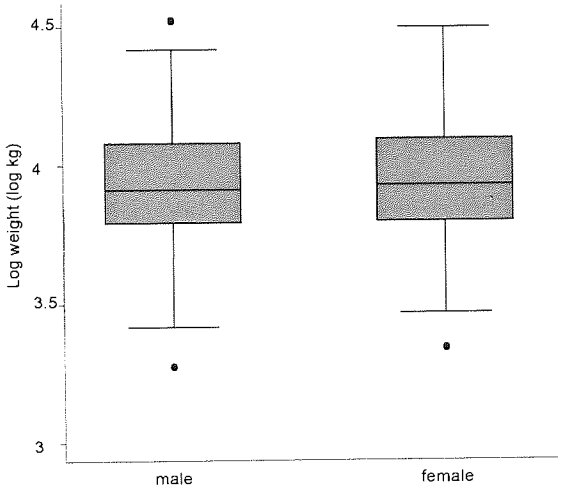


Figure 7.4.28 Year 8 plot of log weight by gender

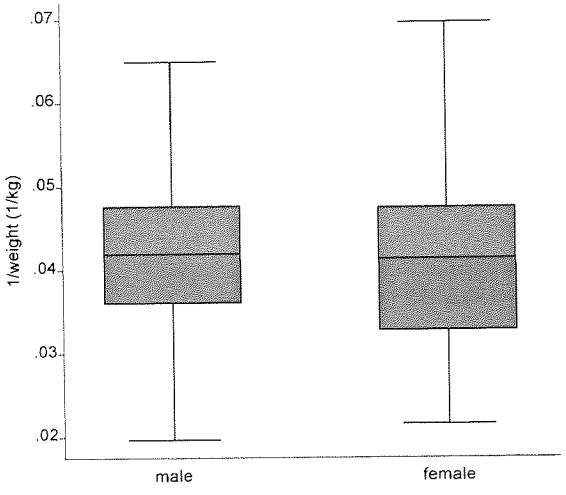


Figure 7.4.29 Year 2 plot of 1/weight by gender

It can be seen that height and weight did not vary by gender within both age groups although systematic differences in biometry were found between males and females (Section 7.4.4).

7.4.6 Biometry, Anthropometry and Refractive Group

7.4.6.1 Differences between refractive groups

Year 8

The following section investigates the association between the refractive group of a child (myope, hyperope and emmetrope) as established by AES definitions and mean biometric measures.

In support of the established correlation between SER and AL (Larsen *et al.*, 1971), a significant difference in mean AL values between the 3 refractive groups was determined (Table 7.4.9, one way between-groups ANOVA, F= 30.87, p< 0.001). For Scheffe *post-hoc* analysis findings, refer to Figures 7.4.30 - 7.4.32.

Refractive Group	N	AL (mm)	SD	CR (mm)	SD	ACD (mm)*	SD	Height (cm)¶	SD	Log weight† (logkg)	SD
Emmetrope	193	23.33	0.75	7.80	0.27	3.61	0.29	159.93	9.33	3.95	0.25
Myope	87	23.97	0.81	7.67	0.24	3.72	0.26	159.75	7.47	3.91	0.22
Hyperope	16	22.60	1.02	7.90	0.35	3.57	0.28	159.93	10.43	3.95	0.18

*N= 182 emmetropes, 84 myopes, 15 hyperopes
†N= 184 emmetropes, 83 myopes, 15 hyperopes
¶ N= 186 emmetropes, 83 myopes, 15 hyperopes

Table 7.4.9 Year 8 mean ocular component values by refractive group

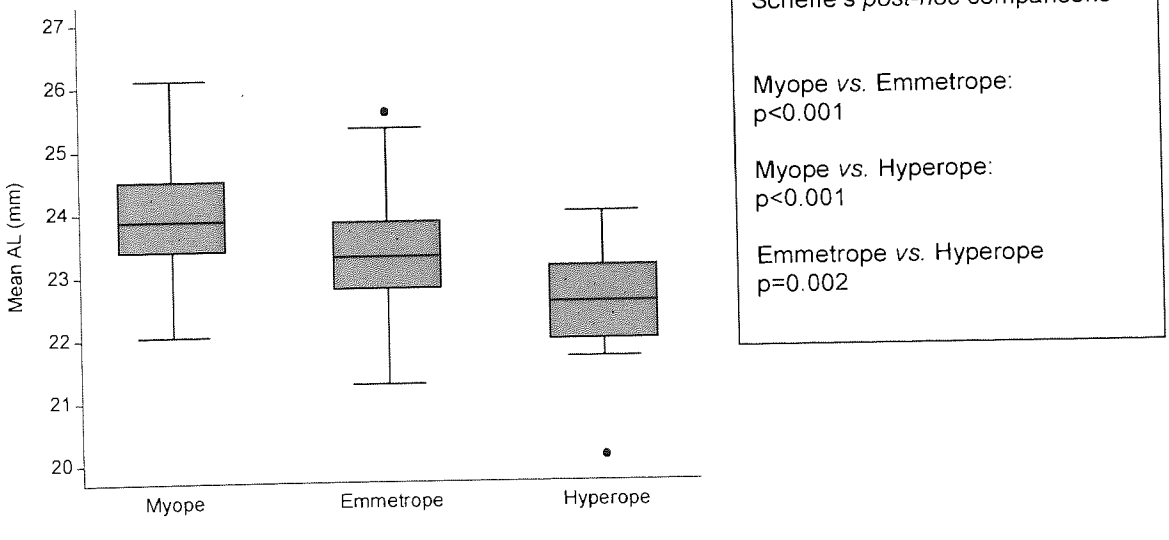


Figure 7.4.30 Year 8 box plot of AL by refractive group with *post-hoc* significance values

Mean corneal radius in myopes was significantly steeper than in both emmetropes and hyperopes (F= 10.13, p<0.001) although emmetropes did not differ from hyperopes (p=0.41).

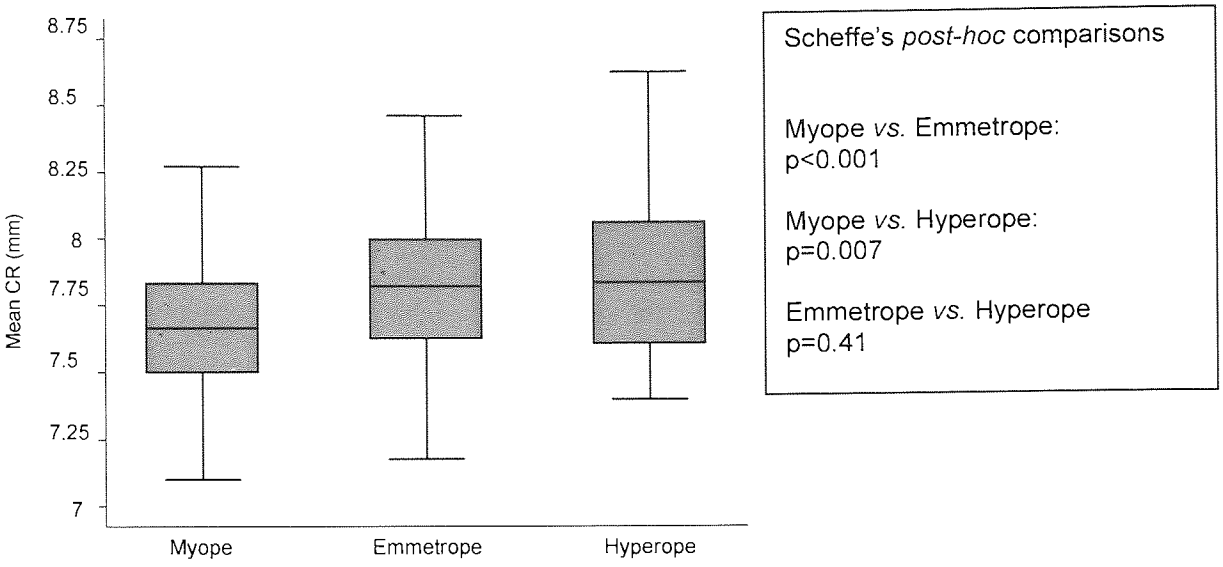


Figure 7.4.31 Year 8 box plot of CR by refractive group with *post-hoc* significance values

Mean ACD was found to differ between refractive groups (F= 4.48, p= 0.012). Myopes showed a deeper mean ACD compared to emmetropes (Figure 7.4.31) although not compared to hyperopes, an unexpected finding in view of the considerable difference in mean ACD between myopes and hyperopes (Table 7.4.11) possibly attributable to low power within the test. Hyperopes also had a deeper mean ACD relative to emmetropes, although this was not statistically significant.

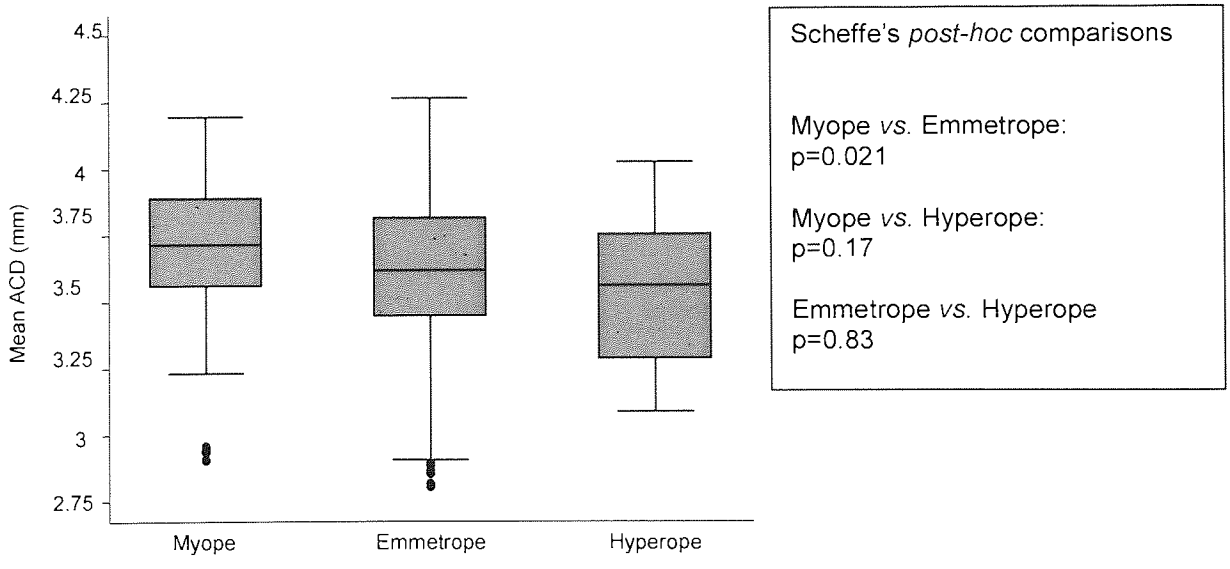


Figure 7.4.32 Year 8 box plot of ACD by refractive group with *post-hoc* significance values

Neither height (F= 0.01, p= 0.99) or weight (F= 0.96, p= 0.38) showed considerable deviation as a function of refractive group (Figures 7.4.33 - 7.4.34).

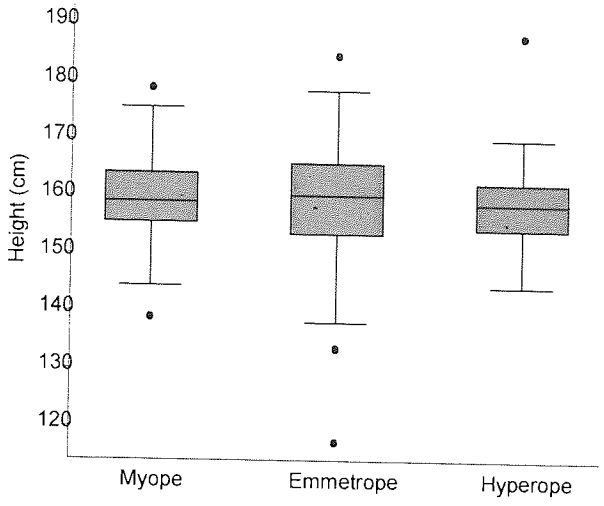


Figure 7.4.33 Year 8 box plot of height by refractive group

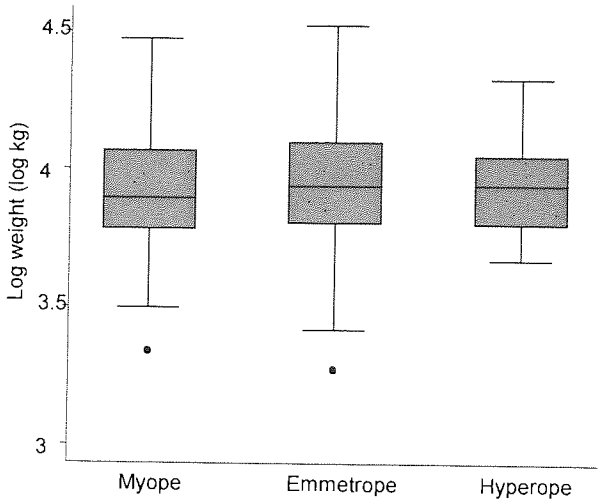


Figure 7.4.34 Year 8 box plot of log weight by refractive group

It may therefore be said that on average in Year 8 myopes, AL was longer, CR was steeper and ACD was deeper compared to emmetropes. Neither height nor weight varied as a function of refractive group.

Year 2

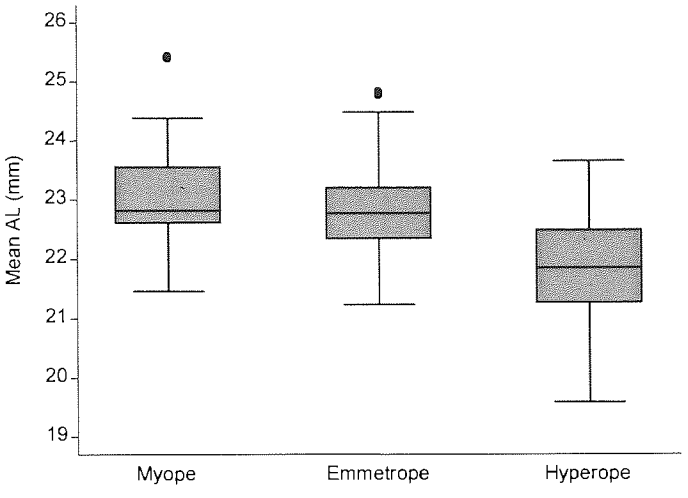
Mean values for measured parameters in the younger cohort as a function of refractive group is displayed in Table 7.4.10.

Refractive Group	N	AL (mm)	SD	CR (mm)	SD	ACD (mm)*	SD	Height (cm)¶	SD	1/ weight† (kg^{-1})	SD
Emmetrope	236	22.80	0.64	7.80	0.25	3.53	0.22	124.19	5.96	0.041	0.01
Myope	30	23.08	0.95	7.59	0.27	3.50	0.24	123.19	6.51	0.043	0.01
Hyperope	36	21.88	0.86	7.80	0.32	3.42	0.22	122.96	6.21	0.043	0.01

* N= 234 emmetropes, 28 myopes, 36 hyperopes ¶ N= 234 emmetropes, 30 myopes, 35 hyperopes
† N= 234 emmetropes, 29 myopes, 35 hyperopes

Table 7.4.10 Year 2 mean ocular component values by refractive group

A significant difference was elicited between refractive groups for AL (F= 31.19, p<0.001). *Post*-hoc multiple comparison results are shown alongside box plots below (Figures 7.4.35 – 7.4.37). Unexpectedly, a significant difference was not found between the mean AL values of myopes and emmetropes (p=0.13)



Scheffe's *post-hoc* comparisons

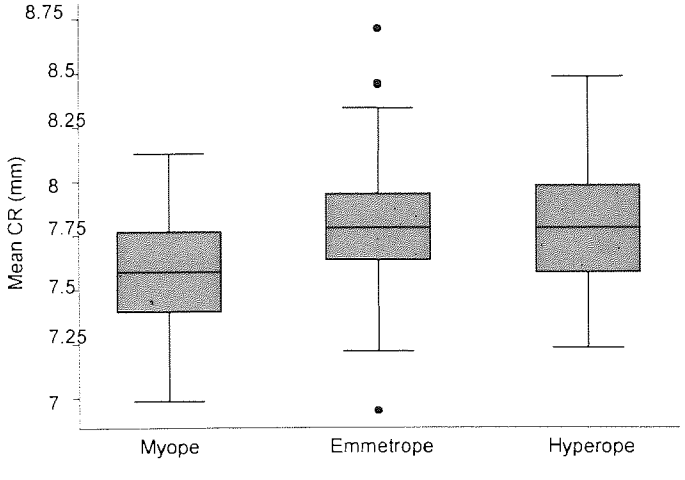
Myope *vs.* Emmetrope:
p=0.13

Myope *vs.* Hyperope:
p<0.001

Emmetrope *vs.* Hyperope
p<0.001

Figure 7.4.35 Year 2 box plot of AL by refractive group with *post-hoc* significance values

Corneal radius varied between refractive groups (F= 6.01, p=0.003), with a steeper cornea in myopes compared to both emmetropes and hyperopes (Figure 7.4.36). This was a similar finding to that of Year 8 children (Figure 7.4.31).



Scheffe's *post-hoc* comparisons

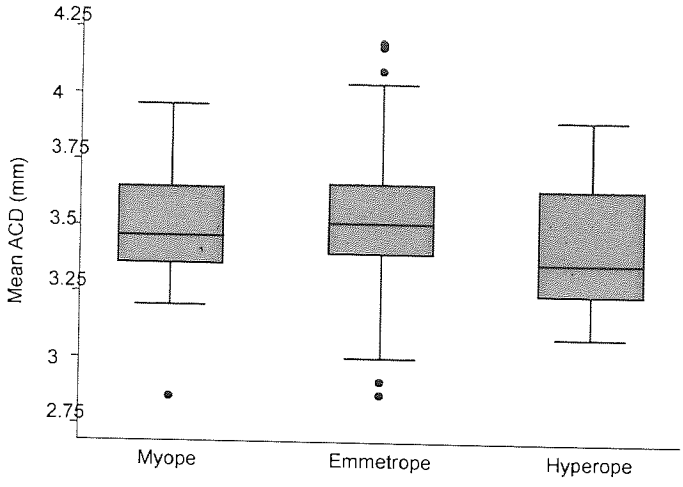
Myope *vs.* Emmetrope:
p<0.001

Myope *vs.* Hyperope:
p=0.005

Emmetrope *vs.* Hyperope
p=0.97

Figure 7.4.36 Year 2 box plot of CR by refractive group with *post-hoc* significance values

Mean ACD was found to differ between refractive groups (F= 4.01, p= 0.02) with the main difference attributable to a difference between emmetropes and hyperopes (Figure 7.4.37).



Scheffe's *post-hoc* comparisons

Myope *vs.* Emmetrope:
p=0.71

Myope *vs.* Hyperope:
p=0.42

Emmetrope *vs.* Hyperope
p=0.02

Figure 7.4.37 Year 2 box plot of ACD by refractive group with *post-hoc* significance values

As with the older cohort, neither height (F= 0.88, p=0.41) nor weight (F= 0.96, p=0.39) varied between refractive groups (Figures 7.4.38 – 7.4.39).

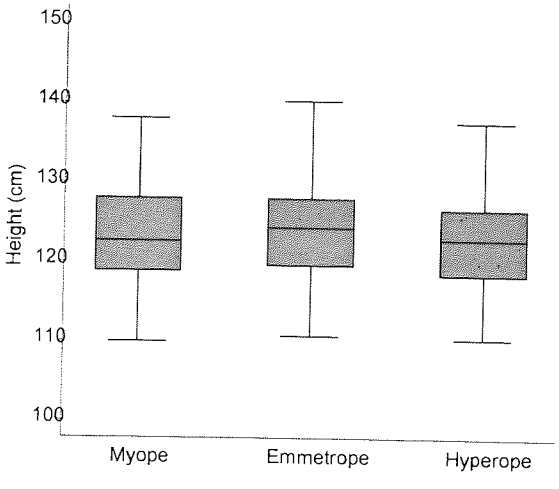


Figure 7.4.38 Year 2 box plot of height by refractive group

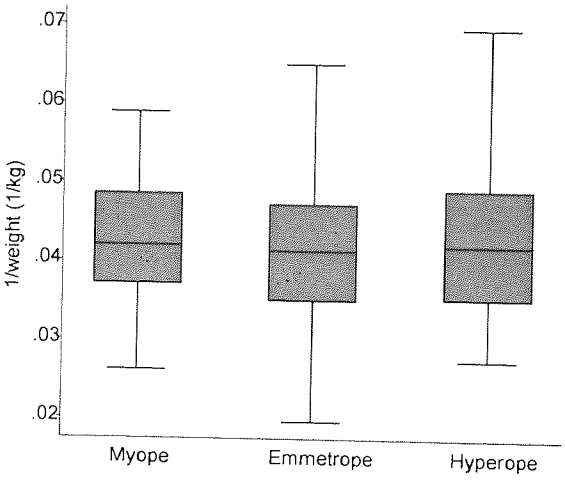


Figure 7.4.39 Year 2 box plot of 1/weight by refractive group

It was found overall that myopes in Year 2 had a steeper CR compared to emmetropes. AL was greater in myopes compared to emmetropes but not to a significant degree. ACD did not show a difference between myopes and emmetropes.

7.5 DISCUSSION

The distribution of ocular components derived in the AES is comparable to that determined by the Sydney Myopia Study (Ojaimi *et al.*, 2005a; Ip *et al.*, 2007). The significant correlation coefficients between many ocular components in the AES (Table 7.4.5-7.4.6) suggest that the components, though respectively distributed normally, are highly coordinated.

7.5.1 Distribution

Both axial length (AL) and corneal radius (CR) were normally distributed, in line with previous child epidemiological studies (Sorsby *et al.*, 1961; Ojaimi *et al.*, 2005a). Anterior chamber depth was found to be non-normally distributed with a strong negative skew. The IOLMaster is sensitive to variations in ACD alignment and it is suggested that the optimal method of measuring ACD on patients is to align the fixation point viewed by the investigator in front of the lens image on the screen (IOLMaster manual, 2003). A greater familiarisation with measurement techniques developed as the investigators became experienced with the IOLMaster, however earlier measurement errors may have contributed to the recurrence of low ACD values determined and the skewed ACD distribution. Eliminating 27 Year 8 children (>2 SD from mean) and 4 Year 2 children (>3 SD from mean) with extreme ACD values normalised the respective distributions of both age groups (Figure 7.4.4 & Figure 7.4.8).

7.5.2 Age

Between age groups, it was found that both AL ($p<0.001$) and ACD ($p=0.005$) increased in size. These effects are qualitatively identical to that determined in the longitudinal CLEERE study (Zadnik *et al.*, 2003). However the cornea was not found to differ significantly between age groups ($p=0.71$). The stability of the cornea supports literature refuting a change in its dimensions with time (Zadnik *et al.*, 1993; Jones *et al.*, 2005), though some studies have shown a slight flattening with age (Friedmann *et al.*, 1996; Zadnik *et al.*, 2004).

However the AES temporal inferences drawn are inferred from cross-sectional findings and used as a basis for longitudinal variation in the individual. The consequence of incorrect temporal inference is illustrated by a study that measured corneal radii changes with age (Friedmann *et al.*, 1996). No difference was found with age using cross-sectional data, although longitudinal data produced a flattening. Thus longitudinal follow-up on the same AES subjects would confirm initial inferences on the temporal nature of ocular component growth between the ages of 6 and 13 years, similar to the CLEERE study (Zadnik *et al.*, 2003).

7.5.3 Ocular components and refractive error

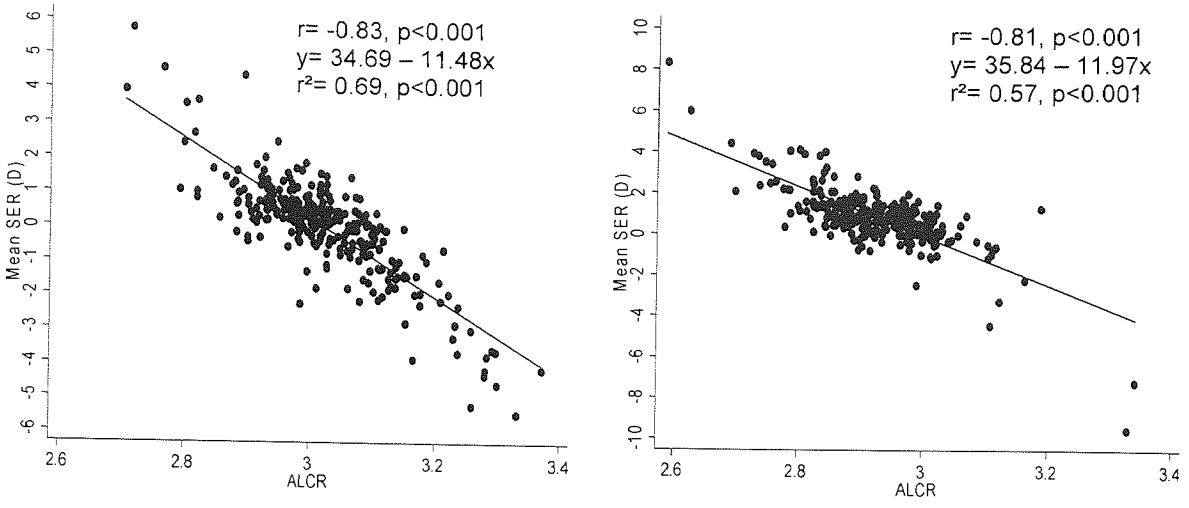
The use of partial correlation coefficients revealed strong correlations between all ocular components to mean SER in both age groups. Linear regression models constructed with mean SER as the outcome measure determined a significant relationship between mean AL and mean SER, with AL accounting for between 28-29% of the variance in SER in children, such that a larger AL was associated with a more negative refractive error. The partial correlation coefficient for AL with SER, adjusted for CR and ACD, was -0.82 and -0.84 in Year 8 and 2 children respectively. These values agree with those determined by van Alphen (1961), who calculated the second order correlation coefficients between mean AL and mean SER (adjusted for mean CR and mean ACD) to be -0.85.

Corneal radius also correlated positively with mean SER, the correlation strengthening after controlling for AL and ACD. The positive correlation between mean CR and mean SER implies that the cornea steepens as refractive error becomes more negative, supporting work reported by Grosvenor and Scott (1994). Thus the cornea does not appear to compensate for AL growth but contributes to refractive error.

To confirm the contributory nature of the cornea, the axial length/corneal radius (AL/CR) ratio was regressed against mean SER (Figure 7.5.1). The mean AL/CR ratio for the Year 8 group (± SD) was 3.02 ± 0.10 and for Year 2 children it was 2.92 ± 0.09, considerably lower than the values calculated by Grosvenor (1988) for White participants in the study by Sorsby *et al.* (1961).

It can be seen that a strong association exists between AL/CR and mean SER (Figure 7.5.1). In addition, the coefficient of determination of AL/CR (r^2= 0.69 Year 8, 0.57 Year 2) is higher that that of AL (r^2= 0.29 Year 8, 0.27 Year 2) or CR alone (r^2= 0.05 Year 8, 0.02 Year 2).

An increased AL/CR is associated with an increased myopic refractive error, due to an increased axial length, a reduced (steepened) corneal radius or both occurring together. The strengthened coefficient of determination (r^2) of AL/CR compared to AL and CR alone suggests that the combined role of the parameters is effective in accounting for a greater proportion of the variance in SER and that CR contributes to the determination of refractive error, albeit to a lesser extent than the axial length. Thus the compensatory component offsetting the effect of ocular elongation in the eye must principally be the lens (Grosvenor and Scott, 1994).



A Year 8 **B Year 2**

Figure 7.5.1 Linear regression of AL/CR with mean SER by age group

The negative coefficients of ACD when correlated with mean SER appeared due to a masking effect of AL and CR, as the partial coefficient after adjustment for AL and CR was positive in both age groups and supports the results of van Alphen (1961). The presence of a positive correlation between ACD and mean SER indicates that ACD becomes shallower with a more negative SER. ACD values included in the multiple regression tables contributed significantly to refractive error in both age groups (Tables 7.4.1-2). However, the ACD results should be interpreted with some caution as the IOLMaster utilises the corneal radius to determine the ACD and the incorporation of a bias is likely where the measure of a component is dependent on another (Ludlam *et al.*, 1965). Further independent assessment of the ACD is required before accurate partial correlations can be drawn between the ACD and CR.

7.5.4 Ethnicity, gender and biometry

There did not appear to be a notable difference in biometric measures as a function of ethnic group, with only ACD found to vary with marginal significance between Whites and Asians in Year 2. Considering the significant disparities in refractive error and myopia prevalence between ethnic groups demonstrated in Chapter 6 (in particular Year 8 Whites *vs.* Asians), the similarity in ocular components by ethnicity points to a refractive error aetiology of miscorrelation, echoing the sentiments of Sorsby and colleagues (1957). It appears that although the ocular components of Asian children are of similar dimensions to those of White children, it is the correlation between these components that differs such that the resultant refractive error is more myopic in Asian relative to White children. An analysis of the AL/CR ratio by ethnic group would provide support for this notion,

as the AL/CR would provide a measure of the relative levels at which the AL and CR were synchronised.

On examination of the 3 main ethnic groups within the Year 8 cohort (Whites, Asians and Blacks), a significant difference in AL/CR ratios between the 2 groups with the largest difference in mean refraction (Whites vs. Asians, mean AL/CR= 3.00 ± 0.10 *vs.* 3.05 ± 0.11 respectively) was detected (one way between-groups ANOVA F= 6.99, p= 0.001; Scheffe's *post-hoc* Whites *vs.* Asians p= 0.001). However, the difference in Year 2 AL/CR ratios as a function of ethnicity was not significant (one way between subjects ANOVA, F= 0.57, p= 0.56).

Thus Year 8 Asian children had on average a larger AL/CR ratio compared to Whites, due to a combination of an increased AL and decreased CR, neither of which were significantly different in isolation. The finding of similar AL/CR ratios in Year 2 children implies a temporal variation in AL/CR and an increase in the Asian AL/CR ratio with age relative to White children. The cause of the higher AL/CR ratio measured in Asian children cannot be speculated upon nor whether the correlation of AL and CR in Asians in some way implies a faulty regulatory 'end-point' mechanism or an adaptive modification to a near visual environment, such that the eye is prompted to grow towards what it believes is an emmetropic near state.

Variations in biometry as a function of gender were systematic for all ocular components. Females of both age groups were found, on average, to have shorter eyes (shorter AL and ACD) and steeper corneae compared to males, a relationship found in other studies (Lam and Goh, 1991; Zadnik *et al.,* 2003; Ip *et al.,* 2007). The AL/CR ratios did not vary by gender in either Year 8 (two-tailed t=0.2, p=0.85) or Year 2 (two-tailed t= 1.17, p= 0.24) children, indicating a similar concordance between the components. It appears as though the eyes of males undergo a greater level of 'size' factor expansion (van Alphen, 1961) relative to females, accounting for their longer AL and flatter CR. However, a higher myopia prevalence level was detected in females (Section 6.5.2.2), which although rendered statistically insignificant by the addition of ethnicity to multivariate models (Table 6.5.9), did retain an OR>1. One putative hypotheses may be cited to account for the gender difference in prevalence involving eye shape. It may be that the female eye is more prolate in shape peripherally relative to males, as suggested by Mutti *et al.* (2000a) who found a more hyperopic relative peripheral refraction in females in relation to males. Prolate peripheral eye shapes have been associated with myopia (Logan *et al.,* 2004b; Mutti *et al.,* 2007).

7.5.5 Anthropometry and biometry

Although there was a lack of association between height and refractive error (mean SER), a weak correlation was derived between ocular components and height, such that taller children had longer eyes, flatter corneae and deeper ACDs. These findings are in accordance with work establishing a relationship between height and biometry but not between height and refractive status (Wong *et al.,* 2001). Therefore, although height may not necessarily affect the refractive outcome of the eye, it may exert a positive influence on eye growth through pre-ordained mechanisms unrelated to visual input. Using the analogy of the eye as an inflatable globe (van Alphen, 1961), an increase in height with a concurrent expansion of the globe (increase in the size factor) would alter lens shape. The lens would become flatter with ocular expansion (Mutti *et al.,* 1998), offsetting the AL growth caused by an increase in height and accounting for the lack of association between SER and height, even after controlling for AL and CR (Figures 7.4.8 – 7.4.9). Chinese subjects have shown a thinning in lens size with increasing height (Wong *et al.,* 2001; Saw *et al.* 2002c), a finding which supports the aforementioned balloon analogy of van Alphen (1961) as an attempt by the eye to offset axial elongation.

In addition, the cornea would also flatten with an increase in size factor (supported by the positive correlation between CR and height in both age groups, Tables 7.4.5 – 7.4.6), further offsetting ocular elongation.

Therefore the proportion of an individual's ocular biometry that is genetically pre-ordained may be the proportion that correlated weakly with height, whilst the remaining growth in ocular components would be driven by visual feedback, such that the eye becomes emmetropic/ametropic. The low correlation between stature and ocular biometry may further represent physiological feedback mechanisms preventing excessively tall/short people from having ALs outside the normal range by virtue of their stature alone.

Weight values were transformed to provide normal distributions and these transformed values were used within all analyses. The transformed weight values correlated well with all ocular components within children of both year groups (Figures 7.4.5 - 7.4.6). However, partial correlation coefficients controlling for height removed significance of all weight links to ocular components (Table 7.4.7) and implied that weight had developed an indirect association with AL, CR and ACD values through height.

Studies have derived a relationship between anthropometry and the AL/CR ratio (Saw *et al.,* 2002c). However, neither height nor weight were significantly correlated with this variable in either AES cohort (Year 8: height r= 0.03, p=0.62; log weight: r= -0.03, p= 0.59; Year 2: height r= 0.001, p=0.86; 1/weight: r=0.02, p=0.76).

In the Year 2 group, Black children were taller than Whites and Asians. However, in the elder cohort, Asians were found to be significantly shorter compared to White children. Though this may appear unexpected in view of the increased susceptibility of Asians to myopia (and the link between height and mean AL), it supports the view that refractive error is not a result of a longer AL, but rather a propensity for miscorrelation between ocular components.
With regards to weight, Year 8 Asian children were found to be lighter than Whites although for the younger age group, this difference was not present.

No differences were found for height and weight by gender (Table 7.4.10) in either age group, opposing results derived from the SCORM study, where males were found to be taller and heavier than females (Saw *et al.*, 2002c). The findings by Saw *et al.*, (2002c) may represent a geographical disparity in stature between Singapore Chinese children and multi-ethnic UK children.

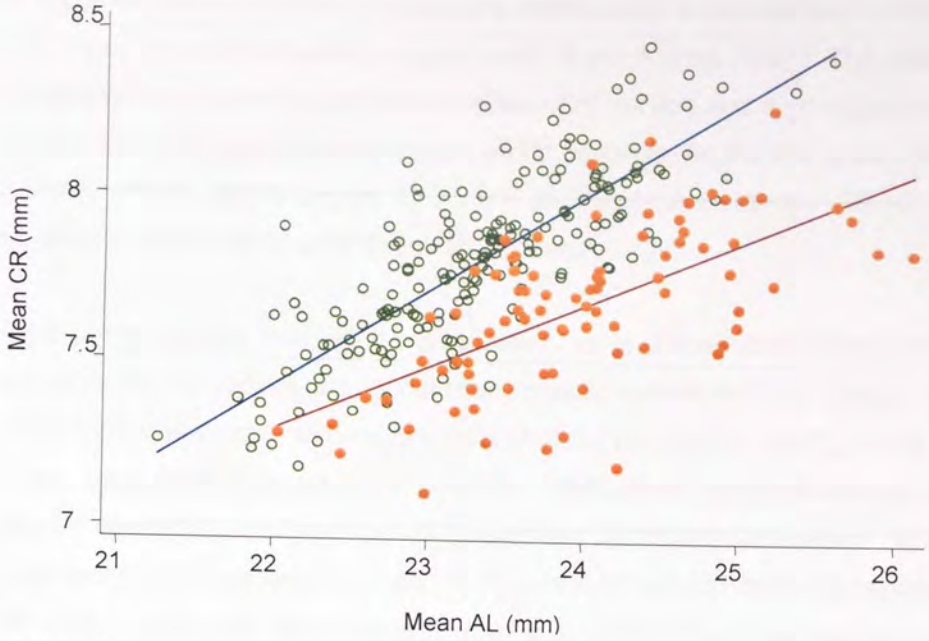
7.5.6 Refractive Groups

7.5.6.1 Axial length

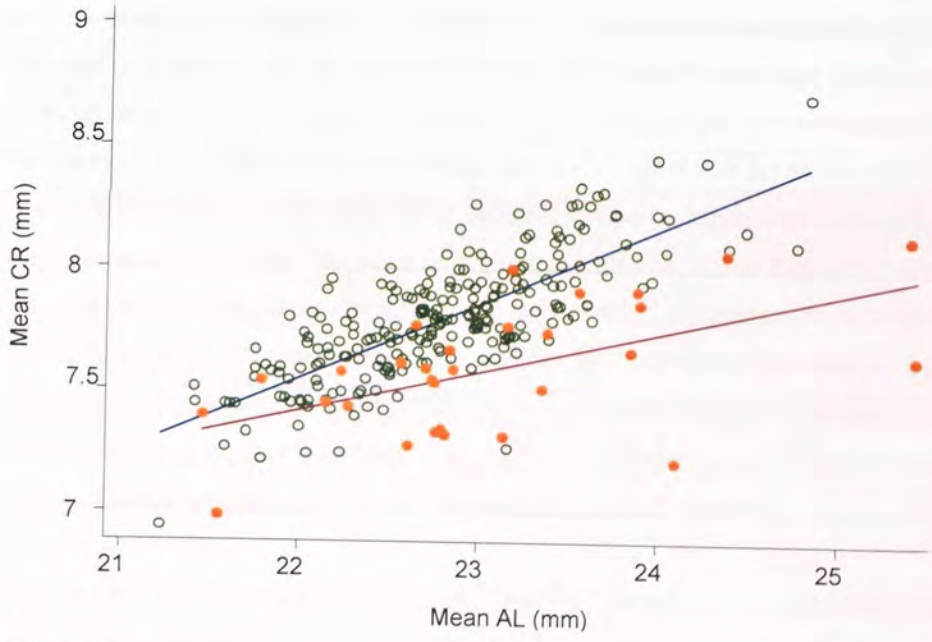
As expected, Year 8 myopes were found to have a significantly longer axial length compared to emmetropes (Figure 7.4.30). This is in line with work showing larger axial lengths in myopes (Jones *et al.*, 2005). However, although Year 2 myopes did have a longer AL compared to emmetropes, unusually this was found to be statistically insignificant.
Height and weight did not differ by refractive group in either age group, supporting findings by Edwards *et al.*, (1996).

7.5.6.2 Corneal radius

The corneal findings of this chapter raise an interesting paradox. AL and CR were found to be positively correlated such that a longer AL was accompanied by a flatter CR (Figure 7.4.5 – 7.4.6). However, myopes were also found to have longer eyes and steeper corneae compared to emmetropes in both Year 2 and Year 8 children (Figure 7.5.2).



A Year 8



B Year 2

Figure 7.5.2 Relationship between corneal radius and axial length for emmetropes and myopes to illustrate the corneal paradox. Emmetropes: Open green circles. Myopes: Filled orange circles. It can be seen that a positive correlation exists between AL and CR and that myopes have on average a steeper cornea compared to emmetropes

A hypothesis to account for the apparent contradiction was proposed by Scott and Grosvenor (1993) and is based upon the significant early work of van Alphen (1961). The positive correlation between AL and CR can be attributed to the size factor of the eye and an endogenous mechanism that causes the eye to grow analogous to an inflated globe. As the eye grows, its AL increases and CR flattens, with AL accounting for 31.3% and 37.2% of the variance in CR for Year 8 and Year 2 children respectively (r^2 values) by AES findings.

Concurrent to ocular inflation, it is postulated that in susceptible children, on exposure to myopiagenic risk factors, equatorial ciliary muscle resistance (van Alphen, 1986) prevents spherical expansion of the globe and initiates axial stretch (van Alphen, 1961), giving rise to a prolate eyeball. At the same time there may be a reduction in the rate of corneal flattening, either due to ciliary muscle resistance or a factor as yet unidentified (Scott and Grosvenor, 1993). The combination of axial stretch, lower corneal flattening and equatorial tension forces (preventing compensatory lens flattening) would lead to the onset of myopia. It is this stretch and relative loss of corneal flattening that would account for the finding of a steeper cornea in myopes.
An alternative hypothesis professes a temporal reversal of the association: a steepening of the cornea occurs in predisposed children during the predominant growth phase of the cornea i.e. before the age of 2 years. The cornea then flattens with global expansion (size factor), albeit remaining steeper in susceptible children relative to those who will remain emmetropic. On eventual exposure to myopiagenic risk factors, the steeper cornea initiates a relative peripheral hyperopic refraction, possibly through a signal cascade or tension forces on equatorial expansion. The relative peripheral hyperopia would cause the onset of myopic symptoms, either through incomplete lens thinning secondary to equatorial restriction, or by driving axial elongation to exceed the rate of lenticular compensation (Mutti *et al.,* 1998). Support for this theory comes from a longitudinal case control analysis by Goss and Jackson (1995), who found that children who developed myopia during the course of the study (n= 29, mean age: 11.3 ± 1.5 years) had steeper corneae at baseline than those who remained emmetropic (n= 58, mean age: 10.8 ± 1.4 years).

The above theories are based upon the central cornea and keratometric readings. However, it is recognised that the CR does not adequately depict the entire corneal plane. The cornea is an aspheric surface and has been described as an ellipse with a flattening curvature (prolate) relative to its apical radius (Figure 7.5.3, Kiely *et al.,* 1982). With age the peripheral cornea becomes less prolate (Davis *et al.,* 2005), although the degree of flattening has been shown to be lower in myopes (Carney *et al.,* 1997) leaving the myopic cornea relatively oblate in shape.

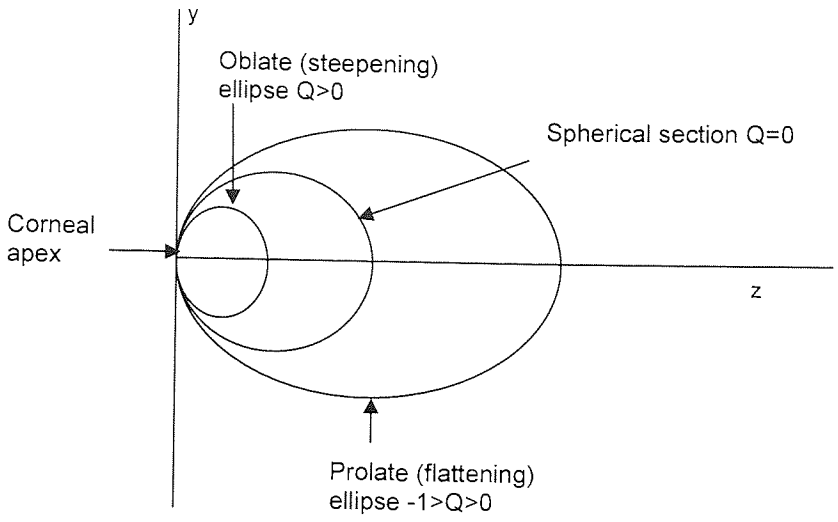


Figure 7.5.3 Conic section showing the effect of asphericity (Q) on corneal profile, assuming a constant apical radius between sections

Longitudinal studies differ regarding the predictive power of initial asphericity on the progression of refractive error. A study on refractive error progression in myopes (n= 48) over 5 years by Horner *et al.*, (2000) found that initial asphericity correlated significantly with myopia progression ($r= +0.29$, $p<0.05$) and that the refractive error of subjects with relatively prolate corneae at baseline progressed faster over the duration of the study. This contrasted with work by Davis *et al.*, (2005) who did not determine a relationship between initial asphericity and 5 year progression (n= 175) and suggested that corneal shape is of little value in predicting future refractive error progression. However, the number of myopes in the study by Davis and colleagues was low and may have precluded sufficient power in the analysis.

In summary, central corneal radius and asphericity values do not appear to be related (Carney *et al.*, 1997; Davis *et al.*, 2005) and it appears that central CR and asphericity have limited value in predicting refractive progression (Grosvenor and Goss, 1998; Horner *et al.*, 2000; Davis *et al.*, 2005). However, there may be a role for the cornea and peripheral refractive error in the prediction of myopia onset.

To the author's knowledge, studies do not exist that have evaluated the role of corneal topography and relative peripheral refraction in prospective, longitudinal cohort studies as a function of children who develop myopia compared to children who remain emmetropic. A study of this nature was conducted recently to assess the role of axial length and relative peripheral refractive error (Mutti *et al.*, 2007) and it would be beneficial to extend this approach to examine the effect of the cornea.

7.5.6.3 Anterior chamber depth

Many studies correlating ACD with mean SER have determined negative zero-order coefficients (Larsen, 1971b; Scott and Grosvenor, 1993), which suggests a deepening of the ACD with an increasing myopic refraction. In addition, the ACD was found to be deeper in Year 8 myopes compared to emmetropes and hyperopes. However, the partial coefficient of ACD correlated to mean SER, after adjustment for AL and CR, was positive, supporting work by van Alphen (1961) and showing that, for eyes of a constant AL and CR, the ACD shallows with an increasing myopic refraction.

These findings present a paradox of the ACD, although it does not appear to have been highlighted in previous literature. However, the ACD is a dimension bounded by the morphology of the cornea and lens. Artificial deepening of the ACD in myopes may be inferred by a steepening of the cornea and/or a thinning of the lens, both of which have been shown to vary by refractive status (Jones *et al.,* 2005). Verification of the actual effect on the ACD with refractive error would require knowledge of lens parameters. In addition, an independent measure of ACD is required which is not reliant upon the input of the corneal radius.

7.5.7 Summary

In conclusion, AL and CR appear to play a predominant role in determining a myopic refractive error. The AL/CR correlated significantly with mean SER and accounted for a greater proportion of SER variance than explained by AL alone. CR was also found to be deeper in myopes. ACD had an impact on the final refractive outcome although its true positive correlation on SER was masked by AL and CR.

The weak correlation of height to ocular components suggests a role of stature in determining the raw dimensions of the eye, although not the final refractive outcome. Weight was shown to be indirectly associated with ocular components due to its relationship with height.

The role of the cornea in myopia appears understated. A steeper cornea may not contribute to a myopic refractive error as considerably as AL, however its role in initiating myopia onset and whether corneal steepening is associated with a relatively prolate peripheral retina appears an avenue as yet unexplored.

Measurement of crystalline lens thickness and corneal thickness using high resolution non-contact partial coherence interferometry (PCI) methods (Drexler *et al.,* 1997) will permit the elucidation of further individual ocular component contributions to refractive error. A commercially available PCI device for the anterior segment, the *Zeiss* ACMaster, is advocated for such future studies

(Kriechbaum *et al.*, 2006) in addition to the IOLMaster. A method of calculating lens power using the data available is demonstrated in Appendix 9 alongside its associated shortcomings.
The strengths of this study include a comprehensive insight into the biometric correlates of refractive error in urban UK children and data on multi-ethnic children obtained through rigorous epidemiological sampling procedures. Ocular biometry was taken using the *Zeiss* IOLMaster (Jena, GmbH), enabling resolution of measurements to a considerably greater degree compared to A-scan ultrasound. In addition, children were very receptive to the machine due to its non-contact nature and it is likely to become the new gold standard for ocular biometric measurements along the primary visual axis and in time, as a measure of peripheral ocular dimensions (Mallen and Kashyap, 2007).

A limitation of this study concerns principally the degree of measurement error that occurred during the initial stages of the AES while measuring ACD. A second limitation refers to the inferences of age effects based on cross-sectional data. Longitudinal extension to cross-sectional AES data using the IOLMaster will evaluate the veracity of biometric inferences drawn to date and their variations with refractive error.

CHAPTER 8

QUESTIONNAIRE ANALYSIS AND THE ELUCIDATION OF PUTATIVE MYOPIAGENIC RISK FACTORS

8.1 INTRODUCTION

Myopia is for many children a relatively benign and easily correctable condition. Nevertheless, it is invariably a lifelong condition and can have social, economic and pathological implications for an individual. Thus as a result of these ramifications and the evident global prevalence rise in children (Saw, 2003; Gilmartin, 2004; Morgan and Rose, 2005), myopia is a discipline demanding a detailed understanding surrounding its aetiology and pathophysiology.

Myopia incurs social costs through negative connotations associated with spectacle wear, blurred vision and accompanying effects on quality of life (Rose *et al.,* 2000). Myopes have been described as introverted characters with reclusive tendencies (Lanyon and Giddings, 1974; Beedle and Young, 1976). It has also been determined that children wearing spectacles (of whom myopes will predominate) are more at risk of bullying/acts of victimisation compared to non-spectacle wearers (Horwood *et al.,* 2005).
However recent evidence from the USA COMET study found myopia not to impact significantly upon the self-esteem of a child (Dias *et al.,* 2005), perhaps due to a general acceptance of spectacle wear in society today. Notwithstanding this finding, spectacle wearing is not favoured by many children in that it is liable to occur at a time of pubertal change when levels of self-consciousness are enhanced.

The economic costs of myopia occur in many guises. The regular purchase of spectacles with supplementary aesthetic procurements (e.g. contact lenses, hi-index lenses) is a financial burden exacerbated by the increased likelihood of a greater frequency of refractive change in myopes (Lam *et al.,* 1999). Collectively, the financial burden of distance correction has been estimated recently to lie between US $3.9 - $7.2 billion a year (Vitale *et al.,* 2006), though this may be considered a conservative range due to the exclusion of professional fees and secondary care costs in the calculation.

The pathological risk myopia presents is a strong incentive to further understand its aetiology. High myopes have axially stretched eyes (Curtin, 1985; Tokoro, 1988), causing a thinning of the retinal layer and predisposing the eye to pathologies e.g. retinal detachment and myopic maculopathy. With studies showing the escalation of myopia onset in young children (Lin *et al.,* 2004) and a greater

progression of myopia with younger ages of onset (Hyman *et al.,* 2005; Gwiazda *et al.,* 2007a), it is evident that that the incidence of pathological complications secondary to high myopia could concurrently rise with ascending prevalence.

The discovering of a myopia aetiology will elucidate important therapeutic and prophylactic methods to arrest and/or regress the development of the condition. A mutually exclusive root of causality between nature and nurture was stipulated by earlier research (Wold, 1949; Angle and Wissman, 1980; Richler and Bear, 1980) though current consensus proposes an interaction between genes and the environment (Goldschmidt, 2003), such that a genetic susceptibility to myopiagenic environmental stimuli exists. The exact level of interaction and relative contribution of each variable is not yet fully understood (Saw *et al.,* 1996; Goldschmidt, 2003).

The Aston Eye Study (AES) is an urban population-based epidemiological eye study instigated in October 2005 to investigate the distribution of refractive error (with particular focus on myopia) and associated biometric correlates in a sample of 6/7 year old (Year 2) and 12/13 year old (Year 8) UK school children. The current chapter details the analysis of questionnaire data in relation to measurements taken, in an attempt to confirm the association or otherwise of putative myopic risk factors. The use of questionnaires in epidemiological work is extensive and provides a wide range of information to investigators at minimum cost (Walline *et al.,* 1996).

8.2 METHODS

The methodology of the AES is comprehensively described in Chapter 5. Full ethical approval was obtained from the Aston University Ethics Committee and the study adhered to the tenets of the Declaration of Helsinki. Informed written consent was obtained from the parents of all participants and from Year 8 children; verbal assent was gained from all Year 2 children and documented by an investigator at the time of study. Population sample characteristics are detailed in Section 6.4.

To summarise methodological details, local primary and secondary schools in Birmingham were invited to participate in the AES and were chosen through a random cluster sampling strategy devised in collaboration with epidemiologists at St. Georges, University of London. On agreement of participation, an initial meeting was organised at a school and parental consent forms distributed to all Year 2 (primary) or Year 8 (secondary) children.
All examination procedures (Section 5.5.3) were performed by experienced UK registered optometrists and consisted of the following protocol:

- Uncorrected vision/presenting visual acuity measurements (if the child was wearing spectacles at the time of examination) were taken monocularly using an electronic test chart with logMAR notation (City 2000 test chart, Thompson Software Solutions, Herts) calibrated for a 3 metre working distance.
- Oculomotor balance status at distance (3m) and at near (33cm) with and without spectacles.
- Cycloplegia induced under a regime of 1 drop 0.5% proxymetacaine *Minims®* (Chauvin Pharmaceuticals, Surrey) in both eyes followed by 1 drop of 1% cyclopentolate HCl *Minims®* (Chauvin Pharmaceuticals, Surrey) 1 - 2 minutes later.
- Height and weight measures using a standard height chart (Leicester Height Measure, Seca Ltd, Birmingham) and digital weighing scales (Tanita Model 2000, Tanita Corporation). Heavy blazers and coats were removed prior to measurement. In addition Year 2 children removed their shoes.
- Once a child was deemed to be cyclopleged (accommodative amplitudes < 2D monocularly measured with a RAF rule), 3 measures of distance sphero-cylindrical refraction were taken in each eye using a Shin Nippon SRW-5000 autorefractor (Shin Nippon, Japan).
- Thereafter, ocular biometry was recorded using a non-contact device (*Zeiss* IOLMaster, Jena GmbH). Three measures of axial length (AL) and corneal radius (CR) were taken in each eye. The anterior chamber depth (ACD) was also measured bilaterally, with 5 rapid readings provided by the IOLMaster for every measurement initiated by the investigator. All refractive and biometric measures were averaged across both eyes to provide a single representative value per individual.

On completion of tests, each child was handed a questionnaire to be completed by their parent/guardian and posted directly back to the AES team. In addition to the parental questionnaire, a child questionnaire was constructed for the AES and completed by Year 8 participants at the time of the study. The child questionnaire allowed parental responses to be compared to those of the child and provided information for the child as a proxy in the absence of a parental questionnaire.

8.2.1 Questionnaire derivation

Both the parent and child questionnaires are based on studies examining large samples of children. Principal modification was from the CHASE study (www.chasestudy.ac.uk, accessed 15/05/2007), a child heart-health study (n= 5,000) extended from the TenTowns study based at St. Georges, University of London (Whincup *et al.*, 1996). In addition, a number of questions were modified from the Sydney Myopia Study questionnaires (www.cvr.org.au/sms.htm, accessed 24/06/2007), a study which determined the prevalence of myopia in approximately 4,000 children (Ojaimi *et al.*, 2005a; Ip *et al.*, 2007).

The parental questionnaire consists of 91 items and covered aspects such as the medical/ocular history of the child, night lighting, near work habits, physical activity, diet and family history of spectacle use (Appendix 8). The child questionnaire consists of 64 items with an additional 26 questions investigating the psychological profile of the child (Appendix 8).
Respondents (parents and children) were encouraged to complete all items and to contact the AES team if they did not understand or felt uncomfortable answering a question.

8.2.2 Questionnaire reminder

Three to four weeks following a study, a questionnaire reminder (Appendix 8) was sent out to those parents who had not returned their questionnaires. An A5 booklet version of the questionnaire was included with the reminder letter, in the event that the parent had misplaced their original copy. It was envisaged that the smaller questionnaire would encourage parents daunted by the size of the original questionnaire to respond. The reminders were addressed and posted directly to those parents who had provided an address for correspondence on consent forms. Direct postage minimised the risk of the parent not having received a questionnaire through their child.

8.2.3 Questionnaire response rates

Year 8

All Year 8 children completed their child questionnaires (response rate= 100%). Parental questionnaire response rates (Figure 8.2.1) based on the initial questionnaire distributed was 41.2% (122 of 296 questionnaires returned). Following the circulation of reminder letters, 39 further questionnaires were returned (13.2%), resulting in a total response rate of 54.4% (161 questionnaires returned).

Year 2

Of the questionnaires initially distributed to parents following the study, 93 (30.8%) were returned at the first attempt (Figure 8.2.1). On sending a reminder to non-respondents, 63 further questionnaires were sent back (20.9%), resulting in a total response rate of 51.7% (156 sent back in total).

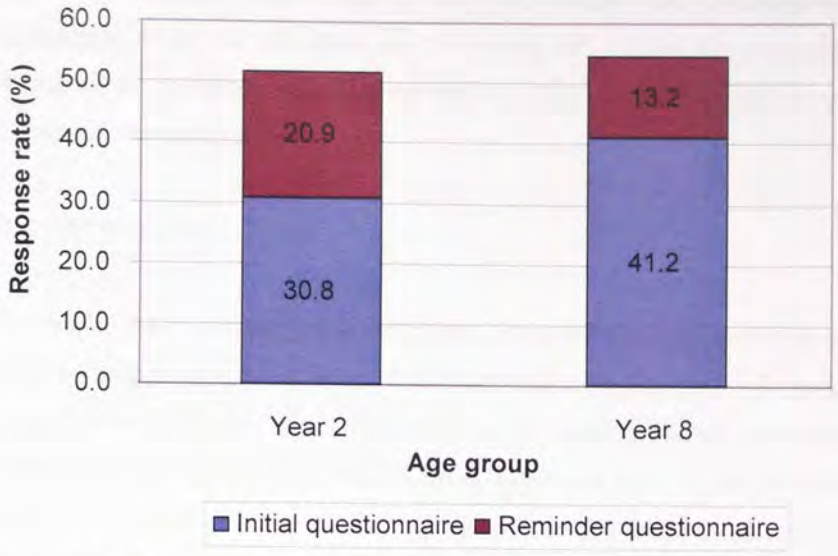


Figure 8.2.1 Parental questionnaire response rates following initial and reminder versions distributed by age group

8.2.4 Socioeconomic Status

Refractive error has been shown to vary by socioeconomic group, with a greater preponderance of myopia in wealthier classes (Angle and Wissman, 1980; Sperduto *et al.*, 1983; Saw *et al.*, 2002). It is thought that socioeconomic status (SES) may act as a surrogate for confounding variables including education, near work and intelligence, all of which are independently linked to myopia (Rosner and Belkin, 1987; Zylbermann *et al.*, 1993; Quek *et al.*, 2004).

SES was surmised from Index of Multiple Deprivation (IMD) values for the region encompassing the home postcode of each child. The IMD 2004 is a directory of deprivation indices for the United Kingdom produced by the Oxford University Social Disadvantage Research Centre. It is an update of the IMD values used for stratification purposes during construction of AES school sampling lists produced in 2000 (Section 5.1).

IMD values range from 0-100, with lower scores representing a lower index of deprivation i.e. higher SES. The values are an overall aggregate weighted score of deprivation within a Super Output Area (SOA). SOAs are split into 3 layers (Lower, Middle and Upper layers), of which the Lower layer areas are relevant to the AES. There are 32,482 Lower layer SOA's in England, each of which has a minimum of 1,000 residents (mean of 1,500) based on National Census data (National Statistics Office, 2001). SOAs have been devised to provide statistics for smaller regions after taking account of population density.

From the addresses that the AES team had been provided with (n= 243, Year 2 children; n= 250, Year 8 children), a list of corresponding IMD values was derived with assistance from collaborating epidemiologists from St. Georges, University of London. Each postcode was assigned an IMD value to represent its deprivation characteristics. Children without attached IMD values were excluded from analyses concerning SES.

8.3 DEFINITIONS

Refractive error definitions were based on the RESC corpus of research (Negrel *et al.*, 2000) and the Sydney Myopia Study (Ip *et al.*, 2007) and were agreed by AES investigators to represent clinically significant boundaries at which a child would require optical correction for a visual defect. Myopia was defined as mean SER ≤-0.50D in at least one eye. Hyperopia was termed as a mean SER ≥+2.00D in either/both eyes, as long as neither eye was myopic. Emmetropia was reported in subjects with mean SER >-0.50D and a mean SER <+2.00D (less than 2 Dioptres) in both eyes. Astigmatism was defined by a cylindrical power ≤-1.00DC in either eye.

8.4 QUESTIONNAIRE COMPARISON

The following section details the method of comparison between child and parental questionnaire to determine whether the child questionnaire could be used in the absence of a returned/completed parental questionnaire. The section is relevant only to Year 8 children.

To compare questionnaires, responses across both questionnaires were evaluated for agreement of categorical responses. An objective screening question was initially compared, followed by 3 categorical questions examining subjective responses. The answers to these questions were compared only in those subjects who had returned both questionnaires and had completed the relevant sections fully. A statistical measure of agreement (kappa statistic) for categorical data was used to establish validity (Landis and Koch, 1977).

The initial objective question compared is shown below from the child questionnaire:

8.0 How many brothers and sisters do you have in all (not counting step brothers & sisters)? ☐

The equivalent question from the parental questionnaire:

4.0 How many brothers and sisters does this child have in all (excluding step brothers & sisters) ? ☐

The above question was evaluated as a basic screening technique, as it was expected that a very high level of agreement would be obtained due to the factual nature of its response. A poor level of agreement at this stage would indicate very low validity of the child questionnaire and preclude further comparisons.

A weighted kappa statistic was used to compare the questions (Woodward, 2005), as the magnitude of disparity between the responses was also relevant in assessing agreement i.e. if the parental questionnaire had stated that the child had 3 siblings, ideal agreement would have been for the child to answer with 3 siblings. However, if the child did not state 3 siblings, then it was of importance that the answer was close to 3. The level of disparity between methods is accounted for by the weighted kappa statistic. The level of agreement for this question was excellent (kappa= 0.84, $p<0.001$) and permitted further comparison of subjective responses.

The following 3 questions are concerned with the amount of homework performed by a child every night, the level of physical activity performed by a child outside school and the level of near vision activity performed by the child outside school. The parental and child versions of the questions follow:

Child Questionnaire

4.0 Which of the following best describes your level of physical activity outside school?

Tick one box only

Spend all or most leisure time watching television, going to the cinema and in other seated activities	☐
Spend time occasionally in light physical activities (e.g. walking, bicycling, table tennis)	☐
Take part in regular sporting activities for up to 3 hours a week (e.g. soccer, swimming, gymnastics, tennis, skating)	☐
Take part in regular sporting activities for more than 3 hours a week (e.g. soccer, swimming, gymnastics, tennis, skating)	☐

4.2 How many hours each day do you spend doing school homework?

Tick one box only

None	☐
Less than 1 hour	☐
1-2 hours	☐
2-3 hours	☐
more than 3 hours	☐

4.3 Which of the following best describes your level of near vision activities outside school?

Tick one box only

- Spend all or most leisure time reading books, writing, and / or using a computer (for computer games or the internet) ☐
- Spend time frequently reading books, writing and / or using a computer (for computer games or the internet) ☐
- Spend time occasionally reading books, writing and / or using a computer (for computer games or the internet) ☐
- Spend little time reading books, writing and / or using a computer (for computer games or the internet) ☐

Parent Questionnaire

3.0 Which of the following best describes your child's level of physical activity outside school ?

Tick one box only

- Spends all or most leisure time watching television, going to the cinema and in other sedentary activities ☐
- Spends time occasionally in light physical activities (e.g. walking, bicycling, table tennis) ☐
- Participates in regular sporting activities for up to 3 hours a week (e.g. soccer, swimming, gymnastics, tennis, skating) ☐
- Participates in regular sporting activities for more than 3 hours a week (e.g. soccer, swimming, gymnastics, tennis, skating) ☐

3.2 How many hours each day does this child spend doing school homework ?

Tick one box only

- None ☐
- Less than 1 hour ☐
- 1-2 hours ☐
- 2-3 hours ☐
- More than 3 hours ☐

3.4 Which of the following best describes your child's level of near vision activities outside school?

Tick one box only

- Spends **all or most** leisure time reading books, writing, and / or using a computer (for computer games or the internet) ☐
- Spends time **frequently** reading books, writing and / or using a computer (for computer games or the internet) ☐
- Spends time **occasionally** reading books, writing and / or using a computer (for computer games or the internet) ☐
- Spends **little** time reading books, writing and / or using a computer (for computer games or the internet) ☐

The questions intentionally requested the performance of tasks outside of school, as parents may not be fully aware of the precise duration of tasks conducted by the child during school hours.

Based on the arbitrary description of agreement by Landis and Koch (1977), the level of agreement for responses concerning physical activity (Question 4.0 *vs.* 3.0, child and parent questionnaire respectively) was fair (weighted kappa= 0.37, $p<0.001$). For the second comparison, amount of homework (Question 4.2 *vs.* 3.2), agreement was slight (kappa= 0.18, $p<0.001$). The final question detailed the level of near vision activities undertaken by the child outside school (Question 4.3 *vs.* 3.4). The level of agreement on this question was also found to be slight (kappa= 0.20, $p<0.001$). Overall, the results indicate a slight to fair agreement between questionnaires. Similar findings have been determined by Rah *et al.,* (2002) in their comparison of child and parental questionnaires for the Orinda Longitudinal Study of Myopia. It does not therefore appear justified to utilise child questionnaires as a proxy in the absence of parental responses; the forthcoming analysis will thus display both parental and child responses separately.
In view of the disparity in responses between parents and children, it is difficult to validate the questionnaires in terms of accuracy i.e. which of the responses is 'correct'. Whereas parents would be more aware of factual details and historical information in relation to their children, children may be less prone to bias and more honest when answering subjective questions. They may also be more aware of the time spent on certain activities than parents, whose answers would be confounded by the level of interest they take in their child.

8.5 DATA ANALYSIS

Recordings taken during the AES were tabulated and the results from each child processed alongside an alphanumeric code unique to each participant. Data was entered into a statistical package, Stata Intercooled version 9 (Statacorp, Texas) and used in both univariate and multivariate models to elucidate putative risk factors for myopia. All logistic regression models have been adjusted for cluster sampling design, a statistical control that adjusts the standard error obtained in a regression model by the number of clusters (schools) in the sample. Examples of statistical output tables in Stata are displayed in Appendix 7.

8.6 RESULTS

Questionnaire analyses were conducted on 156 Year 2 children and 162 Year 8 children for whom parental questionnaires had been returned. In addition, Year 8 child questionnaire responses were analysed (n= 296). The analyses covered in this chapter are restricted to primary risk factors postulated in recent literature to be strongly associated with myopia.

8.6.1 Physical Activity

The results in this section are based on Question 3.0 from the parental questionnaire and Question 4.0 from the child questionnaire.

Year 8

Using child questionnaire responses, logistic regression establishing the association of levels of child physical activity to a binary outcome (myopia/non-myopia) yielded insignificant results (χ^2 of model = 2.81, p= 0.42). However from the parental questionnaire, a significant risk of myopia was present in children that performed occasional light physical activities compared to children deemed sedentary (category 2 *vs.* category 1; OR 3.21, 95%CI: 1.60 - 6.43, p= 0.001). This was an unexpected finding in that children performing some physical activity were more likely to be myopic than those who performed very little/no physical activity (Figure 8.6.1).

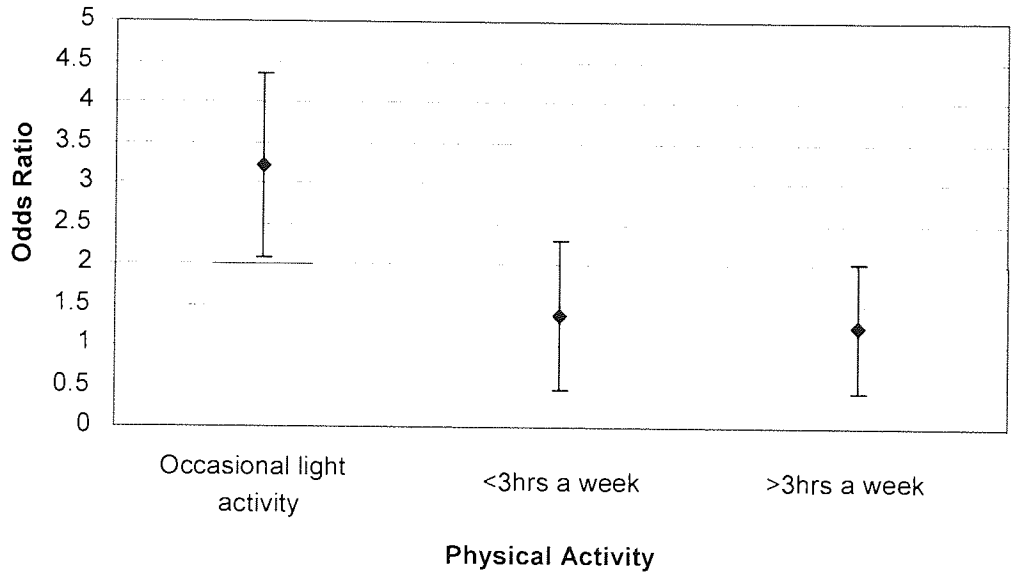


Figure 8.6.1 Odds Ratio (± SE bars) showing the effect of varying levels of physical activity on the odds of becoming myopic relative to a Year 8 child living a sedentary lifestyle. Based on responses from parental questionnaire

Year 2

Logistic regression found a significant association between myopia and physical activity (χ^2= 6429, p<0.001); children undertaking >3hrs regular exercise a week (i.e. most active) were significantly less at risk of myopia compared to children living a sedentary lifestyle (least active), although the OR is extreme due to the low numbers of Year 2 children in this category (OR 1.75×10^{-15}, p<0.001). A greater sample size would be needed to verify this association.

8.6.2 Near work

The following results are based on Question 3.4 (parental questionnaire) and 4.3 (child questionnaire).

Year 8

Logistic regression on parental responses (χ^2= 23.73, p<0.001) showed a significant protective effect of child myopia on children who spent time frequently on computers and near work (response 2) relative to children who spent all/most of their time on computers and near work (OR 0.41, 95%CI: 0.28 - 0.61, p<0.001). The effect was not reproduced in other responses within the question (Figure 8.6.2) and was not supported by the child questionnaire model (χ^2= 2.79, p= 0.43).

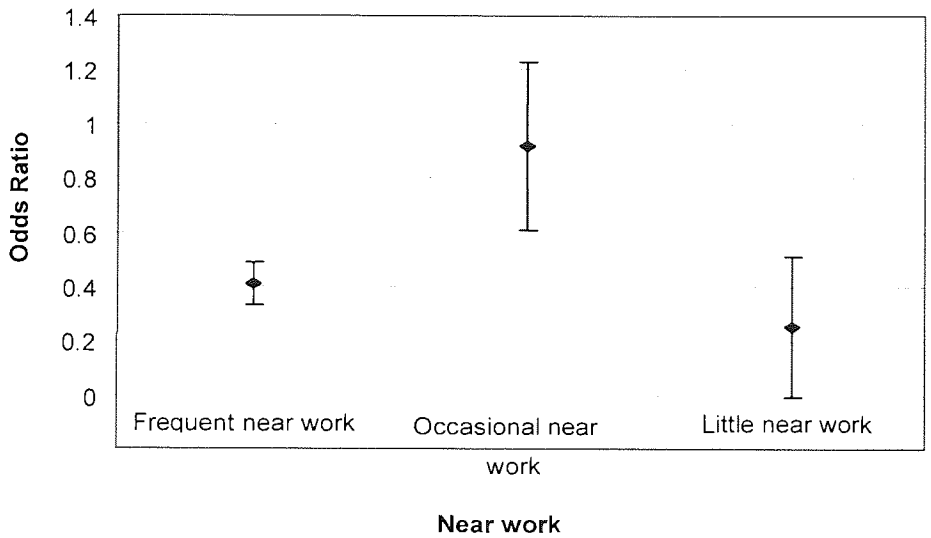


Figure 8.6.2 Year 8 odds ratios showing the effect of varying levels of near work on the odds of becoming myopic relative to a child who spends all/most of their time on near work tasks. Based on responses from parental questionnaire

Year 2

Logistic regression on the risk of myopia as a function of categories of near work did not show a significant effect of near work (χ^2= 1.76, p= 0.62) in this age group.

8.6.3 Family history

8.6.3.1 Parental history

Year 8

Child myopia/non-myopia was explored with respect to parental refractive status. Using parental questionnaire responses (Figure 8.6.3), it was determined that the odds of a child becoming myopic were significantly higher if the mother was myopic compared to if the mother was emmetropic (OR 1.87, 95%CI: 1.08 - 3.23, p= 0.03) and if the father was myopic compared to a paternal emmetrope (OR 3.52, 95%CI: 1.74-7.13, p<0.001).

Point estimates of a hyperopic parent were found to associate protectively with a myopic proband although not to statistically significant levels (mother hyperopia OR 0.31, 95%CI: 0.04 - 2.42, p= 0.26; father hyperopia OR 0.65, 95%CI: 0.18 - 2.40, p= 0.52).

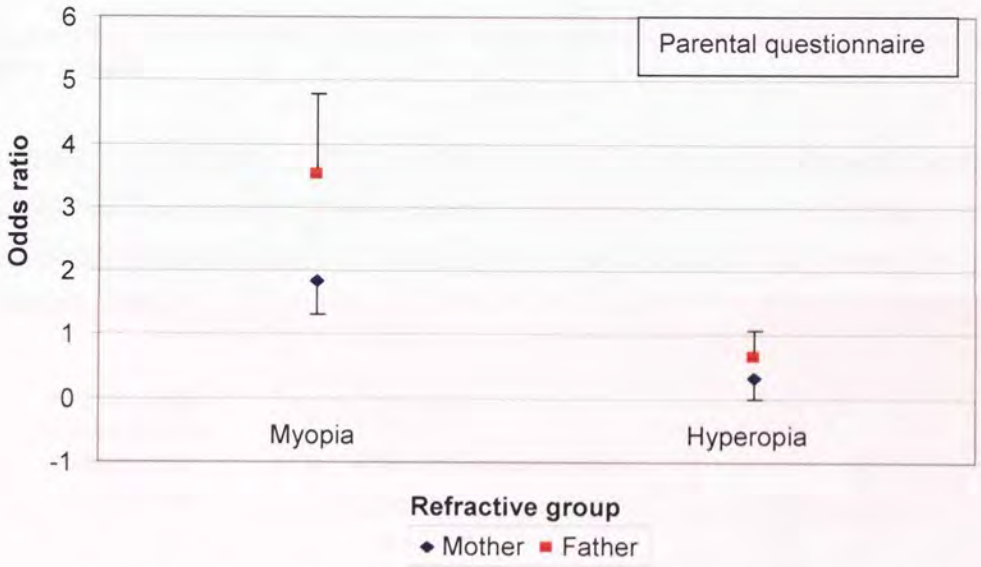


Figure 8.6.3 Year 8 parental questionnaire: the odds ratio of child myopia as a function of parental refractive status (x-axis). Odds ratios are relative to a parent with an emmetropic refraction

The pattern was reinforced by child questionnaire responses (Figure 8.6.4), with myopic parents showing a greater tendency to have myopic children compared to respective emmetropic parents (myopic mother OR 2.04, 95%CI: 1.07 - 3.86, p= 0.029; myopic father OR 3.54, 95%CI: 1.41 - 8.92, p= 0.007). A hyperopic parent was not associated significantly with child myopia (mother hyperopia OR 0.88, 95%CI: 0.47 - 1.63, p= 0.67; father hyperopia OR 1.82, 95%CI: 0.81 - 4.10, p= 0.15).

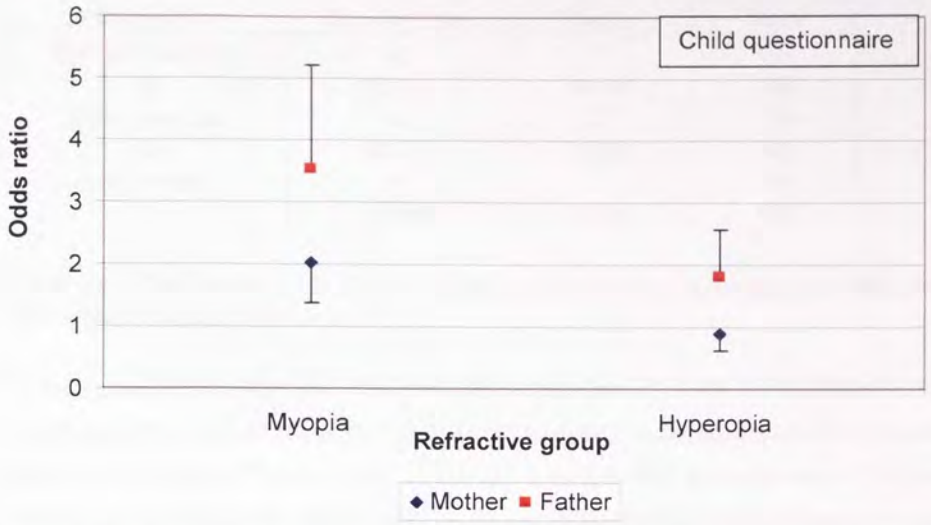


Figure 8.6.4 Year 8 child questionnaire: the odds ratio of child myopia as a function of parental refractive status (x-axis)

The risk of child myopia as a function of the number of myopic parents was examined, following studies that have shown a dose-dependent relationship between the number of myopic parents in a family and the risk of myopia in their progeny (Gwaizda *et al.*, 1993; Pacella *et al.*, 1999; Wu and Edwards, 1999).

Yr 8 Parental questionnaire responses	Child refractive group		
Parental Rx	Non myope	Myope	Total
Both emmetropic	24	4	28
%	***85.71***	***14.29***	***100***
Either myopic	42	21	63
%	***66.67***	***33.33***	***100***
Both myopic	15	11	26
%	***57.69***	***42.31***	***100***

Table 8.6.1 The proportion of Year 8 myopes as a function of joint parental refractive error. Determined by parental questionnaire responses

Yr 8 Child questionnaire responses	Child refractive group		
Parental Rx	Non myope	Myope	Total
Both emmetropic	46	9	55
%	***83.64***	***16.36***	***100***
Either myopic	44	27	71
%	***61.97***	***38.03***	***100***
Both myopic	4	7	11
%	***36.36***	***63.64***	***100***

Table 8.6.2 The proportion of Year 8 myopes as a function of joint parental refractive error. Determined by child questionnaire responses

It can be seen from both parental and child responses (Tables 8.6.1-2) that a dose-dependency exists and that a greater number of myopic parents in a family is reflected by an increased risk of myopia in the child (Figure 8.6.5). However, only the child questionnaire ORs were found reach statistically significant levels (Table 8.6.3), with a presumable lack of power in parental responses due to a lower number of questionnaires returned.

Parental refractive group	Parental questionnaire		Child questionnaire	
	OR	p value	OR	p value
Both emmetropic	1	-	1	-
Either myopic	3	0.16	3.14	**0.05**
95% CI	*(0.65-13.82)*		*(1.03-9.57)*	
Both myopic	4.4	0.07	8.94	**<0.001**
95% CI	*(0.87-22.19)*		*(3.13-25.54)*	

Table 8.6.3 Odds Ratios for child myopia as a function of number of myopic parents in a family. Significant p values in bold

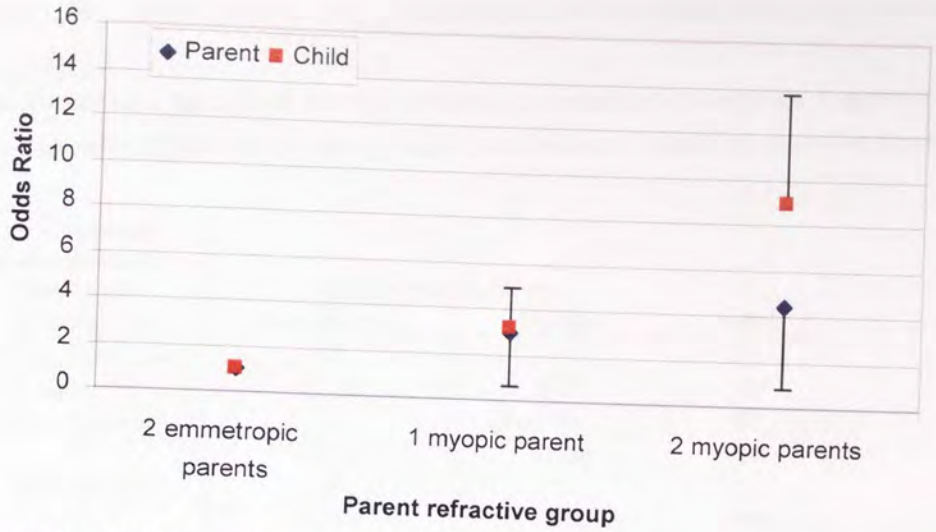


Figure 8.6.5 Year 8 variation in child myopia risk with increasing number of myopic parents by questionnaire type (child or parent)

Year 2

The presence of maternal myopia within Year 2 participants did increase the risk of myopia in a child, although this was not found to be significant (OR relative to emmetropic mother 2.46, 95%CI: 0.62-9.75, p=0.20). A protective estimate of risk was determined with a myopic father, though this was also deemed to be insignificant (OR 0.69, 95%CI: 0.17-2.84, p=0.60) (Figure 8.6.6).

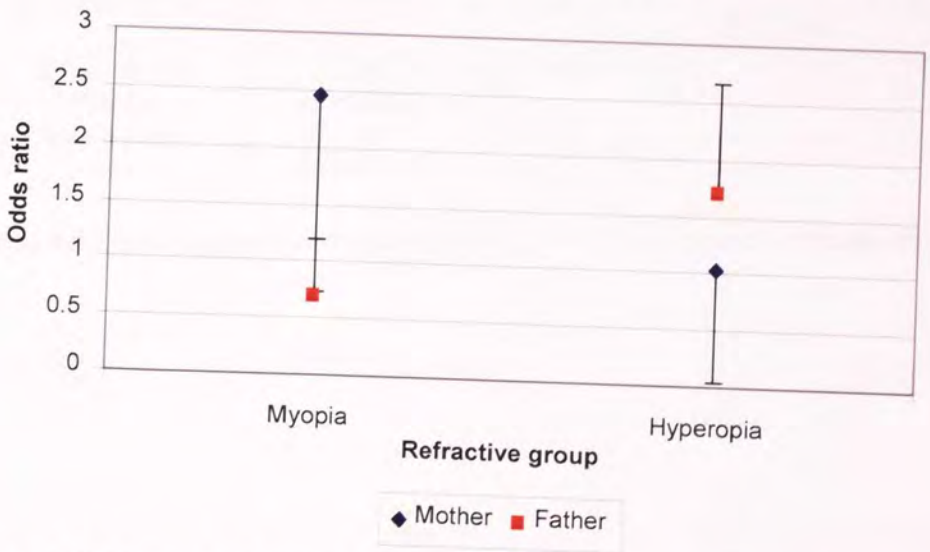


Figure 8.6.6 Odds ratio of myopia in Year 2 children as a function of parental refractive status

A hyperopic mother or father was not found to significantly affect the risk of myopia in their child (mother OR 1.02 95%CI: 0.16-6.68, p=0.98; father OR 1.69 95%CI: 0.55-5.18, p=0.36).

Child myopia as a function of number of myopic parents was investigated to determine whether the dose-dependent relationship found in Year 8 children was present at an earlier age (Table 8.6.4).

Yr 2 Parental questionnaire responses	Child refractive group		
Parental Rx	**Non myope**	**Myope**	**Total**
Both Emmetropic	50	4	54
%	***92.59***	***7.41***	***100***
Either myopic	40	7	47
%	***85.11***	***14.89***	***100***
Both myopic	9	1	10
%	***90.00***	***10.00***	***100***

Table 8.6.4 The proportion of Year 2 myopes as a function of joint parental refractive error

Although an increase in the number of myopic children was evident if either parent was myopic (Table 8.6.4), the ORs determined were not significant (Table 8.6.5 and Figure 8.6.7).

Parental refractive group	**Parental questionnaire**	
	OR	**p value**
Both emmetropic	1	-
Either myopic	2.19	0.21
95% CI	*(0.65-7.37)*	
Both myopic	1.39	0.78
95% CI	*(0.14-13.65)*	

Table 8.6.5 Odds ratio of Year 2 myopes as a function of joint parental refractive error

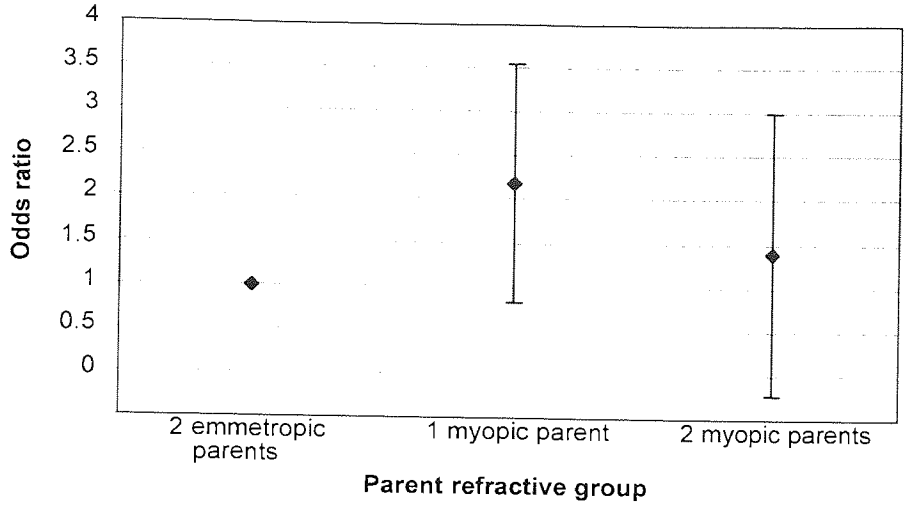


Figure 8.6.7 Odds ratio of Year 2 child myopia with increasing number of myopic parents

8.6.3.2 Sibling history

Sibling information derived from the parent questionnaire focused on whether siblings of the proband wore spectacles and if so, the nature of their refractive error (i.e. myopia, hyperopia). However, the child questionnaire did not enquire as to the type of refractive error, therefore Year 8 child questionnaire responses are excluded from this section.

Year 8

Based upon parental responses, an analysis of the risk of proband myopia as a function of the number of myopic siblings was conducted (Table 8.6.6):

Number of myopic siblings	Non myope	Myope	Total	OR	95% CI	p value
No siblings	7	3	10	1.95	0.51 - 7.51	0.33
%	***70***	***30***	***100***			
0	91	20	111	1 (referent)	-	-
%	***81.98***	***18.02***	***100***			
1	14	12	26	3.9	1.38 - 10.98	**0.01**
%	***53.85***	***46.15***	***100***			
2	5	3	8	2.73	0.89 - 8.36	0.079
%	***62.5***	***37.5***	***100***			
3	0	1	1	n/a	-	-
%	***0***	***100***	***100***			
Total	117	39	156			
%	***75.00***	***25.00***	***100***			

Table 8.6.6 Child refractive status as a function of myopic siblings within the family in Year 8 children. ORs are given relative to '0 myopic siblings' i.e. proband has siblings, none of whom are myopic. Significant p value in bold

A single myopic sibling was found to increase the odds of a myopic proband relative to a child with no myopic siblings (OR 3.9, 95%CI: 1.38 - 10.98, p= 0.01). A dose-dependent association with an increasing number of myopic siblings was not elucidated (Table 8.6.6), although this appears to be due to the low numbers of probands with 2 or more myopic siblings. To increase the power of the analysis, probands with myopic siblings were combined and a reanalysis comparing the effect of ≥1 myopic siblings *vs.* no myopic siblings *vs.* no siblings is displayed by the blue data points in Figure 8.6.8. A significant risk of proband myopia was determined if more than one sibling in the family had myopia (OR relative to proband with 0 myopic siblings 3.83, 95%CI: 1.55 - 9.49, p= 0.004).
The term 'no sibling' refers to a proband without any brothers and sisters. This category was constructed to compare whether the presence of a sibling, irrespective of refractive status, influenced the predisposition of the proband to ametropia. A significant difference was not found between the 2 groups (children with no siblings *vs.* children with 0 myopic siblings; OR 1.95, 95%CI: 0.51 – 7.51, p= 0.33) suggesting that this was not the case (Figure 8.6.8, blue diamond data point in second column).

Year 2

An analysis was conducted on Year 2 children to determine whether a dose-dependent relationship existed between the number of myopic siblings and the odds of proband myopia (Table 8.6.7).

Number of myopic siblings	Nonmyope	Myope	Total	OR	95%CI	p value
No siblings	10	1	11	0.81	0.09-7.69	0.85
%	***90.91***	***9.09***	***100***			
0	97	12	109	1 (referent)	-	
%	***88.99***	***11.01***	***100***			
1	15	2	17	1.08	0.26-4.41	0.92
%	***88.24***	***11.76***	***100***			
2	4	1	5	2.02	0.20-20.42	0.55
%	***80.00***	***20.00***	***100***			
3	1	0	1	n/a		
%	***0***	***100***	***100***			
Total	127	16	143			
%	***88.81***	***11.19***	***100***			

Table 8.6.7 The proportion of Year 2 proband myopia as a function of myopic siblings within the family. ORs are not given for 3 myopic siblings due to the very low sample involved

As with Year 8 children, it was considered that combining all myopic siblings and comparing this to probands without myopic siblings would increase the power of the analysis (Figure 8.6.8 red square data points). A significant risk of proband myopia given that at least one sibling was myopic was not established (OR relative to proband with 0 myopic siblings 1.21 95%CI: 0.37 - 3.97 p= 0.75). Having no siblings at all did not show up as a risk factor either (OR 0.80, 95%CI: 0.09 – 7.69, p= 0.85).

Figure 8.6.8 Odds ratio of proband myopia as a function of sibling myopia

8.6.3.3. Multiple regression models

Year 8

Multiple logistic regression models were constructed to determine the relative effects of parental and sibling refractive status on proband myopia, after mutual adjustment. The models incorporated mother, father and sibling refractive status as explanatory variables, with proband myopia/non-myopia as a binary outcome measure.

Using parental questionnaire responses, it was found that having a myopic father (OR 3.00, 95%CI: 1.53-5.90, p= 0.001) and having 1 or more myopic siblings (OR 5.49, 95%CI: 1.36-22.25, p=0.017) increased the odds of a proband becoming myopic, whilst a myopic mother no longer remained a risk factor (OR 1.66, 95%CI: 0.71-3.89, p=0.24). Unexpectedly, having no siblings at all proved to be a risk factor (Table 8.6.8, OR 3.16, 95%CI: 1.18-8.50, p=0.022).

Multiple logistic regression	Year 2		Year 8	
	Adjusted OR	p value	Adjusted OR	p value
Father myopia	0.57	0.48	3.00	**0.001**
95% CI	***0.12-2.69***		***1.53-5.90***	
Mother myopia	2.23	0.26	1.66	0.34
95% CI	***0.55-8.99***		***0.71-3.89***	
≥1 myopic sibling	0.85	0.83	5.49	**0.017**
95% CI	***0.18-3.91***		***1.36-22.25***	
No siblings	1.08	0.96	3.16	**0.022**
95% CI	***0.08-14.03***		***1.18-8.50***	

Table 8.6.8 Multiple logistic regression to determine relative effects of parental and sibling myopia on proband odds of myopia after mutual adjustment. Significant p values in bold

Year 2

It was found that neither parental nor sibling myopia (Table 8.6.8) influenced the odds of myopia in Year 2 children after mutual adjustment (χ^2 model= 5.39, p= 0.61). Thus a strong family history of myopia was evident in Year 8 children but not in Year 2.

8.6.4 Socioeconomic status

8.6.4.1 Univariate analysis

Index of Multiple Deprivation (IMD) values assigned to each Super Output Area in Birmingham (Section 8.2.3) were utilised for analysis of socioeconomic status (SES). The continuous range of IMD values were categorised into quartiles of IMD to facilitate logistic regression models.

Year 8 quartile allocation		
Group	N	IMD range
I	62	56.03 - 76.64
II	61	28.95 - 55.66
III	64	14.32 - 27.99
IV	63	3.86 - 14.30

Table 8.6.9 Year 8 SES quartile categories

Year 2 quartile allocation		
Group	N	IMD range
I	53	59.45 - 77.37
II	53	56.03 - 59.37
III	75	41.45 - 55.66
IV	62	12.88 - 41.32

Table 8.6.10 Year 2 SES quartile categories

Groups I – IV represent quartile categories of SES (Tables 8.6.9-10), with ordinal progression from most deprived (Group I, highest IMD values) to least deprived (Group IV, lowest IMD values).

Year 8

A breakdown of myopia prevalence by SES revealed an increase in myopia odds of children in Group II relative to Group I (OR 1.84, 95%CI: 1.39-2.44, p<0.001).

IMD group	Myopia Prevalence (%)	95% CI	OR	95% CI	p value
I	27.42	16.00 - 38.84	1 (referent)		
II	40.98	28.28 - 53.68	1.84	1.39 -2.44	**<0.001**
III	23.44	12.77 - 34.10	0.81	0.46 -1.43	0.47
IV	23.81	13.00 - 34.62	0.83	0.44 -1.54	0.55

Table 8.6.11 Year 8 myopia prevalence and odds ratios by SES. Significant p value in bold

The effect was not found to be dose-dependent and further affluent classes (Groups III and IV) did not have a higher OR of proband myopia (Table 8.6.11). Indeed higher SES children presented with a lower prevalence of myopia compared to Group II children, suggesting that children from families with a moderate level of deprivation are more at risk of myopia compared to children from either severely deprived or highly affluent backgrounds.

Year 2

Quartiles of SES were not deemed a risk factor for myopia in younger children on the basis of logistic regression models (Table 8.6.12).

IMD group	Myopia Prevalence (%)	95% CI	OR	95% CI	p value
I	9.43	1.30 – 17.57	1 (referent)		
II	13.21	3.79 - 22.63	1.46	0.45-4.71	0.53
III	10.67	3.52 – 17.82	1.15	0.47-2.80	0.77
IV	11.29	3.19 – 19.39	1.22	0.30-4.97	0.78

Table 8.6.12 Year 2 myopia prevalence and odds ratios by SES

An increase in myopia prevalence can be seen between Group I and II, though not to a significant degree (p= 0.53). The prevalence drops from Group II onwards in children of higher social classes. Although parallels are present in both age groups in displaying Group II children with a higher myopia prevalence, a comparison between cohorts is not feasible as the SES range within Year 2 Group II and Year 8 Group II is not similar (compare Figures 8.6.9 and 8.6.10).

8.6.4.2 Multiple regression analysis

The inclusion of SES in previously derived models is important as it identifies confounding effects of SES on significant AES findings.

8.6.4.2.1 Ethnicity, Gender and Grammar schooling

The addition of SES into a multiple logistic model with ethnicity (Whites, Blacks and Asian), gender and grammar schooling (Year 8 only) was performed to determine if mutual adjustment would reveal further insight into the relative contributions of these factors to the risk of myopia in children.

In Year 8 children (overall model χ^2= 40, p<0.001), it was found that Asian ethnicity (OR 2.54, 95%CI: 1.30 – 4.97, p= 0.006) and grammar schooling (OR 2.42, 95%CI: 1.49 – 3.93, p<0.001) were significant for proband myopia after mutual adjustment and adjustment for SES and gender (Table 8.6.13). Female gender was found to increase the odds of myopia, though not to statistically significant levels (OR 1.24, p= 0.41). These findings suggest that SES did not confound the original model determined in Chapter 6 (Table 6.5.9).

Excluding grammar schooling from the model in Table 8.6.13 (not shown) rendered SES group II significant for myopia (OR 2.02, 95%CI: 1.21 – 3.39, p= 0.007), indicating a confounding effect of grammar schooling on SES.

	Adjusted OR	95% CI	p value
Ethnicity			
White	1	-	
Asian	2.54	1.3 – 4.97	**0.006**
Black	1.31	0.22 - 7.70	0.76
SES Group			
I	1	-	
II	1.43	0.95 – 2.16	0.09
III	0.82	0.38 – 1.77	0.61
IV	0.7	0.40 – 1.23	0.22
Gender			
Male	1	-	
Female	1.24	0.74 – 2.06	0.41
Grammar schooling			
No	1	-	
Yes	2.42	1.49 – 3.30	**<0.001**

Table 8.6.13 Multivariate adjusted odds ratios for myopia in Year 8 children. Significant p values in bold

Year 2 multivariate analysis (Table 8.6.14) elicited that SES, ethnicity and gender were not found to influence the risk of myopia significantly (overall model χ^2= 2.73, p= 0.43).

	Adjusted OR	95% CI	p value
Ethnicity			
White	1	-	
Asian	2.12	0.38 – 11.73	0.39
Black	2.27	0.38 – 13.48	0.37
SES Group			
I	1	-	
II	1.63	0.47 – 5.73	0.44
III	1.24	0.49 – 3.12	0.65
IV	1.65	0.24 – 11.50	0.61
Gender			
Male	1	-	
Female	2.12	0.81 – 5.55	0.12

Table 8.6.14 Multivariate adjusted odds ratios for myopia in Year 2 children

8.6.4.2.2 Anthropometry

Social class has been found to correlate positively with height (Whincup *et al.*, 1988) and may act as a surrogate for anthropometric variables such as height and weight. Therefore an evaluation of AES findings in relation to these factors was conducted.

Height and weight (untransformed compared to Chapter 7) were divided into quartiles to facilitate multiple logistic regression analysis. The allocated range per group is illustrated in Tables 8.6.15-18.

Year 2 quartiles		
Group	N	Height range (cm)
1	71	110.0 - 119.4
2	71	119.5 - 123.8
3	72	123.9 – 128.0
4	70	128.1 – 140.3

Table 8.6.15 Year 2 height quartile categories

Year 8 quartiles		
Group	N	Height range (cm)
1	71	117.4 – 154.4
2	71	154.5 – 159.8
3	72	160.0 – 165.5
4	70	166.0 – 188.3

Table 8.6.16 Year 8 height quartile categories

Year 2 quartiles		
Group	N	Weight range (kg)
1	75	14.4 – 21.0
2	80	21.2 – 24.2
3	69	24.4 – 28.2
4	74	28.4 – 51.0

Table 8.6.17 Year 2 weight quartile categories

Year 8 quartiles		
Group	N	Weight range (kg)
1	73	26.4 – 44.6
2	68	44.8 – 50.6
3	71	50.7 – 59.6
4	70	59.8 – 92.0

Table 8.6.18 Year 8 weight quartile categories

	Year 8				Year 2			
	Univariate OR	95% CI	Adjusted OR	95% CI	Univariate OR	95% CI	Adjusted OR	95% CI
Height Group								
1	1	-	1	-	1	-	1	-
2	1.95	0.63 - 6.07	2.13	0.65 - 6.93	0.90	0.47 –1.73	0.97	0.44 - 2.13
3	1.22	0.62 - 2.40	1.37	0.67 - 2.78	0.62	0.18 –2.12	0.70	0.19 –2.57
4	1.18	0.45 - 3.09	1.47	0.38 - 5.63	0.88	0.47 -1.41	0.80	0.20 – 3.14
Weight Group								
1	1	-	1	-	1	-	1	-
2	1.04	0.63 - 1.72	0.73	0.41 - 1.28	0.81	0.29 –2.26	0.86	0.30 – 2.50
3	0.69	0.30 - 1.60	0.61	0.14 - 2.69	0.83	0.40 –1.73	0.88	0.25 – 3.03
4	0.71	0.42 - 1.19	0.74	0.36 - 1.50	0.53	0.19 –1.47	0.58	0.11 – 3.15
SES Group								
I	1	-	1	-	1	-	1	-
II	1.84	**1.39 - 2.44***	1.87	**1.27 - 2.77***	1.46	0.45 –4.71	1.50	0.47 - 4.77
III	0.81	0.46 - 1.43	0.78	0.38 - 1.57	1.15	0.47 –2.80	1.37	0.49 – 3.27
IV	0.83	0.44 - 1.54	0.77	0.40 - 1.46	1.22	0.30 –4.97	1.68	0.31 – 5.40

*p<0.005

Table 8.6.19 Univariate and multivariate modeling of height, weight and SES on Year 2 and Year 8 AES children.

Year 8

The higher risk of myopia posed by Year 8 children in SES Group II compared to Group I was maintained (Table 8.6.19) after controlling for height and weight (Adjusted OR 1.87, 95%CI: 1.29 – 2.71, p=0.001), indicating that anthropometry did not confound the effects of SES.

Increasing quartiles of height consistently had a higher point estimate for myopia compared to the lowest quartile of height whereas increasing quartiles of weight had a lower OR for myopia compared to the lowest quartile of weight (Table 8.6.19). However these comparisons were found not to reach statistical significance.

Year 2

Both univariate and multivariate ORs for height and weight quartiles projected a protective effect with increasing stature (Table 8.6.19) relative to children in Group I. However, these differences were not found to be significant. Increasing SES quartiles were associated with an increasing risk of myopia relative to Group I; these figures also failed to achieve statistical significance.

8.7 DISCUSSION

Following a single reminder letter, over 50% of questionnaires sent out to all parents/guardians were completed and returned for analysis.

In Year 8 children, as a result of only a moderate level of agreement between parental and child responses, both questionnaires were analysed separately to elucidate putative myopiagenic risk factors.

8.7.1 Physical Activity and Near work

8.7.1.1 Physical Activity

It was found through Year 8 parental responses that children performing occasional light physical activities were more at risk of myopia compared to sedentary children. This finding is contrary to that which was expected, as it has been shown that increased outdoor activity is protective for myopia (Rose *et al.,* 2006; Jones *et al.,* 2007). A protective effect was demonstrated in Year 2 children who undertook regular activity (>3hrs a week). It may be that Year 8 children who perform occasional light physical activities are generally more active in all tasks (Jones *et al.,* 2007), including those initiating myopia i.e. computer work. Alternatively, intelligence has been linked independently to myopia (Saw *et al.,* 2004), which may offset a protective effect, if present, of participation in activities. A higher level of intelligence may be present in the group participating in light physical outdoor activities, overriding the protective effect of activities against myopiagenesis by virtue of the greater potency of intelligence. An analysis of physical activity and intelligence would be of great interest to elicit the nature of a relationship, if present, between the variables.

A factor not identified in the AES analysis was whether physical activities were performed outside, as it is the outdoor nature of activities that is specifically thought to instigate a protective effect against myopia (Ip *et al.,* 2007a). It is not yet known what aspect of outdoor activity causes this effect i.e. higher light levels, non-visual effects (Jones *et al.,* 2007). Research on dopamine, a neurotransmitter released in the presence of light, has found that the chemical prevents the development of form-deprivation myopia in chicks (McCarthy *et al.,* 2007), providing a tentative neurophysiological link between light levels and refractive changes.

8.7.1.2 Near work

A higher level of near work was presented as a myopic risk factor in Year 8 children according to parental responses i.e. children who spend all/most of their leisure time on near work tasks had a higher OR for myopia compared to children who spend a frequent amount of free time on near work tasks. However a lack of dose-dependency existed for lower levels of near work and indicated that children performing very low amounts of near work were equally likely to become myopic as those undertaking sustained periods of near work .

It may be that the threshold of near work required to induce myopia is high. Therefore only prolonged exposure to near work would initiate myopic changes through hyperopic defocus caused by an increased accommodative lag in susceptible individuals. Extended amounts of hyperopic defocus have been required for the induction of ocular elongation in animals (Shaikh *et al.,* 1999) although myopic progression can be offset by small periods of relative myopic defocus (Zhu *et al.,* 2003; Wallman and Winawer, 2004). Therefore, reducing exposure to tasks requiring sustained near work or interrupting near vision with brief periods of relative myopic defocus ought to act protectively against sustained defocus and subsequent myopia. However the finding of an equally high propensity of myopia in children performing low levels of near work suggests that perhaps in these children, intelligence is again a confounding variable. Children performing low levels of near work may be at risk of myopia through their higher intelligence levels, which were not incorporated into the AES models.

Year 2 children were not found to be influenced by the effects of near work, possibly due to lower periods of time spent on concentrated near tasks or a lower susceptibility of the eye to visual stimuli, in comparison to Year 8 children.

Recent research has questioned the causal role of near work in school myopia (Saw *et al.,* 2006; Rose *et al.,* 2006; Jones *et al.,* 2007). However strong associations between the variables have been demonstrated in previous literature (reviewed by Rosenfield and Gilmartin, 1998). Many studies appear to be hindered by study design and measurement techniques, thus further longitudinal analysis on both physical activity and near work using a greater sample size and more direct measurement techniques are recommended to confirm the actual nature of these environmental effects. Diaries recording the magnitude of near work/physical activity undertaken over a period of time require a high level of subject compliance, whereas direct observation is an expensive and intrusive method of analysis (Rah *et al.,* 2002). An extension of the 'experience sampling method', validated by Rah *et al.* (2006), to include measures of outdoor activity alongside that of near tasks may prove more accurate than questionnaire recall.

Transient axial elongation has been demonstrated on response to accommodation (Mallen et al. 2006) supporting a role for accommodative tasks (near work) in ocular growth. Expanding on the findings of Mallen and co-workers, a randomized prospective clinical trial evaluating the induction of

relative myopic defocus (i.e. breaks from sustained near work) on short-term refractive and biometric changes would be of interest. The measurement of continuous ocular refraction and biometry over a period of time while varying the frequency and duration of interruptions to near work would elicit the relative potency of defocus on biometric changes in humans.

8.7.2 Family history

In Year 8 subjects, a higher risk of proband myopia was elicited if the mother or father was myopic, an association determined in both child and parental questionnaires. Identical findings from both questionnaires evidently strengthens the association between child and parental refractive status. A myopic father remained significantly associated with proband myopia in multiple logistic regression models. Child questionnaire responses showed a dose-response relationship in that having two myopic parents increased the risk of myopia in the child more than having one parent (Table 8.6.3). This is in line with similar findings of strong dose-dependent familial links on proband myopia (Table 1.4.1).
Year 2 children did not show a significant association with parental myopia (Table 8.6.4). It is clear that a majority of children will manifest ametropia at an age later than 6/7 years, therefore strong associations with parental refractive error would not be expected in Year 2 children.

Sibling myopia was examined through parental responses only. In Year 8 children, it was found that the risk of proband myopia increased with one or more myopic siblings compared to no myopic siblings, an effect which remained in multivariate models adjusted for mother and father myopic status (Table 8.6.8). The Framingham Offspring Eye Study (Framingham Offspring Eye Study Group, 1996) showed a strong risk of proband myopia when a sibling was myopic (OR 2.81, $p<0.001$), in agreement with findings of the present study. Overall, AES results suggest that a strong genealogical link exists with myopia, particularly when a sibling or father is found to be myopic.

It may be postulated that father and sibling myopia indicates either a genetic aetiology of myopia or surrogates for shared environmental factors, such as education and a culture of reading. It is not known why there was a loss of association with maternal myopia in the multivariate analysis; this may be a suggestion of a predominant patriarchal influence on a child. Therefore a myopic father is more likely to transfer a myopia phenotype to his child compared to a myopic mother, whether it is by virtue of a transfer of genes, environmental exposures or a combination of the two. In contrast, multivariate analysis conducted by Robinson (1999) on 6 year old myopes in Canada suggested a strong association of child myopia with maternal spectacle use, with paternal spectacle use failing to achieve statistical significance. However, the work by Robinson differs widely to the methodology of the AES thus comparison between studies is not feasible.

In addition to paternal and sibling associations with proband myopia, a significant association was found in Year 8 children with no siblings for which an explanation is not known. Perhaps children without siblings are subjected by parents to partake/achieve in activities which constitute myopiagenic risk factors, due to a higher level of undivided attention received. However, it was also found that affluent families tended towards a smaller family size (X^2= 44.66, p=0.002), therefore variables such as SES may have confounded the association between number of siblings and proband myopia.

It would be of interest to study the relationship between the order of birth (i.e. whether the proband is the eldest child in the family) and the risk of child myopia, as this will provide an insight into whether children with a lower birth order receiving less attention from parents are relatively protected from myopiagenesis.
A reanalysis of Goldschmidt's data on high myopes (n= 9,000, 13-14 years of age) by Guggenheim *et al.*, (2000) found an increased risk ratio of proband myopia if only siblings elder to the subject were analysed. The inclusion of younger siblings in the analysis lead to an underestimation of the risk ratio as many were below the conventional ages of myopiagenesis. Extending this method further, the exclusion of all siblings under the age by which the majority of school myopia is thought to occur (i.e. 12 years of age) irrespective of whether elder or younger to the proband, may improve the sensitivity of the proband-sibling analysis and minimise the unnecessary exclusion of siblings.
Year 2 myopes were found not to demonstrate a strong association with sibling myopia, though this may be accounted for by the general lower age of both Year 2 children and their siblings, some of whom will become myopic at a later age.

8.7.3 Socioeconomic status

Socioeconomic status (SES) was examined through a proxy measure of IMD values in univariate and multivariate logistic regression models. Year 8 children from Group II were found to be more at risk of myopia relative to the most deprived Group I after adjustment for anthropometric factors such as height and weight (Table 8.6.18). This effect was not established to be dose-dependent, but instead showed a peaked OR in Group II children. A peak was noted in Group II children within the Year 2 cohort though not to statistically significant levels. However as mentioned, comparison between Year 8 and Year 2 children would not be feasible due to the disparate range of SES boundaries between the age groups.
To the author's knowledge, a peaked trend demonstrated in Group II children from Year 8 has not been reported previously. It implies that children from areas of extreme deprivation (high or low) are protected from myopia relative to those from moderate backgrounds, who are at greatest risk.
Following on from strong genealogical links with child myopia from Section 8.7.2 and to examine

whether myopia family history accompanied the peaked OR of myopia in Group II children, a trend of parental (mother or father) or sibling myopia was not found by SES group (mother: χ^2= 4.69 p= 0.58; father: χ^2= 6.19 p= 0.40; ≥1 myopic sibling: χ^2= 6.74 p= 0.35).

Height and weight were not found to associate strongly with a risk of myopia in either Year 2 or Year 8 children, a finding that supports the weak association of anthropometry with refractive error (Section 7.4.5.2).

Evaluating Table 8.6.13 which illustrates a Year 8 multivariate model including SES, ethnicity, gender and grammar schooling, it can be seen that children from grammar schools and Asian ethnicity were independently at a significantly increased risk of myopia. In addition the significant univariate effect of Group II SES was neutralised by the addition of grammar schooling to the overall model. Thus the lack of a multivariate effect of SES on child myopia can be attributed a confounding effect of grammar schooling.

A tentative hypothesis to account for the Year 8 multivariate findings may be proposed as follows. Based on AES results, Year 8 children at greatest risk of myopia are shown to come from a moderately deprived socioeconomic background (i.e. Group II). This level of deprivation would consist of working class families unable to afford private education for their children. Children from this socioeconomic background attending grammar schools may be under a greater demand from parents to succeed at school, the applied pressure manifesting in the form of increased exposure to myopiagenic risk factors e.g. a greater amount of studying in conjunction with a reduced level of outdoor activities. Hence more grammar schooled Group II children would become myopic relative to other SES groups. Children from the higher SES groups (Groups III and IV) would be protected from myopiagenesis perhaps through a greater undertaking of outdoor activities afforded by their relative prosperity, irrespective of whether a grammar school was attended.

Asian subjects are likely to match the Group II socioeconomic description as second/third generation UK-born children whose parents are of a working class background and instill a strong ethos to study and read in their children. Nevertheless, Asian ethnicity remained strongly associated with myopia even after controlling for SES and grammar schooling, therefore a strong Asian risk of myopia appears prevalent due to a factor unrelated to those within the multiple model (Table 8.6.13). Asian children, like grammar schooled children, may be influenced under a strong cultural ethos to study and read for long periods of time (Wilson *et al.,* 2006) which would lead to myopia. Alternatively, the role of intelligence in myopia has been postulated as a risk factor after adjustment for SES (Saw *et al.,* 2004). A somewhat contentious notion of higher intelligence levels in Asian children to account

for their higher myopia propensity secondary to cultural values may be hypothesised, which would require empirical verification.

8.7.4 Summary

Both near work and physical activity showed some association with the presence of myopia in AES subjects. However, a more detailed and continuous method of observation of these risk factors is proposed below, incorporating quantitative measures based on the 'experience sampling method' (ESM; Rah *et al.,* 2006). Subjects would be provided with a handheld mobile email device which they would keep on their person at all times. Upon receipt of an alert sent at random intervals during the day, the subject would respond by sending an email detailing the type and duration of activity they are partaking in at that time. The ESM is not as intrusive or cumbersome as diaries or direct measurement and avoids potential pitfalls of recall bias, as subjects would be encouraged to respond immediately to messages. Using email channels would in addition make it a more convenient overall method, as the subject would not be required to telephone a voicemail system to provide their responses as with the ESM. Notwithstanding the benefits of this approach, a study of this nature will require adequate access to resources to provide the necessary apparatus.

A strong genealogical link to myopia does appear to exist, particularly where fathers and siblings are found to be myopic. Whether this is the result of shared environments or shared genes in the cohort is unclear. Recent work evaluating the accuracy of questionnaires in determining family history of myopia concluded that questionnaires have limited accuracy as a method of ascertaining family history (Garoufalis *et al.,* 2007). Nevertheless, they do remain a cost-effective and less time-consuming alternative to physical measurement of parental refractive error (Ip *et al.,* 2007b), justifying their inclusion in epidemiological protocols.

The resolution of South Asian ethnicity as a risk factor after multivariate adjustment points either to a genetic link or to cultural myopiagenic risk factors prevalent within the South Asian community. The persistence of grammar schooling affirms a longstanding association between education and myopia (Sperduto *et al.,* 1983; Quek *et al.,* 2004) and further research is advocated to partition education into to its surrogate associations (i.e. near work, intelligence) to elucidate precisely which factor is responsible for myopia onset.

A limitation of this analysis is the questionnaire response rate from parents in both age groups, which was just above 50%. This leaves the study open to patient recall bias, in that parents who returned their questionnaires may have been of a different demographical background compared to those that did not return their documents. To ameliorate this, supplementary questionnaire reminders would

have promoted further successful return of questionnaires, although with a limited number of AES investigators, repeated questionnaire reminders was not feasible.

The current chapter restricted its analyses to primary risk factors of myopia. Future analyses will expand upon the continued progress of the AES in addition to drawing links between myopia and questionnaire data not analysed in this chapter (e.g. breast feeding, night lighting, diet). It is expected that these evaluations under the robust AES banner will provide further insight into putative associates of myopic refractive error and biometric corollaries.

CHAPTER 9

DISCUSSION

9.1 SUMMARY

It is estimated that up to a billion people worldwide may be myopic (Norton *et al.,* 2005). Though a relatively benign ocular condition, myopia interferes significantly with normal visual function, whether as a mere visual hindrance or as a precursor to secondary pathologies. It is evident from Chapter 1 that a large amount of research is being undertaken on myopia and from a number of perspectives, all of which reveal important insights into the condition.

It appears that the prevalence of myopia in children is rising. This has been demonstrated by epidemiological studies and statistical evidence collated worldwide (Goldschmidt, 2003; Gilmartin, 2004), with a principal focus in East Asia (Saw, 2003). However, there has been a dearth of data on child refractive error and ocular biometry in the UK. Since the publication of the last study (Sorsby *et al.,* 1961), refractive studies conducted in the UK have been restricted by selection bias (McBrien and Adams, 1997; Pointer, 2001) and methodological limitations (Williams *et al.,* 2005). The lack of contemporary and comprehensive UK data instigated the Aston Eye Study (AES), a population-based study providing epidemiological data on refractive error and ocular biometry in UK urban school children (Chapter 2).

To reveal an unequivocal change in prevalence over time, methodological disparities must be minimised between studies and a shared protocol should be adhered to by all research groups. A central aim of this thesis has been to establish AES protocols in line with those of WHO[1] accredited global studies on children. Definitions of refractive error and clinical protocols adopted were comparable to those of the RESC[2] (Negrel *et al.,* 2000) and the Sydney Myopia Study (Ojaimi *et al.,* 2005).

The AES benefited greatly from its access to modern instrumentation (Chapter 3). Refractive error was measured under cycloplegia using the Shin-Nippon SRW-5000 autorefractor (Shin Nippon, Japan), which by means of its open-field system, measures refractive error in 'natural' conditions, minimising proximal accommodative interference.

Ocular biometry, namely axial length and anterior chamber depth, has until recently required invasive contact methods of measurement (e.g. A-scan ultrasound). The *Zeiss* IOLMaster (Jena, GmbH) enabled precise measurements of axial length, corneal radius and anterior chamber depth on

[1] World Health Organisation
[2] Refractive Error Study in Children

children without a need for corneal contact. Many studies now advocate the IOLMaster as the gold-standard measure of ocular biometry (Carkeet *et al.*, 2004; Sheng *et al.*, 2004).

All instrumentation and protocols were tested successfully in a feasibility study (Chapter 4). A stratified random cluster sampling design was used to invite select schools for participation in the main study (Chapter 5), which was conducted between January 2006 and June 2007 in primary (Year 2 children) and secondary (Year 8 children) schools. To date, 296 Year 8 and 302 Year 2 children have been measured.

The overall prevalence of myopia has been found to be 19.6%, with the prevalence in Year 8 and Year 2 measured at 29.4% and 9.9% respectively (Chapter 6). These levels are higher than those found in the Sydney Myopia Study (Ojaimi *et al.*, 2005a; Ip *et al.*, 2007) although lower than the proportions determined in East Asia (Fan *et al.*, 2004; Lin *et al.*, 2004). In addition, the AES prevalence estimates suggest a rise in the number of elder UK myopic children in relation to findings by Sorsby *et al.*, (1961, see Table 1.2.5). Using the criterion for myopia employed by Sorsby and co-workers (≤1.00D SER), if the myopia prevalence in children under 10 years of age (4.1%) is compared to the AES Year 2 cohort (4.3%) and the prevalence in children 10 years and older (10%) is compared to the AES Year 8 cohort (19.9%), a cohort effect in elder children is implied. The proportion of younger myopes appears remarkably similar between studies, and suggests that the prevalence of early-onset myopia (which would account for a notable proportion of myopia in children aged 6/7 years of age) has not varied considerably since the era of Sorby and colleagues.

In addition to prevalence estimates, an updated distribution of refractive error as a function of age group was determined by the study (Chapter 6), which provides sound baseline data for future investigations. Furthermore, comparisons of refractive error by ethnicity, age, gender and grammar schooling revealed informative insights, including evidence for more myopic refractions in older children, Asian children and children attending grammar schools.

The subsequent chapter (Chapter 7) investigated biometric associates of refractive error and demonstrated a strong association of axial length and corneal radius of curvature with myopia, most evidently through the use of the AL/CR ratio.

Chapter 8 examined AES outcome measures in relation to questionnaire responses. Associations of child myopia with near work, physical activity and genealogy were affirmed and shown to be statistically significant.

Major findings from the AES are discussed below alongside limitations of the current study. In addition, putative theories of myopiagenesis are postulated with recommendations for future work

9.2 SUSCEPTIBILITY OF ASIAN SUBJECTS TO MYOPIA

A major finding of the study was the differential susceptibility across ethnic groups, with myopia prevalence in South Asian children (i.e. Indian, Pakistani and Bangladeshi) higher in both Year 8 and Year 2 cohorts compared to White children, though only Year 8 children demonstrated statistical significance. To the author's knowledge, the AES is the first study to have reported the distribution of refractive error and ocular biometry specifically across White, South Asian and Black children.

A higher Year 8 relative risk to myopia in Asians remained after multivariate analysis adjusted for socioeconomic status, gender and grammar schooling (Chapter 8), suggesting that a factor unrelated to the above is responsible for the predisposition of UK urban Asian children to myopiagenesis relative to Whites.

Cultural values extolling the importance of studying and academic progression have been proposed to account for the high achievement of South Asian children in schools (Wilson *et al.,* 2006). Sustained exposure to near work, a lack of protective outdoor activities or greater intelligence in Asian children may account for the disparity in myopia prevalence between ethnic groups. Physiologically, the distribution of ocular components did not vary between ethnic groups (Chapter 7) therefore it is a greater frequency of miscorrelation between the contributory (i.e. axial length and corneal radius) and compensatory (i.e. lens) elements in the eye that is responsible for higher estimates of myopia prevalence in Asians.

Future work should attempt to determine the specific risk factors responsible for a higher prevalence of myopia in Asians. A longitudinal cohort study examining children from the age of 6 years to mid-teenage years is proposed, investigating the incidence and prevalence of myopia as a function of ethnic group and exposure to myopiagenic factors.

9.3 UNCORRECTED REFRACTIVE ERROR

A further key finding of the study was the unexpectedly high levels of uncorrected refractive error in Birmingham schools. Thirty-eight Year 8 children (12.84%) and 46 Year 2 children (15.23%) were uncorrected ametropes (myopia and hyperopia) according to AES definitions. These are significant estimates considering the current universal application of pre-school vision screening (aged 4-5 years) present in Birmingham. The levels may be an overestimation given the possibility of selection bias in the study i.e. parents suspecting that their child had a problem may have been more likely to give consent for participation. However this overestimation can be countered by the fact that the AES was not sensitive to detecting non-refractive visual defects e.g. amblyopia and colour vision defects. A majority of ametropes will not manifest refractive error until long after they have been screened during their pre-school years though it is recognized that pre-school screening serves an essential function in detecting early cases of amblyopia and strabismus.

Therefore, based on AES results a case for additional vision screening is recommended at an older age *circa* 11 years, principally to detect refractive error. At this age, many ametropes will have manifested signs of their visual defect yet may still be unaware of their reduction in vision (Logan and Gilmartin, 2004). In addition, an increased awareness should be generated within schools of the availability of free optometric eyecare under the NHS[3] for children under the age of 16 years.

9.4 FAMILY HISTORY

A strong family history of myopia was evident from AES data (Chapter 8). Having a myopic father or more than 1 myopic sibling significantly increased the odds of a Year 8 child being classified myopic. In addition, a dose-dependent increase in Year 8 myopia risk was found with an increase in the number of parents who were myopic.

Studies have shown that refractive error is highly heritable (Young *et al.,* 2007), implying a genetic aetiology of myopia. A strong association between parental and child myopia (Pacella *et al.,* 1999; Guggenheim *et al.,* 2003) and high concordance of refraction between monozygotic relative to dizygotic twins (Hammond *et al.,* 2001; Lyhne *et al.,* 2001; Dirani *et al.,* 2006) further supports this hypothesis. However, other work purports the role of genes to be negligible, with the environment playing a predominant role in determining school myopia in children (Morgan and Rose, 2005). The genealogical links with myopia determined in the AES infer that a familial trait is associated with proband myopia, although further work would be required to determine the exact source of variation. It would be of considerable interest to measure refractive error and biometry directly in immediate family members of the proband. In addition, investigator-led interviews on family members would enable accurate determination of exposure to risk factors (e.g. near work, diet), eliminating the need for parental questionnaires and the potential biases they introduce.

9.5 LIMITATIONS AND RECOMMENDATIONS FOR FURTHER WORK

9.5.1 Sample selection

The principal limitation of the AES was the low response rate achieved by both schools and parents within schools. Approximately a third of schools invited partook in the study; of the children invited from these schools, a third were given consent to take part by parents. Therefore, the overall sample cannot preclude the influence of selection bias in recruitment.

It is not known why a low school response rate existed for the AES. Identical recruitment protocols were employed in a child study in Northern Ireland - the Ulster University Eye Study (UUES - O'Donoghue, personal communication), with much higher response rates. In the AES many schools

[3] National Health Service

refused participation due to lack of available time within a busy curriculum. Low parental response rates were similar between studies (AES and UUES) and may be symptomatic of a general apathy towards research in the UK. Alternatively it may be a result of apprehensive parents unwilling to consent to cycloplegia due to a lack of trust towards research involving medical agents; had the study protocol not entailed cycloplegia, it is anticipated that the parental response rate would have been considerably greater.

It is recommended that AES protocols be expanded to include other cities/regions in the UK, in a manner similar to that of the TenTowns child Heart-Health study (Whincup *et al.,* 1992). Such an extension would increase sample size and enable extrapolation of results to account for the general urban child population. Through the employment of identical recruitment sampling methods and clinical protocols as the AES, a map of child UK refractive error distribution can be created and utilised to identify areas at risk of refractive error. In addition, a comprehensive study on refractive error and ocular biometry is also warranted on adults in the UK, which could be combined with geographical extensions to the child study.

9.5.2 Biometry

Both axial length (AL) and corneal radius (CR) were found to act as contributory factors to refractive error. A limitation to measurements was the lack of lens parameter data taken and future epidemiological work should include measurements of lens dimensions, as it appears to be the principal compensatory component to ocular elongation (Mutti *et al.,* 1998). The advent of non-contact anterior segment measurement techniques based on principles such as partial coherent interferometry (Drexler *et al.,* 1997; Kreichbaum *et al.* 2006) will benefit future child study protocols.

The AL/CR ratio is suggested to have a strong predictive value for future myopia, with values >3.0 thought to be a risk factor in emmetropes (Grosvenor, 1988). It would be of great interest to follow AES Year 2 emmetropes in a longitudinal cohort study as a function of baseline AL/CR to determine the predictive value of the ratio and in addition whether baseline AL/CR correlates with age of myopia onset i.e. what are the threshold AL/CR values as a function of age that will distinguish children who will go on to develop myopia from those who will remain emmetropic?
Finally, the cornea appears to be an understudied ocular component which, although independently is not a vast contributor to the variance in myopic refractive error, may underlie the pathophysiology of myopia via its connection with peripheral refraction prior to myopia onset. Though research conducted has shown corneal radius to lack predictive power for future myopia progression (Horner *et al.,* 2000; Davis *et al.,* 2005), the role of the cornea in myopia onset requires longitudinal work to be performed in pre-myopic children from infancy, when predominant growth occurs. As suggested in

Chapter 7, longitudinal work on changes in corneal topography with peripheral refraction prior to the onset of myopia will provide considerable insight into the relationship between the two variables.

9.5.3 Longitudinal follow-up

The cross-sectional nature of the AES places evident limitations in determining causality from associations. To confirm causal relationships, longitudinal studies are necessary and it would be beneficial to revisit the AES cohort in 2-3 years and repeat measurements. Outcome measures could then be correlated against baseline values to determine the extent of change in children as a function of demography. The cohorts participating in the current AES will remain at the same school for the following 3 years (providing no loss due to relocation), thereby facilitating capture of these pupils for longitudinal follow-up.

9.5.4 Astigmatism

The distribution of astigmatism in children and its correlation with ocular biometry was not considered in this thesis. Simplification of a sphero-cylindrical prescription into a spherical equivalent refraction may conceal actual associations between refractive error and physiological mechanisms, particularly in view of the fact that spherical refraction is predominantly a result of axial changes whilst cylindrical aspects are due to anterior segment variations *viz.* cornea and lens. Consider for example that a sphero-cylindrical refraction of +1.00/-2.50 x 180 will equate to an SER value of -0.25D. The subject will have clinically significant biometric changes conducive to the refractive error i.e. corneal astigmatism, although will be classed an emmetrope. Therefore in addition to SER, future work should incorporate astigmatic error through the use of methods such as power vector analysis (Thibos *et al.,* 1997).

9.6 PROSPECTS FOR MYOPIA RESEARCH

Driven by the financial and pathological implications of a growing myopic population alongside an increasing public health concern of the condition in some countries, there has been a surge of interest in the therapeutic treatment of myopia. The two main lines of treatment are optical and pharmacological, both of which have had limited success to date (discussed in Section 1.5). Pirenzepine, a pharmacological agent which proved successful in retarding myopia progression in children during Phase II trials (Tan *et al.,* 2005), has yet to be thoroughly evaluated for long term safety and efficacy, though the drug (or its anti-muscarinic equivalents) does hold promise for the future.

However, prior to the administration of myopia remedies and/or prophylactic interventions that transpire in the near future, a thorough awareness of refractive error distribution, myopia risk factors

and demographical variations in susceptibility must be understood. This is the role of epidemiology and a primary rationale behind the Aston Eye Study. The AES has provided a valuable insight into the epidemiology of myopia in UK urban school children. Evidence has been presented in support of previous literature suggesting that myopia prevalence varies according to ethnicity, type of schooling and family history of the condition. In addition the levels of uncorrected ametropia in urban regions of the UK highlight a cause for concern for relevant child health public bodies and should be addressed. Overall, solid data foundations have been established in this cross-sectional study and it is anticipated that continuance of the study will expand on current findings and broaden the knowledge base of child refractive error and ocular biometry in the UK.

Myopia is a fascinating research topic and one that becomes increasingly complex the further it is explored. The level of awareness of the condition is increasing substantially at a time when myopia prevalence in children is being described as 'epidemic' (Grosvenor, 2003). It is very important that all spheres of myopia research collaborate to heighten understanding of the subject. Much of the work conducted in fields of myopia (e.g. epidemiology, animal studies, genetics) is complementary and many networks can be developed between areas.

In order to fully comprehend myopia, it has to be approached holistically with an understanding of all facets. A neglect of these synergies may prove the greatest myopia of all.

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APPENDIX 1

FEASIBILITY STUDY APPROVAL AND DATA

CONTENTS

ASTON UNIVERSITY

MEMORANDUM

REGISTRY & PLANNING SERVICES

DATE: 10 November 2004

TO: Dr Nicola Logan,
Life & Health Sciences

FROM: John Walter,
Head of Registry & Planning Services

SUBJECT: **Project 05/P: Refractive error: prevalence and ocular component data in a sample of UK school children..**

I am pleased to inform you that a Sub-Group of the University's Ethics Committee has, on behalf of the Committee, approved the above-mentioned project, subject to the information for children and parents including a statement that children should refrain from cycling and other similar activities after taking part in the study during the period (stating number of hours) when they may suffer from blurred vision.
The Sub-Group asked me to convey to the Project Team its appreciation of the clarity and user-friendliness of the information for child volunteers which is an example of good practice.
The details of the investigation will be placed on file. You should notify me of any difficulties experienced by the volunteer subjects, and any significant changes which may be planned for this project in the future.

Aston University

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Secretary to the Ethics Committee

ID	Age (yrs)	Sex	Race	Specs	Vision RE (logMAR)	Vision LE (logMAR)	Dist OMB	Near OMB	Height (m)	Weight (kg)	RE Non-cyclo SER (D)	LE Non-cyclo SER (D)	Mean Non-cyclo SER (D)
PERAM1	5	F	C	N	0.22	0.26	NMD	NMD	1.2	21.6	0.37	1.25	**+0.81**
PERLD2	5	M	C	N	0.26	0.22	NMD	NMD	1.12	20.6	-0.25	0.25	**+0.00**
PERHW3	5	M	C	N	0.22	0.22	NMD	XOP	1.11	20.4	0.07	-0.01	**+0.03**
PERFA4	5	F	C	N	0.12	0.12	XOP	XOP	1.1	18	-0.12	0.62	**+0.25**
PERMG5	5	M	C	N	0.12	0.22	NMD	NMD	1.24	25.4	0.37	-0.19	**+0.09**
PERRF6	6	M	C	N	0.22	0.22	NMD	XOP	1.19	23.4	0.00	0.44	**+0.22**
PERTH7	5	M	C	Y	0.12	0.12	NMD	NMD	1.12	21.6	0.07	0.06	**+0.07**
PERHW8	5	M	C	N	0.04	0.12	NMD	NMD	1.11	19.6	0.50	0.00	**+0.25**
PERON9	5	F	C	N	0.22	0.12	NMD	NMD	1.15	20.2	0.07	0.37	**+0.22**
PERLS10	6	F	C	N	0.22	0.22	NMD	NMD	1.23	21.8	0.19	0.50	**+0.35**
PERDM11	5	F	A	N	0.12	0.00	NMD	NMD	1.14	19.4	0.44	0.32	**+0.38**
PERLC12	5	M	C	N	0.12	0.12	NMD	NMD	1.16	21.8	0.44	0.44	**+0.44**
PERCD13	5	M	C	N	0.12	0.12	NMD	NMD	1.25	25	0.31	0.25	**+0.28**
PERKC14	6	F	C	N	0.22	0.26	XOP	XOP	1.23	32.2	0.62	0.75	**+0.69**
PERAH15	6	M	C	N	0.26	0.12	NMD	NMD	1.27	26	0.50	0.57	**+0.54**
PERDP16	5	M	C	N	0.12	0.20	NMD	XOP	1.2	23	0.63	0.13	**+0.38**
PERCB17	5	M	C	N	0.36	0.40	NMD	NMD			1.56	1.00	**+1.28**
PERET18	6	M	C	N	0.22	0.12	NMD	NMD			0.56	0.69	**+0.63**
PERSPS19	5	M	C	N	0.22	0.22	NMD	NMD			0.25	0.38	**+0.32**

ID	RE Cyclo SER (D)	LE Cyclo SER (D)	Mean Cyclo SER (D)	Av. AL(mm)		Av. CR (mm)		Av. ACD(mm)		AL/CR	
				RE	LE	RE	LE	RE	LE	RE	LE
PERAM1	1.25	1.31	**+1.28**	22.21	22.26	7.83	7.85			2.84	2.84
PERLD2	0.69	0.19	**+0.44**	22.28	22.18	7.49	7.53			2.97	2.95
PERHW3	0.25	0.25	**+0.25**	22.70	22.67	7.72	7.72	3.56	3.53	2.94	2.94
PERFA4	1.06	0.82	**+0.94**	21.72	21.71	7.62	7.59			2.85	2.86
PERMG5	0.82	0.94	**+0.88**	23.08	23.07	8.10	8.11	2.87	2.87	2.85	2.85
PERRF6	1.69	1.87	**+1.78**	22.67	22.58	8.29	8.17			2.74	2.76
PERTH7	0.81	0.44	**+0.63**	22.38	22.37	7.48	7.47	2.28	2.83	2.99	2.99
PERHW8	0.56	0.37	**+0.47**	22.60	22.63	7.76	7.75	3.57	3.57	2.91	2.92
PERON9	0.94	1.94	**+1.44**								
PERLS10	1.50	1.25	**+1.38**	21.50	21.57	7.50	7.56	3.16	3.19	2.87	2.85
PERDM11	0.31	0.38	**+0.35**	22.74	22.69	7.72	7.77	3.08	3.16	2.95	2.92
PERLC12	0.81	1.00	**+0.91**	21.56	21.58	7.34	7.31	3.26	3.37	2.94	2.95
PERCD13	0.62	0.31	**+0.47**	21.68	21.70	7.54	7.53	1.99	2.11	2.87	2.88
PERKC14	1.07	1.00	**+1.04**	21.97	21.99	7.48	7.47	3.37	3.41	2.94	2.94
PERAH15	0.82	0.56	**+0.69**	23.29	23.37	8.07	8.07	3.61	3.62	2.89	2.90
PERDP16	0.44	1.19	**+0.82**	23.17	23.34	7.83	8.02	2.12		2.96	2.91
PERCB17				21.97	21.90	7.62	7.61			2.89	2.88
PERET18											
PERSPS19											

APPENDIX 2

ASTON EYE STUDY ETHICAL SUBMISSION AND APPROVAL

CONTENTS

ASTON UNIVERSITY

PROJECT NO.....

THE SENATE

REG/00/174

HUMAN SCIENCE ETHICAL COMMITTEE

Application for approval of a research project involving human volunteers

Please read the enclosed guidelines before completing this form - in typescript or black ink - and return the form to: The Secretary of the Human Science Ethical Committee, Registry. If you intend to administer any substance or expose the volunteers to a physical procedure other than simple venepuncture **you must also submit an experimental protocol.**

Project title:

Prevalence of refractive error in UK children. A study of spectacle wear in children and variations with age and ethnicity

Outline Scientific Purpose/Objectives for Project and Potential Benefits:

This project will measure prevalence levels of refractive error, with particular focus on myopia, within a UK child population using cycloplegic autorefraction. Ocular component data will also be taken using the Zeiss *IOL Master* and *AC Master* to quantify structural correlates of myopia.
It has been over 40 years since any substantial data was gathered on prevalence of refractive error and significant variation in ethnic demographics and environmental influences have occurred since that time.
The data obtained may be of use to local Health departments in assessing the need for vision screening in schools.

Investigator(s):	**Department/address:**	**Telephone:**
(First name should be a member of Aston's Academic staff who will act as main contact)		
Dr. Nicola Logan	NRI, School of Life & Health Sciences	204 4128.....
Mr Parth Shah	NRI, School of Life & Health Sciences	204 4091.....
Professor Bernard Gilmartin.....	NRI, School of Life & Health Sciences	204 3881.....

A
Details of sponsoring/collaborating organisation (if any)

1. Name: None
2. Does the sponsoring/collaborating organisation provide insurance? N/A
3. If drugs are used, do any require a clinical trials certificate or clinical trials exemption certificate? NO

*If yes, please provide a copy of the certificate

B
Summary of Project

1 Starting date: April 2005

2 Duration: 3 years

3 Location: The study will take place at schools in the West Midlands region and also within the Neurosciences Research Institute at Aston University.

4 Physical procedures:

- Vision testing using a logMAR computerised test chart (i.e. City 2000)
- Oculomotor status as determined by means of a standard cover test
- Focimetry (i.e. measurement of power) of current spectacles (if any)
- Colour vision and stereoacuity
- Non-cycloplegic and cycloplegic refractive error using an infra-red open field autorefractor (Shin-Nippon NVision-K 5001)
- Height and weight measurement
- Axial length, corneal curvature and anterior chamber depth measured using the Zeiss *IOLMaster*
- Lens and corneal thickness measured using the Zeiss *AC Master*
- Amplitude of accommodation using a standard RAF rule

Many of the above procedures are standard clinical optometric procedures familiar to the investigators involved in the project. More specific investigations use the Zeiss *IOL Master* and *AC Master* in paediatric ophthalmology clinics. However the investigators involved have extensive experience of using these instruments.

5. Substances to be administered (a substance is anything other than normal food - chemical constituents of food stuffs, ethanol and variation of the diet should be included here) and method of delivery should be specified:

Topical anaesthetic: ~30μl 0.5% proxymetacaine HCl (single dose applicator, *Minims®, Chauvin Pharmaceuticals*) as a single dose per eye.

Topical cycloplegic: ~30μl 1.0% cyclopentolate HCl (single dose applicator, *Minims®, Chauvin Pharmaceuticals*) as a single dose per eye.

6 Psychological assessment:

None

7. Questionnaires: (only to be completed when project contains questionnaire(s) which fall within the types of questionnaire requiring HSEC approval [Guidelines D (3)])

(see attached)
Two questionnaires will be used; the first to be completed by the parent/guardian of both 6 and 12 year old cohorts whilst the second is to be completed by each member of the 12 year age group themselves. All information will be strictly confidential and restricted to use for the study.

The questionnaire requests information on the medical history of the child and his/her ethnic origin. Details of previous ocular/spectacle history will be required together with current spectacle wearing habits. The child's environment and basic life style will also be assessed to determine whether a particular type of child has an increased susceptibility to ametropia.
Finally, information on parental and familial history of refractive error will be obtained to aid in determining the heritability of myopia within families.

Volunteers

1 Number of volunteers to be used: 4000

2 Over what time span? 3 years

3 Age of volunteers: 5 to 13 years

4 Sex of volunteers: Male and female

5 Source: Primary and secondary schools located in the West Midlands region

6 Will payments be made to the volunteers and if so, how much will each be paid? No

7 Are the volunteers patients or healthy volunteers? (If patients, give diagnosis, clinic/responsible practitioner).

Healthy volunteers

8 Will any volunteers be excluded and if so, on what grounds?

If volunteers do not want to participate in the study, they will under no circumstances be under any duress to do so. Any previous ophthalmic reactions to drugs will also prohibit involvement in the study.Lastly, any child with a greater risk to adverse effects of the drops, including children with Downs Syndrome and Cerebral Palsy will also be excluded.

9 Is the activity of the volunteer to be restricted in any way either before or after the procedure? (eg diet, driving)

The procedure requires the topical instillation of the mild cycloplegic cyclopentolate. It is a form of drug routinely used on young children in clinical optometric practice. This drug will, at most, cause mild visual blurring (at distance and near) for at least 8 hours after instillation. The volunteer may also suffer from mild glare sensitivity due to the pupil dilation that accompanies cycloplegia.

10 Consent: Please attach a copy of the consent form you intend to use, detailing how procedures and hazards will be explained.

Attached

D

Risk Assessment: *a thorough Risk Assessment of the project must be undertaken (including for example welfare issues arising from the procedure, and the possible risk of residual effects in volunteers and the consequences thereof).*

1. Please give full details of any hazards which could affect the health, safety or welfare of any volunteer, or any other person who might be harmed as a result of the experiment.

Ocular adverse reactions to cyclopentolate are rare. Dilated pupils may impede work due to slight blurring of vision and increased susceptibility to glare which should subside usually within four to six hours of instillation.
Systemic adverse reactions are extremely rare. They may include a transient episode of drowsiness lasting between 1-5 hours, disorientation, restlessness, ataxia and emotional disturbance.

Ocular adverse reactions to proxymetacaine HCl are also rare. Sensitivity reactions have only been reported with repeated instillation of the drug. A rare adverse reaction has been reported with the use of topical anaesthetics with an incidence of 1 in 1000 patients over 55 years of age. The reaction is desquamation of the corneal epithelium which results in a significant reduction in visual acuity for up to 2 hours, but is self-limiting with no permanent effects. Adverse effects have been reported with repeated instillation of proxymetacaine, only a single dose will be used in this study.

2. What levels of risk are associated with these hazards ?

Very low. Cycloplegia with cyclopentolate begins to recover after 8 hours with no permanent effects. Adverse reactions to proxymetacaine are minimal when small volumes of the drug are used. Data is not available for young adults and children, however there have been only 3 incidences of adverse reactions reported within a student population at Aston University over the last 10 years. Corneal anaesthesia wears off approx. 30mins after instillation.

3. How do you propose to control the risks associated with these hazards?

Any risks can be minimised by avoiding over dosage of the drug. The puncta will be occluded as a preventative measure against systemic absorption.
Additional risks can be minimised by parents and children being fully aware of any side effects and by swift recognition of any signs or symptoms. Before consenting to the study both parents and children will have been informed of what to expect after cycloplegia (they will have been given an information sheet detailing the effects of cycloplegia). Children will be advised to wear sunglasses if they have them after taking part in the study to minimise discomfort. They will also be discouraged from taking part in heavy physical activities (e.g. cycling, competitive sports)
After corneal anaesthesia, children will be told not to rub their eyes for an hour and inform us or their teachers if their eyes begin to hurt or their vision deteriorates. Corneal anaesthesia should have recovered by the time the child's measurements are taken thus any adverse reactions can be identified swiftly by an experienced practitioner.

4. What criteria have you used to determine whether the risks are acceptable?

The ophthalmic literature indicates that the risks posed are minimal. Furthermore, all three of the investigators are qualified optometrists and have extensive clinical experience in these procedures. The drops will be instilled by one of the qualified optometrists.
The investigators will only be performing parts of an eye examination typical to that which is undertaken currently in optometric practice. The Zeiss *IOLMaster* is an instrument that is routinely used in paediatric ophthalmology clinics. The investigators also have extensive clinical knowledge and experience in using all instruments e.g. Shin-Nippon, Zeiss *AC Master* and *IOL Master.*

5. Is there any precedent for these experiments? If so, please give details with references if possible.

Aston University Project 05/Q: Epidemiology of myopia in a UK child population. Approved 10th Nov 2004. Has continued without incident.

Aston University Project 05/P: Refractive error: prevalence and ocular component data in a sample of UK school children. Approved 10th Nov 2004. Has continued without incident.

6. Has this project been considered/is it being considered by any other Ethical Committee? If so, please give details and decision made.

No

E

STATEMENT BY NAMED INVESTIGATORS, HEAD OF SCHOOL AND (if necessary) RESEARCH SUPERVISOR

I consider that the details given constitute a true summary of the project and that the hazards and potential risks to any volunteer are accurately described. The Principal Investigator is the main point of contact for the Human Sciences Ethical Committee, and accordingly should be a member of academic staff of the University (this implies that supervisors of research students will be the main point of contact)

Principal Investigator or Supervisor of Student ..... date.....

Investigator..... date.....

Investigator..... date.....

Head of School..... date.....
(or nominee)

The following should be attached:

* volunteer consent form
* insurance certificate (if available)
* clinical trials certificate or clinical trials exemption certificate (if appropriate)
* experimental protocol

ASTON UNIVERSITY

MEMORANDUM

REGISTRY & PLANNING SERVICES

DATE: 18 August 2005

TO: Dr Nicola Logan,
Life & Health Sciences

FROM: John Walter,
Head of Registry & Planning Services

SUBJECT: **Project 05/22: Prevalence of refractive error in UK children. A study of spectacle wear in children and variations with age and ethnicity.**

I am writing to inform you that a Sub-Group of the University's Ethics Committee has approved the above project proposals as amended in the light of the Sub-Group's comments.

The details of the investigation will be placed on file. You should notify me of any difficulties experienced by the volunteer subjects, and any significant changes which may be planned for this project in the future.

Aston University

Secretary to the Ethics Committee

Mr John Walter
Secretary to University Research Ethics Committee

10th August 2006

Dear Mr Walter

Re: Approved ethics Project 05/22: Prevalence of refractive error in UK children. A study of spectacle wear in children and variations with age and ethnicity

The above study is an epidemiology study to assess the prevalence of refractive error in UK children. For the study data to be meaningful we require a response rate of approximately 70% or better and therefore we continually monitor the response and participation rate. As our current response rate is 50% we have reviewed our study recruitment procedures. Consequently changes have been made to the documentation. I have enclosed all the revised documentation for consideration by the Ethics Committee.

I look forward to hearing from you,

Aston University

Nicola Logan
Lecturer
School of Life & Health Sciences

ASTON UNIVERSITY

MEMORANDUM

REGISTRY & PLANNING SERVICES

DATE: 22 November 2006

TO: Dr Nicola Logan,
Life & Health Sciences

FROM: John Walter,
Head of Registry & Planning Services

SUBJECT: **Project 05/22: Prevalence of refractive error in UK children. A study of spectacle wear in children and variations with age and ethnicity.**

I am writing to inform you that a Sub-Group of the University's Ethics Committee has considered the proposed changes to the above project, on behalf of the Ethics Committee. The Sub-Group agreed that the revised project be approved but asked me to emphasise the importance of the role of the school teacher in identifying those students who might be distressed/disturbed by questions about their parents. The Sub-Group also suggest that further consideration is given to the item "I fight a lot. I can make other people do what I want" which appears to conflate two concepts - members felt that it is possible to improve on the validity of an item included in previously published work without seriously affecting the comparability of its results with your study.

The details of the investigation will be placed on file. You should notify me of any difficulties experienced by the volunteer subjects, and any significant changes which may be planned for this project in the future.

Aston University

Secretary to the Ethics Committee

APPENDIX 3

SCHOOL CORRESPONDENCE

CONTENTS

- Example of revised Year 8 school contact letter & reply form. The letter was sent out to schools following initial contact by a principal member of the AES team. Correspondent name and school addresses have been masked to retain anonymity.

9th August 2006

Dear Mr [redacted]

Further to our recent telephone conversation, we are writing to thank you for your interest in the Aston Eye Study. This is the first large scale survey to provide detailed information on the health of children's eyes from different ethnic groups in Britain. The study aims to examine factors that are associated with poor vision in young children. We have specifically invited your school to participate because of its location and the ethnic composition of the school. This letter is to provide you with a summary of the key points of the study along with information regarding future stages.

What are the benefits of participating in this study for your schoolchildren?
The primary benefit for your school would be similar to that of a basic vision screening service; to identify any visual defects present in children involved in the study, a proportion of whom may never have had their eyes examined before. We will be specifically looking at children in Year 8 (12/13 years) as this is an age when short-sightedness (myopia) commonly manifests and leads to complaints of distance objects becoming blurred

Where will the study take place?
We aim to make participation as simple as possible for schools involved in the survey. All preparation of invitations and other study materials will be carried out by our Research Team. No costs will be incurred by participating schools. We are able to come to your school to take measurements and **we will provide** all necessary equipment and staffing for the study to minimise any disruption to your normal timetable. We do request that you provide a room (wholly or partly) for the duration of the study at your school. This will typically be between one to two days, dependant upon the response from children and their parent/guardians. All researchers are Criminal Records Bureau (CRB) checked.

What will the study entail?
A series of tests will be undertaken to assess the child's sight, all of which are standard tests used by the optometrists involved. Measurements will include testing how well the child can see, whether they need spectacles, the size and shape of the eyeball as well as the child's height and weight. If we do find a child has a particular problem concerning their eyesight, we will write to their parent/guardian advising them to take their child along to an optometrist of their choice for a full eye examination.

Next stage
Our next stage is to arrange a brief initial meeting with you to discuss the logistics of the study, distribute consent forms for Year 8 parents and answer any queries that you may have. Please contact the study co-ordinator Mr Parth Shah either by telephone, email or letter (self-addressed envelope enclosed) to arrange this.

Thank you once again for your interest in this important study and we look forward to hearing from you with regards to a suitable meeting date.

Yo

Aston University

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Professor Bernard Gilmartin	Dr. Nicola Logan	Mr. Parth Shah
Study Director	*Study Leader*	*Study Co-ordinator*

REPLY FORM

School: [redacted]

Name of correspondent: _____

Position: _____

I/We are interested in our school participating in the study and would like to arrange an initial meeting ☐

Please inform us of preferred times, days and dates you are/are not free in the coming weeks in order for us to provisionally schedule a meeting with you:

_____

_____

_____

_____

_____

Email and /or telephone number _____

I/We would not like our school to participate in the study ☐

Please return this reply slip in the enclosed envelope (no stamp needed) or alternatively, contact the Eye Study team using the email/telephone details below.

Thank you for your time.

APPENDIX 4

PARENTAL CORRESPONDENCE

CONTENTS

- Example of revised Year 8 parental letter introducing the AES
- Year 8 information sheet for parent and child
- Parental consent form
- Parental reminder letter
- Drug information sheet distributed on completion of measurements

Dear Parent / Carer

January 2007

We are a team of registered optometrists from Aston University and we are writing to you to invite your child (and other children in your child's school) to take part in an important study examining the eyesight of children. Research suggests that seeing well in childhood can have important effects on vision and the ability to learn in later life. We are very keen to include your child in this study, whether he/she uses glasses or not, to ensure that this study provides a true picture of eye health in today's children.

What would taking part in the study involve?

For your child Your child (along with other children) will have their eyes examined at school. We will measure the shape and length of your child's eyes very accurately; **these tests are very quick, painless and do not touch the eye**. To measure the eyes accurately we will need to put some drops into each eye which will make the pupils larger (the black part in the middle of the eye). The drops may irritate for a few seconds when they are first put into the eyes. Your child may find lights brighter than usual for approximately 12 hours after the drops are put in (rarely up to 24 hours), hence we will provide a pair of disposable sunglasses to all children who participate in the study and we advise that your child does not take part in physical activities or sports during this time. Vision may be blurred slightly up close whilst reading for up to 12 hours after we put the drops in, however distance vision should remain unaffected.

Very rarely, the drops can cause a reaction (in less than 1 in 10,000 people). When it occurs a rash appears on the face and the child feels hot and light-headed. These reactions go away **naturally the same day without treatment**. We will also measure your child's height and weight. The eye examination itself will take half an hour or so. Finally, your child will be asked to complete a short questionnaire on his/her health and habits. He/she will be given a special certificate and pen at the end of the examination along with the disposable sunglasses. Our Research Team will have visited the school in advance to explain our study arrangements and to answer any questions.

For you After your child has been measured, you will be asked to fill in a short questionnaire on your child's health and development and on the eye health and circumstances of your family. This questionnaire will help us to interpret the results from your child's examination.

What will happen after the study?

We will look at the results carefully. If we feel your child requires further examination, we will send you a report on your child's eyes once we have received your questionnaire.

We hope very much that your child will be able to take part in the survey – many other children have now taken part and have found it both enjoyable and interesting. **All information from the study will be treated in complete confidence**. Please discuss the study with your child (details of the measurements are shown on the information sheet for children accompanying this letter) and fill in the consent form enclosed to say whether or not your child will take part. The form should be signed by a parent or legal guardian. Please put the reply form in the envelope provided and give it to your child to return to school **as soon as possible**. If you would like any further information please telephone us on 0121 204 4091 or email shahp4@aston.ac.uk.

Th

Aston University

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Professor Bernard Gilmartin
Study Director

Dr Nicola Logan
Study Leader

Mr Parth Shah
Study Co-ordinator

Child information sheet

We are writing to ask you and other children in your class to help us with an important study where we will be looking at how well children can see. We hope that the study will help us find out more about the health of children's eyes and understand why people do not see clearly.

What will the study involve?

On the day of the study we will ask you to come and have your eyes examined by an optician. He or she will measure:-

- **How well you can see-** by reading some letters on a chart (or recognising some shapes), and whether you might need glasses to help you see better.
- **Your height and weight-** using scales and a height chart.

- **The shape and length of your eye-** to do this we will need to put special drops in your eyes. The drops can tingle for a few seconds when they are first put into your eyes. The drops will make your pupils (the black part in the middle of the eye) larger for several hours. You will not be able to play sports on the day that we test your eyes and you may also find that lights are brighter than usual. For this, we will **give you a pair of disposable sunglasses** that you can use for the day and keep. You may have some difficulty reading although your normal distance vision should be fine. These effects do not last long and your eyes will soon be back to normal.

- **A questionnaire-** We will ask you to fill in a short questionnaire to tell us about your health, what you like to eat, and what you do in your free time.

What happens when I have finished the tests?

- **Pen and certificate-** To show that you have played an important part in this research, we will give you a pen and a special certificate to say 'Thank You'.

Thank you for reading this letter. We hope you will be able to take part in this study. Please fill in the reply form with your parent or carer. If you have any questions, you can contact us by telephone, email or by writing to us.

Parth Shah, Aston Eye Study, School of Life and Health Sciences, Aston University, Birmingham, B4 7ET.

Aston University ac.uk

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ASTON EYE STUDY

CONSENT FORM FOR PARENT/GUARDIAN

Confidentiality of Information

Your child's results will be kept in a confidential file accessible by the Research Team only. The results will be transferred to a computer but your child's name will not appear with their results.

Consent

Please read the information sheet and letter very carefully. Complete the form below and tick the appropriate box as to whether or not you consent to your child participating in the study. It is very important that we receive your reply, whether or not you wish for your child to participate.

Name of child_____ **Date of birth** _____

Please discuss the study with your child, TICK THE APPROPRIATE BOX AND SIGN BELOW.

☐ **Yes, I give permission for my son / daughter to take part in the Aston Eye Study as explained to me by the information sheet. My child has been informed that he/she is free to withdraw at any time.**

☐ **No, I do not wish my son / daughter to take part in the Aston Eye Study**

Signature of Parent or Legal Guardian _____ **Date** _____

Name of Parent or Legal Guardian (please print) _____

School_____

YOUR CHILD'S HEALTH If your child has any specific health problem(s) which you think might be important please give details here.

ADDRESS Please write your FULL address (including postcode) here, so that we can keep in touch with you about the study.

If you are not sure about any part of this consent form or wish to discuss it with us, please telephone or email us (details shown below).

PLEASE RETURN THIS FORM TO SCHOOL IN THE ENVELOPE PROVIDED AS SOON AS POSSIBLE.

THANK YOU FOR YOUR HELP

Dear Parent / Carer

May 2007

We are a group of optometrists from Aston University and we wrote to you recently about an Eye Study we are conducting across schools in Birmingham. The aim of this study is to determine the number of children who need to wear spectacles and possible reasons why they may be predisposed to their particular visual problem. We would like to include your child in our study, whether he/she currently wears glasses or not as this will give us a true picture of the state of children's eyesight in the UK.

As yet, we have not received a reply from you. We would be very grateful if you could take the time to complete and return the form below to your child's teacher, even if you do not wish for your child to take part in the study. This will help us in ascertaining parental response rates

Full information on the eye study is on the original letter we distributed to you and we advise you to read this letter before completing this form. If you would like another copy of the letter or if you have any queries please contact the Eye Study team using the details below.

Aston University

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Professor Bernard Gilmartin
Study Director

Dr Nicola Logan
Study Leader

Mr Parth Shah
Study Co-ordinator

To The Aston Eye Study Team

Name of child_____

Date of birth _____

Please discuss the study with your child, TICK THE APPROPRIATE BOX AND SIGN BELOW.

☐ **Yes, I give permission for my son / daughter to take part in the Aston Eye Study as explained to me by the information sheet. My child has been informed that he/she is free to withdraw at any time.**

☐ **No, I do not wish my son / daughter to take part in the Aston Eye Study**

Signature of Parent or Legal Guardian _____ **Date** _____

Name of Parent or Legal Guardian (please print) _____

School_____

The name of the eye drops that were instilled into your child's eyes today is CYCLOPENTOLATE 1.0%.
The drops are used to allow an accurate reading of your eyes prescription by suspending its focusing system. The drops take about 30 to 45 minutes to work and around 12-24 hours to wear off.
The large pupils will make your child more sensitive to light and distant and near objects may appear slightly blurred.
The optometrist will have recommended therefore that your child shouldn't perform any physical activities such as cycling for at least 12 hours after the drops have been instilled. On a bright day, sunglasses may be advisable also.
It is very unlikely, but should your child experience any unusual symptoms such as severe pain and/or blood shot around the eye and cloudy vision during this period please contact us on 0121 204 4091 or your GP as he/she may be experiencing an adverse reaction to the drops.
ASTON UNIVERSITY EYE STUDY TEAM

The name of the eye drops that were instilled into your child's eyes today is PROXYMETACAINE 0.5%.
The drops are a mild local anaesthetic used to numb the surface of your child's eye to enhance absorption and facilitate instillation of the drops that reduce the focusing power of the eye. The drops take about 60 seconds to work and around 25 minutes to wear off.
Your child should avoid situations where he/she may get dust or grit into his/her eyes for a few hours, as he/she will not be able to feel any discomfort straight away.
It is very unlikely, but should your child experience any unusual symptoms such as pain, soreness or blurred vision during this period please contact us on 0121 204 4091 or your GP, as he/she may be experiencing an adverse reaction to the drops.
ASTON UNIVERSITY EYE STUDY TEAM

APPENDIX 5

ASTON EYE STUDY SHEETS

CONTENTS

- Equipment list
- Year 8 consent form
- Year 2 assent form
- Example of completed recording sheets (Year 8 n=3, Year 2 n=3). Sheets have been rendered anonymous to protect the identity of the individuals involved.

Equipment List

	Present
Test chart/Laptop with City 2000 test chart	
Occluder spectacles	
Cover stick	
Shin Nippon SRW-5000	
Zeiss IOLMaster	
Height chart	
Weighing scales	
Tape measure	
Budgie stick	
RAF rule	
Maltese cross	
Cycloplegic drops Cyclopentolate 1%	
Anaesthetic drops Proxymetacaine 0.5%	
Stickers/Pens/Certificates	
Tissues	
Extension lead(s)	
Ruler	
Alcohol Gel	
Spreadsheet with children's name on	
Assent forms 6 and 12 years	
Drug info sheet	
Recording sheet	
Questionnaires	
Trolley	
Chair (adjustable)	
Focimeter	
Video + activities	
BluTack and stapler	
Storage box	
Ready Readers	
Yellow and black tape	
Sunglasses	

ASTON UNIVERSITY REG/00/175

HUMAN SCIENCE ETHICAL COMMITTEE

CHILD CONSENT FORM

PROJECT TITLE

Aston University Eye Study
Prevalence of refractive error in UK children

What will happen to me in this study?
This is a study to check how well children can see. We will be testing your eyes to make sure you do not need to wear glasses. Many of these tests you will have had done before when you previously went to your optician.

Can anything bad happen to me?
We will need to put some drops into your eyes to make sure our results are more accurate. Initially, these drops will sting very slightly for a short period of time.

Can anything good happen to me?
If we find that you are not seeing as clearly as you should be, we will advise your parent/guardian to arrange an appointment at your opticians.

Do I have other choices?
You can choose not to be in this study.

Who can I talk to about the study?
You can ask questions at any time. You can ask your parents to talk to us or you can ask us any questions you may have on the day.

What if I do not want to do this?
You don't have to be in this study. No one will be angry at you if you don't want to do this. If you don't want to be in this study, you just have to tell us. And, remember, you can say "yes" now and change your mind later. It's up to you.

Do you understand this study and are you willing to participate?

☐ *YES* ☐ *NO*

_____ _____
Signature of Child **Date**

ASTON UNIVERSITY

REG/00/175

HUMAN SCIENCE ETHICAL COMMITTEE

CHILD ASSENT FORM

PROJECT TITLE

Aston University Eye Study
Prevalence of refractive error in UK children

What will happen to me in this study?
This is a study to check how well children can see. We will be testing your eyes to make sure you do not need to wear glasses. Many of these tests you will have had done before when you previously saw your optician.

Can anything bad happen to me?
We will need to put some drops into your eyes to make sure our results are more accurate. Initially, these drops will sting very slightly for a short period of time.

What good will come of the study?
If we find that you are not seeing as clearly as you should be, we will advise your parent/guardian to arrange an appointment at your opticians.

Do I have other choices?
You can choose not to be in this study.

Who can I talk to about the study?
You can ask questions any time. You can ask your parents to talk to us or you can ask us any questions you may have on the day.

What if I do not want to do this?
You don't have to be in this study. No one will be angry at you if you don't want to do this. If you don't want to be in this study, you just have to tell us. And, remember, you can say "yes" now and change your mind later. It's up to you.

Assent:
"I was present when _____ read this form and gave his/her verbal assent."

Name of person who obtained assent _____

*Signature*_____ *Date*_____

HRAA

Record Sheet- Aston Eye Study

School Initials: HR

Consent Form signed: ✓

Name: [redacted] Age: 12 [redacted] Race: [redacted]

	Specs worn? Y / N If yes, complete here first:					
VA:	R +1 6/6	L 6/6-2	Vision:	R 6/48	L 6/60	
Dist OMB	ND		Dist OMB	ND		
Near OMB	ND		Near OMB	4xOD		
Focimetry:			Height (m)	1.637		
R	+2.00					
L	+2.00		Weight (kg)	64.0		

Biometry		1	2	3	Ave.
AL	R				
	L				
CR	R H V				
	L H V				

		1	2	3	4	5	Ave.
ACD	R						
	L						

Cycloplegia

0.5% proxymetacaine: ✓ 1% cyclopentolate: ✓ Time: 10am

Amplitude of Accom

Pre-cyclo: R L

Time after insertion: 1230

Post-cyclo R L <20

Cycloplegia achieved: ✓

Cycloplegic autorefraction

R 1 2 3 L 1 2 3

Child Questionnaire completed: ✓

Main questionnaire and drug info sheet handed out ✓

Routine letter

HRA A

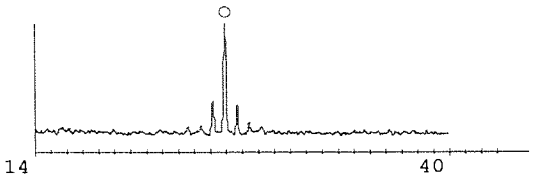
Name: [redacted] Date of Birth: [redacted]

ID: [redacted] Exam Date: **27-04-2007**

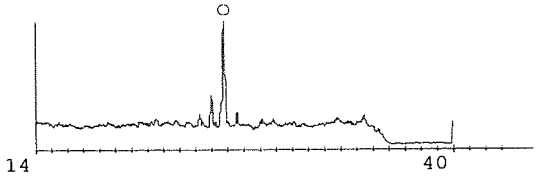
ZEISS

OD (right)		axial length values		OS (left)	
AL	SNR	AL	SNR	AL	SNR
25.70 mm	3.0			25.51 mm	4.8		
Error				> 25.53 mm	< 10.6		
Error				25.51 mm	4.0		
> 25.72 mm	< 6.5						
25.71 mm	4.8						

average AL: 25.71 mm



average AL: 25.52 mm



OD (right)			corneal curvature values		OS (left)		
R1: 8.04 mm @ 7°	41.98 D			R1: 8.02 mm @ 163°	42.08 D	
R2: 7.96 mm @ 97°	42.40 D			R2: 7.90 mm @ 73°	42.72 D	
ΔD: -0.42 D @ 7°				ΔD: -0.64 D @ 163°		
R1: 8.05 mm @ 8°	41.93 D			R1: 8.03 mm @ 163°	42.03 D	
R2: 7.96 mm @ 98°	42.40 D			R2: 7.89 mm @ 73°	42.78 D	
ΔD: -0.47 D @ 8°				ΔD: -0.75 D @ 163°		
R1: 8.06 mm @ 5°	41.87 D <			R1: 8.02 mm @ 166°	42.08 D <	
R2: 7.95 mm @ 95°	42.45 D			R2: 7.89 mm @ 76°	42.78 D	
ΔD: -0.58 D @ 5°				ΔD: -0.70 D @ 166°		
n: 1.3375				n: 1.3375		

OD (right)			anterior chamber depth values		OS (left)				
3.96 mm	3.98 mm	3.96 mm	4.00 mm	4.00 mm	4.03 mm	4.01 mm	4.01 mm	4.01 mm	4.03 mm
ACD: 3.98 mm					ACD: 4.02 mm				

NAME
27 2007 11:38
FRAME V0=10

<R>	SPH	CYL	AX
	- 2.25	-0.50	46
	- 2.12	-0.25	45
	- 1.87	-0.50	44
	- 2.12	-0.50	44

<L>	SPH	CYL	AX
	- 2.00	-0.37	179
	- 1.75	-0.37	173
	- 1.87	-0.25	177
	- 1.87	-0.37	179

PD = 61

SN[redacted]

A1.

HRSA

Record Sheet- Aston Eye Study

School Initials: HH

Consent Form signed: ✓

Name: [redacted] Age: 13 [redacted] Race: [redacted]

	Specs worn? Y / N If yes, complete here first:				
	R ↓	L		R	L
VA:			Vision:	6/-1	6/10
Dist OMB			Dist OMB	6/5	
Near OMB			Near OMB	N5	
Focimetry:			Height (m)	1.567	
R					
L			Weight (kg)	44.8	

Biometry		1	2	3	Ave.
AL	R				
	L				
CR	R H				
	V				
	L H				
	V				

		1	2	3	4	5	Ave.
ACD	R						
	L						

Cycloplegia

0.5% proxymetacaine: ✓ 1% cyclopentolate: ✓ Time: 10-08

Amplitude of Accom

Pre-cyclo: R

L

Time after insertion: 10.35

Post-cyclo R 4.25

L

Cycloplegia achieved: ✓

Cycloplegic autorefraction

R 1

2

3

L 1

2

3

Child Questionnaire completed: ✓

Main questionnaire and drug info sheet handed out ✓

16 myope

HRSA

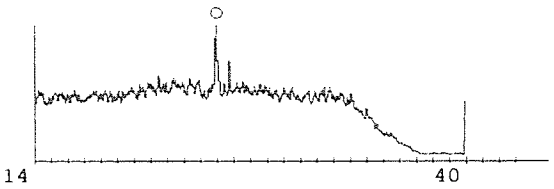
Name: [redacted] Date of Birth: [redacted]

ID: Exam Date: 27-04-2007

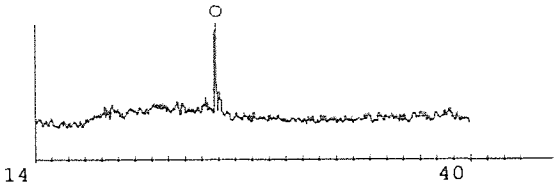
ZEISS

OD (right)		axial length values		OS (left)	
AL	SNR	AL	SNR	AL	SNR
> 24.81 mm	< 6.5			> 24.76 mm	< 3.4		
24.78 mm	2.3			25.00 mm	2.3		
24.80 mm	4.0			25.01 mm	3.1		
				24.99 mm	3.2		

average AL: 24.80 mm



average AL: **Evaluation !**



OD (right)		corneal curvature values		OS (left)		
R1: 8.06 mm @ 37°	41.87 D		R1: 8.05 mm @ 139°	41.93 D	
R2: 7.94 mm @ 127°	42.51 D		R2: 7.95 mm @ 49°	42.45 D	
ΔD: -0.64 D @ 37°			ΔD: -0.52 D @ 139°		
R1: 8.06 mm @ 37°	41.87 D		R1: 8.06 mm @ 131°	41.87 D	× ×
R2: 7.95 mm @ 127°	42.45 D		R2: 7.95 mm @ 41°	42.45 D	○ ○
ΔD: -0.58 D @ 37°			ΔD: -0.58 D @ 131°		○ ○
R1: 8.08 mm @ 42°	41.77 D <		R1: 8.05 mm @ 139°	41.93 D <	
R2: 7.95 mm @ 132°	42.45 D		R2: 7.96 mm @ 49°	42.40 D	
ΔD: -0.68 D @ 42°			ΔD: -0.47 D @ 139°		
n: 1.3375			n: 1.3375		

OD (right)					anterior chamber depth values					OS (left)
3.93 mm	3.95 mm	3.95 mm	3.95 mm	3.95 mm	3.88 mm	3.90 mm	3.90 mm	3.88 mm	3.88 mm	
ACD: 3.95 mm					ACD: 3.89 mm					

Apr 27 2007 11:31
FRAME AD=10

(R)	SPH	CYL	AX
	- 0.25	-0.50	86
	- 0.25	-0.50	112
	+ 0.12	-0.62	56
	+ 0.12	-0.37	86

(L)	SPH	CYL	AX
	- 0.75	-0.	75
	- 0.75	-0.37	107
	- 0.75	-0.25	115
	- 0.75	-0.37	115

PD = 63

Carl Zeiss IOLMaster™ V. 3.01

Printed on: 27-04-2007 at 12:51 PM.

HRTC

Record Sheet- Aston Eye Study

School Initials: HH

Consent Form signed: ☑

Name: [redacted] Age: 13 Race: [redacted]

	Specs worn? Y / N If yes, complete here first:				
	R ↓	L		R	L
VA:			Vision:	6/12	6/24 +2
Dist OMB			Dist OMB	☐	
Near OMB			Near OMB	☐	
Focimetry:			Height (m)	1.567	
R			Weight (kg)	40.8	
L					

Biometry		1	2	3	Ave.
AL	R				
	L				
CR	R H	764@97			
	V	735@87			
	L H				
	V				

		1	2	3	4	5	Ave.
ACD	R						
	L						

Cycloplegia

0.5% proxymetacaine: ☑ 1% cyclopentolate: ☑ Time: 10-10

Amplitude of Accom

Pre-cyclo: R

L

Time after insertion: 10-42 10.50

Post-cyclo R 3D 4D

L 2D

Cycloplegia achieved: ☐ ☑ ☐

Cycloplegic autorefraction

R		L	
	1		1
	2		2
	3		3

Child Questionnaire completed: ☑

Main questionnaire and drug info sheet handed out ☑

Refer - myope.

HR7C

Name: [redacted] Date of Birth: [redacted]

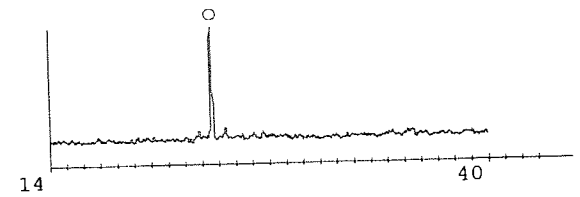
ID: Exam Date: 27-04-2007

ZEISS

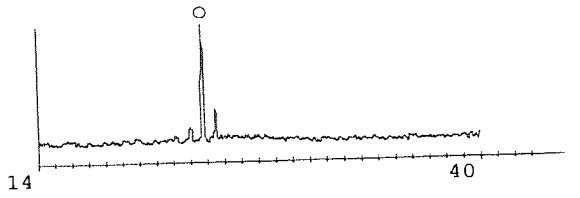
axial length values

OD (right) AL	OD (right) SNR	OD (right) AL	OD (right) SNR	OS (left) AL	OS (left) SNR	OS (left) AL	OS (left) SNR
23.06 mm	3.6			23.14 mm	2.3		
> 23.05 mm <	5.4			23.14 mm	2.3		
23.01 mm	2.4			Error			
				> 23.13 mm <	6.6		

average AL: 23.04 mm



average AL: 23.14 mm



corneal curvature values

OD (right)			OS (left)	
Error !		× × / ○ ○ / ○ ○	R1: 7.58 mm @ 3°	44.53 D
			R2: 7.36 mm @ 93°	45.86 D
			ΔD: -1.33 D @ 3°	
R1: 7.63 mm @ 174°	44.23 D	○ ○ / ○ ○ / ○ ×	R1: 7.56 mm @ 176°	44.64 D
R2: 7.32 mm @ 84°	46.11 D		R2: 7.37 mm @ 86°	45.79 D
ΔD: -1.88 D @ 174°			ΔD: -1.15 D @ 176°	
R1: 7.56 mm @ 173°	44.64 D <		R1: 7.57 mm @ 2°	44.58 D <
R2: 7.38 mm @ 83°	45.73 D		R2: 7.36 mm @ 92°	45.86 D
ΔD: -1.09 D @ 173°			ΔD: -1.28 D @ 2°	
n: 1.3375			n: 1.3375	

anterior chamber depth values

OD (right)					OS (left)				
3.56 mm	3.56 mm	3.56 mm	3.56 mm	3.56 mm	3.55 mm	3.55 mm	3.55 mm	3.55 mm	3.55 mm
ACD: 3.56 mm					ACD: 3.55 mm				

[redacted]

NAME
APR 27-2007 11:43
AGE =10

	SPH	CYL	AX
	- 1.30	-0.12	80
	- 0.75	-0.25	65
	- 0.75	-0.37	57
	- 0.75	-0.25	65

	H	CYL	AX
	0.62	-0.50	60
	- 0.62	-0.12	78
	- 0.50	-0.37	96
	- 0.62	-0.50	60

PD = 60

Carl Zeiss IOLMaster™ V. 3.01

Printed on: 27-04-2007 at 01:08 PM.

WYAM

Record Sheet- Aston Eye Study

School Initials: W4

Consent Form signed: ☑

Name: [redacted] Age: [redacted] Race: [redacted]

	Specs worn? Y / N If yes, complete here first:				
	R ↓	L		R	L
VA:			Vision:	6/5 -2	6/4 -2
Dist OMB			Dist OMB	☑	
Near OMB			Near OMB	6x ap	
Focimetry: R L			Height (m)	118.4	
			Weight (kg)	22.8	

Biometry		*1*	*2*	*3*	*Ave.*
AL	R				
	L				
CR	R H				
	R V				
	L H				
	L V				

		1	*2*	*3*	*4*	*5*	*Ave.*
ACD	R						
	L						

Cyclopegia

0.5% proxymetacaine: ☑ 1% cyclopentolate: ☑ Time: 1.23

Amplitude of Accom

Pre-cyclo: R

L

Time after insertion: 1.50 2.00pm

Post-cyclo R 2.5 <2D

L 2.5

Cycloplegia achieved: ☐ ☑ ☐

Cycloplegic autorefraction

R 1

2

3

L 1

2

3

Child Questionnaire completed: ☑

Main questionnaire and drug info sheet handed out ☑

W4AM

Name: [redacted] Date of Birth: [redacted]

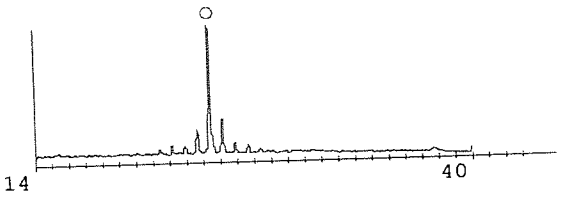
ID: Exam Date: 24-04-2007

ZEISS

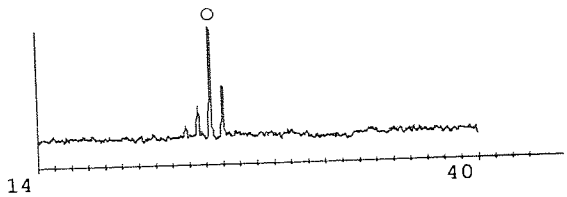
axial length values

OD (right) AL	OD (right) SNR	OD (right) AL	OD (right) SNR	OS (left) AL	OS (left) SNR	OS (left) AL	OS (left) SNR
22.82 mm	3.9			22.64 mm	2.4		
Error				22.72 mm	2.7		
22.88 mm	3.0			> 22.71 mm < 5.0			
> 22.83 mm < 16.0							
22.84 mm	3.4						

average AL: 22.84 mm



average AL: 22.69 mm



corneal curvature values

OD (right)			OS (left)		
R1: 7.85 mm @ 79°	42.99 D		R1: 7.83 mm @ 19°	43.10 D	
R2: 7.83 mm @ 169°	43.10 D		R2: 7.76 mm @ 109°	43.49 D	
ΔD: -0.11 D @ 79°			ΔD: -0.39 D @ 19°		
R1: 7.86 mm @ 179°	42.94 D		R1: 7.79 mm @ 172°	43.32 D	
R2: 7.76 mm @ 89°	43.49 D		R2: 7.75 mm @ 82°	43.55 D	
ΔD: -0.55 D @ 179°			ΔD: -0.23 D @ 172°		
R1: 7.87 mm @ 164°	42.88 D <	○ ×	R1: 7.87 mm @ 68°	42.88 D <	
R2: 7.77 mm @ 74°	43.44 D	○ ○	R2: 7.78 mm @ 158°	43.38 D	
ΔD: -0.56 D @ 164°		○ ○	ΔD: -0.50 D @ 68°		
n: 1.3375			n: 1.3375		

anterior chamber depth values

OD (right)					OS (left)				
2.67 mm	3.42 mm	3.41 mm	3.42 mm	3.42 mm	3.39 mm	3.41 mm	3.41 mm	3.41 mm	3.41 mm
ACD: 3.42 mm					ACD: 3.41 mm				

[redacted]

NAME
APR 24 2007 14:40
FRAME UD=10

<R>	SPH	CYL	AX
	+ 1.25	-0.12	180
	+ 1.37	-0.37	14
	+ 1.50	-0.37	68
	+ 1.37	-0.37	14

<L>	SPH	CYL	AX
	+ 1.12	-0.62	7
	+ 1.25	-0.50	172
	+ 1.25	-0.50	170
	+ 1.25	-0.50	172

PD = 51

Carl Zeiss IOLMaster™ V. 3.01

Printed on: 24-04-2007 at 04:03 PM.

W4KK.

Record Sheet- Aston Eye Study

School Initials: ✓ W4

Consent Form signed: ☐

Name: [redacted] Age: [redacted] Race: [redacted]

	Specs worn? Y / N If yes, complete here first:			
	R ↓	L		
VA:			Vision:	R 6/6 +2 L 6/6 +3
Dist OMB			Dist OMB	✓
Near OMB			Near OMB	✓
Focimetry: R L			Height (m)	128.9.
			Weight (kg)	40.8.

Biometry		*1*	*2*	*3*	*Ave.*
AL	R				
	L				
CR	R H 7.50 @ 1 V 7.33 @ 91				
	L H V				

		1	*2*	*3*	*4*	*5*	*Ave.*
ACD	R						
	L						

Cycloplegia

0.5% proxymetacaine: ☐✓ 1% cyclopentolate: ☐✓ Time: 1.20

Amplitude of Accom

Pre-cyclo: R

L

Time after insertion:

Post-cyclo R

L

Cycloplegia achieved: ☐ ☐ ☐

Cycloplegic autorefraction

R 1 2 3

L 1 2 3

Child Questionnaire completed: ☐

Main questionnaire and drug info sheet handed out ☐

W4KK

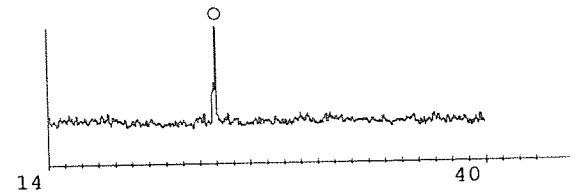
Name: [redacted] Date of Birth: [redacted]

ID: Exam Date: 24-04-2007

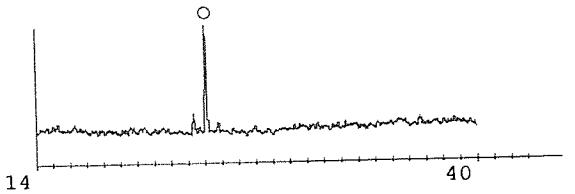
ZEISS

OD (right)		axial length values		OS (left)	
AL	SNR	AL	SNR	AL	SNR
Error				> 22.52 mm	< 4.2
> 22.46 mm	< 3.4			22.49 mm!	1.6
22.45 mm	2.1			22.52 mm	3.4
22.45 mm	2.1			Error	
				22.50 mm	2.0

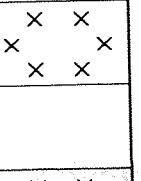
average AL: 22.45 mm



average AL: 22.51 mm



OD (right)		corneal curvature values	OS (left)	
R1: 7.47 mm @ 4°	45.18 D		Error !	
R2: 7.35 mm @ 94°	45.92 D			
ΔD: -0.74 D @ 4°				
R1: 7.46 mm @ 8°	45.24 D		R1: 7.61 mm @ 125°	44.35 D
R2: 7.29 mm @ 98°	46.30 D		R2: 7.39 mm @ 35°	45.67 D
ΔD: -1.06 D @ 8°			ΔD: -1.32 D @ 125°	
R1: 7.45 mm @ 11°	45.30 D <		R1: 7.56 mm @ 172°	44.64 D <
R2: 7.29 mm @ 101°	46.30 D		R2: 7.32 mm @ 82°	46.11 D
ΔD: -1.00 D @ 11°			ΔD: -1.47 D @ 172°	
n: 1.3375			n: 1.3375	



OD (right)					anterior chamber depth values				OS (left)
3.37 mm	3.32 mm	3.37 mm	3.32 mm	3.37 mm	3.44 mm	3.44 mm	3.44 mm	3.46 mm	3.46 mm
ACD: 3.35 mm					ACD: 3.45 mm				

W4KK.

NAME
APR 24 2007 14:34
FRAME UD=10

<R>	SPH	CYL	AX
	- 0.12	0.00	
	+ 0.12	0.00	
	+ 0.12	0.00	
	+ 0.12	0.00	

<L>	SPH	CYL	AX
	+ 0.12	0.00	
	+ 0.25	-0.12	39
	+ 0.25	-0.12	26
	+ 0.25	-0.12	39

PD = 56

Carl Zeiss IOLMaster™ V. 3.01

Printed on: 24-04-2007 at 04:02 PM.

WYMB

Record Sheet- Aston Eye Study

School Initials: WY

Consent Form signed: ☑

Name: [redacted] Age: [redacted] Race: [redacted]

Specs worn? Y / N
If yes, complete here first:

	R	L		R	L
VA:			Vision:	6/6 +1	6/5 -2
Dist OMB			Dist OMB	N9	
Near OMB			Near OMB	N9	
Focimetry: R			Height (m)	115.9	
L			Weight (kg)	17.8	

Biometry

		1	2	3	Ave.
AL	R				
	L	$			
CR	R H				
	V				
	L H	8.39@1, 8.38@3			
	V	8.18@91, 8.22@98			

		1	2	3	4	5	Ave.
ACD	R						
	L						

Cycloplegia
0.5% proxymetacaine: ☑ 1% cyclopentolate: ☑ Time: 1.52

Amplitude of Accom
Pre-cyclo: R
L
Time after insertion: 2:28
Post-cyclo R
L 20
Cycloplegia achieved: ☑ ☐ ☐

Cycloplegic autorefraction

R		L	
	1		1
	2		2
	3		3

Child Questionnaire completed: ☑

Main questionnaire and drug info sheet handed out ☑

APPENDIX WYMB.

Name: [redacted] Date of Birth [redacted]

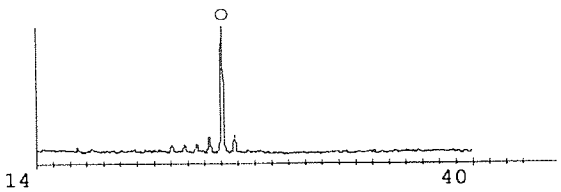
ID: Exam Date: 24-04-2007

ZEISS

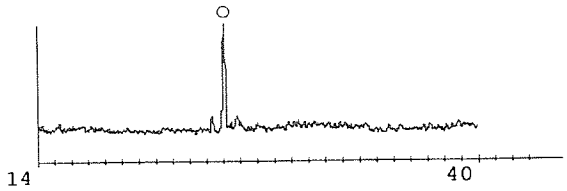
axial length values

OD (right) AL	OD (right) SNR	OS (left) AL	OS (left) SNR
23.52 mm	5.0	23.33 mm	3.8
> 23.49 mm <	11.8	23.53 mm	4.1
23.49 mm	9.5	> 23.48 mm <	4.3
		23.51 mm	2.4

average AL: 23.50 mm



average AL: **Evaluation !**



corneal curvature values

OD (right)			OS (left)		
R1: 8.35 mm @ 179°	40.42 D		Error !		
R2: 8.16 mm @ 89°	41.36 D				
ΔD: -0.94 D @ 179°					
R1: 8.35 mm @ 171°	40.42 D		Error !		× ○ ○ ○ ○ ○
R2: 8.15 mm @ 81°	41.41 D				
ΔD: -0.99 D @ 171°					
R1: 8.37 mm @ 171°	40.32 D <		R1: 8.38 mm @ 2°	40.27 D <	
R2: 8.14 mm @ 81°	41.46 D		R2: 8.16 mm @ 92°	41.36 D	
ΔD: -1.14 D @ 171°			ΔD: -1.09 D @ 2°		
n: 1.3375			n: 1.3375		

anterior chamber depth values

OD (right)					OS (left)				
Error	Error	3.21 mm	3.23 mm	3.23 mm	3.25 mm	3.14 mm	2.93 mm	3.14 mm	3.14 mm
ACD: 3.22 mm					ACD: 3.17 mm				

[redacted]

NAME
APR 24 2007 15:07
FRAME VD=10

<R>	SPH	CYL	AX
	+ 0.62	-0.87	4
	+ 0.87	-0.37	151
	+ 1.00	-0.75	173
	+ 0.87	-0.75	173

<L>	SPH	CYL	AX
	+ 0.37	-0.12	64
	+ 1.37	-0.75	165
	0.00	-0.50	46
	+ 0.37	-0.12	64

PD = 58

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Printed on: 24-04-2007 at 04:23 PM.

APPENDIX 6

ASTON EYE STUDY DATA

CONTENTS

An example of the Stata database used to store and analyse AES measurements is provided.

- Year 8 results (n= 30)
- Year 2 results (n= 30)

ID	DOB	Dostudy	Age yrs	Ethnicity	ethnic1	Gend	Gram	IMD4	IMDhome	Specs	visRE logMAR	visLE logMAR	MeanVA logMAR
BV3DL	30/06/1993	30/06/2006	13.00	White British	White	male	yes	4	7.43	no	0.06	0.04	0.05
BV3DS	01/10/1992	30/06/2006	13.74	Asian Indian	Asian	male	yes	4	15.01	no	-0.14	-0.18	-0.16
BV3DS1	21/10/1992	30/06/2006	13.69	White British	White	male	yes	4	8.07	no	-0.08	1.2	0.56
BV3HU	27/02/1993	30/06/2006	13.34	Asian Indian	Asian	male	yes			no	-0.18	-0.16	-0.17
BV3JK	26/05/1993	30/06/2006	13.10	White British	White	male	yes	4	6.99	no	-0.08	-0.08	-0.08
BV3JK1	29/03/1993	30/06/2006	13.25	White British	White	male	yes	4	9.77	no	-0.06	-0.14	-0.1
BV3JK2	21/02/1993	30/06/2006	13.35	White British	White	male	yes	3	31.52	no	-0.08	-0.08	-0.08
BV3JM	01/08/1993	30/06/2006	12.91	White British	White	male	yes	4	17.09	yes	0.74	0.82	0.78
BV3JY	08/01/1993	30/06/2006	13.47	White British	White	male	yes	4	7.02	no	-0.2	-0.1	-0.15
BV3RW	18/08/1993	30/06/2006	12.87	White British	White	male	yes	4	17.09	no	-0.14	-0.18	-0.16
BV3TG	31/08/1993	30/06/2006	12.83	White British	White	male	yes	4	14.4	no	-0.16	-0.06	-0.11
BV3TJ	15/10/1992	30/06/2006	13.71	White British	White	male	yes	4	12.84	yes	0.22	0.2	0.21
GBAI	21/07/1993	08/03/2006	12.63	Asian Pakistani	Asian	male	no	3	21.89	no	0.2	0.1	0.15
GBCH	26/02/1993	08/03/2006	13.03	White British	White	female	no	3	34.97	yes	0.36	1	0.68
GBJM	20/02/1993	08/03/2006	13.04	White British	White	female	no	3	22.39	no	0	0.1	0.05
GBJM1	28/09/1992	08/03/2006	13.44	White British	White	male	no	3	22.39	yes	0	0.3	0.15
GBJM2	28/09/1992	08/03/2006	13.44	White British	White	female	no	3	22.39	no	-0.04	0	-0.02
GBJW	02/06/1993	08/03/2006	12.76	White British	White	male	no	4	21.46	no	0.02	0.7	0.36
GBKW	03/10/1992	08/03/2006	13.43	White British	White	female	no	3	21.71	no	-0.04	-0.08	-0.06
GBLF	22/02/1992	08/03/2006	14.04	White British	White	female	no	4	20.89	no	0	0	0
GBLH	15/04/1993	08/03/2006	12.90	White British	White	male	no	4	18.13	no	-0.1	-0.06	-0.08
GBLW	09/11/1992	08/03/2006	13.33	White British	White	female	no	2	58.93	yes	0.6	0.9	0.75
GBRD	14/01/1993	08/03/2006	13.14	White British	White	female	no	1	65.03	no	0.08	0.1	0.09
GBRP	28/06/1993	08/03/2006	12.69	Asian Indian	Asian	male	no	4	20.36	no	0.04	0.1	0.07
GBRT	06/12/1992	08/03/2006	13.25	White British	White	female	no	2	51.62	no	0.04	0.04	0.04
GBSB	07/12/1992	08/03/2006	13.25	White British	White	male	no	4	20.72	no	0.08	-0.02	0.03
GBSD	24/03/1993	08/03/2006	12.96	White British	White	male	no	4	18.19	no	0.4	0	0.2
HLAA	13/04/1993	22/03/2006	12.94	Asian Pakistani	Asian	male	no	2	48.37	no	0	0	0
HLAG	30/01/1993	29/03/2006	13.16	Asian Bangladeshi	Asian	male	no	3	45.73	no	0.2	0.08	0.14
HLAH	16/08/1993	22/03/2006	12.60	Black African(Somalian)	Black	female	no	1	64.55	no	-0.16	-0.18	-0.17

distOMBs	nearOMBs	vaRE logMAR	vaLE logMAR	dOMBc	nOMBc	focREsph D	focRECyl D	focREax	focLEsph D	focLECyl D	focLEax	droptime	Height cm	logweight logkg
NMD	NMD											1156	164	4.06
NMD	4SOP											1019	160	3.96
LHyperXOT	LHyperXOT											1028	170.3	4.17
2XOP	2XOP											1200	157	3.83
NMD	6XOP											1005	167.9	4.03
NMD	NMD											1015	166.1	3.90
NMD	NMD											1024	175.2	4.42
NMD	NMD	-0.06	0.04	NMD	NMD	-1.75	-0.25	50	-1.5	-0.25	110	1154	163.8	3.87
NMD	4XOP											1158	167.1	4.01
NMD	6SOP											1152	156.2	3.79
NMD	4XOP											1010	158.7	3.85
NMD	NMD	-0.08	0.06	NMD	NMD	1.5	-2	97	1.5	-1.5	75	1032	188.3	4.33
NMD	NMD											1037	143.5	3.42
20LSOT	20LSOT	0.2	1	10LSOT	10LSOT	4	-0.5	7.5	4.25	-1.5	65	1333	144.5	3.67
NMD	4 XOP											1350	161	4.34
LSOT	LSOT	forgot										1030	156	3.87
NMD	3SOP											1320	152	3.82
NMD	NMD											1022	167.3	4.07
NMD	3SOP											1351	141.5	3.50
NMD	L/R											1321	160	3.93
NMD	NMD											1022	148	3.84
NMD	8SOP	0.1	0.2	NMD	8SOP	-0.5	-0.5	97.5	-1.5	-0.25	90	1345	156	4.01
NMD	NMD											1321	167	4.38
NMD	NMD											1033	148.8	3.52
NMD	5XOP											1325	161	4.00
NMD	NMD											1022	168	4.17
NMD	NMD											1026	165.5	3.97
NMD	NMD											1302	151	4.03
NMD	10XOP											1125	155.8	3.78
NMD	NMD											1322	169.5	3.93

Weight kg	postREamp	postLEamp	REax1 mm	REax2 mm	REax3 mm	REaxAv mm	LEax1 mm	LEax2 mm	LEax3 mm	LEaxAv mm	MeanAL mm	REkH1 mm	REkH1ax mm	REkV1 mm	REkV1ax mm	REkH2 mm
58.2	<2D	<2D	24.11	24.14	24.13	24.13	24.26	24.24	24.25	24.25	24.19	8.34	175	8.25	85	8.35
52.6	<2D	<2D	24.56	24.53	24.52	24.54	24.46	24.49	24.44	24.46	24.5	8.16	16	8.02	106	8.14
64.6	<2D	<2D	24.24	24.26	24.25	24.25	23.67	23.59	23.43	23.59	23.92	8	169	7.96	79	8
46	<2D	<2D	23.5	23.49	23.52	23.5	23.41	23.41	23.41	23.41	23.455	7.84	168	7.69	78	7.85
56	<2D	<2D	22.91	22.88	22.9	22.9	22.8	22.81	22.81	22.81	22.855	7.89	2	7.73	92	7.89
49.6	<2D	<2D	23.44	23.48	23.47	23.46	23.65	23.65	23.67	23.66	23.56	8.09	40	7.92	130	8.1
82.8	<2D	<2D	24.23	24.23	24.26	24.24	24.18	24.2	24.21	24.2	24.22	8.03	2	7.93	92	8.03
48	<2D	<2D	25.24	25.18	25.2	25.21	25.04	25.05	25.07	25.05	25.13	8.05	13	7.96	103	8.1
55.2	<2D	<2D	23.22	23.19	23.22	23.21	23.23	23.24	23.22	23.23	23.22	7.79	176	7.67	86	7.81
44.2	<2D	<2D	23.52	23.49	23.53	23.51	23.49	23.46	23.4	23.44	23.475	8.22	18	8.09	108	8.3
47.2	<2D	<2D	23.73	23.76	23.73	23.74	23.67	23.7	23.71	23.7	23.72	8.12	27	8.05	117	8.1
75.6	<2D	<2D	24.1	24.12	24.12	24.11	23.87	23.86	23.86	23.86	23.985	8.6	94	8.23	4	8.6
30.5	<2D	<2D	24.19	24.16	24.17	24.17	24.08	24.1	24.1	24.09	24.13	7.97	145	7.9	55	8
39.2	<2D	<2D	20.55	20.55	20.58	20.56	19.66	19.62	19.61	19.63	20.095	7.63	16	7.19	106	7.63
76.4	<2D	<2D	22.08	22.07	21.99	22.05	22.12	22	22.07	22.07	22.06	7.93	7	7.87	97	7.96
48	<2D	<2D	22.37	22.4	22.42	22.4	22.39	22.37	22.38	22.38	22.39	7.47	19	7.33	109	7.49
45.7	<2D	<2D	21.88	21.89	21.9	21.89	22.2	22.17	22.16	22.18	22.035	7.28	16	7.21	106	7.29
58.6	<2D	<2D	23.35	23.33	23.34	23.34	23.93	23.91	23.86	23.9	23.62	7.69	8	7.54	98	7.7
33	<2D	<2D	22.76	22.78	22.76	22.77	22.8	22.79		22.79	22.78	7.75	8	7.54	98	7.74
50.7	<2D	<2D	22.78	22.77	22.83	22.79	22.64	22.67	22.69	22.67	22.73	8	11	7.87	101	8
46.6	<2D	<2D	22.84	22.82	22.84	22.83	22.56	22.59	22.57	22.57	22.7	7.6	59	7.55	149	
55.2	<2D	<2D	23.73	23.74	23.73	23.74	24.01	23.99	24	24	23.87	7.68	157	7.51	67	7.71
79.6	<2D	<2D	23.4	23.41	23.41	23.41	23.4	23.42	23.41	23.41	23.41	7.96	1	7.81	91	7.96
33.8	<2D	<2D	22.28	22.26	22.24	22.26	22.08	22.1	22.1	22.09	22.175	7.24	3	7.13	93	7.2
54.5	<2D	<2D	24.12	24.07	24.09	24.1	24.08	24.08	24.09	24.08	24.09	7.9	17	7.84	107	7.9
64.5	<2D	<2D	23.16	23.14	23.13	23.14	23.3	23.28	23.33	23.3	23.22	7.85	58	7.75	148	7.82
53	<2D	<2D	24.64	24.63	24.65	24.64	24.65	24.65	24.61	24.64	24.64	8.31	26	8.25	116	8.34
56	<2D	<2D	22.27	22.26	22.26	22.26	22.34	22.35	22.34	22.34	22.3	7.42	164	7.47	74	7.45
44	<2D	<2D	24.42	24.41	24.39	24.41	24.4	24.38	24.42	24.4	24.405	7.95	103	7.92	13	7.95
50.8	<2D	<2D	23.72	23.73	23.71	23.72	23.76	23.77	23.77	23.77	23.745	8.01	2	7.83	92	8.02

REkH2ax mm	REkV2 mm	REkV2ax mm	REkH3 mm	REkH3ax mm	REkV3 mm	REkV3ax mm	AvREkH mm	AvREkV mm	REmeanK mm	LEkH1 mm	LEkH1ax mm	LEkV1 mm	LEkV1ax mm	LEkH2 mm	LEkH2ax mm
178	8.25	88	8.34	179	8.24	89	8.34	8.25	8.30	8.41	158	8.35	68	8.42	161
180	7.97	90					8.15	8.00	8.07	8.15	174	8.03	84	8.16	180
17	7.96	107	7.99	157	7.95	67	8.00	7.96	7.98	8.22	13	8.1	103	8.22	8
168	7.7	78	7.85	169	7.7	79	7.85	7.70	7.77	7.81	174	7.71	84	7.81	177
178	7.73	88	7.89	178	7.72	88	7.89	7.73	7.81	7.84	171	7.66	81	7.84	176
32	7.93	122	8.08	32	7.95	122	8.09	7.93	8.01	8.14	164	8.02	74	8.15	156
177	7.93	87	8.03	2	7.94	92	8.03	7.93	7.98	8.04	155	8	65	8.03	114
10	7.96	100	8.11	9	7.95	99	8.09	7.96	8.02	8.07	155	7.93	65	8.07	153
1	7.68	91	7.79	172	7.68	82	7.80	7.68	7.74	7.78	11	7.7	101	7.8	9
174	8.17	84	8.27	171	8.1	81	8.26	8.12	8.19	8.22	13	8.06	103	8.21	6
9	8.06	99	8.12	18	8.08	108	8.11	8.06	8.09	8.13	152	8.05	62	8.11	158
84	8.27	174	8.6	92	8.24	2	8.60	8.25	8.42	8.64	84	8.27	174	8.59	87
145	7.88	55	7.97	156	7.81	66	7.98	7.86	7.92	7.97	131	7.9	41	7.97	127
13	7.19	103					7.63	7.19	7.41	7.61	174	7.18	84	7.6	176
14	7.87	104	7.94	4	7.87	94	7.94	7.87	7.91	7.91	150	7.88	60	7.93	173
17	7.33	107	7.47	12	7.31	102	7.48	7.32	7.40	7.42	162	7.37	72	7.4	179
5	7.2	95	7.28	1	7.22	91	7.28	7.21	7.25	7.36	154	7.29	64	7.36	154
6	7.54	96	7.68	6	7.55	96	7.69	7.54	7.62	7.77	171	7.55	81	7.78	169
6	7.52	96	7.75	4	7.44	94	7.75	7.50	7.62	7.79	175	7.54	85	7.8	176
11	7.86	101	8	10	7.84	100	8.00	7.86	7.93	7.97	160	7.82	70	8	157
							7.60	7.55	7.58	7.52	9	7.47	99	7.5	5
169	7.55	79	7.7	167	7.59	77	7.70	7.55	7.62	7.56	6	7.59	96	7.61	176
172	7.79	82	7.93	7	7.79	97	7.95	7.80	7.87	7.96	178	7.78	88	7.97	173
14	7.15	104	7.27	6	7.22	96	7.24	7.17	7.20	7.23	4	7.09	94	7.2	176
21	7.83	111	7.88	24	7.84	114	7.89	7.84	7.87	7.9	157	7.75	67	7.92	157
52	7.74	142	7.78	29	7.75	119	7.82	7.75	7.78	7.84	150	7.78	60	7.82	137
44	8.26	134	8.33	37	8.27	127	8.33	8.26	8.29	8.31	165	8.27	75	8.29	166
45	7.43	135	7.45	38	7.41	128	7.44	7.44	7.44	7.49	163	7.4	73	7.48	170
114	7.93	24	7.95	117	7.92	27	7.95	7.92	7.94	7.96	156	8	66	7.95	162
2	7.82	92	8.02	2	7.83	92	8.02	7.83	7.92	8	174	7.79	84	8.01	172

Working database of Year 8 children (n=30)

LEkV2 mm	LEkV2ax mm	LEkH3 mm	LEkH3ax mm	LEkV3 mm	LEkV3ax mm	AvLEkH mm	AvLEkV mm	LEmeanK mm	MeanK mm	REacd1 mm	REacd2 mm	REacd3 mm	REacd4 mm	REacd5 mm
8.34	71	8.4	165	8.36	75	8.41	8.35	8.38	8.34	3.65	3.67	3.65	3.65	3.65
8.01	90	8.16	176	8.02	86	8.16	8.02	8.09	8.08	3.61	3.62	3.64	3.64	3.64
8.07	98	8.24	3	8.05	93	8.23	8.07	8.15	8.06	3.71	3.71	3.71	3.71	3.72
7.69	87	7.83	173	7.69	83	7.82	7.70	7.76	7.76	3.7	3.63	3.63	3.63	3.63
7.67	86	7.83	171	7.66	81	7.84	7.66	7.75	7.78	3.7	3.68	3.7	3.68	3.68
8.02	66	8.13	160	8.03	70	8.14	8.02	8.08	8.05	3.71	3.71	3.71	3.71	3.71
8	24	8.03	115	8	25	8.03	8.00	8.02	8.00	3.78	3.78	3.79	3.78	3.78
7.93	63	8.08	154	7.93	64	8.07	7.93	8.00	8.01	4.07	4.08	4.08	4.08	4.08
7.69	99	7.81	12	7.69	102	7.80	7.69	7.75	7.74	3.58	3.59	3.59	3.59	3.58
7.98	96	8.21	3	7.99	93	8.21	8.01	8.11	8.15	3.44	3.42	3.42	3.42	3.42
8.04	68	8.11	148	8.04	58	8.12	8.04	8.08	8.08	3.5	3.5	3.5	3.5	3.5
8.27	177	8.59	87	8.28	177	8.61	8.27	8.44	8.43	3.81	3.81	3.81	3.81	3.81
7.9	37	8	137	7.85	47	7.98	7.88	7.93	7.93	3.92	3.92	3.92	3.92	3.92
7.17	86					7.61	7.18	7.39	7.40	3.08	3.08	3.08	3.08	3.08
7.88	83	7.91	126	7.87	36	7.92	7.88	7.90	7.90	3.62	3.6	3.57	3.58	3.58
7.36	89	7.39	161	7.35	71	7.40	7.36	7.38	7.39	3.47	3.47	3.51	3.49	3.47
7.26	64	7.35	156	7.26	66	7.36	7.27	7.31	7.28	3.5	3.48	3.5	3.48	3.48
7.49	79	7.77	173	7.55	83	7.77	7.53	7.65	7.63	3.88	3.86	3.86	3.86	3.86
7.55	86	7.79	175	7.55	85	7.79	7.55	7.67	7.65	3.84	3.82	3.82	3.82	3.84
7.75	67	8.01	154	7.74	64	7.99	7.77	7.88	7.91	3.38	3.39	3.38	3.38	3.38
7.44	95					7.51	7.46	7.48	7.53	3.64	3.64	3.64		
7.54	86	7.65	174	7.52	84	7.61	7.55	7.58	7.60	3.96	3.95	3.96	3.96	3.95
7.8	83	7.95	172	7.79	82	7.96	7.79	7.88	7.87	3.56	3.56	3.56	3.56	3.56
7.1	86	7.2	178	7.09	88	7.21	7.09	7.15	7.18	3.84	3.84	3.84	3.86	3.84
7.73	67	7.9	157	7.79	67	7.91	7.76	7.83	7.85	4.13	4.13	4.13	4.13	4.13
7.78	47	7.84	131	7.76	41	7.83	7.77	7.80	7.79	3.61	3.61	3.61	3.61	3.61
8.26	76	8.29	149	8.26	59	8.30	8.26	8.28	8.29	3.65	3.67	3.67	3.65	3.67
7.4	80					7.49	7.40	7.44	7.44	3.68	3.66	3.66	3.66	3.66
8.01	66					7.96	8.01	7.98	7.96	3.91	3.89	3.89	3.91	3.89
7.81	82	8	178	7.82	88	8.00	7.81	7.91	7.91	3.79	3.79	3.79	3.79	3.79

REacdAv mm	LEacd1 mm	LEacd2 mm	LEacd3 mm	LEacd4 mm	LEacd5 mm	LEacdAv mm	newACD mm	MeanACD mm	REsph1 D	REcyl1 D	REaxis1	REsph2 D	REcyl2 D	REaxis2
3.65	3.67	3.67	3.67	3.67	3.67	3.67	3.66	3.66	0.62	-0.37	34	0.75	-0.25	16
3.63	3.61	3.61	3.61	3.61	3.62	3.61	3.62	3.62	-0.25	-0.37	51	0.12	-0.75	38
3.71	3.78	3.8	3.8	3.78	3.77	3.79	3.75	3.75	0.5	-0.87	54	0.37	-0.62	50
3.64	3.56	3.56	3.56	3.56	3.56	3.56	3.6	3.6	-0.37	0	0	-0.25	0	0
3.69	3.71	3.7	3.71	3.7	3.71	3.71	3.7	3.7	0.87	-0.37	176	0.87	0	0
3.71	3.64	3.64	3.64	3.64	3.66	3.64	3.675	3.675	1.37	-1.5	54	1.75	-1.75	49
3.78	3.78	3.78	3.76	3.76	2.71	3.77	3.775	3.775	0.12	-0.5	64	0.25	-0.12	45
4.08	4	4	4	3.98	3.98	3.99	4.035	4.035	-1.5	-1.62	41	-1.37	-0.75	49
3.59	3.63	3.63	3.64	3.63	3.64	3.63	3.61	3.61	0.37	-0.62	61	0.25	-0.25	74
3.42	3.38	3.38	3.38	3.38	3.38	3.38	3.4	3.4	1.5	-0.5	122	1.37	-0.5	84
3.5	3.45	3.45	3.45	3.47	3.45	3.45	3.475	3.475	1.12	-0.62	115	1.25	-0.75	76
3.81	3.74	3.76	3.76	3.74	3.76	3.75	3.78	3.78	2	-2.37	99	2.25	-2.5	101
3.92	3.91	3.93	3.93	3.93	3.93	3.93	3.925	3.925	0	-0.75	117	0.12	-0.62	116
3.08	3.09	3.11	3.11	3.11	3.01	3.09	3.085	3.085	4.62	-1.5	14	4.87	-1.37	13
3.59	3.62	3.6	3.62	3.6	3.6	3.61	3.6	3.6	1	-0.37	122	0.87	0	0
3.48	3.47	3.47	3.46	3.47	3.47	3.47	3.475	3.475	0.5	-1.25	177	1	-1.25	3
3.49	3.54	3.52	3.52	3.52	3.54	3.53	3.51	3.51	1.5	-0.62	103	1.37	-0.25	99
3.86	3.9	3.9	3.9	3.91	3.91	3.9	3.88	3.88	-0.25	-0.37	35	-0.25	-0.25	26
3.83	3.78	3.78	3.78	3.78	3.78	3.78	3.805	3.805	1.5	-1	54	1.37	-0.37	65
3.38	3.37	3.37	3.39	3.39	3.39	3.38	3.38	3.38	1.12	-0.12	124	1.75	-0.87	26
3.64	3.73	3.73	3.73	3.72	3.72	3.73	3.685	3.685	2.12	-2.87	72	1.5	-2.5	54
3.96	3.98	3.98	3.98	3.96	3.94	3.97	3.965	3.965	-0.87	-0.25	111	-0.75	-0.37	111
3.56	3.58	3.58	3.58	3.58	3.58	3.58	3.57	3.57	0.25	-0.5	136	0.25	-0.37	159
3.84	3.87	3.85	3.87	3.87	3.87	3.87	3.855	3.855	-0.12	0	0	0.12	-0.37	82
4.13	4.06	4.06	4.06	4.06	4.06	4.06	4.095	4.095	0	-0.12	173	0.25	-0.37	177
3.61	3.63	3.63	3.61	3.61	3.61	3.62	3.615	3.615	0.87	-1	64	1	-1	133
3.66	3.62	3.63	3.63	3.63	3.62	3.63	3.645	3.645	0.87	-0.62	67	1	-0.5	72
3.66	3.54	3.54	3.56	3.54	3.54	3.54	3.6	3.6	1	0	0	1	0	0
3.9	3.86	3.86	3.86	3.84	3.84	3.85	3.875	3.875	-0.75	-0.25	82	-0.62	-0.12	96
3.79	3.84	3.84	3.84	3.84	3.84	3.84	3.815	3.815	0.12	0	0	0.62	-0.87	135

REsph3 D	REcyl3 D	REaxis3	REsphAv D	RECylAv D	REaxisAv	REmeanSER D	LEsph1 D	LEcyl1 D	LEaxis1	LEsph2 D	LEcyl2 D	LEaxis2	LEsph3 D	LEcyl3 D
0.5	0	0	0.75	-0.25	16	0.52	1	-0.62	162	1.25	-0.75	4	0.87	-0.5
0.12	-1	41	0.12	-0.75	38	-0.36	0.12	-1.12	43	0.12	-1	51	-0.25	0
0.37	-0.62	58	0.37	-0.62	50	0.06	3	-2	43	2.62	-1.25	-52	2.75	-1.25
-0.25	0	0	-0.25	0	0	-0.29	0.62	-0.5	49	0.75	-0.62	31	0.75	-0.62
1.12	0	0	1.12	0	0	0.89	1.62	-1	8	1.62	-0.62	175	1.75	-0.75
1.37	-1.25	51	1.37	-1.5	54	0.75	0.75	-0.5	38	0.62	0	0	0.87	-0.37
0.25	-0.5	48	0.25	-0.5	48	0.02	0.87	-0.75	18	0.75	-0.37	11	1.25	-0.87
-1	-1.12	48	-1.37	-1.12	48	-1.87	-1.25	-0.75	160	-1.5	-0.5	160	-1.62	0
0.25	-0.37	60	0.25	-0.37	60	0.08	0.12	0	0	0.62	-0.12	29	0.62	-0.12
1.37	-0.37	164	1.5	-0.37	164	1.19	1.5	-0.37	47	1.75	-0.5	49	1.75	-0.75
1.25	-0.5	97	1.25	-0.5	97	0.90	1	-0.87	76	1.12	-0.37	55	1	0
2.25	-2.37	99	2.25	-2.37	99	0.96	3.5	-2.37	74	3.62	-2.62	75	3.87	-2.87
0.12	-0.5	123	0.12	-0.62	116	-0.23	0.12	-1	94	0.25	-1.12	95	0.25	-1.25
5.25	-1.87	19	4.87	-1.5	14	4.12	8.12	-1.62	17	8.25	-2.37	167	8.87	-2
1	-0.37	101	1	-0.37	122	0.83	1.5	-0.87	62	1.62	-0.5	92	1.62	-0.5
0.75	-1.25	20	0.75	-1.25	3	0.13	1.25	-0.5	44	0.62	-0.62	98	1.12	-0.25
1.5	-0.5	69	1.5	-0.5	69	1.23	1.5	-0.87	109	1.62	-0.62	85	1.5	-0.37
0	-0.62	38	-0.25	-0.37	35	-0.37	-2.75	-0.75	158	-2.25	-1.12	170	-2.25	-1
1.37	-0.25	46	1.37	-0.37	65	1.14	1.37	-0.37	54	1.37	-0.5	28	1.12	0
1.25	-0.12	135	1.25	-0.12	124	1.19	1.37	-0.37	59	1.5	-0.62	143	1.62	-0.75
1.75	-2.25	62	1.75	-2.25	62	0.52	2	-1.12	28	3	-1.62	11	1.87	-1.12
-1	0	0	-0.87	-0.25	111	-0.98	-1.75	-0.5	172	-1.75	-0.37	4	-1.87	0
0.37	-0.5	144	0.25	-0.5	144	0.06	1	-1.25	162	1	-1.37	30	1	-1.25
			0	0	0	-0.09	0.12	-0.37	23	0.5	-0.5	58	0.25	0
0.25	-0.25	159	0.25	-0.25	159	0.04	0.37	-0.62	136	0.37	-0.37	5	0.37	-0.37
0.75	-0.5	94	0.87	-0.5	94	0.46	1.12	-0.75	106	0.62	-0.87	78	0.87	-0.62
0.87	-0.5	80	0.87	-0.5	72	0.64	1.12	-0.87	130	2	-2.87	140	1.25	-0.87
1	0	0	1	0	0	1.00	0.87	-0.25	20	0.87	0	0	0.87	-0.12
-0.5	-0.37	100	-0.62	-0.25	82	-0.75	-0.37	-0.5	95	-0.37	-0.37	78	-0.37	-0.37
0.25	-0.25	131	0.25	-0.25	131	0.14	0.75	-1.25	124	0.37	0	0	0.62	-0.25

Working database of Year 8 children (n=30)

LEaxis3	LEsphAv D	LEcylAv D	LEaxisAv	LEmeanSER D	MeanSER D	refgp	bilatrefgp	myopia	hyperopia	Astig	cluster	myopeuncorrect
4	1	-0.5	4	0.73	0.62	Emmetrope	Emmetrope	nonmyope	nonhypero	0	0	0
0	-0.12	-1	51	-0.36	-0.36	Emmetrope	Emmetrope	nonmyope	nonhypero	0	0	0
50	2.75	-1.25	50	2.04	1.05	Hyperope	Emmetrope	nonmyope	hyperope	1	0	0
31	0.75	-0.62	31	0.42	0.06	Emmetrope	Emmetrope	nonmyope	nonhypero	0	0	0
176	1.62	-0.75	176	1.27	1.08	Emmetrope	Emmetrope	nonmyope	nonhypero	0	0	0
40	0.75	-0.37	40	0.60	0.67	Emmetrope	Emmetrope	nonmyope	nonhypero	0	0	0
18	0.87	-0.75	18	0.63	0.32	Emmetrope	Emmetrope	nonmyope	nonhypero	1	0	0
0	-1.5	-0.5	160	-1.67	-1.77	Myope	Myope	myope	nonhypero	0	0	0
84	0.62	0	0	0.41	0.25	Emmetrope	Emmetrope	nonmyope	nonhypero	1	0	0
26	1.75	-0.5	49	1.40	1.29	Emmetrope	Emmetrope	nonmyope	nonhypero	0	0	0
0	1	-0.37	55	0.83	0.86	Emmetrope	Emmetrope	nonmyope	nonhypero	0	0	0
73	3.62	-2.62	75	2.35	1.66	Hyperope	Emmetrope	nonmyope	hyperope	1	0	0
93	0.25	-1.12	95	-0.36	-0.29	Emmetrope	Emmetrope	nonmyope	nonhypero	1	0	0
167	8.25	-2	167	7.42	5.77	Hyperope	Hyperope	nonmyope	hyperope	1	1	0
90	1.62	-0.5	90	1.27	1.05	Emmetrope	Emmetrope	nonmyope	nonhypero	0	1	0
164	1.12	-0.25	164	0.77	0.45	Emmetrope	Emmetrope	nonmyope	nonhypero	1	1	0
71	1.5	-0.62	85	1.23	1.23	Emmetrope	Emmetrope	nonmyope	nonhypero	0	1	0
170	-2.25	-1	170	-2.90	-1.63	Myope	Emmetrope	myope	nonhypero	0	1	1
0	1.37	-0.5	28	1.14	1.14	Emmetrope	Emmetrope	nonmyope	nonhypero	0	1	0
146	1.62	-0.75	146	1.21	1.20	Emmetrope	Emmetrope	nonmyope	nonhypero	0	1	0
5	2	-1.12	5	1.65	1.08	Emmetrope	Emmetrope	nonmyope	nonhypero	1	1	0
0	-1.75	-0.37	4	-1.94	-1.46	Myope	Myope	myope	nonhypero	0	1	0
17	1	-1.25	17	0.36	0.21	Emmetrope	Emmetrope	nonmyope	nonhypero	1	1	0
0	0.5	-0.5	58	0.15	0.03	Emmetrope	Emmetrope	nonmyope	nonhypero	0	1	0
24	0.37	-0.37	5	0.14	0.09	Emmetrope	Emmetrope	nonmyope	nonhypero	0	1	0
110	0.87	-0.75	106	0.50	0.48	Emmetrope	Emmetrope	nonmyope	nonhypero	0	1	0
130	1.25	-0.87	130	0.69	0.67	Emmetrope	Emmetrope	nonmyope	nonhypero	1	1	0
167	0.87	-0.12	167	0.81	0.90	Emmetrope	Emmetrope	nonmyope	nonhypero	0	2	0
92	-0.37	-0.37	92	-0.58	-0.66	Myope	Myope	myope	nonhypero	0	2	1
118	0.62	-0.25	118	0.33	0.24	Emmetrope	Emmetrope	nonmyope	nonhypero	0	2	0

Working database of Year 8 children (n=30)

hyperuncorrect	ametropeuncorrect	ALCR
0	0	2.90
0	0	3.03
1	1	2.97
0	0	3.02
0	0	2.94
0	0	2.93
0	0	3.03
0	0	3.14
0	0	3.00
0	0	2.88
0	0	2.93
0	0	2.84
0	0	3.04
0	0	2.72
0	0	2.79
0	0	3.03
0	0	3.03
0	1	3.09
0	0	2.98
0	0	2.88
0	0	3.02
0	0	3.14
0	0	2.97
0	0	3.09
0	0	3.07
0	0	2.98
0	0	2.97
0	0	3.00
0	1	3.07
0	0	3.00

ID	DOB	DoStudy	Age yrs	presumethnic	ethnic1	Gend	Specs	IMD4	IMDhome	visRE logMAR	visLE logMAR	meanVA logMAR	distOMBs	nearOMBs
PHRS	07/09/1999	14/03/2007	7.52	indian	Asian	male	false			-0.04	-0.04	-0.04	NMD	NMD
PHSB	26/07/2000	14/03/2007	6.63	pakistan	Asian	female	false	2	53.42	-0.02	-0.04	-0.03	NMD	NMD
PHSH	11/02/2000	14/03/2007	7.09	white	White	male	false	2	46.78	0.06	-0.04	0.01	NMD	NMD
SCKP	16/04/2000	07/03/2007	6.89	white	White	male	false	3	28.73	0.04	0.06	0.05	NMD	NMD
SCSI	22/12/1999	07/03/2007	7.21	pakistan	Asian	female	false			-0.18	-0.12	-0.15	NMD	NMD
SCSN	03/09/1999	07/03/2007	7.51	white	White	female	false	4	20.4	0.04	0	0.02	NMD	NMD
SCSW	17/11/1999	07/03/2007	7.30	white	White	female	false	4	20.45	0.04	0.04	0.04	NMD	4XOP
SFAE	01/01/2000	18/04/2007	7.29	black african	Black	male	false	1	67.96	-0.06	-0.1	-0.08	NMD	NMD
SFAK	24/01/2000	18/04/2007	7.23	pakistan	Asian	male	false	3	45.81	-0.04	0.24	0.1	NMD	4XOP
SFAN	26/05/2000	18/04/2007	6.89	pakistan	Asian	male	false	3	41.45	-0.04	-0.02	-0.03	NMD	NMD
SFAS	01/04/2000	18/04/2007	7.04	pakistan	Asian	female	false	3	45.81	-0.04	-0.02	-0.03	NMD	NMD
SFCJ	27/01/2000	18/04/2007	7.22	mixed	Mixed	female	false	2	54.85	0.06	0.04	0.05	NMD	NMD
SFGM	18/09/1999	18/04/2007	7.58	white	White	female	false	3	41.45	-0.1	-0.1	-0.1	NMD	NMD
SFHK	26/12/1999	18/04/2007	7.31	pakistan	Asian	male	false	3	45.81	-0.04	-0.04	-0.04	NMD	4XOP
SFHQ	22/12/1999	18/04/2007	7.32	pakistan	Asian	male	false	2	46.48	0.26	0.2	0.23	NMD	NMD
SFMS	16/09/1999	18/04/2007	7.59	black african	Black	male	false	2	50.63	-0.02	-0.02	-0.02	NMD	4XOP
SFND	04/01/2000	18/04/2007	7.29	white	White	male	false	3	33.12	-0.02	0.1	0.04	NMD	6XOP
SFNK	19/01/2000	18/04/2007	7.24	pakistan	Asian	female	true	3	41.45	1.1	1.1	1.1	NMD	10XOP
SFNM	28/11/1999	18/04/2007	7.39	pakistan	Asian	male	false	3	41.45	-0.06	-0.06	-0.06	NMD	NMD
SMAG	06/01/2000	02/03/2007	7.15	mixed	Mixed	female	false	3	39.53	-0.1	-0.06	-0.08	NMD	NMD
SMAP	03/10/1999	02/03/2007	7.41	white	White	female	true	4	17.09	0.2	0.44	0.32	NMD	NMD
SMAS	31/03/2000	01/03/2007	6.92	white	White	male	false	3	44.46	0.2	0.12	0.16	NMD	NMD
SMBJ	04/05/2000	01/03/2007	6.82	white	White	male	false	1	68.16	-0.04	0	-0.02	NMD	NMD
SMCC	13/10/1999	01/03/2007	7.38	white	White	female	false	2	50.25	0.2	0	0.1		
SMCC1	17/08/2000	01/03/2007	6.54	white	White	female	false	3	41.32	0	0	0	NMD	4XOP
SMCC2	23/02/2000	02/03/2007	7.02	white	White	male	false	3	39.53	0	-0.02	-0.01	NMD	4SOP
SMCD	17/09/1999	02/03/2007	7.46	white	White	male	false	3	34.97	0.1	0.06	0.08	NMD	4XOP
SMCE	06/11/1999	02/03/2007	7.32	white	White	female	false	3	45.19	-0.04	0.02	-0.01	NMD	NMD
SMCJ	12/05/2000	02/03/2007	6.80	white	White	female	false	3	41.32	-0.08	0.02	-0.03	NMD	NMD
SMCM	15/08/2000	01/03/2007	6.54	white	White	male	false	3	33.63	-0.02	-0.02	-0.02	NMD	NMD

vaRE logMAR	vaLE logMAR	dOMBc	nOMBc	focREsph D	focREcyl D	focREax	focLEsph D	focLEcyl D	focLEaxis	droptime	Height cm	Weight kg	Recipweight 1/kg	postREamp
										11:04	129.1	23.8	0.0420168	<2D
										11:00	116.6	23.4	0.042735	<2D
										10:18				<2D
										10:06	117.2	21.6	0.0462963	<2D
										10:00	118.4	22	0.0454545	<2D
										10:10	133.4	36.8	0.0271739	<2D
										10:15	123	33.2	0.0301205	<2D
										11:11	120	22.2	0.045045	<2D
										11:50	116.8	19.8	0.0505051	<2D
										11:12	118.9	27.8	0.0359712	<2D
										10:35	125.2	24.4	0.0409836	<2D
										10:40	125.2	28.8	0.0347222	<2D
										11:13	113.6	20.6	0.0485437	<2D
										11:25	126.4	30.8	0.0324675	<2D
										11:44	127.8	29.4	0.0340136	<2D
										11:42	136.6	27.8	0.0359712	<2D
										10:37	113.4	20.2	0.0495049	<2D
0.16	0.16	NMD	6SOP	-8.25	-2.25	20	-7.5	-2.5	165	11:00	110	17.8	0.0561798	<2D
										11:15	120.6	23.6	0.0423729	<2D
										13:30	133	37.8	0.026455	<2D
0.06	0.2	NMD	NMD	1	-1	12	1.5	-1.5	170	11:15	125.5	23.4	0.042735	<2D
										13:25	130	26.6	0.037594	<2D
											117	20.4	0.0490196	<2D
										10:25	132	40.6	0.0246305	<2D
										10:58	122	32.8	0.0304878	<2D
										11:17	123	21.8	0.0458716	<2D
										10:10	129	24.4	0.0409836	<2D
										10:15	135.3	39.8	0.0251256	<2D
										13:25	124.9	35.8	0.027933	<2D
										11:08	117	23.6	0.0423729	<2D

postLEamp	REax1 mm	REax2 mm	REax3 mm	REaxAv mm	LEax1 mm	LEax2 mm	LEax3 mm	LEaxAv mm	MeanAL mm	REkH1 mm	REkH1ax mm	REkV1 mm	REkV1ax mm	REkH2 mm	REkH2ax mm	REkV2 mm
<2D	23.04	23.03	22.99	23.02	22.9	22.89	22.9	22.9	22.96	7.69	171	7.55	81	7.67	118	7.59
<2D	22.42	22.49	22.48	22.46	22.46	22.43		22.45	22.455	7.71	3	7.54	93	7.72	5	7.55
<2D	21.8	21.77	21.79	21.79	21.86	21.82	21.86	21.85	21.82	7.77	93	7.67	3	7.75	91	7.67
<2D	23.61	23.62	23.63	23.62	23.6	23.56	23.58	23.58	23.6	7.9	43	7.85	133	7.92	137	7.86
<2D	22.74	22.74	22.75	22.74	22.64	22.61	22.65	22.63	22.685	7.89	173	7.83	83	7.94	179	7.78
<2D	22.91	22.89	22.89	22.9	22.77	22.78		22.77	22.835	8.04	179	7.88	89	8.01	4	7.88
<2D	23.03	23.02	22.99	23.01	23.08	23.05	23.04	23.06	23.035	7.85	3	7.65	93	7.87	176	7.67
<2D	22.11	22.09	22.08	22.09	22.11	22.1	22.1	22.1	22.095	7.59	15	7.5	105	7.6	173	7.53
<2D	22.78	22.78	22.76	22.77	22.21	22.2	22.24	22.22	22.495	7.95	159	7.81	69	7.98	176	7.87
<2D	23.46	23.42	23.48	23.45	23.4	23.38	23.41	23.4	23.425	8.23	2	8.1	92	8.23	169	8.12
<2D	23.21	23.21	23.23	23.21	23.14	23.16	23.21	23.17	23.19	7.78	160	7.74	70	7.8	11	7.72
<2D	20.73	20.69	20.71	20.7	20.71	20.74	20.71	20.72	20.71	7.41	7	7.14	97	7.39	5	7.16
<2D	22	22.02	22.02	22.01	22.1	22.08	22.03	22.07	22.04	7.76	170	7.68	80	7.75	173	7.66
<2D	22.9	22.93	22.88	22.9	22.8	22.81	22.8	22.8	22.85	7.81	180	7.69	90	7.84	164	7.66
<2D	23.87	23.86	23.93	23.89	23.82	23.78	23.82	23.81	23.85	7.69	165	7.61	75	7.69	16	7.61
<2D	23.09	23.11	23.06	23.09	22.99	22.96	22.99	22.98	23.035	7.91	170	7.79	80	7.84	23	7.75
<2D	22.69	22.69	22.72	22.7	22.52	22.53	22.51	22.52	22.61	8.11	15	7.96	105	8.08	39	8.02
<2D	24.11	24.08		24.1	24.09	24.08	24.14	24.1	24.1	7.46	9	7.07	99	7.43	10	7.02
<2D	22.57	22.57	22.57	22.57	22.54	22.48	22.49	22.5	22.535	7.88	176	7.73	86	7.87	3	7.72
<2D	22.99	22.99	22.99	22.99	23.08	23.14	23.04	23.08	23.035	8.15	12	7.92	102	8.14	19	7.99
<2D	22.13	22.14	22.12	22.13	22.15	22.19		22.17	22.15	7.64	180	7.33	90	7.62	6	7.33
<2D	22.8	22.85	22.82	22.82	22.78	22.75	22.77	22.77	22.795	7.53	28	7.17	118	7.47	20	7.24
<2D	22.17	22.18	22.18	22.18	22.28	22.3		22.29	22.235	7.6	159	7.53	69	7.56	169	7.47
<2D	21.77	21.79	21.77	21.78	21.73	21.73	21.73	21.73	21.755	7.72	177	7.65	87	7.72	17	7.61
<2D	22.57	22.58	22.58	22.58	22.68	22.67	22.66	22.67	22.625	8.03	1	7.7	91	7.98	5	7.72
<2D	23.68	23.65	23.63	23.65	23.6	23.7	23.65	23.65	23.65	8.36	12	8.27	102	8.38	178	8.2
<2D	22.66	22.64	22.65	22.65	22.58	22.61	22.63	22.61	22.63	7.83	17	7.64	107	7.81	75	7.79
<2D	23.57	23.62	23.55	23.57	23.63	23.63		23.63	23.6	7.99	1	7.66	91	7.96	179	7.66
<2D	23.34	23.37	23.34	23.35	23.05	23.05	23.05	23.05	23.2	8.06	11	7.93	101	8.11	176	7.92
<2D	23.01	22.99	22.96	22.99	23.02	22.99	23.03	23.02	23.005	8.09	36	8.06	126	8.09	50	8.06

REkV2ax mm	REkH3 mm	REkH3ax mm	REkV3 mm	REkV3ax mm	AvREkH mm	AvREkV mm	REmeanK mm	LEkH1 mm	LEkH1ax mm	LEkV1 mm	LEkV1ax mm	LEkH2 mm	LEkH2ax mm	LEkV2 mm	LEkV2ax mm
28	7.64	172	7.56	82	7.67	7.57	7.62	7.59	9	7.53	99	7.63	4	7.53	94
95					7.72	7.55	7.63	7.71	176	7.54	86	7.69	179	7.55	89
1	7.78	95	7.65	5	7.77	7.66	7.72	7.76	157	7.71	67	7.76	120	7.72	30
47	7.96	104	7.86	14	7.93	7.86	7.89	7.87	167	7.78	77	7.87	175	7.84	85
89	7.91	163	7.8	73	7.91	7.80	7.86	7.85	9	7.76	99	7.86	176	7.77	86
94	8.03	7	7.89	97	8.03	7.88	7.96	7.99	162	7.96	72	7.99	156	7.91	66
86	7.84	2	7.68	92	7.85	7.67	7.76	7.85	8	7.67	98	7.84	180	7.66	90
83	7.59	179	7.53	89	7.59	7.52	7.56	7.6	155	7.43	65	7.56	166	7.45	76
86	8.01	173	7.85	83	7.98	7.84	7.91	8.1	162	7.98	72	8.11	161	7.86	71
79	8.25	2	8.13	92	8.24	8.12	8.18	8.21	172	8.09	82	8.22	166	8.09	76
101	7.8	169	7.73	79	7.79	7.73	7.76	7.73	139	7.68	49	7.73	157	7.66	67
95	7.41	8	7.14	98	7.40	7.15	7.28	7.45	166	7.15	76	7.45	165	7.16	75
83	7.76	141	7.6	51	7.76	7.65	7.70	7.74	5	7.62	95	7.76	9	7.6	99
74	7.78	11	7.71	101	7.81	7.69	7.75	7.79	167	7.64	77	7.8	7	7.62	97
106	7.74	11	7.61	101	7.71	7.61	7.66	7.67	116	7.63	26	7.77	47	7.57	137
113	7.91	2	7.78	92	7.89	7.77	7.83	7.85	179	7.71	89	7.88	169	7.64	79
129	8.13	8	7.9	98	8.11	7.96	8.03	8.05	166	7.82	76	8.05	158	7.78	68
100	7.41	8	6.99	98	7.43	7.03	7.23	7.44	177	6.91	87	7.42	178	6.99	88
93	7.88	3	7.72	93	7.88	7.72	7.80	7.82	8	7.65	98	7.83	176	7.62	86
109	8.11	2	7.94	92	8.13	7.95	8.04	8.1	174	7.89	84	8.14	171	7.98	81
96					7.63	7.33	7.48	7.64	172	7.2	82	7.66	173	7.2	83
110	7.57	22	7.11	112	7.52	7.17	7.35	7.36	157	7.25	67	7.41	116	7.3	26
79	7.58	176	7.51	86	7.58	7.50	7.54	7.68	2	7.56	92	7.66	164	7.56	74
107	7.81	27	7.66	117	7.75	7.64	7.70	7.7	23	7.58	113	7.67	50	7.6	140
95	8	3	7.72	93	8.00	7.71	7.86	8.02	177	7.77	87	8.02	176	7.79	86
88	8.37	11	8.27	101	8.37	8.25	8.31	8.39	158	8.24	68				
165	7.83	18	7.64	108	7.82	7.69	7.76	7.79	171	7.62	81	7.75	167	7.61	77
89	7.97	177	7.66	87	7.97	7.66	7.82	8.03	174	7.76	84	8.03	175	7.81	85
86	8.1	175	7.95	85	8.09	7.93	8.01	8.03	167	7.88	77	7.98	6	7.78	96
140	8.11	61	8.06	151	8.10	8.06	8.08	8.1	162	8	72	8.12	150	7.99	60

LEkH3 mm	LEkH3ax mm	LEkV3 mm	LEkV3ax mm	AvLEkH mm	AvLEkV mm	LEmeanK mm	MeanK mm	REacd1 mm	REacd2 mm	REacd3 mm	REacd4 mm	REacd5 mm	REacdAv mm	LEacd1 mm	LEacd2 mm
7.63	177	7.53	87	7.62	7.53	7.57	7.60	3.93	3.93	3.93	5.23		3.93	3.81	3.81
7.7	170	7.54	80	7.70	7.54	7.62	7.63	3.5	3.5	3.52			3.51	3.57	3.57
7.76	135	7.73	45	7.76	7.72	7.74	7.73	3.35	3.35	3.35	3.35	3.35	3.35	3.3	3.28
7.87	174	7.82	84	7.87	7.81	7.84	7.87	4.01	3.99	4.01	4.03	4.03	4.01	3.84	3.84
7.85	6	7.77	96	7.85	7.77	7.81	7.83	3.73	3.73	3.73	3.73	3.75	3.73	3.68	3.68
7.95	151	7.89	61	7.98	7.92	7.95	7.95	3.39	3.39	3.38	3.38	3.38	3.38	3.32	3.32
7.82	176	7.75	86	7.84	7.69	7.77	7.76	3.77	3.77	3.75	3.77	3.77	3.77	3.68	2.61
7.56	146	7.49	56	7.57	7.46	7.52	7.54	3.5	3.48	3.5	3.5	3.52	3.5	3.45	3.46
8.09	168	7.98	78	8.10	7.94	8.02	7.97	3.25	3.24	3.24	3.25		3.25	3.2	3.22
8.24	170	8.09	80	8.22	8.09	8.16	8.17	3.44	3.46	3.46	3.46	3.46	3.46	3.49	3.49
7.74	148	7.64	58	7.73	7.66	7.70	7.73	3.47	3.49	3.51	3.49	3.49	3.49	3.47	3.47
7.47	166	7.17	76	7.46	7.16	7.31	7.29	3.11	3.11	3.11	3.12	3.12	3.11	3.23	3.25
7.78	13	7.59	103	7.76	7.60	7.68	7.69	3.47	3.45	3.47	3.47	3.47	3.47	3.47	3.47
7.79	174	7.58	84	7.79	7.61	7.70	7.73	3.66	3.66	3.66	3.66	3.66	3.66	3.68	3.73
7.73	144	7.65	54	7.72	7.62	7.67	7.66	1.95	2.06	2.08	2.02	2.02	2.03	2.17	1.92
7.88	177	7.7	87	7.87	7.68	7.78	7.80	3.6	3.6	3.58	3.58	3.58	3.59	3.54	3.54
8.03	157	7.82	67	8.04	7.81	7.93	7.98	3.54	3.57	3.57	3.59	3.59	3.57	3.6	3.6
7.42	175	6.99	85	7.43	6.96	7.20	7.21	3.36	3.36	3.36	3.36	3.38	3.36	3.38	3.36
7.82	179	7.62	89	7.82	7.63	7.73	7.76	3.34	3.34	3.32	3.32	3.34	3.33	3.35	3.35
8.1	169	7.95	79	8.11	7.94	8.03	8.03	3.31	3.31	3.29	3.29	3.31	3.3	3.34	3.34
7.66	170	7.22	80	7.65	7.21	7.43	7.46	2.2	4.26	4.24	4.21	4.19	4.23	4.17	4.17
7.43	122	7.29	32	7.40	7.28	7.34	7.34	3.66	3.68	3.68	3.66	3.66	3.67	3.66	3.64
				7.67	7.56	7.62	7.58	3.34	3.38	3.39	3.45	4.23	3.39	3.45	3.47
				7.69	7.59	7.64	7.67	3.16	3.18	3.18	3.18	3.19	3.18	3.14	3.14
				8.02	7.78	7.90	7.88	3.51	3.51	3.51	3.51	3.51	3.51	3.48	3.46
				8.39	8.24	8.32	8.31	3.55	3.48	3.53	3.58		3.53	3.55	3.53
7.8	167	7.62	77	7.78	7.62	7.70	7.73	3.45	3.45	3.45	3.47	3.45	3.45	3.33	3.33
8.01	2	7.81	92	8.02	7.79	7.91	7.86	2.97	4.24	4.22	4.22	4.22	4.22	1.77	4.15
8.04	170	7.77	80	8.02	7.81	7.91	7.96	3.36	3.36	3.36	3.36	3.36	3.36	3.36	3.36
8.07	122	8.04	32	8.10	8.01	8.05	8.07	3.33	3.33	3.35	3.33	3.33	3.33	3.33	3.33

LEacd3 mm	LEacd4 mm	LEacd5 mm	LEacdAv mm	MeanACD mm	newACD mm	REsph1 D	REcyl1 D	REaxis1	REsph2 D	REcyl2 D	REaxis2	REsph3 D	REcyl3 D	REaxis3
3.82	3.82	3.82	3.82	3.875	3.875	1.62	-0.62	102	1.62	-0.12	91	2	-0.75	38
3.57	3.57	3.57	3.57	3.54	3.54	1.12	-0.75	123	1.37	-1.12	53	1.25	-0.75	127
3.28	3.28	3.28	3.28	3.315	3.315	2.62	-0.62	96	3.12	-1.12	84	2.87	0	0
3.84	3.84	3.84	3.84	3.925	3.925	0.25	0	0	0.87	-0.25	69	0.75	-0.37	149
3.7	3.68	3.68	3.68	3.705	3.705	1	-0.25	51	0.87	-0.12	168	1.12	-1	180
3.32	3.32	3.32	3.32	3.35	3.35	1.25	-0.75	144	1.62	-1.12	137	1.87	-0.75	163
3.63	3.65	3.65	3.65	3.71	3.71	2	-1	139	1.87	-0.37	167	2.12	-0.5	161
3.46	3.46	3.46	3.46	3.48	3.48	1.12	-0.12	72	1.25	-0.25	56	1.5	-0.5	77
3.22	3.22	3.22	3.22	3.235	3.235	1.87	-0.25	92	1.87	-0.12	160	2.12	-0.12	69
3.49	3.47	3.49	3.49	3.475	3.475	0.5	-0.37	74	1	-0.5	77	0.87	-0.62	61
3.47	3.47	3.47	3.47	3.48	3.48	0.62	-1.25	89	0.25	-1.12	76	0.75	-1	103
3.23	3.21	3.19	3.22	3.165	3.165	3	-0.5	23	3.37	-0.62	23	3.25	-0.37	10
3.47	3.49		3.48	3.475	3.475	1.87	-0.37	118	1.37	-0.12	99	1.37	0	0
3.68	3.62	3.64	3.67	3.665	3.665	0.25	0	0	0.5	-0.25	180	0.5	-0.62	88
1.89	1.93	1.97	1.93	1.98		-0.5	-0.37	66	-0.5	-0.5	133	-0.37	-0.37	59
3.54	3.53	3.54	3.54	3.565	3.565	1.12	-0.75	90	1	-0.12	171	1.12	-0.12	16
3.62	3.6	3.6	3.6	3.585	3.585	2.12	-0.37	43	2.12	0	0	2.5	-0.12	17
3.36	3.36	5.95	3.36	3.36	3.36	-7.12	-2.87	180	-6.12	-2.37	14	-6	-2.37	17
3.37	3.37	3.35	3.36	3.345	3.345	0.5	-0.37	55	0.25	0	0	0.5	-0.37	59
3.33	3.34	3.34	3.34	3.32	3.32	1.12	-0.37	60	1.25	-0.37	55	1.5	-0.62	49
4.17	4.17	4.17	4.17	4.2	4.2	2	-1	25	2	-0.87	23	2.12	-1.12	30
3.64	3.64	3.64	3.64	3.655	3.655	-0.62	0	0	-0.12	-0.5	109	-0.12	-0.5	83
3.48	3.5	3.48	3.48	3.435	3.435	-1	-1.12	92	0.62	-1.12	98	0	-0.37	151
3.14	3.14	3.14	3.14	3.16	3.16	0.75	-2	42	1.75	-0.5	180	2.12	-0.37	81
3.46	3.48		3.47	3.49	3.49	0.87	-0.37	89	1.25	-0.25	116	1.5	0	0
3.55	3.55	3.55	3.55	3.54	3.54	1.37	-0.75	49	1.25	-0.62	53	1	0	0
3.33	3.35	3.35	3.34	3.395	3.395	1.75	-0.37	23	1.87	-0.37	91	2	-0.75	19
4.15	4.15		4.15	4.185	4.185	1.12	-0.37	38	1	-0.87	3	1.62	-1.37	17
3.36	3.36	3.36	3.36	3.36	3.36	1.25	-0.5	10	1.37	-0.62	31	1.25	-0.5	25
3.33	3.33	3.33	3.33	3.33	3.33	1.75	-0.37	47	1.87	-0.5	40	1.87	-0.62	44

Working database of Year 2 children (n=30)

REsphAv D	REcylAv D	REaxisAv	REmeanSER D	LEsph1 D	LEcyl1 D	LEaxis1	LEsph2 D	LEcyl2 D	LEaxis2	LEsph3 D	LEcyl3 D	LEaxis3	LEsphAv D	LEcylAv D
1.62	-0.12	91	1.50	2.25	-1.37	73	1.5	-0.62	60	1.5	-0.75	69	1.5	-0.75
1.25	-0.75	123	0.81	1.12	-0.37	41	1.37	-0.37	111	1.37	-0.12	75	1.37	-0.37
3.12	-1.12	84	2.58	2.25	-0.25	120	2.5	-0.37	136	2.75	-0.75	147	2.5	-0.37
0.75	0	0	0.52	0.62	-0.87	157	0.25	-1.25	8	0.62	-1	143	0.62	-1.25
1.12	-1	180	0.77	0.62	-0.37	100	0.87	-0.5	175	0.75	-0.12	152	0.87	-0.12
1.62	-0.75	144	1.14	1.62	-0.5	86	1.75	-0.75	60	1.75	-0.37	97	1.75	-0.75
2	-0.5	161	1.69	2.12	-0.37	39	1.75	-0.5	43	1.75	-0.5	79	2.12	-0.5
1.25	-0.25	56	1.15	1	-0.37	149	1.37	-0.62	130	1.25	-0.37	101	1.25	-0.37
2.12	-0.12	69	1.87	2.75	-0.5	156	3.12	-0.62	147	1.87	-0.75	113	3.12	-0.62
0.87	-0.5	77	0.54	0.75	-0.12	16	0.62	0	0	0.62	0	0	0.75	-0.12
0.62	-1.25	89	-0.02	0.25	-0.25	64	0.25	-0.5	47	0.37	-0.37	98	0.25	-0.5
3.25	-0.5	23	2.96	3	-0.25	9	3.5	-0.87	177	3.37	-0.37	172	3.37	-0.37
1.37	-0.12	99	1.46	1.87	0	0	1.87	0	0	1.87	-0.5	23	1.87	0
0.5	0	0	0.27	0.75	-0.62	8	0.75	-0.37	23	0.5	-0.25	42	0.75	-0.37
-0.37	-0.37	66	-0.66	-0.75	-0.5	111	-0.37	-0.87	76	-0.62	-0.37	77	-0.62	-0.37
1.12	-0.12	171	0.92	0.75	-0.12	70	0.75	0	0	0.62	-0.37	20	0.62	-0.37
2.5	-0.37	43	2.17	2.12	-0.75	74	2.62	-0.5	146	2.37	-0.37	8	2.37	-0.37
-6.12	-2.37	14	-7.68	-5.75	-2	166	-5.75	-2.12	166	-5.62	-2.25	168	-5.75	-2.12
0.5	-0.37	55	0.29	0.25	-0.25	165	0.62	-0.5	166	0.37	-0.25	7	0.37	-0.25
1.25	-0.37	55	1.06	1.75	-0.5	162	1.87	-0.12	22	2.12	-1.37	157	1.87	-0.5
2.12	-1	25	1.54	2.12	-1.62	167	2.5	-2.12	160	2.25	-1.5	165	2.37	-1.62
-0.12	-0.5	109	-0.45	-0.37	-0.62	78	-0.37	-0.5	103	-0.5	-0.12	90	-0.37	-0.5
0.62	-1.12	92	-0.56	0.75	-1.37	69	0	-0.87	18	-0.25	0	0	0	-0.87
2.12	-2	42	1.06	1.75	-0.62	18	1.87	-0.75	15	1.87	-0.12	54	1.87	-0.62
1.25	-0.25	116	1.10	1.37	0	0	1.37	-0.37	95	1.37	-0.12	26	1.37	-0.12
1.37	-0.62	53	0.98	0.75	-0.62	170	1.12	-0.87	167	0.87	-0.5	10	0.87	-0.62
2	-0.75	19	1.63	1.12	-0.37	106	1.87	-0.75	83	1.75	-0.12	114	1.75	-0.37
1.12	-0.87	3	0.81	1.37	-0.75	46	1.25	-0.62	13	1.62	-0.62	20	1.37	-0.62
1.25	-0.5	25	1.02	1.25	-0.5	180	1.25	-0.5	175	1.25	-0.37	177	1.25	-0.5
1.87	-0.5	40	1.58	1.62	-0.5	88	1.87	-0.25	63	1.62	-0.25	70	1.62	-0.25

LEaxisAv	LEmeanSERD	MeanSERD	Refgp	Bilatrefgp	Myopia	Hyperopia	Astig	cluster	myopeuncorr	hyperuncorr
69	1.29	1.40	Emmetrope	Emmetrope	0	0	0	7	0	0
41	1.14	0.98	Emmetrope	Emmetrope	0	0	0	7	0	0
136	2.27	2.43	Hyperope	Hyperope	0	1	0	7	0	1
8	-0.02	0.25	Emmetrope	Emmetrope	0	0	1	8	0	0
152	0.58	0.68	Emmetrope	Emmetrope	0	0	0	8	0	0
60	1.44	1.29	Emmetrope	Emmetrope	0	0	0	8	0	0
43	1.65	1.67	Emmetrope	Emmetrope	0	0	0	8	0	0
149	0.98	1.06	Emmetrope	Emmetrope	0	0	0	9	0	0
147	2.27	2.07	Hyperope	Emmetrope	0	1	0	9	0	1
16	0.64	0.59	Emmetrope	Emmetrope	0	0	0	9	0	0
47	0.10	0.04	Emmetrope	Emmetrope	0	0	1	9	0	0
172	3.04	3.00	Hyperope	Hyperope	0	1	0	9	0	1
0	1.79	1.62	Emmetrope	Emmetrope	0	0	0	9	0	0
23	0.46	0.37	Emmetrope	Emmetrope	0	0	0	9	0	0
77	-0.87	-0.77	Myope	Myope	1	0	0	9	1	0
20	0.63	0.77	Emmetrope	Emmetrope	0	0	0	9	0	0
8	2.10	2.13	Hyperope	Hyperope	0	1	0	9	0	1
166	-6.77	-7.23	Myope	Myope	1	0	1	9	0	0
165	0.25	0.27	Emmetrope	Emmetrope	0	0	0	9	0	0
162	1.58	1.32	Emmetrope	Emmetrope	0	0	0	10	0	0
167	1.42	1.48	Emmetrope	Emmetrope	0	0	1	10	0	0
103	-0.62	-0.54	Myope	Emmetrope	1	0	0	10	1	0
18	-0.21	-0.38	Myope	Emmetrope	1	0	0	10	1	0
18	1.58	1.32	Emmetrope	Emmetrope	0	0	0	10	0	0
172	1.29	1.20	Emmetrope	Emmetrope	0	0	0	10	0	0
170	0.58	0.78	Emmetrope	Emmetrope	0	0	0	10	0	0
106	1.37	1.50	Emmetrope	Emmetrope	0	0	0	10	0	0
20	1.08	0.95	Emmetrope	Emmetrope	0	0	0	10	0	0
175	1.02	1.02	Emmetrope	Emmetrope	0	0	0	10	0	0
70	1.54	1.56	Emmetrope	Emmetrope	0	0	0	10	0	0

ametropeuncorr	ALCR
0	3.02
0	2.94
1	2.82
0	3.00
0	2.90
0	2.87
0	2.97
0	2.93
1	2.82
0	2.87
0	3.00
1	2.84
0	2.87
0	2.96
1	3.11
0	2.95
1	2.83
0	3.34
0	2.90
0	2.87
0	2.97
1	3.10
1	2.93
0	2.84
0	2.87
0	2.85
0	2.93
0	3.00
0	2.91
0	2.85

APPENDIX 7

STATA OUTPUT TABLES

Below are examples of statistical outputs obtained during analysis of AES data. Varied tests are displayed to provide an illustration of the breadth of analysis conducted on datasets. Tables are shown on Year 8 children only unless tests are shown comparing children as a function of age group.

Chapter 6

1. Two-sample t test with equal variances

Examining the difference in mean SER by age group (Year 2 vs. Year 8)

```
------------------------------------------------------------------------------
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
   year2 |     302    .8543074   .0807297   1.402932    .6954414    1.013173
   year8 |     296   -.0213837   .0823463    1.41674   -.1834444    .140677
---------+--------------------------------------------------------------------
combined |     598    .4208549   .0603248   1.475185    .3023803    .5393295
---------+--------------------------------------------------------------------
    diff |            .8756911   .1153065                .6492347    1.102147
------------------------------------------------------------------------------
    diff = mean(year2) - mean(year8)                              t =   7.5945
Ho: diff = 0                     degrees of freedom =      596

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 1.0000         Pr(|T| > |t|) = 0.0000          Pr(T > t) = 0.0000
```

2. One-way between-subjects Analysis of Variance with Scheffe's *post-hoc* analysis

Examining the difference in mean SER by ethnic group

```
      Source       SS         df       MS          F     Prob > F
-----------------------------------------------------------------
Between groups  68.4904812     5    13.6980962    7.59    0.0000
Within groups   523.619063    290   1.80558298
-----------------------------------------------------------------
       Total    592.109544    295   2.007151

Bartlett's test for equal variances:  chi2(5) =  10.8244  Prob>chi2 = 0.055

Comparison of MeanSER by 0=white 1=asian 2=black 3=mixed 4=chinese 5=other
                        (Scheffe)
Row Mean-|
Col Mean    White     Asian     Black     Mixed    Chinese
---------+-------------------------------------------------
  Asian |  -.874222
      p |     0.000
  Black |  -.548308    .325914
      p |     0.425     0.883
  Mixed |    .10022   .974442   .648528
      p |     1.000     0.226     0.770
Chinese | -2.26022  -1.386    -1.71192  -2.36044
      p |     0.021     0.406     0.209     0.044
  Other |  -1.15799  -.283764  -.609679  -1.25821  1.10224
      p |     0.430     0.998     0.942     0.524    0.854
```

3. Two-way between-subjects Analysis of Variance

Examining the main effects of ethnicity and gender on mean SER

Number of obs = 296 R-squared = 0.1790
Root MSE = 1.3083 Adj R-squared = 0.1472

Source	Partial SS	df	MS	F	Prob > F
Model	106.002417	11	9.63658337	5.63	0.0000
ethnic1	64.7989202	5	12.959784	7.57	0.0000
gend	.002996962	1	.002996962	0.00	0.9667
ethnic1*gend	31.8393365	5	6.36786731	3.72	0.0028
Residual	486.107127	284	1.71164481		
Total	592.109544	295	2.007151		

4. Relative risk

Examining the relative risk of myopia prevalence as a function of gender

	gender		
	Exposed (Females)	Unexposed (Males)	Total
myopia Cases	57	30	87
Noncases	108	101	209
Total	165	131	296
Risk	.3454545	.2290076	.2939189
	Point estimate		[95% Conf. Interval]
Risk difference	.1164469		.0142614 .2186325
Risk ratio	1.508485		1.033724 2.20129
Attr. frac. ex.	.3370832		.0326239 .5457209
Attr. frac. pop	.2208476		

1-sided Fisher's exact P = 0.0194
2-sided Fisher's exact P = 0.0299

5. Chi-squared test of independence

Examining myopia prevalence as a function of age group

school type prim/sec	myopia No	Yes	Total
year2	272	30	302
%	90.07	9.93	100.00
year8	209	87	296
%	70.61	29.39	100.00
Total	481	117	598
%	80.43	19.57	100.00

Pearson chi2(1) = 35.9642 Pr = 0.000

6. Linear regression

Examining the relationship between mean SER and mean axial length (AL)

Linear regression

Number of obs = 296
F(1, 6) = 19.96
Prob > F = 0.0042
R-squared = 0.2915
Root MSE = 1.1915

Number of clusters (cluster) = 7

MeanSER	Coef.	Robust Std. Err.	t	P>|t|	[95% Conf.	Interval]
MeanAL	-.8972254	.2008049	-4.47	0.004	-1.388577	-.4058735
_cons	21.0426	4.547655	4.63	0.004	9.914893	32.17032

7. Partial correlation

The partial correlation coefficients of mean AL, CR and ACD with mean SER

(obs=281)
Partial correlation of MeanSER with

Variable	Corr.	Sig.
MeanAL	-0.8532	0.000
MeanK	0.8088	0.000
MeanACD	0.3528	0.000

8. Multiple linear regression

Multiple regression of ocular biometry (AL, CR and ACD) with mean SER

Linear regression

Number of obs = 281
F(3, 6) = 280.99
Prob > F = 0.0000
R-squared = 0.7554
Root MSE = .70806

Number of clusters (cluster) = 7

MeanSER	Coef.	Robust Std. Err.	t	P>|t|	[95% Conf.	Interval]
MeanAL	-1.785046	.0808636	-22.07	0.000	-1.982912	-1.58718
MeanK	4.327421	.1786903	24.22	0.000	3.890182	4.764661
newACD	1.043068	.1246007	8.37	0.000	.7381814	1.347955
_cons	4.442997	2.094874	2.12	0.078	-.682974	9.568968

Chapter 8

9. Weighted Kappa statistic

Measuring agreement between parental and child questionnaire responses

Expected Agreement	Agreement	Kappa	Std. Err.	Z	Prob>Z
96.82%	81.14%	0.8312	0.0492	16.88	0.0000

10. Logistic regression

Univariate association of number of myopic parents on risk of proband myopia. Using child questionnaire responses.

Logistic regression — Number of obs = 137; Wald chi2(2) = 16.80; Prob > chi2 = 0.0002

Log pseudolikelihood = -78.879431 — Pseudo R2 = 0.0746

(Std. Err. adjusted for 7 clusters in cluster)

myopia	Odds Ratio	Robust Std. Err.	z	P>|z|	[95% Conf.	Interval]
1myopicparent	3.136364	1.785981	2.01	0.045	1.027343	9.574968
2myopicparent	8.944444	4.787933	4.09	0.000	3.132621	25.5387

11. Multiple logistic regression

Multiple association of ethnicity, SES, gender and grammar schooling on risk of proband myopia.

Logistic regression — Number of obs = 234; Wald chi2(4) = .; Prob > chi2 = .

Log pseudolikelihood = -127.27737 — Pseudo R2 = 0.0729

(Std. Err. adjusted for 7 clusters in cluster)

myopia	Odds Ratio	Robust Std. Err.	z	P>|z|	[95% Conf.	Interval]
Asian	2.542233	.8694154	2.73	0.006	1.30051	4.969547
Black	1.313109	1.184807	0.30	0.763	.2240108	7.697198
SES II	1.433031	.3009369	1.71	0.087	.9495172	2.162759
SES III	.8172048	.3217323	-0.51	0.608	.3777585	1.767859
SES IV	.7014277	.2023833	-1.23	0.219	.3984605	1.234754
gend	1.238769	.3215322	0.82	0.409	.7448249	2.06028
grammar	2.421248	.598202	3.58	0.000	1.491895	3.929525

APPENDIX 8

QUESTIONNAIRES

CONTENTS

Aston University Eye Study 2005-2007

Dear Parent/Guardian,

Your child has now been examined by our Research Team. It will be of great help to us in interpreting the test results if you can complete this questionnaire. All questions are relevant to general health and the health of the eyes.

To answer the questions, please tick the appropriate box ☑ or write in the space provided. All your answers will be treated in **strictest confidence** and will **only** be seen by the Research Team. If you feel uncomfortable with any of the questions, please leave them out and answer as many as you can. Alternatively, if you do not understand a question, please phone us on 0121 204 4091 and leave your telephone number so that we can call you back.
When you have completed the questionnaire, please put it in the envelope provided and post it back to us.
NO STAMP IS REQUIRED ON THE ENVELOPE, IT IS A FREEPOST SERVICE

Thank you very much for your help.

Yours faithfully,

Aston University

Content has been removed for copyright reasons

Professor Bernard Gilmartin	Dr. Nicola Logan	Mr. Parth Shah
Study Director	*Study Leader*	*Study Co-ordinator*

Child's full name

THE ASTON UNIVERSITY EYE STUDY

QUESTIONS 1 TO 3 ARE ABOUT THE CHILD IN THE STUDY

1.0 What is this child's date of birth ? ☐☐/☐☐/☐☐☐☐ (dd/mm/yyyy)

1.1 What is the child's sex ? Male ☐ Female ☐

1.2 What is your relationship to this child ?
- Mother ☐
- Father ☐
- Other relative ☐
- Guardian (unrelated) ☐

1.3 How much did this child weigh at birth ? (If you don't know, please do not guess, but tick 'Not known')

☐☐ lb ☐☐ oz **OR** ☐☐ kg **OR** Not known ☐

1.4 Was this child born:
- On time, (i.e. within a week of the expected date) ☐
- Early by a week or more ☐
- Late by a week or more ☐
- Not known ☐

If EARLY or LATE, by how many weeks ? ☐☐ weeks

1.5 Was this a multiple birth ? (i.e. a twin, triplet, etc .) Yes ☐ No ☐

1.6 Was the child born in the United Kingdom (UK) ? Yes ☐ No ☐

If NO, in which country was the child born ? _____

How old was the child when he/she came to the UK ? _____ years

1.7 Did the child sleep with a bedroom light or night light on in early life (under the age of 2 years) ? Yes ☐ No ☐

If YES, was the light a
- Bedroom light ☐
- Night light (or low illumination light) ☐

MEDICAL HISTORY AND EYE HEALTH

2.0 **On average**, how often has this child visited their local General Practitioner in the **last 4 years** ?
- More than four times per year ☐
- Twice to four times a year ☐
- Once a year ☐
- Not at all ☐

2.1 Does this child regularly take any medications (Tablets, Medicines, Inhalers) ? Yes ☐ No ☐

If YES, please give details: _____

_____

2.2 Has this child been admitted to hospital or eye hospital for any reason in the **last 4 years**? Yes ☐ No ☐

If YES, please give details: _____

_____

2.3 Has this child **ever** had eye surgery and/or been told to wear an eye patch? Yes ☐ No ☐

If YES, please give details (including which eye): _____

_____

2.4 Has this child ever worn spectacles? Yes ☐ No ☐ (go to 2.5

If YES,
- Are they worn most / all of the time ☐
- Are they worn for certain activities but not full time ☐
- Advised to wear them but does not ☐
- Stopped wearing them because no longer needed ☐

If this child **currently** wears spectacles, is he/she...(tick all that apply)
- Shortsighted (needs spectacles to see far away e.g. blackboard) ☐
- Longsighted (needs spectacles more for close up work e.g. reading, computer) ☐
- Astigmatic (i.e. has astigmatism or sometimes called 'rugby ball' shaped eyes) ☐
- Not known ☐

If this child **currently** wears spectacles or **no longer wears** spectacles, please give the age at which they were first prescribed and details of the last spectacle prescription (if available)

_____

_____

2.5 How often does this child have their eyes examined?

Twice a year or more often	☐
Once a year	☐
Once per 2 years	☐
Less often or not at all	☐

2.6 When did this child last have an eye examination at an opticians? ☐☐/☐☐☐☐ (mm/yyyy)
Tick here if the date is not known ☐

EXERCISE, OTHER ACTIVITIES AND DIET

3.0 Which of the following best describes your child's level of physical activity outside school ?

	Tick one box only
Spends all or most leisure time watching television, going to the cinema and in other sedentary activities	☐
Spends time occasionally in light physical activities (e.g. walking, bicycling, table tennis)	☐
Participates in regular sporting activities for up to 3 hours a week (e.g. soccer, swimming, gymnastics, tennis, skating)	☐
Participates in regular sporting activities for more than 3 hours a week (e.g. soccer, swimming, gymnastics, tennis, skating)	☐

3.1 Compared to other children of the same age and sex, how physically active is your child ?

	Tick one box only
Much less active	☐
Somewhat less active	☐
About average	☐
Somewhat more active	☐
Much more active	☐

3.2 How many hours each day does this child spend doing school homework ?

	Tick one box only
None	☐
Less than 1 hour	☐
1-2 hours	☐
2-3 hours	☐
More than 3 hours	☐

3.3 Compared to other children of the same age and sex, how well is this child doing at school?

	Tick one box only
Much better than others	☐
About the same as others	☐
Not quite as well as others	☐
Not as well as others	☐

3.4 Which of the following best describes your child's level of near vision activities outside school ?

	Tick one box only
Spends **all or most** leisure time reading books, writing, and / or using a computer (for computer games or the internet)	☐
Spends time **frequently** reading books, writing and / or using a computer (for computer games or the internet)	☐
Spends time **occasionally** reading books, writing and / or using a computer (for computer games or the internet)	☐
Spends **little** time reading books, writing and / or using a computer (for computer games or the internet)	☐

3.5 Does the child usually sleep with a bedroom light or night light on? Yes ☐ No ☐

If YES, is the light a Bedroom light ☐
Night light (or low illumination light) ☐

3.6 How was this child fed in the first 3 months of life ?

Breast fed only ☐
Fed on formula milk only ☐
Fed on both breast and formula milk ☐
Not known or unsure ☐

Formula milk refers to non-breast milk feeds (e.g. cows milk preparations such as SMA, C&G and Soya milk)

3.7 If the child was breast fed (wholly or partly), for how long was this continued from birth ? _____ months

3.8 How often does this child eat the following foods ? (Please tick the appropriate box for each food item)

	More than once a day	Once a day	Most days	One or two days a week	Less than once a week	Never
Fresh fruit	☐	☐	☐	☐	☐	☐
Green vegetables	☐	☐	☐	☐	☐	☐
Fish (all kinds)	☐	☐	☐	☐	☐	☐

BROTHERS AND SISTERS

4.0 How many brothers and sisters does this child have in all (excluding step brothers & sisters) ?

_____

4.1 How many brothers and sisters are older than this child (excluding step brothers & sisters) ?

_____

4.2 Please give details of this child's brothers and sisters beginning with the oldest :-

	Oldest brother or sister	Second brother or sister	Third brother or sister	Fourth brother or sister
Age	☐ yrs	☐ yrs	☐ yrs	☐ yrs
Full / Half sister or brother	Full ☐ Half ☐	Full ☐ Half ☐	Full ☐ Half ☐	Full ☐ Half ☐
Sex	Boy ☐ Girl ☐	Boy ☐ Girl ☐	Boy ☐ Girl ☐	Boy ☐ Girl ☐
Does this child currently wear spectacles?	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐
If YES, is the child ?				
Shortsighted	☐	☐	☐	☐
Longsighted	☐	☐	☐	☐
Not known	☐	☐	☐	☐
Age at which child began wearing spectacles ?	☐ yrs	☐ yrs	☐ yrs	☐ yrs

If there are more than 4 brothers and sisters please write extra details in the comments box at the end of the questionnaire.

THE FOLLOWING QUESTIONS ARE ABOUT THE CHILD'S NATURAL PARENTS. PLEASE ANSWER THESE QUESTIONS FOR BOTH THE NATURAL MOTHER AND FATHER

	Natural Mother	Natural Father
5.0 Do the parents live with the child ?	Yes ☐ No ☐	Yes ☐ No ☐
5.1 In which country was each parent born ?	_____	_____

5.2	What is the ethnic group of each parent ? (tick all that apply)		
	White	☐	☐
	Indian	☐	☐
	Pakistani	☐	☐
	Bangladeshi	☐	☐
	Black - African	☐	☐
	Black - Caribbean	☐	☐
	Chinese	☐	☐
	Japanese	☐	☐
	Other – please give details	_____	
5.3	How tall is each parent ?		
	Feet and inches **OR**	____ feet ____ inches	____ feet ____ inches
	Metres and centre meters	____ metres ____ cms	____ metres ____ cms
5.4	How much does each parent weigh ?		
	Stones and pounds **OR**	____ st ____ lbs	____ st ____ lbs
	Kilograms	____ kgs	____ kgs
5.5	Do the parents wear spectacles ?	Yes ☐ No ☐	Yes ☐ No ☐
	If YES, are they… (tick all boxes that apply)		
	Shortsighted (needs spectacles to see far away)	☐	☐
	Longsighted (needs spectacles more for close up work)	☐	☐
	Astigmatic (i.e. has astigmatism)	☐	☐
	Not known	☐	☐

3

THE NEXT QUESTIONS ARE ABOUT THE PARENTS / GUARDIANS WHO LIVE WITH THE CHILD NOW – WHETHER OR NOT THEY ARE THE NATURAL PARENTS

If there is only one parent or guardian living with the child, questions for the other parent can be left blank

		Mother / Female Guardian	Father / Male Guardian
6.0	Which of these options best describes the work situation of each parent?		
	in full-time paid work	☐	☐
	in part-time paid work	☐	☐
	unemployed	☐	☐
	looks after family full-time	☐	☐
	in full time education	☐	☐
	other (please give details)	_____	_____

Please answer the following questions about the present or most recent employment of each parent:

6.1	What type of firm or organization does (did) each parent work in, what does (did) the firm make or do ?	_____	_____
6.2	Did he/she need a particular training to obtain this job ?	_____	_____
6.3	What was the highest level of qualification the parent obtained in full or part-time education ?	_____	_____
6.4	Has the parent ever smoked cigarettes regularly ?	Yes ☐ No ☐	Yes ☐ No ☐
6.5	How many cigarettes does the parent usually smoke each day at present ?	_____	_____

HOME CIRCUMSTANCES

7.0 How many rooms does your accommodation contain ?
(Do not count bathrooms, toilets and kitchens) ☐

7.1 How many people, **including the child in our survey,**
live in your household altogether ? ☐

THANK YOU VERY MUCH FOR YOUR HELP IN COMPLETING AND RETURNING THIS QUESTIONNAIRE.

Please check that you have answered all relevant questions. **All information you have provided will be treated confidentially and will only be seen by our research team.** Please seal the questionnaire in the reply paid envelope provided and post it back to us. **No stamp is required.**

On receipt of the questionnaire we will send you a report on your child's eyes if we feel he/she requires further referral.

For comments

Freepost RLZL-HAAB-HGJT, Dr Nicola Logan, Aston University Eye Study, Vision Sciences, Aston University, Birmingham, B4 7ET. Tel: 0121 204 4091. Email: shahp4@aston.ac.uk

Child Questionnaire

Your full name

Aston University Eye Study 2005-2007

Please answer these questions as fully and truthfully as you can. The answers you give will be treated as confidential and will not be told to your school or your parents. Please tick the boxes that you feel apply to you the most or write the answer in the space given.

Thank you very much for your help.

1.0 What is your date of birth?

☐☐/☐☐/☐☐☐☐
Day Month Year

1.1 Are you? Male ☐ **OR** Female ☐

1.2 Were you born in the United Kingdom? Yes ☐ No ☐

IF NO, i) What country were you born in? _____

ii) What age were you when you came to live in the UK_____

MEDICAL HISTORY AND EYE HEALTH

2.0 On average, how often do you visit your local General Practitioner (doctor)?

More than four times a year ☐
Two to four times a year ☐
Once a year ☐
Not at all ☐

2.1 Do you regularly take any medications (Tablets, Medicines, Inhalers)?

Yes ☐ No ☐

If YES, please give details: _____

_____

2.2 Have you been a patient at a hospital or eye hospital for any reason in the **last 4 years**?

Yes ☐ No ☐

If YES, please give details: _____

_____

2.3 Have you **ever** had eye surgery and/or been told to wear an eye patch?

Yes ☐ No ☐

If YES, please give details (including which eye):_____

_____

_____

2.4 Have you ever worn spectacles? Yes ☐ No ☐ go to 2.5

If YES,
- Are they worn most/all of the time ☐
- Are they worn for certain activities but not full time ☐
- Advised to wear them but do not ☐
- Stopped wearing them because no longer needed ☐

If you **currently** wear spectacles, are you… (tick all that apply)

- Shortsighted (need spectacles to see far away e.g. blackboard) ☐
- Longsighted (need spectacles more for close up work e.g. reading, computer) ☐
- Astigmatic (i.e. have astigmatism or sometimes called 'rugby ball' shaped eyes) ☐
- Not known ☐

If you **currently** wear spectacles or **no longer wear** spectacles, at what age did you first start wearing spectacles?

_____

_____

_____

2.5 How often do you have your eyes examined at an opticians?

- Two or more times a year ☐
- Once a year ☐
- Once every few years ☐
- Not at all ☐

2.6 When did you last have an eye examination at an opticians?

☐☐/☐☐☐☐

Month Year

Tick here if you do not know ☐

DIETARY HABITS

3.0 How often do you eat the following foods?

(Please tick the appropriate box for each food item)

	More than once a day	Once a day	Most days	One or two days a week	Less than once a week	Never
Fresh fruits in summer	☐	☐	☐	☐	☐	☐
Fresh fruits in winter	☐	☐	☐	☐	☐	☐
Salads in summer	☐	☐	☐	☐	☐	☐
Salads in winter	☐	☐	☐	☐	☐	☐
Green vegetables	☐	☐	☐	☐	☐	☐
Fish (all kinds)	☐	☐	☐	☐	☐	☐
Poultry (chicken, turkey)	☐	☐	☐	☐	☐	☐
Red meat (include beef, lamb, ham, bacon)	☐	☐	☐	☐	☐	☐
Processed meat (include burgers, sausages and pies)	☐	☐	☐	☐	☐	☐
Cheese	☐	☐	☐	☐	☐	☐

EXERCISE AND OTHER ACTIVITIES

4.0 Which of the following best describes your level of physical activity outside school?

Tick one box only

Spend all or most leisure time watching television, going to the cinema and in other seated activities	☐
Spend time occasionally in light physical activities (e.g. walking, bicycling, table tennis)	☐
Take part in regular sporting activities for up to 3 hours a week (e.g. soccer, swimming, gymnastics, tennis, skating)	☐
Take part in regular sporting activities for more than 3 hours a week (e.g. soccer, swimming, gymnastics, tennis, skating)	☐

4.1 Compared to other children of the same age and sex, how physically active are you?

Tick one box only

Much less active	☐
Somewhat less active	☐
About average	☐
Somewhat more active	☐
Much more active	☐

OTHER ACTIVITIES

4.2 How many hours each day do you spend doing school homework?

Tick one box only

None	☐
Less than 1 hour	☐
1-2 hours	☐
2-3 hours	☐
more than 3 hours	☐

4.3 Which of the following best describes your level of near vision activities outside school?

Tick one box only

Spend all or most leisure time reading books, writing, and / or using a computer (for computer games or the internet)	☐
Spend time frequently reading books, writing and / or using a computer (for computer games or the internet)	☐
Spend time occasionally reading books, writing and / or using a computer (for computer games or the internet)	☐
Spend little time reading books, writing and / or using a computer (for computer games or the internet)	☐

4.4 Compared to other children of the same age and sex, how well are you doing at school ?

Tick one box only

Much better than others	☐
About the same as others	☐
Not quite as well as others	☐
Not as well as others	☐

4.5 Do you plan to stay on at school or go to college after Year 11? Yes ☐ No ☐

THE NEXT QUESTIONS ARE ABOUT YOUR MOTHER

5.0 Does she live with you? Yes ☐ No ☐

5.1 What was her country of birth _____

5.2 Does your mother wear spectacles? Yes ☐ No ☐

If YES, is she
- Shortsighted (needs spectacles to see far away) ☐
- Longsighted (needs spectacles more for close up work) ☐
- Astigmatic (i.e. has astigmatism) ☐
- Not known ☐

5.3 Has she ever smoked cigarettes regularly? (at least 1 cigarette / day for 12 months) Yes ☐ No ☐

THE NEXT QUESTIONS ON THIS PAGE ARE ABOUT YOUR FATHER

6.0 Does he live with you? Yes ☐ No ☐

6.1 What was his country of birth _____

6.2 Does he wear spectacles? Yes ☐ No ☐

If YES, is she
- Shortsighted (needs spectacles to see far away) ☐
- Longsighted (needs spectacles more for close up work) ☐
- Astigmatic (i.e. has astigmatism) ☐
- Not known ☐

6.3 Has he ever smoked cigarettes regularly? (at least 1 cigarette / day for 12 months) Yes ☐ No ☐

YOUR HOME

7.0 Who do you live at home with at present? (where you can, please say how they are related to you e.g. mother, stepfather, brother).

_____

_____

7.1 Does your family have any of the following?

	YES	NO
a car	☐	☐ If Yes, how many_____
a dishwasher	☐	☐
a home computer	☐	☐

(Please don't count video games)

7.2 Thinking about the house or flat your family live in at the moment, do your family own it or is it rented?

- Own ☐
- Rented ☐
- Don't know ☐

7.3 If you live with your mother, stepmother or foster mother and she has a job, please tell us what job she does

_____

7.4 If you live with your father, stepfather or foster father and he has a job, please tell us what job he does

_____

BROTHERS AND SISTERS

8.0 How many brothers and sisters do you have in all (not counting step brothers & sisters)? ☐

8.1 How many brothers and sisters are older than you (not counting step brothers & sisters)? ☐

8.2 Please give details of your brothers and sisters beginning with the oldest:-

	Oldest brother or sister	Second brother or sister	Third brother or sister	Fourth brother or sister
Age	☐ yrs	☐ yrs	☐ yrs	☐ yrs
Sex	Boy ☐ Girl ☐	Boy ☐ Girl ☐	Boy ☐ Girl ☐	Boy ☐ Girl ☐
Does this brother / sister currently wear spectacles ?	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐

If there are more than 4 brother and sisters, it would be helpful if you could write the extra details on the blank page at the back of the questionnaire.

9.0 *STRENGTHS AND DIFFICULTIES*

	Not true	Somewhat true	Certainly true
I am considerate of other people's feelings	☐	☐	☐
I am restless. I cannot stay still for long	☐	☐	☐
I get a lot of headaches, stomach-aches or sickness	☐	☐	☐
I usually share with others (food, games, pens etc.)	☐	☐	☐
I get very angry and often lose my temper	☐	☐	☐
I am rather solitary. I usually play alone or keep to myself	☐	☐	☐
I usually do as I am told	☐	☐	☐
I worry a lot	☐	☐	☐
I am helpful if someone is hurt, upset or feeling ill	☐	☐	☐
I am constantly fidgeting or squirming	☐	☐	☐
I have at least one good friend	☐	☐	☐
I fight a lot. I can make other people do what I want	☐	☐	☐
I am very often unhappy, down hearted or tearful	☐	☐	☐
Other people my age generally like me	☐	☐	☐
I am easily distracted, I find it difficult to concentrate	☐	☐	☐
I am nervous in new situations. I easily lose confidence	☐	☐	☐
I am kind to younger children	☐	☐	☐
I am often accused of lying or cheating	☐	☐	☐
Other children or young people pick on me or bully me	☐	☐	☐
I often volunteer to help others (parents, teachers, children)	☐	☐	☐
I think things out before acting	☐	☐	☐
I take things that are not mine from home, school & elsewhere	☐	☐	☐
I get on better with adults than with people my own age	☐	☐	☐
I have many fears, I am easily scared	☐	☐	☐
I see tasks through to the end. My attention is good.	☐	☐	☐
I am considerate of other people's feelings	☐	☐	☐

THANK YOU VERY MUCH FOR YOUR HELP IN COMPLETING THIS QUESTIONNAIRE.

All information you have provided will be treated confidentially and will only be seen by our research team.

August 2006

Dear Parent/Guardian,

During our recent clinical study examining the eyesight of children at [redacted] School, we examined your child and handed out a questionnaire to be filled out by their parent/guardian.

As yet, we have not received the questionnaire back from you. The questionnaire is of importance as it will allow us to draw links between your child's eyesight and his/her environment (including both family history and lifestyle).

If you have misplaced the previous questionnaire sent out to you, there is a copy enclosed with this letter along with a freepost envelope. Please complete the questionnaire and send it back in the envelope (no stamp required).

Please be reassured: all information provided in the questionnaire will be **treated in strictest confidence** and only processed for purposes of the Eye Study.

Please do not hesitate to contact us if you have any further queries.

Yours sincerely,

Aston University

Content has been removed for copyright reasons

Professor Bernard Gilmartin
Study Director

Dr Nicola Logan
Study Leader

Mr Parth Shah
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Aston University
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B4 7ET

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Email Mr. Shah: shahp4@aston.ac.uk

APPENDIX 9

THE CALCULATION OF LENS POWER

Crystalline lens parameters were not measured in the AES, but a method of lens power calculation has been demonstrated in Rabbetts (2007). The required factors for calculation were measured in the AES: axial length (AL), corneal radius of curvature (CR), anterior chamber depth (ACD), refractive error (mean SER) and the vertex distance for which refractive error is measured (BVD). Refer to Chapter 3 for details on biometry measurement.

The lens power calculation assumes a thin lens surface (hence ignoring its thickness) and follows a step-along vergence method of calculation as described.

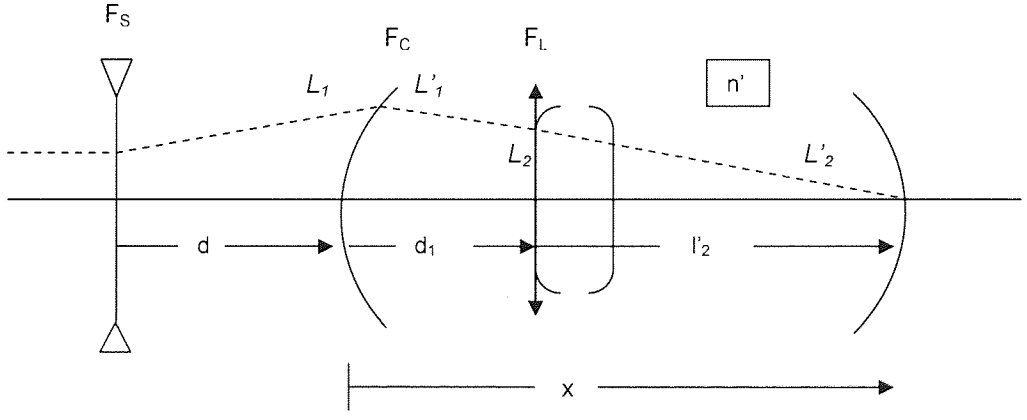


Figure A9.1 The set-up of the eye and an equivalent thin lens (F_L) placed at the anterior lens surface

The initial vergence determined is that at the corneal vertex (L_1). This is calculated using the equation:

$$L_1 = \frac{F_S}{1 - dF_S} \qquad \text{Equation A9.1}$$

with F_S as the spectacle lens refractive power and d as the back vertex distance. The power of the cornea (F_c) is derived using the corneal radius of curvature (r_c) and the refractive index of the aqueous (n') which is assumed at 1.336:

$$F_c = \frac{n' - 1}{r_c} \qquad \text{Equation A9.2}$$

The exit vergence of light from the cornea (L'_1) assuming a single refracting surface is the sum of Fc and L_1, where

$$L'_1 = F_c + L_1 \qquad \text{Equation A9.3}$$

The vergence of light arriving at the lens (L_2) is calculated after taking the anterior chamber depth (d_1) into account:

$$L_2 = \frac{L'_1}{1-([d_1/n']\ L'_1)} \qquad \text{Equation A9.4}$$

The exit vergence of light leaving the lens (L'_2) is the dioptric value of the distance from the assumed lens position to the retina (l'_2), which can be determined by subtracting the anterior chamber depth (d_1) from the axial length (x) in a refractive medium of the vitreous (n' = 1.336) :

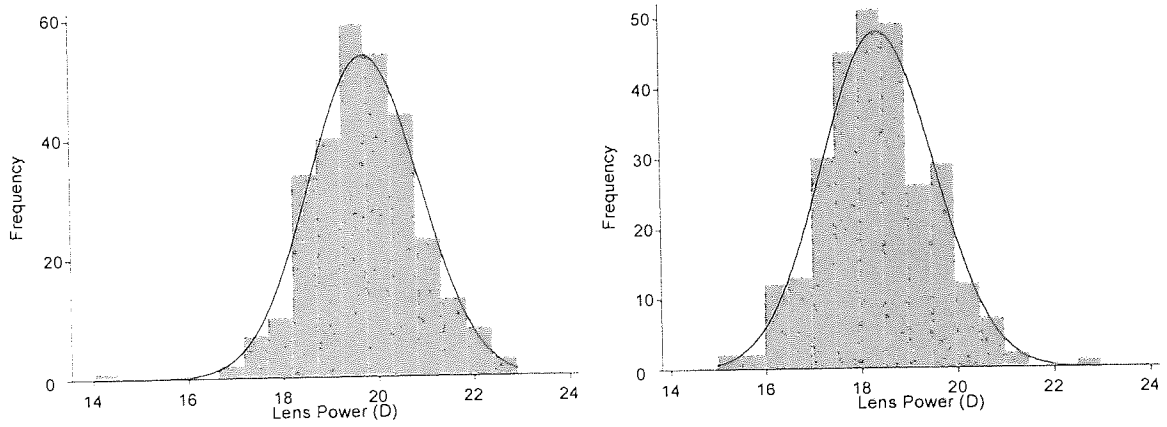
$$L'_2 = \frac{n'}{x - d_1} \qquad \text{Equation A9.5}$$

Therefore the power of the lens (F_L) is deduced as the difference between the results of equations A9.5 and A9.4, such that:

$$F_L = L'_2 - L_2 \qquad \text{Equation A9.6}$$

From Figure A9.1, it can be seen that the calculated lens power is for an equivalent thin lens located at the anterior lens vertex.

Lens power distributions were determined for the AES cohort by age group (Figure A9.2):



A **Year 2** **B** **Year 8**

Figure A9.2 Distributions of calculated lens power for the measured AES cohort by age group

It appears from the above histograms that lens power is lower in elder children. However, further analysis using lens power as a dependent variable was not pursued as it was felt that a variation in unmeasured parameters such as the posterior radius of curvature and refractive index would be concealed by the ascription of subject variation to lens power alone. For example, it would be erroneous to state that the mean lens power was lower in Year 8 children compared to Year 2, even though a statistically significant difference existed between the mean lens power measures of each
age group (mean lens power Year 2 *vs.* Year 8: 19.7±1.2D *vs.* 18.4±1.2D, two-tailed t=13.9, p<0.001). Without having measured parameters such as refractive index, lens radii of curvature and lens thickness -

all of which would constitute a change in calculated lens power – it would be impossible to attribute a change in lens power to a specific morphological change in the eye.
In addition, the correlation of lens power to measured biometric components would be invalid as these components are required to determine the lens power initially therefore a correlation would be expected due to their interdependency (Ludlum *et al.*, 1974). The mean lens powers calculated appear considerably lower than those of the Orinda Longitudinal Study of Myopia who did measure lens thickness and radii of curvature (age 6: ~21.5D, age 12: ~20D; estimated from Figure 4, Mutti *et al.*, 1998), highlighting a further inaccuracy of the calculation.

In summary, the calculation of equivalent lens power was conducted based on assumptions of a thin lens surface located at the anterior lens vertex. However, further analysis using these values was not performed due to potential inaccuracies in assumptions and erroneous data inferred from comparative findings. Actual measurement of lens parameters is advocated for future work.

APPENDIX 10

SUPPORTING PUBLICATIONS

CONTENTS

Refereed published abstracts of conference proceedings

Shah, P., Logan, N. S., Gilmartin, B., Rudnika, A. R. and Owen, C. G. (2006). The Aston Eye Study: methodology for a population-based study of myopia in UK urban school children. 11th International Myopia Conference, Singapore. *Ophthalmic Physiol Opt,* **26**: P016.

Logan, N.S., Shah, P., Rudnicka, A.R., Owen, C.G. and Gilmartin, B. (2006). The epidemiology of refractive error in UK children: The Aston Eye Study. EVER Congress, Portugal. *Acta Ophthalmol Scan*, **84**,2215.

Logan, N.S., Rudnicka, A.R., Shah, P., Gilmartin, B. and Owen, C.G. (2007). The Epidemiology of Refractive Error in UK Children: The Aston Eye Study Methodology. ARVO Conference, Florida. *Invest. Ophthalmol. Vis. Sci*, **48**: E-abstract 4847.

The Aston Eye Study: methodology for a population-based study of myopia in UK urban school children

Parth Shah[1], Nicola S. Logan[1], Alicja R. Rudnika[2], Christopher G. Owen[2] and Bernard Gilmartin[1]

[1] School of Life and Health Sciences, Aston University, Birmingham, UK

[2]Epidemiology and Medical Statistics, St. George's, University of London, London, UK

OBJECTIVES: To describe the methodology of the Aston Eye Study (AES), a prospective cross-sectional study, starting October 2005, which will determine the prevalence of refractive error in a large sample of UK school children. The recruitment of children from a large metropolitan area having diverse educational and ethnic backgrounds will facilitate evaluation of recent reports highlighting the significant role of urbanisation and education in the prevalence of myopia.

METHODS: The target population for the AES has been identified by random cluster sampling of schools in the West Midlands area that have been stratified for both socioeconomic index of specific sub-areas and ethnicity. To encompass onset and development phases of child myopia two separate samples are currently being examined over the study period: 1,700 aged 6/7 years and 1,200 aged 12/13 years.

All procedures requiring informed consent (parents) and assent (children) have been approved by the Aston University Ethical Committee. Examinations include: assessment of visual acuity; cover test for oculomotor status; non-contact ocular biometry (i.e. axial length, corneal radius of curvature and anterior chamber depth using IOLMaster *Zeiss, Jena, GmbH*); cycloplegia (proxymetacaine 0.5%:cyclopentolate 1%); binocular open-field autorefraction (Shin-Nippon SRW5000, *Japan*) and measures of height and weight. An 91-item parental questionnaire and 64-item child questionnaire include sections that address potential risk factors and gene-environment interactions related to myopia: e.g. family history of spectacle wear, education, nutrition, ethnicity and lifestyle.

RESULTS: The initial stages of data collection (N=87) and protocols have been well received by both parents and children and without any adverse incidents or effects.

CONCLUSIONS: To date, the AES design and methodology appears sufficiently robust, comprehensive and accessible to provide a valuable database for the target population. The standardized protocols used will, for the first time in over 40 years, allow comparison of UK data with other international population-based data.

CR: None

Support: Central Local Optical Committee (LOC) Fund, UK

Presented at the 11th International Myopia Conference, Singapore (2006).

The epidemiology of refractive error in UK children: the Aston Eye Study

N.S. Logan[1], P.Shah[1], A.R. Rudnicka[2], B.Gilmartin[1] and C.G. Owen[2].

[1]School of Life & Health Sciences, Aston University, Birmingham, United Kingdom
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Purpose The Aston Eye Study (AES) is a 3-year prospective cross-sectional study (started October 2005) to determine the prevalence of refractive error and to describe ocular biometry in a large multi-racial sample of school children from the West Midlands (England).

Methods Schools are selected by random sampling within the West Midlands area, stratified by area deprivation index (a measure of socio-economic status). Schools with pupils predominantly from a single race are excluded. Sample size calculations account for the likely participation rate and the clustering of individuals within schools. Two separate age groups are being sampled: 1700 Year 2 children (age 6/7 years) and 1200 Year 8 children (age 12/13 years). Visual acuity, non-contact ocular biometry (axial length, corneal radius of curvature and anterior chamber depth using IOLMaster Zeiss, Jena) and cycloplegic (proxymetacaine 0.5%:cyclopentolate 1%) open-field autorefraction (Shin-Nippon SRW5000, Japan) are measured in both eyes. Oculomotor balance (cover test), height and weight are also assessed. Questionnaires for parents and older children will allow the influence of environmental factors on refractive error to be examined.

Results The initial stages of data collection (N=226) and protocols have been well received by both parents and children. No adverse incidents or effects have been reported to date. Currently almost 1 in 15 children require refractive correction but do not have the provision of spectacles.

Conclusions The AES will allow the ocular characteristics of 2900 children from a large metropolitan area of England to be described. The association between educational status, ethnic background and other environmental influences on refractive outcome will be determined.

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The Epidemiology of Refractive Error in UK Children: The Aston Eye Study Methodology

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Purpose: The Aston Eye Study (AES) is a cross-sectional study (started October 2005) to determine the prevalence of refractive error and its associated ocular biometry in a large multi-racial sample of school children from the metropolitan area of Birmingham, United Kingdom.

Methods: A target sample of 1700 Year 2 (age 6-7 years) and 1200 Year 8 (age 12-13 years) children is being selected from Birmingham schools selected randomly with stratification by area deprivation index (a measure of socio-economic status). Schools with pupils predominantly (>70%) from a single race are excluded. Sample size calculations account for the likely participation rate and the clustering of individuals within schools. Procedures involve standardised protocols to allow for comparison with international population-based data. Visual acuity, non-contact ocular biometry (axial length, corneal radius of curvature and anterior chamber depth using *IOLMaster* Zeiss, Jena) and cycloplegia (proxymetacaine 0.5% corneal anaesthesia followed by cyclopentolate 1%) binocular open-field autorefraction (Shin-Nippon SRW5000, Japan) are measured in both eyes. Distance and near oculomotor balance (cover test), height and weight are also assessed. Questionnaires for parents (91 items) and Year 8 children (64 items) will allow the influence of environmental factors on refractive error to be examined.

Results: Data collection is ongoing (currently N=330) with protocols being well received by both parents and children. No adverse incidents or effects have been reported to date. Current data indicate that almost 1 in 10 Year 8 children (N=286) require refractive correction but do not have the provision of spectacles.

Conclusions: The AES will allow the ocular characteristics of 2900 children from a large metropolitan area of the United Kingdom to be described. The association between educational status, ethnic background and other environmental influences on refractive outcome will be determined.

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