THE EFFECTS OF ENVIRONMENT AND LIFESTYLE ON EYE GROWTH

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Doctor of Philosophy

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SUMMARY

Aims: To investigate the association between subjectively and objectively measured environmental and lifestyle factors on eye growth.

Rationale: Emmetropisation is the process of visual regulation of eye growth towards an optimal refraction. Disruptions in emmetropisation have been thought to lead to the development of myopia which has increased in prevalence worldwide. It is a condition which brings significant socio-economic burden and sight-threatening complications. This has led to a significant interest in furthering our understanding of the influential factors driving eye growth, which is the focus of this thesis.

Methods: Two age cohorts were recruited, 226 aged 7 – 12 years and 87 aged 18 – 25 years. 55.3% (n=173) were followed up longitudinally after 12 months and 18.5% (n=58) after 24 months. Time spent outdoors was measured by both subjective and objective methods, including questionnaires, a wrist-worn actigraphy device and a surrogate biomarker, Conjunctival UV autofluorescence (CUVAF). Other lifestyle factors were assessed via questionnaires.

Results: Significant differences in objectively measured light exposure were found between seasons and day of the week. UK children were found to spend more time outdoors on weekdays than weekends. This study has shown for the first time a lack of CUVAF in UK children and a low prevalence of CUVAF in UK young adults. This suggests that CUVAF may not be a suitable surrogate measure of time outdoors in the UK. A normative dataset of sleep patterns of UK children is presented and has shown emerging evidence that sleep/wake cycles are altered in myopes. Urbanisation, BMI and birth weight were found to be significantly associated with eye growth, however all other factors were found not be to significant.

Conclusions: The role of illuminance and eye growth is a prominent area of current research and this study has provided valuable data on environmental risk factors in the UK.

Keywords: time outdoors, light exposure, sleep, CUVAF, eye growth, myopia

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"If you put your mind to it,
you can accomplish anything"
– Marty McFly

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LIST OF ABBREVIATIONS

AC	Anterior chamber
ACES	Anyang Childhood Eye Study
AES	Aston Eye Study
AL	Axial length
AL/CR	Axial length: Corneal Radius ratio
ALSPAC	Avon Longitudinal Study of Parents and Children
ANOVA	Analysis of variance
AoA	Amplitude of Accommodation
ATOM	Atropine for Treatment of Myopia
BLINK	Bifocal Lenses In Nearsighted Kids
BMI	Body Mass Index
BMPS	Beijing Myopia Progression Study
BST	British Summer Time
CCT	Central corneal radius
CENTRAL	Cochrane Central Register of Controlled Clinical Trials
CHASE	Child Heart and Health Study in England
CHAMP	Childhood Atropine for Myopia Progression
CI	Confidence interval
CIBSE	Chartered Institute of Building Services Engineers
CLEERE	Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error
cm	Centimetres
COMET	Correction of Myopia Evaluation Trial
CONTROL	Control of Nearsightedness-TRial Of Lenses
CPM	Counts per minute
CR	Corneal radius
CREAM	Consortium on Refractive Error and Myopia
CUVAF	Conjunctival ultraviolet autofluorescence
D	Dioptres
DA	Dopamine
DBS	Disclosure and Barring Service
Diff	Difference
DOPAC	3,4-Dihydroxyphenylacetic acid
ETDRS	Early Treatment in Diabetic Retinopathy Study
FDM	Form Deprivation Myopia
GEM	Genes in Myopia
GOAT	Guangzhou Outdoor Activity Trial
GOS	General Ophthalmic Services
GMT	Greenwich Mean Time

hr	Hour
ICC	Intraclass correlation coefficient
ILM	Internal limiting membrane
IMD	Index of Multiple Deprivation
IMI	International Myopia Institute
IOP	Intraocular pressure
IQ	Intelligence quotient
IQR	Interquartile range
KF	Katherine Franklin
kg	Kilograms
km	Kilometre
κ_w	Weighted kappa
LAMP	Low-concentration Atropine for Myopia Progression
lb	Pounds
LCD	Liquid-crystal display
LE	Left eye
LED	Light emitting diode
LOA	Limits of Agreement
LogMAR	Logarithm of the minimum angle of resolution
LT	Lens thickness
lux	SI derived unit of illuminance
m	Metres
max	Maximum
MD	Mean difference
MF	Multifocal
min	Minimum
mm	Millimetres
MOSAIC	Myopia Outcome Study of Atropine in Children
n	Sample size
NA	Not applicable
NHS	National Health Service
NICER	Northern Ireland Childhood Errors of Refraction
NIM	North India Myopia Study
NL	Nicola Logan
OCT	Optical Coherence Tomography
OLCI	Optical low coherence interferometry
OLSM	Orinda Longitudinal Study of Myopia
OR	Odds ratio
OrthoK	Orthokeratology
oz	Ounces

PALs	Progressive addition lenses
PCI	Partial coherence interferometry
POM	Prescription-only medication
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
PSQI	Pittsburgh Sleep Quality Index
r	Pearson's correlation coefficient
r_s	Spearman's rank correlation
RAF	Royal Air Force
RE	Right eye
REHS	Raine Eye Health Study
RESC	Refractive Error Study in Children
RCT	Randomised control trial
RGP	Rigid gas permeable
ROC	Recess outside classroom
RPE	Retinal pigment epithelium
SATs	Standard attainment tests
SAVES	Sydney Adolescent Vascular and Eye study
SCORM	Singapore Cohort Study of the Risk factors for Myopia
SD	Standard deviation
SE	Standard error
SECS	Sujitan Eye Care Study
SENCO	Special educational needs coordinator
SER	Spherical equivalent refraction
SIMD	Scottish Index of Multiple Deprivation
SMS	Sydney Myopia Study
SNP	Single nucleotide polymorphism
SNR	Signal to noise ratio
STAMP	Study of Theories about Myopia Progression
UK	United Kingdom
USA	United States of America
USD	United States dollar
UV	Ultraviolet
UVB	Ultraviolet-B
VA	Visual Acuity
VC	Vitreous chamber depth
VC/AC	Vitreous chamber: Anterior chamber ratio
VDU	Visual display unit
VI	Visual impairment
χ^2	Chi square
YA	Young Adult

WHO	World Health Organization
©	Copyright symbol
®	Registered trademark symbol
^{o}C	Degrees Celsius
^{o}N	Degrees North
^{o}	Degrees
%	Percentage
<	Less than
>	Greater than
≤	Less than or equal to
≥	Greater than or equal to
±	Plus or minus
ʎ	Wavelength
µm	Micrometre

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Chapter 1: A review of refractive error development and emmetropisation

1.1 Introduction

The aim of this chapter is to summarise the current literature on refractive error starting with its classification and distribution as well as discussing the current mechanisms behind its development and the role of emmetropisation. The worldwide prevalence of refractive is also discussed alongside the public health and economic implications of refractive error and current myopia control strategies that are available to practitioners.

1.2 Classification of refractive error

Refractive error occurs when there is a breakdown in the correlation between the power of the eye's optical system, the lens and cornea, and the length of the eye (Sorsby, 1956, Benjamin et al., 1957). During childhood, elongation of the eye must be accompanied by a compensatory change in cornea and/or lens curvature in order to maintain a clear focused image at the fovea. If this coordination occurs successfully, emmetropia is obtained and there is no requirement for spectacle or contact lens wear, see Figure 1.1. If this coordination does not occur, then either a myopic or hyperopic refractive error develops. Axial length has been found to be the main contributory refractive component involved in determination of refractive error, followed by lens power and to a lesser extent corneal curvature (Olsen et al., 2007).

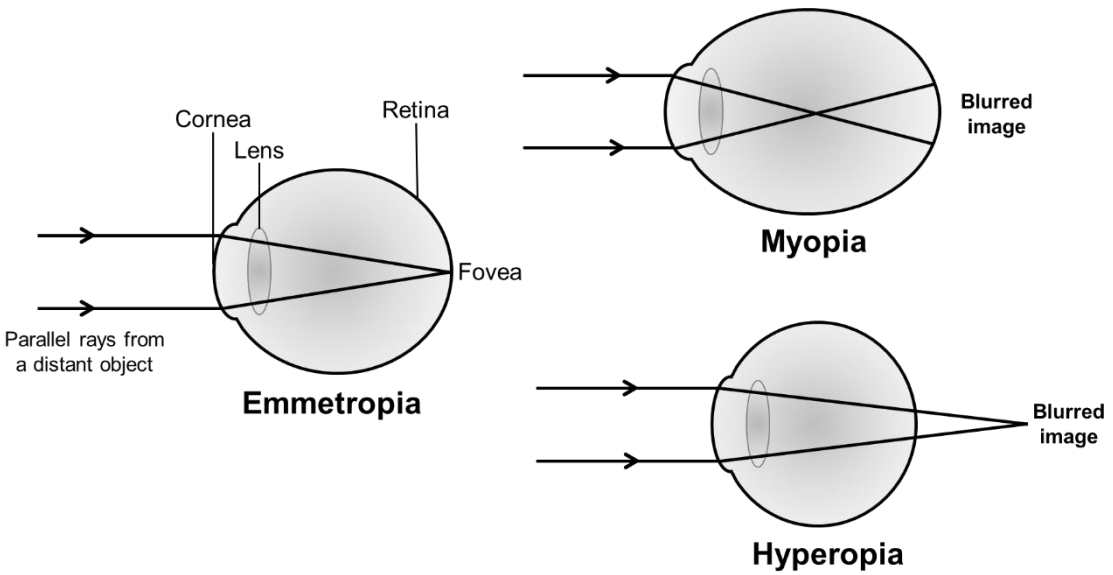


Figure 1.1: Optical representation of emmetropia, myopia and hyperopia

1.2.1 Myopia

Myopia or short sightedness occurs when the image is focussed anterior to the retinal plane projecting a blurred image onto the fovea and causing distance objects to be out of focus, see Figure 1.1, (Bennett and Rabbetts, 1998, Atchison and Smith, 2002). This occurs when coordination of the ocular components does not occur, and this can either be because the eye is too powerful i.e. the cornea is too curved, the lens is too powerful or the eye is too long.

The terminology for the classification of myopia varies greatly in the literature including by age of onset, amount of myopia and even its progression pattern. A recent publication from the International Myopia Institute (IMI) has aimed to outline a set of standards for defining and classifying myopia for epidemiological studies (Flitcroft et al., 2019). The qualitative and quantitative definitions are summarised in Appendix A.1.1.

Myopia is corrected with a concave or negative lens which focuses the image onto the fovea, simulating the state observed in an emmetropic eye (Bennett and Rabbetts, 1998, Atchison and Smith, 2002, Tunnacliffe, 1993). The power of the lens needed to correct for the refractive error is determined by the distance between the fovea and image. Most myopes are reliant on their spectacles for everyday tasks such as driving or seeing the board at school. Contact lenses are a widely available alternative however, in children, their accessibility is limited to those who have the support from parents and are able to afford them.

1.2.2 Hyperopia

Hyperopia or long sightedness occurs when the image is focussed posterior to the retinal plane, when the accommodation is relaxed, projecting a blurred image onto the fovea, see Figure 1.1, (Bennett and Rabbetts, 1998, Atchison and Smith, 2002). This occurs because the cornea is too flat, lens is too weak or the axial length is too short.

Hyperopia can be divided into three categories: simple, pathological and functional (Benjamin and Borish, 2006). Simple hyperopia develops as a result of ocular physiological features related to axial length and refractive components. Pathological hyperopia is caused by an abnormal ocular anatomy primarily caused by congenital defects such as nanophthalmia which can produce hyperopia of between +8.00 and +24.00D (Carricondo et al., 2018). Functional hyperopia arises from paralysis of accommodation, for example in third nerve palsies. The vast majority of hyperopia are classified as simple which are physiological in nature resulting from insufficient ocular power from the lens, a flat cornea or a short axial length.

Hyperopia can be corrected with a convex or positive lens or alternatively pre-presbyopic individuals can accommodate to overcome this deficit, which is driven by the ability of the lens to change shape to move the image onto the fovea (Bennett and Rabbetts, 1998, Atchison and Smith, 2002, Tunnacliffe, 1993). This allows objects at distance and near to be seen clearly. This process occurs reflexively and hyperopic individuals are often unaware of their refractive error; however it also has the potential to cause asthenopic symptoms associated with prolonged close tasks (Bennett and Rabbetts, 1998, Atchison and Smith, 2002). The power of the lens needed to correct for the refractive error, similarly to myopia, is determined by the distance between the fovea and image as well as the amount of residual accommodation.

1.2.3 Astigmatism

Astigmatism is characterised by a variation in the dioptric power of the eye from one meridian to another (Benjamin and Borish, 2006). This creates a cylindrical cross section which is usually caused by one or more refracting surfaces, most commonly the anterior cornea, having a toroidal shape (Atchison and Smith, 2002). This produces 2 principal foci each of which need to be independently corrected as a result astigmatism requires a cylindrical lens correction. Astigmatism can be associated with myopia or hyperopia. Astigmatism is generally classified as either with-the-rule or against-the-rule. The steepest meridian in with-the-rule astigmatism is the vertical meridian, whereas in against-the-rule astigmatism, the steepest meridian is horizontal (Atchison and Smith, 2002, Tunnacliffe, 1993).

1.3 Refractive error distribution

1.3.1 Distribution of refractive error in young adults

Interestingly, refractive error does not follow the usual Gaussian distribution of other biological variables such as height and weight. Adult refractive error distribution is leptokurtic with a negative skew (Stenstrom, 1948). This distribution is demonstrated in Figure 1.2 which shows data from a UK study by Sorsby et al (1960) of army recruits aged 17 and 27 years old. Note that there is an increased number centred around the marginally hyperopic mean and also a negative skew with a slight tendency for a myopic refraction.

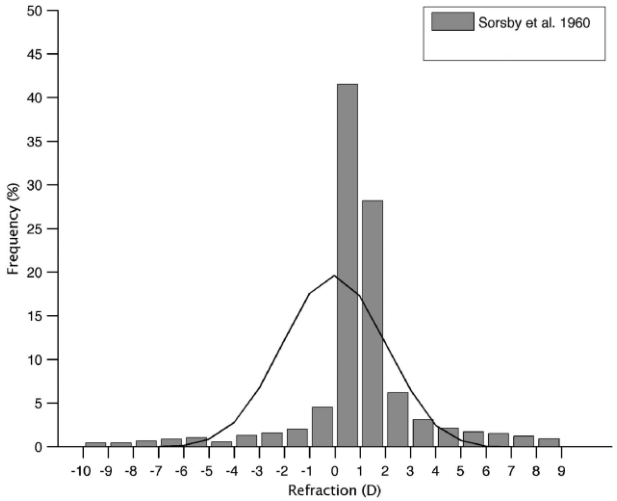


Figure 1.2: UK young adult refractive error distribution from Sorsby et al (1960) study Reproduced with permission from Flitcroft et al (2014)

This negative skew is becoming more prominent in recent years, primarily in East Asian countries, but also within the UK where the incidence of myopia is increasing. This can be seen in Figure 1.3 which shows a more recent refractive distribution of a sample ofUK undergraduate students (n=373) aged 17 – 30 years (Logan et al., 2005). On comparison to Figure 1.2 the increased negative skew towards a myopic refraction is noticeable.

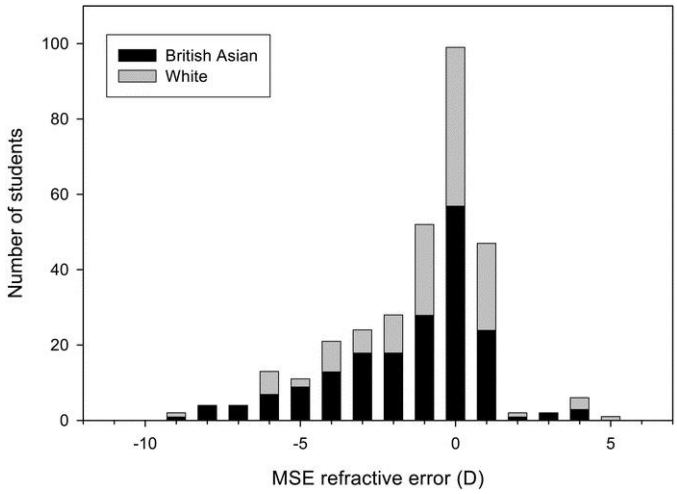


Figure 1.3: Refractive error distribution of a UK university student population Reproduced with permission from (Logan et al., 2005). MSE: Mean Spherical Equivalent

1.3.2 Distribution of refractive error in children

The distribution of refraction in children is significantly different to that displayed for adults in the section above. A leptokurtic distribution emerges which unlike the adult distribution is positively skewed (Ojaimi et al., 2005b, Watanabe et al., 1999). At birth

the majority of neonates demonstrate a significant amount of hyperopia which is considered normal at this early stage of development (Wildsoet, 1997). Emmetropia and myopia is a rare finding at this age (Cook and Glasscock, 1951, Saunders et al., 1995). However, this hyperopia diminishes throughout childhood as the ocular components grow and change (Mutti et al., 2005). This developmental process by which the structural components of the eye change in order to coordinate the eyes optical power to its size and shape towards an ideal refractive state is termed emmetropisation (McBrien and Barnes, 1984).

This emmetropisation process takes place during infancy and as a result the distribution of refractive error varies greatly with increasing age. Between 3 months and 3 years the mean refractive error shifts from +2.00 to +0.75D (Flitcroft, 2014). This is considered the optimal progression towards emmetropia or low hyperopia. After the age of 6 a distribution with a negative skew emerges with an increasing prevalence of myopia. This distribution has been shown in data from the Northern Ireland Childhood Errors of Refraction (NICER) study of 6 – 7 year old UK children McCullough et al (2016). Myopia rates at this age are relatively low compared to older age groups. In addition, it is interesting to observe the increase in skew towards myopia in the NICER data compared with data from Sorsby et al (1961) seen in Figure 1.4. The myopia prevalence was found to have increased two-fold over the 50 year period further supporting the literature that myopia prevalence has increased rapidly over the past few decades (Dolgin, 2015).

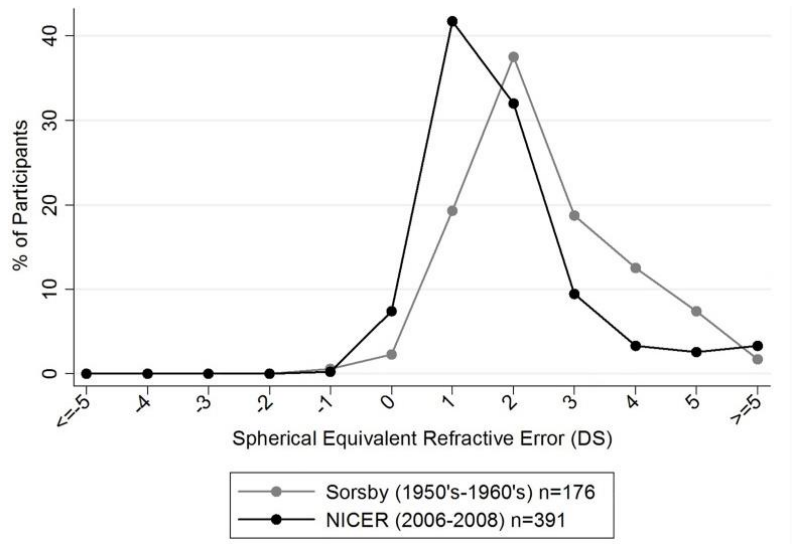


Figure 1.4: Distribution of refraction in 6-7 year old children in NICER and Sorsby et al (1961) Reproduced with permission from McCullough et al (2016)

A number of studies have demonstrated an increase in myopia prevalence with age. NICER found an increase from 1.9% to 14.6% between the 6 – 7 year old cohort and 12

– 13 year old cohort respectively (O'Donoghue et al., 2010a). Similarly, in Australia French et al (2013a) found an increase from 1.4% to 14.4% between the same age groups and 29.6% in those aged 17 years. Figure 1.5 demonstrates this trend of increasing myopia with age found in a cohort of school children conducted over a 13-year period in Japan.

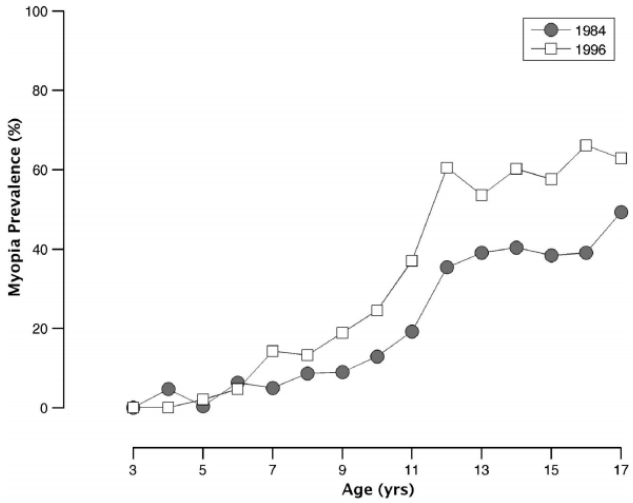


Figure 1.5: Myopia prevalence in Japanese school children from ages 3 – 17 years
Reproduced with permission from Matsumura and Hirai (1999)

This increase in prevalence after the primary emmetropisation period suggests that myopia is caused by a failure to maintain this emmetropic state rather than a failure of the primary emmetropisation process (Flitcroft, 2014). The development of hyperopia and myopia are discussed in detail in Section 1.5. However, in order to understand these processes, a more in depth understanding of emmetropisation is required which is discussed in the next section.

1.4 Emmetropisation

Emmetropisation is considered to be the process of visual regulation of eye growth towards an optimal refraction and involves the coordination of ocular structures. In humans the optimal refraction is emmetropia, whereby the optical structures of eye, namely the cornea and lens, are coordinated with the ocular axial length such that light is focused on the fovea and there is no requirement for spectacle correction, see Figure 1.1. The average neonate has a hyperopic refraction of +2.00D and a rapid reduction in refraction to approximately +0.75D occurs within the first few years of life (Flitcroft, 2014). However, the eye grows from 15mm in newborns to approximately 24mm in early adulthood, this change represents a refractive change of more than 40 dioptres (Iribarren, 2015). As the axial length elongates it is counteracted by an equal but

opposite change in corneal and lens power such that the ocular refraction progresses towards an optimal refractive state which in humans is emmetropia (Robinson, 1999). Straub, cited in Sorsby et al (1932), termed this process emmetropisation.

Sorsby and Leary (1969) stated that this process has 2 phases: a rapid infantile growth phase which occurs between birth and three years followed by a much slower juvenile phase up to early teenage years. During the rapid infantile growth phase, the structures of the eye must compensate for a large increase in axial length of 5mm. Both cross sectional and longitudinal studies have suggested that emmetropisation primarily begins between the first three to nine months of life (Mutti et al., 2005, Mayer et al., 2001, Pennie et al., 2001). As mentioned previously, there is a progressive myopic shift in refraction in childhood towards low hyperopia or emmetropia (Flitcroft, 2014). Biometric data have shown that corneal and lenticular power reduce during the rapid infantile phase alongside axial elongation (Mutti et al., 2005). Emmetropisation begins to slow after the first three years of life but a clear leptokurtic distribution emerges at school age see Figure 1.4 (French et al., 2012, Ojaimi et al., 2005b, Watanabe et al., 1999, McCullough et al., 2016).

The slower juvenile phase period occurs from three years old up until adolescence, during this period corneal and lens changes continue to occur but at a much slower rate. Continued growth of the eye between the ages of 6 and 15 year was demonstrated by Zadnik et al (2004) with an upward trend of axial length, anterior chamber depth, and vitreous chamber depth.

The majority of physiological myopia occurs during this slow juvenile phase and is thought to occur as a result of a failure to maintain an emmetropic state (Grosvenor, 1987). Myopia is often evident by the age of nine and is followed by a rapid phase of myopic refractive shift which plateaus towards a relatively stable refraction in adulthood (Flitcroft, 2014, Goss, 1990, Goss and Winkler, 1983, Thorn et al., 2005). What triggers this sudden acceleration of myopia and initiates the cessation is currently unknown (Flitcroft, 2014).

1.4.1 Evidence of visual cues in emmetropisation

Extensive investigations on animal models have provided key evidence that emmetropisation is an active process which is regulated, and can be modified, through environmental visual cues (Chakraborty et al., 2020). A wide variety of animal species have been used to demonstrate these mechanisms including chickens, tree shrews, guinea pigs, cats, macaque and marmoset monkeys (Troilo et al., 2019, Wildsoet, 1997,

Schaeffel and Feldkaemper, 2015). The most fundamental discoveries include eye growth responses to and recovery from form deprivation and optically induced defocus. A review of the large body of literature in this field is discussed below.

1.4.1.1 Form Deprivation

Form deprivation is designed to deprive all aspects of spatial vision and was initially employed through the use of surgical eyelid sutures and subsequently induced by the use of translucent diffusers over the eye. Increased axial elongation and subsequent myopic refraction from form deprivation has been shown in a number of animal species including monkeys, cats and chicks (Hubel and Wiesel, 1970, Wiesel and Raviola, 1977, Smith et al., 1987, Thorn et al., 1981, Gottlieb et al., 1987, Vonnoorden and Crawford, 1978). This outcome has been coined Form Deprivation Myopia (FDM). Most interestingly it has also been demonstrated in humans in individuals with ptosis and congenital cataracts (Oleary and Millodot, 1979, Vonnoorden and Lewis, 1987). FDM has been found to be primarily the result of an increased vitreous chamber as well as thinning of the choroid (Howlett and McFadden, 2006, Troilo et al., 2000, Smith and Hung, 2000, Hung et al., 2000, Wildsoet and Wallman, 1995).

Recovery from FDM has provided clear evidence that eye growth and emmetropisation is an active process as on removal of the form deprivation, for example by removal of the diffuser, myopic defocus is experienced and a resultant rapid reduction in the experimentally induced myopia has been shown to occur (Howlett and McFadden, 2006, Shen et al., 2005, Qiao et al., 2001, Wildsoet and Schmid, 2000, Wallman and Adams, 1987, Troilo et al., 2000). This recovery has been primarily found to be related to changes in vitreous chamber elongation rates. Qiao-Grider et al (2001) demonstrated this in macaque monkeys treated monocularly with a spectacle diffuser. On removal of the diffuser, the vitreous chamber of the untreated control eye continued to grow at the normal rate however the grow rate of the treated eye virtually ceased. Once the control eye caught up with the treated eye in terms of vitreous chamber depth and refractive error such that both eyes were more similarly matched, the formerly deprived eye begun to grow again. It has also been demonstrated that localised retinal changes can be observed by using diffusers that cover only part of the visual field which result in axial elongation limited to the affected part of the retina (Smith et al., 2009, McFadden, 2002, Diether and Schaeffel, 1997, Wallman et al., 1987).

1.4.1.2 Optically induced defocus

Compensatory eye growth responses to both hyperopic and myopic defocus have provided compelling evidence that emmetropisation is an active process driven by visual

cues (Wildsoet, 1997, Wallman and Winawer, 2004, Troilo, 1992). This was first shown by Schaeffel et al (1988) who demonstrated that chicks who wore positive or negative spectacles lenses compensated for the defocus with appropriate eye growth in order to maintain an emmetropic state. Specifically, the use of negative lenses creates hyperopic defocus (image focussed behind the retina) which induced eye growth and myopia development. Conversely, positive lenses produce myopic defocus (image focussed in front of the retina) which led to inhibition of eye growth and hyperopia development. These experiments suggest that the eye has the ability to detect and distinguish defocus and adapt accordingly in the appropriate direction. This compensation for lens induced defocus has been replicated in chicks, tree shrews, guinea pigs, mice and monkeys (Troilo et al., 2019, Wildsoet, 1997, Smith et al., 2009). Chicks have been shown to have the largest compensation range with an ability to adapt to spectacle lens powers between -10 and +20D (Irving et al., 1992).

Similarly to FDM, lens induced defocus can be localised and produce regionally selective compensatory changes (Diether and Schaeffel, 1997, Irving et al., 2015). Also interestingly chicks reared in cages designed to have close ceilings induced localised myopia in the inferior field as a result of a relatively hyperopic superior field induced by the cage ceiling (Miles and Wallman, 1990).

1.4.1.3 Other optical characteristics

In addition to the large body of literature demonstrating the visual regulation of emmetropisation and refractive error development in form deprivation and optically induced, other characteristics of light and its aberrations also need to be considered.

The spectral characteristics of light encompasses a number of factors including longitudinal chromatic aberration (LCA), wavelength and intensity. LCA causes short wavelengths (red) to be focused in a more myopic plane than long wavelengths (blue). Altering the chromaticity of light has been shown to act as a directional cue. It has been shown to induce and reverse refractive error in chicks and guinea pigs. More specifically red light induced myopia cold be reversed to hyperopia in chicks by changing red light to blue light (Foulds et al., 2013) and blue light inhibited axial eye growth in guinea pigs (Jiang et al., 2014). Studies in rhesus monkeys have also shown that animals reared in light dominated by long wavelength light resulted in a more hyperopic refraction (Hung et al., 2018). This was also demonstrated with the use of red filters over one or both eyes and interestingly following removal of the filter, recovery from the induced hyperopic error was observed (Smith et al., 2015).

Numerous studies have also shown increased illuminance to be protective against the development of FDM in animal models. Young chicks exposed to both high levels of sunlight (30,000 lux) or laboratory light (15,000 lux) slowed the development of form deprivation myopia by 65% (Ashby et al., 2009, Ashby and Schaeffel, 2010). Similar findings were found in infant monkeys and tree shrews exposed to high ambient lighting (Smith et al., 2012, Siegwart et al., 2012, Wang et al., 2015). Furthermore, light levels have been found to modulate the emmetropisation process in chicks. Cohen et al (2011) reared chicks in three different light conditions: high (10,000 lux), medium (500 lux) and low (50 lux). The chicks reared in the low light condition all progressed to a myopia refraction (mean refraction -2.4±1.2D) whereas no chicks in the high light condition developed myopia and instead exhibited a stable hyperopic refraction (mean refraction +1.1±0.2D). The medium intensity group had a mean refraction of +0.03±0.5D. Increased time outdoors and illuminance has also been shown to be protective against myopia onset and development in children, this is discussed in detail in the next Chapter in Section 2.2.

Another optical characteristic to consider are higher order monochromatic aberrations (HOAs) such as spherical aberration, coma and trefoil. These aberrations have been shown to change during emmetropisation and also with refractive error (Brunette et al., 2003, Coletta et al., 2010, de la Cera et al., 2006, Ramamirtham et al., 2007). Rhesus monkeys reared with optically induced defocus or form deprivation showed a higher amount of aberrations in treated eyes at the end of the lens rearing period (Ramamirtham et al., 2007). Following recovery from the experimentally induced refractive error higher order aberrations also decreased. These results suggest that differences in HOAs between refractive errors are a consequence of differences in optical components rather than playing an active role in the visual regulation of emmetropisation and refractive error development. HOAs are directly influenced by the shape and configuration of the eyes optical components which are known to change during the process of emmetropisation and are discussed below.

1.4.2 Ocular component change during emmetropisation

From birth to early adulthood structures of the eye grow and develop and the process of emmetropisation is designed to ensure that the eye develops into an “ideal” refractive state. For humans this is low levels of hyperopia or emmetropia. In other animals species such as guinea pigs the residual refraction is low myopia (Schaeffel and Feldkaemper, 2015). This difference could be suggestive of a varying emmetropisation

process however it could also be an adaptation to their caged environment (Troilo et al., 2019).

Coordination of the ocular components, primarily the axial length, cornea and crystalline lens during this process will determine the residual refraction in school aged children and teenagers. As the eye elongates with age, a reciprocal change in the cornea and lens is vital in order to maintain an optimal refractive state. If there is a mismatch in this process and emmetropisation fails, then ametropia occurs as a result (Flitcroft, 2013).

A recent large longitudinal study provided comprehensive average growth curves of refractive error and ocular components in children aged 3 months to 6.5 years (Mutti et al., 2018). The Berkeley Infant Biometry Study confirmed this biphasic process of emmetropisation with most of the change occurring in the first two years of life during a rapid exponential growth phase followed by a much slower phase of growth. As expected, the axial length increased during follow up on average +3.35 ± 0.64mm from 3 months to 6.5 years. A reduction in power of the cornea and lens was found which was associated with flattening of both radii and lens thinning.

The Orinda Longitudinal Study of Myopia (OLSM) provides information about changes that occur in emmetropic children in the later stage of childhood between the ages of 6 and 15 years (Zadnik et al., 2004). Axial elongation was found to be have slowed with an average increase of less than 1mm elongation and vitreous elongation was suggested as the driving force behind the myopic shift in refraction. Only minimal corneal flattening occurs, however significant flattening of the crystalline lens was found to occur with increasing age making it the most likely candidate in the mediation of emmetropisation (Mutti et al., 2005, Zadnik et al., 2004).

1.4.2.1 Axial Length

Axial length is measured as the distance from the anterior surface of the cornea to the anterior retina. This includes the central cornea thickness, anterior chamber, the area between the cornea and the anterior crystalline lens surface, lens thickness and the vitreous chamber, the area between the posterior crystalline lens and the retina, see Figure 1.6. The retina comprises of 10 layers and different biometric techniques measure to different layers, discussed in Section 4.3. The retina is supported by two further structures called the choroid, a vascular layer and the sclera, a fibrous outer protective layer.

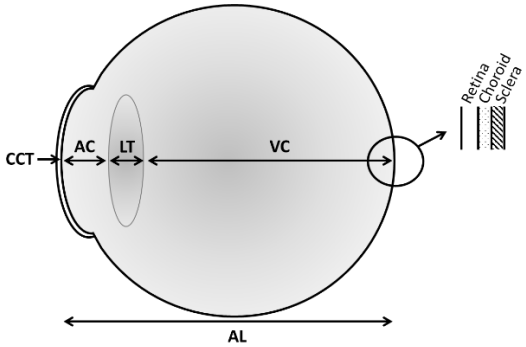


Figure 1.6: Ocular biometry components CCT: Central Corneal Thickness AL: Axial Length AC: Anterior Chamber LT: Lens Thickness VC: Vitreous Chamber

A rapid rate of growth in the infant eye is well documented (Mutti et al., 2005, Mutti et al., 2018, Pennie et al., 2001, Zadnik et al., 2004). Between the ages of 3 and 9 months a significant increase from 19.03±0.58mm to 20.23±0.64mm (difference +1.20±0.51mm, $p<0.0001$) has been found (Mutti et al., 2005). In line with the biphasic nature of the emmetropisation process, a much larger change was found between the ages 3 months and 6.5 years, 19.19±0.69 and 22.39±0.71 mm respectively (difference +3.35±0.64mm, $p<0.001$) (Mutti et al., 2018). This growth was found to slow between the ages 6 and 14 years, 22.57 mm to 23.30 mm respectively (difference +0.73mm) (Zadnik et al., 2004). In all three of these studies the axial length elongation was associated with an increased anterior chamber depth (AC) and vitreous chamber depth (VC). These findings are also in agreement with data from the Singapore Cohort Study of the Risk factors for Myopia (SCORM) and Northern Ireland Childhood Errors of Refraction (NICER) study (Saw et al., 2005, Breslin et al., 2013). Axial elongation has been found to stabilise earlier in females (14.6 – 15.3 years) compared to males (15.0 – 16.7 years), which typically coincides with the end of puberty and the cessation of body growth (Goss et al., 1990)

Axial length is considered the primary determinant of refractive error (Young et al., 2007, Olsen et al., 2007) and is widely used to classify different types of refractive error (Flitcroft et al., 2019). The correlation between axial length and refractive error is greater than with any other ocular component (van Alphen, 1961). Excessive axial elongation is the primary precipitant for myopia development (McBrien and Adams, 1997, Mutti et al., 2007, McBrien and Millodot, 1987). For low levels of myopia there is not a consistent pattern of axial length in relationship to myopia and axial length can fall within the normal range for emmetropia. In these cases, it is likely that other ocular structures such as the cornea and crystalline lens are responsible for the myopia.

1.4.2.2 Cornea

The cornea is the anterior ocular surface and is an important component of the optical properties of the eye. It is responsible for two-thirds of the eyes dioptric power and it's power is directly related to its curvature (Gipson, 2007). Steeper corneas have an increased refractive capability relative to flatter corneas and as a result produce a relatively more myopic focus.

Between the ages of 3 and 6 months a reduction in corneal power has been found, alongside an associated flattening of the cornea from 43.90 to 42.83D (7.69 to 7.88 mm) (Mutti et al., 2005). However, between the ages 6 and 14 years corneal power remains reasonably stable with only minimal corneal flattening occurring, 43.69 to 43.63 D (7.72 to 7.74 mm) despite axial elongation occurring (Zadnik et al., 2004). This is supported by data from the Correlation of Myopia Evaluation Trial (COMET) study that measured changes in biometry over 14 years, in a cohort of 469 6 – 12 year old myopic children (Scheiman et al., 2016). A small but significant ($p<0.0001$) flattening in corneal curvature was found but only in the flattest meridian during the first 5 years. This is consistent with the 3 year longitudinal data from SCORM study in Singapore (Saw et al., 2005).

Corneal curvature has also been found to vary depending on refractive error. Myopic eyes have been found to have steeper corneas than emmetropes (Garner et al., 2006, Goss et al., 1997). Paradoxically, larger emmetropic eyes have been found to have flatter corneas (Grosvenor and Scott, 1993). As part of the Sydney Myopia Study (SMS), corneal radius in emmetropes (defined as -0.49 to +0.49D and moderate hyperopes (+2.00D or greater) was compared in children aged 6 to 12 years (Ip et al., 2008b). Children with moderate hyperopia had flatter corneas than those of age matched emmetropic children ($p<0.05$).

In addition to measurements of central corneal radius, some researchers have investigated the Axial Length:Corneal Radius (AL/CR) ratio as a method of exploring the role of the cornea in the development of refractive error (He et al., 2015b, Grosvenor, 1988). It has been suggested that an emmetropic eye would be expected to have an AL/CR ratio of 3.0 (Goss and Jackson, 1995, Grosvenor and Scott, 1994). Grosvenor and Scott (1993) found that with increasing amounts of myopia the axial lengths were longer and the corneal radii steeper resulting in a larger AL/CR ratio. Baseline data from the COMET study of 469 myopic children found that the ratios of 95% of the cohort were greater than 3.0 (Gwiazda et al., 2002). Longitudinal data from the same study found the average AL/CR ratio increased from 3.15 at baseline to 3.31 at the 14-year follow

up (Scheiman et al., 2016). In addition, a number of studies have found a better correlation between refractive error and AL/CR compared to axial length alone (Scheiman et al., 2016, Ip et al., 2007a, He et al., 2015b). As a result AL/CR has been suggested as a more useful marker in monitoring the progression of refractive error especially myopia than axial length alone as well as the potential to predict eyes that are likely to become myopic (Goss and Jackson, 1995).

A number of studies have explored the relationship between corneal curvature, sex and ethnicity. COMET, CLEERE and SMS all found that females had a significantly steeper corneas than boys (Twelker et al., 2009, Gwiazda et al., 2002, Ip et al., 2008a, Fan et al., 2004). In the COMET study, this was despite a similar mean spherical equivalent refraction (-2.40D versus -2.35D respectively) (Gwiazda et al., 2002). CLEERE also investigated differences between ethnicity and corneal curvature. They found a marked difference with Native Americans and Hispanics, both having a statistically significant and clinically meaningful (≥0.50D) flatter cornea in the horizontal meridian compared to Caucasian (Twelker et al., 2009). An Australian cohort of children aged 11 – 15 years found that European Caucasians and South Asian ethnicities had the steepest corneas (Ip et al., 2008a).

Corneal changes do appear to have a significant role in the emmetropisation process but only at an early stage and it's emmetropisation ability appears to be limited up to a certain point.

1.4.2.3 Crystalline Lens

The crystalline lens accounts for the remaining third of the eye's dioptric power and is an ocular structure that continues to grow throughout childhood into adult life (Flitcroft, 2014). It undergoes changes in its thickness, curvature and refractive index over time.

A comprehensive picture of crystalline lens changes in childhood was found by the OLSM study which provides longitudinal biometric data from baseline 6 year old children until 14 years of age (Zadnik et al., 2004, Mutti et al., 1998). This study confirmed the typical decreasing lens thickness pattern with age previously reported in children (Zadnik et al., 1995) as well as flattening of the lens curvature.

In addition, the calculated power of the crystalline lens was found to have decreased by 2.11D between the ages 6 and 14 years, losing 8.4% of its power (Zadnik et al., 2004). The resultant flattening of the radii of curvature as well as a reduction in refractive index is the likely cause of the loss of power. Interestingly over the course of the study on average the eyes grew by 0.73mm which is equivalent to a 1.94D myopic shift. In light

of the fact that the majority of children did not become significantly myopic to that extent indicates that the lens plays a significant role in the maintenance of an optimal refractive error alongside changes in axial elongation. It was suggested that the concurrent thinning and flattening of the lens, alongside the increase in axial length, was a result of mechanical stretching caused by the equatorial growth of the eye during childhood (Mutti et al., 1998). However, some research has shown minimal changes in the anterior segment growth after the age of two (Brown and Bron, 1996) and so it has been proposed that the "redistribution of the gradient index structure within the lens contributes to the loss of lens power" (Iribarren, 2015).

The progression of various features of the crystalline lens during childhood has been well documented and point to its importance in maintaining emmetropia. However, literature on changes in the crystalline lens with myopia are scarce. However, myopic children have been found to consistently have lower lens thickness and lower lens power (Jones et al., 2005, Mutti et al., 2005, Zadnik et al., 2003, Shih et al., 2009, Gwiazda et al., 2002). Further research into the development of the crystalline lens could provide an insight into the mechanism of emmetropisation and also how emmetropia can be lost resulting in refractive error, such as myopia.

1.4.3 Conclusions

Research investigating the role of vision in the regulation of ocular growth suggests that visual feedback is necessary to actively coordinate ocular growth and emmetropisation. In form deprivation, the lack of stimulus results in an eye that continues to elongate unregulated with seemingly no visual cues to stop. In lens induced defocus it has been shown that the eye is able to detect and respond accordingly to both hyperopic and myopic defocus with a perceived aim of creating an optimal refractive state, in humans this is emmetropia.

The understanding behind the mechanisms involved in the regulation of eye growth and emmetropisation are still being understood. Experiments that removed obvious neural inputs and outputs to the eye through surgical removal of the optic nerve did not interfere with the development of FDM (Troilo et al., 1987, Wildsoet and Pettigrew, 1988). Thus showing that the processes are local in nature and that neural input into the eye is not essential to regulate ocular growth. Direct evidence of the localised control of eye growth within the retina has been demonstrated in experiments in which visual experience has varied across the visual field (Diether and Schaeffel, 1997, Smith et al., 2009, Wallman et al., 1987, Irving et al., 2015). Furthermore, monocular differences produced in animals where one eye has been treated and the other used as a control

have shown that the effects of vision are largely independent in two eyes with identical environmental and genetics factors minimising any confounding effect.

1.5 Refractive error development

The question still remains that if the process of emmetropisation exists and is an active process that has the ability to respond and adapt to visual stimuli, how does refractive error develop? This question is explored below.

1.5.1 Mechanism of myopia development

Myopia is thought to develop because of an inability to maintain an emmetropic refractive status as a result of a break down in the maintenance of emmetropia. A trend for increasing myopia prevalence worldwide has been well documented (Holden et al., 2016). This has led to a significant interest in furthering our understanding the mechanism of myopia development in an attempt to explain its rapid insurgence. Subsequently, this understanding has been vital in the development of myopia control strategies designed to slow the onset/progression of myopia. There has been a large amount of literature surrounding the influence of environmental and lifestyle factors, such as time outdoors, on myopia onset and progression which is discussed in Chapter 2. Research using animal models has shown that myopia can be induced through form deprivation and hyperopic defocus created through the use of spectacle lenses which appear to act as a signal for axial elongation. The role of both peripheral and central hyperopia in myopia development are discussed.

1.5.1.1 Relative peripheral hyperopic defocus

Studies examining myopia progression have found increasing axial length to be the primary growth response (Chua et al., 2006, Gwiazda et al., 2003). As a result of this longitudinal elongation the eye shape is altered. Four potential models for the nature of this growth have been proposed: Global expansion, equatorial expansion, posterior polar expansion and axial expansion (Strang et al., 1998b, Verkicharla et al., 2012), see Figure 1.7. In all four models for an uncorrected eye there is less myopia in the periphery than the centre of the retina due to the posterior ocular surface contour, resulting in relative peripheral hyperopia compared to the fovea. The number of individuals that fit into each expansion model has been evaluated and no single model was found to fit all myopes (Atchison et al., 2005a). The majority fitted into either the global or axial expansion models.

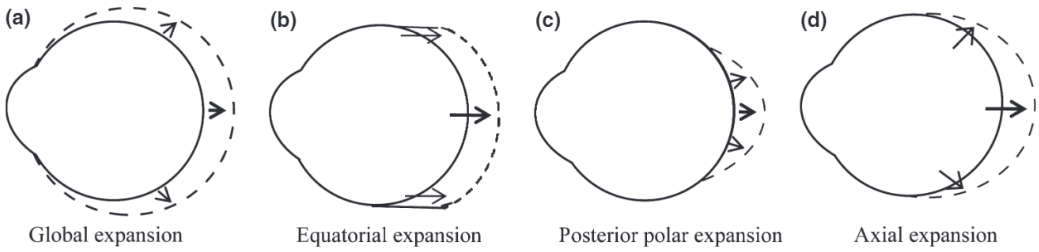


Figure 1.7: Models of retinal stretching in myopia: a) global b) equatorial c) posterior polar and d) axial expansion. The solid circles represent the shape of the retina of an emmetropic eye; the dashed shapes represent the myopic retinas, and the arrows indicate the regions of stretching. Reproduced with permission from Verkicharla et al (2012)

Myopic eyes have been associated with relatively prolate globe shapes (Gilmartin et al., 2013, Lim et al., 2020, Mutti et al., 2000b). Peripheral refraction studies have supported these findings with relative hyperopic refraction found peripherally (Mutti et al., 2007, Logan et al., 2004, Rotolo et al., 2017) . The amount of relative hyperopic refraction has been found to increase in magnitude with increasing eccentricity (Atchison et al., 2005b, Calver et al., 2007, Millodot, 1981, Seidemann et al., 2002). It is this peripheral hyperopic defocus that is thought to provide a strong signal for myopic growth and is considered by many to be the driving factor behind myopia development and axial elongation (Smith et al., 2007, Smith, 2011, Mutti et al., 2007, Schmid, 2011, Benavente-Perez et al., 2014). A longitudinal study assessing children's eyes before and after the onset of myopia concluded that relative peripheral hyperopia is a useful predictor of myopia onset (Mutti et al., 2007). Results from clinical studies indicate that peripheral treatment strategies such as orthokeratology and multifocal contact lenses are effective at slowing myopic progression (Huang et al., 2016). Orthokeratology was not initially designed for this purpose and was instead developed as an alternative to daily spectacle/contact lens wear through the temporary reshaping of the cornea. Through the reverse geometry design of the rigid gas permeable (RGP) lens used in orthokeratology the image shell is altered reducing the amount of hyperopic peripheral refraction, demonstrated in Figure 1.8B. Multifocal contact lenses use concentric rings of alternative powers to create a dual-focus optical design comprises of a central zone correcting the refractive error and peripheral zones of hyperopic power to create simultaneous myopia retinal defocus.

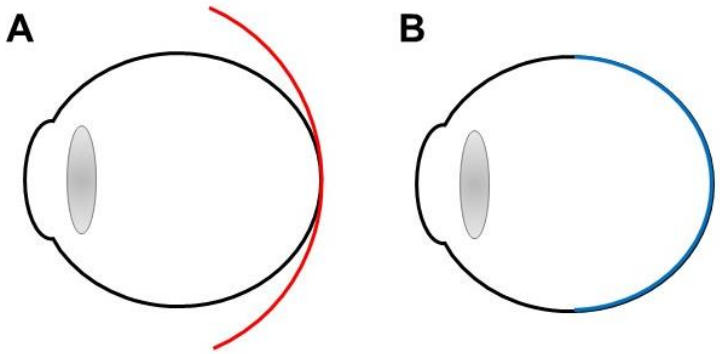


Figure 1.8: Peripheral refraction image shells A) Demonstrates the image shell produced by conventional single vision spectacles or contact lenses where the image is focused at the fovea but results in relative peripheral hyperopic defocus B) Demonstrates the image shell produced when both central and peripheral refraction is corrected

1.5.1.2 Accommodative lag and central hyperopic blur

As well as peripheral hyperopic blur, central hyperopic blur caused by a lag of accommodation during near tasks has been linked with abnormal axial growth (Charman, 1999, Goss and Rainey, 1999). This is supported by clinical observations that have found myopes to have a reduced accommodative response compared to emmetropes (Gwiazda et al., 1993b, Mutti et al., 2006, Gwiazda et al., 1995, Schmid and Strang, 2015). It has therefore been theorised that this lag in accommodation produces hyperopic blur at the fovea which provides the aberrant signal for increased axial growth. This theory is supported by the Correction of Myopia Evaluation Trial (COMET) and the Study of Theories about Myopia Progression (STAMP) which both found that the use of progressive addition lenses was effective at slowing myopia progression in myopes with high accommodation lag (Gwiazda et al., 2004, Berntsen et al., 2012). Furthermore, the response in animal models to minus lenses which stimulate hyperopic defocus also strongly supports this theory (Schaeffel et al., 1988, Hung et al., 1995, Shaikh et al., 1999, Irving et al., 1992). However, if the lag of accommodation is thought to only be present during near tasks, then the hyperopic defocus would be interspersed with periods of clear vision when the individual is not focussing on a near target. Periods of clear vision have been shown, in animal models, to eliminate the “grow” signal (Norton et al., 2006, Schmid and Wildsoet, 1996). More recently in marmosets, short daily interruptions to imposed hyperopic defocus effectively blocked axial elongation and myopia development (Benavente-Perez et al., 2019).

The cause for the association between myopes and insufficient accommodative power has been found to be related to a developmental failure in the lens and ciliary body. Failure of the ciliary body to expand creates mechanical tension anteriorly (Mutti et al., 1998, Zadnik et al., 1995, Berntsen et al., 2012). This tension in the anterior portion of the globe reaches a critical point whereby the expansion of the globe is restricted. It is hypothesised that this tension inhibits equatorial growth resulting in a rapid axial elongation producing myopia (Berntsen et al., 2012). Subsequently, the lens is unable to compensate for this axial elongation as it can no longer decrease in power by thinning and stretching (Mutti et al., 1998, Zadnik et al., 1995). Furthermore, the tension also increases the accommodative effort which is the likely cause of the increased accommodative lag (Mutti et al., 2006) and AC/A ratio (Mutti et al., 2000a) found in myopes. Thus, this theory suggests that accommodative lag is a by-product of myopia as opposed to the precipitating factor. This has been shown to be the case in marmosets (Troilo et al., 2007). The mechanical tension induced may also explain the diversity in eye shape evident in myopes and why not one consistent model of retinal stretching has been found (Atchison et al., 2005a, Verkicharla et al., 2012).

1.5.2 Mechanism of hyperopia development

Hyperopia appears to stem from a failure of the emmetropisation process. In comparison to the vast amount of research on myopia development there is only minimal information about the mechanism of hyperopia development. The reasoning for this has been suggested to be two fold in nature; (1) the prevalence of hyperopia is comparatively lower than myopia and (2) the nature of hyperopia development is significantly different to myopia (Strang et al., 1998a). Generally, hyperopic children are hyperopic from an early age and their refraction remains relatively stable. This is in contrast to myopia which tends to occur at a later stage around 7 – 12 years old and is progressive in nature. The majority of evidence suggests that hyperopic eyes have shorter axial lengths as well as shallower anterior chambers which puts them at an increased risk of closed angle glaucoma which is potentially sight threatening if not treated swiftly (Stenstrom, 1948, Lowe, 1970, Bonomi et al., 2000). The majority of hyperopia, similar to myopia, has been found to be axial in nature (Strang et al., 1998a). Hyperopia has been suggested to arise from a lack of completion of emmetropisation (Mutti, 2007, Atkinson et al., 2000).

As discussed previously, hyperopic defocus has been implicated in the development of myopia. As result there has been research investigating the effect of full and partial correction of hyperopia in children which to date has been inconclusive. Atkinson et al

(2000) reported that at the age of 3 there was no difference between children who had worn spectacle correction and those that had not. Alternatively, Ingram et al (2000) found that emmetropisation was impeded by spectacle wear from 6 month of age until 42 months. This is supported more recently by Yang et al (2014) who compared the negative shift in SER associated with emmetropisation in age matched children between 3 – 8 years old, over a 2 year period, who were prescribed either partial or full correction of hyperopia. Although both groups showed an overall negative SER shift over the follow up period, the shift was more rapid in children wearing partial correction which was found to be the only factor associated with a more negative shift (OR, 2.414; 95% CI, 1.202–4.849; P = 0.013). Consequently, there is still debate regarding prescribing guidelines for hyperopic children and whether full or partial correction is the most effective management option (Leat, 2011, Mutti, 2007). However, it should be noted that in partial correction the hyperopic defocus produced is likely to be eliminated by activation of the accommodative system and thus the aberrant signal for growth may not be experienced by the individual.

1.6 Prevalence of refractive error

Comparison of global refractive error prevalence is made difficult by the varying study protocols and differing definitions of refractive error that are used. An overview of prominent epidemiological refractive error studies in the literature are summarised in Appendix A.1.2.

Cycloplegic autorefraction is considered the gold standard for determination of refractive error. However, many studies use non-cycloplegic autorefraction to establish refractive status however this is known to overestimate the amount of myopia and underestimate hyperopia (Fotouhi et al., 2012). The most common refractive error definitions use the spherical equivalent refraction (SER) calculated by using: sphere + ½ cylinder. However, there is a diverse range of cut off values used for classification, particularly in regard to myopia, see Table 1.1. The most common definition of myopia is an SER ≤-0.50D in at least one eye (Logan et al., 2011, Rudnicka et al., 2010, O'Donoghue et al., 2010c, Ojaimi et al., 2005c) and hyperopia as an SER ≥ +2.00D (Logan et al., 2008, Negrel et al., 2000).

A study by Quek et al (2004) investigated the prevalence of myopia in high school students in Singapore demonstrated how different myopia definitions can alter the prevalence. By using 3 definitions of ≤-0.50D, ≤-0.75D and ≤-1.00D prevalence varied from 73.9%, 63.4% and 56.1% respectively.

Study	Myopia	Hyperopia	Emmetropia
AES (Logan et al., 2011)	SER ≤-0.50 in at least one eye	SER ≥ +2.00 in either/both eyes as long as neither eye was myopic	-0.25 to +1.75
RESC (Negrel et al., 2000)	SER ≤-0.50 in at least one eye	SER ≥ +2.00 in either/both eyes as long as neither eye was myopic	Emmetropes neither myopic or hyperopic
NICER (O'Donoghue et al., 2010b)	SER ≤-0.50 in either eye	Hyperopia - SER ≥ +0.50 - +2.00 Moderate Hyperopia ≥ +2.00 or higher	-0.50 to +0.50
BMPS (Lin et al., 2004)	SER ≤-0.50 in either eye	SER ≥ +0.50	Emmetropes neither myopic or hyperopic
CLEERE (Zadnik et al., 2003)	SER≤-0.75 in both meridians	≥ +1.25 in both meridians	Emmetropes neither myopic or hyperopic
SMS (Ojaimi et al., 2005c)	SER ≤-0.50	SER ≥ +0.50	-0.50 to +0.50

Table 1.1: Refractive error definitions in other myopia studies AES: Aston Eye Study, RESC: Refractive Error Study in Children, NICER: Northern Ireland Childhood Errors of Refraction, BMPS: Beijing Myopia Progression Study, CLEERE: Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error, SMS: Sydney Myopia Study

Alternatively, some studies have used visual acuity as a measure of myopia prevalence, one used a VA ≤ 6/9 to identify myopia while another used VA ≤6/18 (Cummings, 1996, Au Eong et al., 1993). Using visual acuity to define myopia does not provide an accurate representation of refractive error as various other uncorrected refractive errors such as astigmatism and high levels of hyperopia as well as pathological conditions such as amblyopia and ocular disease can account for reduced visual acuity. However, a study of school aged children found that visual acuity measurement was reliable for detecting myopia but not hyperopia or astigmatism (O'Donoghue et al., 2012).

With these disparities in mind, a standardised protocol was developed as part of the Refractive Error Study in Children (RESC) (Negrel et al., 2000). The RESC allowed a representative, population-based sample of children to be compared in multiple centres worldwide including China, India, South Africa, Nepal and Malaysia. This has provided an invaluable resource for comparison of myopia prevalence in school age children of different ethnicities.

Within the UK, prevalence data has been captured by a number of studies. The Northern Ireland Childhood Errors of Refraction (NICER) study was a population based study (n = 1068) investigating refractive error in school children (O'Donoghue et al., 2010c). The phase 1 cross-sectional data revealed a myopia prevalence of 2.8% (95% CI 1.3-4.3%) in children aged 6 – 7 years and 17.7% (95% CI 13.2-22.2%) in children aged 12 – 13 years (O'Donoghue et al., 2010a). Further data was collected longitudinally at 3 yearly intervals for 6 years, named Phase 2 and Phase 3 respectively (Breslin et al., 2013, McCullough et al., 2016). This allowed the prospective change in refractive error and myopia prevalence over a six-year period to be demonstrated. Of the Phase 1 participants, 42.3% (n=438) took part in the six-year phase 3 follow up.

Over the six-year period the prevalence of myopia increased significantly in the younger cohort, between the ages 6 – 7 years and 12 – 13 years, 1.9% and 14.6% respectively, see Figure 1.9. Whereas only a small increase in prevalence was found in the older cohort, between the ages 12-13 years and 18-20 years, 16.4% vs 18.6%.

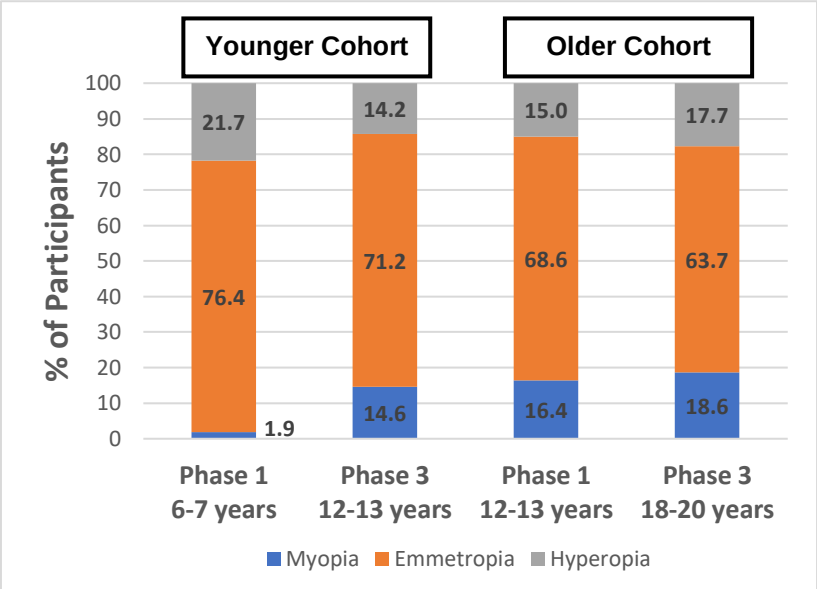


Figure 1.9: Refractive error prevalence in the NICER study at baseline (Phase 1) and at six year follow up (Phase 3) Redrawn from data in McCullough et al (2016)

In addition, the median change in spherical equivalent refraction (SER) was higher in the younger cohort, -1.38D (IQR -0.63 to -2.75D), compared to -0.63D (IQR -0.13 to -1.00D) in the older cohort. This supports the evidence that children are more likely to develop myopia between the ages 6 – 7 years and 12 – 13 years. As expected, hyperopia prevalence, reduced slightly from 76.4% in 6-7 year old to 63.7% in 18-20 year old. This data can be compared to historical data from Sorsby et al (1961) if the definition of myopia is adjusted to SER <0 dioptres as defined by Sorsby. This alters the myopia prevalence in the 12 – 13 year old to 23% in the NICER study. This is

compared to 10% prevalence found by Sorsby in 10 – 16 year olds in 1961 and highlights a 2 fold increase in myopia over the past five decades within the UK.

The Aston Eye Study (AES) was a cross sectional study which aimed to determine the ethnic difference in refractive error and ocular biometry in UK children (n=655) (Logan et al., 2011). The same study protocol and sampling procedures as NICER were used to minimise bias and allow comparisons. Preliminary published data found a myopia prevalence of 9.4% (95% CI 6.3-12.5%) in children aged 6 – 7 years and 29.4% (95% CI 24.2-34.6%) in children aged 12 – 13 years. These results are significantly higher than those found in the NICER study which found 2.8% (95% CI 1.3-4.3%) and 17.7% (95% CI 13.2-22.2%) respectively (O'Donoghue et al., 2010a). This difference can be accounted, in part, by the large differences in ethnicity in the AES. In the NICER study 99% of participants were white Caucasian compared to only 29% in AES, with the majority being South Asian ethnicity (50%). This difference is not due to bias sampling but due to the diverse multi-cultural nature of the city of Birmingham as opposed to the predominantly white population of Northern Ireland. By looking specifically at only the white participants in the AES the prevalence reduces significantly to 5.7% (95% CI 0.2-11.2%) at 6 – 7 years and 18.6% (95% CI 11.1-25.4%) at 12 – 13 years which is much more similar to those found in the NICER study. This again shows the difficulty in comparing prevalence data between studies, even within the same country, without taking ethnicity into consideration.

A study conducted at Aston University investigating refractive error prevalence in university students, mean age 19.55±2.99 years, again found a considerably higher value compared to that found in the NICER study, 52.7% vs 18.6% (Logan et al., 2005, McCullough et al., 2016). This difference can however be accounted for by sample bias as the population sampled by Logan et al (2005) consisted of solely Aston University optometry students. Whereas those NICER were participants who had been followed up from their involvement in Phase 1 and as such likely included a much more diverse population. This comparison introduces the idea of a hypothesised myopia risk factor of level of education which has been thought to increase myopia prevalence, see Section 2.3.2.1. This is also known as “academic myopia.” In addition, it could be argued that optometry students are more likely to be myopic as if they have worn glasses from a younger age and had multiple eye examinations they have been more exposed to optometry and therefore chosen their course accordingly. Similar prevalence levels in undergraduate students in the UK have been reported at Aston University previously and at Cardiff University, 55.5% and 64.0% respectively (Bullimore et al., 1989, Guggenheim et al., 2003).

Although there is a plethora of literature regarding the prevalence of refractive errors worldwide, the comparison between these studies is difficult due to varying cohort characteristics, methodology protocols and refractive classification which has been highlighted in a number of studies. As a result, there is little limited data on the prevalence of refractive errors across the world as a whole.

A recent meta-analysis has pooled data from 163 articles detailing refractive error prevalence between 1990 to 2016 from across the world in an attempt to estimate the prevalence of hyperopia, myopia and astigmatism in adults and children (Hashemi et al., 2018). Children were classified as less than 20 years and an estimated pooled prevalence (EPP) for myopia of 11.7% (95% CI 10.5 – 13.0), hyperopia 4.6% (95% CI 3.9 – 5.2) and astigmatism 14.9% (95% CI 12.7 – 17.1) were found. In adults aged over 30 years the EPP for myopia was significantly higher at 26.5% (95% CI 23.4 – 29.6), hyperopia EPP was 30.9% (95% CI 26.2 – 35.6) and astigmatism 40.4% (95% CI 34.3 – 46.6).

This followed on from another meta-analysis which attempted to calculate global prevalence of myopia and high myopia as well as predict future trends in prevalence levels (Holden et al., 2016). It was estimated that in 2000, 1406 million people were myopic equating to 22.9% of the world population as a whole and 163 million people were highly myopic, defined as $\leq$-6.00D, 2.7% of the world population. The authors predicted a significant increase globally by 2050, with the myopic prevalence estimated to double to be 49.8% and high myopia levels to more than triple to 9.8%. With this predicted increase in myopia prevalence globally, the economic and healthcare implications will also increase, and these are discussed below.

1.6.1 Ocular pathology and public health indications of myopia

In light of the increasing prevalence of myopia, it has been recognised as a serious public health concern and was identified as one of the top 5 ocular conditions that require immediate attention as part of the World Health Organisation's Global Initiative for the Elimination of Avoidable Blindness (Vision 2020) (Pararajasegaram, 1999, McCarty and Taylor, 2000). Myopia carries with it both pathological and economic burdens for the individual but also a significant societal cost for the country they reside in.

The majority of myopia can be corrected by optical means such as single vision spectacles, contact lenses or refractive surgery and most obtain good visual acuity. However, the physiological axial length changes associated with the progression of myopia is the precipitating factor in a number of ocular conditions, some of which are

sight threatening resulting in loss of best corrected visual acuity. These include a range of structures and include myopic maculopathy (Vongphanit et al., 2002), retinal detachment (Ogawa and Tanaka, 1988), cataract (Lim et al., 1999) and glaucoma (Marcus et al., 2011, Mitchell et al., 1999). The relative risk of these conditions increases with increased myopia. A recent meta-analysis calculated that myopic maculopathy costs $6 billion in global potential productivity loss annually (Naidoo et al., 2019). Furthermore, simply improving spectacle correction for myopes was estimated to potentially gain $244 billion in productivity annually.

Myopia has historically been classified as pathological and physiological based on refractive error. Physiological referring to low levels of myopia (less than -6.00D) and pathological classified as more than -6.00D and is a classed as a medical condition with associated ocular complications (Flitcroft, 2012). However, the literature suggests that this arbitrary classification is incorrect as ocular complications can also occur at lower levels of myopia. This has been shown in myopic maculopathy, see Figure 1.10, with an odds ratio of 2.2 for myopia refractions between -1.00 and -2.99D showing a definitive increased risk (Vongphanit et al., 2002). The relevance of this can be compared with the ubiquitous awareness of the association between hypertension and stroke. The odds ratio of a cardiovascular event based on systolic blood pressure and smoking habit has been found to be between 1.6 – 3.4 (Du et al., 1997, Woo et al., 2004). However, the odds ratio of myopic maculopathy from so called “physiological myopia” (less than -6.00D) can be as high as 40.6 (Vongphanit et al., 2002) and for retinal detachment 3.1 – 9.0 (Ogawa and Tanaka, 1988). Thus, interestingly the risk associated with cardiovascular events from hypertension compared to ocular complications from myopia is much lower and a much higher risk association can be found with the latter.

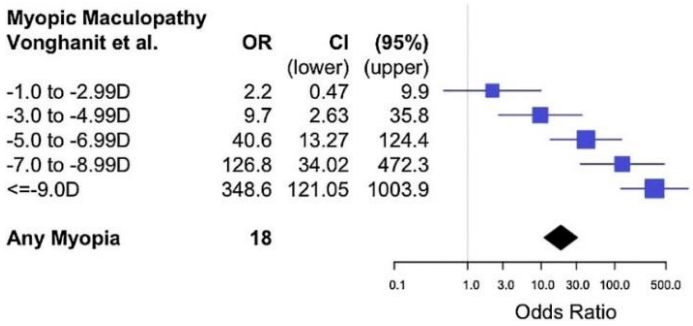


Figure 1.10: Forest plot of odds ratio for myopic maculopathy for different refractive errors derived from the Blue Mountains Eye Study Reproduced with permission from Flitcroft (2012)

A similar association is observed with retinal detachment with refractive errors of -1.00 to -3.00D which has been found to have a fourfold increased risk of retinal detachment

compared to non-myopes (Yannuzzi et al., 1993). There is a clear monotonic relationship associated with the incidence of retinal detachments and myopia which is primarily due to changes in the peripheral retina e.g. lattice degeneration. Lattice degeneration was found to be associated with 60% of retinal detachments in high myopes, but it was also present in 20% of non-myopic retinal detachments (Burton, 1985). It has therefore been suggested that the term 'pathological' myopia is misleading and has resulted in a new classification of myopia terminology being agreed, see Appendix A.1.1. There is no "safe" level of myopia and all myopia should be considered a potential risk factor.

Visual impairment due to ocular complications as a consequence of myopia is increasing in prevalence worldwide (Shih et al., 2006). Tideman et al (2016b) investigated the association of axial length and visual impairment (VI) (n = 15,693). They found that the odds ratio of visual impairment increased with axial length. The cumulative risk of visual impairment for individuals aged 75 years and over is indicated in Table 1.2. High levels of myopia (<-10D) have been associated with the same impaired quality of life similar to that of a keratoconic patient (Rose et al., 2000). In addition, a dependence on spectacles for myopia correction have been shown to leave some individuals feeling despondent and has been found to be a hindrance to the social development of children (Safir, 1979).

Axial Length (mm)	Cumulative Risk of VI (%)
<24	6.9
24 - <26	3.8
26 - <28	25.4
28 - <30	26.6
30 +	90.6

Table 1.2: Cumulative risk of visual impairment (VI) compared to axial length in participants over 75 years (Tideman et al., 2016b)

With the increasing prevalence of myopia worldwide the burden on the economy and health service is exceeding. It is being suggested that public policies need to be put in place to combat the increasing prevalence of myopia (Morgan, 2016, Verkicharla et al., 2016), this includes the implementation of mandatory programs some of which are already in place in East Asia to encourage time outdoors and regular vision screening to identify children who are myopic at its onset. This needs to be coupled with public awareness of the myopia epidemic and education of its possible ocular complications.

Myopia management guidelines for eye care practitioners have been released by the College of Optometrists this year (College of Optometrists, 2019) as well as a clinical management report by the International Myopia Institute (IMI) (Gifford et al., 2019). These resources aim to provide the education, support and training for healthcare professionals to appropriately manage myopic patients, particularly children, to aim to reduce progression or even prevent onset of myopia. This can be through patient/parent education and also through implementation of myopia control strategies detailed in the next section.

1.7 Summary

The prevalence and incidence of myopia is increasing worldwide and is being described as a global epidemic. There is evidence that the myopia prevalence is doubling in white Caucasian children within the UK (McCullough et al., 2016). Data from other studies worldwide have shown that this is a global phenomenon with Asian countries such as China, Singapore and Taiwan at the forefront. Estimates of global prevalence suggests that this trend will continue to increase and by 2050 myopic prevalence is predicted to more than double from 22.9% to 49.8% of the world population (Holden et al., 2016. Alongside this myopia is being recognised as a public health concern due to the pathological and economic consequences it brings. A number of myopia control strategies are starting to be implemented in clinical practice in an attempt to prevent the development of and also the progression of myopia. There is accumulating data from studies of refractive development and emmetropisation using animal models to suggest that young eyes can control their refractive state in a more active way in response to detected focusing errors. This data has potentially important clinical implications, as they imply that refractive errors may be manipulated, either intentionally or otherwise, through clinical management decisions. In order to further understand the natural history of refractive error influential environmental and lifestyle factors also need to be evaluated.

Chapter 2: Environment and lifestyle factors associated with refractive error

2.1 Introduction

Epidemiological and animal studies have shown that an individual's environment and lifestyle play a key role in refractive error development particularly in myopia (Flitcroft, 2012). It has been suggested that the rapid increase in myopia prevalence worldwide over a relatively short period of time cannot be accounted for solely by genetics and as such environmental factors must also play an influential role (Ramamurthy et al., 2015). A recent population-based prospective birth-cohort study found that axial elongation and myopia onset were independently associated ($p<0.05$) with several environmental and lifestyle parameters such as time spent outdoors, amount of near work and participation in sport (Tideman et al., 2019). The extent that these factors, along with numerous other identified environmental and lifestyle factors, are responsible for the trend towards a rapid increase in myopia prevalence dominates a large area of myopia research worldwide. These risk factors are discussed in depth below.

2.2 Time spent outdoors and myopia

There has been a large increase in research exploring the hypothesis that increased time outdoors protects against myopia which was first reported by Kathy Rose and colleagues in school aged children as part of the Sydney Myopia Study (SMS) (Rose et al., 2008a). The relationship between time outdoors and myopia has been extensively researched in the past decade. A mixture of cross sectional, longitudinal and interventional study designs have been used. The literature can be categorised in three ways; evidence for an association between time outdoors and myopia, protection from myopia onset and protection from myopia progression depending on the study design. These three study outcomes are discussed below and summarised in Table 2.1.

2.2.1 Association between time outdoors and myopia

A number of studies have investigated the association between time outdoors and myopia, see Appendix A.2.1. The SMS found that increased time outdoors was associated with a more hyperopic refraction and reduced myopia prevalence in children aged 12 years (Rose et al., 2008a). SCORM, a large cross sectional study in Singapore investigated the relationship between myopia and time outdoors in teenagers aged 11 – 20 years (n=1249) (Dirani et al., 2009). The total amount of outdoor time per day was

significantly associated with myopia, OR 0.90 (95% CI 0.84 to 0.96, p=0.004) after adjusting for a number of factors including age, sex, ethnicity, school type, books read per week, height, parental myopia, parental education and intelligence level. Overall the 868 myopic teenagers spent on average 3.09±1.92 hours per day undertaking outdoor activities compared to 3.59±2.03 by the 381 non-myopes (p<0.001).

The Beijing Myopia Progression Study investigated 386 children aged 6 – 17 years old (Lin et al., 2014). A high level of outdoor time (hours per day) was significantly associated with a less myopic refraction, however this was only found in younger children (6 – 12 years) (P_{trend} = 0.005) but not in the older children (13 – 17 years) (P_{trend} = 0.16). This trend in the younger age group was still significant after adjusting for age, sex, parental refractive error and amount of near work (P_{trend} = 0.0003). This study was hospital based rather than population based and therefore participants were more likely to have a myopic refraction. Lin et al (2014) suggested that this could have influenced the results and therefore the association found as well as possibly introducing an upper limit refractive saturation effect.

Similarly, Guo et al (2013) found that less time outdoors was associated with a longer axial length (p=0.02) and myopia (p=0.04) in both 5 – 7 year and 8 – 13 year olds. However, this was not a populated based study and therefore could be influenced by selection bias and although autorefraction was undertaken, cycloplegia was not used. The use of cycloplegia is recommended by the International Myopia Institute (IMI) in studies where refractive progression as a primary outcome, as in this study (Wolffsohn et al., 2019) and is considered the gold standard for epidemiology studies (Morgan et al., 2015). Lack of cycloplegia has been shown to lead to misclassification of refractive error in children (Hu et al., 2015).

Ethnicity has been found to also be a key factor influencing myopia prevalence with much higher levels of myopia being found in East Asia. However, an interesting study by Rose et al (2008b) compared myopia in students of Chinese ethnicity living in Singapore and Sydney. They found that those living in Singapore were significantly more myopic (29.1%) than those of same ethnicity living in Singapore (3.3%) (p<0.001). They hypothesised that the most significant factor associated with this difference was the average amount of time spent outdoors between the two locations (13.75 vs 3.05 hours per week) rather than ethnicity.

The majority of this literature is based on questionnaire data and therefore could be influenced by recall bias. Two studies have found that estimations of time spent outdoors are consistently overestimated compared to objective light sensor data

(Alvarez and Wildsoet, 2013, Ostrin, 2017). In addition, not all of the literature adjusted for factors such as age, sex, ethnicity and other environmental/lifestyle factors discussed in this chapter, such as amount of near work. These limitations must be taken into consideration when analysing the literature and comparing data between studies.

2.2.2 Myopia onset and time outdoors

In addition to the association between myopia and time outdoors, a similar association has been found between myopia onset and time outdoors. A large cohort study (ALSPAC) based in the UK analysed data from children over a 7 year period at ages 7, 10, 11, 12 thr and 15 years (Guggenheim et al., 2012). Parental questionnaire data were used to classify children into two time outdoors groups: either low (<3 hours per day) or high (3+ hours per day). Children classified as spending a ‘‘low’’ amount of time outdoors at age 8–9 years were about 40% more likely to have myopia between the ages of 11 to 15 years, compared to those classified as spending a ‘‘high’’ amount of time outdoors. A follow up analysis from the same study examined data on time outdoors from a much younger age: 2 to 9 years. Shah et al (2017) reported that from 3 years of age onwards greater time outdoors is associated with a reduced risk of incident myopia, independent of other factors such as number of myopic parents.

Similarly, the Sydney Adolescent Vascular and Eye Study (SAVES) found that children that became myopic spent less time outdoors than those that did not develop myopia (16.3 hours vs 21.0 hours per week, $p < 0.0001$) (French et al., 2013b). Analysis of data from the CLEERE study found that children aged 6 – 14 years with incident myopia spent 10-20% less time engaged in outdoor activities during the 4 year period prior to myopia onset (Jones-Jordan et al., 2011). The OLSM, another study based in the USA, followed up children from grade 3 (aged 8 – 9 years) to grade 8 (13 – 14 years) (n=514) (Jones et al., 2007). Over this period 21.6% became myopic and the number of hours spent undertaking outdoors sports and outdoor activities per week at baseline prior to myopia onset were significantly associated with future myopia (11.65 ± 6.97 hours for non-myopes vs. 7.98 ± 6.54 hours for future myopes, $p < 0.001$).

In total four interventional randomised control trials have taken place with school aged children based in China and Taiwan. These studies are summarised in Table 2.1. He et al (2015a) added an extra 40 minute class of outdoor activity daily to 6 schools in Guanghou, China. In addition, parents of children (n=952) at the 6 interventional schools were encouraged to undertake outdoor activities at weekends and outside school hours. Comparatively 6 control schools continued their usual daily pattern of outdoor activities and no encouragement was given to parents. The 3 year cumulative myopia incidence

rate difference was 9.1%, with a myopia incidence of 30.4% in the intervention group and 39.5% in the control group (p<0.001).

Author (Year) Country	Intervention daily	Baseline Age (years)	Group	Myopia Incidence rate (%)	Progression rates	
					SER (D/year)	AL (mm/year)
Wu et al (2013), Taiwan	80 min ROC program 1 year RCT	7 – 11 (n=571)	Intervention	8.41	-0.25±0.68	NA
			Control	17.65	-0.38±0.69	NA
			Diff	**9.24% p=0.001***	**0.13D/year p=0.029***	**NA**
Jin et al (2015), China	40 min ROC program 1 year RCT	6 – 14 (n=3051)	Intervention	3.70	-0.10±0.65	0.16±0.30
			Control	8.50	-0.27±0.52	0.21±0.21
			Diff	**4.8% p=0.048***	**0.17D/year p=0.005***	**0.05mm/year p=0.034***
He et al (2015a), China	40 min activity class 3 year RCT	6 – 7 (n=1903)	Intervention	30.4	-1.42 (95%CI -1.58 to -1.27)	0.95 (95%CI 0.91 to 1.00)
			Control	39.5	-1.59 (95%CI -1.76 to -1.43)	0.98 (95%CI 0.94 to 1.03)
			Diff	**9.1% p<0.001***	**0.17D/year p=0.04***	0.03mm/year p=0.07
Wu et al (2018), Taiwan	40 min ROC program	6 – 7 (n=693)	Intervention	14.5	-0.35±0.58	0.28±0.22
			Control	17.4	-0.47±0.74	0.33±0.35
			Diff	2.9% p=0.054	**0.12D/year p=0.002***	**0.05mm/year p=0.003***

Table 2.1: Myopia outdoor intervention studies showing myopia incidence and progression rates All studies used cycloplegic autorefraction and a myopia SER definition ≤-0.50. *AL: Axial length. Diff: difference. NA: Not available. RCT: Randomised control trial. ROC: recess outside classroom*.

In an earlier smaller study (n=571) 80 minutes of recess outside classroom (ROC) was introduced into the daily timetable (Wu et al., 2013). During this time classroom lights were turned off and emptied and the children encouraged to go outside. A larger myopia incidence difference of 9.24% was found between the interventional (8.41% incidence) and control (17.65% incidence). In a larger scale study (n=3051), Jin et al (2015) introduced two additional 20 minute ROC in the school timetable which had to be undertaken outside the classroom i.e. outdoors. They reported a reduction in myopia incidence rate of 4.8% in the intervention group (incidence rate 3.70% vs 8.50% in intervention vs control groups respectively). Most recently a study of Taiwanese children (n=693) introduced 40 minutes of ROC a day (Wu et al., 2018). Teachers were also

encouraged to give homework that involved outdoor work and parents and children were encouraged to undertake outdoor activities. Light exposure was measured with wearable sensors. A moderate incidence difference of 2.9% (p=0.054) was found between the two groups. The non-significant difference could be attributed to two nationwide incentives initiated by the Ministry of Education of Taiwan during the study period to encourage all children to spend more time outdoors. The “Tien-Tien 120” promoted 120 minutes per day of outdoor activity during school hours and “Sports and Health 150” which promoted 150 minutes of exercise per week. Three of the four studies showed a significant reduction in myopia incidence rates.

A meta analysis of 7 cross sectional studies summarised the association between time outdoors and myopia in children and adolescents (up to 20 years) and concluded that for every additional hour of outdoor time per week it reduced the risk of myopia by 2% (OR 0.981 95% CI, 0.973–0.990; P<0.001) (Sherwin et al., 2012c).

2.2.3 Myopia progression and time outdoors

The majority of studies are cross sectional in nature and are therefore unable to provide data regarding the association between myopia progression and time outdoors. However, the four interventional studies discussed above also monitored refractive and biometry progression on the children and their results are summarised in Table 2.1. He et al (2015a) showed a significant reduction in SER in the intervention group (-0.10D/year) compared to the control group (-0.27D/year) (p = 0.005). Jin et al (2015) also found less myopic progression in the intervention group compared to the control and in addition found a significant reduction in axial length (AL) in the intervention group compared to the control group, 0.16mm/year vs 0.21mm/year respectively (p = 0.034). A similar result was found by the most recent study with both myopic and non-myopic children in the intervention group exhibiting a less myopic shift than those in the control group (Wu et al., 2018). This was most pronounced for children that were myopic at baseline with a 0.23D difference between the intervention and control groups (myopic progression of -0.57D vs -0.79D respectively). Children in the intervention group also had less AL growth than the control (0.28mm vs 0.33mm respectively, diff: 0.05mm, p=0.003).

Seasonal trends in myopia progression has also been found which have been interpreted as indirect evidence of light exposure influencing myopia progression. Donovan et al (2012) found that myopia progression was significantly slower in summer (-0.31±0.25D) than winter (-0.53±0.29D) (p<0.001) in Chinese children aged 6 – 12 years. Myopia progression in summer was found to be approximately 60% of that in

winter and an increase in AL was similarly less in summer. Similar differences were found in the US based COMET study of 358 ethnically diverse children aged 6 – 12 years (Gwiazda et al., 2014b). Mean progression in winter was -0.35±0.34D compared to -0.14±0.32D in summer (difference: 0.21D, p<0.0001).

2.2.4 Opposition to the association between time outdoors and myopia

In addition to the large amount of compelling evidence for an association between time outdoors and myopia there is also a number of studies that failed to find an association. A study of young Singapore Chinese children aged 6 – 72 months found no association between myopia and time outdoors (n=3009) (Low et al., 2010). Time outdoors information was obtained through parental questionnaire data and the lack of association could be related to the age of the cohort which is younger than the typical onset of myopia. Zhou et al (2015a) also found no significant protective effect of increase time outdoors in Chinese schoolchildren (mean age 10.4±1.03 years). The definition of myopia was based on an unaided VA ≤6/12 which does limit the comparison with other studies.

Sherwin et al (2012a) assessed time outdoors by both objective and subjective methods on adult participants (mean age 54.1±16.2, n=636). Subjectively participants were asked to complete a questionnaire and were categorised into three groups when asked how much of the day they spend outside: none/< ¼ day, approximately ½ or > ¾ day. In this study conjunctival ultraviolet autofluorescence (CUVAF) was used as an objective measure of outdoor light exposure. This is a biomarker that has been found to provide a measure of sun exposure and therefore has been suggested as a surrogate measure of time outdoors (Sun et al., 2017). It involves photography of the conjunctival using special filters and illumination allowing the autofluorescence to become visible. It is discussed in detail in Chapter 10. A statistically significant trend in agreement with the protective association of increased time outdoors and myopia was found (P_{trend} = 0.03), however time outdoors was not associated with myopia when a multivariable model was used to account of other factors such as age and sex. Despite self-reported time outdoors not associated with myopia, a protective association between increased CUVAF and myopia was found. This disparity could be attributed to the broad categories used in the questionnaire which likely reduced the ability to detect any association.

Li et al (2015) investigated the association between time outdoors and myopia progression over 2 years in Chinese children aged 10 – 16 years as part of the ACES study (n=1997). They concluded that time outdoors was not associated with myopia progression and only a very small association between time outdoors and change in

axial length was found (high vs low amounts of time outdoors, -0.016mm/year, p=0.053). Saw et al (2006) also found no association between time outdoors and incident myopia in a 3 year cohort study of school children in Singapore. The authors hypothesised that this false negative result could be explained by the relatively low amount of time outdoors reported in the questionnaire data. Analysis of data from the CLEERE study examining 835 myopes aged 6 – 14 years found no association between myopia progression and reduced time outdoors (Jones-Jordan et al., 2012). This study suggested that time outdoors may be more influential prior to myopia onset rather than slow its progression.

The majority of literature supports the theory that increased time outdoors is protective against myopia and literature in opposition is limited. The conflicting findings found by studies in opposition to this theory can be attributed to differences in study design, cohort age and myopia classification.

2.2.5 Protective mechanism of time outdoors

Despite the large body of epidemiological studies that point to the protective effect of time outdoors in myopia progression, the exact mechanism behind this effect is still unclear. Several theories have been proposed and they are discussed below.

2.2.5.1 Outdoor light composition

The difference in light levels in outdoors environments is significantly different from indoors. This includes differences in light intensity, UV wavelength exposure and spectral composition of the light. The intensity of light from indoor has been found to be less than 1000 lux which in contrast to outdoor light intensity can often be up to 100,000 lux on a sunny day (Wu et al., 2018). A longitudinal observational study of children aged 10 – 15 years in Australia measured ocular biometry at 6 monthly intervals over a 18 month period (Read et al., 2015). Light exposure was measured objectively via a wrist worn sensor, Actiwatch 2 (Philips Respironics, USA). A modest but statistically significant association between greater average daily light exposure and slower axial eye growth was observed (p=0.047). Mean daily light exposure was used to categorise children into 3 groups: “low daily light exposure” (average light exposure <651 lux), “moderate daily light exposure” (average light exposure 652 – 1019 lux) or “high daily light exposure” (average light exposure ≥1020 lux). Children experiencing “low daily light exposure” exhibited significantly greater axial length elongation (0.13m/year) than both high (0.065mm/year) and moderate (0.060mm/year) daily light exposure (p<0.05). Interestingly there was no statistically significant difference between the axial elongation

of those with high or moderate light exposure ($p<0.05$). This supports the theory that there is a potential threshold of light that slows AL growth.

Research in animal studies has provided direct evidence that high illuminance levels can have a protective effect, see Section 1.4.1.3.

There is some evidence that in addition to light intensity other differences such as chromaticity and spectral composition of outdoor light could play a role. Violet light has been suggested as a vital component of outdoor light. Visible violet light is defined as a wavelength between 360 – 400nm which is part of the lower limits of visible light and overlaps with the upper end of Ultraviolet A spectrum (Krutmann et al., 2014). Violet light only exists in outdoor lighting and is absent in indoor lighting such as LEDs and fluorescent lights, in addition violet light doesn't pass through UV protected surfaces such as sunglasses and windows. Studies in guinea pigs and rhesus monkeys have shown that exposure to wavelengths towards the blue/violet end of the spectrum have reduced myopia progression (Liu et al., 2011, Liu et al., 2014). It has also been found to potentially suppress myopia progression in humans (Torii et al., 2017a, Torii et al., 2017b). A retrospective study in students aged 13 – 18 years who wore violet light-transmitting and violet light-non-transmitting contact lenses, found a smaller axial length elongation and lower myopia progressionin those who had worn violet light-transmitting contact lenses (Torii et al., 2017a). In addition, Torii et al (2017a) found that violet light had a protective effect on myopia progression in chicks and that it upregulates EGR1, an established myopia protective gene (Pardue et al., 2013). However, some speculation has arisen with regard to the validity of these results and further investigation was suggested to corroborate these findings (Schaeffel and Smith, 2017). However, more recently exposure to short-wavelength (violet) light has been shown to slow refractive eye growth in mice (Strickland et al., 2020). Interestingly this effect did not occur in mice with dysfunctional cones suggesting that cone signalling might play a role in the response of eye growth to violet light.

Longitudinal chromatic aberration causes the focus of different wavelengths of light to vary relative to the retina, such that short wavelength (blue light) is focussed in front of the retina and long wavelength (red light) is focussed behind the retina. As mentioned previously longitudinal chromatic aberrations of the eye have been found to be an important visual cue during emmetropisation in experimental animal models with the ability to influence eye growth (Rucker, 2013), see Section 1.4.1.3. Altering the chromaticity of light has been shown to induce and reverse myopia in chicks and guinea pigs. More specifically red light induced myopia cold be reversed to hyperopia in chicks

by changing red light to blue light (Foulds et al., 2013) and blue light inhibited axial eye growth in guinea pigs (Jiang et al., 2014). Therefore, given the difference in spectral composition of outdoor light, with a larger short wavelength (violet) component, there is a possibility that longitudinal chromatic aberration could be playing a role in the protective mechanism of increased time outdoors. However, currently the exact mechanism of how longitudinal chromatic aberration is used in emmetropisation is not well understood.

In addition to violet light, the UV component of sunlight has also been investigated as a possible protective light component. Ashby et al (2009) reared chicks under lighting with the UV component (<400nm) filtered out and the protective effect of the high illuminance was still found. This study excluded UV exposure as a requirement of light to slow myopia progression. In further support of this exclusion, Artigas et al (2012) found that the ocular media in phakic humans blocks out a large amount of light below 400 nm with only a minimal amount reaching the retina.

2.2.5.2 Dopamine and Myopia

Dopamine (DA) is a retinal neurotransmitter which has been suggested to be involved in the control of eye growth (Feldkaemper and Schaeffel, 2013, Ashby and Schaeffel, 2010, Cohen et al., 2012, Zhou et al., 2017a). DA levels are regulated by light levels with higher levels during the day and low levels during the night. This diurnal pattern is shown in Figure 2.1 in chickens as a function of 3,4-Dihydroxyphenylacetic acid (DOPAC), a primary dopamine metabolite and robust index of dopamine levels. In addition, the rate of release of dopamine has been shown to increase in a roughly log-linear manner with increasing light intensity (Cohen et al., 2012, Morgan and Boelen, 1996). There are currently no studies in humans to explore this hypothesis, however there is a large body of literature from animal studies. Early work by Stone et al (1989) found that retinal dopamine levels were significantly reduced following visual deprivation in neonatal chicks. Similar findings were also found in 1 year old chicks, tree shrews and guinea pigs (Dong et al., 2011, McBrien et al., 2001, Papastergiou et al., 1998). Furthermore, when half of the visual field is deprived using hemifield diffusers in chicks, only the deprived retinal areas elongated and were found to have reduced DOPAC levels (Ohngemach et al., 1997; Stone et al., 2006). These results were consistent with the hypothesis of an inverse relationship between dopamine release and axial eye growth. Furthermore, dopamine has been identified as a key modulator of circadian rhythms (Korshunov et al., 2017). The role of circadian rhythms in myopia development is emerging, see Section 2.3.5.

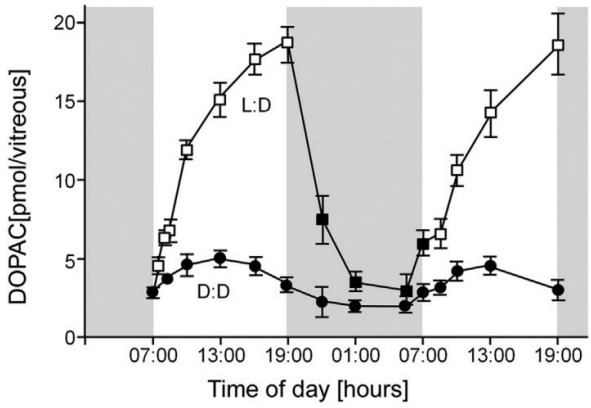


Figure 2.1: Diurnal variation of vitreal DOPAC in chickens Chickens were kept in 12:12 hours of light:dark cycle for 10-12 days. Subsequently half the chickens were kept on the same 12:12 L:D cycle (squares) and other half were kept in constant darkness D:D (circles). Reproduced with permission from Feldkaemper and Schaeffel (2013) redrawn from Megaw et al (2006)

The use of dopamine agonists and antagonists have further supported the role of dopamine in axial elongation. Dopamine agonists have been found to slow the development of experimental myopia (McCarthy et al., 2007, Iuvone et al., 1991). Furthermore, the use of a dopamine receptor antagonist, spiperone, just prior to exposure to bright light, eliminated the protective effect of high light exposure against the development of form deprivation myopia (Ashby and Schaeffel, 2010).

In summary, there is a large body of evidence supporting the role of dopamine in eye growth and could in part be responsible for the protective effects of time outdoors. It appears that dopamine levels are regulated by light levels and to some extent form deprivation. Further research into the potential biochemical pathway linking dopamine with axial growth and its role in humans is yet to be found.

2.2.5.3 Vitamin D

Another proposed mechanism of the protective effect of time outdoors is insufficient vitamin D levels caused by less time outdoors. Vitamin D can be obtained in small amounts in our diet from foods such as oily fish and eggs. However, the majority is synthesised within the skin following sunlight exposure specifically, ultraviolet-B (UVB). A number of studies have investigated serum levels of vitamin D and found lower levels in myopes compared to non-myopes (Choi et al., 2014, Mutti and Marks, 2011, Tideman et al., 2016a, Yazar et al., 2014, Kwon et al., 2016). Historically this was first suggested by Arthur Knapp in 1939 who found myopia was induced in his experimental dogs through vitamin D and calcium deficiency, a condition he called “scleral rickets” (Knapp,

1939). Conversely, a number of large scale studies have found no evidence of an association with vitamin D and myopia (Guggenheim et al., 2014, Williams et al., 2017). Analysis of genetic variants that are known to affect vitamin D levels also showed no evidence of genetically determined vitamin D level and myopia levels (Cuellar-Partida et al., 2017). This study used a mendelian randomisation analysis which is considered an equivalent of a natural randomised controlled trial. This evidence suggests that previous findings of a positive association with low vitamin D levels and myopia are potentially confounded by time spent outdoors and/or sun exposure.

A recent literature review of studies investigating vitamin D and myopia concluded that although there is evidence that lower serum concentrations are associated with myopia it is still unclear as to whether vitamin D is involved in the regulation of myopia onset or progression (Pan et al., 2017). In addition, myopia is not a characteristic of a condition called rickets caused by severe vitamin D deficiency (Reddy et al., 1979). Therefore, the established relationship between time outdoors and vitamin D levels may suggest that levels of vitamin D may be acting as a surrogate biomarker for time outdoors rather than having an inherent protective effect.

2.2.5.4 Accommodation and environment

The viewing environment and accommodation demand on the eye when outdoors is significantly different to indoors. In order to further understand these differences Flitcroft (2012) used computer simulations to create dioptric representations of indoor and outdoor environments, see Figure 2.2. He concluded that there is significantly longer viewing distances and less accommodative demand when outdoors (Flitcroft, 2012). In addition, the dioptric structure of outdoor environments was much more uniform causing minimal amounts of peripheral defocus and eye movements resulting in little variation of retinal focus. Aberrant amounts of central and peripheral hyperopic defocus have been found to be fundamental in the theory behind myopia progression and axial length growth, see Section 1.5.1.1. This optical effect may be further enhanced by the natural process of pupil constriction when outside resulting in increased depth of focus and subsequent reduction in optical aberrations and image blur (Castejon-Mochon et al., 2002, Atchison et al., 1997, Wang and Ciuffreda, 2006). An investigation of higher order aberrations and pupil size revealed that they do not all behave the same with changes in pupil size. Coma aberrations were found to be the most dominant aberrations at all pupil sizes however pupil change was found to have the biggest influence on spherical aberrations (Wang et al., 2003).

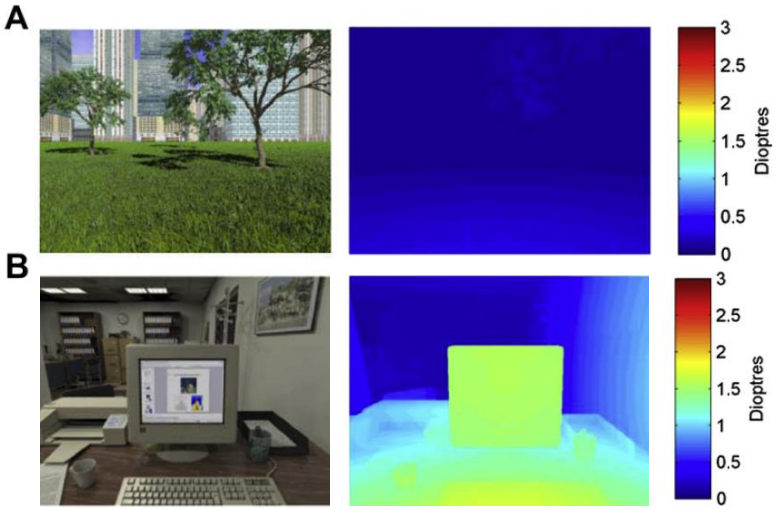


Figure 2.2: Dioptric representation of A) an outdoor scene B) an indoor scene Dioptres were calculated from the reciprocal of the distance in metres and shown as a colour scale from blue (0D) to red (3D). Reproduced with permission from (Flitcroft, 2012)

2.2.5.5 Physical activity

It has been hypothesised that physical activity could be influential in myopia development by way of increased heart rate causing increased optic blood flow or through other health benefits such as reduced glucose levels in more physically active individuals (Herbst et al., 2015, Warburton and Bredin, 2017).

In earlier studies, sport and time outdoors were grouped together in a single questionnaire question so differentiation between the two was difficult (Jones-Jordan et al., 2012, Parssinen and Lyyra, 1993). The Sydney Myopia Study (SMS) and Singapore Cohort study of risk factors for myopia (SCORM) study used a more detailed questionnaire that asked several separate questions about time outdoors and physical activity. Both studies showed that indoor sport was not protective (Dirani et al., 2009, Rose et al., 2008b).

A number of other studies have implemented objective measures of physical activity through accelerometers to quantitatively measure physical activity. Analysis of data from the UK based ALSPAC study used a hip worn accelerometer to measure physical activity over a seven day period (Guggenheim et al., 2012). A significant independent association was found between incident myopia and physical activity. However, the association between time outdoors was much greater. Guggenheim et al (2012) suggested that the association between myopia and physical activity was due to the link between physical activity and time outdoors and not a direct causal relationship between

physical activity and myopia. This theory was further supported by Read et al (2014) who used wrist worn accelerometers and found a significant association between physical activity and light with a trend for greater physical activity when outdoors. However, there was no significant association between physical activity and myopia. Most recently a prospective study with longitudinal objective data on physical data using an accelerometer worn at regular intervals over a 7 year period found no association between physical activity and myopia (Lundberg et al., 2018).

Overall, a recent systematic review concluded that participation in sport or increased physical activity does not seem to be the precipitating factor in myopia onset, and it seems that increased physical activity is merely a result of greater time outdoors (Thykjaer et al., 2017). Although one method of encouraging children to spend more time outdoors is through participation of sports.

2.2.6 Conclusions

The association between time outdoors and myopia is well established however it still remains unclear which element or elements of being outdoors is responsible for the protective effect. Several mechanisms of the protective effects of light and time outdoors have been proposed including neurochemical factors through melanopsin and dopamine cascades as well as optical factors such as longer viewing distances and a flatter dioptric scene leading to less accommodative demand when outdoors. As well as , the natural condition of pupil constriction when outside resulting in increased depth of focus and subsequent reduction in optical aberrations and image blur. The composition of outdoor light varies considerably with indoor light in relation to a number of factors including light intensity and spectral composition, both of which have been found to be key visual cues for emmetropisation and therefore could play a role in the protective effect. Objective measures of time outdoors and quantification of factors such as light intensity through the use of objective devices, such as the Actiwatch 2 device (Philips Respironics, USA) used in this study, are invaluable in studies where quantification of environmental factors are critical. Further research is required to enhance our knowledge and understanding of the mechanism of how time outdoors protects against myopic progression. Despite this, increased time outdoors is considered an effective and straightforward strategy for myopia control and is encouraged by many eyecare practitioners worldwide.

2.3 Additional risk factors

In addition to time outdoors a number of other environmental and lifestyle risk factors have been implicated in myopia onset and progression.

2.3.1 Near work

Another important factor to consider is near work which takes on a number of forms, traditionally this has been largely paper based consisting of reading and writing. However, the rapid increase in myopia prevalence over the past 50 years has occurred simultaneously with the development and adoption of digital devices and communication technologies into our daily lives. The use of these devices such as smartphones, tablets, and computers has dramatically changed the viewing landscape of near work. This has been further enhanced by improvements in screen resolution which allows digital screens to be smaller and handheld which has encouraged children to develop "unhealthy" visual behaviours such as prolonged screen time and a closer working distance (Cao et al., 2020, Wen et al., 2020). The increased use of these devices has been found in children who often regularly using them from a very early age (Escobar-Chaves and Anderson, 2008). In the UK, 52% of children as young as 3-4 years are using these devices to access the internet for 9 hours a week, this increases to 20.5 hours for 12-15 year old (Ofcom, 2018). Furthermore 83% of UK children aged 12-15 own their own smartphone with the majority having no limits on its usage, similar findings of 95% of American teenagers reported ownership or access to a smartphone (Anderson and Jiang, 2018). Digital devices have therefore becoming ubiquitous with modern day life and are being used by children frequency from a young age, therefore it has emerged as a potentially myopiagenic contributory factor. The most recent and relevant literature surround near work and myopia is discussed as well as the proposed mechanisms behind the relationship.

2.3.1.1 The relationship between near work and myopia

Mutti et al (2002) explored the association between near work and myopia through the OLSM using a parental survey investigating the time spent outside school undertaking various activities such as reading for pleasure, studying for school assignments, watching television of children in the eighth grade (aged 13.7±5 years, n=366). Myopic children spent more time studying than emmetropes (11.2 vs 8.9 hours, $p<0.05$) and more time reading for pleasure (5.8 vs 4.1 hours, $p<0.005$). Saw et al (2001a) investigated a similar aged cohort of children living in rural and urban ages of China. Myopic children spent more time reading and writing compared to non-myopic children.

In addition, children spent more time reading and writing outside school in urban areas, where the myopia prevalence was higher, than rural areas (2.2 vs 1.6 hours, $p<0.001$, myopia prevalence 19.3% vs 6.6% respectively). Baseline cross sectional data from SCORM found that children aged 7 – 9 year who read more than two books per week had 3.05 times higher risk of moderate myopia (at least -3.00D) (Saw et al., 2002b).

In a cross sectional study of 12 year old Australian schoolchildren as part of the SMS, the total time spent doing near tasks was not found to be associated with myopia however the intensity of near work was (Ip et al., 2008d). A closer reading distance (<30cm) and periods of continuous reading (>30mins) independently increased the odds of myopia (OR 2.5 and OR 1.5, respectively). The five to six year follow up of the SMS, the Sydney Adolescent Vascular and Eye Study (SAVES) found that children who became myopic undertook more hours of near work per week than those who didn't (19.4 hours vs 17.6 hours) (French et al., 2013b).

More recently a nationwide population based study of Taiwanese children aged 7 – 12 years old examined the association between amount of near activities and incident myopia over a 4 year follow up period (Ku et al., 2019). In Taiwan, attendance at 'cram school' is common practice to enhance children's academic abilities. Private classes are arranged outside the regular school system at evenings and weekends. In this study children spent an average of 2.78±3.53 hours per day on cram school. Children attending cram schools for ≥2 hours a day (hazard ratio 1.31; 95% confidence interval, 1.03-1.68) had a higher risk of incident myopia with the effect attributed to the increase in near visual activity.

A 3 year longitudinal study of Norwegian engineering students (mean age 20.6±1.1 years) found myopic progression was significantly associated with reading scientific literature and undertaking practical near work (both $p<0.001$) but interestingly not computer use (Kinge et al., 2000). This again suggested the hypothesis that it is not just the number of hours doing near tasks but also the type and distance of near work being undertaken. Another study in support of the intensity of near work as a risk factor for myopia progression investigated Singaporean children aged between 7 – 12 years over a 12 month period (n=168) (Tan et al., 2000). Cycloplegic autorefraction measurements were taken 5 times at regular intervals throughout the study period. School examinations took place in the first week of May and last of October and significantly higher levels of myopia progression were recorded after this time periods. The authors interpreted this increase in progression as a delayed effect of the intense near work associated with preparing for the school examinations.

A recent meta analysis investigated the association between time spent on near work and myopia from published articles between 1989 – 2014 with participants <18 years of age (Huang et al., 2015). 12 longitudinal studies and 15 cross sectional studies conducted in Asia, North America, Australia, Europe and the Middle East were identified. Near work was defined as "the sum of activities with short working distances, for example reading, studying, writing, doing homework, watching TV or playing video games etc." All included articles quantified near work through questionnaires completed by parents, children or both and the definition of myopia did vary across the studies. The meta analysis found that more time spent doing near tasks was associated with higher odds of myopia (OR 1.14) (Huang et al., 2015). Myopic children were found to spend more time reading but not studying, watching TV or using the computer than non-myopic children.

As mentioned previously the increased use of digital devices has had an impact on the amount of near work that children are undertaking. A study of 6-14 year old in China (n=566) used detailed parental questionnaires to quantify the use of electronic devices (Liu et al., 2019). Although myopia was not associated with time spent using these devices, mean SER decreased by 0.28D and 0.33D for each hour increase in time spent on smartphones and computers respectively. Furthermore a longer AL was associated with more time spent using smartphones and computers.

Given the known limitations of the use of questionnaires in the quantification of activities such as near work, recent studies have used objective measures to investigate the relationship between near work and myopia. One study used a spectacle mounted device called the Clouclip (HangZhou Glasson Technology Co., Ltd, China), which is able to objectively measure duration of near tasks as well as viewing distance. The device was worn for a week by 86 children (10.13±0.48 years) and myopic children were found to spent more time on average each day on activities at a close distance (<20cm) than non-myopic children (Wen et al., 2020). Another objective method of assessing smartphone use is through the quantity of data usage. McCrann et al (2020)(2020)(2020)(2020)(2020)found that myopic students use almost double the amount of smartphone data per day compared to myopes (1,130.71±1,748.14 MB and 613.63±902.15 MB respectively).

2.3.1.2 In opposition to the relationship between near work and myopia

Both the Beijing Myopia Progression Study and the Northern Ireland Childhood Errors of Refraction (NICER) found that increased near work did not significantly affect SER or risk of myopia development in children (Lin et al., 2014, O'Donoghue et al., 2015).

Instead of using questionnaires to ascertain the numbers of hours undertaking near tasks some studies have used the number of books read per week as a measure of near work (Dirani et al., 2009, Saw et al., 2006). 3 year follow up analysis from SCORM found contradictory results to the baseline data discussed previously and found no association between time spent doing near work or number of books read per week with myopia at follow up (Saw et al., 2006). Jones-Jordan et al (2011) investigated the amount of near work undertaken by children prior to myopia development in the CLEERE study. Again, no significant difference in number of hours undertaking reading activities prior to myopia onset however a significant difference was found at myopia onset. It was noted that instead myopia onset was linked to fewer hours of outdoor activity rather than the amount of near work suggesting that time outdoors exerts a much stronger influence on development of myopia. Consequently, it has been suggested that a combined effect of more hours doing near tasks and less time spent outdoors could be the best predictor of myopia development. This combined effect was investigated by French et al (2013b) in SAVES assessing 2 age cohorts (n=2103), see Figure 2.3.

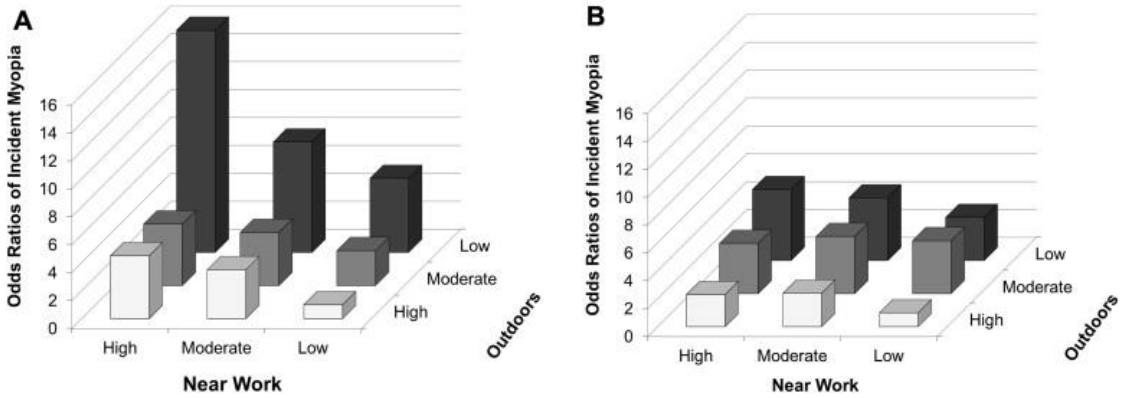


Figure 2.3: Multivariate odds ratios (ORs) of incident myopia by time spent outdoors and near work in the (A) Younger cohort (6 years of age) and (B) Older cohort (12 years of age) Reproduced with permission from (French et al., 2013b) Overall higher odds ratios were found in children that undertook high levels of near work and low levels of time outdoors. Higher odds ratios were found in the younger cohort suggesting that environmental factors are more influential at this age prior to myopia development. It is also interesting to note that time outdoors was found to be the most influential factor when assessing odds ratios of incident myopia with moderate to low levels increasing the odds ratio by more than 3-fold (French et al., 2013b). Conversely, altering the level of near work did not alter this level of risk.

2.3.1.3 Proposed mechanisms

2.3.1.3.1 Accommodative lag and microfluctuations

One theory suggests that the excessive accommodation demand caused by near work could induce foveal hyperopic defocus which is influential in myopia development (Angle and Wissmann, 1980, Mutti et al., 2002). It has been well established that hyperopic blur, simulated by minus lenses, can act as a stimulus for axial elongation and subsequent myopia development in experimental animals such as chicks (Schaeffel et al., 1988). The myopiagenic effect of imposed hyperopic defocus is very consistent across several other species such as tree shrews (Shaikh et al., 1999) and monkeys (Smith and Hung, 1999).

Variations in accommodation response has been found between refractive error groups, with myopic children shown to accommodate significantly less and have a larger accommodative lag compared to emmetropes for near tasks (Nakatsuka et al., 2005, Gwiazda et al., 1993b). Conversely, a large scale 8 year follow up study (CLEERE) evaluated the accommodative lag of children before, during and after the onset of myopia (n=1107) and concluded that accommodative lag was not significantly associated with myopia (Mutti et al., 2006). More recent analysis of the CLEERE study found accommodative lag was not associated with myopia development over a ten year period (Berntsen et al., 2011)

In an effort to slow myopia progression, bifocals and progressive addition lenses (PALs) have been historically prescribed with an aim to reduce the accommodative lag during near work to reduce residual hyperopic defocus (Fulk et al., 2000, Goss and Uyesugi, 1995, Cheng et al., 2014). These studies were found to significantly reduce myopia progression. However, it has been subsequently suggested that bifocals and PALS alter the peripheral image shell as well as affecting accommodative lag by imposing relative myopic defocus in the periphery. It is this peripheral refractive modification that is thought to be the influential factor in their success at slowing myopia progression rather than the effect on accommodation. Peripheral refraction has been well established to be significant in myopia development and been successful in other interventional studies, see Section 1.5.1.1.

Another element of accommodation that has been investigated is the role of accommodative microfluctuations. These are temporal changes in accommodation that occur even under steady viewing conditions. It has been suggested that increased aberrations and depth of focus in myopia may lead to a reduction in blur sensitivity and subsequently increased variability of accommodative response and microfluctuations

(Day et al., 2006, Harb et al., 2006, Langaas et al., 2008). Microfluctuations have traditionally been assessed measuring fluctuations in refractive error using an autorefractor. However, there is some debate as to whether this method of measurement is able to exclusively quantify microfluctuations related to accommodation. A recent study has found that a large number of microfluctuations are not related to accommodation and have proposed a relative rather than absolute approach to measuring microfluctuations (Lupon et al., 2019).

It can be concluded that the majority of studies do not support the theory of accommodative lag as a stimulant for myopia development and further research into microfluctuations is required to further understand its possible role in myopia development.

2.3.1.3.2 Relative Peripheral Retinal Hyperopia

The accommodation system is foveocentric and therefore responds to central stimulus at the point of the fovea (Gu and Legge, 1987). The aim of accommodation is to allow hyperopically defocussed images at near to be focussed through alteration in the lens shape by the ciliary body. However, these refractive changes occur across the whole of the visual field and consequently the retina. As a result, it is likely that during near tasks the accommodation system is activated and the image is pulled forward onto the retina but due to its curved nature relative peripheral hyperopic defocus is produced which is known to be influential in axial elongation, see Section 1.5.1.1. Flitcroft (2012) used dioptric computer simulations to evaluate the retinal image defocus imposed by indoor and outdoor tasks such as reading on a desk, using a computer or standing outside. Indoor environments were found to be more dioptrically varied than outdoors and indoor tasks create larger levels of retinal hyperopic defocus. This is shown in Section 2.1.5.4 in Figure 2.2.

There is conflicting evidence regarding the relative peripheral defocus caused by accommodation. Calver et al (2007) found a small relative myopic shift off axis in emmetropes but not myopes. Lundstrom et al (2009) also found emmetropes to have a peripheral relative myopic shift but found that myopes exhibited either no shift or a small hyperopic shift. This peripheral hyperopic shift in myopes with accommodation has also been demonstrated by Mutti and Walker (2002). The authors found that accommodation induced the ocular shape to become more prolate and suggested tension on the choroid could be influential in altering ocular shape. Conversely other studies have found that accommodation creates a relative peripheral myopic shift in myopes (Whatham et al.,

2009). Some studies have found no change in peripheral refraction with varying amounts of accommodative demand induced (up to 3.00D) (Davies and Mallen, 2009).

The lack of consistency in these studies could be related to the diversity of study designs and methodology and high levels of cohort variation.

2.3.1.4 Conclusion

Although an association between near work and myopia has been shown in a number of studies, it if often weak and inconsistent with a number of studies showing no association at all. Intensity of near work appears to be more prominent factor than duration of near work.

One factor that is integral when comparing results within in the literature is the consistency in quantification of near work. Near vision has primarily been quantified through questionnaire based data with questions varying from the number of books read per week to number of hours spent reading and writing. The number of books read per week can be considered a vague question and can be influenced by a number of factors including reading speed. One child who reads one book per book may take the same amount of time as a quicker reader who can read 3 or 4. However the same amount of time has been spent doing the same near task.

Some studies have shown that the intensity of near work is important. Therefore information about time taken to read a book, duration of periods of near work, details about font size and reading distance would allow a more detailed analysis. Some studies have calculated the number of dioptric hours for near tasks which is defined by: 3 x (hours spent studying + hours spent reading for pleasure) + 2 x (hours spent playing video games or working on the computer at home) + 1 x (hours spent watching television) (Mutti et al., 2002). In addition, there are a number of other activities that children may be undertaking at a close working distance aside from traditional reading. This could include board games, colouring, puzzles, increasing use of tablets and also in situations where parents read to their children in the evening often the children will be looking at the pages as well. With this in mind it is likely that the majority of assessments of near work do not convey a true representation on the amount and type of activities and without objective data is difficult to accurately measure.

It is widely accepted that the use of questionnaires when quantifying activities such as near work are influenced by recall bias and are often completed by the parents so the accuracy of these estimations are put into question. Furthermore, near work comprises a large variety of activities not just reading and writing but also the use of smartphones,

tablets and computers. Given the frequent use of these electronic devices more detailed information on the usage of these devices needs to be investigated when assessing the relationship between near work and myopia onset/development. Research has shown differing levels of association with myopia with different electronic devices (Liu et al., 2019). As a result of these challenges investigations into the relationship between near work and myopia have started to use objective measures of near work including using spectacle mounted devices to quantify duration of near work and also the viewing distance and also smart phone data usage.

It should not be overlooked that a strong association between time outdoors and myopia has been established which could be confounded by near work. It could be theorised that children that spent more time doing near work tasks such as reading and writing consequentially spend less time outdoors. As a result, near work could be acting as a surrogate measure of time outdoors. In addition, there other implications of increased near work, more specifically increased use of digital devices such as smartphone and tablets have been found to disturb and delay sleep (Stiglic and Viner, 2019, Bartel et al., 2019). This could have an impact on circadian rhythms and sleep patterns which have also emerged as a potential environmental factor involved in myopia onset/development, see Section 2.3.5.

It is clear that currently there is mixed research supporting the theory of the influence of near work and myopia. The complex nature of near work and its associations with other factors, primarily time outdoors, mean that current research does not support near work as a stand alone factor associated with near work. Further research using objective measures of environmental factors such as near work and time outdoors will provide insight in their relationship.

2.3.2 Near work associated factors

2.3.2.1 Education and Intelligence quotient (IQ)

As mentioned previously higher levels of myopia have been identified in students from academic degree courses (Logan et al., 2005, Midelfart et al., 1992). Williams et al (2015) also found level of education to be a precipitating factor in myopia prevalence. Prevalence increased from 25.4% in adults who had completed primary school to 29.1% who had completed secondary school and 36.6% for higher education courses. It is difficult to distinguish between education level and amount of near work as separate risk factors as they occur simultaneously as higher education courses require more hours of near work. This can also be said for the association of IQ level and myopia. Saw et al

(2004b) investigated this association by calculating IQ through the nonverbal Raven Standard Progressive Matrix test and assessing refraction and biometry in 1204 Chinese school children aged 10 to 12 years. Children with higher IQ scores had significantly more myopic refractions (-1.86D for children in the highest quartile compared to -1.24D for children in the lowest quartile, p=0.002). In addition, they were also found to have longer axial lengths (24.06 vs 23.80 mm, p=0.022). After controlling for other factors including age, sex, school, parental myopia and amount of near work, IQ was found to be independently associated with myopia. A further study by Saw et al, as part of the Singapore Cohort study Of the Risk factors for Myopia (SCORM) study, found a positive association between school grades and myopia in Singapore children. It found that children aged 10-12 years whose averaged scores for language and mathematics placed them in the top quartile had an odds ratio for myopia of 2.5 compared to those in the lowest quartile (Saw et al., 2007). This is similar to results from the Orinda Longitudinal Study of Myopia (OLSM) which also found that myopes scored higher than emmetropes in both national and local reading ($p<0.013$) and language ($p<0.0069$) (Mutti et al., 2002). In the UK good performances in the standard attainment tests (SATs) reading and mathematics examinations were found to have higher odds ratios of becoming myopia (2.60 and 1.90 respectively) (Williams et al., 2008). Interesting, hyperopes have been reported to score lower in achievement tests and have impaired literacy skills (Rosner, 1997, Williams et al., 2005). It has been hypothesised that there is a link between axial length and cerebral development, through shared genes, which could attempt to explain education/IQ as a possible risk factor (Hirsch, 1959, Storfer, 1999, Miller, 1992).

As mentioned previously the differentiation of IQ/intelligence as an independent risk factor from near work is difficult. This is especially apparent with the use of school grades as a marker for intelligence as these grades are an accumulation of academic ability, intelligence and, arguably, parental influence through their interest, time taken to help with school work and also level of work ethic instilled. It must also be considered that “good” school grades are related to increased time reading and writing and are a product of these activities.

2.3.2.2 Reading Ergonomics

The amount of near work and myopia has been heavily researched in a number of studies as discussed above. In addition to the amount of time undertaking near tasks other ergonomic elements of near work has been assessed including reading distance and position. A recent study of 8 – 13 year children in Finland found that shorter reading

distances were correlated with high myopia in females (Parssinen and Kauppinen, 2016). In addition, myopia progression was found to be greater in children who had a steeper downward angle of gaze when reading and those that read in a sitting position compared to lying on their back. The SMS is in agreement with these findings as it reported that children that undertook near work at a distance of <30 cm were 2.5 times more likely to be myopic (Ip et al., 2008d). Similar findings were found in military conscripts in Taiwan with individuals with a closer near distance associated with myopia and a longer axial length (Lee et al., 2013). Wang et al (2013) studied the reading behaviour of children aged 7 – 12 years and concluded that better ergonomics can reduce asthenopia and help children read better as well as reduce myopia. Furthermore, a greater downward pitch viewing angle was found in progressing myopes compared to non-progressing myopes (Hartwig et al., 2011). Although no difference in head posture was found between myopes and emmetropes, some evidence in difference between head posture and movement during reading was found in progressing myopes which could be attributed to spectacle use.

Another interesting study observed the myopia prevalence of male teenagers in Jewish Orthodox schools who studied religious texts where the font size was very small (in some cases 1mm) up to 16 hours a day. The prevalence of myopia in this group was significant higher than other students in general schools with no strenuous study periods (Zylbermann et al., 1993).

The association between a closer reading distance and myopia has been suggested to derive from the fact that myopes are accustomed to reading at short working distance, particularly unaided (Parssinen and Kauppinen, 2016). In addition some studies have explored the short terms effects of gaze on axial length changes (Ghosh et al., 2012, Ghosh et al., 2014). The greatest elongation change of +18±8μm occurring with inferonasal gaze ($p<0.001$) (Ghosh et al., 2012). Consequently, it has been hypothesised that biomechanical factors (i.e. extraocular muscles forces and ciliary muscle contraction) could play a role in altering the tensions and pressures on the globe during periods of near work altering the ocular biometry. These studies investigated only short term periods of near vision of either 5 or 10 minutes and so analysis of ocular biometry after more prolonged periods of near work need to assessed in order to establish the long lasting effects.

2.3.3 Parental myopia and genetics

There is strong evidence that genetics plays a role in the development of myopia. Twins studies such as the Genes in Myopia (GEM) study has provided useful insight into the

role of genes in myopia (Baird et al., 2010). The most heritable tract was found to be axial length. In addition, the Consortium on Refractive Error and Myopia (CREAM) consortium conducted a genome wide meta-analysis comparing European and Asian cohorts. 16 loci were identified for refractive error in the European cohort and 8 of which were shared with the Asian cohort (Verhoeven et al., 2013). This has recently been extended to identify individual single nucleotide polymorphism (SNP) that are accountable for myopia (Fan et al., 2016).

The heritability of these genes has also been widely researched. The risk of a child developing myopia has been shown to be consistently associated with a family history of myopia. It has been shown that the risk of a child developing myopia when both parents are myopic is 42%. This reduces to 22.5% with one myopic parent and only 8% when neither parent in myopic (Gwiazda et al., 1993a). The Orinda Longitudinal Study of Myopia (OLSM) also found this dose-dependent pattern whereby 32.9% of children with two myopic parents became myopic, this reduced to 18.2% with only one parent and 6.3% with no myopic parents (Mutti et al., 2007). Calculating the odds ratio of becoming myopic further confirmed this pattern as the odds ratio increased from 3.31 to 7.29 by having one or two parents with myopia. Analogous odds ratios were found by Jones et al (2007) with 2.08 for one parent and 5.07 for both parents. An interesting study by Wu and Edwards (1999) investigated the effect of having myopic parents for 3,131 children aged 7 to 17 years in China. Consistent findings of a dose dependent relationship were identified, see Table 2.2. The Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error (CLEERE) study found that a larger proportion of children who were identified as at a high risk of development myopia had two myopic parents (25.4%) (Jones-Jordan et al., 2010).

	12 year old		**17 year old**	
	Prevalence (%)	**Odds**	**Prevalence (%)**	**Odds**
Neither parent myopic	30.8	0.44	54.5	1.20
One parent myopic	41.6	0.59	69.8	2.31
At least one parent myopic	46.5	0.87	69.7	2.30
Both parents myopic	62.5	1.67	69.6	2.29
Overall	35.9	0.51	59.1	1.44

Table 2.2: Prevalence of myopia and odds of becoming myopic in 12 year old (n = 325) and 17 year old (n=254) according to family history of myopia (Wu and Edwards, 1999)

This myopic predisposition based on heritability from myopic parents has been supported by interesting biometric studies. Zadnik et al (1994) found that non-myopic children with two myopic parents had longer eyes and a less hyperopic refraction compared to children with one or no parents with myopia. Saw et al (2002a) also studied non-myopic children and found that axial length was longer and vitreous chamber was deeper in children who had at least one myopic parent.

Furthermore, Lam et al (2008) measured the change in axial length of Chinese children aged 5 to 16 years (n = 7560) longitudinally over a 12 month period. Eye growth and myopic shift in refraction were found to occur more quickly in children with two myopic parents compared to those with none (annual AL growth/myopia progression = 0.37mm/-0.22D and 0.20mm/-0.02D respectively, p = <0.001). The Correction of Myopia Evaluation Trial (COMET) investigated the change in refraction and axial length of children and the role of parental myopia over a 5 year period (Kurtz et al., 2007). They concluded that the number of myopic parents was directly related the rate of myopia progression. A mean rate of -2.59±0.19D was found in children with two myopic parents compared to -1.81±0.18D in those with no myopic parents. The COMET is unique in that it didn't rely on questionnaire data for parental refraction, instead direct autorefractor measurements were taken. Conversly in the SMS, no association of axial length and parental myopia was found (Ip et al., 2007b).

2.3.4 Urbanisation and housing type

The difference in myopia prevalence between rural and urban areas is well documented with a greater prevalence of myopia consistently found in urban areas (He et al., 2007, French et al., 2013b, Rose et al., 2008a, Sherwin et al., 2012c, Lin et al., 2014, Read et al., 2014, He et al., 2015a, Shah et al., 2017). Myopia is also found to be much greater in East Asian countries particularly China which is becoming rapidly urbanised. Environmental factors associated with urbanisation, such as increased population density and housing type, have been investigated to establish the extent to which they influence myopia development. Ip et al (2008c) examined this association by dividing the Sydney area into five urban regions based on their population density, from the least populated outer suburban region (<100 persons/km^2) to the most populated inner city region (>3000 persons/km^2). Myopia prevalence was found to be lowest in the outer suburban region (6.9%) and nearly triple in the inner city region (17.8%). This pattern was consistent for both European Caucasian and East Asian ethnicities. Population density was also found to an independent risk factor for myopia in Chinese children (Zhang et al., 2010, Choi et al., 2017).

The influence of housing type has also been investigated and myopia was found to be more prevalent in children living in apartments (26.3%) compared to separate houses (11.3%) (χ^2<0.001) (Ip et al., 2008c). This difference in housing type was evaluated further by Wu et al (2016) who found that myopia was more prevalent in children living in higher floors within an apartment block, 29.2% (1-3 Floor) compared to 39.4% (7+ floor). However, interestingly in Singapore adult myopia has been associated with a large dwelling size (Wong et al., 2000). This association was also related to increased educational level, increased income and professional occupations which have likely resulted in larger homes.

The specific reasoning behind the association of urbanisation and myopia has yet to be established however it has been theorised that it could be linked to protective effects of time outdoors that has been found in several studies, see Section 2.2. Closely confined environments such as apartments may not only limit the amount of light through windows but may also act as a barrier for the accessibility for children to be outdoors especially those on higher floors. Furthermore, living in a more confined environment may also increase the baseline accommodative demand experienced by these children and therefore result in myopia development. The myopia prevalence in China is increasing alongside increasing levels of urbanisation. The percentage of China's population residing in urban environments has increased from 11.8% in 1950 to 55.5% in 2015 and is projected to increase further to 80% in 2050 (United Nations, 2018).

It has also been hypothesised that the spatial frequency of urban and indoor environments differs from natural outdoor environments. A recent study by Flitcroft et al (2020) has shown that the spatial frequency of urban and indoor environments is relatively deficient in high spatial frequency and is similar to slightly defocussed (blurred) images equivalent to 0.66 to 1.51D. This is similar to the spatial feature created by diffusing filters that have been found to induce form deprivation myopia in animal models.

The use of the simple dichotomy of rural and urban does not account for the complex spectrum of environmental and social factors that are at play. Urbanisation has the ability the improve access to health services and education, however it has also been linked to a number of health risks, including cardiovascular conditions (Gong et al., 2012). Urban areas have also been linked with increased pollution (Schwela, 2000), noise (Hoffmann et al., 2009) and disrupted sleep (Haseli-Mashhadi et al., 2009). All of which could have a detrimental effect on individuals and could be contributing to myopia

development. The impact of sleep patterns and circadian rhythms is an emerging field in myopia and is discussed in the next section.

2.3.5 Circadian rhythms and sleep patterns

Circadian rhythms are internal 24 hour cycles that regulate processes within the human body to coordinate environmental variations with behavioural and physiological activities, such as sleep/wake cycles. Increasing evidence implicates diurnal and circadian rhythms in eye growth and refractive error development (Chakraborty et al., 2018). As mentioned previously dopamine, a key neurotransmitter in circadian rhythms, has been postulated to be integral in the mechanism behind the protective effect of time outdoors, see Section 2.2.5.2. Melatonin is a neurohormone which is also under circadian control and its levels are influenced by light levels but inversely to dopamine (Cahill et al., 1991). Melatonin synthesis is stimulated in darkness and inhibited in light and therefore acts as a 'night' signal. This is the reverse of dopamine which acts as a 'light' signal, see Figure 2.1 in Section 2.2.5.2. As discussed previously there is a protective effect of increased time outdoors in myopia development. It was therefore postulated that less exposure to outdoor light could lead to higher melatonin concentrations and ultimately promote myopic growth. This was first investigated by the removal of the pineal gland in chicks, which is critical for melatonin synthesis. However, removal of the pineal gland did not influence ocular growth (Li and Howland, 2006).

Wahl et al (2011) investigated the influence of melatonin eye drops on the refractive error of chicks. Administration of up to 4 drops of melatonin daily caused a myopic shift in chicks exposed to constant light for 2 weeks. This suggests that melatonin promotes myopia growth and also inhibits the protective effect of bright light. Furthermore, administration of a melatonin receptor antagonist (Luzindole) caused a hyperopic shift. This research in chicks therefore suggested that increased melatonin levels promote myopic development and decreased melatonin levels promote hyperopic development.

A recent study has investigated the serum melatonin levels in young adults (aged 19.1±0.81 years, n=45) (Kearney et al., 2017). This study reported for the first time in humans that myopes exhibited higher serum melatonin concentrations than non-myopes ($p<0.001$). This study is likely to pave the way for future research into circadian rhythms and neurochemicals with future research likely to focus on younger cohorts where active myopic progression is present.

In addition to maintaining circadian rhythms, melatonin also plays a pivotal role in regulation of sleep patterns (Huang et al., 2013, Rodenbeck et al., 1998). Studies

investigating the relationship between sleep and refractive error primarily assess sleep through sleep duration recall or sleep specific questionnaire data. One study investigated the relationship between sleep duration and myopia in Korean adolescents aged 12-19 years old (n=3625) and found an inverse relationship between sleep duration and myopia (Jee et al., 2016). The odds of myopia were 41% less in participants who had >9 hours sleep compared to those with less than 5 hours (p=0.006). It was also found to have a dose-response with the risk of myopia decreasing by 10% per hour increase of sleep (p=0.012). This is consistent with a previous study of 15,316 Chinese children which found that children who had <7 hours of sleep had a 3.37 times higher risk of myopia than those with >9 hours (Gong et al., 2014). Another study used a sleep specific questionnaire (Pittsburgh Sleep Quality Index (PSQI)) to assess sleep quality in children aged 10 – 19 year old (Ayaki et al., 2016). It found that children with high myopia (≤-6.00D) had a poorer PSQI score than non-myopes (p<0.01). It concluded that myopic children were late and short sleepers and myopes tended to go to bed approximately 1 hour (74 minutes) later than non-myopes.

The exact mechanism behind this association between sleep duration and myopia is difficult to pinpoint when based on questionnaire data which for children populations are almost exclusively based on parental recall. One hypothesis for the association between sleep and myopia is that the lack of sleep or sleep deprivation is a result of the high amounts of near work children are undertaking, thus suggesting that the amount of near work is the precipitating factor. The intensity of education in Asian countries is much higher with school often starting between 07:00-08:30 and finishing between 16:30-18:00. In addition, often children attend private tuition sessions in the evenings sometimes until 21:00 or even 24:00 (Yang et al., 2005). Korean adolescents have been shown to have higher amounts of chronic sleep deprivation compared to adolescents in other countries (Yang et al., 2005). Another theory that has been suggested is that the retinal damage and stretch caused by axial elongation in myopia, primarily high myopia, could damage the intrinsically photosensitive retinal ganglion cells which are responsible for light perception (Ayaki et al., 2016). This deficiency could result in a disrupted circadian rhythm.

Due to the currently scarce amount of literature on this topic it is difficult to establish the causal relationship between sleep and myopia and understand whether altered sleep is a result of intensive established myopiagenic activities such as near work or whether an intrinsic mechanism such as disruption of the circadian rhythm is responsible. In order to understand the relationship between sleep, circadian rhythms and myopia using more objective measures need to be used to record sleep, for example the use of an actigraph,

such as the Actiwatch 2 (Philips Respironics, USA) used in this study which allows sleep/wake times to be evaluated more accurately.

2.3.6 Demographic risk factors

Several factors associated with the demographic of populations have been investigated and found to have a link with myopia prevalence. These are discussed below.

2.3.6.1 Ethnicity

The worldwide prevalence of myopia has clearly shown an increased prevalence in Asian countries such as Singapore and China compared to the UK. Ethnicity has been recognised as a risk factor for myopia with a number of epidemiological studies reporting higher myopia levels in East Asian children. The SMS found that in 11 – 15 years olds (n=2352) the myopia prevalence was 4.6% in Caucasian children, 39.5% in East Asian and 31.5% in South Asian (Ip et al., 2008a). In addition, Caucasians had a more hyperopic mean SER (+0.82D) and shorter mean axial length (23.23mm). East Asian children had the most myopic SER (-0.69D) and the greatest mean axial length (23.86mm). Similar findings were found by the AES with South Asian children aged 12-13 years having a prevalence of 36.8% compared to 18.6% in white Europeans. White Europeans also had a more hyperopic refraction (+0.45D) compared to South Asian (-0.42D) (Logan et al., 2008). The difference was even larger in another UK based study of 10 – 11 year olds which again showed a higher prevalence in South Asian (25.2%) than white European children (3.4%) (Rudnicka et al., 2010).

The CLEERE study, examined four ethnic groups in school children aged 5–17 years, and also found that Asians had the highest prevalence of myopia (18.5%) followed by Hispanics (13.2%) and European ancestry children had the lowest prevalence of myopia (4.4%), which was not significantly different from African Americans (6.6%) (Kleinstein et al., 2003). Although there is an established difference in prevalence between ethnicities it should be noted that this difference is unlikely to be purely genetic in nature and may also reflect different patterns in lifestyle between different countries, cultures and religions. One study that demonstrates this examined the prevalence of myopia in two age-matched cohorts both of Chinese ethnicity living in Singapore and Sydney. The prevalence of myopia was 29.1% vs 3.3% in Singapore vs Sydney (Rose et al., 2008b).

These ethnic differences have been attributed to a potentially genetic origin however it has also been suggested that differences in cultural norms and habits could also be playing a significant role (Chiang et al., 2020).

2.3.6.2 Sex

A recent meta-analysis of 142 published studies spanning 42 countries found a higher prevalence of myopia in females compared to males aged 9 year old (Rudnicka et al., 2016). This association become more pronounced with age. The association between males and females in other myopia related studies is shown in Table 2.3.

Study	Sample size	Country	Age (years)	Females (%)	Males (%)
Fan et al (2004)	7560	China	5 – 16	37.9	37.1
O'Donoghue et al (2015) NICER	661	Northern Ireland	12 – 13	20	16
Rudnicka et al (2010) CHASE	1179	England	10 – 11	12	11.7
Saxena et al (2015) NIM	1884	India	5 – 15	13.2	11.6
Ojaimi et al (2005b) SMS	1765	Australia	5 – 6	1.62	1.24

Table 2.3: Comparison of sex differences in myopia prevalence NICER: Northern Ireland Childhood Errors of Refraction, CHASE: Child Heart and Health Study in England, NIM: North India Myopia Study, SMS: Sydney Myopia Study

Similar trends in sex differences have been found in a number of other studies. A 5 year study of the progression of refractive error in Chinese children aged 6 – 15 years (n=1858) found that myopic progression was larger in females than males, -2.41D compared to -1.99D respectively (Zhou et al., 2016a). This is in agreement with two other studies on school aged children based in China (Zhao et al., 2002, Fan et al., 2004). A 12 year follow up of Finnish children (aged 9.3±1.9) found a greater myopic progression in females compared to males (Parssinen et al., 2014). Conversely, SAVES found no significant difference in myopia prevalence between males and females over a 5-6 year follow up period (French et al., 2013a). Two UK based studies, NICER and CHASE, found no significant association between females and myopia (O'Donoghue et al., 2015, Rudnicka et al., 2010).

The majority of the literature does provide evidence that myopia is more prevalent in female school children compared to their male counterparts. Investigations into the different activities of these two groups, namely time outdoors and amount of near work, have found that females have a more myopiagenic pattern and are more likely to spend

time indoors doing near tasks then spent outdoors (Fan et al., 2004, Parssinen et al., 2014, French et al., 2013a). In addition it should be speculated that this discrepancy is related to an earlier myopia onset in female compared to males, as females experience an earlier onset of puberty and earlier 'growth spurts' (Yip et al., 2012). Therefore, cohort age should be considered when assessing sex difference in myopia prevalence.

2.3.6.3 Season of birth

A correlation between season of birth and myopia prevalence has been found in Israeli conscripts (Mandel et al., 2008). June/July births had a higher prevalence of moderate and severe myopia (defined <-3.00D), 11.8% and the lowest in December/January 10.4%. This was followed up by McMahon et al (2009) on a UK population examining the records of 74,459 participants aged 18 – 100 years. Similarly, to Mandel et al (2008) an association between season of birth and myopia prevalence was found, however it only related to high myopia (<-6.00D). Individuals born in Summer and Autumn were 16% more likely to be highly myopic compared to winter births. It has been hypothesised that this association could be related to light exposure and the duration of daylight hours (photoperiod). The role of light exposure in refractive error development and emmetropisation has been discussed previously in Sections 1.4.1 and 2.2.5.1. The association between myopia and perinatal photoperiod was examined by Mandel et al (2008) who found an increased odds ratio for severe myopia in those born in shorter photoperiod compared to a longer photoperiod ($p<0.001$). This is in agreement with a similar trend found by in Finland by Vannas et al (2003) who found a trend of higher myopia in individuals born in the north of the country (where the photoperiod is extremely long in summer months and reciprocally short in winter months) compared to those in the south. However, no association between season of birth and myopia was found. The association of photoperiod and myopia was also investigated in a UK population by McMahon et al (2009) who found only a weak association (OR = 0.94, $p=0.019$) and the directional effect was opposite to that observed by Mandel et al (2008). McMahon et al (2009) concluded that perinatal photoperiod is an unlikely risk factor for myopia development in the UK.

Although the evidence for an association between perinatal photoperiod and myopia is contradictory, a similar agreement in a summer season of birth and myopia was found by both McMahon et al (2009) and Mandel et al (2008). It must be considered however, that the season of birth has been found to be influential in a number of factors, including melatonin production which could confound the association. Sivan et al (2001) found infants born in June has the highest levels of melatonin at 8 weeks and lowest in

December. Furthermore, season of birth has a strong association with birth weight (McGrath et al., 2005). In addition to light levels the season of birth is also associated with differences in environmental variations such as temperate, rainfall and pollen count. Increasing body temperature in rabbits has been found to increase myopia (1970). Thus, although an association between season of birth and myopia has been found there are a number of confounding factors that make the reason for the correlation difficult to identify.

2.3.6.4 Socioeconomic status

Socioeconomic status can be considered by assessing a number of different factors including parental education, housing type and/or household income (Quek et al., 2004). Two UK based studies have used the Index of Multiple Deprivation (IMD) as a measure of relative deprivation (O'Donoghue et al., 2015, Goverdhan et al., 2011). The IMD incorporates details on income, employment and accessibility of services based on the place of residence (via postcodes).

Assessment of socioeconomic status in children is limited. One study found that socioeconomic status did not predict rate of progression of myopia in children aged 6 – 12 years (Saw et al., 2001b). These findings were based on a very limited range of socioeconomic statuses within the population. Similarly the SAVES study based in Australia found no significant difference in the amount of incident myopia with parents with higher education attainment or employment status (French et al., 2013b). Conversely Xiang et al (2012) found that myopic Chinese children had higher parental educational levels as well as higher incomes and parental occupation. Similarly, Lim et al (2012) found that higher parental incomes were associated with myopia in Korean children (mean age 9.36 years, n=8633). However, parental myopia was not accounted for. Wu et al (2015) did account for parental myopia and similarly found an association between myopia and parental income. A study based in Delhi found that higher socioeconomic status was associated with a higher risk of myopia in school children (mean age 11.6±2 years, n=9884) (Saxena et al., 2015). NICER, a UK based study on a similar age group (12-13 years) did not find a significant association (O'Donoghue et al., 2015).

In adults there is a very strong association between education level and occupation with myopia with a higher prevalence found in individuals in higher education and professional careers such as Medicine and Optometry (Lin et al., 1996, Logan et al., 2005). A higher prevalence of myopia was found in Chinese and Japanese individuals with a higher education level, near work occupations (for example managers and office

workers), higher incomes and better housing (Wong et al., 2000, Shimizu et al., 2003). In addition higher educational status was also found to correlate with longer axial length and vitreous chamber depth (Wong et al., 2003). In UK adults a linear association between IMD score and axial length was found with increasing deprivation associated with a decreased axial length (Goverdhan et al., 2011). However, no association between IMD score and spherical refraction was found.

It appears that there is conflicting evidence regarding socioeconomic status and myopia. These discrepancies could be attributed to differences and limitations of cohort populations. In addition, definition and classifications of socioeconomic status with some studies using the location of residence to establish deprivation level (O'Donoghue et al., 2015) compared to other variations such as schooling fees (Saxena et al., 2015). However, it is difficult to decipher whether individuals living in less deprived families with arguably more academically successful parents may be influenced by other factors that could account for this association. For example, parental input and academic pressures leading to increased concentration tasks which has been implicated in myopia development. Socioeconomic status is also related to housing size and type and has been found to be influential in myopia development.

2.3.6.5 Birth order and family size

A number of studies have assessed the relationship between birth order and myopia prevalence and found an increased prevalence in first born children (Peckham et al., 1977, Rudnicka et al., 2008). However, these studies classified myopia based on unaided VA which is not considered the gold standard for classification. However analysis of four cohorts from four different countries using data from ALSPAC, SCORM, Raine Eye Health Study (REHS) and Israeli Pre-recruitment Candidates found a small increased risk of myopia in first born children compared to non-first born individuals (Guggenheim et al., 2013). It also had the novel finding that “only children” i.e. families with only one child were at a similarly elevated risk of myopia. One potential cause of this association between birth order and myopia was thought to be related to parental investment in their children’s education (Morgan and Cotch, 2013). Studies have shown that parental investment does vary depending on birth order with parents reported to direct more of their resources to earlier born children which as a result leads to better educational attainment compared to later born individuals (Booth and Kee, 2009, Fergusson et al., 2006). As a result, parents may be exposing their earlier born children to a more myopiagenic environment with increased near work and reduce time outdoors. This is also in line with data from the NICER study that showed that children in larger

families were less likely to be myopic (O'Donoghue et al., 2015). In a follow up analysis from his earlier work, Guggenheim et al (2015) attempted to adjust for education level to establish if the same association between myopia and birth order remained. Prior to adjusting for education, first born individuals were 10% more likely to be myopic having a refractive error of less than -0.25D more negative than non-first born individuals. However, after adjusting for education this association was attenuated, therefore, concluding that the relationship between birth order and myopia is confounded by educational exposure and parental input. It is interesting to note that demographic changes worldwide have led to an increased prevalence of smaller families. This is particularly prominent in China where the single child policy was implemented in 1979 (Hesketh et al., 2005) which coincides with the a continent with one of the highest prevalence of myopia.

In conclusion, it appears that the link between education level and birth order could potentially be confounded by other factors namely increased amount of near work from external parental pressure on first born children.

2.3.6.6 Height and Weight

In children, the development of myopia and the growth of the eye occur at the same time when body stature is increasing. A recent study by Rim et al (2017) found that increased height was associated with myopia in children. A similar trend was found in a young cohort of Singapore Chinese children aged 6 – 72 month old children (Low et al., 2010). For each 1 cm increase in height, the SER was more myopic by 0.01 dioptres. Huang et al (2014a) investigated how refraction and axial length change is related to changes in height in 7 – 9 years old Taiwanese schoolchildren over a 3 year period. Axial length change was found to be positively correlated to height change ($p<0.001$). Although a myopic shift in refraction was correlated with axial length changes ($p=0.000$), it was not correlated with height change. A similar correlation between axial length and height but not refraction was found by Ojaimi et al (2005a). Children in the lowest quintile for height had a mean axial length of 22.39±0.01mm compared to those in the highest quintile with a mean axial length 22.76±0.04mm. This result was also found in a study of Chinese adults and concluded that taller people were more likely to have a longer axial length, with +0.23mm longer axial length found for every 0.1m difference in height (Wong et al., 2001). A similar trend was found in Singaporean children with a +0.29mm longer axial length in boys and +0.32 longer axial length in girls for every 0.1m difference in height (Saw et al., 2002a). Considering that axial length is a key determinant in myopia a number of other studies, including the Singapore Cohort Study of Risk Factors for

Myopia (SCORM) study, assessed the relationship between myopia and height. In many of these studies greater height was associated with a more myopic refraction (Lee et al., 2018, Sharma et al., 2010, Rim et al., 2017), however this is not consistent with many finding no relationship (Jung et al., 2012, Rosner et al., 1995, Lim et al., 2010, Jacobsen et al., 2007).

In addition to height, the relationship between weight and refraction has been investigated. Dirani et al (2008) explored the relationship between body stature and myopia using the Genes in Myopia (GEM) twin study in twins aged 18 to 86 years. They found that the heaviest individuals were at a significantly higher risk of myopia (OR 1.48, p=0.01) compared to the lighter individuals. However, when sex was analysed separately this increased risk only remained for females (OR 1.79, p=0.01). Conversely Wu et al (2007) found that heavier individuals were more likely to be hyperopic and Wong et al (2001) found those with a higher body mass index (BMI) were likely to be hyperopic than lighter leaner individuals. This was explained by Gunes et al (2015) who reported that the amount of retrobulbar fat is limited by the orbital space and therefore prevents expansion. Therefore obese individuals tend to be more hyperopic with short vitreous chambers (Wong et al., 2001). Interestingly low birth weight has been associated with myopia (Rahi et al., 2011). However, some studies have found no relationship between BMI and myopia (Jung et al., 2012, McKnight et al., 2014). It seems, similarly to height, inconsistent findings between weight and myopia have been found and therefore the relationship between BMI, height and weight with myopia is inconclusive.

The definitive relationship between increasing height and increasing axial length but not myopia is in line with our understanding of the active process of emmetropisation. More specifically as children age, they increase in height and the eye naturally elongates. Alongside this the ocular components within the eye, namely the lens and cornea, change in order to compensate for this elongation to maintain an emmetropic state, Section 1.4.

2.3.6.7 Smoking

Investigations into experimental myopia in laboratory animals has identified a number of retinal neurotransmitters involved in regulating refractive error development. One prominent neurotransmitter identified is acetylcholine which acts through muscarinic or nicotine acetylcholine receptors which are found throughout the body including the retina. Nicotinic receptor antagonists have been found to inhibit experimental myopia in chicks (Stone et al., 2001). This led to the investigation of the association of nicotine,

the primary component of tobacco cigarettes, and myopia. Conflicting results are found in the literature with a number of cross sectional studies, including the SMS, STARS and SCORM studies, finding passive smoking in children to be associated with a more hyperopic refractive (Ip et al., 2008b, Iyer et al., 2012, Saw et al., 2004a). A recent meta-analysis of the association between maternal smoking and childhood refractive error agreed with these findings (Li et al., 2016). Conversely, a study of myopia prevalence in 3 year old children in Singapore found a 2.8 times increased risk of myopia in children who have been exposed to passive smoke from birth to 6 months of age (Chua et al., 2016). This risk increased to 4 times if the parental smoking occurred at home, in the family car or in the presence of the child. Interestingly a study based in the UK found that myopia was positively associated with maternal smoking in the first trimester of pregnancy which was also factor to be a marker for socioeconomic status (Rahi et al., 2011).

These conflicting findings can be attributed to the nature of the studies which were mainly cross sectional and questionnaire based. Larger prospective studies with longer follow up visits are required to gain a better understanding of the link between passive smoking and refractive error development. In addition, the use of objective measures for smoking would be beneficial. This could include analysis of urinary levels of cotinine. A metabolite of nicotine which is a biomarker for smoke exposure. A study of 300 children aged 5 – 12 years found a positive correlation between urinary cotinine levels and hyperopia, suggesting that hyperopes had higher passive smoking indices (El-Shazly, 2012).

As with many demographic risk factors discussed in this section it is difficult to establish a direct correlation without considering possible confounding factors. For example, smoking is less common in highly educated individuals (Gilman et al., 2008) and higher levels of parental education are associated with an increased myopia prevalence (Mirshahi et al., 2014). Therefore, the exact causal relationship and mechanism of passive smoking and refractive error, if there is one, is difficult to distinguish and could be confounded by other factors such as education level.

2.3.7 Diet

Another possibly influential environmental factor is diet. The human diet has evolved and diversified compared to our “hunter gather” predecessors. The variety and type of food has changed from high protein, moderate fat and low carbohydrate to the reverse in modern society (Cordain et al., 2000). In particular, an increase in high glycaemic food intake which promotes the development of hyperinsulinaemia has been thought to

facilitate unregulated sclera growth and therefore play a role in myopia (Cordain et al., 2002).

Diet has been investigated in relationship to a number of ocular diseases including cataracts and macular degeneration (Chiu and Taylor, 2007, Montgomery et al., 2010). Literature in this area of myopia research is very variable and the majority rely on questionnaire data which is reliant on good recall and often find conflicting results. Edwards et al (1996) investigated the variation in nutritional intake between non-myopes and incident myopes. A significantly lower food intake was recorded for incident myopes compared to the non-myopes, 1484.2 calories vs 1713.8 calories respectively (p=0.024). However, Lim et al (2010) concluded that higher saturated fat and cholesterol intake are associated with longer AL. Breastfeeding has been found to have a protective effect and is associated with a more hyperopic spherical refraction (Sham et al., 2010). A small number of studies have investigated the levels of micronutrients such as zinc and copper. Findings of lower levels of these micronutrients in myopes compared to controls have been found (Wang, 2009, Huo et al., 2006, Xie et al., 2003). However, two recently published articles in Korean and US populations of 12 – 19 year olds found no significant association between serum zinc and myopia (Burke et al., 2020, Burke et al., 2019). These mixed results could be attributed to the limited sensitivity of biomarker for zinc status. Vitamin D is another important dietary factor that has been investigated however this has been primarily related to the association of vitamin D and time outdoors, see Section 2.2.5.3.

2.4 Summary

It is widely accepted that most myopia is polygenic, resulting from a combination of genetic susceptibility and environmental factors. It is evident that there is an increasing prevalence of myopia worldwide and the primary reason behind this increase is thought to be associated with changes in environment and lifestyle that have occurred over the past century. Most notably the increased urbanisation globally and the technology boom which has occurred meaning that children are spending less time outdoors and more time using electronic devices at a closer working distance which is thought to be influential in myopia development. The majority of literature assessing these environmental and lifestyle factors is through questionnaire data however objective data is more likely to produce more accurate picture of the associations at play in myopia development. However, many of risk factors identified are plagued by potential confounding factors that make underpinning the exact factors and mechanisms that underpin myopia onset and development difficult.

Chapter 3: Introduction to study design, rationale and objectives

3.1 Study rationale

It is widely accepted that the development of myopia is a multifactorial process involving environmental factors. The amount of time spent outdoors has been shown to be an important environmental factor in myopia development providing a protective effect, see Section 2.2. Despite this consistent finding across a number of studies, the exact mechanism behind this process remains unclear. One theory has suggested that this effect can be attributed to the exposure of sunlight when outdoors. Sunlight provides a much higher illuminance level compared to indoor light (Wu et al., 2018) and in addition it contains visible violet light. Preliminary data has shown that this wavelength is a vital component of outdoor light (Liu et al., 2011, Liu et al., 2014, Torii et al., 2017b). Furthermore, research in animal studies has provided direct evidence that high illuminance levels can have a protective effect against myopia development, this has been discussed in detail in Section 2.2.5.1.

Research into the protective effect of light levels on myopia onset and progression has emerged as a rapidly evolving field of myopia research over the past few decades. In order to demonstrate the growth of this area of research a systematic search was conducted of three databases – PubMed, Web of Science and the Cochrane Central Register of Controlled Clinical Trials (CENTRAL) – from their inception until March 2020. The following search strategy was used: “myop*” AND “light”. The search results from the three databases were collated and duplicates removed. Abstracts were reviewed for each publication to allow exclusion of irrelevant papers (those not related to myopia research) and also removal of records relating to conference papers if subsequent published data was available. The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow diagram can be found in the Appendix A.3.1. Initially 4,926 records were identified from the three databases and 1,187 duplicates were removed. The remaining 3,739 titles and their abstracts were screened and only 310 articles related to myopia research remained. Full-text articles were then retrieved for these 310 articles which were then further screened for their eligibility. 180 articles remained and a histogram was created to demonstrate the increase in the number of articles published related to myopia and light, see Figure 3.1. These articles were then further subdivided into 14 categories related to the area of research.

It is clear from Figure 3.1 that there has been a dramatic increase in published articles over the past decade, with the peak between 2018-2019 (n=32). Over recent years the majority of research in myopia and light has been centred around the composition of light, mainly the wavelength, circadian rhythms, dopamine and objective light exposure measurements. These align with the current theories of the protective mechanism of time outdoors, see Section 2.2.5.

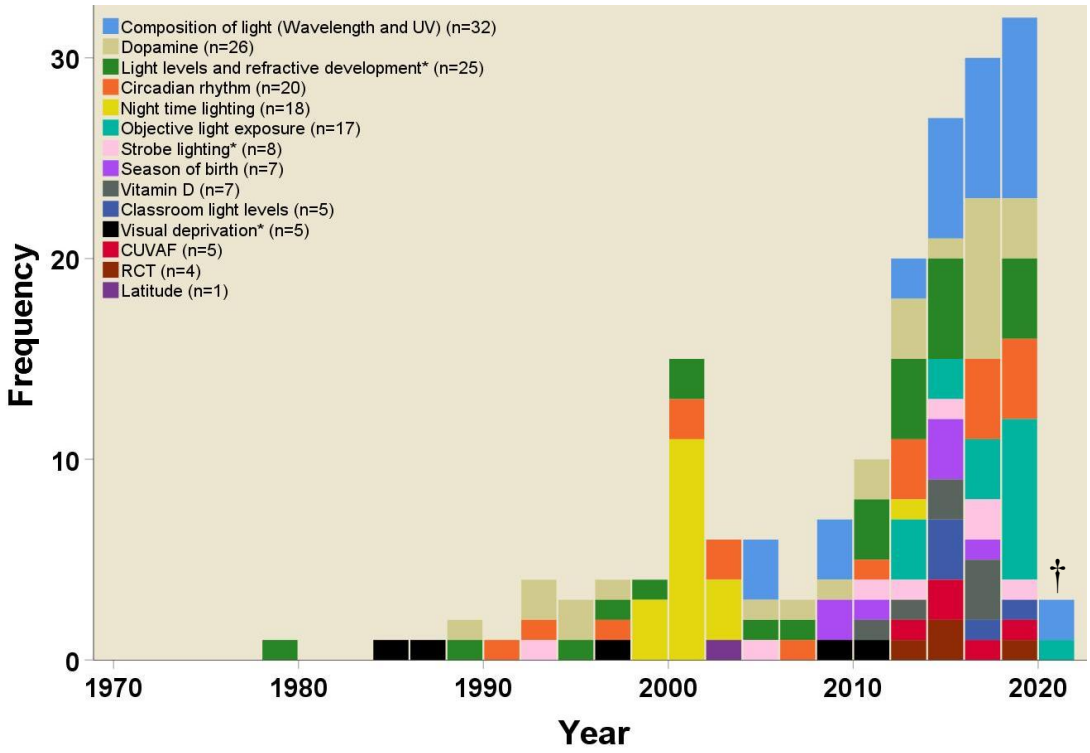


Figure 3.1: Trends of published articles relating to a systematic literature search using "myop*" AND "light" from database inception to March 2020 *: animal studies only. †: Article published until March 2020 only displayed. An enlarged version of this histogram can be found in the Appendix A.3.2.

This study discusses three sets of objective data related to light levels: objective measures of light exposure measured with a wrist worn device (Actiwatch 2, Philips Respironics, USA), identification of Conjunctival UV Autofluorescence (CUVAF), considered a surrogate measures of light exposure, and also classroom illuminance levels. It is clear from Figure 3.1 that these are all emerging areas of research within myopia and light and this study hopes to provide data from UK based participants, primarily children aged 7-12 years, in these key areas, which is currently not published in the literature . In addition, a number of other environmental and lifestyle factors are subjectively quantified through the use of parental and participant questionnaires. The study is longitudinal in nature to allow eye growth and SER progression to be analysed

alongside these factors to investigate their potential influence. The study design is discussed in detail below.

3.2 Study design

This thesis has been written to describe the effects of environment and lifestyle on refractive outcome, with an emphasis eye growth The study was designed to be longitudinal in nature recruiting participants from two cohorts. The first cohort: children aged 7 to 12 years, the age at which myopia is likely to develop (Logan et al., 2011, McCullough et al., 2016). This age group is also in line with other longitudinal observatiional studies such as NICER, SMS and CLEERE (O'Donoghue et al., 2010c, Ojaimi et al., 2005c, Mutti et al., 2007). The second cohort comprises of young adults aged 18 to 25 years, the age at which myopia is found to continue to progress in 50% of individuals (Dong et al., 2013, Kinge et al., 2000). Both cohorts were followed up longitudinally for 2 years (1 yearly intervals), this required three visits: Baseline, Year 1 follow up and Year 2 follow up. All participants were followed up at 12 months ± 6 weeks intervals, see Figure 3.2.

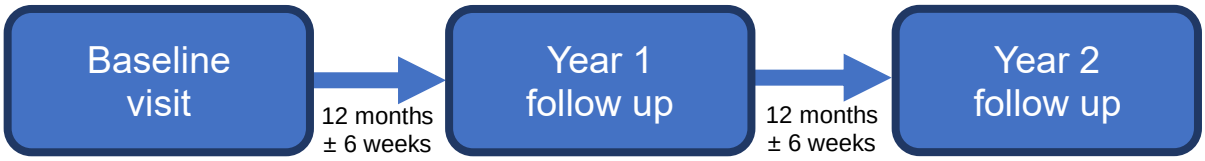


Figure 3.2: Study design follow up outline

At each visit the same protocol was adhered to, as detailed in Section 5.1, including cycloplegic refraction, ocular biometry, questionnaires and conjunctival UV autofluorescence (CUVAF) photography. Full ethical approval for this study was obtained from the Aston University Ethics Committee, see Appendix A.3.3. and all protocols adhere to the tenets of the Declaration of Helsinki. In the Child cohort, following initial recruitment, an extension of recruitment to schools at different latitudes, namely the North and South of the UK, was undertaken to determine if differences in light exposure and refractive error development across a cross section of the UK.

The investigation of myopiagenic risk factors was originally designed to be largely centred around responses from questionnaires however this analysis has been limited by the low number of myopes recruited in the Child cohort. In addition, a high attrition rate has meant that longitudinal comparisons have also been limited. Despite this, valuable objective data on time outdoors was gathered through the use of a wrist worn light sensor (Actiwatch 2, Philips Respironics, USA) providing objective data on light

exposure patterns within the UK and estimations of time outdoors. This allowed direct comparisons with previous literature from Australia, USA and Singapore to be undertaken. In addition, this device has also allowed novel exploratory data on sleep patterns to be captured and analysed. This coupled with the investigation of conjunctival UV autofluorescence, a surrogate biomarker of time outdoors, has provided an interesting insight into environmental factors within the UK. Alongside this, valuable biometric data has been collected using the Aladdin (HW3.0, Topcon, Tokyo, Japan) a new biometer that utilises optical low coherence interferometry and has the ability to measure Axial length (AL), Anterior Chamber (AC) and Corneal Radius (CR) as well as Lens Thickness (LT) and Central Corneal Thickness (CCT). This has allowed the role of LT and CCT in refractive error determination to be investigated, as well as establish its validity and agreement with the gold standard biometer, IOLMaster 500 (Carl Zeiss, Jena, Germany).

To clarify the outline of this thesis and to assist the reader, an explanation of the research chapters is detailed below:

Chapter 6: outlines the validity and agreement of the new generation Aladdin (HW3.0, Topcon, Tokyo, Japan) biometer to the gold standard IOLMaster 500 (Carl Zeiss, Jena, Germany) with regard to AL, AC and CR measurements.

Chapter 7: investigates the association of environmental and lifestyle factors, quantified through questionnaires, with eye growth

Chapter 8: explores objectively measured sleep patterns of UK children and assesses the influence of season and day of the week. In addition, the association of between sleep patterns and eye growth and SER progression are explored

Chapter 9: examines the relationship between objectively measured light exposure and longitudinal changes in axial eye growth in children. In addition, seasonal variation in light exposure in a UK cohort is explored.

Chapter 10: assesses the viability of the CUVAF as a surrogate measure of time outdoors in the UK

Chapter 11: explores the illuminance levels in UK classrooms analysing seasonal and within classroom variation

3.3 Study objectives

The primary study objectives are outlined below:

- To assess the validity and agreement between IOLMaster 500 (Carl Zeiss, Jena, Germany) and Aladdin (HW3.0, Topcon, Tokyo, Japan) biometry devices
- To assess risk factors for increased eye growth in UK children and young adults
- To determine if faster eye growth is associated with environmental and lifestyle factors
- To objectively assess light exposure of UK children and determine if latitudinal and seasonal differences exist as well as establish the influence of light exposure on longitudinal axial length growth in UK children
- To assess the viability of CUVAF as a surrogate measure of outdoor exposure in the UK and analyse the ability of a bespoke handheld device to detect the presence of CUVAF
- To determine if axial length growth is associated with lower levels of conjunctival UV autofluorescence in UK population
- To assess light levels in UK classrooms and discover if variability occurs within the classroom and throughout the course of a calendar year
- To provide exploratory normative data on sleep patterns of UK children and determine if any differences in sleep patterns exist between children with varying eye growth and SER values

Chapter 4: Instrumentation

This chapter outlines the technical specifications of instrumentation used for data collection.

4.1 Vision and visual acuity measurement

Vision and visual acuity were measured in LogMAR notation. For participants aged 18 – 25 years measurements were taken in the Ophthalmic Research Labs on Aston University Campus and a free standing backlit Early Treatment in Diabetic Retinopathy Study (ETDRS) 4 metre chart (Precision Vision, La Salle, USA) was used, see Figure 4.1. The chart was positioned in the same location for all participants, this ensured consistent ambient lighting conditions.

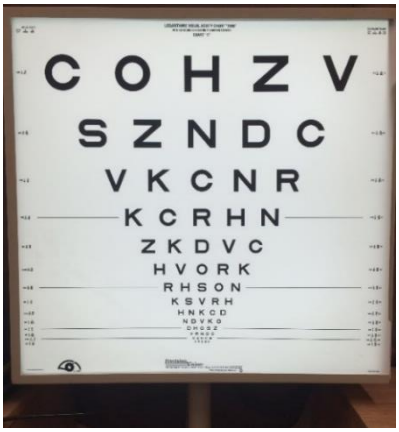


Figure 4.1: Image of free standing backlit ETDRS 4 metre chart used in the Young Adult cohort

Participants aged 7 – 12 years were seen at different locations on each school site therefore transporting the ETDRS chart was impractical due to its size. Therefore, a computerised LogMAR test chart (Thomson Software Solutions®, Herts, Version 1.45) was used on a 14 inch laptop screen. Ambient room lighting was variable depending on the size of the study room/area provided by the schools. For consistency it was ensured that the laptop screen was set to full brightness and positioned perpendicular to the line of sight at eye level. Visual inspection of the screen ensured that no glare from ceiling lighting or windows obscured the screen. One of the advantages of using the computerised test chart software was the ability to randomise the optotypes which aimed to prevent a potential learning effect. This was invaluable in the participants aged 7 – 12 years as they tended to be tested in groups of up to six at a time. In this scenario vision/visual acuity were undertaken sequentially and therefore the facility to change the letters was beneficial. In addition, due to the variation in working environments and

therefore variability of the screen location the software was able to be calibrated for different viewing distances. The software has a calibration function to allow different viewing distances, see Figure 4.2. The distance at each site was measured accurately with a measuring tape, ensuring a minimum of 3 metres, and inputted to calibrate the appropriate optotype size. All participants were able to read the letter optotypes on the LogMAR chart so there was no need for picture optotypes. The right eye was always measured first followed by the left eye.

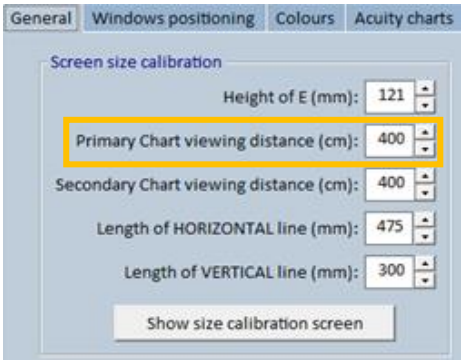


Figure 4.2: Viewing distance calibration for Test Chart 2016 (Thompson Software Solutions, Herts, Version 1.45)

LogMAR charts provide a reliable precise measure of vision and visual acuity and are widely accepted as the gold standard for use in research studies (Ferris and Bailey, 1996, Elliott, 2016). Visual acuity measurement with a LogMAR chart have been found to be twice as repeatable compared to a Snellen chart (Lovie-Kitchin, 2015). A LogMAR chart adheres to the designed principles set out by Bailey and Lovie including 5 letters on each line, consistent interrow and interletter spacing down the chart and each line equates to 0.1 LogMAR (each letter 0.02) LogMAR) (Bailey and Lovie, 1976). Therefore, each optotype read correctly improves acuity by 0.02.

4.2 Refractive Error

Objective cycloplegic autorefraction was used to measure refractive error in this study. It has been found to be the most reliable and repeatable measure of refractive error compared to retinoscopy and subjective refraction (Zadnik et al., 1992). This has been confirmed by Hashemi et al (2015) as part of the Tehran Eye Study, who found that subjective measurements were more myopic compared to cycloplegic autorefraction, -0.32±1.61 D versus +0.31±1.80 respectively ($p<0.001$). The largest variation was found in 5 – 10 year olds with a difference of 1.11D±0.60D found between subjective refraction and cycloplegic autorefraction. Therefore, use of cycloplegia minimises the overestimation of myopia as well as allowing identification of latent hyperopes and

pseudomyopes. Cycloplegic refraction is more sensitive and repeatable than subjective refraction when measuring refractive error and as such plays a pivot part in this study design. The WAM-5500 autorefractor (Grand Seiko Co. Ltd, Hiroshima, Japan) was used in this study for refractive error measurements.

4.2.1 WAM-5500 (Grand Seiko, Tokyo, Japan)

The WAM-5500 (Grand Seiko, Tokyo, Japan) is an open field autorefractor and keratometer with the ability to measure spherical refractive error spheres between ±22DS and cylinders between ±10DC in 0.01D, 0.12D or 0.25D increments. The vertex distance can be adjusted (0, 10, 12, 13.5 or 15mm). This instrument allows binocular fixation of a distance target in an open field configuration which promotes relaxation of accommodation. This is the gold standard for research purposes as closed view autorefractors are known to induce instrument myopia (Smith, 1983, Rosenfield and Ciuffreda, 1991). A 5.6 inch monitor allows visualisation of the anterior eye to ensure accurate alignment and allows monitoring of fixation throughout. An in-built thermal printer allows hard copies of the data to be easily obtained, see Figure 4.3.

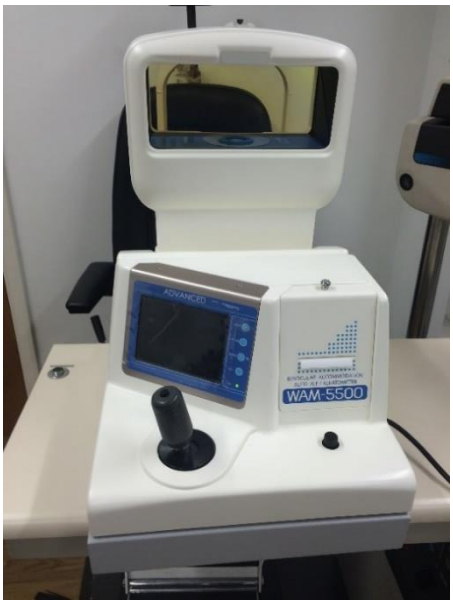


Figure 4.3: Photo of WAM-5500 autorefractor

The WAM-5500 (Grand Seiko, Tokyo, Japan) calculates refractive error in two stages, the same way as the Shin Nippon SRW-5000. An infrared image of a ring is projected into the eye and reflected off the retina. This image is initially brought into focus using an internal motorised lens system. Following this, the image of the ring is then digitally analysed to calculate a toroidal refractive prescription (Mallen et al., 2001, Mallen et al.,

2015). The image of the ring is smaller in hyperopia, larger in myopia and oval in astigmatism (Wolffsohn et al., 2001).

Sheppard and Davies (2010) have clinically evaluated the validity and repeatability of the WAM-5500 compared with non-cycloplegic subjective refraction (n=150). Only a small difference was found compared to subjective refraction (-0.01 ± 0.38D) over a wide range of refractive errors (-6.38D to +4.88D). 61% of spherical components and 74% of cylindrical components were within ±0.25D of subjective refraction. Assessment of cylinder axis for cylinder powers ≥0.75D was found to be even more similar with 80% within ±10^{o} and 95% within ±20^{o}. Intratest variability was assessed by analysis of the standard deviations of the 5 consecutive readings. This was found to be very low at 0.09D for the spherical component and 0.14D for the cylindrical component. Furthermore, Sheppard and Davies (2010) found a slight myopic bias in intertest repeatability in both spherical and cylindrical measurements, see Table 4.1. Arguably intertest variability is more important than intratest variability as it requires consistency with alignment and accurate remeasuring of the same participant at a different time (Mallen et al., 2001, Davies et al., 2003). Overall Sheppard and Davies (2010) concluded that the WAM-5500 is a 'reliable and valid objective refraction tool.'

Parameter	Sphere	Cylinder
Mean difference (D)	-0.04	-0.07
SD of differences (D)	±0.26	±0.29
Within ±0.12 D (%)	30	36
Within ±0.25 D (%)	75	66
Within ±0.50 D (%)	93	95
Within ±1.00 D (%)	100	100

Table 4.1: Intertest repeatability of the refractive components measured with WAM-5500 Adapted from (Sheppard and Davies, 2010)

More recently this has been confirmed by Moore et al (2014) who assessed repeatability centrally and eccentrically at 20, 30 and 40 degrees nasal and temporal in normal eyes and also those treated with orthokeratology. In the normal eyes the between-visit repeatability (defined as 1.96 x standard deviation of the difference) was found to be ±0.21D centrally increasing to ±0.73D 40^{o} nasally and ±0.88D 40^{o} temporal. Moore at al (2014) agreed that WAM-5500 is a valid repeatability instrument when assessing central refraction however peripheral measurements are less repeatable with increasing eccentricity.

Other features of the WAM-550 which have not been required in this study include measurement of corneal radii in the range 5.0-10.0mm (0.01mm steps) and pupil size (minimum size 2.3mm). It is also widely used in research to assess both static and dynamic accommodation (Aldaba et al., 2015, Aldaba et al., 2017, Win-Hall et al., 2010, Nemeth et al., 2013). The WAM-5500 has the ability to take monocular readings whilst providing a binocular accommodative stimulus. By connecting the WAM-5500 to a computer, rapid continuous dynamic measurements can be recorded at a frequency of 5 Hz.

The WAM-5500 was calibrated daily prior to any data collection using the calibration tool provided. All calibration readings were within tolerance and confirmed that the WAM-5500 was valid for use in this study.

4.2.2 Cycloplegia

In order to ensure reliability and repeatability, prior to refractive error measurements, all participant's accommodation was controlled with cycloplegia. Cycloplegia has been found to be the most reliable means of controlling accommodation compared to other methods such as extended optical fogging (using a +2.00 lens for 20 minutes) (Hopkins et al., 2012). Cycloplegia is a fundamental and essential component of a valid research protocol when investigating refractive error. The use of cycloplegia is recommended by the International Myopia Institute (IMI) in where studies refractive progression as a primary outcome, as in this study (Wolffsohn et al., 2019). The Shandong Children Eye Study concluded that non-cycloplegic measurements lead to a misclassification of refractive errors in children (Hu et al., 2015). As a result cycloplegic refraction is considered the gold standard for epidemiology studies (Morgan et al., 2015).

There are a variety of different topical drugs available that can induce cycloplegia, they include: Cyclopentolate Hydrochloride, Tropicamide and Atropine. All of these drugs are synthetic non-selective muscarinic antagonist which prevent the binding of acetylcholine at the iris sphincter and ciliary body smooth muscle. This results in mydriasis and cycloplegic (Eperjesi and Jones, 2005). Each drug varies we regard to its time of onset and duration.

Atropine is the most potent cycloplegic drug and it is rarely used in research for cycloplegia, as it requires instillation several days prior to refraction to ensure an adequate depth of cycloplegia is achieved. In addition, it can take up to 14 days to wear off (depending on the dosage) during this period glasses are required for all near vision tasks and patients often report a large amount of glare. The risk of toxicity with atropine

is much higher than any other cycloplegic drug. The most common adverse reactions range from mild itching to convulsions to even death (Bartlett and Jannus, 2008). Cyclopentolate and Tropicamide have more desirable pharmacokinetic properties as they take between 20 – 60 minutes to take action and their recovery times vary between 6 – 24 hours. Tropicamide has a shorter recovery time of between 2 – 6 hours (Mutti et al., 1994).

The type of cycloplegic drug and dosage used varies between studies, see Table 4.2. In some studies, two cycloplegics were used and in others a corneal anaesthetic prior to cycloplegic instillation is additionally used. This aimed to reduce the stinging sensation caused by cycloplegics (Shah et al., 1997). However, this additional drop itself causes mild stinging and therefore could affect compliance and ultimately increase dropouts. It has been shown that instillation of a topical anaesthetic does not increase the rate of onset of the cycloplegic (Haddad et al., 2007). Consequently, no corneal anaesthetic was used in this study due to the minimal beneficial effect and was therefore not considered essential.

Two different cycloplegics were selected for use in this study. 1 drop of 1.0% Cyclopentolate Hydrochloride was used on participants in the Child cohort (aged 7 – 12 years) and 1 drop of 1.0% Tropicamide was used on participants in the Young Adult cohort (aged 18 – 25 years). Cyclopentolate Hydrochloride was selected for the Child cohort as this is the most widely used cycloplegic used in studies with a similar design to this study, see Table 4.2, and this would therefore allow better comparison to the published literature.

Furthermore, Cyclopentolate Hydrochloride Minims® (Bausch and Lomb, Surrey) is an extensively used paediatric cycloplegic and has an increased depth of cycloplegia which is essential in this age group who possess a higher level of accommodation (Egashira et al., 1993, Rosenfield and Linfield, 1986). It should be noted that Tropicamide has also been found to be an effective cycloplegic in children (Manny et al., 2001). Tropicamide 1.0% Minims® (Bausch and Lomb, Surrey) was selected for participants in the Young Adult cohort as it has been found to be as effective as Cyclopentolate in this age group with the added benefit of a shorted recovery time and reduced side effects (Mutti et al., 1994, Yazdani et al., 2018). Furthermore, another study comparing the effectivity of Cyclopentolate and Tropicamide found that the participants preferred Tropicamide (Hofmeister et al., 2005).

Study	Author/Year	Topical Anaesthetic	First Cycloplegic	Secondary Cycloplegic
ACES	Li et al (2015)	0.5% Proparacaine	1.0% Cyclopentolate	1.0% Tropicamide
AES	Logan et al (2011)	0.5% Proxymetacaine	1.0% Cyclopentolate	-
BMPS	Lin et al (2014)	-	1.0% Cyclopentolate	-
CLEERE	Zadnika et al (2003)	0.5% Proparacaine	1.0% Tropicamide	1.0% Cyclopentolate
GOAT	He et al (2015)	-	1.0% Cyclopentolate	-
NICER	O'Donoghue et al (2015)	0.5% Proxymetacaine	1.0% Cyclopentolate	-
SECS	Jin et al (2015)	-	0.5% Tropicamide	-
SMS	Ojaimi et al (2005c)	1.0% Amenothocaine	1.0% Cyclopentolate	1.0% Tropicamide

Table 4.2: Summary of cycloplegics used in published myopia studies ACES: Anyang Childhood Eye Study. AES: Aston Eye Study. BMPS: Beijing Myopia Progression Study. CLEERE: Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error. GOAT: Guangzhou Outdoor Activity Trial. NICER: Northern Ireland Childhood Errors of Refraction. SECS: Sujitan Eye Care Study. SMS: Sydney Myopia Study.

Both Cyclopentolate Hydrochloride and Tropicamide do not have the ability to achieve absolute cycloplegia and often residual accommodation of ~1.50D is found (Leat et al., 1999). However, this small amount of residual accommodation means that no refractive adjustment is needed to compensate for ciliary muscle tonus (Harvey and Gilmartin, 2004). To ensure adequate cycloplegia had been achieved prior to refraction measurements residual amplitude of accommodation was measured using a Royal Air Force (RAF) rule (Richmond Products, Albuquerque, NM). The acceptable level of residual accommodative for refractive purposes has been suggested at less than 2 dioptres (Milder, 1961). Therefore, a cut off of <2D of accommodation was judged as acceptable in this study and this typically occurred 25-40 minutes post instillation. In participants with darker irides an additional drop was instilled if accommodation was found not be <2D after 40 minutes.

4.3 Biometry

Non-contact optical biometers are widely used in research studies and in clinical practice. Historically axial length (AL) and anterior chamber depth (AC) were measured used contact ultrasound instruments such as A-Scan and corneal radius by keratometry. However, the IOLMaster 500 (Carl Zeiss, Jena, Germany), is now considered the gold standard for biometry measurements. Not only is it non-contact, thus reducing the risk of corneal abrasion and instillation of anaesthetic drops and therefore more favourable with adults and children, but it is also been found to be much more precise and repeatability when compared to ultrasound techniques (Carkeet et al., 2004, Hussin et al., 2006). The resolution of the IOL Master 500, for AL and AC, is much higher (±0.01mm) compared to conventional ultrasound methods (±0.15mm) (Santodomingo-Rubido et al., 2002).

In this study two optical biometers were used; the IOLMaster 500 (Carl Zeiss, Jena, Germany), and the Aladdin (HW3.0, Topcon, Tokyo, Japan). Both machines are able to measure AL, AC and corneal radius (CR) but the Aladdin (HW3.0 Topcon, Tokyo, Japan) is also additionally able to measure lens thickness (LT), central corneal thickness (CCT) and full corneal topography which are becoming more important in refractive research studies. The Aladdin (HW3.0 Topcon, Tokyo, Japan) has not been widely used in research studies with children so the results provide some novel information. However, as mentioned above the IOLMaster 500 is considered the gold standard and thus was used to allow comparison of parameters with other research papers as well as investigate the reliability and validity of the Aladdin.

Both machines were calibrated daily prior to any measurement being taken and measures were taken after cycloplegia which has been found to have no significant effect on AL measurements (Sheng et al., 2004). Another important reason that the biometry took place after cycloplegia is because the Aladdin will measure LT. If cycloplegia is not applied, then the accommodative status of the eye will influence the measurement which is particularly important when taking measurements in children who have a large amount of accommodation.

4.3.1 IOLMaster 500 (Carl Zeiss, Jena, Germany)

The IOLMaster 500 (Carl Zeiss, Jena, Germany), see Figure 4.4, is considered the gold standard in optical biometry. It is able to measure axial length (AL) (range 14.0-38.0mm), corneal radius (CR) (range 5.0 – 10.0mm) and anterior chamber depth (AC) (range 1.5-6.5mm).

Figure 4.4: Photograph of IOLMaster 500 (Carl Zeiss, Jena, GmbH)

The IOLMaster 500 is highly repeatable in both non-cycloplegic and cycloplegic participants with the 95% limits of agreement of -0.11mm to +0.07mm and -0.06mm and +0.05mm respectively (Sheng et al., 2004). Santodomingo-Rubido (2002) also found a good agreement between repeated measures of the AL and AC. The mean difference for AL was 0.00±0.04mm (p=0.75) and for AC -0.01±0.08mm (p=0.24). This repeatability has been found to be consistent even when taking measurements from children (Carkeet et al., 2004). The IOLMaster was shown to be more repeatable than the ultrasound measurements of AL in this cohort. The IOLMaster has become the gold standard for optical biometry and dominates the majority of research literature including many myopia studies including AES (Logan et al., 2008), NICER (O'Donoghue et al., 2010b) and SMS (Ojaimi et al., 2005c) .

4.3.1.1 Measurement of Axial Length

The IOLMaster 500 measures AL using partial coherence interferometry (PCI), see Figure 4.5. A laser diode (LD) produces an infrared light (ʎ = 780nm) of short coherence length. This light then passes through a beam splitter (BS1) and is split into 2 equal coaxial beams (CB1 and CB2) which are projected into the eye. They are reflected off the cornea (C) and retina (R). After leaving the eye they pass through another beam splitter (BS2) and the difference in frequency in the coaxial beams from each interface is detected by the photodetector (PHD). The mirror M1 is then moved at a constant speed and measures interference patterns between the reflected beams until a particular interference condition is fulfilled (Santodomingo-Rubido et al., 2002). This allows accurate measurements of AL (cornea to retina). Interestingly the coaxial beam reflected from the retina penetrates to the retinal pigment epithelial (RPE) whereas in techniques that measure by ultrasound axial length is measured from the cornea to the internal limiting membrane (ILM) (Lam et al., 2001). This would mean that the IOLMaster

500 would measure a longer axial length compared to ultrasound techniques. However, the manufacturer has incorporated a conversion factor to account for this discrepancy.

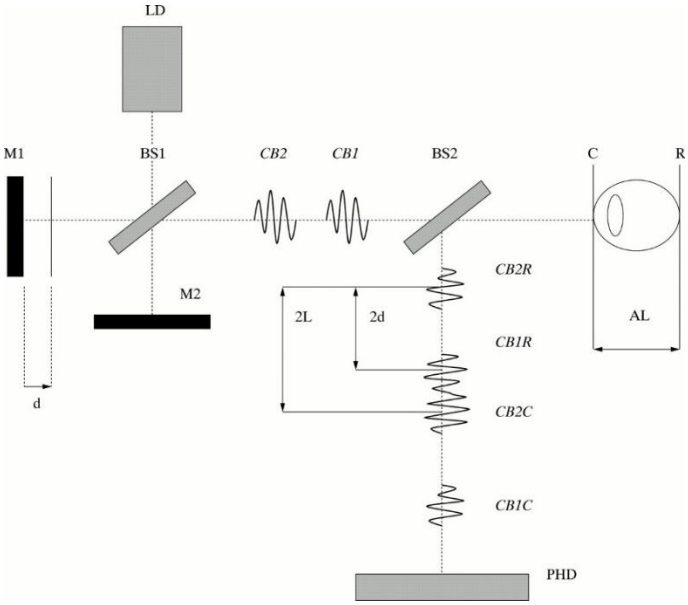


Figure 4.5: Operating mechanism of the IOLMaster 500 Reproduced with permission from Santodomingo-Rubido et al (2002)

Alongside each measurement a Signal-to-Noise Ratio (SNR) value is displayed which acts as a marker for the quality of the measurement. Measurements were classed as valid if the SNR (signal:noise ratio) was greater than 2.0 which is in line with the manufacturer recommendation (Emerson and Tompkins, 2003). Borderline measurements (SNR 1.6 – 2.0) were noted by an '!' and were excluded from the analysis along with outliers identified in red print. Measurements were repeated until a minimum number of 3 valid readings were obtained per eye.

4.3.1.2 Measurement of Corneal Radius

Corneal Radius (CR) is measured through an image analysis method. Six symmetrical points of light are reflected onto the corneal mid-periphery arranged in a 2.3mm hexagonal pattern (Elbaz et al., 2007). Through manual manipulation of the joystick these lights are focussed and aligned using a traffic light display (green is optimal), see Figure 4.6. The IOLMaster software derives the CR values by comparing the actual known separation of each of the 3 pairs of opposite lights with the image separation following projection onto the cornea. 5 individual measurements are taken for a single keratometry measurement within 0.5 seconds. Following this CRs and principal meridians are displayed. CR measurements with the IOLMaster have been shown to have good agreed with those measured with a manual Javal-Schiötz Keratometer (Santodomingo-Rubido et al., 2002).

Figure 4.6: IOLMaster 500 corneal radius measurement

4.3.1.3 Measurement of Anterior Chamber Depth

Anterior Chamber Depth (AC) is measured using an image-based slit lamp system. It uses a 0.7mm wide slit beam of light which is directed at a 30 degree angle into the anterior chamber (Emerson and Tompkins, 2003). An image of the cornea and anterior lens are visible on screen and fine adjust of the joystick is required to align them and focus them within a rectangle on screen, see Figure 4.7.

Figure 4.7: IOLMaster anterior chamber depth measurement

Similar to the CR measurement, a traffic light display is used to guide the observer to a focussed optimal image. 5 internal measurements are taken within 0.5 seconds. It has been reported that the IOLMaster measures greater values for AC compared to ultrasound (Lam et al., 2001, Mallen et al., 2001). This discrepancy is suggested to be due to compression of the globe with ultrasound which does not occur with the IOLMaster's non-invasive technique. Furthermore, it has been suggested that the IOLMaster is not in fact measuring axial AC as the light source is temporal. In addition, it takes keratometry measurements into account when calculating AC. The use of optical coherence tomography (OCT) has revolutionised imaging of the anterior and posterior eye. Zeiss has developed the IOLMaster 700 which uses this new technology. Akman et al (2016) found that AC measurements were high correlated between the IOLMaster

500 and 700 however the IOLMaster 700 did consistently read shorter AC then the IOLMaster 500. This is consistent with the IOLMaster 500 comparison with ultrasound and could be attributed to the factors listed above as the IOLMaster 700 does not use keratometry values but does take on axis measurement.

4.3.2 Aladdin (HW3.0, Topcon, Tokyo, Japan)

The Aladdin (HW3.0, Topcon, Tokyo, Japan) is a new addition to interferometry biometers using optical low coherence interferometry (OLCI) and is becoming increasingly popular (Kiss, 2013). The Aladdin combines a biometer and a placido-ring topographer, see Figure 4.8. It therefore has the ability to measure 8 parameters including AL, AC, CR, central corneal thickness (CCT), lens thickness (LT), pupillometry, white-to-white and corneal topography. The manufacturer states the Aladdin is able to take all these measurements in less than 5 seconds.

Figure 4.8: Image of illuminated placido rings used by the Aladdin to measure corneal topography

The instrument has a 10.1 inch colour touch screen which allows visualisation for alignment and also displays all recorded readings. To take the measurements the image of the placido rings needs to be brought into focus using the joystick, see Figure 4.9. Once the image is focussed, pressing down on the button on the top of the joystick engages the alignment software. Good alignment is indicated by a green display, however blue arrows indicate that the instrument is too close to the eye and needs to be moved backwards and red arrows indicate that the instrument is too far away and needs to be moved forward, see Figure 4.9. Full Data acquisition (K-AL-ANT) is performed in two stages. The first press of the joystick after initial alignment as discussed above performs Keratometry and Axial Length acquisition. Following this a subsequent re-alignment is performed before pressing the joystick a second time for Anterior Chamber Depth, Central Corneal Thickness and Lens Thickness acquisition.

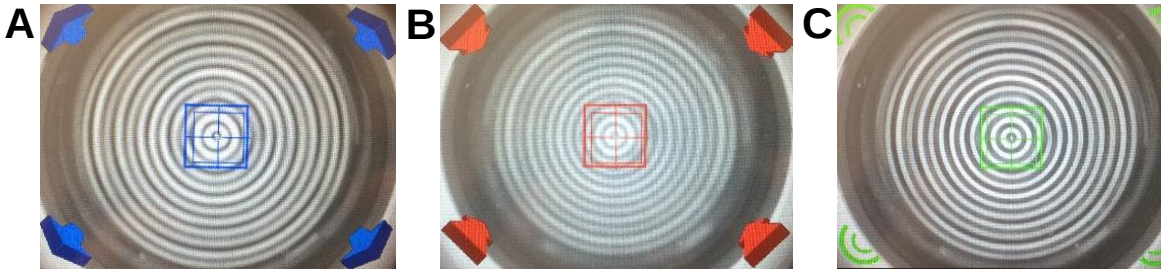


Figure 4.9: Aladdin alignment software A) blue arrows indicating that the instrument is too close to the patient B) red arrows indicating that the instrument is too far away C) green display indicating good alignment

The Aladdin software highlights inconsistent measurements caused by errors such as bad focus, closed eyelid or movement with a warning sign ⚠. These measurements were repeated. However, it must be noted that in some participants primarily in the child cohort (aged 7 – 12 years) obtaining a result not denoted by this warning sign was challenging and, in some cases, not possible. Unlike the IOLMaster individual values for inconsistency such as SNR ratio were not available and alternatively inconsistent measurement warnings were denoted for the measurement as a whole.

4.3.2.1 Measurement of Axial Length

Biometry is measured by an optical low coherence interferometry (OLCI) system using a super luminescent diode 830nm, see Figure 4.10. The interference signal is reflected by the retinal pigment epithelium (RPE). To allow accurate comparison the software automatically adjusts for the distance between the ILM and RPE similarly to the IOLMaster. Six AL readings are recorded within the range 15.0 – 38.0mm with a 0.01mm resolution.

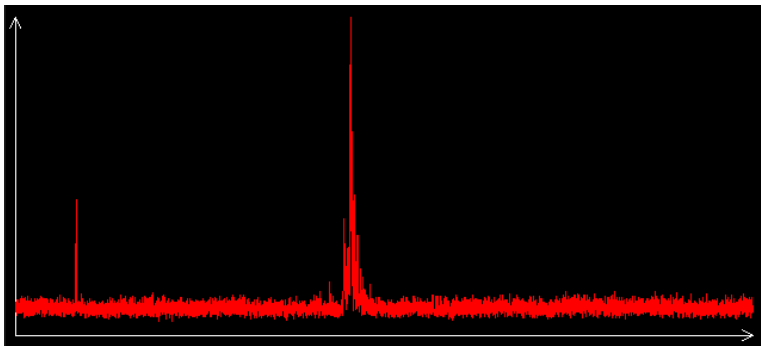


Figure 4.10: Aladdin axial length interferometry image

4.3.2.2 Measurement of Corneal Radius

Corneal radii are measured alongside corneal topography through the reflection of the 24 placido rings, see Figure 4.8, at a controlled working distance 80mm from the ocular

surface. This technique analyses over 100,00 points over the central 9.8mm of the cornea. The CR readings reported are a representative of the central 3.0mm and are extrapolated from the placido disc data. Three CR readings are taken for each eye in the range 5.00 – 12.00mm (28.00 – 67.50D) with a 0.01mm/0.01D resolution.

4.3.2.3 Measurement of Anterior Segment (AC-CCT-LT)

Anterior segment measurements (AC-CCT-LT) are simultaneously measured using the same method as AL using OLCI, using a 830nm LED, see Figure 4.11. AC is defined as the distance between the anterior surface of the lens and the corneal epithelium measured along the central axis. This is different to the IOLMaster 500 which is measured off axis. Three AC readings are recorded within the range 1.50mm – 6.50mm with a 0.01mm resolution in phakic eyes. CCT is defined as the distance between the corneal epithelium and endothelium within the range 0.300 – 0.800mm with a 0.001mm resolution. LT is defined as the distance between the anterior surface and the posterior surface of the crystalline lens within the range 1.50 – 6.50 mm with a 0.01mm resolution.

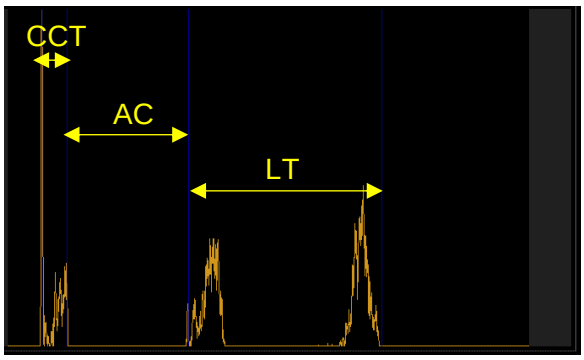


Figure 4.11: Aladdin anterior segment interferometry image CCT = Central Corneal Thickness, AC = Anterior Chamber Depth, LT = Lens Thickness

4.4 Conjunctival UV Autofluorescence Photography

The device used to photograph the conjunctiva to visualise Conjunctival UV Autofluorescence (CUVAF) was a modified smartphone (iPhone 6 plus 16G, Apple, USA, iOS 8.4) with a built in 8-mega pixel camera. The photography system was derived from the principles of the Wood's lamp as well as from the CUVAF photography system set out by Coroneo and colleagues (Ooi et al., 2007, Ooi et al., 2006, Asawanonda and Taylor, 1999). The Wood's lamp emits a wavelength of between 340-400nm and has historically been used in dermatology to elicit autofluorescence from bacterial and fungal skin infections and UV damage (Asawanonda and Taylor, 1999). It was subsequently suggested that this short wavelength of light could be used to visualise UV damage on the conjunctival (Ooi et al., 2006).

The novel device used in this study was a modified smartphone design using two Ultra Bright Deep Violet 5mm diameter light emitting diode (LEDs) (ʎ = 375nm) to provide an excitatory light source. This was a similar wavelength to the system used by Coroneo and colleagues (300 – 400nm, peak 365m) and the Wood's lamp detailed above (Ooi et al., 2007, Ooi et al., 2006)

A yellow filter (Aston Fluorescein Enhancement Filter) traditionally used for fluorescein enhancement was used as a short wavelength cut off filter, see Figure 4.12. This eliminated the excitatory emission spectra produced by the Ultra Bright Deep Violet LEDs and acted to enhance the visibility of the conjunctival fluorescence. The device also consisted of a macro 6x magnification lens and a lithium rechargeable battery, see Figure 4.13. The app Camera+© (tap tap tap, USA) was used as it provided further control of camera settings such as shutter speed and exposure.

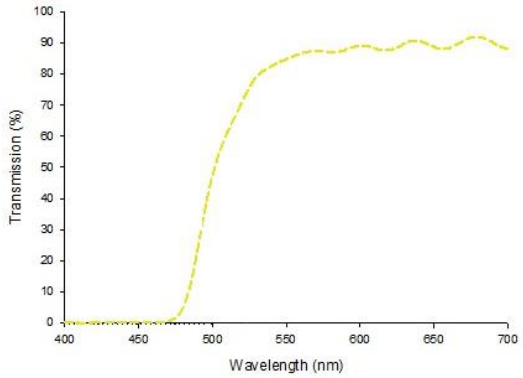


Figure 4.12: Aston fluorescein enhancement filter wavelength transmission

Specially designed housing was developed to align the magnification lens and filters directly in front of the camera as well as hold the LED light sources. This housing extended out from the phone backing by 3.2cm to provide an eyebrow rest for the device to provide stability during photography as well as ensure equidistance to the anterior eye across all participants.

Figure 4.13: Image of UV device used for CUVAF photography

Optimal photographs are taken in low illumination with the housing also acting as a shield from any aberrant external light sources. Examples image taken with this device can be seen in Figure 4.14. CUVAF image analysis is discussed in detail in Chapter 10.

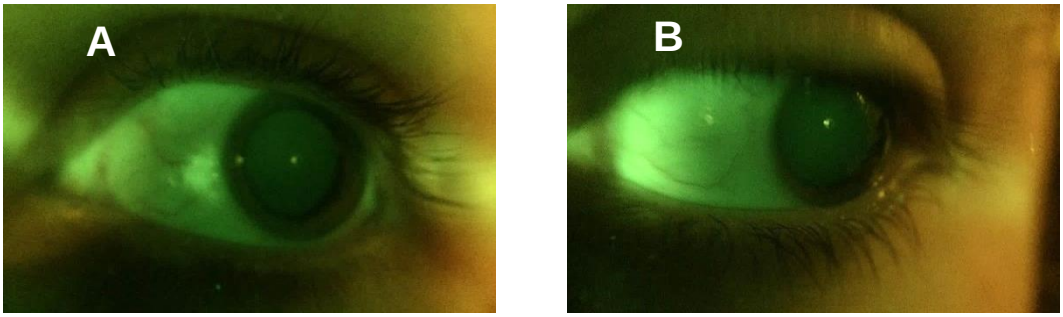


Figure 4.14: Example images of CUVAF captured from participants in the Young Adult cohort A) CUVAF is present on the nasal conjunctiva (participant YA027) B) No CUVAF present on the nasal conjunctiva (participant YA041)

4.5 Actiwatch 2 (Philips Respironics, USA)

Light exposure and physical activity was measured with the Actiwatch 2 (Philips Respironics, USA). This is a lightweight wrist worn device with a silicon photodiode light sensor, see Figure 4.15, which measures visible light illuminance (wavelength range 400 – 900 nm, peak wavelength 570nm). It can measure illuminance within the range 5 – 100,000 lux, 24 hours a day at specific intervals either every 15 seconds, 30 seconds or minute. It has a rechargeable battery to allow up to 30 days of data collection and it was originally advised that it was waterproof for 1 metre for up to 30 minutes. However, it was later reported that this recommendation was based on a cold water test and when tested using hot water (40^{o}C) it was found that the seals were prone to leaking. Therefore, all participants were subsequently advised to not swim, shower or bath with the watch on.

Figure 4.15: Image of Actiwatch 2 (Philips Respironics, USA)

The device is also able to quantify physical activity through a piezo-electric accelerometer which takes 32 samples per minute to provide number of 'activity counts per minute' (CPM).

In addition, the Actiwatch is able to provide objective data about actigraphy or sleep patterns. A number of daily sleep statistics were extracted from the Actiware software (version 6.0.9) including bed time, total sleep time and sleep efficiency.

4.6 C.A 810 Illuminometer (Chauvin Arnoux, Slough, UK)

Classroom illuminance was measured using the C.A 810 lightmeter (Chauvin Arnoux, Slough, UK), see Figure 4.16. This illuminometer has the ability to measure from 0.01 to 20,000 lux using a silicon photo diode. The LCD display shows illuminance readings and can be adjusted to four different ranges: 20, 200, 2,000 and 20,000. It is portable and lightweight weighing only 250 grams.

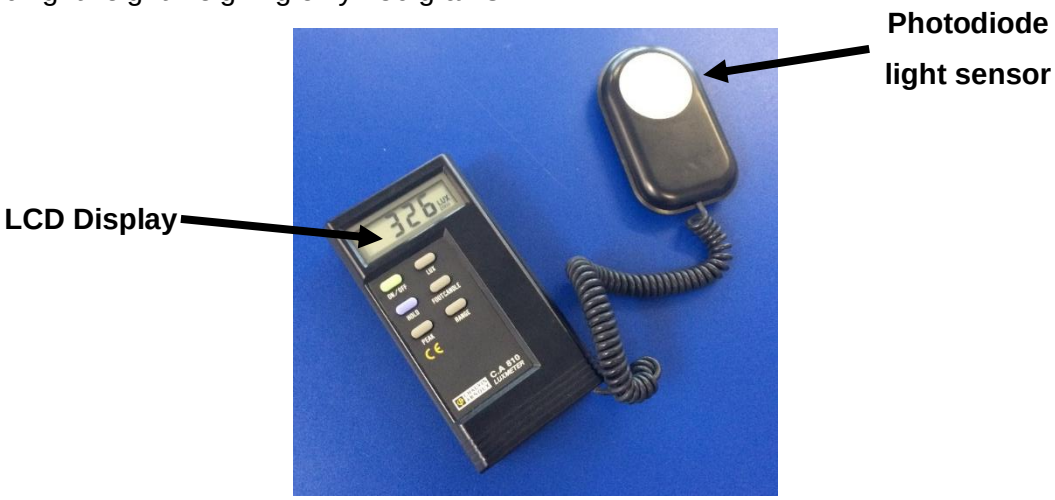


Figure 4.16: C.A 810 Illuminometer (Chauvin Arnoux, Slough, UK)

Chapter 5: Methodology

This chapter outlines the methodology behind this study, including recruitment of participants and clinical protocol design as well the instrumental and operator procedures adopted.

5.1 Study Protocol

A rigid procedure protocol was put in place to ensure continuity and reliability of results and was adhered to throughout the data collection process.

5.1.1 Set up and Consent/Assent

Data collection for the Child cohort was undertaken on the school site. This required all equipment to be transported to the school and set up on the morning of the data collection. The Young Adult data collection took place on campus in the vision science building and so all equipment was present on site. In both cases prior to data collection all equipment was calibrated to ensure accuracy and supplies e.g. printer paper, tissues, steriwipes were replenished if required.

The exact layout of the equipment was variable depending on availability of classrooms in the schools. A minimum distance of 3 metres was required to ensure the accurate vision testing using the computerised test chart. An example set up at one of the schools can be seen in Figure 5.1.

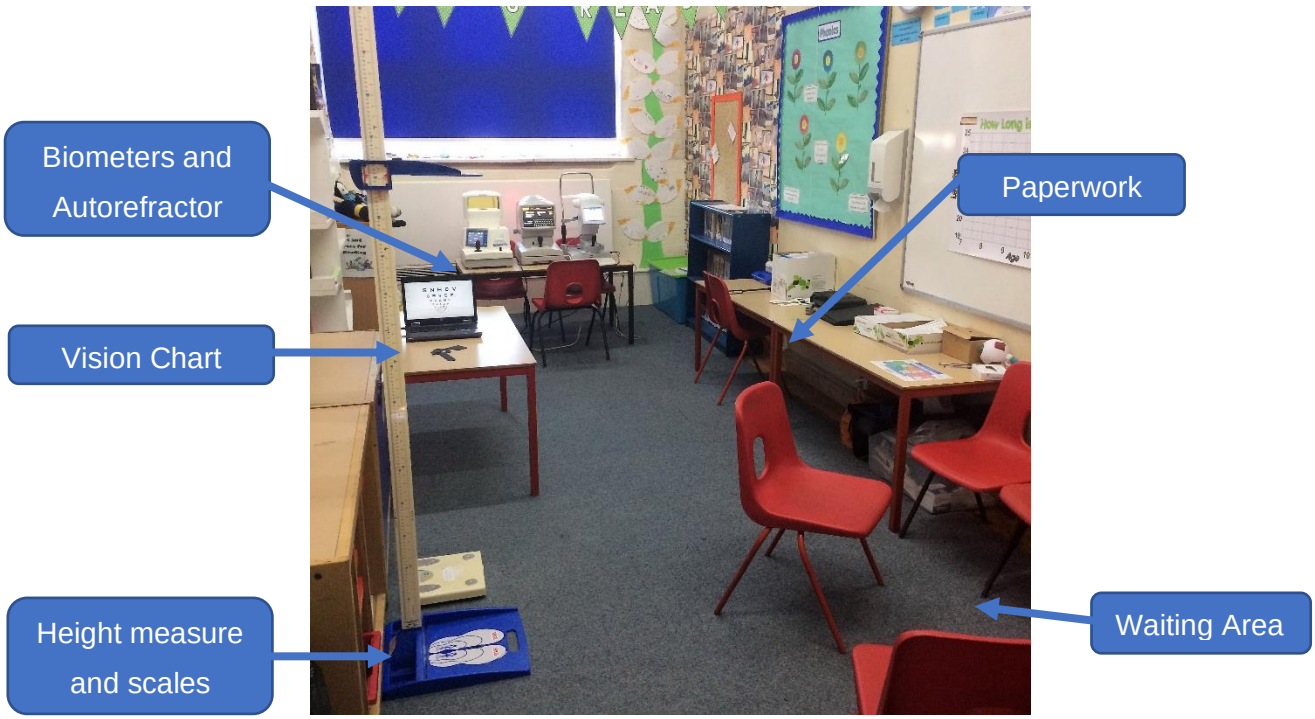


Figure 5.1: Example school equipment set up

Prior to commencement of the study direct consent was obtained from those aged 18 – 25 years and assent was obtained from those aged 7 – 12 years, who had already had parental consent confirmed, see Appendix A.5.4. Information about what the study would entail was discussed prior to consent/assent forms being completed. All participants were made aware that this is a voluntary study and that they could withdraw at any time.

5.1.2 Study Procedure

The same study protocol framework was used for both age cohorts, as detailed chronologically in Figure 5.2 below. Only a few minor alterations were made between the groups including the addition of Intraocular pressure (IOP) and anterior chamber angle measurement in the older age group and the difference in the specific drug used for each age group, the rationale for this can be found in Section 4.2.2.

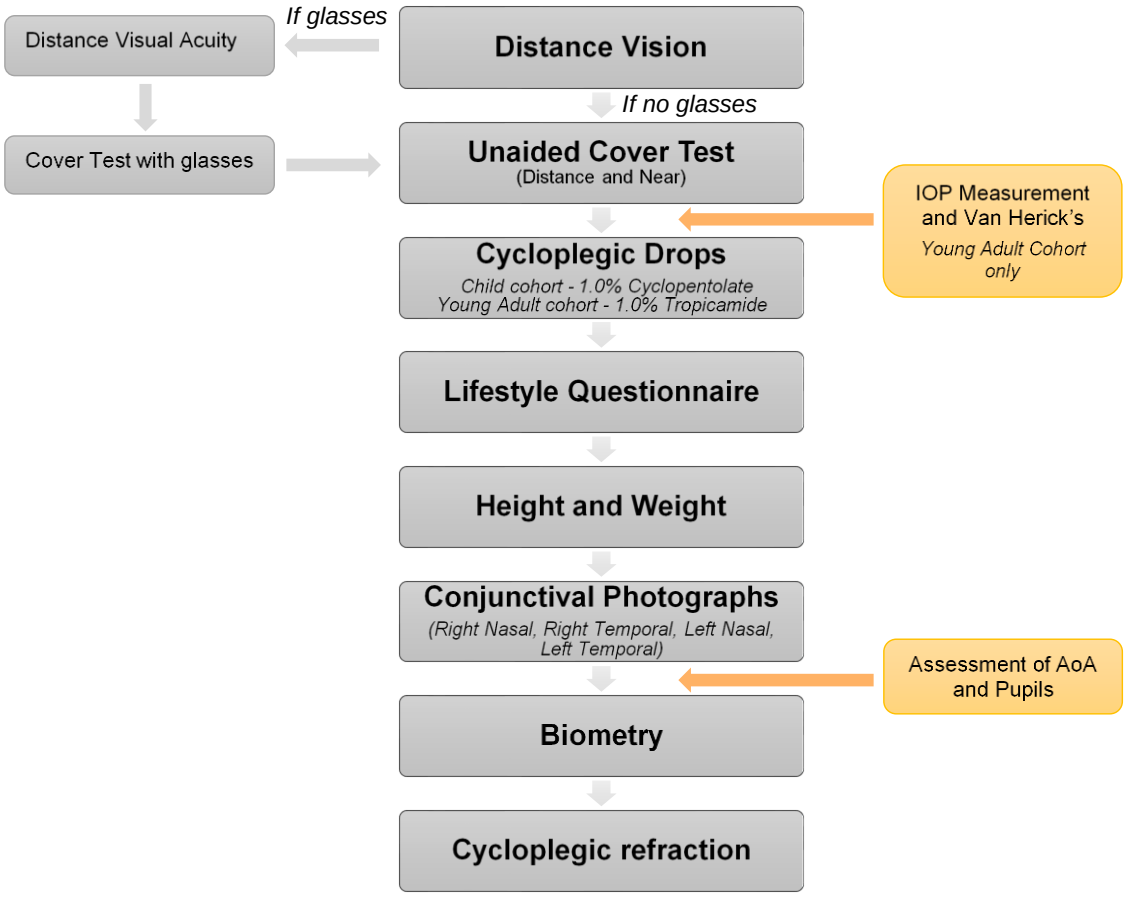


Figure 5.2: Clinical protocol flow chart AoA: Amplitude of Accommodation

Participants aged 18 – 25 years tended to attend the study visit individually or with other participants (maximum attendance at one session was 5). As the participants aged 7 – 12 years took part in school, measures were taken to reduce disruption to the school

day and teachers as well as minimise the amount of time the participants were away from the classroom. As such groups of children between 3 – 5 took part in the study at the same time. Due to the number of procedures needed to be undertaken, it was decided not to be effective to instil the cycloplegic drops and then take the children back to class and take a second group. Instead, a group of children undertook the study in its entirety before returning to class.

The procedure for each stage of the protocol is detailed below and a proforma was used for data recording to ensure all measurements were taken:

1. **Vision/Visual Acuity:** Monocular and binocular visions were taken for all participants and if wearing spectacles, visual acuity. For the 18 – 25 age group this was measured using a back illuminated 4 metre ETDRS chart (Precision Vision, La Salle, USA). For participants aged 7 – 12 years a computerised LogMAR test chart was used instead (Thomson Software Solutions®, Herts, Version 1.45).
2. **Oculomotor balance:** a cover test involving both cover/uncover and alternate cover was implemented to assess oculomotor balance. This was performed at distance (fixation of a letter target) and also at near ~33cm (fixation at a target on a budgie stick), with and without spectacles as necessary. The size and type of deviation was evaluated by the two practitioners (KF and NL).
3. **Instillation of drops for cycloplegia:** cycloplegia was induced with the instillation of 1 drop of 1.0% Cyclopentolate Hydrochloride Minims® (Bausch and Lomb, Surrey) in each eye in the participants aged 7 – 12 years and 1 drop of 1.0% Tropicamide Minims® (Bausch and Lomb, Surrey) in each eye for participants aged 18 – 25 years. 15 – 20 minutes post dilation cycloplegia was assessed and in some individually, primarily those with dark irides, an additional drop was instilled.
4. **Lifestyle questionnaire:** a 39 point and 22 point questionnaire was undertaken by the participants aged 18 – 25 years and 7 – 12 years respectively, see Appendix A.5.5. This was performed immediately following cycloplegic instillation as it was felt that the effect on accommodation and consequential ability to read at this early stage was minimal. In the younger cohort, depending on age and competence some children were able to complete the questionnaire independently however some children did require the questions to be read out to them and completed with the help of the practitioner.
5. **Height and Weight:** height was measured using a portable stadiometer (Leicester Height Measure, Seca, Birmingham) to the nearest 0.1cm and weight

was measured using digital weighing scales to the nearest 0.1kg (Tanita Model 2000, Tanita Corporation, Japan).

6. **Conjunctival photography:** Photographs of the conjunctiva were taken using a modified camera to identify conjunctival UV autofluorescence, (CUVAF) see Section 4.4. Four photographs were taken per eye (Right Nasal, Right Temporal, Left Nasal, Left Temporal) with room lights off. The use of a digital device allowed image quality to be instantly verified and retaken where necessary. For example, poor alignment, image defocus or obscured conjunctiva by eyelashes or eyelid, examples of these are shown in Figure 5.3.

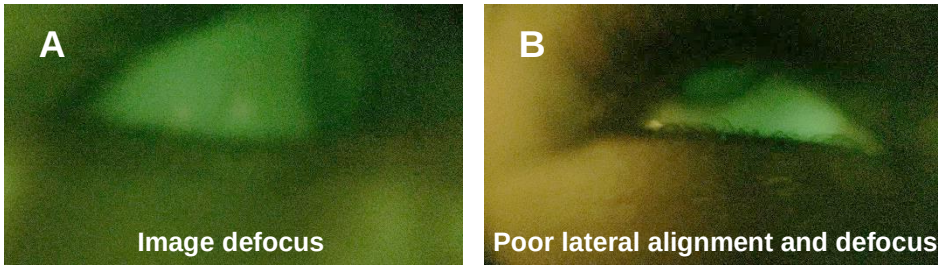


Figure 5.3: Examples of poor CUVAF photographs

7. **Assessment of Amplitude of Accommodation (AoA) and pupil reactions:** full cycloplegia was confirmed when the push up AoA was found to be <2D with a Royal Air Force (RAF) rule (Richmond Products, Albuquerque, NM) and no pupil reactions to light from a pen torch were observed. If full cycloplegia was not achieved these measurements were repeated at 5 minute intervals until full cycloplegia was obtained.
8. **Biometry:** Ocular biometry was first undertaken with the IOLMaster 500 (Carl Zeiss, Jena, Germany). Axial Length (AL), Corneal radius (CR) and Anterior Chamber Depth (AC) were measured. A minimum of 3 individual measurements of AL were taken and values were averaged to give a mean AL. Measurements were classed as valid if the SNR (signal:noise ratio) >2.0 which is in line with the manufacturer recommendation and measurements not identified as outliers highlighted in red. AL, CR, AC as well as Lens Thickness (LT) and Central Corneal Thickness (CCT) were measured with the Aladdin (Topcon, Tokyo, Japan). Measurements identified as inaccurate denoted with a yellow triangle symbol, ⚠, were repeated as per the manufacturer recommendation.
9. **Refractive error:** Finally, cycloplegic autorefraction was undertaken with the WAM 5500 (Grand Seiko, Tokyo, Japan) a binocular open field autorefractor. Participants were advised to focus on a distance fixation target of a maltese cross at 3 metres. 10 measurements of refraction were taken in each eyes and

averaged to establish a mean refraction. Mean spherical equivalent refraction (SER) for each eye was calculated using the equation sphere + ½ cylinder.

On completion of the study, all young adult participants were given a College of Optometrists' Tropicamide information leaflet detailing possible side effects and what to do should they occur. In the case of the Child cohort a College of Optometrists' Cyclopentolate information leaflet was accompanied by a cover letter for their parent/guardian as well as a parental questionnaire for them to complete and return. All participants aged 7 – 12 years were given a thank you certificate, see Appendix A.5.7 and branded pencil as a gesture of goodwill for taking part. In addition, in one school on request from the Special Educational Needs Coordinator (SENCO) as part of a school incentive, each participant was given a 'character' sticker to show appreciation for helping others.

5.1.3 Study Personnel

The principal study practitioners were 2 UK General Optical Council (GOC) registered Optometrists (KF and NL). KF was present at all data collection and NL assisted with data collection as necessary. All personnel had up to date Disclosure and Barring Service (DBS) checks and were familiar with the equipment and protocol.

5.1.4 Data entry, analysis and statistics

All raw data was inputted electronically by investigator KF into Microsoft Excel® (Office 365, Version 2001) spreadsheets. Data from the Aladdin was able to be directly exported with manufacturer software into a Microsoft Excel® (Office 365, Version 2001) spreadsheet. All participants were given a 5-digit code to anonymise them. Participants in the young adult study were given the pre-fix "YA" followed by their participation number e.g. YA001. The pre-fix used for the children was the initials of the school e.g. MA, GP, ST followed by their participation number. A separate password protected spreadsheet with the participant names and their corresponding code was created to anonymise all raw data. After data collection was completed all data entries including refractive error data from autorefractor printouts, questionnaire and biometry data were rechecked to ensure the accuracy and validity of data input.

All data was analysed using SPSS® Version 25 and sample size calculations using G*Power software (version 3.1.9.4).

5.1.5 Refractive error definitions

Refractive error was defined by first calculating the spherical equivalent refraction (SER) for each eye using the equation: sphere + ½ cylinder. The refractive error classifications definitions used in this study are summarised in Table 5.1.

Category	Definition
Myopia	SER ≤ -0.50D in at least one eye
Emmetropia	SER > -0.50D to <+2.00D in both eyes
Hyperopia	SER ≥ +2.00D in at least one eye as long as neither eye was myopic
Astigmatism	Cylindrical power ≤ -1.00 DC in either eye

Table 5.1: Refractive error classification definitions

These definitions are in line with other myopia epidemiology studies including AES, NICER and the standardised protocol developed as part of the Refractive Error Study in Children (RESC), see Table 1.1 in Section 1.6 (Logan et al., 2005, O'Donoghue et al., 2010b, Negrel et al., 2000). The myopia definition of SER ≤-0.50D in at least one eye has also proposed as a suitable cut off in the recently published International Myopia Institute white papers (Flitcroft et al., 2019).

5.1.6 Referral Criteria

After collation and analysis of the results, some participants were advised to see their local optometrist for a full sight test or to update their glasses. In the case of the participants aged 7 – 12 years this will be done via a letter to their parent/guardian. The referral criteria used to identify these individuals is specified below:

- Uncorrected vision ≤ 0.2 LogMAR (6/10) in either eye
- Uncorrected Myopic SER ≤ -0.50DS in either eye
- Uncorrected Hyperopic SER ≥ +2.00DS in either eye
- Uncorrected Astigmatism ≤ -1.00DC in either eye
- Strabismus present

The referral did state that if a sight test had been performed within the last 3 months then to disregard this letter.

5.1.7 Risk Assessment

A risk assessment was completed alongside ethical approval to ensure the safety of participants. Despite the low risk associated with the use of cycloplegic eye drops, safety and precautionary measures were implemented. These are detailed below:

- Prior to instillation of either drug the examiner identified if the participant has had an intolerance or allergic to the drug previously and any contraindications e.g. medication that may interfere with the drug or any diagnosed ocular condition. If any of the above were found to apply the participant was not be eligible to take part in the study.
- All considerations outlined in the 'ORG guidelines for topical drugs in research' document were adhered to prior to instillation.
- Drug instillation was performed by a qualified optometrist with experience of topical drug instillation.
- The participants and their parent/guardian (applicable to participants aged 7 – 12 years) were informed pre and post drug instillation of possible side effects and emergency protocol. A College of Optometrist leaflet was provided on the day of instillation, either to the participant directly or via a parental information envelope, detailing possible side effects and what to do should they occur.
- In participants aged 18 – 25 years both anterior chamber angles and IOP measurements were taken prior to instillation to identify those at a possible increased risk of acute angle closure glaucoma.
- All adult participants were advised not to drive home after the study and child participants and their parents were informed not to cycle home after the study. This advice was also detailed on the information leaflet.

5.2 Recruitment

5.2.1 Child cohort (aged 7 – 12 years)

5.2.1.1 School recruitment

Education for children in the UK is compulsory until aged 18 and children start primary school at 5 years of age until 12 years of age. Therefore, primary schools were targeted as they conveniently contained the target age group and negated the need for door-to-door recruitment or national advertising. Schools in the Midlands were targeted primarily due to the ease of accessibility. This recruitment area was widened to Scotland and Plymouth to provide data from a cross section of the UK in two different areas with

different latitudes. Recruitment of primary schools was undertaken in 3 stages, as illustrated in Figure 5.4:

Stage 1: Contact with the schools was made with a telephone call to provide initial information about the study and ascertain if the school would be interested in being involved. All of these phone calls were fielded by the office staff and I was unable to be transferred to the primary decision maker either headteacher, deputy headteacher or special educational needs coordinator (SENCO) in any case. A further information pack was then sent to the school either via post or e-mail, depending on the school's preference. This included an information sheet specifically designed for headteachers as well as a covering letter, see Appendix A.5.1. Most schools were happy to receive the further information pack and only 2 schools declined any information at this stage citing reasons that either the school did not take part in external studies or in one case a school had recently been placed in special measures by Ofsted.

Stage 2: A follow up phone call within 1-2 weeks was made to all schools who agreed to receive further information. This was to ensure that they had received the information and that it had been forwarded to the appropriate person in school and also to arrange a subsequent face to face meeting or phone call with the headteacher to discuss the study further if the school was interested.

Stage 3: A face-to-face meeting or phone call was made with the schools who were interested in taking part. During this meeting I explained the study further and an example parental information pack was shown to the headteacher. An offer of undertaking an assembly or workshop in school prior to the data collection was offered and taken up by one of the schools. At this meeting a date for data collection was also established.

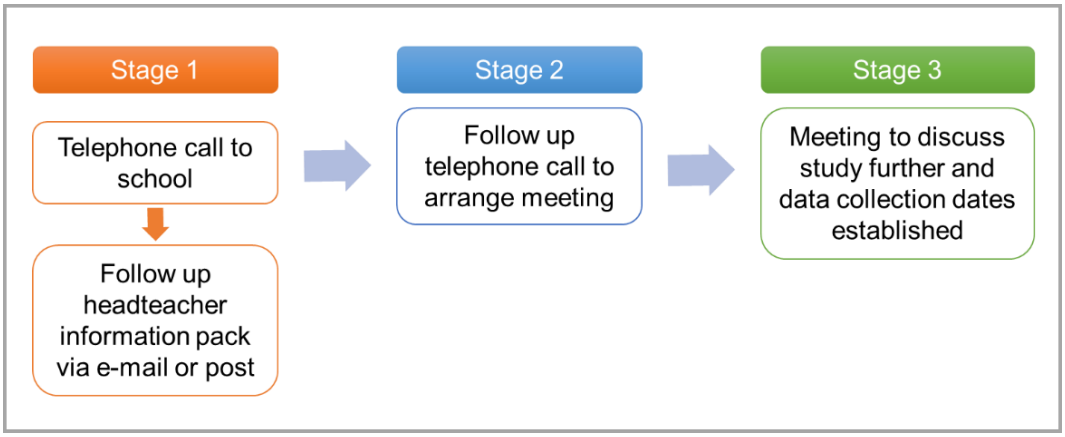


Figure 5.4: School recruitment flow chart

5.2.1.2 School response rates

In total 100 schools were contacted, and 8 schools agreed to take part in the study. The success at each stage of the recruitment process can be seen in Figure 5.5. Stage 1 comprised of the initial phone call to the school and shows those that accepted a follow up e-mail or letter regarding the study. Stage 2 compromised of a one week follow up phone call following receipt of the further information package and shows those that arranged a face to face meeting or phone call with the headteacher. Stage 3 compromised of those that agreed to take part in the study and booked data collection dates. This process for school recruitment was performed at regularly intervals throughout the study period (March 2017 to July 2019) and schools who had previously declined were contacted again to ascertain if their circumstances had changed and were able to take part at a later date. One school withdrew one week prior to data collection as a safeguarding issue was reported within the school. Attempts were made to rearrange the data collection however the issue took a long time to resolve and the school declined further involvement in the study. As a result, 7 schools took part in the study at baseline.

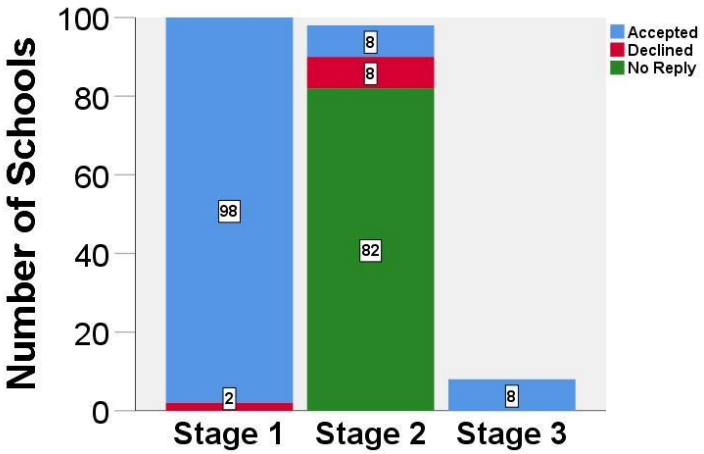


Figure 5.5: Primary school response rates at different stages of recruitment5.2.1.3 School Information

7 schools in total took part in the study from 5 locations: Nottingham, Church Stretton (Shrewsbury), Abington (Glasgow), Lauceston (Cornwall) and Plymouth, see Figure 5.6.

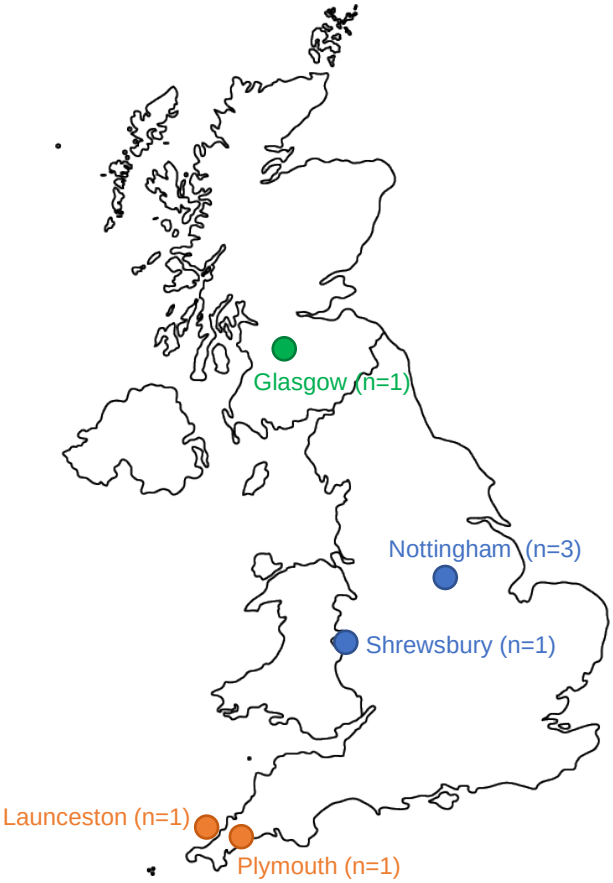


Figure 5.6: UK map of school locations

These school locations were chosen to gain a geographical cross section of the UK at different latitudes as well as to provide information from potentially contrasting urban and rural locations. This allowed schools to be classified as the Midlands, North or South depending on their location to allow future comparisons, see Table 5.2.

School	Closest Town/City	Region Classification	Northern Latitude (°N)	Rural/Urban Classification	Eligible Pupils (n)
AB	Glasgow	North	55.494611	Rural	39
BP	Nottingham	Midlands	52.962014	Urban	120
GP	Nottingham	Midlands	52.921211	Urban	180
MA	Nottingham	Midlands	52.898375	Urban	186
ST	Shrewsbury	Midlands	52.544135	Rural	164
PG	Launceston	South	50.692339	Rural	50
PH	Plymouth	South	50.372328	Urban	152
				Total	**891**

Table 5.2: Child cohort school characteristics

The mean northern latitude for the schools classified as North was 55.49461^{o}, Midlands 52.83143^{o}N and South 50.53233^{o}N. In addition, the schools were classified as either rural or urban from the mean population density (persons per hectare) for each school which was derived from the postcodes of participants from each school. For further information regarding this process, see Section 7.3.5. Schools were broadly classified as living in a rural area if the population density was <10 persons per hectare and urban ≥ 10 persons per hectare. This is the same classification used in other similar myopia studies, for example the NICER study (O'Donoghue et al., 2010c).

5.2.1.4 School participation duration

Recruitment was continuous across the study period following ethical approval (March 2017 to July 2019). Baseline data was collected from all schools however as recruitment was continuous over 29 month period, depending on the time of baseline recruitment not all participants at each school were able to take part in the 1 year and/or 2 year follow up. Due to early recruitment of 2 schools, MA and GP, 2 year follow up data was able to be obtained for some participants. Conversely due to recruitment later in the study period for schools PG and PH, less than 12 months remained before cessation of the study and therefore only baseline data was able to be obtained for these participants. The duration of each school's participation in this study is shown in Figure 5.7.

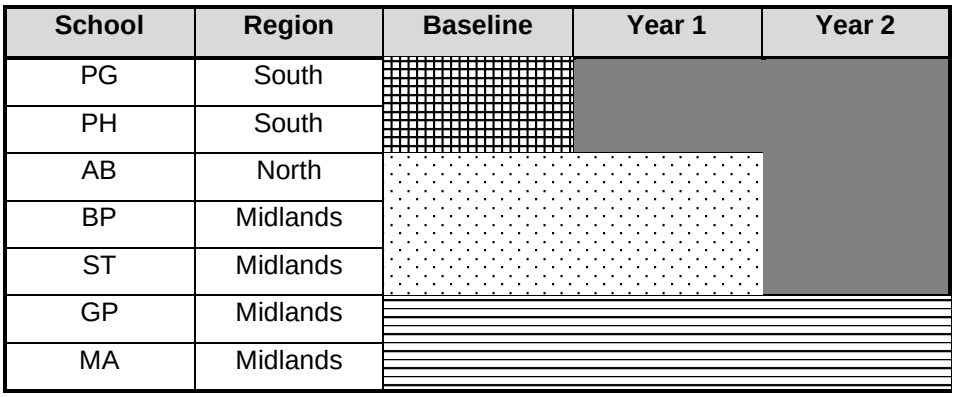


Figure 5.7: Illustration of individual school participation duration

5.2.1.5 Participant recruitment strategy

Following agreement with a school to participate in the study, approximately 6-8 weeks prior to the agreed data collection date parental information packs were distributed to all eligible children aged 7 – 12 years old, see Appendix A.5.2. The information pack consisted of:

1) **Cover letter** – outlined who I was and my role in the study as well as the rationale behind the study. A deadline for 2 weeks prior to the data collection date was also included on this letter.
2) **Parental information leaflet** – outlined in more detail what the study would involve and what would happen after the study as well as providing my contact details to ensure they could easily ask me any questions or queries they may have.
3) **Children information sheet** – a simplified version of the parental information leaflet written in lay-person language detailing what will happen in the study. Parents were encouraged to discuss the study with their child prior to completing the consent form.
4) **Consent form** – required to be completed by the parent/guardian to allow their child to participate in the study.

All returned consent forms were collated prior to commencement of data collection. During the data collection period, additional study packs were available and handed out to children, who had not already returned completed consent forms. This allowed eligible children to return completed parental consent forms continuously throughout the data collection period and increase participation rates.

Parental consent was obtained at each subsequent visit (Year 1 and Year 2) for all eligible children. In line with these visits, study information packs were again distributed to children who had not yet taken part in the study to allow continuous recruitment of participants. For those participants for which re-consent was being obtained, parental contact details were obtained from their previous consent forms which allowed these parents to be contacted directly via text message and/or e-mail to reminder them to return consent forms to the school office. Once again additional information packs were made available during the data collection period to allow increased recruitment opportunities.

5.2.1.6 Inclusion and exclusion Criteria

A number of inclusion and exclusion criteria were adhered to during the recruitment process. These are outlined in Table 5.3 below. Reaffirmation of this criteria was undertaken at each subsequent follow up stage and an additional question regarding myopia control intervention was included in the Year 1 and Year 2 follow up questionnaires for further confirmation. It was also made clear to the children on the day of the data collection that they were able to withdraw at any time.

Inclusion Criteria
• Aged 7 – 12 years old • Consent form signed and completed by parent/guardian • Assent from participant
Exclusion Criteria
• No parental/guardian consent form signed and completed • No assent from participant • Previous adverse reaction to use of cycloplegic drops • Participant with a diagnosed ocular condition requiring the use of medication • Participant is taking any prescription or non-prescription medicine that may interact with the cycloplegic drug • Undergoing or have previously had any form of myopia control intervention (any history of use of atropine, orthokeratology, multifocal soft contact lenses, bifocal or progressive addition spectacle lenses)

Table 5.3: Inclusion and exclusion criteria for the children's study

5.2.2 Young adult cohort (aged 18 – 25 years)

UK undergraduate students were recruited from Aston University, Birmingham continuously throughout the study period following ethical approval (March 2017 to July 2019). Due to the longitudinal nature of the study first year undergraduates were primarily targeted to ensure full follow up, however some second year and final year students did take part. Awareness of the study was initially done via a short talk to eligible students detailing the study and how to get in contact. A week after this talk an e-mail was distributed to all students outlining the rationale of the study with an information sheet attachment explaining what is involved in the study, see Appendix A.5.3. This e-mail was also distributed every 2-3 months to the all student at the university to allow continuous recruitment. On reply to this e-mail, appointments for data collection were made available via an online calendar to increase participant flexibility with various times and days available.

Undergraduate students from a variety of discipline including Optometry, Engineering, Accountancy and Maths across the university were invited to take part in the study. However, the majority of participants that took part were from the Optometry department. Due to the age of this cohort consent was obtained from the participants themselves, see Appendix A.5.3.

Prior to Year 1 and Year 2 visits participants were contacted via e-mail to invite them to attend the study. The follow up period was classified as 12 months ± 6 weeks, allowing

a 12 week window for participation. Participants were contacted at the beginning of this window to allow sufficient time for data collection to take place and greater flexibility for participants to attend.

5.2.2.1 Inclusion and Exclusion Criteria

A number of inclusion and exclusion criteria were adhered to during the recruitment process. These are outlined in Table 5.4 below.

Inclusion Criteria
• Aged 18 – 25 years old • Consent form signed and completed by participant
Exclusion Criteria
• No consent form completed • Previous adverse reaction to use of cycloplegic drops • Participant with a diagnosed ocular condition requiring the use of medication • Participant is taking any prescription or non-prescription medicine that may interact with the cycloplegic drug • Undergoing or have previously had any form of myopia control intervention (any history of use of atropine, orthokeratology, multifocal soft contact lenses, bifocal or progressive addition spectacle lenses)

Table 5.4: Inclusion and exclusion criteria for the young adult study

Reaffirmation of this criteria was undertaken at each subsequent follow up stage and an additional question regarding myopia control intervention study participation was included in the Year 1 and Year 2 follow up questionnaires for further confirmation. It was also made clear to the participant on the day of the data collection that they were able to withdraw at any time.

5.3 Response Rates

5.3.1 Child cohort

5.3.1.1 Baseline

School response rates are discussed in Section 5.2.1.2 and were lower than anticipated at 8.0%. In total 100 primary schools were contacted and 8 agreed to take part in the study. However one school dropped out of the study a week prior to data collection due to a safe guarding issue within the school, as a result 7 schools took part in the study. At Baseline 891 parental consent forms were distributed to all eligible children prior to

data collection. The proportion of parental consent forms returned varied between schools, see Figure 5.8.

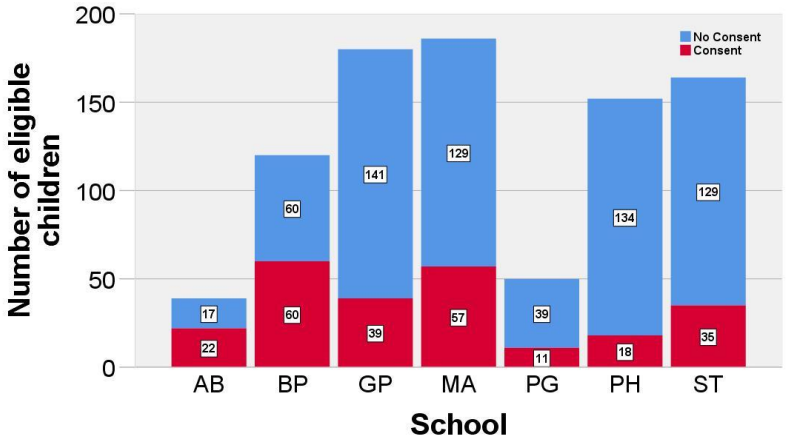


Figure 5.8: Baseline parental consent form returns per school

The mean baseline parental response rate was 27.2% (range 11.8 – 56.4). This response rate was significantly lower than those obtained in other school-based myopia studies such as the SMS (79%) and NICER (62%) (Ojaimi et al., 2005c, O'Donoghue et al., 2010c). It aligns more favourably with rates found in the CLEERE study (30-50%) and the AES (31.1%) (Zadnik et al., 2003, Logan et al., 2011).

Baseline parental response rates varied between schools, see Table 5.5. This variation can, in part, be attributed to the level of enthusiasm shown by the school towards the study. Schools where a senior member of staff took an active interest in the study and were proactive at reminding children to return the consent forms had the highest parental response rates (AB and BP, 56.4% and 50.0% respectively).

School	Participants contacted (n)	Returned Parental Consent Forms (n)	Parental Response Rate (%)	Number of Participants examined (n)	Participation Rate (%)
AB	39	22	56.4	21	95.5
BP	120	60	50.0	56	93.3
GP	180	39	21.7	38	97.4
MA	186	57	30.6	51	89.5
PG	50	11	22.0	10	90.9
PH	152	18	11.8	15	83.3
ST	164	35	21.3	35	100.0
Overall	**891**	**242**	**27.2**	**226**	**93.4**

Table 5.5: Baseline parental response rates and participation rates in each school

Of the 242 children for whom parental consent was received, an excellent baseline participation rate on the day of the study was found at 93.4% (n=226), see Table 5.5. The discrepancy in those children with parental consent and those that participated in the study is attributed to those that did not provide assent on the day of the study (n=13). In addition, 2 participants were not in attendance on the day of the study and 1 participant with severe learning disability was excluded from the study by the investigators as they were unable to complete all necessary parts of the study.

5.3.1.2 Year 1

Of the 226 participants that took part at baseline, 85.4% (n=193/226) of these children were eligible to take part in the Year 1 follow up. 33 children were ineligible as due to late recruitment this follow up visit fell outside the time constraints of the study period. 54.4% (n=105/193) of participants were examined in the Year 1 follow up cohort. 28.5% (n=55/193) had left the data collection school, 15.0% (n=29/193) did not have parental consent, 1.0% (n=2/193) did not provide assent and 1.0% (n=2/193) were not in attendance on the day(s) of data collection.

Year 1 parental response rate was high at 79.0% (n=109/138). Of those participants with parental consent, an excellent study participation rate of 96.3% (n=105) was also achieved. The discrepancy between the parental response rate and participation rate was a result of 2 potential participants with parental consent were not in attendance on school on the day(s) of the data collection and 2 participants did not provide assent to take part. For Year 1 follow up parental response rates and participation rates, see Table 5.6.

School	Participants contacted (n)	Returned Parental Consent Forms (n)	Parental Response Rate (%)	Participants examined (n)	Participation Rate (%)
AB	8	7	87.5	7	100.0
BP	39	30	76.9	29	96.7
GP	31	23	74.2	23	100
MA	33	28	84.8	26	92.9
ST	27	21	80.8	20	95.2
Overall	**138**	**109**	**79.0**	**105**	**96.3**

Table 5.6: Year 1 parental response rates and participation rates in each school

5.3.1.3 Year 2

Due to early recruitment of schools MA and GP a Year 2 follow up was able to be obtained, as a result for the Year 2 visit only 46.7% (49/105) were eligible to take part.

53.1% (n=26/49) of participants were examined at the Year 2 follow up. 38.8% (n=19/49) had left the data collection school, 6.1% (n=3/49) did not have parental consent and 2.0% (n=1/49) were not in attendance on the day(s) of data collection.

26 participants (86.7%) were examined at the Year 2 follow up. Parental response rate was high at 90.0% (n=27/30) and an excellent participation rate was achieved at 96.3% (n=26/27). Only one participant with parental consent did not take part as they were not in attendance on the day(s) of the study. For Year 2 parental response rates and participation rates, see Table 5.7.

School	Participants contacted (n)	Returned Parental Consent Forms (n)	Parental Response Rate (%)	Participants examined (n)	Participation Rate (%)
GP	16	14	87.5	13	92.9
MA	14	13	92.9	13	100.0
Overall	**30**	**27**	**90.0**	**26**	**96.3**

Table 5.7: Year 2 parental response rates and participation rates in each school

5.3.2 Young adult cohort

5.3.2.1 Baseline

The recruitment method used for the Young Adult cohort was much broader than the children's study with contact to all major discipline areas across the university. As such the exact number of eligible participants contacted at baseline cannot be accurately traced. 88 participants took part at baseline, however subsequently one participant (YA059), a high hyperope (RE SER +15.50D LE SER +14.44D) was excluded from the study due to aberrant biometry measurements, see Section 6.3.2.2. As a result, 87 participants were used in all subsequent data analysis.

5.3.2.2 Year 1

Of the 87 participants that took part at baseline, 100% (n=87/87) participants were eligible to take part at the Year 1 follow up. 68 participants (78.2%) were examined in the Year 1 follow up cohort. 14.9% (n=13/87) had left the university and 6.9% (n=6/87) did not reply to correspondence to take part. A good response rate of 78.2% (n=68/87) was achieved at Year 1, see Table 5.8.

5.3.2.3 Year 2

Of the 68 participants that took part in the Year 1 follow up, 61.8% (n=42/68) were eligible to take part at the Year 2 follow up. 26 participants (38.2%) were ineligible to

take part as this visit fell outside the time constraints of the study period due to late recruitment.

32 participants (76.2%) were examined in the Year 2 follow up cohort. 19.0% (n=8/42) had left the university and 4.8% (n=2/42) did not reply to correspondence to take part. A good response rate of 76.2% (n=32/42) was achieved at Year 2, see Table 5.8.

Year	Participants contacted (n)	Ineligible† participants (n)	Participants examined (n)	Response rate (%, n)
Year 1	87	0	68	78.2 (68/87)
Year 2	42	26	32	76.2 (32/42)

Table 5.8: Young adult Year 1 and Year 2 follow up participation rates †Ineligible participants were those for whom the follow up fell outside the time constraints of the study and were therefore unable to take part

5.3.3 Summary participant recruitment numbers and attrition rates

Summary of the number of participants examined in each cohort at each stage of the study are shown in Table 5.9.

	Stage		
Cohort	**Baseline**	**Year 1**	**Year 2**
Child	226	105	26
Young Adult	87	68	32
Overall	**313**	**173**	**58**

Table 5.9: Total number of participants examined at each stage of the study

Participant contactability, participation and ineligibility for all cohorts from Baseline to Year 1 are summarised in Figure 5.9 and from Year 1 to Year 2 in Figure 5.10.

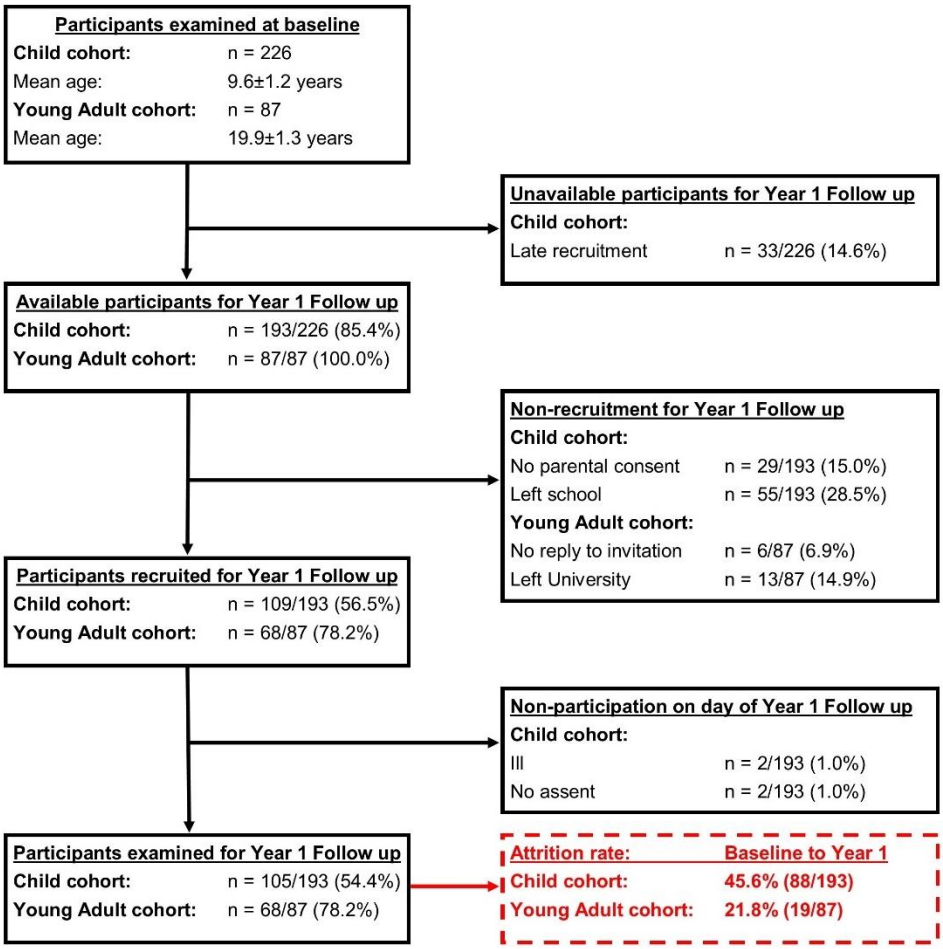


Figure 5.9: Summary flow chart of all participants contactability, participation and attrition rates from Baseline to Year 1 follow up Late recruitment was defined as participants who had baseline measurements taken less than 12 months prior to the end of the study period, as a result Year 1 follow up was not possible.

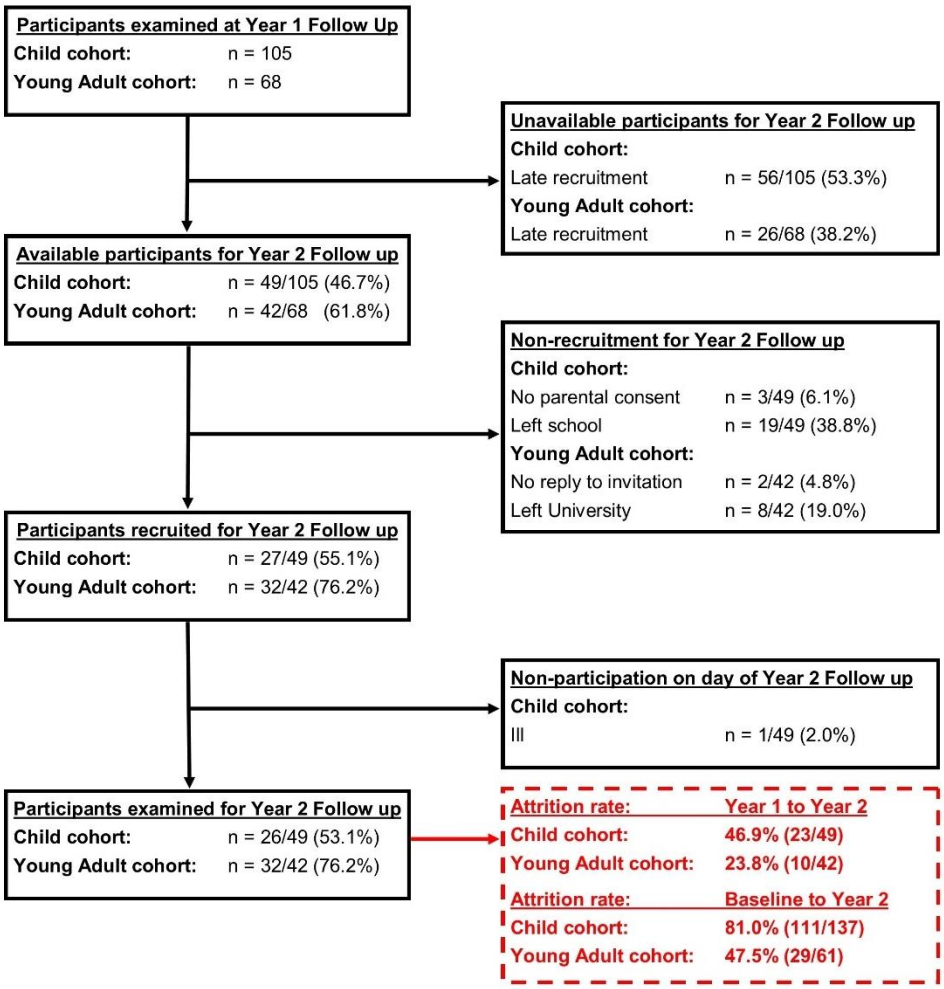


Figure 5.10: Summary flow chart of all participants contactability, participation and attrition rates from Year 1 follow up to Year 2 follow up Late recruitment was defined as participants who had Year 1 measurements taken less than 12 months prior to the end of the study period, as a result Year 2 follow up was not possible.

5.3.3.1 Attrition rates

In the Child cohort, 46.4% (n=105/226) of participants who took part at Baseline were examined at Year 1. However, 14.6% (n=33/226) were unable to take part in Year 1 as later recruitment meant that this follow up visit fell outside the time constraints of the study. After consideration of these participants, the attrition rate between Baseline and Year 1 was 45.6% (n=88/193). In Year 2, 24.8% (n=26/105) of participants who took part at Year 1 were examined at Year 2. Similarly to Year 1, for some participants due to later recruitment this follow up visit fell outside the time constraints of the study, at Year 2 this was 53.3% (n=56/105). After consideration of these participants, the attrition rate between Year 1 and Year 2 was 46.9% (n=23/49).

Overall, the attrition rate between Baseline and Year 2 for the Child cohort, after consideration of those participants (n=89) who were unable to be followed up due to later recruitment, was 81.0% (n=111/137). The reason for drop out was 54.0% (n=74/137) of participants had left the data collection school, 1.5% (n=2/137) did not provide assent on the day of the study and 2.2% (n=3/137) were not in attendance on the day(s) of data collection. The remainder, 23.3% (n=32/137), did not return a signed parental consent form.

In the Young Adult cohort, 78.2% (n=68/87) of participants who took part at Baseline were examined at Year 1. The attrition rate between Baseline and Year 1 was 21.8% (n=19/87). In Year 2, 47.1% (n=32/68) of participants who took part at Year 1 were examined at Year 2. Similarly to the Child cohort, due to later recruitment for some participants this follow up visit fell outside the time constraints of the study and these participants could therefore not take part in the Year 2 visit. This was 38.2% (n=26/68). After consideration of these participants, the attrition rate between Year 1 and Year 2 was 23.8% (n=10/42).

Overall, the attrition rate from Baseline to Year 2 in the Young Adult cohort, after consideration of those participants (n=26) who were unable to be followed up due to late recruitment, was 47.5% (n=29/61). The reason for drop out was 34.4% (n=21/61) had graduated and were therefore not able to return for the follow up and 13.1% (n=8/61) did not respond to communication regarding the follow up visit.

5.4 Questionnaires

5.4.1 Questionnaire design

Three questionnaires were designed, one for completion by the participants aged 7 – 12 years, one for completion by their parent/guardian and one for completion by the participants aged 18 – 25 years, see Appendix A.5.5. All questionnaires consisted of 5 sections: About you (or your child in the parent/guardian questionnaire), Ocular History, Your Activities (Your Child's Activities in the parent/guardian questionnaire), Diet and Parent Details. Both the parental/guardian questionnaire and young adult questionnaire were longer, 38 and 39 questions respectively however the child's questionnaire was adapted and consisted of 22 questions. The additional question asked in these questionnaires included ethnicity, birth weight and levels of parental education. Furthermore, more in depth questions regarding activities were asked including amount of time doing various tasks during seasons (Summer and Winter) and weekday or weekend. The rationale behind the children's questionnaire was to provide basic

information regarding potential influential environmental and lifestyle factors and gauge validity of the parent/guardian questionnaire through comparing responses. The children's questionnaire was also thought to provide information in the absence of a returned parental questionnaire.

5.4.1.1 Ethnicity

Ethnicity was categorised into six main groups based on the classification of ethnicity from the 2011 census for England and Wales (Office for National Statistics, 2019b). For the purposes of this thesis and for continuity with previous published literature participants from a South Asian heritage are referred to as 'Asian' and those from East Asian heritage are referred to as 'Chinese'. The categories used are listed below:

- White: White British, Irish, Other White
- Asian: South Asian: India, Pakistan, Bangladesh
- Chinese: East Asian: China, Singapore, Japan, Taiwan, Vietnam
- Black: African, Caribbean, Other Black
- Mixed: Combination of White, South Asian or Black
- Other: Any ethnicity not stated above

5.4.2 Questionnaire distribution

Both the children's and young adult questionnaires were completed on the day of the study. In the first instance, the parent/guardian questionnaires were distributed as hard copies to parents/guardians on the day of the data collection alongside the study participation letter. Completed questionnaires were then handed in to the school office where they were collected by KF. A section for contact details for parent/guardians was provided on the consent form completed at the start of the study, this allowed follow up contact to be established if the questionnaire was not returned. 4-6 weeks following distribution all parent/guardians were sent a reminder via text message or e-mail to return completed questionnaires to the school office. In an attempt to improve questionnaire return rates an electronic questionnaire was created using Google forms® (Google, California, United States). Extensive steps were taken in the design of the electronic form such that it had the same appearance, content and layout of the hard copy to ensure no discrepancies between hard copy and electronic completion. Parents/guardians who had not yet returned a completed questionnaire were again contacted via text message or e-mail to return the hard copy questionnaire to the school office or complete the electronic version via weblink.

At each subsequent visit, all children with outstanding questionnaires were given another hard copy to return alongside the Year 1/Year 2 consent form. All outstanding questionnaires following these multiple attempts were followed up via a phone call to complete the questionnaire over the phone.

5.4.3 Questionnaire response rates

Questionnaires for all participants aged 7 – 12 years (n=226) and 18 – 25 years (n=87) were completed on the day of the study (response rate 100%).

Parental questionnaire response rate was high at 83.2% (n=188/226). The majority of questionnaires were returned in hard copy form (n=119/188, 63.3%), followed by over the phone (n=38/188, 20.2%) and via the electronic form (n=31/188, 16.5%). The parental questionnaire responses per school can be found in Table 5.10.

School	Participants (n)	Parent questionnaires returned (n)	%
MA	51	38	74.5
GP	38	34	89.5
AB	21	17	81.0
ST	35	35	100.0
BP	56	40	71.4
PG	10	10	100.0
PH	15	14	93.3
Total	**226**	**188**	**83.2**

Table 5.10: Parental questionnaire response rates

5.5 Cohort Characteristics

The cohort demographic, refractive and biometric characteristics are discussed below. Biometric data in this section is presented from data obtained with the Aladdin (HW3.0, Topcon, Tokyo, Japan). This biometric data was selected to be presented in opposition to that collected from the IOLMaster 500 (Carl Zeiss, Jena, Germany) as both biometers are capable of measuring three of the main ocular biometric parameters: AL, AC and CR with good agreement (see Chapter 6). However, the Aladdin is able to measure two addition parameters: LT and CCT. LT is a key component of refractive error assessment. CR was defined as the Mean K (average of K1 and K2). The resolution of AL, AC, CR and LT was 2 decimal places whereas the CCT was 3 decimal places.

5.5.1 Child cohort

5.5.1.1 Demographic characteristics

The mean±SD age at baseline was 9.6±1.2 years (range 7.1 – 11.8, n=226). Due to the age of the participants in the Child cohort ethnicity data was obtained from completed and returned parental questionnaires. The parental questionnaire response rate was 83.2% (n=188). As a result, no ethnicity data was available for 38 child participants. The majority of participants were of White (67.0%), Asian (14.4%) and Chinese (8.5%) ethnicity, see Table 5.11. Due to the limited sample size of Chinese, Black, Mixed and Other ethnic groups any findings found in these groups cannot be considered a representation of the respective population. A relatively equal sex composition was found with only a slight female tendency at 56.2% (n=127) compared to 43.8% male (n=99). No significant difference in age was found between females and males (mean age 9.6±1.2 years and 9.7±1.2 years respectively, t=-0.517, p=0.606).

Ethnic Group	n	%
White	126	67.0
Asian	27	14.4
Chinese	4	2.1
Black	9	4.8
Mixed	16	8.5
Other	6	3.2

Table 5.11: Child cohort ethnicity composition

5.5.1.2 Refractive characteristics

5.5.1.2.1 SER characteristics and distribution

Mean RE SER was +1.06±1.35D (range -4.81 to +6.00) in 226 eyes measured and mean LE SER was +1.13±1.30D (range -3.81 to +6.44) in 225 eyes measured. The discrepancy between number of right eyes and left eyes is because participant BP046 only had one eye (RE) following an accident to her LE in early childhood. Refractive error distribution for the RE was more negatively skewed compared to the LE, see Figure 5.11. Normality assessments were performed, see Appendix A.5.8, and it was concluded that, following removal of extreme outliers (>2SD), RE SER was normally distributed (p=0.011) but LE SER was not normally distributed (p=0.002).

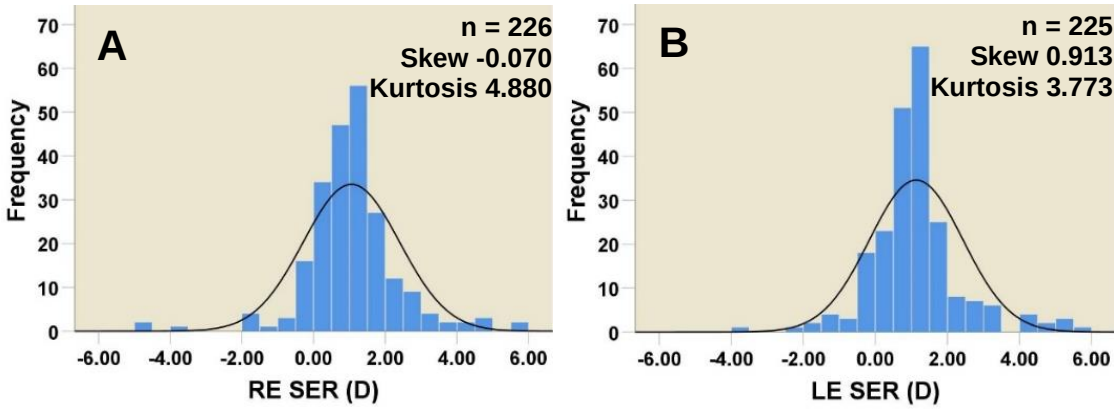


Figure 5.11: Child cohort SER distribution A) Right eye distribution B) Left eye distribution. A normal distribution curve is shown by the solid black line.

5.5.1.2.2 SER RE vs LE correlation

Correlation between RE and LE was initially assessed using a simple scatterplot, see Figure 5.12. Outliers measurements were defined as ≥2SD from the mean difference (RE SER – LE SER, mean±SD -0.08±0.66D). Two outliers were identified in this assessment and are highlighted in red on the scatter plot, see Figure 5.12A. On examination of these participants both were excluded as outliers in this correlation analysis as one individual (BP006) was highly astigmatic in one eye which had caused the SER equation to create a disproportionate difference between the eyes and the other (MA008) was amblyopic with SER RE -4.75D LE +0.13D. On removal of these outliers the R^2 value increased to 0.877 from 0.765, see Figure 5.12B.

RE SER and LE SER were subsequently found to be significantly correlated (Pearson's correlation coefficient r = 0.937, p<0.001). ICC was good at 0.875.

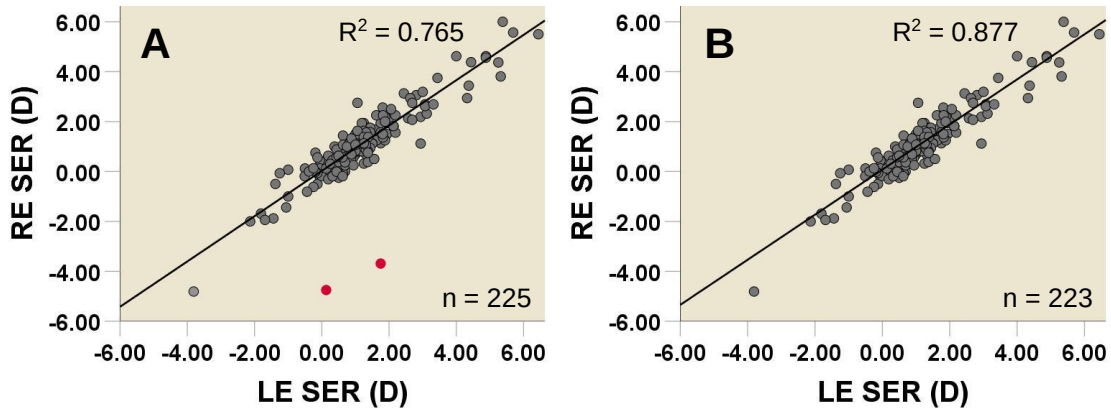


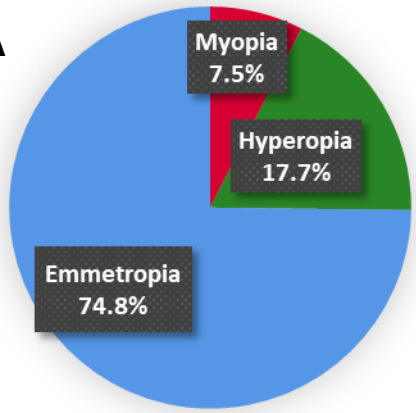
Figure 5.12: RE and LE SER correlation Child cohort A) Complete data set B) Data set without outliers. Outliers (>2SD from mean difference (RE SER – LE SER) shown in red

5.5.1.2.3 Proportion of refractive error

Participants were classified as myopes, hyperopes or emmetropes as per the refractive error definitions outlined in Section 5.1.5.

The proportion of each refractive error in the Child cohort is shown in Figure 5.13. Of the 226 participants, 7.5% were classified as myopic (n=17), 17.7% hyperopic (n=40) and the majority, 74.8%, emmetropic (n=169). The proportion of astigmatism was 18.5% (n=42).

A



B

Refractive error	n
Hyperopia	40
Emmetropia	169
Myopia	17

Figure 5.13: A) Refractive error composition and B) number of participants per refractive error category in the Child cohort

Of the 7.5% classified as myopic (n=17), 41.2% were bilateral myopes (n=7). Altering the definition of myopia did alter the myopia proportion, see Table 5.12. When using a ≤1.00D definition the proportion reduced by 2.2% (n=5).

Myopia SER definition and myopia %		
≤-0.50D	≤-0.75D	≤-1.00D
7.5 (n=17)	5.8 (n=13)	5.3 (n=12)

Table 5.12: Proportion of myopia using different SER definitions in the Child cohort

5.5.1.3 Biometric characteristics

5.5.1.3.1 Ocular parameters

The mean±SD and range of ocular parameters in the Child cohort can be found in Table 5.13, alongside RE and LE correlation analysis. All measurements were found to significantly correlated between RE and LE with mean R^2=0.897 (range 0.835 to 0.962), see Appendix A.5.10. Pearson's correlation coefficient also showed an overall strong correlation with mean r=0.947 (range 0.914 to 0.981). CR was found to be the most

correlated parameter (R^2=0.962, r=0.981, p<0.001) and AL was the least correlated parameter (R^2=0.835, r=0.914, p<0.001). The distributions of each ocular parameter can be found in the Appendix A.5.9.

Ocular parameter	Eye	n	Mean±SD	Range	R^2	r	p value
AL	RE	188	22.84±0.84	20.33 - 25.64	0.835	0.914	**p<0.001**
	LE	202	22.92±0.83	20.39 - 25.27			
AC	RE	197	3.68±0.24	2.99 – 4.24	0.935	0.967	**p<0.001**
	LE	196	3.67±0.24	3.05 – 4.39			
CR	RE	133	7.80±0.26	7.07 – 8.36	0.962	0.981	**p<0.001**
	LE	136	7.78±0.26	7.08 – 8.36			
LT	RE	175	3.43±0.17	2.94 – 4.06	0.864	0.930	**p<0.001**
	LE	176	3.42±0.18	2.96 – 4.04			
CCT	RE	198	0.547±0.034	0.440 – 0.640	0.890	0.944	**p<0.001**
	LE	193	0.549±0.034	0.430 – 0.640			

Table 5.13: Ocular parameter characteristics in the Child cohort and RE vs LE correlation All parameters measured in mm. r: Pearson's correlation coefficient.

5.5.1.3.2 SER and biometry correlation

Correlation between each ocular biometry parameter and SER can be found in Table 5.14 and linear regression graphs can be found in the Appendix A.5.11. AL correlated well with SER (Pearson's correlation, r =-0.590, p<0.001) and accounted for 34.8% of variation in SER (R^2=0.348) using the IOLMaster. There was a weak negative correlation between AC and SER (R^2=0.115, r=-0.339, p<0.001) with only 11.5% of variation in SER accounted for. No significant correlation between CR, LT or CCT with SER was found.

Parameter (mm)	n	R^2	r	p value
AL	188	0.348	-0.590	**p<0.001**
AC	197	0.115	-0.339	**p<0.001**
CR	133	0.001	0.037	p=0.671
LT	175	0.002	0.049	p=0.520
CCT	198	0.002	0.050	p=0.486

Table 5.14: Correlation between biometry measurements and SER in the Child cohort r: Pearson's correlation coefficient

To determine the relative contribution of each parameter to the overall refractive status of the eye a multiple linear regression model was constructed with SER as the outcome variable and the five ocular parameters as explanatory variables, see Table 5.15. The multiple linear regression statistically significantly predicted SER ($F(5,89) = 29.553$, $p<0.001$), adjusted $R^2=0.603$, indicating that 60.3% of variability in SER is explained by AL, CR, AC, LT and CCT, see Table 5.15.

The multiple linear regression found that AC depth (p=0.102) and CCT (p=0.831) did not significantly contribute to this model. A subsequent multiple linear regression was run without these parameters with only AL, CR and LT remaining. It was found that this follow up multiple linear regression could also significantly predict SER at a slightly lower 55.5% ($F(3,96) = 42.085$, $p<0.001$, adjusted $R^2=0.555$).

Parameter (mm)	Regression Coefficient	Standard error of coefficient	t value	p value
AL	-1.748	0.168	-10.390	**p<0.001**
AC	0.717	0.435	1.650	p=0.102
CR	3.825	0.499	7.673	**p<0.001**
LT	-1.168	0.540	-2.163	**p=0.033**
CCT	-0.639	2.976	-0.215	p=0.831

Table 5.15: Multiple linear regression of ocular parameters on SER in the Child cohort

5.5.2 Young Adult cohort

5.5.2.1 Demographic characteristics

The mean±SD age at baseline was 19.9±1.3 years (range 18.2 – 24.5. n=87). Ethnicity was self-reported in this cohort, the majority of participants were of White (41.4%) and Asian (43.7%) ethnicity, see Table 5.16.

Ethnic Group	n	%	Mean age±SD (years)
White	36	41.4	19.9±1.3
Asian	38	43.7	19.8±1.2
Chinese	5	5.7	19.6±0.8
Black	6	6.9	19.9±0.8
Mixed	1	1.1	24.5±0.0
Other	1	1.1	19.6±0.0

Table 5.16: Young Adult cohort ethnicity composition

A predominantly female composition of participants was found, 66.7% (n=58) compared to 33.3% males (n=29). No significant difference in age was found between females and males (mean age 20.0±1.3 years and 19.8±1.1 years, respectively, t=0.837, p=0.405).

5.5.2.2 Refractive characteristics

5.5.2.2.1 SER characteristics and distribution

Mean RE SER was -0.81±2.60D (range -7.81 to +8.00, n=87)) and mean LE SER was -0.76±2.66D (range -7.63 to +10.00, n=87). The refractive error distribution for the RE was slightly more negatively skewed compared to the LE, see Figure 5.14. Normality assessments were performed, see Appendix A.5.8 and it was concluded that, following removal of extreme outliers (>2SD), both RE SER and LE SER were not normally distributed (p=0.003 and p<0.001 respectively).

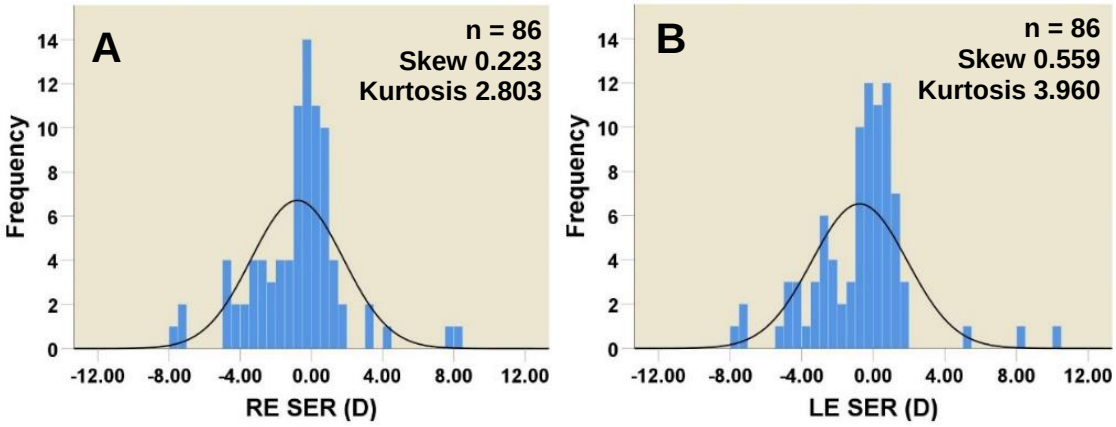


Figure 5.14: Young Adult cohort SER distribution A) Right eye distribution B) Left eye distribution. A normal distribution curve is shown by the solid black line.

5.5.2.2.2 SER RE vs LE correlation

RE and LE SER correlation was also primarily assessed with a scatterplot, see Figure 5.15. No outliers were visually identified. R^2 was high at 0.924. RE SER and LE SER were found to be significantly correlated (Pearson's correlation coefficient r = 0.961, p<0.001). ICC was good at 0.961.

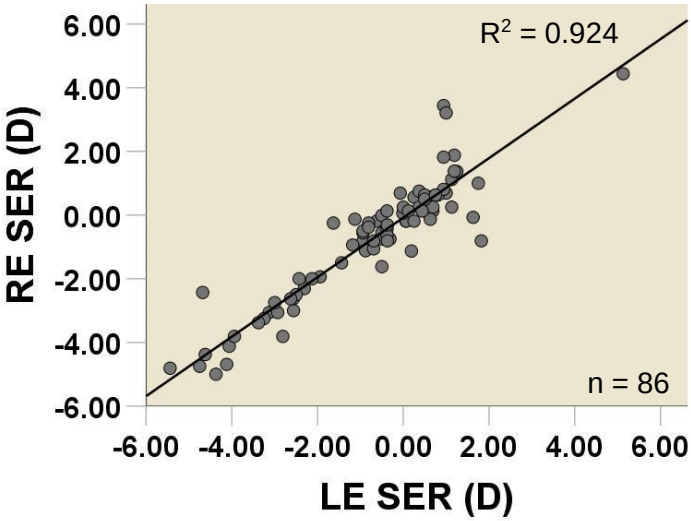


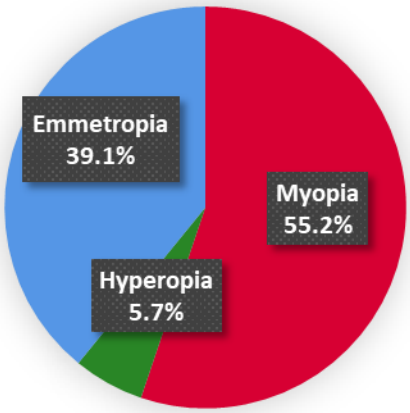
Figure 5.15: RE and LE SER correlation Young Adult cohort

5.5.2.2.3 Proportion of refractive error

Participants were classified as myopes, hyperopes or emmetropes as per the refractive error definitions outlined in Section 5.1.5.

The proportion of each refractive error in the Young Adult cohort is shown in Figure 5.16. Of the 87 participants, 55.2% were classified as myopic (n=48), 5.7% hyperopic (n=5) and 39.1% emmetropic (n=34). The proportion of astigmatism was 28.7% (n=25).

A



B

Refractive error	n
Hyperopia	5
Emmetropia	34
Myopia	48

Figure 5.16: A) Refractive error composition and B) number of participants per refractive error category in the Young Adult cohort

Of the 55.2% classified as myopic (n=48), 77.1% were bilateral myopes (n=37). As expected, altering the definition of myopia did alter the myopia proportion, see Table 5.12. When using a ≤1.00D definition the proportion reduced by 17.3% (n=15).

Myopia SER definition and myopia %		
≤ -0.50D	**≤ -0.75D**	**≤-1.00D**
55.2 (n=48)	50.6 (n=44)	37.9 (n=33)

Table 5.17: Proportion of myopia using different SER definitions in the Young Adult cohort

5.5.2.3 Biometric characteristics

5.5.2.3.1 Ocular parameters

The mean±SD and range of ocular parameters in the Young Adult cohort can be found in Table 5.18, alongside RE and LE correlation analysis. All measurements were found to significantly correlated between RE and LE with mean, R^2=0.957 (range 0.941 to 0.970). Pearson's correlation coefficient also showed a strong correlation with mean, r=0.978 (range 0.970 to 0.985). AC was found to be the most correlated parameter (R^2=0.970, r=0.985, p<0.001) and LT was the least correlated parameter (R^2=0.941, r=0.970, p<0.001). The distributions of each ocular parameter can be found in the Appendix A.5.9.

Ocular parameter	Eye	n	Mean±SD	Range	R^2	r	p value
AL	RE	86	24.08±1.32	20.57 – 27.65	0.952	0.975	**p<0.001**
	LE	84	24.05±1.33	20.07 – 27.55			
AC	RE	86	3.78±0.27	3.16 – 4.46	0.970	0.985	**p<0.001**
	LE	86	3.76±0.27	3.16 – 4.43			
CR	RE	85	7.80±0.23	7.30 – 8.39	0.963	0.981	**p<0.001**
	LE	83	7.79±0.22	7.32 – 8.37			
LT	RE	86	3.49±0.18	3.09 – 3.88	0.941	0.970	**p<0.001**
	LE	84	3.49±0.19	3.08 – 3.90			
CCT	RE	86	0.544±0.037	0.460 – 0.640	0.959	0.979	**p<0.001**
	LE	85	0.56±0.038	0.450 – 0.650			

Table 5.18: Ocular parameter characteristis in the Young Adult cohort All parameters measured in mm. r: Pearson's correlation coefficient

5.5.2.3.2 SER and biometry correlation

Correlation between each ocular biometry parameter and SER can be found in Table 5.19 and linear regression graphs can be found in the Appendix A.5.11. A similar good correlation between AL and SER was also found in the Young Adult cohort (Pearson's correlation, r=-0.851, p<0.001) and accounted for large of variation in SER at 72.4% (R^2=0.724). A weak correlation between AC and SER was found (R^2=0.148 r=-0.384

p=0.148) with 14.8% of variation in SER accounted for. A weak but positive correlation was found between LT and SER was found (R^2 = 0.111, r=0.333, p=0.002) with only 11.1% of variation in SER accounted for. No significant correlation between CR or CCT with SER was found.

Parameter (mm)	n	R^2	r	p value
AL	86	0.724	-0.851	**p<0.001**
AC	86	0.148	-0.384	**p<0.001**
CR	85	0.004	0.060	p=0.583
LT	86	0.111	0.333	**p=0.002**
CCT	86	0.013	0.114	p=0.298

Table 5.19: Correlation between biometry measurements and SER in the Young Adult cohort r: Pearson's correlation coefficient

To determine the relative contribution of each parameter to the overall refractive status of the eye a multiple linear regression model was constructed with SER as the outcome variable and the five ocular parameters as explanatory variables, see Table 5.20. The multiple linear regression statistically significantly predicted SER (F(5,79) = 182.424, p<0.001), adjusted R^2=0.915, indicating that 91.5% of variability in SER is explained by AL, CR, AC, LT and CCT. The multiple linear regression found that CCT (p=0.361) did not significantly contribute to this model. A subsequent multiple linear regression was run without CCT and it was found that this follow up multiple linear regression could also significantly predict SER at the same level, 91.5% (F(4,80) = 228.268, p<0.001, R^2 = 0.915).

Parameter (mm)	Regression Coefficient	Standard error of coefficient	t value	p value
AL	-2.299	0.086	-26.773	**p<0.001**
AC	2.029	0.422	4.808	**p<0.001**
CR	5.403	0.409	13.198	**p<0.001**
LT	-1.130	0.558	-2.026	**p=0.046**
CCT	2.130	2.320	0.918	p=0.361

Table 5.20: Multiple linear regression of ocular parameters on SER in the Young Adult cohort

5.6 Summary

- In the Child cohort, 226 participants were recruited from 7 schools from three regions of the UK (North, Midlands and South). 46.5% (n=105) were re-examined at a Year 1 visit and 11.5% (n=26) at a Year 2 visit
- In the Young Adult cohort, 87 participants were recruited and consistently of predominantly university undergraduate students. 78.2% (n=68) were re-examined at a Year 1 visit and 36.8% (n=32) at a Year 2 visit
- Attrition rates were higher than expected and were higher in the Child cohort compared to the Young Adult cohort (46.4% vs 21.8% at Year 1 and 81.0% vs 47.5% at Year 2).
- The gold standard of cycloplegic autorefraction was undertaken in this study
- A rigid study procedure was adhered to throughout which included vision/visual acuity, cover test, instillation of cycloplegic drops, completion of a lifestyle questionnaire, height and weight, conjunctival photography, biometry and autorefraction
- A good parental questionnaire response rate of 83.2% (n=188/226) was achieved using a variety of communication methods
- The Actiwatch 2 (Philips Respironics, USA) light sensor device was used to measure the ambient light exposure and physical activity of study participants in the Child cohort
- Excellent correlations between RE and LE measurements were found for SER and all ocular parameters (AL, AC, CR, LT, CCT)

Chapter 6: Validity and agreement between IOLMaster 500 (Carl Zeiss, Jena, Germany) and Aladdin (HW3.0, Topcon, Tokyo, Japan) biometry devices

6.1 Introduction

Optical biometers are widely used in research centres and hospital sites across the world to measure ocular parameters such as AL, AC and CR. Their use in clinical practice has primarily been in intraocular lens (IOL) calculations and cataract surgery but their use is increasing in the area of myopia control where AL measurement is used as a key indicator of myopia progression and the efficacy of the control method. The ability to measure AL, in addition to refractive error, in clinical practice provides useful information which can be used to gauge the individual's risk of certain pathologies, such as retinal detachment. Furthermore, keratometry and topographic corneal measurements are also essential in contact lens based myopia control strategies such as orthokeratology lens design and fitting.

The IOLMaster 500 (Carl Zeiss, Jena, Germany) is considered the gold standard of modern optical biometry devices. It uses the principle of partial coherence interferometry (PCI) discussed in detail in Section 4.3.1. A 780nm laser diode infrared light is used to measure AL and AC is measured through image analysis of a 0.7mm wide lateral slit beam at a 30 degree angle. CR is also measured through an image analysis method through analysis of 6 reference points in a hexagonal configuration on the central 2.3mm optical zone. The Aladdin (HW3.0, Topcon, Tokyo, Japan) is a relatively new biometer and uses optical low coherence interferometry (OLCI) system using a super luminescent diode (830nm) to measure AL, ACD, CR and, additionally to the IOLMaster 500, LT and CCT as well corneal topography. CR is measured using a 24 placido disc corneal topographer which analyses more than 100,000 data points over an 9.8mm corneal area. The CR readings reported are a representative of the central 3.0mm and are extrapolated from the placido disc data.

The accuracy and repeatability of the Aladdin compared with the gold standard biometer, the IOLMaster 500, has been investigated and to date most studies have investigated the accuracy of the Aladdin in cataract patients as correct selection of an appropriate IOL is crucial to ensure an optimal refractive error post cataract surgery (Ortiz et al., 2018, Hoffer et al., 2016, Sabatino et al., 2016, Mandal et al., 2014). Preoperative biometry measurements of AL, ACD and K can be applied to a power calculation formula

to determine the correct IOL. Minimal information about the repeatability and accuracy of the Aladdin compared to the IOLMaster 500 in children and young adults is published which is explored in this study.

6.2 Rationale

The aim of this chapter is to assess the validity of the new generation Aladdin (HW3.0, Topcon, Tokyo, Japan) in a Child and Young Adult cohort which is currently not available in the literature. The majority of current literature has largely been centred around older populations with cataracts. The biometers will be assessed on a number of key measures of validity, including:

- Data acquisition ability takings into account the number of failed and inconsistent measurements allowing the number of successful data acquisition measurements to be calculated
- Direct comparison of parameter measurements between the two devices

These comparisons will confirm whether the Aladdin's biometric ocular measurements of AL, AC and CR are statistically different compared to the IOLMaster 500 and assess the clinical relevance of any discrepancies. If a good agreement between these two biometers is found it will allow the use of Aladdin biometric data in subsequent chapters allowing the analysis of an additional two parameters, LT and CCT measurements.

6.2 Methodology

6.2.1 Biometric parameters

Biometric parametric data was obtained following the clinical protocol set out in Section 5.1. In summary for all participants post-cycloplegic biometric measurements were taken with the IOLMaster 500 and Aladdin at three stages (Baseline, Year 1 and Year 2).

In the Child cohort, biometric measurements of AL and CR and in the Young Adult cohort, AL, AC and CR were obtained for both devices. For all Child cohort participants AC measurements were measured as it was automatically taken as part of the biometry acquisition process. However, for the IOLMaster 500 a separate AC measurement had to be selected supplementary to AL and CR measurement. Although initially attempts were made to measure AC with the IOLMaster 500, poor compliance from the Child cohort participants was noted, likely a result of the bright light used to acquire this measurement. AC was not considered a primary biometric measure in this study,

therefore due to the time constraints attributed to the field based nature of this study AC was not measured in the Child cohort.

CR measurements are analysed as K1 (keratometry at the flattest meridian), K2 (keratometry at the steepest meridian) and mean K (average measurements of K1 and K2) measurements.

6.2.2 Data acquisition

Data acquisition ability was calculated by taking into account failed and inconsistent measurements of AL and CR in the Child cohort and AL, AC and CR in the Young Adult cohort. Failed measurements were classed as those where no measurement was able to be recorded, despite repeated attempts.

For inconsistent measurements, both biometers have in built systems to highlight measurements that are deemed inconsistent caused by errors such as bad focus or movement during acquisition. These are discussed in Section 4.3.

In summary, IOLMaster 500 AL measurement is accompanied by a SNR value, any value <2.0 was removed. Furthermore, values flagged in red as outliers were also removed. After removal of these values, a minimum of 3 measurements was needed to remain in order to class the measurement as consistent.

The Aladdin identified inconsistencies/errors during the acquisition for all parameters (AL, AC and CR) with this warning sign: ⚠ on the data acquisition screen. This can result from bad focus, closed eyelid, tear film irregularity, movement or high standard deviation in multiple measurements. Unlike with the IOLMaster 500, this is not assigned to the individual measures but rather to the ocular component as a whole. Therefore, an equivalent removal of these data points, as with the IOLMaster 500, was not possible. Advice from the manufacturers was to repeat these measures until a non-flagged value i.e. a reliable consistent measurement without errors was taken. This was not possible in all participants, with subsequent repeated measurements still flagged with the warning sign. All Aladdin data was directly exported from the device into a Microsoft Excel® (Office 365, Version 2001) spreadsheet using the manufacture software. Measurements identified as inconsistent by the Aladdin (denoted by ⚠ on the acquisition screen) were easily identifiable in the exported spreadsheet as yellow highlighted cells and removed.

Data acquisition ability for each device was calculated by dividing the number of valid measurements that were taken by the total number of potential measurement

opportunities. The discrepancy between the number of valid and potential measurements is those measurements that failed or were classified as inconsistent.

A repeated-measures within-subjects ANOVA was run with instrument, eye and visit as factors to control for any bias caused by the inclusion of data from both eyes and multiple visits for each participant in the analysis, see Table 6.1. Each data collection visit was 12±3 months apart. Due to the comparatively low numbers in the Year 2 data collection only data from Baseline and Year 1 were used in this analysis.

	Child cohort			Young Adult cohort			
Factor	**AL**	**K1**	**K2**	**AL**	**AC**	**K1**	**K2**
Instrument*Eye	F=0.450 p=0.505	F=1.756 p=0.204	F=3.010 p=0.101	F=0.580 p=0.449	F=0.119 p=0.732	F=2.045 p=0.158	F=2.907 p=0.094
Instrument*Visit	F=0.681 p=0.412	F=0.000 p=0.989	F=0.015 p=0.905	F=2.325 p=0.132	F=3.019 p=0.088	F=0.559 p=0.458	F=0.180 p=0.673
Eye*Visit	F=0.647 p=0.424	F=0.103 p=0.753	F=0.384 p=0.544	F=0.017 p=0.898	F=0.267 P=0.607	F=0.001 p=0.977	F=0.169 p=0.682
Instrument*Eye*Visit	F=1.145 p=0.289	F=0.006 p=0.937	F=0.631 P=0.438	F=0.170 p=0.681	F=0.024 p=0.878	F=0.251 p=0.619	F=0.190 P=0.665

Table 6.1: Repeated-measures within subjects ANOVA for individual ocular parameters in each cohort with instrument, eye and visit as factors

The outcome confirms the lack of interaction between eye and visit on ocular parameter measurements, concluding that each eye and visit can be considered an independent measure and therefore an opportunity to assess the accuracy and validity of the Aladdin biometer. Therefore, both right and left eyes were included in the analysis which is in accordance with similar previous studies (Akman et al., 2016, Jasvinder et al., 2011, Rohrer et al., 2009). Furthermore, data from all three years of data collection (Baseline, Year 1 and Year 2) was also included.

6.2.3 Statistical analysis and sample size calculation

The data from the two cohorts were analysed separately. For the Child cohort: AL and CR (K1, K2 and Mean K) were evaluated between the two devices and for the Young Adult cohort: AL, AC and CR (K1, K2 and Mean K) were evaluated. Mean K was calculated by averaging the corneal curvatures (K1 and K2) to give an average K measurement. All statistical analyses were carried out using SPSS® Version 25.

To evaluate normality histograms were plotted and Shapiro-Wilk test was applied. All ocular biometric parameters in both cohorts were normally distributed, with the exception of AL in the Young Adult cohort for both devices (IOLMaster 500 p=0.039 and Aladdin

p=0.048). However, examination of both histograms showed a symmetrical distribution with an approximate Gaussian curve, albeit with a positive skew likely a result of a large proportion of myopic participants. No strong reasoning was found to use non-parametric analysis with this data. Therefore, normality was assumed for all ocular components in both cohorts allowing the use of parametric tests.

The level of agreement between the two biometers for each parameter was quantified by using the Limits of Agreement (LOA) graphical method, a statistically valid method outlined by Bland and Altman (Bland and Altman, 1999), as well as the ICC. The assessment of the mean difference between each parameter measured with each device was assessed with paired samples t-test. Differences in categorical variables was assessed with the χ^2 test (data acquisition ability between cohorts).

A sample size calculation was performed using G*Power software (version 3.1.9.4) to calculate an effect size of 0.10 (power of 95%, significance 5%) considering 2 repeated eyes and 3 repeated visits per individual. The results indicated a total sample size of 166. The sample sizes used in this study for the assessment of agreement between the two devices are shown in Table 6.2. The sample size was therefore found to be sufficient for each parameter assessed.

	Cohort sample size (n)	
Ocular parameter	**Child**	**Young Adult**
AL	614	370
AC	NA	353
CR	388	355

Table 6.2: Sample sizes for each parameter used in the comparison of IOLMaster 500 and Aladdin biometers

6.3 Results

6.3.1 Data acquisition ability

Biometry with both the IOLMaster 500 and Aladdin was attempted on all participants on both eyes throughout the study (Child cohort n=713, Young Adult cohort n=374). In some instances, measurements were attempted however their measurement failed to be recorded by the biometer, for example due to blinking or eyelid closure. Table 6.3 shows the number of failed measures for AL, AC and CR for the IOLMaster 500 and Aladdin. Please note that AC data was not recorded in the Child cohort. Of all the AL, CR and AC measurements, the IOLMaster 500 was unable to record 6.12% (n=156/2548) of measurements and the Aladdin 11.50% (n=293/2548).

		Measurement Failures (%)							
		IOLMaster 500				Aladdin			
Cohort	**Parameter**	**RE**	**LE**	**Total**	**Overall**	**RE**	**LE**	**Total**	**Overall**
Child	**AL**	1.12 (n=4)	1.97 (n=7)	1.54 (n=11)	1.01 (n=11/1087)	3.64 (n=13)	4.21 (n=15)	3.93 (n=28)	2.58 (n=28/1087)
Young Adult		0.00 (n=0)	0.00 (n=0)	0.00 (n=0)		0.00 (n=0)	0.00 (n=0)	0.00 (n=0)	
Child	**AC**	NA	NA	NA	4.81 (n=18/374)	NA	NA	NA	1.07 (n=4/374)
Young Adult		5.35 (n=10)	4.28 (n=8)	4.81 (n=18)		1.07 (n=2)	0.00 (n=0)	0.53 (n=2)	
Child	**CR**	17.09 (n=61)	17.13 (n=61)	17.11 (n=122)	11.68 (n=127/1087)	36.41 (n=130)	34.55 (n=123)	35.48 (n=253)	24.01 (n=261/1087)
Young Adult		1.07 (n=2)	1.60 (n=3)	1.34 (n=5)		2.67 (n=5)	1.60 (n=3)	2.14 (n=8)	
		Overall			**6.12 (n=156/2548)**	**Overall**			**11.50 (n=293/2548)**

Table 6.3: Comparison of the number of measurement failures by the IOLMaster 500 and Aladdin for AL, AC and CR

In addition to measurement failures, inconsistencies during the data acquisition process were also able to be identified by the biometers. As mentioned previously for the IOLMaster 500 each individual measure was assigned a measure of its consistency through a SNR. Following removal of these inconsistent measures, 100% of participants had three remaining consistent values. For the Aladdin, information regarding consistency was provided for the parameter as a whole and in some participants all measurements were flagged as inconsistent, despite repeated measures. Table 6.4 summarises the number of inconsistent measurements which were flagged by the Aladdin.

		Inconsistent Measurements (%)			
Parameter	**Cohort**	**RE**	**LE**	**Total**	**Overall**
AL	**Child**	10.76 (n=37)	6.74 (n=23)	8.76 (n=60)	6.04 (n=64/1059)
	Young Adult	0.53 (n=1)	1.60 (n=3)	1.07 (n=4)	
AC	**Child**	NA	NA	NA	0.54 (n=2/370)
	Young Adult	0.54 (n=1)	0.00 (n=0)	0.27 (n=1)	
CR	**Child**	1.32 (n=3)	1.72 (n=4)	1.52 (n=7)	1.69 (n=14/826)
	Young Adult	1.65 (n=3)	2.17 (n=4)	1.91 (n=7)	
				Overall	**3.55 (n=80/2255)**

Table 6.4: Data acquisition entries flagged as inconsistent by the Aladdin

0.00% of IOLMaster 500 measurements were deemed inconsistent. For the Aladdin 3.55% (n=80/2255) of measurements CR recorded by the Aladdin were inconsistent. After removal of this inconsistent data values and taking into account the number of failed measurements, as shown in Table 6.3, the data acquisition ability was calculated for each biometer for each cohort and is shown in Table 6.5.

	Data Acquisition Ability (%)					
	IOLMaster 500			Aladdin		
Parameter	Child (n=713)	Young Adult (n=374)	Overall	Child (n=713)	Young Adult (n=374)	Overall
AL	98.46 (n=702)	100.00 (n=374)	98.99 (n=1076/1087)	87.66 (n=625)	98.93 (n=370)	91.54 (n=995/1087)
AC	NA	95.19 (n=356)	95.19 (n=356/374)	NA	99.20 (n=371)	99.2 (n=371/374)
CR	82.89 (n=591)	98.66 (n=369)	88.32 (n=960/1087)	63.53 (n=453)	95.99 (n=359)	74.70 (n=812/1087)
Overall	**90.67 (n=1293/1426)**	**97.95 (n=1099/1122)**	**93.88 (n=2392/2548)**	**75.60 (n=1078/1426)**	**98.04 (n=1100/1122)**	**85.48 (n=2178/2548)**

Table 6.5: Comparison of successful data acquisition ability between the IOLMaster 500 and Aladdin in both cohorts for AL, AC and CR

The IOLMaster 500 had a significantly higher data acquisition ability compared to the Aladdin ($\chi^2(1)=97.086$, $p<0.001$, 93.88% vs 85.48% respectively). This discrepancy was largest between the biometers in the Child cohort with the Aladdin losing 15.07% more data compared to the IOLMaster 500. Between the devices, no significant difference in data acquisition ability was found in the Young Adult cohort ($\chi^2(1)=0.023$, $p=0.880$) however the Aladdin had a significant reduced data acquisition in the Child cohort compared to the IOLMaster 500 ($\chi^2(1)=115.598$, $p<0.001$).

The ocular parameter with the lowest overall acquisition percentage was CR (IOLMaster 500, 88.32% and Aladdin 74.70%). The data acquisition ability for both biometers was affected by the cohort, with the Child cohort causing a significant reduction in acquisition ability compared to the Young Adult cohort (IOLMaster 500 $\chi^2(1)=57.852$ $p<0.001$, Aladdin $\chi^2(1)=254.812$ $p<0.001$). This is likely a result of the influence of age on compliance as the Child cohort was significantly younger than Young Adult cohort (9.9±1.2 and 20.5±1.4 respectively, independent samples t-test $p<0.001$).

The study took place over a 2 year period and in order to assess whether data acquisition changed over the course of the study, the data was analysed for each device at each stage of the study (Baseline, Year 1 and Year 2). This is shown in Table 6.6. The data acquisition of both devices increased over the 2 year period, for the Aladdin by 12.22% and for the IOLMaster 500 3.24%. The increase in data acquisition ability was

relatively stable between each stage for both devices, IOLMaster 500: 1.40% and 1.84% between Baseline and Year 1 and Year 1 and Year 2 respectively and Aladdin 5.19% and 7.03%. For both devices a significant difference in data acquisition ability was found between Baseline and Year 2 (IOLMaster 500 $\chi^2(1)=4.287$ p=0.038, Aladdin $\chi^2(1)=27.910$ p<0.001).

	Data Acquisition ability (%)		
	Baseline	**Year 1**	**Year 2**
IOLMaster 500	93.05 (n=1325/1424)	94.44 (n=782/828)	96.28 (n=285/296)
Aladdin	82.37 (n=1173/1424)	87.56 (n=725/828)	94.59 (n=280/296)

Table 6.6: Overall device data acquisition ability over time for IOLMaster 500 and Aladdin

6.3.2 Ocular parameter measurement agreement

6.3.2.1 Child Cohort

For AL 614 eyes from 219 participants were included and for CR (K1, K2 and Mean K) 388 eyes from 182 participants. Table 6.7 summarises the AL, K1, K2 and Mean K data values for the IOLMaster 500 and Aladdin.

Parameter (mm)	n	Device	Mean	SD	Paired t-test	Range	ICC
AL	614	IOLMaster 500	22.94	0.82	p<0.001	20.36 to 25.65	0.971
		Aladdin	22.91	0.83		20.33 to 25.64	
K1	388	IOLMaster 500	7.88	0.26	p=0.218	7.11 to 8.50	0.987
		Aladdin	7.89	0.26		7.11 to 8.68	
K2	388	IOLMaster 500	7.72	0.25	p<0.001	7.02 to 8.32	0.979
		Aladdin	7.73	0.25		7.02 to 8.54	
Mean K	388	IOLMaster 500	7.80	0.25	p<0.001	7.09 to 8.36	0.985
		Aladdin	7.81	0.25		7.07 to 8.61	

Table 6.7: Comparisons of values from the IOLMaster 500 and Aladdin in the Child cohort ICC: Intraclass correlation

Although the agreements between the two devices were outstanding regarding AL, K1, K2 and Mean K (mean ICC: 0.981, range 0.971 to 0.987), paired t tests showed statistically significant differences between AL, K2 and Mean K values.

Table 6.8 summarises the mean differences between the two devices. The AL measurements were measured slightly shorter by the Aladdin compared to the

IOLMaster 500 (mean difference -0.03mm, 95% CI -0.39 to 0.33, p<0.001). The Aladdin showed slightly flatter K2 and Mean K measurements which were statistically significant (+0.01mm, 95% CI -0.08 to 0.09, p<0.001 for both).

Parameter	Mean Difference (mm)	SD	95% CI of the differences
AL	-0.03	0.18	-0.39 to 0.33
K1	+0.00	0.04	-0.08 to 0.09
K2	+0.01	0.05	-0.09 to 0.12
Mean K	+0.01	0.04	-0.08 to 0.09

Table 6.8: Mean differences between IOLMaster 500 and Aladdin in the Child cohort Mean difference was calculated by subtracting IOLMaster 500 values from Aladdin values

Bland-Altman plots for comparisons between IOLMaster 500 and Aladdin are shown below in Figure 6.1 to Figure 6.4.

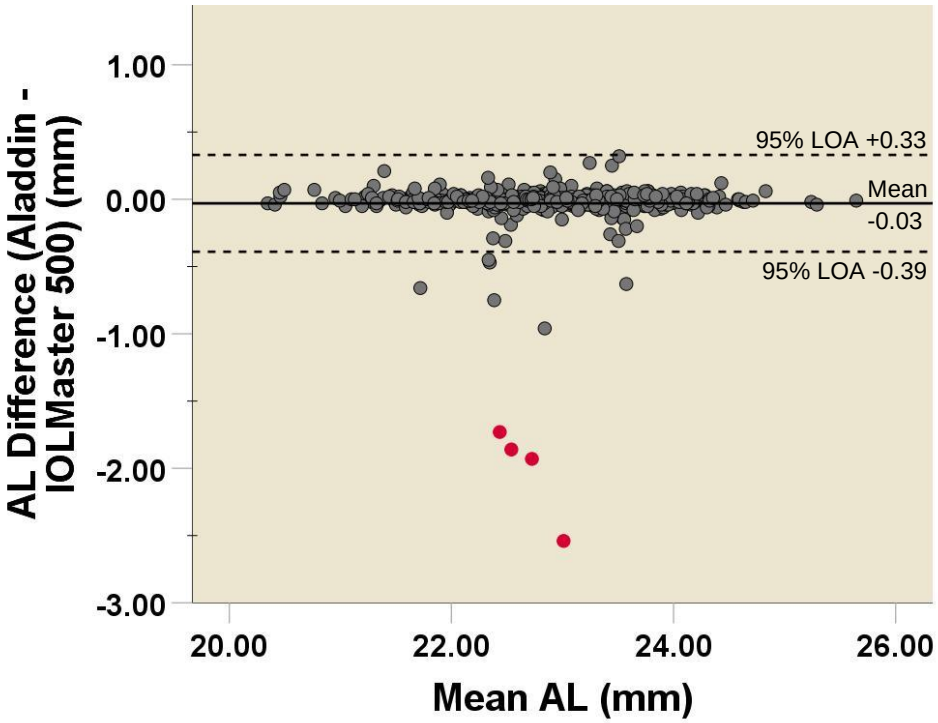


Figure 6.1: Bland-Altman plot for AL comparing Aladdin with IOLMaster 500 in the Child cohort Mean±SD difference: -0.03±0.18 mm. 95% limits of agreement (LOA) were -0.39 to +0.33, indicated by dotted lines. Extreme outliers (≥6SD) shown in red.

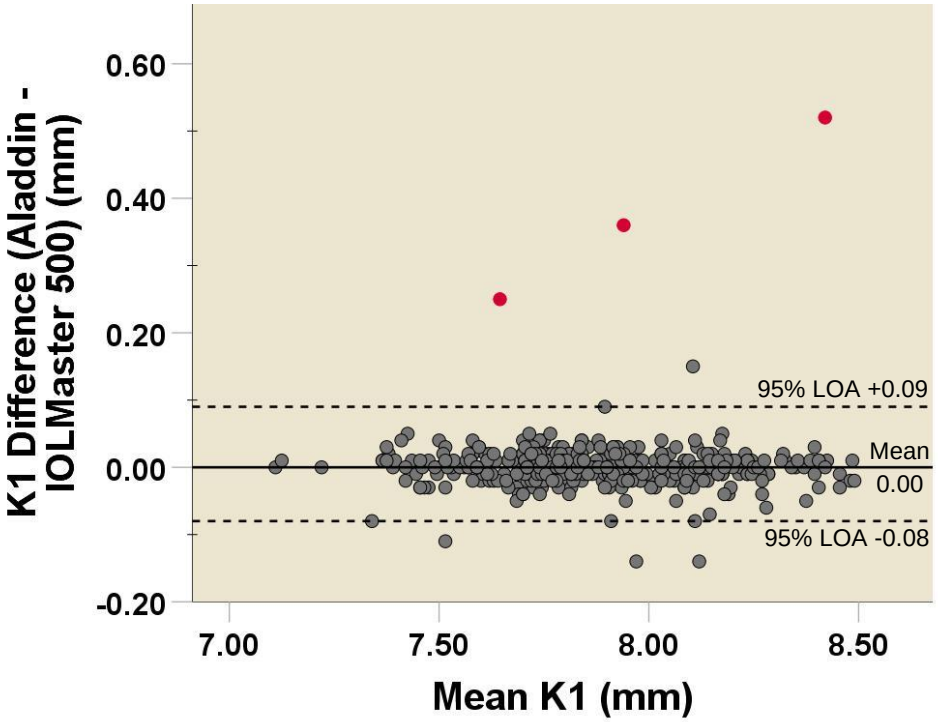


Figure 6.2: Bland-Altman plot for K1 comparing Aladdin with IOLMaster 500 in the Child cohort Mean±SD difference: 0.00±0.04mm. 95% limits of agreement (LOA) were -0.08 to +0.09, indicated by dotted lines. Extreme outliers (≥6SD) shown in red.

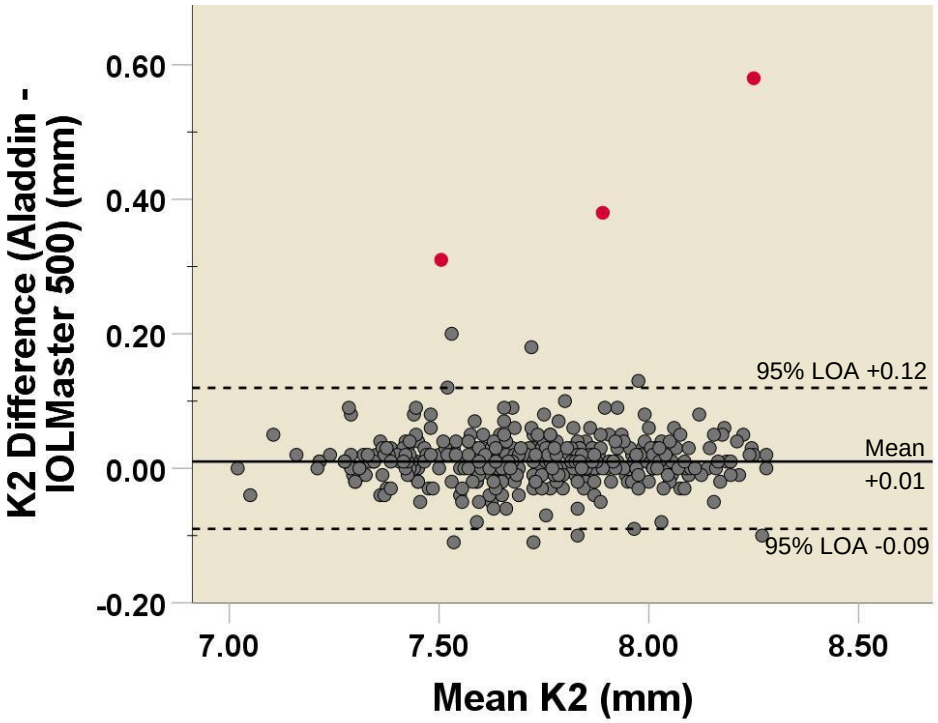


Figure 6.3: Bland-Altman plot for K2 comparing Aladdin with IOLMaster 500 in the Child cohort Mean±SD difference: +0.01±0.05mm 95% limits of agreement (LOA) were -0.09 to +0.12, indicated by dotted lines. Extreme outliers (≥6SD) shown in red.

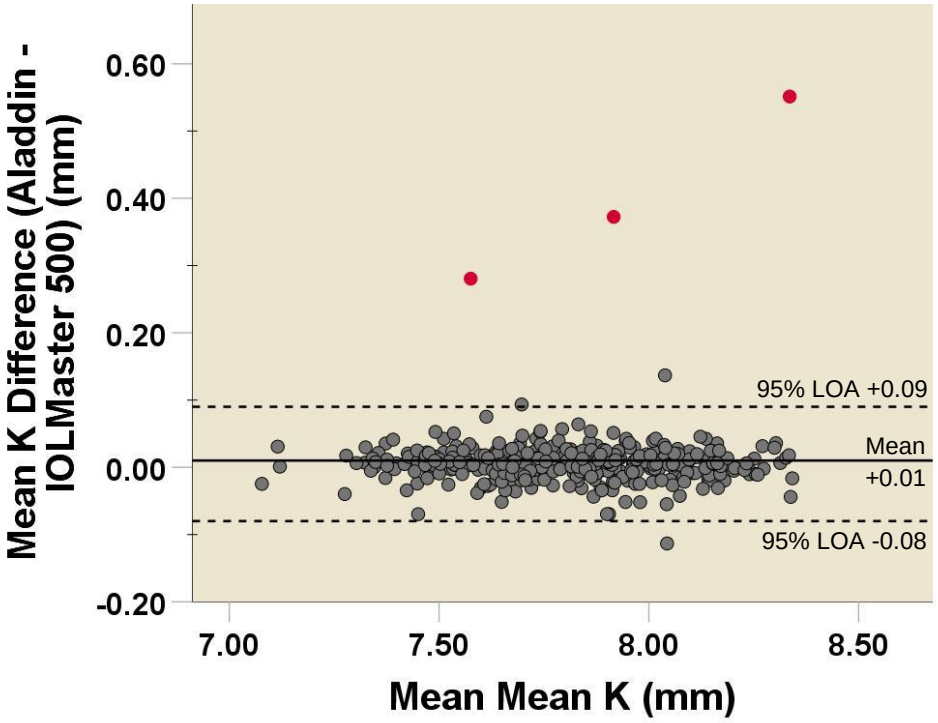


Figure 6.4: Bland-Altman plot for Mean K comparing Aladdin with IOLMaster 500 in the Child cohort Mean±SD difference: +0.01±0.05mm 95% limits of agreement (LOA) were -0.08 to +0.09, indicated by dotted lines. Extreme outliers (≥6SD) shown in red.

Extreme outlier measurements were defined as ≥6SD from the mean difference: 7 outlier measurements were identified and were highlighted in red on the appropriate Bland-Altman: 4 were AL measurements (Figure 6.1) and 3 CR measurements (Figure 6.2-Figure 6.4). These 7 measurements were from 7 different participants. The characteristics of the AL outliers are shown in Table 6.9 and CR outliers in Table 6.10. Outlier participant (n=7) mean±SD age was 9.4±0.8 years and 57.1% were females (n=4). 71.4% (n=5) were RE measurements and 71.4% (n=5) were taken at baseline the remainder at Year 1. All the participants were classified as emmetropes with a mean±SD SER of +0.30±0.30D.

Participant	Eye	Age	IOLMaster 500 (mm)	Aladdin (mm)	Difference (mm)
MA044	RE	10.1	24.28	21.74	-2.54
BP005	RE	10.8	23.69	21.76	-1.93
BP036	RE	8.9	23.47	21.61	-1.86
BP029	RE	8.8	23.30	21.57	-1.73

Table 6.9: Participant and measurement characteristics of AL outliers from comparison of Aladdin and IOLMaster 500 in the Child cohort The difference was calculated by subtracting IOLMaster 500 values from Aladdin values

			IOLMaster 500 (mm)			Aladdin (mm)			Difference (mm)		
Participant	**Eye**	**Age**	**K1**	**K2**	**Mean K**	**K1**	**K2**	**Mean K**	**K1**	**K2**	**Mean K**
ST002	LE	8.8	8.16	7.96	8.06	8.68	8.54	8.61	+0.52	+0.58	+0.55
BP038	LE	9.5	7.76	7.70	7.73	8.12	8.08	8.10	+0.36	+0.38	+0.37
ST001	RE	8.8	7.52	7.35	7.44	7.77	7.66	7.72	+0.25	+0.31	+0.28

Table 6.10: Participant and measurement characteristics of CR outliers from comparison of Aladdin and IOLMaster 500 in the Child cohort The difference was calculated by subtracting IOLMaster 500 values from Aladdin values

Clinical Relevance

Although differences in mean ocular parameter measurements were found between the two devices the assessment of these from a clinical perspective also need to be assessed. The proportion of readings within set boundaries are shown in Table 6.11. For AL measurements, 93.6% of readings were within ±0.10mm. For CR measurements 98.2% of K1, 96.9% of K2 and 98.7% of Mean K were within ±0.10D.

AL (mm)	**% (n)**	**K1 (mm)**	**% (n)**	**K2 (mm)**	**% (n)**	**Mean K (mm)**	**% (n)**
No difference	13.2 (81)	No difference	19.6 (76)	No difference	15.7 (61)	No difference	20.1 (78)
<0.05	80.3 (493)	<0.1	98.2 (381)	<0.1	96.9 (376)	<0.1	98.7 (383)
<0.10	93.6 (575)	<0.2	99.2 (385)	<0.2	99.0 (384)	<0.2	99.2 (385)
<0.50	98.7 (606)	<0.3	99.5 (386)	<0.3	99.2 (387)	<0.3	99.5 (386)
<1.0	99.3 (610)	<0.4	99.7 (387)	<0.4	99.7 (387)	<0.4	99.7 (387)
<2.0	99.8 (613)	<0.6	100.0 (388)	<0.6	100.0 (388)	<0.6	100.0 (388)
<3.0	100.0 (614)						

Table 6.11: Clinical relevance of differences in measurements between IOLMaster 500 and Aladdin in the Child cohort

6.3.2.2 Young Adult Cohort

For AL 370 eyes from 87 participants were included, for AC 353 eyes from 86 participants and for CR (K1, K2 and Mean K) 355 eyes from 87 participants. Table 6.7 summarises the ocular parameter values for the IOLMaster 500 and Aladdin.

Parameter (mm)	n	Device	Mean	SD	Paired t-test	Range	ICC
AL	370	IOLMaster 500	24.12	1.44	p <0.001	20.09 to 27.74	1.00
		Aladdin	24.09	1.44		20.07 to 27.70	
AC	353	IOLMaster 500	3.69	0.27	p <0.001	3.07 to 4.45	0.973
		Aladdin	3.77	0.27		3.15 to 4.46	
K1	355	IOLMaster 500	7.90	0.29	p=0.395	7.33 to 9.35	0.997
		Aladdin	7.90	0.29		7.33 to 9.33	
K2	355	IOLMaster 500	7.71	0.29	p <0.001	6.97 to 9.28	0.994
		Aladdin	7.72	0.29		6.93 to 9.28	
Mean K	355	IOLMaster 500	7.81	0.29	p=0.004	7.27 to 9.32	0.997
		Aladdin	7.81	0.28		7.25 to 9.29	

Table 6.12: Comparisons of values from the IOLMaster 500 and Aladdin in the Young Adult cohort ICC: Intraclass correlation

Although the agreements between the two devices were outstanding (mean ICC: 0.992, range 0.973 to 1.00), paired t tests showed statistically significant differences between AL, AC, K2 and Mean K values. Table 6.13 summarises the differences between the devices.

Parameter	Mean Difference (mm)	SD	95% CI of the differences
AL	-0.02	0.04	-0.10 to 0.05
AC	+0.09	0.06	-0.03 to 0.22
K1	+0.00	0.02	-0.05 to 0.05
K2	+0.01	0.03	-0.05 to 0.08
Mean K	+0.00	0.02	-0.05 to 0.05

Table 6.13: Mean differences between IOLMaster 500 and Aladdin in the Young Adult cohort Mean difference was calculated by subtracting IOLMaster 500 values from Aladdin values

AL measurements were measured slightly shorter by the Aladdin compared to the IOLMaster 500 (mean difference -0.02mm, 95%CI -0.10 to 0.05, p<0.001). The Aladdin showed deeper AC measurements (mean difference +0.09mm, 95% CI -0.03 to 0.22, p<0.001). The Aladdin showed slightly flatter K2 and Mean K measurements which were statistically significant (p<0.001). Bland-Altman plots for comparisons between IOLMaster 500 and Aladdin are shown below in Figure 6.5 to Figure 6.9.

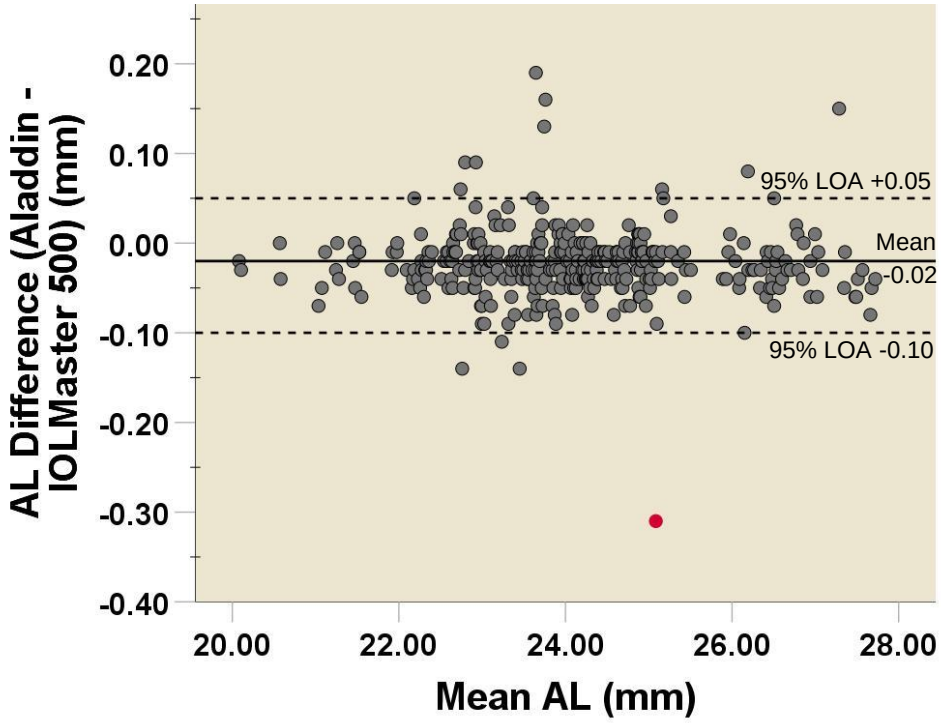


Figure 6.5: Bland-Altman plot for AL comparing Aladdin with IOLMaster 500 in the Young Adult cohort Mean±SD difference:-0.02±0.04mm. 95% limits of agreement were -0.10 to +0.05, indicated by dotted lines. Extreme outliers (≥6SD) shown in red.

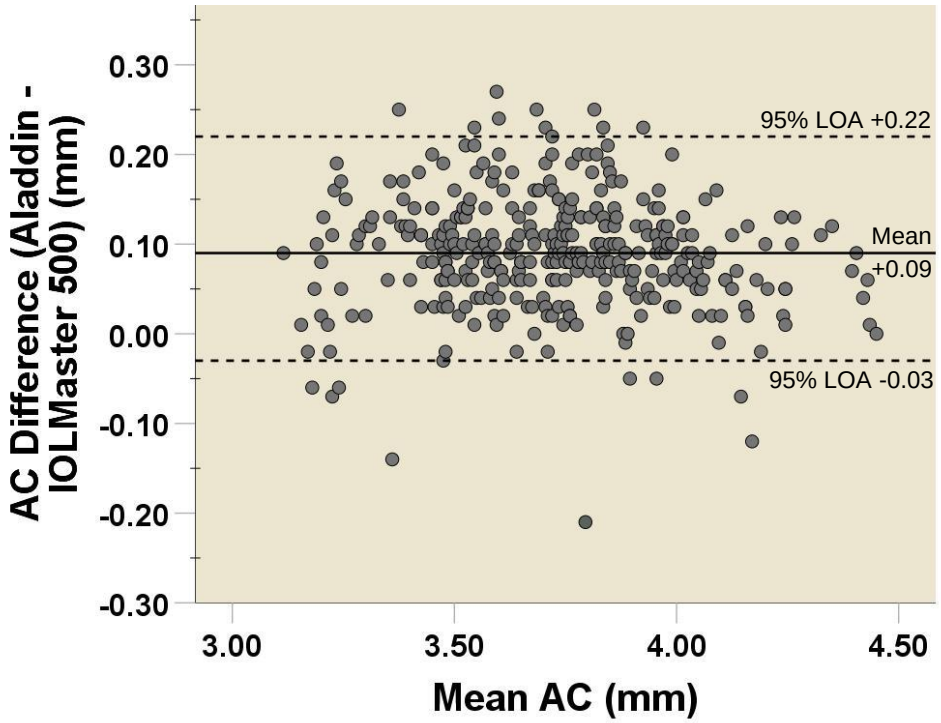


Figure 6.6: Bland-Altman plot for AC comparing Aladdin with IOLMaster 500 in the Young Adult cohort Mean±SD difference: +0.09±0.06mm. 95% limits of agreement were -0.03 to +0.22, indicated by dotted lines.

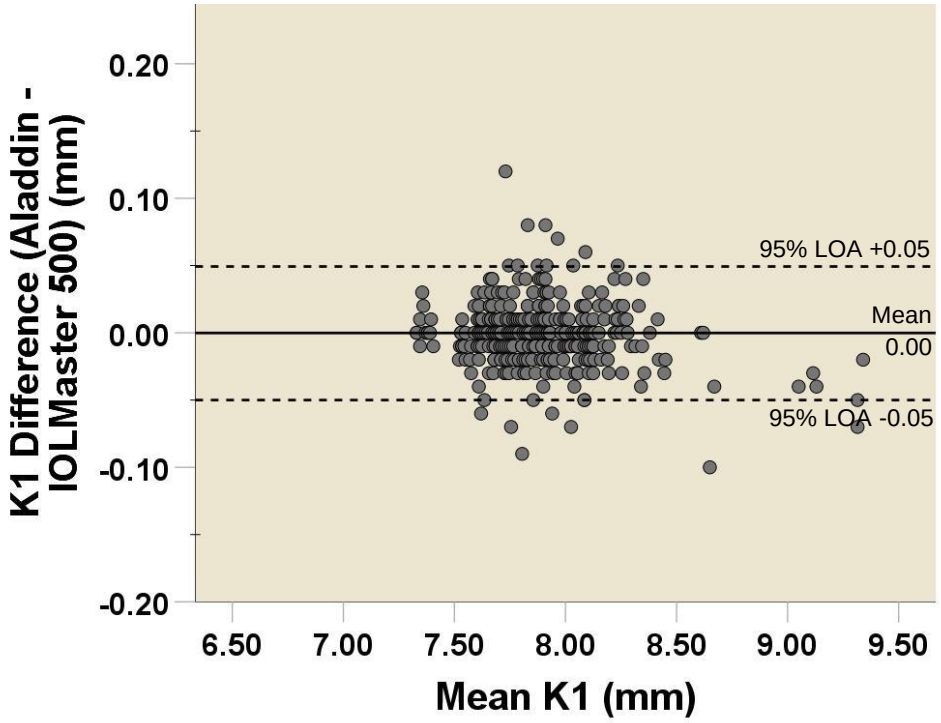


Figure 6.7: Bland-Altman plot for K1 comparing Aladdin with IOLMaster 500 in the Young Adult cohort Mean±SD difference: 0.00±0.02mm. 95% limits of agreement were -0.05 to +0.05, indicated by dotted lines.

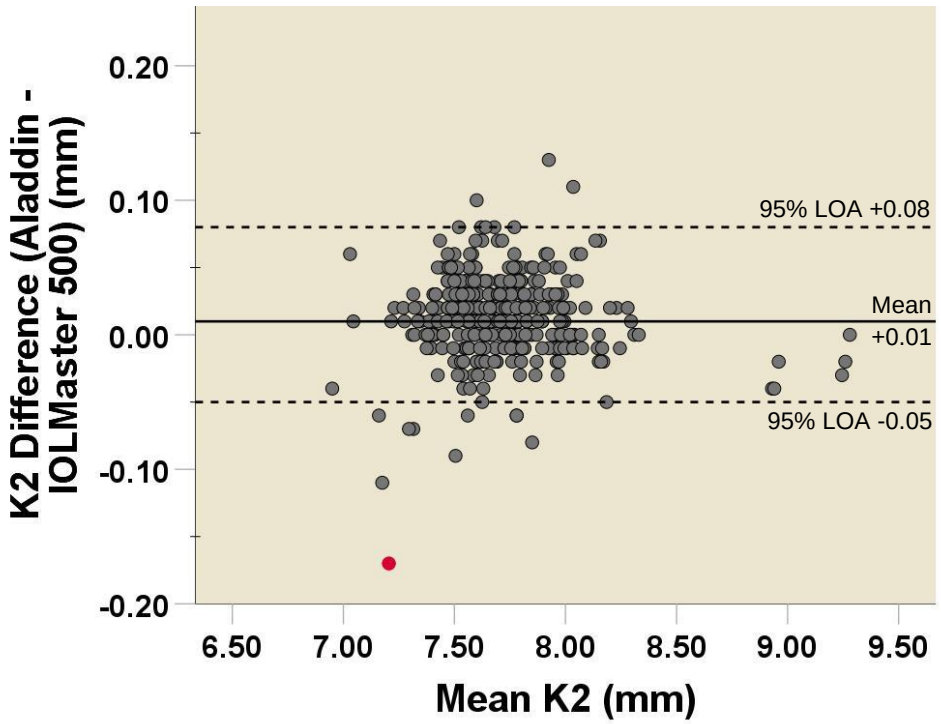


Figure 6.8: Bland-Altman plot for K2 comparing Aladdin with IOLMaster 500 in the Young Adult cohort Mean±SD difference:+0.01±0.03mm. 95% limits of agreement were -0.05 to +0.08, indicated by dotted lines. Extreme outliers (≥6SD) shown in red.

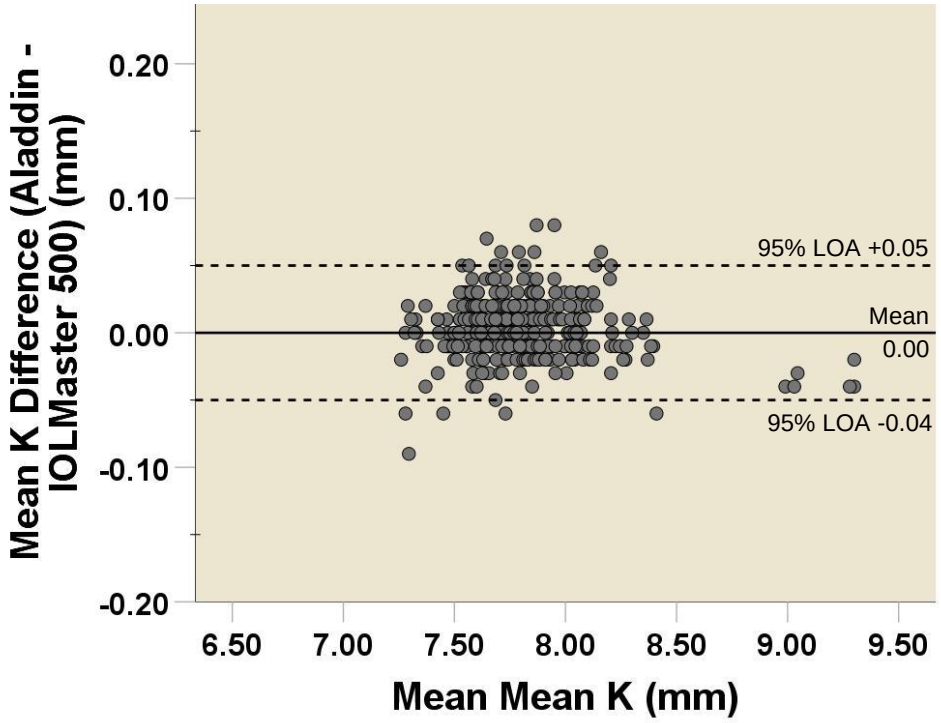


Figure 6.9: Bland-Altman plot for Mean K comparing Aladdin with IOLMaster 500 in the Young Adult cohort Mean±SD difference: 0.00±0.02mm. 95% limits of agreement were -0.04 to +0.05, indicated by dotted lines.

Extreme outlier measurements were defined as ≥6SD from the mean difference: 2 outlier measurements were identified and highlighted in red on the appropriate Bland-Altman plot: 1 was a AL measurement (Figure 6.5) and 1 K2 measurement (Figure 6.8). These 2 measurements were from 2 different participants. The characteristics of these outliers are shown in Table 6.14. Both outliers were taken at different stages of data collection (Year 1 (n=1) and Year 2 (n=2)). One outlier was classified as an emmetrope and the other a myope.

Participant	Eye	Sex	Age	Parameter	IOLMaster 500 (mm)	Aladdin (mm)	Difference (mm)
YA032	RE	Male	20.8	AL	25.24	24.93	-0.31
YA036	LE	Female	20.3	K2	7.29	7.12	-0.17

Table 6.14: Participant and measurement characteristics of outliers from comparison of Aladdin and IOLMaster 500 in the Young Adult cohort The difference was calculated by subtracting IOLMaster 500 values from Aladdin values

It should also be mentioned that participant YA059 from the Young Adult cohort was excluded due to aberrant biometry measurements recorded by the Aladdin. RE AL measured 15.75mm and 27.10mm on the IOLMaster 500 and Aladdin respectively and

their LE AL measured 15.67mm and 27.07mm respectively. This consistent abnormality persisted despite repeat measures on different days. This is within the AL range for the Aladdin outlined in the manual (15.0mm – 38.0mm) which is just slightly less than that of the IOLMaster 500 (14.0 – 38.0mm). The manufacturers were informed of this aberrant result, but no response has been received yet.

Clinical relevance

Assessment of clinical relevance and demonstration of the proportion of readings within set boundaries is shown in Table 6.15. For AL measurements, 97.6% of readings were within ±0.10mm and for AC 51.3% were within ±0.10mm. For CR measurements 99.4% of K1, 98.6% of K2 and 100.0% of Mean K were within ±0.10D.

AL (mm)	% (n)	AC (mm)	% (n)	K1 (mm)	% (n)	K2 (mm)	% (n)	Mean K (mm)	% (n)
No difference	7.0 (26)	No difference	1.1 (4)	No difference	23.1 (82)	No difference	13.0 (46)	No difference	16.6 (59)
<0.05	77.0 (285)	<0.02	4.0 (14)	<0.1	99.4 (353)	<0.1	98.6 (350)	<0.1	100.0 (355)
<0.10	97.6 (361)	<0.1	51.3 (181)	<0.2	100.0 (355)	<0.2	100.0 (355)		
<0.20	99.7 (369)	<0.2	94.1 (332)						
<0.40	100.0 (370)	<0.3	100.0 (353)						

Table 6.15: Clinical relevance of differences in measurements between IOLMaster 500 and Aladdin in the Young Adult cohort

6.4 Discussion

In this study, the Aladdin and IOLMaster 500 provided similar measurements although the agreement was not perfect and some differences, namely AC, did not allow the devices to be considered interchangeable. The results were similar across both the Child and Young Adult cohort.

This is the only published data on the comparison of the ocular parameter measurements between these devices in a Child and Young Adult study. Previously the literature has been centred around assessing the agreement in older populations with cataracts. These studies are summarised in Table 6.16 alongside the results of this study.

Study	n	Cohort age (years)	Cohort type	Mean AL difference (mm)	Mean AC difference (mm)	Mean K difference (D)
This study	226	9.6±1.2	Healthy	**-0.03±0.18* p<0.001**	NA	**-0.04* p<0.001**
	87	19.9±1.3		**-0.02±0.04* p<0.001**	**+0.09±0.06* p<0.001**	**0.00* p<0.001**
Mandal et al (2014)	97	74.9±8.5	Cataracts & Healthy	+0.01±0.06 p=0.0695	0.00±0.11 p=0.874	-0.08±0.51 p=0.354
Hoffer et al (2016)	60	75±10	Cataracts	+0.01 p=0.770	**+0.16* p<0.001**	**-0.14* p<0.001**
	56	26±3	Healthy	-0.01 p=0.062	**+0.05* p<0.001**	**-0.14* p<0.001**
Ortiz et al (2018)	231	67.9±13.0	Cataracts	**+0.04* p=0.03**	+0.10 p>0.05	+0.10 p>0.05
Sabatino et al (2016)	215	70.5 (IQR 15.8)	Cataracts	**+0.005* p<0.05**	**+0.02* p<0.05**	**-0.08* p<0.05**

Table 6.16: Comparison studies of IOLMaster 500 vs Aladdin Mean difference defined as IOLMaster 500 values subtracted from Aladdin values. For the purposes of comparison with the literature mean K difference measurements from this study are displayed as dioptres following conversion from millimetres.

Regarding AL measurement, an excellent correlation was found between the IOLMaster 500 and Aladdin in the Young Adult cohort with an ICC value of 1. This correlation was slightly less in the Child cohort of 0.971 but still high. For both cohorts the Aladdin measured slightly shorter AL measurements. This difference was found to be statistically significant ($p<0.001$ in both), although this difference was within the calibration tolerances of the IOLMaster 500 (±0.05mm) and therefore deemed clinically insignificant. Previous studies have also found a significant difference between the biometers for AL measurement, however with opposing findings of the Aladdin measuring slighter longer than the IOLMaster (Ortiz et al., 2018, Sabatino et al., 2016). Both studies did find a good correlation between the measurements and, similarly to this study, have concluded that these differences were clinically insignificant. The opposing findings of these studies could be related to the different lens densities sampled in each cohort, as in this study no participants had cataracts.

AC comparison was only available for the Young Adult cohort and showed that Aladdin measurements were well correlated (ICC: 0.973) with IOLMaster 500. However, when comparing the mean difference, the Aladdin was found to measure deeper than the IOLMaster 500. These findings are in agreement with those previously reported (Hoffer

et al., 2016, Sabatino et al., 2016). Although the mean difference was found to be small for clinical significance, they were statistically significant ($p<0.001$) and outside the calibration tolerances of the IOLMaster 500 (±0.02mm). Only 4.0% of Aladdin values were within the calibration tolerances. This discrepancy is likely a result of the different AC measurement methods. The IOLMaster 500 measures AC by using an optic section with illumination at 30 degrees temporal. Whereas the Aladdin measures on axis using OLCI. Both the Lenstar and AL-scan, which uses a similar OLCI technique, gives mean higher AC than the IOLMaster 500 (Huang et al., 2014b, Ortiz et al., 2018). Arguably axial AC measurements are a more accurate representation of the actual AC depth.

Similarly to the other ocular parameters all K values (K1, K2 and mean K) showed a good correlation to the IOLMaster 500 in both cohorts and all mean differences were within the calibration tolerances of the IOLMaster 500 (±0.03mm). These differences were not felt to be clinically significant with 98.6% of all K readings within ±0.10mm. Both mean K and K2 values were found to be statistically significantly flatter in both cohorts which agrees with previously published studies (Hoffer et al., 2016, Sabatino et al., 2016, Mandal et al., 2014). The difference can again be derived from the method of measurement. The IOLMaster 500 measures a smaller corneal diameter (2.3mm) compared to the Aladdin (3.0mm (extrapolated from 9.8mm). The majority of corneas have a prolate shape (Nieto-Bona et al., 2009) indicating that they are steeper in the centre. Therefore, as the Aladdin is measuring a large diameter it is likely to record a flatter K value.

The data acquisition ability for both biometers was high, however the IOLMaster 500 was found to have a significantly higher acquisition ability (93.88% vs 85.48%, $p<0.001$). The Aladdin had a higher measurement failure rate compared to the IOLMaster 500 (11.50% vs 6.12%). All IOLMaster 500 readings were deemed consistent however for the Aladdin only 96.45% of readings were deemed consistent. The discrepancy is likely a result of the method of inaccurate measurement identification between the two systems. The IOLMaster 500 has the ability to provide each reading with a SNR. As a result, these readings were easily able to be excluded, and following our methodology, allowed a minimum of 3 readings to remain in order for the measurement to be deemed accurate. For the Aladdin if an error occurs during the data acquisition process such as movement or blinking than the parameter as a whole is flagged as inconsistent. As a result, inconsistent measurements could not be removed on an individual basis as with the IOLMaster 500. For some participants consistent measurements were not able to be recorded despite repeated attempts, this was the case in both cohorts. This could have contributed to a lower data acquisition ability compared to the IOLMaster 500 for

all parameters. As expected, an overall pattern of increased failed/inconsistent measurement failures in the Child cohort compared to the Young Adult cohort was evident for both devices and all parameters. Based on the odds ratio, the odds of a failed/inconsistent measurement was 4.92 times higher in the Child cohort than the Young Adult cohort. This was likely a result of reduced compliance in the younger cohort.

Another factor to consider when comparing the data acquisition ability of these biometers in this study is the potential methodological implication of a consistently consecutive order of devices. In this study the IOLMaster 500 was performed first followed by the Aladdin in all cases. This protocol was chosen as the IOLMaster 500 is considered the gold standard and therefore data acquisition with this device was deemed a priority. Due to the field based nature of the study there were limitations that arose with regard to study space which would have made randomisation of the devices challenging. In addition, the majority of data acquisition was performed by a single practitioner (KF) and this would have meant that masking would not have been possible. The validity and agreement between the IOLMaster 500 and Aladdin was not a primary objective of this study and in light of the objective non-contact nature of the devices and rapid measurement capability it was not felt that the order of biometers would have an influence on the data acquisition. Therefore, in the interest of consistency for primary analyses this methodological approach was used. The data acquisition ability in the Young Adult was consistent and not statistically different between the devices (IOLMaster 500: 97.95% vs Aladdin: 98.04%, $p=0.880$). However, a significantly reduced data acquisition ability was found with the Aladdin in the Child cohort compared to the IOLMaster 500 (IOLMaster 500: 90.67% vs Aladdin: 75.60%, $p<0.001$). The order of device usage could have contributed to a reduced data acquisition of the Aladdin in this cohort as a result of fatigue and compliance of the participants due to the cohort age. Although it was not objectively measured in this study, the speed of data measurements with the IOLMaster 500 were felt to be quicker and more consistent requiring less than the Aladdin.

Data acquisition did improve over time, more so with the Aladdin improving by 12.22% from Baseline to Year 2 compared to 3.24% with the IOLMaster 500, which was more consistent to start with. The increase in data acquisition ability was relatively stable between each stage for both devices. Data acquisition was performed by two practitioners (KF and NL) so single practitioner use could not be accountable for this increase. Practitioner NL had extensive experience with the IOLMaster 500 but comparatively less experience with the Aladdin whilst practitioner KF had equal

experience with both devices at the start of data acquisition at baseline. Practitioner KF performed the majority of the data collection and so increased practitioner experience is assumed to be equal across both devices. A more influential factor is likely participant age which naturally increased over the study period alongside device familiarity. These factors likely contributed to an increased compliance, most prominently, in the Child cohort. Furthermore, for logistical reasons the Child cohort were sampled in groups, as opposed to a one-to-one basis in the Young Adult cohort. As a result of decreasing participant numbers as the study progressed from Baseline to Year 2, the group sizes were smaller which could have reduced the number of distractions and ultimately improved compliance and consequently data acquisition ability.

6.5 Conclusions

In conclusion, the Aladdin and IOLMaster 500 provided well correlated and provided similar results for AL and CR measurements. The differences in AL and CR appear to be negligible and clinically insignificant with the mean difference falling within the recognised calibration tolerances of the IOLMaster 500. However, the difference in AC should not be overlooked. The data acquisition ability was consistent in the Young Adult cohort for both devices however in the Child cohort the Aladdin acquisition ability was significantly reduced compared to the IOLMaster 500.

It should also be highlighted that the Aladdin has the addition advantageous features of LT, CCT and corneal topography measurement. The use of these supplementary parameters in the design and fitting of contact lens makes it a useful clinical tool for those implementing myopia control strategies such as Orthokeratology as well as monitoring its efficacy.

6.6 Summary

- Data acquisition ability was higher in the IOLMaster 500 compared to the Aladdin
- Cohort age had a marked effect on data acquisition ability
- AL, AC and CR measurements were well correlated between the devices
- Differences in AL and CR readings were considered to be clinically negligible. However AC measurements with the Aladdin were found to be significantly deeper than the IOLMaster 500
- Agreement increased in the older cohort suggesting better accuracy with increased age

Chapter 7: The effects of environment and lifestyle on eye growth

7.1 Introduction

With an increasing prevalence of myopia worldwide, over the past few decades both epidemiological and animal studies have attempted to shed light on the potential environmental and lifestyle factors that could be at play. These factors include the amount of time spent outdoors, near work, educational attainment, urbanisation, socioeconomic status, parental myopia, parental occupation, sleep patterns and diet and are discussed in detail in Chapter 2. It is widely accepted that the development of refractive error, more specifically myopia, is multifactorial in nature. In addition, to environment and lifestyle factors, a strong case for a genetic contribution has been found. Parental myopia has been shown to have a significant impact on the likelihood of myopia in their children. It has been shown that the risk of a child developing myopia when both parents are myopic is 42%. This reduces to 22.5% with one myopic parent and only 8% when neither parent in myopic (Gwiazda et al., 1993a). The introduction of new technologies such as smartphones and tablets have changed our visual landscape and increased the duration of near tasks (McCrann et al., 2020).

Several epidemiological studies have used questionnaires to identify risk factors associated with myopia including Avon Longitudinal Study of Parents and Children (ALSPAC) (Guggenheim et al., 2012), Orinda Longitudinal Study of Myopia (OLSM) and the follow up Collaborative Longitudinal Evaluation of Ethnicity and Race (CLEERE) study (Mutti et al., 2002, Jones et al., 2007), Northern Ireland Childhood Errors of Refraction Study (NICER) (O'Donoghue et al., 2015), Sydney Myopia Study (SMS) and the follow up Sydney Adolescent Vascular and Eye Study (SAVES) (French et al., 2013b) and Singapore Cohort Study of the Risk Factors for Myopia (SCORM) (Saw et al., 2002b). Despite the extensive amount of research on a wide variety of environmental and lifestyle factors, there is conflicting evidence on the key contributory factors, see Chapter 2.

7.2 Rationale

This Chapter is designed to investigate self-reported and parental reported questionnaire responses related to environmental and lifestyle behaviours among children aged 7-12 years and young adults aged 18-25 years in a UK population to determine whether any associations exist with eye growth. In particular, amount of time

spent outdoors and performing near and VDU tasks will be explored as well as investigation of the patterns of these behaviours to determine any seasonal or day of the week differences. Alongside this other factors such as rural/urban residence, school performance, school achievement, BMI, birth weight and gestation and their potential influence on eye growth will be explored. The role of familial factors such as parental myopia will be also evaluated. This Chapter aims to provide a comprehensive analysis of environmental and lifestyle factors and their influence on eye growth using subjective responses.

7.3 Methodology

7.3.1 Questionnaire design

A key component of this study is the use of questionnaires to elicit potential myopiagenic risk factors. The format and content was based on questionnaires used in the CHASE study (Rudnicka et al., 2010), Sydney Myopia Study (Ojaimi et al., 2005c) and Aston Eye Study (Logan et al., 2011).

The questionnaire designs are outlined in detail in Section 5.4. In summary, three questionnaires were designed, one for completion by the participants aged 7 – 12 years, one for completion by their parent/guardian and one for completion by the participants aged 18 – 25 years, see Appendix A.5.5. All questionnaires consisted of 5 sections: About you (or your child in the parent/guardian questionnaire), Ocular History, Your Activities (Your Child's Activities in the parent/guardian questionnaire), Diet and Parent Details. Both the parental/guardian questionnaire and young adult questionnaire were longer, 38 and 39 questions respectively however the child's questionnaire was adapted and consisted of 22 questions. The additional questions asked in these questionnaires included ethnicity, birth weight and levels of parental education.

7.3.2 Questionnaire response rates

Questionnaires for all participants aged 7 – 12 years (n=226) and 18 – 25 years (n=87) were completed on the day of the study (response rate 100%). The parent/guardian questionnaires, for the Child cohort only, were distributed as hard copies on completion of the study. A section for contact details for parent/guardians was provided on the consent form completed at the start of the study, this allowed follow up contact to be established if the questionnaire was not returned. 4-6 weeks following distribution all parent/guardians were sent a reminder via text message or e-mail to return the hard copy to the school office. They were also offered the option to complete the questionnaire electronically via a weblink. Extensive steps were taken in the design of

the electronic form such that it has the same appearance, content and layout of the hard copy to ensure no discrepancies between hard copy and electronic completion. Following the 4-6 week reminder all outstanding questionnaires were followed up via a phone call to the remaining parents to complete the questionnaire over the phone.

Parental questionnaire response rate was high at 83.2% (n=188/226). The parental questionnaire responses per school can be found in Table 7.1.

School	Participants (n)	Parent questionnaires returned (n)	%
MA	51	38	74.5
GP	38	34	89.5
AB	21	17	81.0
ST	35	35	100.0
BP	56	40	71.4
PG	10	10	100.0
PH	15	14	93.3
Total	**226**	**188**	**83.2**

Table 7.1: Parental questionnaire response rates

Due to the good parental response rate and the consideration of likely inaccurate responses due to young age of the Child cohort (7 – 12 years), only parental questionnaire responses were analysed in this chapter. This also gave the added detail of more in depth seasonal and day of the week responses of time outdoors and daily tasks such as near tasks from the parental questionnaires.

7.3.3 Biometry assessment

Two biometers were used for axial length (AL) measurement in this study: IOLMaster 500 (Carl Zeiss, Jena, Germany) and Aladdin (HW3.0, Topcon, Tokyo, Japan). AL data from the Aladdin biometer will be presented in this chapter due to the good agreement with the IOLMaster 500, see Chapter 6. An assessment of right eye (RE) and left eye (LE) biometric correlations at baseline, in Sections 5.5.1.3.1 and 5.5.2.3.1, found a highly significant strong correlation in both cohorts (Child cohort: average R^2=0.897, r=0.947 all p<0.001; Young Adult cohort: average R^2=0.957, r=0.978, all p<0.001). Therefore, only data from RE data is presented in this chapter. The only exception, participant YA016 in the Young Adult cohort for whom LE data is reported as between Baseline and Year 1 follow up they experienced a RE retinal tear which was treated with a scleral buckle, thus excluding RE data from the analysis.

Details of the technical specifications and biometric measurement acquisition method can be found in Section 4.3. AL measurements were undertaken at 2 time points: Baseline (0 months) and Year 1 (12 months), allowing longitudinal changes in AL and therefore eye growth to be calculated. Year 1 eye growth data was available for 32.7% (n=74/226) in the Child cohort and 67.8% (n=59/87) in the Young Adult cohort examined at baseline.

7.3.4 Socioeconomic status

For participants in the Child cohort only, an assessment of socioeconomic status was undertaken using the Index of Multiple Deprivation (IMD) for those residing in England and the Scottish Index of Multiple Deprivation (SIMD), the Scottish equivalent. The IMD and SIMD are official measures of relative deprivation for small areas in England and Scotland calculated by their equivalent government bodies. The most up to date IMD was undertaken in 2019 and SIMD in 2016. IMD/SIMD are comprised of information from seven domains which are combined to provide an overall relative measure of deprivation. These 7 domains can be seen in Figure 7.1.

Figure 7.1: Seven Domains that contribute the Index of Multiple Deprivation in England and Scotland

To allow equal comparison of IMD and SIMD scores across the respective countries, they were subdivided into smaller areas. In England, these areas are called Lower-Layer Super Output Areas (LSOA) and in Scotland are called Data Zones (DZ). LSOAs are larger in population than DZ, maximum 3,000 population compared to maximum 1,000 population however taking into account the geographical size variation between England and Scotland they were considered comparative. Therefore, from this point forward LSOA and DZ will be collectively called small areas

For each of these small areas an overall IMD/SIMD score is calculated using information about the seven domains shown in Figure 7.1. Using the IMD/SIMD scores the small areas are ranked from most to least deprived. To allow comparison between different small areas, they are divided into 10 equal groups to provide a deprivation decile, shown

in Figure 7.2. As the sample size in the Child cohort was relatively small (n=226) these deciles were further categorised into quintiles to allow a better comparison between socioeconomic status, see Figure 7.2. This a similar method used in the NICER study for classification of socioeconomic status in UK children (O'Donoghue et al., 2015).

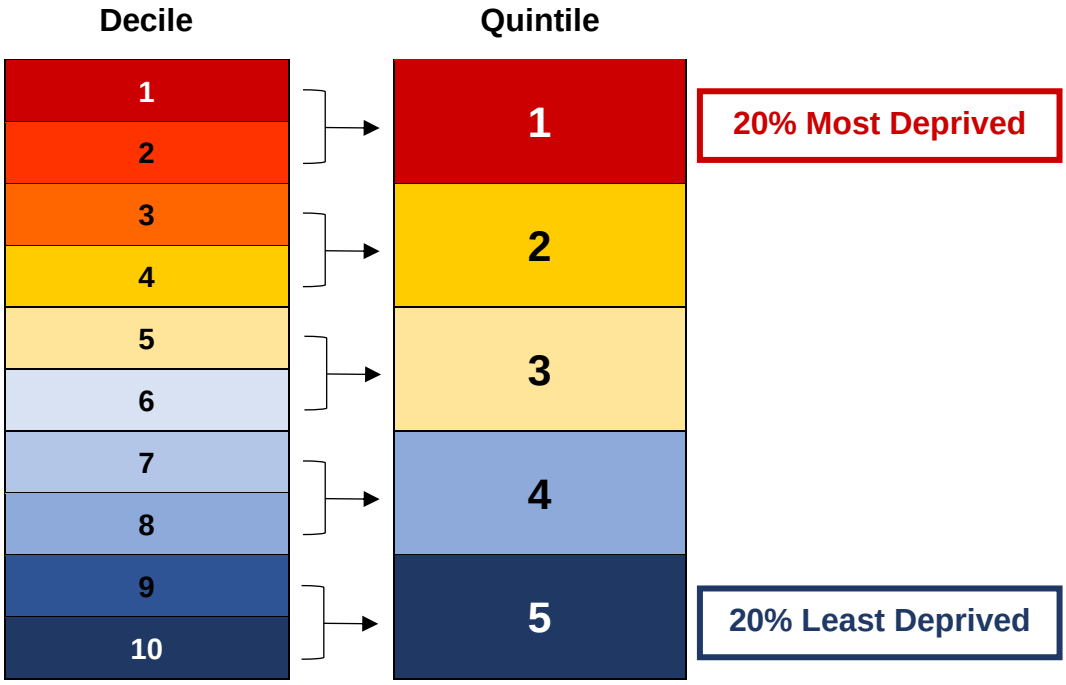


Figure 7.2: Indices of Multiple Deprivation deciles and quintiles

Each parent/guardian was asked to provide a residential postcode, this was completed by 97.3% (n=220/226). These postcodes were then inputted into the English government website run by the Ministry of Housing, Communities and Local Government to provide the IMD data (Ministry of Housing Communities and Local Government, 2019). All Scottish postcodes were inputted into a dedicated website run by the Scottish Government website for SIMD data (Scottish Government, 2016).

7.3.5 Rural/Urban residence

In the Child cohort only, classification of participants as residing in rural or urban environments was done through assessment of the population density as defined by their residential postcode. This was available for 97.3% of participants (n=220/226). Population density is defined as the number of persons per hectare. Population density data for postcode was available from the Office for National Statistics website for England (Office for National Statistics, 2019a) and National Records of Scotland census website for Scotland (National Records of Scotland, 2019). Using these data individuals were broadly classified as living in a rural area if the population density <10 persons per

hectare and urban ≥ 10 persons per hectare. This is the same classification used in other similar myopia studies, for example the NICER study (O'Donoghue et al., 2010c).

As all participants in the Young Adult study were university students from the centre of Birmingham, they were all classified as having an urban residence as the majority lived on campus and spent the majority of their time on campus which is based in the city centre.

7.3.6 Body Mass Index (BMI)

In the Young Adult study, Body Mass Index (BMI) was calculated using the universally recognised formula, shown below:

$$\text{BMI} = \frac{\text{weight (kg)}}{\text{height}^2 \text{ (m)}}$$

BMI attempts to quantify an individual's tissue mass and is used to categorise individuals as underweight, normal weight, overweight or obese. The World Health Organization (WHO) and National Institute for Health and Clinical Excellence (NICE) have defined the cuts offs for each category which can be seen in Table 7.2 (World Health Organization, 1995, NICE, 2014).

BMI value	Category
< 18.5	Underweight
18.5 – 24.9	Healthy weight
25.0 – 29.9	Overweight
≥ 30	Obese

Table 7.2: Adult Body Mass Index (BMI) categories and cut off values

There are a number of recognised limitations with using BMI as a measure of adiposity or body fat levels. Most notably it doesn't take into account age or sex (Nuttal, 2015). Although BMI is widely used in research and by healthcare practitioners for adults, it is not suitable for those under 18 years of age. This is because a child's height and weight changes at different amounts and rates depending on their age and sex. As a result, fixed thresholds such as those used for adults cannot be accurately applied to participants in the Child cohort. Instead of fixed thresholds, variable thresholds are used which are based on age and sex. Therefore, instead of discrete categories as for adult values, children BMI thresholds are defined in percentiles, see Table 7.3. For this study the percentiles were calculated by using an online BMI calculator powered by the NHS

(NHS, 2015). Using the percentile, the child's BMI category was established, see Table 7.3.

Percentile	Category
≤ 2nd	Underweight
3rd – 90th	Healthy weight
91st – 97th	Overweight
≥ 98th	Obese

Table 7.3: Child Body Mass Index (BMI) categories and cut off percentile values

7.3.7 Birth weight and gestation

Questions regarding birth weight and gestation were asked on the Parental Questionnaire (Q5 and 6) and on the Young Adult participant Questionnaire (Q5 and 6), see Appendix A.5.5. Birth weight can be recorded in metric units e.g. kilograms (kg) or imperial units e.g. pounds (lb) and ounces (oz), therefore both of these options were available on the questionnaire for completion, see Figure 7.3.

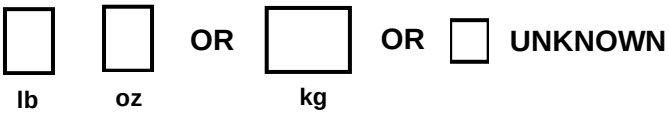


Figure 7.3: Birth weight questionnaire response options

However, for consistency all imperial units (lbs and ozs) were converted to metric units (kgs) to allow a linear scale. First lb and oz responses were converted to lbs using the conversion that 1oz = 0.0625lb. Following this lbs were converted to kgs using the conversion 1lb = 0.45359kg.

Gestation/time of birth is typically defined in terms of the number of completed weeks. The categories used in this questionnaire were Late (42 weeks or more), On time (37-41 weeks), Early (32-36 weeks), Very Early (31 weeks or less) or Not known, see Figure 7.4. These categories are widely used in Obstetrics (Quinn et al., 2016).

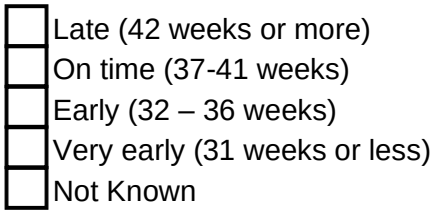


Figure 7.4: Gestation/time of birth questionnaire response options

7.3.8 School achievement

For the Child cohort only, school achievement was assessed. In England, National Curriculum Assessments (or SATs) are undertaken at the age 10 – 11 years of age. SATs in Maths, Reading and Spelling/Punctuation/Grammar are undertaken. For each of these tests the raw test scores are converted to scaled scores to ensure accurate comparison of performance over time i.e. between years. Scaled scores range from 80 – 120. In Scotland, national standardised assessments were only recently introduced in 2017 so currently no scoring is available. Therefore, no data on school achievement was available for participants based in Scotland (school AB, n=21).

In the Young Adult study, all participants had a similar highest level of school achievement with 90.8% (n=79/87) achieving A-level qualifications, 8.0% (n=7/87) achieving a University degree and only 1.1% (n=1/87) achieving GCSE qualifications as their highest level of education.

7.3.9 Statistical analysis and power calculations

All data were analysed using SPSS® Version 25. The main focus of the analysis was to explore the association between some of the key proposed risk factors with eye growth. Eye growth (mm) was found to be normally distributed (Shapiro-Wilk $p<0.001$), the characteristics of eye growth in both cohorts is discussed below. In addition, the biometric eye growth data in the Child cohort was investigated further to attempt to differentiate normal physiological eye growth attributed to emmetropisation in this age group and abnormal/aberrant axial length change related to myopia development. This was done through the use of a Bland-Altman plot and calculation of 95% Limits of Agreements (LOAs).

The majority of data in this chapter was from questionnaire responses which was ordinal in nature. In order to assess differences in patterns of behavioural factors such as of time spent outdoors, performing near or VDU tasks and the influence of day of the week and season, related samples Wilcoxon Signed Rank test was used. For comparisons between cohorts and these tasks a Mann Whitney U-test was performed. In order to assess the association between categorical risk factor responses of factors with more than 3 categories such as time outdoors, near and VDU tasks, family history of myopia, socioeconomic status, BMI and gestation stage with eye growth, a one-way ANOVA test was used. For urbanisation status where only 2 categories were present, rural vs urban, an independent t-test was used. Continuous data responses including birth weight and SATs were assessed for normality using Shapiro-Wilk and were all shown to be normally

distributed (p>0.05). The correlation between these continuous variables and eye growth was assessed with scatterplots and their associated R^2 values and Pearson's correlation coefficient (r).

7.4 Results

7.4.1 Eye growth characteristics

For 77 participants in the Child cohort eye growth data was available between Baseline and Year 1, the mean eye growth was +0.16±0.24mm (range -0.25 to +2.00) which was found to be normally distributed (Shapiro-Wilk p<0.001). On visualisation of the data and observation of the histogram a number of potential outliers were identified, most notably those that showed a reduction in eye growth at follow up and one participant who showed +2.00mm of eye growth over the 12 month period. Firstly, all data was re-checked to ensure it had been inputted correctly to rule out any administrative errors. Following this as biometry was recorded on the IOLMaster 500 and Aladdin, a comparison of the eye growth measured by each biometer was undertaken to assess the validity of these outliers and allow identification of potentially inconsistent measurements. These inconsistent measures could have been caused by errors during the measurement acquisition process such as blinking or participant movement during acquisition which were not flagged up by the intrinsic software of the biometers. The mean difference between the biometer measurements was found to be +0.03±0.23 (range -0.41 to 1.79). Using the 95% LOA for AL measurements, -0.39 to +0.33, determined in Chapter 6 for the Child cohort, 3 data values were found to be outside of the LOA and therefore identified as inconsistent measures and removed from all analyses. The details of these measurements are shown in Table 7.4.

Participant	IOLMaster 500 (mm)	Aladdin (mm)	Difference (mm)
ST012	+0.16	-0.25	-0.41
AB002	-0.49	+0.16	+0.65
BP036	+0.21	+2.00	+1.79

Table 7.4: Inconsistent eye growth measurements in the Child cohort

For the Young Adult cohort, axial length growth data was available for 67 participants between Baseline and Year 1. The mean eye growth was +0.03±0.08mm (range -0.16 to 0.29) and it was also found to be normally distributed (Shapiro-Wilk p<0.001). As with the Child cohort, the data was analysed for any inconsistent measurements between the

two biometers. The mean difference between the biometer measurements was 0.00±0.04mm (range -0.13 to 0.07). Using the 95% LOA for AL measurements, -0.10 to +0.05, determined in Chapter 6 for the Young Adult cohort, 8 data values were found to be outside of the LOA and therefore identified as inconsistent measures and removed from all analyses. The details of these measurements are shown in Table 7.5.

Participant	IOLMaster 500 (mm)	Aladdin (mm)	Difference (mm)
YA026	-0.01	-0.14	-0.13
YA003	0.15	0.02	-0.13
YA040	0.02	0.08	0.06
YA051	0.03	0.09	0.06
YA055	0.02	0.09	0.07
YA024	0.22	0.29	0.07
YA043	0.04	0.11	0.07
YA071	0.01	0.08	0.07

Table 7.5: Inconsistent eye growth measurements in the Young Adult cohort

7.4.2 Physiological vs abnormal/aberrant eye growth

As discussed previously emmetropisation is an active process of visual regulation of eye growth from birth until early adulthood, see Section 1.4. Due to the age of the Child cohort (7-12 years) there is a possibility that the biometric eye growth found between the follow up visits could be attributed to a normal physiological axial length growth rather than an abnormal/aberrant axial length change related to myopia development. In order to investigate this further for each participant the predicted axial length at Baseline and Year 1 was calculated using formulae derived from axial length growth curves developed by Jones et al (2005). These growth curves were modelled on children aged 6 to 14 years which is similar to this study. From these predicted axial length values the predicted axial length change between Baseline and Year 1 was derived. The mean difference between the actual axial length change and predicted axial length change was then calculated and found to be +0.02±0.09mm (range -0.14 to +0.31), n=74. The agreement between the actual and predicted axial length growth was assessed using a Bland-Altman plot, see Figure 7.5.

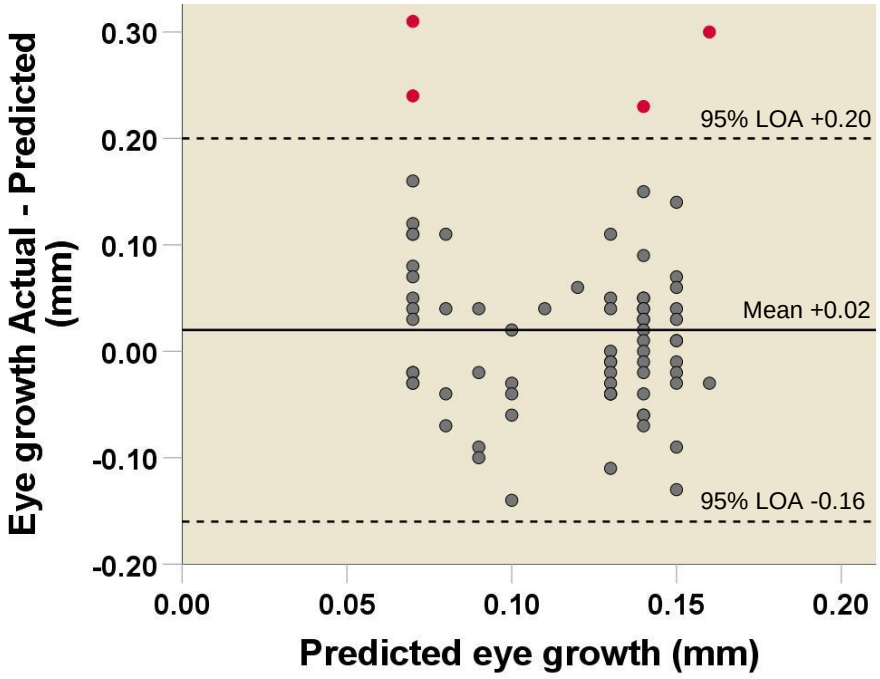


Figure 7.5: Bland-Altman plot comparing the predicted eye growth and the actual eye growth in the Child cohort data points outside the 95% LOA are shown in red.

4 participant's eye growth was found to be outside the 95% LOA (-0.16 to +0.20), shown in red on Figure 7.5. The characteristics of these outliers can be found in Table 7.6. These outlier participants were 50% (n=2) females and from a mixture of ethnic backgrounds (White (n=2), East Asian (n=1) and Mixed Race (n=1). For all 4 participants a faster than predicted eye growth was measured which, as expected, was associated with a negative shift in SER. This suggests that the eye growth for 94.6% (n=70/74) of participants between Baseline and Year 1 could be attributed to a normal physiological axial length growth and only 5.4% (n=4/74) could be considered abnormal/aberrant axial length change related to myopia development.

Participant	Age	Baseline SER (D)	Year 1 SER (D)	SER change Baseline to Year 1 (D)	Actual eye growth (mm)	Predicted eye growth (mm)	MD (mm)
BP054	10.4	-0.50	-1.25	-0.76	0.38	0.07	+0.31
ST007	7.6	+2.25	+1.06	-1.19	0.46	0.16	+0.30
GP016	10.3	-0.18	-0.50	-0.38	0.31	0.07	+0.24
GP002	8.2	+1.50	+0.94	-0.57	0.37	0.14	+0.23

Table 7.6: Participant and measurement characteristics of eye growth outliers from comparison of actual and predicted eye growth measurements in the Child cohort MD: mean difference, calculated by subtracting actual from predicted values.

7.4.3 Time outdoors

Time outdoors responses was available for 83.2% (n=188/226) of Child cohort participants and 100.0% (n=87/87) of Young Adult participants. The distributions of responses are shown in Figure 7.6. The most common frequency of time outdoors on weekdays in Winter was less than 1 hour (n=68) in the Child cohort and 1-2 hours (n=48) in the Young Adult cohort, on weekends in Winter was 2 or more hours (n=69) in the Child cohort and 1-2 hours (n=40) in the Young Adult cohort, on weekdays in Summer was 2 or more hours (n=90) in the Child cohort and 2 or more hours (n=50) in the Young Adult cohort and on weekends in Summer was 2 or more hours (n=121) in the Child cohort and 2 or more hours (n=56) in the Young Adult. The weekly frequencies of time outdoors as a function of day of the week and season for both cohorts are shown in the Appendix A.7.1.

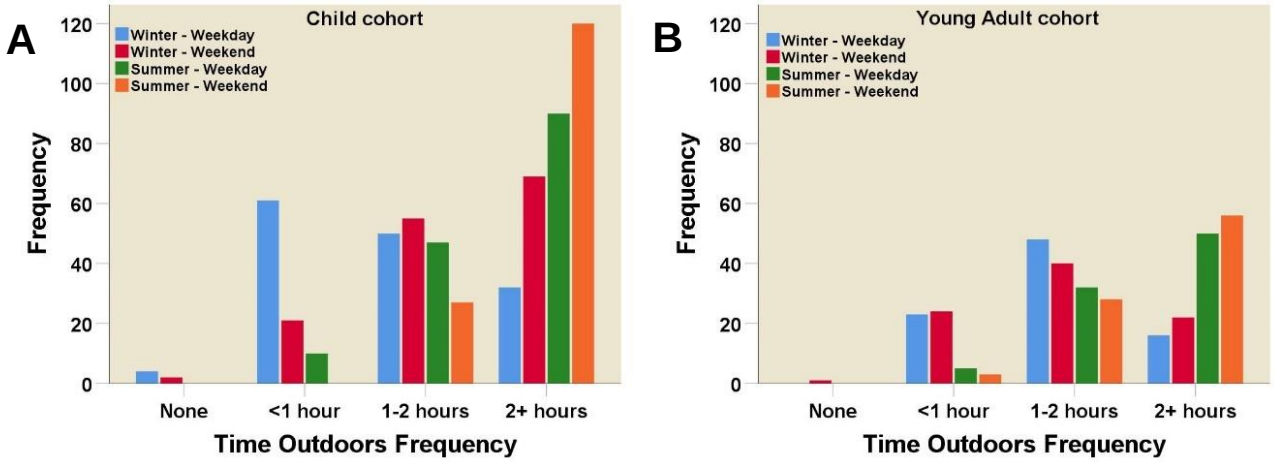


Figure 7.6: Time outdoors questionnaire responses for A) Child cohort B) Young Adult cohort Child cohort n=188, Young Adult n=87

In Winter, the Child cohort spent significantly more time outdoors on weekends compared to weekdays (Wilcoxon Signed rank: z=6.315, p<0.001) however no significant difference was found in the Young Adult cohort (Wilcoxon Signed rank: z=0.364, p=0.716). Similar findings were found in Summer with the Child cohort spending more time outdoors on weekends compared to weekdays (Wilcoxon Signed rank: z=5.152, p<0.001) and no difference in the Young Adult cohort (Wilcoxon Signed rank: z=1.509, p=0.117).

Seasonal differences between time spent outdoors was also explored. In the Child cohort and the Young Adult cohort, time spent outdoors was significantly more in Summer than Winter on weekdays and weekends (Wilcoxon Signed rank: Child cohort:

Weekdays z=8.430, p<0.001, Weekends z=7.343, p<0.001. Young Adult cohort: Weekdays z=2.313, p=0.021, Weekends z=6.095, p<0.001).

In addition, differences in time outdoors between the cohorts as a function of season and day of the week were also analysed. No significant differences in time spent outdoors on weekdays in Summer or Winter was found between the cohorts (Mann Whitney U-test: Winter Weekday z=-1.950, p=0.051, Summer Weekday z=1.064, p=0.287). However, on weekends, in both Summer and Winter the Child cohort spent more time outdoors than the Young Adult cohort (Mann Whitney U-test: Winter Weekend z=3.430, p=0.001, Summer Weekend z=3.052, p=0.002).

No statistically significant difference in eye growth was found between time spent outdoors by either season or weekday in either the Child cohort (Summer-Weekday p=0.849, Summer-Weekend p=0.217, Winter-Weekday p=0.122, Winter-Weekend p=0.260) or the Young Adult cohort (Summer-Weekday p=0.885, Summer-Weekend p=0.356, Winter-Weekday p=0.780, Winter-Weekend p=0.126). Eye growth characteristics for each category can be found in the Appendix A.7.2.

7.4.4 Near and VDU tasks

Near work and visual display unit (VDU) questionnaire responses for 83.2% (n=188/226) of Child cohort participants and 100.0% (n=87/87) of Young Adult participants were available. The distributions of responses are shown in Figure 7.7. The most common weekly frequency of near work in the Child cohort irrespective of day of the week or season was less than one hour and in the Young Adult cohort was 2 or more hours except weekends in Summer which was less than 1 hour. The most common weekly frequency of VDU use in the Child cohort was 1-2 hours on weekdays in Winter, 1-2 hours and 2+ hours on weekends in Winter, less than 1 hour on weekdays in Summer and 1-2 hours on weekends in Summer. Alternatively, in the Young Adult cohort irrespective of day of the week or season the weekly frequency of VDU use was 2 or more hours. The weekly frequencies of near and VDU tasks as a function of day of the week and season for both cohorts are shown in the Appendix A.7.1.

In Winter, no significant difference in time spent performing near tasks between weekdays and weekends was found in either cohort (Wilcoxon Signed rank: Child cohort z=1.836, p=0.066, Young Adult cohort: z=-1.591, p=0.112). Comparatively, time spent on a VDU was found to be significantly higher in the Child cohort on weekends compared to weekdays (Wilcoxon Signed rank: z=5.663, p<0.001) and no significant difference was found in the Young Adult cohort (Wilcoxon Signed rank: z=-1.591, p=0.112).

In Summer, the Child cohort continued to show no difference in time spent doing near tasks between weekdays and weekends (Wilcoxon Signed rank: z=-0.315, p=0.753) but the Young Adult cohort spent statistically significantly less time doing near tasks at weekends compared to weekdays (Wilcoxon Signed rank: z=-3.556, p<0.001). With regard to time spent on a VDU, the Child cohort spent more time on a VDU at weekends compared to weekdays (Wilcoxon Signed rank: z=2.600, p=0.009) whilst no significant difference between weekday and weekend time was found in the Young Adult cohort (Wilcoxon Signed rank: z=-1.255, p=0.210).

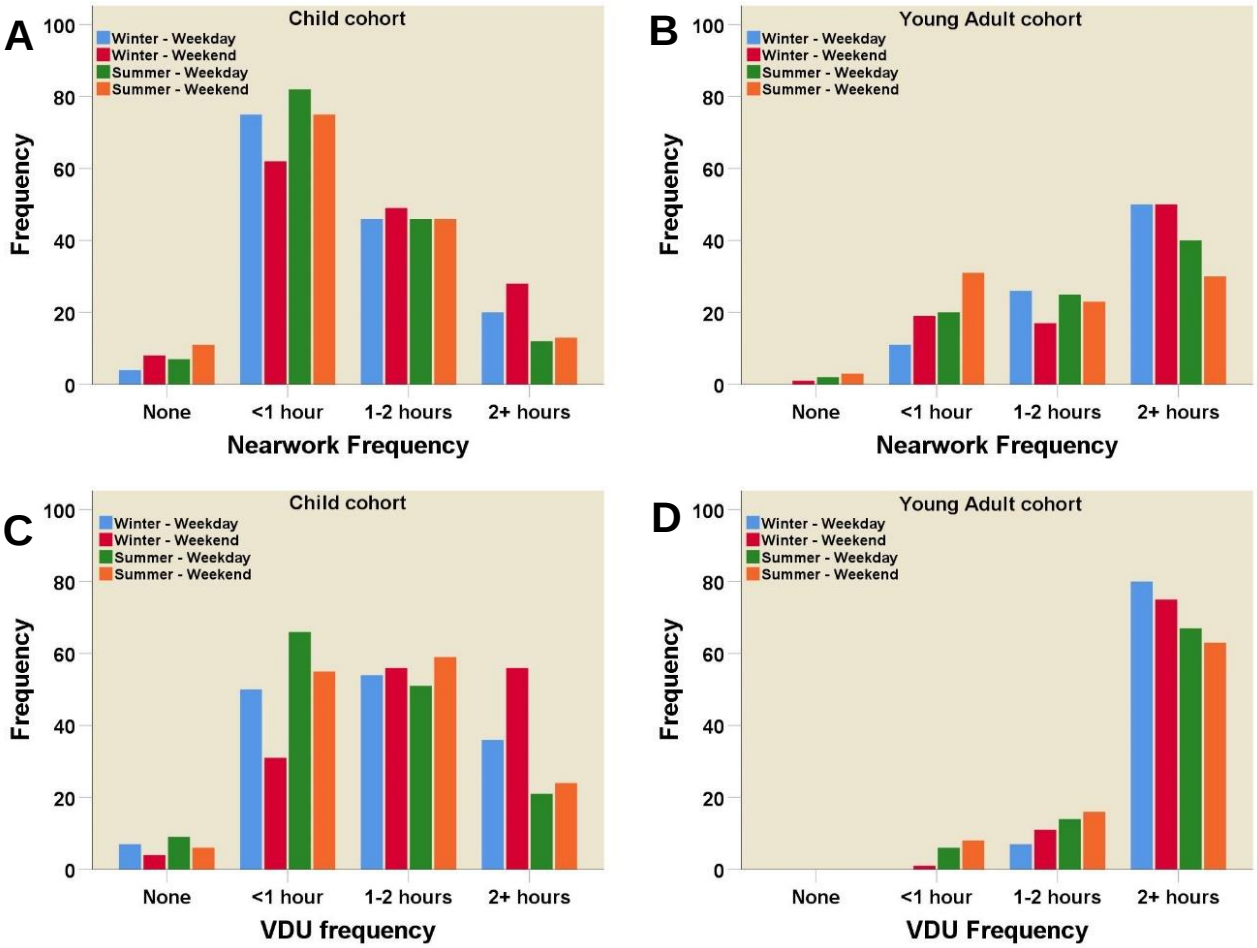


Figure 7.7: Nearwork questionnaire responses for near work in the Child cohort (A) and Young Adult cohort (B) and VDU questionnaire responses for the Child Cohort (C) and Young Adult cohort (D) Child cohort n=188, Young Adult n=87

Seasonal differences between time spent performing near and VDU tasks were also explored. In the Child cohort and the Young Adult cohort, time spent performing near and VDU tasks was significantly less in Summer than Winter on weekdays and weekends (Wilcoxon Signed rank: all p<0.05), see Table 7.7.

		Summer vs Winter	
		Child cohort	**Young Adult cohort**
Near tasks	Weekday	z=-3.124, p=0.002	z=-2.882, p=0.004
	Weekend	z=-4.892, p<0.001	z=-3.894, p<0.001
VDU tasks	Weekday	z=-4.465, p<0.001	z=-3.477, p=0.001
	Weekend	z=-6.392 p<0.001	z=-3.578, p<0.001

Table 7.7: Comparison of seasonal differences in time spent performing near and VDU tasks between day of the week in the Child and Young Adult cohort Wilcoxon Signed Rank results reported

In addition, differences in time spent performing near and VDU tasks between the cohorts as a function of season and day of the week were also analysed. The Young Adult cohort spent more time performing both near and VDU tasks than the Child cohort for both weekdays and weekend days in Summer and Winter (Mann Whitney U-test all p<0.001), see Table 7.8.

	Child vs Young Adult cohort	
	Near tasks	**VDU tasks**
Winter – Weekdays	z=-7.695, p<0.001	z=-9.554, p<0.001
Winter – Weekends	z=-5.494, p<0.001	z=-7.252, p<0.001
Summer – Weekdays	z=-6.013, p<0.001	z=-8.696, p<0.001
Summer – Weekends	z=-4.057, p<0.001	z=-8.106, p<0.001

Table 7.8: Comparison of near and VDU tasks between the cohorts by season and day of the week Mann Whitney U-test results reported

No statistically significant difference in eye growth was found between time spent performing near or VDU tasks by either season or weekday in either the Child cohort (Near tasks: Summer-Weekday p=0.186, Summer-Weekend p=0.242, Winter-Weekday p=0.319, Winter-Weekend p=0.882. VDU tasks: Summer-Weekday p=0.686, Summer-Weekend p=0.786, Winter-Weekday p=0.123, Winter-Weekend p=0.279) or the Young Adult cohort (Near tasks: Summer-Weekday p=0.375, Summer-Weekend p=0.804, Winter-Weekday p=0.317, Winter-Weekend p=0.842. VDU tasks: Summer-Weekday p=0.237, Summer-Weekend p=0.172, Winter-Weekday p=0.176, Winter-Weekend p=0.172). Eye growth characteristics for each category can be found in the Appendix A.7.3.

7.4.5 Family history of myopia

Family history of myopia was classified depending on the number of parents self-reporting as myopic for the Child cohort and was available for 68.6% (n=155/226) of participants. In the Young Adult cohort, this classification was made from participant self-reporting of parental myopia and was available for 81.7% (n=71/87) of participants. The proportion of myopic parents in each cohort are shown in Table 7.9.

Number of myopic parents	Child cohort (%)	Young Adult (%)
0	51.6 (n=80)	29.6 (n=21)
1	40.0 (n=62)	47.9 (n=34)
2	8.4 (n=13)	22.5 (n=16)

Table 7.9: Proportion of number of myopic parents in the Child cohort and Young Adult cohort

Eye growth and number of myopic parents data was available for 52 participants in the Child cohort and 45 participants in the Young Adult cohort, see Table 7.10.

	Child cohort			Young Adult cohort		
Number of myopic parents	**n**	**Mean±SD (mm)**	**One-way ANOVA**	**n**	**Mean±SD (mm)**	**One-way ANOVA**
0	23	+0.15±0.10	p=0.569	12	+0.01±0.05	p=0.280
1	22	+0.13±0.08		24	+0.05±0.07	
2	6	+0.12±0.07		9	+0.02±0.07	

Table 7.10: Number of myopic parents and eye growth characteristics (mean±SD) for the Child and Young Adult cohort

No statistically significant difference in eye growth was found in either the Child cohort (n=52, one-way ANOVA p=0.569) or the Young Adult cohort (n=45, one-way ANOVA p=0.280).

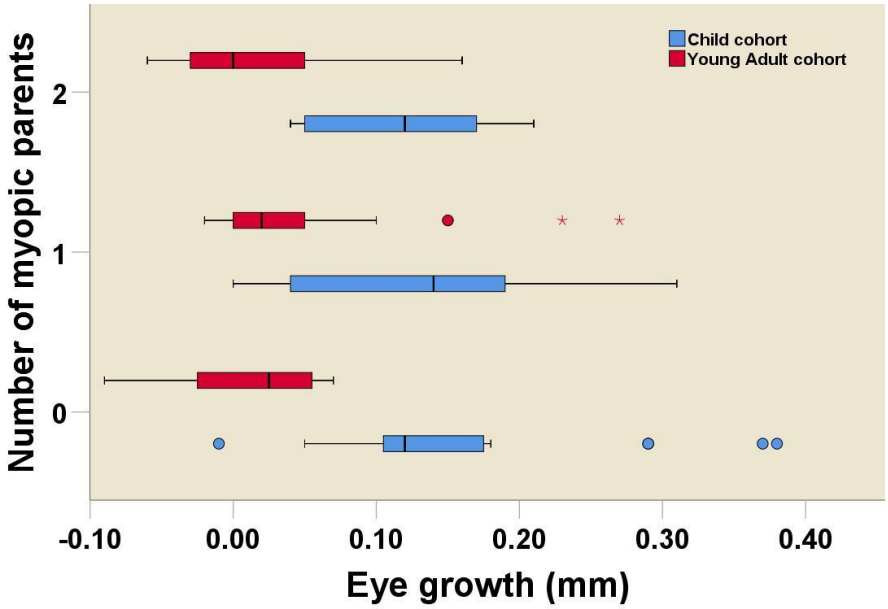


Figure 7.8: Eye growth (mm) as a function of number of myopic parents in the Child and Young Adult cohort

7.4.6 Socioeconomic status

Index of Multiple Deprivation (IMD) quintile values were used as a measure of socioeconomic status. The IMD quintile proportions are shown in Table 7.11. The majority of participants, 42.3% (n=93/220), were classified within IMD quintile 1 i.e. 20% most deprived. A Kruskal Wallis test showed that IMD quintile did not differ by region (p=0.541).

	IMD Quintile proportion (%)				
	1	**2**	**3**	**4**	**5**
North	0.0 (n=0)	71.4 (n=15)	28.6 (n=6)	0.0 (n=0)	0.0 (n=0)
Midlands	50.0 (n=87)	8.6 (n=15)	7.5 (n=13)	16.1 (n=28)	17.8 (n=31)
South	24.0 (n=6)	48.0 (n=12)	16.0 (n=4)	4.0 (n=1)	8.0 (n=2)
Total	**42.3 (n=93)**	**19.1 (n=42)**	**10.5 (n=23)**	**13.2 (n=29)**	**15.0 (n=33)**

Table 7.11: Index of Multiple Deprivation (IMD) quintile proportions

Eye growth and IMD data was available for 72 participants in the Child cohort, see Table 7.12. There was no statistically significant difference between IMD quintile and eye growth in the Child cohort (n=72, one-way ANOVA p=0.177), see Figure 7.9.

	Child cohort		
IMD quintile	**n**	**Mean±SD (mm)**	**One-way ANOVA**
1	33	+0.15+0.10	p=0.177
2	16	+0.11±0.06	
3	5	+0.17±0.13	
4	10	+0.10±0.08	
5	8	+0.17±0.07	

Table 7.12: Index of Multiple Deprivation (IMD) quintile and eye growth characteristics (mean±SD) for the Child and Young Adult cohort

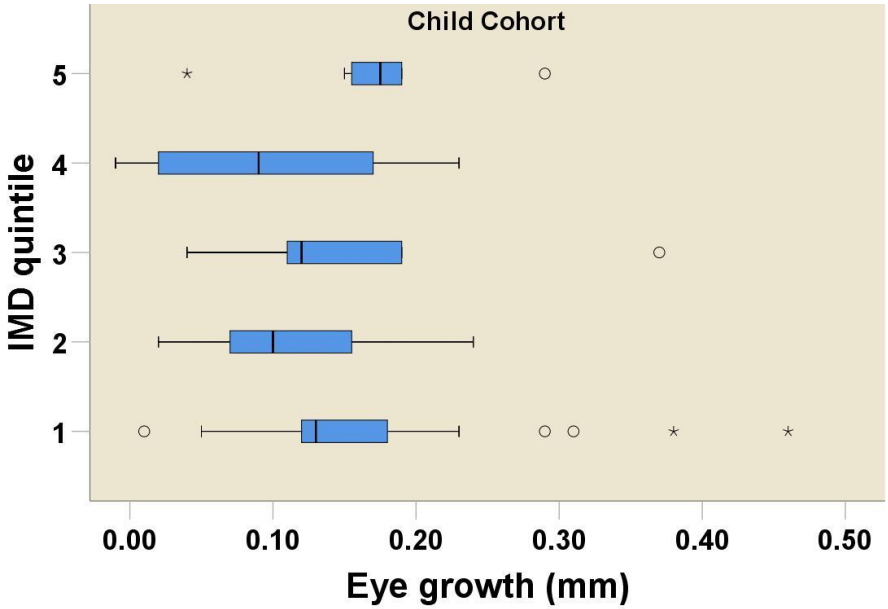


Figure 7.9: Eye growth (mm) as a function of Index of Multiple Deprivation (IMD) quintile in the Child cohort

7.4.7 Rural/Urban residence

Participants in the Child cohort were classified as living in urban or rural areas depending on the population density of the area calculated by their postcodes. This was available for 97.3% (n=220/226) of participants and 30.0% (n=66/220) were classified as rural and 70.0% (n=154/220) were classified as urban, see Table 7.13. The North region was entirely of rural composition whilst Midlands and South regions had a predominantly urban composition (79.9% and 60.0% respectively).

	%			
	Rural		Urban	
North	100.0	(n=21)	0.0	(n=0)
Midlands	20.1	(n=35)	79.9	(n=139)
South	40.0	(n=10)	60.0	(n=15)
Total	**30.0**	**(n=66)**	**70.0**	**(n=154)**

Table 7.13: Rural and urban regional composition

Eye growth and urbanisation classification data was available for 74 participants in the Child cohort, see Table 7.14.

	Child cohort		
Urbanisation classification	**n**	**Mean±SD (mm)**	**t-test†**
Rural	24	+0.11±0.07	p=0.177
Urban	50	+0.15±0.09	

Table 7.14: Urbanisation category and eye growth characteristics (mean±SD) for the Child and Young Adult cohort †:independent t-test

A statistically significant difference between rural and urban classification was found (n=74, independent t-test p=0.033), see Figure 7.10. Urban participants were found to have a faster eye growth by +0.05±0.02 (95%CI 0.00 to +0.09) than rural participants.

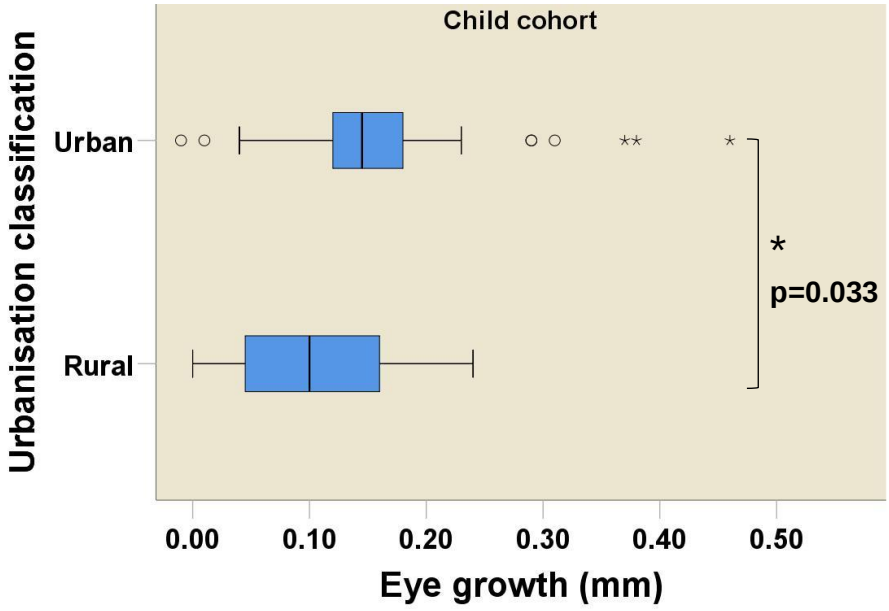


Figure 7.10: Eye growth (mm) as a function of urbanisation classification (rural vs urban) in the Child cohort

7.4.8 Body Mass Index (BMI)

Body mass index (BMI) was classified into four categories: Underweight, healthy, overweight and obese. The proportions of each BMI category are shown in Table 7.15. The majority of participants were classified as healthy (Child cohort 73.9% (n=167) and Young Adult cohort 58.6% (n=51)). No difference in BMI category between males and females was found in both cohorts (Mann Whitney U-test: Child cohort p=0.140, Young Adult cohort: p=0.170).

	%	
	Child cohort (n=226)	**Young Adult cohort (n=87)**
Underweight	1.8 (n=4)	10.3 (n=9)
Healthy	73.9 (n=167)	58.6 (n=51)
Overweight	13.7 (n=31)	24.1 (n=21)
Obese	10.6 (n=24)	6.9 (n=6)

Table 7.15: BMI category proportions for both cohorts

Eye growth and BMI data was available for 74 participants in the Child cohort and 59 participants in the Young Adult cohort, see Table 7.16.

	Child cohort			Young Adult cohort		
BMI category	**n**	**Mean±SD (mm)**	**One-way ANOVA**	**n**	**Mean±SD (mm)**	**One-way ANOVA**
Underweight	1	+0.31	p=0.159	7	+0.01±0.05	p=0.007
Healthy	54	+0.13±0.09		33	+0.01±0.04	
Overweight	11	+0.17±0.09		16	+0.07±0.08	
Obese	8	+0.14±0.07		3	+0.00±0.05	

Table 7.16: BMI category and eye growth characteristics (mean±SD) for the Child and Young Adult cohort

A statistically significant difference in BMI and eye growth was found in the Young Adult cohort (n=59, one-way ANOVA p=0.007). Post-hoc tukey only found a significant difference between healthy and overweight participants (p=0.006), see Figure 7.11. Overweight participants were found to have a faster eye growth than healthy participants, mean difference +0.06±0.02 (95%CI 0.01 to 0.11). There was no statistically significant difference between BMI and eye growth in the Child cohort (n=74, one-way ANOVA p=0.159).

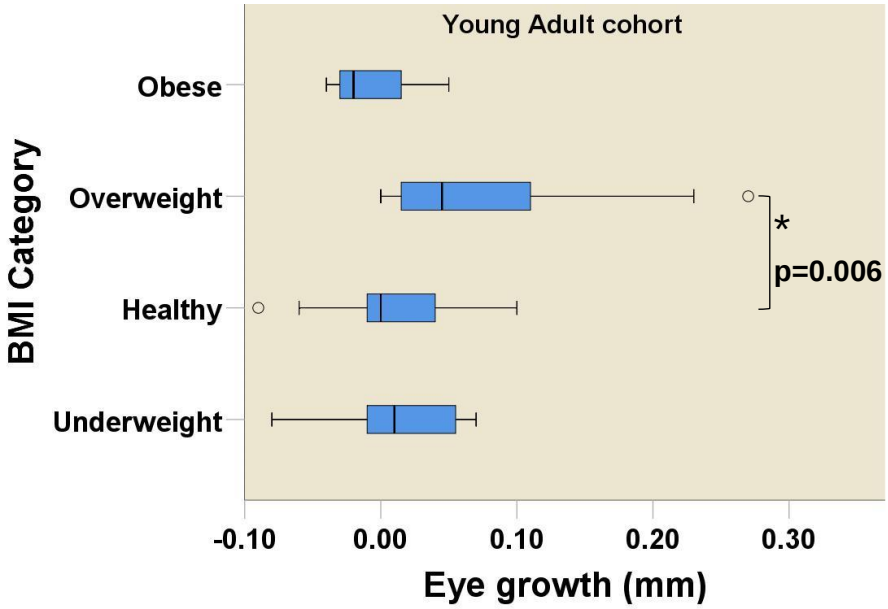


Figure 7.11: Eye growth (mm) as a function of Body Mass Index (BMI) category in the Young Adult cohort

7.4.9 Birth weight and gestation

Birth weight was available for 67.3% (n=152/226) for the Child cohort and 28.7% (n=25/87) of the Young Adult cohort. The mean±SD birth weight for the Child cohort was 3.29±0.63kg and for the Young Adult cohort was 3.52±1.06kg, the distribution of birth weight are shown in Figure 7.12.

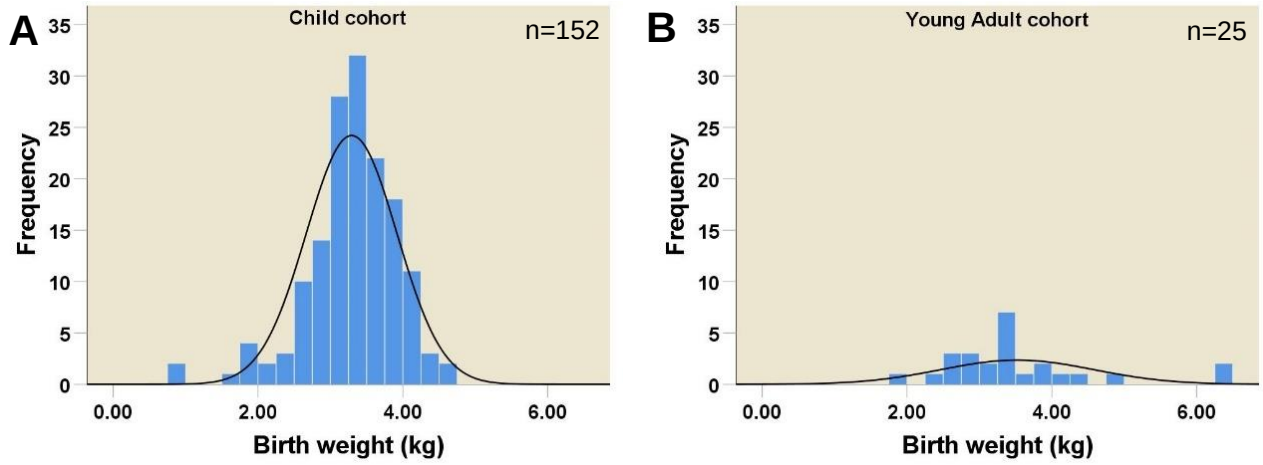


Figure 7.12: Birth weight (kg) distribution in A) Child cohort B) Young Adult cohort

A significant correlation was found in the Child cohort between eye growth and birth weight (R^2=0.099, r=-0.314 p=0.028, n=49), see Figure 7.13. However, no correlation was found in the Young Adult cohort (R^2=0.000, r=-0.019 p=0.939, n=25).

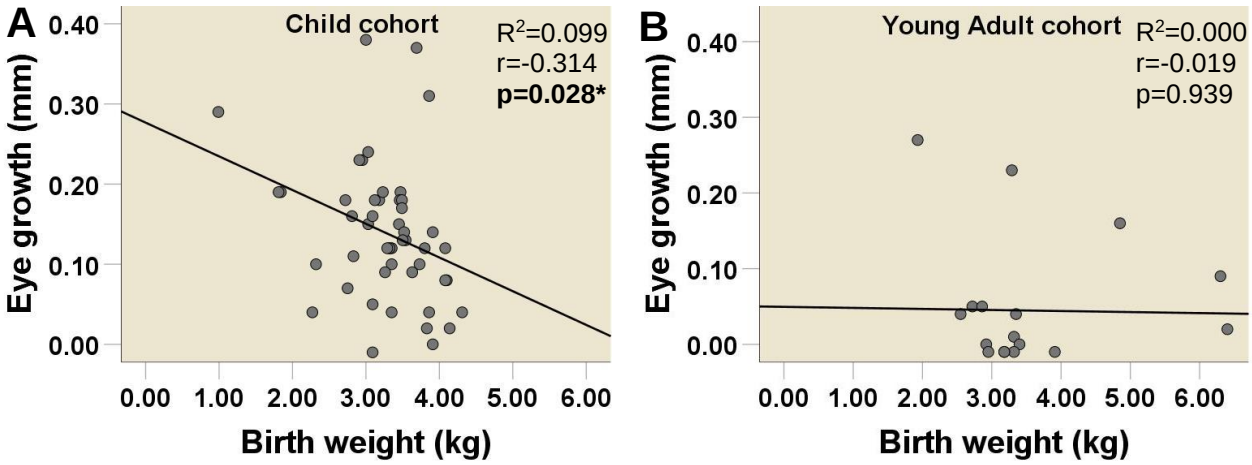


Figure 7.13: Correlation between eye growth (mm) and birth weight (kg) in the A) Child cohort (n=49) B) Young Adult cohort (n=25)

Gestation/time of birth data was available for 81.9% (n=185/226) for the Child cohort and 81.2% (n=71/87) for the Young Adult cohort, see Figure 7.14 for distribution of responses.

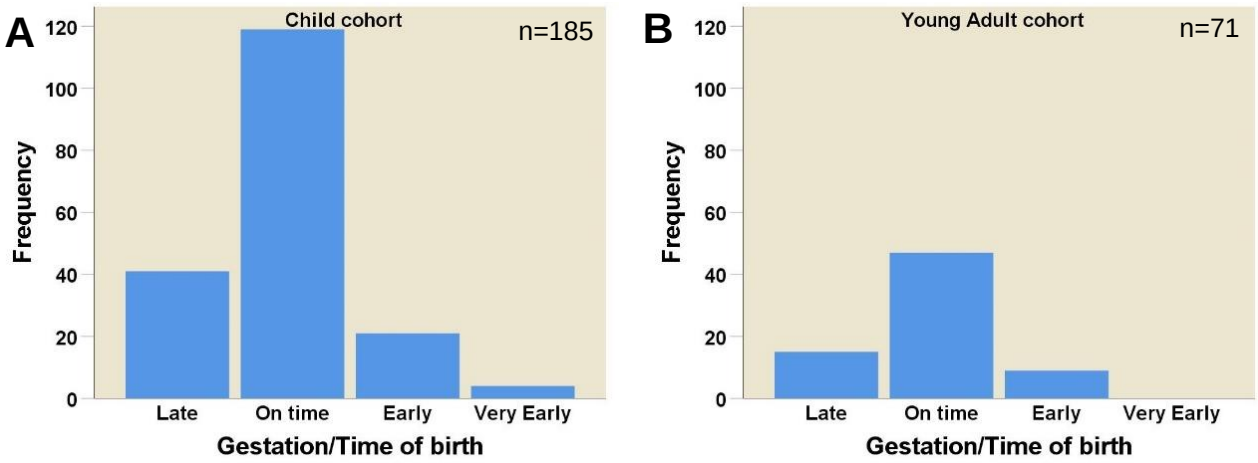


Figure 7.14: Gestation/Time of birth frequency bar chart A) Child cohort B) Young Adult cohort

Eye growth and gestation category was available for 57 participants in the Child cohort and 47 participants in the Young Adult cohort, see Table 7.17. There was no statistically significant difference between gestation/time of birth category and eye growth in either the Child cohort (n=57, one-way ANOVA p=0.183) or Young Adult cohort (n=47, one-way ANOVA p=0.172), see Figure 7.15.

Gestation	Child cohort			Young Adult cohort		
	n	Mean±SD (mm)	One-way ANOVA	n	Mean±SD (mm)	One-way ANOVA
Late	16	+0.16±0.09	p=0.183	11	0.00±0.04	p=0.172
On time	31	+0.12±0.08		30	+0.05±0.07	
Early	8	+0.16±0.05		6	+0.04±0.04	
Very Early	2	+0.23±0.08		0	NA	

Table 7.17: Gestation and eye growth characteristics (mean±SD) for the Child and Young Adult cohort

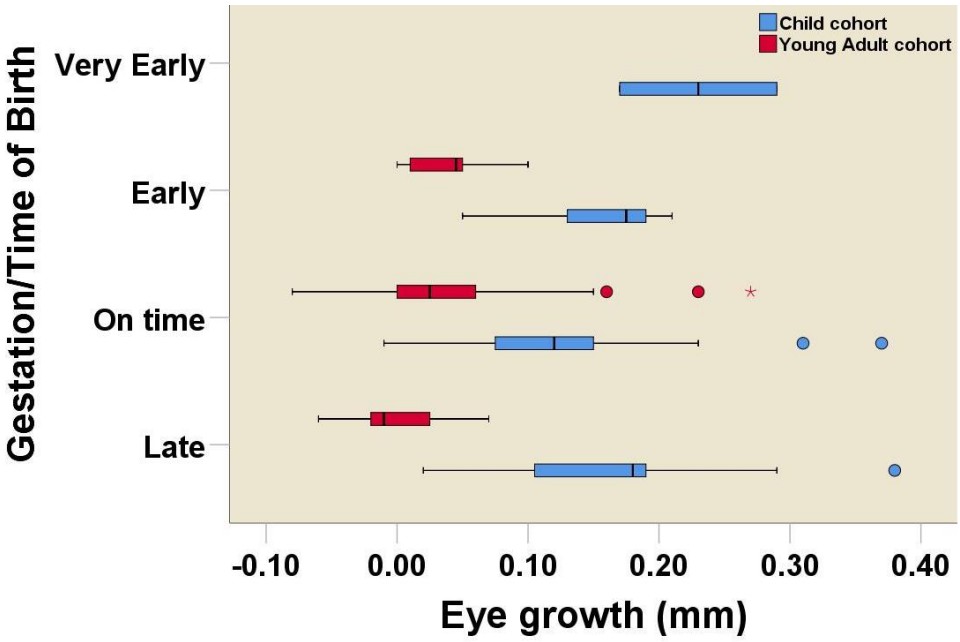


Figure 7.15: Eye growth (mm) as a function of gestation/time of birth category in the Child and Young Adult cohort

7.4.10 School achievement

School achievement data was derived from SATs results and were available for 19.9% (n=45/226) of participants in the Child cohort. The mean±SD score for Reading was 104±7 (range 82 – 118), Spelling 107±7 (range 92 – 120), Maths 105±5 (90 – 113) and overall score 106±5 (range 94 – 116), see Figure 7.16. The two outliers for Maths and Reading were not the same participant. A significant correlation between Reading and Spelling scores (r=0.641, p<0.001), Reading and Maths scores (r=0.418, p=0.004) and Spelling and Maths scores (r=0.600, p<0.001) was found.

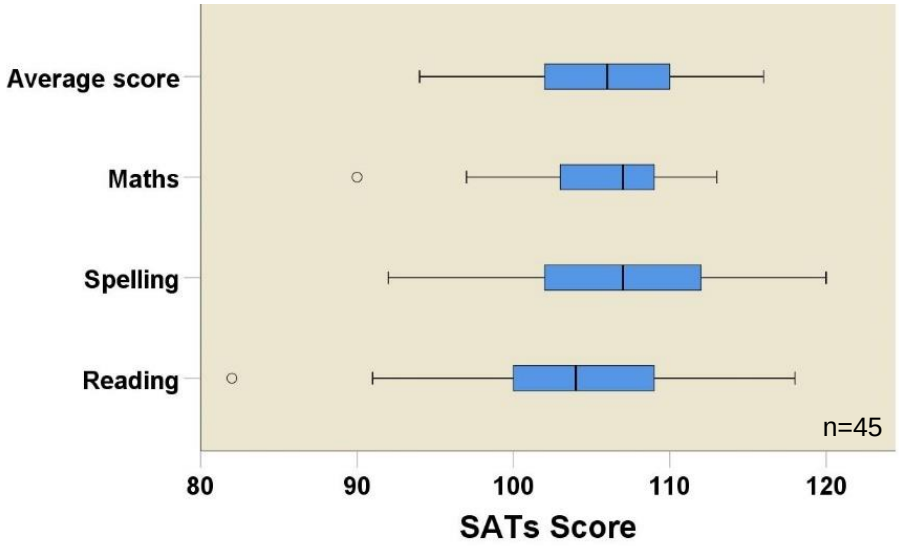


Figure 7.16: SATs scores for reading, spelling, maths and average overall scores

No correlations between reading score (R^2=0.038, r=0.194 p=0.426), spelling score (R^2=0.059, r =0.243 p=0.316), maths score (R^2=0.020, r=-0.142, p=0.561) or average score (R^2=0.025, r=0.157 p=0.521) with eye growth (n=19) were found, see Figure 7.17.

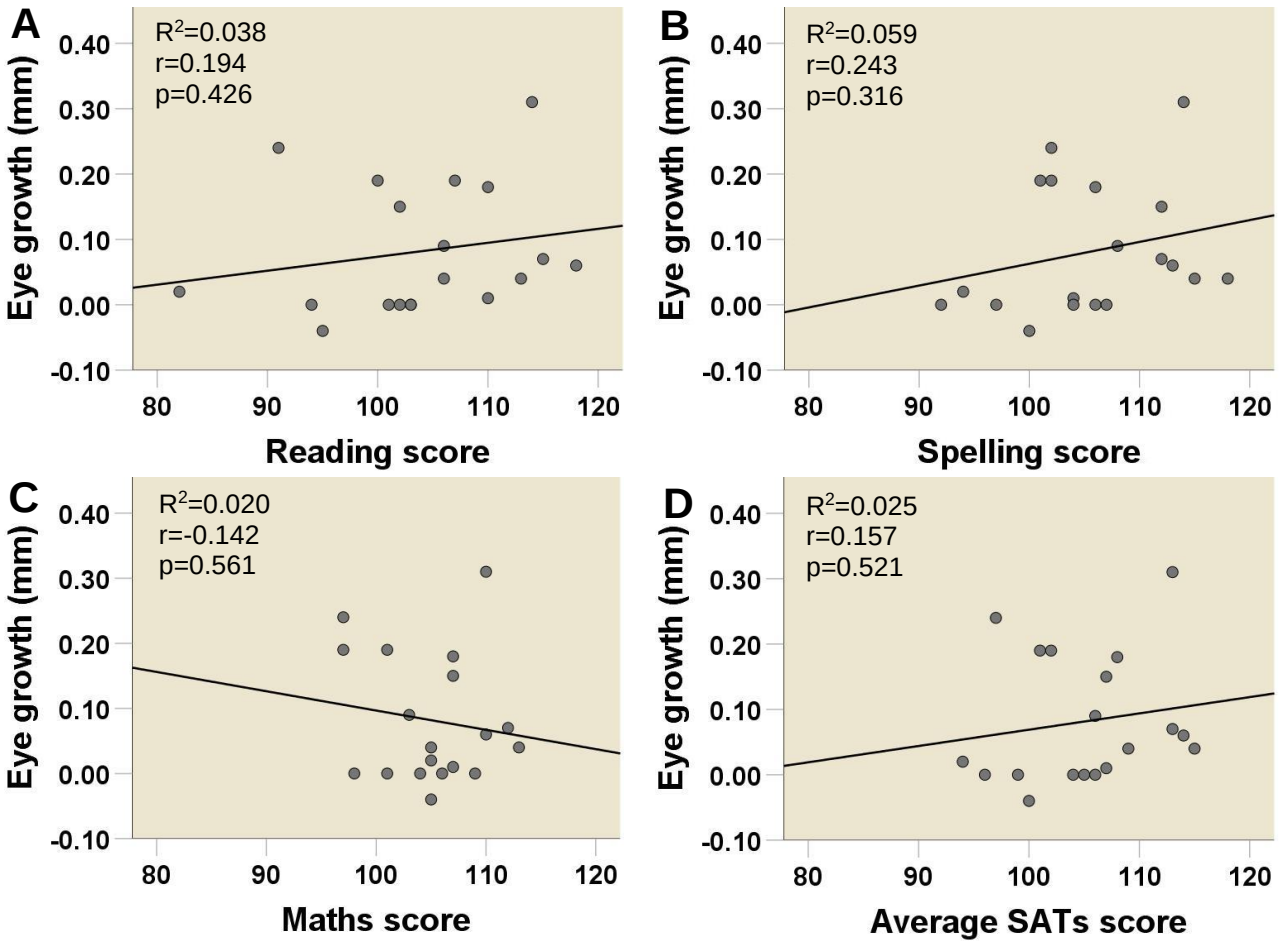


Figure 7.17: Correlation between eye growth (mm) (n=19) and A) Reading score B) Spelling score C) Maths score D) Average SATs score

7.5 Discussion

In this chapter the behaviours of school children and young adults within the UK have been shown to vary by day of the week and by season. Children were reported to spend more time outdoors on weekends than weekdays. This correlates with an increased opportunity for time outdoors at weekends when they are not restricted to the school schedule where time outdoors during the school day is limited. Although no difference in the time spent doing near tasks was found between weekdays and weekends, time spent using VDUs was significantly higher on weekends than weekdays. Again, this is likely a result of the increased opportunity for VDU use and increased accessibility to these devices when not at school. Children are the fastest growing population of smartphone users (Terras and Ramsay, 2016) and it has been reported that 99% of students aged 10-33 years old own their own smartphone (McCrann et al., 2020). This also introduces the factor of parental influence and attitude on children's behaviours. It was recently reported that the majority of parents feel that they limit their child's screen time however children still spent over 14 hours a week on average at a screen (McCrann et al., 2018). At this age, children are dependent on their parents for decision making and access to these devices. However, in the Young Adult cohort irrespective of day of the week or season the weekly frequency of VDU use was 2 or more hours. Furthermore, those in the Young Adult cohort were found to have significantly higher VDU use than the Child cohort in both seasons and day of the week. Participants in the Young Adult cohort (18 – 25 years) are more independent and the majority were living away from home and therefore their activities were not influenced by external factors such as parent's attitudes and accessibility to devices as in the Child cohort. The high level of VDU tasks in this cohort could be attributed to the use of smartphones which are ubiquitous in this age group and are increasingly used for tasks such as social media and communication methods and also the use of laptops/PCs are university work. In addition, the academic university environment of the Young Adult is synonymous with studying and due to the ease of accessibility and their ease of use this is predominately done on VDUs. Whilst VDUs are used in some primary schools to aid learning, they are not located within the classroom and are not used every day. The majority of schoolwork and homework at primary school level is paper based. In addition, smartphone use was included in "VDU tasks". The advent of smartphone has increased our accessibility to information through the internet and provided on demand features such as the ability to watch TV and films anywhere. They have now become ubiquitous with modern life. A review of epidemiological studies investigating the association between myopia and near tasks prior to smartphone or tablet invention, showed much lower levels of near

tasks than more recent studies. For example, Mutti et al (2002) used questionnaires to estimate that schoolchildren (mean age 13.7±0.5 years, n=366) spent on average 2.3±3.3 hours per week on videogames/computer. However more recent objective data extracted from smartphone devices has shown that students (16.77±4.4 years, n=418) spent on average 4 hours 32±169 minutes a day on smartphone use alone (McCrann et al., 2020). Although this study population incorporated a proportion of older students it demonstrates how the advent of smartphones have greatly increased the amount of time spent doing near tasks.

As expected for both cohorts a significantly increased time spent outdoors was reported for Summer compared to Winter. This is likely a reflection of the significant differences in climate characteristics that are experienced within the UK during Summer and Winter months, this is explored in Section 9.4.4. Summer days were found to be warmer and longer with less rainfall compared to shorter cooler and wetter days in Winter months. The climate conditions of Summer are more favourable for spending time outdoors and the longer day length provides more opportunity for light exposure and therefore increased duration. In addition, for both cohorts the amount of time spent performing near and VDU tasks was significant less in Summer than Winter. This could be attributed to the increased time spent outdoors or that over Summer school/university are closed. As a result, there is a reduction in the necessary near work required, by means of no homework or school classes to attend. A reduction in the amount of near work required by school children and university students would mean an increased opportunity to spend time outdoors coupled with the more favourable climate conditions. This highlights the interconnected relationship between time outdoors and near tasks. There is some debate in the literature as to whether this relationship results in a confounding effect such that the amount of time spent doing either behaviour influences the amount of time available for the other. Conversely it has also been suggested that this relationship could have a combined effect on myopia development. The odds ratio of incident myopia in school children was found to be higher in those that had a combination of high near work and low time outdoors (French et al., 2013b).

A significant association between urbanisation and eye growth was found in this study. With children living in urban areas found to have a faster eye growth. The difference in myopia prevalence between rural and urban areas is well documented with a greater prevalence of myopia consistently found in urban areas, see Section 2.3.4. It has been theorised that this association could be linked to the protective effects of time outdoors, see Section 2.2. Closely confined environments such as apartments may not only limit the amount of light through windows but may also act as a barrier for the accessibility

for children to be outdoors especially those on higher floors. In addition, urban areas have been linked with disruptive sleep (Haseli-Mashhadi et al., 2009) which is another factor that has been investigated in this study, see Chapter 8. It has also been hypothesised that the spatial frequency of urban and indoor environments differs from natural outdoor environments. A recent study by Flitcroft et al (2020) has shown that the spatial frequency of urban and indoor environments is relatively deficient in high spatial frequency and is similar to the spatial feature created by diffusing filters that have been found to induce form deprivation myopia in animal models.

Another interesting finding of this study is that overweight young adults were found to have a faster eye growth than healthy participants. It has been hypothesised that those with a higher BMI are more likely to be myopic as they are more likely to have a sedentary lifestyle (Mitchell et al., 2014). As a result, increased BMI could be a confounded factor as it could led to or be caused by less time spent outdoors and increased time performing near and VDU tasks which have been shown to be related to myopia progression. Conversely to this, children who were born with a lower birth weight were found to have a faster eye growth. Birth weight has been shown to provide a unique insight into development of milestone achievements and also a strong predictor of health outcomes and achievement of developmental milestones (Gill et al., 2013). Low birth weight has been associated with myopia (Rahi et al., 2011).

The lack of association between time outdoors, near and VDU tasks and eye growth in this study, which is well established in the literature see Chapter 2, could be attributed to the relatively crude assessment of these behaviours. The use of categories and the limited number of categorical options available on the questionnaires was perhaps not sensitive enough to fully establish any association. For time outdoors, for both cohorts 50% of questionnaire responses for time spent outdoors in Summer on weekdays and weekends was 2 or more hours. As mentioned previously, in the Young Adult cohort VDU use was 2 or more hours irrespective of day of the week or season. A re-design of the questionnaire would be warranted to ascertain more specific estimations of these tasks through asking participants to report the number of hours for each task rather than using categories. For near work previous studies have also used calculation of a dioptre-hours variable to quantify exposure to near work not just in terms of time but also accommodative effort. Dioptre-hours has been defined as 3 × (hours spent studying + hours spent reading for pleasure) + 2 × (hours spent playing video games or working on the computer at home) + 1 × (hours spent watching television) (Mutti et al., 2002, Jones-Jordan et al., 2012). Due to the categorical nature of the questionnaire responses in this study this calculation was not possible. This further suggests that responses

provided as number of hours as a single number is a more valuable output and reduces the chance of loss of data through the use of categories.

A genetic predisposition to myopia as a function of parental myopia is well established in the literature and has been shown to be dose-dependent, see Section 2.3.3. However, neither cohort showed a significant association with parental myopia. This could be attributed to the age range of the Child cohort and the development of myopia and associated eye growth may not have occurred yet. In addition, identification of parental myopia was reliant on accurate recall of parents own and other parent's refractive error. Steps were made to try and differentiate between myopia and hyperopia on the questionnaire using phrases such as "needs glasses to see far away e.g. driving, TV" for myopia and also a space to record their refraction. Other studies have used more objective ways to determine parental myopia for example in the COMET study non-cycloplegic autorefraction or recent eye examination records were used (Kurtz et al., 2007). Due to the field based nature of this study with data collection taking part in a school setting, direct contact with parents was not possible so this would not have been possible. Interestingly, the parental myopia, particularly in the Child cohort, was much lower than would be expected in an adult cohort at only 8.4%. This may explain the low prevalence of myopia in the Child cohort as parental myopia has been shown to be a strong indicator of childhood myopia. On reflection, it is unclear if this is related to a potential recruitment bias whereby myopic parents and therefore myopic children are already being seen regularly by an Optometrist so did not feel the need to take part in the study. Conversely, emmetropic individuals may not have had a sight test themselves as they are not symptomatic and therefore may not have taken their children for a sight test, despite a free eyecare in the UK for under 18s, and therefore may have been more interested in the taking part in the study. Conversely, in the Young Adult cohort the majority were undergraduate Optometry students so it was felt that they would likely be able to accurately identify the refractive error of their parents. In addition, the examiner KF was present at the time of questionnaire completion for this cohort so was able to answer any possible questions regarding parental refraction that arose.

As with any other study analysing questionnaire data, it must be acknowledged that it is subjective in nature and therefore subject to recall bias. Studies have shown that participants tend to overestimate the amount of time spent outdoors compared to objective measures (Ostrin, 2017, Alvarez and Wildsoet, 2013). For the parental questionnaire there may also have been a bias towards what the parents wants the perception of their child's behaviours to be as it is widely acknowledged that increased time on VDUs and smartphones are bad. Although it is made clear on the questionnaires

that all data will remain anonymise this also could have contributed to bias in the responses. The use of objective measures would provide a better and more accurate estimations of environmental factors. Objective measures of near work are currently available through the use of devices such as the Clouclip (HangZhou Glasson Technology Co., Ltd, China) and Vivior monitor (Vivior, Switzerland). These devices are glasses mounted devices are able to provide detailed information on reading distance, duration and angle. The Clouclip has recently been shown to actively modify near work behaviours by alerting the wearer, using a vibration, when their working distance is too short or after continuous periods of near work (Cao et al., 2020). This device therefore also provides the potential opportunity to be used in interventional studies to further our understanding of the relationship between near work and eye growth and myopia development. The combination of objective measures of near work with objective measures of light exposure using light sensor devices such as the Actiwatch 2 (Philips Respironics, USA), discussed in Chapter 9, would allow the relationship between near work and time outdoors to be more extensively and accurately explored.

7.6 Conclusions

The behaviour patterns of UK school children and young adults were established in this study. Significant associations between urbanisation, BMI and birth weight with eye growth were found. The questionnaire design limited the scope of the analysis within this Chapter. Future studies designed to address the limitations in this study are required to further explore the relationship between the effects of environment and lifestyle on eye growth. Modifications to the recruitment and retention strategies would also benefit this study to increase the sample sizes and also a longer study duration would allow the association between these factors and eye growth to be explored more extensively.

7.7 Summary

- A good parental questionnaire response rate was achieved of 83.2% (n=188/226)
- Children were found to spend more time outdoors and on VDUs at weekends compared to weekdays
- Young Adult spent significant less time outdoors and more time performing near and VDU tasks than children
- No significant associations between time outdoors and near and VDU tasks and axial length growth

- A significant association between urban residence and fast eye growth was found
- Overweight young adults were found to have a faster eye growth compared to those with a healthy BMI
- A trend for children born with a low birth weight to have faster eye growth was found

Chapter 8: Objective assessment of sleep patterns of UK children and the influence of eye growth

8.1 Introduction

In addition to the environmental and lifestyle factors explored in the previous Chapter, recent literature has suggested that circadian rhythms could play a role in eye growth (Chakraborty et al., 2018). Circadian rhythms are internal 24 hour cycles that regulate processes within the human body to coordinate environmental variations with behavioural and physiological activities, such as sleep/wake cycles. Diurnal fluctuations in ocular structures such as axial length and choroidal have been observed in adult and child populations (Burfield et al., 2018, Chakraborty et al., 2011, Ostrin et al., 2019, Stone et al., 2004). This suggests a possible important implication of circadian rhythms in eye growth and myopia development.

The most important signal for circadian rhythms is light which directly influences and regulates the sleep/wake cycle. The key neurohormone under circadian control is melatonin, whose levels are stimulated by darkness and inhibited in light (Cahill et al., 1991). A recent study has reported for the first time differences in melatonin levels between myopes and non-myopes in a young adult population (Kearney et al., 2017). Myopes were found to have significantly higher serum melatonin concentration, suggesting a possible link between circadian rhythms, light exposure and myopia.

Sleep is a crucial cycle regulated by circadian rhythms and several recent studies have investigated sleep in relation to refractive error. One study investigated the relationship between sleep duration and myopia in Korean adolescents aged 12-19 years old (n=3625) and found an inverse relationship between sleep duration and myopia (Jee et al., 2016). The odds of myopia were 41% less in participants who had >9 hours sleep compared to those with less than 5 hours (p=0.006). It was also found to have a dose-response with the risk of myopia decreasing by 10% per hour increase of sleep (p=0.012). This is consistent with a previous study of 15,316 Chinese children which found that children who had <7 hours of sleep had a 3.37 times higher risk of myopia than those with >9 hours (Gong et al., 2014). Another study used a sleep specific questionnaire (Pittsburgh Sleep Quality Index (PSQI)) to assess sleep quality in children aged 10 – 19 year old (Ayaki et al., 2016). It found that children with high myopia (≤-6.00D) had a poorer PSQI score than non-myopes (p<0.01). It concluded that myopic children were late and short sleepers and myopes tended to go to bed approximately 1 hour (74 minutes) later than non-myopes. However, two large scale studies based in

China found no evidence of an association between refractive error and sleep patterns in children (Wei et al., 2020, Zhou et al., 2015b). Wei et al (2020) were also able to show no association between sleep duration or bedtime with myopia progression or axial length due to the longitudinal nature of the study. All of these studies used subjective means for determination of sleep patterns which could explain the inconsistent findings.

Sleep patterns can be assessed objectively through a variety of methods including polysomnography, which involves observation of sleep in a clinic or laboratory setting where a number of biological features are recorded including brain waves, heart rate, respiratory rate and body movements. More recently non-invasive methods of monitoring sleep, termed actigraphy, have been developed, such as the Actiwatch 2 (Philips Respironics, USA) device used in this study. Light exposure data from the light sensor and physical activity through the accelerometer are combined to provide objective estimates of a number of sleep characteristics. The Actiwatch 2 has been shown to be as accurate as traditional methods of sleep analysis such as polysomnography (Pesonen and Kuula, 2018). Although a number of studies have used objective measures to evaluate sleep, there is currently only one published paper that has examined the differences in sleep between myopic and non-myopic children using objective means (Ostrin et al., 2020). This Australian based study showed that myopic children aged 10 – 15 years tended to have a more variable sleep duration than non-myopes. However, no significant influence of refractive error on bedtime, wake time and sleep duration was found.

With the known protective effect of light exposure and myopia, see Section 2.2, and the influence of light on sleep patterns, it is of interest to investigate this potential relationship further.

8.2 Rationale

Currently the only reference dataset for sleep duration for children in the UK is based on subjective responses from parental questionnaires as part of the ALSPAC, a prospective birth cohort, study (Blair et al., 2012). A recent meta-analysis has utilised objective sleep data from worldwide sources to establish normative values for paediatric sleep patterns (Galland et al., 2018). However, there is currently no normative objective dataset of sleep characteristics for children aged 7 – 12 years specifically in the UK. This Chapter will therefore provide detailed objectively measured sleep data of UK children aged 7 – 12 years old which could form the basis for a normative dataset. It will explore differences in sleep patterns as a function of day of the week and also season. In

addition, analysis of sleep patterns in relation eye growth will also be explored. The objective nature of this data will allow comparison of data sets from outside the UK.

8.3 Methodology

8.3.1 Actiwatch 2 (Philips Respironics, USA)

The Actiwatch 2 (Philips Respironics, USA), a wrist worn device, was used to provide objective information on actigraphy, more commonly known as sleep patterns. This device is able to combine information on light exposure from a light sensor and activity data from a piezo-electric accelerometer to provide sleep characteristics. The characteristics extracted directly from the device include: bed time, wake up time, total sleep time and number of awakenings, their definitions can be found in Table 8.1.

Sleep Statistic	Definition	Unit
Bed time	The start time of the longest rest interval in the 24-hour day	hr:min
Wake up time	The end time of the longest rest interval in the 24-hour day	hr:min
Total sleep time	Time between bed time and get up time	hr:min
Number of awakenings	The total number of wake bouts within the sleep intervals associated with the 24-hour day	Frequency

Table 8.1: Sleep statistics calculated from the Actiwatch 2 data and their definitions

8.3.2 Actiwatch schedule

The Actiwatch 2 device was worn by study participants in the Child cohort only (7 – 12 years). The device was programmed to record light exposure and physical activity every 30 seconds, equating to 2880 measurements/epochs per day. Participants were advised to wear the device on their wrist for 24 hours a day over an 11 day period during term time, see Figure 8.1.

Data Collection Period										
1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Fri	**Sat**	**Sun**	**Mon**	**Tue**	**Wed**	**Thu**	**Fri**	**Sat**	**Sun**	**Mon**

Figure 8.1: Schedule of Actiwatch wear Weekend days are highlighted in orange. Mon: Monday, Tue: Tuesday, Wed: Wednesday, Thu: Thursday, Fri: Friday, Sat: Saturday, Sun: Sunday

The devices were set to start recording at 12:00pm on a Friday and finish recording at 12:00pm on the following Monday. This allowed data on 10 consecutive bed times, 10 consecutive wake times and 10 consecutive full nights sleep to be collected. The devices were distributed a few days prior to the collection period to ensure that any initial potential alteration in sleep patterns had subsided prior to data recording and were collected on the following Tuesday.

Weekend bedtimes, sleep time and number of awakenings were classified as data collected on a Friday or Saturday evening i.e. the night before a weekend day and weekday bedtimes were classified as those prior to a weekday (this included Sunday, Monday, Tuesday, Wednesday and Thursday). Weekend wake up times were classified as those on a Saturday or Sunday. The sleep data from the Actiwatch 2 device was only included on datasets when the device had been worn for a minimum of 5 nights across the data collection period, this was assessed by observing the actogram created by the Actiware software (Version 6.0.9) and through the activity and light exposure data.

Logistically all participants were not able to wear the device over the same 11 day period and instead data was obtained over a 25 month period between May 2017 and June 2019. Data were subdivided into summer and winter seasons using the established cut offs implemented in the United Kingdom by British Summer Time (BST) to indicate the start of summer and the return to Greenwich Mean Time (GMT) to indicate the start of winter. The dates of which can be found in Table 8.2.

Year	British Summer Time (BST)	Greenwich Mean Time (GMT)
2017	26/03/17	29/10/17
2018	25/03/18	28/10/18
2019	31/03/19	27/10/19

Table 8.2: Start dates of British Summer Time (BST) and to Greenwich Mean Time (GMT) used for Summer and Winter season cut-off

8.3.3 Statistical analysis and sample size calculation

All data were analysed using SPSS® Version 25. All sleep characteristics, total sleep time, bed time, wake up time and number of awakenings, were continuous and were assessed for normality using Shapiro-Wilk and were all shown to be normally distributed ($p>0.05$). The correlation between these sleep characteristics with SER and eye growth as continuous variables were assessed with scatterplots and their associated R^2 values and Pearson's correlation coefficient (r). In addition, differences in sleep characteristics as a function of refractive status (myopic and non-myopic) and speed of eye growth

(slow and fast) with an independent t-test. Furthermore, analysis of differences in sleep characteristics between weekdays and weekends and season was assessed for participants with both datasets with a paired t-test.

8.4 Results

8.4.1 Participant characteristics

90 valid sleep data sets were obtained (Summer n=39 and Winter n=51) from 67 participants (23 participants had both Summer and Winter data).

The mean±SD age of participants was 9.2±1.1 years (range 7.5 – 11.3) with a predominantly female participant composition of 62.7% (n=42). The mean SER was +1.19±1.45D (range -4.75 – +5.57). Only 4.4% (n=3/67) were classified as myopic (SER ≤-0.50D in at least one eye).

8.4.2 Seasonal differences in sleep characteristics

Firstly, Seasonal differences in sleep patterns were explored by analysing the data from participants that had valid sleep data for both Summer and Winter (n=23), see Table 8.3.

In both Summer and Winter, participants woke up significantly later on weekends compared to weekdays (paired t-test $p<0.001$ mean difference +33 minutes and $p=0.001$ mean difference +32 minutes respectively). In addition, in Summer and Winter participants went to bed significantly later on weekends compared to weekdays (paired t-test $p<0.001$ mean difference +37 minutes and $p<0.001$ mean difference +36 minutes respectively). No significant difference in number of awakenings and total sleep duration was found between weekdays and weekends in Summer (paired t-test $p=0.951$ and $p=0.308$ respectively) or in Winter (paired t-test $p=0.772$ and $p=0.752$ respectively).

To allow comparison of seasonal sleep patterns only those participants with both valid Summer and Winter data were included in this analysis (n=23). No significant difference in bed time, wake up time, total sleep time or number of awakenings between Summer and Winter was found (paired t-test all $p>0.05$, see Table 8.3). Similarly, no seasonal differences in sleep characteristics between weekdays and weekends were found (paired t-test all $p>0.05$, see Table 8.3).

		Summer (n=23)	Winter (n=23)	p value†
Bed time (hr:min)	**All**	21:27±0:55 (19:44 – 23:03)	21:26±0:42 (20:13 – 22:43)	p=0.916
	Weekday	21:23±0:56 (20:06 – 23:46)	21:12±0:35 (20:11 – 22:07)	p=0.316
	Weekend	22:00±0:54 (20:06 – 23:46)	21:49±1:04 (19:33 – 23:47)	p=0.224
Wake up time (hr:min)	**All**	07:12±0:42 (05:56 – 09:05)	07:14±0:29 (06:26 – 08:21)	p=0.736
	Weekday	06:58±0:37 (05:46 – 08:31)	07:02±0:24 (06:01 – 07:57)	p=0.602
	Weekend	07:31±0:52 (05:46 – 09:47)	07:34±0:47 (06:19 – 09:06)	p=0.780
Total sleep time (hr:min)	**All**	8:09±0:24 (7:13 – 8:52)	8:18±0:23 (7:36 – 8:57)	p=0.089
	Weekday	8:13±0:28 (7:07 – 9:09)	8:21±0:21 (7:40 – 9:00)	p=0.177
	Weekend	8:03±0:38 (7:10 – 9:59)	8:18±0:42 (6:49 – 9:28)	p=0.120
Number of awakenings	**All**	43±9 (31 – 64)	42±10 (25 – 62)	p=0.762
	Weekday	43±10 (28 – 66)	43±11 (24 – 64)	p=0.977
	Weekend	43±9 (29 – 62)	42±11 (26 – 70)	p=0.807

Table 8.3: Seasonal sleep characteristics measured for participants with both Summer and Winter seasons (n=23) †: Paired t-test

8.4.3 Baseline sleep characteristics

As no seasonal differences in sleep characteristics were found the data from both seasons were collated in order to calculate daily sleep characteristics (n=67). For individuals with both Summer and Winter data (n=23), random assignment of either Summer or Winter dataset inclusion was undertaken whilst ensuring that an equal number of each season was included (Summer n=12, Winter n=11). Daily sleep characteristics are shown in Table 8.4 and the distribution in Appendix A.8.1.

The mean bed time was found to be significantly later on weekend days (22:08±1:08) compared to weekdays (21:22±0:51) (paired t-test $p<0.001$, mean difference +45 minutes). The mean wake up time was also found to be significantly later on weekends (07:41±1:00) compared to weekdays (07:04±0:34) (paired t-test $p<0.001$, mean difference +37 minutes). The distributions of weekday and weekend data for bed time

and wake up time are shown in Figure 8.2. Total sleep time and number of awakenings were found to not be significantly different between weekdays and weekends (paired t-test p=0.681 and p=0.522 respectively). No significant differences in sleep characteristics between males (n=25) and females (n=42) were found (independent t-test: bed time p=0.425, wake up time p=0.161, total sleep time p=0.631, number of awakenings p=0.963).

	Mean±SD (range) (n=67)			
	All days	**Weekdays**	**Weekends**	**p value†**
Bed time (hr:min)	21:39±0:53 (19:41 – 23:14)	21:22±0:51 (19:36 – 22:51)	22:08±1:08 (19:33 – 01:28)	**p<0.001**
Wake up time (hr:min)	07:18±0:40 (05:16 – 09:05)	07:04±0:34 (05:11 – 08:31)	07:41±1:00 (05:25 – 10:18)	**p<0.001**
Total sleep time (hr:min)	8:16±0:30 (6:56 – 9:43)	8:18±0:35 (6:50 – 9:44)	8:17±0:39 (6:15 – 9:36)	p=0.681
Number of awakenings	42±8 (25 – 64)	42±8 (24 – 65)	41±9 (21 – 63)	p=0.522

Table 8.4: Daily Sleep characteristics †: paired t-test

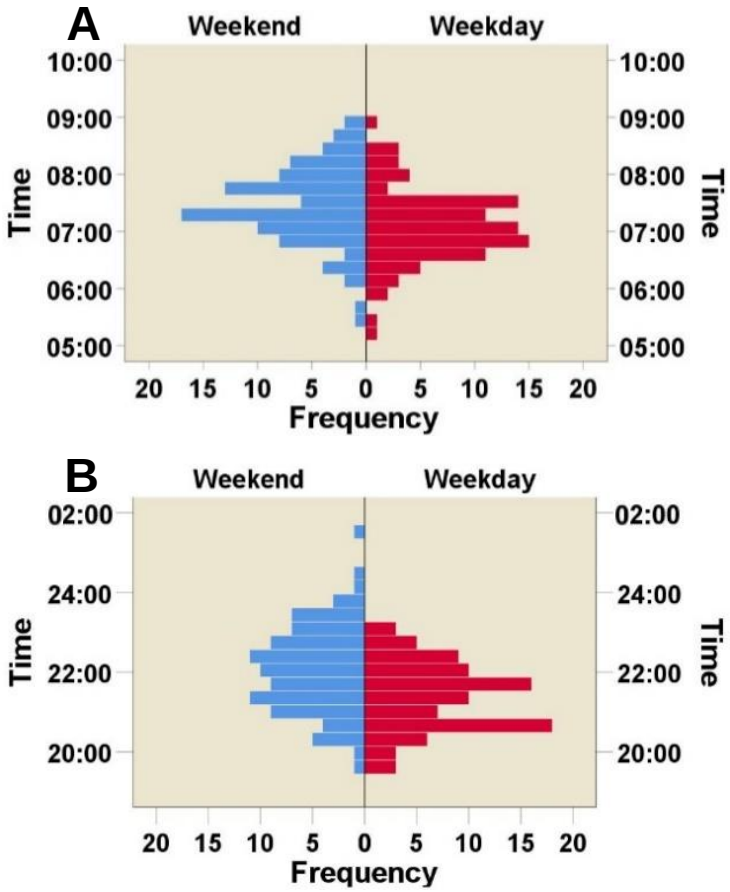


Figure 8.2: Distribution of weekend and weekday A) Bed time B) Wake up time

8.4.4 Sleep characteristics and SER

Sleep characteristics, refractive status and SER were also explored. No significant differences in bed time, wake up time, total sleep time or number of awakenings was found between myopes (n=3) and non-myopes (n=64) (independent t-test: bed time p=0.160, wake up time p=0.642, total sleep time p=0.079 and number of awakenings p=0.783).

No significant correlations were found between SER, change in SER between Baseline and Year 1 and change in SER between Baseline and Year 2 and sleep characteristics were found, see Table 8.5.

	SER			Change in SER					
				Baseline to Year 1			Baseline to Year 2		
	R^2	r	p	R^2	r	p	R^2	r	p
Bed time	0.032	-0.180	0.146	0.002	0.047	0.752	0.018	-0.135	0.646
Wake up time	0.002	-0.048	0.697	0.004	-0.063	0.673	0.111	-0.333	0.245
Total sleep time	0.025	0.157	0.203	0.034	-0.185	0.214	0.002	-0.044	0.882
Awakenings	0.000	0.002	0.989	0.001	-0.032	0.830	0.039	0.197	0.501

Table 8.5: Correlation of SER (n=67), change in SER (D) between Baseline and Year 1 (n=47) and Baseline and Year 2 (n=14) with sleep characteristics

As significant differences in bed time and wake up time between weekdays and weekends were found, correlations between SER and change in SER were also assessed by day of the week for these parameters. However again no significant correlations were found (SER: bed time weekday R^2=0.041, r=-0.202 p=0.101, weekend R^2=0.000, r=-0.016 p=0.899; wake up time weekday R^2=0.003, r=-0.052 p=0.077, weekend R^2=0.006, r=0.077 p=0.537. Change in SER Baseline to Year 1: bed time weekday R^2=0.001, r=-0.034 p=0.820, weekend R^2=0.009, r=0.094 p=0.529; wake up time weekday R^2=0.014, r=-0.118 p=0.429, weekend R^2=0.002, r=-0.046 p=0.758. Change in SER Baseline to Year 2: bed time weekday R^2=0.090, r=-0.301 p=0.296, weekend R^2=0.003, r=0.056 p=0.849; wake up time weekday R^2=0.104, r=-0.322 p=0.261, weekend R^2=0.192, r=-0.438 p=0.117).

The Winter and Summer season datasets were also analysed separately to identify any differences in sleep patterns within each season with regard to refractive status and SER, change in SER. In Summer, a significant difference in total sleep time between myopes (n=2) and non-myopes (n=37) was found (independent t-test p=0.018, mean difference -40 minutes). A similar difference was found in Winter between myopes (n=2)

*

and non-myopes (n=49) however it was not statistically significant (independent t-test: p=0.127, mean difference -38 minutes), see Figure 8.3.

For all remaining characteristics no significant difference was found between myopes and non-myopes (independent t-test: Winter: bed time p=0.347, wake up time p=0.876, and number of awakenings p=0.678. Summer: bed time p=0.347, wake up time p=0.876, and number of awakenings p=0.678).

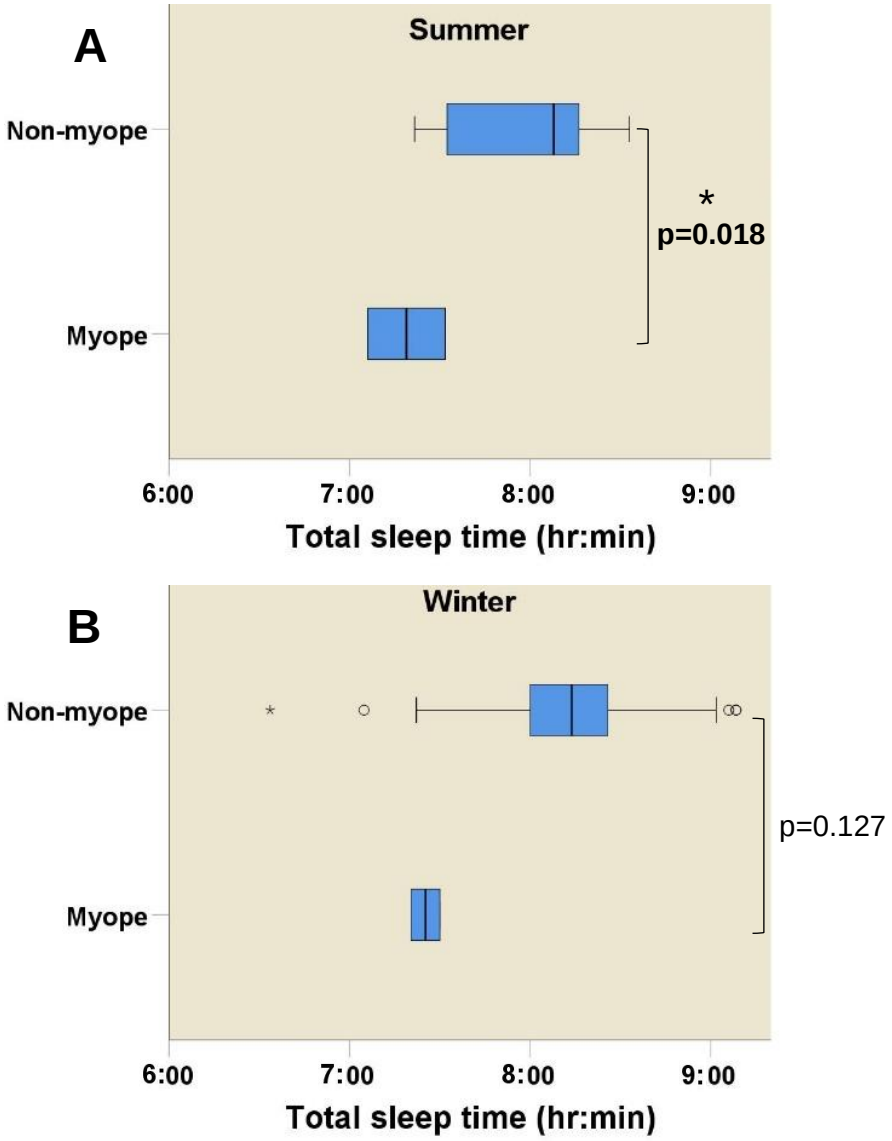


Figure 8.3: Total sleep time (hr:min) as a function of refractive error status in Summer and Winter

The correlation of SER with sleep characteristics was also analysed in each season. In Winter (n=51), a significant correlation between SER and total sleep was found (R2=0.100, r=0.317 p=0.024), however in Summer (n=39) no significant correlation was found (R2=0.011, r=-0.106 p=0.519), see Figure 8.4.

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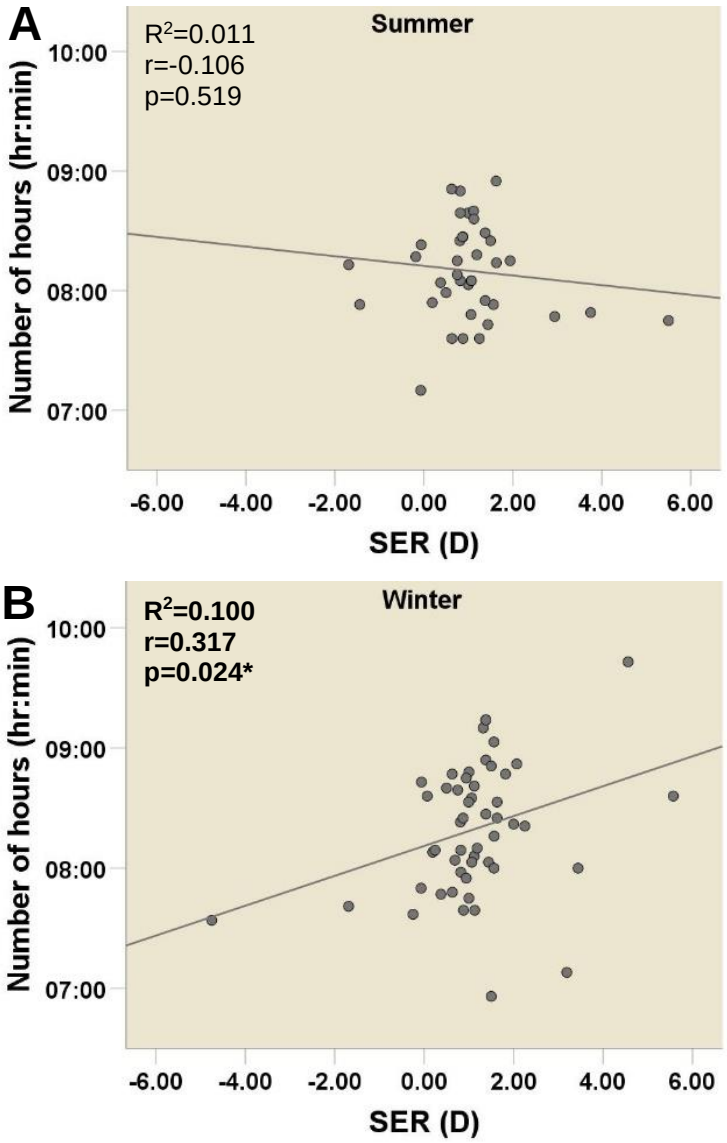


Figure 8.4: Correlation of SER and Sleep duration in A) Summer (n=39) B) Winter (n=51)

For all other sleep characteristics no correlations with SER were found (Summer: bed time R^2=0.000, r=-0.024 p=0.884, wake up time R^2=0.005 r=-0.073 p=0.659 and number of awakenings R^2=0.009, r=-0.096 p=0.561. Winter: bed time R^2=0.064, r=-0.252 p=0.074, wake up time R^2=0.001 r=-0.038 p=0.792 and number of awakenings R^2=0.005, r=0.069 p=0.630).

Correlations with sleep characteristics with change in SER between Baseline and Year 1 (B-Y1) and Baseline and Year 2 (B=Y2), were performed, see Appendix A.8.2. In Summer, two significant correlations were found between change in SER (B-Y1) and bed time (R^2=0.187 r=-0.432 p=0.019) and change in SER (B-Y1) and wake up time

(R^2=0.191 r=-0.436 p=0.018), see Figure 8.5. In Winter no significant correlations between any sleep characteristics and change in SER were found.

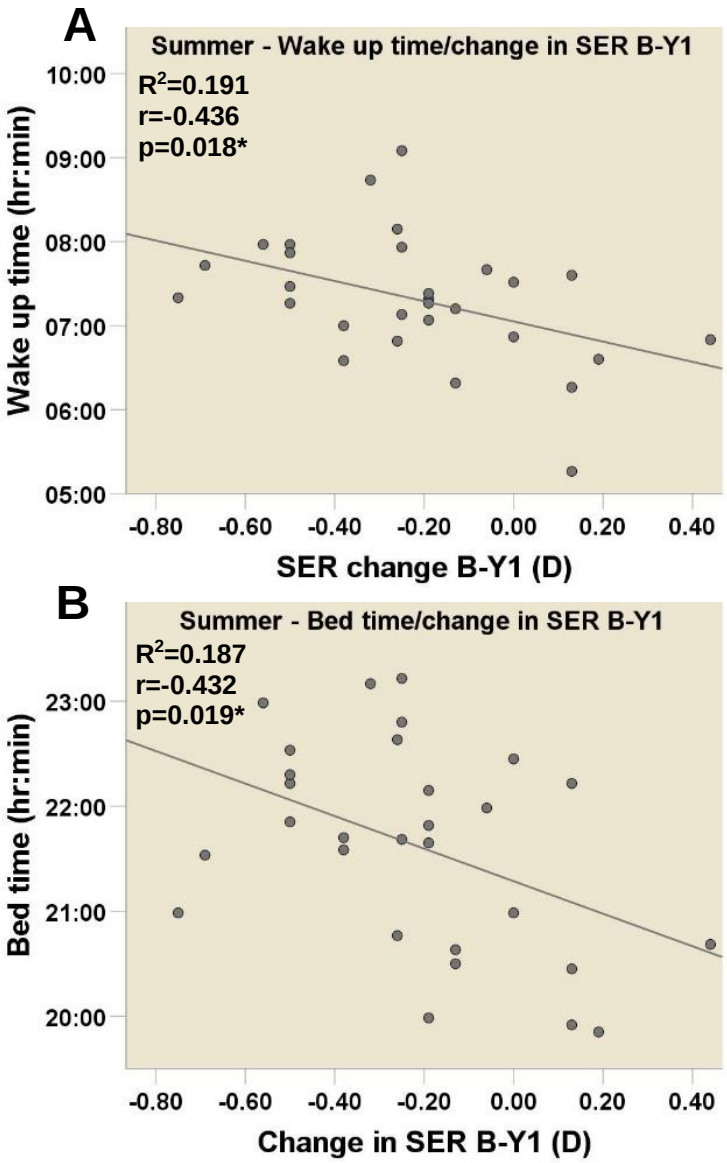


Figure 8.5: Significant correlations found in Summer between A) Wake up time and SER change B-Y1 (D) (n=29) B) Bed time and SER change B-Y1 (D) (n=29)

8.4.5 Sleep characteristics and eye growth

No significant correlations were found between AL, change in AL between Baseline and Year 1 and between Baseline and Year 2 and sleep characteristics were found, see Table 8.6.

	AL			Change in AL					
				Baseline to Year 1			Baseline to Year 2		
	R^2	r	p	R^2	r	p	R^2	r	p
Bed time	0.011	-0.106	0.395	0.003	-0.054	0.723	0.060	0.245	0.361
Wake up time	0.042	-0.204	0.100	0.018	0.135	0.372	0.000	-0.004	0.987
Total sleep time	0.003	-0.058	0.645	0.010	0.098	0.517	0.011	-0.106	0.696
Awakenings	0.003	-0.051	0.685	0.036	0.191	0.204	0.193	-0.439	0.089

Table 8.6: Correlation of AL (n=67), change in AL (mm) between Baseline and Year 1 (n=46) and Baseline and Year 2 (n=16) with sleep characteristics

As significant differences in bed time and wake up time between weekdays and weekends were found, correlations between AL and change in AL were also assessed by day of the week for these parameters. However again no significant correlations were found (AL: bed time weekday R^2=0.024, r=-0.154 p=0.216, weekend R^2=0.008, r=-0.091 p=0.468; wake up time weekday R^2=0.043, r=-0.207 p=0.095, weekend R^2=0.056, r=-2.37 p=0.056. Change in AL Baseline to Year 1: bed time weekday R^2=0.000, r=-0.005 p=0.975, weekend R^2=0.015, r=-0.124 p=0.410; wake up time weekday R^2=0.033, r=-0.182 p=0.226, weekend R^2=0.003, r=-0.052 p=0.734. Change in AL Baseline to Year 2: bed time weekday R^2=0.060, r=0.244 p=0.362, weekend R^2=0.036, r=0.189 p=0.484; wake up time weekday R^2=0.019, r=-0.137 p=0.612, weekend R^2=0.074, r=-0.273 p=0.307).

The Winter and Summer season datasets were also analysed separately to identify any differences in sleep patterns within each season with regard to AL and eye growth.

Correlations with sleep characteristics with axial length (AL) and eye growth between Baseline and Year 1 (B-Y1) and Baseline and Year 2 (B-Y2) were performed, see Appendix A.8.2. In Summer, one significant correlations was found between change in AL (B-Y2) and bed time (R^2=0.416 r=0.654 p=0.044) and in Winter, only one significant correlation was found with AL and wake up time (R^2=0.087 r=-0.294 p=0.038), see Figure 8.6.

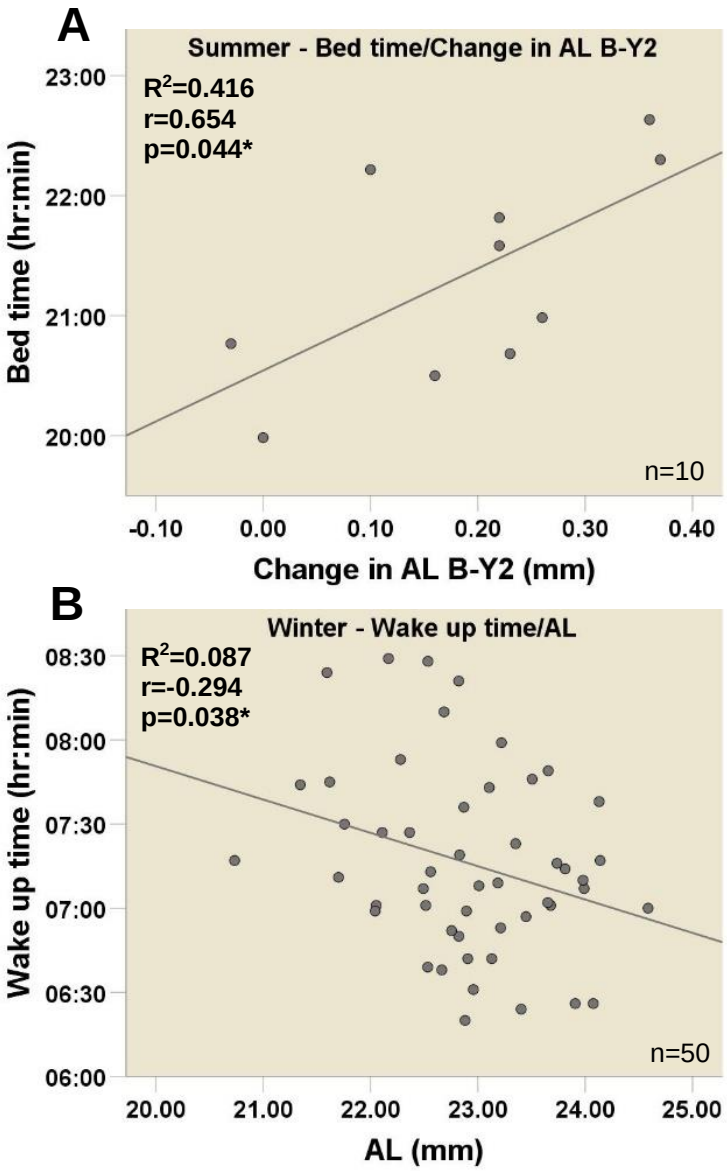


Figure 8.6: Significant correlations found in Summer between A) Bed time and change in AL B-Y2 (mm) (n=10) and in Winter between B) Wake up time and AL (mm) (n=50)

8.5 Discussion

Sleep/wake cycles are closely entwined with circadian rhythms which are internal 24-hour cycles that regulate processes within the human body and coordinate environment variations with behavioural activities. There is emerging evidence that circadian rhythms are atypical in myopic eyes (Chakraborty et al., 2018). The use of a wrist worn device to measure sleep patterns allowed exact bed time, wake time and total sleep duration to be objectively quantified. Previous studies have relied upon questionnaire responses which rely on considerable recall bias. The Actiwatch 2 device used in this study has been shown to be as accurate as traditional methods of sleep analysis such as

polysomnography (Pesonen and Kuula, 2018). It is arguably a more natural representation of sleep which is less invasive as participants are able to be monitored at home in their normal sleeping environment. This study has been able to investigate differences in sleep patterns during term time by day of the week and also seasonal variations as the data was collected over a 25 month period. As expected, children went to bed significantly later on weekends compared to weekdays and they woke up later on a weekend day compared to a weekday, this pattern was consistent across both Winter and Summer periods. However interesting no difference in total sleep time or number of awakenings was found by day of the week of season. This data suggests that during school term time sleep patterns remain constant throughout the week and the year, this is despite significant seasonal differences in weather and day length, explored as part of the next chapter, see Section 9.4.4. As data collection took place during school term time, it would be interesting to collect data of sleep patterns during school holidays and observe if differences occur compared to term time sleep patterns. This is a limitation of this study as term time sleep patterns could be influenced by school start times and without this requirement sleep patterns may be altered. For example, outside of term time children may not need to wake up at a certain time to ensure they arrive at school on time and equally they may be allowed to stay up later. As a result, this could cause the sleep/wake cycle to take on a different pattern more attuned to their natural biological rhythm rather than artificially altered through the use of alarm clocks. In addition, children's daily activities are also likely to be altered outside of term time which could influence their sleep pattern. For example, they may spend more time undertaking physical activities rather than sitting in a classroom during term time and therefore may be more physically exhausted and require more sleep. The logistical barriers of distribution and collection of devices outside of term time would need to be considered as in this study all data collection and communication was done through the schools themselves.

Despite a low number of sleep pattern datasets for myopes in this study, 4.4% (n=3/67), a significant difference in the sleep duration was found in Summer, with myopes having significant less sleep than non-myopes on average by 40 minutes In Winter, although a similar difference in sleep duration was found, with myopes found to sleep for 38 minutes less than non-myopes, however it was not significant. The correlation of SER with sleep characteristics was explored and when the datasets were analysed all together, no significant correlations were found. However, exploring the data by season, in Winter a significant correlation was found with less sleep associated with a more myopic SER. The Summer correlation of SER and sleep duration was found to be not

significant. The Winter correlation was aided by a participant with an SER of -4.75D who was not captured in the Summer data. Removal of this data point made the correlation not significant (R^2=0.064, r=-1.06 p=0.519), this shows that recruitment of participants with myopic SER would greatly benefit the analysis of these correlations.

The trend for less sleep associated with a more myopic SER found in this study, is consistent with previously published data that also found an inverse relationship between myopia and sleep in children and teenagers (Jee et al., 2016, Gong et al., 2014). Both studies found that the risk of myopia was significantly higher in those that had less sleep. In addition, a dose-response with the risk of myopia decreasing by 10% per hour increase of sleep has been found (Jee et al., 2016). Both of these studies used questionnaire responses to estimate sleep duration. No subjective estimate of sleep duration was obtained in this study however comparison of responses of Chinese participants aged 6 – 18 by Gong et al (2014) (n=15,101) to the Winter sleep data from this study (n=51) is shown in Table 8.7.

Sleep duration	Gong et al (2014) (n=15,101)	This study (n=51)
9 hours or more	37.6% (n=5,675)	41.2% (n=21)
8 hours	32.2% (n=4,859)	53.0% (n=27)
7 hours or less	30.2% (n=4,567)	5.9% (n=3)

Table 8.7: Comparison of sleep duration data from subjective questionnaire responses of Chinese participants aged 6 – 18 years (Gong et al, 2014) and objective measurements during the Actiwatch 2 device in this study of UK children aged 7 – 12 years The frequency of 7 hours or less was lower in this study compared to Gong et al (2014), (5.9% vs 30.2% respectively). These differences could be attributed to an underestimation of self-reported sleep duration from questionnaire responses. However, they also could be indicative of differences in lifestyle between the UK and China. The intensity of the education in Asian counties is much higher with school often starting between 07:00-08:30 and finishing between 16:30-18:00 compared to an average 09:00 start and 15:00 finish in the UK. In addition often children attend private tuition sessions in the evenings sometimes until 21:00 or even 24:00 (Yang et al., 2005).

Sleep characteristics and longitudinal changes in refraction and axial length growth were also explored and showed some interesting results. In Summer, a more myopic SER change between Baseline and Year 1 was correlated with waking up and going to be bed significantly later. In addition, the strongest correlation (R^2=0.416) was found

between bed time and axial length growth between Baseline and Year 2, with those with a faster AL growth going to bed significantly later. In Winter, only one significant correlation was found with those with a longer AL getting up significantly earlier. These significant correlations also provide support for sleep characteristics playing a role in myopia onset and development.

In addition to objective sleep patterns through the use of devices such as the Actiwatch 2 used in this study, further objective measures of circadian rhythms could be explored through the sampling of melatonin levels through blood or saliva collection. A previous study has shown that myopes have significantly higher melatonin levels compared to non-myopes (Kearney et al., 2017).

8.6 Conclusions

This is an emerging field of myopia research and this study has provided exploratory data on sleep patterns of UK children and their correlation with refractive and AL parameters. There is currently no normative objective dataset of sleep characteristics for children aged 7 – 12 years specifically in the UK and therefore this study could be considered the basis of a normative objective dataset. Further recruitment of myopic children alongside longitudinal data on AL change will provide insight into the role of sleep and myopia development.

8.7 Summary

- Explorative objective data on sleep patterns in a UK child cohort aged 7 – 12 years was collected and forms the basis of normative dataset
- Children went to bed later and got up later on weekends compared to weekdays. No seasonal differences in sleep patterns was found.
- A significant correlation of SER with total sleep was found with less sleep associated with a more myopic SER.
- A more myopic SER shift was associated with a later bed time and wake up time
- A faster AL growth was also associated with a later bed time

Chapter 9: Patterns of daily outdoor light exposure and eye growth in UK children

9.1 Introduction

There is growing evidence from both human and animal studies showing that various aspects of light including illuminance levels and spectral composition are important visual cues involved in the regulation of eye growth, see Section 1.4.1.3. High illuminance levels have been found to directly impact on axial length growth and protect against the development of form deprivation myopia in chicks (Ashby et al., 2009, Ashby and Schaeffel, 2010). Similar findings were found in infant monkeys and tree shrews exposed to high ambient lighting (Smith et al., 2012, Siegwart et al., 2012, Wang et al., 2015). Seasonal variations in eye growth have been found in school children with consistent findings of slower eye growth in summer compared to winter (Donovan et al., 2012, Fulk et al., 2002, Gwiazda et al., 2014a). These support the potential role of light exposure in the control of human eye growth. In addition, consistent findings of increased time outdoors providing a protective effect against myopia development and progression further support this theory, as discussed in Section 2.2.

Historically estimations of light exposure have been based on subjective responses from children or their parent/guardian through the use of questionnaires. These rely heavily on memory recall and ultimately may not give an accurate estimate or representation of light exposure. Alvarez and Wildsoet (2013) investigated the accuracy of self-reported light exposure in 27 young adults (18 – 25 years) compared with objective data recorded via a light sensor (HOBO Pendant) worn over a two week period on the upper arm. This demonstrated a recall bias with consistent overestimate of time spent outdoors and indoors, see Figure 9.1.

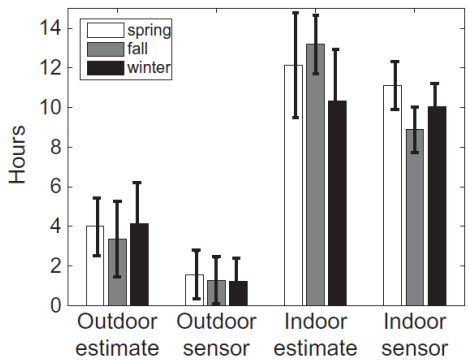


Figure 9.1: Comparison of questionnaire response of time spent indoors and outdoors compared to sensor measurements Reproduced with permission from (Alvarez and Wildsoet, 2013)

A similar overestimation of time outdoors was found in a recent study by Ostrin (2017) who found that participants (aged 21 – 65 years) overestimated on average 0:25±1:19 hours per day (range -1:49 to +4:29 hours) spent outdoors.

Objective light exposure can be measured through the use of light sensors which have the ability to quantitatively measure light exposure and also provide information on, not only the duration, but also the intensity of light. These sensors can be wrist worn, for example the Actiwatch 2 (Philips Respironics, USA) used in this study, pendant style which can be fixed onto clothing, for example HOBO Pendant (Onset Computer Corp., USA) or glasses mounted, for example Clouclip (HangZhou Glasson Technology Co., Ltd, China) and Vivior monitor (Vivior, Switzerland). A recent pilot study has compared a wrist worn sensor (Actiwatch 2) and a pendant style sensor (HOBO Pendant) worn on the shirt, with 10 adult participants simultaneously wearing these devices (Read et al., 2018). The HOBO pendant was found to overestimate the light exposure however estimates of time spent outdoors were similar. This could be explained by the positioning of the device as the Actiwatch 2 is worn on the wrist whereas the HOBO pendant was positioned on the shirt.

The use of objective light measurements has emerged in the area of myopia research in only a small number of recent studies primarily based in USA and Australia and also in Singapore (Ostrin, 2017, Ostrin et al., 2018, Read et al., 2014, Read et al., 2015, Ulaganathan et al., 2019, Read et al., 2018, Dharani et al., 2012). A significant relationship between objectively measured light exposure and eye growth has been shown in children (10 to 15 years) and young adults (18 to 30 years) with more light exposure resulting in a slower axial growth (Ulaganathan et al., 2019, Read et al., 2015, Ostrin et al., 2018). Read et al (2015) found the annual eye growth of children aged 10 – 15 years exposed to low light exposure, defined as less than mean daily light exposure ≤ 651 lux, was significantly faster than those exposed to high light exposure, defined as ≥1020 lux, 0.13mm/year compared to 0.065mm/year respectively. This is consistent with previously published literature that has shown the protective effect of time outdoors using primarily questionnaire data, discussed in Section 2.2.

In this longitudinal study, objectively measured light exposure will be correlated with refractive and biometric data to provide a more comprehensive insight into the role of light exposure and eye growth within a UK population. The use of the light sensor will provide objective data on, not only duration, but also intensity of light exposure and also frequency of outdoor exposure. Furthermore, data from a cross section of the UK will be sampled to allow identification of variations in light exposure across different

latitudes. The ability to measure light exposure objectively is invaluable in this study where quantification of environmental factors is essential.

9.2 Rationale

There is currently no published data on objectively measured light exposure of UK children. This Chapter will explore the average daily light exposure experienced by school children in UK as well as investigate the impact of season, day of the week and latitude on this exposure. From the light exposure data objective measures of outdoor exposure can be evaluated to assess the quantity of time spent outdoors. By using similar methodologies to studies investigating light exposure in children from other countries including Australia and the USA, direct comparisons in light and outdoor exposure can be made. The longitudinal nature of this study will also provide novel data on the influence of light exposure upon eye growth in UK children. This in turn could help to further our understanding of possible mechanism of the protective effect of time outdoors. In addition, the impact of light sensor orientation on recorded light exposure measurements will also be evaluated to allow a better understanding of the influence of positioning when using wrist worn sensors.

9.3 Methodology

9.3.1 Actiwatch 2 (Philips Respironics, USA)

Light exposure and physical activity were measured using the Actiwatch 2 (Philips Respironics, USA), a wrist worn device using a silicon photodiode light sensor. The technical specifications can be found in Section 4.5. The study was conducted with a total of 16 Actiwatch 2 devices; 4 of which were lost and 3 were broken during the duration of the study. All 16 devices were calibrated prior to data acquisition to ensure consistent light exposure readings between the devices. The watches were mounted side by side and carried between four different lighting environments: outdoors (high illuminance), outdoors (low illuminance), indoors (high illuminance) and indoors (low illuminance). All sixteen watches were programmed to record illuminance every 15 seconds and were placed in each environment for a 15 minute period equating to 60 time points or epochs.

When the data were extracted from the watches there was an error with watch 5 and no data could be retrieved. Data from the other watches were analysed and the correlation coefficients were calculated and can be found in Table 9.1. The correlation coefficient was found to be at least 0.99 for all watches except watch 6.

Watch	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1																
2	1.00															
3	0.99	0.99														
4	0.99	0.99	0.99													
5	X	X	X	X												
6	0.90	0.90	0.90	0.89	X											
7	1.00	1.00	0.99	0.99	X	0.90										
8	0.99	0.99	0.99	0.99	X	0.90	0.99									
9	1.00	1.00	0.99	0.99	X	0.90	1.00	0.99								
10	1.00	1.00	0.99	0.99	X	0.90	1.00	0.99	1.00							
11	0.99	1.00	0.99	0.99	X	0.91	0.99	0.99	1.00	1.00						
12	0.99	0.99	0.99	0.99	X	0.89	0.99	0.99	0.99	0.99	0.99					
13	1.00	1.00	0.99	0.99	X	0.90	1.00	0.99	1.00	1.00	1.00	0.99				
14	0.99	1.00	1.00	0.99	X	0.90	0.99	0.99	0.99	0.99	1.00	0.99	1.00			
15	0.99	0.99	0.99	0.99	X	0.90	0.99	0.99	0.99	0.99	0.99	0.99	0.99	0.99		
16	0.99	0.99	1.00	0.99	X	0.90	0.99	0.99	0.99	0.99	0.99	0.99	1.00	0.99	0.99	

Table 9.1: Correlation coefficients for each watch in the first calibration study

A repeat calibration study was performed, and another error occurred with watch 5 and watch 6 was still found not to be calibrated. These two watches were sent to the manufacturer who replaced one and repaired the other. A third calibration study was undertaken with watches 5 and 6 and two of the other calibrated watches. Following on from this calibration study both watch 5 and 6 were found to be calibrated, see Table 9.2.

Watch	5	6	8	9
5				
6	1.00			
8	1.00	1.00		
9	1.00	1.00	1.00	

Table 9.2: Correlation coefficients for four watches in the third calibration study

9.3.2 Actiwatch schedule

The Actiwatch 2 (Philips Respironics, USA) light sensor device was used to measure the ambient light exposure and physical activity of study participants in the Child cohort only (7 – 12 years). The devices were programmed to record light exposure and physical activity every 30 seconds, equating to 2880 measurements/epochs per day. This is in line with other studies evaluating light exposure and refractive error change (Read et al., 2014, Read et al., 2015). Illuminance levels were measured over an 11 day period during term time (9 full days and 2 half days). The devices were set to start recording at 12:00pm on a Friday and finish recording at 12:00pm on the following Monday. This

ensured that 1 full week and 2 full weekends were sampled, see Figure 9.2. This period was selected as weekends were felt to be the most variable part of the week. The devices were distributed a few days prior to the collection period to ensure that any initial potential alteration in activity had subsided prior to data recording and were collected on the following Tuesday.

Data Collection Period										
1	2	3	4	5	6	7	8	9	10	11
Fri	Sat	Sun	Mon	Tue	Wed	Thu	Fri	Sat	Sun	Mon

Figure 9.2: Schedule of Actiwatch wear Weekend days are highlighted in orange. Mon: Monday, Tue: Tuesday, Wed: Wednesday, Thu: Thursday, Fri: Friday, Sat: Saturday, Sun: Sunday

Participants were advised to wear the device on their wrist for 24 hours a day even during sleep and were advised to ensure that it is not obstructed by clothing especially when outside in winter due to the increased likelihood of coverage due to coat sleeves. It was only advised to be removed when swimming, showering or bathing. For information sheet distributed to participants see Appendix A.9.1.

Logistically all participants were not able to wear the device over the same 11 day period and instead data was obtained over a 25 month period between May 2017 and June 2019. Data were subdivided into summer and winter seasons using the established cut offs implemented in the United Kingdom by British Summer Time (BST) to indicate the start of summer and the return to Greenwich Mean Time (GMT) to indicate the start of winter. The dates of which can be found in Table 9.3.

Year	British Summer Time (BST)	Greenwich Mean Time (GMT)
2017	26/03/17	29/10/17
2018	25/03/18	28/10/18
2019	31/03/19	27/10/19

Table 9.3: Start dates of British Summer Time (BST) and to Greenwich Mean Time (GMT) used for Summer and Winter season cut-off

9.3.3 Actogram

Following the return of the Actiwatches the data from each device was extracted, using the Actiware software Version 6.0.9, into Microsoft Excel® (Office 365, Version 2001) spreadsheets detailing the amount of white light (lux) and activity (cpm) per each 30

second time point or epoch. For each data acquisition period an Actogram was produced, see Figure 9.3 and the raw data on light illuminance and activity were exported for further analysis. This was used to assist with screening compliance of Actiwatch wear.

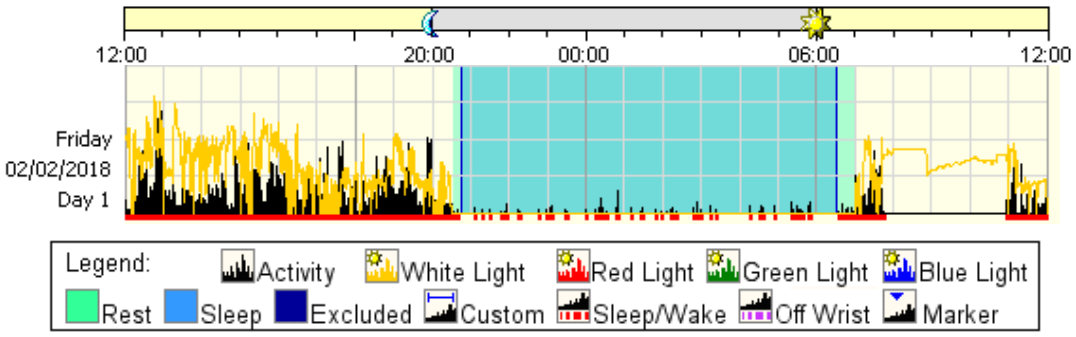


Figure 9.3: Example 24 hour actogram

9.3.4 Screening for compliance and data analysis

The screening protocol used in this study is taken from published data from Australia to allow direct comparison (Read et al., 2014).

Only data from full days was included in screening and analysis. Daytime hours were defined as between 7am and 7pm (12 hour period). Data from the two half days (day 1 and day 11) were removed prior to analysis, allowing a 9 day period to analysed and assessed for compliance.

In order to assess for compliance, the data were initially screened to remove any invalid data, this included periods when the watch had been removed, defined as 15 minutes or more when zero activity was recorded during daytime hours (7am-7pm) and periods when the light sensor had been covered, for example with clothing, defined as 15 minutes or more when illuminance was recorded as 0.01 lux (indicating total darkness) during daytime hours (7am-7pm). These periods can be visualised by examining the Actogram. For example in Figure 9.3, between the hours of 8:00am and 11:00am no physical activity is recorded, it can be assumed that the watch was not worn during this period. Additionally, intermittently throughout the daytime hours the white light level, indicated by the yellow line touches the x-axis indicating extremely low light levels and it can be assumed that during these periods the light sensor was covered or obscured. Although these periods can be visualised on the actograms, these periods were more accurately identified through analysis of the exported individual data points in a Microsoft Excel® (Office 365, Version 2001) spreadsheet.

As data were obtained every 30 seconds, invalid periods of 30 consecutive data points or more (indicating a 15 minute period or more) which either showed total darkness (<0.01 lux) or inactivity (0 cpm) during the daytime hours (7am – 7pm) were identified and removed. Only days that included 90% valid data between daytime hours (7am – 7pm) were included in the analysis. For these valid days the removed data were substituted with average data for the same time period on valid days. This equated to a maximum of 144 invalid data points out of 1440 per day, allowing a maximum of 72 minutes of substituted data per day. As mentioned previously, this is in line with previously published data from Australia to allow a direct comparison (Read et al., 2014).

Following the screening and substitution of the data, analysis was only performed on data sets that had a minimum of 5 valid days of data i.e. >90% daily valid data with the remainder substituted with averaged data from the same time period. These data were used to determine average hourly and daily light exposure and time outdoors between weekdays/weekends and summer/winter. Each individual data set was analysed to determine average number of minutes spent in light levels >1000 lux to estimate outdoor exposure. A cut off of 1000 lux for outdoors was used which has been established in other studies examining light levels and refractive error change (Ostrin, 2017, Dharani et al., 2012, Alvarez and Wildsoet, 2013, Ostrin et al., 2018, Read et al., 2015, Read et al., 2014).

9.3.5 Light sensor orientation analysis

The Actiwatch 2 (Philips Respironics, USA), as mentioned previously, is a wrist worn device. As the device is worn on the wrist the direction of the sensor varies constantly with movement of the arm and subsequently the wrist. Therefore, the light sensor is rarely perpendicular the nearest light source, for example ceiling lights, when indoors and the sun, when outdoors. The degree to which this rotational orientation may affect the light exposure readings was investigated by placing five watches at five orientations 0 degrees, 45 degrees, 90 degrees, 135 degrees and 180 degrees to a horizontal plane, this is illustrated in Figure 9.4. These watches were placed in touching proximity and they simultaneously recorded illuminance levels in four conditions: Outdoors (high illuminance), Outdoors (low illuminance), Indoors (high illuminance) and Indoors (low illuminance). The devices were set to collect data every 30 seconds during a 15 minute period in each condition, equating to 30 data points/epochs for each device. This was performed on the same day and consecutively using five previously calibrated devices.

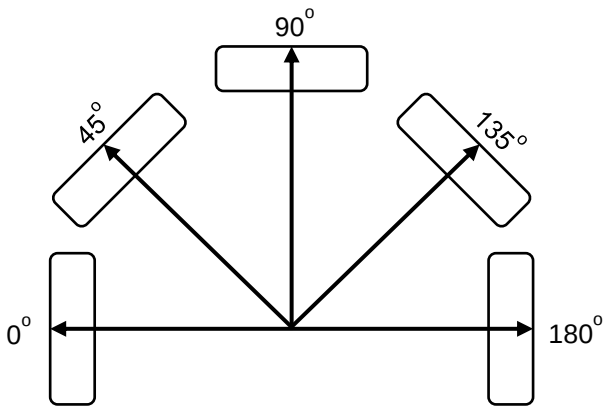


Figure 9.4: Diagram of the light sensor rotational directions along the horizontal plane

9.3.6 Refractive error assessment

Refractive error was measured using cycloplegic autorefraction and defined by first calculating the spherical equivalent refraction (SER) using the equation: sphere + ½ cylinder. The refractive error classifications definitions used in this study are summarised in Table 9.4. These definitions are in line with previously published data, see Table 1.1 in Section 1.6.

An assessment of right eye (RE) and left eye (LE) SER correlation at baseline found a highly significant strong correlation (R^2=0.877, r=0.937 p<0.001), see Section 5.5.1.2.2. Therefore, only data from RE data are presented in this Chapter.

Category	Definition
Myopia	SER ≤ -0.50D in at least one eye
Emmetropia	SER > -0.50D to <+2.00D in both eyes
Hyperopia	SER ≥ +2.00D in at least one eye as long as neither eye was myopic
Astigmatism	Cylindrical power ≤ -1.00 DC in either eye

Table 9.4: Refractive error classification definitions

9.3.7 Biometry assessment

Consistent with the other research chapters, only RE data on axial length (AL) from the Aladdin biometer will be presented in this chapter due to the good agreement with the IOLMaster 500, see Chapter 6. Details of the technical specifications and biometric measurement acquisition method can be found in Section 4.3.

9.3.8 Questionnaire data

The questions regarding amount of time outdoors varied between the two questionnaires, see Section 7.3.1 and Appendix A.5.5.

Child questionnaire responses

In the Child questionnaire, due to the age of the participants a single question was asked regarding time outdoors, “How many hours do you spend outdoors each day?” This was followed by four categorical options: none, less than 1 hour, 1-2 hours or 2 or more hours. Questionnaire responses were taken on the day of the study and these were categorised as Summer or Winter estimates of time outdoors using the agreed cut offs outlined in this chapter, see Section 9.3.2. These questionnaire responses were then compared to the objective responses only if they were from the same season.

Parental questionnaire responses

Parental questionnaire data was available for 95.8% (n=91/95) of objective data sets and direct seasonal comparisons were able to be compared. In the Parental questionnaire, more in depth questioning regarding time outdoors was undertaken. This included: “How much time does your child spent outdoors on a weekday/weekend in Winter/Summer?” As a result, four estimates of time outdoors were obtained from the parental questionnaire using four categorical options: none, less than 1 hour, 1-2 hours or 2 or more hours.

In order to compare the subjective responses of parental questionnaires with the child questionnaire responses and assess the ability to accurately estimate time outdoors, only data on weekdays and the corresponding seasons as outlined by the child responses was used.

9.3.9 Statistical analysis and sample size calculation

All data were analysed using SPSS® Version 25. All parameters were assessed for normality using Shapiro-Wilk, Q-Q normality plots and observation of histogram distributions. The primary outcomes of mean hourly and daily light exposure, maximum light exposure and minutes >1000 lux were all not normally distributed (Shapiro Wilk $p<0.001$), therefore non-parametric statistics were used in their analysis. Comparison of these parameters between day of the week (weekdays vs weekends) and season (Summer and Winter) were assessed with a related samples Wilcoxon Signed Rank test. Previously published data have reported parametric statistics and therefore to

allow direct comparison with this data, mean±SD will alternatively be presented in the Appendix A.9.4 and will be used in this discussion for comparison purposes.

The correlation between longitudinal eye growth over a 12 month period and average light exposure and outdoor exposure was examined with scatterplots and their associated R^2 values, Pearson's correlation coefficient (r). In addition, differences in axial length (AL) in three average light exposure categories, low, average and high was also examined. Summer data sets were selected for this analysis due to the increased range in light exposure compared to Winter which would allow better differentiation of the categories. Categorical differences were assessed with Kruskal Wallis for those with 3 or more categories (geographical region and categorical light and outdoor exposure groups) and Mann Whitney U test for those with 2 categories (sex) and also as a post-hoc for significant Kruskal Wallis outcomes. The correlation between seasonal differences in mean daily light exposure and outdoor exposure was assessed with scatterplots and their associated R^2 values, Pearson's correlation coefficient (r).

To compare child and parental questionnaire responses to the objective measure of time outdoors, estimated by number of minutes >1000 lux from the Actiwatch 2 device, a weighted kappa (κ_w) statistic was used. Prior to this analysis all objective measures were converted into categorical data using the same categories given in the questionnaires (None, less than 1 hour, 1-2 hours or 2 or more hours) thus allowing direct comparison. Frequencies of correct responses were obtained by comparison of the questionnaire responses to the objective time outdoors estimate (considered as reference) with an expectation of 1:1 using chi squared goodness of fit test. Contingency tables were also used to assess the relationship between subjective and objective categorical responses to the amount of time spent outdoors. Further comparison was undertaken by calculating the amount and direction of subjective over or under estimation of the amount of time spent outdoors by calculating the deviation of the subjective category of the objective categorical estimate (considered the reference). For example, if the subjective response was 1-2 hours and the objective estimate was within the 2 or more hours category this would be given a -1 score i.e. the subjective response underestimated the amount of time spent outdoors by 1 category.

Illuminance levels recorded in the four conditions at different sensor orientations were found to be not normally distributed as assessed by Shapiro-Wilk's test ($p<0.05$). Analysis of the impact of the sensor orientation on illuminance values was assessed with Kruskal Wallis test with post hoc Mann Whitney U test.

Due to the exploratory nature of these primary outcomes and limited comparative published literature, sample size and power calculations were performed post-hoc using G*Power software (version 3.1.9.4) and are presented in the discussion.

9.4 Results

9.4.1 Data acquisition, screening and valid data sets

167 data acquisition sessions, from 109 participants, took place over a 25 month period between May 2017 and June 2019. 18 unsuccessful data acquisition sessions took place: 6 had battery problems during data collection resulting in <75% of data recorded, 3 were broken during data collection (one the strap broke, one had a crack in the housing which was repaired by the participant using cellotape which obscured the light sensor so was excluded and the other would not connect to dock for data extraction), 4 were not returned, 2 did not record activity data so validity could not be assessed and 3 were excluded as the watch numbers returned did not match the allocated watches suggesting the watches had been mixed up between participants. These unsuccessful acquisition sessions were removed.

As a result, 89.2% (n=149/167) successful data sets were obtained. These data sets were then screened for compliance, the screening protocol is outlined in Section 9.3.4. Following screening for compliance, days with less than 90% valid data were removed, in line with previously published data (Read et al., 2015, Read et al., 2014). 39.7% of all days collected were deemed invalid (i.e. <90% valid data) and removed (n=533/1341). For the 149 data sets, the mean±SD number of valid days per participant was 5.4±2.9 (range 0.0 – 9.0). Only data sets with 5 days or more of valid data (i.e. >90%) were included in the analysis. 36.2% of data sets (n=54/149) were removed due to poor compliance (5 days or more of <90% valid data). Therefore, a total of 95 data sets were included in the analysis from 68 participants. 27 participants had valid data for both Summer and Winter months.

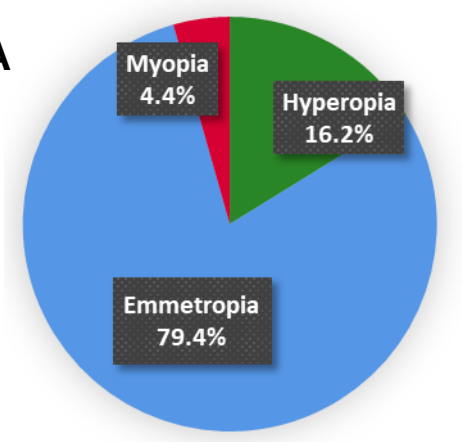
Of these 95 valid data sets, data that were removed following screening for compliance was substituted with averaged data from the same time period. Using the 90% of valid daily data cut off, a maximum of 72 minutes of substituted data per day was allowed. The final data analysed included on average 7±17 minutes of data per day (range 0-72 minutes per day) that was estimated based on substituted averaged data. As a result, 1.1% (n=10,649/993,600) of light exposure data analysed was based upon estimated averaged data.

The participants were sampled from five schools, these schools were classified into 3 UK regions: North, Midlands and South, see Section 5.2.1.3. In this analysis, 1 school from the North, 3 from Midlands and 1 from South was sampled. The mean±SD school start time was 08:59±0:06 and the mean school finish time was 15:15±00:10. The mean start time of the first school break was between 10:28±00:11 and 10:42±00:10 and the mean time of the second school break (lunch) was from 12:10±00:07 until 13:07±00:07.

9.4.2 Participant characteristics

Of the 226 available participants at Baseline, 68 (30.1%) participants were included in this analysis. The mean±SD age of participants was 9.2±1.1 years (range 7.5 – 11.3) with a predominantly female participant composition of 61.8% (n=42). The mean SER was +1.20±1.44D (range -4.75 to +5.57). The proportion of each refractive error in the cohort is shown in Figure 9.5. Of the 68 participants, 4.4% were classified as myopic (n=3), 16.2% hyperopic (n=11) and the majority, 79.4%, emmetropic (n=54).

A



B

Refractive error	n
Hyperopia	11
Emmetropia	54
Myopia	3

Figure 9.5: A) Refractive error composition and B) number of participants per refractive error category in the Child cohort

Due to the age of these participants ethnicity data was obtained from returned parental questionnaires and was available for 95.6% (n=65/68) of participants. The ethnicity composition of participants can be found in Table 9.5.

Ethnic Group	n	%
White	55	85.9
Asian	3	4.7
Chinese	1	1.6
Black	0	0.0
Mixed	5	7.8
Other	0	0.0

Table 9.5: Ethnic group composition of participants with valid Actiwatch 2 data

Year 1 follow up data was available for 75.1% (n=49) of participants and Year 2 follow up data for 23.5% (n=16).

9.4.3 Daily objective light exposure measurements

Daily objective light exposure characteristics are shown in Table 9.6. Analysis of data from all 95 valid data sets from 68 participants showed daily light exposure (7am-7pm) on weekdays, median 203 lux (IQR 71 – 567), to be significantly higher than at weekends, median 91 lux (IQR 22 – 468), (related samples: Wilcoxon signed rank $p<0.001$, median difference +56 lux). Similarly, maximum daily light exposure on weekdays, median 22,212 lux (IQR 12,327 – 45,211) was significantly higher than at weekend, median 10,396 lux (IQR 1,676 – 41,144) (related samples: Wilcoxon signed rank $p<0.001$, median difference +6,064 lux).

	Median (IQR) (n=95)		
	All days	**Weekdays**	**Weekends**
Daily light exposure (7am-7pm), lux	164 (59 – 593)	203 (71 – 567)	91 (22 – 468)
Maximum daily light exposure, lux	20,679 (9,679 – 42,673)	22,212 (12,327 – 45,211)	10,396 (2,573 – 40,103)

Table 9.6: Daily objective light exposure characteristics measured over the 9-day period of Actiwatch wear for all data sets (Summer and Winter inclusive)

Figure 9.6 illustrates the median hourly light exposure for all 95 data sets on weekdays and weekends. On weekdays, peaks in light exposure were observed between 8 and 9 am, 10 and 11 am, 12 and 1 pm and 3 and 4 pm, all of which correlate to school start, break one, break two and school finish, see Section 9.4.1. The maximum hourly light exposure occurred between 12 and 1 pm (1315 lux IQR 388 – 3141). On weekends, median hourly light exposure was consistently below 1000 lux with a moderately elevated period of light exposure observed between 10 am and 4 pm, with a peak between 2 and 3 pm (208 lux IQR 31 – 1085). Significant differences in hourly light exposure between weekdays and weekends were observed at a number of time points with significantly greater light exposure (related samples: Wilcoxon signed rank $p<0.05$) on weekdays compared to weekends for each hour between 6 and 11 am, 12pm and 4 pm, 6 and 7 pm. Significantly higher (related samples: Wilcoxon signed rank $p<0.05$) light exposure was recorded between 10 and 11pm and 12 and 1 am at weekends compared to weekdays. All p values for each hour can be found in the Appendix A.9.2.

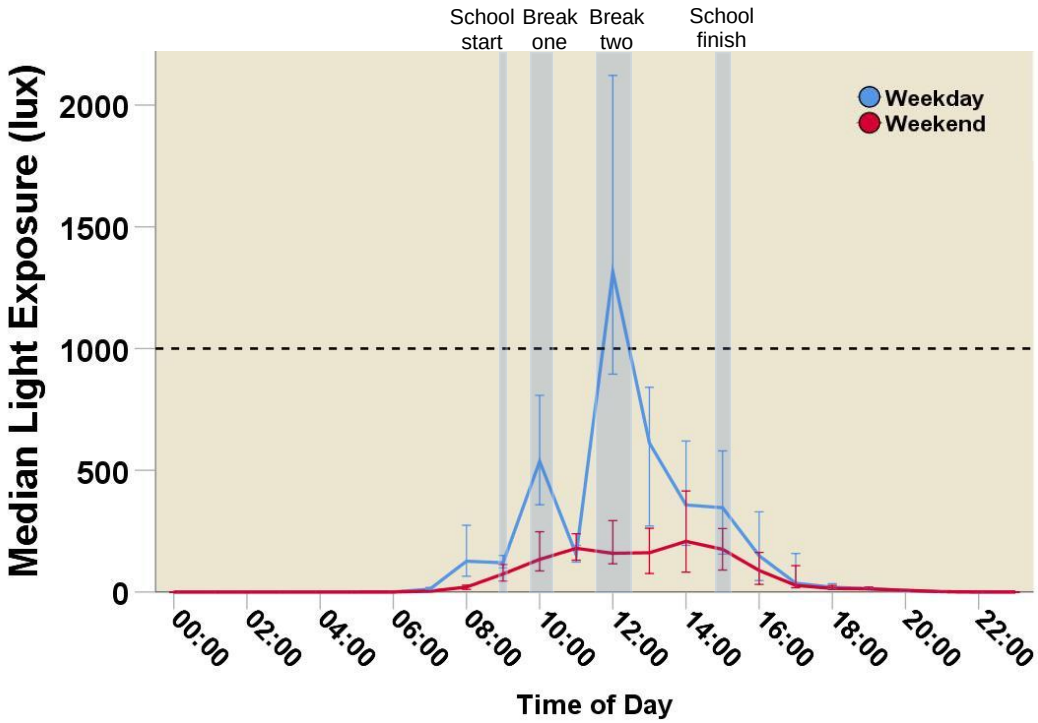


Figure 9.6: Median hourly light exposure (lux) for all 95 data sets for weekdays (blue) and weekends (red) 1000 lux reference line shown with a dotted line. Blue shading indicates school start and finish and break times.

No significant difference in daily light exposure or maximum daily light exposure was found between males and females (Mann Whitney U test: p=0.324 and p=0.504, respectively).

9.4.4 Seasonal objective light exposure measurements

The 95 valid data sets were divided into Summer and Winter seasons using the established cut offs implemented in the United Kingdom by British Summer Time (BST) to indicate the start of summer and the return to Greenwich Mean Time (GMT) to indicate the start of winter, see Section 9.3.2. 42 data sets were classified as Summer and 53 as Winter, 27 participants had a Summer and Winter data sets. Only participants who had valid Summer and Winter data sets were analysed for seasonal light exposure measurements. The mean age was 9.1±1.0 years with a 63.0% (n=17) female composition. The ethnicity composition was 85.2% (n=23) White, 7.4% (n=2) South Asian and 7.4% (n=2) Mixed Race.

Table 9.7 shows the average climate conditions and day length for Summer and Winter months during which data were collected. All climate parameters including maximum and minimum temperature, daily rainfall, sunrise and sunset and day length, were statistically significantly different between the two data collection periods (independent t-test: all p<0.001).

	Mean±SD (range)		
	Summer (n=88)	**Winter (n=99)**	**p-value†**
Maximum daily temperature (°C)	17.0±6.5 (3.4 – 28.8)	7.6±4.0 (-2.6 – 17.3)	**p<0.001**
Minimum daily temperature (°C)	7.9±4.3 (-1.4 – 16.0)	2.1±3.7 (-5.1 – 11.1)	**p<0.001**
Mean daily rainfall (mm/d)	1.7±3.7 (0.0 – 22.0)	4.8±4.3 (0.0 – 13.9)	**p<0.001**
Mean sunrise (24-hr time)	05:09±31min (04:08 – 06:07)	07:33±33min (06:16 – 08:12)	**p<0.001**
Mean sunset (24-hr time)	20:54±58min (18:29 – 22:01)	17:07±57min (15:48 – 18:55)	**p<0.001**
Mean day length (hr:min)	15:44±1:26 (12:22-17:30)	9:34±1:26 (7:41-12:06)	**p<0.001**

Table 9.7: Mean±SD climate conditions and day length for Summer and Winter months †: independent t-test

Daily objective light exposure characteristics for Summer and Winter are shown in Table 9.9.

		Median (IQR)	
		Summer (n=42)	**Winter (n=53)**
Daily light exposure (7am-7pm), lux	**All**	515 (264 – 914)	39 (17 – 110)
	Weekday	647 (481 – 898)	76 (33 – 151)
	Weekend	506 (291 – 854)	29 (11 – 70)
Maximum daily light exposure, lux	**All**	43,425 (22,674 – 57,549)	4,008 (1,117 – 18,658)
	Weekday	50,482 (32,640 – 56,563)	13,323 (5,023 – 21,852)
	Weekend	38,454 (26,407 – 51,077)	3,473 (1,271 – 12,265)

Table 9.8: Median (IQR) light exposure measured over the 9-day period of Actiwatch wear for Summer and Winter seasons

Figure 9.7 illustrates the median hourly light exposure for the Summer data sets (n=42) on weekdays and weekends. On weekdays, peaks in light exposure were observed between 8 and 9 am, 10 and 11 am, 12 and 1 pm and 3 and 4 pm, all of which correlate school start, break one, break two and school finish, see Section 9.4.1. The maximum hourly light exposure occurred between 12 and 1 pm (3083 lux IQR 1538 – 3785). On weekends, peaks in light exposure were observed between 10 and 11 am, 1 and 2 pm and 3 and 4 pm. The maximum hourly light exposure occurred between 3 and 4 pm (1464 lux IQR 366 – 2517). Significant differences in hourly light exposure between

weekdays and weekends in Summer were observed at a number of time points with significantly greater light exposure (related samples: Wilcoxon signed rank p<0.05) on weekdays compared to weekends for each hour between 6 and 9 am, 12 and 1 pm and 6 and 7 pm. All p values for each hour can be found in the Appendix A.9.2. No significant difference in daily light exposure (related samples: Wilcoxon signed rank p=0.118) or maximum daily light exposure (related samples: Wilcoxon signed rank p=0.212 was found between weekdays and weekends.

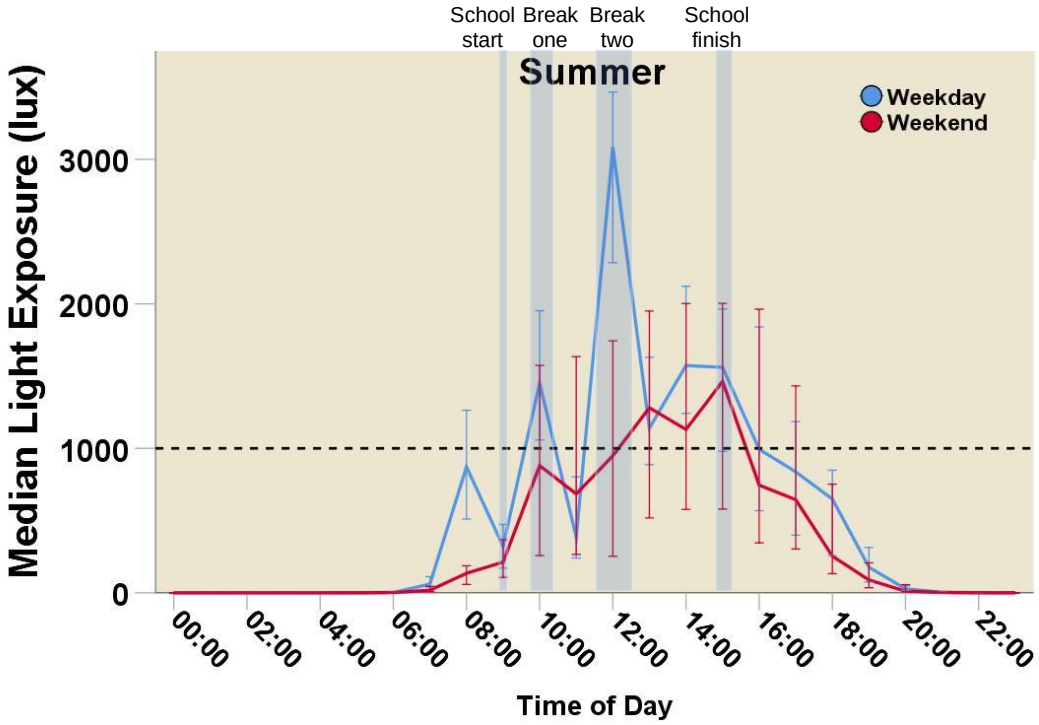


Figure 9.7: Median hourly light exposure (lux) in Summer for weekdays (blue) and weekends (red) (n=42) 1000 lux reference line shown with a dotted line. Blue shading indicates school start and finish and break times.

Figure 9.8 illustrates the median hourly light exposure for the Winter data sets (n=53) on weekdays and weekends. On weekdays, peaks in light exposure were observed between 10 and 11 am and 12 and 1 pm, both of which correlate to break one and break two timings, see Section 9.4.1. The maximum hourly light exposure occurred between 12 and 1 pm (567 lux IQR 102 – 1394). On weekends, no definitive peaks in light exposure were observed, however a slightly elevated light exposure was recorded between 10 am and 2 pm. The maximum hourly light exposure occurred between 12 and 1 pm (91 lux IQR 28 – 219). Significant differences in hourly light exposure between weekdays and weekends in Winter were observed at a number of time points with significantly greater light exposure (related samples: Wilcoxon signed rank p<0.05) on weekdays compared to weekends for each hour between 7 and 11 am and 12 and 5 pm. All p values for each hour can be found in the Appendix A.9.2. In Winter, a

statistically significant higher daily light exposure was found on weekdays compared to weekends (related samples: Wilcoxon signed rank p=0.005, mean difference +22 lux) and a higher maximum daily light exposure was also found on weekdays compared to weekends (related samples: Wilcoxon signed rank p=0.009, mean difference +3,123 lux).

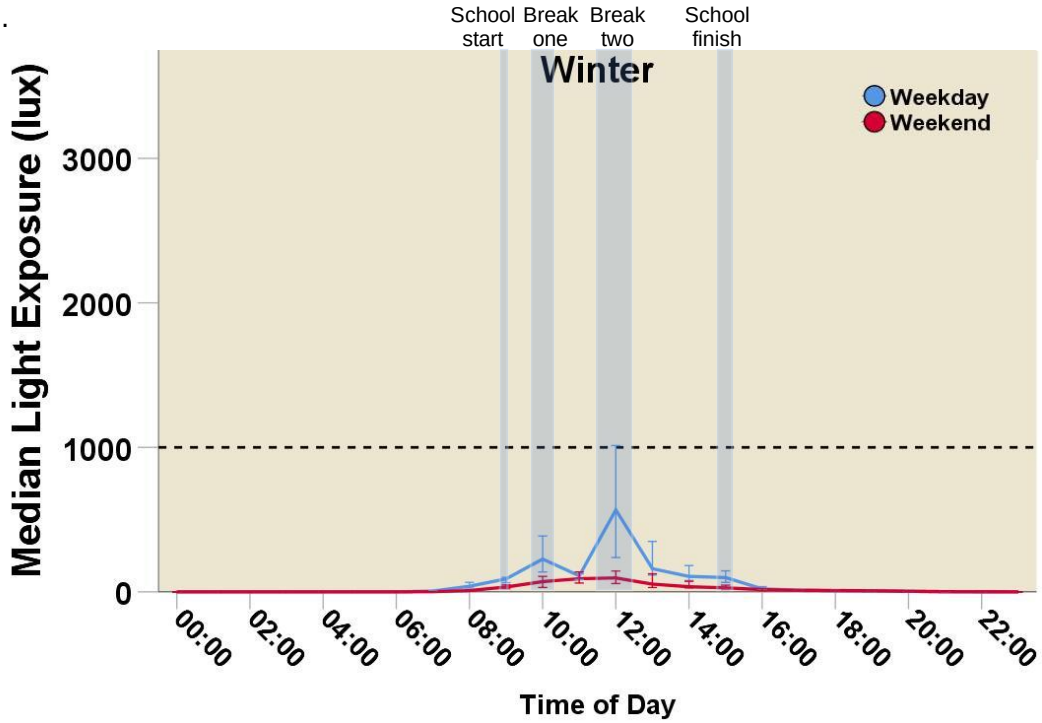


Figure 9.8: Median hourly light exposure (lux) in Winter for weekdays (blue) and weekends (red) (n=53) 1000 lux reference line shown with a dotted line. Blue shading indicates school start and finish and break times

In order to directly compare the two seasons, only data from participants who had valid data sets for Summer and Winter was analysed (n=27). Daily objective light exposure characteristics for these participants in Summer and Winter are shown in Table 9.9. Comparison of daily light exposure (7am-7pm) and maximum daily light exposure between the two seasons were all found to be statistically significantly different (related samples: Wilcoxon signed rank, all p<0.001).

		Summer (n=27)	Winter (n=27)	p value†
Daily light exposure (7am-7pm), lux	**All**	653 (439 – 832)	55 (24 – 75)	**p<0.001**
	Weekday	618 (476 – 879)	70 (27 – 121)	**p<0.001**
	Weekend	483 (259 – 748)	23 (11 – 46)	**p<0.001**
Maximum daily light exposure, lux	**All**	42,618 (30,441 – 49,996)	7,096 (3,013 – 14,083)	**p<0.001**
	Weekday	47,521 (24,579 – 56,339)	9,672 (2,145 – 18,391)	**p<0.001**
	Weekend	35,436 (25,097 – 47,699)	3,165 (1,328 – 7,001)	**p<0.001**

Table 9.9: Median (IQR) light exposure measured over the 9-day period of Actiwatch wear for participants with both Summer and Winter seasons (n=27) †: Wilcoxon signed rank test

Figure 9.9 illustrates the median hourly light exposure for all 27 participants in Summer and Winter. In Summer, peaks in light exposure were observed between 8 and 9 am, 10 and 11 am, 12 and 1 pm and 2 and 3 pm, all of which correlate school start, break one, break two and school finish, see Section 9.4.1. The maximum hourly light exposure occurred between 12 and 1 pm (1846 lux IQR 265 – 3360). In Winter, median hourly light exposure was consistently below 1000 lux with a minimally elevated period of light exposure between 10 and 3 pm, with peaks between 10 and 11 am (127 lux IQR 34 – 387) and 12 and 1 pm (123 lux IQR 53 – 472). Significant differences in hourly light exposure between Summer and Winter were observed in all median hourly light exposure between 5 am and 10 pm (related samples: Wilcoxon signed rank p<0.001). All p values for each hour can be found in the Appendix A.9.2.

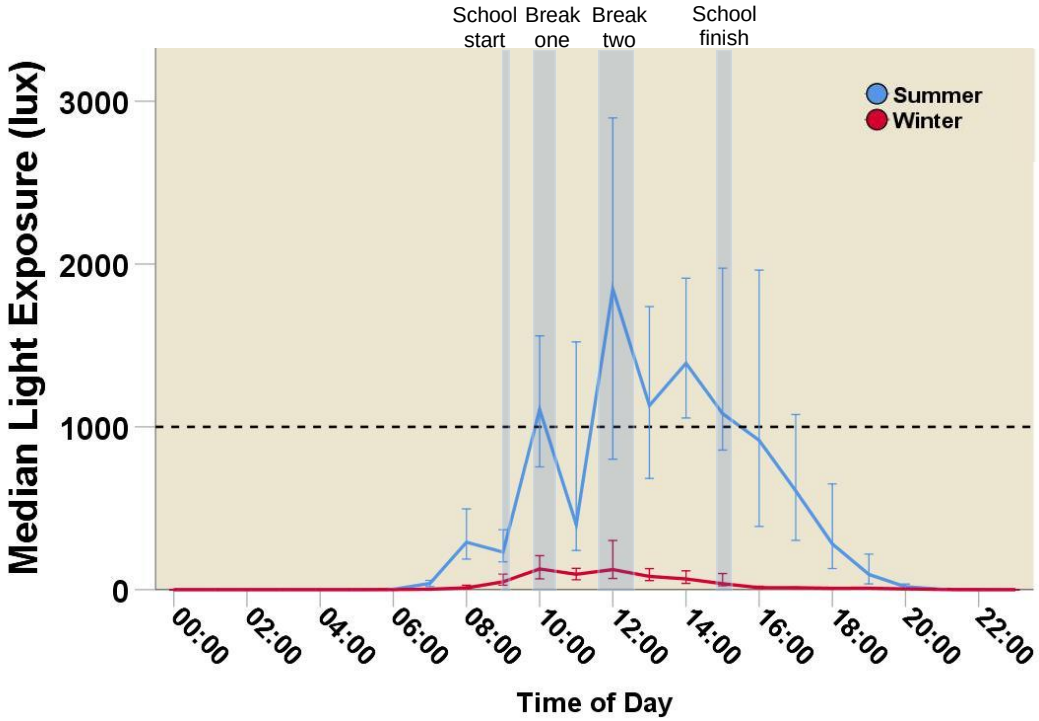


Figure 9.9: Median hourly light exposure (lux) for all 27 participants with both Summer (blue) and Winter (red) data sets 1000 lux reference line shown with a dotted line. Blue shading indicates school start and finish and break times.

No correlation between mean Summer and Winter daily light exposure (lux) (R^2=0.005, r=0.073 p=0.716) was found.

9.4.5 Objective estimate of time outdoors

The median daily minutes spent outdoors i.e. >1000 lux was 38 minutes (IQR 14 – 114). The number of minutes spent outdoors on weekdays (median 44 minutes (IQR 15 – 119)) was significantly higher than at weekends (median 28 minutes (IQR 4 – 98)), median difference +15 minutes) (related samples: Wilcoxon signed rank, p=0.005).

Figure 9.6 illustrates the median hourly light exposure for all 95 data sets on weekdays and weekends. On weekdays, peaks in time spent outdoors i.e. minutes >1000 lux were observed between 10 and 11am and 12 and 1 pm which correlates to break 1 and break 2 in the school schedule. The greatest hourly outdoor exposure was between 12 and 1 pm (Median 16 lux (IQR 5 – 23). Conversely on weekends no distinct peaks of outdoor exposure were observed. Outdoor exposure occurred between 10 am and 3 pm, although each hour saw less than 5 minutes of outdoor exposure. Significant differences in hourly outdoor exposure between weekdays and weekends were observed at a number of time points with significantly greater outdoor exposure (related samples: Wilcoxon signed rank $p<0.05$) on weekdays compared to weekends for each hour between 6 am and 12 pm, 3 and 5 pm and 6 and 7 pm. All p values for each hour of day can be found in the Appendix A.9.3.

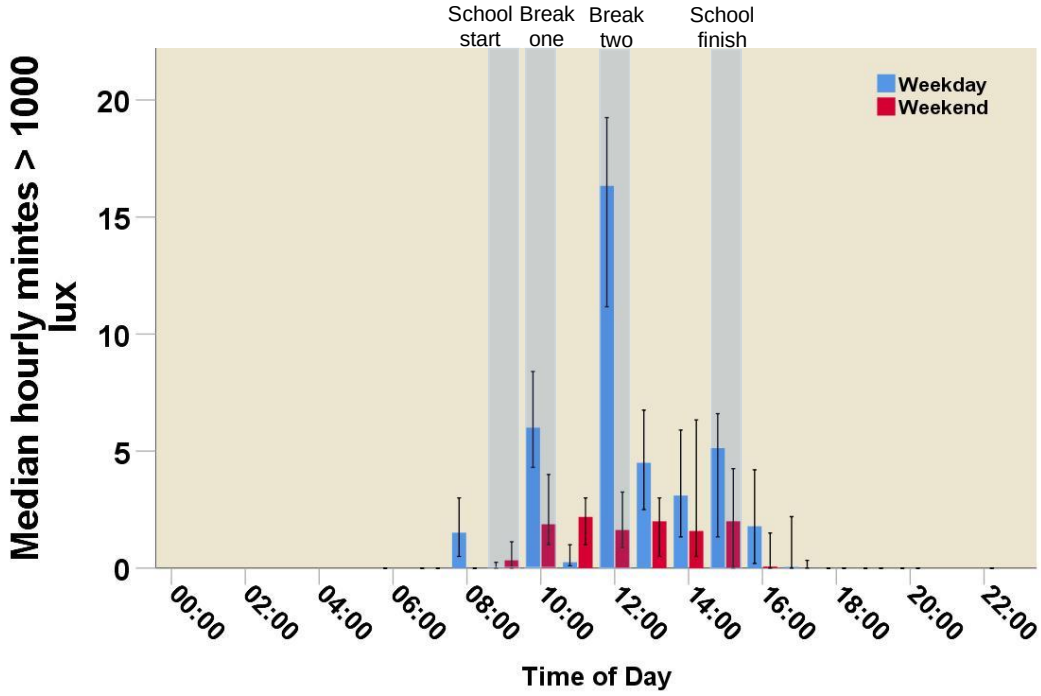


Figure 9.10: Median hourly minutes spent over 1000 lux for all 95 data sets for weekdays (blue) and weekends (red) Blue shading indicates school start and finish and break times.

No significant difference in median minutes >1000 lux was found between males and females (Mann Whitney U test: p=0.334 respectively).

Seasonal differences in time spent outdoors on weekdays and weekends was explored, see Table 9.10. In Summer, no significant difference in the amount of time spent outdoors was found between weekdays and weekends (related samples: Wilcoxon signed rank, p=0.152). However, in Winter, the amount of time spent outdoors was

significant higher on weekdays than weekends (related samples: Wilcoxon signed rank, p=0.005).

	Minutes >1000 lux (Median, IQR)	
	Summer (n=42)	**Winter (n=53)**
All	120 (88 – 161)	14 (4 – 31)
Weekday	133 (93 – 157)	21 (4 – 41)
Weekend	106 (57 – 166)	7 (1 – 20)

Table 9.10: Median (IQR) daily minutes > 1000 lux measured over the 9-day period of Actiwatch wear for Summer and Winter seasons

In Summer, on weekdays, peaks in time spent outdoors i.e. minutes >1000 lux were observed between 8 and 9 am, 10 and 11am and 12 and 1 pm which correlates with before school start, break 1 and break 2. The greatest hourly outdoor exposure was between 12 and 1 pm (median 22 minutes (IQR 15 – 28)). Conversely on weekends no distinct peaks of outdoor exposure were observed. Instead outdoor exposure occurred between 10 am and 5 pm. The greatest hourly outdoor exposure between 1 and 2 pm (median 13 minutes (IQR 2 – 21)). Significant differences in hourly outdoor exposure between weekdays and weekends were observed at a number of time points with significantly greater outdoor exposure (related samples: Wilcoxon signed rank $p<0.05$) on weekdays compared to weekends between 6 and 9 am, 12 and 1 pm and 6 and 7 pm. All p values for each hour of day can be found in the Appendix A.9.3.

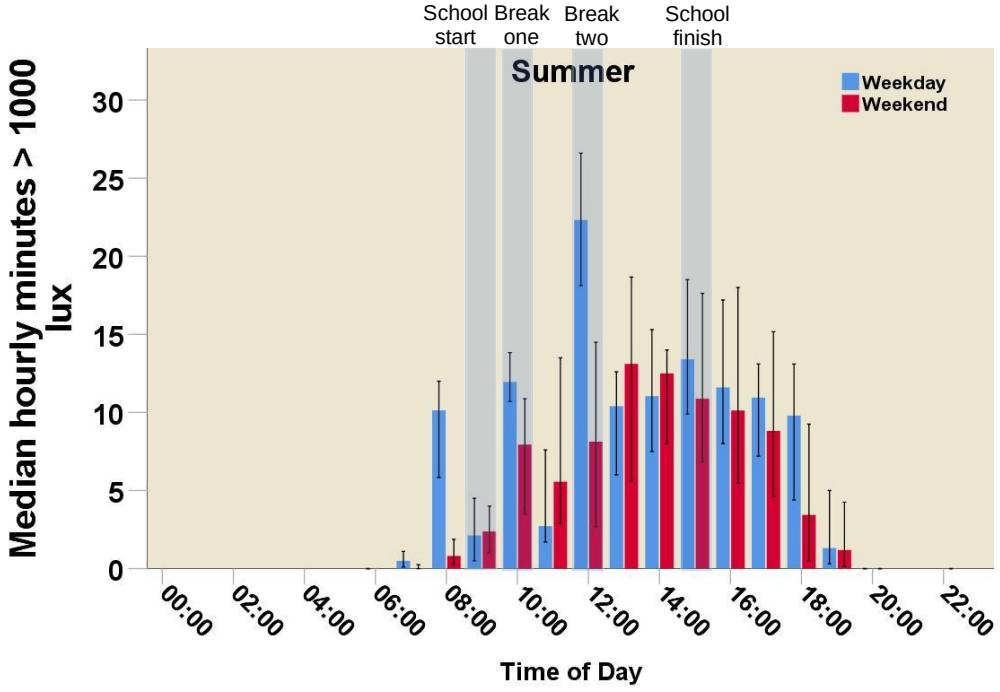


Figure 9.11: Median hourly minutes spent over 1000 lux in Summer for weekdays (blue) and weekends (red) (n=42) Blue shading indicates school start and finish and break times.

In Winter on weekdays, peaks in time spent outdoors i.e. minutes >1000 lux were observed between 10 and 11am and 12 and 1 pm which correlates with break 1 and break 2. The greatest hourly outdoor exposure was between 12 and 1 pm (median 7 minutes (IQR 1 – 18)). Conversely on weekends no distinct peaks of outdoor exposure were observed. Instead outdoor exposure occurred between 10 am and 1 pm, although each hour saw less than 5 minutes of outdoor exposure. Significant differences in hourly outdoor exposure between weekdays and weekends were observed at a number of time points with significantly greater outdoor exposure (related samples: Wilcoxon signed rank $p<0.05$) on weekdays compared to weekends between 8 and 2 pm and 3 and 4 pm. All p values for each hour of day can be found in the Appendix A.9.3.

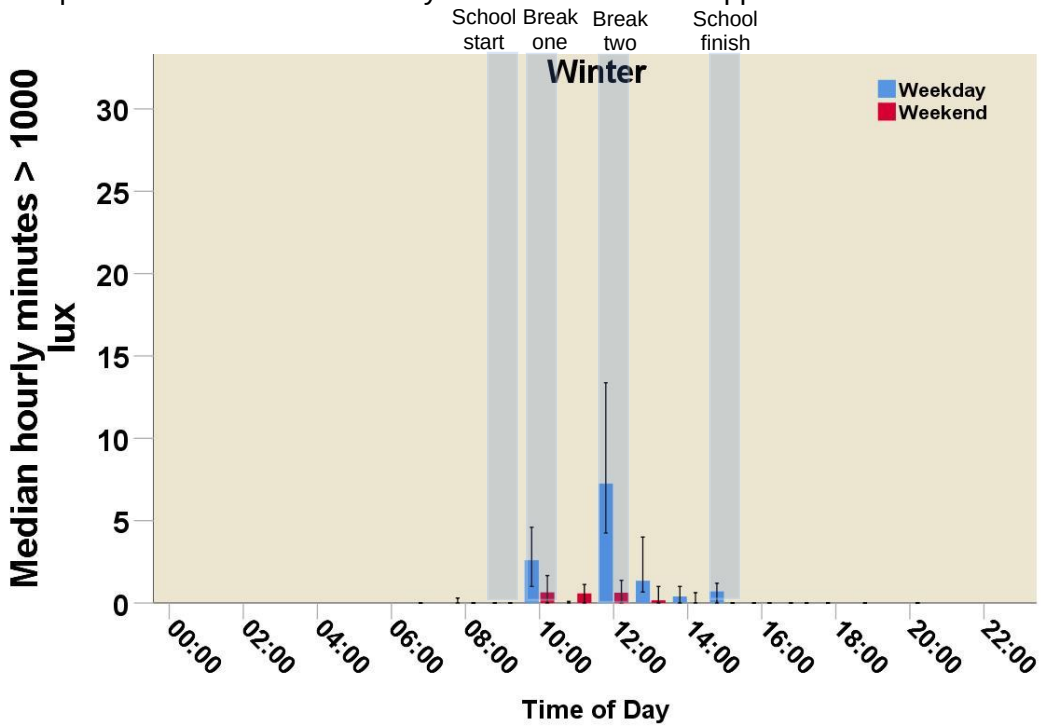


Figure 9.12: Median hourly minutes spent over 1000 lux in Winter for weekdays (blue) and weekends (red) (n=42) Blue shading indicates school start and finish and break times.In order to directly compare the amount of time spent outdoors between the two seasons, only data from participants who had valid data sets for Summer and Winter were analysed (n=27). Number of daily minutes >1000 lux in Summer and Winter for these participants are shown in Table 9.11.

The amount of time spent >1000 lux between the two seasons and day of the week were found to be statistically significantly different (related samples: Wilcoxon signed rank, all $p<0.001$).

	Summer (n=27)	Winter (n=27)	p value†
All	117 (78 – 159)	11 (2 – 22)	**p<0.001**
Weekday	133 (93 – 156)	12 (2 – 28)	**p<0.001**
Weekend	96 (53 – 158)	7 (2 – 17)	**p<0.001**

Table 9.11: Median (IQR) daily minutes > 1000 lux measured over the 9-day period of Actiwatch wear for participants with both Summer and Winter data †: Wilcoxon signed rank test

In Summer, a peak in time spent outdoors i.e. minutes >1000 lux was observed between 12 and 1 pm (median 14 minutes (IQR 2 – 25)). All hours between 10 and 11 am, 12 and 5 pm the median hourly minutes >1000 lux were over 10 minutes. However, in Winter all median hourly outdoor exposure was consistently below 5 minutes. Significant seasonal differences in hourly outdoor exposure were observed at a number of time points with significantly greater outdoor exposure (related samples: Wilcoxon signed rank p<0.05) in Summer compared to Winter between 7am and 9 pm. All p values for each hour of day can be found in the Appendix A.9.3.

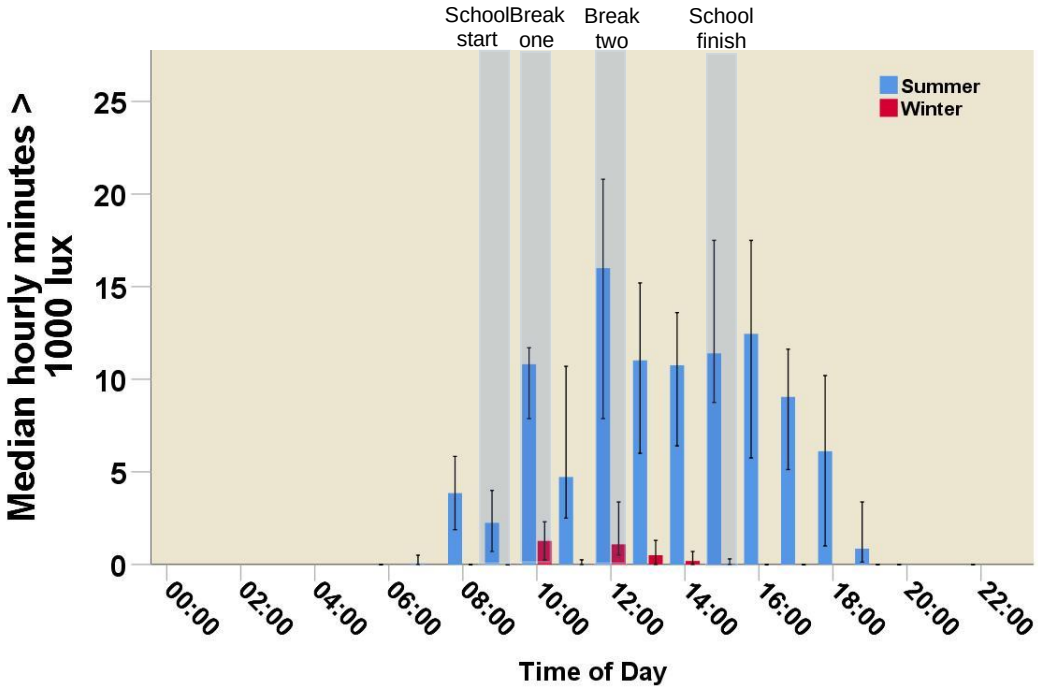


Figure 9.13: Median hourly minutes spent over 1000 lux for all 27 participants with both Summer (blue) and Winter (red) data sets Blue shading indicates school start and finish and break times.

No correlation between Summer and Winter mean daily minutes >1000 lux (R^2=0.003, r=0.053 p=0.792) was found, see Figure 9.14.

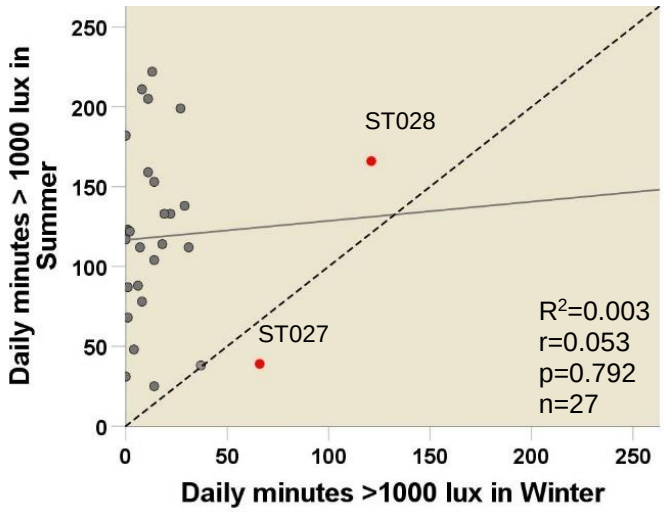


Figure 9.14: Correlation between Summer and Winter mean daily minutes >1000 lux Dotted line represents a perfect correlation (x = y) relationship for reference

Two participants stand out in this correlation and shown in red on Figure 9.14. Participant ST028 spent above median time outdoors in Summer and nearly 10 times the median time outdoors in Winter (Summer: 166 lux, Winter: 106 lux). Participant ST027 spent more time outdoors in Winter than Summer (Summer: 39 minutes, Winter: 66 minutes).

9.4.6 Light exposure and latitude

The data obtained about light exposure was from five schools which were classified into regional groups: North, Midlands or South, according to their latitude to allow comparison of light exposure from across the UK, see Section 5.2.1.3. The majority of data were obtained from the Midlands (77.9%, n=74/95), see Table 9.12.

	All		Summer		Winter	
Region	**n**	**%**	**n**	**%**	**n**	**%**
North	5	5.3	2	4.8	3	5.6
Midlands	74	77.9	33	78.6	41	77.4
South	16	16.8	7	16.7	9	17.0
Total	**95**	**100.0**	**42**	**100.0**	**53**	**100.0**

Table 9.12: Participant numbers for each region and season

Seasonal light exposure characteristics for each region are shown in Table 9.13 and Figure 9.15.

		Region			
	Season	**North**	**Midlands**	**South**	**p value†**
Daily light exposure (7am-7pm), lux	**Summer**	877 (533 – 1,221)	749 (491 – 864)	435 (195 – 539)	**p=0.048**
	Winter	101 (69 – 137)	60 (29 – 147)	59 (23 – 69)	p=0.370
Maximum daily light exposure, lux	**Summer**	61,017 (58,842 – 63,193)	53,036 (39,719 – 56,622)	20,485 (15,589 – 26,890)	**p=0.006**
	Winter	17,113 (17,009 – 23,776)	12,614 (4,367 – 19,933)	4,655 (2,727 – 8,867)	p=0.056
Daily minutes >1000 lux	**Summer**	147 (96 – 199)	123 (105 – 166)	87 (31 – 112)	p=0.059
	Winter	27 (22 – 51)	14 (6 – 32)	14 (1 – 14)	p=0.173

Table 9.13: Median (IQR) light exposure regional characteristics measured over the 9-day period of Actiwatch wear for Summer and Winter seasons †: Kruskal Wallis test. Sample sizes: Summer: North (n=2), Midlands (n=33) and South (n=7). Winter: North (n=3), Midlands (n=41) and South (n=9).

In Summer, significant regional differences in daily light exposure and max daily light exposure were found (Kruskal Wallis: p=0.048 and p=0.006 respectively). Post hoc analysis of daily light exposure revealed no statistically significant difference between North and Midlands (Mann Whitney U test: p=0.524) however a statistically significant difference was found between Midlands and South (Mann Whitney U test: p=0.018). Post hoc analysis of maximum daily light exposure found similar results with no statistically significant difference between North and Midlands (Mann Whitney U test, p=0.084) however a statistically significant difference was found between Midlands and South (Mann Whitney U test: p=0.005). No significant regional difference in minutes spent >1000 lux was found in Summer (Kruskal Wallis: p=0.059).

In Winter, no significant regional differences in daily light exposure, maximum daily light exposure or minutes spent >1000 lux were found (Kruskal Wallis: p=0.370, p=0.056, p=0.173 respectively).

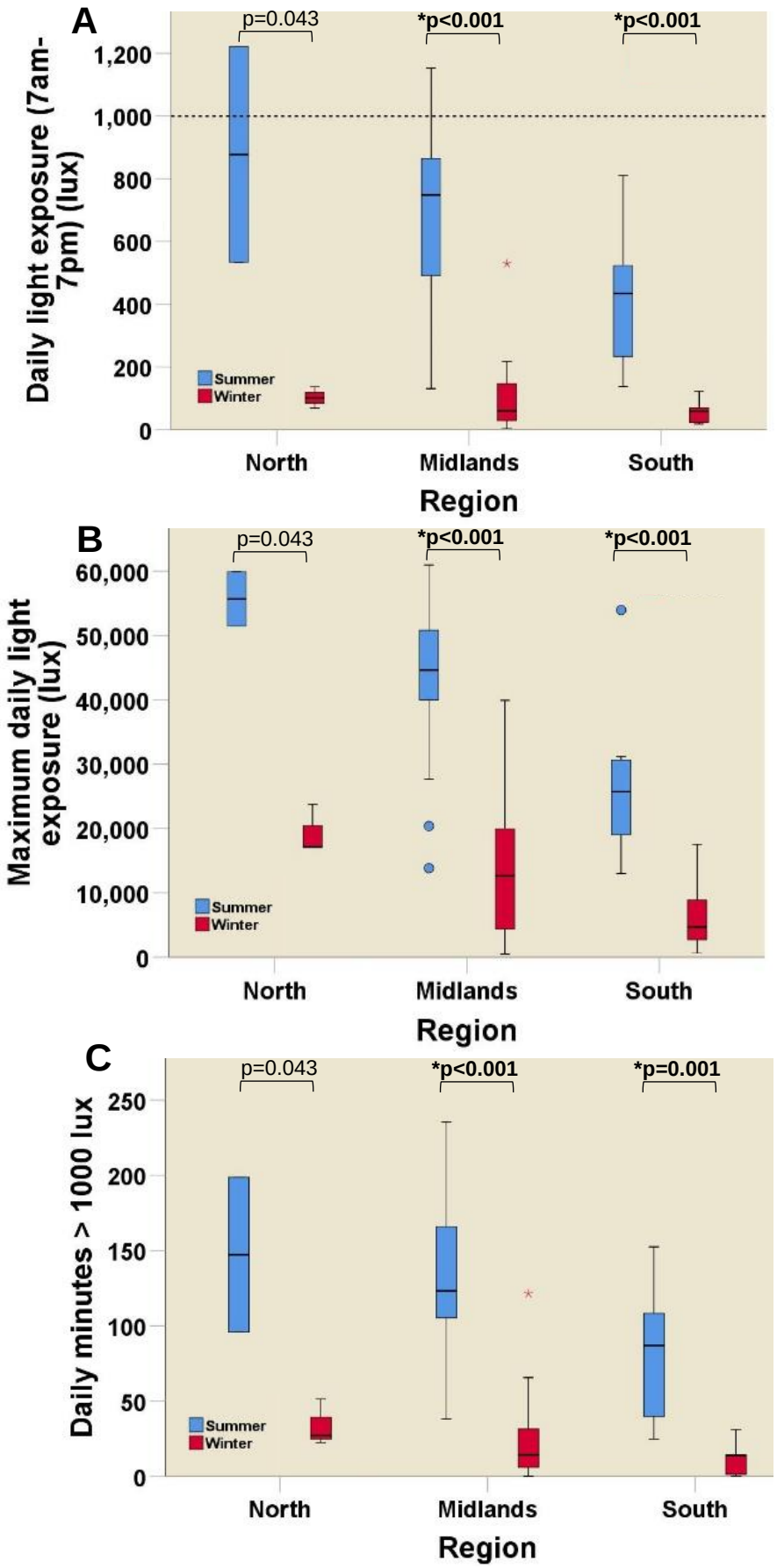


Figure 9.15: Regional light exposure characteristics A) Daily light exposure (7am-7pm) (lux) B) Maximum daily light exposure (lux) C) Mean daily minutes >1000 lux

9.4.7 Light exposure and longitudinal changes in axial length

Of the 42 participants with valid Summer light exposure data, 59.5% (n=25/42) had longitudinal annual data on axial length growth. No significant correlation was found between axial length growth and daily light exposure (R^2=0.006, r=0.078 p =0.712), see Figure 9.16.

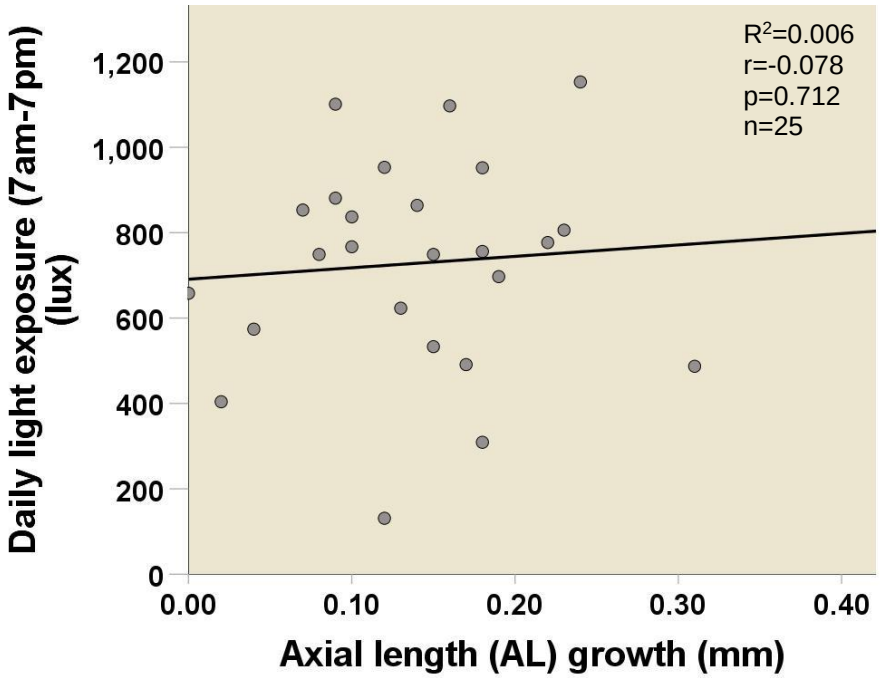


Figure 9.16: Correlation of axial length (AL) growth (mm) and daily light exposure (7am=7pm) (lux)

Participants (n=25) were categorised according to their average daily light exposure in Summer. Children were classified as experiencing low daily light exposure (average daily light exposure ≤ 642 lux) (n=8), average light exposure (average daily light exposure between 643 – 840 lux) (n=9) and high light exposure (average daily light exposure ≥ 841 lux) (n=8), this was based on a tertile split of the average daily light exposure.

The change in axial length growth between the categories can be found in Table 9.14 and Figure 9.17. Analysis of the axial length change between Baseline and Year 1 between the three categories found no significant difference (Kruskal Wallis: p=0.946).

Light exposure	Low (n=8)	Average (n=9)	High (n=8)
Median (IQR) Axial length growth (mm)	0.14 (0.08 – 0.18)	0.15 (0.10 – 0.19)	0.13 (0.09 – 0.17)

Table 9.14: Median (IQR) axial length growth (mm) in the three light exposure categories

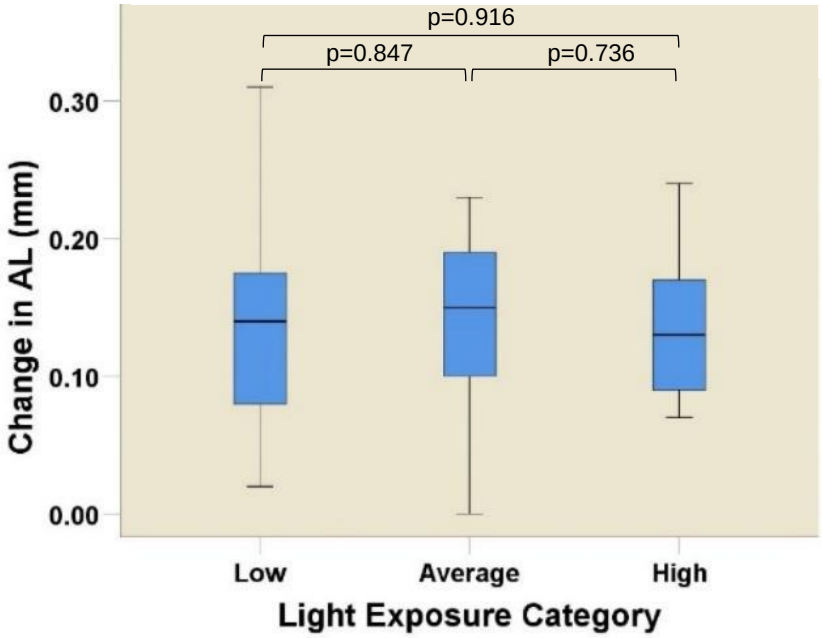


Figure 9.17: Change in axial length (AL) in low (n=8), average (n=9) and high (n=8) light exposure participants

The correlation between axial length growth and outdoor exposure time was assessed. No significant correlation was found (R^2=0.006, r=0.079 p=0.709), see Figure 9.18.

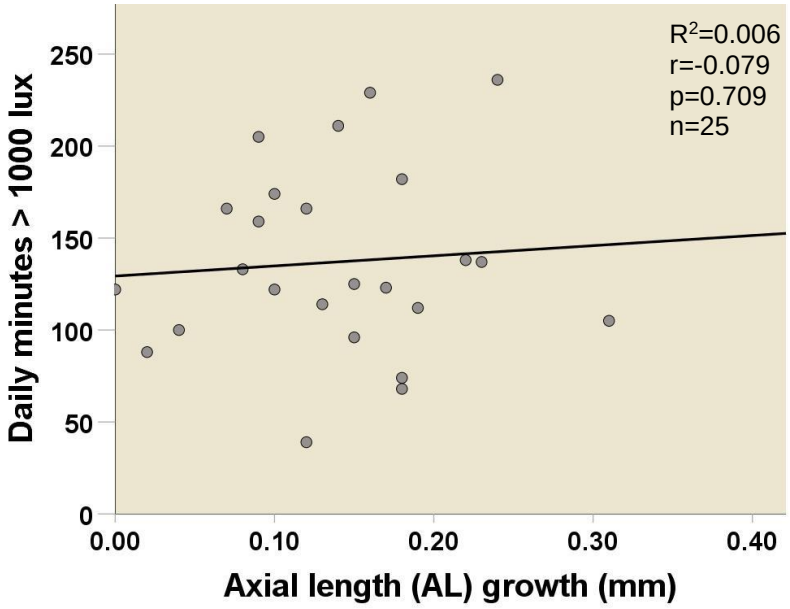


Figure 9.18: Correlation of axial length (AL) growth (mm) and daily minutes > 1000 lux

Participants were classified as experiencing low daily outdoor exposure (average daily light exposure ≤ 113 minutes) (n=8), average outdoor exposure (average daily light exposure between 114 – 160 minutes) (n=9) or high light exposure (average daily light exposure ≥ 161 minutes) (n=8), this was based on a tertile split of the daily number of minutes spent >1000 lux.

The change in axial length growth between the categories can be found in Table 9.15 and Figure 9.19. Analysis of the axial length change between Baseline and Year 1 between the three categories found no significant difference (Kruskal Wallis: p=0.835).

Outdoor exposure	Low (n=8)	Average (n=9)	High (n=8)
Median (IQR) Axial length growth (mm)	0.16 (0.08 – 0.19)	0.13 (0.09 – 0.17)	0.13 (0.10 – 0.17)

Table 9.15: Median (IQR) axial length growth (mm) in the three outdoor exposure categories

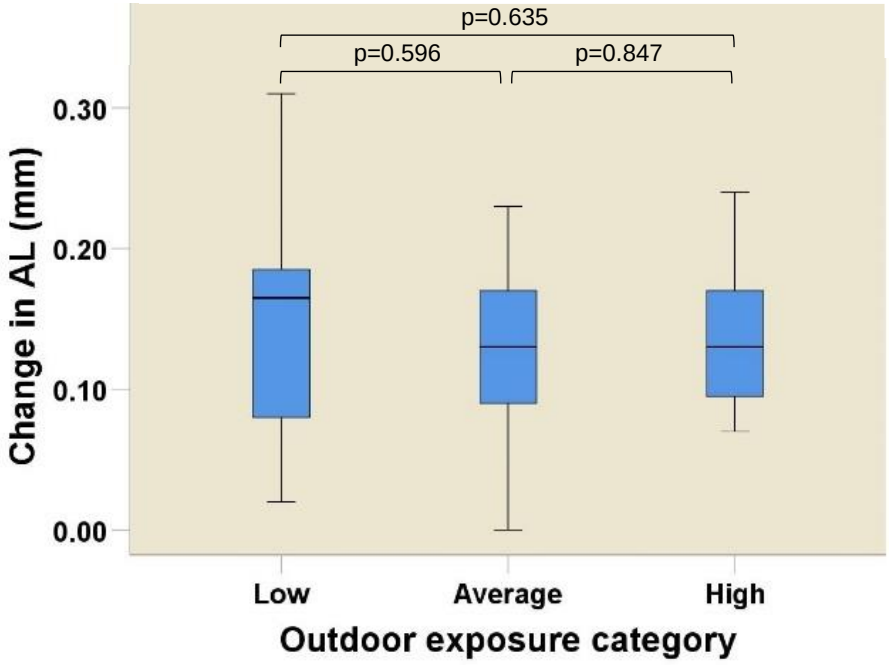


Figure 9.19: Change in axial length (AL) in low (n=8), average (n=9) and high (n=8) outdoor exposure participants

9.4.8 Subjective vs Objective quantification of time outdoors

Subjective data on time outdoors was assessed via questionnaires, one by the participants themselves and one by their parent/guardian. Parental questionnaire data was available for 95.8% (n=91/95) of objective data sets.

58 children had valid objective measures of time outdoors and completed questionnaires undertaken in the same season has the objective data collection (Summer n=24, Winter n=34). The level of agreement between the child and parental responses and the objective measure of time outdoors was fair (Child responses: κ_w = 0.229, Parental response: κ_w = 0.327). Frequencies of correct responses were obtained by comparison of the questionnaire responses to the objective time outdoors estimate with an expectation of 1:1 using chi squared goodness of fit test. No significant difference in the ability of the child or parent to correctly estimate the amount of time spent outdoors (χ^2 = 0.04). Compared to the objective data, 44.6% (n=25/56) children correctly estimated the amount of time they spent outdoors and 46.4% (n=26/56) of parents estimated correctly.

Contingency tables were used to assess the relationship between the subjective responses from the Child and Parental questionnaires compared to the objective estimates of time outdoors, see Table 9.16 and Table 9.17.

		Objective estimate			
		None	< 1 hour	1-2 hours	2+ hours
Child response	None	0	1	0	0
	Less than 1 hour	0	3	0	1
	1-2 hours	1	8	8	10
	2+ hours	0	5	5	14

Table 9.16: Contingency table of the comparison of child questionnaire responses and objective estimate of the amount of time spent outdoors

		Objective estimate			
		None	< 1 hour	1-2 hours	2+ hours
Parental response	None	0	0	2	0
	Less than 1 hour	1	10	8	4
	1-2 hours	0	5	3	8
	2+ hours	0	2	0	13

Table 9.17: Contingency table of the comparison of parental questionnaire responses and objective estimate of the amount of time spent outdoors

The frequencies of categorical deviations were calculated for all incorrect responses. The median incorrect child response was one category higher than the objective estimate i.e. overestimation (median +1 IQR -1 to +1, n=31) whilst the median incorrect parental response was one category lower than the objective estimate i.e. underestimation (median -1 IQR -1 to +1, n=30). However, the categorical deviations

were found to not be significantly different between the two groups (related samples: Wilcoxon signed rank, p=0.058). The comparison of these categorical differences compared to the objective estimate is shown in Figure 9.20.

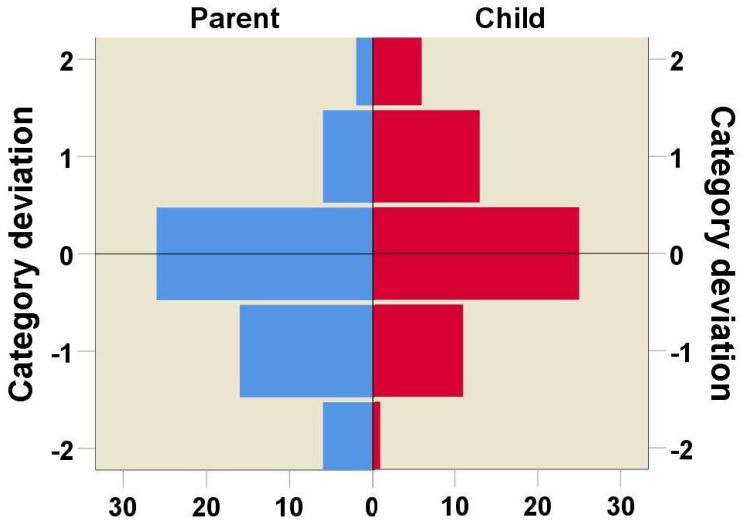


Figure 9.20: Category deviation of child and parental questionnaire responses regarding the amount of time spent outdoors compared to an objective measure

9.4.9 Light Sensor Orientation

Mean light exposure (lux) in each condition are shown in Table 9.18. In all conditions median light exposure (lux) was higher when the device was in the 90 degrees orientation i.e. the light sensor was facing directly up towards the light source. This is illustrated in Figure 9.21.

	Device Orientation (degrees)				
	0	**45**	**90**	**135**	**180**
Outdoors (High)	5,669 (5,428 – 5,669)	6,317 (6,182 – 6,317)	52,773 (49,452 – 42,773)	7,117 (7,039 – 7,512)	5,565 (5,371 – 5,565)
Outdoors (Low)	273 (262 – 285)	408 (386 – 412)	3,444 (3,371 – 3,520)	403 (370 – 431)	242 (221 – 286)
Indoors (High)	89 (87 – 91)	71 (70 – 73)	120 (115 – 123)	79 (78 – 83)	83 (81 – 83)
Indoors (Low)	7 (7 – 8)	10 (10 – 11)	16 (16 – 16)	7 (7 – 8)	5 (5 – 5)

Table 9.18: Light exposure values in five orientations along the horizontal plane
All values are median (IQR).

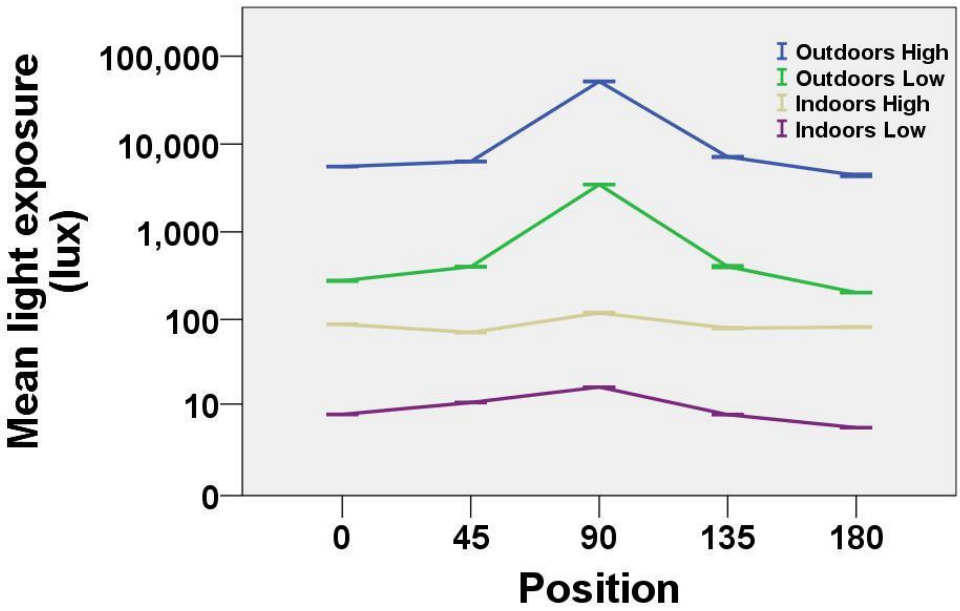


Figure 9.21: Line graph illustrating median illumination values (lux) for different device orientations in different environmental conditions

As excepted, no significant difference was found between illuminance values recorded at 0 and 180 (Mann Whitney U test: p=0.765) and 45 and 135 (Mann Whitney U test: p=0.570). Therefore, a Kruskal-Wallis test was run to determine if there were differences in illuminance values between 0, 45 and 90 orientation in the four conditions. A statistically significant difference in illuminance levels was found between the orientation in each condition (Kruskal Wallis test: Outdoors High: p=<0.001, Outdoors low: p=<0.001, Indoors High: p=<0.001, Indoors Low: p=<0.001). Post hoc analysis of illuminance values revealed a statistically significant difference all orientations i.e. 0, 45 and 90 across all conditions (Mann Whitney U test: all p<0.001), see Table 9.19.

	Outdoors High	Outdoors Low	Indoors High	Indoors Low
0-45	p<0.001	p<0.001	p<0.001	p<0.001
0-90	p<0.001	p<0.001	p<0.001	p<0.001
45-90	p<0.001	p<0.001	p<0.001	p<0.001

Table 9.19: Post hoc analysis, using Mann Whitney U test, of illuminance values in each condition comparing 0, 45 and 90 degree orientation

9.5 Discussion

This study has provided valuable objective data on daily light exposure and duration experienced by UK children. This has allowed the influence of weekday and season to be evaluated and compared with other studies with similar methodologies. Daily light

exposure and maximum daily light exposure were found to be significantly higher on weekdays than weekends. Closer observation of the hourly light exposure showed four distinct peaks in light exposure and outdoor exposure in the weekday data which correlated with the school schedule (school start, morning break, lunch break and school finish). This shows that on weekdays the light exposure and duration are clearly dictated by the rigid constraints of the school schedule where mandatory periods of time outdoors for all children are observed and outdoor play is encouraged. In addition, many children have to walk to and from schools and recreational parks are often found close to schools and it is common for children to spent time in these after school. This is reflected in an significant amount of outdoor exposure between 3 and 5pm on weekdays suggesting that after school children may spend time playing outside with friends and also potentially attend after school clubs during this time which incorporate outdoor activities.

As expected at weekends patterns of light exposure and time spent outdoors did not show these distinct peaks but instead showed a moderately elevated light exposure between 10am and 4pm. This suggests much more variability in light exposure at weekends and suggests other behavioural factors that could influence time spent outdoors and as a result light exposure. One of the biggest factors to consider is the influence of parental behaviour on child's activities. This data suggests that children spent less time outdoors at weekends which could result from lack of parental encouragement to spent time outdoors. In addition, the use of electronic devices such as tablets, smartphones and computers are also now widely used in this age group and have become ubiquitous with modern day life from an early age. 37% of UK children aged 8-11 years own their own smartphone and 49% have their own tablet with the majority having no limits on its usage (Ofcom, 2018). In addition, 99% were found to watch TV or films for 10 hours 30mins a week and 74% watch YouTube for 10 hours a week. Using these estimates that equates to nearly 3 hours a day of TV and VDU/tablet usage. These tasks are performed outside of school time and the majority at weekends and therefore it is likely that this is contributing to the difference in light exposure patterns shown between weekdays and weekends. This was confirmed in this study, see Chapter 7, where subjective estimates of electronic devices including VDU were higher on weekends than weekdays. In addition, it was recently reported that the majority of parents feel that they limit their child's screen time however children still spent over 14 hours a week on average at a screen (McCrann et al., 2018).

Comparison of these findings with that of Australian data investigating slightly older children aged 10 – 15 years, found the mean daily light exposure to be nearly three times lower than levels recorded in Australia and maximum light exposure was much

lower at nearly half the maximum light exposure level in the UK (Read et al., 2014). see Table 9.20. In addition, UK children spent less time outdoors than in Australia. Although an identical pattern of weekday light exposure was found in the Australian with clear peaks aligning with the school schedule. An opposite pattern of these parameters by day of the week was found in the Australian cohort, with Australian children spending more time outdoors on weekends than weekdays. This could be attributed to differences in lifestyle between the two countries and the comparably sedentary weekend lifestyle of children in the UK. It appears that this encouragement for outdoor activity is not apparent on weekends within in the UK resulting in reduced outdoor exposure.

	Mean±SD					
	This study, UK (n=95)			Read (2014), Australia (n=101)		
	All	Weekdays	Weekends	All	Weekdays	Weekends
Mean daily light exposure (lux)	361 ±517	373 ±488	342 ±561	1,072 ±571	1,009 ±527	1,231 ±1,145
Mean maximum daily light exposure (lux)	25,973 ±24,605	27,926 ±24,444	22,876 ±24,589	49,066 ±11,713	50,058 ±11,860	46,438 ±21,428
Mean minutes >1000 lux	67 ±65	71 ±66	63 ±79	107 ±47	105 ±44	112 ±85

Table 9.20: Comparison of Mean±SD light exposure from this UK based study with the data from Australia Data from (Read et al., 2014)

In addition to findings demonstrating the influence of day of week on light exposure and duration, significant seasonal differences were also found. The UK experiences significant seasonal differences throughout the year which have a direct influence on environmental climate conditions, contributing to significantly warmer and longer days in Summer months with less rainfall compared to shorter cooler and wetter days in Winter months. The climate conditions of Summer are more favourable for spending time outdoors and the longer day length provides more opportunity for light exposure and therefore increased duration. This is confirmed in the Summer data sets which were found to have 12 times higher average daily light exposure than Winter and 10 times higher outdoor exposure. In addition, the maximum light exposure was also significantly higher in Summer compared to Winter.

In Summer, on weekdays four distinct peaks correlating to the school schedule were observed, as mentioned previously and similar patterns of increased outdoor exposure between these times was also demonstrated. However, on weekdays in Winter only two peaks were visible, correlating with morning break and lunch break. Outdoor exposure across the whole day was also only limited to these times and on average was less than

5 minutes. It is interesting to see this difference in weekday pattern between Winter and Summer despite the same school schedule in place. This discrepancy suggests that children are no longer walking to and from school and are possibly being driven instead as a result of the shorter day lengths resulting in darker mornings and evenings and also lower temperatures. In addition, they are likely to be going to and from school directly without visiting the park and playing after school in Winter as is shown by the lack of outdoor activity between 3 and 5 pm which is found in Summer.

The seasonal patterns of weekdays and weekends also differed. In Summer, the daily light exposure was not statistically significantly different between weekdays and weekends however in Winter daily light exposure was statistically significantly higher on weekdays than weekends. Part of the school schedule on weekdays incorporates two compulsory breaks, during which children are encouraged to go outdoors. However, it appears without this encouragement children are not spending time outdoors and experiencing higher light exposure and are instead spending time indoors. This again points to a more sedentary indoor-centric lifestyle of children at weekends, particularly in Winter.

In line with other studies a cut off of 1000 lux was used to calculate time outdoors (Ostrin, 2017, Dharani et al., 2012, Alvarez and Wildsoet, 2013, Ostrin et al., 2018, Read et al., 2015, Read et al., 2014). However, the findings of a mean outdoor exposure of 24±23 minutes on weekdays in Winter despite two compulsory school breaks where outdoor exposure is encouraged should equate to on average 1h 11 minutes a day of outdoor exposure, although weather dependent these breaks do sometimes take place inside this data was not collected. This hints that despite time outdoors light levels in Winter in the UK do not reach the 1000 lux threshold for classification of time outdoors and therefore may not be accurately assessed by objective means using this criteria. Significant steps were taken in the provisional of comprehensive instructions were given to all participants and their parents regarding not allowing the sensor to be covered by clothing in particular coats in winter. In addition, a comprehensive screening regime was implemented to appropriately remove times when the watch was not worn and crucially covered by clothing. Therefore it was felt it was unluckily that this potential limitation of usage of a wrist worn sensor was responsible for the findings. It has currently not been confirmed in the research the exact element of outdoor light that is required to provide a protective effect to myopia onset/progression, it has been hypothesised as attributed to wavelength, duration and intensity and depends combination. Read et al (2015) have suggested that the mechanisms controlling eye growth may be sensitive to intensity of outdoor light and those of brighter light intensities

(>3000 lux) may have an even greater influence on eye growth. If it is intensity that is the key factor in the protective effect of time outdoors on myopia onset/progression then current guidelines in place in other countries such as Malaysia and Australia to slow myopia progression through recommending more time outdoors may not have a place in the UK, especially during the Winter months as the daily light exposure recorded in this study in Winter was only 55 lux. Or at least may require more specific recommendations, for example using the data from this study to advise increased time outdoors during specific hours of the day when light exposure levels are maximal and are sufficient to reach a particularly threshold.

As mentioned previously the UK experiences significant seasonal differences in day length and climate conditions. Table 9.21 compares these climate and day light characteristics to published data collected during light exposure measurements from Australia (Read et al., 2014) and Singapore (Dharani et al., 2012).

	This study (UK)			Australia	Singapore
	Overall	**Summer**	**Winter**	**Overall**	**Rainy season**
Daily maximum temperature (ºC)	12.0±7.1 (-2.6 – 28.8)	17.0±6.5 (3.4 – 28.8)	7.6±4.0 (-2.6 – 17.3)	26.3±2.5 (22.3 – 30.3)	31.8±0.6 (30.7 – 32.7)
Daily minimum temperature (ºC)	4.8±5.0 (-5.1 – 16.0)	7.9±4.3 (-1.4 – 16.0)	2.1±3.7 (-5.1 – 11.1)	15.9±2.5 (12.6 – 21.3)	25.1±0.5 (24.1 – 25.7)
Daily rainfall (mm)	3.2±4.3 (0.0 – 22.0)	1.7±3.7 (0.0 – 22.0)	4.8±4.3 (0.0 – 13.9)	2.1±3.0 (0.0 – 15.4)	5.3±4.9 (0.3 – 14.9)
Day length (hr:min)	12:27±3:24 (7:41-17:30)	15:44±1:26 (12:22-17:30)	9:34±1:26 (7:41-12:06)	11:58±1:11 (11:08-13:12)	12:10±0.01 (12:08-12:11)

Table 9.21: Mean±SD climate characteristics and day length during light exposure measurements collected in this study (UK), Australia and Singapore (Read et al., 2018)

The Australian data was collected over an 18 months period for children aged 10 – 15 years and no separation of seasons was accounted for. The Singapore data was collected over a much shorter period of time of only 3 months between April and June for children aged 6 – 12 year. As Singapore is close to the equator it does not experience the conventional four seasons but instead has 'wet' and 'dry' seasons. Comparing these characteristics shows significant differences in climate characteristics between the UK and Australia and Singapore. The UK temperatures are much lower with an average overall daily maximum temperature of 12.0±7.1ºC compared to 26.3±2.5ºC in Australia and 31.8±0.6ºC in Singapore. Interestingly, no obvious difference in daily rainfall was found between the three countries. However, there is a striking difference in day length between seasons within the UK with a range of nearly 10 hours compared to a range of

2 hours in Australia. Comparison of the day length in Singapore is not possible due to the limited information of only a 3 month period compared to 25 months in the UK and 18 months in the Australian study. The differences in climate between these countries, and also inherently different lifestyle cultures, could be attributing to different patterns of activities of children. Longer and warmer days encourage and allow more opportunities for outdoor activities and subsequently a higher and longer light exposure.

A novel element of this study was the investigation of light exposure at different cross-sectional latitudes across the UK: North, Midlands and South to evaluate any latitudinal differences. Consistent findings of a significantly higher light exposure, maximum illuminance levels and outdoor exposure in Summer compared to Winter were found at each latitude, with the exception of the North which did show this trend but was not significantly. The lack of significance could be attributed to the low sample size of North participants (Summer n=2, Winter n=3).

In Summer, the comparison of daily light exposure across the three regions was found to be statistically significantly different, with the Midlands recording nearly twice as much daily average light exposure than the South. In addition, the maximum daily light exposure was found to be higher in the Midlands than the South by more than two-fold. These findings are opposite to those that were expected, as it was hypothesised that as the Southern latitude is closer to the equator they would likely experience a higher maximum daily light exposure. In Winter, no statistically significant regional differences in daily light exposure and maximum daily light exposure were found, this could be attributed to more consistent light levels across the UK in Winter. No statistically significant differences were found between either the Midlands or South region with the North region for daily light exposure, maximum daily light exposure or outdoor exposure. Due to the low number of Northern regional participants (n=5), post-hoc power calculations were performed using G*Power software (version 3.1.9.4, Wilcoxon signed-rank test (two groups):two tailed) to assess the power for each comparison, the results of these calculations are shown in Table 9.22. These calculations show insufficient power for comparison of daily light exposure and time outdoors between the latitudes. This suggests that a larger sample size would be required in order to assess any significant differences in daily light exposure and outdoor exposure between the three regions.

Regional Comparison	Daily light exposure		Maximum daily light exposure		Time outdoors	
	Summer	Winter	Summer	Winter	Summer	Winter
North*Midlands	0.34	0.32	0.99	0.80	0.34	0.39
North*South	0.56	0.25	0.99	0.99	0.52	0.80

Table 9.22: Post-hoc power calculations for the comparison of regional differences in daily light exposure and maximum daily light exposure in Summer

A significant link between objectively measured low light exposure and increased axial length growth has been shown in both children and young adults in previously published studies (Read et al., 2015, Ostrin et al., 2018, Ulaganathan et al., 2019). In this study, no significant correlation between eye growth and light exposure or time outdoors was found. Following classification of light exposure and outdoor exposure into three tertiles, low, average and high, no significant statistical difference was found between these categories. A post-hoc power calculation was performed using G*Power software (version 3.1.9.4, Wilcoxon signed-rank test (two groups):two tailed). The results showed a low insufficient power of 0.14 suggesting a larger sample size would be required in order to assess any significant differences in axial length growth between low and high light exposure. Only 25 participants were able to be included in the analysis of axial length growth and light exposure. This low sample size was in part due to the large proportion of data sets (43.1%) classified as invalid due to poor compliance and compounded by the high attrition rate at the Year 1 follow up visit across the whole study, see Section 5.3. As a result, this limited the available longitudinal biometric data for this chapter and only 59.5% (n=25/42) had this data available. In addition, only 4.4% (n=3) of participants samples were myopic which meant that the comparison of light exposure between refractive error groups was not able to be performed.

Due to consistent methodological criteria, the comparison of the objective estimates of time outdoors from recorded light exposure in this study can be compared with those from Australia (Brisbane), Singapore and USA (Houston, Texas), using the same >1000 lux cut off see Table 9.23 (Dharani et al., 2012, Read et al., 2014, Ostrin et al., 2018). The age range of participants for the Singapore data (8 – 12 years) was similar to that of this study (7 – 12 years) however the Australian data was from older children (10 – 15 years) and the USA data included a younger cohort (5 – 10 years).

	This study			Australia†	Singapore†	USA‡			
	All (n=95)	Summer (n=42)	Winter (n=53)	All (n=43)	All* (n=69)	All (n=60)	Summer (n=60)	Spring (n=60)	Fall (n=60)
All days	67±65	125±54	21±22	105±42	61±40	92±259	111±46	94±30	72±31
Weekday	71±66	129±56	24±23	106±39	55±44	NA	NA	NA	NA
Weekend	63±79	121±86	16±25	105±77	76±50	NA	NA	NA	NA

Table 9.23: Mean daily minutes of outdoor exposure (>1000 lux) in UK, Australian, Singaporean and American Children †: data from Read et al., (2018) ‡: data from Ostrin et al., 2018). *: Singapore data was collected over a 3 month period during their rainy season

When considering the mean daily minutes of outdoor exposure across the year, i.e. not differentiating by season, the UK and Singapore recorded similar findings (67±65 and 61±40 minutes, respectively). Both USA and Australian estimates of outdoor exposure were higher (105±45.8 and 105±42 minutes, respectively). It could be that children in the UK, similarly to Singapore, are more indoor-centric and spend less time outdoors than Australia, where outdoor activities play a central role in communities and therefore these differences could be attributed to differences in children's lifestyles between the three countries. This was suggested by Read et al (2018) who found similar climate characteristics between the two countries, with the exception of increased rainfall in Singapore. However, this study has shown the significant seasonal variation that occurs in the UK with a 6 fold difference in daily outdoor exposure between Summer and Winter, 125±54 and 21±22 minutes respectively. Similar significant seasonal differences in minutes per day outdoors were found in the USA however the fluctuation was not as marked as within the UK data. As mentioned previously, within the UK more outdoor exposure was recorded on weekdays compared to weekends however in Australia no significant difference was found between weekdays and weekends and in Singapore the opposite was true with more outdoor exposure on weekends (Read et al., 2018).

Both children and their parent/guardian subjective responses of time outdoors had a fair level of agreement when compared to objective estimates and no significant difference in the ability of the child or parent/guardian to correctly estimate the amount of time outdoors. The accuracy of self-reported light exposure has previously been assessed in adult cohorts, both studies found that participants tended to overestimate the amount of time spent outdoors (Alvarez and Wildsoet, 2013, Ostrin, 2017). This is in line with the child responses in this study who tended to overestimate the time they spent outdoors however responses from parent/guardians were found to be underestimated.

This is consistent with recent data from the USA where parents were also found to underestimate their child's time outdoors (Ostrin et al., 2018).

Another interesting finding of this study is the evaluation of the influence of light sensor orientation on light exposure reading. The orientation of the light sensor was found to significantly alter the light exposure reading. Under all lighting conditions, as expected, the highest light exposure value was recorded when the sensor was directed towards the light sensor i.e. 90^0 and the lowest light exposure value was measured when the sensor was perpendicular to the light sensor i.e. $0/180^o$. This difference was felt to be clinically significant for outdoor values as for both low and high illuminance outdoors, it was nearly 10 times lower. For indoors values the orientation of the sensor did not have as big of an impact. With a wrist worn sensor the orientation of the sensor is likely to be constantly moving especially when the children are playing outside. The selection of the 30 second collection interval rather than 60 seconds aimed to allow more regular sampling with this is mind. However, the use of a wrist worn light sensor has been shown to be well correlated with those recorded at eye level (Jardim et al., 2011, Okudaira et al., 1983). Jardim et al (2011) reported that 69% of all light exposure values recorded using simultaneous sensors at wrist and eye level were within ±50 lux. As mentioned previously alternative non-wrist worn devices to measure light exposure are available. This includes sensors that fix to clothing, for example HOBO Pendant (Onset Computer Corp., USA) or glasses mounted, for example Clouclip (HangZhou Glasson Technology Co., Ltd, China) and Vivior monitor (Vivior, Switzerland). The glasses mounted devices also have the ability to provide more useful objective information in addition to light exposure data but also information on behavioural factors related to near work. The Vivior monitor is able to measure reading distance, orientation and also detailed information on motion with cloud based data processing. The Clouclip is able to measure reading distance, reading duration and reading angle. All data from the Clouclip is transferred to an app which can be made available to parents/guardians so they can self-monitor. Furthermore, it has an innovative alert function that can vibrate if the wearer is reading at less than 33cm to encourage them to increase their working distance and also to encourage breaks from near tasks as it alerts the wearer after 45 minutes of continuous near work. This function has been shown to significantly modify near work behaviours by encouraging longer reading distances and reducing the frequency of continuous periods of near work (Cao et al., 2020). It therefore could be used as a potential strategy for managing myopia.

A limitation of this study is the relatively small sample size meant that comparisons relating to light exposure differences and time spent outdoors with eye growth, latitude

and refractive status did not have sufficient power and were therefore unable to be assessed in this study. Although a large number of data sets were acquired (n=167), only 56.9% (n=95/167) were able to be included in the final data analysis. This large drop out was largely the result of poor compliance, with 32.3% (n=54/72) of data sets removed for this reason. Although poor compliance is expected in this population due to their age (7 – 12 years) it was more than expected and resulted in a considerable loss of data. Read et al (2017) reported the removal of only 0.98% (n=1/102) of data sets for poor compliance in a slightly older cohort (10 – 15 years) following identical screening criteria. For this participant only seven valid hours over the 2 week period was recorded. In this study four participants recorded zero valid data points across the nine day period. 6.5% (n=11/167) of removed data sets were attributed to technical problems with the devices, some of which were avoidable for example insufficient battery charging and incorrect programming setting which resulted from inexperience at the beginning of the study whilst irreparable breakage of the devices also did occur.

Although a larger sample size would be required in order to successfully assess these factors, there are significant logistical elements to consider when collecting this type of data. Due to the limited number of Actiwatch devices available (n=16) it was not possible to capture light exposure for the exact same time periods in Summer and Winter for all participants. Furthermore, inevitably some devices were not returned (n=4) or damaged (n=3) which further reduced the numbers. In order to obtain one data set the device needs to be charged for 24 – 48 hours, programmed, given to the participant prior to the start of data collection, collected 11 days later and the data extracted before starting this cycle again. In this study, only five charging docks were available for 16 devices which impacted the charging phase which had elongated the time between data collection opportunities. In this study, 54 data sets equating to 32.3% of those collected were removed due to poor compliance. Therefore in future not only increasing the sample size but also improving compliance would directly impact the number of data sets. This could be done through the development of a child friendly leaflet detailing information about the device and how much to wear it etc rather than only using an adult designed leaflet intended for their parent/guardian as in this study. This would further enhance the ownership of the compliance to the child themselves, rather than being solely reliant on their parent/guardian input. In addition, increased contact with the participants through their schools and through regular text alerts to their parent/guardian reminding them to ensure they are wearing the device.

A novel aim of this study was the investigation of potential latitudinal differences across the UK. However, the majority of data was captured from the Midlands and a limited

sample was obtained from Southern and Northern regions which again meant the comparison was underpowered and therefore unable to be sufficiently assessed. The main reason behind the sample size discrepancy is the late recruitment of schools in the North and South towards the end of the second year of data collection. This was coupled with the logistical difficulties of distributing the devices to the participants in these areas which was considerable time consuming. This was done almost entirely via post and as a result relied heavily on the school office staff to collect the devices and return them. Across this study a high attrition rate a Year 1 follow up was achieved which limited the availability of eye growth data. Improvements in recruitment and retention strategies, would be beneficial to enhance the sample size and therefore statistical power.

Future studies with improved compliance and a lower attrition rate in a larger population measuring eye growth and light exposure are likely to provide more precise estimates regarding the effects of light exposure on eye growth in the UK. Furthermore, longer duration studies will provide greater insights into the relationship between light on axial length growth throughout childhood. There are well documented seasonal variations in eye growth (Gwiazda et al., 2014b, Donovan et al., 2012) so more regular axial length measurements would be beneficial more closely elucidate the underlying role of light exposure and eye growth across different times of year.

This study is the first to provide objectively measured data on light exposure and outdoor exposure for schoolchildren in the UK. It demonstrates the significant seasonal variation of these measures across the calendar year within the UK alongside other environmental climate conditions. Comparison with published data from Australia, Singapore and USA have shown that, not only, are these seasonal variations unique to the UK but the behaviour of schoolchildren with regard to light and outdoor exposure are different between these countries. These findings have shown that UK schoolchildren experience lower levels of light intensity and also duration.

9.6 Conclusions

This study has provided some novel objective data on light exposure and time spent outdoors for UK children. As expected, it has demonstrated that there are significant seasonal variations in light exposure and time spent outdoors, both of which were much higher in Summer compared to Winter. Significant differences in daily temperature and day length could be attributing to these differences. Furthermore, light exposure and time spent outdoors were significantly higher on weekdays than weekends, this suggests that child's behaviours could be influenced by their parents and introduces the

potentially modifiable factor of parental encouragement and involvement in outdoor activities.

The exact mechanism behind the protective nature of increased light exposure and myopia has still yet to determined. However, if it is attributed to light intensity i.e. the requirement for a certain level of light exposure in order to exhibit a protective effect, this study has shown significant seasonal variation in light exposure and the amount of outdoor exposure. It raises the question as to the viability of recommendation and encouragement for increased time outdoors as protective strategy for myopia for UK children, especially during Winter months. This strategy is implemented in other countries such as Australia which this study have shown experience much higher levels of light exposure. This may lead to the introduction of other methods of increasing light exposure, for example through practical approaches to increasing classroom lighting and also identifying other possible modifiable risk factors, such as reduced near tasks particularly electronic devices which are now commonly used by young children on a regular basis.

Future studies designed to address the limitations in this study, including sample size, are required to further explore objectively measured light exposure and eye growth and refractive error, as well as identify any possible latitudinal varies within the UK.

9.7 Summary

- UK children spend more time outdoors on weekdays compared to weekends
- In Summer, light exposure was 13 times higher and objectively measured time spent outdoors was 10 times longer than in Winter
- Light sensor orientation significant impacted on light exposure recordings
- There was insufficient sample size to compare differences in eye growth and latitude with differences in light exposure and objective estimates of time outdoors
- Subjective responses of time outdoors were overestimated by children and underestimated by parents/guardians compared to objective estimates

Chapter 10: Assessing the viability of Conjunctival UV autofluorescence (CUVAF) as a biomarker in the UK

10.1 Introduction

The relationship between myopia and time outdoors has been investigated extensively over the past few decades and increased time outdoors has been found to have a protective effect on the development of myopia, see Section 2.2. Historically time spent outdoors and light exposure in research has been quantified using self-reported questionnaire data. This is not a reliable source of data as it is reliant on participant recall. It has been hypothesised that Conjunctival UV Autofluorescence (CUVAF) could act as a surrogate biomarker of time outdoors and provide an objective quantifiable measure of ocular UV light exposure (Sherwin et al., 2011).

CUVAF is based on the premise that conjunctival cells that have been exposed to ultraviolet (UV) radiation emit visible fluorescence when excited with a specific wavelength. Ultraviolet (UV) light is thought to damage conjunctival components, such as elastin and collagen which emit fluorescence upon exposure to an excitatory light source (Sandby-Moeller et al., 2004, Asawanonda and Taylor, 1999). UV radiation exposure from the sun has long been linked with several ocular conditions including basal cell carcinomas, cataracts and pterygium (Situm et al., 2008, McCarty and Taylor, 2002, Taylor, 1994, Zhou et al., 2016b). CUVAF has been associated with both pingueculae and pterygia (Ooi et al., 2007). As a result, a photography system was developed as a method to detect and record this fluorescence. It was derived from Wood's lamp which is used to assess dermatological changes (Asawanonda and Taylor, 1999). CUVAF can be observed through the use of a mounted camera system on a slit lamp or, as in this study, a novel handheld modified smartphone system, outlined in Section 4.4.

Ooi et al (2006) explored CUVAF in Australian children aged 3-15 years. The study reported that CUVAF was found in children with established pingueculae, but also those without. This led to the notion that this technique could be used in the identification of individuals with conjunctival UV damage which could be acting as a pre-cursor prior to the development of clinical manifestations. On a clinical level, this would allow the monitoring of individuals identified as at risk of the development of ocular conditions such as pterygia and allow implementation of possible prevention strategies and advice. It also emerged that CUVAF could act as a surrogate biomarker to quantify time outdoors.

This has led to a number of studies investigating CUVAF (McKnight et al., 2015, Sherwin et al., 2011, Wolffsohn et al., 2014, Kearney et al., 2019, Sherwin et al., 2012c, Haworth and Chandler, 2017). The largest study to investigate CUVAF was the Norfolk Island Eye Study which recruited 641 participants aged 15-89 years old from Norfolk Island, an external territory of Australia located in the South Pacific Ocean located in the Southern hemisphere (Sherwin et al., 2011). This study found that total CUVAF area was not normally distributed and declined with age. This non-parametric distribution has been supported by subsequent studies (McKnight et al., 2015, Sherwin et al., 2011, Wolffsohn et al., 2014). Whilst Sherwin et al (2011) concluded that the area of CUVAF was larger in males than females (34.4mm^2 vs 23.2mm^2 respectively, $p<0.001$), Wolffsohn et al (2014) found no difference in sex (male 2.69±4.19mm^2 and female 2.27±3.33mm^2). The area of CUVAF per eye reported by Wolffsohn et al (2014) was considerably smaller than that by Sherwin et al (2011) (2.58±3.73mm^2 vs 17.5mm^2 (IQR 7.1-25.4)). The large difference between these areas is likely attributed to the differences in geographical location of the two recruitment cohorts. Whilst Sherwin et al (2011) cohort was exclusively from Norfolk Island in the Southern hemisphere, Wolffsohn et al (2014) captured CUVAF from 307 individuals across the Northern hemisphere (Czech Republic, Germany, Greece, Kuwait, Netherlands, Sweden, Switzerland, United Arab Emirates and the United Kingdom). Therefore, the discrepancy is likely a result of the differences in sunlight exposure and intensity of light experienced in these differing locations.

The area of CUVAF was speculated to be greater nasally than temporally due to the peripheral light focussing or Coroneo effect. This effect is caused by the optics of the eye intensifying light directed towards the temporal limbus onto the nasal limbus (Twelker et al., 2005, Coroneo et al., 1991). This correlates with the typical presentation and distribution of pterygia (McKnight et al., 2015) and this distribution in CUVAF has been confirmed by McKnight (2015) and Wolffsohn (2014).

The amount of CUVAF and time spent outdoors has been found to be positively correlated (McKnight et al., 2014, Sherwin et al., 2012a, Kearney et al., 2016). The relationship between CUVAF and myopia has been investigated in two Australian based studies (McKnight et al., 2014, Sherwin et al., 2012a). Sherwin et al (2012a) investigated CUVAF in 636 adults (aged 19 – 64 years) from Norfolk Island. A protective association between increasing CUVAF and myopia was found with the median CUVAF found to be significantly less in myopes compared to non-myopes (16.6mm^2 vs 28.6mm^2 respectively, $p<0.001$). Data from mainland Australia also found myopes to demonstrating a significantly smaller CUVAF area than non-myopes (31.9mm^2 vs

47.9mm^2 respectively, p<0.001) (McKnight et al., 2014). Both studies concluded that myopia was inversely related to UV exposure and therefore, indirectly, time outdoors. Interestingly sun exposure prevention methods such as the wearing of sunglasses and hats and even UV-blocking contact lenses have been shown to have no effect on CUVAF likely due to incomplete coverage of the conjunctiva (McKnight et al., 2014, Sherwin et al., 2012a, Wolffsohn et al., 2014).

The literature surrounding our understanding of CUVAF is still in its infancy and more research is required to get a more conclusive picture of its distribution and associations worldwide.

10.2 Rationale

There is currently limited data on the presence and quantity of CUVAF in an exclusively UK population and no published data of CUVAF characteristics of children in the UK. This Chapter will assess the viability of using CUVAF as a biomarker for time outdoors in the UK. In addition, it will provide data on the ability of a bespoke handheld device to detect the presence of CUVAF and assess the quality of the images captured. This study will also provide exploratory data on longitudinal changes in CUVAF.

10.3 Methodology

10.3.1 Image acquisition

Nasal and temporal conjunctival photos were taken using the device detailed in Section 4.4 on all participants. The app Camera+© (tap tap tap, USA) was used and the setting set at 1/8 (shutter speed), 400ISO (exposure) and Shade (filter setting). All images were taken in low illumination with the room lights off to ensure aberrant visible light did not interfere with the images. Attempts were made to ensure the minimum external illumination however in some schools, room illumination could not be easily reduced because of uncovered windows or ceiling lights. Four images were taken (Right Nasal, Right Temporal, Left Nasal, Left Temporal) at each visit (Baseline, Year 1 and Year 2). The use of a digital device allowed image quality to be instantly verified and retaken where necessary. Each eye was photographed at 1.0x magnification.

All images were downloaded from the smartphone and coded for identification using the following sequence: Visit Number (V1/V2/V3)_Participant Code_Eye(OD/OS) _Location (Nasal/Temporal). For example, a photo of participant YA001 taken on the first visit of their right nasal conjunctiva would have the code V1_YA001_OD_Nasal.

All images were taken by a single practitioner (KF) and due to the novel nature of this device, prior to image acquisition on participations training sessions were undertaken. These training sessions demonstrated how to set up the device in relation to pre-determined optimised settings by the manufacturer and methods of accurate alignment. In addition, all images were taken prior to biometry and autorefraction data reducing the risk of bias in the photography process.

10.3.2 CUVAF Image Analysis

Quantitative analysis of the images was done using ImageJ software (Version 1.51j8: http://rsbweb.nih.gov/ij/). Prior to this analysis the quality of each image was graded as poor, adequate or good using the assessment matrix in Table 10.1. Examples of each image quality grade can be found in the Appendix A.10.1.

	Poor	Adequate	Good
Sharpness	Image out of focus: poor definition of conjunctival blood vessels	Adequate focus: adequate definition of conjunctival blood vessels	Image in good clear focus: good definition of conjunctival blood vessels
Visibility of conjunctiva	Poor/no visibility of conjunctiva. Obstruction by eyelid or eyelashes	Adequate visibility	Good visibility. No obstruction of conjunctiva
External illumination	Excessive resulting in inability to visualise potential CUVAF present	Adequate allowing potential CUVAF visualisation	Optimal allowing clear visualisation of potential CUVAF

Table 10.1: CUVAF image quality grading matrix

Only images of adequate or good quality were assessed for the presence of CUVAF. Overall, 23.0% (n=275) of images were classed as good, 42.8% (n=513) as adequate and 34.2% (n=410) as poor. Prior to analysis of CUVAF area all images were converted to greyscale and the contrast increased to 75 using Adobe Photoshop (Adobe Systems Inc, San Jose, California, USA). This improved identification of areas of CUVAF from non-CUVAF areas, see Figure 10.1.

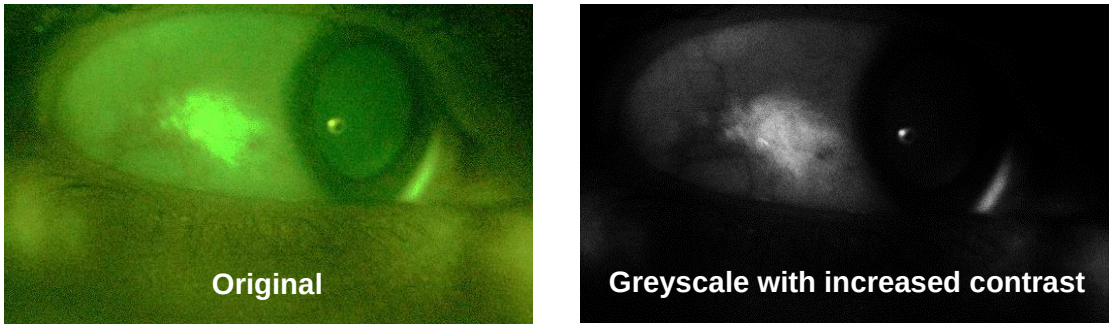


Figure 10.1: The visibility of CUVAF was enhanced by converting images to greyscale and enhancing the contrast

Following this image enhancement, all images were reviewed and those with visible CUVAF were analysed. The edges of the CUVAF were subjectively outlined using the ImageJ software, see Figure 10.2. This is a similar method employed in other studies to establish CUVAF area (Kearney et al., 2016, Wolffsohn et al., 2014). The software provided an area in pixels which was then converted to millimetres. Total CUVAF area (mm^2) for an individual was calculated by summing the temporal and nasal areas of the right and left eye.

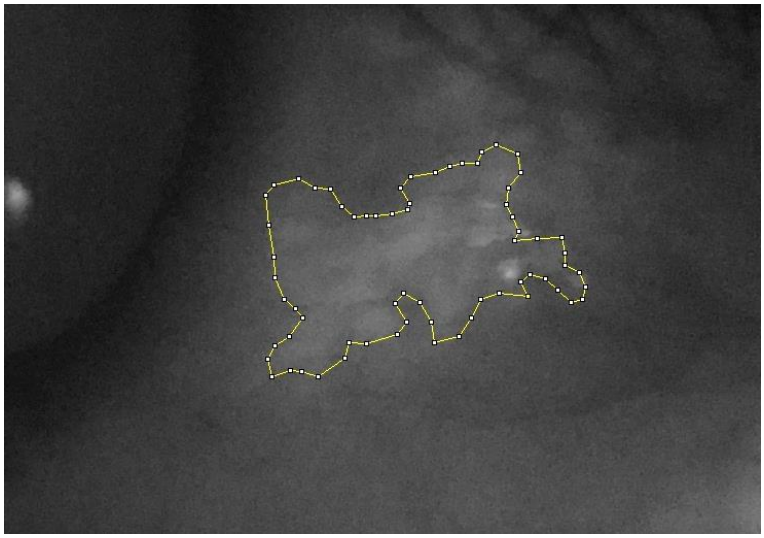


Figure 10.2: Image analysis of area of CUVAF using ImageJ

10.3.3 Converting the pixel area to millimetres-squared (mm^2)

The area of fluorescence measured with the ImageJ software was calculated in $pixels^2$. To convert this area to millimetres-squared (mm^2), the number of pixels per millimetre (mm) was calibrated from the image of a ruler using the same camera system, see Figure 10.3.

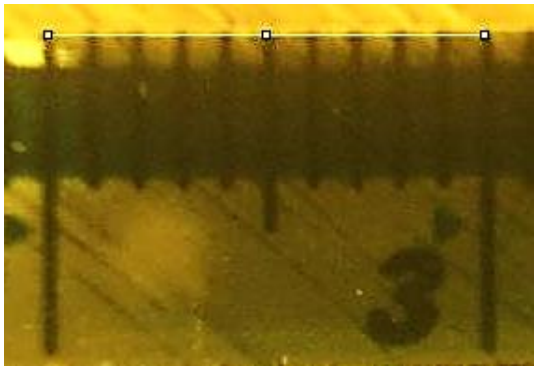


Figure 10.3: Image of ruler taken with the UV camera system used for pixels-mm calibration The yellow line was drawn with the ImageJ software.

The number of pixels per centimetre (cm) was measured 10 times. The average was then used to calculate the number of pixels per mm which was found to be 88.0±0.3mm. It was therefore determined that 1 mm^2 equated to 88 x 88 pixels (7744 $pixels^2$). The following equation was then used to covert pixel area to mm^2:

$$mm^2 = \frac{\text{pixel area}}{7744}$$

10.3.4 CUVAF analysis intra-examiner repeatability

CUVAF photography has been previously found to have high inter and intra-examiner reliability (Sherwin et al., 2012b, Kearney et al., 2014). Both of these studies used a slit lamp mounted photography system. The handheld modified smartphone UV device used in the study is described in Section 4.4. and uses the same principles outlined by Coroneo and colleagues (Ooi et al., 2007). Due to the bespoke nature of the device, its repeatability and validity needed to be established.

Repeatability has been defined as the variation in repeat measurements under identical conditions. Any variation found using this method can subsequently be attributed to the measurement process (Bartlett and Frost, 2008). All images were captured and analysed by the same examiner (KF) therefore only intra-examiner repeatability was investigated.

To evaluate intra-examiner repeatability, a random sample of 15 images with visible CUVAF from 15 participants (mean age 20.0±2.0 years, range 18.8 – 24.5 years) were analysed in two separate sessions to ensure consistency in demarcation and area calculation. The images were analysed one week apart to prevent recall bias. At each session each image was analysed three times and an average taken. The images were randomised and re-labelled to further prevent recall bias and to ensure the examiner was masked. The mean difference (MD) between the two measurements was calculated for each image. The agreement between the repeat measurements was analysed using the Limits of Agreement (LOA) graphical method, a statistically valid method outlined by Bland and Altman (Bland and Altman, 1999). A narrow LOA is required in order to attribute any change in CUVAF area to a 'true' change in CUVAF area rather than a measurement error. A Bland-Altman plot for comparison of the CUVAF area measured at the two time points was drawn, see Figure 10.4.

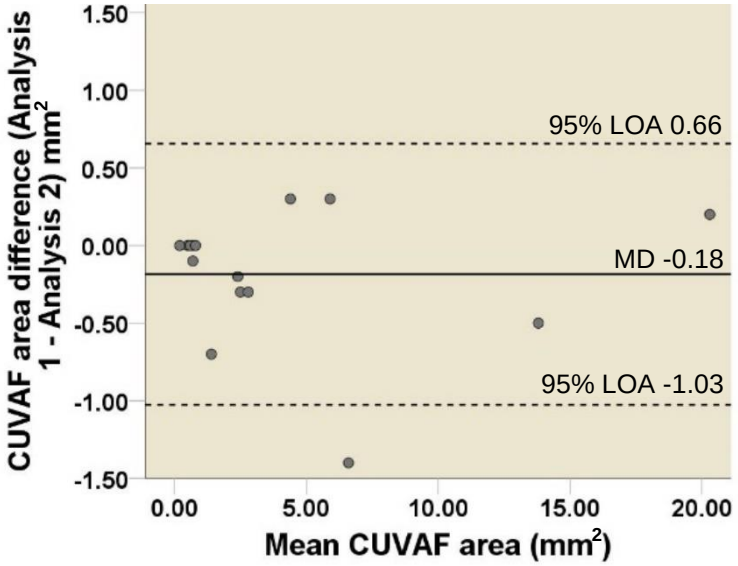


Figure 10.4: Bland-Altman plot demonstrating intraobserver repeatability for CUVAF area measurement (mm^2) The mean difference (MD) is shown with a solid line and the 95% Limits of agreement (LOA) are shown with the dashed lines.

Examination of the Bland and Altman plot shows a narrow LOA and small MD which indicates a high intra-examiner agreement. The intra-examiner reliability and repeatability of CUVAF captured with a different image system than that employed in this study has previously been assessed and was found to be high (Sherwin et al., 2012b). Table 10.2 shows the comparison between the 95% LOA and MD values for CUVAF area measurement for this study and Sherwin et al (2012b).

Study (sample size)	Age (mean±SD)	MD (mm^2)	95% LOA (mm^2)
This study (n=15)	20.0±2.0	-0.18	-1.03 to 0.66
Sherwin et al (2012b) (n=15)	53.3±14.2	-1.41	-5.23 to 2.39

Table 10.2: Intra-examiner repeatability of CUVAF area measurement found in this study and a previous study performed by Sherwin et al (2012b) MD: Mean difference. LOA = Limits of Agreement

The MD in this study is much closer to zero than Sherwin et al (2012b) suggesting that the intra-examiner repeatability in this study was higher. The LOA is narrower in this study further suggesting a greater intra-examiner repeatability. This provides confidence that the method used in this study has a high intra-examiner repeatability and is highly likely be able to establish small changes in CUVAF area. A high degree of

intra-examiner reliability was also found in the study by calculating the intraclass correlation (ICC). The ICC was 0.998 (95% CI from 0.995 – 0.999).

To further assess the repeatability of the technique a single image was measured 10 times. The coefficient of variation (CV) was then calculated. The CV allows the extent of variability within a data set to be established in relation to the mean. It is the ratio of standard deviation (SD) to the mean using the following formula:

$$CV = \frac{SD}{Mean} \times 100$$

The CV was calculated as 1.6% (mean±SD 8.76±0.14 mm^2). This low CV indicated a low dispersion of data from the mean and therefore shows a relatively low variability in the measurements. This suggests that the technique employed in this study to assess CUVAF is a repeatable technique.

10.3.5 Refractive error assessment

Refractive error was established through cycloplegic autorefraction and defined by first calculating the spherical equivalent refraction (SER) using the equation: sphere + ½ cylinder. The definitions used in this study are summarised in Table 10.3. These definitions are in line with previously published data, see Table 1.1 in Section 1.6.

Category	Definition
Myopia	SER ≤ -0.50D in at least one eye
Emmetropia	SER > -0.50D to <+2.00D in both eyes
Hyperopia	SER ≥ +2.00D in at least one eye as long as neither eye was myopic
Astigmatism	Cylindrical power ≤ -1.00 DC in either eye

Table 10.3: Refractive error classification definitions

10.3.6 Self-reported time outdoors and sun protection strategies

A questionnaire providing demographic information such as ethnicity and lifestyle information including amount of time spent outdoors in summer and winter and weekdays and weekends, use of sun bed, sun protection strategies in the summer such as the use of sunglasses and a hat that protects from the sun and if applicable time spent abroad and duration. Time spent outdoors categorical responses were none, less than 1 hour, 1-2 hours or 2 or more hours. Use of sunglasses and hat wear categorical responses were Never, Occasionally, Usually and Always, see Appendix A.5.5. The questionnaire was completed by the participants themselves in the Young Adult cohort (18 – 25 years). In the younger Child cohort (aged 7 – 12 years) this questionnaire was

completed by a parent or guardian and a simpler questionnaire enquiring about time of outdoors in general (i.e. non-seasonal) and sun protection strategies was completed by the child on the day of data collection. A parental questionnaire return rate of 83.2% (n=188) was achieved however only 65.5% (n=148) of returned questionnaire had all required responses relating to this analysis completed. Ethnicity information for participants in the Child cohort was only available for those with returned parental questionnaires.

10.3.7 Statistical analysis and sample size calculation

All data was analysed using SPSS® Version 25. Total CUVAF area (mm^2) was found to be not normally distributed (Shapiro Wilk p=0.128), therefore non-parametric statistics were used. Differences in categorical variables were assessed with the χ^2 test (image quality comparison between cohorts), differences in continuous data with categorical variables were assessed with the Mann Whitney U test (sex, ethnicity and sun protection strategies) and the Kruskal Wallis test (time outdoors, refractive error classification and longitudinal change in CUVAF area). Differences in nasal and temporal CUVAF areas was assessed with a related samples Wilcoxon Signed Rank test. All images graded as poor were excluded from the analysis.

Due to the exploratory nature of CUVAF in this study with a novel photography system that, to date, has not be used in published literature, sample size calculations were performed post-hoc using G*Power software (version 3.1.9.4) and are presented in the discussion.

10.4 Results

10.4.1 Baseline characteristics including questionnaire responses

Two cohorts were examined in this study, 87 participants in the Young Adult cohort (mean age 19.9±1.3 years, range 18.2-24.5 years) and 226 in the Child cohort (mean age 9.6±1.2 years, range 7.1-11.8 years). All participants were current residents of the UK. In the Young Adult cohort participants were recruited from Aston University and therefore consisted of primarily undergraduate students. In the Child cohort participants were sampled from seven primary schools from a cross section of the UK, see Section 5.2.1.3. 56.2% (n=127) of participants in the Child cohort were female and 66.7% (n=58) in the Young Adult cohort were female. The main ethnic groups sampled in both cohorts were White and Asian (Child cohort: White 67.0% (n=126), Asian 14.4% (n=27) and Other 18.6% (n=35). Young Adult: White 41.4% (n=36), Asian 43.7% (n=38) and Other 14.9% (n=13)).

Table 10.4 provides a summary of self-reported questionnaire responses of sun protection strategies frequencies in the Child cohort and the equivalent parental questionnaire responses.

	Frequency sunglasses are worn (%)		Frequency a hat is worn (%)	
Frequency	**Self-reported†**	**Parental‡**	**Self-reported†**	**Parental‡**
Always	0.9 (n=2)	2.7 (n=4)	4.9 (n=11)	12.2 (n=18)
Usually	13.7 (n=31)	12.2 (n=18)	16.8 (n=38)	36.5 (n=54)
Occasionally	65.9 (n=149)	64.2 (n=95)	56.6 (n=128)	45.9 (n=68)
Never	19.5 (n=44)	20.9 (n=31)	21.7 (n=49)	5.4 (n=8)

Table 10.4: Questionnaire responses (%) for frequency of sun protection strategies self-reported by participants in the Child cohort and reported in the parental questionnaire responses †n=226, ‡n=148

In the Child cohort, 52.2% (n=118) of participants self-reported more than 2 hours of time outdoors a day, 38.1% (n=86) 1-2 hours a day, 9.3 (n=21) less than 1 hour a day and 0.4% (n=1) reported no time outdoors. The parental questionnaire responses for the Child cohort can be subdivided into season and weekday/weekend and is shown in Table 10.5.

Frequency	Weekday Summer† (%)	Weekend Summer† (%)	Weekday Winter† (%)	Weekend Winter† (%)
None	0.0 (n=0)	0.0 (n=0)	2.7 (n=4)	1.4 (n=2)
<1 hour	6.8 (n=10)	0.0 (n=0)	41.2 (n=61)	14.2 (n=21)
1-2 hours	32.0 (n=47)	18.2 (n=27)	34.5 (n=51)	37.8 (n=56)
2 or more hours	61.2 (n=90)	81.8 (n=121)	21.6 (n=32)	46.6 (n=69)

Table 10.5: Parental questionnaire responses (%) for time spend outdoors in summer/winter and weekday/weekend reported in the Child cohort †n=148

In the Young Adult cohort, the amount of time spent outdoors in each season and weekday/weekend is shown in Table 10.6. 5.7% (n=5) of participants always wore sunglasses. 16.1% (n=14) usually wore sunglasses, 55.2% (n=48) occasionally worse sunglasses and 23.0% (n=20) never wore sunglasses. 1.1% (n=1) always wore a hat, 23% (n=2) usually wore a hat, 33.3% (n=29) occasionally wore a hat and 63.2% (n=55) never wore a hat. For sun bed use, 97.7% (n=85) of participants had never used a sunbed and 2.3% (n=2) used a sunbed a few times a year.

Frequency	Weekday Summer† (%)	Weekend Summer† (%)	Weekday Winter† (%)	Weekend Winter† (%)
None	0.0 (n=0)	0.0 (n=0)	0 (n=0)	1.1 (n=1)
<1 hour	5.7 (n=5)	3.4 (n=3)	26.4 (n=23)	27.6 (n=24)
1-2 hours	36.8 (n=32)	32.2 (n=28)	55.2 (n=48)	46.0 (n=40)
2 or more hours	57.5 (n=50)	64.4 (n=56)	18.4 (n=16)	25.3 (n=22)

Table 10.6: Questionnaire responses (%) for time spend outdoors in summer/winter and weekday/weekend reported by participants in the Young Adult cohort †n=87

Image quality assessment of the Young Adult cohort images (total n=342) found 38.3% (n=131) to be classed as good, 37.4% (n=128) as adequate and 24.3% (n=83) as poor. In the Child cohort (total n=856), 16.8% (n=144) were good, 45.0% (n=385) as adequate and 38.2% (n=327) as poor. A significant association between cohort and image grade was found ($\chi^2(2) = 66.24$, $p<0.001$). More specifically a significantly higher proportion of images in the Child cohort were rated as poor compared to good than in the Young Adult cohort ($\chi^2(1) = 57.50$, $p<0.001$). Based on the odds ratio, the odds of a poor image were 3.58 times higher in the Child cohort than the Young Adult cohort.

10.4.2 CUVAF characteristics

Of the 313 participants that took part in this study, 3.8% (n=12) showed visible CUVAF. In the Child cohort, no eyes examined showed evidence of CUVAF. In the Young Adult study, 12.6% of eyes (n=22) showed visible CUVAF from 12 participants. The median CUVAF area per eye (Nasal and Temporal combined) was 9.08mm^2 (IQR 4.51-15.85mm^2) and median total CUVAF area per individual (both eyes combined) was 18.79mm^2 (IQR 7.70-29.27). No significant difference was found between the median area of CUVAF nasally (median 5.44mm^2, IQR 2.12-7.92 mm^2) and temporally (median 2.89mm^2, IQR 0.24-7.40 mm^2) (related samples: Wilcoxon signed rank p=0.733). The total CUVAF area was not related to sex (independent samples: Mann Whitney U p=0.149) or ethnicity (independent samples: Mann Whitney U p=0.921).

10.4.3 Time outdoors and CUVAF

CUVAF area and self-reported time spent outdoors by season and weekday/weekend is shown in Table 10.7. The area of CUVAF was not related to time spent outdoors in summer during weekdays (Kruskal Wallis test p=0.492), time spent outdoors in summer during weekends (Kruskal Wallis test p=0.268), time spent outdoors in winter during

weekdays (Kruskal Wallis test p=0.415) or time spent outdoors in winter during weekends (Kruskal Wallis test p=0.845).

	Median total CUVAF area (mm^2) (IQR)			
Frequency	**Weekday Summer**	**Weekend Summer**	**Weekday Winter**	**Weekend Winter**
None	NA	NA	NA	NA
<1 hour	**26.25** (n=1) (26.25-26.25)	NA	**16.18** (n=5) (7.33-25.24)	**17.83** (n=4) (5.28-25.74)
1-2 hours	**13.81** (n=6) (3.67-25.74)	**24.22** (n=5) (13.81-44.43)	**15.46** (n=6) (6.28-38.36)	**16.18** (n=5) (5.46-46.45)
2 or more hours	**21.40** (n=5) (8.31-52.25)	**9.51** (n=7) (3.82-30.28)	**41.88** (n=1) (41.88-41.88)	**21.40** (n=3) (9.51-NA)
Kruskal Wallis	p=0.492	p=0.268	p=0.415	p=0.845

Table 10.7: Total CUVAF area (mm^2) and self reported time spent outdoors in summer/winter and weekday/weekend All values are median with accompanying IQR

10.4.4 Refractive error and CUVAF

Of participants with visible CUVAF, 58.3% (n=7) were emmetropic (median CUVAF area 21.40mm^2 (IQR 7.10-41.88)) and 41.7% (n=5) were myopic (median 16.18mm^2 (IQR 7.63-28.37)), see Figure 10.5. Total CUVAF area was not related to refractive error classification (Mann Whitney U test p=1.000).

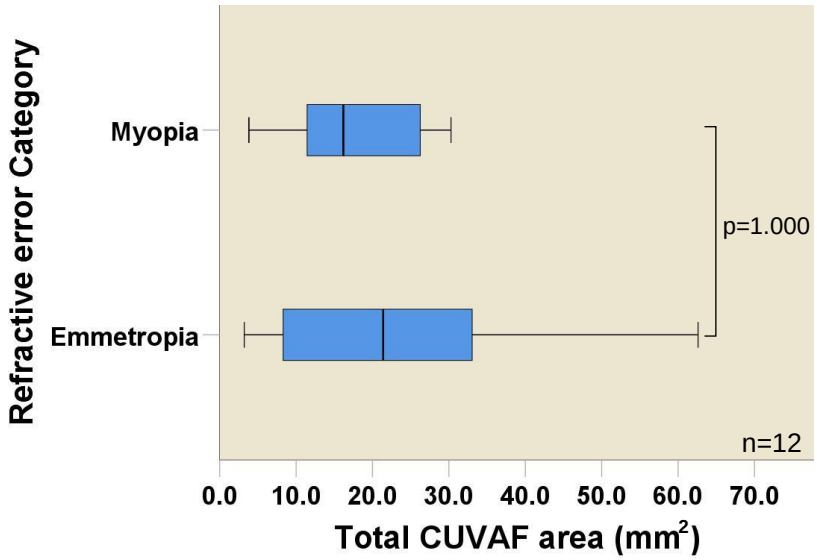


Figure 10.5: Total conjunctival UV autofluorescence (CUVAF) area with refractive error category

Analysis of total CUVAF area and refractive error as a continuous variable revealed no significant correlation (R^2=0.000, r=-0.014 p=0.965), see Figure 10.6.

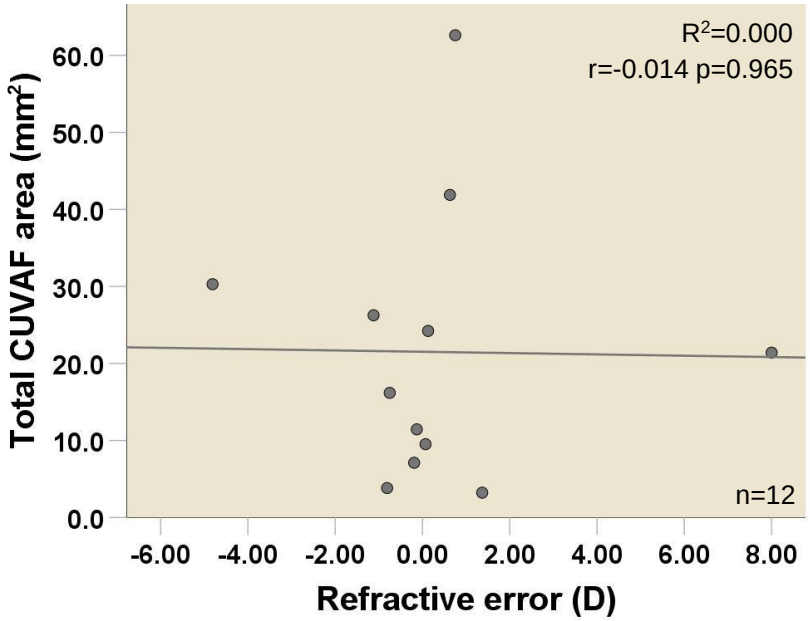


Figure 10.6: Correlation of total conjunctival UV autofluorescence (CUVAF) area with refractive error

10.4.5 Eye growth and CUVAF

Of the 12 participants with visible CUVAF at Baseline, 58.3% (n=7) had adequate images for re-assessment at the 1 year follow up. The CUVAF at Year 1 was compared to the average eye growth between Baseline and Year 1, see Figure 10.7. No significant correlation was found (R^2=0.008, r=0.088 p=0.851).

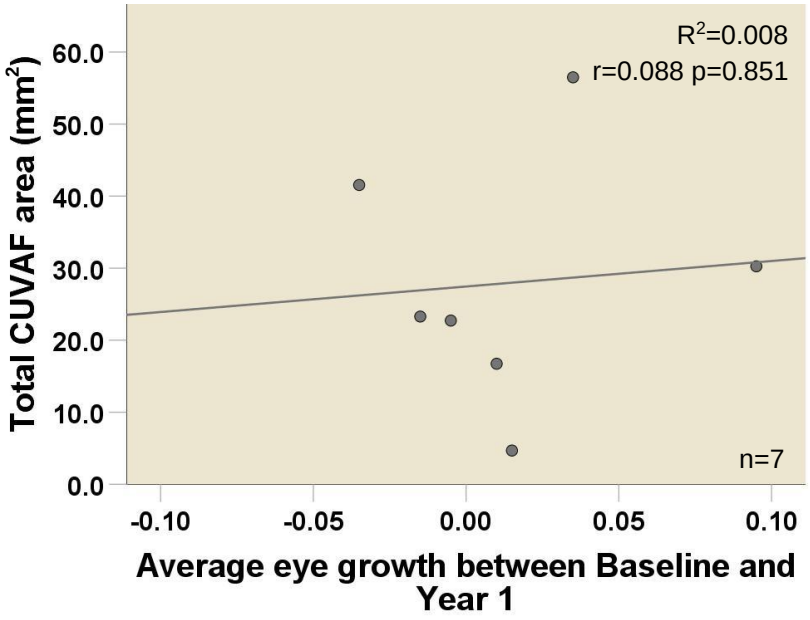


Figure 10.7: Correlation of total conjunctival UV autofluorescence (CUVAF) area with average eye growth between Baseline and Year 1

10.4.6 Sun protection strategies and CUVAF

Questionnaire responses for frequency with which sunglasses were worn was limited to occasionally (75%, n=9, median CUVAF area 24.22mm^2) and usually (25%, n=3, median 3.82mm^2). Total CUVAF was not related to frequency of sunglass use (independent samples: Mann Whitney U test p=0.064).

Questionnaire responses for frequency of hat use was limited to occasionally (25%, n=3, median CUVAF area 7.10mm^2) and never (75%, n=9, median 24.22mm^2). Total CUVAF was related to frequency of hat use (independent samples: Mann Whitney U test p=0.036).

10.4.7 Sun bed use and CUVAF

100% (n=12) of participants with visible CUVAF responded that they had never used a sun bed. Of the 2.2% of participants (n=2) that responded that they use sunbeds a few times a year no visible CUVAF was found.

10.4.8 Time spent living abroad and CUVAF

33.3% (n=4) of participants with visible CUVAF responded that they had spent time living abroad. This included Czech Republic for 14 years, Malawi for 5 years, Kenya from birth to 18 years old and Canada from birth to 22 years old. Total CUVAF was not related to time spent living abroad (independent samples: Mann Whitney U test p=0.283).

10.4.9 Longitudinal changes in CUVAF

Of the 12 participants with visible CUVAF at Baseline, 58.3% (n=7) had adequate images for re-assessment at the 1 year follow up and 16.7% (n=2) at a 2 year follow up. The mean difference in CUVAF between Baseline and Year 1 was 2.11mm^2 and between Year 1 and Year 2 -0.51mm^2. No significant difference in CUVAF area between visits was found (Kruskal Wallis test p=0.669). No participants who had previously been recorded as having no visible CUVAF developed CUVAF over the two year period.

10.5 Discussion

Of the 626 eyes examined in this study only 3.5% (n=22) exhibited any visible CUVAF from 12 participants. This is markedly different from the findings from an Australian based study which found 96.3% (n=1234/1282) of participants had CUVAF (Sherwin et al., 2011). The cohort was older and had a larger age range (15 to 89 years) compared to this study. Similar differences were also found in the total area of CUVAF, which was

smaller in this study (18.79mm^2, IQR 7.70-29.27mm^2) than that of the Norfolk Island eye study based in Australia (28.2mm^2, IQR 14.5-48.2mm^2) (Sherwin et al., 2011). It was more in line other northern hemisphere based studies such as Kearney et al (2016) where the median area of CUVAF was 4.9mm^2 (IQR 2.2-9.4mm^2). Interestingly, in this study no participants in the Child cohort (aged 7 to 12 years) demonstrated any visible CUVAF this is conflicting with previous literature on school aged children (aged 3 to 15 years) in Australia where 32% (n=23/71) demonstrated CUVAF (Ooi et al., 2007). The previous Chapter demonstrated significant differences in climate, light intensity and time spent outdoors compared to other countries, most notably Australia. These factors directly influence the exposure to UV light and consequently CUVAF prevalence and quantity. These environment differences will also likely have a direct impact on behavioural and lifestyle factors, for example influencing participation in outdoor activities, which could contribute to the discrepancy between the findings of this study and other studies based outside the UK.

No relationship between sex and total CUVAF area was found which is in agreement with two other northern hemisphere studies (Kearney et al., 2016, Wolffsohn et al., 2014). Furthermore, ethnicity was also found to not be related to CUVAF.

The area of CUVAF was speculated to be greater nasally than temporally due to the peripheral light focussing or Coroneo effect. This effect is caused by the optics of the eye intensifying light directed towards the temporal limbus onto the nasal limbus (Twelker et al., 2005, Coroneo et al., 1991). This correlates with the typical presentation and distribution of pterygia (McKnight et al., 2015) and this distribution in CUVAF has been confirmed by McKnight (2015) and Wolffsohn (2014). In this study CUVAF area showed a trend for a larger area nasally (median 5.44mm^2) than temporally (median 2.89mm^2) however this was not found to be statistically significant. A sample size calculation for this data was performed using G*Power software (version 3.1.9.4, Wilcoxon signed rank test (matched pairs):two tailed) to calculate the sample size needed to show a difference of 1mm between nasal and temporal regions with a power of 95% and significance 5%. The effect size was calculated using the mean nasal and temporal area (5.86mm^2) and the SD using the intra-examiner repeatability calculated in Section 10.3.4 of 0.43mm^2. The results indicated a total sample size of 6 would be required and 12 participants were measured in this study, thus confirming a sufficient sample size was obtained. Kearney et al (2016) also did not find a difference in CUVAF area nasally and temporally, but did find a difference in the CUVAF intensity which was greatest nasally.

The quantification of time outdoors varies between studies and is based on self-reported average values. Two studies used sunbathing habits to gauge UV exposure, using terminology such as 'sun worshipper', 'adequate sun exposure' and 'sun avoider' (Kearney et al., 2016, Wolffsohn et al., 2014). Both of these studies found no association between this measure of UV exposure and CUVAF area which could be related to broad relatively ambiguous categorisation. More similarly to this study, Sherwin et al (2012a), elicited information on the amount of time spent outdoors, using the proportion of the day as a measure (none, < ¼ of day, approximately ½ day and > ¾ of day) rather than number of hours. However again no statistically significant association was found between time outdoors and CUVAF area. The results of this study align with these studies with no association between time outdoors and CUVAF, irrespective of season or weekday/weekend. The use of subjective responses and broad categories, such as those used in this study, is likely to result in a reduction in power to detect any associations. The use of an objective wearable light sensor such as the Actiwatch 2 (Philips Respironics, USA) would allow a more sensitive and accurate assessment of duration of time spent outdoors as well as providing information of intensity of illuminance. In this study, this data were only available for the Child cohort, within which no CUVAF was observed, so this data was unable to be analysed.

The relationship between CUVAF and sun protection strategies, primarily the use of sunglasses and hats, is unclear. Contrary to expectation a reduced area of CUVAF has not be associated with the use of sunglasses and sunhats (McKnight et al., 2014, Sherwin et al., 2012a, Wolffsohn et al., 2014). However a more recent study did find a negative association between sunglass wear and CUVAF area suggesting sunglasses may be protective against CUVAF (Kearney et al., 2016). In this study no association with CUVAF area was found with sunglass wear, however, a significant association with hat use was found. Those who wore a hat occasionally had a significantly smaller CUVAF area than those who never wore a hat. None of the participants with visible CUVAF reported the use of sunbeds and as such in order to ascertain the potential effect sunbeds have on CUVAF a population including participants who regularly use sunbeds would be beneficial. No association between time spent abroad and CUVAF was found in this study.

It has been hypothesised that CUVAF can be used a biomarker for UV exposure and therefore as a surrogate measure of time outdoors. In the literature increased time outdoors has been shown to have a protective effect against myopia, see Section 2.2. Therefore it was theorised that the area of CUVAF would be larger in emmetropes compared to myopes as a direct result of increased time outdoors and consequential

UV exposure. This has been investigated in two Australian based studies, both finding a smaller CUVAF area in myopes (McKnight et al., 2014, Sherwin et al., 2012a). Both studies had a considerably larger sample size than this study at 636 and 1344 compared to 12 in this study. Of the 313 participants examined in this study only 3.8% (n=12) showed visible CUVAF. This suggests that comparatively to Australia the prevalence of CUVAF is significantly lower. Of the 12 participants identified with CUVAF 7 were emmetropic and 5 were myopic and no significant difference in CUVAF was found between these refractive groups. A post-hoc power calculation was performed using G*Power software (version 3.1.9.4, Wilcoxon signed-rank test (two groups):one tailed). The effect size was calculated using the mean±SD total CUVAF area of myopes (17.59±10.79mm^2) and emmetropes (24.28±21.39mm^2) with a 5% significance. The results showed a low power of 0.15 suggesting a larger sample size would be required in order to assess any significant differences between total CUVAF area between refractive error categories. Due to the longitudinal nature of the data collection in this study the comparison of CUVAF with eye growth was able to be explored, data on which has yet to be published. In this study no significant correlation was found between eye growth and total CUVAF area. Sample size for this analysis was limited twofold, firstly by the high attrition rate between Baseline and Year 1 and secondly by the low prevalence of CUVAF in the study population. Further recruitment would allow this analysis to be more accurately

This study has demonstrated that the novel CUVAF modified smartphone photography system used in this study has the capacity to detect CUVAF. Further adjustments need to be made to ensure a consistently good quality image can be captured in order to allow accurate demarcation and measurement of CUVAF area. As expected, this was more apparent in the Child cohort where good compliance was lacking with some participants. This device provides a useful portable alternative to slit lamp based photography systems for field based research such as in this study. In the absence of a current standardised system or agreed gold standard for CUVAF photography comparison of images taken with this device with other slit lamp based systems would be beneficial to ascertain any potential differences in the amount of detectable CUVAF.

The research surrounding CUVAF is still in its infancy and one key question that is yet to be fully answered regarding CUVAF is the exact duration of UV exposure that is required to produce CUVAF. It has been postulated that it provides information about acute/recent light exposure, similar to a suntan, rather than a cumulative exposure over a lifetime (Sherwin et al., 2011). This has been supported by a recent study investigating the seasonal effect on CUVAF on 50 participants located in Ohio, USA (Haworth and

Chandler, 2017). Higher levels of CUVAF were measured during the winter seasons of collection compared to Spring. It was concluded that this was a result of the conjunctival tissue retaining the UV autofluorescent properties for several months following chronic UV exposure and therefore a representation from a longer period than that suggested by Sherwin and colleagues. This study has provided exploratory information on the natural history of CUVAF through the re-examining of the same individuals over time. No significant difference in size of CUVAF area was found over a 2 year period and interestingly no development of new CUVAF occurred over the study period. All measurements were taken at the same time of year (within ±6 weeks) which could explain the lack of change over time or new development of CUVAF however this would also assume that the participants exposure to UV was consistent across the time period compared to previous years. Alternatively it could be interpreted that CUVAF damage is more permanent then simply a suntan and hence why the total CUVAF area remained consistent over time. Further investigation of CUVAF at more regular intervals will provide further insight into its natural history. This would be further enhanced by recruiting participants from a larger range of age groups to understand the distribution of CUVAF within the UK population as a whole and also compare the quantity of CUVAF with age.

10.6 Conclusions

This study has shown for the first time a lack of CUVAF in UK based children and a relatively low prevalence of CUVAF in UK young adults. This suggests that CUVAF may not be a suitable biomarker for use as a surrogate measure of time outdoors in the UK. Further work is required to assess CUVAF with objective measures of time outdoors and also determine the longevity of CUVAF.

10.7 Summary

- No child aged 7 – 12 years showed any CUVAF and only 3.5% of Young Adults aged 18 – 25 years demonstrated CUVAF
- Total CUVAF area was smaller than Australian data which is in line with a lower objective levels of light exposure measured in the UK compared to Australia found in the previous chapter
- Participants who never worn a hat had a significantly larger area of CUVAF
- No association between subjectively reported time outdoors or sunglass use and CUVAF area was found
- No significant change in CUVAF area was found over the 2 year follow up

Chapter 11: Quantification of illuminance levels in UK classrooms

11.1 Introduction

Epidemiological studies have suggested that increased time outdoors is protective against myopia in children (Dirani et al., 2009, French et al., 2013b, Guggenheim et al., 2012, Guo et al., 2013, Jones et al., 2007, Jones-Jordan et al., 2012, Rose et al., 2008a, Shah et al., 2017). Four intervention studies all found that implementing additional time outdoors resulted in a reduction in myopia incidence and progression rates in school aged children (He et al., 2015a, Jin et al., 2015, Wu et al., 2018, Wu et al., 2013). Despite the large body of evidence demonstrating the protective effect of time outdoors, the exact mechanism is not well understood. Several theories have been proposed and investigated, see Section 2.2.5. One of the most promising theories is the influence of outdoor illumination namely the light intensity and composition. Outdoor light intensity can often be up to 100,000 lux on a sunny day (Wu et al., 2018). A cut off of 1000 lux has been used to distinguish between indoor and outdoor light in studies examining light levels and refractive error change (Ostrin, 2017, Dharani et al., 2012, Alvarez and Wildsoet, 2013, Ostrin et al., 2018, Read et al., 2015, Read et al., 2014). Animal studies have shown that exposure to high levels of light (Ashby et al., 2009, Cohen et al., 2011) have reduced myopia progression as well as wavelengths towards the blue/violet end of the spectrum which are only present in outdoor light (Liu et al., 2011, Liu et al., 2014). Interestingly, there has also been some research regarding the impact of classroom lighting on circadian rhythm stimulation (Leslie et al., 2010, Rea and Figueiro, 2018, Figueiro and Rea, 2010), which has also proposed as a possible mechanism of myopia development, see Section 2.3.5. Eleven teenagers (aged 14-15 years) wore orange tinted glasses, which removed short wavelengths of light, during the school week. Delays in the circadian clock and the onset of melatonin production were found (Figueiro and Rea, 2010).

One recent study has examined the practicality of the development of a novel “Bright Classroom” prototype, designed to expose children to light levels and light composition more closely related to outdoors than a traditional classroom (Zhou et al., 2017b). The bright classroom design constructed of a four sided building with light diffusing glass for all walls and roof, with the exception of the bottom one metre of each wall which was clear glass. Fourteen large (1m x 1.5m) glass windows were also present. Comparisons were made between the light intensity and light spectrum of the bright classroom and a

traditional classroom. The median light intensity across a 12 month period was higher in the bright classroom (median 2,540 lux, IQR 1,330-4060) compared to a traditional classroom (median 477 lux, IQR 245-738). In addition, the light spectrum more closely resembled that of outdoors. Overall satisfaction scores from teachers and students were higher in the bright classroom, although masking was not possible, and excellent feedback on the design was received. This suggests that increasing light levels could also enhance the learning environment within the classroom as well as providing a potential protective effect from myopia development. Rittner and Robbin (2002) found that students were able to retain and learn information better under daylight conditions. However, excessive lighting has been found to have a detrimental impact of student learning and student behaviour (Fenton and Penney, 1985, Schreiber, 1996).

The UK government alongside the Chartered Institute of Building Services Engineers (CIBSE) have published recommendations for classroom illuminance levels. It is recommended that 300 lux is suitable for general tasks and a higher value of 500 lux is ideal for detailed tasks (CIBSE, 2011). However, myopia research did not inform this criteria.

11.2 Rationale

This Chapter will provide novel data on the classroom illuminance levels from two UK schools taken over an 11 month period and establish the variation in light levels to which primary school children are exposed to in a classroom setting.

11.3 Methodology

Classroom illuminance readings from 10 classrooms at two midlands-based schools (GP and MA). Only classrooms in which children who had taken part in the study were taught were sampled.

Illuminance levels (lux) were assessed using an illuminometer (C.A 180 Chauvin Arnoux, Slough, UK) placed horizontally in the centre of the desk. Prior to measurement, it was ensured that all indoor ceiling lighting was switched on and all blinds/curtains were open. In addition, desks were cleared to ensure adjacent objects did not interfere with the reading. Readings were taken 5 seconds after the sensor had been centred on the desk. A sketch plan of the desk layout, as well as door and window locations, was created for each classroom. This plan was used at each visit to record illuminance levels, see Figure 11.1. Within each classroom, the desks were classified as ‘window or ‘no window’ desks based on their location in the classroom and its proximity to a

window. For example, in Figure 11.1, desks 1, 2, 4 and 5 were classed as window desks and desk 3 no window.

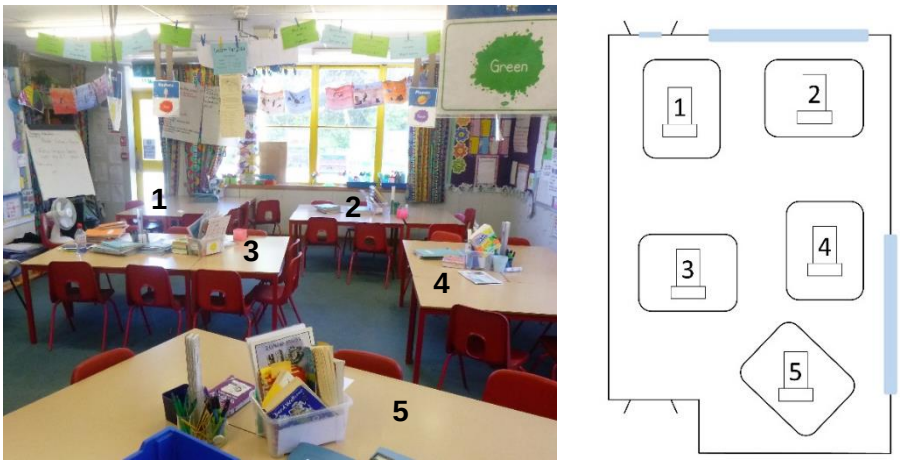


Figure 11.1: A) Photograph of a classroom with numbered desks B) Sketch plan of a classroom layout

Measurements were taken monthly over an 11 month period between 22nd September 2017 and 20th July 2018. No access to the classroom was available in the month of August due to school closures for school holidays. Measurements were taken 4-5 weeks apart depending on the month. Measurements were only taken on Fridays between 12:00pm and 1:00pm. This was the most convenient time as it was the lunchbreak so there was easy access to the classrooms with minimal disruption. Access to one classroom was unavailable on 3 occasions due to choir and dance practice taking place. Due to the close geographical nature of the two schools (4.0 miles), both schools were able to be measured on the same day consecutively. GP was always visited first followed by MA.

The uniformity of light across all areas of classroom was not measured in this study as it was felt that measurement of the illuminance on the desk plane would be a more accurate representation of light reflecting into and experienced at eye level.

11.3.1 Statistical analysis and sample size calculation

All data was analysed using SPSS® Version 25. The illuminance levels were not normally distributed (Shapiro Wilk $p<0.001$), therefore non-parametric statistics were used. Differences in continuous data with categorical variables were assessed with the Mann Whitney U test (desk and classroom illuminance between schools and desk location). Differences in classroom illuminance in different seasons was assessed with a related samples Wilcoxon Signed Rank test.

Due to the exploratory nature of the classroom illuminance levels no comparative studies could be used to calculate sample size a priori. Sample size calculations were therefore performed post-hoc using G*Power software (version 3.1.9.4) and are presented in the discussion.

11.4 Results

A total of 614 readings were taken from 58 desks in 10 classrooms across two schools throughout the study (28 desks at GP, 30 desks at MA). The mean number of desks sampled per classroom was 5.8 (range 5 – 8).

The overall median classroom illuminance was 593 lux (IQR 459-822). No significant difference was found in the median classroom illuminance between the two schools (GP median classroom illuminance 682 lux (IQR 521-826), MA 539 lux (IQR 413-843) Mann Whitney U test p=0.133).

The overall median illuminance per desk was found to be 558 lux (IQR 410-558). The median difference in illuminance values of desks within the same classroom was 452 lux (IQR 309-731). Desks located near a window had a statistically significantly higher illuminance reading than those not adjacent to a window (691 lux (IQR 504-919) and 465 lux (IQR 355-651) respectively Mann Whitney U test p<0.001).

The mean monthly classroom illuminance over the 11 month period can be seen in Figure 11.2. Overall, the highest monthly classroom illuminance was in July (median 846 lux (IQR 627-1116)) and lowest in October (median 382 lux (IQR 263-598)). Both schools had a peak mean classroom illuminance in July (MA 878 lux and GP 761 lux). The lowest classroom illuminance was in October (265 lux) for school MA and in December (471 lux) for school GP.

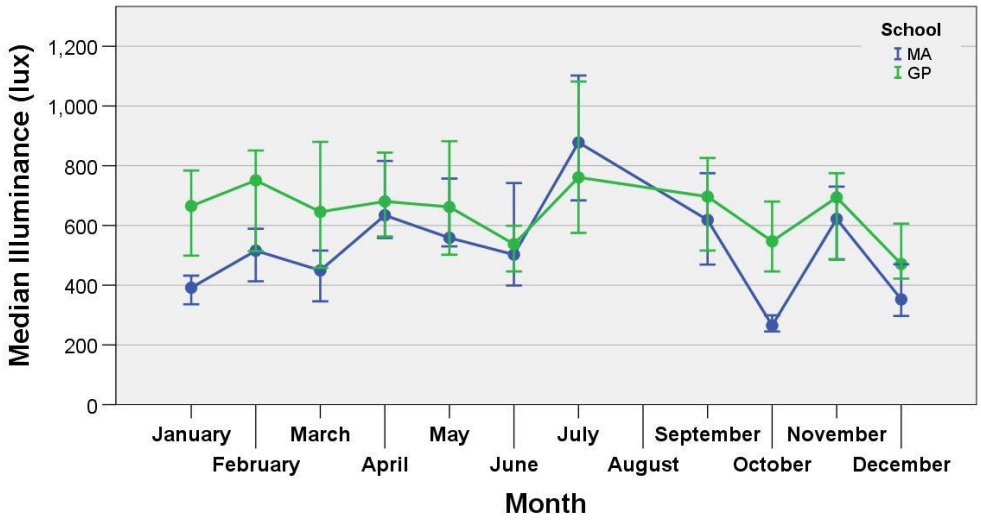


Figure 11.2: Classroom Illuminance levels over an 11 month period

Using the same cut off dates used for the Actiwatch data classification, as previously outlined in Section 9.3.2, the classroom illuminance measurements were divided into Summer and Winter seasons. The illuminance characteristics of each can be found in Table 11.1.

	Summer	Winter
Median (IQR) (lux)	692 (471-851)	571 (440-724)
Maximum illuminance (lux)	1,383	1,200
Minimum illuminance (lux)	256	119

Table 11.1: Summer and Winter classroom illuminance levels

A comparison of illuminance in summer and winter found no statistically significant difference in illuminance (median difference 19 lux (IQR -109-145) related samples Wilcoxon Signed rank p=0.438).

The median fluctuation in individual desk illumination over the 11 month period was 545 lux (IQR 311-862). The largest variation (2009 lux) was found in School MA Classroom 2 Desk 4 which was situated directly by a window (minimum 294 lux and maximum 2303 lux). The smallest variation (172 lux) was found in School GP Classroom 1 Desk 5 which was in the centre of the classroom (minimum 448 lux and maximum 620 lux).

The distribution of desk illuminance reading shows a positively skewed distribution, see Figure 11.3. For reference a 1000 lux mark is outlined on the distribution with a dotted line. Only 12.7% (n=78/614) of desk readings recorded illuminance values of >1000 lux across the study period.

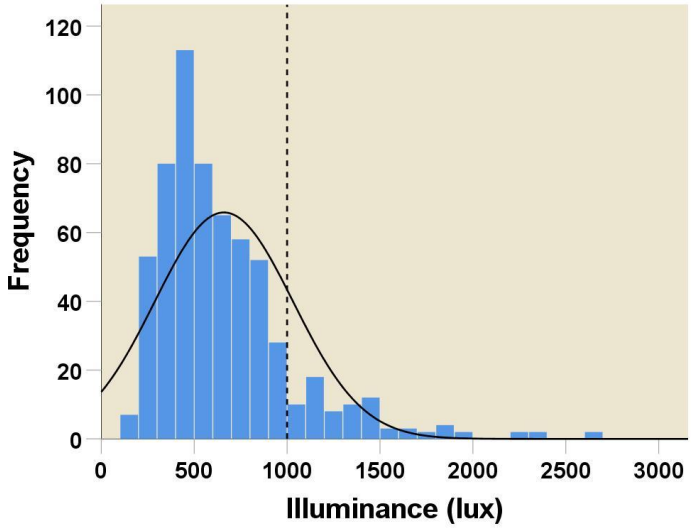


Figure 11.3: Desk illuminance reading distribution 1000 lux reference line shown with a dotted line

Referring to the CIBSE guidelines (CIBSE, 2011), 90.2% (n=554/614) of desk readings across the 11 month period were recorded at >300 lux, which is recommended for general tasks and 58.8% (n=361/614) at >500 lux recommended for detailed tasks. Interesting only 53.4% (n=31/58) of desks consistently measured >300 lux at each visit, 19.0% (n=11/58) consistently measured >500 lux and only 1.7% (n=1/58) consistently measured >1000 lux.

11.5 Discussion

The classroom illuminance was relatively constant over the 11 month period (September to July) in both schools with no significant difference between summer and winter months. Post-hoc sample size calculation was performed using G*Power software (version 3.1.9.4, Mann Whitney test (matched pairs):one tailed) to calculate the sample size needed to show a difference in illuminance between the two seasons with a power of 95% and significance 5%. The effect size was calculated using the mean illuminance and SD from the illuminance data in summer and winter (687±262 lux and 613±233 lux respectively). The results indicated a total sample size of 155 classrooms would be required and 108 classrooms were measured in this study, thus the sample size was not sufficient to test this hypothesis. Therefore to definitively report that no differences in classroom illuminance is present between summer and winter months further measurements would be required. The median classroom illuminance (593 lux) was similar to that recorded in two other studies measuring classroom illuminance in China of 477 lux (Zhou et al., 2017b) and 340 lux ((Wu et al., 2018).

As expected only a small proportion of desks measured illuminance values of >1000 lux which is the cut off illuminance used to represent the levels experienced outdoors. Only 1 desk consistently measured values above this threshold and was directly adjacent to a window. Nearly 10% of desks did not record values over 300 lux which is the illuminance recommended for general tasks by the CIBSE (CIBSE, 2011).

There was a large within classroom variation in desk measurements of 452 lux and as expected desks located directly adjacent to a window recorded higher illuminance levels. Post-hoc sample size calculation was performed using G*Power software (version 3.1.9.4, Mann Whitney test 2 groups:one tailed) to calculate the sample size needed to show a difference between desks location with a power of 95% and significance 5%. The effect size was calculated using the mean illuminance and SD from the data from desks adjacent and those not adjacent to a window (794±423 lux and 526±250 lux respectively). The results indicated a total sample size of 78 (39 in each group) would be required and a total of 637 desks (317 adjacent to a window and 320 not adjacent to

a window) were measured in this study, thus confirming a sufficient sample size was obtained.

As no significant difference in classroom illuminance between the two schools was found, differences in refractive error prevalence and progression were not able to be explored in this study. In order to provide a better insight into the possible relationship between classroom illuminance and refractive error development, identification of participants seating locations within the classroom i.e. desk location would allow a more detailed analysis the illuminance experienced by each participant within the classroom. However in primary schools this is difficult as there is often movement between desks for different activities and also between classrooms, meaning that children are not consistently in the same location throughout the school day.

11.6 Conclusions

Overall, these results suggest that classroom illuminances in the UK remain relatively constant across the school year with the main variation in illuminance dependent on desk location within the classroom. The recorded classroom illuminance levels in this study fell below that experienced outdoors. As the role of illuminance and myopia emerges and our understanding of the required protective level of illuminance to produce a protective effect against myopia develops, architectural approaches such as the bright classroom design (Zhou et al., 2017b) could be a future practical approach to influence classroom lighting to increase illuminance levels throughout the school day and year.

11.7 Summary

- Classroom illuminance stayed relatively constant over the year
- Median classroom illuminance was 593 lux, however a large variation in desk illuminance within the classroom was found (309 – 731 lux)
- Desks locations adjacent to windows recorded higher illuminance levels

Chapter 12: Final discussion and future work

12.1 Introduction

Emmetropisation is the process of visual regulation of eye growth towards an optimal refraction. Both environmental and lifestyle factors have been found to be influential in coordinating this process. A disruption in emmetropisation has been thought to lead to the development of myopia. The prevalence of myopia is increasing worldwide and is being described as a global epidemic (Morgan et al., 2018). In addition to the requirement of optical correction, myopia also brings significant socioeconomic burden and crucially can lead to sight threatening ocular complications. No "safe" level of myopia has been identified (Flitcroft, 2012). In the UK, the prevalence of myopia in school aged children has more than doubled over the past 50 years (McCullough et al., 2016). As a result, there has been an increased interest in understanding the mechanisms and environmental factors involved in driving eye growth and the regulation of emmetropisation, which is explored in this thesis.

In recent years, one of the most widely researched risk factors for myopia and it's associated eye growth is the amount of time spent outdoors. Literature has supported a protective effect of increased time outdoors and myopia development. The exact mechanism of this protective effect has not been fully identified and is likely multifactorial in nature. The composition of outdoor light has been found to be significantly different from indoor light, most notably regarding the light intensity (Wu et al., 2018). To date, research exploring the association between time outdoors and myopia has been largely subjective in nature through the use of questionnaires. Although this study did use questionnaires to quantify risk factors, objective measurements of light exposure were also measured through a wrist worn sensor and through the identification of CUVAF. By furthering our understanding of myopia development and the role of environment and lifestyle, it will allow eye care practitioners to be better placed to provide advice to their patients. This enhanced knowledge coupled with developments in myopia interventional strategies could be the key to slowing down myopia progression, with an ultimate aim of preventing myopia onset.

12.2 Summary of main findings

This thesis describes the rationale, study design and results of a field based longitudinal study aimed at investigating the influence of environmental and lifestyle factors on eye

growth, with an emphasis on light levels, in school children and young adults in the UK. The main findings are discussed below.

Optical biometers are widely used in research and increasingly being used in clinical practice especially in the area of myopia control where AL measurement is used as a key measure of myopia progression and indicator of the effectivity of intervention strategies. The IOLMaster 500 is considered the gold standard in ocular biometry however the Aladdin, a new biometer has recently been introduced. The current comparative published literature between these biometers has been largely centred on participants with cataracts with a view for accurate IOL measurements. However, this study has provided valuable data on the validity and agreement of these two biometers in healthy Child and Young Adult cohorts. AL and CR measurements were both well correlated, however AC measurements with the Aladdin were found to be significantly deeper than the IOLMaster 500. This is likely attributed to the method of AC measurement. Differences in AL and CR readings were considered to be clinically negligible with the mean difference falling within the recognised calibration tolerances of the IOLMaster 500. However, the difference in AC should not be overlooked. These data show that the Aladdin produced comparable AL and CR measurements to the IOLMaster 500 however data acquisition was markedly lower in the Child cohort. It should also be highlighted that the Aladdin has the additional advantageous features of LT, CCT and corneal topography measurement. The use of these supplementary parameters in the design and fitting of contact lens makes it a useful clinical tool for those implementing myopia control strategies such as Orthokeratology as well as monitoring its efficacy.

Potential myopiagenic risk factors were investigated through questionnaires. Across both cohorts only a limited number of significant correlations were found. In the Child cohort, a significant correlation between urban residence and a fast axial growth was found. This compliments the well documented greater prevalence of myopia consistently in urban areas. The specific reasoning behind this association has not yet been established but it has been theorised that it could be linked to protective effects of time outdoors and the potential lack of accessibility in urban areas. Furthermore, living in a more confined environment may also increase the baseline accommodative demand experienced by these children which is thought to stimulate increased eye growth. In addition, the spatial frequency of urban and indoor environments is relatively deficient in high spatial frequency and is similar to the spatial feature created by diffusing filters that have been found to induce form deprivation myopia in animal models. Overweight young adults were found to have a faster eye growth which is thought to be a result of a

sedentary lifestyle (Mitchell et al., 2014). However, it should be highlighted that BMI could be a confounded factor as it could led to or be caused by less time spent outdoors and increased time performing near and VDU tasks which have been shown to be related to myopia progression. Conversely to this, children who were born with a lower birth weight were found to have a faster eye growth. Birth weight has been shown to provide a unique insight into development of milestone achievements and also a strong predictor of health outcomes and achievement of developmental milestones (Gill et al., 2013). Low birth weight has been associated with myopia (Rahi et al., 2011).

Sleep/wake cycles are closely entwined with circadian rhythms which are internal 24-hour cycles that regulate processes within the human body and coordinate environment variations with behavioural activities. There is emerging evidence that circadian rhythms are atypical in myopic eyes (Chakraborty et al., 2018). This study has provided exploratory objective data on sleep patterns of UK children and their correlation with refractive and AL parameters. Despite a low number of sleep pattern datasets for myopes, a significant difference in the sleep duration was found, with myopes having significant less sleep than non-myopes on average by 40 minutes in Summer. In addition, a more myopic SER shift was associated with a later bed time and wake up time and a faster AL growth was also associated with a later bed time. This study has provided a normative dataset of sleep patterns of UK children and has shown emerging evidence that sleep/wake cycles are altered in myopes.

This study has also provided novel objective data on light exposure and time spent outdoors for UK children and allowed comparisons with Australia, Singapore and the USA. Significant differences in daily and seasonal patterns of light exposure were also found within the UK. It has highlighted different behaviour patterns between UK and Australian children, with UK children spending more time outdoors on weekdays compared to weekends, which is the opposite finding to Australia children suggesting a difference in lifestyle of UK children (Read et al., 2014). Although seasonal differences in light exposure within the UK were expected, the size of the difference is marked. In Summer, light exposure was 13 times higher and objectively measured time spent outdoors was 10 times longer than in Winter. These findings have provided invaluable data on light exposure in the UK which has not been reported before. Although the mechanism of the protective effect of time outdoors is yet to be established, if light intensity is determined as a key factor, this study questions the validity of the role of increased time outdoors as a protective strategy for myopia for UK children in particular in Winter months where light levels were consistently low.

A bespoke modified smartphone system for assessment of CUVAF was found to successfully detect CUVAF. This work reported for the first time the lack of CUVAF in children aged 7 – 12 years living in the UK. CUVAF was found in a small percentage of young adult participants and the total area of CUVAF was considerably smaller than reported by Australian studies (Sherwin et al., 2011). This could be attributed to the considerably reduced light exposure reported in this study for the UK compared to Australian data. Comparisons of CUVAF between myopes and non-myopes showed no significant difference and could have resulted from the limited sample size but also could be due to the comparatively lower exposure in this population.

The role of illuminance and myopia development is a prominent area of current myopia research and this study has provided valuable data on objective measures of light exposure and time outdoors for children aged 7 – 12 years within the UK. It also questions whether a threshold light exposure level is required to provide the protective effect of increased time outdoors and whether light exposure experienced within the UK is high enough to provide a protective effect throughout the year.

This study has provided a wealth of novel data most notably providing the first objectively measured dataset of sleep and light exposure in UK schoolchildren. It has demonstrated that significant seasonal variation in light exposure and time outdoors are experienced in the UK. Furthermore, the use of comparative methodologies with Australian and USA studies has allowed direct comparisons to be performed and has highlighted significantly lower light levels and outdoor exposure within the UK. This study has also provided data on the low prevalence and quantity of CUVAF in an exclusively UK population and has reported for the first time the lack of CUVAF in UK children aged 7-12 years. As a result, this study has suggested that CUVAF is not a suitable biomarker for use a surrogate measure of time outdoors in schoolchildren and young adults in the UK. This study has also provided novel data on classroom illuminance levels in the UK and has demonstrated that levels remain relatively constant across the school year with the main variation in illuminance dependent on desk location within the classroom. The association between time outdoors and myopia is well established however it still remains unclear which element or elements of being outdoors is responsible for the protective effect. With the investigation of illuminance levels at the forefront of research this study has provided valuable data from the UK that will only aid our knowledge of understanding of the protective effect of time outdoors.

12.3 Limitations

The limitations within each chapter have already been discussed, however an overview of the most significant limitations are outlined below.

The recruitment for this study was limited due to a low school response rate and also poor parental response rate within the recruited schools. In addition, the attrition rates over the 2 years follow up was higher than expected. The use of cycloplegia may have contributed to the low recruitment rate and also the high attrition rate. In addition, recruitment of primary schools only meant that children aged 11 – 12 years could not be followed up and therefore resulted in a loss of longitudinal data for those at the upper end of the age range in the Child cohort. In the Young Adult cohort, the sample is not representative of the population as the majority were undergraduate students primarily studying Optometry.

In Chapter 7, the influence of potential myopiagenic risk factors was investigated through questionnaire responses. These responses are subjective in nature and therefore can be affected by recall bias. However, previously validated questionnaires were used to formulate the questionnaire design in this study. In the Child cohort, parental questionnaires were used to the quantification of risk factors such as time spent outdoors and performing near tasks. However, it could be argued that these responses may not be a true representation of their child's daily activities as they may not be fully aware of the tasks or activities their child is undertaking throughout the course of the day. However, due to the age of the Child cohort (7 – 12 years) it was felt that the parental questionnaires would be more accurate and also allowed more detailed information on their activities to be examined, for example time outdoors was subdivided into season and day of the week which was no possible in the Child questionnaire. Furthermore, the categorical nature of the questionnaire could have contributed to a lack of differentiation of particular tasks, primarily near tasks and VDU tasks which only had four categories available: None, less than 1 hour, 1-2 hours or 2+ hours. A re-design of the questionnaire would be warranted to ascertain more specific estimations of these tasks through asking participants to report the number of hours for each task rather than using categories. Furthermore, the use of objective measures of near tasks through the use of spectacle mounted devices, coupled with the objective measures of light exposure would provide valuable analysis of the role of these two tasks in eye growth. However due to the spectacle mounted nature of these devices it could possibly limit data collection to those who wear spectacles full time. If plano spectacles with this device were issued to children who are previous non-spectacle wearers there should be

a consideration of how this could impact of their behaviours also a potential compliance issue.

In Chapter 9, objective measures of light exposure through the use of a wrist worn sensor was explored in the Child cohort only. Due to significant seasonal variations in climate characteristics such as temperature and day length, datasets were classified as Summer or Winter using established cut offs implemented in the UK by BST and GMT. Therefore, the light exposure data analysed in this study assumes that a single measure over a 9-day period is a reliable and consistent assessment of light exposure for each season. In addition, data collection only occurred during school term so no data on light exposure during school holidays was captured. Furthermore, the use of a wrist worn sensor means that it is susceptible to being covered by clothing which may present limitations in assessing light exposure in Winter, a colder season where coats are necessary when spending time outdoors. However, steps were taken to screen the data for times when the light sensor was covered or taken off. Furthermore, the use of a wrist worn sensor does pose some limitations regarding its representation of light exposure at eye level, although the correlation has been shown to be good (Jardim et al., 2011, Okudaira et al., 1983). This study has also shown that the orientation of the light sensor can have a significant effect on the light exposure reading. The short follow up time and high attrition rate meant that longitudinal analyses were also limited.

Investigation of CUVAF in this study was undertaken with a novel portable modified smartphone system. As CUVAF is a relatively new discovery, there is currently no standardised system established as a gold standard, so validity of the system used in this study was not able to be assessed.

12.4 Future work

Future work related to this study would involve a recruitment of a larger sample size, in particular an increased number of myopic participants in the Child cohort. In addition, further extension of the longitudinal nature of this thesis would allow greater insight into the impact of environmental and lifestyle factors on eye growth. In addition, recruitment could be expanded to other cities and regions in the UK which would increase the sample size and also enable extrapolation of the data for the entire UK population.

The measurement of light exposure using the Actiwatch 2 device was a key component of this thesis and provided accurate reliable objective data. The analysis of this in combination with objective measures of near tasks would also be invaluable in ascertaining the role these factors play in refractive error development. This could be

done through the use of the Clouclip (HangZhou Glasson Technology Co., Ltd, China) or Vivior monitor (Vivior, Switzerland). These devices have the added benefit of being spectacle frame mounted and therefore may allow a better representation of light exposure at eye level and also are not subject to changes in orientation or being covered by clothing. In addition, further data collection in school holidays may also allow differences in light exposure and time spent performing near tasks to be identified. This could aid previous literature that has shown seasonal differences in eye growth (Gwiazda et al., 2014b, Donovan et al., 2012, Fulk et al., 2002).

The exploratory sleep pattern data showed some interesting and promising results and would greatly benefit from a larger sample size and more myopic individuals. In addition, further objective measures of circadian rhythms could be explored through the sampling of melatonin levels through blood or saliva collection. A previous study has shown that, in young adults aged 18 – 20 years, myopes have significantly higher melatonin levels compared to non-myopes (Kearney et al., 2017).

This study has shown that the novel CUVAF modified smartphone photography system used in this study has the capacity to detect CUVAF. Further adjustments need to be made to ensure a consistently good quality image is able to be captured in order to allow accurate demarcation and measurement of CUVAF area. Further investigation of CUVAF in a UK population to assess the longevity of CUVAF and further understand its natural history of CUVAF could not only benefit myopia research through the use of an objective measure of time outside but also other areas of Optometry, allowing identification of individuals at risk of other ocular pathologies related to high UV exposure such as pterygiums and age-related macular degeneration.

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Appendix

A.1.1 Qualitative and quantitative definitions of myopia

Term	Definition
Qualitative Definitions	
Axial myopia	A myopic refractive state primarily resulting from a greater than normal axial length
Refractive myopia	A myopic refractive state that can be attributed to changes in the image forming structures of the eye i.e. the cornea and lens
Secondary myopia	A myopic refractive state for which a single, specific cause (e.g., drug, corneal disease or systemic clinical syndrome) can be identified that is not a recognized population risk factor for myopia development.
Quantitative definitions	
Myopia	A condition in which the spherical equivalent refractive error of an eye is ≤ -0.50 D when ocular accommodation is relaxed.
Low Myopia	A condition in which the spherical equivalent refractive error of an eye is ≤ -0.50 and > -6.00 D when ocular accommodation is relaxed.
High Myopia	A condition in which the spherical equivalent refractive error of an eye is ≤ -6.00 D when ocular accommodation is relaxed.
Pre-myopia	A refractive state of an eye of ≤ +0.75 D and > -0.50 D in children where a combination of baseline refraction, age, and other quantifiable risk factors provide a sufficient likelihood of the future development of myopia to merit preventative interventions.

Table A.1: Summary of qualitative and quantitative definitions of myopia Adapted from IMI white papers (Flitcroft et al., 2019)

Study	Location	Study Type	n	Time period	Age (years)	Ethnicity Composition	Myopia definition
AES (Aston eye Study)	UK	Population based (cross sectional)	655	Initiated 2006	6-7 12-13	29% Caucasian 50% South Asian 12% Black 9% Mixed/East Asian	Cycloplegic SER ≤-0.50 in at least one eye
ALSPAC (Avon Longitudinal Study of Parents and Children)	UK	Multidisciplinary study recruiting pregnant women (longitudinal)	13,867	Initiated 1991 (to date 19-22 year follow up achieved)	ND	Majority Caucasian	Non-cycloplegic SER≤-1.50DS
CLEERE (Collaborative Longitudinal Evaluation of Ethnicity and Race)	USA	Multicentre observational (longitudinal) (Extension of OLSM)	3,618	Initiated 1995	5-17	36% Caucasian 28% Hispanic 20% Black 16% Asian	Cycloplegic SER≤-0.75 in both meridians
NICER (Northern Ireland Childhood Errors of Refraction Study)	UK	Prospective population based (longitudinal)	1,068	Initiated 2006. Three phases over a 6 year period. Extension to a fourth phase approved.	6-7 12-13	98.8% Caucasian 1.2% Other	Cycloplegic SER ≤-0.50 in either eye
OLSM (Orinda Longitudinal Study of Myopia)	USA	Population based (longitudinal)	1,246	Initiated 1989	6-14	Majority Caucasian	Cycloplegic SER≤-0.75 in both meridians
SAVES (Sydney Adolescent Vascular and Eye Study)	Australia	Population based (5-6 year Follow up of SMS)	2,760	Initiated 2009	12-17	65% Caucasian 14% East Asian 21% Other	Cycloplegic SER ≤-0.50
SCORM (Singapore Cohort Study of the Risk Factors for Myopia)	Singapore	Prospective population based (cross sectional)	1,005	1999-2002	7-9	72.5% Chinese 19.4% Malays 5.6% Indians 2.5% Other	Cycloplegic SER ≤-0.50 in either eye
SMS (Sydney Myopia Study)	Sydney, Australia	Population based (cross sectional)	4,118	Initiated 2004	6 and 12	62.2% Caucasian 16.1% East Asian 6% Middle Eastern 3.9% South Asian 11.8% Other	Cycloplegic SER ≤-0.50

Table A.2: Overview of epidemiological refractive error studies

A.2.1 Overview of time outdoors and myopia association studies

Author (Year) Country	Baseline Age (years)	Study Design	Conclusion and Main Findings
Rose et al (2008a) Australia, SMS	6 and 12 (n=1765)	Cross sectional	Increased time outdoors associated with more hyperopic SER. 6 years β = +0.05, p=0.009. 12 years β = +0.07, p<0.0003
Dirani et al (2009) Singapore, SCORM	11 – 20 (n=1249)	Cross sectional	Less time spent outdoors associated with myopes compared to non-myopes: 3.09±1.92 hours vs 3.59±2.03 hours, p<0.001. OR 0.90 (95% CI 0.84 to 0.96) (p =0.004)
Lin et al (2014) China, BMPS	6 – 12 13 –17 (n=386)	Cross sectional	Increased time outdoors associated with more hyperopic SER. 6-12 years β = +0.27, p=0.03. 13-17 years β = +0.04, p=0.70
Shah et al (2017) UK, ALSPAC	2 (n=2833)	Population-based birth longitudinal cohort	Increased time outdoors was associated with a reduced risk of incident myopia. The HR for myopia at 3 years 0.90 (95% CI 0.83 to 0.98, p=0.012), at 9 years 0.86 (95% CI 0.78 to 0.93, p=0.001) for each additional unit of time spent outdoors per day.
French et al (2013b) Australia, SAVES	6 and 12 (n=2103)	Population-based longitudinal cohort	Less time outdoors associated with increased incidence of myopia compared to non-myopes. Younger cohort: 16.3 vs 21.0 hours, p<0.0001 OR 2.84 (95% CI 1.56 to 5.17, p<0.0001), Older cohort: 17.2 vs 17.6 hours, p=0.02) OR 2.15 (95% CI 1.35 to 3.42 p=0.003)
Jones-Jordan et al (2011) USA, CLEERE	6 – 14 (n=731)	Multicentre longitudinal cohort	Less time outdoors in incident myopes compared to emmetropes. Mean hour difference -1.42 (99% CI -2.00 to -0.83)
Jones et al (2007) USA, OLSM	8 – 9 (n=514)	Population-based longitudinal cohort	Less time outdoors associated with myopia incidence. 11.65 ± 6.97 hours for non-myopes vs. 7.98 ± 6.54 hours for future myopes, p<0.001. OR = 0.91 (95% CI = 0.87 to 0.94).
Guggenheim et al (2012) UK, ALSPAC	7 (n=4837-7747)	Population-based birth longitudinal cohort	Increased time outdoors was associated with a reduced risk of incident myopia. HR 0.76 (95% CI 0.60–0.96, p=0.02)

Table A.3: Overview of time outdoors and myopia association studies

SER: spherical equivalent refraction, OR: odds ratio, HR: hazard ratio

A.3.1 Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram

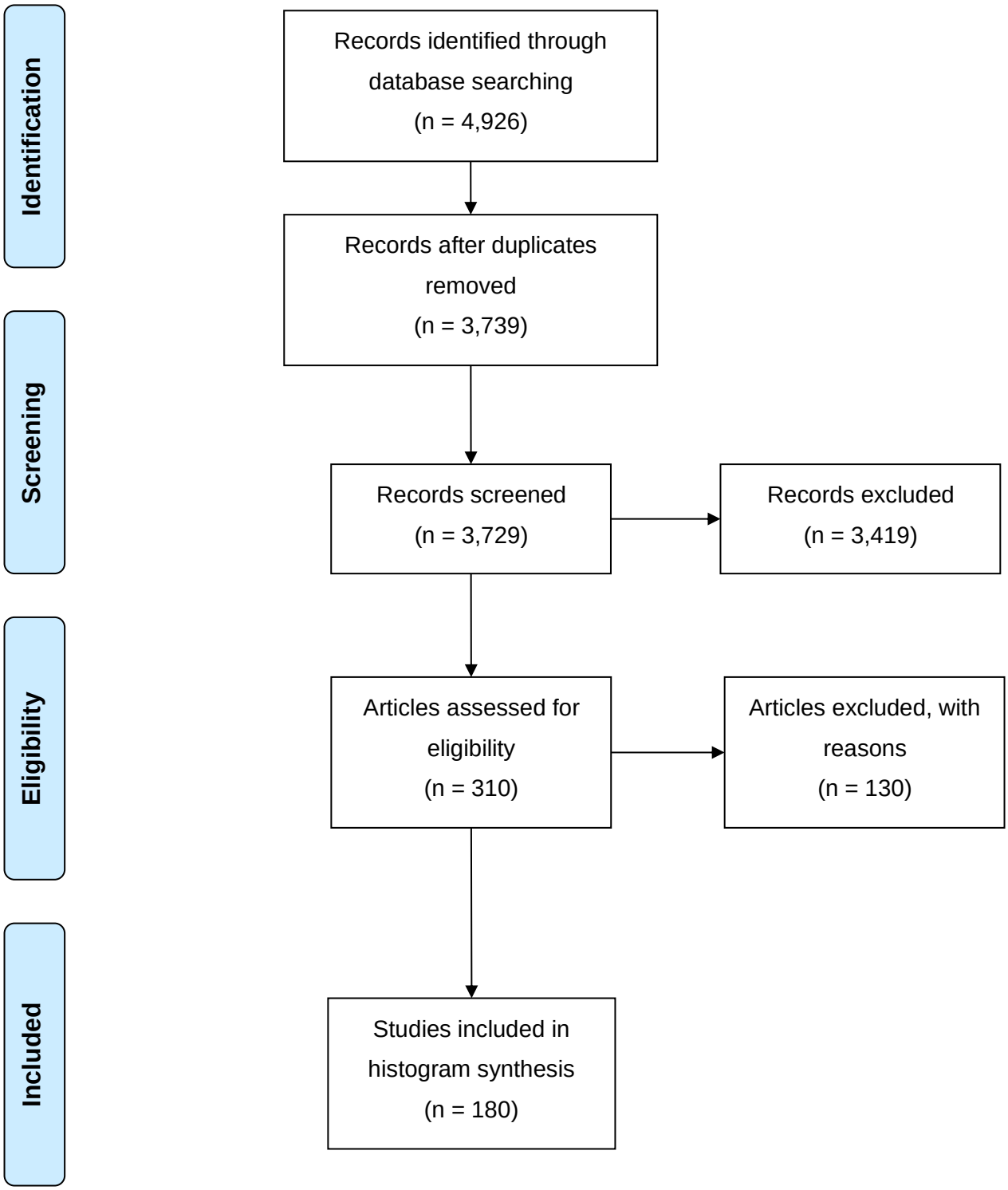


Figure A.1: Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for the search "myop*" AND "light" from database inception for March 2020.

A.3.2 Enlarged Figure 3.1: Trends of published articles relating to a systematic literature search using " myop*" AND " light"

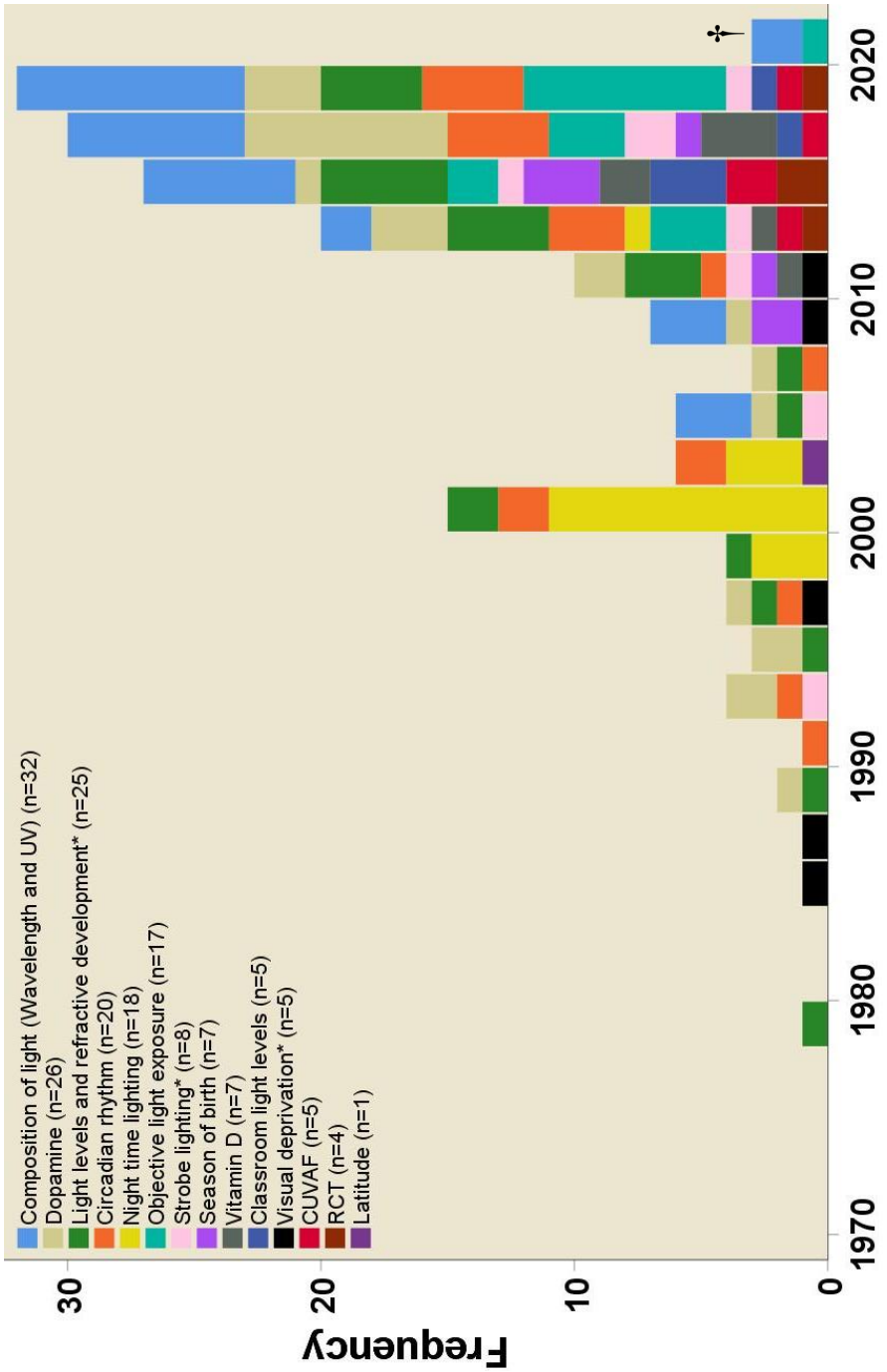


Figure A.2: Trends of published articles relating to a systematic literature search using "myop*" AND "light" from database inception to March 2020 *: animal studies only. †: Article published until March 2020 only displayed

A.3.3 Ethics approval

Aston University

Aston University
Aston Triangle
Birmingham
B4 7ET
0121 204 3000

Date: 06/03/2017

Nicola Logan
[*School of Life and Health Sciences*]

Study title:	The effects of environment and lifestyle on refractive outcome
REC REF:	Ethics application 1044

Confirmation of Ethical Opinion

On behalf of the Committee, I am pleased to confirm a favourable opinion for the research.

Documents approved

Document	*Version*	*Date*
Assent form- children	1	14/11/16
Consent form – young adult	2	23/12/16
Consent form- parent	2	23/12/16
Example email	1	14/11/16
Information leaflet – young adult	2	23/12/16
Information leaflet- headteacher	2	09/02/17
Information leaflet- parent	1	14/11/16
Information sheet- primary school children	1	09/02/17
Information sheet- secondary school children	2	09/02/17
Letter to parents	1	14/11/16
Letter to schools	1	14/11/16
Poster- Young Adult	3	09/02/17
Questionnaire- child	4	27/02/17
Questionnaire- young adult	4	27/02/17
Questionniare- parent	4	27/02/17

With the Committee's best wishes for the success of this project.
Yours sincerely

Chair of the University Research Ethics Committee

A.5.1 Headteacher information pack – cover letter and leaflet

Aston University

Aston University,
University Triangle,
Birmingham,
B4 7ET

Dear Headteacher,

I am Katie Franklin a qualified Optometrist and current PhD student at Aston University. I am looking to recruit schools for an exciting study looking at children's eyes.

The study is focusing on myopia, also known as short sightedness, in children in the UK and aims to identify environmental and lifestyle factors that could be influential in its onset. Worldwide the number of children that are short sighted has increased dramatically over the past decade. In the UK alone it has doubled since the 1960s. In countries in East Asia the prevalence in school children has increased to 80%. Being short sighted puts you at an increased risk of potentially sight threatening ocular conditions. There has been a lot of research in this area which has tentatively suggested that increased time outdoors has a protective effect and increased time spent doing near tasks may be contributing.

This study aims to look at the reasons why more children are becoming short sighted in the UK and ultimately aims to find ways that can prevent or slow the onset of short sightedness.

I have enclosed a school information guide which details what the study will involve and what benefits you will gain from the study.

I would like to **arrange a meeting** to discuss this opportunity further with you, my e-mail is [redacted] or if you would prefer to call my number is 0**********.

I look forward to hearing from you.

Your Sincerely,

Katie Franklin BSc(Hons) MCOptom

Clinical Supervisors: Dr Nicola Logan BSc(Hons) PhD MCOptom FHEA PGCertHE

Dr Janis Orr BSc(Hons) PhD MCOptom DipTp(IP) FHEA PGCertHE

Version [1] Date [14/11/16]

Who do I contact?

If you interested in being involved and would like any further information we would be delighted to hear from you. Please contact Katie Franklin, the lead investigator:

Tel: 0**********

[redacted]

Clinical Supervisors: Dr Nicola Logan and Dr Janis Orr

Address: Aston University, Aston Triangle, Birmingham, B4 7ET

Aston University

A study of Myopia (short sightedness) in children in the UK

Head Teacher Information Guide

Version [2] Date 09/02/17]

Why are we doing this study?

The prevalence of **myopia** (short sightedness) is increasing globally and in some countries is becoming an **epidemic** with up to 80% of children becoming myopic. If we can further understand why children are becoming myopic we can aim to try and slow its onset and progression. This study aims to look at **why** children are becoming myopic and the **environment and lifestyle factors** that could be involved.

How will the study benefit your school?

- The study will provide **vision screening** for all children involved. If it is found that the child needs a full sight test or needs to update their glasses, we will write to the parents advising them to take their child to see their local optometrist (optician).
- It is an exciting opportunity to be involved in a **pioneering study** looking at children's eyes
- I am happy to offer **talks** or **workshops** to the children to further their understanding of the eye

Who is eligible for the study?

Children are eligible to take part in the study if they are:

- **Aged between 7 and 12 years old**

Children are NOT eligible to take part in the study if they:

- **Previously had a reaction to cycloplegic eye drops**
- **They are taking medication for an ocular condition or medical condition that may interact with the eye drops**
- **Undergoing or have had any form of myopia control intervention**

Consent is required from their parent/guardian and the child themselves before they are able to be involved in the study.

What do we require from you?

- This study is provided at no cost.
- We will require time and space to undertake the necessary measurements and we would also like to gain access to the children's SATS scores

What would taking part in the study involve?

Taking part in the study will involve:

- The children's eyes will be tested by an **experienced qualified optometrist** (optician). A simple eye test will be performed to assess how well they can see and also assess their eye muscles.
- We will use special instruments that can measure the **shape and size** of their eyes, these are very quick and painless and don't touch the eye.
- In order to make sure we take accurate measurements we will need to **insert drops** into the children's eyes. These are the same drops used by high street optometrists (opticians). There is a very low risk that the drops will cause any side effects.
- We will also be taking a **photograph** of the front of the children's eyes to assess any damage that may be present from UV light. This is nothing more than a normal camera with a special filter.
- The children's **height** and **weight** will be measured
- A **questionnaire** will need to be completed by the child's parent/guardian and this will give further insight in their lifestyle and environment.
- We will also be measuring **light levels** in classrooms.
- We would like to monitor the growth of the children's eyes and so would be interested in doing a follow up study next year and the following year.

How will the children and their parents be informed of the study?

- I have an information pack that I will send out to all eligible children's parents.
- This will contain a letter inviting their child onto the study, a parental information leaflet detailing what the study involves, a children's information sheet and a consent forms.

Please note: this study does not replace a routine eye examination

A.5.2 Parental information pack – cover letter, leaflet, child leaflet and consent form

Aston University

Aston University,
University Triangle,
Birmingham,
B4 7ET

Dear Parent/Guardian,

I am Katie Franklin a qualified Optometrist and current PhD student at Aston University. I am looking for children aged 7 to 12 years old to be involved in an exciting study looking at children's eyes.

The study is focusing on myopia, also known as short sightedness, in children in the UK and aims to identify environmental and lifestyle factors that could be influential in its onset. Worldwide the number of children that are short sighted has increased dramatically over the past decade. In the UK alone it has doubled since the 1960s. In countries in East Asia the prevalence in school children has increased to 80%. Being short sighted puts you at an increased risk of potentially sight threatening ocular conditions. There has been a lot of research in this area which has tentatively suggested that increased time outdoors has a protective effect and increased time spent doing near tasks may be contributing.

This study aims to look at the reasons why more children are becoming short sighted in the UK and ultimately aims to find ways that can prevent or slow the onset of short sightedness.

I have enclosed an information guide to provide further information about the study. Please complete the enclosed parental consent form and discuss the children's information sheet with your child. Once the consent form is complete please return it to your child's school.

Please do not hesitate to contact me if you require any further information.

Your Sincerely,

Katie Franklin BSc(Hons) MCOptom

Tel: 0**********

[redacted]

Clinical Supervisors: Dr Nicola Logan BSc(Hons) PhD MCOptom FHEA PGCertHE

Dr Janis Orr BSc(Hons) PhD MCOptom DipTp(IP) FHEA PGCertHE

Version [1] Date [14/11/16]

Aston University

A study of Myopia (short sightedness) in children in the UK

Parental Information Guide

Version [1] Date 14/11/16]

Why are we doing this study?

The prevalence of **myopia** (short sightedness) is increasing globally and in some countries is becoming an **epidemic** with up to 80% of children becoming myopic. If we can further understand why children are becoming short sighted we can aim to try and slow its onset and progression. This study aims to look at **why** children are becoming short sighted and the **environment and lifestyle factors** that could be involved.

Whether your child wears glasses or not, we are keen for them to be involved.

What would taking part in the study involve?

Taking part in the study will involve:

- Your child's eyes will be tested by an **experienced qualified optometrist** (optician) in your child's school. A simple eye test will be performed to assess how well your child can see and also assess their eye muscles.
- We will use special instruments that can measure the **shape and size** of your child's eyes, these are very quick and painless and don't touch the eye.
- The eye drops used in the study are used to allow an accurate reading of your eyes prescription by suspending its focusing system. These are the same drops used by high street optometrists (opticians).
  - When applied to the eye, they may sting for a few moments.
  - The drops take about **30 to 45 minutes** to work and around **12 hours** to wear off (in some cases up to 24 hours.) The resultant large pupils will make your child more sensitive to light, whilst distant and near objects may appear slightly blurred.
  - Consequently, your child shouldn't perform any activities such as cycling for at least 12 hours after the drops have been inserted. On a bright day, disposable sunglasses will be provided.
  - It is very unlikely, but should your child experience any unusual symptoms such as pain and/or blood shot around the eye during this period please contact **Katie Franklin, franklkj@aston.ac.uk** and/or your optometrist/GP as you may be experiencing an adverse reaction to the drops.
- We will also be taking a **photograph** of the front of your child's eye to assess any damage that may be present from UV light. This is nothing more than a normal camera with a special filter.
- Your child's **height and weight** will be measured.
- Some children may be asked to wear a **wrist worn light sensor** to monitor their light exposure for a 10-14 day period.

What will happen after the study?

Once the information has been collected we will look at the results carefully. If we find that your child needs a sight test or needs to update their glasses, **we will write to you advising that you take them to see their local optometrist (optician)**.

We would like to monitor the growth of your child's eyes over the next 2 years by taking the same measurements next year and the following year.

What happens next?

We ask that you discuss this study with your child and complete and sign the enclosed **consent form** indicating whether or not you would like your child to be involved in the study. The form needs to be signed by a parent or legal guardian. Please put the form in the envelope provided and hand it back to your child's school.

Once we have taken the measurements we will ask you to complete a **short questionnaire** about your child's health and lifestyle and return this to your child's school.

We will also use your child's **SATS scores** as part of the study to see whether academic achievement plays a role in myopia. This information will be strictly confidential and will not be linked to your child in any publications.

Please note: this study does not replace a routine eye examination

Who do I contact?

If you have any questions please do not hesitate to get in touch with Katie Franklin, the lead investigator:

[redacted]

Clinical Supervisors: Dr Nicola Logan

Dr Janis Orr

Address: Aston University, Aston Triangle, Birmingham, B4 7ET

Child's Information sheet

to be read with your parent/guardian

We are writing to you and other children in your class to help us with a study where we will be looking at how well children can see. We want to find out why some people don't see as clearly as others and why some children need glasses and some don't.

What will the study involve?

How well you can see

A qualified optician will get you to read some letters (or shapes) on a chart

Questionnaire

We will ask you to answer some questions about what you like to do and how much time you spend outside

Height and weight

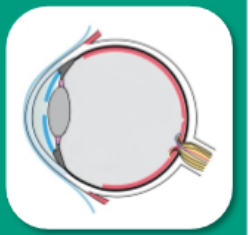
We will measure how tall you are and how much you weigh using scales and a height chart.

Photograph

We will take some photographs of your eyes

Shape and Length of your eyes

A machine will measure your eyes and will tell us how long it is. It will also tell us what shape it is. In order to take these measurements we will need to put some special drops in your eyes. These may tingle for a few seconds when they go in. The drops will make your pupils (the black part in the middle of your eye) larger for several hours. You may find that lights feel brighter than usual so we will give you a pair of disposable sunglasses to keep. You may also find reading a bit difficult with the drops in. These effects do not last long and your eyes will soon be back to normal.



What happens when I have finished the tests?

To show that you have played an important part in this study we will give you a **pencil/pen** and a **special certificate** to say:

I hope you would like to take part in this study!

Version [2] Date 09/02/17]

Code:

Aston University

A Study of Myopia (short sightedness) in children in the UK

Parental Consent Form

IF YOU WOULD LIKE YOUR CHILD TO TAKE PART IN THIS STUDY PLEASE COMPLETE THIS FORM

Please initial each box if you agree with the statement. *Please note you must initial all boxes to be eligible to take part in the study.*

1	I confirm that I have read the information sheet *(Version [1] Date [14/11/16])* for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
2	I understand that participation is voluntary and that I am free to withdraw my child at any time without giving any reason, without my legal rights being affected.	
3	I understand that eye drops will be used in this study.	
4	I give permission for the study to gain access to my son / daughter's SATS score.	
5	I give permission for my son / daughter to take part in the above study.	

Child's Name:

Date of Birth:

School: **Class:**

Signature:

Name: **Date:**

Address: *This will allow us to keep you updated about the results of the study.*

Postcode:

Contact Number:

E-mail:

Confidentiality

Please be assured that all data and records that contains any personal information will be kept strictly confidential. The data will be anonymised and no identifying information will be published. All electronic data will be password protected. Hard copies of consent forms and data collection forms will be stored in a locked filing cabinet.

All study data will be stored in accordance with the Data Protection Act (1998) and the University data storage policies for research data.

Clinical Investigator: Katie Franklin [redacted]
Clinical Supervisors: Dr Nicola Logan and Dr Janis Orr

Version [2] Date [23/12/16]

A.5.3 Young adult information sheet and consent form

Aston University

Th effect of environment and lifestyle on refractive outcome in Young Adults in the UK

Why are we doing this study?

The prevalence of **myopia** (short sightedness) is increasing globally and in some countries is becoming an **epidemic.** In the UK 20% of white teenagers and 40% of South Asian teenagers are myopic. If we can further understand why people are becoming short sighted we can aim to try and slow its onset and progression. This study aims to look at **why** people are becoming myopic and the **environment** and **lifestyle factors** that could be involved.

Whether you wear glasses or not, we are keen for you to be involved and give you some interesting information about your eyes.

What would taking part in the study involve?

Taking part in the study will involve:

- A **simple eye test** will be performed by a qualified optometrist (optician) in the Aston Optometry Department on campus and they will assess how well your can see.
- We will use special instruments that can measure the **shape and size** of your eyes, these are very quick and painless and don't touch the eye.
- The eye drops used in the study are used to make the pupils larger than normal allowing the investigator to take accurate measurements. These are the same drops used my high street optometrists (opticians).
  - When applied to the eye, they may sting for a few moments.
  - The drops take about **15 to 30 minutes** to work and around **6 hours** to wear off (in some cases up to 24 hours.) The resultant large pupils will make you more sensitive to light, whilst distant and near objects may appear slightly blurred.
  - Consequently, you shouldn't perform any activities such as driving and/ or cycling for at least 12 hours after the drops have been instilled. On a bright day, sunglasses may be advisable.
  - It is very unlikely, but should you experience any unusual symptoms such as severe pain and/or blood shot around the eye and cloudy vision during this period please contact **Katie Franklin, franklkj@aston.ac.uk** and/or your optometrist/GP as you may be experiencing an adverse reaction to the drops.
- We will also be taking a **photograph** of the front of your eyes to assess any damage that may be present from UV light. This is nothing more than a normal camera with a special filter.
- Your **height** and **weight** will also be measured
- You will be asked to complete a **short questionnaire** about your health and lifestyle.

Am I eligible?

You are eligible to take part in the study if you are:

- **Aged between 18 and 25 years old**

You are NOT eligible to take part in the study if you:

- **Previously had a reaction to cycloplegic eye drops**
- **You are taking medication for an ocular condition or medical condition that may interact with the eye drops**
- **Undergoing or have had any form of myopia control intervention**

What happens next?

If you would like to be involved in this study then please **contact me** (details are below) and arrange a time when you can come to the Aston Optometry Department.

You will be required to sign a **consent form** at the appointment.

Who do I need to contact?

If you would like to be involved in the study or if you have any questions please do not hesitate to get in touch with Katie Franklin, the lead investigator:

[redacted]

Clinical Supervisors: Dr Nicola Logan
Dr Janis Orr

Address: Aston University, Aston Triangle, Birmingham, B4 7ET

Version [2] Date [23/12/16]

Code:

Aston University

A Study of Myopia (short sightedness) in Young Adults in the UK

Participant Consent Form

IF YOU WOULD LIKE TO TAKE PART IN THIS STUDY, PLEASE COMPLETE THIS FORM

Please initial each box if you agree with the statement. *Please note you must initial all boxes to be eligible to take part in the study.*

1	I confirm that I have read the information sheet *(Version [2] Date [23/12/16])* for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
2	I understand that participation is voluntary and that I am free to withdraw at any time without giving any reason, without my legal rights being affected.	
3	I understand that eye drops will be used in this study.	
4	I understand that this does not replace a routine eye examination.	
5	I agree to take part in the above study.	

Signature:

Name: **Date:**

Address: *This will allow us to keep you updated about the results of the study.*

Postcode:

Contact Number:

E-mail:

Confidentiality

Please be assured that all data and records that contains any personal information will be kept strictly confidential. The data will be anonymised and no identifying information will be published. All electronic data will be password protected. Hard copies of consent forms and data collection forms will be stored in a locked filing cabinet.

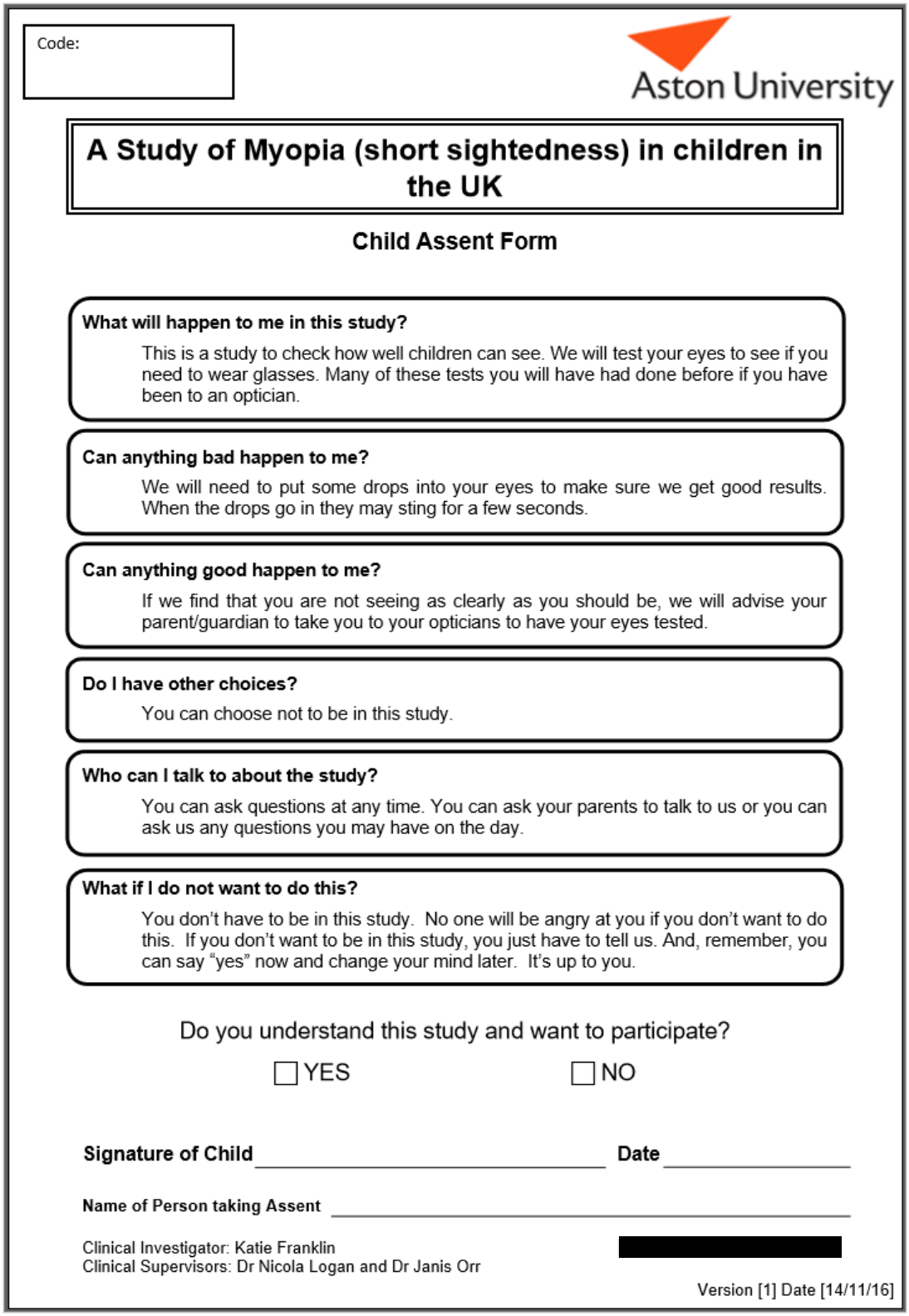
All study data will be stored in accordance with the Data Protection Act (1998) and the University data storage policies for research data.

Name of Person taking Consent _____

Clinical Supervisors: Dr Nicola Logan and Dr Janis Orr
Student: Katie Franklin

Version [2] Date [23/12/16]

A.5.4 Child assent form



Code:

Aston University

A Study of Myopia (short sightedness) in children in the UK

Child Assent Form

What will happen to me in this study?

This is a study to check how well children can see. We will test your eyes to see if you need to wear glasses. Many of these tests you will have had done before if you have been to an optician.

Can anything bad happen to me?

We will need to put some drops into your eyes to make sure we get good results. When the drops go in they may sting for a few seconds.

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 take you to your opticians to have your eyes tested.

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 want to participate?

☐ YES ☐ NO

Signature of Child _____ **Date** _____

Name of Person taking Assent _____

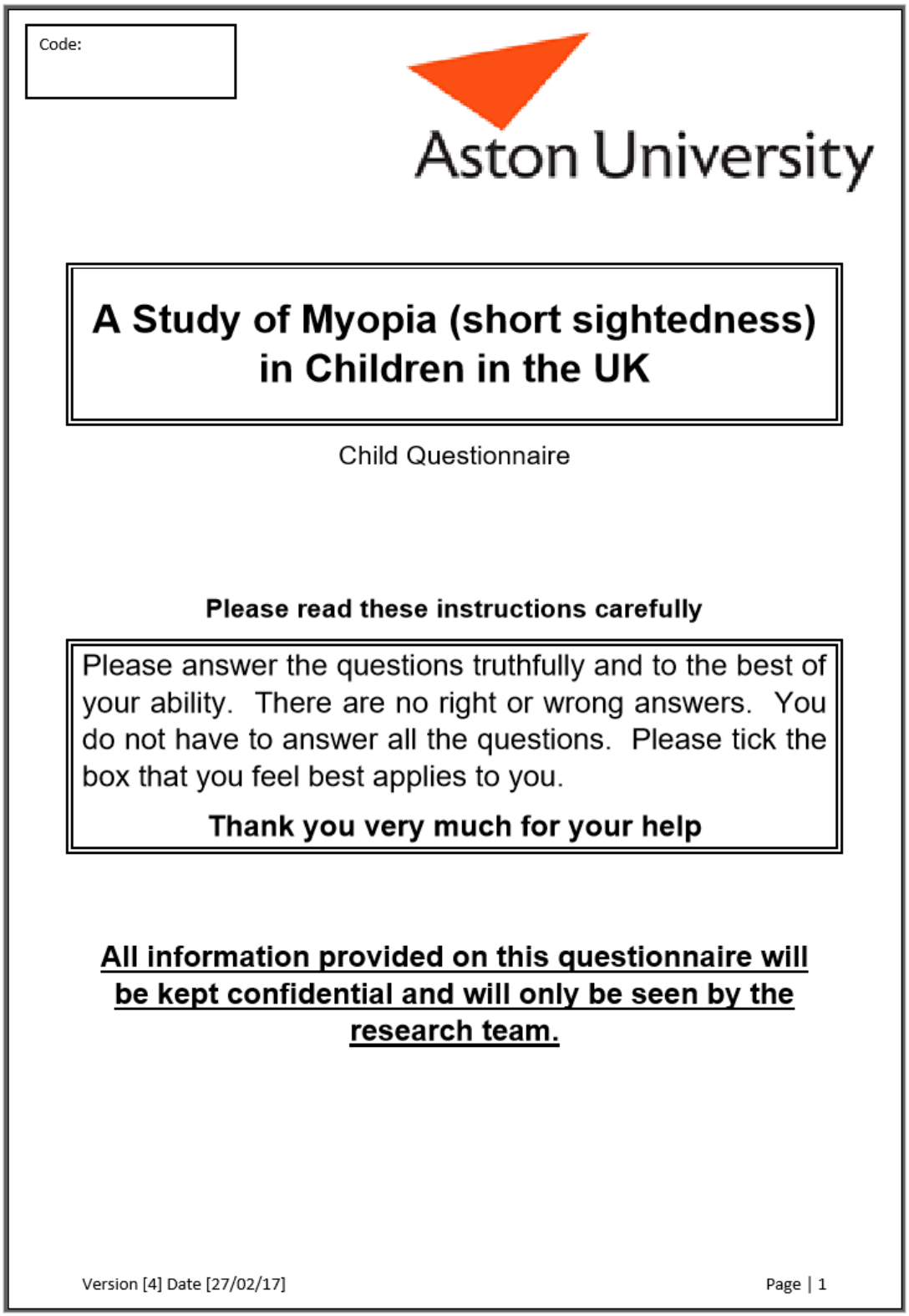
Clinical Investigator: Katie Franklin
Clinical Supervisors: Dr Nicola Logan and Dr Janis Orr

[redacted]

Version [1] Date [14/11/16]

A.5.5 Lifestyle questionnaires

A.5.5.1 Child questionnaire



Code:

Aston University

A Study of Myopia (short sightedness) in Children in the UK

Child Questionnaire

Please read these instructions carefully

Please answer the questions truthfully and to the best of your ability. There are no right or wrong answers. You do not have to answer all the questions. Please tick the box that you feel best applies to you.

Thank you very much for your help

All information provided on this questionnaire will be kept confidential and will only be seen by the research team.

Version [4] Date [27/02/17]

Page | 1

1 About you

In this section, we would like to know some more information about you.

1. Name:

2. Are you:

☐ **Boy** ☐ **Girl**

3. When were you born?

☐☐ DAY ☐☐ MONTH ☐☐ YEAR

4. How many brothers and sisters do you have?
(not counting step brothers or sisters)

☐

2 Ocular history

In this section, we would like to know more about your eyes

5. Have you **ever** had to go to the hospital for your eyes?

Yes ☐ No ☐

6. Have you **ever** had surgery on your eyes and/or worn an eye patch?

Yes ☐ No ☐

7. Have you **ever** had to wear glasses or contact lenses?

Yes ☐ No ☐

8. If you wear glasses or contact lenses, what do you wear them for?

☐ I need glasses to see far away e.g. whiteboard, TV
☐ I need glasses for reading and writing
☐ I have rugby ball shaped eyes
☐ I don't know

3 Your Activities

In this section, we would like to know more about what you like to do.

9. How many hours do you spend **outdoors** each day

☐ None
☐ Less than 1 hour
☐ 1-2 hours
☐ 2 or more hours, ***how many hours*** ☐

10. How many hours do you spend doing the following activities each day

	None	Less than 1 hour	1-2 hours	2 or more hours
Reading printed text or writing	☐	☐	☐	☐
Using a computer, tablet or smartphone	☐	☐	☐	☐
Watching TV	☐	☐	☐	☐
Playing video games	☐	☐	☐	☐
Playing sport **outdoors**	☐	☐	☐	☐

11. How often do you wear sunglasses?

☐ Never
☐ Occasionally
☐ Usually
☐ Always

12. How often do you wear a hat that protects from the sun e.g. with a cap?

☐ Never
☐ Occasionally
☐ Usually
☐ Always

4 Diet

In this section, we would like to find out more about what you eat

13. How many different types of fruit you **usually** eat each day?

- ☐ I don't eat fruit
- ☐ 1 serving
- ☐ 2 servings
- ☐ 3 servings
- ☐ 4+ servings

14. How many different vegetables do you **usually** eat each day?

- ☐ I don't eat vegetables
- ☐ 1 serving
- ☐ 2 servings
- ☐ 3 servings
- ☐ 4+ servings

15. How often do you eat red meat e.g. beef, mince, lamb, liver?

- ☐ Never or rarely
- ☐ Less than once a week
- ☐ 1-3 times a week
- ☐ 4-6 times a week
- ☐ 7 or more times a week

16. How often do you eat oily fish e.g. salmon, sardines, mackerel?

- ☐ Never or rarely
- ☐ Less than once a week
- ☐ 1-3 times a week
- ☐ 4-6 times a week
- ☐ 7 or more times a week

17. How often do you eat eggs (including the yolk)?

- ☐ Never or rarely
- ☐ Less than once a week
- ☐ 1-3 times a week
- ☐ 4-6 times a week
- ☐ 7 or more times a week

5 Parent details

This section we would like to find out more about your parents.

18. Does your mum wear glasses or contact lenses?

Yes ☐ No ☐

19. If your mum wears glasses or contact lenses do they:

- ☐ Need glasses to see far away e.g. TV
- ☐ Need glasses for reading
- ☐ Have rugby ball shaped eyes
- ☐ I don't know

20. Does your dad wear glasses or contact lenses?

Yes ☐ No ☐

21. If your dad wears glasses or contact lenses do they:

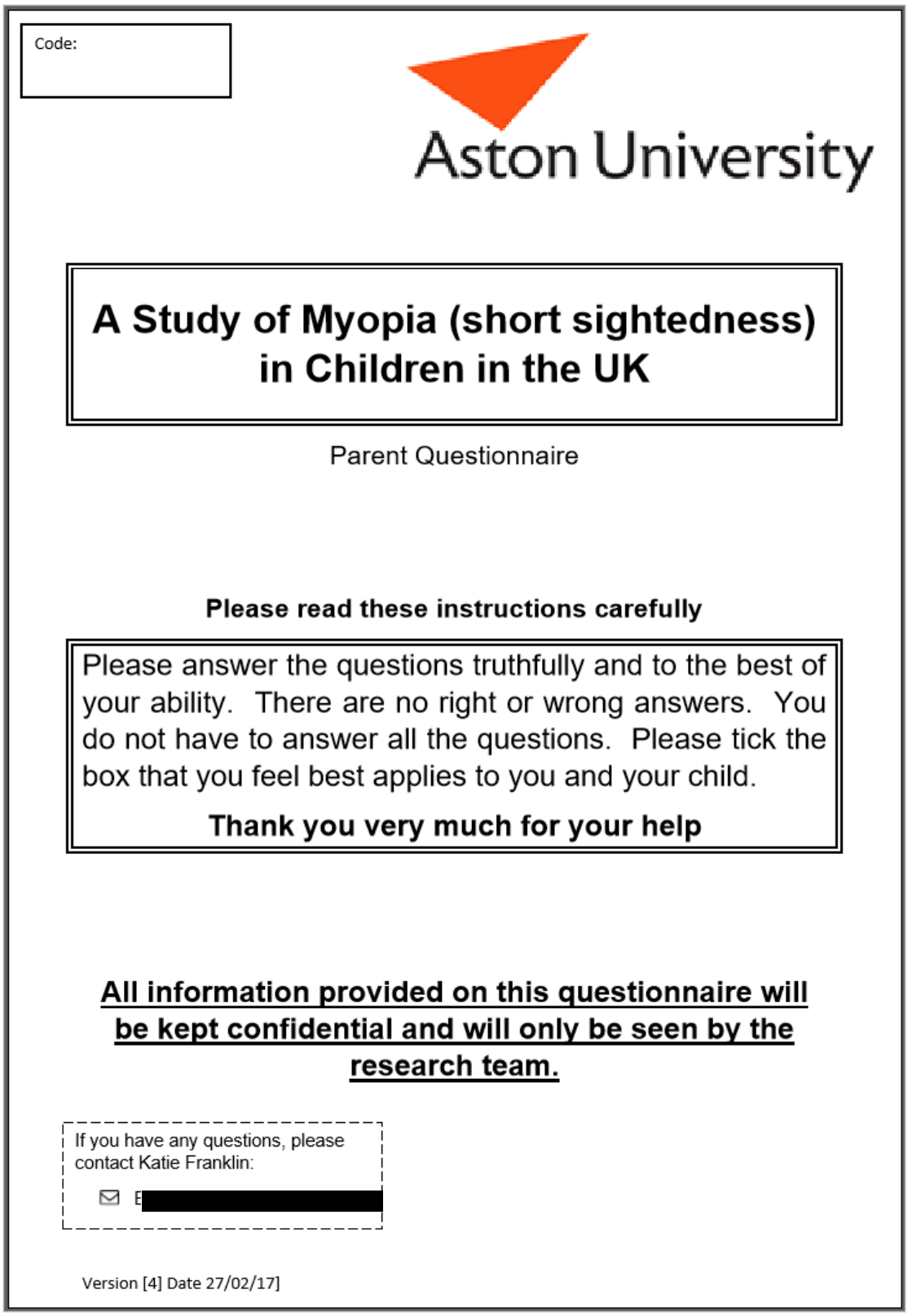
- ☐ Need glasses to see far away e.g. TV
- ☐ Need glasses for reading
- ☐ Have rugby ball shaped eyes
- ☐ I don't know

22. Does either you mother or father smoke?

Yes ☐ No ☐

Thank you very much for completing this questionnaire

A.5.5.2 Parental questionnaire



Code:

Aston University

A Study of Myopia (short sightedness) in Children in the UK

Parent Questionnaire

Please read these instructions carefully

Please answer the questions truthfully and to the best of your ability. There are no right or wrong answers. You do not have to answer all the questions. Please tick the box that you feel best applies to you and your child.

Thank you very much for your help

All information provided on this questionnaire will be kept confidential and will only be seen by the research team.

If you have any questions, please contact Katie Franklin:

E [redacted]

Version [4] Date 27/02/17]

1 About your child

In this section, we would like to know some more information about your child who is taking part in the study.

1. Write your child's full name in this box

2. What is your child's gender?

☐ **Male** ☐ **Female**

3. What is your child's date of birth?

DAY MONTH YEAR

4. What is your child's ethnicity?

☐ **White**

☐ **Black**

Asian

☐ East Asian (e.g. China, Singapore, Japan etc)

☐ South Asian (e.g. Indian, Pakistan, Bangladesh etc)

☐ **Mixed race**, *please specify below*

☐ **Other**, *please specify below*

5. What was your child's birth weight?

lb oz OR kg OR ☐ **UNKNOWN**

6. Was your child born:

☐ Late (42 weeks or more)

☐ On time (37-41 weeks)

☐ Early (32 – 36 weeks)

☐ Very early (31 weeks or less)

7. How many brothers and sisters does your child have?
(not counting step brothers or sisters)

2 Ocular history

In this section, we would like to know more about your child's eyes and their eye health

8. Have you **ever** had to take your child to the hospital for their eyes?

Yes ☐ No ☐

If **YES**, please give details:

9. Have they **ever** had surgery on their eyes and/or worn an eye patch?

Yes ☐ No ☐

10. Has your child **ever** had to wear glasses?

Yes ☐ No ☐

11. If your child wears glasses, are they:

☐ Short sighted (need glasses to see far away e.g. whiteboard, TV)

☐ Long sighted (need glasses for close tasks e.g. reading, writing)

☐ Astigmatic (often described as rugby ball shaped eyes)

☐ Not known

12. When did they last have an eye examination at their local opticians?

MONTH YEAR

☐ Unknown

☐ Never

3 Your child's activities

In this section, we would like to know more about your child's activities on school days and weekends.

13. How much time does your child spend **outdoors** on a **week day**, outside of school hours, **IN WINTER**? *This can include time walking to and from school.*

- ☐ None
- ☐ Less than 1 hour
- ☐ 1-2 hours
- ☐ 2 or more hours, ***please specify*** ☐

14. How much time does your child spend doing the following tasks on a **week day**, outside of school hours, **IN WINTER**?

	None	Less than 1 hour	1-2 hours	2 or more hours
Reading printed text or writing	☐	☐	☐	☐
Using a computer, tablet or smartphone	☐	☐	☐	☐
Watching TV	☐	☐	☐	☐
Playing video games	☐	☐	☐	☐
Playing sport **outdoors**	☐	☐	☐	☐

15. How much time does your child spend **outdoors** on a **weekend day IN WINTER**?

- ☐ None
- ☐ Less than 1 hour
- ☐ 1-2 hours
- ☐ 2 or more hours, ***please specify*** ☐

16. How much time does your child spend doing the following tasks on a **weekend day IN WINTER**?

	None	Less than 1 hour	1-2 hours	2 or more hours
Reading printed text or writing	☐	☐	☐	☐
Using a computer, tablet or smartphone	☐	☐	☐	☐
Watching TV	☐	☐	☐	☐
Playing video games	☐	☐	☐	☐
Playing sport **outdoors**	☐	☐	☐	☐

17. How much time does your child spend **outdoors** on a **week day**, outside of school hours, **IN SUMMER**? *This can include time walking to and from school.*

- ☐ None
- ☐ Less than 1 hour
- ☐ 1-2 hours
- ☐ 2 or more hours, ***please specify*** ☐

18. How much time does your child spend doing the following tasks on a **week day**, outside of school hours, **IN SUMMER**?

	None	Less than 1 hour	1-2 hours	2 or more hours
Reading printed text or writing	☐	☐	☐	☐
Using a computer, tablet or smartphone	☐	☐	☐	☐
Playing video games	☐	☐	☐	☐
Watching TV	☐	☐	☐	☐
Playing sport **outdoors**	☐	☐	☐	☐

19. How much time does your child spend **outdoors** on a **weekend day IN SUMMER**?

- ☐ None
- ☐ Less than 1 hour
- ☐ 1-2 hours
- ☐ 2 or more hours, ***please specify*** ☐

20. How much time does your child spend doing the following tasks on a **weekend day IN SUMMER**?

	None	Less than 1 hour	1-2 hours	2 or more hours
Reading printed text or writing	☐	☐	☐	☐
Using a computer, tablet or smartphone	☐	☐	☐	☐
Watching TV	☐	☐	☐	☐
Playing video games	☐	☐	☐	☐
Playing sport **outdoors**	☐	☐	☐	☐

21. IN SUMMER, how often does your child wear sunglasses?

- ☐ Never
- ☐ Occasionally
- ☐ Usually
- ☐ Always

22. IN SUMMER, how often does your child wear a hat that protects from the sun e.g. with a cap?

- ☐ Never
- ☐ Occasionally
- ☐ Usually
- ☐ Always

23. Has your child ever lived outside the UK? If YES please indicate below the country and duration

4 Diet

In this section, we would like to find out more about your child's diet.

24. How many servings of fruit does your child **usually** eat each day?

- ☐ They don't eat fruit
- ☐ 1 serving
- ☐ 2 servings
- ☐ 3 servings
- ☐ 4+ servings ***please specify*** ☐

25. How many servings of vegetables does your child **usually** eat each day?

- ☐ They don't eat vegetables
- ☐ 1 serving
- ☐ 2 servings
- ☐ 3 servings
- ☐ 4+ servings ***please specify*** ☐

26. How often do they eat red meat e.g. beef, mince, lamb, liver?

- ☐ Never or rarely
- ☐ Less than once a week
- ☐ 1-3 times a week
- ☐ 4-6 times a week
- ☐ 7 or more times a week

27. How often do they eat oily fish e.g. salmon, sardines, mackerel?

- ☐ Never or rarely
- ☐ Less than once a week
- ☐ 1-3 times a week
- ☐ 4-6 times a week
- ☐ 7 or more times a week

28. How often do they eat eggs (including the yolk)?

- ☐ Never or rarely
- ☐ Less than once a week
- ☐ 1-3 times a week
- ☐ 4-6 times a week
- ☐ 7 or more times a week

29. Do they take a vitamin D supplement?

- ☐ Never
- ☐ Occasionally
- ☐ Once a week
- ☐ Daily

30. Do they take cod liver oil supplement?
This can either be via capsules or liquid

- ☐ Never
- ☐ Occasionally
- ☐ Once a week
- ☐ Daily

5 Parent details

In this section, we would like to find out more about your child's biological parents. If you are not the child's natural parents, you do not need to complete this section.

31. Do you wear glasses or contact lenses?

Yes ☐ No ☐

32. If you **do** wear glasses or contact lenses are you:

- ☐ Short sighted (need glasses to see far away e.g. whiteboard, TV)
- ☐ Long sighted (need glasses for close tasks e.g. reading, writing)
- ☐ Astigmatic (often described as rugby ball shaped eyes)
- ☐ Not known

If you know your prescription then please complete the boxes below:

	Sph	Cyl	Axis		Add
R					
L					

33. Does the child's other biological parent wear glasses or contact lenses?

Yes ☐ No ☐

34. If they **do** wear glasses or contact lenses are they:

- ☐ Short sighted (need glasses to see far away e.g. whiteboard, TV)
- ☐ Long sighted (need glasses for close tasks e.g. reading, writing)
- ☐ Astigmatic (often described as rugby ball shaped eyes)
- ☐ Not known

If you know their prescription then please complete the boxes below:

	Sph	Cyl	Axis		Add
R					
L					

35. Which of these qualifications best describes the **highest level of education** obtained by each parent?

	Mother	Father
Primary school not completed	☐	☐
Primary school completed	☐	☐
Secondary school completed	☐	☐
GCSE qualifications/ O-level or equivalent	☐	☐
A-level qualifications/ equivalent	☐	☐
University degree qualification	☐	☐
Higher degree (e.g. MA, PhD)	☐	☐

36. What is your occupation?

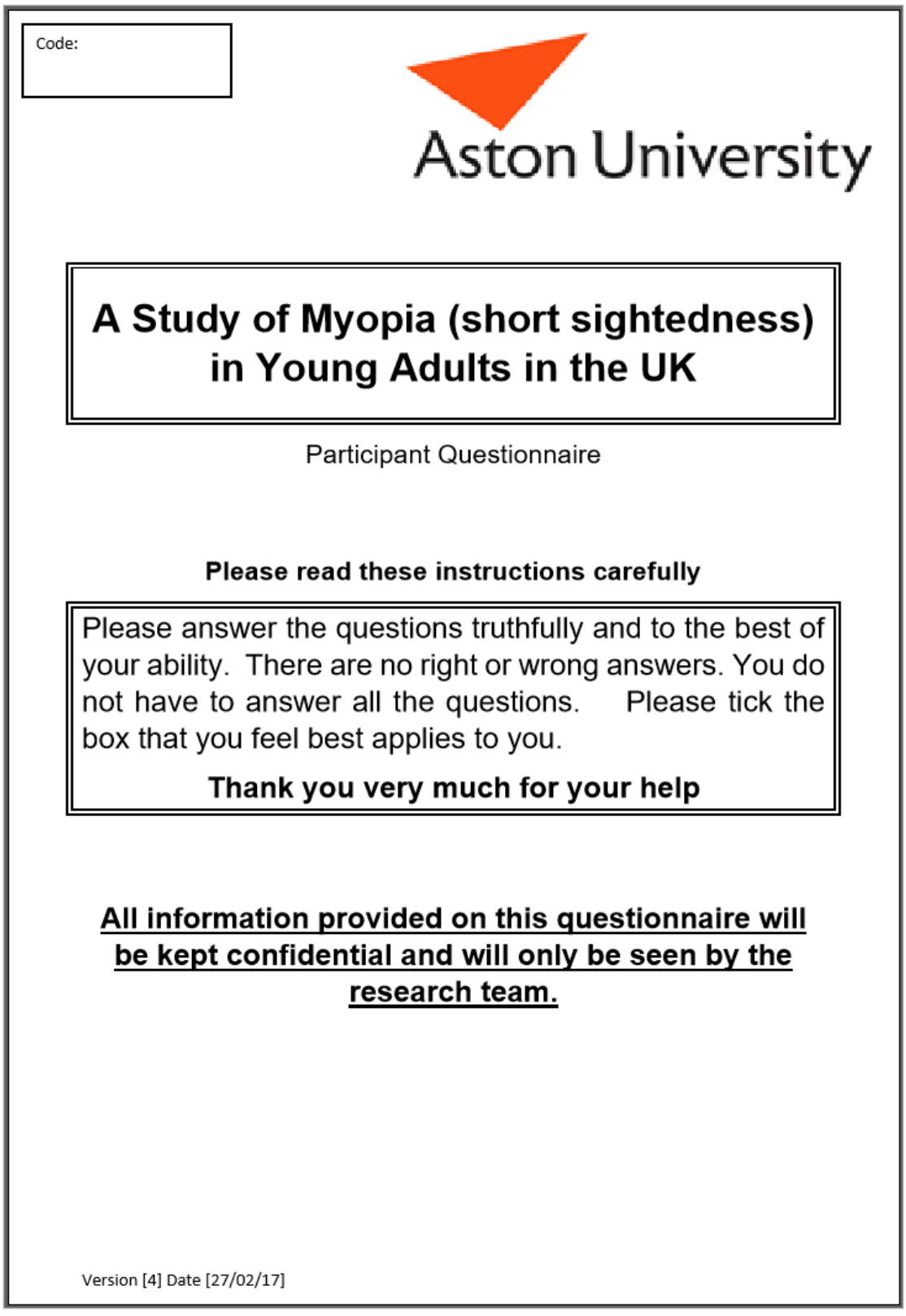
37. What is your child's other biological parent's occupation?

38. Does either your or your partner smoke?

Yes ☐ No ☐

Thank you very much for completing this questionnaire

A.5.5.3 Young adult questionnaire



Code:

Aston University

A Study of Myopia (short sightedness) in Young Adults in the UK

Participant Questionnaire

Please read these instructions carefully

Please answer the questions truthfully and to the best of your ability. There are no right or wrong answers. You do not have to answer all the questions. Please tick the box that you feel best applies to you.

Thank you very much for your help

All information provided on this questionnaire will be kept confidential and will only be seen by the research team.

Version [4] Date [27/02/17]

1 About you

In this section, we would like to know some more information about you.

1. Your Full Name:

2. What is your date of birth?

DAY MONTH YEAR

3. Are you:

☐ **Male** ☐ **Female**

4. What is your ethnicity?

☐ **White**

☐ **Black**

Asian

☐ East Asian (e.g. China, Singapore, Japan etc)

☐ South Asian (e.g. Indian, Pakistan, Bangladesh etc)

☐ **Mixed race**, *please specify below*

☐ **Other**, *please specify below*

5. What was your birth weight?

☐ lb ☐ oz **OR** ☐ kg **OR** ☐ **UNKNOWN**

6. Were you born:

☐ Late (42 weeks or more)
☐ On time (37-41 weeks)
☐ Early (32 – 36 weeks)
☐ Very early (31 weeks or less)
☐ Not Known

7. How many brothers and sisters do you have?
(not counting half/step brothers or sisters)

☐

8. Which of these qualifications best describes the **highest level of education** that you have obtained?

☐ Primary school not completed
☐ Primary school completed
☐ Secondary school completed
☐ GCSE qualifications
☐ A-Level qualifications
☐ University degree qualification
☐ Higher degree (e.g. MA, PhD)

2 Ocular history

In this section, we would like to know more about your eyes and your eye health

9. Have you **ever** had to go to the hospital for your eyes?

Yes ☐ No ☐

If **YES**, please give details:

10. Have you **ever** had surgery on your eyes and/or worn an eye patch?

Yes ☐ No ☐

11. Have you **ever** had to wear glasses or contact lenses?

Yes ☐ No ☐

12. If you wear glasses or contact lenses, are you:

- ☐ Short sighted (need glasses to see far away e.g. whiteboard, TV)
- ☐ Long sighted (need glasses for close tasks e.g. reading, writing)
- ☐ Astigmatic (often described as rugby ball shaped eyes)
- ☐ Not known

13. When did you last have an eye examination at your local opticians?

☐☐ MONTH ☐☐☐☐ YEAR

- ☐ Unknown
- ☐ Never

3 Your Activities

In this section, we would like to know more about your activities on week days and weekends.

14. How much time do you spend **outdoors** on a **week day IN WINTER**?
This can include time walking to and from lectures.

- ☐ None
- ☐ Less than 1 hour
- ☐ 1-2 hours
- ☐ 2 or more hours, ***please specify*** ☐

15. How much time do you spend doing the following tasks on a **week day**, **IN WINTER**?

	None	Less than 1 hour	1-2 hours	2 or more hours
Reading printed text or writing	☐	☐	☐	☐
Using a computer, tablet or smartphone	☐	☐	☐	☐
Watching TV	☐	☐	☐	☐
Playing video games	☐	☐	☐	☐
Playing sport **outdoors**	☐	☐	☐	☐

16. How much time do you spend **outdoors** on a **weekend day IN WINTER**?

- ☐ None
- ☐ Less than 1 hour
- ☐ 1-2 hours
- ☐ 2 or more hours, ***please specify*** ☐

17. How much time do you spend doing the following tasks on a **weekend day IN WINTER**?

	None	Less than 1 hour	1-2 hours	2 or more hours
Reading printed text or writing	☐	☐	☐	☐
Using a computer, tablet or smartphone	☐	☐	☐	☐
Watching TV	☐	☐	☐	☐
Playing video games	☐	☐	☐	☐
Playing sport **outdoors**	☐	☐	☐	☐

18. How much time do you spend **outdoors** on a **week day IN SUMMER**?
This can include time walking to and from lectures.

- ☐ None
- ☐ Less than 1 hour
- ☐ 1-2 hours
- ☐ 2 or more hours, ***please specify*** ☐

19. How much time do you spend doing the following tasks on a **week day**, **IN SUMMER**?

	None	Less than 1 hour	1-2 hours	2 or more hours
Reading printed text or writing	☐	☐	☐	☐
Using a computer, tablet or smartphone	☐	☐	☐	☐
Watching TV	☐	☐	☐	☐
Playing video games	☐	☐	☐	☐
Playing sport **outdoors**	☐	☐	☐	☐

20. How much time do you spend **outdoors** on a **weekend day IN SUMMER**?

- ☐ None
- ☐ Less than 1 hour
- ☐ 1-2 hours
- ☐ 2 or more hours, ***please specify*** ☐

21. How much time do you spend doing the following tasks on a **weekend day IN SUMMER**?

	None	Less than 1 hour	1-2 hours	2 or more hours
Reading printed text or writing	☐	☐	☐	☐
Using a computer, tablet or smartphone	☐	☐	☐	☐
Watching TV	☐	☐	☐	☐
Playing video games	☐	☐	☐	☐
Playing sport **outdoors**	☐	☐	☐	☐

22. How often do you wear sunglasses?

- ☐ Never
- ☐ Occasionally
- ☐ Usually
- ☐ Always

23. How often do you wear a hat that protects from the sun e.g. with a cap?

- ☐ Never
- ☐ Occasionally
- ☐ Usually
- ☐ Always

24. How often do you use sunbeds?

- ☐ Never
- ☐ A few times a year
- ☐ Once a month
- ☐ Once a week
- ☐ Couple of times a week

25. Have you ever lived outside the UK? If YES, please indicate below the country and duration

4 Diet

In this section, we would like to find out more about your diet.

26. How many servings of fruit do you **usually** eat each day?

- ☐ I don't eat fruit
- ☐ 1 serving
- ☐ 2 servings
- ☐ 3 servings
- ☐ 4+ servings ***please specify*** ☐

27. How many servings of vegetables do you **usually** eat each day?

- ☐ I don't eat vegetables
- ☐ 1 serving
- ☐ 2 servings
- ☐ 3 servings
- ☐ 4+ servings ***please specify*** ☐

28. How often do you eat red meat e.g. beef, mince, lamb, liver?

- ☐ Never or rarely
- ☐ Less than once a week
- ☐ 1-3 times a week
- ☐ 4-6 times a week
- ☐ 7 or more times a week

29. How often do you eat oily fish e.g. salmon, sardines, mackerel?

- ☐ Never or rarely
- ☐ Less than once a week
- ☐ 1-3 times a week
- ☐ 4-6 times a week
- ☐ 7 or more times a week

30. How often do you eat eggs (including the yolk)?

- ☐ Never or rarely
- ☐ Less than once a week
- ☐ 1-3 times a week
- ☐ 4-6 times a week
- ☐ 7 or more times a week

31. Do you take a vitamin D supplement?

- ☐ Never
- ☐ Occasionally
- ☐ Once a week
- ☐ Daily

32. Do you take cod liver oil supplement? *This can either be via capsules or liquid*

- ☐ Never
- ☐ Occasionally
- ☐ Once a week
- ☐ Daily

33. Do you smoke?

Yes ☐ No ☐

5 Parent details

This section we would like to find out more about your biological parents.

34. If your mother wears glasses or contact lenses is she:

- ☐ Short sighted (need glasses to see far away e.g. TV)
- ☐ Long sighted (need glasses for close tasks e.g. reading, writing)
- ☐ Astigmatic (often described as rugby ball shaped eyes)
- ☐ Not known
- ☐ She does not wear glasses

If you know her prescription then please complete the boxes below:

	Sph	Cyl	Axis		Add
R					
L					

35. If your father wears glasses or contact lenses is he:

- ☐ Short sighted (need glasses to see far away e.g. TV)
- ☐ Long sighted (need glasses for close tasks e.g. reading, writing)
- ☐ Astigmatic (often described as rugby ball shaped eyes)
- ☐ Not known
- ☐ He does not wear glasses

If you know his prescription then please complete the boxes below:

	Sph	Cyl	Axis		Add
R					
L					

36. Which of these qualifications best describes the **highest level of education** obtained by each of your parents?

	Mother	Father
Primary school completed	☐	☐
Secondary school completed	☐	☐
GCSE qualifications/ O-level or equivalent	☐	☐
A-level qualifications or equivalent	☐	☐
University degree qualification	☐	☐
Higher degree (e.g. MA, PhD)	☐	☐

37. What is your mother's occupation?

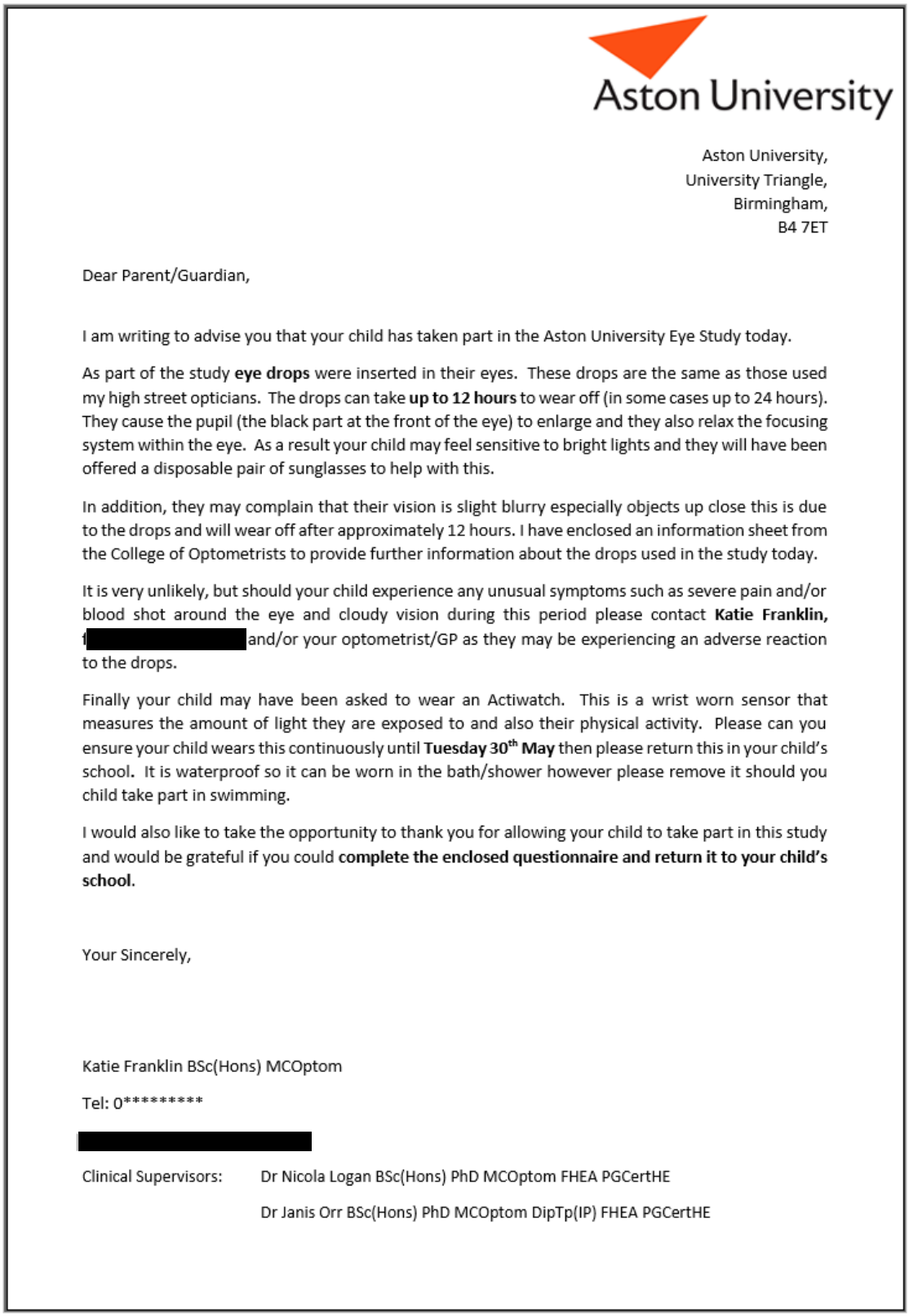
38. What is your father's occupation?

39. Does either you mother or father smoke?

Yes ☐ No ☐

Thank you for completing this questionnaire

A.5.6 Parental day of study letter



Aston University

Aston University,
University Triangle,
Birmingham,
B4 7ET

Dear Parent/Guardian,

I am writing to advise you that your child has taken part in the Aston University Eye Study today.

As part of the study **eye drops** were inserted in their eyes. These drops are the same as those used my high street opticians. The drops can take **up to 12 hours** to wear off (in some cases up to 24 hours). They cause the pupil (the black part at the front of the eye) to enlarge and they also relax the focusing system within the eye. As a result your child may feel sensitive to bright lights and they will have been offered a disposable pair of sunglasses to help with this.

In addition, they may complain that their vision is slight blurry especially objects up close this is due to the drops and will wear off after approximately 12 hours. I have enclosed an information sheet from the College of Optometrists to provide further information about the drops used in the study today.

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 **Katie Franklin,** [redacted] and/or your optometrist/GP as they may be experiencing an adverse reaction to the drops.

Finally your child may have been asked to wear an Actiwatch. This is a wrist worn sensor that measures the amount of light they are exposed to and also their physical activity. Please can you ensure your child wears this continuously until **Tuesday 30th May** then please return this in your child's school. It is waterproof so it can be worn in the bath/shower however please remove it should you child take part in swimming.

I would also like to take the opportunity to thank you for allowing your child to take part in this study and would be grateful if you could **complete the enclosed questionnaire and return it to your child's school**.

Your Sincerely,

Katie Franklin BSc(Hons) MCOptom

Tel: 0*********

[redacted]

Clinical Supervisors: Dr Nicola Logan BSc(Hons) PhD MCOptom FHEA PGCertHE

Dr Janis Orr BSc(Hons) PhD MCOptom DipTp(IP) FHEA PGCertHE

A.5.7 Participation certificate

A.5.8 SER normality assessment

A.5.8.1 Child cohort

The data was assessed for normality using Shapiro-Wilk and was found not to be normally distributed in either eye (RE $p<0.001$, LE $p<0.001$).

Normality was also assessed through normality Q-Q plots, see Figure A.3A. Principal outliers that deviated from the normal line were visible towards the extremes of the refractive error. These outliers (≥2SD) were identified and excluded from the normality assessment. For the RE 16 values were classed as outliers (7.1%) and for the LE 15 values (6.7%).

Following removal of these outliers, normality Q-Q plots were redrawn, see Figure A.3B. The remaining data from both eyes produced a near straight line which was more prominent in the RE SER data compared to the LE SER data. This was reflected in repeat Shapiro-Wilk analysis on this modified data set which found RE SER to be normally distributed ($p=0.011$) but LE SER to still not be normally distributed ($p=0.002$).

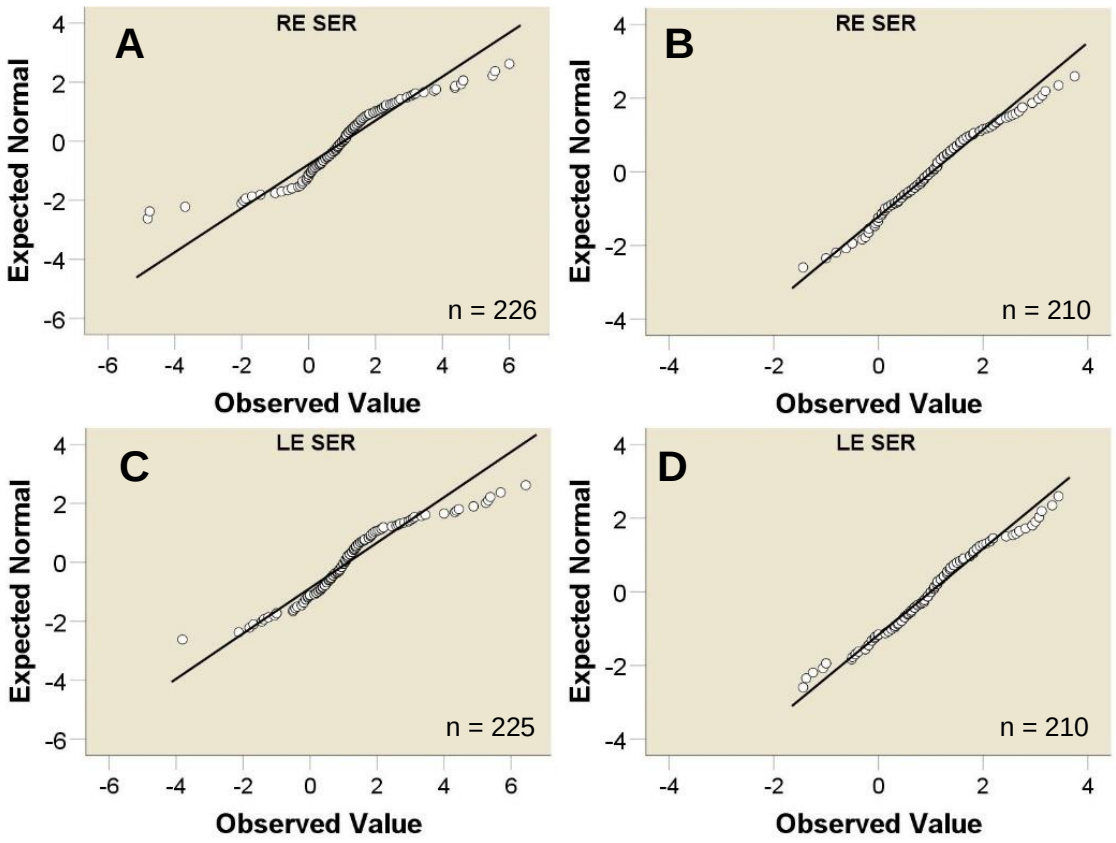


Figure A.3: SER normality Q-Q Plots for the Child cohort with and without outliers (≥2SD from mean) A) RE with outliers B) RE without outliers C) LE with outliers D) LE without outliers

A.5.8.2 Young adult cohort

The data was assessed for normality using Shapiro-Wilk and was found not to be normally distributed in either eye (RE p<0.001, LE p<0.001). Normality Q-Q plots are shown in Figure A.4A. Similar to the Child cohort, the outliers that deviated from normal were primarily in the extremes of refractive error. The outliers (≥2 SD) were excluded, for each eye 6 values were classified as outliers (6.9% per eye). Redrawn normality Q-Q plots still did not produce a straight line, see Figure A.4B. This was confirmed with repeat Shapiro-Wilk analysis which continued to show both RE SER and LE SER were not normally distributed (p=0.003 and p<0.001 respectively).

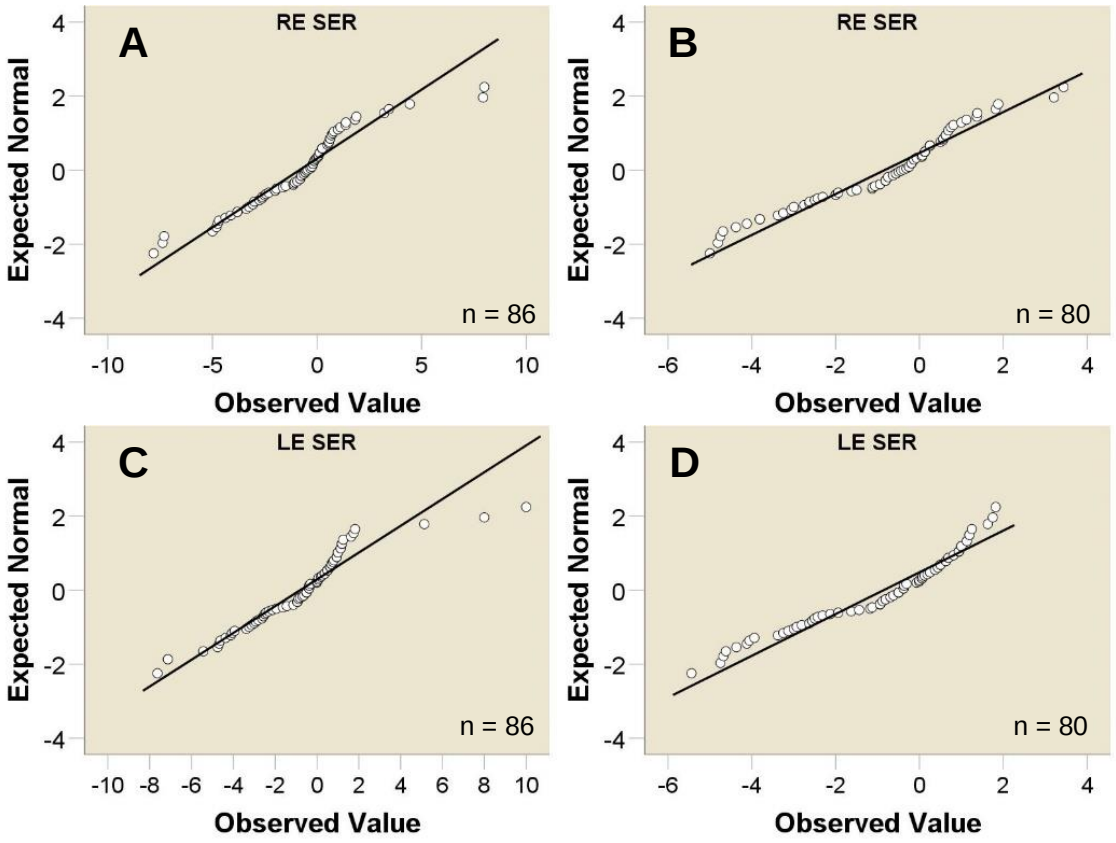


Figure A.4: SER normality Q-Q Plots for the Young Adult cohort with and without outliers (≥2SD from mean) A) RE with outliers B) RE without outliers C) LE with outliers D) LE without outliers

A.5.9 Distribution of ocular parameters and assessment of normality

A.5.9.1 Child cohort

The distributions of the ocular parameter are shown in Figure A.5.

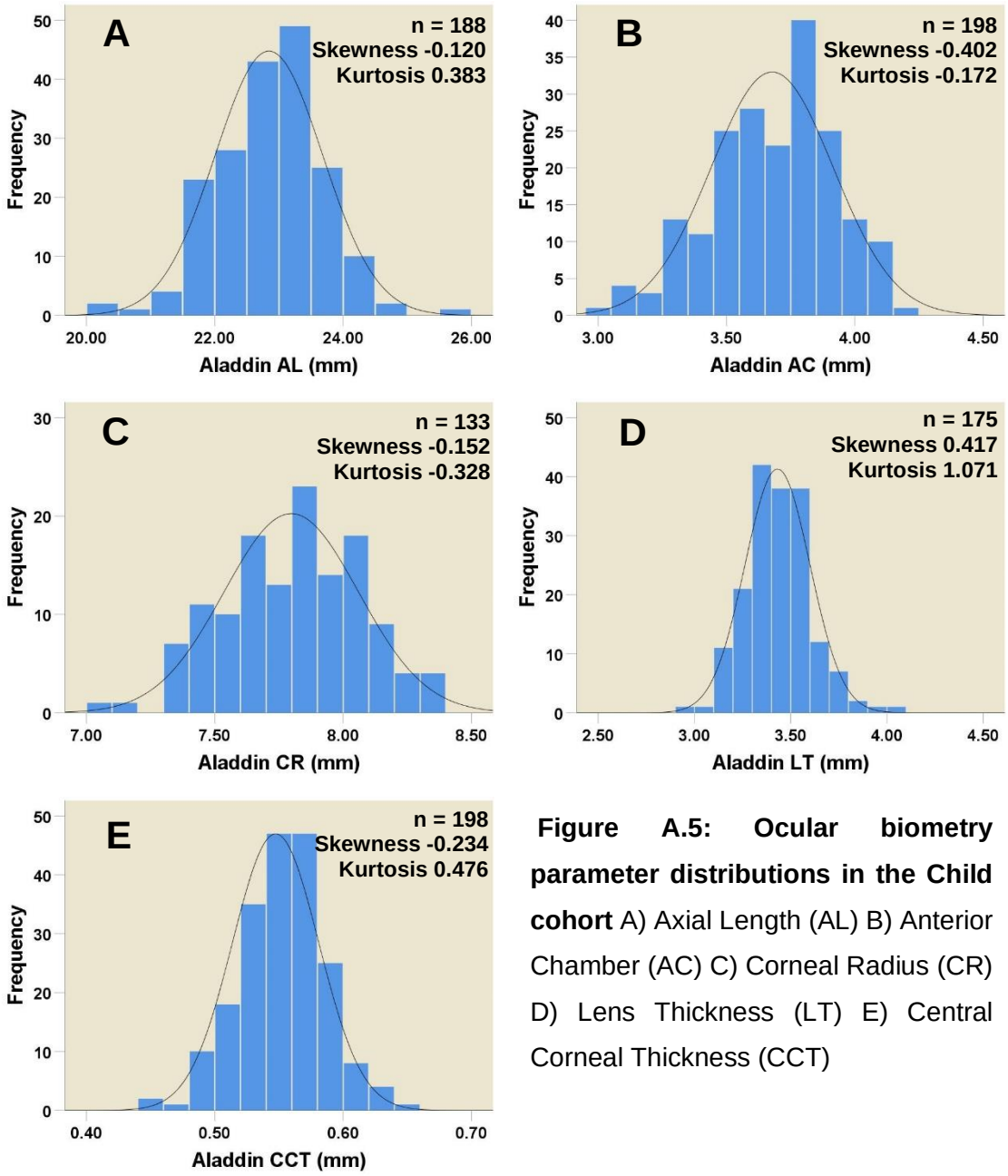


Figure A.5: Ocular biometry parameter distributions in the Child cohort A) Axial Length (AL) B) Anterior Chamber (AC) C) Corneal Radius (CR) D) Lens Thickness (LT) E) Central Corneal Thickness (CCT)

Associated Q-Q normality plots which were used to ascertain normality, see Figure A.6. Shapiro-Wilk values can be found in Table A.4. Following inspection of the histograms and Q-Q plots alongside the Shapiro-Wilk analysis AL, CR and LT were all found to be normally distributed. However, AC and CCT were found to be not normally distributed (p=0.030 and p=0.048, respectively). Inspection of AC and CCT histograms showed a

symmetrical distribution with an approximate Gaussian curve. No strong reasoning was found to use non-parametric analysis with this data.

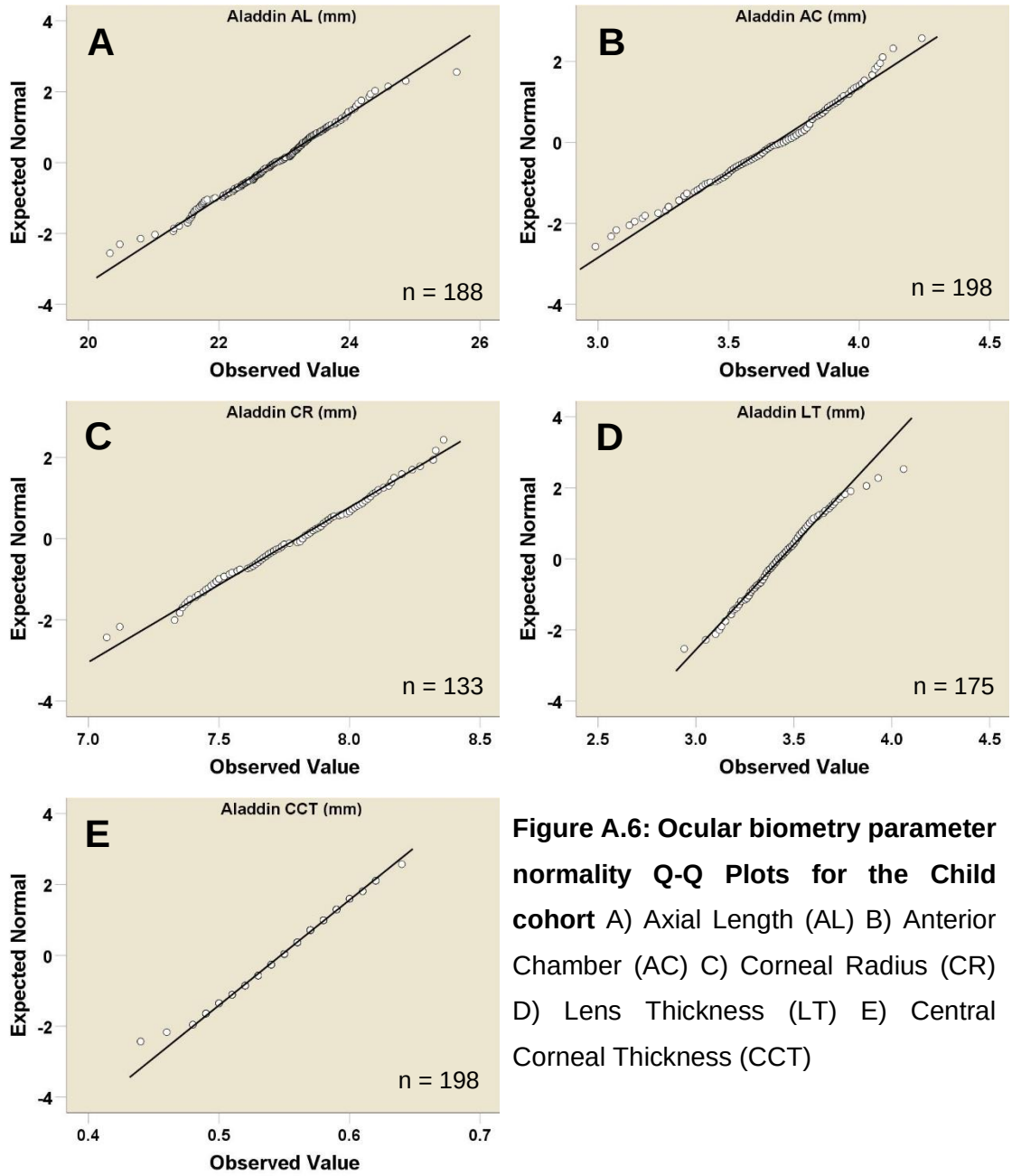


Figure A.6: Ocular biometry parameter normality Q-Q Plots for the Child cohort A) Axial Length (AL) B) Anterior Chamber (AC) C) Corneal Radius (CR) D) Lens Thickness (LT) E) Central Corneal Thickness (CCT)

Parameter (mm)	Child cohort
AL	p=0.486
AC	**p=0.030**
CR	p=0.524
LT	p=0.074
CCT	**p=0.048**

Table A.4: Shapiro-Wilk values for each ocular parameter measurement in the Child cohort

A.5.9.2 Young adult

The distributions of the ocular parameters are shown in Figure A.7.

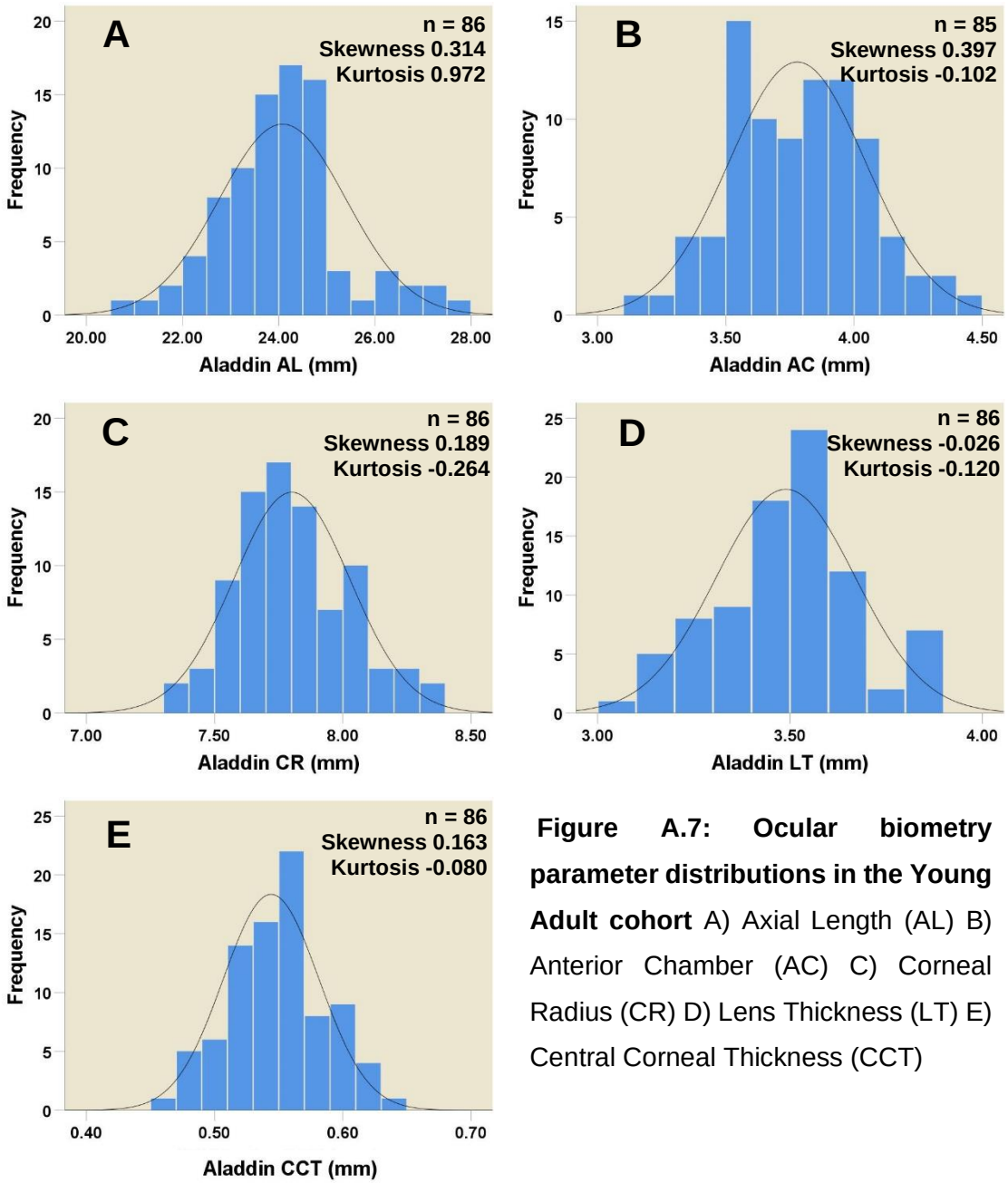


Figure A.7: Ocular biometry parameter distributions in the Young Adult cohort A) Axial Length (AL) B) Anterior Chamber (AC) C) Corneal Radius (CR) D) Lens Thickness (LT) E) Central Corneal Thickness (CCT)

Associated Q-Q normality plots which were used to ascertain normality, see Figure A.8. Shapiro-Wilk values can be found in Table A.5. Unlike in the Child cohort all parameters were normally distributed except AL (p=0.048). However, examination of both histograms showed a symmetrical distribution with an approximate Gaussian curve, albeit with a positive skew likely a result of a large proportion of myopic participants. No strong reasoning was found to use non-parametric analysis with this data.

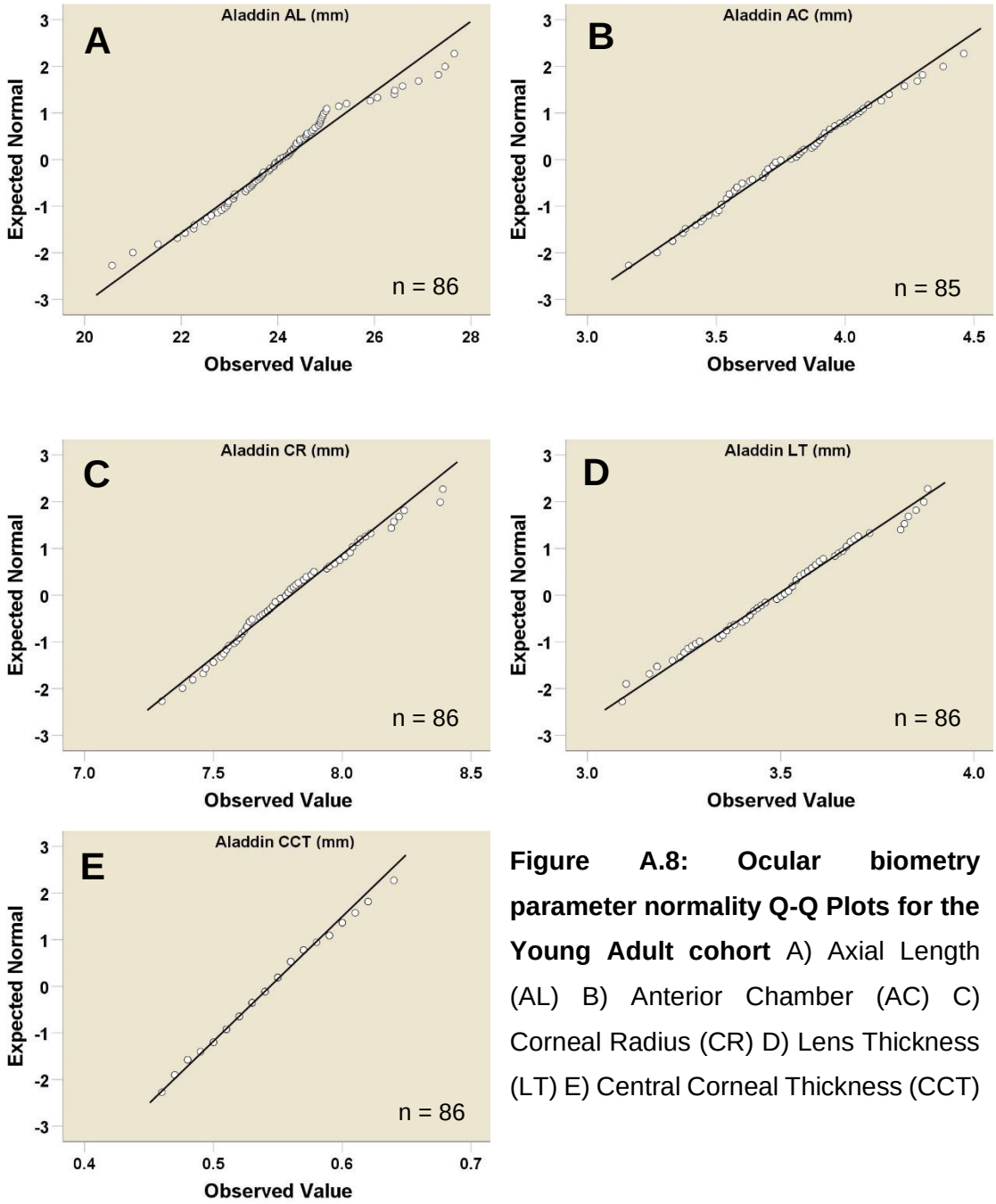


Figure A.8: Ocular biometry parameter normality Q-Q Plots for the Young Adult cohort A) Axial Length (AL) B) Anterior Chamber (AC) C) Corneal Radius (CR) D) Lens Thickness (LT) E) Central Corneal Thickness (CCT)

Parameter (mm)	Young Adult cohort
AL	**p=0.048**
AC	p=0.872
CR	p=0.355
LT	p=0.394
CCT	p=0.405

Table A.5: Shapiro-Wilk values for each ocular parameter measurement in the Young Adult cohort

A.5.10 Biometry RE vs LE correlation

A.5.10.1 Child cohort

The correlation of RE and LE biometry measurements are shown in Figure A.9.

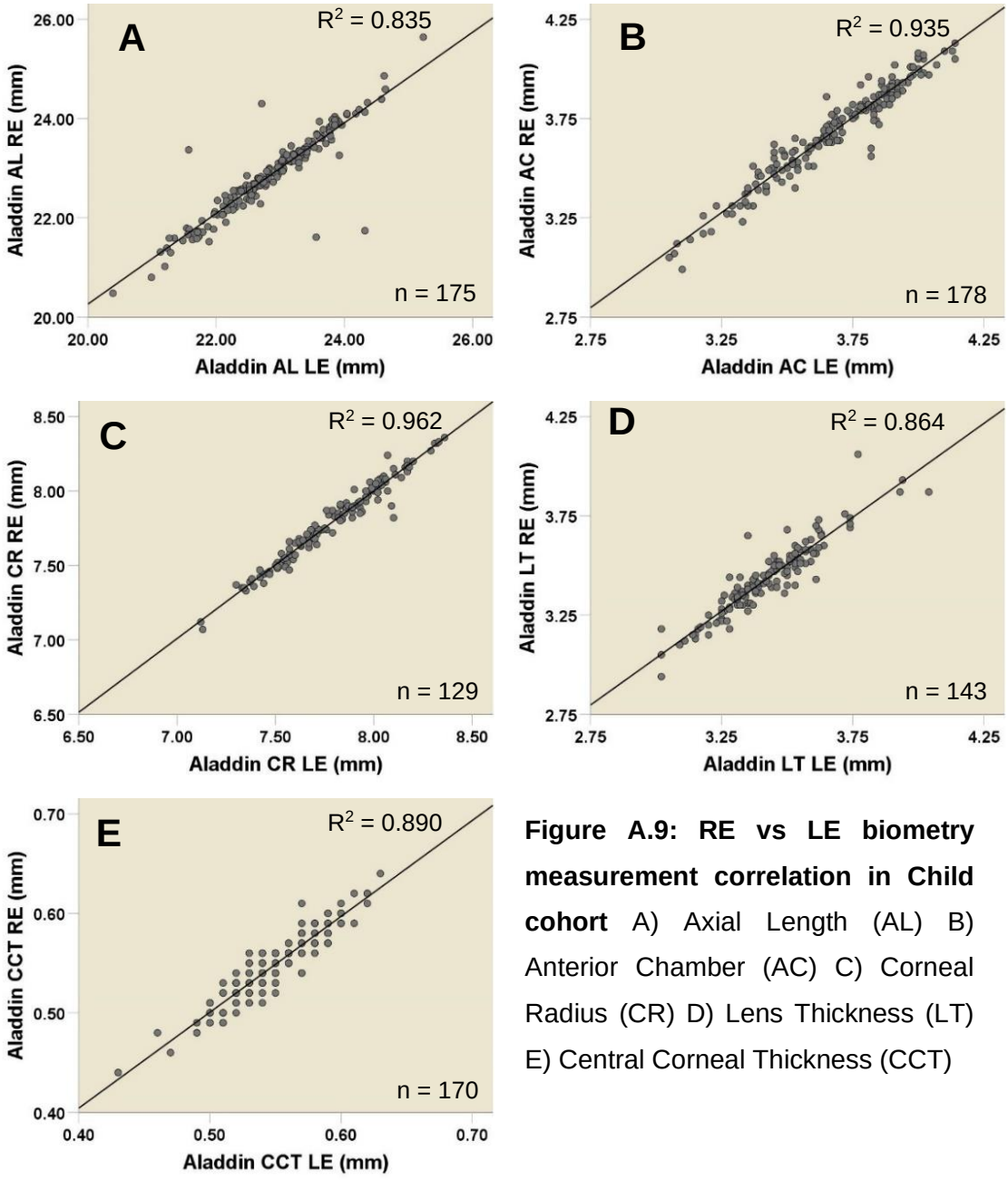


Figure A.9: RE vs LE biometry measurement correlation in Child cohort A) Axial Length (AL) B) Anterior Chamber (AC) C) Corneal Radius (CR) D) Lens Thickness (LT) E) Central Corneal Thickness (CCT)

A.5.10.2 Young adult cohort

The correlation of RE and LE biometry measurements are shown in Figure A.10.

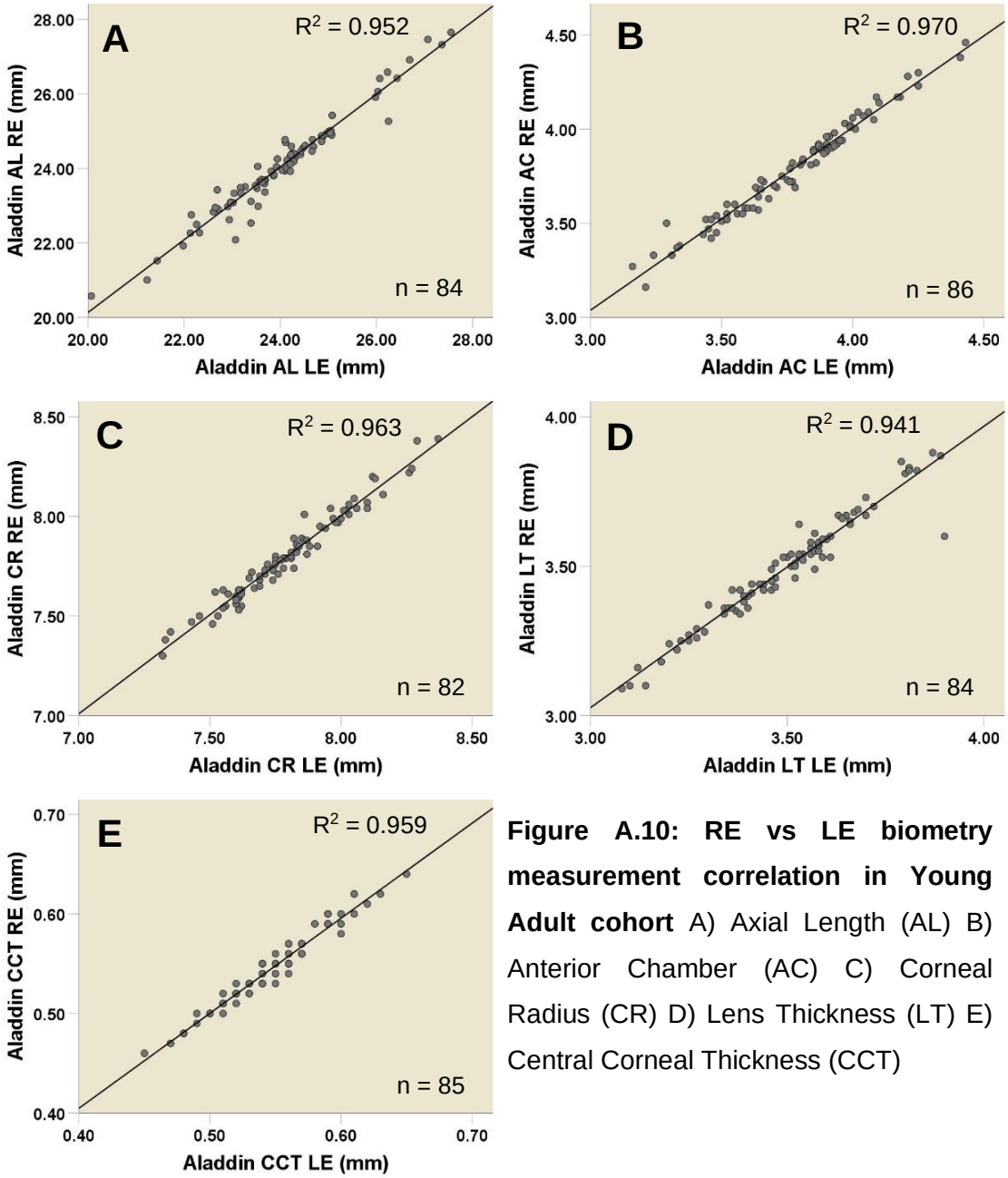


Figure A.10: RE vs LE biometry measurement correlation in Young Adult cohort A) Axial Length (AL) B) Anterior Chamber (AC) C) Corneal Radius (CR) D) Lens Thickness (LT) E) Central Corneal Thickness (CCT)

A.5.11 Ocular biometric parameters and SER correlation

A.5.11.1 Child cohort

The correlation of RE ocular biometer parameters and RE SER are shown in Figure A.11.

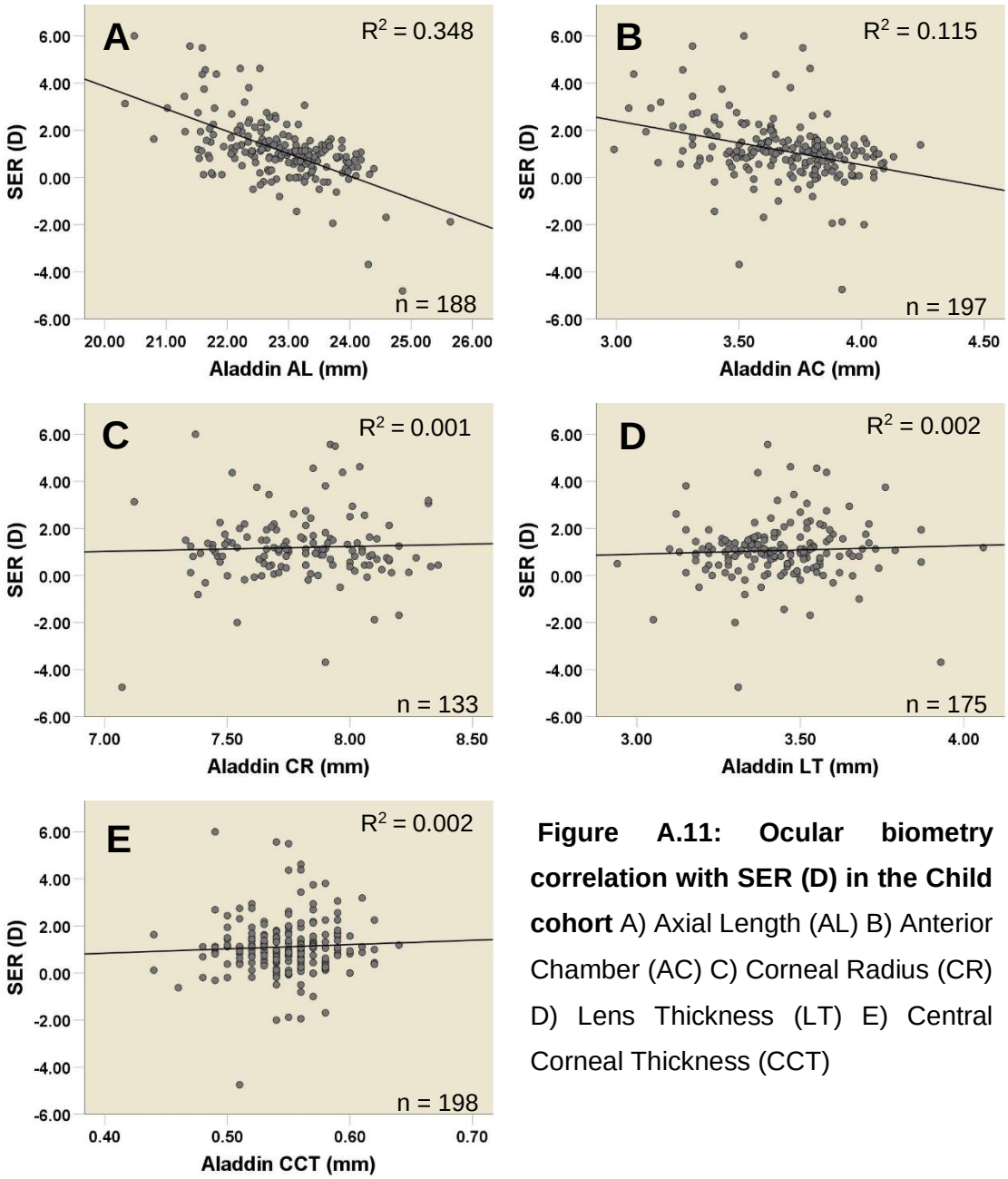


Figure A.11: Ocular biometry correlation with SER (D) in the Child cohort A) Axial Length (AL) B) Anterior Chamber (AC) C) Corneal Radius (CR) D) Lens Thickness (LT) E) Central Corneal Thickness (CCT)

A.5.11.2 Young adult cohort

The correlation of RE ocular biometer parameters and RE SER are shown in Figure A.12.

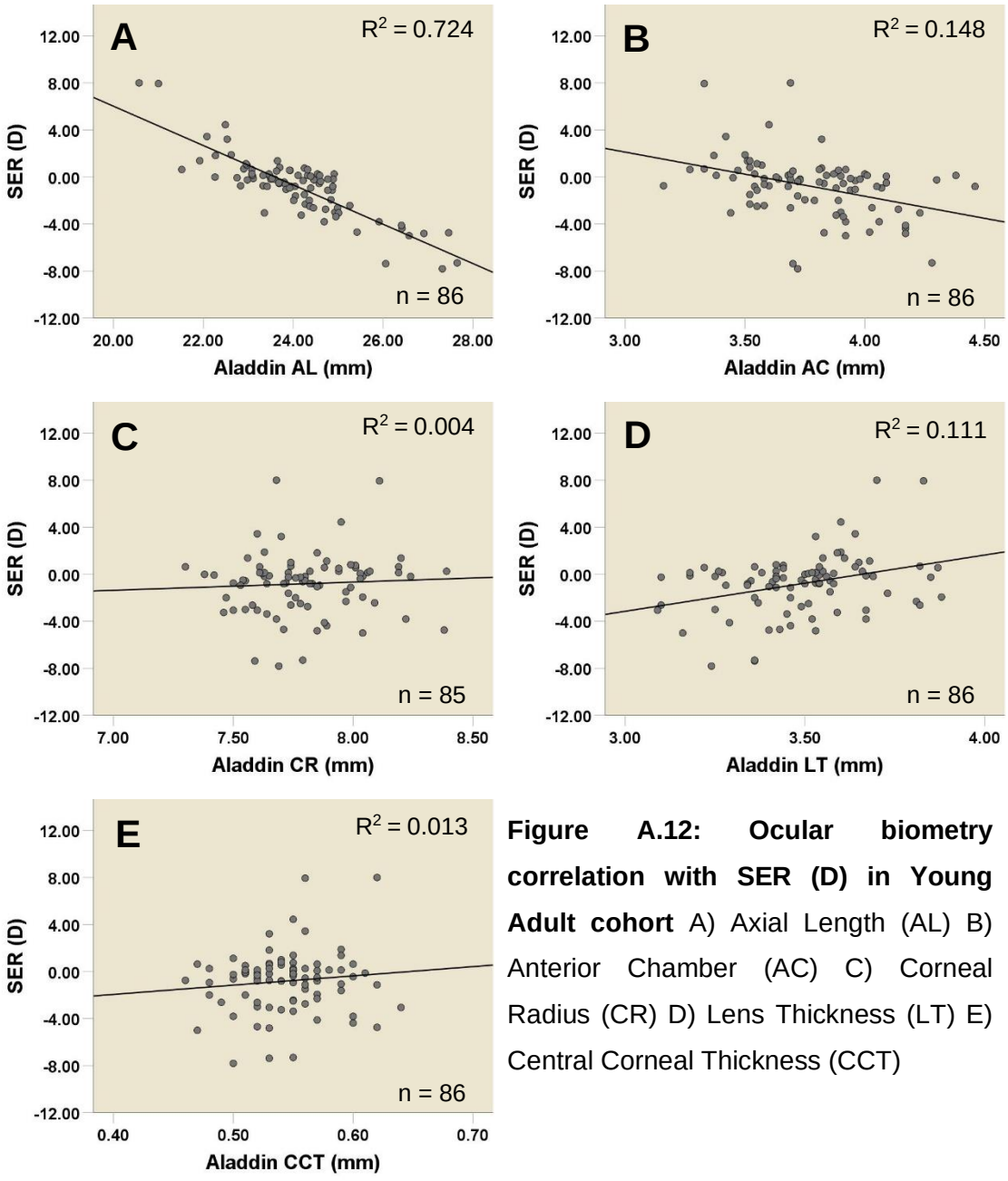


Figure A.12: Ocular biometry correlation with SER (D) in Young Adult cohort A) Axial Length (AL) B) Anterior Chamber (AC) C) Corneal Radius (CR) D) Lens Thickness (LT) E) Central Corneal Thickness (CCT)

A.7.1 Questionnaire response frequencies for time outdoors, near work and VDU use

		Child cohort (n=188)			Young Adult cohort (n=87)		
		Time outdoors	**Near work**	**VDU use**	**Time outdoors**	**Near work**	**VDU use**
Winter – Weekday	None	5	5	7	0	0	0
	< 1 hour	**68**	**88**	57	23	11	0
	1-2 hours	66	62	**65**	**48**	26	7
	2+ hours	48	29	58	16	**50**	**80**
Winter – Weekend	None	2	8	4	1	1	0
	< 1 hour	21	**62**	32	24	19	1
	1-2 hours	56	50	**56**	**40**	17	11
	2+ hours	**69**	28	**56**	22	**50**	**75**
Summer – Weekday	None	0	7	9	0	2	0
	< 1 hour	10	**82**	**67**	5	20	6
	1-2 hours	47	47	51	32	25	14
	2+ hours	**90**	12	21	**50**	**40**	**67**
Summer – Weekend	None	0	11	6	0	3	0
	< 1 hour	0	**75**	56	3	**31**	8
	1-2 hours	27	47	**59**	28	23	16
	2+ hours	**121**	13	24	**56**	30	**63**

Table A.6: Frequencies of questionnaire responses for time outdoors, near work and VDU by day of the week and season for the Child cohort and Young Adult cohort highest frequency for each activity is highlighted in red

Time outdoors	Summer – Weekday			Summer – Weekend			Winter – Weekday			Winter - Weekend		
	n	Mean±SD	p value	n	Mean±SD	p value	n	Mean±SD	p value	n	Mean±SD	p value
None	1	+0.09	0.849	0	NA	0.217	1	+0.05	0.112	2	+0.17±0.01	0.260
<1 hour	3	+0.11±0.07		0	NA		22	+0.12±0.07		5	+0.20±0.15	
1-2 hours	19	+0.15±0.10		10	+0.17±0.09		17	+0.17±0.09		22	+0.13±0.08	
2+ hours	34	+0.15±0.08		39	+0.14±0.08		9	+0.15±0.07		20	+0.14±0.06	

Table A.7: Time spent outdoors and eye growth characteristics (mean±SD) for the Child cohort

Near tasks	Summer – Weekday			Summer – Weekend			Winter – Weekday			Winter - Weekend		
	n	Mean±SD	p value	n	Mean±SD	p value	n	Mean±SD	p value	n	Mean±SD	p value
None	2	+0.16±0.18	0.186	4	+0.16±0.10	0.242	1	+0.17	0.319	2	+0.15±0.04	0.882
<1 hour	31	+0.12±0.07		28	+0.12±0.07		31	+0.13±0.08		25	+0.14±0.09	
1-2 hours	15	+0.16±0.09		10	+0.18±0.10		13	+0.16±0.09		13	+0.14±0.08	
2+ hours	9	+0.18±0.10		6	+0.17±0.08		4	+0.19±0.08		9	+0.16±0.07	

Table A.8: Time spent performing near tasks and eye growth characteristics (mean±SD) for the Child cohort

VDU tasks	Summer – Weekday			Summer – Weekend			Winter – Weekday			Winter - Weekend		
	n	Mean±SD	p value	n	Mean±SD	p value	n	Mean±SD	p value	n	Mean±SD	p value
None	5	+0.16±0.03	p=0.686	4	+0.17±0.01	p=0.786	5	+0.16±0.03	p=0.123	3	+0.17±0.02	p=0.279
<1 hour	24	+0.13±0.07		20	+0.13±0.08		13	+0.10±0.07		7	+0.15±0.05	
1-2 hours	13	+0.15±0.11		15	+0.14±0.10		17	+0.16±0.09		21	+0.12±0.10	
2+ hours	15	+0.16±0.09		9	+0.16±0.08		14	+0.15±0.08		18	+0.16±0.07	

Table A.9: Time spent performing VDU tasks and eye growth characteristics (mean±SD) for the Child cohort

Time outdoors	Summer – Weekday			Summer – Weekend			Winter – Weekday			Winter - Weekend		
	n	Mean±SD	p value	n	Mean±SD	p value	n	Mean±SD	p value	n	Mean±SD	p value
None	0	NA	0.885	0	NA	0.356	0	NA	0.708	1	+0.05	0.126
<1 hour	3	+0.03±0.06		2	-0.01±0.04		16	+0.03±0.08		18	+0.01±0.07	
1-2 hours	23	+0.03±0.07		21	+0.01±0.04		32	+0.02±0.04		26	+0.05±0.07	
2+ hours	33	+0.02±0.06		36	+0.04±0.07		11	+0.04±0.09		14	+0.01±0.04	

Table A.10: Time spent outdoors and eye growth characteristics (mean±SD) for the Young Adult cohort

Near tasks	Summer – Weekday			Summer – Weekend			Winter – Weekday			Winter - Weekend		
	n	Mean±SD	p value	n	Mean±SD	p value	n	Mean±SD	p value	n	Mean±SD	p value
None	2	+0.02±0.01	0.375	3	+0.02±0.02	0.804	0	NA	0.317	0	NA	0.842
<1 hour	14	+0.01±0.05		21	+0.02±0.06		8	+0.03±0.04		14	+0.02±0.05	
1-2 hours	17	+0.02±0.04		14	+0.02±0.04		16	+0.01±0.06		8	+0.03±0.11	
2+ hours	26	+0.04±0.08		21	+0.04±0.08		35	+0.04±0.07		37	+0.03±0.06	

Table A.11: Time spent performing near tasks and eye growth characteristics (mean±SD) for the Young Adult cohort

VDU tasks	Summer – Weekday			Summer – Weekend			Winter – Weekday			Winter - Weekend		
	n	Mean±SD	p value	n	Mean±SD	p value	n	Mean±SD	p value	n	Mean±SD	p value
None	0	NA	0.237	0	NA	0.172	0	NA	0.176	0	NA	0.172
<1 hour	5	+0.04±0.07		1	-0.02		0	NA		1	-0.02	
1-2 hours	11	+0.05±0.08		8	+0.06±0.10		5	+0.06±0.07		8	+0.06±0.10	
2+ hours	43	+0.02±0.06		50	+0.02±0.06		54	+0.02±0.06		50	+0.02±0.06	

Table A.12: Time spent performing VDU tasks and eye growth characteristics (mean±SD) for the Young Adult cohort

A.8.1 Sleep characteristic distributions

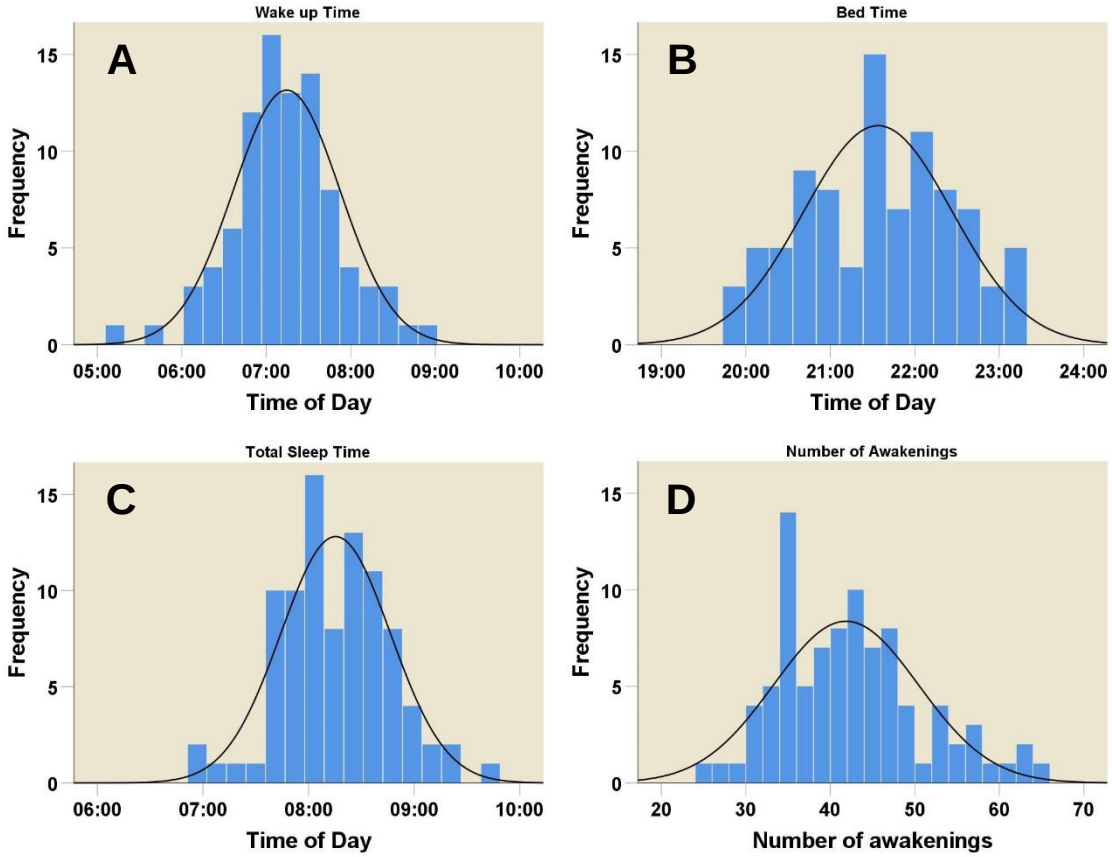


Figure A.13: Sleep characteristic distributions A) Bed time B) Wake up time C) Total Sleep Time D) Number of Awakenings

		Bed time (hr:min)			Wake up time (hr:min)			Total sleep time (hr:min)			Number of awakenings		
	Season	**R^2**	**r**	**p**	**R^2**	**r**	**p**	**R^2**	**r**	**p**	**R^2**	**r**	**p**
Change in SER (B-Y1)	Summer (n=29)	**0.187**	**-0.432**	**0.019***	**0.191**	**-0.436**	**0.018***	0.012	-0.109	0.572	0.124	0.353	0.061
	Winter (n=33)	0.059	0.243	0.173	0.021	0.144	0.425	0.066	-0.257	0.149	0.000	-0.026	0.885
Change in SER (B-Y2)	Summer (n=9)	0.418	-0.646	0.060	0.236	-0.486	0.185	0.427	0.654	0.056	0.310	0.556	0.120
	Winter (n=9)	0.005	0.070	0.858	0.049	-0.221	0.568	0.068	-0.260	0.499	0.043	0.208	0.591
AL	Summer (n=38)	0.011	-0.107	0.524	0.017	-0.132	0.430	0.000	-0.009	0.957	0.000	0.001	0.995
	Winter (n=50)	0.000	-0.007	0.961	**0.087**	**-0.294**	**0.038***	0.062	-0.248	0.082	0.042	-0.206	0.151
Change in AL (B-Y1)	Summer (n=28)	0.037	0.192	0.327	0.127	0.356	0.063	0.015	0.120	0.541	0.008	0.089	0.654
	Winter (n=32)	0.061	-0.247	0.173	0.018	-0.133	0.468	0.015	0.123	0.502	0.023	0.152	0.406
Change in AL (B-Y2)	Summer (n=10)	**0.416**	**0.654**	**0.044***	0.086	0.294	0.410	0.027	0.163	0.652	0.172	-0.415	0.233
	Winter (n=12)	0.065	0.256	0.422	0.013	-0.112	0.728	0.047	-0.216	0.500	0.172	-0.415	0.180

Table A.13: Correlations of sleep characteristics with Change in SER between Baseline and Year 1 (B-Y1) and Baseline and Year 2 (B-Y2), Axial length (AL), Change in AL between Baseline and Year 1 (B-Y1) and Baseline and Year 2 (B-Y2)

A.9.1 Actiwatch information sheet

ACTIWATCH WEARER'S GUIDE

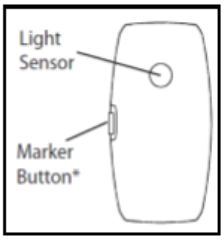
Thank you for participating in this research project. For this part of the project, we are recording children's typical activities (amount of physical activity and how much light you are exposed to) with the use of an A*ctiwatch.* We are asking each participating child to wear an A*ctiwatch* for a continuous 14 day period during the school term. The A*ctiwatch* is small and lightweight and should not interfere with your child's normal activities, so we ask over this time that they continue to carry out all of their regular daily activities.

What is an Actiwatch?
The *Actiwatch* is a small, lightweight device, worn on the wrist that that records motion and light.

Where and how do I wear it?
Your child should wear the A*ctiwatch* snugly and securely on their non-dominant wrist (i.e. on their LEFT wrist if they are RIGHT handed, or on their RIGHT wrist if thet are LEFT handed). Please can they wear the A*ctiwatch* continuously over the next 2 weeks, during day and night and while awake and asleep. **It is important when wearing the A*ctiwatch*, that the face of the watch can be seen and is exposed to light. The A*ctiwatch* should not be covered by long sleeved clothing.**

Is the Actiwatch water resistant?
Yes. However, it is no longer recommended to be worn in the shower, bath or swimming pool so must be removed at these times. Please recommence wear as soon as they are out of the water.

Removal of the Actiwatch?
If for any reason your child does need to remove the watch, upon removal it is important to press the marker button on the side of the watch, so we know that the watch has been removed. We also ask that you fill in the attached diary to document the activities performed when the watch was removed. Please recommence wear of the A*ctiwatch* as soon as you can after any periods of removal.



A.9.2 Seasonal and day of the week hourly light exposure analysis

Time of day	All weekdays vs weekends (n=95)	Summer weekdays vs weekend (n=42)	Winter weekdays vs weekend (n=53)	Summer vs Winter (n=27)
01:00	p=0.923	p=0.178	p=0.123	p=0.284
02:00	p=0.753	p=0.372	p=0.136	p=0.737
03:00	p=0.919	p=0.344	p=0.322	p=0.409
04:00	p=0.509	p=0.248	p=0.090	p=0.411
05:00	p=0.906	p=0.286	p=0.086	**p<0.001**
06:00	**p=0.012**	**p=0.023**	p=0.237	**p<0.001**
07:00	**p<0.001**	**p=0.001**	**p<0.001**	**p<0.001**
08:00	**p<0.001**	**p<0.001**	**p<0.001**	**p<0.001**
09:00	**p=0.024**	p=0.213	**p=0.041**	**p<0.001**
10:00	**p=0.006**	p=0.204	**p=0.001**	**p<0.001**
11:00	p=0.122	p=0.071	p=0.785	**p<0.001**
12:00	**p<0.001**	**p<0.001**	**p<0.001**	**p<0.001**
13:00	**p=0.016**	p=0.896	**p<0.001**	**p<0.001**
14:00	**p=0.007**	p=0.253	**p=0.006**	**p<0.001**
15:00	**p=0.014**	p=0.427	**p=0.001**	**p<0.001**
16:00	p=0.164	p=0.995	**p=0.006**	**p<0.001**
17:00	p=0.311	p=0.945	p=0.113	**p<0.001**
18:00	**p=0.004**	**p=0.029**	p=0.145	**p<0.001**
19:00	p=0.211	p=0.285	p=0.263	**p<0.001**
20:00	p=0.773	p=0.578	p=0.233	**p<0.001**
21:00	p=0.640	p=0.572	p=0.193	p=0.005
22:00	**p=0.028**	p=0.197	p=0.091	p=0.690
23:00	p=0.087	p=0.257	p=0.307	p=0.602
24:00	**p=0.033**	p=0.118	p=0.411	p=0.209

Table A.14: p values for the comparison of day of the week and seasonal differences in hourly light exposure (related samples: Wilcoxon signed rank) Significant p values are highlighted in orange

A.9.3 Seasonal and day of the week hourly outdoor exposure analysis

Time of day	All weekdays vs weekends (n=95)	Summer weekdays vs weekend (n=42)	Winter weekdays vs weekend (n=53)	Summer vs Winter (n=27)
01:00	p=1.000	p=1.000	p=1.000	p=1.000
02:00	p=1.000	p=1.000	p=1.000	p=1.000
03:00	p=1.000	p=1.000	p=1.000	p=1.000
04:00	p=1.000	p=1.000	p=1.000	p=1.000
05:00	p=1.000	p=1.000	p=1.000	p=1.000
06:00	**p=0.017**	**p=0.017**	p=1.000	p=0.109
07:00	**p=0.006**	**p=0.007**	p=0.317	**p<0.001**
08:00	**p<0.001**	**p<0.001**	**p<0.001**	**p<0.001**
09:00	**p=0.031**	p=0.327	**p=0.026**	**p<0.001**
10:00	**p=0.003**	p=0.057	**p=0.013**	**p<0.001**
11:00	**p=0.003**	p=0.058	**p=0.008**	**p<0.001**
12:00	**p<0.001**	**p<0.001**	**p<0.001**	**p<0.001**
13:00	p=0.369	p=0.299	**p<0.001**	**p<0.001**
14:00	p=0.803	p=0.975	p=0.958	**p<0.001**
15:00	p=0.023	p=0.202	**p=0.045**	**p<0.001**
16:00	p=0.249	p=0.323	p=0.327	**p<0.001**
17:00	p=0.754	p=0.791	p=0.878	**p<0.001**
18:00	**p=0.013**	**p=0.014**	p=0.317	**p<0.001**
19:00	p=0.446	p=0.544	p=0.059	**p<0.001**
20:00	p=0.588	p=0.546	p=0.317	**p<0.001**
21:00	p=1.000	p=1.000	p=1.000	p=1.00
22:00	p=0.317	p=0.317	p=1.000	p=0.317
23:00	p=1.000	p=1.000	p=1.000	p=1.000
24:00	p=1.000	p=1.000	p=1.000	p=1.000

Table A.15: p values for the comparison of day of the week and seasonal differences in hourly time spent outdoors (related samples: Wilcoxon signed rank) Significant p values are highlighted in orange

A.9.4 Daily patterns of mean light exposure and time outdoors

	Mean±SD		
	All days	**Weekdays**	**Weekends**
Mean daily light exposure (7am-7pm), lux	361±517	373±488	342±561
Mean maximum daily light exposure, lux	25,973±24,605	27,926±24,444	22,876±24,589
Mean minutes >1000 lux	67±65	71±66	63±79

Table A.16: Mean±SD light exposure measured over the 9-day period of Actiwatch wear for all data sets (Summer and Winter inclusive) (n=95)

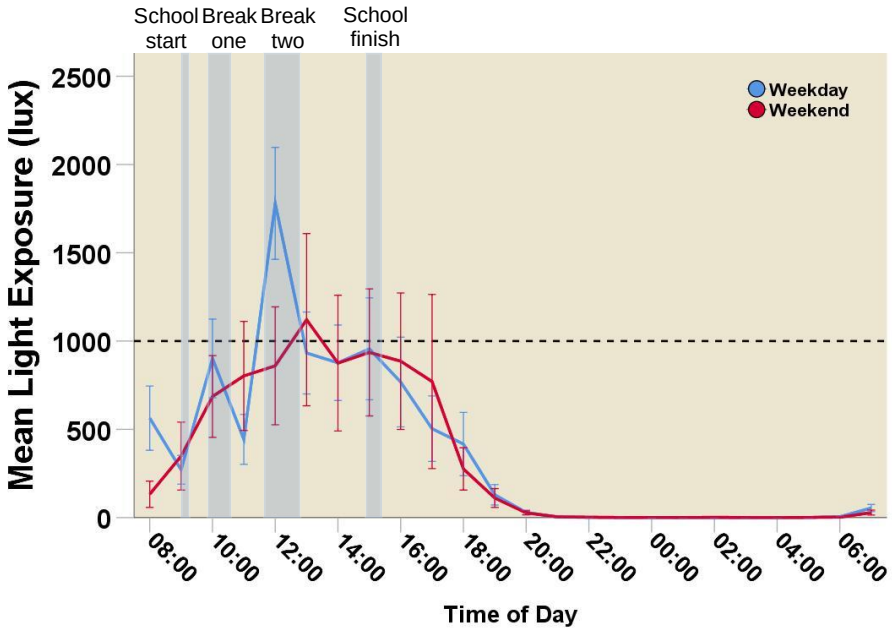


Figure A.14: Mean hourly light exposure (lux) for all 95 data sets for weekdays (blue) and weekends (red) 1000 lux reference line shown with a dotted line. Blue shading indicates school start and finish and break times.

		Summer (n=42)	**Winter (n=53)**
Mean daily light exposure (7am-7pm), lux	**All**	659±570	104±275
	Weekday	674±482	127±330
	Weekend	638±680	64±130
Mean maximum daily light exposure, lux	**All**	41,360±360	12,695±17,666
	Weekday	44,056±20,882	14,760±18,556
	Weekend	37,399±24162	9,194±15,488
Mean minutes >1000 lux	**All**	125±54	21±22
	Weekday	129±56	24±23
	Weekend	121±86	16±25

Table A.17: Mean±SD light exposure measured over the 9-day period of Actiwatch wear for Summer and Winter seasons

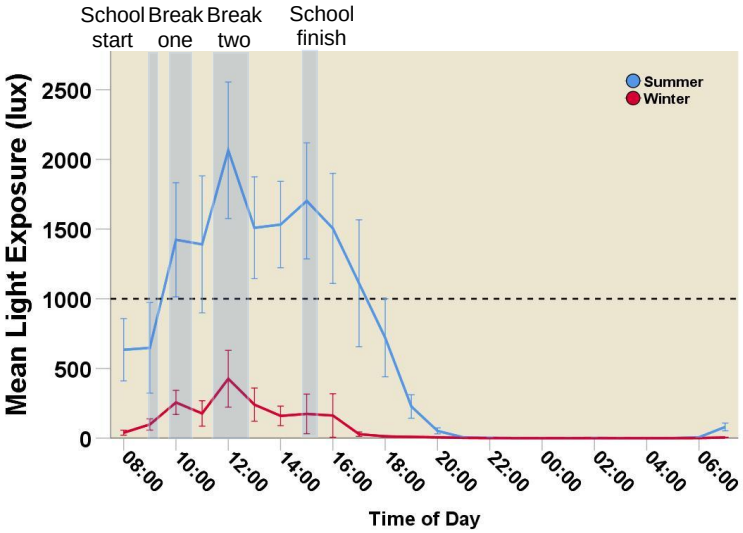


Figure A.15: Mean hourly light exposure (lux) for all 27 participants with both Summer (blue) and Winter (red) data sets 1000 lux reference line shown with a dotted line. Blue shading indicates school start and finish and break times.

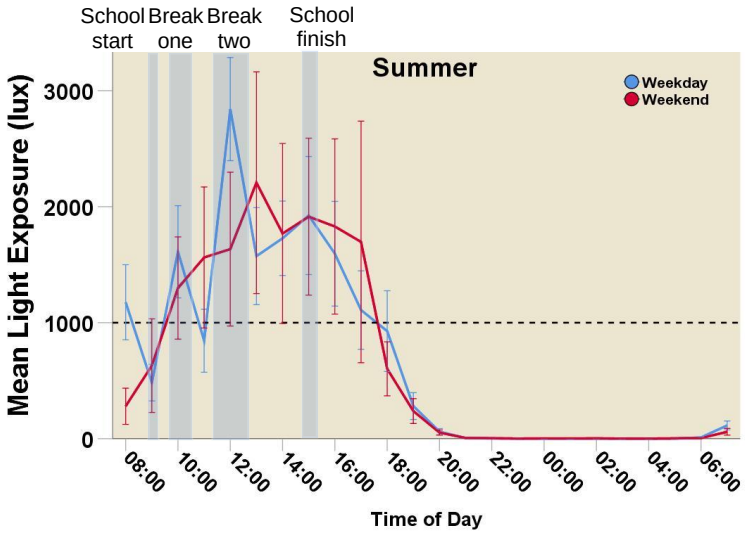


Figure A.16: Mean hourly light exposure (lux) in Summer for weekdays (blue) and weekends (red) (n=42) 1000 lux reference line shown with a dotted line. Blue shading indicates the standard deviation of school hours and break times.

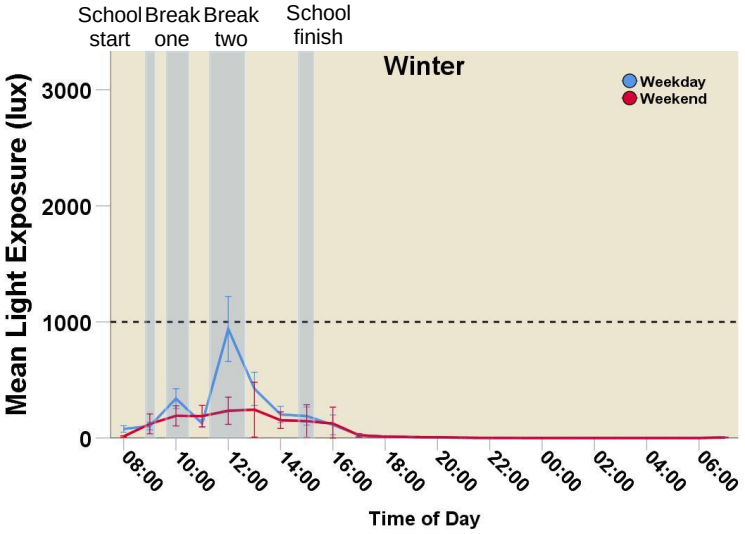


Figure A.17: Mean hourly light exposure (lux) in Winter for weekdays (blue) and weekends (red) (n=53) 1000 lux reference line shown with a dotted line. Blue shading indicates school start and finish and break times.

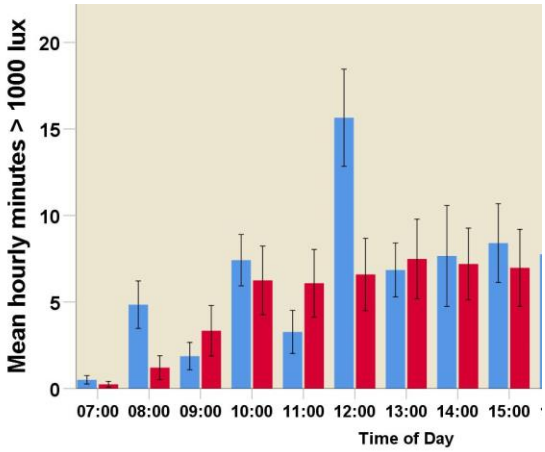


Figure A.18: Mean hourly minutes spent over 1000 lux for all 95 data sets for weekdays (blue) and weekends (red)

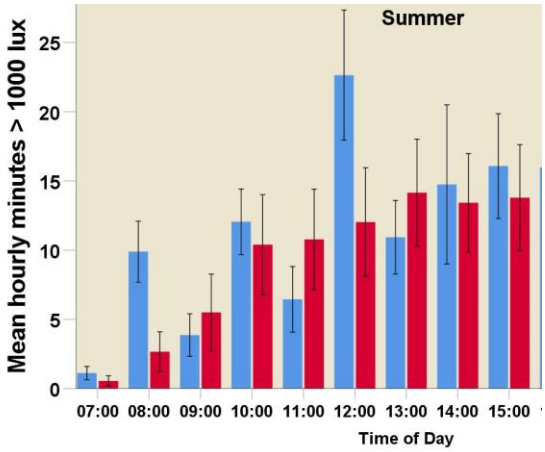


Figure A.19: Mean hourly minutes spent over 1000 lux in Summer for weekdays (blue) and weekends (red) (n=42)

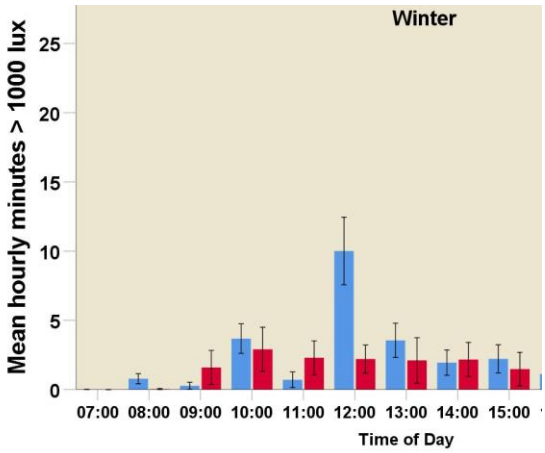


Figure A.20: Mean hourly minutes spent over 1000 lux in Winter for weekdays (blue) and weekends (red) (n=42)

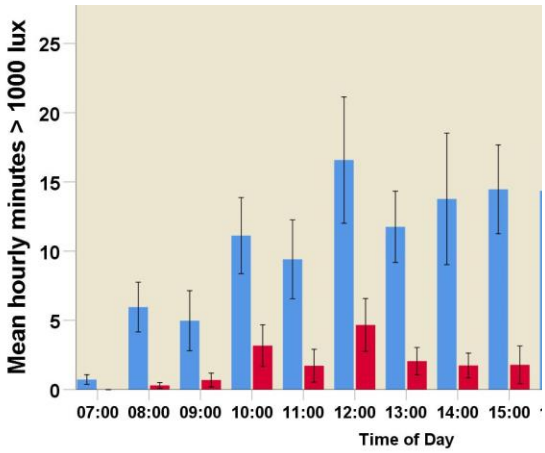
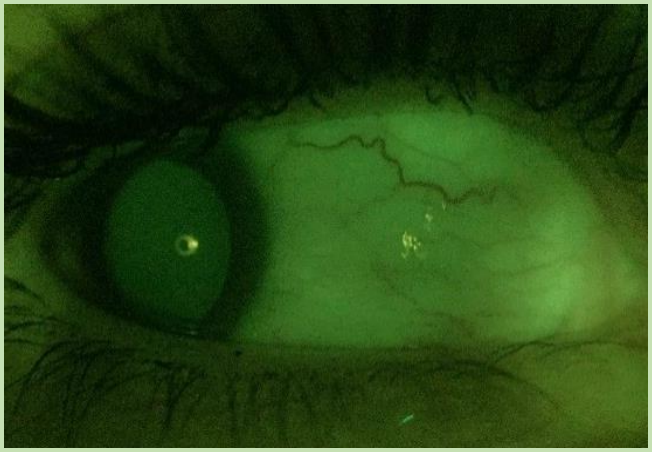


Figure A.21: Mean hourly minutes spent over 1000 lux for all 27 participants with both Summer (blue) and Winter (red) data sets

A.10.1 CUVAF image quality assessment examples

Image Quality Grade	Example Image
Good	
Adequate	
Poor