MYOPIA RESEARCH: IMPROVING THE QUANTIFICATION OF RISK FACTORS

Long Phan
BPharm, MOrth

Primary Supervisor: Prof. Kathryn Rose

Co-supervisor: Dr. Amanda French

Submitted in fulfilment of the requirements for the degree of
Doctor of Philosophy

Discipline of Orthoptics

Graduate School of Health
University of Technology Sydney
2022

Statement of Original Authorship

I, Long Phan, declare that this thesis, is submitted in fulfilment of the requirements for the award of Doctor of Philosophy, in the Graduate School of Health at the University of Technology Sydney.

The work contained in this thesis has not been previously submitted to meet requirements for an award at this or any other higher education institution. To the best of my knowledge and belief, the thesis contains no material previously published or written by another person except where due reference is made.

This research was supported by an Australian Government Research Training Program Scholarship.

Signature: Production Note: Signature removed prior to publication.

Date: 18 JULY 2022

Acknowledgements

Firstly, I am thankful to everyone who has directly or indirectly helped me during the course of this journey.

Most of all, I have sincere gratitude towards my supervisors, Professor Kathryn Rose and Dr Amanda French for providing me with the opportunity to pursue my ambition of making a contribution to the world of science. I am extremely appreciative of all the guidance and support you have provided me throughout these years, which was evident even before undertaking this thesis. I would also like to extend these thanks to Professor Ian Morgan, who has selflessly provided me with copious amounts of knowledge which has been instrumental in allowing me to reach the end of the tunnel.

Thank you to all the staff members within the Discipline of Orthoptics at the University of Technology, Sydney, who have all been welcoming throughout my time on campus. Special thanks to fellow HDR candidates (now Dr's) Mythili and Sahar for being extra kind and friendly, as well as Prem for being my lunch buddy throughout these years.

Thank you to Dr Thomas Hong and all those at Sydney Retina who have provided me opportunity to be involved with the alternate world of clinical research and supporting me professionally throughout this time.

To my mum and dad, thank you for raising me and making sacrifices which have allowed me to become the best that I can be. Finally to my partner Lynn, thank you for always being there for me and for providing endless unconditional support. This would not have been possible without you all.

Table of Contents

Abstract

In recent decades, rapid increases in the prevalence and severity of myopia (short-sightedness) have been documented across the globe. In several populations, this has now reached epidemic proportions, becoming a major concern for eye care professionals. The increasing prevalence of high myopia suggest that there will be an increased risk of sight threatening pathologies that conventional treatment does not prevent. The myopia epidemic and looming rates of associated visual impairment, stimulated further studies of the aetiology of myopia, in order to develop more effective preventive intervention strategies.

This thesis aims to improve study methods in myopia research by identifying accurate and reliable tools for capturing behavioural exposures and by investigating an effective non-invasive means to relate these exposures to refractive changes. Initial direct comparisons of light intensity measures from three previously used portable light data loggers (LDLs) (Actiwatch 2, HOBO Pendant UA-002-64, and Clouclip M2) revealed strong correlations to a standard fixed industrial illuminometer (Yokogawa 51012). However, proportionally biased measurement errors were seen, indicating that light intensity measures with different portable LDL devices were reliable and reproducible, but differed between devices. These differences likely reflect the use of different sensors, and variations in control of measurement direction between different devices. Such errors inevitably lead to inaccuracies in the objective measurement of two key parameters relevant for myopia development: time spent outdoors and the intensity, duration and frequency of outdoor light exposure. Further reductions in reliability and incongruities in light exposure measures seen between LDLs during real-world validation suggested that sensor orientation was a major factor influencing device accuracy. It was concluded that spectacle-mounted LDLs appear to be the most viable option for capture of intraocular light exposures than other device wearing modalities.

In addition, by comparing longitudinal refractive and biometric data from two large population-based studies, an alternative to cycloplegic refraction using an indirect and non-contact method of determining refractive error and myopia risk was identified. In school-children aged 6 and 12 years, changes in the biometric AL/CR variable over 6–7 years were more strongly and linearly related to refractive changes than any single biometric measure. In myopic children, changes in the AL/CR variable over time could predict myopic progression with a reasonable level of accuracy. By considering this relationship, the collection of biometric data can potentially provide insight into the changes occurring in an individual's refractive status at more frequent intervals than typically able to be captured with cycloplegic refraction.

Overall, this thesis provides evidence for the presence of measurement errors occurring at several levels between commonly used portable LDL devices used to objectively capture time outdoors in myopia research. Greater knowledge of the limitations of these devices will enable more accurate capture of data and improve its interpretation. Similarly, greater understanding of the AL/CR value and its relationship to age and refractive errors can be a valuable supplement to standard cycloplegic measures in order to assess short-term refractive changes. Together this allows for more detailed measurements of causal and explanatory variables in myopia epidemiological studies. These findings also indicate a need for future methodological standardisation in myopia research, enabling more effective and reliable studies to further investigate the various relationships between behavioural environmental risk factors and myopia.

Publications and Presentations

Published Peer Reviewed Abstracts:

- **Phan, L.,** French, A. N., Rose, K. A. (2018) Emerging tools in the measurement of time spent outdoors. *Australian Orthoptic Journal*, 50.
- **Phan, L.,** French, A. N., Morgan, I. G., Rose K. A. (2019) Sunlight and myopia, how much is really enough? *Australian Orthoptic Journal*, 51.
- **Phan, L.,** French, A. N., Morgan I. G., Rose K. A. (2021) Biometric risk factors for myopia and the role of the AL/CR ratio. *Australian Orthoptic Journal*, 53.

National & International Scientific Presentations

- **Phan, L** (2018) Emerging tools in the measurement of time spent outdoors. ***75th Orthoptics Australia Annual Scientific Conference***, Adelaide, Australia
- **Phan, L** (2019) Investigating Patterns of Light Exposure in Young Adults. ***17th International Myopia Conference,*** Tokyo, Japan
- **Phan, L** (2019) Sunlight and myopia, how much is really enough? ***76th Orthoptics Australia Annual Scientific Conference***, Sydney, Australia
- **Phan, L** (2021) AL/CR for prediction of myopia and monitoring of management for progression. ***Orthoptics Australia NSW Virtual August Scientific Meeting Paediatric Symposium,*** Sydney, Australia
- **Phan, L** (2022) Ocular biometric changes during childhood refractive development and the role of the axial length to corneal radius ratio in predicting myopia onset. ***77th Orthoptics Australia Annual Scientific Conference***, Brisbane, Australia

Other Authored and Co-authored Published Peer-reviewed Papers

- **Phan, L. T**., Broadhead, G. K., Hong, T. H., & Chang, A. A. (2021). Predictors of Visual Acuity after Treatment of Neovascular Age-Related Macular Degeneration–Current Perspectives. *Clinical Ophthalmology (Auckland, NZ)*, 15, 3351. **(Appendix 1)**
- Spooner, K., **Phan, L**., Cozzi, M., Hong, T., Staurenghi, G., Chu, E., & Chang, A. A. (2021). Comparison between two multimodal imaging platforms: Nidek Mirante and Heidelberg Spectralis. *Graefe's Archive for Clinical and Experimental Ophthalmology*, 1-12. **(Appendix 2)**
- Spooner, K., Fraser-Bell, S., Hong, T., **Phan, L.**, Wong, J. G., & Chang, A. (2021). Long-term Anti–Vascular Endothelial Growth Factor Treatment for Neovascular Age-Related Macular Degeneration: The LATAR Study: Report 1: Ten-Year, Real-World Outcomes. *Ophthalmology Retina*, 5(6), 511-518. **(Appendix 3)**

List of Figures

List of Tables

List of Abbreviations

Abbreviation	Full term
ACD	Anterior chamber depth
AL	Axial length
AL/CR	Axial length to corneal radius ratio
ANOVA	Analysis of variance
CI	Confidence interval
CR	Corneal radius
D	Dioptre
FDM	Form deprivation myopia
GWAS	Genome-wide association study
HR	Hazard ratio
LDL	Light data logger
LIM	Lens-induced myopia
LoA	Limits of agreement
LOESS	Locally estimated scatterplot smoothing
LP	Crystalline lens power
MMD	Myopic macular degeneration
OK	Orthokeratology
OR	Odds ratio
ROC	Receiver operating curve
SAVES	Sydney Adolescent and Vascular Eye Study
SER	Spherical equivalent refraction
SD	Standard deviation
SMS	Sydney Myopia Study
SNP	Single Nucleotide Polymorphism
SPSS	Statistical Package for the Social Sciences
VA	Visual acuity
WHO	World Health Organisation

Chapter 1: Literature Review

1.1 Overview

1.1.1 The rising prevalence of myopia

Myopia has traditionally been thought of as a simple benign optical anomaly, readily corrected with spectacle or contact lenses. However, epidemiologists and eye care professionals now consider myopia to be a major public health issue, due to the occurrence of epidemics of myopia and high myopia in developed countries of East and South East Asia.[1] A meta-analysis has projected these increases through to the year 2050, estimating that up to up to 50% of the world's population will be myopic, alongside rates of high myopia at approximately 10%.[2] Apart from the initial costs and healthcare resources required to provide refractive correction and eye-care services, the main concerns with the rises in myopia relates to the development of pathological myopia, given its association with high myopia,[3] as well as increases in retinal detachment, which occurs at even moderate levels of myopia.[4] These consequences have begun to be evident in areas with high rates of myopia, where complications relating to pathological myopia, such as choroidal neovascularisation, have become the main source of vision impairment and blindness in middle aged adults and older.[5-9] Associated reductions in visual-specific functioning,[10] may lead to substantial financial costs due to lost productivity during peak working life.

1.1.2 Myopia control through modifiable risk factors

Effective myopia control strategies are therefore needed in order to combat the consequences of both myopia and high myopia. These have taken various forms ranging from an array of treatments provided on an individual level to slow myopia progression, up to broad public health reforms conducted at national levels. Research to advance the understanding of the risk factors underlying myopia, has provided the scientific basis to develop several of these interventions. For example, the identification of a new causal modifiable risk factor, namely limited time outdoors, has allowed for public health initiatives to prevent incident myopia in schoolchildren,[11-13] who are most prone to

myopia development. While seemingly effective so far,[12, 13] these initiatives have the potential for further achievements, given that a complete understanding of the role of time outdoors in myopia development and progression has yet to be realised.

1.1.3 Investigating human light exposures to guide myopia control

In recent years, evidence has accumulated from animal experimental studies to support the hypothesis that light-stimulated retinal dopamine release is the mediator behind the protective effects of outdoor time against myopia.[14-16] Although it is unlikely that human light exposures can be strictly modulated in the same fashion as in animal models, the detailed study of human light exposures may provide insights into more effective ways of implementing time outdoors in children exposed to the myopigenic environments created during their schooling years.

Currently, only a few studies have been conducted examining human light exposure in the context of myopia. Effective investigation of human light exposure humans may be hampered by methodological limitations for the capture of light exposure over time and the accurate measurement of refractive errors. As it is not possible to directly measure ocular light exposures in vivo, investigators have employed and developed various wearable light data loggers, which capture light intensity across different areas of the body. In addition to capturing the underlying factor behind myopia protection, the analysis of light exposure provides investigators with an objective way of determining time outdoors. However, due to the heterogeneity among currently used light data loggers, it is not clear whether data obtained in studies using different devices are comparable or reproducible, and limited validation of such devices have been performed.

1.1.4 The importance of cycloplegic refraction and the need for alternative measures

The accurate determination of refractive errors is fundamental to both the investigation and management of myopia, with cycloplegic refraction universally accepted to be the gold standard technique for children and young adults.[17] However, logistical challenges may arise using this

method, as achieving complete cycloplegia is a relatively time consuming and invasive process, particularly in children and on a mass scale. From a public health perspective, dealing with the epidemic of myopia requires school screening to be performed for the systematic correction of myopia and control of its progression as well as the identification of at-risk pre-myopic individuals. At the same time, in myopia research, there is now a need to obtain quite frequent measures of refraction. Evidence suggests that fluctuations in environmental exposures dictate changes in eye growth, as myopia progression slows in winter compared to summer seasons.[18] Whether this is related to seasonal differences in light exposure needs confirmation, which would also provide causal evidence to support the role of time outdoors in myopia progression. However, cycloplegic refractive data has been captured at best, annually in most longitudinal studies, making short term comparisons difficult. While it is possible to perform cycloplegic refractions at shorter intervals, increases in attrition rates may be expected which may diminish the quality of data in larger studies.

As a result, alternative methods to determine refractive error have been employed in population screening and myopia surveillance programs, with most relying on either visual acuity or more recently, non-cycloplegic refractive measurements. However, other indirect methods to determine refraction may be more effective. Due to technological advances over the years, biometric component measures can now be measured efficiently and non-invasively. It has been known for some time that a strong correlation exists between selected optical component measures and cycloplegic refraction, [19-23] as ultimately variations in these components are what underlie refractive errors.

Since light exposure is the mediator behind the protective effects of time outdoors and biometric component measures are the underlying variables determining refractive error, further investigation into the utility of these core measures may optimise the capture of causal and explanatory variables. In a research context, this has the potential to improve data quality, whilst in a clinical context, it would allow for more efficient assessment of risk factors and treatment monitoring.

This chapter reviews the current body of evidence in myopia research, covering the natural history of refractive errors; including biometric changes during refractive development, the epidemiology of myopia and its current management options as well as the current understanding of its aetiology. Finally, this chapter will outline and justify the aims of this thesis in light of these considerations.

1.2 The Anatomy of the Human Eye and its Optical System

The eye is a sensory organ which collects light to be converted into nerve impulses for the brain. This underpins visual perception, but also supports other functions including: adaptation to light levels for scotopic and photopic vision, control of eye movements and control of central circadian functions.

1.2.1 Anatomic structures of the eye

The largely spherical shape of the eye (termed globe) can be divided into three general layers. The outermost layer, known as the fibrous tunic, is comprised of the sclera: an opaque sheet of connective tissue which encapsulates and protects approximately 85% of the globe, as well as the cornea: a transparent structure of highly uniform lamellar fibrils, which lies at the anterior-most portion of the globe. In the middle lies the vascular tunic or uvea, containing three distinct segments of continuous vascular tissue from posterior to anterior, the choroid, ciliary body and iris. The choroid supplies blood to the outer layers of the retina. The ciliary body includes the ciliary muscle, which contracts to control the shape of the crystalline lens via attached connective tissues called zonules; this process, which allows the power of the crystalline to be increased, is termed accommodation. The iris is the most anterior segment of the uvea and acts as an aperture to control pupil size and hence; light entering the eye, through the constriction of two muscle types: sphincter and radial dilator muscle fibres.

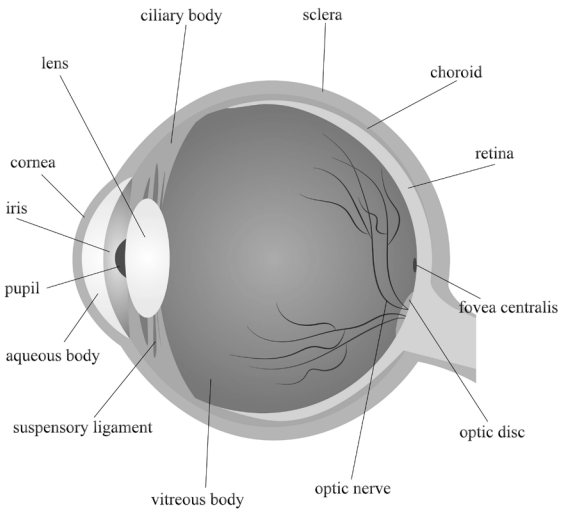


Figure 1.1: Cross-sectional view of the human eye, cut on the transverse plane.

The innermost tunic of the posterior portion of the eye is the retina, the neural area containing a network of cells ordered to form 10 distinct layers, three of which are neuronal. The outermost neuronal layer contains the cell bodies of two types of photoreceptors, rods and cones. These photoreceptors are the cells responsible for the detection of light, in the form of electromagnetic waves, and their transduction into an electrochemical impulse, initiating the cascade of signal transmission along the visual system. The wavelengths of light that these photoreceptors respond to is termed the visible spectrum that lies between 390 and 700 nanometres. While rods and cones have similar structure and function, each responds to different forms of light, with rods being more sensitive to low intensity light providing night vision, and cones being more sensitive to bright light; with three sub-types containing pigment sensitive to different wavelengths of light, providing the basis for colour vision during the day. The distribution of rods and cones in the retina varies, with the highest density of cone cells found in the central region of the posterior retina. This area is called the macula and is responsible for sharp central vision.

Following transduction of light at the photoreceptor layer a chain of events occur, involving propagation of electric signals regulating the release of transmitters at synapses. This electro-chemical signal is transmitted forwards towards the inner retina to bipolar cells that modulate the

signal along with input from horizontal cells. The bipolar cells then transmit the visual signal into the innermost neural layer of the retina either directly or indirectly (via amacrine cells which further modulate the signal) to retinal ganglionic cells which collectively receive input from multiple bipolar cell groups and amacrine cells and process their signals based upon intensity form, orientation and color. Axons of retinal ganglion cells then exit the globe via the optic nerve head into the optic nerve. Ordered signals are then projected to corresponding areas of the brain, predominantly the visual cortex via the visual pathway.

The eye contains two major compartments, the anterior and posterior vitreous chamber, separated by the internal crystalline lens. The vitreous chamber houses the vitreous humour, a clear gel-like substance responsible for maintaining the pressure and shape of the globe. The anterior chamber is filled with aqueous humour, a transparent watery fluid produced by epithelial cells of the ciliary body. Aqueous humour is also responsible for maintaining intraocular pressure of the globe as well as providing nutrition to local areas such as the posterior cornea and anterior lens.

1.2.2 Optical system of the eye

Light entering the eye passes through a number of structures before reaching the retina. The structures that manipulate and control the passage of light within the eye are the optical components of the eye. Firstly, light enters the eye through the transparent window of the cornea, where the majority of refraction occurs based upon two properties of Snell's law: the difference in refractive index between the air and corneal interface, as well as the curvature of the anterior corneal surface. There is slight refraction as the light leaves the posterior corneal surface and enters into the anterior chamber. Further refraction occurs as the light passes through the biconvex crystalline lens and exits into the vitreous cavity. The anterior surface of the cornea and the curvature of the crystalline lens have the largest influence on the refractive power of the eye. A smaller radius of curvature at the anterior corneal interface indicates a steeper curve and thus a

stronger refractive power, whilst a larger corneal radius indicates a flatter corneal surface and a consequent weaker refractive power.

The optical power of the eye is quantified in dioptres (D), a unit equal to the reciprocal of the focal length of the combined optical structures, that is the distance to the location where the light rays entering the come to a focal point following refraction. The average power of the human cornea and lens is 44 D and 20 D respectively, making the total optical power of an average eye to be approximately 64 D. When the focal point of the eye falls onto the plane of the foveal pit (in the absence of external optical modification and/or additional optical power provided by the accommodative reflex), maximum image sharpness is achieved and this optical refractive state is referred to as emmetropia; though the term is usually reserved for when this occurs. Therefore, along with corneal and lens power, the axial length of the eye (distance from corneal apex to the foveal pit) must be considered and a perfect balance between these three components is required for clarity of vision.

1.2.2.1 The accommodation reflex

The accommodation reflex of the eye is its ability to increase its optical power in response to viewing near objects. Light rays from distant objects are essentially parallel but become increasingly divergent as objects are brought closer to the eye. This means that for an emmetropic eye at rest (no accommodation), light rays from a nearby object will be focussed (virtually) at a point behind the retina, creating relative hyperopia. This stimulates a reflex where contraction of the ciliary body muscle and relaxing of the tension applied by the zonules results in increased curvature and hence the optical power of the crystalline lens brings the focal point forward to the plane of the retina.

1.3 Refractive Errors

1.3.1 Types of refractive error

Refractive errors (ametropias) occur when light focusses at a point along the visual axis other than the retina, due to a mismatch between the optical power of the eye and its axial length. Different forms of refractive errors are defined based upon on the location of the focal point of the eye and where it is located along the visual axis in relation to the position of the retina. These include: hyperopia, myopia and astigmatism.

Hyperopia, or long-sightedness, occurs when the focal point from parallel rays of light fall beyond the outer segments of the photo-receptors at the fovea. This suggests that the optical components of the eye are not powerful enough to converge and focus light onto the retina. This may be corrected with the use of convex lenses to help converge light rays. Alternatively, if there is adequate accommodative ability of the lens, the accommodation system can be evoked to provide additional optical power and symptomatic relief. With age, there is a progressive loss of accommodative ability, termed presbyopia. This causes relative hyperopia when focussing on near objects and is accompanied by both lenticular and extra-lenticular physiological changes including sclerosis of the crystalline lens nucleus, as well as decreased elasticity of the lens capsule and zonules.

Conversely, myopia, or near-sightedness, occurs when the focal point from parallel rays of light falls in front of the fovea. This suggests that the axial length of the eye is too long relative to the focal point produced by the optical power of the eye. Myopia causes blurry vision when viewing objects at a distance, and can be compensated by using concave lenses or by bringing target objects closer to increase the angle of diverging light. Unlike, hyperopia, the visual effects of myopia are more apparent and predictable, as there is no internal mechanism like accommodation able to reduce optical power within the eye.

Whilst both myopia, hyperopia and presbyopia are spherical refractive errors, astigmatism is a cylindrical refractive error caused by a mismatch of the focal point along an axis, creating two meridians of different optical power. There are two types of astigmatism, the first being regular astigmatism, where the two principal meridians lie perpendicularly to each other and have uniform power centred on the cornea. When the plane of steepness is in line with the vertical meridian 90° (± 22.5), it is termed with-the-rule astigmatism, whereas against-the-rule astigmatism indicates that the horizontal meridian of 180˚ (± 22.5) is steeper. If the angle of steepness lies outside either vertical or horizontal bounds then it is termed an oblique astigmatism. Regular astigmatism is the more common form of astigmatism, with with-the-rule astigmatism found more commonly in young children, whilst against-the-rule astigmatism more commonly appears in the older children and adults. Irregular astigmatism, occurs when the two principal meridians of optical power do not lie perpendicularly to each other and there is non-uniform power along each axis. This less common form of astigmatism is primarily associated with corneal structural pathologies such as keratoconus. Astigmatism is predominantly corneal in origin, especially for childhood astigmatism, however there can be some internal sources such as from the crystalline lens or at a retinal level.

1.3.2 Measurement of refractive error

1.3.2.1 Direct measures of refraction and the necessity of cycloplegia

There are several methods to identify and quantify the presence of refractive errors. A subjective refraction is a procedure where combinations of incremental lens power are presented to the patient in order to eliminate blur and achieve the best-corrected visual acuity as perceived by the individual. Other methods of obtaining refractive error measurements are autorefraction; an objective method where a computer refines the focus of an infrared light reflected from the retina using magnification; and retinoscopy, where the movement of a streak of light on the retina is manually neutralised by an examiner using lenses.

Subjective refraction is the gold standard in clinical practice, as the improvement of VA is most often the purpose for determining refractive state. However in epidemiology, where researchers are usually more concerned with the true optical state of the eye, it is generally preferred to use objective measures of refraction. When determining refraction in epidemiology, a key consideration is to eliminate the influence of accommodation, as both objective and subjective measures may be compromised by induced accommodation. This unwanted effect of accommodation has the potential to cause myopic shifts in the measured refraction, resulting in the overestimation of myopia and an underestimation of hyperopia in population studies.[24-26] This can be overcome by using a cycloplegic agent to paralyse the ciliary muscle and hence accommodation. There are other techniques used in both retinoscopy and autorefraction to reduce accommodation, such as fogging the target fixation image, however, residual effect of accommodation in refraction still remain.[27-29] While cycloplegic refraction has been universally agreed to be the best practice in childhood cohorts, there is some belief that cycloplegia may not be necessary in older subjects due to declines in accommodative ability with age. However, significant overestimations of myopia and underestimations of hyperopia with non-cycloplegic methods of refraction have been seen, in young adults,[30, 31] and those up to 50-60 years old.[32, 33] Additionally, studies have measured clinically significant levels of accommodative amplitudes into adulthood.[34-37] These combined findings indicate that cycloplegic refraction remains crucial in the measurement of refraction for epidemiological studies.[17]

There are a number of agents available for cycloplegia. Atropine (1%) was traditionally regarded as the gold standard agent of choice for achieving complete cycloplegia, particularly in children. However it has not been used routinely in clinical practice, and even less so in epidemiology, due to its intrusive regime, which requires at least four instillations one day prior to refraction,[38] and its duration of effect (lasting several days) as well as its rather toxic systemic side effects, such as fever, neurological effects and tachycardia. Therefore, investigators have turned to other short-acting drugs in the form of cyclopentolate and tropicamide, which can produce cycloplegia in as little as

20–25 minutes. While the two can be used in combination, there is a general consensus that cyclopentolate is the superior choice for paralysing accommodation when considered individually. A study using pooled results confirmed these standings when examining different measurement techniques, across age groups, with higher and statistically significant dioptric changes in pre-and post-cycloplegic refraction found using cyclopentolate over tropicamide: in retinoscopy versus autorefraction, in children versus adults and in hyperopic and mixed refractions, versus myopic refractive errors.[39]

With regard to number of instillations, the guidelines are not as clear, with as little as 1 drop of 1% cyclopentolate may be sufficient in children and young adults.[40] However to err on the side of caution, the majority of investigators favour a two or three drop regimen which involves a waiting interval of at least 5 minutes between installations. In individuals with darker iris colours, cycloplegia is more difficult to achieve due to increased binding of the drug by pigment cells in the eye causing a delay in onset and reduced magnitude of paralysis.[41] In these cases, further instillations (up to five), or the combination of both cyclopentolate and tropicamide may be required to ensure complete cycloplegia.[42, 43] Further variations may arise from tearing and blinking, thus it is often desirable in epidemiological studies to confirm whether adequate cycloplegia has occurred. This can be done by monitoring for the absence of a pupillary light reflex and ensuring a minimum dilated pupil size has been achieved.

1.3.2.2 Other means to detecting refractive errors

1.3.2.2.1 Visual acuity as a determinant of refractive error

VA can be used to indirectly determine refractive status as reduced vision is the most common clinical manifestation of refractive errors. This is useful in a clinical sense, since screening programmes are mostly concerned with identifying correctable vision impairment. However, this method may not be sufficiently accurate from an epidemiological point of view, when the purpose of identifying refractive errors is to capture the imbalance between axial length and optical power,

describe prevalence and perform risk factor analysis. VA has been used to indirectly determine population prevalence's of myopia in several countries such as Singapore[44], Taiwan[12] and China,[45] though there has been a recent preference for using non-cycloplegic refractions.

Leone et al[46] found that VA was a strong predictor of myopia in schoolchildren, with a cut-off of 6/9.5 detecting myopia of -1.00 D or more with a sensitivity of 97.8% and a specificity of 97.1%. On the other hand, there was less reliability in detecting hyperopia with VA, with a sensitivity of 69.2% and specificity of 58.1%%. Similar findings have been reproduced by O'Donoghue et al,[47] using data from the Northern Ireland Childhood Errors of Refraction (NICER) study. Meanwhile for the detection of astigmatism, this relationship is more complex as its effect on VA is dependent on the presence co-existing spherical refractive errors. Leone et al[46] found that pure astigmatism significantly affected VA in a stepwise manner with increasing cylinder power. However, for those with hyperopia, only high levels of astigmatism (-1.50 DC or less) had impacts on VA. Meanwhile for myopia, co-existing astigmatism did not appear to have any independent impacts on VA. No similar studies have been performed in older adults. However, it can be presumed that VA remains reliable in the absence of ocular pathology, as adults of presbyopic age are less able to use accommodative reserves to overcome manifest hyperopia.

1.3.2.2.2 Correlation of ocular biometric measures and refraction

Refractive errors may also be determined by considering measures of an individual's ocular biometrics. This approach is also intuitive, as refractive errors fundamentally arise from an imbalance between the axial length (AL) of the eye relative to its optical power (generated by both the surfaces of the cornea and crystalline lens, and the refractive indices of all the internal ocular media). Assuming that there is little inter-individual variation in refractive index (except for pathologically induced refractive errors), its role can be excluded, and thus variations in refraction can be attributed to inter-individual differences in biometric measures. For the case of myopia, this can either mean that the AL of the eye may be too long in relation to its optical power (axial

myopia), or that the curvature of either cornea or crystalline lens may be too steep (e.g keratoconus), whereas for cases of hyperopia, the opposites would be true.

Studies comparing the correlation between biometric measures of individual ocular components and refraction, find that AL has the strongest correlation with spherical equivalent refraction.[20, 21] While this suggests that refractive errors are primarily axially driven, in reality some myopes have relatively short eyes, some hyperopes have relatively long eyes, and those with emmetropia are seen to have a relatively broad range of axial lengths. A classic example of this relationship occurs between genders, as men generally exhibit longer AL than females, yet are not significantly more myopic.

The axial length to corneal radius ratio (AL/CR) is a proposed unit which partially accounts for these differences. Grosvenor and Scott first investigated the AL/CR variable and found that 84% of the variance in SER was determined by differences in AL/CR.[48] Furthermore, unlike measures of individual ocular components which are normally distributed, ALCR has a leptokurtic distribution curve similar to that of SER, suggesting it may be more closely related to overall refraction. This has been confirmed by several studies which find stronger correlations between AL/CR and SER compared to AL alone.[19-23] If this relationship is linear, an individual's refraction; either the purely spherical component or spherical equivalent refraction (SER); could therefore be indirectly determined from their AL/CR value by applying a simple scaling factor obtained from linear regression analysis. However, differences in levels of correlation between AL/CR and SER have been seen between refractive categories, age groups and ethnicity (Table 1). As the dynamics of these variables have not yet been investigated thoroughly to provide a model to accurately determine refraction, AL/CR has not been used to determine refraction in clinical or epidemiological settings.

The largest variation in the relationship between AL/CR and SER is seen across the spectrum of refractive errors. While this relationship has been commonly illustrated to be linear within the literature, further inspection suggests it may not be strictly linear, given that AL/CR seems to underestimate SER at both higher levels of hyperopia and myopia.[23, 49, 50] Further indication comes

from the comparison of correlation and gradient coefficients obtained from AL/CR vs SER plots between refractive error categories, with both higher correlation and gradient coefficients seen in higher myopes compared to low myopes, and in low myopes compared to emmetropes.[22, 23, 48, 50-52] Though one study reports a stronger correlation coefficient in emmetropes compared to myopes/hyperopes,[49] these differences suggest that the accuracy of determining SER from AL/CR may be influenced by the refractive state of the individual.

It also appears that variations in the relationship between AL/CR and refraction occurs with age, as studies in adults and relatively older children generally report stronger correlation co-efficients than those in younger children.[23, 52, 53] While this may result from confounding effects with age-related increases in myopia, Further age-related effects are seen in studies which find increases in mean levels of AL/CR with age, independent to changes in refraction.[50, 54] Another factor may be that the AL/CR variable does not take into account involvement of the crystalline lens. Changes in lens power occurs with age, [55] however no studies have investigated its role in determining the relationship between AL/CR and refraction.

Similar variations appear with ethnicity, as Garner et al reported that AL correlated more strongly with refraction in Malay children compared to Melanesian children.[56] Similarly, Ip et al found that East Asian children had a stronger correlation between AL/CR and SER compared to European children.[57] However, these apparent differences may be confounded by population differences in biometric component measures and increased levels of myopia, as correlations inherently appear stronger across a broader range of axial lengths.

Table 1.1: Studies investigating the relationship between AL/CR and refractive error.

Paper	n	Age (years)	Ethnicity	Mean ALCR	Regression coefficient (β)	Correlation coefficient (r)	Determination coefficient (r^2)
Foo et al 2016[22]	349	3	South East Asian	2.81*	-7.4	-0.53	0.33
Guo et al 2017[54]	1127	5 (3-6)	East Asian	2.88	-0.67	-0.63	0.40
Ojaimi et al 2005[21]	1765	6.7	Mixed	2.906	n/a	-0.66	0.43
He et al 2015[23]	3922	6-12	East Asian	2.973	-10.66	-0.81	0.66
Tao et al 2020[52]	1697	6-14	East Asian	**G1:** 2.95 **G3:** 3.02 **G5:** 3.08 **G7:** 3.14	**NM:** -0.28 to -1.80 **LM:** -3.40 to -6.20 **HM:** -3.37 to -11.34	-0.82	0.68
Scheiman et al 2016[53] **(baseline)**	462	9.3	Mixed	3.15	n/a	-0.55	0.30
Kimura et al 2007[58]	95	10.8 (7-13)	East Asian	3.27	-25	-0.76	0.58
Ip et al 2007[57]	2353	12.7	Mixed	3.01	-15.5	-0.81	0.64
Jong et al 2018[50]	**LM:** 732 **HM:** 308	**LM:** 10.1 **HM:** 12.8	East Asian	**LM:** 3.2 **HM:** 3.6	**LM:** -6.7 **HM:** -12.2	**LM:** -0.64 **HM:** -0.65	**LM:** 0.41 **HM:** 0.42
Grosvenor & Scott 1994[48]	194	18-30	White	n/a	-18.35	-0.92	0.84
Karunakar et al 2016[59]	296	20-30	Indian	2.98	-13.67	-0.93	0.87
Elmadina 2019[60]	200	16-35	African	3.14**	-11.9	-0.76	0.58
Yebra-Pimentel et al 2004[51]	192	22	Hispanic	n/a**	-13.36	-0.80	0.64
Scheiman et al 2016[53] **(follow-up)**	362	24.1	Mixed	3.31	n/a	-0.79	0.62
Iyamu et al 2011[19]	70	27.9	African	3.03**	-17.24	-0.78	0.61
Badmus et al 2017[61]	350	18-60	African	3.04	-8.89	-0.31	0.51
Hashemi et al 2013[49]	5190	40-64	Middle Eastern	3.034	-12.1	-0.78	0.61

*Median, **Non-cycloplegic refraction, **G(1-7):** Grades 1-7, **NM:** no myopia, **LM:** low myopia, **HM:** high myopia

β signifies the amount of change in SER lead for a 1 unit change in AL/CR

r is a measure of the strength of the linear relationship between AL/CR and SER

r^2 is the proportion of the variance in SER that is predictable from AL/CR

1.3.3 Classification of refractive errors

Refractive errors are quantified on a continuous scale using the dioptre (D) unit. With zero as the reference point for emmetropia, negative dioptre values are representative of myopia and positive values for hyperopia. However, refractive errors need to be been categorically defined for the purposes of clinical diagnosis and epidemiological investigation. This raises a number of issues, as there have been variations in the thresholds for each refractive category. In particular, for epidemiology, selecting appropriate definitions is crucial, as it has the potential to drastically affect observed prevalence and incidence rates. For example, using lower cut-offs for myopia can dramatically overestimate prevalence in countries with high rates of myopia.[62] Two common methods of selecting cut-offs exist. The approach commonly used in epidemiology is to allow for measurement error and variation between examiners and on repeated occasions. Under this paradigm, a cut-off of ±0.50 D for both hyperopia and myopia is most commonly used. Evidence has shown that there is a 95% agreement between repeated measures using both autorefraction and conventional subjective refraction within this threshold.[63] The second approach is based on clinical outcomes. Under this paradigm, refractive errors are defined when functional vision loss begins to occur and optical correction is required to maintain visual function. This definition however, causes the cut-off points to vary between the classes of refractive error as well as across age groups depending on what is considered “normal” or the ideal state of refraction.

In clinical practice, despite being a continuous variable, refractive errors are typically captured in 0.25 D increments based upon the traditional power increments of loose lenses available for subjective refraction and for the prescription of spectacles. Meanwhile in epidemiology, refractive errors are often reported as SER, unlike in clinical practice where spherical and astigmatic errors are addressed separately. This transformation into SER takes the sum of the base spherical power and half of the astigmatic power and results in a power representative of the meridional balance of an astigmatic eye, placing the circle of least confusion onto the retinal plane. An alternative method is

to convert the clinical notation of refraction into a power vector format. This allows a Fourier analysis of refraction as the power of these three component lenses may be interpreted as (x,y,z) coordinates of a vector representation of the power profile. This provides a way to express sphere, cylinder and axis statistically, in contrast to "spherical equivalent". Though more statistically meaningful, this method has not been used as commonly as the spherical equivalent notation.

1.3.3.1 Myopia

The clinical definition of myopia remains close to what is commonly used in epidemiological studies at ≤ -0.50 D. However, as there is no standardised threshold, some studies have also used higher cut-off points such as -0.75 D and -1.00 D whilst fewer have used thresholds of -0.25 D. Further variations have occurred between the uses of < or ≤. Under the umbrella term of myopia, numerous subcategories have been defined based upon its heterogenic manifestations with a variety of different terminologies. These terms have predominantly revolved around certain features of myopia involving aetiology, age of onset, degree of myopia and associated anatomical complications.

The most common sub-classification that has been to define myopia is based upon its severity. Within this classification, the term 'high myopia' is used to indicate a state when individuals have an increased risk of irreversible vision loss and associated ocular complications.[64] In epidemiology, the most common cut-offs for high myopia has been at ≤ -6.00 D and < -6.00 D, however thresholds of < -5.00 D and ≤ -5.00 D have also been used. In rarer instances, high cut-offs at -8.00 D, -10.00 D and -12.00 D have been used, as well as an axial length definition of > 26 mm. Much like the threshold for general myopia, there is no agreed standard established for the limit of high myopia however; there have been some proposed guidelines by large international groups. In 2015, after a global scientific meeting on myopia, the World Health Organisation (WHO) released a report suggesting that the cut-off for high myopia should be defined as ≤ -5.00 D. This was based upon a clinical approach that -5.00 D of myopia produces a visual impairment worse than the threshold of < 3/60 for legal

blindness. Later in 2019, the International Myopia Institute, released a white paper detailing a standardised set terminologies, definitions and thresholds for myopia and its associated complications.[65] Its contributors acknowledged the previous definition for high myopia, however recognised that in the context of epidemiological studies, the ≤ -6.00 D threshold should remain for consistency. More importantly, a defining feature of this white paper was that the concept of pre-myopia was introduced, considered to be SER of between < -0.50 D to ≤ +0.75 D.[65] Current classification systems would consider individuals within this category to be emmetropic, however this term implies that zero dioptres is the ideal state of refraction. In the real world, a perfect optical state of exactly zero diopters is rarely achieved in the population as the endpoint of natural refractive development tends to leave children in a state of mild hyperopia.[66] As evidence suggests that biometric changes towards myopia occur prior to the emergence of myopia using classic definitions,[67-70] the pre-myopia category has strong clinical relevance in determining at-risk individuals particularly when preventative interventions are being considered.

When discussing high myopia, the terms pathologic and degenerative myopia have been commonly brought into association. These terms refer to a state of myopia where structural complications exist due to excessive axial elongation of the eye. But while there is a considerably higher risk of irreversible vision loss and related ocular pathologies at higher levels of myopia,[71] high myopia should not be confused with and used interchangeably with pathological myopia, as myopic maculopathy is not always present at high degrees of myopia.[72]

Other commonly used terms are school myopia or juvenile-onset, which refer to myopia that appears during childhood around late-primary or early secondary school years. This is the most common form of myopia seen, which is characterised by continued gradual progression of myopia into early adulthood. Another common term used is familial myopia, which is associated with a clear inheritance pattern and is characterised by an earlier onset and relatively faster progression rate than classic school myopia.

1.3.3.2 Hyperopia

Similar to myopia, thresholds for hyperopia are not universally defined. Whilst the statistical threshold of +0.50 D may be an accurate limit to identify optical hyperopia, there is little associated clinical significance, as it is known that hyperopia correlates less strongly with VA; due to the ability to accommodate. Additionally, due to natural growth of the eyes from birth, a small level of hyperopia has been considered normal at younger age groups. For school-children, ≥ +2.00 D is generally considered to the threshold for clinically significant hyperopia. This has also been commonly used within epidemiological studies, however alternative definitions between +0.50 D and +1.50 D have also been used. For adult populations, there is a bit more consistency as the majority of studies use a threshold of ≥ +0.50 D for hyperopia. Considerable variations also exist for the definition of high hyperopia; which sometimes is associated with levels considered to be amblyogenic; with studies using thresholds between +3.50 to +6.00 D. Unlike for myopia, consensus definitions for the limits of high hyperopia have not been proposed.

1.3.4 Summary

The methodology used to measure and classify refractive errors must be carefully selected with respect to the purpose of investigation, as there are several factors which can influence its accuracy and reliability. These factors also need to be considered when interpreting studies of refraction and in particular, the exploration of associated risk factors.

In clinical settings, subjective refraction is the gold standard as it provides the best visual outcomes for refractive correction for the individual. In epidemiology, as investigators are primarily concerned with the optical and biometric state of the eye, objective methods such as autorefraction are required. In order to accurately capture these, the accommodation reflex needs to be eliminated via cycloplegic eye drops, preferably with cyclopentolate 1%, or 0.5% in children under one year. Tropicamide 1% can also be used but is not as effective as cyclopentolate, particularly in younger children.[39] With regards to the number of instillations to achieve cycloplegia, this must be

considered on a case-by-case basis. A minimum of two to three drops, administered in five minute intervals is generally required. Younger individuals and those with more pigmented irises commonly requiring more instillations (up to five). Confirmation that an adequate level of cycloplegia has occurred, by examining the pupillary light reflex and measurement of pupil size at least 30 minutes after initial instillation, is critical in minimising measurement errors. While this can be considered to be the ideal practice methods, this protocol has not been universally followed. Inadequate or non-existent cycloplegic methods gives rise to pseudo-myopia, which in prevalence studies will overestimate the prevalence of myopia and underestimate the prevalence of hyperopia, [30-33] particularly individuals with low myopia and low hyperopia respectively.

Apart from a direct measurement, refractive status can be determined using indirect measures. Visual acuity can reliably detect myopia, but not so much hyperopia or coexisting astigmatism.[73] There will be a tendency for false positives due to the capture of pathological visual impairment, which will overestimate prevalence rates, however this may not be a concern in the context of a screening program. It is also possible that substantial hyperopic refractive errors may be missed, due to the capacity of children in particular to exert a high level of accommodation for the duration of the test in order to obtain clear vision. Alternatively, there is some evidence to suggest that measurements of ocular biometric components, in particular the AL/CR variable, could serve as a more reliable determinant of refraction in the absence of cycloplegia, given its strong association with, and underlying role in determining refractive errors. This has potential to supplement cycloplegic refractive measurements in large longitudinal studies where repeated measures of refraction are required, however its utility has not been explored thoroughly so far.

Alongside measurement considerations, thresholds for classifying refractive errors are not discrete, with a wide variety of definitions adopted between clinical practice and within epidemiological studies. In epidemiology, the most appropriate definitions will depend on the methodology being used to measure refraction in the study, the context and population of interest in the research

question, as well as any relevance to possible biological mechanisms involved. For example, in epidemiological studies of myopia, while a spherical equivalent refraction of ≤ -0.50 D has been the most widely adopted cut-off, studies using non-cycloplegic data may need to consider more myopic thresholds, to reduce the inclusion of pseudo-myopes. While this may bring prevalence rates closer to values obtained by cycloplegia, it must be recognised that a number of true low myopes will be excluded. This has the potential to reduce the statistical integrity of risk factor analysis.

For classifying high myopia, more myopic thresholds may alter the composition of the sample population to include myopia with syndromic origin rather than high myopia resulting from school/common myopia. Inclusion of an axial length threshold (e.g. > 26 mm) would be likely to exclude myopia of non-axial origin such as those with keratoconus, though again an AL/CR ratio may provide even better identification of such cases. Recently, thresholds for a pre-myopia category for children has been proposed (< -0.50 D to ≤ +0.75 D), which has clinical importance for identification of those suitable for intervention and is based upon biological understanding of likely progression of myopia throughout childhood and adolescence, given that low hyperopia appears to be the natural endpoint for refractive development.[66] Again, cut-offs for this threshold may need to be relatively adjusted based upon the population being sampled, as individuals within populations with a high prevalence of myopia may exhibit more rapid myopigenic changes and larger reductions in mildly hyperopic refractive error at an early age.

1.4 Natural History of Eye Growth and the Development of Refractive Errors

Throughout an individual's lifetime, several distinct changes in refraction occur. Also within a population, characteristic changes in the distribution of refraction are also seen. These patterns reflect the natural development of refractive errors and refractive changes of the eye with age. While these patterns have never been truly captured using cycloplegic refraction in a longitudinal study from birth to senescence, population based cross-sectional studies can provide a comprehensive summary of the major refractive changes that occur over an individual's lifetime. Whilst those which span across large age groups could be influenced by large inter-generational changes in refractive error prevalence's, a number of longitudinal studies also exist that examine the same individuals over a shorter time periods. These studies have captured similar patterns of change in refraction as well as in biometric components.

1.4.1 Newborns and infancy

There is a wide range of refractive errors present in newborns. Despite this large range, most newborns tend to be hyperopic and the variation of refraction is distributed in a normal Gaussian curve, peaking at around 2–3 D with a standard deviation of approximately 2 D.[74-78]

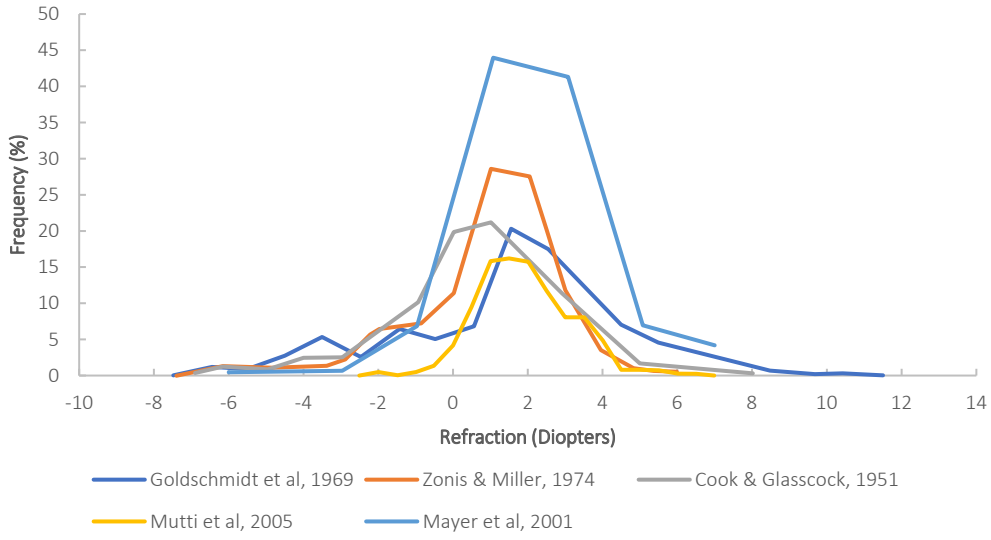


Figure 1.2: Refractive error distributions at birth.

Over the first year of life, this distribution is seen to narrow, becoming more leptokurtic. During this time, the mean refractive error also shifts to reach a state of mild hyperopia. Thus eyes appear to be undergoing emmetropization, a development process where regulated eye growth occurs to achieve optical emmetropia.[79]

Early longitudinal data documenting infantile refractive development came in 1991 by Marion Edwards,[80] who measured changes in cycloplegic refraction in 50 Hong Kong Chinese infants. Substantial 'emmetropization' was seen with each subsequent visit at 10-weekly intervals, as the mean SER rapidly decreased, beginning at +2.98 D at 10 weeks and decreasing to +0.80 D by 40 weeks. This change was also accompanied by a reduction in the variance of refraction, with the SD of mean SER reducing from 1.55 at 10 weeks to 1.19 by 40 weeks. Similar changes in infants within their first year of birth have subsequently been reported in several longitudinal studies.[81, 82],[76, 78, 83] Studies which also examine biometric component measures, find that multiple ocular components undergo significant change during emmetropization.[76, 83] As the eye grows, expansion of the globe occurs, which results in the AL and corneal radius (CR) to increase. Alongside this, thinning of the crystalline lens occurs, seen by the flattening or reductions of the anterior and posterior radii. A slight increase in equivalent refractive index has also been seen during this time.[76] These component changes result in reductions in corneal and lenticular optical power and act in favour of hyperopia. However, there is a net result of myopic shift, suggesting that axial elongation is the primary determinant of refraction during emmetropization. This was supported by Mutti et al,[76] who found that changes in refractive error (or reductions in hyperopia) were only associated with AL changes but not corneal or lens power changes.

Part of the shift in refractive errors towards emmetropia has been attributed to simple scaling factors as total optical power would be expected to decrease with proportional growth of the eye. However, this passive process does not explain the rapid changes in refractive error distributions and the individual changes in biometric components seen. As while the overall distribution of

refractive error narrows to become leptokurtic, biometric components remain normally distributed and grow at differing rates with age. Findings that eye growth is dependent on initial refraction also dispute this and strongly suggests a mechanism which is visually guided. This process is referred to as active emmetropization.

Through regression analyses, Saunders et al,[81] and Mutti et al, [76] found that changes occurring during emmetropization were primarily determined by the level of baseline refraction. Infants with initially higher levels of hyperopia at birth experienced larger myopic shifts and AL growth than those less hyperopic, who experience relatively smaller degrees of myopic shift and axial elongation. However, there appears to be some exceptions. Pennie et al,[83] noted a case where a child developed a high level of hyperopia (+5.00 D) at 3 months of age and remained stable in refraction throughout the remainder of the year. Correspondingly, Mutti et al,[76] found that the relationship between initial refraction and subsequent ocular changes was linear in nature only for those moderately hyperopic at baseline. Meanwhile, for those already close to emmetropia and those with initial refractions > +5.00 D, only minimal changes in refractive error and axial growth were seen. These findings are suggestive of a possible failure of the emmetropization process in highly hyperopic eyes as well as a possible lack of stimulus to emmetropize eyes already close to emmetropia.

1.4.1.1 Evidence for active emmetropization from animal models

Evidence for the presence of an active mechanism underlying emmetropization also comes from observing refractive changes in animals such as chickens,[84, 85] tree shrews[86] and apes.[87] Similar to humans during infancy, a reduction in hyperopia and refractive variance is also seen in these animals immediately following birth.[88, 89] This process appears to be visually guided, as it can be altered by placing artificial lenses in front of the eyes during development. Making the eye relatively hyperopic by covering with a minus lens, stimulates axial elongation in that particular eye which continues until the lens is corrected for. Conversely, making an eye relatively myopic by way of positive lens wear, causes axial growth to slow in comparison to its fellow untreated eye, until the induced refractive

error is compensated for. These growth patterns also adjust accordingly when the defocus is altered or removed, suggestive of an active regulatory component.

However as also seen in humans, this process does not occur for all cases, as there also seems to be an optimum range of refraction that animals are able to compensate for, which for chickens is quite large at between -10 and +15 D.[90] On the other hand, when animal eyes are deprived of vision, they grow uncontrollably towards myopia, suggesting a failure of emmetropization has occurred and indicating the requirement for clear vision as a regulator for growth. Parallels can be seen in humans where abnormal axial myopia develops following visual deprivation at birth due to pathologies such as vitreous haemorrhage,[91] optic nerve hypoplasia,[92] corneal opacification,[93] congenital cataracts[94, 95] and ptosis.[96, 97]

1.4.2 Early childhood

Following infancy, refractive error changes and eye growth slows significantly. In 1979, Ingram and Barr[98] measured refraction in 148 children at ages 1 and 3.5 years and found no significant differences in hyperopia prevalence between the two age groups. Furthermore, distribution curves for both age groups did not appear markedly dissimilar.

In 2013, Lan et al[43] measured refractive errors in students from Chinese preschools who were three to six years of age. While there were statistically significant age-related reductions in hyperopia, these overall changes were minimal, and the mean SER remained mildly hyperopic for those aged three and six (+1.44 D & +1.33 D respectively). Another study of Chinese pre-school children in 2017,[54] found similar mean refractive errors (mean SER aged 3 = +1.37 D, aged 6 = +1.23 D) again with a slight myopic shift in the mean refractive error in the older children. In both studies, refractive error distribution curves appeared more kurtotic with increasing age, suggesting the continuation of an emmetropization process. However, mild hyperopia remained the dominant refractive status at age six, occurring in over 75% of children. In the study by Guo and colleagues,[54] there was a slight increase in the prevalence of myopia and emmetropia, but as there was no clear pattern in changes

to the prevalence's of myopia and hyperopia with increasing age groups, it appears that the endpoint of emmetropization at this early age leaves children in a state of mild hyperopia rather than optical emmetropia. This is supported by data from older populations, where a high proportion of mild hyperopia remains into late childhood[66], and adulthood.[99, 100]

In the Shenzhen Kindergarten Eye Study,[54] ocular biometry was also measured in the 1,133 Chinese pre-schoolers aged three to six years. Unsurprisingly, it was found that AL increased with age, with a difference of 0.44 mm between the 3 and 6 year olds. There were no differences in corneal radius between age groups however, there was a loss of crystalline lens power (LP) of approximately 1.9 D. The combination of AL, CR and LP changes was able to account for 80% of the variance in SER. In comparison, changes in AL/CR and AL alone accounted for 39.8% and 18.6% respectively. This suggests that changes in all three biometric components make a significant contribution to refractive development at this age. As CR remained stable, the loss of LP was likely to be the main parameter balancing the myopic shift produced by continuing axial elongation seen in this age group.

Further insight into ocular component changes came in 2018, by Mutti et al[101] who published follow-up data from Berkeley Infant Biometry Study (BIBS), which continued at ~1.5 year intervals until 6.5 years of age. After the initial decrease in hyperopia experienced between 3 and 9 months,[76] the mean SER decreased slightly and remained relatively stable from 18 months of age until the final visit, with subjects finishing with a mean spherical equivalent of +1.10 ± 1.01 D at age 6.5 years. In terms of ocular component data, AL continued to increase, however at a reduced rate than in infancy. This increase was driven by steady increases in both anterior and vitreous chamber growth. Reductions in corneal power slowed abruptly, with only a minor reduction in power from 18 months to 6.5 years as opposed to the initial reduction in corneal power seen from 3 to 18 months of age (0.3 vs 1.2 D). Thinning of the crystalline lens seemed to continue, as both anterior and posterior lens radii increased. However, rates of lens thinning were slower, characterised by a quadratic pattern rather than the exponential change seen in infancy. Interestingly, after reaching a maximum

at 18 months of age, the refractive index of the crystalline lens began to decline, resulting in a refractive index at 6.5 years of age slightly below that seen at baseline. Overall, these corneal and crystalline lens changes caused a continuous net loss in optical power up to the age of 6.5 years.

1.4.3 Childhood to adolescent years

Following the period of stable refractive growth that occurs until about 6 years of age, rates of ocular growth and refractive distributions begin to differ by population as the prevalence of myopia rises coupled with differing rates of axial elongation.[66] This is due to differences in exposures to environmental influences for myopia (discussed in Section 1.9). In populations where the prevalence of myopia is high, faster rates of myopic shift and higher incidence rates of myopia, creates a tail in the distribution of SER and the highly kurtotic distribution of refractive errors diminishes. Meanwhile in populations where the rates of myopia remain low, there is a continuous shift in refraction towards myopia occurring into the schooling years. These slow with increasing age but overall in these populations a hyperopic mean SER and tight distribution of refractive errors are maintained. Data on non-human primates, not influenced by myopigenic influences, provides a similar picture,[102] indicating that mild hyperopia is the preferred endpoint for human refractive development.

More detailed analyses on prevalence rates, distributions and risk factors of refractive error within this age group will be discussed in Section 1.5 of this chapter. What follows is an examination of general age-related refractive changes during late childhood and adolescent years.

Despite differences across populations, there is a general trend for a mean myopic shift to continue throughout childhood.[103-110] The earliest studies by Sorsby et al,[103, 104] followed changes in refraction and optical component measures using cycloplegia and found that axial length continued to grow by about 1 mm between the ages of 3 and 13 years. This was associated with smaller changes in refraction towards myopia, as the expected myopic shift appeared to be compensated by limited reductions in corneal power as well as significant reductions in the optical power of the crystalline lens.

Zadnik et al,[106] reported on cross-sectional and longitudinal data from the Orinda Longitudinal Study of Myopia (OLSM), where refractive and biometric data were collected across four years from children within the United States. Between 6–14 years, there was a gradual reduction in low hyperopia and an increasing proportion of myopia indicating an ongoing shift towards myopia. Crystalline lens thinning was seen most markedly between the ages of 6 to 9, reaching a relative plateau after that age, however there was a continuous steady decline in lens power throughout the entire period. Overall axial length also increased, at a declining rate with increasing age. No changes in corneal power with age were seen. Following this, the OLSM study became the Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error (CLEERE) study,[107] after additional sites were included to capture children of different ethnicities. Similar trends were seen, but this time continued crystalline lens thinning and flattening occurred through to 14 years of age.

Jones et al,[108] examined longitudinal data of ocular parameters captured between 6 and 14 years of age from the children in the original OLSM study and from this data developed growth curves for each biometric component. As expected, there was a gradual increase in axial length with age, with the rate of change declining with increasing age but no significant changes in corneal power. A similar investigation by Wong et al,[109] examined similar ocular component changes in children from the Singapore Cohort Study of the Risk Factors for Myopia (SCORM) study and found the same pattern of ocular biometric development.

Both studies found that the changes in the crystalline lens were however, more complex. The lens thickness profile, exhibited a U-shaped trend where there was continuous thinning that occurred until 9.5 years (Jones et al) and around 10 years in the Chinese children (Wong et al) followed by subsequent thickening. The refractive index of the crystalline lens continuously decreased, but the rate of change declined with increasing age. Combined, these changes caused crystalline lens power to decline with age, at a rate which also decreased with age. Lens power calculations by Iribarren et

al using the Singaporean data,[68] produced similar growth curves to the OLSM study, confirming that the rate of crystalline lens power reduction decreases with age.

1.4.3.1 Ocular component changes during the onset of refractive errors

In addition to age-related trends for ocular component growth, patterns are also seen between individuals of different refractive errors. While AL has long been known to be the primary determinant of refractive errors, studies that examine differences in ocular component growth curves between individuals with different refractive courses have also identified potential influences from other parameters.

Jones et al,[108] stratified children from the OLSM study to examine baseline and growth differences between children based on their refractive course over the study: myopes, emmetropes, emmetropizing hyperopes and persistent hyperopes. At baseline, AL was the variable which differed the most between groups, with myopes having longer AL than emmetropes, who in turn had longer AL than both emmetropizing hyperopes and persistent hyperopes. There were also smaller differences, in particular, myopes had higher initial corneal power, suggesting that the effects of axial elongation may be more pronounced in those with steeper corneas. Meanwhile, persistent hyperopes had lower initial lens powers, crystalline refractive indices as well as a shallower vitreous than other groups. Alongside baseline differences, those in different refractive groups exhibited differences in growth rates of certain ocular parameters. This was most notable for myopes, who maintained a high rate of axial elongation compared to other groups who exhibited a slowing of elongation with age. Though there is minimal change in corneal power during this age group, persistent emmetropes and persistent hyperopes exhibited relatively large declines in corneal power with age (~0.25–0.50 D).

A similar investigation was done by Wong et al, using data from SCORM.[109] Unlike in OLSM, myopes were considered as either persistent or newly developed myopes. Like in OLSM, persistent and newly developed myopic children were characterised by higher rates of axial elongation than the

other refractive groups, who displayed similar growth patterns to children who remained emmetropic. This same pattern was also observed for vitreous chamber depth elongation, demonstrating that myopic axial elongation primarily occurs in the posterior segment of the eye. Unlike in OLSM, minimal increases in corneal curvature were seen with age, with non-significant differences seen between refractive error groups, indicating that changes in corneal power have little to no effect in the development of refractive errors, especially for myopia. Unlike in OLSM, where all groups displayed similar crystalline lens changes (lens thinning & refractive index reduction), differences in crystalline lens profile changes over time seen in the SCORM data. All groups displayed a U-shaped pattern of lens thickness changes; characterised by a trough where crystalline lens thinning ceases and is followed by thickening; except persistent hyperopes who had no changes in lens thickness over time. Meanwhile, emmetropizing hyperopes and persistent emmetropes experienced an earlier trough, at ~9 years of age, whereas newly-developed and persistent myopes experienced a later trough, occurring at ~10 years of age. These effects on crystalline lens power, were calculated by Irribarren et al,[68] finding that newly-developed myopes had the greatest rates of crystalline lens power loss over time. This meant that although newly-developed myopes began with similar baseline levels of crystalline lens power to the non-myopic groups, they resulted in a final lens power that was similar to that of persistent myopes, who began with significantly lower lens powers than other refractive groups at baseline. This suggested that lens thinning and lens power losses were a major early process during the development of myopia. Although it was previously suggested that these lens thinning and lens power loss were mechanically induced by the equatorial growth of the eye alongside axial elongation,[111] analysis between emmetropes and newly-developed myopes from the CLEERE study,[112] found that lens power losses (due to thinning and flattening) ceased within ±1 year of myopia onset, even though axial length continued to elongate thereafter. This was also shown from a decline in correlation between lens power and axial elongation at follow-up after the onset of myopia in the SCORM data.[68] Findings of rapid SER progression around the time of myopia onset,[67, 69, 70] suggests that myopic refractions

develop following a decoupling of posterior and anterior segment growth, where excessive axial elongation begins to exceed the loss of lens power generated by natural lens thinning that occur early in life.

1.4.4 Adulthood

Shifts towards myopia continue into adolescence, seen by concurrent decreasing proportions of hyperopia as well as increases of incident myopia with age. At some point, the progression towards myopia ceases, and the mean refractive error begins to shift back in a hyperopic direction. This backward shift occurs later in populations more heavily influenced by environmental myopigenic stimuli, where eye growth remains high and continues into young adulthood. These general changes can be visualised from cross-sectional data from the Tehran Eye Study,[100] which found myopia to stabilise after the age of 25 through to 70 years of age until it increases again. Meanwhile, the prevalence of hyperopia stabilises until about 40 years of age and also beings to increase into adulthood (Figure 1.4).

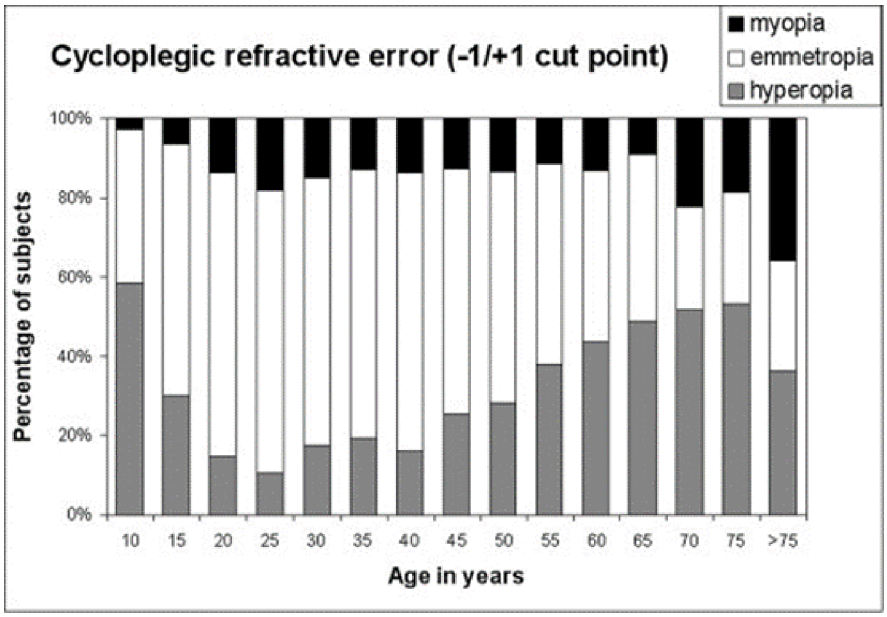


Figure 1.3: Prevalence of refractive errors across age groups, using cross-sectional data from the Tehran Eye Study,[100] illustrated and presented with permission by Iribarren et al.[113]

The most significant contributor to these refractive changes seems to be physiological changes of the crystalline lens rather than changes to axial length or corneal curvatures.[36, 114] This is seen by reductions in anterior chamber depth[36] as well as steepening of both anterior and posterior lens surfaces indicating lens thickening[115] due to an increased number of cortical lens fibres. From these changes, increases in crystalline lens power would be expected, resulting in further shifts towards myopia. However, the opposite is observed, as the lens power reductions seen initially from childhood, continue. This phenomenon is known as the 'lens paradox'. The leading theory explaining the lens paradox suggests that although the crystalline lens thickens, the total refractive index of the crystalline lens decreases, counteracting the myopic effects imposed by the structural lens changes. Although the origin of these refractive index changes have not been entirely confirmed, it is generally agreed that this change in refractive index is due to a decrease in the variation or gradient of refractive index change; specifically between cortex and nucleus. These lens power changes combined with some continuing axial elongation result in the stability of refraction seen until about 40 years of age, where further significant hyperopic changes occur. This also coincides with the symptomatic onset of presbyopia. Later in life around the age of 65–70, there is another shift back towards myopia[116-119] due to the development of nuclear sclerotic cataract, which increases the refractive index of the crystalline lens and its optical power.

1.4.5 Summary

Natural changes in the prevalence and distribution of refractive errors occur with age. This begins immediately following birth, as the large variance in refractive errors present in newborn reduces and rapidly shifts towards emmetropia by the first year of life. During this phase, the axial length of the eye elongates; driven by a mechanism involving the adjustment of growth rates in response to retinal defocus signals; while the cornea flattens and loses power. Concurrently there is a smaller degree of lens power reduction from crystalline lens thinning which also partially compensates for axial growth. This process ends sometime in late infancy, as changes in corneal power slow significantly and there is little further change with age. However axial elongation continues, causing a myopic shift in mean refractive error to be seen, which continues to be partly minimised by ongoing lens power reduction. Although lens thinning reverses sometime during childhood, the lens still continuously loses power, resulting in a hyperopic shift once axial elongation slows in adolescence.

During childhood school years average refraction starts to differ between populations worldwide, due to varying levels of myopia development influenced primarily by environmental factors (discussed in Section 1.9). Individuals with high rates of ocular axial elongation tend to develop myopia, whereas those with shorter eyes, most commonly achieve mild hyperopia to emmetropia, or can remain hyperopic as normal eye growth fails to achieve emmetropia. While axial length change is the primary determinant of refractive errors in childhood, changes in refraction in adults primarily occurs due to refractive index changes of the crystalline lens, which causes a hyperopic shift in refraction until the onset of cataracts in late adulthood, causing myopic shifts in those affected.

1.5 Epidemiology of Myopia

Myopia has become a public health concern following rapid increases in prevalence which have occurred over the last few decades. However, this has only affected certain populations and to varying degrees, with some countries seeing epidemic levels of myopia and high myopia, whilst others have seen little to no change in prevalence over time. As a result, in addition to age-related variations in refractive errors, there is now considerable variability in the prevalence and distribution of refractive errors across the globe, between countries and within ethnic groupings.

In this section, evidence for an epidemic of myopia will be first presented, followed by an overview of the prevalence rates of myopia across different geographic regions and across each age group from population-based studies. As earlier described, since the accuracy of a refractive measurement can vary significantly from various factors, care must be taken when comparing prevalence rates from different sources, particularly those using different methodologies and definitions for myopia. Findings from repeated birth cohort studies examined to introduce the myopia epidemic can be interpreted with a fair level of confidence since they typically employ the same methodology and sample characteristics, whereas studies examined as part of the global epidemiology of myopia will be interpreted with caution due to increased heterogeneity.

There will be a focus on studies using cycloplegic refraction, which provide the most precise figures. However, this may not be available for all cohorts such as in adult populations and large population studies. In this case, data derived from non-cycloplegic refraction, or other indirect methods such as visual acuity or spectacle data may be presented. In these cases, it must be noted that non-cycloplegic refractions will always tend to over-estimate the prevalence of myopia, even in adults.[24, 26, 32, 100] Meanwhile, visual acuity on its own will also have a tendency to over-estimate prevalence rates, due to the capture of pathological visual impairment. This may be minimised by excluding uncorrectable vision impairment but will also begin to underestimate the prevalence of low myopia depending on the cut-off used. In contrast, data derived from spectacle prescriptions will have a

tendency to underestimate prevalence rates, given that refractive correction may not be required at low degrees of myopia. Finally, in combination with the method of refraction and whether cycloplegia has been used, thresholds for myopia also need to be carefully considered when interpreting prevalence figures. For example, more myopic thresholds (-0.75 and above) will likely capture more true myopes when non-cycloplegic refractions are measured, and naturally underestimate prevalence rates compared to less myopic thresholds. These errors are likely to be more significant in populations where the prevalence of myopia is relatively low, because the greatest differences are seen for hyperopic refractions. Reliable comparisons between prevalence rates can be made by considering studies using similar methodological parameters.

1.5.1 The myopia epidemic

Evidence for rises in myopia prevalence was first documented in the 1970's by Young et al,[120] and Morgan et al,[121] who investigated the refraction and ocular components of Inuit Eskimo families and their offspring in North America. They observed that the younger generation of Eskimo's, who were less than 30 years of age at the time, were significantly more myopic than compared to their elders in the previous generation. As simple genetics could not explain the large differences in myopia seen, it was thought that this "epidemic" was due to environmental causes, such as cultural factors which had changed school attendance patterns.[122] Since then the understanding of the aetiology of myopia has progressed significantly, and current paradigms will be reviewed in Sections 1.8 and 1.9. Meanwhile, significant rises in the prevalence of myopia have been seen elsewhere in various parts of the globe. Evidence for these rises come from population studies comparing myopia prevalence at specific ages from different birth cohorts (Figure 1.4).

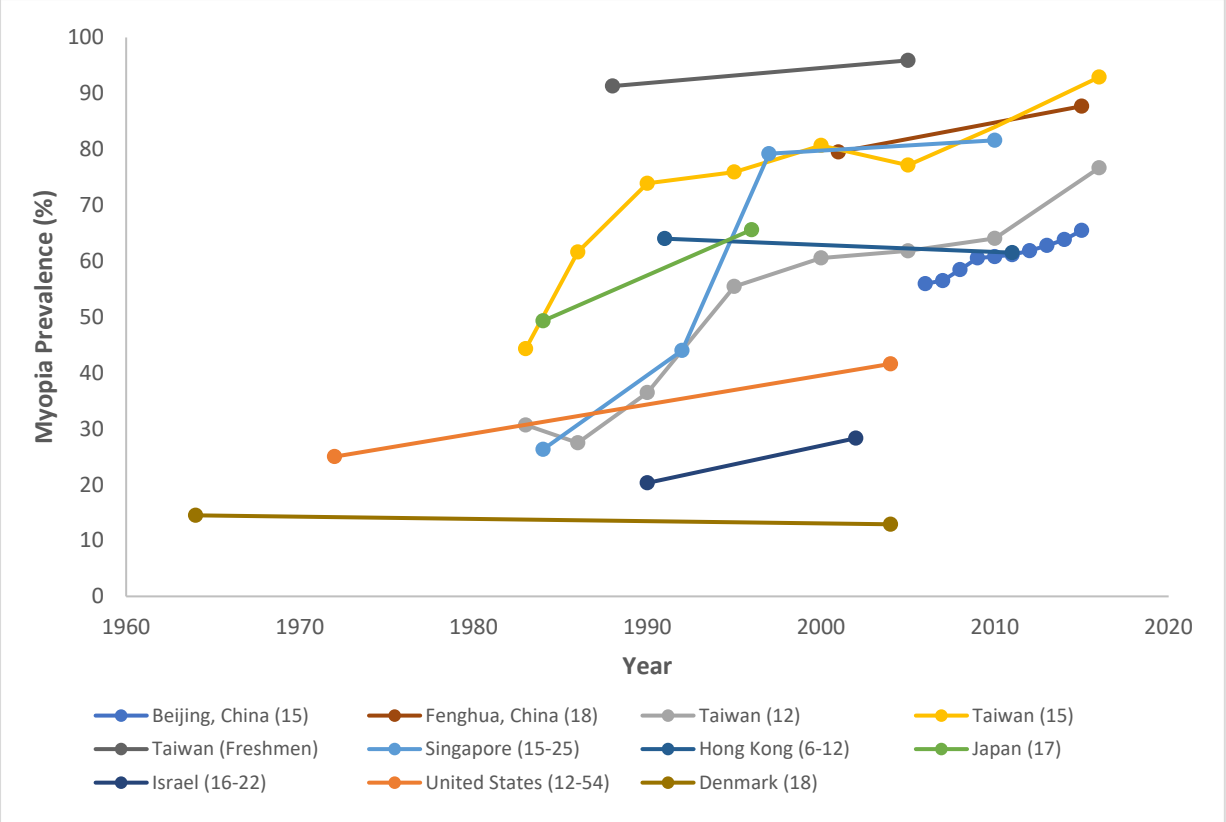


Figure 1.4: Changes in prevalent myopia over time from repeated birth cohort studies conducted within different populations and their age ranges.

1.5.1.1 Evidence from studies reporting rises in prevalent myopia

East Asian countries have seen the most rapid rises in myopia prevalence since the 1960s. Lin et al,[123] Tsai et al,[124] have reported on the prevalence of myopia (≤ -0.25 D) in Taiwanese schoolchildren aged 7–18 years from eight nationwide surveys conducted between 1983 and 2016. Significant increases in prevalent myopia were seen in all age groups. This was most severe for primary school children in youngest age group (aged 7 years), where the prevalence of myopia increased almost five-fold from 5.4% in 1983 to 25% in 2016. At this latest survey, the myopia rate reached a plateau of approximately 90% among junior and senior high school students aged 13–18. Alongside these rises, the prevalence of high myopia (≤ -6.00 D) also increased significantly by approximately 3x. These rises were more evident in the older age groups, such as in those aged 15, where the prevalence of high myopia rose from 4.37% in 1983 to 15.36% in 2000. Meanwhile, Wang et al[125]

captured rises in prevalent myopia among freshmen in National Taiwan University from 1998 to 2005. Though already exceptionally high to begin with, the prevalence of myopia rose from 91.3% in 1988 to 95.9% in 2005. Most notably, there was a ~5% reduction in prevalence of both low myopia (-0.25 to -3.0 D) and moderate myopia (-3.0 D to -6.0 D) whilst the high myopia rate (< -6.0 D) increased from 25.5% to 38.4%.

In Singapore where military enlistment for males is compulsory between the ages of 15–25, medical examinations have provided data for examining the changes in myopia over the years.[126] The earliest report examined conscripts between 1974 and 1984 and estimated myopia prevalence to be 26% using a VA cut-off of ≤ 6/18.[127] A second report in 1993 examined conscripts between 1987 and 1992 using the same criteria for myopia, and found a higher prevalence rate of 44%.[44] These estimates were based on VA alone and not cycloplegic refraction, so it must be noted that while low cases of myopia might've been missed, these estimates would have also been overestimated, due to the capture of other ocular conditions and possible malingering to avoid conscription. Despite this, two subsequent data points have been collected using non-cycloplegic autorefraction and have found further increases in prevalent myopia, at 79% in 1996-1997 and 82% in 2009–2010.[126] While non-cycloplegic refraction will also overestimate the proportion with myopia, it is unlikely to account for the entire increase in myopia,[100] especially as further increases were seen using the same protocol thereafter. In terms of high myopia, small increases in prevalence were also seen, from 13% in 1996–1997 to 15% in 2009–2010.

In Japan, Matsumura and Hirai[128] reported on 13 year changes in myopia prevalence using data from mass ophthalmologic examinations conducted between 1984 and 1996 in students aged 3–17 years old. Rises in prevalent myopia were seen for all students aged 7 and above, which were most notable for those aged 17, where the prevalence increased from 49% to 66%.

In China, evidence of increases of myopia were complicated by the fact that levels of myopia had always appeared to be relatively high, and early studies did not provide cycloplegic data. The first

definitive studies to identify high rates of myopia using cycloplegic refraction were by Zhao et al,[129] who reported prevalences of 36.7% and 55.0% in 15 year old males and females respectively within Shunyi district (rural) between 1988–1998, as well as He et al,[130] who also reported myopia prevalences of 69.3% and 77.5% in 15 year old boys and girls resepctively, within Guangzhou (urban) between 2002–2003. Evidence of increases in China were first provided by Xiang et al, using VA measurements collected from school screening in Guangzhou, [131] showing that the prevalence of reduced unaided VA increased between 1988 and 2007 [from 6.2% to 14.5% in Grade 1 students (aged 6 years) and from 62.5% to 84.11% in Grade 12 students (aged 17 years)]. And then by Sun et al, who used a similar approach.

Subsequent studies have reported smaller increases over time. In Haidian district of Beijing (urban), Li et al[132] examined grade 9 junior high school students (aged ~15 years) annually using cycloplegic refraction from 2006 to 2015 in population-based survey. There was an increase in total myopia prevalence, from 56% to 65%, as well as an increase in the prevalence of high myopia (< -6.00 D), from 4% to 6.7%. While there was a decrease in the prevalence of low myopia (-3.0 ≤ SER < -0.5 D); from 32.3% to 20.7%; a larger proportion of students progressed into moderate myopia (-6.0 ≤ SER < -3.0 D), which almost doubled from 20% to 38%. Similar findings were reported by Chen et al,[133] who collected refractive data (non-cycloplegic auto-refraction) from grade 12 high school students (aged ~18 years) in Fenghua city (urban) over a 15-year survey. From 2001 to 2015, the prevalence of overall myopia rose from 80% to 88%. Although the prevalence of low myopia (-3.0 < SER < -0.5 D) decreased (from 33% to 24%), the prevalence of both moderate (-6.0 ≤ SER < -3.0 D) and high myopia (< -6.00 D) increased, from 39% to 46% and from 8% to 17% respectively.

In Hong Kong, changes in prevalent myopia were seen by Wu and Edwards in 1999,[134] who investigated the prevalence of myopia in three generations; children aged 7–17 years old, their parents and their grandparents. A relationship between prevalent myopia and generation was seen, with increasing levels of prevalent myopia for younger generations. This was demonstrated by odds

ratios which were highest in the children (OR: 0.35) followed by their parents (OR: 0.26) and finally their grandparents (OR: 0.06), who were least likely to be myopic. Larger differences in prevalent myopia between the parents and grandparents compared to between the parents and their children, suggest that the prevalence changes primarily occurred between the two older cohorts.

While most data has come from East Asian countries, increases in myopia prevalence have also been seen elsewhere across the globe. In the United States, Vitale et al[135] compared population estimates of myopia in individuals aged 12–54 years of age, using data from the 1971–1972 National Health and Nutrition Examination Survey (NHANES) and a subsequent survey conducted 30 years later in 1999–2004. Although myopia rates were estimated without cycloplegia, from an algorithm which used a combination of lensometry, pinhole VA, presenting VA and retinoscopy results, this method was replicated in the follow-up survey to allow adequate comparison. This found rises in prevalent myopia (< -2.00 D), from 25% in 1999–2004 to 42% in 1971–1972. The prevalence of high myopia (≤ -7.90 D) also rose dramatically during this time, from 0.2% to 1.6%. Investigation of non-cycloplegic refractive data obtained in the second survey, indicated a lower myopia prevalence (33.1%),[136] suggesting that the true prevalence rates and change pattern would be even lower than reported.

In Israel, Dayan et al[137] analysed data from a series of prevalence surveys conducted over 13 consecutive years in military service candidates aged 16–22 years old. From 1990 through to 2002, the overall prevalence of myopia (≤ -0.50 D) rose from 20% to 28%. As this was determined by non-cycloplegic refraction, the true prevalence rates are likely to be lower.

In countries with populations of European ancestry there have not been any repeated birth cohort studies. However, there are some indications of gross prevalence changes over time from the comparison of studies conducted within similar populations. Parssinen,[138] reviewed changes in myopia prevalence within Finland and described an increase in prevalent myopia among school-children aged 14–15 years old, which approximately doubled from 10.6% in 1927 to ~21% by the 1980's. In adults an increase was also seen, with prevalent myopia being < 10% amongst those born

in the first three decades of the 20th century, compared to those born in the second half of the 20th century, for whom the prevalence of myopia was 21–30%. Williams et al[139] investigated myopia prevalence across Europe by conducting a meta-analysis of population-based, cross-sectional studies from the European Eye Epidemiology (E3) Consortium. This included 15 population-based studies conducted between 1990 and 2013, but was based on non-cycloplegic refractions. There was a significant birth cohort effect seen within adults aged 44–78 years, with a small independent increase in myopia prevalence with later birth decades. This was 17.8% in those born between 1910 and 1939 and rose to 23.5% in those born between 1940 and 1979. Given that the prevalence of myopia determined through cycloplegic refraction is below 20% by the end of schooling years in countries with populations of European ancestry,[140] these changes raise the question of whether the higher prevalence reported from adult studies without cycloplegia was only higher due to lack of cycloplegia, or to further development of myopia in young adults. Evidence suggesting this was a possibility can be seen in Australia, by Mackey et al.[141] Myopia prevalence from two Western Australian studies of adults aged 49-70 years conducted in the 2010s; the Busselton Healthy Ageing Study (BHAS) and the 26 year follow-up interval of Generation 1 cohort of the Raine Study (G1RS); were compared to two earlier studies conducted in the early–mid 1990s; the Blue Mountains Eye Study (BMES) and the Visual Impairment Project (VIP). All studies used non-cycloplegic refraction. Age-standardised myopia prevalences were higher in both recent studies. Comparing urban cohorts, there was a myopia prevalence of 29.2% in G1RS compared to 16.4%, and 23.9% in VIP and BMES. Meanwhile in regional cohorts, myopia prevalence was 19.4% in BHAS compared to 13.8% in VIP.

1.5.1.2 Studies not reporting rises in prevalent myopia

Not all populations have seen rises in myopia prevalence over time. In Denmark, Jacobsen et al[142] found a decrease in myopia prevalence within 18 year old military conscripts from 14.5% in 1964 to 12.9% in 2004. Given rather low levels of prevalent myopia, it suggests that this particular population may not be subject to the external forces proposed by Young et al, which seemed to be

driving the myopia epidemic in other countries. However, it is to be noted that cycloplegic refraction was not used and that the methods used to obtain refractive status and definitions changed between studies.

A similar trend was observed in 2011 by Lam and colleagues[143] who compared data gathered from 2,651 schoolchildren in Hong Kong (aged 6–12); from a school vision screening service held during 2005–2010; to an earlier study in 1991,[144] where refraction was obtained in a smaller sample of 383 schoolchildren. Over these two decades, prevalent myopia did not appear to increase, being 64% in 1991 and 61.5% in 2005–2010. The prevalence of high myopia also appeared stable at 4% and 3.8% respectively. Given that existing rates of myopia were already high in the 1991 study, it suggests that prevalence increases may have already reached a maximum threshold for that young age. Data described earlier, suggests that rises in prevalence has indeed occurred previously.[134] Similar findings have also recently been reported by Yam and colleagues,[145] where the prevalence of myopia (using cycloplegic refraction) in 6-8 year old children remained similar between 2019 to an earlier Hong-Kong cross-sectional study in 2004 (17% vs 13%, at age 6, 28% vs 24% at age 7 and 38% vs 36% at age 8).[146]

1.5.2 Global prevalences of myopia

1.5.2.1 Prevalence of myopia in infants

There have only been a few population-based studies investigating the prevalence of myopia in infants (Table 1.2). In 2010, the Strabismus, Amblyopia and Refractive error in young Singaporean children (STARS) study[147] reported that the overall prevalence of myopia (≤ −0.50 D) was 11%, decreasing to 8.1% and 5.2% when using myopia definitions of ≤ -0.75 and ≤ -1.00 D respectively. Meanwhile, the prevalence of high myopia (≤ −6.00 D) was rare, occurring in only 0.2% of the population. Myopia remained fairly high from ages 6 to 11, 12 to 23 and 24 to 35 months, being present in 15.8%, 14.9% and 20.2% of children respectively. This dropped and began to steadily

decrease thereafter from 36 to 47, 48 to 59, and 60 to 72 months: 8.6%, 7.6%, and 6.4% respectively.

Within the United States, two large population-based studies have been conducted. The Baltimore Pediatric Eye Disease Study[148] (BPEDS) was an evaluation of the prevalence of ocular disorders in 1030 White and 1268 African-American children aged 6 to 71 months within Baltimore, Maryland. Overall the prevalence of myopia (≤ −1.00 D) was 3.3%, and appeared significantly lower in White children (0.7%) compared to African-American children (5.5%). The second population-based study in the United States was the Multi-Ethnic Paediatric Eye Disease Study (MEPEDS), which also investigated children of similar ages from Los Angeles County and Riverside County, California. Its first report in 2010,[149] provided information for 2994 African-American and 3030 Hispanic children. Similar to BPEDS,[148] there appeared to be inter-ethnic differences in myopia prevalence, with rates of myopia (≤ −1.00 D) being higher in African-American children (6%) than Hispanic children (3.7%). A combined analysis of the BPEDS and MEPEDS data in 2011,[150] provided a report for a total of 4,306 African-American, 3,076 Hispanic and 2,403 White children. Similar trends were noticed from both individual studies, with the prevalence of myopia being highest in African-American children (6%), followed up Hispanic children (3%) and being the least in White children (1%). The third report of MEPEDS data released in 2013, provided information on 3,008 children of White and Asian ethnicity.[151] Again the prevalence of myopia among White children was low (1.2%), while children of Asian ethnicity appeared to have a higher prevalence of myopia (3.98%).

In Australia, the Sydney Paediatric Eye Disease Study (SPEDS),[152] was another population-based study aimed at investigating causes of vision impairment among preschool children. From 1,188 children aged 30–72 months who underwent cycloplegic autorefraction, myopia (≤ −0.50 D) was found in only 0.67% of subjects. Although European Caucasians were the dominant ethnic group (47.1%), there was a more diverse set of ethnicities, which included East Asians (21.4%), South Asians (13.5%), Middle Easterns (8.2%) and those with other ethnicities/mixed ethnicities (9.8%). As

the overall prevalence of myopia was low, ethnic differences in myopia prevalence were unable to be investigated.

A few other studies in East Asia have investigated myopia prevalence rates in slightly older populations of pre-school children. In Hong Kong children aged 36–72 months, Fan et al[153] reported that rates of myopia to be 6.3% using a cut-off of ≤ −0.50 D. In Taiwan, Lai et al,[154] reported that 5.5% of children aged 36–72 months were myopic using a higher cut-off of ≤ −1.00 D. Meanwhile in China, the prevalence of myopia within children of similar age groups have been found to be very low at approximately 1–2%.[155-157]

In these infantile populations, it must be considered that these varying degrees of prevalence, while seemingly suggestive of geographic and possible ethnic variations, are likely marred by methodological issues involving the adequacy of cycloplegia and subtle differences in myopia definitions. In studies of children aged less than 12 months, namely BPEDS, MEPEDS, STARS and SPEDS which employed similar methodologies, a lower dose of cyclopentolate was administered to infants aged ≤ 12 months (typically 2 drops of 0.5%) as opposed to the 1% cyclopentolate used in the older children. Given that in older children, up of 4 drops of cyclopentolate 1% are often required to achieve adequate cycloplegia,[155] significant inflations in myopia prevalence from pseudo-myopia can be assumed, especially when confirmation of adequacy of cyloplegia was not employed. As also discussed in STARS,[147] there was the propensity for measurements from hand-held autorefractors, used predominantly for children aged under two years of age, to shift refractions in a myopic direction, further over-estimating prevalence rates. The significant reductions in prevalence rate when using higher myopia cutoffs, as well as the limited proportion (5.1%) of hyperopic children (≥ +2.00 D) in gives further indication of pseudo-myopia occuring in STARS. These errors may be more evident in children with darker iridies, such that in the MEPEDS data it can be seen that the mean SER shifts towards hyperopia after 11 months of age and that the proportion of children with myopia < -1.00 D also lessens after 11 months of age for both African American and Hispanic children.[150]

Given that the prevalence rates in Guangzhou pre-schoolers provided by Lan et al,[155] using a rigorious cycloplegic protocol, was comparable to what is seen in the white European populations from previous studies, it is likely that the true prevalence rates of myopia in other infantile cohorts, especially in ethnic subgroups with dark iridies (e.g. African-Americans) are lower than presented.

Table 1.2: Population-based studies reporting the prevalence of myopia in infants and children of pre-school age.

Author, Year	Location	n	Age (months)	Method of refraction	Myopia definition/s	Myopia (%)	High Myopia (%)
Giordano et al, [148] **2009**	United States *BPEDS*	3,990	6-71	C, A/R	**M:** ≤ −1.00 D	**Total:** 3.3 **White:** 0.7 **African-American:** 5.5	N/A
Dirani et al,[147] **2010**	Singapore *STARS*	3,009	6-72	C, A/R	**M:** ≤ −0.50 D **HM:** ≤ −6.00 D	**Total:** 11	0.2
Multi-Ethnic Pediatric Eye Disease Study Group[149] **2010**	United States *MEPEDS*	6,026	6-72	C, A/R	**M:** ≤ −1.00 D	**Hispanic:** 3.7 **African-American:** 6.6	N/A
Borchert et al,[150] **2011**	United States *BPEDS + MEPEDS*	9,970	6-72	C, A/R	**M:** ≤ −1.00 D	**White:** 1 **Hispanic:** 3 **African-American:** 6	N/A
Wen et al,[151] **2013**	United States *MEPEDS*	3,008	6-72	C, A/R	**M:** ≤ −1.00 D	**White:** 1.2 **Asian:** 3.98	N/A
Pai et al,[152] **2011**	Australia *SPEDS*	1,188	30-72	C, A/R	**M:** ≤ −0.50 D	**Total:** 0.67	N/A
Lai et al,[154] **2009**	Taiwan	618	36-72	C, R	**M:** ≤ −0.50 D	**Total:** 5.5	N/A
Fan et al,[153] **2011**	Hong Kong	823	36-72	C, A	**M:** ≤ −1.00 D	**Total:** 6.3	N/A
Lan et al,[155] **2013**	China (urban)	2,480	36-72	C, A & R	**M:** ≤ −0.50 D	**Total:** 1	N/A
Wang et al,[157] **2014**	China	2,255	24-80	C, R	**M:** ≤ −1.00 D	**Total:** 0.9	N/A
Ma et al,[156] **2016**	Shanghai, China *SCES*	8,398	3-10	C, A & S	**M:** ≤ −0.50 D **HM:** ≤ −6.00 D	**3 year-olds:** 1.8 **6 year-olds:** 5.2	0

C = Cycloplegic, A = Auto-refraction, R = Retinoscopy, S = Subjective refraction, M = Myopia, HM = High Myopia

1.5.2.2 Prevalence of myopia in school-aged children

In school-aged children, the prevalence of myopia increases with age, seen as part of the natural history of refractive errors. However, changes in the prevalence of myopia between cohorts appears to differ depending on geographic region, with some cohorts experiencing more sudden increases (Table 1.3). While ethnic differences may contribute to between-country differences in prevalence, large within-country differences between areas of rural and urban areas suggest that environmental differences are likely to be predominantly driving these changes instead.

A series of early population-based, cross-sectional studies called the Refractive Error Studies in Children (RESC), were designed to assess the prevalence of refractive errors and vision impairment in children between the ages of 5 and 15 of different ethnicities and in different countries. Many subsequent studies have employed a similar study design, allowing comparison of refractive error prevalences between different regions. Table 1-2 summarises the prevalence of myopia in various countries within each of the major continents, with a focus on studies using cycloplegic refraction.

1.5.2.2.1 East Asia

In general, the prevalence of myopia appears to be the highest in urbanised areas of many East Asian countries. In Taiwan, Lin et al[123] reported a nationwide myopia prevalence (≤ -0.25 D) of 20% in primary school children aged 7. This rate sharply increased to 61% in 12 year-olds and 81% in the 15 year-olds. Rates of high myopia (< −6.00 D) also increased with age group, being 3.4% in 12 year-olds, 13% in 15 year-olds and 21% in 18 year-olds. Similarly high prevalence rates of general myopia were also reported by Hsu et al[158] who found 36.4% of Taiwanese school-children aged 8 to be myopic (≤ −0.50 D). These rates are also fitting with the relatively high rates of myopia seen in Taiwanese pre-schoolers.[154]

In mainland China, a wider prevalence range has been seen across its large geographic landscape. In early studies, large divides were seen between rural and urban areas as previously described.[159] One

of the first RESC studies held within Shunyi;[129] a rural district within China; found a myopia rate of 14.9% in children aged 5–15 years old. A similar prevalence of 13.7% has been found in a relatively less developed area of western China in children of the same age group.[160] A low prevalence rate of 5% has been seen in rural northern China,[161] however, higher rates have been seen in other rural areas, such as in Handan province,[162] where there was a prevalence of 23.3% in a slightly older group aged from 6–17 years. The Mojiang Myopia Progression Study,[163] examined myopia prevalence in students within a rural county and reported a myopia rate of 2.4% in those grade 1 (aged 7–8 years) and 29.4% in grade 7 (aged 13–14 years) students. These rates are similar to the age-specified rates seen within Shunyi. Older rural samples report higher rates, such as in Yangxi County (a semi-rural setting)[164] where 42.4% of adolescent children aged 13–17 years were found to be myopic. In a more remote location of outer Mongolia, in three schools from a rapidly growing city in the Gobi Desert Children Eye Study,[165] 60% of children aged 6–21 years were myopic, however this rate should be interpreted with caution as the authors used the refractive error of the worse eye rather than right eye to calculate this prevalence in conjunction with an older age group.

In contrast to rural populations, prevalence rates of myopia and high myopia in urban areas of China have all been generally high. In children aged 3–10 years in Shanghai, rates of myopia have been reported to be 20% by Ma et al.[156] Meanwhile using a RESC-based protocol, He et al[130] reported that 38.1% of children aged 5–15 years within Guangzhou were myopic. The rate of myopia in an older sample of children (aged 14–16 years) within Beijing was 65.5%.[132]

In Hong Kong, the prevalence of myopia in school-children is similar to urban areas of China, with Fan et al[146] finding that myopia was prevalent in 36.7% of children aged 5–16 years. In those aged 7, the prevalence was already high at 28.9% in contrast to preschool rates of 6.3%.[153] This rose further with increasing age to reach 53.1% in those aged 11-16.

1.5.2.2.2 Countries with populations of European ancestry – Europe, Australia & the United States

There are only several population-based studies within western countries that report the prevalence of myopia. Notable studies include the Generation R study in the Netherlands,[166] the Aston Eye Study (AES) in the United Kingdom,[167] the Northern Ireland Childhood Errors of Refraction (NICER) and Ireland Eye Study (IES) studies in Ireland,[168, 169] the Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error (CLEERE) in the United States, and the Sydney Myopia Study (SMS) as well as its follow-up the Sydney Adolescent Vascular Eye Study (SAVES) in Australia.[21, 105] Reported rates of myopia in school-children within these countries have been generally similar, and are relatively lower than in comparison to that seen in East Asia.

Upon entry to primary school at ages 6–7, prevalences for myopia in the Netherlands,[166] Ireland[168, 169] and Australia[21] are low; and similar to levels at preschool ages; at between 1.4–3.3%. In the United Kingdom however, higher prevalence rates of 9.4% were reported in the AES.[167] By age 12, rates of myopia in Ireland and Australia rise to 17–19%[105, 168, 169]. Meanwhile rates of prevalent myopia remain higher (29.4%) in the United Kingdom.[167] Moderately low levels of myopia have also been reported in the United States with a prevalence of 10.5% in 5–17 year olds,[170] and in Poland where 13.3% of 6–18 year olds were found to be myopic.[171] In Sweden, high rates of myopia was seen by Villarreal et al,[172] who reported that 49.7% of 12–13 year old teenagers were myopic. However, part of this high rate seen may have been influenced by incomplete cycloplegia through the use of 0.5% tropicamide, compared to most other studies that used at least 1% cyclopentolate.

1.5.2.2.3 Africa

The prevalence of myopia among schoolchildren within African countries is low. Studies using cycloplegic refraction find the prevalence of myopia in children around the ages of 5–18 to often be below 10%,[173-180] with pooled analysis suggesting an overall rate of 4.2%.[181] These prevalence rates remain low in older samples, with Kumah et al,[182] reporting a prevalence of 3.2% in private schoolchildren aged 12–15 years in Ghana.

1.5.2.2.4 South America

Within South America, a RESC study by Maul et al,[183] reported an extremely low prevalence of 3.4% myopia in 5-year olds within La Florida, Chile. This increased with age to be approximately 15% by the age of 15. Lira et al,[184] reported similar rates in Campinas, Brazil, with a prevalence of 2.8% in 6 year olds which increased to 19.5% in 17 year olds.

1.5.2.2.5 The Middle East

In the Middle East, prevalence rates for myopia come from studies across different regions of Iran. This may not provide an accurate representation of the entire Middle East, as Iran places higher emphasis on education relative to other neighbouring countries. This likely means that rates of myopia seen are higher, due to environmental differences associated with education. Overall, rates of myopia in Iran are generally lower compared to East Asian and Western countries. Rural and semi-rural areas report the lowest levels of myopia of between 2.5–2.6%.[185, 186] Predominantly semi-urban areas such as Shiraz,[187] Masshhad[188] and Bojnourd[189] have all reported slightly higher rates of myopia at 4.4%, 3.6% and 4.3% respectively. Meanwhile, rates of myopia in Tehran; the capital and most urbanised city of Iran; was the highest at 7.2%.[100]

1.5.2.2.6 South East Asia

Varying levels of myopia are seen across different countries within South East Asia. In Singapore, the prevalence of myopia appears to increase dramatically from infants, with the SCORM study reporting 32.7% of children aged 7–9 years being myopic at baseline.[190] These rates are comparable to the rates seen in Hong Kong and Urban China. Meanwhile Malaysia records moderately high prevalences, being 10–16% in 7–9 year olds and increasing to 34% in 15 year olds.[191] Slightly lower rates are seen in Thailand being 11.1% in children aged 6–12.[192]

1.5.2.2.7 South Asia

In India, a RESC study conducted in an urban population of New Delhi, reported a myopia prevalence rate of 7.4%,[193] whereas in Andhra Pradesh, a rural region, myopia was reported to be lower at 3.8% in children of the same ages.[194] In the neighbouring country of Nepal, one of the original RESC studies conducted in the rural Mechi Zone, reported the lowest myopia prevalence of 1.2%, even though many of these children would have largely been of Tibetan/East Asian descent.[195] A later study in Kathmandu, Nepal reported a much higher prevalence of 19% in children aged 10–15 years.[196] Although the population within Kathmandu was more urbanised than in Mechi zone and sampled older students from an upper to middle socio-economic group in elite schools, these differences were potentially overestimated, as children with VA better than 6/12 had their refraction obtained without cycloplegia.

Table 1.3: Population-based studies reporting the prevalence of myopia using cycloplegia in school-aged children. Prevalence values from repeated cohort studies are taken from the most recent year.

Author, Year	Location	n	Age (years)	Method of refraction	Myopia definition/s	Myopia (%)	High Myopia (%)
Countries with populations of European ancestry (Europe, North America & Australia)							
Ojaimi et al,[21] 2005	Sydney, Australia *SMS*	1,724	6-7	C, A	**M:** ≤ −0.50 D	1.4	N/A
Tideman et al,[166] 2018	Netherlands *Generation R study*	5,711	6	C, A	**M:** ≤ −0.50 D	2.4	N/A
O'Donoghue et al,[168] 2010	Northern Ireland *NICER*	392	6-7	C, A	**M:** ≤ −0.50 D	2.8	N/A
Harrington et al,[169] 2018	Ireland *IES*	728	6-7	C, A	**M:** ≤ −0.50 D	3.3	N/A
Logan et al,[167] 2011	United Kingdom *AES*	327	6-7	C, A	**M:** ≤ −0.50 D	9.4	N/A
Kleinstein et al,[170] 2003	United States *CLEERE*	2,523	5-17	C, A	**M:** ≤ −0.50 D	10.5	N/A
Czepita et al,[171] 2007	Poland	4,422	6-18	C, R	**M:** ≤ −0.50 D	13.3	N/A
French et al,[105] 2013	Sydney, Australia *SAVES*	863	12	C, A	**M:** ≤ −0.50 D **HM:** ≤ −6.00 D	18.9	0.1
O'Donoghue et al,[168] 2010	Northern Ireland *NICER*	661	12-13	C, A	**M:** ≤ −0.50 D	17.7	N/A
Harrington et al,[169] 2018	Ireland *IES*	898	12-13	C, A	**M:** ≤ −0.50 D	19.9	N/A
Logan et al,[167] 2011	United Kingdom *AES*	269	12-13	C, A	**M:** ≤ −0.50 D	29.4	N/A
Villarreal et al,[172] 2000	Sweden	1,045	12-13	C, R	**M:** ≤ −0.50 D **HM:** ≤ −5.00 D	49.7	2.5
Ip et al,[197] 2008	Sydney, Australia *SMS*	2,353	11-15	C, A	**M:** ≤ −0.50 D	11.9	N/A
French et al,[105] 2013	Sydney, Australia *SAVES*	1,196	17	C, A	**M:** ≤ −0.50 D **HM:** ≤ −6.00 D	30.8	1.9
Africa							
Naidoo et al,[180] 2003	South Africa *RESC*	4,890	5-15	C, R	**M:** ≤ −0.50 D	2.9	N/A
Ovenseri-Ogbomo and Omuemu,[177] 2010	Ghana	961	5-19	C, R	**M:** ≤ −0.50 D	6.9	N/A
Atowa et al,[176] 2017	Nigeria	6,192	8-15	C, A	**M:** ≤ −0.50 D	2.7	N/A
Anera et al,[173]	Morocco	545	6-16	C, A	**M:** ≤ −0.50 D	6.1	N/A

2009							
Soler et al,[178] 2015	Equatorial Guinea	425	6-16	C, A	**M:** ≤ −0.50 D	10.4	N/A
Alrasheed et al,[174] 2016	Sudan	1,678	6-15	C, A	**M:** ≤ −0.50 D	6.8	N/A
Yamamah et al,[179] 2015	Egypt	2,070	6-17	C, A	**M:** ≤ −0.50 D	3.1	N/A
Assem et al,[175] 2019	Ethiopia	601	6-18	C, S	**M:** ≤ −0.50 D	10.8	2.33
Kumah et al,[182] 2013	Ghana	2,435	12-15	C, R	**M:** ≤ −0.50 D	3.2	N/A
South America							
Maul et al,[183] 2000	La Florida, Chile *RESC*	5,303	5-15	C, R	**M:** ≤ −0.50 D	5.8	N/A
Lira et al,[184] 2017	Campinas, Brazil	778	6-17	C, A	**M:** ≤ −0.50 D	9.6	N/A
East Asia							
Fan et al,[146] 2004	Hong Kong	7,560	5-16	C, A	**M:** ≤ −0.50 D **HM:** ≤ −6.00 D	36.7	1.2
Pan et al,[163] 2018	China (rural)	2,432	7-8	C, A	**M:** < −0.50 D **HM:** < −6.00 D	2.4	0.1
Hsu et al,[158] 2016	Taipei, Taiwan	11,590	8	C, A	**M:** ≤ −0.50 D	36.4	N/A
Lin et al,[123] 2004	Taiwan	10,878	7-18	C, A, R	**M:** ≤ −0.50 D **HM:** < −6.00 D	**7y:** 20 **12y:** 61 **15y:** 81	**12y:** 3.4 **15y:** 13 **18y:** 21
Ma et al,[156] 2016	China (urban) *SCES*	8,398	3-10	C, A	**M:** ≤ −0.50 D **HM:** ≤ −6.00 D	20.1	0.3
Zhao et al,[129] 2000	China (rural) *RESC*	5,884	5-15	C, R	**M:** ≤ −0.50 D	14.9	N/A
He et al,[130] 2004	China (urban)	4,364	5-15	C, R	**M:** ≤ −0.50 D	38.1	N/A
Pi et al,[160] 2012	China (semi-rural)	3,079	6-15	C, R	**M:** ≤ −0.50 D	13.7	N/A
Lin et al,[162] 2014	China (rural)	585	6-17	C, A	**M:** ≤ −0.50 D **HM:** < −5.00 D	23.3	0.7
Li et al,[161] 2014	China (rural)	1,675	5-18	C, S	**M:** ≤ −0.50 D	5	N/A
Pan et al,[163] 2018	China (rural)	2,346	13-14	C, A	**M:** < −0.50 D **HM:** < −6.00 D	29.4	0.4
He et al,[164] 2007	China (rural)	2,400	13-17	C, A	**M:** < −0.50 D	42.4	N/A
Li et al,[132] 2017	China (urban)	3,676	14-16	C, A	**M:** ≤ −0.50 D **HM:** < −6.00 D	65.5	6.7
Guo et al,[165] 2015	Ejina, China	1,565	6-21	C, A	**M:** ≤ −0.50 D **HM:** ≤ −6.00 D	60	**All:** 2.9 **11y:** 3.4

							18+y: 9.9
South Asia							
Pokharel et al,[195] 2000	Mechi Zone, Nepal *RESC*	5,067	5-15	C, R	**M:** ≤ −0.50 D	1.2	N/A
Sapkota et al,[196] 2008	Kathmandu, Nepal	4,282	10-15	C, S*	**M:** ≤ −0.50 D	19	N/A
Murthy et al,[193] 2002	India (urban) *RESC*	6,447	5-15	C, R	**M:** ≤ −0.50 D	7.4	N/A
Dandona et al,[194] 2002	India (rural)	4,074	7-15	C, R	**M:** ≤ −0.50 D	3.8	N/A
Middle East							
Jamali et al,[185] 2009	Shahrood, Iran	815	6	C, R	**M:** ≤ −0.50 D	1.7	N/A
Hashemi et al,[100] 2004	Tehran, Iran (urban) *TES*	809	5-15	C, S	**M:** ≤ −0.50 D	7.2	N/A
Hashemi et al,[186] 2018	Iran (rural)	3,314	5-15	C, A	**M:** ≤ −0.50 D	2.6	N/A
Fotouhi et al,[198] 2007	Dezful, Iran (semi-rural)	5,544	7-15	C, A	**M:** ≤ −0.50 D	2.5	N/A
Yekta et al,[187] 2010	Shiraz, Iran (urban)	1,872	7-15	C, A	**M:** ≤ −0.50 D	4.4	N/A
Ostadimoghaddam et al,[188] 2011	Mashhad, Iran	865	≤ 15	C, R	**M:** ≤ −0.50 D **HM:** < −6.00 D	3.6	0
Rezvan et al,[189] 2012	Bojnourd, Iran (urban)	1,551	6-17	C, A	**M:** ≤ −0.50 D	4.3	N/A
South East Asia							
Yingyong,[192] 2010	Thailand	2,340	6-12	C, A	**M:** ≤ −0.50 D	11.1	N/A
Goh et al,[191] 2005	Gombak District, Malaysia	4,634	7-15	C, R	**M:** ≤ −0.50 D	19.3	N/A
Saw et al,[190] 2005	Singapore *SCORM*	981	7-9	C, A	**M:** ≤ −0.50 D	32.7	N/A

*Only those with VA < 20/40 in at least one eye received cycloplegia

C = Cycloplegic, A = Auto-refraction, R = Retinoscopy, S = Subjective refraction, M = Myopia, HM = High Myopia

1.5.2.3 Prevalence of myopia in young adults

There are fewer population-based studies investigating myopia prevalence in older teenagers and young adults compared to those in school-aged children (Table 1.4). The most complete population-based figures come from countries where compulsory military service is required and data is collected from medical examinations upon enlistment. This typically only covers male subjects, however, as age groups between cohorts are consistent (typically at 19 years of age) and participant numbers are high, comparisons in prevalence between various countries can be readily made with a fair level of confidence, so long as the method of refraction remains consistent.

1.5.2.3.1 East Asian countries

There is a further increase in the prevalence of myopia within East Asian countries from school-children to young adults. It is here where we see the highest prevalence's recorded in any cohort, with the prevalence of myopia reaching epidemic proportions in many of these populations.

South Korea contains the highest rates of myopia, where a prevalence of 96.5% myopia and 21.6% high myopia were seen using cycloplegic refraction in a group of male military conscripts from Seoul; a highly urban location.[199] Slightly lower rates were seen in a smaller group of Korean conscripts from a more rural location, where the prevalence of myopia and high myopia were 83.3% and 6.8% respectively.[200]

In Taiwanese male military conscripts, the prevalence of myopia and high myopia is also high at 86.1% and 21.2% respectively.[201] Although this was not determined using cycloplegia, similar rates of 84% myopia and 21% high myopia were found in 18 year old Taiwanese high school leavers using cycloplegia,[123] but at a lower myopia cut-off at < -0.25 D.

In mainland China, similar rates have been found in 18 year old urban high school students in Fenghua,[133] with a prevalence of 87.7% myopia and 16.6% high myopia. Even higher levels have been documented from urban university students in Shanghai, at 95% and 19.5% respectively,[202]

however neither of these studies used cycloplegia. A more recent study in 7,971 young adults from Anyang University which did employ cycloplegia, reported a prevalence rate of 83.2% and 11.1% for myopia and high myopia respectively using the same definitions. Compared to their non-cycloplegic measures, the prevalences of myopia and high myopia were overestimated by 12.1% and 6.1% respectively, indicating that the figures from Fenghua and Shanghai were likely overestimated, and confirming the necessity of cycloplegia in young adults.

1.5.2.3.2 South East Asia

Following the previous trend in schoolchildren, Singapore also records high rates of myopia in young adults, and remains comparable to East Asia, with a prevalence of 81.6% myopia and 14.7% high myopia in its own sample of male military conscripts aged 19 years old.[126] Lower rates of myopia reported in Cambodia (54.7% in 19–29 year olds)[203] and Indonesia (46.3% in 21–29 year olds)[204] suggests that the prevalence rates in this region are heterogenous.

1.5.2.3.3 The Middle East

In contrast, while rates of myopia also continue to increase in the Middle East, they do not reach the levels seen in East Asia or Singapore. In Tehran, Iran, a survey using cycloplegia in residents aged 16-25 years old found that 22.5% of individuals were myopic.[100] Slightly, higher rates have been found in a larger study in Israel, where 28.3% of nationals aged 16–22 were myopic.[137] Though this rate likely was overestimated as cycloplegia was not used.

1.5.2.3.4 Countries with populations of European ancestry

Despite a limited number of studies using cycloplegic refraction, the prevalence rate of myopia in European populated countries appears relatively low compared what is seen in East and South East Asia. What is even more notable, is the stark difference in prevalence rates of high myopia found in these countries compared to those in East Asia, which ranges from 0.3–2.8% in predominantly

European Caucasian populations compared to urban populations of East Asia, where high myopia rates lie between 15–20% (Table 1.3).

From spectacle prescription data, Jacobsen et al, [142] reported that 12.8% of male conscripts in Denmark were myopic. Meanwhile in Australia, examination of participants from the RAINE birth cohort at ages 19–22 years using cycloplegia found that 23.7% of the cohort was myopic.[205] In the United States, the only available population-based data in young adults come from its National Health Nutrition Examination Survey (NHANES) in 1971–1972,[206] where 27.7% of participants had myopia. Though this was highly prone to overestimation, as refractive data was mostly obtained from presenting spectacle prescriptions and all degrees of myopia were included. Relatively high myopia rates (35%) were initially reported in Norwegian residents aged 20–25 years.[207] However again, results may have been overestimated, given that myopia and high myopia rates of 12.7% and 0.3% were reported in 16-19 year olds under cycloplegia in a later study by Hagen et al.[140]

Table 1.4: Summary of population-based studies reporting the prevalence of myopia in young adults. Prevalence values from repeated cohort studies are taken from the most recent year.

Author, Year	Location	n	Population	Age (years)	Method of refraction	Myopia definition/s	Myopia (%)	High Myopia (%)
East Asia								
Chen et al,[133] 2018	China (urban)	2,932	High school students	18.3 ± 0.6	NC, A	**M:** < -0.50 D **HM:** < -6.00 D	87.7	16.6
Sun et al,[202] 2012	China (urban)	5,083	University students	20.2 ± 2.8	NC, A	**M:** < -0.50 D **HM:** < -6.00 D	95.5	19.5
Sun et al, [31] 2018	China (urban)	7,971	University students	20.2 ± 1.5	C, A	**M:** < -0.50 D **HM:** < -6.00 D	83.2	11.1
Jung et al,[199] 2012	Korea (urban)	23,616	Male military conscripts	19	C, A	**M:** < -0.50 D **HM:** < -6.00 D	96.5	21.6
Lee et al,[200] 2013	Korea (rural)	2,805	Male military conscripts	19	C, A	**M:** < -0.50 D **HM:** < -6.00 D	83.3	6.8
Lin et al,[123] 2004	Taiwan	1,439	High school students	18	C, A, R	**M:** < -0.25 D **HM:** < -6.00 D	84	21
Lee et al,[201] 2013	Taiwan	5,048	Male military conscripts	18-24	NC, A	**M:** ≤ -0.50 D **HM:** ≤ -6.00 D	86.1	21.2
South East Asia								
Koh et al,[126] 2014	Singapore	28,908	Male military conscripts	19.8 ± 1.2	NC, A	**M:** < -0.50 D **HM:** < -6.00 D	81.6	14.7
Saw et al,[204] 2002	Indonesia	341	Rural villages	21-29	NC, A	**M:** ≤ -0.75 D	46.3	N/A
Shin et al,[203] 2018	Laos	859	Adults	19-29	NC, A	**M:** ≤ -0.75 D	54.7	N/A
The Middle East								
Hashemi et al,[100] 2004	Iran, Tehran	820	Tehran residents	16-25	C, S	**M:** ≤ -0.50 D	22.5	N/A
Dayan et al,[137] 2005	Israel	839,66	Israeli nationals	16-22	NC, A	**M:** ≤ -0.50 D **HM:** < -6.00 D	28.3	1.2
Countries with populations of European ancestry								
Sperduto et al,[206] 1983	United States	9,882	NHANES cohort 1971-1972	18-24	NC, S/R*	**M:** All **HM:** ≤ -7.90 D	27.7	0.3
Jacobsen et al,[142] 2007	Denmark	4,681	Male military conscripts	19.3 ± 1.6	NC, S**	**M:** ≤ -0.50 D **HM:** < -6.50 D	12.8	0.3
McKnight et al,[205] 2014	Australia	1,344	Participants from RAINE birth cohort	19-22	C, A	**M:** < -0.50 D **HM:** < -6.00 D	23.7	1.3
Hagen et al,[140] 2018	Norway	393	Secondary school students	16-19	C, A	**M:** ≤ -0.50 D **HM:** ≤ 6.00 D	12.7	0.5

Midelfart et al,[207] 2002	Norway	1,248	Norway residents	20-25	NC, S	**M:** ≤ -0.50 D **HM:** < -5.00 D	35	2.8

*Refraction obtained from presenting spectacle prescriptions. For those >20/40 that improved on pinhole, retinoscopy or subjective refraction was performed.

**Refraction obtained from presenting spectacle prescriptions only.

C = Cycloplegic, NC = Non-cycloplegic, A = Auto-refraction, R = Retinoscopy, S = Subjective refraction, M = Myopia, HM = High Myopia

1.5.2.4 Prevalence of myopia in adults

Unlike in young adults, more studies have examined the prevalence of myopia within older populations. However, the use of cycloplegia becomes increasingly rare, even though some populations cover pre-presbyopic individuals of ages 20 or 30–40 years old. What is essential however, is the exclusion of pseudophakic individuals as well as phakic individuals with significant cataract, as the development of nuclear sclerosis with age (especially in those aged ≥ 70 years old) will overestimate the prevalence of myopia, due to myopic shifts in refraction. Table 1.5 summarises studies which investigate the prevalence of myopia in cohorts of adults across various countries. Unless the use of cycloplegia is specifically noted, the data reported here is derived from non-cycloplegic refraction.

1.5.2.4.1 East Asian countries

In contrast to the extremely high rates of myopia found in young adults within East Asian countries, the prevalence of myopia among Chinese adults is much lower, and exhibits a clear rural versus urban divide. In 2005, the Beijing Eye Study reported refractive status in adults aged ≥ 40 years, from the urban Haidian district of Beijing and the rural village of Yufa, south of Beijing.[208] The overall rate of myopia was 22.9%, with the urban population between the ages of 40 to 69 significantly more myopic than those from the rural areas; a difference not found in the older populations in this study. In the Liwan Eye Study, which examined a highly urban population in Guangzhou, higher rates of myopia (32.5%) with 5% high myopia (< -5.00 D) were found.[209] In the Handan Eye Study,[210] which

examined a rural population, there were slightly lower rates of myopia (26.7%) with 1.8% having high myopia (< -5.00 D), however, the inclusion of the younger population aged 30 to 49, who demonstrated significantly more myopia than those aged 50 to 69 (see Figure 2;[210]) would account for the somewhat higher prevalence observed in this rural population. Additionally, it also indicates that myopia prevalence is increasing in younger generations, despite their rural location. Meanwhile in urban and rural regions of Mongolia, 17.2% of the population aged ≥ 40 years were myopic, but this was predominantly related to myopic shift in older persons related to onset of nuclear cataract.[211] These lower rates would suggest that the environmental influences driving increases in myopia were not uniform across China at this time.

In other East Asian countries with higher rates of urbanisation, there are limited studies examining rural and urban differences in older populations, but consistently lower rates of myopia are found in older person than observed in younger adults. Two studies from Japan however, do see an urban versus rural difference in myopia rates. The Tajimi study, reported relatively high rates of myopia (41.8%) in persons aged ≥ 40 years living in an urban environment, with the highest rate in the youngest age group 40–49 years, where approximately 69% were myopic.[212] Meanwhile, in the Kumejima study,[213] which studied a rural population, a lower rate of myopia (29.5%) was seen in those aged ≥ 40 years. High myopia rates followed a similar pattern of difference at 8.2 vs 1.9% respectively. In the Shihpai Eye Study,[214] 19.4% of urban residents of Taiwan aged ≥ 65 were myopic, with the prevalence peaking in the 75–79 years age group, indicating cataracts. In Korea, higher prevalence rates of myopia are seen in a national sample of adults (65.3% in those aged 40-44 years),[215] with lower prevalence rates seen in strictly rural populations (20.5% in residents aged ≥ 40 years).[216]

1.5.2.4.2 South East Asia

In Singapore, three studies have investigated the prevalence of myopia across its three major ethnic groups. Wong et al,[217] examined adult Chinese Singaporeans (aged 40–79 years) and found a myopia

prevalence of 38.7%. Rates of high myopia in this population were also high at 9.1%. Using the same protocol, two further studies examined the prevalence of myopia in the other two main ethic groups in Singapore and found that those of Malay[218] and Indian background[219] had lower rates of myopia (30.7% and 28.0% respectively), than the Chinese adult population in Singapore. High myopia prevalence's were also lower at 3.9% and 4.1% respectively. In Sumatra Indonesia, 28.8% of those aged 40–49 and 39.7% of those aged 50+ were found to be myopic,[220] suggesting that unlike in young adults, adult myopia prevalence across South East Asia are more similar.

1.5.2.4.3 South Asia

In Southern Asia, prevalence rates of adult myopia seems to be associated with the development of nuclear cataract. Bangladesh records low rates of myopia, being 5.16% (≤ 1.00 D) in those aged 30–39 and remaining low (< 20% until 60 years old) in those without significant cataract.[221] Meanwhile, adults in Pakistan appear to have the highest rates of myopia,[222] with ~43% of those aged 30-39 seen to be myopic. Urban areas of India show slightly lower rates, with the Andhra Pradesh Eye Disease Study reporting 19.2% myopia in those aged 40–49 years compared to 25% in Pakistan.[223]. Slightly lower rates were found in rural India (Tamil Nadu), with an overall prevalence of 15.6% among those of the same age group.[224]

1.5.2.4.4 The Middle East

Within the Middle East, Hashemi and colleagues have performed a number of refractive surveys in Iran. The first of these was in Tehran in the early 2000s and crucially used cycloplegic refraction, finding a prevalence of 19.6% in those aged 36–55 years old.[100] This marginally increased to 22.5% in those older than 56 years. A later study in Shahroud, a relatively urban city, which also used cycloplegic refraction, found a higher rate of myopia (30.2%) of adults aged ≥ 40 years.[225] A third study in a rural location used non-cycloplegic refraction and found a myopia prevalence of 28.5% in those aged 36–54 years.[226] Also using non-cycloplegic methods, a second Iranian rural study, the Yazd Eye Study,[227], found an overall higher prevalence (36.5%) of myopia, which unusually did not

vary substantially with age (40–80 years). More recently, a study using non-cycloplegic methods in two highly rural locations,[228] reported an overall prevalence rate of 16.2% in adults aged 41–60 years.

1.5.2.4.5 Countries with populations of European ancestry

In European populated countries, prevalence rates of myopia in adults are highly variable. Some rates have been compared as part of the European Eye Epidemiology (E^3) consortium,[229] which compared 15 population-based studies between 1990 and 2013 using a myopia cut off of ≤ −0.75 D.

Within the United Kingdom, the Norfolk Eye Study,[230] reported 27.8% of British adults aged 48–89 years to be myopic (≤ -0.50 D). Similarly, 31.4% of twins of ages 16–85 years were myopic from the national TwinsUK database.[229] Meanwhile, refractive data collected from those in the 1958 British birth cohort at 44–46 years of age, suggested a higher myopia (≤ -0.75 D) prevalence of 48.7%.[231] However, analysis of data from the UK Biobank Study suggested otherwise, reporting a prevalence rate of 27% in adults aged 40–69 years old.[232]

In Germany, rates of myopia appear to be similar to the United Kingdom. The Gutenburg Health Study reported that the prevalence of myopia (≤ -0.50 D) was 35.1% in a large sample of 13,959 adults aged 35–74 years.[233] A similar prevalence rate of 36.1% myopia (≤ -0.75 D) was also found from the KORA study in individuals aged 35–84 living in Ausberg.[229]

In France, three studies have investigated the prevalence of myopia, the ALIENOR study, the Montrachet Study and POLA study. The prevalence of myopia found within these three studies were all much lower than that found in the United Kingdom and Germany, at 16.7%, 19.1% and 16.2% respectively. This is despite investigating a much higher age bracket than the UK studies (60–93 years). A similar prevalence rate of 14.2% has also been found in Greek adults of similar ages (60–94 years) from the Thessaloniki eye study,[229] suggesting that prevalence rates in Southern Europe may be similar to that of France.

In the Netherlands, rates of myopia are in between that of France and the United Kingdom. The Erasmus Rucphen Family Study reported a myopia prevalence of 21.2% in individuals aged 14–87 years old.[229] Meanwhile, data from the third Rotterdam Elderly Study collected during 2005–2008 found a higher prevalence of 32.5%, despite having a cohort of more elderly adults aged 46–97. Myopia (≤ -0.50 D) rates in Norway also appear to be similar, with a prevalence of 30.3% in adults aged 40–45 years. The Tromsø Eye Study reported a lower rate at 19.4%, though they included an older sample aged 35–87, and used a higher cut-off for myopia (≤ -0.75 D).[229]

In the United States, four studies have investigated myopia prevalence across its major ethnic groups in adults aged ≥ 40 years old. The Baltimore Eye Study studied a population of both Black and White residents and reported a myopia prevalence of 22.7%.[234] In the Barbados Eye Study,[235] which examined an entirely Black population, a similar prevalence rate of 21.9% was seen. Meanwhile in Latino-Americans, the Los Angeles Latino Eye Study, reported a slightly lower rate of 16.8% [236] which may be due to a higher myopia cut-off (-1.00 D). The highest rates of myopia (35.1%) have been found within Chinese Americans from the Chinese American Eye Study (CHES), with those in the two youngest age categories (50–59 and 60–69 years old) displaying the highest rates of myopia (36.1% and 36.6% respectively).[237] High prevalence's of high myopia were also found being 7.4% in total. These rates are similar to that seen of Chinese adults living in urban China[209] and Singapore.[217] Given that the critical period of myopia develop occurs in childhood/adolescence, it is not clear whether the adults sampled in the CHES were of immigrant background or grew up within the United States.

In Australia, the prevalence of myopia in adults is also relatively low. The Blue Mountains Eye Study (BMES) reported myopia (≤ -0.50 D) and high myopia (≤ -4.00 D) prevalences of 15% and 3% from adults aged 49–97 years.[238] Similar rates were also found during the Visual Impairment Project study, where 17% of adults in urban and rural Victoria were found to be myopic.[239] Though a lower rate of high myopia rate was found (1.5%), likely due to a higher cut-off used (≤ -5.00 D).

1.5.2.4.6 Africa

In African countries, the prevalence of myopia among adults is low. In a national sample of Nigerian adults ≥ 40 years of age, myopia and high myopia prevalence's were 16.2% and 2.1% respectively.[240] Meanwhile, a lower prevalence of 11.4% was found in a smaller sample of residents living in suburban provinces of Durban, South Africa.[241]

1.5.2.4.7 South America

In South America, similar rates are seen to Africa, with 15.7% of adults 30–55 years of age residing in urban districts of Colombia found to be myopic.[242] Though lower rates were seen in its rural districts, where 9.2% were myopic.

Table 1.5: Summary of population-based studies reporting the prevalence of myopia in adults. Prevalence values from repeated cohort studies are taken from the most recent year.

Author, Year	Location	n	Population	Age (years)	Method of refraction	Myopia definition/s	Myopia (%)	High Myopia (%)
East Asia								
He et al,[209] 2009	China (urban)	1,405	Liwan District, Guangzhou *Liwan Eye Study*	≥ 50	NC, S	**M:** < -0.50 D **HM:** < -5.00 D	32.3	5
Liang et al,[210] 2009	China (rural)	6,491	Handan *Handan Eye Study*	≥ 30	NC, S	**M: <** -0.50 D **HM:** < -5.00 D	26.7	1.8
Xu et al,[208] 2004	China	4,319	Urban and rural Beijing *Beijing Eye Study*	40–90	NC, A, S	**M:** < -0.50 D **HM:** < -6.00 D	22.9	2.6
Cheng et al,[214] 2003	Taiwan	2,045	Shihpai district *Shihpai Eye Study*	≥ 65	NC, A, S	**M:** < -0.50 D **HM:** < -6.00 D	19.4	2.4
Han et al,[215] 2019	Korea (urban)	737	*Korea National Health and Nutrition Examination Survey*	40-44	NC, A	**M:** ≤ -0.50 D **HM:** ≤ -6.00 D	65.3	7.6
Yoo et al,[216] 2013	Korea (rural)	1,532	Namil-myeon *Namil Study*	≥ 40	NC, A	**M:** < -0.50 D **HM:** < -6.00 D	20.5	1
Sawada et al,[212] 2008	Japan (urban)	3,021	Tajimi *Tajimi study*	≥ 40	NC, S	**M:** < -0.50 D **HM:** < -5.00 D	41.8	8.2
Nakamura et al,[213] 2018	Japan (rural)	2,384	Kumejima *Kumejima study*	≥ 40	NC, S	**M:** < -0.50 D **HM:** < -5.00 D	29.5	1.9
Wickremasinghe et al,[211] 2004	Mongolia	620	Ömnögobi	≥ 40	NC, A	**M:** < -0.50 D	17.2	N/A
South East Asia								
Wong et al,[217] 2000	Singapore	1,113	Chinese	40-79	NC, S	**M:** < -0.50 D **HM:** < -5.00 D	38.7	9.1
Saw et al,[218] 2008	Singapore	2,974	Malays *Singapore Malay Eye Survey*	40-80	NC, A, S	**M:** < -0.50 D **HM:** < -5.00 D	30.7	3.9
Pan et al,[219] 2011	Singapore	2,805	Indians *Singapore Indian Eye Study*	≥ 40	NC, A, S	**M:** < -0.50 D **HM:** < -5.00 D	28	4.1
Saw et al,[220] 2002	Indonesia	1,043	Riau Province	≥ 21	NC, A	**M:** ≤ -1.00 D **HM:** ≤ -6.00 D	26.1	0.8

South Asia								
Bourne et al,[221] 2004	Bangladesh	11,624	National sample	≥ 30	NC, A, S	**M:** < -0.50 D **HM:** < -5.00 D	22.1	1.8
Shah et al,[222] 2008	Pakistan	14,490	National sample	≥ 30	C, A	**M:** < -0.50 D **HM:** < -5.00 D	36.5	4.6
Krishnaiah et al,[223] 2009	Indian (mostly urban)	10,293	*Andhra Pradesh Eye Disease Study*	≥ 40	NC, R, S	**M:** < -0.50 D **HM:** < -5.00 D	34.6	4.5
Raju et al,[224] 2004	Indian (rural)	2,508	Tamil Nadu	> 39	NC, R, S	**M:** < -0.50 D **HM:** < -5.00 D	27.0	3.7
The Middle East								
Hashemi et al,[100] 2004	Iran	3,544	Tehran (urban)	5-96	C, S	**M:** ≤ -0.50 D **HM:** < -6.00 D	**All:** 17.2 **≥56 yo:** 22.5	**All:** 5.2
Hashemi et al,[225] 2012	Iran	4,864	Shahroud (urban)	40-64	C, A, S	**M:** ≤ -0.50 D **HM:** < -6.00 D	30.2	1.9
Hashemi et al,[226]	Iran	2,001	Khaf County (rural)	16-90	NC, A, R	**M:** < -0.50 D **HM:** < -6.00 D	**All:** 28.0 **> 40yo:** 32.5	**Total:** 1.5
Ziaei et al,[227] 2013	Iran	2,098	Yazd (rural) *Yazd Eye Study*	40-80	NC, R, S	**M:** < -0.50 D **HM:** ≤ -6.00 D	36.5	2.3
Hashemi et al,[228] 2018	Iran	943	Shahyoun & Kajour (rural)	41-60	NC, A, R, S	**M:** < -0.50 D	16.2	N/A
Countries with populations of European ancestry								
Sherwin et al,[230] 2012	United Kingdom	4,428	Norfolk *EPIC-Norfolk Eye Study*	48-89	NC, A	**M:** ≤ -0.50 D	27.8	N/A
Williams et al,[229] 2015	United Kingdom	2,495	1958 British birth cohort	44-46	NC, A	**M:** ≤ -0.75 D	48.7	N/A
Williams et al,[229] 2015	United Kingdom	6,095	National TwinsUK database	16-85	NC, A	**M:** ≤ -0.75 D	31.4	N/A
Williams et al,[229] 2015	France	618	*ALIENOR study*	73-93	NC, A	**M:** ≤ -0.75 D	16.7	N/A
Williams et al,[229] 2015	France	576	*Montrachet Study*	76-92	NC, A	**M:** ≤ -0.75 D	19.1	N/A
Williams et al,[229] 2015	France	2,315	*POLA study*	60-93	NC, A	**M:** ≤ -0.75 D	16.2	N/A
Williams et al,[229] 2015	Netherlands	2,662	*Erasmus Rucphen Family Study*	14-87	NC, S	**M:** ≤ -0.75 D	21.2	N/A
Williams et al,[229] 2015	Netherlands	3,624	Rotterdam *Rotterdam Elderly Study III*	46-97	NC, S	**M:** ≤ -0.75 D	32.5	N/A
Midelfart et al,[207] 2002	Norway	1,889	Residents in Norway	40-45	NC, S	**M:** ≤ -0.50 D **HM:** < -5.00 D	30.3	3.3
Williams et al,[229] 2015	Norway	5,792	*Tromsø Eye Study*	38-87	NC, A	**M:** ≤ -0.75 D	19.4	N/A

Wolfram et al,[233] 2014	Germany	13,959	Gutenberg *Gutenberg Health Study*	35-74	NC, A	**M:** < -0.50 D	35.1	N/A
Williams et al,[229] 2015	Germany	2,372	Augsburg *KORA Study*	35-84	NC, A	**M:** ≤ -0.75 D	36.1	N/A
Williams et al,[229] 2015	Greece	1,952	*Thessaloniki eye study*	60-94	NC, S	**M:** ≤ -0.75 D	14.2	N/A
Katz et al,[234] 1997	United States	5,036	African-Americans & Caucasians *Baltimore Eye Study*	≥ 40	NC, S	**M:** < -0.50 D	22.7	N/A
Wu et al,[235] 1999	United States	4,036	African-Americans *Barbados Eye Study*	40-84	NC, A	**M:** < -0.50 D	21.9	N/A
Tarczy-Hornoch et al,[236] 2006	United States	5,927	Latinos *Los Angeles Latino Eye Study*	≥ 40	NC, A	**M:** ≤ -1.00 D **HM:** ≤ -5.00 D	16.8	2.4
Verma et al,[237] 2017	United States	4,144	Chinese-Americans *The Chinese American Eye Study*	≥ 50	NC, A, S	**M:** < -0.50 D **HM:** < -5.00 D	35.1	7.4
Attebo et al,[238] 1999	Australia	3,654	*Blue Mountains Eye Study*	49-97	NC, S	**M:** < -0.50 D **HM:** ≤ -4.00 D	15	3
Wensor et al,[239] 1999	Australia	5,744	Urban and rural Victoria *Visual Impairment Project*	≥ 40	NC, S	**M:** < -0.50 D **HM:** < -5.00 D	17	1.5
Africa								
Ezelum et al,[240] 2011	Nigeria	13,599	National sample	≥ 40	NC, A	**M:** ≤ -0.50 D **HM:** ≤ -5.00 D	16.2	2.1
Mashige et al,[241] 2016	South Africa	1,939	Durban, KwaZulu-Natal Province	35-90	NC, A, R, S	**M:** < -0.50 D	11.4	N/A
South America								
Galvis et al,[242] 2018	Colombia	3,608	Residents from urban and rural Colombian districts	35-55	NC, R	**M:** ≤ -0.50 D	**Urban:** 15.7 **Rural** 9.2	N/A

C = Cycloplegic, NC = Non-cycloplegic, A = Auto-refraction, R = Retinoscopy, S = Subjective refraction, M = Myopia, HM = High Myopia

1.5.3 Future projections of myopia prevalence

A number of meta-analyses have pooled data from various studies of prevalent myopia in an attempt to broadly visualise changes in prevalent myopia over time across larger groups. However, one must consider that the prevalence of myopia can vary significantly even within smaller population groups such as within individual countries, due to ethnic and geographic differences. Hashemi et al,[243] performed meta-regression using pooled data from 157 studies which reported prevalent myopia rates between 1990 and 2016 and showed a global increase in the prevalence of myopia, from 10.4% in 1993 to 34.2% in 2016 (P = 0.097). Similarly, Holden et al[2] conducted a meta-analysis of 145 studies published from 1995 and estimated that worldwide prevalence of myopia was 22.9% in 2000 (95% CI: 15.2–31.5%), with high myopia rates being 2.7% (95% CI: 1.4–6.3%). Extrapolations of future myopia prevalence were also made, with 49.8% of the world's population predicted to become myopic and 9.8% being highly myopic by 2050. While a startling statistic, some caution may be needed as the projection equations were derived from six particular longitudinally repeated cross-sectional studies which all reported increases in prevalence over time.[123, 125, 126, 128, 135, 137] Meanwhile, the two studies which have not reported changes in prevalence were not included.[138, 143] These two studies provide two key aspects on the nature of changes in global myopia prevalence which need to be considered (Discussed in Section 1.5.1.2). Firstly, the data from Finland,[138] suggested that not all populations may be susceptible to rises in myopia prevalence to the same degree, such as some rural populations not subject to intense educational loads. Secondly, what was seen in Hong Kong,[143] suggests that countries with existing high rates of myopia (such as in East Asia) may have reached a saturation point of myopia prevalence and are unlikely to see further significant increases. Additionally, given that four of the six studies were also derived from East Asian populations, the projections may not carry enough external validity to be applied to other populations. Assumptions were also made in regions with low myopia prevalence that constant prevalence rate increases would occur (3.26% increase per year). As this did not allow for myopia prevalences to remain stable, it may likely have overestimated future prevalence rates.

1.5.4 Summary

Over the past couple of decades, there has been an increase in the prevalence of myopia which has affected certain locations across the world. These changes were most severe in urban locations in countries of East Asia, where epidemic rises were seen, occurring in school-aged children and young adults. While age-specific prevalences of myopia appears to differ between countries, differences in prevalence rates seen within ethnic groups residing between urban and rural cities, indicates that factors relating to differences in geographic locations may also contribute to the development of myopia. Meanwhile, in older adults, the prevalence of myopia remains relatively low. Although natural hyperopic shifts in refraction with age may contribute to a decrease in myopia prevalence, there is still a large difference in prevalence of both myopia and high myopia seen between groups of young adults and older adults, even in East Asian countries. This difference has been termed a "generational gap" which reflects the large rapid increase in myopia prevalence seen across a single generation. This is also indicative of a myopia epidemic.

1.6 Impact of Myopia

1.6.1 Visual implications of myopia

Out of all the refractive errors, myopia has the most severe visual consequences.[71] In addition to the known correctable decline of visual acuity which occurs linearly with higher levels of myopia, there are additional visual implications which arise, each carrying increasing risks of irreversible vision impairment at higher degrees of myopia.

1.6.1.1 Myopia and glaucoma

Myopia has been associated with an increased risk of glaucoma. Several cross-sectional population-based studies across different ethnicities have found a higher prevalence of open-angle glaucoma in individuals with high myopia. In the Blue Mountains Eye Study (BMES),[244] there was a higher prevalence of open angle glaucoma in low myopes (-1.00 D to -3.00 D) (4.1%, OR: 2.3) and moderate to high myopes (≥ -3.00 D) (4.4%, OR: 3.3), compared to emmetropes (1.5%). Meanwhile in the Beijing Eye Study,[245] a higher prevalence of glaucomatous optic nerve damage was seen in highly myopic eyes (> -6.00 D) compared to hyperopic eyes, emmetropic eyes and eyes with low to moderate myopia. Further associations between general myopia and glaucoma have been found in the Barbados Eye Study,[246] Beaver Dam Eye Study,[247] the Tajimi Study,[248] the Singapore Indian Eye Study[249] and the Malmo eye survey.[250] A meta-analysis in 2011 by Marcus et al,[251] confirmed these associations reporting that even low levels of myopia (up to -3.00 D) was associated with an increased risk (pooled OR: 1.77) for developing open-angle glaucoma.

1.6.1.2 Myopia and cataract

While it is known that aged-related nuclear sclerosis of the lens causes a myopic shift in refraction, evidence suggests that myopia may also lead to the early development of cataracts. Though many early findings were from cross-sectional studies,[217, 235, 252-254] making it difficult to distinguish the causal effect, there is evidence from longitudinal studies, such as the Visual Impairment Project,[255]

where myopia (> 1.00 D) was found to be an independent risk factor for the development of cortical cataracts (RR: 2.0) but not nuclear or posterior sub-capsular cataracts. Further longitudinal evidence came in 2014 from the 10 year follow-up of the Blue Mountains Eye Study,[256] which found that myopes at baseline were more likely to develop posterior sub-capsular cataracts compared to emmetropes (OR: 2.12). For nuclear cataracts, only baseline high myopia (≥ -6.00 D) was associated with incident nuclear cataracts (OR: 3.01), whereas mixed results were seen for cortical cataracts as there was an association with only moderate myopia (OR: 1.79). Overall, myopes were also more likely to require cataract surgery (OR: 2.75), with increasing risks for higher levels of myopia.

1.6.1.3 Myopia and retinal detachment

Myopic eyes are also associated with a higher risk of rhegmatogenous retinal detachment. In the literature, most reports investigating the relationship between myopia and retinal detachment come from case-control studies due to the incidence of retinal detachments being low in the general population.[257-261] Pooled results by Haarman et al in 2020,[4] indicate that higher odds for retinal detachment in all myopes compared to emmetropes (OR: 3.5), with increasing risks at higher degrees of myopia (moderate myopia OR: 8.7, high myopia OR: 12.6). Highly myopic eyes also have a worse surgical prognosis than non-myopes, as they achieve lower levels of post-operative visual acuity[258, 262, 263] and require more reoperations to achieve success.[264-267]

1.6.1.4 Myopia-related pathologies

In addition to raised risks of other ocular conditions, there are a number of myopic pathologies which directly occur as a result of excessive myopic axial elongation. The term “pathologic myopia” is commonly used in this scenario, which has historically been considered in a similar manner as high myopia, using a refractive error cut-off for definition. However, the latest definition proposed by Ohno-Matsui et al,[3] utilises sole pathological biomarkers, and defines pathologic myopia as having either myopic chorioretinal atrophy and/or in the presence of posterior staphylomas. Posterior staphylomas are an outpouching of a circumscribed area of sclera at the posterior pole, which occur

following excessive axial elongation of the globe. While they do not directly cause visual impairment, they commonly lead to, and are associated with other sight threatening myopic pathologies such as macular retinoschisis, myopic optic neuropathy. Myopic chorioretinal atrophy on the other hand, encompasses a spectrum of myopic macular progression changes which lead to the development of macular atrophy. While these progressive changes occur gradually, two types of lesions may arise that lead to sudden significant vision impairment: 1) lacquer cracks; which represent breaks in Bruch's membrane; and 2) the development of myopic choroidal neovascularisation.[268]

While the overall prevalence of pathologic myopia is relatively low, occurring in 0.9-3.8% of the general adult population,[64, 269-272] prevalence rates rise exponentially with increasing levels of myopia. For example, in the rural Chinese population, myopic retinopathy was seen in 0.3% of those with myopia ≤ -5.0 D, 11.1% of those with myopia from -5.0 D to -7.9 D, and in 65.7% of those with ≤ -8.0 D of myopia.[270] Meanwhile in an urban Chinese population; where prevalence rates of myopia are higher; myopic retinopathy was seen in 3.8% of eyes with ≤ -4.0 D, and reached 89.6% in eyes with ≤ -10.0 D.[271] The presence of pathologic myopia is associated with higher rates of vision impairment, with Shih et al,[273] reporting that 50% of patients older than 40 years with myopic maculopathy had a deterioration in visual acuity of more than 2 lines over 10 years, compared to only 4.3% of those without any myopic maculopathy.

Collective impacts of myopia related vision impairment was assessed in 2014 by Verhoeven et al,[71] who examined the prevalence and causes of vision impairment (defined using the WHO criteria for low vision of 6/12 unilaterally and 6/19 bilaterally) using data form the Rotterdam Study I and II. Overall, high myopes were found to have a significantly higher lifetime risk of visual impairment compared to emmetropes, with a 3.4 OR for those with myopia between -6.0 D and -10.0 D, and a 22.0 OR for those with myopia -10.0 D or worse. Myopic macular degeneration (MMD) was the most common cause of visual impairment, followed by cataracts and primary open-angle glaucoma.

There is potential for rates of vision impairment occurring from myopia related pathologies to rise in the near future, as individuals affected by the myopia epidemic begin to reach adult age groups. This can be further exponentiated, as the proportions individuals with high myopia are seen to be higher in populations with higher levels of myopia. Fricke et al,[274] pooled data from 17 papers which reported prevalence rates of MMD induced vision impairment, to produce a predictive model to estimate prevalence rates of vision impairment (WHO definition) associated with MMD from 2000 to 2050. This estimated that in the year 2000, vision impairment due to MMD affected 4.2 million people (0.07% of the world's population) and predicted that rates would increase eight-fold over time, affecting 55.7 million people by 2050 (0.57%).

1.6.2 Economic costs of myopia

Alongside the visual consequences of myopia, there exists both considerable economic, societal and personal impacts which place burdens for individuals affected as well as for government and healthcare systems involved. On an individual level, financial costs associated with myopia include basic costs of eye care, purchasing optical correction and treatment costs associated with downstream complications and secondary eye conditions. While on a broader level, there are also costs to the government and healthcare system, such as the operating cost of facilities such as hospitals, aged care services, pharmaceutical subsidies and the employment of staff and carers.

Within Australia, Taylor et al examined the economic costs of vision loss and found that refractive errors were the second most costly eye condition (after cataracts), costing Australia $261.3 million in 2004.[275] While this estimate represented cost of managing refractive errors as a whole, it can be safely assumed that a large proportion of this value was from myopic correction, given that myopia is the more common form of refractive error. Furthermore, it only considered direct healthcare costs and not indirect costs. Additional indirect costs of vision impairment relating to myopia which were not captured in this estimate reflect potential costs associated with years of healthy life lost, carer costs as well as potential losses in earnings and productivity. Compared to direct costs for vision

disorders as a whole, which was estimated to cost $1.8 billion, indirect costs were reported to lie at $3.2 billion. Therefore it should be unsurprising that the true costs associated with myopia are much larger than described in current reports. In Singapore, the annual direct costs of myopia in adults was estimated to be $755 million USD,[276] with refractive correction (optometry visits, costs of spectacles and contact lenses) accounting for the majority (65%) of the total costs. Meanwhile for children, median direct costs have been estimated to be around $25 million USD per year.[277] In the United States, estimates of direct costs for refractive correction from NHANES data between 1999 and 2002, were $3.8 billion per year across the whole population.[278] On a global scale, Naidoo et al estimated using meta-analysis, that the global potential loss associated with vision impairment for that year was $244 billion USD per annum from uncorrected myopia and $6 billion USD per annum from MMD in 2015.[279] in comparison, previous estimates in 2007 of the operating costs required to provide refractive care services for these individuals were between $20–28 billion.[280]

1.6.3 Psychosocial impacts of myopia

While not as evident as the financial costs of myopia, there are a number of potential psychosocial issues associated with myopia and its vision impairment which may negatively impact an individual's quality of life. Wong et al,[281] reported lower scores in quality of life measures, psychosocial functioning and school functioning among individuals with vision impairment.[281] However, as refractive errors were not directly associated with reductions in any of these measures, it suggested that these issues arose primarily due to general vision impairment. On the other hand, Rose et al,[282] surveyed a sample of adult patients electing to undergo refractive correction, and found that higher degrees of myopia were associated with significantly poorer subjective reports of visual function and an overall reduced quality of life. This level of impairment was comparable to individuals who also presented with keratoconus, however, given that high myopia was defined at ≥ -10.00 D, and the sample of participants were self-elected to undergo refractive surgery, they may have represented a highly selected sample of individuals who were dissatisfied with myopic symptoms. Meanwhile Chen

et al,[283] compared vision-related quality of life among emmetropes, myopes who had refractive surgery and myopes who wore spectacles and/or contact lenses, and found that spectacle and/or contact lens wearers had significantly increased odds of having concerns about injuring themselves (OR: 11.5), difficulties coping with demands in life (OR: 23.6), difficulties fulfilling roles (OR: 5.6) and less confidence joining in everyday activities (OR: 30.6) compared to emmetropes. In contrast, previous myopes who underwent refractive surgery for correction, reported no differences in quality of life measures compared to emmetropes, indicating the potential for psychosocial improvements with treatment of myopia. In the extreme end, Takashima et al evaluated functional and quality of life outcomes in patients with pathological myopia and found that compared to control subjects, 3 major influencing factors were contributing to reduced functional and quality of life outcomes; 1) disability factors, which impaired performance in activities on an individual level; 2) handicap factors, which restricted participation in social activities; and 3) support related factors, which encompassed physical, social, and attitudinal settings in which people live and conduct their lives within the environment.[284]

1.6.4 Summary

Although the initial visual impacts of myopia is generally benign at first and is easily corrected via optical aids such as spectacles and contact lenses, there are various underlying consequences which can follow. Immediate impacts experienced are usually related to financial costs to the individual, due to costs associated with eye care and treatment. However, there are also pathological risks associated with myopia that occur later in life and in individuals with higher degrees of myopia, which often lead to significant uncorrectable visual impairment. On a broader level, refractive errors also place a considerable burden on society, due to significant direct financial costs as well as more insidious indirect costs of service provision. As many of the consequences of myopia occur exponentially in proportional to the severity and prevalence of myopia, measures to prevent the early onset and rapid progression of myopia during childhood are required to reduce impending

functional and economic strains on individuals and society in the near future. This is especially important in new developing countries with lower socioeconomic status and are at risk of rapid myopia rises, as they may not have the capacity and resources to cater for significant increases in financial demand and healthcare requirements.

1.7 Strategies for Myopia Control

Conventional treatment of basic myopia improves visual acuity and some vision-related quality of life associated with vision impairment, however does not alter the underlying biometric status of the eye nor its future refractive trajectory. Fortunately myopia control is possible, with several strategies now available. These fall into three broad areas: pharmacotherapy, optical manipulation and environmental/behavioural modification. Within these are also several sub-categories, defined by differences in underlying mechanisms of effects. Some strategies are able to influence myopic shifts prior to myopia development, which reduces incident myopia, while others have been developed to reduce the progression of existing myopia.

1.7.1 Modification of refractive errors in animal studies

In animal models, refractive errors can be artificially induced, demonstrating that refractive errors are not always inherently pre-determined and can be altered after birth using external inputs. During Wiesel and Raviola's Nobel Prize winning investigation into the effects of monocular visual deprivation on the development of binocular cortical neurons,[285] they noticed that eyes of monkeys subject to lid fusion, developed high myopia as a result of severe axial elongation. Around the same time, similar findings were reported in tree-shrews by Sherman et al[286] and chickens by Wallman et al.[287] Since then, this behaviour has been demonstrated in a wide variety of animals including mice,[288] fish,[289] guinea pigs,[290] rabbits[291] and birds.[292] This method of experimentally induced myopia has been termed "Form-Deprivation Myopia" (FDM). In the following decades, a second method of experimentally induced myopia was discovered after optical defocus was also found to induce compensatory changes in eye growth and hence alter underlying refractive errors.[84, 86, 87, 288, 293-296] When a negative lens is placed in front of the eye, hyperopic focus is induced as the image shifts behind the retina. This causes the eye to grow in its axial direction, creating a myopic shift until the defocus is cleared and the eye appears emmetropic. This principle has been used to induce myopia in animal models, referred to as "Lens-Induced Myopia" (LIM). On the other hand, when a positive

lens induces myopic defocus, eye growth is inhibited, allowing changes in the anterior eye and loss of crystalline lens power to produce hyperopic shifts.

1.7.2 Pharmacological treatments for myopia control

The earliest method of myopia control began with the use of atropine drops. Although other pharmacological agents have been studied, such as pirenzepine[297-299] and 7-methylxanthine[300], neither have been incorporated into routine clinical practice due to limited levels of efficacy (Table 1.6)

Atropine is a non-selective muscarinic acetylcholine receptor antagonist historically derived from the *Atropa belladonna* plant. In modern ophthalmological practice, 1% of atropine solution is typically used for its long-acting mydriatic and cycloplegic properties: in order to accurately measure refractive errors, to provide therapeutic relief in anterior uveal inflammation and to penalise the contralateral eye in the management of childhood amblyopia. Atropine is also known for its harsh side effect profile; both ocular and systemic; which include blurred vision, photophobia, allergic reactions, dry mouth/throat, increased heart rate and increased blood pressure.

While the first cited uses of atropine for myopia control was recorded by Dutch ophthalmologist Donders in 1864,[301] it was only in the 1970's when strong evidence began to accumulate for its positive effects, with early trials finding that both 0.5% and 1% atropine could slow myopic progression more significantly than placebo as well as cyclopentolate controls.[302-306] Initially, this was believed to occur via blocking accommodation,[307] however, animal studies suggested otherwise, as the anti-myopic effects of atropine remain active in chickens,[308] despite chickens having an accommodative response mediated by nicotinic receptors rather than muscarinic. Although currently the exact mechanism by which atropine exerts its anti-myopic effects has not been confirmed, it is widely believed that atropine acts either directly or indirectly on retinal or scleral tissue.[309] This initiates a biochemical signalling cascade, leading to downstream inhibition of scleral

fibroblast proliferation and hence scleral thinning or stretching is avoided, and thereby eye growth.[310]

The Atropine for the Treatment of Myopia (ATOM) 1 and 2 clinical trials, were two large randomised studies which investigated the effects of various atropine doses on myopia progression over a 2 year period. ATOM1 compared 1% atropine to placebo,[311] whilst ATOM2 investigated 0.5%, 0.1% and 0.01% doses and compared results to the control group of ATOM1.[312] Combined results from both trials demonstrated a direct dose-related response, with higher doses of atropine inhibiting progression of myopia more effectively than lower doses after the first year of use. This remained following the second year of study, however overall differences in myopia progression between doses were clinically similar with only a 0.19 D and 0.14 mm difference in myopic progression and axial elongation between the 0.5% and 0.01% doses. Following on from the first phase of the ATOM1&2 studies, a 12-month washout period was placed. During this phase, significant dose-dependent rebound effects were observed, where groups treated with the highest dose had the largest changes in myopic progression.[313, 314] Overall, this resulted in children who were originally given the lowest dose of atropine (0.01%) showing the least myopia progression after 3 years. In the third year of the ATOM study, all children (regardless of initial dose) who progressed more than 0.50 D of myopia year 2, were restarted on 0.01% atropine for a further 2 years. Dose dependent effects remained, as fewer children in the original 0.01% group required re-treatment compared to those who started with 0.1% or 0.5% (24% vs 59% and 68% respectively).[315] This resulted in the overall 5-year progression of myopia to be the lowest in those originally receiving 0.01% atropine compared with those who received 0.1% or 0.5% (-1.38 D vs -1.83 D and -1.98 D respectively), with axial elongation being equivocal between dosage groups (P = 0.185).

Following the ATOM studies, two smaller RCTs have been conducted investigating atropine (at 1% and 0.5%) in children with low myopia (-0.50 to -2.00 D).[316, 317] Both studies reported hyperopic shifts in SER alongside small reductions in AL elongation after 1 year, suggesting that myopic reversal may

be possible, however, the reductions in myopia observed may have reflected the process of lens thinning occurring during this age group, or an incomplete cycloplegic refraction at baseline which may have been revealed by the strong cycloplegic actions of atropine at such high concentrations. Longer studies using 1% atropine such as in ATOM1, suggests that this apparent effect does not persist after the first year of treatment.[311]

The Low-concentration Atropine for Myopia Progression Study (LAMP), was a recent RCT comparing three low concentrations of atropine (0.01%, 0.025% and 0.05%) in 438 Hong Kong children aged 4-12.[318] Like in the ATOM studies, significant dose-dependent effects against myopia progression and AL elongation were seen after the first year, with ocular side effects which did not significantly affect visual acuity or vision-related quality of life scores. This suggested that 0.05% atropine could be better than 0.01% atropine whilst being well tolerated. This efficacy was maintained into year 2, with those who were started with 0.05% atropine exhibiting the least progression and elongation. In the third year of the LAMP study, where half of the subjects in each dosing group ceased treatment, dose dependent rebound effects occurred in all groups, suggesting that continued treatment with 0.05% atropine remained the most effective regimen.[319]

Table 1.6: Summary of studies investigating pharmacological treatments for myopia control.

Author, Year (Country)	Sample Size & Baseline Mean Age	Treatment(s)	Control	Study Duration (years)	Difference in Myopia Progression [Control - Treatment, D(%)]	Difference in Axial Elongation [Control - Treatment, mm(%)]
Chua et al, 2006 (Singapore)[311]	n = 400 (6-12)	Atropine 1%	Placebo eye drops	2	-0.92 (77)	+0.40 (105)
Chia et al, 2012 (Singapore)[312]	n = 400 (6-12)	Atropine 0.5%, 0.1% or 0.01%	ATOM1 placebo (historical control)	2	**0.5%:** -0.90 (75) **0.1%:** -0.82 (68) **0.01%:** -0.71 (59)	**0.5%:** +0.11 (29) **0.1%:** +0.10 (26) **0.01%:** -0.03 (-8)
Yi et al, 2015 (China)[316]	n = 132 10 (7-12)	Atropine 1%	Placebo eye drops	1	+0.47 (155)	+0.35 (109)
Wang et al, 2017 (China)[317]	n = 126 9 (5-10)	Atropine 0.5%	Placebo eye drops	1	-1.20 (60)	+1.60 (320)
Yam et al, 2019 (Hong Kong)[318]	n = 438 8 (4-12)	Atropine 0.05%, 0.025% or 0.01%	Placebo eye drops	1	**0.05%:** -0.54 (67) **0.025%:** -0.35 (43) **0.01%:** -0.22 (27)	**0.05%:** +0.21 (51) **0.025%:** +0.12 (29) **0.01%:** +0.05 (12)
Yam et al, 2019 (Hong Kong)[320]	n = 438 8 (4-12)	Atropine 0.05%, 0.025% or 0.01%	Placebo group switched to 0.05% during 2nd year	2	**0.05%:** -0.45 (45) **0.025%:** -0.15 (15) **0.01%:** +0.12 (-12)	**0.05%:** +0.19 (33) **0.025%:** +0.08 (14) **0.01%:** -0.01 (-2)
Siatkowski et al, 2004 (USA)[297]	n = 174 10 (8-12)	2% pirenzepine gel twice daily	Placebo gel	1	-0.27 (51)	+0.04 (13) *
Siatkowski et al, 2008 (USA)[298]	n = 84 10 (8-12)	2% pirenzepine gel twice daily	Placebo gel	2	-0.41 (41)	+0.12 (30) *
Tan et al, 2005 (Singapore, Thailand & Hong Kong)[299]	n = 353 9 (6-13)	% pirenzepine gel daily (P1D) or twice daily (P2D)	Placebo gel	1	**P2D:** -0.37 (44) **P1D:** -0.14 (17) *	**P2D:** +0.13 (39) **P1D:** +0.03 (10) *
Trier et al, 2008 (Denmark)[300]	n = 68 11 (8-13)	7-methylxanthine tablets 400mg daily	Placebo tablets	3	**Moderate baseline AXL growth rate:** -0.33 (22) * **High baseline AXL growth rate:** -0.27 (12) *	**Moderate baseline AXL growth rate:** +0.18 (24) * **High baseline AXL growth rate:** +0.09 (8) *

AXL = Axial Length, *P > 0.05

1.7.3 Optical modifications

Initially, optical modifications to control myopia were targeted under the belief that excessive levels of accommodation were responsible for inducing myopia during near work. However several lines of evidence within animal and epidemiological studies have not supported the relationship between accommodation and myopia as a mechanism (discussed in Section 1.9.3.4.1). More recently, retinal defocus has been the focus of optical myopia control, based on the principles seen in animal models. Several interventions employing myopic defocus have shown profound effects at reducing myopia progression. However, there is considerable heterogeneity within this category, therefore it is crucial to treat different strategies separately, based on the results of their clinical studies.

1.7.3.1 Myopic spectacle under-correction

Optical under-correction of myopia was considered to slow myopia progression by reducing extra accommodative demands during near work. Though this strategy also complies with more recent hypotheses surrounding myopic defocus, as fully corrected spectacle lenses are seen to induce more relative peripheral hyperopic defocus,[321, 322] meaning that myopic under-correction can potentially reduce peripheral ametropia and slow progression.

Currently the evidence does not support the role of under-correction in myopia control. While early observational studies found slower rates of myopia progression in undercorrected subjects,[323, 324] results from randomised clinical trials have shown otherwise (Table 1.7), with two trials finding that under-correction conversely resulted in increased myopia progression.[325, 326] Although a recent non-randomised observational study in Beijing reported a small significant benefit with undercorrection,[327] baseline differences between groups may have led to significant confounding being involved, as uncorrected myopes had an older age of myopia onset, were less myopic and had shorter axial lengths at baseline compared to fully corrected myopes.

Table 1.7: Summary of peer-reviewed studies investigating under-correction (UC) or no correction (NC) compared to full correction (FC) of spectacle lenses for myopia control.

Author, Year (Country)	Sample Size & Baseline Mean Age	Treatment	Control	Study Duration (years)	Difference in Myopia Progression [Control - Treatment, D(%)]	Difference in Axial Elongation [Control - Treatment, mm(%)]
Chung et al,[326] 2002 (Malaysia)	n = 94 12 (9-14)	+0.75D UC	Full correction	2	+0.23 (-30)	+0.05 (8)
Adler et al,[325] 2006 (UK)	n = 48 10 (6-15)	+0.50D UC	Full correction	1.5	+0.17 (-21) *	N/A
Koomson et al,[328] 2016 (Ghana)	n = 150 (10-15)	+0.50D UC	Full correction	2	-0.04 (7) *	N/A
Li et al,[329] 2015 (China) **	n = 253 13 (10-16)	No correction	Full correction	1	-0.04 (6) *	0 (0) *
Sun et al,[327] 2017 (China) **	n = 121 13 (10-16)	No correction	Full correction	2	-0.29 (28)	+0.08 (26)

*P > 0.05, **non-randomised, observational study

1.7.3.2 Bifocal & multifocal spectacles

Like under-correction, bifocal and multi-focal spectacles were considered to reduce accommodation in an attempt to slow myopia progression. However, there is also evidence to suggest that these lenses may induce peripheral myopic defocus particularly in the superior retina.[330] Despite this, studies investigating bifocals have generally yielded poor results (Table 1.8), with the majority finding myopic progression between children wearing bifocal spectacles compared to single vision spectacles to be equivocal.[331-333] However, there have been some isolated observations within subsets of children who have accommodative lag as well as near esophoria,[334] and when including a base-in prism within the add zone.[335]

Multi-focal or progressive addition lenses (PAL's) are an alternative to bi-focal lens designs, which are thought to impose more consistent levels of defocus in the peripheral retina for varying distances of near fixation. But while most studies investigating either +1.50 or +2.00 D PAL's lenses find reduced myopia progression compared to single vision lenses,[336-339] most are minimal and not

deemed clinically significant (Table 1.8). Similar to bifocal uses, enhanced effects in individuals with accommodative lag and near esophoria are also seen but the effects remain small.[340]

Table 1.8: Summary of control studies investigating bifocal (BF) and multi-focal (MF) spectacle lenses for myopia control.

Author, Year (Country)	Sample Size & Mean Age at Baseline	Treatment	Control	Study Duration (years)	Reduction in Myopia Progression [Control – Treatment, D (%)]	Reduction in Axial Elongation [Control – Treatment, mm (%)]
Pärssinen et al,[333] 1989 (Finland)	n = 240 11 (9-12)	BF lenses (+1.75 add)	SV spectacles (full time)	3	-0.12 (8) *	N/A
Grosvenor et al,[332] 1987 (USA)	n = 207 (6-15)	**1.** BF (+1.00 add) **2.** BF (+2.00 add)	SV spectacles	3	**+1BF:** +0.02 (-6)* **+2BF:** 0 (0) *	N/A
Goss et al,[331] 1986 (USA)	n = 112 (6-15)	BF lenses	SV spectacles	?	-0.07 (16) *	N/A
Fulk et al,[334] 2000 (USA)	n = 82 11 (6-15)	BF lenses (+1.50 add)	SV spectacles	2.5	-0.25 (20)	N/A
Cheng et al,[335] 2014 (Canada)	n = 135 10 (8-13)	**1.** BF (+1.50 add) **2.** BF (+1.50 add) & 3Δ base-in near prism.	SV spectacles	3	**BF:** -0.81 (39) **ΔBF:** -1.05 (51)	**BF:** +0.25 (30) **ΔBF:** +0.28 (34)
Leung et al,[336] 1999 (Hong Kong) **	n = 90 10 (9-12)	**1.** MF (+1.50 add) **2.** MF (+2.00 add)	SV spectacles	2	**MF+1.5:** -0.47 (38) **MF+2.0:** -0.57 (46)	N/A
Gwiazda et al,[337] 2003 (USA)	n = 469 9	MF lenses (+2.00 add)	SV spectacles	3	-0.20 (14)	+0.11 (15)
Hasebe et al,[338] 2008 (Japan) ***	n = 92 10 (6-12)	MF lenses (+1.50 add)	SV spectacles	1.5 (per phase)	**Phase 1:** -0.31 (26)	N/A
Yang et al,[339] 2009 (China)	n = 178 11 (7-13)	MF lenses (+2.00 add)	SV spectacles	2	-0.26 (17)	**VCD elongation:** +0.11 (16)
COMET2 et al,[340] 2011 (USA)	n = 118 10 (8-12)	MF lenses (+2.00 add)	SV spectacles	3	-0.28 (24)	N/A

*P > 0.05, **non-randomised, ***crossover trial, VCD = Vitreous Chamber Depth, SV = Single Vision

1.7.3.3 Basic contact lenses

Both soft and gas-permeable contact lenses have been found to induce more peripheral myopic defocus compared to single vision spectacles.[322] However, neither have demonstrated any convincingly significant effects especially in reducing axial elongation in RCTs (Table 1.9).[341-344] Apparent reductions in myopic progression found using contact lenses are likely due to transient flattening of the cornea,[341, 345] rather than a reduction in axial elongation.

Table 1.9: Randomised control trials investigating soft (SCL) and rigid-gas permeable (RGP) contact lenses for myopia control.

Author, Year (Country)	Sample Size & Baseline Mean Age	Treatment	Control	Study Duration (years)	Reduction in Myopia Progression [Control – Treatment, D (%)]	Reduction in Axial Elongation [Control – Treatment, mm (%)]
Horner et al,[346] 1999 (USA)	n = 175 (11-14)	SCL wear	SV spectacles	3	-0.15 *	N/A
Walline et al,[343] 2008 (USA)	n = 584 10 (8-11)	SCL wear	SV spectacles	3	+0.19 (-17) *	-0.04 (7) *
Katz et al,[342] 2003 (USA)	n = 564 8 (6-12)	RGP wear	SV spectacles	2	+0.05 (-4) *	-0.05 (6) *
Walline et al,[341] 2004 (USA)	n = 116 10	RGP wear	SCL wear	3	-0.63 (29)	-0.05 (7) *

*P > 0.05, SV = Single Vision

1.7.3.4 Orthokeratology

Typical orthokeratology (OK) therapy involves the overnight wear of a rigid gas-permeable lens to temporarily reshape the cornea, resulting in the symptomatic visual correction of myopia. While corneal reshaping is responsible for the effects of OK on myopia correction, OK therapy has been seen to also induce relative peripheral myopia, most likely due to making the cornea more oblate.[347]

Four RCTS have compared the effectiveness of OK wear with promising results (Table 1.10). The Retardation of Myopia in Orthokeratology (ROMIO) study conducted in Hong Kong,[348] found that OK

could slow axial length in children with low-moderate myopia (0.50–4.00 D) by approximately 43% over 2 years compared to full spectacle correction. This same group subsequently studied the effects of partially correcting high myopia using orthokeratology in the HM-PRO study.[349] Although subjects receiving OK were under-corrected and required extra spectacle correction, individuals in this group experienced approximately 63% less axial elongation than pure spectacle wearers over a 2-year period. Swarbrick et al, used a cross-over design to compare myopia progression between eyes wearing OK and contralateral eyes which wore GP lenses.[350] During each 6-month period of the study, eyes who wore OK lenses did not experience any significant growth of axial length compared to baseline, whilst eyes which wore GP lenses, experienced progressive axial length growth across the duration of wear. While effective at slowing axial elongation during use, rebound effects have been reported following treatment cessation,[350] which could indicate that the effects on axial elongation are occurring through an anterior chamber depth reduction rather than a decrease posterior chamber elongation. In the most recent trial by Jakobsen & Møller,[351] OK wear produced reductions in axial elongation of 59% over 18 months compared to spectacle wear. Notably, there were no fast progressors (> 0.75 D/year) in the OK group, in contrast to 22% of the spectacle group.

Table 1.10: Randomised control trials investigating orthokeratology (OK) treatment for myopia control

Author, Year (Country)	Sample Size & Baseline Mean Age	Treatment	Control	Study Duration (years)	Difference in Axial Elongation (Control - Treatment) mm,%
Cho et al,[348] 2012 (Hong Kong)	n = 102 9 (6-10)	OK	SV spectacles	2	+0.26 (41)
Charm et al,[349] 2012 (Hong Kong)	n = 79 10 (8-11)	Partial reduction OK	SV spectacles	2	+0.32 (63)
Swarbrick et al,[350] 2015 (Australia) **	n = 26 13 (10-17)	**1.** OK **2.** RGP	RGP	0.5 per phase	**Phase 1:** **OK:** +0.02 * **RGP:** -0.04
Jakobsen & Møller,[351] 2021 (Denmark)	n = 47 (6-12)	OK	SV spectacles	1.5	+0.24 (59)

*P > 0.05, **contra-lateral crossover study, SV = Single Vision, RGP = Rigid Gas Permeable

1.7.3.5 Novel multifocal lens designs

Novel multifocal lens designs represent the most recent endeavours into optical myopia control, which impose simultaneous distance correction and myopic defocus across the retina. A variety of different lens designs have been developed which can achieve this effect. However, a common element they all share is that they contain a central zone, which is corrected for distance viewing. Soft contact lens designs are the most common implementation, where regions of positive power are added to the periphery of a soft contact lens. This power can be introduced by either a gradient/progressive transitional increase in power towards the periphery, or instead through concentric rings of constant positive and distance power, which alternate towards the periphery (Figure 1.5). Further variances in the amounts of defocus provided between lenses are seen, and treatment effects between different designs have been seen. As the optimum design has not yet been identified, and newer lens designs are constantly being produced, different lens designs must be considered individually.

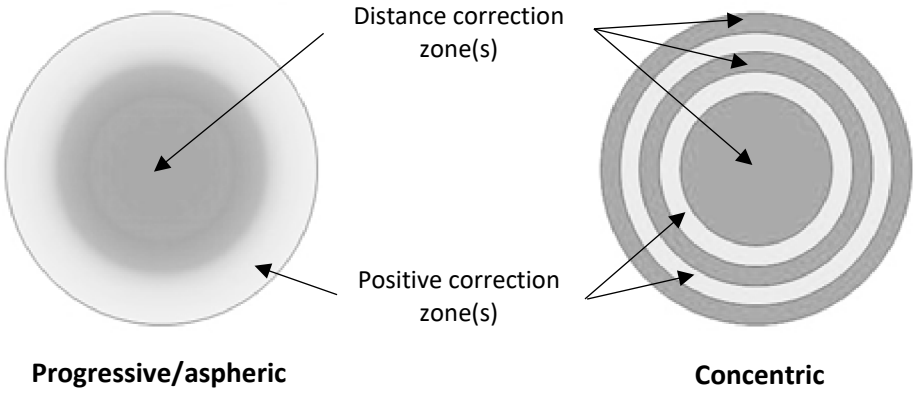


Figure 1.5: Differences between designs of 'dual focus' contact lenses. Shaded areas indicate regions of standard distance correction whereas lighter areas represent regions where positive power is added

Three prospective studies have demonstrated that progressive ring designs can slow myopia progression,[352-354] however, only one study used randomisation in their study design.[352] On the other hand, Fujikado et al was not able to find any significant differences in either axial elongation or myopia progression rates in eyes treated with a low add (+0.50 D) progressive contact lens.[355] When examining the relative peripheral refractive errors, they found no significant differences in amounts

of myopic defocus imposed by the multifocal contact lens as opposed to the mono-focal control. However, this may have been due to their use of a +0.50 D progression compared to other progressive lens designs which have an add zone reaching at least +2.00 D in the periphery.

On the other hand, results from RCT's investigating soft contact lenses with concentric ring designs have been highly consistent as significant reductions in both myopia progression and slowing of axial length elongation have been seen in all studies to date.[356-360] Several of these designs are now commercially available such as the Vistakon Acuvue Bifocal contact lens and the MiSight lens (CooperVision Inc., Pleasanton, CA). In particular, the MiSight lens has gained US FDA approval for the indication of myopia control following two successful RCTs. The MiSight Assessment Study Spain (MASS), compared the MiSight lenses to SV spectacles and found a reduction of 39% and 36% in SER and AL change.[359] No rebound effect was seen following cessation of treatment after an additional year.[361] The second RCT compared the MiSight lenses to equivalently manufactured soft contact lenses and found that the MiSight lenses could reduce both SER and AL by 59% and 52% respectively after 3 years of treatment.[360]

Specialised defocus lenses within spectacles have also been studied. In 2010, Sankaridurg et al. published results investigating three types of novel spectacle lenses.[362] All lenses had a central clear aperture with varying amounts of plus defocus in the periphery. Unfortunately, there was no significant effect on myopic progression with all three designs compared to single vision lenses. However, in a subgroup of younger children aged 6–12 who had parental myopia, the type-3 lens (where the central aperture extended into the horizontal and inferior meridians with a peripheral power of +1.90 D) resulted in significantly less myopia progression of ~30%. This lens design was later commercialised as "MyoVision" lenses. However, a recent RCT conducted by Kanda et al investigating this particular lens design,[363] found no differences in myopia progression nor change in axial elongation between groups of myopic Japanese children aged 6–12 with parental myopia, who either wore MyoVision spectacles or single vision distance spectacles over a period of 2 years.

Defocus-Incorporated Multiple Segment (DIMS) spectacle lenses use the same principle of dual-focus as contact lenses, however instead of a concentric ring design, these lenses utilise a single band in the periphery containing multiple focal segments 1.03 mm in length of +3.50 D power to induce myopic defocus. A central zone spanning 9 mm in diameter is retained for clear distance viewing. Results from a clinical trial, showed a reduction in SER and AL elongation of 52% and 62% respectively in children wearing DIMS spectacles when compared to children wearing single vision spectacle lenses after 2 years.[364] Additionally, 21.5% of the children who wore DIMS spectacles had no myopia progression compared to 7.4% who wore SV spectacles during the study period. These effects were maintained in the third year of the study and also extended to children who switched from initially using SV lenses to the DIMS group.[365] In a similar fashion, the Essilor Stellest, are spectacle lenses which contain 11 concentric rings of contigious aspherical lenslets which also generates myopic defocus. Compared to single vision spectacles, children wearing spectacles containing aspheric lenslets exhibited less myopia progression and less AL elongation after a 2 year clinical trial.[366] Dose dependent effects were also seen, as lenses with higher asphericity (HAL) provided greater myopia control than those of lower asphericity. Additionally, longer wearing hours (> 12 hours/day) resulted in better myopia control efficacy for the HAL lenses.

Table 1.11: Control trials investigating special lens designs for myopia control

Author, Year (Country)	Sample Size & Baseline Mean Age (Range)	Treatment	Control	Study Duration (years)	Reduction in Myopia Progression [Control – Treatment, D (%)]	Reduction in Axial Elongation [Control – Treatment, mm (%)]
Sankaridurg et al,[362] 2010 (China)	n = 210 11 (6-16)	**1:** Progressive +1.00D peripheral add **2:** Progressive +2.00D peripheral add **3:** Asymmetric horizontal astigmatism reducing lens, max +1.90D	SV spectacles	1	**1:** +0.03 (-4) * **2:** +0.03 (-4) * **3:** -0.12 (16) *	**1:** 0 (0) * **2:** +0.01 (3) * **3:** +0.05 (14) *
Anstice et al,[356] 2011 (New Zealand)**	n = 40 13 (11-14)	Dual-Focus soft contact lens – concentric +2.00D rings	SCL	10 months per period	**Period 1** -0.25 (36)	**Period 1** +0.11 (50)
Sankaridurg et al,[352] 2011 (China)	n = 85 11 (7-14)	Progressive soft contact lens – +2.00D progressive peripheral power	SV spectacles	1	-0.30 (36)	+0.15 (38)
Walline et al,[353] 2013 (USA)***	n = 40 10 (8-11)	Multifocal soft contact lens – +2.00D progressive peripheral power	SCL (historical control)	2	-0.52 (50)	+0.12 (29)
Fujikado et al,[355] 2014 (Japan)**	n = 24 (10-16)	Low-addition contact lens – +0.50D progressive add power, nasally decentred	SCL	1 per period	+0.22 (-35) *	+0.05 (25) *
Lam et al,[357] 2014 (Hong Kong)	n = 221 10 (8-13)	Defocus Incorporated Soft Contact (DISC) lens – concentric +2.50D rings	SCL	2	-0.20 (25)	+0.12 (32)
Paune et al,[354] 2015 (Spain)***	n = 100 13 (9-16)	Soft radial refractive gradient contact lenses – +6.00D maximum progressive add	SV spectacles	2	-0.42 (43)	+0.14 (27) *
Cheng et al,[367] 2016 (USA)	n = 109 10 (8-11)	Positive spherical aberration soft contact lens	SCL	1	-0.13 (19)	+0.14 (38)
Aller et al,[358] 2016 (USA)	n = 86 13 (8-18)	Acuvue Bifocal soft contact lens – 5 concentric add rings (individualised power)	SCL	1	-0.57 (72)	+0.19 (79)
Ruiz-Pomeda et al,[359] 2018 (Spain)	n = 89 11 (8-12)	MiSight contact lenses – concentric +2.00D rings	SV spectacles	2	-0.28 (38)	+0.17 (38)
Kanda et al,[363] 2018 (Japan)	n = 207 10 (6-12)	MyoVision (MV) spectacles – Asymmetric horizontal astigmatism reducing lens, max +1.90D	SV spectacles	2	+0.04 (-3) *	-0.04 (-6) *
Chamberlain et al,[368] 2019 (USA)	n = 135 10 (8-12)	MiSight contact lenses – concentric +2.00D rings	SCL	3	-0.53 (43)	+0.32 (52)
Lam et al,[364] 2019 (Hong Kong)	n = 183 (8-13)	Defocus Incorporated Multiple Segments (DIMS) spectacles – multiple +3.50D segments in ring surrounding central zone	SV spectacles	2	-0.44 (52)	+0.34 (62)
Bao et al,[366] 2022	n = 157 (8-13)	Spectacle lenses with highly aspherical lenslets (HAL) or slightly aspherical lenslets (SAL)	SV spectacles	2	**HAL:** -0.80 (55) **SAL:** -0.42 (29)	**HAL:** +0.35 (51) **SAL:** +0.18 (26)

*P > 0.05, SV = Single Vision, SCL = Scleral Contact Lens

1.7.4 Environmental/Behavioural modification

A number of detailed epidemiological studies have emerged within the past few decades that indicate that the environment plays a major role in the development of myopia (See Section 1.9). While there are several risk factors for myopia, only a few are modifiable. However, this approach is vital because it represents the only possible means of myopia prevention.

1.7.4.1 Increasing time outdoors

Greater time spent outdoors is protective against myopia development. A comprehensive review of the evidence surrounding this association, and detailed results of these studies will be discussed in Section 1.9.4. After initial observations from the SMS[369] and the OLSM studies,[370] a number of clinical trials using school-based strategies aimed at increasing daily outdoor exposures in children have been developed, which have all been effective at reducing the onset of myopia. An early study in Taiwanese schoolchildren found that 80 minutes of additional outdoor recess time per day reduced incident myopia after 1 year.[371] Apparent dose-response effects were also seen from a second study in Guangzhou,[372] where a 23% reduction in incident myopia was seen with 40 minutes of extra outdoor activity, however this occurred over a three year period. A third study in Northeast China, has reported profound effects in a subgroup of primary and junior high school students, with a 56% reduction in incident myopia seen over 1 year, following the inclusion of two 20-minute outdoor recess programs during school days.[373] The most recent trial conducted again in Taiwan, found more modest results following the promotion of 11 hours or more outdoor time every week, as a 17% reduction in incident myopia reported.[374] While lower than previous trials, these effects were likely to be reduced as the control group was also exposed to a form of intervention, due to the introduction of a number of nationwide initiatives by the Taiwanese government aimed at promoting increased outdoor time: the “Tien-Tien 120” policy, designed to promote 120 minutes of outdoor time per day and the “Sport & Health 150”, which promoted an additional 150 minutes of exercise time per week.

Extra outdoor time in clinical trials also appears to reduce the progression of myopia. Although the effects seen in the early studies were small and conflicting at times, these were likely due to the effects being reported for the entire cohort which consisted of a majority of non-myopes. However in existing myopes of the 2018 ROCT711 study, Wu et al found that the SER and axial elongation reduced by 0.23 D (28%) and 0.15 mm (25%) respectively,[374] suggesting that outdoor initiatives may be effective in reducing myopia progression.

Other issues from trials of outdoor time are that while participants all receive the same intervention, individual outdoor times may differ, as existing myopes and pre-myopes are more likely to be spending lower levels of outdoor time at baseline and may not achieve a therapeutic dose from the intervention. For more effective implementation of outdoor time as a public health intervention for myopia, more studies are required to identify dose-response relationships while considering individual levels of outdoor exposures. This may be assisted by the use of personal smart devices, such as wearable light meters, which are an additional aspect of myopia control currently in development.

Table 1.12: Randomised control studies investigating the addition of outdoor activity to control myopia.

Author, Year (Country)	Sample Size & Baseline Mean Age	Treatment(s)	Control	Study Duration (years)	Baseline Myopia Prevalence (%)	Difference in Myopia Incidence (Control – Treatment) %, (effect size %)	Difference in SER Progression (Control – Treatment) D, (effect size %)	Difference in Axial Elongation (Control – Treatment) mm, (effect size %)
Wu et al, 2013 (Taiwan)[371] **ROC**	n = 571 9 (7-11)	Recess outside the classroom (ROC) program – 80 minutes of outdoor recess time per day	No ROC program	1	48	-9.3 (48)	**All:** -0.13 (34) **Myopes:** -0.12 * **	N/A
He et al, 2015 (China)[372] **GOAL**	n = 1903 7 (6-7)	Extra 40 minute outdoor activity class per day + after school outdoor time promotion	No extra class or promotion	3	1.9	-9.1 (23)	-0.17 (11)	+0.03 (3) *
Jin et al, 2015 (China)[373]	n = 391 11 (6-14)	Two additional 20-minute outdoor recess programs	No extra program	1	~33.2	-4.8 (56)	-0.17 (63)	+0.05 (24)
Wu et al, 2018 (Taiwan)[374] **ROC**	n = 693 6 (6-7)	Recess Outside Classroom Trial 711 program – promotion of 11 hours or more outdoor time every week	Standard myopia initiatives (Sport & Health 150, Tien-Tien 120)	1	10.5	-2.9 (17) *	**All:** -0.12 (26) **Myopes:** -0.23 (28)	**All:** +0.05 (15) **Myopes:** +0.15 (25)

*P > 0.05, **multivariate adjusted

1.7.4.2 Reductions in near work

The amount of near work performed has also been identified as a risk factor for myopia, however the relationship is not entirely consistent (see Section 1.9.3), and thus near work has not been targeted often in as part of myopia control. While no control trials have been conducted, there have been reports of strategies and behavioural recommendations established in placed aimed at preventing and reducing myopia through near work reductions. There are cases in China, where classrooms are fitted with special desks, each containing a bar which restricts close working distances, and guidelines enforced where breaks after continuous periods of reading/near work are enforced. However, scientific evidence for the effectiveness of such strategies has not been published.

1.7.4.3 Increasing ambient lighting conditions

As the mechanism behind the effects of outdoor time have been attributed to elevated light intensity levels, other classroom modifications aimed at increasing ambient lighting conditions have been considered with some success in preventing myopia onset. In 2015, Hua et al examined the effect of increased ambient lighting levels in a group of Chinese schoolchildren by rebuilding lighting systems to provide higher and more uniform illuminances onto blackboards and desks within their classrooms.[375] After a year of intervention, there was a lower incidence of new myopia in these classrooms (4%) compared to a control school which had no lighting modifications (10%). Rates of axial elongation were also significantly lower for both existing myopes (0.20 vs 0.27 mm, intervention vs control) and non-myopes (0.13 vs 0.18 mm, intervention vs control). While there were no differences in myopia progression in existing myopes, non-myopic students in the intervention group had much smaller myopic shifts (-0.25 D) compared to the control group (-0.47 D) indicating a low potential of effect on myopia progression. Elevated light levels have also been examined in China through the development of a “Bright Classroom”, a room built enclosed by de-polished glass to allow for more ambient lighting.[376] A pilot study showed that this raised mean light

intensity levels by approximately 5x however, the clinical effects of this modification on myopia development has yet to be investigated in a control study.

1.7.4.4 Low-intensity red light therapy

Recent evidence has emerged demonstrating a therapeutic potential for low intensity laser therapy. This was based upon anecdotal reports of increases in choroidal thickness and inhibition of axial elongation in children using low-level red light stimulation for amblyopia treatment.[377] As changes in choroidal thickness and scleral growth underlie axial elongation,[378, 379] this treatment was applied to myopia control, however the mechanism behind these effects have not been confirmed.

In a 1 year clinical trial, children who received 2x 3 minutes/day for 5 days of low intensity laser therapy (650 nm, 1600 lux & 0.29 mW), exhibited less axial elongation (0.26 mm) and myopia progression (-0.59 D) compared to a control group.[377] In another study which used similar lighting and treatment parameters, low intensity laser therapy appeared to be more effective at reducing axial elongation compared to OK therapy over 6 months.[380]

1.7.5 Combination treatment

While there are promising effects with many different forms of myopia intervention, less is known about the therapeutic benefit which combination therapy offers for myopia control as only a few studies have investigated synergistic effects between treatment options.

Kinoshita et al, demonstrated that the combination of OK and 0.01% atropine was more effective in slowing myopia progression than OK monotherapy in a RCT of children aged 8–12.[381] After 1 year, axial elongation in the combination group was 0.09 mm (53%) less than the monotherapy group. Given that 0.01% atropine provided a 0.05 mm difference in axial elongation in LAMP study, suggests that synergistic effects may be occurring. While this was promising, initial results from the combined Atropine with Orthokeratology (AOK) for myopia control study indicated that while there was an additive effect seen between 0.01% atropine and OK in the first 6 months of therapy (0.09 mm

difference), axial elongation rates became similar after 1 year.[382] Another RCT is currently comparing the combination of bifocal contact lenses with atropine treatment,[383] however more long-term studies are required in order to obtain a more comprehensive insight into the most effective strategies to combat the myopia epidemic. This may also include the investigation of other combinations, such as the inclusion of novel multifocal lenses and behavioural interventions such as the promotion of extra outdoor time.

1.7.6 Summary

There are a variety of treatment options to control myopia. Consistent and robust effects have been seen via pharmacological intervention with topical muscarinic agents; namely low-dose atropine 0.01–0.05%. In terms of optical-based approaches, while there are multiple avenues for treatment selection, there is considerable variability in the evidence level between choices with some intended treatments having the potential to induce myopia instead; such as the strategy of spectacle under-correction. Nevertheless, both orthokeratology use and defocus modifying lenses have found positive degrees of effects in clinical studies. Finally, although there are also consistent effects of increased outdoor time as an environmental modification to reduce myopia progression, the degree to which this reduces progression appear to be relatively low in comparison to the aforementioned strategies. Yet increasing time outdoors crucially shows robust effects against incident myopia. The ongoing development and optimisation of these strategies is linked to research aimed at understanding the aetiology and pathophysiology of myopia development.

1.8 Aetiology of Myopia - A role for genetics in school myopia

1.8.1 The nature versus nurture controversy

Early observations were made by Johannes Kepler, who in 1604, published the first comprehensive treatise on the optics of the eye and myopia and attributed his own short-sightedness to intense study.[384] While this view was never discarded in the debate, and was reinforced when Cohn showed strong links between education and the development of myopia in 1886,[385] Nevertheless, the idea that myopia was genetic in origin and environment played little role in the genesis of myopia came to be dominant, largely due the influence of studies on heritability of myopia in twins. This is well illustrated in the response to Francis Young's observation of generational differences in myopia prevalence in Inuit families in Barrow Alaska in the 1960s,[386] and the letter to the editor that this evoked from Professor Arnold Sorsby,[387] who stated that there was "incontrovertible evidence that refraction is genetically determined," based on the study of heritability of refractive error in twins he had conducted in England.[388] But the main problem in attributing school myopia to genes is the rapid rise in myopia prevalence seen in East Asian.[389] Such rapid changes within decades are not compatible with a genetic hypothesis, since gene pools cannot change significantly over a period of a few decades.[390]

Modern twin studies investigate differences in refractive phenotype between pairs of monozygotic (MZ) and dizygotic (DZ) twins and consistently supported Sorsby's initial observations, and have for some decades been the primary evidence used to argue for a role of genetics in school-myopia. These studies have generally found a larger level of agreement in refraction and ocular component for MZ than DZ twins.[391-401] However, a major issue with twin heritability studies is the assumption that the concordance in environmental exposures for members of MZ pairs who are raised together is the same that for members of DZ twin pairs who are raised together, an assumption known as the common environment assumption, that has to be established on a trait-by-trait basis that is almost never tested robustly. To the extent that this assumption does not hold, then estimates of

heritability can be inflated. There is an inherent tendency towards over-estimation, because MZ twin pairs are of the same sex, whereas those of DZ twins are of opposite sex in 50% of cases, and for any trait in which there are significant sex differences in prevalence or in exposure to risk factors, over-estimation must be considered a possibility.

In 2001, Lyhne et al challenged the pure genetic link by finding signs of gene-environment interactions in refractions of 114 twin pairs.[401] Although MZ twins had higher concordance in refractions compared to DZ twins, there was a difference in concordance levels of education, where DZ twins were more likely to be discordant in their years spent in education. Since education is a risk factor for myopia, this finding undermines the calculation of heritability.

Parental myopia status is another well-established risk factor for myopia development.[134, 402-405] While this is commonly used to support the role of genetics, it is also likely that children can "inherit" certain myogenic behaviours, such as educational values and patterns of daily activity while being exposed to the same environments as their parents. This will lead to high familial correlations, but the respective contributions of genetics and environment remains unclear.

In those studies that have investigated parental history of myopia and some identified environmental risk factors, such as the Orinda study,[404] parental history of myopia was found to be the strongest factor that explained the variance in children's myopic refractive error. As no confounding effects were reported between other identified risk factors (near work, school achievement and time in sport) it was proposed that genetics was a main contributor. This was further supported by data from the CLEERE Study when adjustment for shared and individual differences between siblings (including near work and time spent in sport/outdoors) only reduced the intra-class correlation coefficient between parental myopia and refractive status by 0.5%.[406]

On the other hand, Ghorbani Mojarrad et al, found that genetic risk scores (calculated by presence of myopia-associated SNPs) and parental myopia status were both independently predictive of myopia.[407] As there was also only a small difference in the genetic risk scores between children with

and without myopic parents, it indicated that children with a higher number of myopic parents do not necessarily have a greater number of known myopigenic alleles, and that parental myopia as a single association may also capture external influences such as environmental risk factors.

1.8.2 Syndromic and familial high myopia

It is well understood that there are several genetic forms of myopia associated with specific mutations or chromosomal rearrangements. These typically occur in those with familial patterns of high myopia, and in certain genetic disorders where myopia manifests usually in early infancy. Some examples of syndromic myopia include systemic connective tissue disorders such as Marfan's (*FBN1*) and Stickler's syndrome (*COL2A1*, *COL11A1*, *COL9A1*, *COL9A2*), as well as ocular disorders such as retinitis pigmentosa (RPGR), Leber's congenital amaurosis (*TULP1*) and ocular albinism (*OCA2*). However, with a few rare exceptions,[408, 409] mutations associated with these conditions are not regularly linked to common myopia. They probably account for only a low percentage of myopia with a population (~1–2%), since the prevalence of myopia in societies where there was or is little exposure to education for most of the population rarely, if ever, exceeds this level.[195]

Several genetic linkage studies have investigated high myopia and identified a number of implicated genetic loci.[410-415] While a multitude of loci have been found, few experimentally validated single candidate genes have been identified.[416-418] As most have been identified within highly-aggregated families with high-myopia displaying an autosomal dominant inheritance pattern,[410, 412-415, 419, 420]

In 2009 a genome-wide association study (GWAS) compared 411,777 single nucleotide polymorphisms (SNPs) in 830 Japanese individuals with pathologic myopia and 1911 population controls.[421] This analysis identified SNP rs577948 at chromosome 11q24.1 that was thought to regulate mitochondrial-led apoptosis via the *BLID* gene. Changes in mitochondrial function have been proposed to affect the development of myopia, due to the high energy requirements of the retina. However, follow-up studies have not been able to be replicate these findings.[422, 423]

While high myopia has traditionally been regarded as likely to have a genetic or chromosomal aetiology, with the increasing prevalence of early onset myopia in the emerging epidemic, high rates of subsequent progression can produce high myopia, without the need for specific mutations.

1.8.3 Evidence from large GWAS Studies

The introduction of GWAS allowed rapid scanning of a large number of potential SNPs associated with myopia from multiple human assays. However, identified genes are often of small effect and require large sample sizes to gain statistical power.[424] Additionally, findings from GWAS need to be replicated in different populations in order to ensure that identified genotype-phenotype associations represent credible associations and are not due to Type 1 or 2 errors.[425].

Two large cohort studies in western populations examining refractive error, initially identified susceptibility loci on chromosomes 15q14[426] and 15q25[427] but only 15q14 was replicated in later studies.[428, 429] Following these initial findings, two independent large-scale databases, the Consortium of Refractive Error and Myopia (CREAM) group[430] and the personal genomics company 23andMe[431] published findings from independent cohorts. 23andME confirmed the two previously identified loci,[426, 427] and an additional 20 loci associated with myopia with an onset between five to 30 years.[431]. At the same time, the CREAM group conducted a meta-analysis of 35 GWAS cohorts, which included 37,382 individuals of European descent, as well as 12,332 individuals of Asian ethnicity.[430] The CREAM group identified 11 of 20 of the new loci found by 23andMe and confirming an additional five using a more conservative threshold for significance. Though many these loci were further replicated in several independent studies,[432-437] in total they were only able to explain ~3% of the phenotypic variance in refractive error seen.[431] This led to a combined GWAS meta-analysis from CREAM and 23andMe that included 160,420 participants.[438] Findings were further replicated using 95,505 participants from the UK Biobank. The number of validated refractive error loci increased to 161. There was a high genetic correlation (> 0.78) between individuals of European and Asian descent, suggesting that there is not much difference in genetic variation between these two

ethnicities. However despite these additional findings, the proportion of phenotypic variance in refractive error explained by genetics only increased to 7.8%. Again more recent analyses have continued to identify newly associated markers, increasing the predictability level to 12.1%.[439]

1.8.4 Summary

The discussion of the literature regarding the contribution of genes to the development of myopia presented here is not exhaustive as it is not a focus of this thesis. In regards to the most common form of myopia, school myopia is likely to be associated with multiple factors with major environmental drivers in play. While there has been some research looking at the relative contributions of parental myopia and environmental factors, the quantification of the environmental factors has been both subjective and not precisely targeted, such measuring time in outdoor/sport rather than exposure to high light intensities in childhood. Heritability established from twin studies has in the past overemphasised the contribution of genes to concordance values for refractive error and again inclusion of objectively quantified environmental risk factors in such studies may find lower estimates of heritability for myopia. Large GWAS studies have not found a 'myopia gene', rather they find a large number of genes of small effect. Finally, populations whose myopia prevalence has moved from around 35% to 80% within decades, provide the most compelling evidence that myopia is not incontrovertible genetically determined, and that environmental exposures must play a significant role. Considerable evidence suggests that these exposures are largely determined by social factors that control exposure to education and near work, and the balance between time indoor and outdoor environments.

1.9 Aetiology of Myopia - Environmental risk factors

Several environmental risk factors for myopia have now been identified. As previously discussed, this has led to the development of a number of successful intervention strategies to control myopia (Section 1.7.4), confirming that there is indeed a role for the environment in refractive development.

1.9.1 Education

Over 400 years ago, German astronomer and optician Johannes Kepler, claimed that his own short sightedness arose due to the amount of intense studying and reading he had performed throughout his lifetime. Many years later in 1886, ophthalmologist Hermann Cohn saw that children with who were introduced to formal education were more likely to become myopic.[385] These observations have since continued in the literature. Studies investigating education have typically used two broad measures: the level of educational attainment; provided by the number of years spent in schooling, as well as academic performance; which is usually measured via test scores or enrolment in higher academic streams.

1.9.1.1 Myopia and educational attainment in adults

In young adults, there have been several population-based studies primarily based on male military conscripts. In male Danish army recruits, Goldschmidt et al observed increasing prevalence of myopia among occupational groups, being lowest amongst unskilled workers (2.9%) and highest amongst those who attended grammar school or experienced university education (30.1%).[440] They concluded that the higher prevalence was as a result of a higher education level achieved, however, there may have been some confounding, as the occupational groups were ordered based upon estimated near work requirements of their roles. Later also in Danish conscripts, Teasdale et al, reported that myopes scored higher and have spent more time in schooling than non-myopes, with increasing proportions of myopia with higher categories within both parameters.[441] Around the

same time, a study of male Jewish recruits also reported increasing prevalence rates of myopia to be equally associated with more years of schooling, as well as higher IQ.[442]

In Singaporean conscripts, Tay et al observed that proportion of myopia increased in those with higher levels of education, being 15% in those with no formal education and increasing up to 65% in those who underwent university education.[443] These findings were confirmed by Au Eong et al,[44] who matched for age, sex, race and level of urbanisation within each group and by Wu et al, in a subsequent cohort.[444] Also at this time, Saw et al showed that myopes were more likely to have completed pre-university education (OR: 4.1) as well as been previously enrolled in either gifted, special or express educational streams during high school (OR: 3.8).[445] Similar findings have also been observed in studies within Greek[446] and Korean[199] conscripts.

While the data from military conscripts are restricted to males, they are strong in power due to an often large number of participants of similar age and ethnicity. Furthermore, the consistency of results found from these studies across multiple different countries, provides strong general support for the association between the exposure duration of education and myopia. These associations have also been extended into older adult populations.[215, 217, 239, 447-453] Links have also been made between other occupation groups and myopia,[239, 450, 452] as higher academic achievement provides opportunity for more professional roles within the workforce, as well as a degree of confounding from high near-work requiring jobs.

1.9.1.2 Myopia and academic performance in school-children

In children, evidence for the role of education comes from measures of academic performance; such as via examination scores or in the type of academic stream a child is enrolled in. Early studies in school-children have used tests of IQ or general intelligence,[454-457] under the longstanding belief that innate intellectual ability itself was a risk factor for myopia. However, while studies have found correlations between myopia and higher intelligence scores, recent studies investigating more

academically focussed measures of performance have identified stronger associations between myopia and increased reading and language ability.

Early longitudinal data using more academically selective tests came from a series of birth cohort studies in Britain, where medical examinations, cognitive tests and information on education were collected at various intervals throughout life. From the first cohort born in 1948,[458] children who were myopic at 15 years old, scored higher in attainment tests at ages 8, 11 and 15 than those with "perfect vision" (defined as 6/6 or better without glasses). This difference was largely seen in reading scores, rather than in non-verbal tests; suggesting that the relationship may not simply reflect general intelligence or IQ. In the subsequent birth cohort of 1958,[459] children with myopia at age 11, scored higher in reading comprehension, arithmetic and general ability tests than non-myopic children. Like in the first cohort, the relationship was slightly clearer for reading ability than for other skills. These differences were also present when tested at age 7, suggesting a causal effect of academic performance or ability as the majority of these children were non-myopic at this stage. Re-investigation of this cohort in 2011 extended this relationship into adult myopia as well.[459]

Associations between reading ability and myopia have also been seen elsewhere. From the OLSM study,[404] myopic children were more likely to have higher scores in the Iowa Test of Basic Skills (ITBS). This was especially in the reading and language segments (OR: 1.013 & 1.014 respectively) instead of mathematics. Additionally, as ITBS scores do not strongly correlate with IQ scores, it suggested again that the causal factor did not simply lie in general intelligence. Similar findings were also seen in children from the SCORM study,[460] where those who placed in the upper quartile of a nationwide exam were more likely to be myopic than those in the bottom quartile (OR: 2.5) after adjusting for near work (books per week read) and IQ.[461] Again, this association predominantly came from language ability scores rather than in mathematics.

In 2008, Williams et al[462] investigated the predictive value of a variety of performance measures in a large longitudinal cohort of 6871 children at ages 7 and 10 in the UK. At age 7, the school-based

SATS reading and maths tests, the clinic-based WORD test results and verbal IQ scores were all predictive of prevalent myopia, however non-verbal performance IQ scores were not. Like in the previous studies from OLSM and SCORM, scores from the reading test were more strongly associated with prevalent myopia than scores in mathematics (OR: 2.6 vs 1.9). However, when investigating incident myopia by 10 years of age, all measures were associated with the development of myopia.

The type of academic stream a child is participating in is another aspect of education that has been linked to myopia. From as early as the 1970's, Grosvenor noticed that there was a higher number of myopes within "high ability" classrooms compared to those deemed "low ability".[454] In Singapore, students are assigned one of three streams: 'Express', 'Normal Academic' or 'Normal Technical'. These are incremental tiers of educational streams based on their performance in an examination taken on entrance to secondary school at 12 years of age. From their military data, myopes were more likely to have been educated within a higher educational stream during secondary school (OR: 3.8).[445] Incremental levels are seen in grade 9-10 secondary schoolers, where students in the normal academic and express streams were more likely to be myopic than those in the standard normal technical stream (OR: 1.68 & 3.03 respectively).[463] Longitudinal evidence has recently been provided in a 4 year follow-up of 1958 Taiwanese school-children,[464] where those who attended extracurricular "cram" schools for longer than 2 hours per day, were 1.31x more likely to develop myopia.

More broadly, there are also differences in myopia prevalence between schools of differing academic calibre. Zylbermann et al, reported a higher prevalence of myopia in orthodox Jewish boys (81%), who are required to do more intense schooling than their female counterparts (36%), as well as non-orthodox males (27%) and females (32%) in general schools.[465] More recently in Singapore, a higher proportion of highly myopic children were reported in a school ranked within the top 20 (17.2%) compared to one that was ranked in the bottom 20 (4%).[466] Similarly, within a suburban

district of Western China, there was also a higher prevalence of myopia seen in schools that were deemed more academically challenging (32.7%) compared to regular schools (9.8%).[467] This has also been seen in western countries: firstly in Australia from the SMS; where a higher proportion of 12-year-old myopic children were found in public academically selective schools (42%) compared to either private schools (11%) or public non-selective schools (9%);[468] and also for 12-13 year olds in Ireland from the NICER study, between children in grammar schools (25%) vs. non-grammar schools (12%).[469] This effect also extends to children of kindergarten age, with a study of primary school-children in Shanghai finding that attending elite "high-level" schools was associated with higher myopia prevalence in children aged 6 and above (OR: 2.0).[156]

On an even larger scale, a link has been made between the prevalence of myopia across various countries and their level of international educational performance. In 2013, Morgan and Rose investigated data from the Organisation for Economic Cooperation and Development (OECD) Program in Secondary Assessment (PISA),[470] which tested educational outcomes in representative samples of 15 year-old school children from 65 locations, and compared these between the countries with high (> 70%) and low myopia (< 40%) prevalence. They found that all locations which were classified to have high myopia prevalence (Shanghai-China, Hong Kong-China, South Korea, Japan, Singapore and Taiwan), all placed within the top quartile of educational performance for all categories within PISA (Reading, Mathematics & Science). Interestingly, there were other countries such as Australia and Finland that also ranked highly for educational performance, but had a low prevalence of myopia. They found that this was because the locations with a high prevalence of myopia and high educational performance, engaged highly in after-school tutorials, whereas those with a low prevalence of myopia had little engagement in tutorials yet were able to perform well academically. From this, they suggested that the myopigenic stimulus underlying afterschool tutorials involved 'educational load', which encompasses multiple aspects of education such as homework, tutorials and demands of school classes. While this does not isolate a single cause for myopia from education, it demonstrates that it is possible for groups to perform well academically

while avoiding the risk of developing myopia, with the missing link being the mediator on the effects of education on biological systems. On the other end, a low prevalence of myopia has been observed in several societies where education systems are limited in access or undeveloped such as in Africa,[180] Nepal,[195] India,[193, 194] Laos,[471] Cambodia[472] as well as in the Inuit population.[473]

1.9.1.3 Causal role of education

Studies using mendelian randomisation have also been used to demonstrate the causal relationship of education as a myopigenic risk factor. Mendelian randomisation is a process where known polymorphisms or genetic variants of risk factor exposure e.g. education level are used to assess for their effects on an outcome such as refractive error. In 2015, Cuellar-Partida et al, calculated genetic risk scores in 3 cohorts of Caucasian adults (AREDS, BMES and KORA) using loci identified from the Social Science Genetic Association Consortium and found that genetic predisposition to higher education levels were associated with increased myopia.[474] More specifically, for every extra year spent in education, there was an increase of myopia by -0.46 D. This provided the first true causal evidence for the role of educational attainment on refractive error. A similar study using a smaller number of strongly associated educational loci in a larger separate European cohort by Mountjoy et al, [475] found that every year of education was associated with -0.27 D more myopia. Simultaneously by investigating reverse causality, they also disproved the idea that myopic individuals were more prone to spend longer years in education, as myopia related loci were not associated with a longer time in education.

1.9.1.4 Potential genetic susceptibility to education effects

There has been some evidence from studies suggesting that the effects of education on myopia occurs due to the presence of particular gene variants. Verhoeven et al, found that European adults with a high genetic risk score (calculated by the presence of 26 SNPs identified from CREAM) for myopia combined with university level education, had a higher risk for myopia (OR: 51.3) than those with high genetic risk who only achieved primary level schooling (OR: 7.2).[476] In Singaporean cohorts,

similar interactions were reported by Fan et al, where strong associations between the presence of SNPs at three loci (SHISA6-DNAH9, GJD2 and ZMAT4-SFRP1) and myopia was observed only in those who had a higher level of education.[477]

1.9.1.5 Summary

Educational attainment has been consistently demonstrated to be associated with myopia using various measures in observational studies in a large number of cohorts of differing ethnicities and across different age groups. Despite this, the mechanism of action underlying the effects of education has not been identified. Initially, performing increased near work was believed to be the mediator, but has not shown conclusive evidence on its own as a risk factor. More recently, there has been evidence that individuals who spend less time outdoors (such as those engaging in higher or more intensive studies) are more prone to myopia. While both explanations remain plausible, there is a large degree of potential confounding which may exist, requiring further research in order to confirm their respective roles. Evidence for the individual effects of these variables will be discussed in the next section.

1.9.2 Near work

Near work has also long been thought to be associated with the development of myopia. Anecdotally, a higher prevalence of myopia has been noted in several occupations characterised by high periods of continuous near work, such as carpet weavers, seamstresses and monastic scribes. Later on, cross-sectional studies began to report associations between near work performed in childhood and prevalent myopia. In 1980, during their investigation into United States Health Examination Survey data of 12–17 year old children, Angle & Wissmann found that time spent reading, reading test performance and education level were more strongly associated with myopia than other social factors which included gender, race and level of urbanisation.[478] Their findings supported the “use-abuse theory” of myopia at the time, which proposed that myopia arose as the result of habitual use of the eye at near focal lengths, or near-work. Also in that year, a study

involving over 80% of the population of Newfoundland,[479] reported an association between the duration of near work (hours per day performing tasks < 50 cm) and refraction. Adjustment of near work and education significantly reduced within-family correlations (both sib-sib and parent-offspring) of refractive error,[480] suggesting that values from heritability estimates were potentially inflated due to the effects of common environments and gave further support for the role of near work as an environmental risk factor for myopia.

1.9.2.1 Near work and prevalent myopia

Since then, many cross-sectional studies have investigated the relationship between near work and prevalent myopia. These studies have used varying combinations of variables to capture near work time including: time spent reading, number of books read per week, reading distance, television use and video game time. Consequently, there has been a lack of consistency with varying levels association between individual variables. While most studies show some level of association between cumulated near work parameters and myopia,[481] there are also a handful that fail to find any link between near work and myopia.[482]

In 2001, using a validated near-work questionnaire,[483] Saw et al reported that myopic school-children in Xiamen China, spent more time doing near-work related activities outside of school hours than did non-myopes (2.7 vs 2.3 hours/day).[484] This was significant for reading or writing time and time spent studying music notes, but not for other activities such as time using the computer, playing video games or number of books read per week. The same questionnaire was also used in the SCORM study,[485] which found that those who read more than two books per week were more likely to have myopia worse than -3.00 D (OR: 3.0) have axial lengths 0.17 mm longer and vitreous chambers 0.15 mm deeper than those who read two or fewer books.[486] After multivariate adjustment, this was not the case for those who read longer than two hours per day or for eight or more dioptre hours. Yet in a combined analysis of subjects from both cohorts from Xiamen and SCORM, all variables (books per week, time reading, computer use and video games) were

significantly associated with both myopia and high myopia.[485] Similar findings were seen in the OLSM study, which found that myopic children spent more time studying and reading for pleasure compared with emmetropes out of school (OR: 1.02 for each extra dioptre-hour).[404]

Out of several near work variables investigated in the SMS, only time spent reading for pleasure was independently associated with refraction; with those reading a higher number of books per week having a more myopic refraction.[468] There was also an increased risk of myopia in children who read continuously for longer than 30 minutes at a time (OR: 2.5) or those read at close distances < 30 cm (OR: 1.5). Though, as the effects of school type (public, selective or private) were adjusted for during multivariate analysis, differences in near work time seen between schools of different academic calibre may have been masked. A subsequent analysis of total near-work times of both SMS cohorts (which included children aged 6–7 years old), again did not find any direct association between tertiles of near work time and refraction, however, identified independent interactions between near-work activity and outdoor activity.[487] Outdoor activity was shown to be associated with reduced myopia; however, those who performed high near work required higher levels of outdoor activity for protection, which occurred in a step-wise fashion. As both variables were poorly correlated, it indicated near work may still play a role by determining the amount of outdoor time needed for protection.

Since then, two more recent reports; the North India Myopia (NIM) study by Saxena et al,[488] and a school-based study in Guangzhou China by Guo et al;[489] have demonstrated more consistent associations between multiple similar questionnaire-gathered variables of near work and prevalent myopia.

1.9.2.2 Near work and incident myopia

In comparison to cross-sectional evidence, longitudinal evidence to support a causal association between near work and incident myopia is sparse, with several conflicting reports. In the 3-year follow-up of the SCORM study,[490] no significant increases in incident myopia were seen in those who

spent more time in near work, read more books per week or for any extra dioptre-hr week of near work. Similarly, the 5-year follow-up of the OLSM study found that children who became myopic did not spend more time in near-work activities than those who remained non-myopic.[370] Later in the CLEERE study,[491] differences in near work time and dioptre-hours between non-myopes and those who became myopic were seen just 1 year before and following the onset of myopia. Though the lack of any significant differences in the many years prior to onset indicated that it was unlikely to have been causal.

On the other hand, compelling evidence came from the SAVES study, which reported that children in the younger cohort who became myopic spent more time in near work activities at baseline (19.4 h/week) compared to those who remained non-myopic (17.6 h/week). These differences were not seen in the older cohort, suggesting that the role of near work may depend on age. More recently in the Beijing Myopia Progression Study,[492] children who spent a greater time on near work were more likely to develop incident myopia after 3 years (OR: 4.1 for spending ~2.9 h/day near work vs 0.4 h/day reference). Analysis of 4,734 children from the Generation R Study in 2019,[405] found associations between incident myopia and time watching television, number of books read, frequency of continuous near work and a shorter reading distance but not time spent reading and computer use.

1.9.2.3 Near work and myopia progression

For myopia progression, there are also several conflicting reports. During their 3-year RCT of spectacle myopia control in 1993, Parssinen and Lyra reported that children who were in the highest quartile of myopic progression over the course of the study had shorter reading distances (mean difference 2.1 cm), and spent more time reading or in close work per day (mean difference 0.6 h/day) than those who were in the lowest quartile for progression.[493] Though shorter reading distances in higher myopes could be the result of inadequate spectacle correction.

In their 1-year study in Taiwanese grade 2 primary school children, Hsu et al also reported that a shorter reading distance (< 30 cm) was associated with faster myopic progression (OR: 1.45), however there was no association with either time spent in near work (> 2 h/day) or use of computers/cellphones/tablets.[494] Conversely, in the 1-year follow-up of the NIM study,[495] both reading and writing time, and use of computers/video games were independently associated with myopic progression compared to those who did not progress. These effects occurred in a dose-dependent manner, with the odds for myopic shifts increasing with higher levels of both hours/week reading & writing as well as hours spent using computers and playing video games.

On the other hand, while near work was associated with incident myopia in the CLEERE study,[491] hours spent per week in any near work activity (reading for pleasure, studying, computer or TV use) nor in the amount of dioptre-hours spent was associated with annual myopia progression in existing myopes.

1.9.2.4 Possible mechanisms underlying near work

1.9.2.4.1 Excessive accommodation

Initially, excessive use of accommodation was thought to be the stimulus underlying how near work may lead to myopia. This widely held idea was intuitive as the accommodative response is the primary physiological and optical response of the eye that is evoked at near and is required to effectively perform at close distances. However animal experiments, specifically those investigating the accommodation pathway in animals, have challenged these beliefs, by demonstrating that experimental myopia can occur in the absence of accommodation. This was first seen in 1990 by Schaffel et al,[496] who showed that chickens who had areas of their Edinger-Westphal nucleus (the area of the brain responsible for accommodation) ablated, continued to respond to lens defocus and develop myopia. Later in 1993, McBrien et al demonstrated that experimental myopia was also possible in squirrels, which lack a functional accommodative system.[497] Further evidence against comes from observations of that the anti-myopigenic effect of atropine also occurs in chickens,

who's accommodative response occurs via nicotinic rather than muscarinic receptors, as demonstrated separately by both Stone et al,[498] in 1991 and McBrien et al in 1993.[308] Evidence in humans against the role of accommodation come from studies of myopia control, as strategies aiming to reduce myopia progression via reducing accommodative elements such as bifocals, multifocals and undercorrection, have not been widely successful.

1.9.2.4.2 Intraocular pressure

During the time when accommodation was believed to cause myopia, it was thought that forces induced by accommodation created increased tension within the globe, leading to increases in intraocular pressure (IOP).[499-501] These rises in IOP would potentially leave the sclera susceptible to expansion and result in axial myopia. While some cross-sectional studies have shown that myopes have higher IOP,[502, 503] the effects are not strong and don't establish a causal relationship. While there is no longitudinal evidence, animal and human RCT studies using IOP lowering agents such as timolol have not demonstrated any significant effects in slowing myopia progression.[504, 505]

1.9.2.5 Accommodative lag and insufficiency

The paradigm then shifted to believe that a deficient accommodative responses at near was the stimulus for near-work induced myopia. This theory was primarily based upon the principle of hyperopic defocus demonstrated in animal models of emmetropization.[87, 89] It was thought that hyperopic defocus from reduced accommodative ability as well as transient phases of hyperopic defocus caused by accommodative lag, were responsible for myopia by stimulating signals for axial elongation. Though continuous exposure to hyperopic defocus leads to myopia development, brief periods of clear unobstructed vision is capable of nullifying this effect,[86, 506, 507] making this source of near-work induced hyperopic shifts to be less viable in humans in the real world.

In humans, while there are several reports that myopes have reduced total and higher lags of accommodation,[508-514], the role for a causal association for accommodative lag is less clear with

conflicting reports. In 2005, Gwiazda et al found that children who became myopic exhibited accommodative lag 2 years before the onset,[515] suggesting that it may have some contribution towards myopia development. However shortly after, this was challenged by a report from the CLEERE study,[516] which found that pre-myopic children did not display any lags of accommodation until 1 year after becoming myopic. In terms of progression, two longitudinal studies in children have also demonstrated no relationship between accommodative lag and the progression of existing myopia.[517, 518]

1.9.2.6 Relative peripheral defocus

It was then suggested that hyperopic defocus in more peripheral regions of the retina may by the primary driver for myopia. This idea stemmed from early observations of trainee pilots, as those with more prolate eye shapes that had more significant relative peripheral hyperopia, were more likely to develop myopia.[519] Subsequent cross-sectional studies have shown that myopic eyes are relatively more hyperopic towards the periphery, whilst emmetropes have generally no off-axis refractions.[520-522] Conversely, hyperopes tend to show relatively myopic off-axis refractions. Longitudinal studies however, have not been able to find a causal relationship between relative peripheral hyperopia and either myopia onset or progression,[523-526] indicating that relative peripheral hyperopia instead occurs as a result of myopia development.

1.9.2.7 Use of smart phones and other digital devices

Another proposal which has recently gained popularity is the notion that increased use of smart phones and digital devices are behind the rise of myopia in children. While it is clear that there has been an abrupt increase in the use of smartphones over the last two decades, increases in myopia from the epidemic have been documented well before the advent and mainstream use of smartphones. For example, rates of myopia in Singapore and Taiwan have been high since the 1970's, whereas the first smartphone was not developed until 1995, which did not see widespread use until well after the 2000's. Therefore it is highly unlikely that digital device use has been the root

cause of the myopia epidemic. While it still may add to the increasing rates of myopia development today, there have been limited investigation into its effects, with the myopigenic nature of smart phones and digital devices on myopia is still unconfirmed.

Computer usage times in children were investigated in both OLSM and SMS, computer usage times in children and did not find associations between screen time and myopia,[404, 468] however more recent cross-sectional studies in children and teenagers have also found associations between increased computer use and higher myopia risks,[488, 527] suggesting that the relationship may not have taken effect until recently.

In regards to mobile phone usage, recent cross-sectional studies have attempted to look for associations with varying outcomes. In Chinese university students, no association was found between questionnaire derived estimates of daily smartphone usage and prevalent myopia.[528] Similarly, McCrann et al found that myopic children had higher smartphone data usage rates than non-myopic children, but did not see any significant differences in usage time.[529] Differences in data usage rates may relate to the type of applications used between myopes and non-myopes. Meanwhile in a sample of teenagers from the Generation R study, more myopic refractive errors were associated with a higher frequency of continuous smartphone use (≥ 20 minutes).[530] However, this only occurred on weekdays and in those with low outdoor exposures, suggesting a potential protective effect of outdoor time. These findings need further investigation in a prospective study.

An early meta-analysis, published in 2020, included 5 studies and reported no association between digital screen time and myopia.[531] Later, a subsequent meta-analysis, which included 11 articles, found significant associations between myopia and both smart device screen time alone (OR: 1.26) as well as in combination with computer usage time (OR: 1.77).[532] However, there was considerable heterogeneity in these studies, as many did not objectively measure myopia, and measures of smartphone use were often confounded with other risk factors for myopia which were not

controlled for. As a result the authors concluded that the association was plausible but remained unconfirmed.

1.9.2.8 Summary

Though near-work has been thought to cause myopia for centuries, evidence seen from studies of human epidemiology has been mixed. Despite this, a meta-analysis by Huang et al in 2015 has reaffirmed the role of near work calculating the pooled odds of myopia to increase by 2% for each extra dioptre-hour spent in near work per week.[481] While this may seem small, the fact that recent studies published after 2014,[492, 494] which were not included in the meta-analysis, have tended to show more consistent associations, suggests that the overall effects are likely to be larger than currently noted. More evidence is required to confirm these links as well as to identify dose-dependent relationships. Meanwhile, the biological nature of the relationship between near work and myopia remains a mystery as an underlying mechanism has not been clearly defined. Identification of potential pathways involved not only completes the picture, but can also potentially provide further targets for intervention and myopia control.

1.9.3 Time outdoors

In comparison to the longstanding history that education and near work hold as risk factors for myopia, time outdoors has only recently come into the attention as another significant environmental risk factor for myopia. The first scientific indications for this came in 1993 by Parssinen and Lyra during their RCT of spectacle control in myopic school-children,[493] who noted that boys who reported spending a greater amount of time outdoors at the beginning of the trial, had lower rates of myopic progression throughout and finished the trial with a lower degree of myopia. Between the slowest and fastest progressors during the study, those who were in the lowest quartile for myopia progression spent less time on outdoor activities and sports per day (3.2 hours) compared to those in the highest quartile for progression (2.5 hours). Though at the time, this finding was attributed to reductions in reading and near work time and possible effects of distance

viewing occurring while outdoors. However since then, a large amount of accumulating evidence has been uncovered to support the role of time outdoors itself for the protection of myopia. This not only includes evidence from larger longitudinal studies, but also a number of successful clinical trials which have provided a new avenue for myopia control.

1.9.3.1 Time outdoors and prevalent myopia

Further signs for the role of time outdoors did not come until 2002, when Mutti et al reported that myopic children from the OLSM study spent less time playing sports (7.4 hours/week) than both emmetropic (9.7 hours) and hyperopic children (9.8 hours).[404] After adjusting for parental myopia, near work and test scores, a greater time spent playing sports was associated with a lower likelihood for myopia (OR = 0.917). However, like the earlier study by Parssinen and Lyra,[493] this finding was not attributed to time outdoors per se. Instead, Mutti hypothesised that there may exist a protective effect of physical activity itself or alternatively that myopes tended to refrain from sports possibly due to a more introverted personality, or due to the physical limitations of wearing spectacles. In the same year, during their investigation of the relationship between near-work activity, night-lights, and myopia, Saw et al found that children who were myopic spent less time outdoors than those non-myopic,[485] however as this became non-significant after multivariate adjustment, time outdoors was not considered to be influential for myopia. Over the next few years, several studies continued to report associations between increased time in sports, outdoor activities and physical exercise with reduced prevalent myopia. In 2006, Khader et al reported that playing sports outside of school hours was negatively associated with myopia (OR: 0.89) in a group of school-children in Jordan.[533] Similarly, baseline data of a study in Danish medical students found that myopic students spent significantly less time per day performing physical activity (51 minutes) than non-myopic students (60 minutes).[534] Also after two years, each hour/day of physical activity resulted in 0.175D less myopia (95% CI = 0.035–0.315). In another sample of medical students in Turkey, outdoor activity

performed before and at age 7 was reported to be higher in non-myopes (68.4%) than in myopes (48.6%).[535]

It was not until 2008, when Rose et al put forward the notion that it may be in fact time outdoors itself which may be protective against myopia. This was following findings from the SMS, where a greater amount of time spent in outdoor activities was associated with less myopic refractions in both groups of school-children aged 6 and 12.[487] Simultaneously, they also disproved the role of physical activity using the older cohort, as time spent on indoor sport had no association with refractive error ($P = 0.9$), whilst outdoor activities excluding sport, remained significantly associated ($P < 0.0001$). The effect of outdoor time was distinguished from possible reductions in near work, as poor correlations between near work and outdoor activity values ($P = 0.7$), ruled out that substitution effects were occurring between these two parameters. This made sense, given it is possible for an individual to spend both high amounts of time outdoors and in near work, such as in activities like outdoor reading. It was then proposed that it may be the higher levels of light intensity found in outdoor environments which underlie the effects of time outdoors. This was possible, as the release of retinal dopamine; which had been long known to inhibit eye growth;[536] was shown to be stimulated by light.[537] This theory has now become known as the light-dopamine hypothesis.

Following this, further attention shifted towards outdoor time as several reports began to accumulate finding associations between time outdoors and prevalent myopia.[165, 482, 488, 538-546] It also became clear that the effects of physical activity were confounded by time spent in outdoor environments and not exercise itself.[538, 543, 547-549]

Though not all studies investigating outdoor time have found associations with myopia. Some of these were conducted in children of preschool age,[550, 551] who may not be old enough to be susceptible to environmental risk factors for myopia and whose behaviours are still largely under parental control. Others have been conducted in populations known to have excessive levels of school myopia,[489, 552] with children either already engaging in lower levels of outdoor activities than

to other samples, or without enough variance to power statistical differences. Furthermore, due to the cross-sectional nature of these studies, students who were possibly pre-myopic and already spending low amounts of time outdoors may have not been represented adequately in statistical comparison.

1.9.3.2 Geographic variations in time outdoors and prevalent myopia

While there are differences in prevalence rates of myopia between ethnicities, the comparison of prevalence between individuals from the same ethnic group residing between different geographic locations, provides additional support that environmental risk factors can influence the development of myopia. Furthermore, significant differences in outdoor habits between the individuals living between these locations also suggests that time outdoors may be a contributing factor to the differences in myopia prevalence seen.

Significantly lower prevalences of myopia are found amongst Chinese schoolchildren living in Xiamen (19%) compared to those living in Singapore (37%).[485] Children in Xiamen also spent significantly greater time outdoors per week (9 hours) than the children in Singapore (3 hours) which may have contributed to the differences in prevalence rates seen between both cohorts, as there were also independent findings that myopic children spent significantly less time outdoors than those who were non-myopic. Similarities are seen in children with Chinese ethnicity living between Sydney, Australia and Singapore where a lower prevalence of myopia was found in children living in Sydney (3%) compared to those living in Singapore (29%).[553] This was also accompanied by more time spent outdoors per week in children living in Sydney (14 hours) compared to those in Singapore (3 hours). In these combined cohorts, a significant association between time outdoors and refraction was also present, demonstrating another scenario where outdoor time may be contributing to differing geographic prevalence rates of myopia.

Apart from between-country differences, myopia prevalence has also been seen to vary across rural and urban environments, with individuals spending different amounts of outdoor time. Guo et al

compared grade 1 & 4 children from urban and rural areas of Beijing and found that the prevalence of myopia was significantly higher in children living in urban regions compared to those in rural areas (urban vs rural; Grade 1: 30% vs 8%, Grade 4: 53% vs 19%).[540] In accordance with the previous examples, greater outdoor time was associated with reduced myopia, and it was also found that the children living in urban areas spent significantly less amount of time outdoors (1.1 hours/day) compared to their peers in rural locations (2.2 hours/day).

1.9.3.3 Time outdoors and incident myopia

Several longitudinal studies have identified associations between time outdoors and myopia, supporting the link for a causal role. In the OLSM study, children who became myopic spent less time per week on outdoor and sporting activities at baseline than those who remained non-myopic (mean difference: 3.7 hours).[370] This was again evident in the CLEERE study,[554] where children who became myopic were spending 1.1–1.8 hours/week less on outdoor and sporting activities than children who remained emmetropic, a difference which was evident beginning 4 years prior to the onset of and continued to 4 years after the development of myopia. In the SAVES study,[555] both younger and older children who became myopic also spent less time outdoors per week than those remaining non-myopic (mean difference: 4.7 & 2.4 hours, younger and older cohort). This trend for reduced incident myopia occurred in a dose-dependent manner as the odds of myopia decreased with increasing tertiles of outdoor time. Dose-response relationship was also seen in a study of grade 9 Chinese students from Aviation Cadet pre-recruitment classes,[556] where the 2-year incidence of myopia was 27.8% in those spending < 0.5 hour/day outdoors, 18.3% in those spending 0.5–1 hour/day and dropped to 8.6% in those who spent > 1 hour/day outdoors.

1.9.3.4 Time outdoors and myopia progression

In contrast to prevalent and incident myopia, the role of time outdoors in myopia progression is less clear, with several conflicting reports. In addition to the study by Parssinen and Lyyra,[493] three studies have demonstrated an association between time outdoors and myopia progression.[495, 549, 556]

In 2015, Wu et al reported that Chinese schoolchildren who were spending higher levels of time outdoors, were less likely to experience a myopic shift ≥ -0.50 D after a year (OR = 0.87).[549] Similar findings were reported from the 1 year follow-up of the NIM study, where those who spent > 2 hours per day outdoors were also less likely to experience myopic shifts ≥ -0.25 D (OR = 0.54).[495] While these two studies investigated myopia progression categorically Yao et al, found that male aviation cadets spending more than 1 hour per day outside, experienced smaller cumulative myopic shifts after 1 year and 8 months, compared to those who spent less than 1 hour per day outdoors (mean difference: 0.09 D).[556] While these studies indicate that refractive shifts towards myopia may be reduced by time outdoors, only the study by Saxena et al demonstrated that existing myopia progression can be protected, as participants in the two other studies were non-myopic at baseline.

On the other hand, while follow-up results from the CLEERE study found protective effects on incident myopia,[491] there was no association between outdoor time and annual myopia progression in their existing myopes. Investigations of myopes in the Anyang Childhood Eye Study (ACES),[557] and of a small group myopic children by Oner et al,[558] have also failed to find associations between myopia progression rates and outdoor activity.

Despite direct epidemiological evidence being unclear, consistent findings of seasonal differences in refractive progression have provided a strong plausible argument supporting the role of time outdoors in myopia progression.[18, 559-562] Several studies have found myopia to progress more slowly in summer periods than in winter, particularly in school-based cohorts which have summer vacation and are typically accompanied by higher levels of time outdoors and reduced near work.[539] Since individuals in these studies serve as their own controls, the evidence from these studies are arguably more robust, as they overcome the lack of variation in exposure time which may have limited previous studies examining outdoor time in myopes.

1.9.3.5 Intervention trials of time outdoors

To date, four clinical trials have investigated the effects of increased outdoor time in school-aged children (Table 1.12). These studies have provided the strongest lines of evidence supporting the protective relationship between time outdoors and myopia.

The first completed RCT was conducted in two Taiwanese schools.[371] One school was assigned to receive the "recess outside the classroom" (ROC) program, where 80 minutes of outdoor time per day was enforced by restricting access to classrooms during recess periods. After 1 year, incident myopia in the school which received the ROC program was approximately 50% less than seen in a control school which had no program (8.4 vs 17.7% respectively, P = 0.001). Children in the intervention school exhibited less myopic shift than the control school (-0.25 vs -0.38 D respectively, P = 0.029), however this seemed to occur in non-myopic children, as myopia progression in existing myopes was not significantly different between the two groups. This may have been due to the fact that there was a large proportion of myopic children concurrently undergoing atropine treatment in both groups (41% & 24%, intervention & control group).

Shortly after, 3-year results from the GOAL study were published,[372] which was a clustered RCT held in 1st year classes across 12 primary schools within Guangzhou, China. In the intervention schools, a compulsory 40-minute long outdoor sports class was added at the end of each school day and children were also encouraged to spend more time outdoors out of school hours. After 3 years, incident myopia was significantly lower in the intervention schools compared to the control schools (30.4% vs 39.5% respectively, P = 0.001). As the proportion by which this was reduced was approximately of half that seen in the ROC study (23% vs 50%), it indicated a potential dose-response effect. Similar to the ROC study, myopia shifts were also lower in the intervention group compared to the controls (-1.42 vs -1.59 D respectively, P = 0.04), however no significant differences in axial elongation were seen. As there was a low baseline incidence of myopia (~1.9%) these

differences were unlikely to have occurred in existing myopes, thus the effect of time outdoors on myopia progression remained unclear.

In the same year, results from another large-scale intervention study in China was published where extra outdoor time was added in the form of two 20-minute recess programs.[373] Although there were 3,051 students from two primary and two junior high schools who participated, cycloplegic refractive data was only available for a small random subgroup of 391 (12.8%) students. Although the total extra outdoor time provided by the intervention was lower (40 minutes), incidence rates were reduced by a similar proportion (~50%) to what was seen by the ROC study (3.7 vs 8.5%, P = 0.048). Again myopic shifts were lower in the treatment group (-0.10 vs -0.27 D, P = 0.005), however this time axial elongation in the treatment group was significantly lower compared to the controls, albeit by a small margin (0.16 vs 0.21 mm). While this was promising, baseline incidences of myopia in this subgroup were not reported, making it difficult to determine the effects on existing myopes.

A second clinical trial of outdoor time in Taiwan was published in 2018.[374] 1st graders in Taiwan who were encouraged to spent at least 11 hours or more of outdoor time per week as part of the Recess Outside Classroom Trial 711 (ROCT711), had less incident myopia than their controls over a 1 year period, however this was not statistically significant (14.5% vs 17.4% respectively, P = 0.054). The result of this trial may have been complicated by the fact that the control group also received some form of intervention. Since the first ROC trial was conducted, the Taiwanese government introduced two nationwide health promotion programmes, the Tien-Tien 120 program: which encourages 120 minutes of outdoor activities per day, as well as the Sport and Health 150 program: which encouraged at least 150 minutes of exercise time weekly. These combined programs would theoretically have added more outdoor time than the intervention itself. Nevertheless, both myopia progression and axial elongation were significantly reduced in the intervention group (mean difference of -0.22 D, P = 0.007 and 0.09 mm, P = 0.02), suggesting that perhaps a higher level of outdoor activity was needed to slow existing myopia progression.

1.9.3.6 Meta-analyses

So far, two meta-analyses have pooled together results from various studies of time outdoors. An early meta-analysis published in 2012,[563] included results from seven cross-sectional studies and reported on a further 16 studies which met the inclusion criteria. Pooled odds ratios indicated that each additional hour of time outdoors spent per week reduced the odds of myopia by 2% (OR = 0.98, 95% CI = 0.973–0.990). Though these results were rather small as there was limited evidence at this point in time. Two of the included studies only used outdoor sports as a measure of time outdoors,[404, 533] which may have underestimated true outdoor exposures. Another two of the included studies also failed to find any association at all,[551, 552] whereas the majority of the 16 excluded studies reported significant associations.

A later meta-analysis was published in 2017,[564] which included 25 articles out of a pool of 51. A significant protective effect of outdoor time was found for incident myopia from clinical trial studies (RR = 0.536, 95% CI = 0.338–0.850) and longitudinal cohort studies (RR = 0.574, 95% CI = 0.395–0.834), as well as for cross-sectional studies investigating prevalent myopia (OR = 0.964, 95% CI = 0.945–0.982). In their dose-response analysis, increased time outdoors reduced the risk of incident myopia that followed an inverse logarithmic relationship. Pooled results from clinical trials indicated that outdoor time was able to reduce myopic shifts of -0.30 D over 3 years of follow-up. Meanwhile in existing myopes, no significant effects were found, however as earlier described (Section 1.9.3.5) the majority of the RCTs were not geared to examine myopia progression.

1.9.3.7 Proposed mechanisms

1.9.3.7.1 Physical activity

Potential underlying mechanisms were thought to mediate an effect of physical activity against myopia involved possible changes in blood flow to the choroid, leading to increased thickening and inhibitory axial length elongation.[565] However little further evidence for the role physical activity has

been provided, as later epidemiological studies of myopia began to distinguish between outdoor activities and sports separately. This found that strong associations between direct measures of outdoor activity and myopia remained, but not for sporting activities itself.[538, 543, 547, 549] Additionally, recent studies using actigraphy devices to separately capture time outdoors and physical activity, have found associations between outdoor light and myopia but not activity count.[566] Therefore it currently appears that physical activity is unrelated to myopia, and that the associations seen come from confounding effects of time outdoors itself and myopia.

1.9.3.7.2 Reduced near work-related factors

While excessive near work has also been indicated to be involved in myopia development, the effects of time outdoors does not seem to come from a substitutional effect from reducing near work. Poor correlations between the two variables.[370, 487, 538, 555] indicates that any observed effects from near work and time outdoors are occurring independently. This makes sense given that in real life, near work and time outdoors do not occur in opposition, as it is rather common for individuals to perform both activities simultaneously such as reading outdoors. A lack of a viable mechanism underlying near work also adds to the unlikely involvement of near work related factors underlying the effects time outdoors.

1.9.3.7.3 High light intensity and myopia

Higher light exposures has become the most established variable explaining the effects of outdoor time on myopia. This is logical as there is a stark difference in lighting levels between outdoor and indoor environments which is readily perceivable by the human eye. There has since been substantial evidence provided within areas of animal experimentation and in human epidemiology to support this mechanism, which will be reviewed in depth in Section 1.10.

1.9.3.8 Summary

Time spent outdoors has quickly become one of the most well established causative risk factors for myopia development in children. This was first identified in several population based studies, reporting that myopes were spending lower time outdoors compared to non-myopes. Evidence for causality was subsequently demonstrated by a number of longitudinal studies which found that higher outdoor time was associated with reduced incident myopia. Further definitive evidence comes from intervention trials which confirmed the protective role of increased outdoor time against incident myopia. In contrast, while there has also been evidence that higher outdoor time can reduce the progression of existing myopia, it has not been conclusive.

A major underlying issue is that many studies examining progression have been conducted within highly myopic populations. Thus myopigenic influences are expected to be strong and existing myopes may display little variation in behaviours to display significant or clinically meaningful effects. Similar issues may have influenced the control studies, as all participants are given the same degree of behavioural intervention, existing myopes who are likely to be spending the least amounts of time outdoors may not be receiving enough total outdoor exposure to see protection compared to non-myopes. This level of exposure needed might be determined by the amount of individual near work being performed, as indicated by the Sydney Myopia Study,[487, 555] suggesting that future intervention studies may need to accurately determine exposures to several key risk factors on an individual level. Further evidence to support this assertion comes from studies examining light exposure as the protective mediator for outdoor time, which will be discussed in the following section.

1.10 Light Exposure and Myopia

Light intensity, or illuminance, is a measure of the amount of incident light on a surface of a given size. It is measured in SI units of lux (lx) which represents the amount of lumens falling per square meter. Typical indoor lighting conditions using artificial lighting sources usually provide low illuminance values of approximately 500 lux, whereas it is not uncommon for light levels to reach over 100,000 lux outdoors in direct sunlight, a magnitude well over 100 times larger in comparison. Animal studies have suggested that higher light exposures mediates the protective effects of time outdoors on myopia. Subsequently, studies into human epidemiology have begun to investigate light exposures using illuminometers [light meters or light data loggers (LDLs)] in order to verify this relationship in humans and to more accurately assess for protective relationships (Table 1.13).

1.10.1 Animal studies

1.10.1.1 Light intensity and animal myopia

Animal studies investigating the effects of lighting environments on the development of experimentally induced myopia have provided evidence for a protective role of high light intensity against myopia.

Animals developing FDM become less myopic when raised in brighter lighting. Ashby et al,[567] demonstrated that chickens who had 15 minutes of diffuser removal in sunlight (30,000 lux) were less affected by FDM than those who had their diffusers removed in standard laboratory light (500 lux). Chicks wearing diffusers continuously under high-light intensity (15,000 lux) developed less myopic refractions and shorter axial lengths than those reared under normal light levels (500 lux). This reduced the development of FDM by approximately 65% when contralateral control eyes were considered. There were no differences in refraction of form-deprived eyes between those who were raised in low light levels (500 lux) and dim light levels (50 lux), suggesting that a possible minimum threshold of light intensity between 500 and 15,000 lux was required in order to see a protective

effect. This was again shown in a similar experiment, where chickens wearing diffusers who were raised under 15,000 lux had approximately 60% less FDM than those raised under 500 lux.[568]. Similar findings were reported in tree shrews by Siegwart et al, who reported that ~16,000 lux for 7.75 hours per day reduced the development of FDM by 44% after 11 days.[569] This was again demonstrated in rhesus monkeys by Smith et al,[16] who found an 87% reduction in myopic anisometropia in monkeys raised under ~25,000 lux for 6 hours per day for 50–123 days. This effect was promising as it suggested that larger effects could be achieved using higher light levels, in an animal model of myopia which is arguably closest in resemblance to the human eye.

Evidence for a dose-dependent relationship between light intensity and myopia development came in 2015 when Karouta et al found a significant correlation between increasing light intensity levels and the amount of protection received from FDM.[14] This followed an inverse logarithmic dose-response relationship, with levels of 40,000 lux almost completely abolishing the effects of FDM (~95%), while 10,000, 20,000 and 30,000 lux reduced FDM by ~50%, ~70% and ~80% respectively. In a separate experiment, chicks initially raised in 500 lux that switched to 40,000 lux after developing myopia, experienced a subsequent hyperopic shift in refractive trajectory, which stabilised around emmetropia for the remainder of the period. This resulted in their final refraction lying in between those raised in 500 and 40,000 lux, demonstrating that increased light intensity could prevent the progression of existing myopia. In comparison to chickens, Chen et al, reported that mice under FDM receiving 6 hours per day of 2,500–5,000 lux for 4 weeks, had ~46% less myopia compared with those who were only exposed to 100–200 lux lighting.[15] While this may suggest that myopia protection can be achieved in lower lighting environments, the lower threshold may have reflected the relative differences in habitual lighting environments, as mice tend to live in scotopic to low mesopic environments, wheras humans and chickens experience more photopic environments.

While most animal experiments on myopia have used artificially simulated lighting environments, Stone et al, attempted to investigate the impact of outdoor lighting environments on refractive

development in chicks by comparing responses to FDM in chicks who were either raised outdoors during the day or remained in standard laboratory lighting conditions.[570] After four days, there was a 44% reduction in experimental myopia in those who were exposed to outdoor lighting compared to those indoors. However by 11 days, this difference disappeared, with treated eyes in outdoor chickens having more relative myopia (~80%) than indoor eyes. Given that outdoor illuminance was not measured, it was not clear whether this occurred as a result of insufficient light exposure from weather fluctuations.

High light environments also appears to slow the development of LIM, though not demonstrated as consistently as seen with FDM. In chickens, five hours per day of 15,000 lux slowed rates of lens compensation (+7 or -7 D lens wear) but did not alter the final refraction and axial length change in treated eyes compared to those raised in normal 500 lux.[568] Similarly in tree shrews, high lighting environments provided a 39% reduction in LIM after 11 days,[569] before full compensation eventually occurred. Meanwhile, Smith et al, was unable to find any protective effects of 25,000 lux for six hours in their rhesus monkeys subject to LIM.[571] Light levels needed to influence LIM may be higher than required for FDM. Since animal myopia is induced with constant myopigenic stimuli, the protective levels required may exceed levels commonly encountered by humans and may have been overestimated.

1.10.1.2 Duration and frequency of light exposure and animal myopia

In contrast to the number of studies investigating the effect of light intensity on animal refraction, few have investigated temporal aspects of light exposure such as the duration and frequency of bright light exposure. This is rather surprising given that the human data examines outdoor time as a temporal-based variable.

In 2013, Backhouse et al investigated whether a shorter period of higher intensity light exposure was more effective at protecting against myopia than continuous exposure to bright light.[572] Chicks reared under FDM were exposed to either 300 lux (control), constant 2,000 lux or 300 lux + two

hours of 10,000 lux during the light-dark cycle for three days. However, those in the latter group did not have any significant differences in refraction compared to the control, indicating there was no additional benefit to receiving an additional two hours of 10,000 lux. As 10,000 lux is known to protect against myopia in chickens,[14, 573] there may also be a minimum exposure time that is required. Additionally time-of-day effects may be involved, as those who received bright light in the midday were not significantly less myopic than those who experienced continuous exposure to 2,000 lux, whereas the group which received the extra 10,000 lux in the morning or during the evening had significantly less myopia protection. This suggests that the effectiveness of light exposure may be different when given at certain times, with the authors hypothesising that bright light exposure in morning and evening times may disrupt the emmetropisation system, leading to more myopia. Similar time-of-day effects were also seen by Sarfare et al, who exposed chicks with either FDM or LIM to three hours of 30,000 lux in the morning or evening over 6 days.[574] Though changes in refractive error were not seen, significant differences in rates of axial elongation were found, though maximal inhibition of axial elongation occurred in those exposed to bright light in the evening instead.

In 2014, Lan et al conducted two experiments investigating temporal effects of high light exposures on chicks under FDM.[575] Firstly differing durations of high light exposure were investigated by exposing chicks to 5,000 lux continuously for either 1, 2, 5 or 10 hours per day. After 5 days, significant inhibition of myopia (~70%) was seen in those exposed to those exposed to 5 or 10 hours or more of bright light per day compared to those reared under constant 500 lux. On the other hand, no myopia protection was seen in chicks who received either 1 or 2 hours of high light exposure per day who developed myopia similar to the control group. As protection was not seen using higher lux levels than Backhouse et al (15,000 lux 2h/day), this suggested that a minimum exposure time is required to receive myopic protection. Similarities in protection seen between those receiving 5 hours and 10 hours of exposure suggests that an upper threshold may also exist or that there are diminishing returns. In a second experimental paradigm, differences in frequency of bright light

exposure was examined. Again chicks were exposed to 15,000 lux, however 5 hours of total exposure was split into 1:1 on-off cycles applied at either 1, 7, 15, 30 or 60 minute intervals, keeping the total daily duration the same but altering the frequency of attainment. While significant myopic protection was seen in all groups compared to 500 lux controls, larger protective effects were seen in those who received light in 1:1 or 7:7 minute cycles compared to all lower frequencies. At these two levels, near total suppression of FDM was seen as differences between eyes wearing diffusers and their control eyes were non-significant. This indicates that in addition to effects of cumulative exposure time, the episodic delivery of light may also play a large part in determining the effectiveness of light exposure on myopia. Flickering light has already been known to stimulate dopamine release (the likely mediator behind light-induced myopia protection),[576, 577] however this suggested that even extremely low frequencies of light episodes (0.007 Hz) can have an impact on myopia, at a level which is more realistically experienced within the human environment.

1.10.1.3 Mechanisms of light induced myopia protection

1.10.1.3.1 Light intensity and retinal dopamine release

The light-dopamine theory proposed by Rose et al[487] has a strong biological basis from several animal experiments. Retinal dopamine release has long been known to be driven by light,[578-582] linking its involvements with time outdoors. Dopamine (DA) is the major catecholamine neurotransmitter found in subtypes of amacrine and interplexiform cells within the retina. It is synthesized from the amino acid tyrosine in two steps: firstly tyrosine hydroxylase (TH) converts L-tyrosine into 3,4-dihydroxy-L-phenylalanine (L-DOPA) and secondly, L-DOPA converts into DA by DOPA decarboxylase. Once synthesis is complete, DA is transported into synaptic vesicles by the vesicular monoamine transporter. Upon release, DA may either act on postsynaptic, presynaptic or extra synaptic D1 or D2-like receptors. Following activation, DA may either be repackaged into the synaptic vesicles or metabolised by monoamine oxidase to form 3,4-dihydroxyphenylacetic acid (DOPAC). As TH is the rate-limiting enzyme in dopamine synthesis, corresponding levels reflect the

rate of dopamine production. As DOPAC is the primary metabolite of DA in the retina and vitreous, corresponding levels also reflect DA activity.[583, 584] The main hypothesised role for retinal dopamine is that it is a chemical messenger for light adaptation. However, secondary implications for DA have been developed which demonstrate its role as a "stop" signal for eye growth, particularly in experimental myopia

DA has also been known to regulate the development of experimental myopia for some time as well. Stone et al found that synthesis of normal diurnal retinal DA as well as DOPAC were reduced in eyes that received FDM and developed subsequent axial myopia.[536] The causal link underlying this effect was supported upon administration of apomorphine; a DA agonist which inhibited the induced FDM in a dose-dependent fashion. Further confirmation was seen, as co-administration of haloperidol (a dopamine antagonist) nullified the protected effects seen by apomorphine. At the same time Iuvone et al, reported the same finding in rhesus monkeys and also demonstrated that TH was also reduced following FDM.[585] This behaviour has been demonstrated in several studies in a variety of animal models including chickens,[537, 586-589] rabbits,[590, 591] guinea pigs[592, 593] and tree shrews,[587] indicating that increasing DA levels and/or DA activity in the retina can protect against myopia development. Meanwhile, there have been some mixed results particularly in studies on mice[15, 594-598] and those which use lens-induced myopia (LIM).[593, 599-601]

Evidence that retinal DA mediates the protective effects of bright light in FDM was given by Ashby et al, who found that intravitreal injections of spiperone (a dopamine D2 antagonist) could negate the protective effects of high ambient lighting (15,000 lux) on chicks under FDM.[568] Further support was provided by Chen et al, who showed that intraperitoneal injections of SCH39166; a dopamine D1 antagonist; completely reversed the inhibitory effects of bright light on both refraction and ocular elongation.[15] Retinal dopamine has also been shown to be involved in the ability for brief periods of unrestricted vision to protect against FDM.[537] For LIM, Thomson et al[602] found that spiperone

blocked the inhibitory effect of levodopa administration in chicks but not SCH39166, suggesting that the D2 receptor may be the pathway in both models.

1.10.1.3.2 Spectral composition of light

Apart from retinal dopamine release, differences in the spectral composition of light found in outdoor environment has also been proposed to underlie the effects of time outdoors and myopia. In comparison to typical indoor lighting conditions which are often lit artificially and comprises more of longer red wavelengths, outdoor sunlight contains light of shorter wavelengths, such as green, blue and ultraviolet light. Due to the effects of chromatic aberration, shorter wavelengths of light are refracted more anteriorly on the optical axis of the globe compared to longer wavelengths thus potentially inducing similar responses to that of myopic defocus.

In animal studies, there have been conflicting reports on the effects of various wavelength compositions on refractive development between different animal models. On one hand, in chickens[603-606] and guinea pigs,[607] shorter wavelength light (e.g. blue) has been shown to slow eye growth and reduce myopia development, while longer wavelength light (e.g. red) increases eye growth, thus causing myopia. On the other hand, in tree shrews[608-610] and rhesus monkeys[611, 612] the opposite is seen to occur, as increased eye growth and myopia development occurs under short wavelength light whilst longer wavelength light leads to hyperopia. More conflicting reports come from studies demonstrating that the protective effects of bright light still occur, despite the filtering of various spectrums (in particular violet light) from the light source.[14, 16] Finally, doubt that shorter wavelength light is involved in inducing retinal growth signals also comes from the fact that UV light is naturally heavily filtered by the cornea and crystalline lens of the eye,[613] meaning that intensities reaching the retina are relatively low in comparison to other wavelengths.

UV light exposure stimulates retinal vitamin D synthesis. Although there are multiple cross-sectional studies demonstrating an association between vitamin D levels and its biomarker 25-hydroxyvitamin D (25(OH)D) with prevalent myopia;[614-617] which have then been shown to be significant via meta-

analysis;[618] longitudinal studies have been unable to find differences in vitamin D levels in the years precluding myopia onset after multivariate adjustment.[405, 619] Furthermore, mendelian randomization studies of individuals possessing a range of SNP's relating to reduced 25(OH)D levels have failed to find an association with myopia.[620] As no causal relationship can be established, it appears that associations between vitamin D and myopia occurs via confounding effects with time outdoors.

1.10.1.3.3 Circadian rhythms

Changes in the regulation of the circadian rhythm via light has also been thought to underlie the effects of time outdoors and myopia, as diurnal fluctuations have been observed in many of the eyes ocular parameters and physiological processes involved in refractive development. It is generally indicated that eyes are generally longer during the day and shorter at night, conversely fluctuations in choroidal thickness occur in antiphase with daily fluctuations in axial length.[621-623] Dopamine signalling is also related to circadian rhythms. Light exposure is the strongest zeitgeber (time-giver) of the body's circadian rhythm. From the retina, there are tracts sending photic information to the suprachiasmatic nuclei in the brain, which has output pathways via the humoral and automonic nervous system of the body. One such pathway projects to the pineal gland, which produces the sleep-facilitating hormone melatonin and has inverse links to the dopaminergic system.

Animal studies indicate that disruption of ocular diurnal rhythms occur following experimentally induced refractive errors for both FDM[624, 625] and LIM.[626] Furthermore, these disruptions have been correlated to longer term eye-growth, suggesting that they may impact overall refractive development. However, the evidence in humans is limited, with two studies unable to find differences in diurnal rhythms between refractive error groups.[627, 628]

Another aspect suggestive of an influence of circadian rhythms, comes from the relationship between melatonin levels; a biomarker for light induced circadian rhythm regulation; and refractive error, however the evidence has also been inconclusive. Kearney et al found that myopes aged 18–

20 from the NICER study had higher levels of melatonin compared to non-myopes.[629] However two cross-sectional studies in adult samples have failed to find differences in serum melatonin levels between myopes and emmetropes.[627, 630]

Further findings of associations between sleep deprivation and myopia have been reported, which suggests for a role of circadian rhythms as melatonin regulates the body's sleep-wake cycle. However, these studies have also been inconsistent.[545, 631, 632] This may be due to confounding effects occurring from education and near work, as children with higher study loads are more likely to receive less sleep time. More studies are needed to assess the causal nature of altered circadian rhythms and refractive development.

1.10.2 Human light exposures and myopia

Recently, human epidemiological studies have begun using portable illuminometers to capture individual light exposure. Though the early roles of these devices were to provide an objective measurement of outdoor time, investigators have also begun to use these measures to directly assess light exposure itself as a risk factor for myopia. Several metrics have been assessed. To capture time outdoors, a threshold of 1,000 lux has been generally deemed the cut-off to categorically distinguish between indoor and outdoor environments. On the other hand, light exposure can be examined as a continuous variable by quantifying mean light intensities across a certain period of time (usually a day). Temporal aspects can also be investigated, by considering the number of indoor-outdoor alternations or by using higher thresholds to examine bright light exposures. These approaches provide a complete picture of individual light exposure habits and have the potential to truly characterise the relationship between time outdoors and myopia development and its progression.

1.10.2.1 Observational studies of light exposure

Dharani et al first investigated the relationship between light exposure and myopia.[633] In the Family Incentive Trial (FIT), a subset of 117 Singaporean children (55% myopic) aged 6–12 years old wore the HOBO Pendant UA-002-64; a miniature data logging device containing both a temperature and light sensor; over 7 consecutive days of wear. No differences in time outdoors were seen between children who were myopic and those non-myopic as determined by the light meter as well reported from an outdoor activity diary (all $P > 0.05$).

Further findings came in 2014 by Read et al who investigated light exposure and physical activity in children as part of the Role of Outdoor Activity in Myopia (ROAM) study in Australia.[566] 102 children wore the Actiwatch 2, a wrist-worn actigraphy device which contains a light sensor, over 14 days across the school term. Myopic children experienced lower mean daily light intensities (915 lux) than emmetropes (1,272 lux, $P < 0.01$), and spent less time in outdoor environments > 1,000 lux (91 minutes per day) than emmetropes did (127 minutes per day, $P > 0.001$). This was also true for time spent > 2,000 lux and > 5,000 lux. A later analysis of this data also found that the myopic children spent more time in mesopic (1–30 lux) light conditions than non-myopes.[634] AUC analysis indicated that time spent > 2,000 lux was the strongest distinguisher between myopes and emmetropes, possibly indicating the presence of a minimum threshold around this level.[566] Differences in the average daily light intensities between myopic and non-myopic children remained statistically significant during an 18-month follow-up of this study (805 vs 999 lux, myopes vs non-myopes).[635] These reduced light exposures were also independently associated with larger longitudinal changes in axial length, with decreases in axial elongation rate of 0.12 mm/year for every 1 log unit increase in average daily light intensity experienced. In addition to average daily light intensity levels, time spent in environments of higher light intensities were also associated with reductions in rates of axial eye growth, however this was only significant for time spent in environments > 3,000 lux and > 5,000 lux but not > 1,000 lux or > 2,000 lux. Given that time spent > 2,000 lux was able to distinguish prevalent myopia, this suggests that the requirements for protection against myopia progression may lie at a higher intensity threshold than needed to reduce incident myopia.

Data from the FIT and ROAM study were compared,[636] to show that the cohort in Australia; were spending significantly longer time outdoors (105 vs 61 min/day) and were outside more frequently (6.9 vs 4.6 episodes/day) compared to the Singaporean cohort. Differences in outdoor exposure habits were most significant during school hours on weekdays, potentially suggesting that differences in education systems between the two countries may be influencing light exposure habits. However, the sample contained in the ROAM study was unlikely to have adequately represented a typical Australian school cohort, given that it contained a myopia rate of 41%.

Meanwhile, Ostrin et al also failed to find an association between refractive error groups and outdoor light exposure in a longitudinal study of 60 children aged 5-10 years, who wore the Actiwatch 2 device over three 2-week periods over 1-year.[637] Although there was a trend for decreased rates of axial elongation with higher light exposures, the association was poor (r = -0.176) and was non-significant during multivariate analysis. Exposure times to light levels > 1,000, >2000 or >5000 lux did not significantly differ between myopes and non-myopes, however there may have been a lack of statistical power, with only 8 myopes (13%) contained in the study.

More robust findings from a larger sample size was presented in 2018, after objective light exposure data obtained from participants wearing HOBO Pendants in the ROCT711 study was analysed.[374] Children exposed to >200 minutes per week to lighting levels of ≥ 1,000 lux, or ≥ 3,000 lux, experienced significantly less myopic shifts over the study duration (1 year) compared to those spending < 125 minutes per week. Stronger associations were seen in children who were non-myopic at baseline, where those spending > 200 minutes per week in all thresholds (≥ 1,000, ≥ 3,000, ≥ 5,000 and ≥ 10,000 lux) experienced lower myopic shifts than those who spent < 125 minutes per week outdoors. Interestingly for those non-myopic who spent less time outdoors (125–199 minutes per week), only those with exposures ≥ 10,000 lux had less myopic shifts. These results suggests that trade-offs between the effects of light intensity and exposure duration may be possible, as those

spending less time in outdoor lighting environments were only seen to receive protection at higher thresholds of light intensity.

Further evidence came in 2020, when Wen et al provided light exposure data from the newly developed device, the Clouclip.[638] In addition to its capabilities in measuring light intensity, the Clouclip is able to record working distance at an eye level. Associations between refractive error and time spent in higher intensity light were seen, with myopic children spending less time in light levels > 3,000 lux and > 5,000 lux per day compared to non-myopic children. Time spent in levels > 1,000 lux and > 2,000 lux however, were not different between refractive groups, suggesting a potential threshold level between 2,000–3,000 lux. Furthermore, dose-dependent effects were indicated, as the likelihood for myopia decreased with time spent in higher light intensity levels (> 3,000 lux: OR = 0.27, 95% CI = 0.10–0.72; > 5,000 lux: OR = 0.11, 95% CI = 0.02–0.56). While a higher time spent in brighter light environments was associated with reduced myopia, temporal effects were not seen, as the frequency of outdoor light exposures were not significantly different between myopes and non-myopes. Similar findings using the Clouclip were recently reported by Bhandari et al,[639] who found that myopic children spent less daily time outdoors and experienced lower mean daily light exposures than non-myopic children, but did not differ in daily outdoor frequency. Though given the relative large age range and small sample size studied (10–18 years old, n = 40), the samples may have not adequately represented the general population.

In 2021, light exposures from 9-year old children in Singapore were examined by Li et al using a fourth illuminometer: the FitSight device;[640] a wrist-worn watch with light monitoring capabilities. Though subjectively reported time outdoors was associated with reduced myopia (OR: 0.82 for 1 hour increase in daily outdoor time), no differences in light exposures were seen between myopic and non-myopic children. As the average time spent > 1000 lux and average daily light intensity levels in this sample were much lower than in Wen et als study, (37 vs ~100 min/day and 458 vs 730

lux respectively),[638] it is likely that most of the Singaporean children were below the threshold for protection.

1.10.2.2 Intervention studies of light exposure

Whilst most studies have been observational, only one intervention study has investigated the impacts of directly altering light exposures. In Hua et al's RCT study of elevated classroom lighting levels,[375] schools in the intervention arm which had rebuilt lighting systems received increases in average illuminance from less than 100 lux to approximately 500 lux. Schools in the control group had no lighting modifications and their classroom illuminances remained below 100 lux. Their findings (discussed in Section 1.7.4.3) suggested that increased lighting levels could be protective against incident myopia, but what was most profound was that a protective effect was achieved using light levels much lower (~500 lux) than the levels commonly studied using objective devices in humans which are well in excess of 1,000 lux. In animals this difference is even larger, as constant 500 lux exposures are typically used as the control environment when inducing experimental myopia. This suggests that protective light levels may not necessarily need to be acquired from such high light exposures solely from within outdoor environments. In combination with observations that myopes and non-myopes may differ in mesopic light exposures (1–30 lux),[634] raises questions of dose-time interactions. Perhaps protection was achieved through consistently prolonged exposures to moderately intensive light across the entire school day. Although the exact duration of classroom time was not described in the study, these daily exposures are likely longer than the extra periods of outdoor exposures obtained during outdoor intervention trials, which have provided extra outdoor recess times of 40-80 minutes per day. More intervention studies manipulating lighting conditions at different intensity levels are required to examine dose response effects and future studies would need to focus on exposure time as well.

Table 1.13: Summary of studies investigating light exposures in relation to myopia in humans.

Author, Year	Participants	Methodology	Risk factor measure/s	Findings
Dharani et al,[633] 2012 Singapore *FIT*	117 children from the FIT trial *Aged 6-12 years old* *55% myopic*	Cross-sectional *Light exposures and outdoor activity logged over 7 consecutive days*	Outdoor activity diary completed by parents • Adapted from the Child Development Supplement-III 2007 HOBO Pendant UA-002-64, light meter • *Worn on shirt via safety pin with sensor facing outwards, measuring at 5-minute intervals* • *Time spent > 1000 lux considered as outdoor time*	No significant differences in outdoor time were seen between myopic and non-myopic children for values obtained from both diary and light meter estimates (all P > 0.05).
Schmid et al,[641] 2013 Australia	35 university students *Aged 17-25 years old* *13 emmetropes, 12 stable myopes & 10 progressive myopes*	Cross-sectional *Light & UV exposures and outdoor activity obtained over 3 days*	Self-administered questionnaire + 24-h light exposure diary • *Adapted from SMS questionnaire* HOBO Pendant UA-002-08 • *Clipped onto shirt pocket, collar or midline, measuring at 5-minute intervals* Polysulphone film (PSF) dosimeter	Mean daily illuminance did not significantly differ between refractive groups and did not correlate with the magnitude of refractive error (r=0.153, P = 0.438). Time per day >1000 lux and number of indoor/outdoor alternations did not significantly differ between refractive groups. Stable myopes had the greatest UV exposures (0.32 MED) followed by progressive myopes (0.17 MED) and emmetropes (0.17 MED) (P = 0.003).
Read et al,[566] 2014 Australia *ROAM*	102 children (41 myopes, 61 emmetropes) *Aged 10-15 years old* *Mean SER of myopes -2.39D* *Mean SER of emmetropes +0.34D*	Cross-sectional *Light exposures and physical activity data collected over 2 weeks during school term.*	Actiwatch 2 actigraphy device • *Worn on wrist, measuring light and activity counts at 30-second intervals* • *Time of exposure per day above various thresholds (>1000 lux, >2000 lux, >3000 lux, and >5000 lux)*	Myopic children experienced lower average light exposures (915 ± 519 lux) than did emmetropes (1272 ± 625 lux, P < 0.01). Myopic children spent less time >1000 lux per day (91 minutes) than emmetropes (127 minutes, P > 0.001). Time spent >2000 lux and >5000 lux were also lower in myopes. Time spent >2000 lux was the strongest distinguisher for myopes vs emmetropes. Physical activity counts not significantly different between myopes and emmetropes.
Read et al,[635] 2015 Australia *ROAM*	101 children (41 myopes, 60 non-myopes) *Aged 10-15 years old* *Mean SER & AL of myopes -2.39 D & 24.46 mm* *Mean SER & AL of non-myopes +0.34 D & 23.24mm*	Longitudinal (18 month follow-up) *Light exposures and physical activity data collected over 2 weeks during school term at baseline and between 5.3 to 9.4 months afterwards.*	Self-administered questionnaire • *Adapted from SMS questionnaire* Actiwatch 2 actigraphy device • *Worn on wrist, measuring light and activity counts at 30-second intervals* • *Time of exposure per day above various thresholds (>1000 lux, >2000 lux, >3000 lux, and >5000 lux)*	Myopic children experienced lower average daily light exposures (805 ± 427 lux) than non-myopic children (999 ± 468 lux, P < 0.05). This did not vary by season. Greater light exposures were associated with smaller axial length changes (P = 0.047). Higher durations of light exposure >3000 lux and >5000 lux associated with reduced AL elongation (both P < 0.05).

Hua et al,[375] **2015** **China**	317 schoolchildren *Aged 6-14 years old*	Randomised control trial (1 year) *178 students in the intervention arm, had classrooms with rebuilt lighting systems to provide higher illuminance.*	Intervention • *Illuminances of desks and blackboards increased to ~500lux.* Control • *Classroom lighting remained low at <100 lux*	Incident myopia in the intervention arm (4%) was lower than the control group (10%, P = 0.029). Non-myopic students in the intervention group also had smaller myopic shifts (-0.25D) compared to the control group (-0.47D, P = 0.001). All students in the intervention group had lower rates of axial elongation.
Landis et al,[634] **2018** **Australia** ***ROAM***	80 children (40 myopes, 40 emmetropes) *Aged 10-15 years old* *Mean SER of myopes -2.39D* *Mean SER of emmetropes +0.34D*	Cross-sectional *Exposures to dim light levels were evaluated from a subset of participants from the ROAM study*	Actiwatch 2 actigraphy device • *Worn on wrist, measuring light and activity counts at 30-second intervals* • *Time of exposure per day above various thresholds (scotopic: <1-1 lux, mesopic: 1-30 lux, indoor photopic: >30-1000 lux & outdoor photopic: >1000 lux)*	The biggest differences occurred on weekends, where myopic children were exposed to less scotopic light (P = 0.024) and less outdoor photopic light (1.27 hours) than non-myopic children (1.93 hours, P = 0.008). However, myopic children spent more time in mesopic light (6.4 hours) than non-myopic children did (5.75 hours, P < 0.001). In myopic children, more myopic refractive errors were correlated with increased time in mesopic light (R = −0.46, P = 0.002) and decreased time in outdoor photopic light (R = 0.33, P = 0.005).
Ostrin et al,[637] **2018** **United States**	60 children (8 myopes, 52 non-myopes) *Aged 5-10 years old* *13.3% myopic at baseline* *Mean SER +0.85 D at baseline* *Mean AXL 22.61 mm at baseline*	Longitudinal (1 year) *Actiwatch measures obtained over three 2-week periods (fall school, spring school, summer)*	Actiwatch 2 actigraphy device • *Worn on wrist, measuring light and activity counts at 1-minute intervals* • *Time spent > 1000 lux considered as outdoor time* Parent-administered questionnaire • *Adapted from SMS questionnaire*	Axial length elongation decreased with higher light exposures (r = −0.176, P = 0.187), however this was non-significant during multivariate adjustment. There were no differences in exposure time to >1,000 lux, >2,000 lux and > 5,000 lux between refractive groups (all P < 0.01).
Read et al,[636] **2018** **Australia**	69 Singaporean children aged 8-12 vs 43 Australian children aged 10-12 *71% myopic in Singapore, mean SER −2.14 D* *44% myopic in Australia, mean SER −0.71 D*	Comparative study *Light exposure data from ROAM study and FIT trial compared*	HOBO Pendant UA-002-64, light meter • *Worn on shirt via safety pin with sensor facing outwards, measuring at 5-minute intervals* Actiwatch 2 actigraphy device • *Worn on wrist, measuring light resampled at 5-minute intervals*	Children in Australia experienced significantly longer daily outdoor light exposures (105 min/d) compared to children in Singapore (61 min/d, P = 0.005). The largest differences occurred on weekdays during school hours, however outdoor light exposure was not significantly different on weekdays out of school hours. Australian children had more frequent intervals of outdoor light exposure (6.9 episodes per day) compared with Singaporean children (4.6 episodes per day, P = 0.02). There were no significant differences in the mean duration of these episodes (P = 0.54).
Wu et al,[374] **2018** **Taiwan**	693 children from ROCT711 trial *Mean age 6.3 (6-7) at baseline*	Longitudinal (1 year follow-up) *Children who participated in the ROCT711 trial had measures of outdoor light intensities during school and filled out activity diaries out of school for one week.*	Outdoor activity diary • *30 minute activity intervals* HOBO Pendant UA-002-64, light meter • *Worn around the collar, recording at 5-minute intervals*	Participants who had >200 minutes of weekly outdoor time during school hours ≥1000 lux, or ≥3000 lux had a significantly less myopic shift compared to individuals who <125 minutes per week outdoors. Non-myopes at baseline who spent >200 minutes per week of outdoor time during school at all thresholds (≥1000, ≥3000, ≥5000 and ≥10,000 lux) had less myopic shift than those who spent <125 minutes per week outdoors. For those who spent 125-199 minutes per week outdoors, only those who spent this time ≥10,000 lux had less myopic shift.

Ulaganathanet al,[642] **2019** **Australia**	43 university students (22 myopes, 21 emmetropes) *Aged 18-30 years old*	Longitudinal (1 year duration) *14-day measures of light exposure obtained at 3 intervals between summer and winter*	Actiwatch 2 actigraphy device • *Worn on wrist, measuring light resampled at 30-second intervals*	Seasonal differences in outdoor time were seen, with emmetropes receiving 31 minutes more outdoor time in summer than winter, compared to myopes who only received 13 minutes more exposure in summer (P = 0.049) compared to winter. This made daily outdoor times to be significantly greater in emmetropes (67 min) than myopes (35 min, P = 0.05) during summer. Higher durations of outdoor exposure were associated with smaller changes in axial length. Subjects who were exposed to greater light exposures during summer also tended to exhibit less axial length elongation during summer compared to winter.
Wen et al,[638] **2020** **China**	86 schoolchildren *Mean age 10 years old*	Cross-sectional *Light exposures and near work measures obtained over 1 week*	Clouclip device • *Mounted to glasses, measuring light intensity at 2-minute intervals and working distance at 5-second intervals*	Myopic children spent less time in light intensity levels >3000 lux and >5000 lux per day than non-myopic children but not in levels >2000 or >1000 lux. Time spent >3000 lux and >5000 lux were both significantly associated with reduced myopia. (>3000 lux: OR = 0.27, 95% CI = 0.10-0.72; >5000 lux: OR = 0.11, 95% CI = 0.02-0.56). The frequency of outdoor light exposures were not significantly different between myopes and non-myopes.
Li et al,[640] **2021** **Singapore** **GUSTO**	483 schoolchildren *Aged 9 years old*	Cross-sectional *14 days of light exposure measurement*	FitSight • *Worn on wrist, measuring light at 1-minute intervals* Parent-administered questionnaire • *Adapted from SMS questionnaire* 7-day outdoor activity diary	Greater reported time outdoors was significantly associated with lower odds of myopia (OR = 0.82, 95% CI = 0.70-0.95, /hour increase daily, P = 0.009). Average light intensity levels, duration of high light exposures (≥3000, ≥5000 and ≥15 000 lux), timing and frequency of light exposures were not significantly associated with myopia, SE or AL. Higher average weekday light intensity was significantly associated with lower odds for myopia (OR = 0.88 /1000 lux) but not SE or AL.
Bhandari et al,[639] **2022** **United States**	40 children (25 myopes and 15 nonmyopes) Aged 10-18 years old	Cross-sectional *Light exposures and near work measures obtained over 1 week*	Clouclip device • *Mounted to glasses, measuring light intensity at 2-minute intervals and working distance at 5-second intervals*	Mean daily light exposure was lower in myopes (180 ± 174 lux) compared to non-myopes (375 ± 253 lux) (P = 0.01) Daily time outdoors was lower in myopes (0.6 ± 0.1 hours) compared to non-myopes (0.3 ± 0.1 hours) (P = 0.02) Number of indoor-outdoor transitions did not differ between myopes and non-myopes

MED = Minimal Erythema Dose, OR = Odds Ratio, CI = Confidence Interval

1.10.2.3 Light exposure and seasonal variations in myopia progression

Seasonal differences in light exposures in humans have been studied in order to investigate whether seasonal variations in myopia progression are linked to time outdoors. Longer sunlight hours in summer periods compared to in winter, offer greater opportunities for outdoor activities to occur thus providing greater myopic protection.

In a 2013 light exposure study by Alvarez et al, young adult university students experienced higher mean daily light intensities during spring (2,232 lux) compared to both fall and winter (857 and 1,591 lux respectively).[643] Though this was also accompanied by higher outdoor exposure hours, differences in exposure time were not significantly different between seasons, suggesting that seasonal variations in myopia progression may be mediated by light intensity levels rather than exposure duration. However, this is difficult to confirm as the study was small in sample size and compared different cohorts for each seasonal group. Additionally, intensity levels were not the lower compared to fall, and measures during summer were not investigated, due to students being on summer vacation.

Further seasonal differences in light exposure were noticed by Read et al, during their longitudinal follow-up of Australian schoolchildren in 2015, with children experiencing both higher daily light intensities and longer durations of high light exposure on warmer days compared to cooler days.[635] Although myopic children also experienced lower daily light exposures than non-myopic children, this difference remained consistent across all seasons, indicating that seasonal differences in light exposure did not significantly contribute to prevalent myopia.

Similar findings were later reported by Ostrin et al, who obtained light exposures in children across three 2-week periods (fall school, spring school and summer holidays).[637] Significant seasonal differences in outdoor time as measured by the light meter were found, with children spending the longest time outdoors per day during summer (111 minutes), followed by spring and fall (94 and 72 minutes respectively, $P < 0.001$). This was also accompanied by corresponding exposures to higher

light intensities, with children receiving higher average daily light exposures during the summer (~2,000 lux) followed by spring and fall again (~1,500 and ~1,000 lux respectively, P < 0.001). Though similarly to Read's study, these seasonal differences also did not vary by refractive group.[635]

More thorough work came in 2019 by Ulganathan et al, who investigated the association between light exposures and seasonal variations in axial length changes through a 1-year longitudinal study, where 43 university students had 2-week measures of light exposure obtained over 3 intervals between summer and winter.[642] In agreement with previous findings, seasonal differences in outdoor time was seen, with the daily time exposed to outdoor light levels > 1,000 lux being greater in summer (58 minutes) compared to winter (36 minutes, P < 0.001). While total outdoor time between myopes and non-myopes were similar, seasonal differences in outdoor exposure time were seen, with emmetropes receiving 31 minutes more outdoor time in summer than winter, compared to myopes who only received 13 minutes more exposure in summer (P = 0.049). This made daily outdoor times to be significantly greater in emmetropes (67 min) than myopes (35 min, P = 0.05) during summer. This was also accompanied with greater axial elongation changes in myopes (0.040 mm) compared to emmetropes during summer (0.004 mm). This relationship was demonstrated to be causal, as those with higher differences time in outdoor light exposures between summer and winter, tended to exhibit smaller seasonal differences axial length elongation (r = -0.380, P = 0.035). This provided evidence with objective data that the protective effects of outdoor time occurs primarily during summer, and is mediated by higher levels of light exposure. Further investigation is required to examine these patterns in childhood cohorts.

1.10.2.4 Variations in light intensity measures within myopia studies

The need to more accurately and thoroughly capture time outdoors as a risk factor for myopia has driven the development of several unique devices capable of objectively measuring various myopic risk factors. The devices from many of the early studies have roots in other scientific fields (such as the HOBO Pendant in aquamarine/agricultural studies and the Actiwatch in sleep studies). However,

a newer generation of devices have been developed to specifically capture light exposures for determining myopia risk. While additional features of these devices can vary, the common primary variable they capture is light intensity. These devices have several distinct traits and utilities, being made in the form of wristbands, pendants and spectacle mounted devices, however this heterogeneity has the potential to give rise to inter-device variations. To date, limited validation has been performed among these devices and against previously established tools of risk factor capture such as questionnaires and diaries which have been the backbone of myopia epidemiological research.

In the FIT trial, comparison of light-meter derived outdoor time using the HOBO Pendant to parentally completed diary records of outdoor time in children indicated that outdoor times from the light meters were significantly higher than the diaries during the school term.[633] This came from differences during the school term weekdays as no differences were found during school holidays or on school-term weekends. It is possible that these inaccuracies occurred from limitations from the diary as it was completed by parents, who were not able to directly monitor their children during school times. Given most studies in children have utilised parental reports of outdoor time, this study suggests that possible under-reporting of outdoor time may have occurred. Meanwhile, comparison of self-reported measures of outdoor time to objective measures from the HOBO Pendant by Alvarez et al in university students indicated the opposite,[643] as subjective estimates were higher than the objectively derived measures.

Between illuminometers, only one study has explored differences in device estimates of outdoor time and light exposure. During comparison of the ROAM and FIT studies, Read et al, conducted a small pilot experiment to compare differences in light intensity measures between the Actiwatch-2 light sensor (used in the ROAM study) and the HOBO pendant light sensor (used in the FIT trial). Measures from both devices were obtained from 10 adults who simultaneously wore both devices recording at 1-minute intervals for a 60-minute period. While there was a high correlation between

the two devices for both light intensity measures (r = 0.79) and estimated outdoor time (r = 0.95), considerable differences in absolute values and a high variance between the two devices were observed, with light exposures from the HOBO pendant reading ~4,677 ± 11,048 lux higher than the Actiwatch. These differences were not constant and increased in proportion with light intensity, as device differences in mean light levels less than 1,000 lux were 104 ± 151 lux, which increased to 9,760 ± 15,117 lux in levels greater than 1,000 lux. In contrast, differences in derived exposure time to outdoor light, was relatively small with an average difference of 0.4 ± 1.1 extra minutes of outdoor time recorded by the HOBO pendant. These results indicate that while different light meters are comparable in terms of objective outdoor time, absolute light intensity levels between device measures are not reliable, due to the increased variation occurring at higher light environments. Given the fact that protective exposures to light are likely to occur at intensity levels higher than 1,000 lux, future studies investigating light intensity levels as a primary outcome must select the most accurate device to capture light exposures. However, a gold standard portable illuminometer device has not yet been recognized by the research community.

1.10.3 Summary

Since its inception, the light-dopamine theory has become the leading hypothesis underlying the effects of time outdoors on myopia. Primary support has come from animal experiments which demonstrate the protective dose-related effects of light exposure against experimentally induced myopia. Evidence that retinal dopamine; a known inhibitor of axial elongation; mediates this effect has also been confirmed through animal experiments, from the use of anti-dopaminergic medications and the observations that retinal dopamine release is directly stimulated by light exposure. Preliminary data of light exposures within humans have also demonstrated small associations, suggesting that this mechanism may be occurring in human myopia. However, unlike in the animal models, approximate protective thresholds have not been identified. This process is challenging, as human behaviours and environments are more heterogeneous than within

experimental settings, making patterns of light exposure varied between and within individuals. In addition, light exposures are further complicated by an interplay between three parameters: the level of intensity, duration of exposure and the frequency of exposure. All three parameters have been shown to display a protective effect and this interplay has been shown in animals and observed in humans to a small degree. Portable data logging devices have been developed to capture risk factors in human with greater detail and accuracy.

1.11 Chapter Summary and Thesis Aims

As demonstrated in this chapter, environmental risk factors play a major role in the development of common myopia. Spending time outdoors is protective against myopia, while near work time and education are risk factors for myopia. Out of these three risk factors, time outdoors has been the main target for intervention as it is more easily modifiable and its role in preventing myopia has been consistently supported from large observational studies and clinical trials. Currently at least ~2 hours/day of outdoor time appears to be protective, however the optimum requirements for time outdoors is unknown. These levels may be further complicated by the fact that the protective requirements may vary between individuals, depending on the involvement of other risk factors, particularly near work time. Meanwhile, there is less consistent evidence that time outdoors slows the progression of existing myopia, despite pooled analyses finding significant associations.

These issues may relate to the fact that current tools to measure myopic risk factors (e.g. questionnaires) lack the resolving power to detect differences in exposure between existing myopes and those at risk of developing myopia, who inherently spent little time outdoors. The development and use of portable monitoring devices to capture exposure variables provide a more detailed and accurate approach as they are objectively based and for the case of time outdoors, are able to capture the underlying mediator behind myopia development. However, to date, only a limited number of studies have used objectively based methods, and such studies have demonstrated inconsistent findings. This may be attributed to a lack of methodological standardisation in the capture and analysis of these variables. So far a variety of data logging devices have been used, which differ substantially in design however inter-device comparisons and validation have not been performed.

More research is needed to further understand the most effective ways to capture variables involved in examining myopic risk factors. This is necessary to design more effective observational and interventional studies, which will provide findings to subsequently develop and implement

evidence-based public health policies and strategies to combat myopia through the addition of time outdoors.

1.11.1 Thesis aims

This thesis addresses the current issues through the following aims:

- To explore factors which may influence the accuracy and reliability of outdoor exposure and near work measurements. (CH3, 5 & 6)
- To identify different parameters of light exposure relevant for myopia development (CH4 & 6)
- To compare and validate existing portable light data loggers to a standard measure of light intensity (CH5)
- To compare light exposure parameters between different portable light data loggers during real world use (CH6)
- To describe the relationship between ocular component measures and cycloplegic refraction and investigate its utility in determining refractive error (CH7)
- To determine the role of ocular component measures in predicting myopia onset (CH8)

1.11.2 Impact of the 2019 global coronavirus pandemic on original thesis aims

The Covid-19 pandemic was an unforeseen event which has unquestionably impacted millions of individuals on an unprecedented scale. Across the globe, countries have responded to this crisis in a variety of ways, which has impacted several sectors including research, healthcare and tertiary education. Between 2020 and 2021, Sydney Australia experienced two major restrictive periods both of which were associated with the shutting down of non-essential services and stay-at-home orders. During this time, significant changes in university systems have occurred, which has had varying consequences for existing and planned research projects. The following statement outlines the impact of the Covid-19 global pandemic on the overall thesis aims and directions. More specific impacts of the global pandemic on thesis findings will be discussed in their relevant chapters.

The original intention of the thesis was to extend the validation component of LDLs performed in young adults (Chapter 6) in a cohort of school-children. The aim of this study would have been to confirm the accuracy and validity of different LDL measures in a younger cohort alongside gathering preliminary measures of light exposure and objectively derived near work in an Australian environment. Unfortunately due to a number of restrictions, this exploration was not possible within the candidature period. This project was unable to be performed virtually, as it required face-to-face contact in order to perform ocular examinations and other study procedures. As an alternative, the focus of the thesis was changed to also investigate the collection of explanatory variables. While wearable monitoring devices allows for detailed collection of exposure variables, Chapter 7 and 8 examines whether similar enhancements can be made in the collection of explanatory variables e.g. refraction. Overall the consideration of these two aspects must be considered for a holistic assessment of data collection methods in myopia research.

Chapter 2: Methods

2.1 Overview

The findings presented in this thesis have been derived from a number of sources. This not only includes data collected as part of this thesis, but also data from existing studies, which have been reanalysed to explore a number of aims relating to the thesis that have not been previously reported. This chapter details all the research methodologies used in this thesis, including sampling methods, study procedures and details of study tools and equipment.

2.2 Chapter 4: Light Exposures in Young Adults

Chapter 4 contains data from a previously conducted study, which aimed to validate measures of outdoor time from a single LDL (HOBO Pendant UA-002-64) against subjectively derived outdoor estimates obtained from a questionnaire (WHO outdoor activity questionnaire) and a diary. In this thesis, re-analysis of this data was undertaken in order to explore patterns of light exposure amongst young adult participants, and to examine the influence of certain behavioural activities on various light exposure parameters. Details of how this data was originally captured will be described below.

2.2.1 Sample and Recruitment

Participants were recruited via advertisements placed on faculty noticeboards across the campus and through announcements made onto electronic bulletins within the Faculty of Health Science at the University of Sydney, Australia. Over a 10-week period during autumn, 102 students volunteered to participate and were recruited into the study. There was no exclusion criteria applied. All observations were conducted in accordance with the declaration of Helsinki and under ethical approval obtained via the University of Sydney Human Research Ethics Committee.

2.2.2 Study Procedures

Prior to enrolment, participants signed a consent form containing detailed study information including data collection and information storage processes. Participants were then provided a questionnaire to estimate their average daily outdoor activity time. Following completion of the questionnaire, participants were provided the remainder of the study materials, which consisted of a LDL, an armband and an outdoor activity diary. Participants were then instructed to wear the LDL using the armband and simultaneously complete the diary over a four consecutive days (two weekdays and two weekend days). Following this period, participants returned the LDLs and diaries to the investigators.

2.2.3 Study Materials

2.2.3.1 World Health Organisation (WHO) Outdoor Activity Questionnaire

The WHO questionnaire was used to collect subjectively reported outdoor time. As the original design of the questionnaire was geared towards school-children, modifications were made to the wording of certain questions to be appropriate for an older population. This included replacing terms such as “children” with “university students”, and “school” with “university”.

2.2.3.2 HOBO Pendant UA-002-64 Light Data Logger

The HOBO Pendant UA-002-64 (Onset Computer Corporation, Bourne, MA, USA) light data logger, was used to collect light exposure measures during the four day study period. The HOBO LDL is a combined temperature and light data logger, able to record light intensity within measurement ranges of 0–320,000 lux (Figure 2.1). It has a peak wavelength sensitivity at 900 nm and a total detection range between 150 and 1,200 nm. It has a forward-facing sensor and the device is intended to be positioned horizontally such that the sensor is facing upwards towards the direction of light. As this position was not feasible for human use, the LDL was housed vertically in a transparent pocket of an armband fastened to the participant’s non-dominant arm so that the

sensor plane was facing outwards. Participants were instructed to wear the LDL during all activities when possible over their outermost layer of clothing. Otherwise, they were advised to keep the device in close proximity, with the sensor facing upwards in the same environment during activities such as swimming or bathing/showering. The LDL was configured to automatically capture light intensity values (lux) at 10-minute intervals. At the end of the recording period, data contained within the LDL was extracted into an electronic format using HOBOware software.

Figure 2.1: Image of a HOBO Pendant UA-002-64 LDL, showing the location of the light sensor.

2.2.3.3 Activity Diary

Participants recorded all activities performed during the study period into a printed diary template. A previous version of this diary was used in a Singaporean study aimed at increasing sunlight exposure in children and was adapted for this study to suit the older participants in the current study.[633] The diary classified everyday activities into 10 groups: sleep, travel, university, work, physical activity, computer use, studying/completing assignments/reading, tablet/smartphone use, other indoor activities and other general activities: which had to be specified. Logs from the 24-hour diary also specified whether each activity was outdoors or indoors and included start and end time of each activity in order to unite data with LDL measures. For data analysis in this thesis, all activities listed under computer use, studying/completing assignments/reading, tablet/smartphone use and other indoor activities were grouped together and called “passive leisure activities”. A copy of the diary can be found in Appendix 4.

2.3 Chapter 5: Experimental Comparison of Light Data Loggers

2.3.1 Study Procedures

2.3.1.1 Experiment 1: Comparison of light intensity between different LDLs

A comparative experimental design was used to investigate light meter measures (Lux) obtained by the Clouclip M2 (Mirror Technology Co., Ltd. Hangzhou) device and two other portable light sensors, the HOBO Pendant UA-002-64 (Onset Computer Corporation, USA) and the Actiwatch 2 (Philips Respironics, USA). These measures were compared to a standard non-portable LDL, the Yokogawa 51012 Digital LUX meter (Yokogawa Test & Measurement Corporation, Japan) across four separate lighting environments.

Pairs of each LDL were mounted on to a foam block with their respective sensors facing upwards on the same linear plane to allow equal and uniform spread of ambient light exposure between each device (Figure 2.2). Pairs of the same LDL were positioned on the foam block symmetrically to detect and control for potential variations in exposure across the surface of the block. Each of the portable LDLs were configured to continuously record light intensity levels at 2-minute intervals. The reference meter was placed horizontally above the foam block with the centre aligned to the position of the light sensor. As the reference meter was not automated, light intensity readings from the reference light meter were manually captured by the investigator at the same 2-minute intervals as determined by a stopwatch. This was performed over a 1-hour period for a total of 31 data points in each environment. All data was collected during a single cloudy summer day. Due to this being an experimental study, not involving human or animal subjects, ethical approval was not sought.

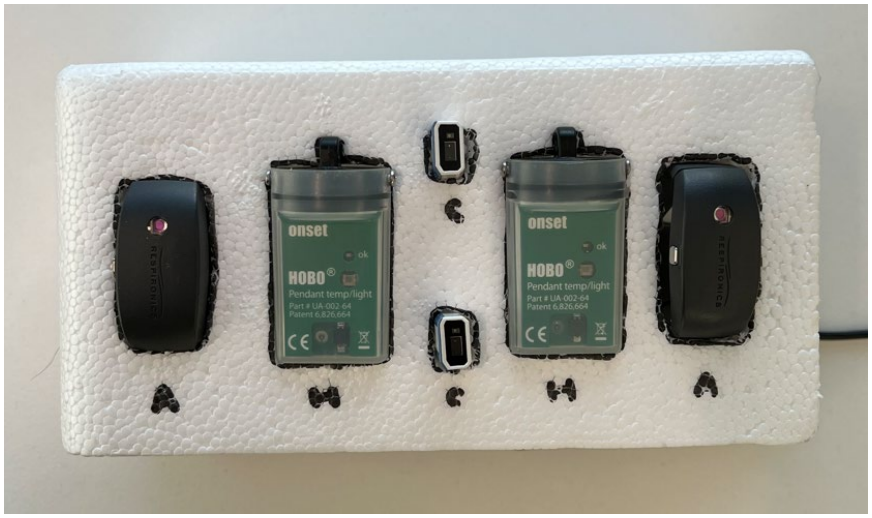


Figure 2.2: Apparatus used to simultaneously collect light intensity from three pairs of different LDLs.

The experiment was repeated in 4 environments of differing light levels classified as low indoors, high indoors, low outdoors and high outdoors. Low indoor light was considered to be the ambient light encountered in the centre of an enclosed room without exposure from open windows, with most of the illuminance, if not all, coming from artificial lighting. This was defined by lux values less than 500 measured using the standard light meter. However, as there were no open sources of external light, in order to capture a broader range of light, the room illumination was gradually reduced in 10-minute intervals across the hour using a dimming switch. The highly illuminated indoor environment consisted of a large indoor room with additional external sources of light from multiple large open windows facing in more than 1 direction, this was set to include lux levels ranging between 500 and 1,000. Low outdoor light levels were representative of an outdoor environment that had no direct line of sight with the sun such as under the shade of a tree or near a high-rise building, with lux levels defined between 1,000 and 10,000. High outdoor light levels were defined as outdoor environments with large open spaces such as in parks and fields where there was a direct line of sight with the sky, capturing lux > 10,000.

2.3.1.2 Experiment 2: Comparison of light intensity between LDLs in different directions

In a second experiment, the influence of directionality on light intensity measurements was investigated. Wearable LDLs (Actiwatch 2, HOBO Pendant and Clouclip M2) were attached to five faces of a square foam block, with their respective sensors orientated at the same plane and facing the same direction. The five directions were considered to be facing A) Upwards B) North C) East D) West and E) South (Figure 2.3).

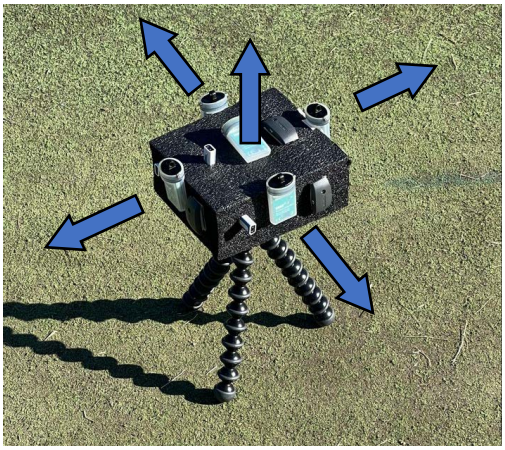


Figure 2.3: Apparatus used to simultaneously collect light intensity from five different directions.

All LDLs were configured to automatically record light intensity at 2-minute intervals. The apparatus was placed outdoors in an open park for 30 minutes to simultaneously capture 16 intervals of light intensity from each LDL in five different directions (Figure 2.4). Measurements were obtained during a partly cloudy winter day.

Figure 2.4: Directions faced by each LDL: A) Upwards B) North C) East D) West and E) South

2.3.1.3 Experiment 3: Comparison of angular light intensity using the Clouclip LDL

In a third experiment, angular variations in light intensity was investigated. A Clouclip LDL was attached to a protractor mounted onto a tripod at four vertical positions A) 90° upward (vertical) B) 45° upward C) 0° (horizontal) D) and 45° downward (Figure 2.5).

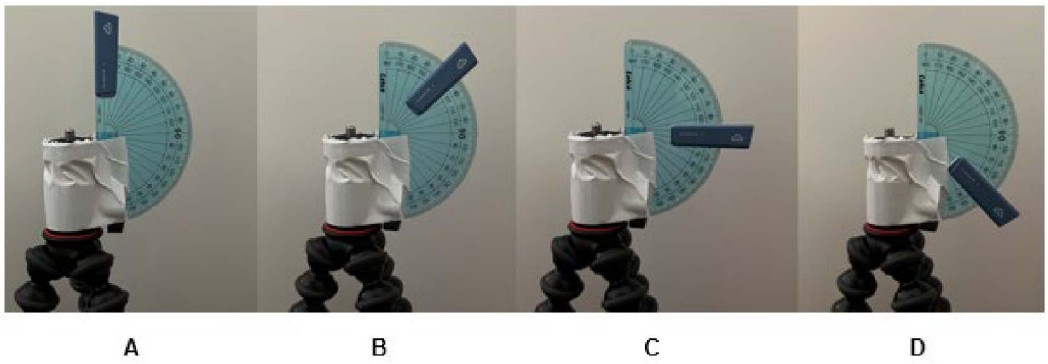


Figure 2.5: Apparatus used to simultaneously collect light intensity from four different angles.

The Clouclip LDL was configured to automatically record light intensity and was placed in two environments A) indoor desk environment with artificial lighting and B) an outdoor environment on a partly cloudy winter day (Figure 2.6). In each environment the position of the LDL was manually adjusted every two minutes to capture light intensity at four different angles.

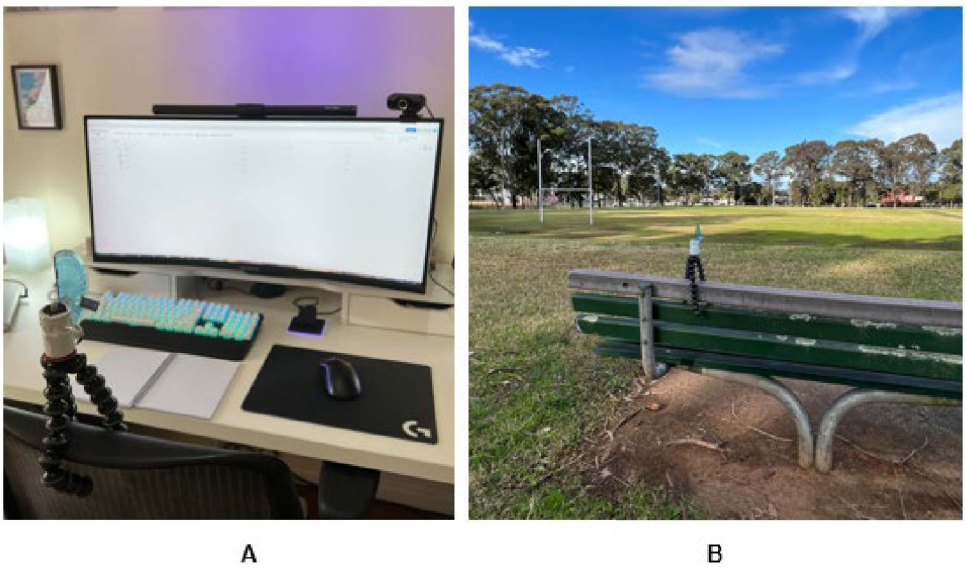


Figure 2.6: Indoor and outdoor environments used to measure angular light intensity

2.3.2 Study Materials

2.3.2.1 Actiwatch 2

The Actiwatch 2 is an activity monitoring device band weighing approximately 16g worn on the wrist which measures sleep patterns, physical activity levels as well as visible light illuminance (Figure 2.7). The silicone photodiode sensor has a wavelength range of 400–900 nm with a peak sensitivity at 570 nm. The device has an illuminance range of 5–100,000 lux with a 10% accuracy at 3,000 lux. Data from Actiwatch devices were transferred onto a PC and collected via the Philips Respironics ActiWare Software.

Figure 2.7: Image of an Actiwatch 2 LDL, showing the location of the light sensor.

2.3.2.2 HOBO Pendant UA-002-64

The HOBO Pendant UA-002-64 is a combined temperature and light data logger. Device specifications have been described earlier in Section 2.2.3.2. For this investigation, an armband was not used to contain the device. Instead the HOBO Pendants were mounted horizontally within the foam block to orient the sensors upwards along with the other LDLs.

2.3.2.3 Clouclip M2

The Clouclip M2 is a portable light meter intended for use in individuals who wear spectacles. It weighs approximately 6 grams and is intended to be attached in line with an arm of the spectacle frame with the front sensor orientated forward in the direction of fixation (Figure 2.8). The Clouclip allows for the continuous measurement of both light intensity (lux) and near work measures (mm). No manufacturer details regarding its light sensor specifications are available at this time. In this study, Clouclip devices were not mounted onto spectacles but were placed vertically within the foam block to orient the sensors upwards. Data from Clouclip devices were transferred via Bluetooth onto a linked mobile device using the Clouclip Medical app.

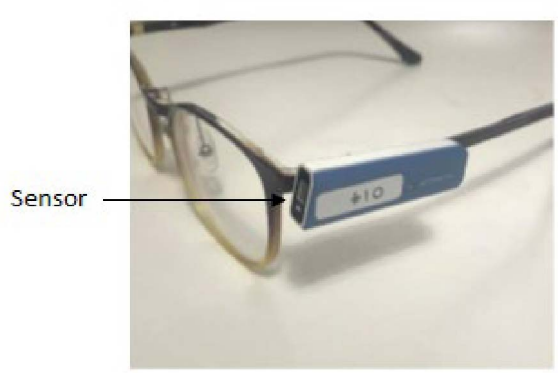


Figure 2.8: Image of a Clouclip M2 LDL mounted onto a spectacle arm and showing the location of the light and near work sensor.

2.3.2.4 Yokogawa 51012 Digital LUX meter

The Yokogawa 51012 Digital LUX meter was used as the standard reference light meter (Figure 2.9). This was because it provides highly accurate illuminance measures complying with standards set by the International Commission on Illumination (CIE 19476:2014 and 231:2019). It has a spectral response curve almost identical to the visible spectrum of the human eye, ranging from 400–700 nm with a peak wavelength sensitivity at 555 nm. It also measures light up to a maximum limit of

999,000 lux, well beyond expected intensities during the day, with a reported accuracy within 3% above 3,000 lux. The device can measure light of oblique incidences up to 70 degrees with a near 0% margin of error.

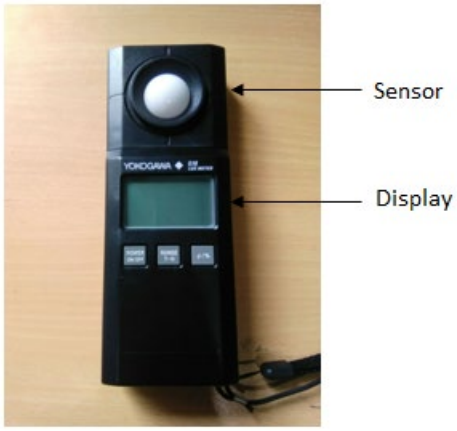


Figure 2.9: Image of a Yokogawa 51012 Digital LUX meter, showing the location of the light sensor and display screen.

2.4 Chapter 6: Real World Comparisons of Light Data Loggers

The study contained in Chapter 6 was a cross-sectional observational study conducted between 2019 and 2021. This study was an extension of the project presented in Chapter 5 and aimed to compare objectively measured light exposures from three separate portable LDLs during real world use.

2.4.1 Sample and Recruitment

Participants were young adults recruited from the student population within the University of Technology, Sydney. Participants were recruited via advertisements placed on faculty noticeboards across the campus and through announcements made onto faculty-wide electronic bulletins (Appendix 5). Students who expressed interest in the study were assessed by the investigator for eligibility prior to inclusion into the study. Participants were excluded from participating in the study based upon the following self-reported criteria:

- Ocular history which may influence refractive status e.g. cataract, keratoconus, pseudo-phakia and prior refractive surgery.
- Systemic disease which may influence refraction e.g. uncontrolled diabetes
- Family history of genetic/hereditable disease with associations with refractive status e.g. Marfan's syndrome

2.4.2 Study Procedures & Materials

2.4.2.1 Baseline outdoor activity questionnaire

At the first study visit, participants completed a questionnaire derived from the WHO Outdoor Activity questionnaire, which was based off the questionnaire used in Chapter 4 (See Section 1.2.3.1). For this study, additional questions were included into the questionnaire to capture participant characteristic data. This included: sex, ethnicity, parental myopia status, current

spectacle/contact lens use, age of onset of refractive error and self-reported reading distance. A copy of this questionnaire can be found in Appendix 6.

Subjectively measured daily outdoor time and near work times from the questionnaire were determined separately for weekdays and weekends and transformed into a weekly average using the formula [(hours spent on weekday) x 5 + (hours spent on weekend day) x 2] / 7. Activities that were performed outside a building during the day, such as riding bicycles, park visits, walking around the neighbourhood, and outdoor sports, were all classified as outdoor activities. Indoor activities were defined as inside a building or an enclosed space or travelling in a car or train. Near work time was calculated from the duration of time spent studying and reading and writing for leisure or work.

2.4.2.2 Categorisation of refractive status

Monocular visual acuity (VA) (with and without spectacle correction) was obtained using an ETDRS logMAR chart. Participants who failed to score logMAR 0.00 (6/6 or 20/20) on VA testing were re-tested with a pinhole occluder to ascertain any improvement in VA. Participants wearing spectacles had their correction measured using a Nikon LM-500 vertometer (Nidek Co. Ltd., Tokyo, Japan). Contact lens wearers were asked to bring in their lens packs and a pair of spectacles if available. The most recent correction from either the contact lens or spectacles was used to determine their refractive status.

Participants were deemed to be myopic if they self-reported themselves to be short-sighted in at least one eye and either 1) presented with a refractive correction with a spherical equivalent refraction (SER) of ≤ -0.75 D and scored a corrected logMAR VA of 0.20 (6/9.5) or better, or 2) scored a logMAR VA worse than 0.20 (6/9.5) and subsequently improved to 0.00 (6/6) or better under a pinhole occluder. All other participants who failed to be categorised as myopic were considered to be non-myopic.

2.4.2.3 Ocular biometric data

Ocular component measurements (axial length, corneal radius of curvature and anterior chamber depth) was obtained using an IOLMaster TM (Carl Zeiss, Meditec AG Jena, Germany). For axial length and anterior chamber depth, a minimum of 5 measures were taken and were considered valid if they were within ± 0.05 mm. For corneal radius, three measures were obtained and considered valid if they were within ± 0.05 D. From the biometric measures, the axial length to corneal radius ratio (AL/CR) was calculated for each eye.

2.4.2.4 Collection of objective light exposure and near work measures

Participants were instructed to simultaneously wear three portable LDLs during waking hours over four consecutive days (two weekdays and two weekend days). Participants were instructed to wear the LDLs during all activities when possible over their outermost layer of clothing. During activities where LDL wear was impractical (such as swimming or bathing/showering) were advised to keep the devices in close proximity, with the sensor orientated upwards within the same environment. All LDLs were configured to automatically capture light intensity values (lux) at 2-minute intervals. All devices were worn on the non-dominant side of the body to minimize variations in sensor positioning resulting from dominant arm movements (Figure 2.10).

Participants without spectacles were given a pair of clear plano-lensed spectacles to wear the Clouclip device during the study period, otherwise participants mounted the Clouclip devices onto their existing spectacles via rubber mounts that were slipped through to the base of a spectacle arm. Contact lens wearers had the choice of wearing their spectacles during the study period or use plano-lensed spectacles to mount the device. Additional mounts were provided to all participants to place on sunglasses for outdoor use.

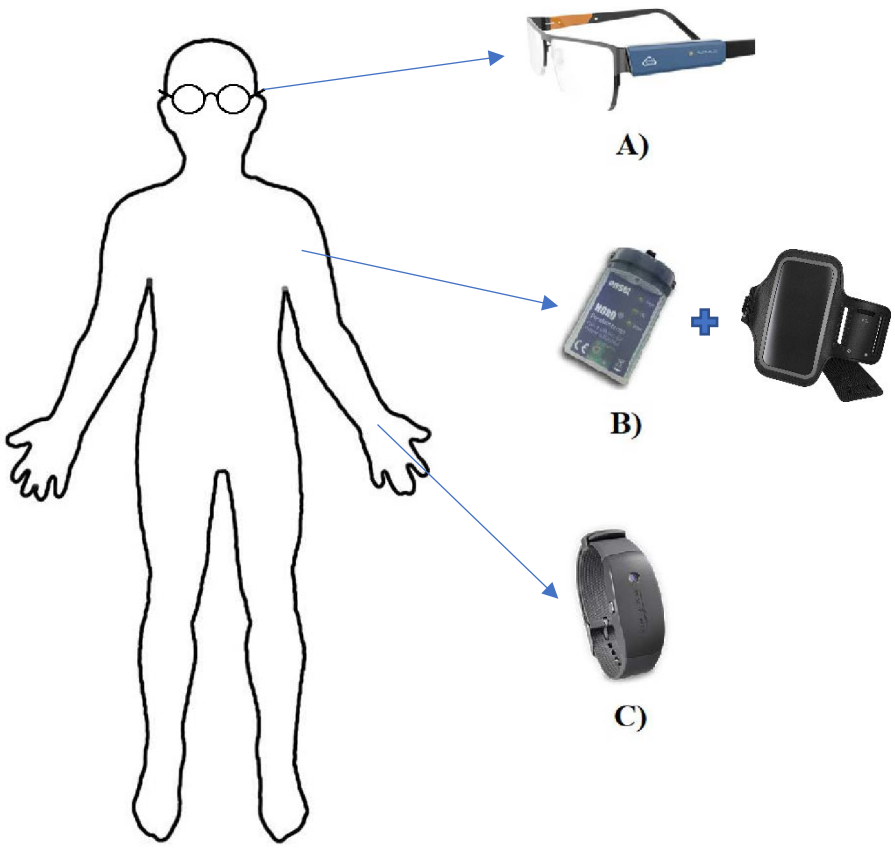


Figure 2.10: LDL mounting locations for A) the Clouclip M2 B) the HOBO Pendant and C) the Actiwatch 2.

2.4.2.5 Outdoor activity diary

During the four days of LDL wear, participants documented their daily activities in a 24-hour diary, previously used for Chapter 4 (see Section 1.2.3.3) (Appendix 4). As a general rule participants were asked to record all unique activities which was performed for longer than 10 minutes regardless of whether the activity was performed indoors or outdoors.

2.4.2.6 Focus groups

Following four days of data capture, participants attended a small focus group of up to five individuals. The investigator prompted discussions regarding participant experiences during the study based on a set of structured questions (Appendix 7). These questions gathered feedback on participants views on the utility of the questionnaires, diary and individual devices. Unstructured questions were also provided by the investigator in response to individual comments when required,

to gather more details from the participant. At the conclusion of the focus groups, participants were given a post-study survey where each of the devices were ranked based on two separate criteria 1) device wearability: how comfortable the devices were and 2) device invasiveness: to what extent did device wear interfere with their daily activities (Appendix 8).

2.4.3 Ethical Considerations

This study adhered to the tenets of the Declaration of Helsinki. Ethical approval for this study was obtained from the institutional review board from the University of Technology, Sydney prior to commencement of the study (HREC# ETH17-1765 & ETH20-4870) (Appendix 9). Written informed consent was obtained from all participants prior to study enrolment and study procedures (Appendix 10).

2.5 Chapters 7 and 8: Longitudinal Changes in Refractive Error and Ocular Biometrics in Australian Schoolchildren

Chapter 7 contains data from two previously conducted studies, the Sydney Myopia Study (SMS) and the Sydney Adolescent and Vascular Eye Disease Study (SAVES). In this thesis, re-analysis of this data was undertaken in order to investigate the relationship between biometric ocular component variables, in particular the axial length to corneal radius ratio (AL/CR) and refraction. Details of how this data was originally captured will be described below.

2.5.1 The Sydney Myopia Study (SMS)

The SMS was the first of the Sydney Childhood Eye Studies, devised primarily to determine the prevalence of myopic refractive errors in light of the epidemic of myopic occurring in a number of countries and to examine possible risk factors that might assist to explain the rapid rise in its prevalence. It was also the first examination of childhood eye conditions in a representative sample of Australian school children. The methodology of the SMS has been previously published. The Sydney metropolitan area was stratified by socioeconomic status (SES) using the 2001 ABS census data into nine strata. A total of 34 primary schools and 21 secondary schools across Sydney were randomly selected with preferential selection of schools from the highest strata. These include five primary schools and two high schools in the top SES and a random but proportionate mix of public, religious and private schools. The study was approved by the Human Ethics Committee of the University of Sydney, the Catholic Education Office and by the New South Wales Department of Education. The research adhered to the tenets of the Declaration of Helsinki. Informed written consent was obtained from at least one parent or guardian. Verbal consent was also obtained from each child prior to commencing the examination on the day.

Each school was approached by the lead researcher inviting participation and with the principal of the school's agreement, information sessions were held with teachers, parents and pupils. Packages

including information sheets, consent forms and questionnaires were sent to all eligible children. Questionnaires were completed by parents of participating children, including questions regarding sociodemographic information such as ethnicity, parental education and employment; the child's birth and medical history and typical daily activities on weekdays and weekends.

Between 2003 and 2005, SMS examined 4093 children in two samples; Grade 1 children with mean age 6 and Grade 7 with a mean age 12 years. The study team included ophthalmologists, medical practitioners, orthoptists and optometrists. Assessments were conducted to examine visual acuity, ocular alignment, ocular pathology and cycloplegic refraction. Visual acuity was measured monocularly using a retro-illuminated EDTRS LogMAR chart (VectorvisionTM CSV-1000; Vectorvision,Inc., Arcanum, OH) at 2.44m and under controlled illumination, near vision was measured using the LogMAR HOTV near vision chart at 33 cm. A matching card is available for children unable to read the letters. After dilation (amethocaine 1%, cyclopentolate 1% and tropicamide 1% twice, 5 minutes apart and 2.5% phenylephrine if still poorly dilated), ocular biometry was measured using the IOLMasterTM (Carl Zeiss, Meditec AG Jena, Germany) and a Haag-Streit slit-lamp (Koeniz, Switzerland) was used to examine the anterior segment of the eye. Refraction was measured on average 25 minutes after the last cycloplegic eye drop was administered using a Canon autorefractor (model RK-F1; Canon, Tokyo, Japan)

2.5.2 The Sydney Adolescent and Vascular Eye Disease Study (SAVES)

In the SMS five to six year follow-up study known as SAVES, the examination procedures and questionnaires were the same as those used in the original study, so that direct comparison could be made between the baseline and follow-up data. Of the original 34 primary schools included in SMS, children were still enrolled in 13 of these primary schools and re-examined at those schools. Of the 21 secondary schools included in SMS, 20 still had the same children enrolled at the school and were re-examined. Children unable to be examined at their original school were invited to attend an eye clinic or at one of the study schools if it was close to their home address. Again the same detailed

questionnaires were administered to parents for demographic data as well as the child's health and ocular health since SMS. Questionnaires were also administered to children to obtain information on daily activities, ocular health and ocular symptoms. A total of 2,130 children from the original SMS were included in SAVES during 2009–2011, representing 52% of the SMS cohort and an attrition rate of 10% per year for the five to six year follow-up, Included in SAVES were a further 941 children enrolled in the schools who participated in the study and consented to be included in SAVES.

2.5.3 Ethics Approval

Ethics approval for SMS and SAVES was obtained from the Human Research Ethics Committee of the University of Sydney, the New South Wales Department of Education and Training, and the Catholic Education Office. Informed written consent was obtained from at least one parent or participants who were over the legal age of consent (18 years) prior to examination. Verbal consent was also obtained from each child prior to commencing the examination on the day.

Chapter 3: Methods to Measure Exposures to Environmental Risk Factors in Myopia Research

3.1 Introduction

Myopia appears to be heterogeneous, with different forms defined by having an aetiology controlled by both genetic and environmental influences, each to varying degrees.[390] As discussed in Chapter 1, Section 1.8.2, there are at least two to three hundred distinct but rare forms of myopia associated with specific mutations or chromosomal rearrangements, which account for at most 1-2% of myopia in any human population. In contrast, the current epidemic of myopia has been produced by marked increase in the prevalence of myopia that develops in association with schooling that is commonly known as school myopia. Detailed genetic work has shown that identified SNPs account for close to 20% of the variation in refraction in western populations,[438] with somewhat less in East Asian populations. For school myopia, environmental factors are therefore believed to play a major role, with changes in three risk factors; education pressures, near work time and outdoor time; found to be involved in the myopia epidemic.[1, 644] Near work and time outdoors can be ethically modified for intervention purposes. However currently, their roles in the development and progression of myopia have yet to be fully understood.

For near work, it has often been considered to be the biological mediator behind the relationship seen with education, however in contrast to the links seen between education and myopia, the effects from near work have been inconsistent and limited, despite meta-analysis confirming an underlying association with myopia.[481] Meanwhile for time outdoors, it has shown to play a strong role in the development of myopia, with several successful clinical trials using increased outdoor time to reduce incident myopia, however, has not adequately demonstrated consistent roles in reducing the progression of existing myopia.[564, 645, 646]

This may be because current epidemiological methods of assessing risk factors, which have traditionally been based on subjective tools; namely questionnaires, are insufficient. While they have been valuable in identifying consistent associations between these risk factors, they are fundamentally limited as they may not accurately capture true levels of exposures. In the case of

time outdoors, findings of seasonal differences, where myopia progression is slower in summer compared to winter, suggests that differences in time outdoors can regulate myopia progression.[18] In order to confirm this, a more thorough investigation of the relationship between risk factors and myopia is required. To elucidate seasonal effects, this requires accurate measurement of risk factors and refractive error at least twice a year. Currently, these measures are typically obtained cross-sectionally or at annual intervals.

Alternative methods of risk factor capture, particularly portable monitoring devices have been investigated. The main advantage provided by these tools is the ability to continuously provide objective measurements of a range of variables, including light intensity as a proxy for time outdoors and working distance to assess near work. More emphasis has been placed in the measurement of outdoor time, as there are discrete differences in light intensity between indoor and outdoor environments. On the other hand, the measurement of working distance is complicated by an ambiguity in the distances what is considered near work. So far, outdoor time has been captured in observational studies[566, 633, 635, 638] and clinical trials,[374] using a variety of devices. However among these options, preferred or "gold standard" methods have not been established and it is unclear whether data obtained from different methods or devices are comparable, as limited validation studies have been performed.

This chapter aims to identify and describe the characteristics and limitations of all available methods used to measure the two modifiable risk factors for myopia, near work and time outdoors. The identification and analysis of factors which differ among these tools may provide clues to develop and/or select more efficient and optimal methods of exposure capture in future studies.

3.2 Subjective methods of risk factor measures

3.2.1 Questionnaires

Questionnaires have been the most popular method of capturing exposures in myopia studies. Questionnaires are a basic epidemiological research instrument where a series of questions are provided to participants for the purposes of gathering information of interest at a single point in time; either retrospectively or at the present time. The key benefit of questionnaires are that they are non-invasive, easy to distribute and quick to complete. This makes them highly cost-effective, allowing investigators to target larger sample sizes for increased statistical power. However, the design and implementation of questionnaires can take many forms, creating multiple avenues for bias, therefore well-designed surveys must be carefully considered in order to obtain data which most accurately reflects the intended variable which the researcher is investigating.

3.2.1.1 Questionnaire design

Questionnaires can be modifiable by the investigator, allowing efficient sampling of multiple variables, such as demographic data and confounding factors. However, questionnaires which are too long and detailed may be influenced by subject fatigue, which can reduce the overall response rate and accuracy of latter questions. A major source of bias comes from the use of non-standardised or un-validated questionnaires, though this is usually unavoidable in early studies when associations between a single particular exposure and outcome have not been identified and questionnaires geared at detailing a single variable of interest have not been developed. Recall bias is another source of inaccuracy in questionnaire data, when past exposures are required to be quantified or described. Errors from recall bias may also be greater when the exposure variable is not easily quantifiable, or consciously taken into consideration by an individual, such as average daily outdoor activity. Further recall bias may also occur in retrospective case-control settings, as

individuals affected by the outcome are more likely to overestimate their exposures to known risk factors, such as the general belief that near work causes myopia.

In early myopia studies, risk variables were gathered from single questions,[404, 485, 493, 552] directly asking for an estimate of the average daily time spent in near work, or time spent outdoors. Early studies into outdoor activity, also contained questions about physical activity/exercise and sports,[534] under the belief that physical activity was related to myopia. Though there were some associations,[533, 534] assessing outdoor time through physical activity leads to bias through the inclusion of indoor sports. While some studies specified outdoor sports only,[404, 491] these would have missed outdoor leisure activities such as picnics.

For investigating near work, detailed studies began use sets of questions quantifying time spent across several near work related activities.[404, 552, 647] In the Orinda Longitudinal Study of Myopia (OLSM) survey, children's near work time was assessed from estimates of four activities: 1) studying for school, 2) reading for pleasure, 3) watching television and 4) playing video/computer games or working on the computer at home.[404] Similar variables were also used in the Singapore Cohort Study of the Risk Factors for Myopia (SCORM) survey,[490] which also included the number of books read per week as an additional variable. For time outdoors, it was not until the Sydney Myopia Study,[487] when a detailed questionnaire was developed to gather outdoor exposures. This multi-item questionnaire established time outdoors based upon questions about playing outdoors, family picnics and barbeques, bicycle riding, bush walking, and outdoor sport. This approach aimed for a more accurate estimate by indirectly capturing outdoor time through a number of smaller estimates. Since the development of the SMS survey, many subsequent studies have either used the exact questionnaire itself,[162, 201, 538, 550, 551, 648] or a similar variant of their own multi-item survey.[372, 373, 469, 649] Although, some continued to use a single question approach.[539, 554] A unified questionnaire structure to gather outdoor activity time was provided by the World Health Organisation (WHO) in 2007–2008, however has not been commonly used to report outdoor time since its inception.

Further variations can be seen in the nature of variables captured by questionnaires. While most surveys quantify exposures using continuous variables, many have also collected data by categorical means,[205, 371, 535, 544, 546, 547, 556, 563, 649] such as the grading of exposure time as high/medium/low or by selecting arbitrarily defined thresholds. This may introduce heterogeneity, as cut-offs for low-high exposures may differ between studies and further subjective bias can occur when exposures are not quantified. On the other hand, during data analysis, some studies have also chosen to analyse continuous numeric estimates into categorical thresholds using population tertiles,[482, 487, 555, 648] This also allows relative comparison within highly myopic populations where there may not be a large variance in risk factor measures and can be useful in identifying dose-response relationships and protective threshold levels.

As questionnaires only collect data at a single point in time, capturing exposures that have temporal variations is difficult. Comparisons of a complex near-work questionnaire repeated 3 weeks apart in the Anyang Childhood Eye Study, found a modest correlations between measures (ICC: 0.63).[648] Clear day to day variations are seen in school students, where environmental exposures and individual behaviours differ between weekdays and weekends, and indeed by day of the week. Well-designed questionnaires gather exposures separately for these different days, gathering exposure more accurately for certain activities, such as the consideration of recess and lunch times during school days as well as after-school extracurricular activities. Average daily exposures are then calculated using the formula: [(hours spent on weekday) x 5 + (hours spent on weekend day) x 2] / 7. While the majority of questionnaires take daily variations into account, some studies have only gathered exposures via a single weekly estimate.[370, 489, 545, 554] This consideration can be taken a step further to examine seasonal variations,[372, 540] as individuals seem to report higher daily outdoor times during summer or sporting seasons,[539] and less near work activity during holiday periods. On a larger scale, exposures to near work and time outdoors are also likely to vary with age, particularly as children advance into more academically demanding/challenging grades within school and exposures to myopigenic risk factors begin to differ. Studies investigating longitudinal changes in

refraction; where outdoor activity habits have been taken at a single point in time (typically at baseline) are more likely to be influenced by this bias, which may have contributed to the inconsistency seen between time outdoors and myopia progression.

3.2.1.2 Questionnaire delivery

The manner in which questionnaires (interviewer administered or self-administered) are delivered can also determine the validity of data. In myopia studies, self-administered questionnaires have been the more popular choice. They are the cheapest and easiest form of delivery as they generally require less involvement and coordination between investigators and study participants. While they can be completed on-site during a study visit, they are also able to be sent out through email, postal mail or digitally via an online survey; though this is usually associated with lower response rates and incompletion.[650] For studies in younger cohorts, subjects may not be literate enough to understand or recall past childhood data, thus these surveys have been directed at parents instead.[405, 489, 490, 545, 547, 550, 551, 555, 558, 649] Parental reports of exposure times are likely to be less accurate compared to self-reported data, as children are not under constant observation from their parents, especially during school hours. Some studies have considered this, and have only asked about out-of-school exposures,[165, 370, 491, 493, 494, 544] however this assumes that children exhibit consistent patterns of behaviour during school periods. Given the association between education and myopia, it likely that the significant differences in exposures may be occurring during school hours. In particular, near work estimate are more likely to be inaccurate using solely out-of-school times, as the majority of exposures occur during school hours. On the other hand, it could be argued that out-of-school estimates of outdoor time are more accurate compared to near work estimates, as more consistent exposures to time outdoors occur during school hours from fixed recess/lunch times, whereas out-of-school light exposures are likely to differ due to individual choices. For more validated measures, some studies have employed estimates from the child's classroom teacher,[165, 488, 494, 495] this may be limited in sensitivity as it is difficult to estimate a specific child's exposures within a large class.

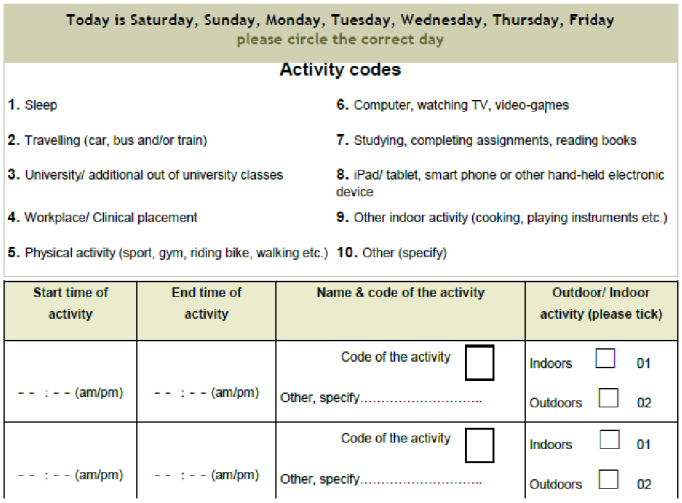
Grading of children using tertile measures may be more useful in these cases. True self-administered questionnaires are commonly used for older children, usually at least 12 years of age,[140, 487, 538, 541, 552, 556] though there have been studies using self-administered questionnaires in grade 4 children (~9 years old).[489]

Interviewer-administered questionnaires may be conducted in person (face-to-face) or over the phone.[534, 551, 557] In comparison to self-administered questionnaires, responses to interviewer-administered questionnaires are generally more reliable as study staff can provide clarification in areas of misunderstanding, whereas the phrasing of questions within self-administered questionnaires need to be considered more carefully, particularly for younger participants, cognitively or intellectually impaired individuals or those of a different linguistic background. As with self-administered questionnaires, interviewer-administered questionnaires have also been used on parents of children who may be too young to comprehend questions provided verbally.

3.2.2 Diaries

Diary sampling, also known as experience/event sampling, is when subjects fill out a personal log of events over a determined length of time, usually daily for a week (Figure 3.1). Diary sampling requires little to no recall of events as they are usually completed at the end of each day. Diaries are generally simpler in design than questionnaires as entries should be quick and not requiring much thought, in order to not disrupt normal behaviour. Diaries also capture day-to-day variations in exposures, making them more reliable than questionnaires. However, a fundamental disadvantage is that they cannot be used for past exposures, making them useful only for cross-sectional or longitudinal studies. While there is generally less recall bias associated with diary measures, there is increased likelihood of the Hawthorne bias, as participants are self-aware of being monitored for particular exposure variables. There may be logistical issues, as diary sampling methods can be consuming for participants and are also burdensome for investigators during data entry and analysis as it often requires manual transcription. In comparison to questionnaires, diary sampling has not

been used as often in observational studies,[651, 652] but has found increasing utility in recent studies as a supplementary measure of exposure alongside objective devices.[374, 633, 653]



Today is Saturday, Sunday, Monday, Tuesday, Wednesday, Thursday, Friday
please circle the correct day

Activity codes

1. Sleep	**6.** Computer, watching TV, video-games
2. Travelling (car, bus and/or train)	**7.** Studying, completing assignments, reading books
3. University/ additional out of university classes	**8.** iPad/ tablet, smart phone or other hand-held electronic device
4. Workplace/ Clinical placement	**9.** Other indoor activity (cooking, playing instruments etc.)
5. Physical activity (sport, gym, riding bike, walking etc.)	**10.** Other (specify)

Start time of activity	End time of activity	Name & code of the activity	Outdoor/ Indoor activity (please tick)
-- : -- (am/pm)	-- : -- (am/pm)	Code of the activity ☐ Other, specify.....	Indoors ☐ 01 Outdoors ☐ 02
-- : -- (am/pm)	-- : -- (am/pm)	Code of the activity ☐ Other, specify.....	Indoors ☐ 01 Outdoors ☐ 02

Figure 3.1: Example of a diary designed to gather near work and outdoor exposures in university students.

3.2.2.1 Comparison of diary sampling to questionnaire measures

Diary sampling has often been compared to questionnaires. Saw et al compared a complex interviewer-administered parental near-work questionnaire; which was eventually used in the SCORM studies; against a 24-hour diary and found that while the questionnaire was consistent in measuring total near work time (given by a high reproducibility score of 0.87) it was only moderately in agreement compared to the diary measures (ICC: 0.50), with the questionnaire underestimating total near work time compared to the diaries (6.6 vs 7.2 hours/day).[483] Lower correlations were seen on weekends compared to weekdays (ICC: 0.22 vs 0.38), as well as during holiday periods compared to during the school term (ICC: 0.21 vs 0.45). In specific activities the highest correlation occurred when using the computer (0.90) or playing video games (0.83), whist the lowest correlations were seen during reading and writing (< 0.34) suggesting that more near-work intensive related activities were captured less reliably.

Contrasting levels of agreement were found in a slightly older sample of children by Rah et al, who performed similar comparisons of a parentally verified self-administered multi-item near work

questionnaire to real-time experience sampling.[654] Average exposure times derived from the questionnaire and experience sampling method were within statistical similarity for total near-work time as well as all individually near-work related activities. These findings suggest there are differences in accuracy between self-reported and parentally assessed measures of near work,[655] suggesting that more accurate methods of capturing exposures in younger children are needed.

3.3 Objective measures of risk factors

3.3.1 Near work

In contrast to subjective measures, objective measurements of near work may only be captured through one variable: working/reading distance, i.e. the distance along the visual axis between an individual's eye and the surface of the object of their focus. Several portable devices are capable of automatically recording working distance. These devices work by projecting and collecting emittance signals to calculate reading distance via the time-of-flight principle. While working distance is the primary marker of these devices, near work time can be deduced by quantifying time spent below a threshold distance. So far, these definitions have been inconsistent, ranging between < 30–60 cm.[197, 479, 494, 656]

The earliest attempt of objectively measuring near work was by Leung et al in 2011,[657] who used an ultrasonic sensor mounted on a headband that continuously measured and recorded viewing distance. Validation of device measures to self-reported reading distances found poor correlations, with errors of at least 10 cm in almost half of the participants. Subjects with closer working distances tended to overestimate their reading distance whereas those with longer working distances tended to underestimate their reading distance, suggesting a tendency for subjective reports to be biased towards a perceived normal/mean value for near work. Subjective estimates of working distance are therefore unlikely to provide a reliable metric of near work.

Three portable devices have recently been developed, the RangeLife (Adafruit, USA), the Clouclip (Glasson Technology Co Ltd, Hangzhou, China) and the Akeso glasses (Beijing Akeso Technology Co., Ltd., Beijing, China). All devices capture working distance at an eye level by using an infra-red based sensor mounted onto spectacle frames. The RangeLife, contains externally connected components (batteries and storage drives), whereas all components of the Clouclip are housed within a single shell. Meanwhile, the Akeso glass's proximity sensor is inbuilt within the right arm of the spectacle.

Validation of the RangeLife device in adults,[658] found no correlations between time spent in near and intermediate work (0.1–1 m) to questionnaire data. On average, objectively derived near work (6.25 D/hour) was significantly lower than subjective measures of daily near work (10.3 D/hour). Meanwhile during validation of the Clouclip in myopic children,[659] objectively derived near work time (< 60 cm) was significantly higher than subjective measures (obtained from both self-administered and parentally-administered questionnaires). Potential reliability differences between adult and child subjects, as well as inter-device differences may exist.

Recently, an inbuilt tablet and smartphone-based software has been developed, capable of measuring working distance using front-facing cameras commonly present in modern day smartphones and hand-held tablets.[660] This uses real-time formulas which derive an approximate working distance from the number of pixels contained within an individual's face as captured by the camera. This requires a one-time calibration for each subject and device, as facial shape varies between individuals. Experimental validation found that this method measured viewing distance with good accuracy (≤ 5 mm) and a high precision (≤ 1 cm) within a range of 40–250 cm.[661] Though in real-life pilot testing, tilting of devices in regular use had the potential to cause significant errors in working distances as the cameras were limited by their field of view due to a fixed focal length. As this device only collects data during hand-held device use, it may require a further development to capture other habitual near-work behaviours such as studying and reading books.

3.3.1.1 Considerations for near-work device selection

Several considerations are required when selecting an appropriate tool to capture near work (Table 1.1). For the portable detection of working distance, two sensor types are available: ultra-sonic based sensors and infrared based sensors. Only the near work analyser by Leung et al,[657] uses an ultrasonic sensor, while the RangeLife and Clouclip devices both contain infrared-based laser sensors. Whilst new in the context of myopia, both these types of sensors have been widely used in the robotics industry for obstacle detection and navigation purposes. Performance differences between these two types of sensors have been identified against various environmental surfaces, with ultrasonic sensors having greater accuracies in detecting sponge, wood, plastic and tiles, whilst infra-red sensors perform better against paper surfaces.[662] Since the majority of near work in school-children occurs against paper surfaces such as during reading and writing activities, devices using infra-red sensors are likely to provide more reliable measures.

In comparison to ultrasonic sensors, infra-red sensors are also typically much smaller and are also able to more accurately measure distances against uneven surfaces. However, while ultrasonic sensors are capable of measuring distances accurately over a broad range of distances, infra-red sensors have a smaller detection range, with significant errors in perceived distance occurring at both extremely short distances and at longer distances.[662] In myopia validation studies, while Leung et al's near work analyser was not tested for distances < 25 cm, it retained stable recording distances up to 200 cm.[657] On the other hand, the Clouclip has a specified detection range of 15–60 cm and was validated at distances between 18–55 cm,[663] whilst the RangeLife device was validated between 10–120 cm.[658]

Ultrasonic based sensors generally have a larger field of view compared to infra-red sensors; which may more realistically capture objects within the environment; however both infrared-based near work devices are spectacle-mounted and lie more closely on the visual axis of the eye. While field of view differences seen between devices have been generally small, and device positioning matters

less when measuring near work, a major limitation of all near work devices is that they are all fixed to the position of the head, meaning that changes in viewing distance when looking away from the primary position will not be estimated accurately. Additionally, capturing working distance may not completely translate into near work given that it is simply a measure of distance to nearest surface. This assumes that this is also where focus and attention is at, which will have a tendency to overestimate measures of time in near viewing.

Methodological limitations with objective near-work measuring devices are that they are significantly more expensive compared to questionnaires, which may limit larger cohort studies. Device wearability should also be considered, which may affect compliance and retention rates, particular in longer-term studies. Though the newer spectacle-mounted devices are increasingly lightweight, they may be intrusive by blocking part of the peripheral visual field. Further discomfort may occur in emmetropic individuals who require the addition of plano-lensed spectacles to mount the devices. Data analysis from objective measures can be complicated in long term studies, as the devices produce high volumes of data, typically one record per 2–10 minutes.

Table 3.1: Comparison of device characteristics of objective near work devices.

	Near work analyser	**RangeLife**	**Clouclip M2**
Sensor type	Ultrasonic	Infrared (940nm)	Infrared
Mounting	Head-mounted	Spectacle-mounted	Spectacle-mounted
Detection range	25-200cm	10-120cm	15-60cm
Reported variance	20mm @ 2.0m	12mm @ 1.0m	-0.78 ± 0.83 mm @ 18-55cm
Approximate field of view	30°	27°	25°
Maximum detection frequency	1Hz	1Hz	1/12Hz

3.3.2 Objective measurement of outdoor activity

There are also methods available to objectively capture outdoor activity. However, unlike for near work where measures have focussed on working distance, several approached have been considered. These includes the measurement of light intensity and UV exposures.

3.3.2.1 Light data loggers (LDLs)

The use of wearable light meters (also known as light data loggers, illuminometers, photometers or luxmeters) has been the most popular method to objectively capture outdoor activity in myopia studies. The average light intensity in outdoor environments is significantly higher than in indoor environments, often at magnitudes of greater than 10-fold. Thus, indoor and outdoor states can be distinguished using a threshold, which has generally considered to be 1,000 lux.[664, 665] Light intensity appears to be the mediator underlying the effects of outdoor time on myopia,[14, 16, 487] indicating that direct measurement of this risk factor could be more reliable.

Light data loggers (LDLs) quantify light intensity via photodiode sensors which convert incoming light into an electrical current. LDLs are characterised by a spectral responsivity curve or luminosity function which indicates the range of wavelengths detectable by the sensor, and its peak frequency where it is most sensitive to. Most industrial LDLs are calibrated with a luminosity function matching the human eye, which ranges between 400 to 700 nm and has a maximal sensitivity at approximately 555 nm in photopic conditions.

3.3.2.1.1 Portable/wearable LDLs

Portable/wearable LDLs are much smaller and can be automated to continuously record and store data at given frequencies for a select period of time. Despite sensor sizes of portable LDLs being smaller than traditional devices, they theoretically remain accurate as the measurement of light intensity (lux) is based upon the concentration of light (lumens) over a unit area. To date, there have been five portable LDLs which have seen use in myopia studies (Figure 3.2).

The HOBO Pendant UA-002-64 (Onset Computer Corporation, Massachusetts, USA) is a miniature LDL capable of simultaneously measuring temperature and light intensity. Though commonly used in biological studies to measure environmental changes in lighting and temperatures, the HOBO Pendant was the earliest device to be utilised in a myopia study.[633] Shortly after, Actiwatch 2 (Respironics Inc., Pennsylvania, USA) devices, which were wrist-worn actigraphy devices able to simultaneously measure light exposures and physical activity counts, were used in the ROAM study.[566] While these early studies were conducted using non-specific LDLs, recent devices have been developed specifically for the investigation of myopia. The Clouclip is one such device, capable of simultaneously capturing light intensity at an eye level alongside its ability to capture working distance.[663] Meanwhile, the FitSight tracker was designed as an intervention tool to modulate myogenic behaviour by aiming to encourage 3 hours of outdoor activity per day. The FitSight tracker was a custom-made smart-phone-linked app, which was loaded onto a commercially available smartwatch (Sony Smartwatch 3; Sony Corp., Tokyo, Japan).[666] The smartwatch has an inbuilt light sensor, which could be programmed by the FitSight app to automatically record illuminance at 1-minute intervals, as well as an accelerometer which could record physical activity via the number of "steps" taken by the wearer. Lastly, while the Akeso glasses also contain an inbuilt light sensor, the device appears to be programmed to primarily capture outdoor time, by categorically assessing light intensity using a 1,500 lux threshold at three minute intervals.[667]

Figure 3.2: Images of wearable light meters including the A) HOBO Pendant UA-002-64 B) Actiwatch 2 C) Clouclip M2 & D) FitSight tracker. Light sensor locations are indicated by red circles.

Studies using wearable LDLs have reported inconsistent associations between light exposure and myopia.[374, 633, 635, 638, 640, 641, 668] Whether these inconsistencies were related to differences in the objective measure requires examination of the comparability between devices and to subjective measures.

3.3.2.1.2 Validation of subjective measures using LDLs

A poor to fair level of agreement was found when outdoor time derived from the HOBO Pendant was compared against a parentally administered 7-day outdoor activity diary in school-children, with objective measures overestimating outdoor time compared to the diary.[633] As the significant differences primarily occurred on weekdays during the school term, the disagreement may reflect biases from parental estimates rather than inaccuracies of device measures. In university students and adults, outdoor time obtained from both the HOBO Pendant and Actiwatch 2 devices were significantly lower compared to self-reported questionnaire measures.[637, 643] While this may reflect differences in reporting accuracy between younger and older age samples, a study using the Clouclip device, found that both parental and self-reported estimates of outdoor time were overestimated compared to device measures.[659] These conflicting reports suggests that there may be potential for discrepancies occurring between different LDLs.

3.3.2.1.3 Comparability of LDLs

Studies comparing different LDL devices have provided further evidence that inter-device variations in exposure measurements are occurring.[636, 669, 670] The cause of these discrepancies has not been confirmed, but a number of factors can be considered, given the heterogeneity seen between wearable LDLs and their specifications (Table 3.2).

Firstly there is a clear external factor, as different wearable LDLs are positioned differently across each part of the body and orientated in different directions. For example, wrist-worn devices are naturally positioned lower and are usually faced laterally than necklaces or spectacle mounted devices which are usually forward facing. As it is unlikely that light intensity is consistent across all

areas of the body at a given point in time, measures from different directions would not be expected to be equivocal, though no studies have investigated the influence of directionality yet. LDLs can also be expected to behave differently during real world use, with those positioned peripherally on the body (wrist-worn devices) and those mounted less securely (necklaces) subject to increased variations from motion. These variations can be expected to occur more so in outdoor environments during physical activity, which may reduce the consistency of outdoor light exposure measures.

Alongside external factors, there may also be internal factors involved, as sensors contained within wearable LDLs exhibit different characteristics. In terms of the luminosity function, the HOBO Pendant appears to capture a wavelength range much broader than the visible spectrum of the eye (400–700 nm), alongside having a peak sensitivity outside the visible spectrum. Meanwhile the Actiwatch 2 device has a luminosity function more similar to the visible spectrum which may indicate that the illuminance measured is likely to be related to a retinal biologic response. Sensor characteristics for the Clouclip and Fitsight devices have not been publically reported.

Table 3.2: Comparison of different device characteristics of portable light meter devices based on publically available specifications.

	Hobo Pendant	**Actiwatch 2**	**Clouclip**	**FitSight**
Typical positioning	Necklace or shoulder-strap	Wrist-worn	Spectacle-mounted	Wrist-worn
Wavelength range	150-1200nm	400-900nm	??	??
Peak wavelength sensitivity	900nm	570nm	??	??
Minimum sampling rate	1Hz	1Hz	1/120Hz	1/60Hz
Light Range	0-320,000lx	5-100,000lx	1-655,336lx	??
Accuracy	??	10% @ 3000lux	-54.3 ± 37.6 @ 100-2000 lux	??
Weight	18g	16g	4.7g	38g
Secondary features	Waterproof (IP68) Temperature logging	Accelerometer	Working distance measures	Accelerometer GPS

3.3.2.1.4 Impact of sampling frequency and duration

Methodological differences, such as differences in recording intervals (sampling frequency) and measurement durations (sampling duration), provide the potential for further variations in light exposure measurements. For example, having a sampling frequency too low may fail to capture short intermittent sessions of light exposure if the action occurs between two logging time points, potentially underestimating mean daily light intensities. Secondly, capturing exposures over a shorter sampling duration, reduces the validity of the data, due to day to day variations in human behaviour. Yet a balance must be struck for both parameters, as having too much data creates logistical issues, since the amount of measures collected from each individual can quickly become overwhelming during data analysis.

Studies using LDLs have used a ranged of sampling parameters, with sampling frequencies ranging from 30 second to 5 minute intervals, whilst sampling durations have either lasted for either 1 or 2 weeks in continuous length.[566, 633] Two studies have investigated the effects of sampling frequency and duration on the validity and resolving power of device estimates. Alvarez and Wildsoet used a range of sampling intervals between 10 and 3,600 seconds from the HOBO Pendant light meter to describe outdoor light exposures in a sample of 27 young adults.[643] Using the shortest sampling interval (10 seconds) as the standard, they found that when sampling frequencies were extended beyond 120 second intervals, device estimates of hours in bright sunlight, cumulative outdoor exposures and total cumulative light exposure, all fell beyond an acceptable deviation of ± 5% in error. As the corresponding values derived using intervals of between 10 and 120 seconds were stable and remained within a 5% margin of error, it was proposed that a sampling interval of two minutes was the most effective frequency to accurately capture light exposures for both duration and intensity. Later investigations by Ulaganathan et al, also found that altering the sampling between 30 second and 10 minute frequencies did not alter the derived time spent outdoors.[671] What differed with decreasing sampling frequency, was an increase in the 95% limits of agreement.

This increase in variation fell beyond a statistically significant margin for frequencies below 2-minutes, confirming the threshold established by Alvarez and Wildsoet. Similar effects on sampling duration were seen, with measurement variability increasing with decreasing sampling durations. For this parameter, exposures obtained using 8-day measurement durations remained statistically similar to 14 days of monitoring.

Differences in optimum sampling duration and frequency also exists between cohorts of adults and children. In general, changes in sampling parameters appear more forgiving in children, as 4-days of measures explained 76% of the variance captured over 14-days, compared to 7-days of measures in adults which could only explain ~70% of the variance in the 14-day data.[671] Similarly for sampling frequencies, measurement intervals of 4 minutes or less in children were comparable to a 30 second sampling rate, whereas 3 minute intervals or less were needed for adults. Between sampling parameters, changes in sampling duration appear to have a greater impact on measurement reliability than sampling frequency, suggesting that studies requiring to collect light exposures more efficiency may need to consider reducing the sampling frequency in favour of maintaining a longer measurement duration.

3.3.3 UV exposures

Despite not directly involved in myopia control, quantitative measures of UV exposures have been explored as a surrogate measure of time outdoors.

3.3.3.1 Conjunctival autofluorescence

Digital UV auto-fluorescence (UVAF) photography allows the visualisation and imaging of areas of conjunctival damage resulting from UV exposures. In contrast to standard photography which captures all visible light, UVAF photography is performed using a flash system which transmits a wavelength range of 300–400 nm. When these images are taken at a fixed focal length and magnification (105 mm & 0.94x), the areas of hyperfluoresence seen in both nasal and temporal

conjunctival quadrants can be analysed to provide an area value representative of UV exposure and hence time spent outdoors. Validation of conjunctival UVAF measurements, find that UVAF measurements are reliable, given by high inter- and intra-observer correlations.[672] However, comparisons against a self-administered outdoor activity questionnaire which categorically assessed outdoor time, reported a poor correlation between total UVAF and outdoor activity (r = 0.29). One major issue is that little is known on the exact exposure period which UV damage represents, which likely both encompasses long term damage and short term exposure. Therefore, it is likely unable to provide a sensitive measure of outdoor time. Digital UVAF also requires trained personnel to capture and analyse the photographs. Additionally, the equipment required is relatively more expensive in comparison to other objective methods, limiting the number of potential participants and feasibility of larger studies.

3.3.3.2 UV dosimeters

UV dosimeters are a group of devices which measure UV exposures. Traditionally, UV dosimetry was performed using chemical badges, which measure cumulative UV exposure via a polysulphone film which undergoes photodegradation when exposed to ultraviolet radiation. This causes a change in its optical absorbency which can be measured by a spectrophotometer and transformed into a unit of UV exposure. Comparisons between daily UV doses measured via polysulfone badges have been found to be moderately correlated (r = 0.63–0.72) with self-recorded diary measures of outdoor time in adults.[673] Meanwhile, comparisons of UV exposure derived outdoor time to estimates of time outdoors derived using HOBO devices demonstrated a poor correlation (r = 0.38).[641]

These older forms of UV dosimeters carry a number of disadvantages in clinical studies. Firstly as they measure cumulative dosing, they cannot investigate temporal patterns of exposure, measure durations of exposure above particular thresholds and cannot investigate maximum intensities. Secondly, as the polysulfone films are a single use item, they can only capture data for a single period at a time (usually one day) before they are interpreted, although modern UV dosimeters have

become electronic, which function similarly to portable light meters by automatically capturing and storying UV exposures at pre-defined intervals. However, poor correlations have been found to survey estimates of outdoor time, and comparisons to other objective measures such as light meters remain moderately correlated.[674]

3.3.4 Location monitoring

Devices which directly monitor location, such as GPS trackers have been considered as a tool to discriminate between indoor and outdoor states.[675] GPS signals become disrupted when indoors due to shielding effects of buildings, these interference patterns can be analysed and quantified to determine whether an individual is currently located indoors or outdoors. In a study of preschool children, GPS trackers (QStarz device) appeared to be more accurate than portable LDLs (Actigraph GT3X+) in determining indoor/outdoor state when compared to direct observation.[676] However, while some portable LDLs appear to also contain GPS tracking capabilities, such as the FitSight device, location monitoring has not been used in any myopia studies to date.

3.4 Conclusion

There has been a shift in focus within the field of myopia epidemiology from using traditional subjective methods of exposure capture, such as questionnaires and diaries, to using methods which provide objective measures, such as portable data logging devices. This is in an attempt to provide more accurate measures of two key modifiable myopic risk factors, time outdoors and near work. For near work, head-mounted devices can measure working distance, where exposure time can be calculated by establishing thresholds. For time outdoors, wearable data loggers which measure light intensity have also been the preferred tools as light intensity likely to be the direct mediator behind the protective effects of outdoor time. Among the variety of light data loggers available, spectacle-mounted devices appear the most promising, due to their close positioning to the eye and capabilities of measuring both risk factors simultaneously. To date, only a handful of studies have been performed using these device. Common limitations of using these objective methods is that they are currently expensive to employ in studies and require more logistical resources for data collection and analysis. Higher rates of non-compliance may be seen as these methods are often associated with additional levels of discomfort. Newer devices may provide increased utility and efficiency in these areas, however given the heterogeneity between available devices validation between instruments is required to ensure that data obtained is accurate and comparable, which may potentially allow further detailed studies such as meta-analyses to be performed.

Chapter 4: Quantifying Light Exposure Patterns in Young Adults

4.1 Abstract

Purpose: Using objective measures to describe patterns of light exposure in young Australian adults engaging in tertiary education.

Methods: 102 university students wore a portable light data logger for a period of four days (2 week and 2 weekend days) during an autumn season. Participants simultaneously completed a 24-hour diary to capture indoor and outdoor exposure and activities undertaken.

Results: Subjects spent approximately 11.3% of daylight hours outdoors, equating to ~81 minutes of exposure to lux ≥ 1,000 on a day with 12 hours of light. Of this, only ~18 minutes was spent ≥ 10,000 lux and ~6 minutes ≥ 40,000 lux. The main activity differentiating behaviour on weekdays versus weekends was tertiary education. However, this made no significant difference to the time spent within all light intensity ranges (0–100,000+ lux) nor in the mean daily light level experienced. Yet there was a graphic difference in the daily pattern of light exposure with overall weekday exposure patterns more sporadic from sunrise to sunset.

Conclusion: Days spent in education accumulates total light exposure in multiple short intervals. Given that phasic dopamine release can occur from intermittent exposure to high intensity light, protective effects may continue if exposure times and intensities are kept above threshold. Very little time was spent at the light levels deemed protective in animal studies, which had used continual myopic stimuli, leading to a possible overestimation of the requirements for protection in humans. Recent epidemiological evidence from Taiwan also suggests that lower light exposures in humans may be protective for myopia.

4.2 Introduction

Within the last few decades, an increased prevalence of common myopia has been observed in various developed countries around the world.[135, 139, 677] In some cohorts myopia has reached epidemic proportions, such as in South Korea, where up to 97% of their male military conscripts are now myopic,[199] or in Taiwanese schools, where approximately 80-90% of children are myopic.[677]

Strong negative associations seen between outdoor time and prevalent myopia in epidemiological studies has suggested that spending time outdoors may protect against the development of myopia.[564, 645] Additionally, the light-dopamine theory provides a clear biological mechanism, where excessive axial length elongation is inhibited in response to light induced retinal dopamine release.[487] Animal model studies confirm this mechanism[14] and that these effects have been also been shown in several intervention trials,[371, 372, 374] provides strong evidence for causality in humans, with higher outdoor time having a protective effect on incident myopia.

Currently, it has not been demonstrated whether or not time outdoors can reduce the progression of existing myopia, as only relatively modest effects have been seen to date.[564, 646] One reason for this may be that the traditional methods of exposure capture, namely questionnaires, have not been able to precisely quantify individual outdoor time. Chapter 3 has identified several areas of variance in questionnaires used in myopia studies to date. These differences have the potential to introduce various levels of bias, resulting in reductions in accuracy and reliability. Therefore, current methods may not be sufficient in the context of investigating myopia progression, given that it requires the discrimination of time outdoors among existing myopes, who may be already spending limited time outdoors compared to their non-myopic counterparts.

Alternatively, investigators have used wearable light data loggers (LDLs) in order to objectively determine time outdoors. In addition, the measurement of light exposure allows investigators to measure other protective variables associated with time outdoors, allowing further detailed

examination of this myopigenic risk factor. While time spent outdoors has been the primary variable associated with myopia in humans, the light dopamine theory and related animal studies have indicated that high light intensities are also needed to achieve myopia protection,[16, 567, 569] with dose-response relationships occurring within moderate intensity levels commonly experienced in outdoor environments.[14] Other experimental studies have suggested that the frequency of high light exposure also plays a major role by enhancing the protective effect of high intensity light.[575] Together these three variables of light exposure: duration, intensity and frequency, allow investigators to comprehensively assess the relationship between outdoor time and myopia. Despite this, most studies using LDLs have only considered light exposure duration by using a measurement threshold of 1,000 lux to distinguish between an indoor and outdoor state. As a result, there has been limited data available to characterize light exposure patterns in humans (duration of outdoor light exposure, light intensity and frequency of bright light), which may exhibit differences between populations of different myopia prevalences.

This chapter aims to use objective measures of light exposure to describe normal light exposure habits of Australian young adults and examine the impact of various behavioural activities on light exposure patterns.

4.3 Methods

4.3.1 Study design

One hundred and two students from the University of Sydney, Australia wore a portable LDL for a period of four days and simultaneously completed an outdoor activity diary during waking hours. This was performed across a 10-week period during an autumn season. Participants were recruited via advertisements placed on faculty noticeboards across the campus and through announcements made on faculty-wide electronic bulletins. There was no exclusion criteria applied.

4.3.2 Light intensity measurements

After study enrolment, participants were instructed to wear a HOBO UA-002-64 LDL (Onset Computer Corporation, Bourne, MA, USA) during waking hours for four consecutive days (two weekdays and two weekend days). The LDL was housed vertically in a transparent pocket of an armband fastened to the participant's non-dominant arm, so that the sensor plane was facing outwards. Participants wore the LDL during all activities over their outermost layer of clothing when possible. Otherwise, they were advised to keep the device in close proximity, with the sensor facing upwards in the same environment during activities such as swimming or bathing/showering. The LDL was configured to automatically capture light intensity values (lux) at 10-minute intervals.

4.3.3 Activity diary

In conjunction with wearing the LDL, participants were asked to document their daily activities in a 24-hour diary. The diary classified everyday activities into eight groups: sleep, travel, university, work, passive leisure activities, and active leisure activities, external university related activities; and other activities: which had to be specified. Passive leisure activity was defined as any non-university related activity undertaken where the activity predominantly involve low frequency movement and mild physical exertion of the individual, whereas active leisure activities consisted of activities in which the individual was in constant motion or had high physical exertion. Actions classed as "other

activities" were then manually sorted into either passive, active, work or university related activities at the discretion of the primary investigator based upon descriptions recorded in the diary log. Logs from the 24-hour diary also specified whether each activity was outdoors or indoors and included start and end time of each activity, in order to unite data with LDL measures.

4.3.4 Ethical considerations

Prior to enrolment, participants signed a consent form containing detailed study information including data collection and information storage processes. All observations were conducted in accordance with the Declaration of Helsinki and under ethical approval obtained via the University of Sydney Human Research Ethics Committee.

4.3.5 Data analysis

For each day, only data during daylight hours were considered for analysis with reference to sunrise and sunset times documented by www.timeanddate.com. Overall, 98 participants had complete data intervals between sunrise and sunset time for both light intensity and diary logs across all four days of recording. Participants were primarily undergraduate students ranging between 18 and 29 years of age, with the exception of eight post-graduate students who were above 40 years of age.

Light intensity values were first compared to diary entry data in order to validate measures obtained from the LDL. A Spearman correlation and Cohen's kappa analysis were performed to compare the agreement between reported states of outdoor time logged in the diaries to estimates of outdoor states from the LDL defined by a threshold of > 1,000 lux,[664, 665] and as used in previous myopia studies.[566, 633-635, 638, 640, 643]

Paired samples t-tests were used to identify individual differences in average daily light exposures levels, average time spent outdoors, as well as differences in the number of indoor-outdoor transitions made on a weekday versus weekend days. Mean light exposure levels at each time interval were calculated and plotted using a LOESS curve to capture the average daily pattern of light

exposures of the cohort. Mean percentage of time spent above incremental thresholds of light intensity were also quantified and compared between weekday and weekend days. The relationship of specified activities as listed in the diary to mean light exposure levels were investigated by an ANOVA analysis. All data analyses were performed using SPSS (version 22, IBM Corp, Armonk, NY, USA). All results were considered statistically significant at an alpha level of 5%.

4.4 Results

4.4.1 Mean light intensity and frequency

The mean daily lux exposure was 1,534.5 ± 2,026 lux. Mean lux exposure during weekdays (1,427 ± 1,550) was slightly lower than on weekend days (1,648.6 ± 3,767), however, this difference was not statistically significant (P = 0.589). Figures 4.1-4.3 show the average light exposure patterns of the participants during daylight hours. On weekdays, individuals were exposed to high light levels in varying episodes spread across the day, between the hours of 7:30am–3:30pm (Figure 4.2). During weekends however, high light exposure episodes clustered more tightly during the day between 9:50–2:50pm, with maximum exposures occurring between 1:00–2:00pm (Figure 4.3). When considering the frequency of outdoor light exposure, individuals transitioned between indoor and outdoor environments more often during weekdays than on weekends (3.0 vs 1.9 instances, P < 0.001).

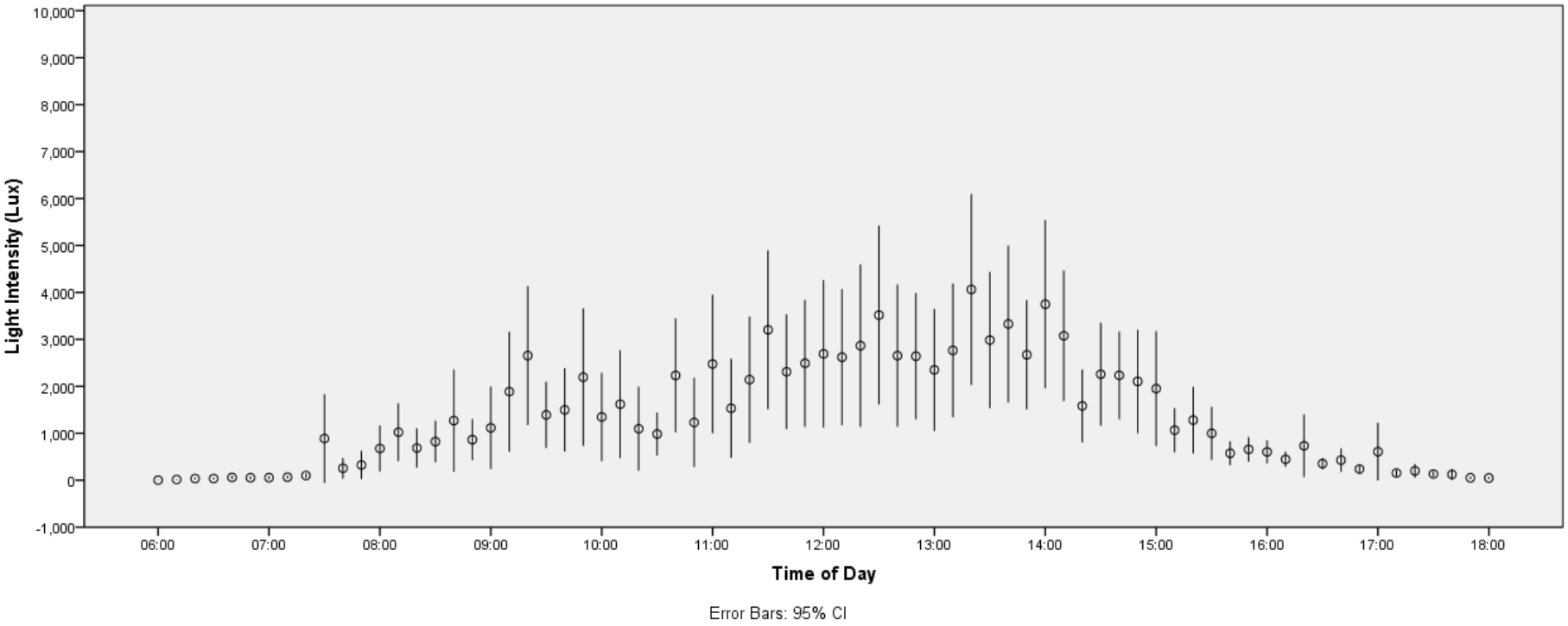


Figure 4.1: Mean light intensity over an average day. Error bars represent 95% CI.

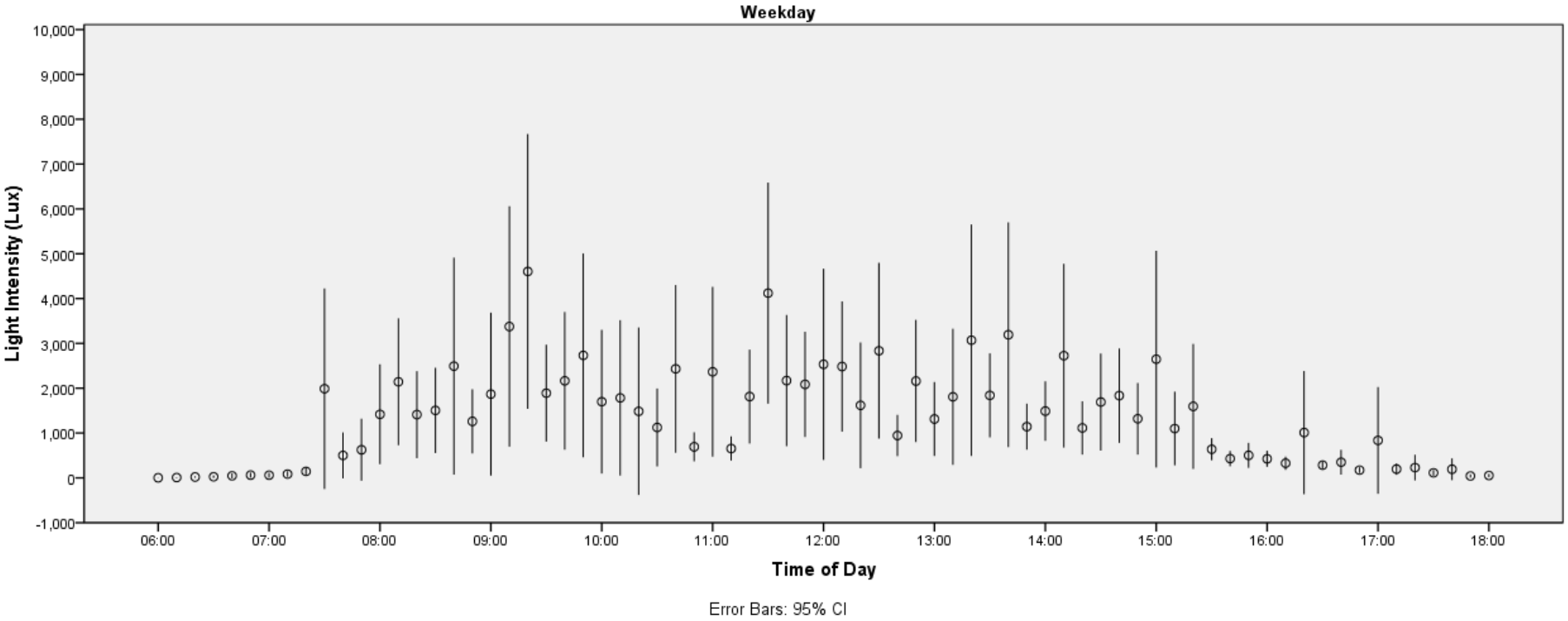


Figure 4.2: Mean light intensity over an average weekday. Error bars represent 95% CI.

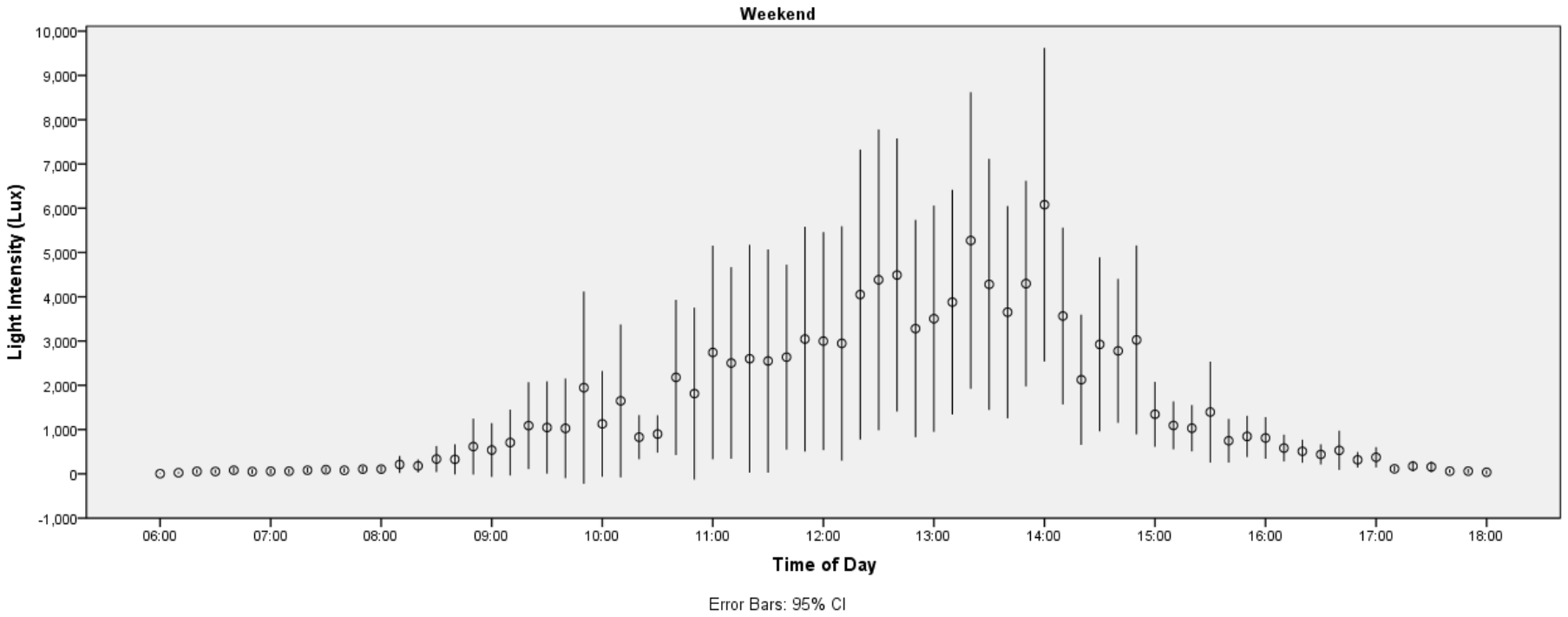


Figure 4.3: Mean light intensity over an average weekend day. Error bars represent 95% CI.

4.4.2 Time outdoors and in high light environments

During daylight hours, participants spent approximately 11.3% of their time outdoors (defined as lux > 1,000) (Table 4.1). This equates to ~81 minutes of outdoor light exposure on a day with 12 hours of daylight and ~68 minutes on a 10-hour day. More time was spent outdoors during weekdays (12.2%) compared to weekend days (10.3%), however, this difference was not significant (P = 0.120). Individuals spent decreasingly less time within higher light intensity environments, with only ~18 minutes spent ≥ 10,000 lux and ~6 minutes ≥ 40,000 lux. There were no significant differences observed in time spent above any lux threshold between weekdays and weekend days (all P > 0.05).

Table 4.1: Time spent above various light intensity thresholds, expressed as a percentage of daylight hours and in minutes during 12 and 10 daylight hour days.

	Mean proportion of daylight hours (%)			**Mean time spent (minutes)**	
Light intensity threshold	***Overall***	***Weekday***	***Weekend***	***12-hour daylight length***	***10-hour daylight length***
0-999 lux	88.7	87.8	89.7	639	532
1,000+ lux	11.3	12.2	10.3	81	68
5,000+ lux	4.2	4.3	4.0	30	25
10,000+ lux	2.5	2.5	2.5	18	15
20,000+ lux	1.4	1.3	1.5	10	9
30,000+ lux	1.1	1.0	1.1	8	6
40,000+ lux	0.8	0.8	0.9	6	5
70,000+ lux	0.5	0.4	0.7	4	3
100,000+ lux	0.3	0.3	0.4	2	2

4.4.3 Agreement between LDL and diary measure of outdoor state

There was a moderate-fair level of agreement between LDL determined indoor-outdoor states and records from the outdoor activity diary (Table 4.2). This was given by a Spearman's correlation coefficient of 0.378 ($P < 0.001$) and a Cohen's kappa value of 0.370 ($P < 0.001$).

Table 4.2: Cross-tabulation of agreement between indoor and outdoor states from the diary and from the LDL (defined as > 1,000lux)

		Number of LDL counts		Total
		Indoors	***Outdoors***	
Diary log during	***Indoors***	19,199	1,283	20,482
count interval	***Outdoors***	2,480	1,580	4,060
Total		21,679	2,863	24,542

4.4.4 Mean light exposures during diary activities

Average light exposures levels experienced by participants while engaging in various activities are listed in Table 4.3. Activities classified as "Active Leisure" provided the most opportunity for light exposure, with a mean light intensity of 5,980 lux. This was followed by "Travel" at a mean 3,474 lux and "Passive Leisure" at 1,160 lux. All other activities had mean light exposure levels below 1,000 lux. Mean light exposure levels did not significantly differ between weekdays and weekend days for all activities except "Travel", which provided higher exposures on weekdays ($P = 0.013$) and "Active leisure", which provided higher mean light exposures on weekends ($P < 0.001$) (Table 4.3–4.5).

Table 4.3: Average light intensity levels recorded in various activity groups.

Activity group	N	Mean lux	SD
Sleep	4,874	134	2,638
Travel	1,957	3,474	13,824
In university	2,604	804	6,740
Work	951	370	1,339
Passive leisure	7,574	1,160	9,180
Active leisure	3,050	5,980	22,508
Study	3,018	811	5,951

Table 4.4: Average light intensity levels recorded in various activity groups on weekdays and weekends. (*P < 0.05)

	N		Mean lux		SD	
Activity group	**Weekday**	**Weekend**	**Weekday**	**Weekend**	**Weekday**	**Weekend**
Sleep	1,774	3,100	119	142	747	3,256
Travel	1,265	692	*4,053	*2,415	15,519	10,019
In university	2,380	224	843	391	7,047	1,429
Work	611	340	392	330	1,221	1,528
Passive leisure	3,147	4,427	1,072	1,223	6,885	10,514
Active leisure	1,400	1,650	*4,369	*7,347	18,233	25,554
Study	1,288	1,730	699	895	5,685	6142

Table 4.5: Activity groups sorted by indoor or outdoor environment as determined by diary entries.

Activity group	Environment	N	Mean lux	SD
Sleep	***Indoors***	4,871	134	2,654
	Outdoors	3	585	423
Travel	***Indoors***	143	2,893	17,520
	Outdoors	1,814	3,520	13,592
In university	***Indoors***	2,503	721	6,557
	Outdoors	79	3,639	13,445
Work	***Indoors***	950	344	1,079
	Outdoors	1	24,800	-
Passive leisure	***Indoors***	7,163	614	4,097
	Outdoors	411	10,673	34,016
Active leisure	***Indoors***	1,376	570	2,217
	Outdoors	1,674	10,427	29,713
Study	***Indoors***	3,002	815	5,936
	Outdoors	0	-	-

4.5 Discussion

This study describes objective parameters of light exposure relevant for myopia development in young adults. The average exposed light intensity and the duration of time spent in high lighting environments by subjects in our study appears to be lower than the light environments commonly used in animal experiments to protect against stimulus driven myopia.[16, 568] For example in chickens, Karouta and Ashby reported that a minimum of 10,000 lux for 6 hours/day was required for inhibition of experimental form deprivation myopia.[14] Meanwhile in our study, only an average of 15–18 minutes per day was spent in environments > 10,000 lux. However, despite this relatively low exposure time, the prevalence of myopia in Australian young adults is still considerably low compared to similarly aged cohorts from countries involved in the myopia epidemic.[202, 678] Additionally, associations between differences in myopia prevalence between Singapore and Sydney with differences in time spent outdoors,[553] indicates that a protective effect is indeed occurring in Australian environments. This suggests that humans may not need such high levels of continuous light exposure as found in animal studies, in order to be protected against myopia.

One reason likely for this is because real-world exposure to myopigenic risk factors; such as near work activities and educational load; occurs intermittently, unlike in experimental animal models where the myopigenic stimulus (either form deprivation or lens defocus) is constant. Therefore, as the driving force for myopia is lower, individuals may not be required to spend as much time outdoors in order to counteract any myopigenic effects. Evidence to support this concept was seen in the Sydney Myopia Study, as children engaging in high near work required higher levels of outdoor activity to see protection from myopia development compared to those engaging low near work, who only required moderate amounts of time spent outdoors.[487] However, another reason may be because light exposure time between human and experimental environments cannot be directly compared. Lighting in laboratory experiments is typically fixed at a single illuminance level, allowing exposure time effects to specific intensities to be accurately determined. Meanwhile in the

real world, there are constant fluctuations and variations in light levels occurs, and a result, outdoor exposure time has been quantified using a minimum intensity threshold. This also means when using a given lux threshold, the average light intensity experienced would naturally be higher than the threshold value. As the protective effect of light occurs via a dose dependent relationship with increasing light intensity,[14] the protective effect would likely be higher in the human environment, given the same exposure times. An alternative may be to consider units such as lux-hours, however this method would still not account for different frequencies of high intensity light. Lan et al showed in chickens, that myopic inhibition achieved from five hours of exposure to 15,000 lux was more potent when delivered in 1 and 7 minute periodic intervals.[575] This suggests that individuals exposed to similar daily frequent outdoor times, have the potential to receive different levels of myopic protection depending on both the frequency and interval duration in which their light exposure is obtained. However, this relationship has not yet been shown in humans, with limited associations between outdoor frequency and myopia status.[641, 643] Future studies comparing light exposure between populations would need to consider light exposure frequency in addition to duration and intensity.

Most studies describing normative light exposure patterns have done so in the context of investigating chronobiology and circadian rhythms rather than myopia, yet have found similar levels of daily light exposure in humans. An early study by Espiritu et al, reported that adults spent ~58 minutes per day in outdoor environments.[679] Later, Savides et al reported that healthy adults spent ~90 minutes per day in > 2,000 lux environments.[680] In 2010, Scheuermaier et al, used the Actiwatch-L light meters to examine habitual light exposure patterns in a group of 22 older subjects (mean age 66) and 22 young adult subjects (mean age 23).[665] Similar to our study, relatively low levels of outdoor light exposure were seen in both cohorts, with the older and younger cohorts respectively spending averages of 14.7% and 9% of their waking day in light environments > 1,000 lux. Light exposure patterns across the day were also similar to our findings, with young adults achieving peak light exposure between 1–3pm.

Levels of outdoor time experienced by our subjects also appear consistent with other myopia-focused studies. Alvarez et al reported that young adult university students from California, USA were exposed to < 10% of the available sunlight during a typical day.[643] Though mean daily light intensity (857 lux during autumn) was lower than our findings, this may have reflected d differences in geographic locality. Average outdoor frequency exposure experienced by subjects in their study was considerably higher (51.4–63.2 intervals) than ours, though this was likely due to their shorter sampling interval of 10 seconds. Schmid et al, have also investigated light exposures in university students, reporting that ~6–10 minutes was spent > 30,000 lux per day.[641] This was similar to the findings in our sample (6–8 minutes/day). Outdoor light exposure frequency among their emmetropes, stable myopes and progressive myopes were higher (3.6–5.2 intervals/day) than our sample, again likely due to a shorter sampling interval of 5 minutes and also due to the fact that outdoor time was quantified using one of two different thresholds, > 10,000 or > 500 lux. Standardization of LDL measurement protocols are required in future studies for adequate comparison light exposure parameters.

So far most reports have been from western countries and in adult populations. However, it is exposures occurring during primary and secondary schooling years that are of greater concern, as this is when most refractive progression occurs. No studies have yet to examine light exposure from a representative sample of Australian school-children or compared differences in light exposure between different levels of schooling. Using HOBO LDLs, Dharani et al found that Singaporean children spent an average of 53 minutes per day outdoors during school weekdays.[633] However, they spent a similar amount of time outdoors to our adult subjects during weekends (81.6 minutes). While geographic location could be a factor, the weekday differences in light exposure are likely related to differences in schooling level. In contrast to primary schooling, where students are typically assigned to a single classroom, secondary and tertiary education systems require students to move between classrooms for subject changes. This likely provides a significant source of light exposure, assuming that students are moving between buildings. In our findings, spending time in

education was the main activity differentiating subject behaviours on weekdays compared to weekends. However, this did not appear to influence the duration or intensity of luminance exposure experienced. What differed was that weekday light exposure patterns were less consistent from sunrise to sunset, and subjects transitioned between indoor and outdoor environments more frequently. This indicates that on weekends, individuals were receiving their light exposures during similar times and for similar durations, whilst on weekdays, individual outdoor activities were distributed more sporadically throughout the day and were more likely to have been shorter in duration and more frequent yet cumulating to the same total exposure. This view is consistent with light exposure patterns seen in Singaporean primary schoolchildren, who instead record lower number of daily light exposure episodes during weekdays than weekends.[640] Increases in light exposure frequency may contribute to a protective effects against myopia, as suggested earlier by animal studies,[575] and may possibly be another component driving myopia development in schoolchildren, alongside reduced outdoor time.

In the ROCT711 trial, Taiwanese schoolchildren aged 6–7 years old who were allocated to the control group, spent an average of 40.7 minutes per day outdoors,[374] approximately half the time our older subjects in Sydney experienced (~81 minutes). Part of these differences were due to the fact that objective light exposures were only captured during school hours for the Taiwanese children. Similar proportional differences in levels of light exposure occurred when considering time spent > 5,000 lux (17 vs 30 minutes) and time spent > 10,000 lux (9 vs 18 minutes) in Taiwan and Sydney respectively. This suggests that a similar ranges of light intensities can be experienced, despite differences in outdoor time. However, the overall time outdoors in Taiwanese children appears to be insufficient to provide good protection from developing myopia in this young control group.[374]

The current study also quantifies light exposures during common routine activities. Participants were exposed to consistently high levels of ambient light intensity when performing activities not relating to education and work (travelling and leisure activities). Of these, activities that were inherently

active in nature (active leisure and travelling) provided the highest average light intensity measures. This appeared to come from the fact that most of the outdoor activities performed by participants fell into one of these two categories. While some elements of this could be considered common sense, as some level of active movement is required to transition into an outdoor environment, it is still possible and not unreasonable for someone to perform other passive activities; such as work, studying and passive leisure; outdoors. This however, suggests that interventions targeting active behaviors are likely to be effective at increasing outdoor time and hence light exposure in humans.

Furthermore, the effectiveness of such interventions may also vary across the week, as we found that travel-related activities provided greater light exposures on weekdays than on weekends, whereas active leisure activities provided greater light exposures on weekends rather than weekdays. Interventions designed for school-aged children may find it more valuable to increase travel on school days, such as encouraging parents to walk their child to school more often, or by changing classrooms throughout the day for children to receive more outdoor exposure. Meanwhile, active leisure activities such as outdoor sport should be encouraged particularly on weekends, as children should then have more available time to spend outdoors.

To our knowledge, this is the first study to report ambient light intensity values during day-to-day activities. Further investigations comparing the effectiveness of different behavioral intervention strategies against myopia are needed to support our findings. The main strengths of this study was its relatively large sample size compared to other studies in young adults, and the use of experience sampling (diary records) to capture behaviors and determine indoor/outdoor states. Experience sampling offers more real-time measures than questionnaires, alongside the ability to capture day-to-day variations. On the other hand, the main limitation of this analysis was that refractive data of participants was not obtained, thus relationships between the variables identified could not be associated with refractive status. Another limitation of our study was the use of a university student sample, which may not adequately represent younger cohorts or other university populations with

different study patterns.

While HOBO LDLs have been previously used in myopia research, our LDL were mounted differently to other studies that usually instructed participants to wear the LDL around the neck. Little is currently known on the impacts of sensor positioning on the body on light exposure measures and a standardized method of collecting human light exposure data has not been adopted. We also used a lower recording frequency of 10 minutes than other studies, who have logged intensities at intervals as low as one-minute. Instances of high light exposure shorter than 10 minutes may have been experienced in between recording intervals and not captured in this study. This would have underestimated time and frequency spent outdoors, though likely only to a minor degree, as it is not typical for individuals to transition between indoor-outdoor states frequently within a 10 minute interval. Additionally, whether light exposure at such high frequencies is clinically significant or not in humans is unknown. While some animal experiments find that high frequency light exposure can produce enhanced effects,[575] findings that brief periods of light exposure can produce long-lasting protective effects against myopigenic stimuli,[507] suggests that there may be limited additive benefit within such a short period of time. Again for future studies, standard validated methods of objective light exposure measures need to be established. Certainly if recording over multiple days, short interval measures may present very large data sets that may not add value to findings, however a minimum sampling interval of 2-minutes has been found to provide the most reliable estimate of outdoor light exposure.[671]

Overall, light exposures experienced by humans in the real world are far more complex than those investigated in laboratory conditions. Multiple parameters of light exposure have been identified to be involved in protecting against myopia (duration of light exposure, light intensity and light frequency) which need to be captured together in order to appropriately quantify human light exposures. Since the requirements for myopia protection also varies depending on the individual (such as the amount of near work being performed), comprehensive multivariate approaches need

to be considered in future studies looking to find associations between light exposures couple with other parameters and the prevention of myopia.

Chapter 5: The Accuracy and Reliability of Portable Light Data Loggers for Measuring Light Intensity

5.1 Abstract

Purpose: To compare light intensity outputs from portable light data loggers (LDLs) with respect to a standard industrial illuminometer.

Methods: Measures of agreement between three pairs of portable LDLs (HOBO Pendant UA-002-64, Actiwatch 2 & Clouclip M2), set to simultaneously record light intensity measures at 2-minute intervals, were compared to a single standard digital illuminance meter (Yokogawa 51012) over a 1-hour period. This was performed within four incremental lighting environments: low indoors (0–499 lux), high indoors (500–999 lux), low outdoors (1,000–9,999 lux) and high outdoors (> 10,000 lux).

Results: Light intensity measurements from the Actiwatch, HOBO and Clouclip LDL were strongly correlated with the standard light meter (ICC: 0.799, 0.860 & 0.884 respectively) however, mean light intensity from each device was significantly different to the standard meter in all environments (all $P < 0.001$). Measurement errors from the portable LDLs displayed proportional bias, with increasing errors at higher illuminances. The Actiwatch and Clouclip LDLs had a tendency to underestimate true illuminance (mean percentage difference: -57.5% & -28.36% respectively). In solely outdoor environments, the HOBO LDL overestimated true illuminance (mean difference: 43.35%).

Conclusion: Portable LDLs are reliable in that they give comparable relative results, however different devices do not measure the same illuminance as experienced by the individual at a given time due to several factors including sensor differences and measurement directions. These differences must be considered when interpreting results from sources using different LDLs in the measurement of time spent outdoors and in future study designs investigating light exposures in humans.

5.2 Introduction

Rapid increases in myopia prevalence have occurred in the past few decades, reaching epidemic proportions in certain countries within East and Southeast Asia.[1] It has been predicted that this rise will affect almost 50% of the world's population by 2050, alongside concurrent increases in the prevalence and proportion of high myopia (≤ -5.00 D) which would occur in ~20% of those myopic.[2] High myopia poses a substantial risk of non-correctable visual impairment from retinal consequences such as choroidal neovascular membranes, posterior staphylomas and retinal detachment.[3] However, even low levels of myopia have higher likelihoods of subsequent glaucoma[251] and cataract.[256]

It is now understood that environmental changes are the major contributors underlying the epidemic.[1, 389, 681] Several epidemiological studies have identified three major risk factors to be associated with myopia development: intensive education, high near work and low time spent outdoors.[682] Near work and time outdoors are variables of interest, as they are more easily modifiable for intervention. Of the two, time outdoors has been the primary focus, since several intervention studies have shown that it has a clear causal relationship to myopia[371-374] and public health programmes have also reported success.[12, 13] However there are a number of unanswered questions. While time outdoors plays a significant role in reducing the onset of myopia, reports on whether outdoor time can reduce the progression of existing myopia have not been consistent.[564] Furthermore, the optimal duration of exposure required for protecting against myopia has not been identified, which may limit the efficacy of future trials and intervention programmes.

One contributing issue is that time spent outdoors has been captured with questionnaires. Values captured may be influenced by recall bias and inaccuracies associated with secondary reporting from parents or teachers in childhood cohorts. Despite this, questionnaires were able to consistently identify causal relationships between time outdoors and myopia, indicating that the association is strong and reproducible, however they are not able to capture more detailed aspects of light

exposure, such as intensity and frequency, which are key elements required for protection as demonstrated in animal models of myopia.[14, 575]

Recent studies have begun to use portable light data loggers (LDLs), also known as illuminometers or light meters, to objectively quantify time outdoors and directly capture light intensity as the primary exposure variable.[566, 633, 636, 638, 643] These devices work by automatically recording light intensity at continuous intervals throughout the day. This more detailed approach is likely to provide greater statistical power and has the potential to reveal protective thresholds for light exposure and illuminate the role that it plays in myopia progression. Early studies comparing estimates of outdoor time between these devices and previously used questionnaires have found poor agreement,[633, 643] suggesting that real-time exposures may be different to what has been previously reported in the literature.

To date, a variety of wearable LDLs have been used in myopia-related studies to capture light intensity, but it is uncertain whether the illuminance measures are consistent between differing devices or how accurate these devices are with respect to a conventional illuminometer. LDLs come in a variety of different forms, which may not allow the capture of identical light sources throughout daily use due to differences in sensor orientations. Additionally, sensors contained within these devices have different specifications and capture light across different wavelength spectrums (Chapter 3), making it difficult to ascertain whether results are a true measure of the light experienced by the human eye on a retinal level, as well as the impact that it may have on the light-dopamine response. Some inconsistencies has been observed between findings of studies comparing measurements between different wearable LDLs,[636, 670, 683, 684] indicating that a greater understanding of the characteristics of LDLs, and their relationship to effective light levels entering the eye are required.

This study aims to directly compare measures of light intensity obtained from three portable LDLs previously used in myopia research in order to assess the accuracy and reliability of their sensors with respect to a standard, non-portable light meter calibrated for industrial use.

5.3 Methods

Detailed study methodology has been described in Chapter 2.

5.3.1 Experiment 1: Comparison of light intensity between different LDLs

A comparative experimental design was used to investigate light meter measures (Lux) obtained by the Clouclip M2 (Mirror Technology Co., Ltd. Hangzhou) device and two other portable light sensors, the HOBO Pendant UA-002-64 (Onset Computer Corporation, USA) and the Actiwatch 2 (Philips Respironics, USA). These measures were compared to a standard non-portable LDL, the Yokogawa 51012 Digital LUX meter (Yokogawa Test & Measurement Corporation, Japan) across four separate lighting environments.

Pairs of each LDL were mounted on to a foam block with their respective sensors facing upwards on the same linear plane to allow equal and uniform spread of ambient light exposure between each device. Pairs of the same LDL were positioned on the foam block symmetrically to detect and control for potential variations in exposure across the surface of the block. Each of the portable LDLs were configured to continuously record light intensity levels at 2-minute intervals. The reference meter was placed horizontally above the foam block with the centre aligned to the position of the light sensor. As the reference meter was not automated, light intensity readings from the reference light meter were manually captured by the investigator (LP) at the same 2-minute intervals as determined by a stopwatch. This was performed over a 1-hour period for a total of 31 data points in each environment.

5.3.1.1 Light environments

The experiment was repeated in four environments of differing light levels classified as low indoors, high indoors, low outdoors and high outdoors. Low indoor light was considered to be the ambient light encountered in the centre of an enclosed room without exposure from open windows with most of the illuminance, if not all, coming from artificial lighting. This was defined by lux values less than 500 measured using the standard light meter. However, as there were no open sources of external light, in order to capture a broader range of light, the room illumination was gradually reduced in 10-minute intervals across the hour using a dimming switch. The highly illuminated indoor environment consisted of a large indoor room with additional external sources of light from multiple large open windows facing in more than one direction, this was set to include lux levels ranging between 500 and 1,000. Low outdoor light levels were representative of an outdoor environment which had no direct line of sight with the sun such as under the shade of a tree or near a high-rise building with lux levels defined between 1,000 and 10,000. High outdoor light levels were defined as outdoor environments with large open spaces such as in parks and fields where there was a direct line of sight with the sky, capturing lux > 10,000.

5.3.2 Experiment 2: Comparison of light intensity between LDLs in different directions

In a second experiment, wearable LDLs (Actiwatch 2, HOBO Pendant and Clouclip M2) were attached to five faces of a square foam block, with their respective sensors orientated at the same plane and facing the same direction. The five directions were considered to be facing 1) upwards 2) north 3) east 4) west and 5) south. All LDLs were configured to automatically record light intensity at 2-minute intervals. The apparatus was placed outdoors in an open park for 30 minutes to simultaneously capture 16 intervals of light intensity from each LDL in five different directions. Measurements were obtained during a partly cloudy winter day.

5.3.3 Experiment 3: Comparison of angular light intensity using the Clouclip LDL

In a third experiment, angular variations in light intensity was investigated. A Clouclip LDL was attached to a protractor mounted onto a tripod at four vertical positions A) 90° upward (vertical) B) 45° upward C) 0° (horizontal) D) and 45° downward (Figure 2.5). The Clouclip LDL was configured to automatically record light intensity and was placed in two environments A) indoor desk environment with artificial lighting and B) an outdoor environment on a partly cloudy winter day (Figure 2.6). In each environment the position of the LDL was manually adjusted every two minutes to capture light intensity at four different angles.

5.3.4 Light data loggers

The Actiwatch 2 is an activity monitoring device band weighing 16 g worn on the wrist which measures sleep patterns, physical activity levels as well as visible light illuminance. The silicone photodiode sensor has a wavelength range of 400–900 nm with a peak sensitivity at 570 nm. The device has an illuminance range of 5–100,000 lux with a reported 10% accuracy at 3,000 lux.

The Clouclip M2 is a portable light meter intended for use in individuals who wear spectacles. It weighs approximately 6 grams and is attached in line with an arm of the spectacle frame with the front sensor orientated forward in the direction of fixation. The Clouclip allows for the continuous measurement of both light intensity (lux) and near work measures (mm) with real-time data transfer via Bluetooth onto a linked mobile device via an app. No manufacturer details regarding its light sensor specifications have been made public at this time.

The HOBO Pendant UA-002-64 is a combined temperature and light data logger with measurement ranges between 0–320,000 lux. It has a peak wavelength sensitivity at 900 nm and a total wavelength range between 150 and 1,200 nm. It weighs 18 grams and has a forward-facing sensor.

A Yokogawa 51012 Digital LUX meter was used as the standard reference light meter for Experiment 1. This was because it provides highly accurate illuminance measures complying with standards set

by the International Commission on Illumination (CIE). It has a spectral response almost identical to the visible spectrum of the human eye, ranging from 400–700 nm with a peak wavelength sensitivity at 555 nm. It also measures light up to a maximum limit of 999,000 lux, well beyond expected intensities during the day, with a reported accuracy within 3% above 3,000 lux.

5.3.5 Ethical considerations

As this experimental study does not involve human subjects nor any biomaterial, approval from research ethics committee was not required prior to commencement of the experiment.

5.3.6 Data analysis

To determine intra-device reliability, light intensity (lux) measured between each pair of LDL across all environments were compared via the intra-class correlation coefficient using a two-way mixed effects, single measures model. Average lux between the LDL pairs were then calculated and used for the remainder of the analyses. For all devices and in all environments, mean lux levels were calculated as well as percentage differences between the portable light meters and the standard light meter. In each environment, Friedman's ANOVA was used to compare mean light intensity among LDLs. Bland-Altman plots were generated to assess the agreement between measures obtained from each LDL with respect to the standard light meter using both absolute and percentage differences. Intra-class and concordance correlation coefficients were calculated to compare reliability of the LDLs with respect to the standard meter. The concordance correlation coefficient, proposed by Lin et al, is a measure of agreement which considers the product of Pearson's correlation coefficient (a measure of precision) and a bias correction factor (Cb); a unit which indicates how far the line of best fit deviates from a 45° line through the origin.[685] The bias correction factor was used to compare the accuracy between each of the LDLs and the standard meter. The influence of direction on light intensity measures was assessed using a one-way ANOVA.

Calculations were performed using Statistical Package for the Social Sciences (SPSS) version 23 (IBM, US) and MedCalc version 18.5 (MedCalc Software, Belgium). Figures were generated using SPSS and Microsoft Excel. All results were considered statistically significant at an alpha level of 5%.

5.4 Results

Measurements were taken during mid-April (early autumn in eastern Australia). In general, all recording periods were between mid-day and late afternoon, during times of peak sun exposure in metropolitan Sydney, Australia. Outdoor measures were all obtained on partly cloudy days to capture a larger variation in light intensity during the recording period.

5.4.1 Intra-device reliability

All pairs of LDL devices showed an excellent level of reliability. Intra-class correlation coefficients between each of the two Actiwatch, HOBO and Clouclip devices were 0.990, 0.995 and 0.998 respectively.

5.4.2 Light intensity measures across environments

5.4.2.1 Low Indoors

Within the low indoor setting, the mean lux level across the hour as measured by the standard light meter was 217.2 ± 84.0 SD. The LDLs all recorded lower illumination values than the standard meter (Table 1). With the reductions in ambient room lighting, all LDLs were able to detect the gradual changes in illumination except the HOBO Pendant, which recorded sporadic fluctuations in illuminance inconsistent with the times at which light levels were altered (Figure 5.1).

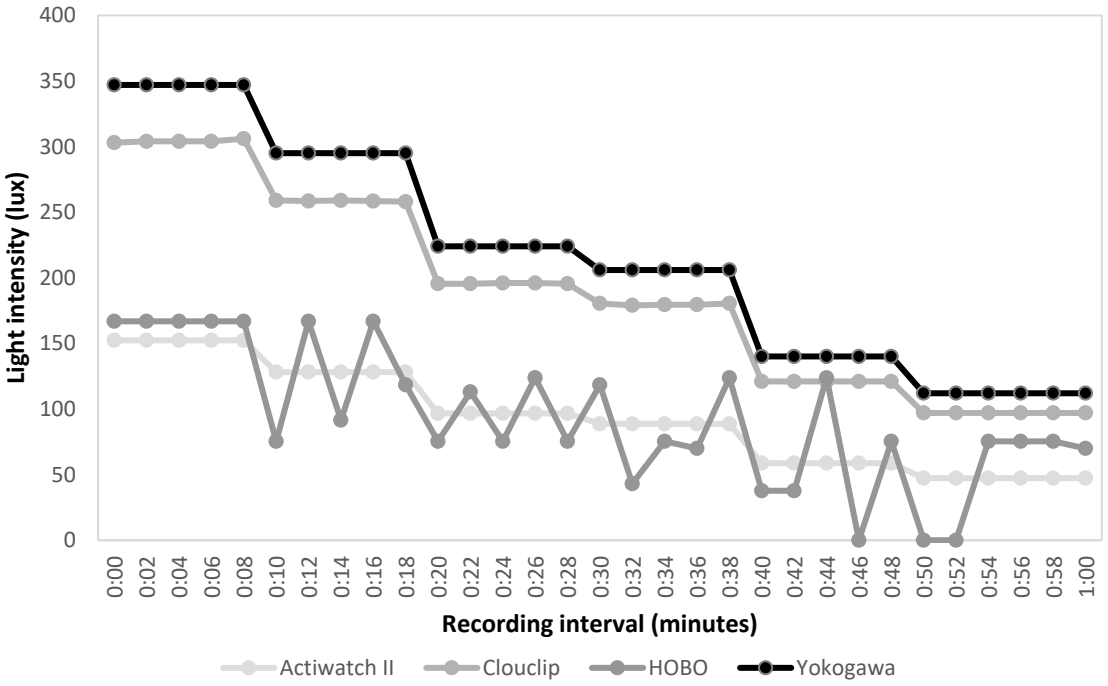


Figure 5.1: LDL recordings in a “low indoor” light environment.

5.4.2.2 High Indoors

In the high indoor setting, mean lux levels for each device were stable across the hour with mild reductions over the hour (Figure 5.2). The standard light meter recorded an average of 760.9 ± 48.5 lux, which ranged from 858 at the start of the recording interval and dropped to 680 by the end of the hour. All LDLs recorded lower illumination values than the standard meter (Table 5.1).

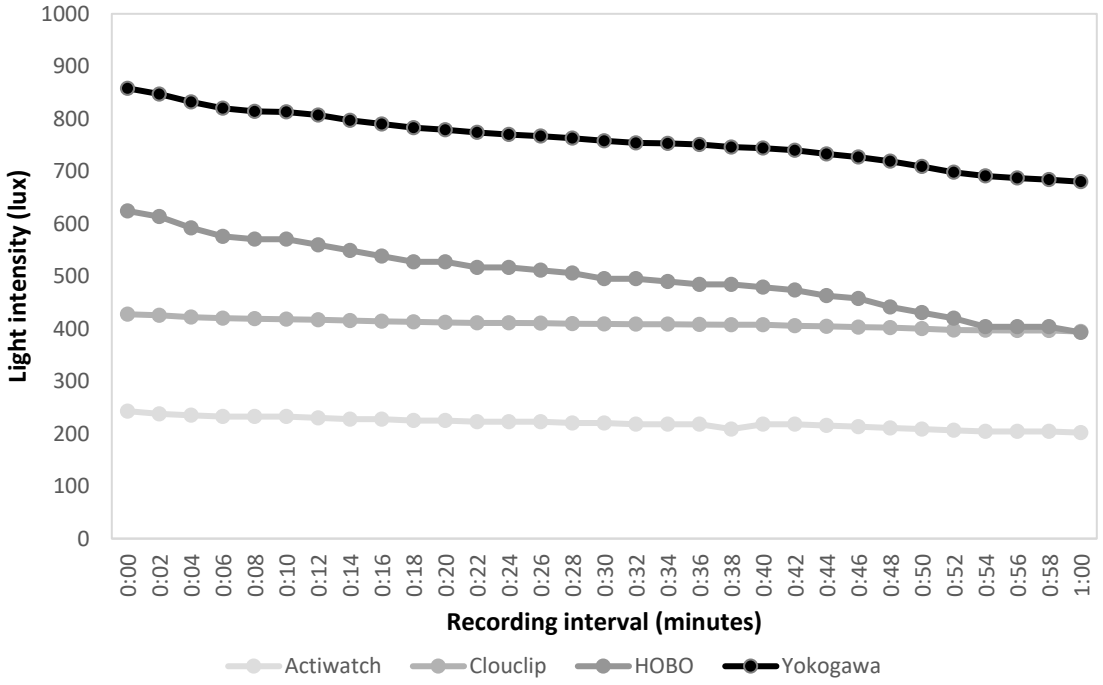


Figure 5.2: LDL recordings in a "high indoor" light environment.

5.4.2.3 Low Outdoors

For low outdoor settings, the standard light meter measured mean lux levels of 3,951.7 ± 541.4. Across the recording period, the illuminance varied more dramatically compared to indoor settings reducing from 4,710 to 3,050 lux (Figure 5.3). Unlike within the indoor settings, the illuminance as measured by the HOBO Pendant was higher than the reference meter at an average of 4,613.9 ± 620.1 lux. However, both the Actiwatch 2 and Clouclip devices measured lower illuminance values than the standard meter (Table 5.1).

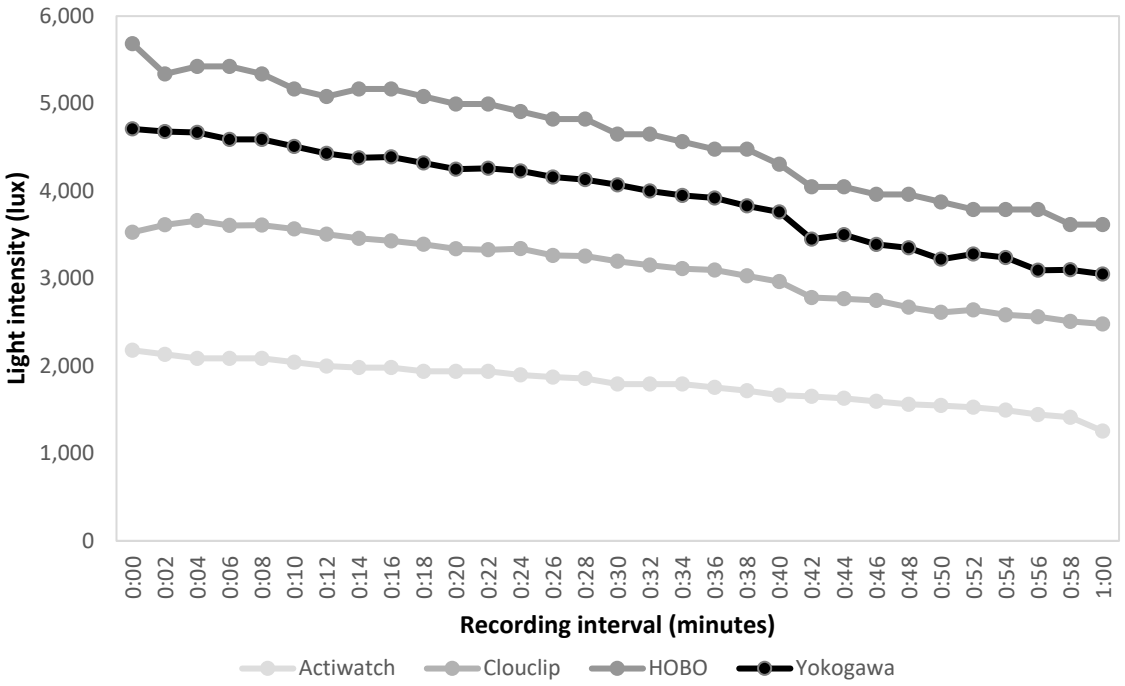


Figure 5.3: LDL recordings in a "low outdoor" light environment.

5.4.2.4 High Outdoors

In high outdoor settings, the standard light meter measured an average illuminance level of 17,932.3 ± 4,430.9 lux across the hour, which ranged from a maximum of 31,100 to a minimum of 11,000 lux (Figure 5.4). This time again, illuminance measures from the HOBO Pendant were considerably higher than the standard meter averaging at 30,544.7 ± 7,836.1 lux, while Actiwatch and Clouclip device measures were lower the standard meter (Table 5.1). There were two instances where a short period of direct sun exposure occurred which was captured by both HOBO and Yokogawa devices but failed to be recognised by the Clouclip and Actiwatch devices.

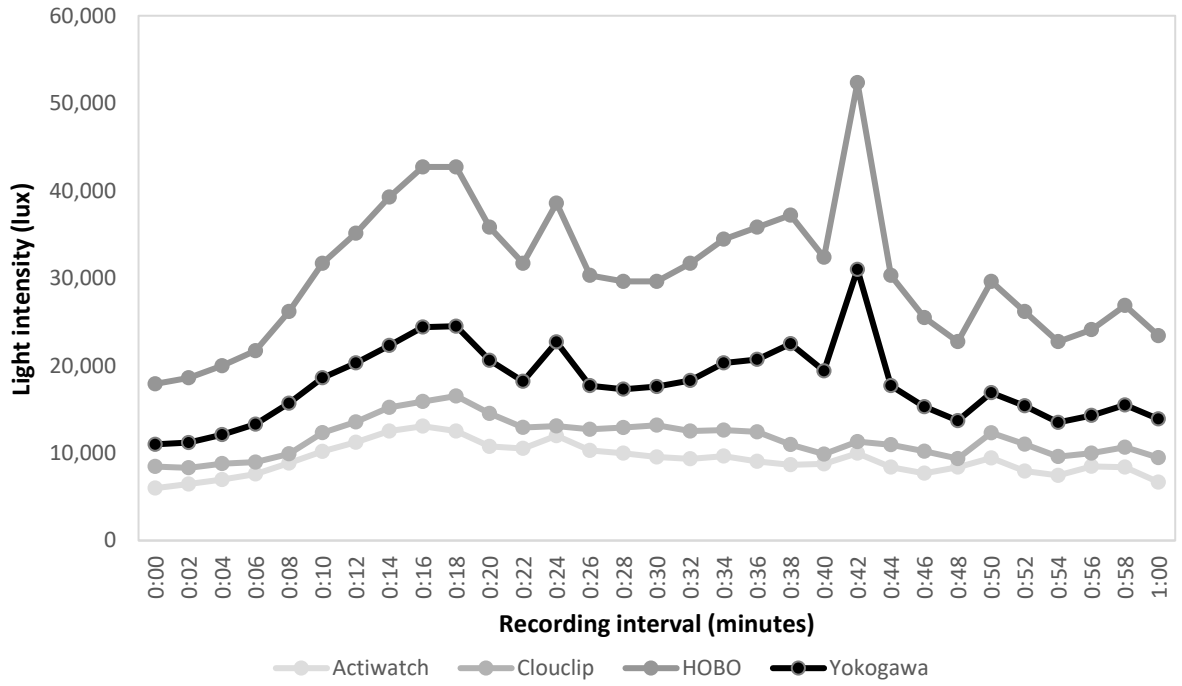


Figure 5.4: LDL recordings in a "high outdoor" light environment.

Table 5.1: Mean ± SD illuminance measures from light meter devices over a 1-hour interval across all light environments.

Environment	LDL	N	Mean (Lux)	Std. Deviation	Range	P value
Low Indoors	**Yokogawa**	31	217.2	84.0	112 - 347	<0.001
	Actiwatch	31	93.8	37.6	47.3 - 152.4	
	Clouclip	31	189.6	74.2	97 - 306	
	HOBO	31	94.1	52.0	0.00 - 166.9	
High Indoors	**Yokogawa**	31	760.9	48.5	680 - 858	<0.001
	Actiwatch	31	220.1	10.8	201.9 - 242.9	
	Clouclip	31	409.4	8.7	394.5 - 427.5	
	HOBO	31	500.5	63.5	392.9 - 624.3	
Low Outdoors	**Yokogawa**	31	3,951.7	541.4	3,050 - 4,710	<0.001
	Actiwatch	31	1,795.5	239.6	1,254.9 - 2,179.5	
	Clouclip	31	3,123.1	386.3	2,480 - 3,662	
	HOBO	31	4,613.9	620.1	3,616.7 - 5,683.4	
High Outdoors	**Yokogawa**	31	17,932.3	4,430.9	11,000 - 31,000	<0.001
	Actiwatch	31	9,250.7	1,812.1	5,987.1 - 13,070.2	
	Clouclip	31	11,633.3	2,181.1	8,310.5 - 16,523	
	HOBO	31	30,544.7	7,836.1	17,911.2 - 52,355.9	

5.4.3 Accuracy and reliability between LDLs

Figure 5.5 compares light intensity measures between LDLs via linear regression. Within all lighting environments, all LDLs recorded significantly different mean lux levels across the hour (all $P < 0.001$) (Table 5.1). Percentage differences between portable LDL measures and the standard meter remained statistically significant between separate environments (all $P < 0.001$).

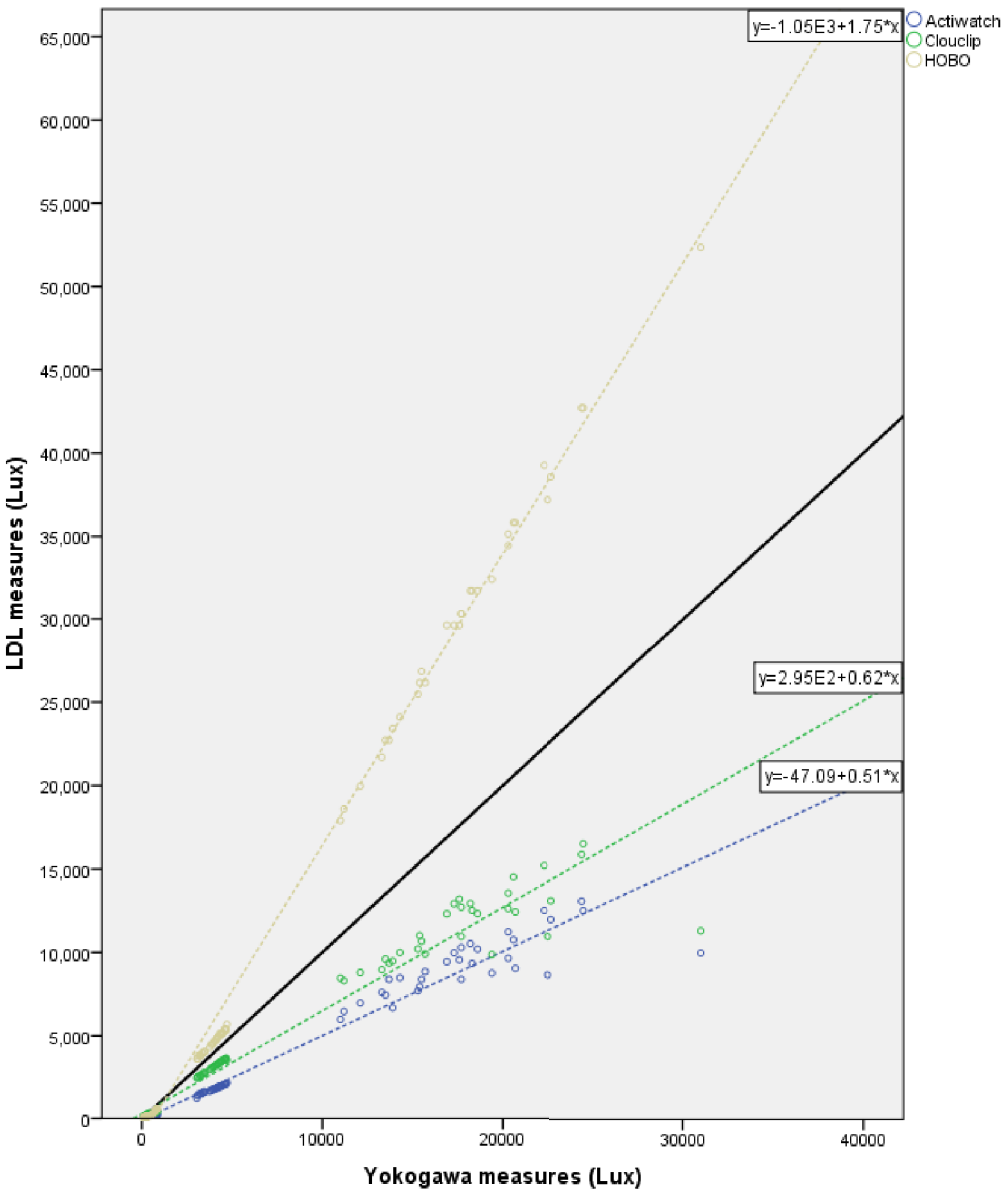


Figure 5.5: Scatter diagram of all portable LDLs measures against the standard light meter. Solid black line represents y = x for the Yokogawa measures.

Bland & Altman plots of mean differences between device measures against the standard meter displayed proportional errors across increasing lux for all devices. Both the Actiwatch and Clouclip displayed inverse proportional differences whilst the HOBO meter had an increase in differential error with higher lux as measured by the reference meter (Figure 5.6). When plotting these differences as a percentage, the errors became horizontally dispersed, confirming the presence of proportional bias (Figure 5.7). When compared to the standard meter, average mean % differences were lowest from the HOBO LDL (-0.28%) followed by the Clouclip (-28.4%) then the Actiwatch (-57.5%). 95% limits of agreement (LoA) ranged from -97.5 to -100%, -2.0 to -54.7% and 39.5 to 79.5%, for HOBO, Clouclip and Actiwatch LDLs respectively. After excluding indoor values from the HOBO device, the mean percentage difference was 43.35% (LoA: -8.9% to 95.7%).

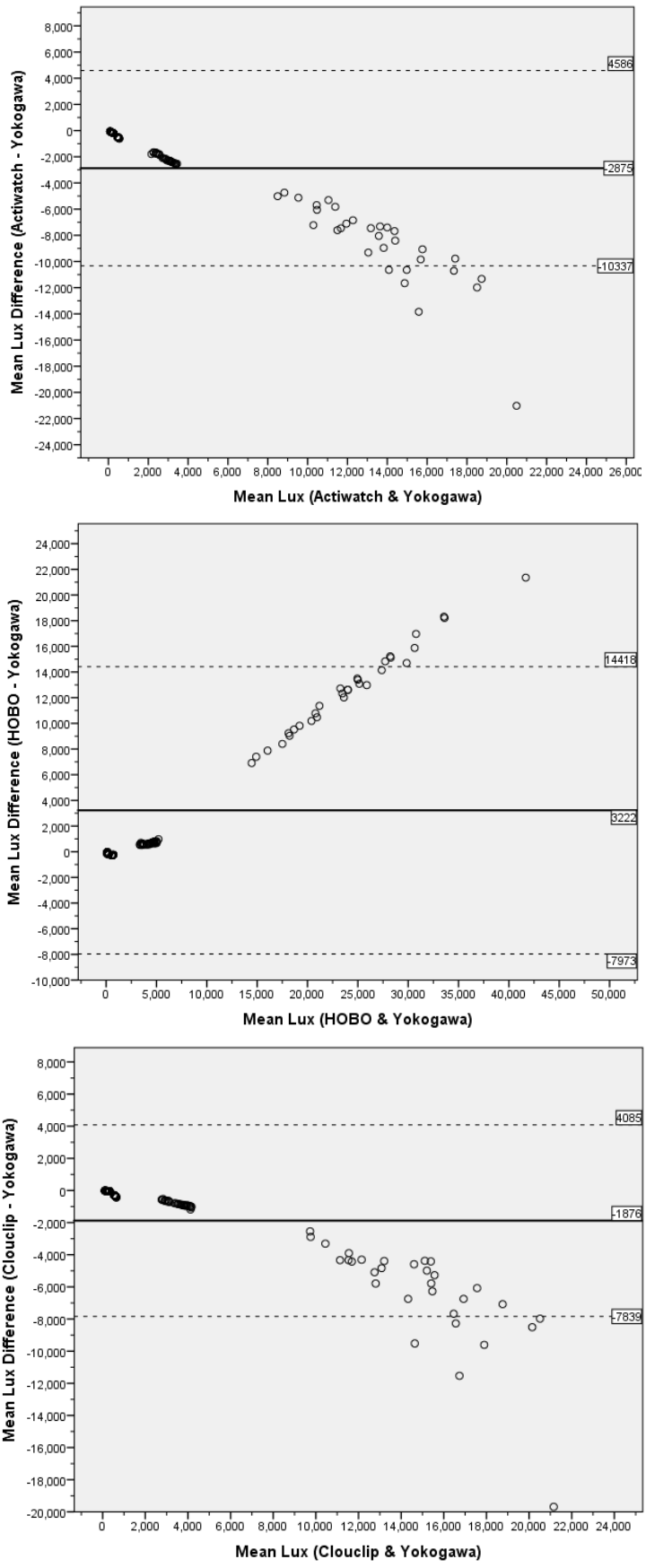


Figure 5.6: Bland & Altman plots showing mean differences for all portable LDLs against the standard light meter. Solid lines represent average mean differences, dotted lines represent 95% limits of agreement.

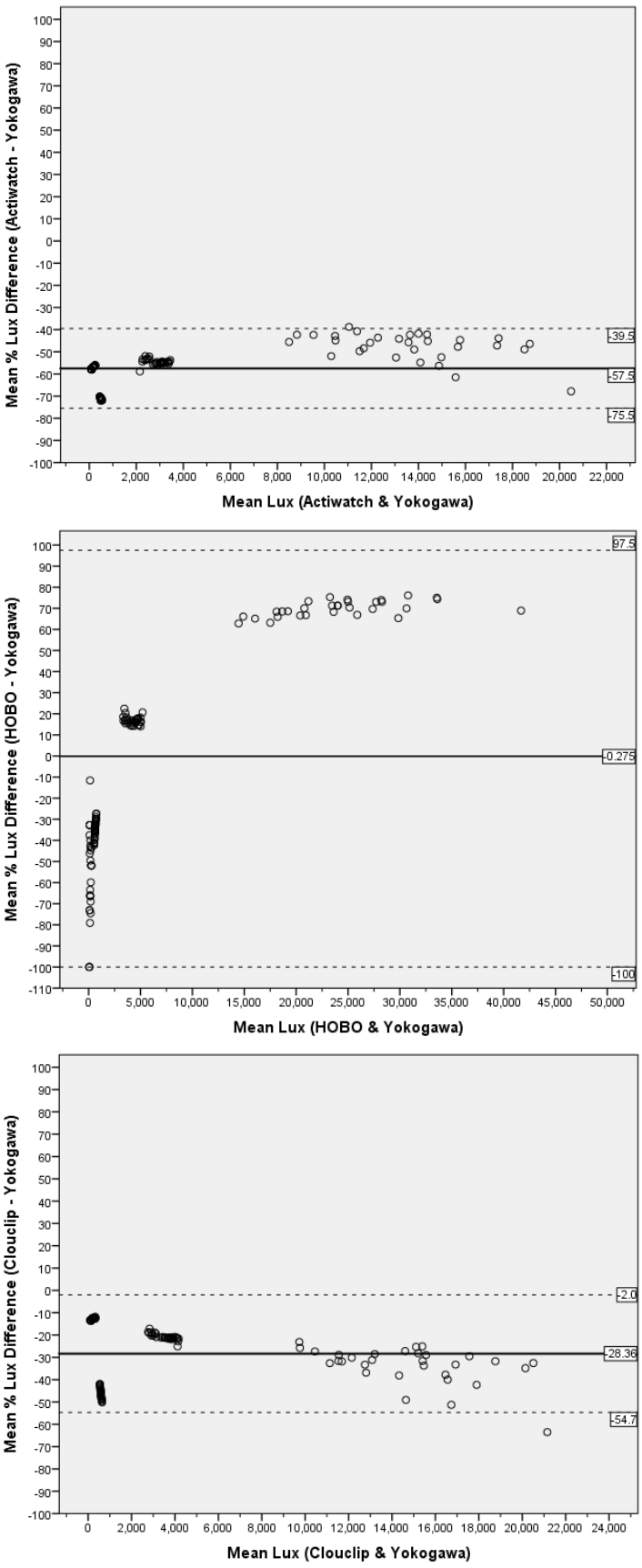


Figure 5.7: Bland & Altman plots showing mean percentage differences for all portable LDLs against the standard light meter. Solid lines represent average mean differences, dotted lines represent 95% limits of agreement.

Intra-class correlation coefficients of measures from each LDL against the standard meter demonstrated highly consistent illuminance measures, with the Clouclip being most reliable followed by the HOBO and Actiwatch (Table 5.2).

Table 5.2: Intra-class correlations (ICC) for each of the light meters with respect to the standard meter

	Yokogawa		
	n	**ICC**	**95% CI**
Actiwatch	124	0.799	0.725-0.855
Clouclip	124	0.884	0.839-0.918
HOBO	124	0.860	0.805-0.899

Levels of agreement between LDLs and the standard meter as determined by the concordance correlation coefficient was poor from all devices (Table 5.3). While all LDLs displayed a high level of precision compared to the standard meter, with Pearson's coefficients all > 0.9, accuracy scores were relatively lower, with the Clouclip being most accurate, followed by the HOBO then Actiwatch devices (Table 5.3).

Table 5.3: Concordance correlation coefficients (CCC), person's correlation coefficients (ρ) and the bias correction factor (Cb) for each of the light meters with respect to the standard meter

	Yokogawa				
	n	**CCC**	**95% CI**	**ρ (precision)**	**C_b (accuracy)**
Actiwatch	124	0.716	0.725-0.855	0.983	0.729
Clouclip	124	0.847	0.839-0.918	0.978	0.866
HOBO	124	0.822	0.805-0.899	0.998	0.824

5.4.4 Influence of measurement direction

For all LDLs, significant differences in light intensity were seen between LDLs facing different directions (all P < 0.001) (Figure 5.8). For the Actiwatch LDLs, north-facing devices recorded significantly higher lux (16,167) than upwards-facing devices (8,099) (P < 0.001). Actiwatches facing east, west and south all recorded similar lux levels (P = 0.705) and were all significantly lower than upwards-facing devices all P < 0.001. For the HOBO LDLs, north-facing devices also recorded significantly higher lux (56,095) than upwards-facing devices (44,778). East- and west-facing LDLs recorded similar lux (22,143 vs 19,141 respectively, P = 0.780), while only west- and south-facing LDLs were similar (19,141 vs 13,482 respectively, P = 0.206). For Clouclip LDLs, north- and upwards-facing LDLs recorded similar lux levels (20,549 vs 16,628 respectively, P = 0.075). Meanwhile, lux from east-, west- and south-facing LDLs were similar (5,424 vs 4,425 vs 4,289 respectively, P = 0.940) but significantly lower than from north- and upwards facing LDLs (all P < 0.001).

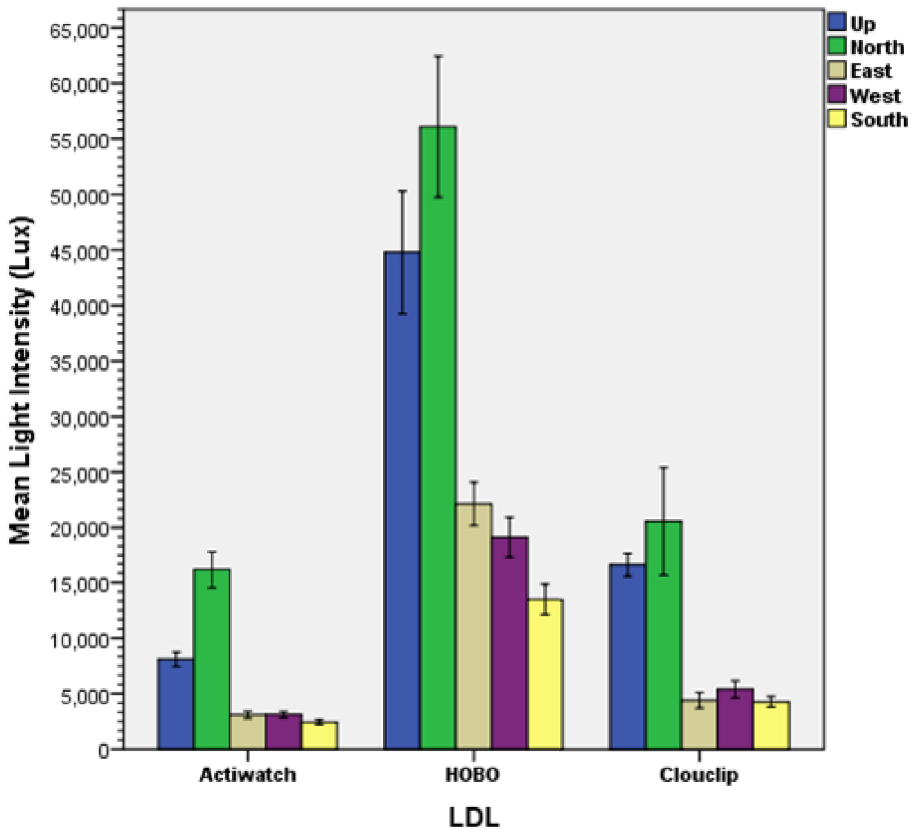


Figure 5.8: Mean light intensity recorded by each LDL when orientated in different directions. Error bars represent 95% CI's

Variations in light intensity measurement from the Clouclip LDL were captured within the vertical plane (Table 5.4). In both indoor and outdoor environments, light intensity was greatest when the LDL was orientated vertically (skywards), followed by 45° upward, horizontal and then 45° downward.

Table 5.4: Angular light intensity measures from the Clouclip M2 within an indoor and outdoor environment

Direction of LDL	Light intensity (lux)	
	Indoor Environment	Outdoor Environment
90° upward (vertical)	221	25529
45° upward	199	9192
0° (horizontal)	104	4463
45° downward	55	4218

5.5 Discussion

In this study, measures of light intensity from portable LDLs were collected across a variety of environments ranging from low indoor to high outdoor light and were compared to measures obtained from a standard light meter calibrated for industrial use. Overall, while each of the portable devices were relatively reliable and consistent, they were inaccurate and produced proportional errors with increasing illumination. There was a tendency for the Clouclip and Actiwatch devices to underestimate true light intensity values, whereas measures from the HOBO LDL had a tendency to overestimate light intensity. These results suggests that measurements of light intensity obtained from such portable devices do not truly reflect the amount of light exposure experienced by the wearer. Differences in errors between individual LDLs also suggest that measures obtained from different devices may not be directly comparable. Additionally, measurement variations occurring between different directions within similar devices suggests that device positioning is another major factor that determines the level of light intensity measures obtained.

Our results are in agreement with two studies which have previously compared light intensity values between portable LDLs to a standard reference light meter.[670, 684] Joyce et al compared light exposures from the Actiwatch 2 LDL to another laboratory-standard light meter, the ILT1700 photometer (International Light Technologies Inc., Massachusetts, United States) and found that the Actiwatch LDL under-reported true illuminance values by approximately 75% under ~20,000 lux of white light and 54% when under ~30,000 lux of artificial sunlight.[684] Since the Actiwatch measures were precise and linear (r^2 = 0.99) they proposed that true illuminance values could be transformed from Actiwatch measures by using a simple correction factor. Despite using more natural light sources in our study, we found the Actiwatch to display similar characteristics, with the LDL displaying a high level of precision (r^2 = 0.97) yet underestimating lux by a mean difference of 57.5%.

In a similar study, Howell et al compared light intensity measurements from Actiwatch 2 and Clouclip M2 devices to a Hagner S2 photometer (Hagner, Sweden) and also found that both portable LDLs

had a tendency to underestimate lux, with absolute mean differences between the Actiwatch and photometer, and Clouclip and photometer at 430.92 and 79.35 lux, respectively. While similar patterns were seen in our study, we found larger absolute mean differences in lux error from the two devices (2,875 & 1,876 lux respectively) and the standard meter. This difference was likely due to the fact that their maximum illuminance range was below 10,000 lux compared to our study which included illuminance ranges up to 31,000 lux from the standard light meter. Evidence of proportional biases occurring with increasing illuminance in both studies further supports this claim, however only limited comparison to our findings is possible as they did not report proportional differences.

For the HOBO LDL, while there has not been data comparing outputs from it to a standard meter, relative comparisons can be made from studies comparing the HOBO device to other portable LDLs. In a small pilot study where 10 subjects simultaneously wore both Actiwatch and HOBO LDLs, Read et al found the HOBO LDL tended to record higher light intensity values than the Actiwatches. Differences in light intensity between these two devices increased in higher lighting environments which is also suggestive of the proportional bias seen in our study, however again proportional differences were not reported for comparison. While their experimental design was not highly controlled and measurement variations may have been influenced by differences in sensor positioning (wrist-worn vs necklace), their findings are largely in agreement with our results, which indicate that HOBO LDLs overestimate light intensity.

Differences in measured light intensity seen between portable LDL devices is likely attributed to the internal sensor variations within each device. In particular, the HOBO Pendant has a reported spectral response range much broader than the visible spectrum of the retina, extending further into both ultraviolet and infrared wavelengths between 150–1,200 nm and having a peak wavelength sensitivity of 900 nm. This is in comparison to the standard light meter, which was calibrated with a spectral response curve matching the human eye at 400–700 nm. This the likely the source of

overestimation from the HOBO Pendant given that the wavelength of light from sun rays can range between 280–2,800 nm.[686] On the other hand, the Actiwatch has a spectral response range closer to the reference sensor, allowing it to capture more similar light outputs to what the human eye experiences. Wavelength sensitivity ranges have not been publically reported for the Clouclip, however our findings suggest they are likely similar to the Actiwatch specifications.

While not investigated in this study, differences in sensor size is another factor possibly involved in producing differences in light output. Sensors contained within portable LDLs have a considerably smaller surface area than those for standard industrial use. In theory this should not influence light intensity readings, since the unit of lux is a concentration measure of luminous flux per unit area (i.e. 1 lux = 1 lumen per m^2). However, it is likely that the smaller sensors contained within portable LDLs are not capturing light from a large field of view, whereas the standard sensor has been designed to oblique sources of light. If this is the case, it indicates that sensor positioning also plays a significant role in determining the accuracy and reliability of light intensity measures. While our first experiment was controlled by the fact that all sensors were positioned in the same orientation, larger errors could be expected during real world use of these devices as they are all mounted at different locations and orientated at different directions on the human body. No studies have yet to report the role of directionality when using wearable LDLs. Experiments 2 and 3 confirmed these speculations by demonstrating that directionality is a major factor influencing light intensity readings. Light exposure at and below the horizontal plane are considerably lower than what is potentially available from within the environment. Since these directions are where the line of sight is typically orientated throughout the day, it is highly likely that the range light exposures experienced by the eye is much lower than what may be expected from outdoor environments. This effect of directionality may partially explain why some studies have reported relatively low daily light intensity measures from LDL readings.[635] Additionally, since the anti-myopigenic effects of light appears to occur at a local level on the retina,[687] this means that spectacle mounted devices such as the Clouclip would be most appropriate for the investigation of causal relationships between light

and myopia, as the device remains in line with the direction and angle of viewing. However, epidemiological myopia studies using this device has been limited at this time.[638, 688]

One other consideration is that light intensity has not been the primary variable measured in human myopia studies, which has predominantly focused on time spent outdoors as a risk factor for myopia. Although this was driven by the fact that early studies used questionnaires to capture risk, recent studies using LDLs have continued to investigate time outdoors by using a light intensity threshold of 1,000 lux. Thus, while non-spectacle mounted LDLs may not accurately capture ocular light intensity, it is not clear how large an effect this error has on objective measurements of time spent outdoors, particularly since it is focussed on differentiating light intensity at lower ranges where less measurement error occurs. Some signs of this can be seen in Read et al's study, where small differences in outdoor light exposure time were seen between LDLs despite having recorded relatively large differences in light intensity.[636] On the other hand, Bhandari et al compared measurements of daily time outdoors between Clouclip and Actiwatch devices from 25 young adults who wore both devices over one week and found that time outdoors measured by the Clouclips were significantly greater than from Actiwatch devices (0.9 vs 0.7 hours/day, P = 0.02).[689] Given these inconsistencies, and that no other studies have examined measures of time outdoors with respect to HOBO LDLs, further comparative real world studies are needed.

The major strengths of this study were that sensors from various LDLs were able to be directly compared across a wide range of lighting environments. Previously conducted studies comparing LDLs examined devices in their intended orientation to simulate real world use, which may mask underlying differences in sensor capabilities. Light intensity data from each LDL was captured from two devices, allowing intra-device variations to be controlled for. Furthermore, the strong correlation seen between the pairs of each LDL indicates that there was uniform light exposure across the testing surface of the LDL mounting block. Limitations of this study was that it was not conducted in a laboratory setting, but in the real world, hence the exact range of light exposures

available for capture was not able to be controlled for by the investigators. In this study the maximum light exposure we encountered was 31,000 lux, which occurred on a partly cloudy day in a high outdoor setting. Higher light intensities well above 100,000 lux can be expected on more sunny days which would potentially lead to larger absolute errors not captured by our analysis, however this is unlikely to change our findings significantly as we examined percentage errors.

In conclusion, our study identifies inconsistencies between sensor configurations contained within portable illuminometers and provides insight on the relative differences in measurements obtained from popular light data logging devices used in myopia research. While they are not a direct substitute for a standardised photometer device in industrial settings, portable LDLs may still be considered a valid tool for measuring light intensity for epidemiology, however objective measures of intensity should not be taken at face value, and the inherent differences between light meter devices utilised should be considered when interpreting data found from such studies. Further studies are needed to examine the impact of these differences during real world use and when interpreting other light exposure parameters used in myopia research such as time spent outdoors.

Chapter 6: Real World Comparison of Outdoor Exposure Parameters between Wearable Light Data Loggers

6.1 Abstract

Purpose: To investigate the real world comparability of wearable light data loggers (LDLs) used to capture light exposure as a risk factor for myopia.

Methods: Fifty nine university students wore three LDLs (Actiwatch 2, HOBO Pendant UA-002-64 and Clouclip M2) simultaneously over 4 days (2 weekdays and 2 weekend days). Various light exposure parameters (absolute light intensity, daily outdoor time, mean daily intensity of outdoor light and mean daily outdoor frequency) from the LDLs were compared between devices alongside two previously used subjective measures of outdoor activity, a questionnaire and a diary.

Results: Light intensity measurements between pairs of portable LDLs were all poorly correlated (r = 0.070–0.225). Measurement errors between pairs of LDLs increased in proportion with light intensity with the HOBO LDLs displaying a tendency to overestimate lux when compared to Actiwatch and Clouclip devices (average mean differences 8,000 and 8,213 lux respectively). Daily outdoor time derived from LDLs were moderate-strongly correlated with each other (r = 0.645–0.805) and were moderately correlated with self-reported outdoor time from a diary (r = 0.473–0.593) however, objectively derived daily outdoor time from all LDLs were significantly lower than self-reported outdoor time (all $P < 0.05$). Mean daily intensity of outdoor light determined between Actiwatch and Clouclip LDLs were similar ($P = 0.086$) but were lower than measures from the HOBO LDL (both $P < 0.001$). Mean daily outdoor frequency between HOBO and Clouclip measures were higher than from the Actiwatch as well as diary measures (all $P < 0.001$).

Conclusion: Parameters of outdoor exposure obtained from different methods have limited direct comparability as they capture light across different areas of the body. These characteristics must be considered when selecting an appropriate tool to capture myopic risk factors and when comparing exposure values obtained using different methods.

6.2 Introduction

Several epidemiological studies have made it clear that increased outdoor time plays an essential protective role in myopia development.[564, 645] While these studies have largely focussed on the temporal aspect of outdoor time, the light-dopamine theory suggests that it is in fact the higher light exposures obtained from outdoor environments that mediate the effects of outdoor time.[487] Several animal studies confirm this, finding that modulation of light intensity can influence myopia development,[16, 567, 569] with higher levels of light intensity (lux) providing greater levels of protection in a dose-dependent fashion.[14] In contrast to human data, there has been limited investigation into the temporal effects of light exposure in animals, however, some available data does indicate that exposure time and frequency may also play a major role.[575] This suggests that both aspects of light exposure (duration and intensity) need to be determined with greater statistical power to accurately capture an individual's exposure and determine their personal level of risk. For investigators, this would help identify protective thresholds for myopia protection and determine the role of time outdoors against myopia progression that currently remains unclear in humans.

Before this can occur, changes in the methodology used to capture myopic risk factors are needed. Until now, questionnaires have been the predominant tool used by investigators to capture outdoor time. While several detailed questionnaires are available, such as those derived from the Sydney Myopia Study and the WHO developed questionnaire, it is not possible to determine light intensity via subjective means. Recently investigators have begun to utilize a variety of portable light data loggers (LDLs, also known as light meters) in order to objectively capture individual light exposures. Using the Actiwatch 2 device (a wrist-worn LDL), Read et al reported that myopic children spent less time in light environments brighter than 1,000, 2,000 lux and 5,000 lux than non-myopic children.[566] Subsequently they found in an 18-month longitudinal study that time spent in environments brighter than 3,000 lux and 5,000 lux were associated with reductions in axial eye growth.[635] Later, during the ROCT711 study, which used the HOBO Pendant meters, Wu et al reported that children who were

exposed to > 200 minutes per week of lighting levels of ≥ 1,000 lux, or ≥ 3,000 lux, experienced significantly less myopic shifts compared to those spending < 125 minutes per week exposed to these light intensities.[374] More recently in a cross-sectional study using the Clouclip, a spectacle mounted LDL, Wen et al reported that myopic children spent less time in environments > 3,000 lux and > 5,000 lux per day, compared to non-myopic children.[638] On the other hand, Dharani et al,[633] Ostrin et al[637] and Li et al,[640] failed to detect differences in light exposure patterns between myopic and non-myopic children using HOBO, Actiwatch and FitSight LDLs respectively. As a meta-analysis to consolidate these inconsistencies has not been provided, the evidence in this field remains unclear.

In Chapter 5, it was established through experimental validation, that light intensity measures from different portable illuminometers have significant variations occurring at a sensor level. These differences have the potential to produce errors in risk factor capture in real world use and may have contributed to the inconsistencies seen in human studies investigating the relationship between myopia and light exposure. This may also restrict the validity of pooled study findings through meta-analysis, by introducing methodological heterogeneity. However, the real-world implications of these variations have not been confirmed. From Chapter 4, we identified that there are more aspects to human light exposure than just absolute light intensities alone. This aligns with current evidence which suggests that rather than just light intensity, it also the duration of light exposure which is associated with myopia prevention; although the threshold requirements for myopia protection have yet to be confirmed (likely around 3,000 lux and a minimum of 2 hours per day).[638] In terms of light intensity, given this relatively low threshold for a clinical effect, the differences in absolute light intensity measured between LDLs identified in Chapter 5 may not impact the association between light intensity and myopia to a significant degree, since the errors occur proportionally at much higher light levels (10,000 lux and beyond). On the other hand, in terms of light exposure duration, an experimental design study does not allow for comparison of outdoor activity and light exposure patterns, therefore further validation is needed to determine the

comparability of these variables in real world use or determine whether measures from different devices can be consolidated by using adjustment factors.

In this chapter, human validation and comparison of light exposure measures was conducted, simultaneously capturing measures across multiple portable LDL devices, alongside two previously validated methods of subjective time outdoors measures; a questionnaire and a diary. The relationship between objective light exposure, near-work and refractive status was also examined as a secondary outcome.

6.3 Methods

Detailed study methodology has been described in Chapter 2.

6.3.1 Study recruitment

This study was a cross-sectional observational study examining objectively measured light exposures in young adults from three separate portable LDLs: the Actiwatch 2 (Respironics Inc., Pennsylvania, USA), the Clouclip M2 (Glasson Technology Co., Ltd, Hangzhou, China) and the HOBO Pendant UA-002-64 (Onset Computer Corporation, Massachusetts, USA). Participants were recruited from students within the University of Technology, Sydney.

6.3.2 Examination process

Participants were deemed to be myopic if they self-reported themselves to be short-sighted in at least one eye and either 1) presented with a refractive correction with a spherical equivalent refraction (SER) of ≤ -0.75 D and scored a corrected logMAR VA of 0.20 (6/9.5) or better, or 2) scored a logMAR VA worse than 0.20 (6/9.5) and subsequently improved to 0.00 (6/6) or better under a pinhole occluder. All other participants who failed to be categorised as myopic were considered to be non-myopic.

6.3.3 Outdoor activity questionnaire

At the first study visit, participants completed an outdoor activity questionnaire derived from the WHO Outdoor Activity questionnaire (Appendix 6). Participant characteristic data gathered from the questionnaire included: sex, ethnicity, parental myopia status, current spectacle/contact lens use, age of onset of refractive error and self-reported reading distance. Subjectively measured daily outdoor time and near work times from the questionnaire were determined separately for weekdays and weekends and transformed into a weekly average using the formula [(hours spent on weekday) x 5 + (hours spent on weekend day) x 2] / 7. Activities that were performed outside a building during the day, such as riding bicycles, park visits, walking around the neighbourhood, and outdoor sports, were all classified as outdoor activities. Indoor activities were defined as inside a building or an enclosed space or travelling in a car or train. Near work time was calculated from the duration of time spent studying and reading and writing for leisure or work.

6.3.4 Light intensity measurement

Participants were instructed to simultaneously wear three portable LDLs (Actiwatch 2, HOBO Pendant & Clouclip M2) during waking hours over four consecutive days (two weekdays and two weekend days). All LDLs were configured to automatically capture light intensity values (lux) at 2-minute intervals.

6.3.5 Activity diary

In conjunction with wearing the LDLs during the study period, participants documented their daily activities into a 24-hour diary (Appendix 4). For each diary entry, participants specified whether each activity was performed outdoors or indoors and included start and end time of each activity in order to unite data with LDL measures.

6.3.6 Focus groups

Following four days of data capture, participants attended a small focus group of up to five individuals. The focus group gathered feedback on participant's views on the utility of the

questionnaires, diary and individual devices. At the conclusion of the focus groups, participants were given a post-study survey where each of the devices were ranked based on two separate criteria 1) device wearability: how comfortable the devices were and 2) device invasiveness: to what extent did device wear interfere with their daily activities (Appendix 8).

6.3.7 Ethical considerations

This study adhered to the tenets of the Declaration of Helsinki. Ethical approval for this study was obtained from the institutional review board from the University of Technology, Sydney prior to commencement of the study (HREC# ETH17-1765 & ETH20-4870). Written informed consent was obtained from all participants prior to study enrolment and study procedures.

6.3.8 Data analysis

After the four days of the study period, light intensity measurements from each of the LDLs were directly obtained via their corresponding software programs. Measurements recorded between 6:00 and 20:00 were included in the analysis as this captured daylight hours for all days during the study and a majority of the waking hours spent by the participants. Light intensity measures from each LDL were then matched at every two-minute interval and collated with diary logs of indoor and outdoor state. Working distance measures from the Clouclip device were averaged over two minutes as the device logged near work at five-second intervals.

A second pool of data was generated, where raw light intensity data from each LDL was adjusted using scaling factors derived from Chapter 5. These were adjusted using the following formulas:

- **Adjusted Actiwatch Lux** = (Raw Actiwatch Lux) / (100 **- 57.5**) * 100
- **Adjusted Clouclip Lux** = (Raw Clouclip Lux) / (100 **- 28.36**) * 100
- **Adjusted HOBO Lux** = (Raw HOBO Lux) / (100 + **43.35**) * 100

All analyses and calculations were performed using the raw dataset, with additional analysis using adjusted data where specified.

For the direct comparison of light intensity between LDLs, measurements from all participants were pooled. To compare light intensity within outdoor environments, only intervals where at least one device recorded a light intensity value of ≥ 1,000 lux were included. Lux values of < 10 were considered to be invalid and the interval was excluded as it indicated that the particular LDL was not in use. This left 2,760 intervals, equivalent to 92 hours in total, where the three LDLs were considered to be simultaneously exposed to an outdoor environment. From this pool of data, Pearson's correlation coefficients were calculated and scatter plots and a Bland-Altman plot were generated. Wilcoxon signed rank tests were used to compare light intensity between pairs of each LDL using both raw and adjusted data.

For the comparison of agreement, all intervals where all three LDLs recorded a minimum of 10 lux were included for analysis. This provided a total of 11,525 intervals or 384 hours where the LDLs were considered to be in valid use. The threshold of ≥ 1,000 lux was used to distinguish between indoor and outdoor states, based on previous studies and data presented in Chapter 5. Cohen's kappa statistic was used to determine the interrater reliability of the LDLs alongside diary measures of indoor/outdoor state. This was performed using both the raw and adjusted LDL data.

There were 135 valid study days where all three LDLs simultaneously recorded light exposure. Pearson's correlation coefficients and related-samples Wilcoxon signed rank tests were used to compare continuous outcomes between LDLs (time outdoors, mean outdoor light intensity and daily outdoor frequency). Diary measures of time outdoors and daily outdoor frequency were also included for comparison. For each individual participant, daily time spent outdoors from each LDL was determined by the number of intervals spent ≥ 1,000 lux, mean outdoor light intensity was determined by the average illuminance values of all intervals ≥ 1,000 lux and daily outdoor frequency was determined by the number of indoor-outdoor transitions. To account for fluctuations in light intensity in outdoor environments, groups of indoor-outdoor transitions, which were

separated by less than 10 minutes, were considered to be a single instance of outdoor exposure (Figure 6.1).

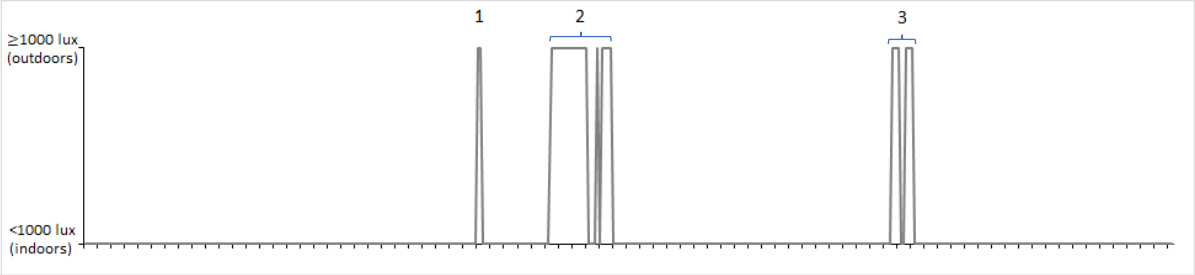


Figure 6.1: Example of a subject's light exposure on one day. Spikes in graph represent an indoor-outdoor transition. Ticks on x-axis represent 10-minute intervals. While the LDL recorded 6 indoor-outdoor transitions, the subject was considered to have experienced 3 instances of outdoor exposure for this day rather than 6.

35 subjects with data from all three LDLs from at least 1 weekday and 1 weekend day were included to compare average weekly outdoor and near work time determined between subjective (questionnaire's & diary) and objective methods (LDLs). Average weekly time outdoors was calculated for each subject using the time spent ≥ 1,000 lux on weekdays and weekend days and applying the formula [(hours spent on weekday) x 5 + (hours spent on weekend day) x 2] / 7. Average weekly near work time was calculated in the same fashion, using a threshold working distance of ≤ 60 cm. Related-samples Wilcoxon signed rank tests were used to compare each measure for both variables.

From subjects with data from all three LDLs, demographic and biometric data were compared between myopic and non-myopic subjects, using independent samples t-tests for continuous variables and chi-squared tests for categorical variables. As measures of axial length and corneal radius between right and left eyes were highly correlated ($r = 0.957$ & 0.961 respectively, $P < 0.001$) data was presented from right eyes only ($n = 35$). No subjects had unilateral myopia in their left eye. Mann-Whitney U tests were used to compare differences in outdoor exposure parameters and near work times between myopes and non-myopes as well as between subjects who participated before and after the advent of the COVID-19 pandemic.

Focus group discussions were recorded and transcribed verbatim for qualitative analysis. Transcripts presenting similar points were then organised and grouped in order to develop a number of relevant themes. Factors of wearability and invasiveness between LDLs determined by the post-study survey was compared using a Friedman test.

All statistical analyses were performed in SPSS (version 25, IBM Corp, Armonk, NY, USA). Normality of all variables were determined by the Kolmogorov-Smirnov test. All results were considered statistically significant at an alpha level of 5%.

6.4 Results

6.4.1 Participant characteristics

Study recruitment began in August 2019 and ended in May 2021. All study data was conducted during the academic calendar of spring and autumn semesters. There were fifty nine participants enrolled into the study. Of these, 36 were female (61%) and 23 (39%) were male, with an average age of 23 ± 2.33 years (range: 19–31 years). Seven of the participants were of 'White' ethnicity, 39 as 'East Asian' and 13 were of 'Other' ethnicity. Thirty six participants were considered to be myopic and the remaining 23 were considered to be non-myopic.

6.4.2 Comparability of light intensity measurements

Figure 6.2 illustrates the comparability of light intensity measurements between LDLs during real-world use using scatter plots. There was a weak positive correlation in light intensity measurements between the HOBO Pendant and Actiwatch LDL's ($r = 0.225$, $P < 0.001$). Correlations between the HOBO LDLs and the Clouclip LDLs were also significant, but extremely weak ($r = 0.093$, $P < 0.001$). Meanwhile, light intensity measurements between the Clouclip and Actiwatch LDLs were not significantly correlated ($r = 0.070$, $P = 0.695$). At each recording interval, light intensity between all pairs of LDLs were significantly different ($P < 0.001$).

Figure 6.3 illustrates the agreement in light intensity measurements between LDLs using Bland-Altman plots. All pairs of LDLs displayed proportional biases in recording light intensity, with increased differences between devices at brighter environments. The largest differences were seen when comparing the Actiwatch and Clouclip against the HOBO Pendant, with average mean differences in light intensity of 8,000 and 8,213 lux respectively. Against the HOBO pendant, 95% limits of agreement (LoA) of the LDLs were also high, at -40,910 to 56,911 lux and -41,808 to 58,234 lux respectively. Meanwhile, the average mean difference between the Actiwatch and the Clouclip LDLs was -212 lux and the 95% LoA were -12,644 and 12,218 lux.

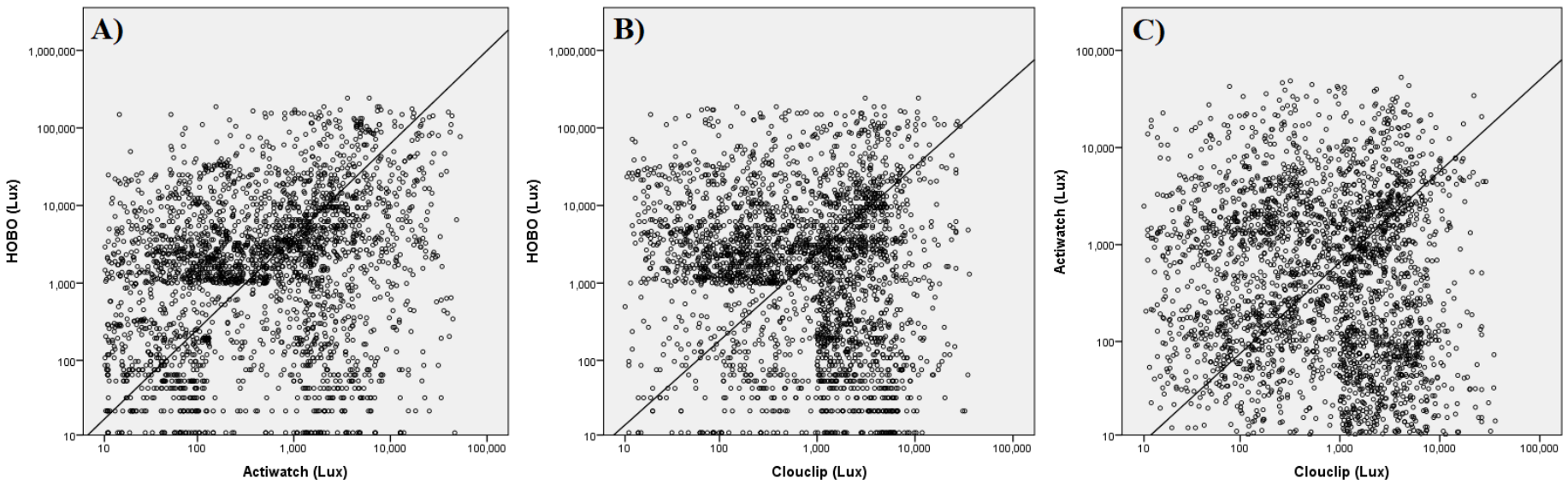


Figure 6.2: Scatter plots comparing light intensity readings between the A) HOBO and Actiwatch LDLs, B) HOBO and Clouclip LDLs and C) Actiwatch and Clouclip LDLs. Dotted lines represent the 95% limits of agreement, solid line represent the mean difference between the two LDLs

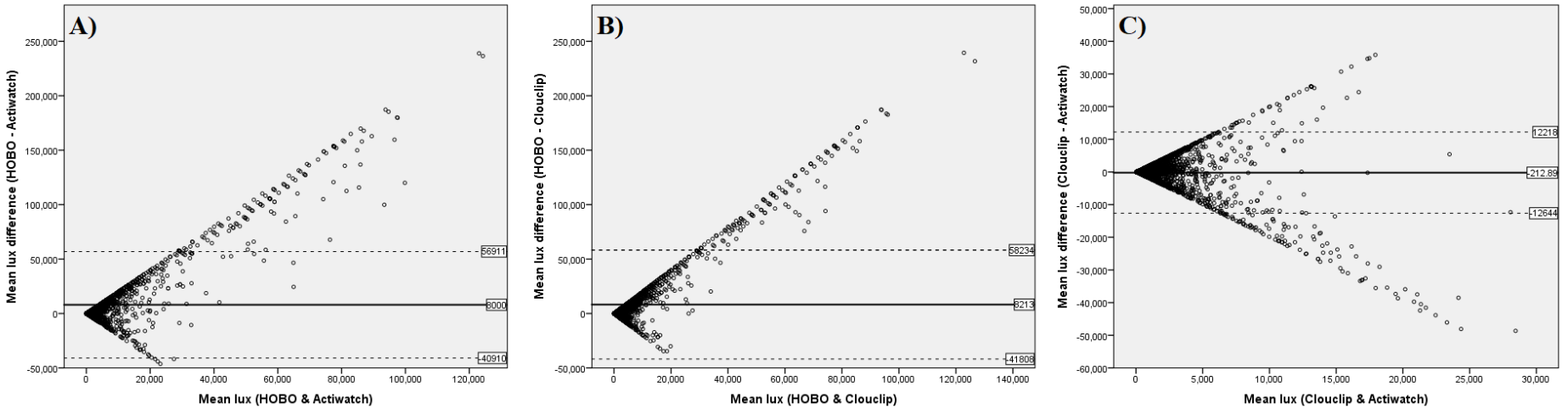


Figure 6.3: Bland-Altman plots comparing the agreement in light intensity readings between the A) HOBO and Actiwatch LDLs, B) HOBO and Clouclip LDLs and C) Actiwatch and Clouclip LDLs. Dotted lines represent the 95% limits of agreement, solid line represent the mean difference between the two LDLs

6.4.3 Agreement in determining outdoor state

Table 6.1 presents Cohens kappa (κ) coefficients for the inter-rater reliability for the determination of outdoor state at each recording interval during the study. There was a fair level of agreement in outdoor state from both the Actiwatch and Clouclip LDLs, when compared to self-reported measures from the outdoor activity diary (κ = 0.377 & 0.312 respectively). There was also a moderate level of agreement between the HOBO LDL and the diary (κ = 0.421). Between LDLs, the Actiwatch and the Clouclip demonstrated the highest agreement (κ = 0.432) followed by the Clouclip and HOBO (κ = 0.378), and then the Actiwatch and HOBO (κ = 0.330). Minimal improvements in agreement between the LDLs were seen when using adjusted LDL measures to determine indoor-outdoor state, except between the diary and HOBO LDL and between the Actiwatch and Clouclip LDL.

Table 6.1: Inter-rater agreements for outdoor status between LDLs and the outdoor activity diary using Cohen's kappa (κ).

	Cohen's kappa (κ)	
	Raw LDL measures	**Adjusted LDL measures**
Diary vs Actiwatch	0.377	0.422
Diary vs HOBO	0.421	0.412
Diary vs Clouclip	0.312	0.334
Actiwatch vs HOBO	0.330	0.511
Actiwatch vs Clouclip	0.432	0.367
HOBO vs Clouclip	0.378	0.398

6.4.4 Comparability of daily time outdoors, mean daily light intensity and daily outdoor frequency

6.4.4.1 Time outdoors

Daily time outdoors between all the devices and the diary were significantly correlated with each other (all P < 0.001). Strong positive correlations were seen between daily time outdoors determined from the Clouclip and Actiwatch (r = 0.805), as well as the Actiwatch and HOBO LDLs (r = 0.708). Estimates of time outdoors between the Clouclip and HOBO devices were moderately positively correlated (r = 0.645). Compared to self-reported outdoor time from the outdoor activity diary, the Clouclip (r = 0.593) and Actiwatch (r = 0.557) LDLs had a moderate level of correlation, whereas there was a poor correlation with the HOBO device (r = 0.473). On an individual level, daily outdoor time determined by each method, all were significantly different to each other (all P < 0.05) (Table 2). Self-reported time outdoors from the diary tended to be the highest reported, followed by the HOBO LDLs, Clouclip and Actiwatch LDLs (Table 2). Measures of time outdoors calculated using adjusted LDL values, were not significantly different between any LDL pair, however, all LDL estimates remained significantly lower than diary reports of time spent outdoor (Figure 6.4).

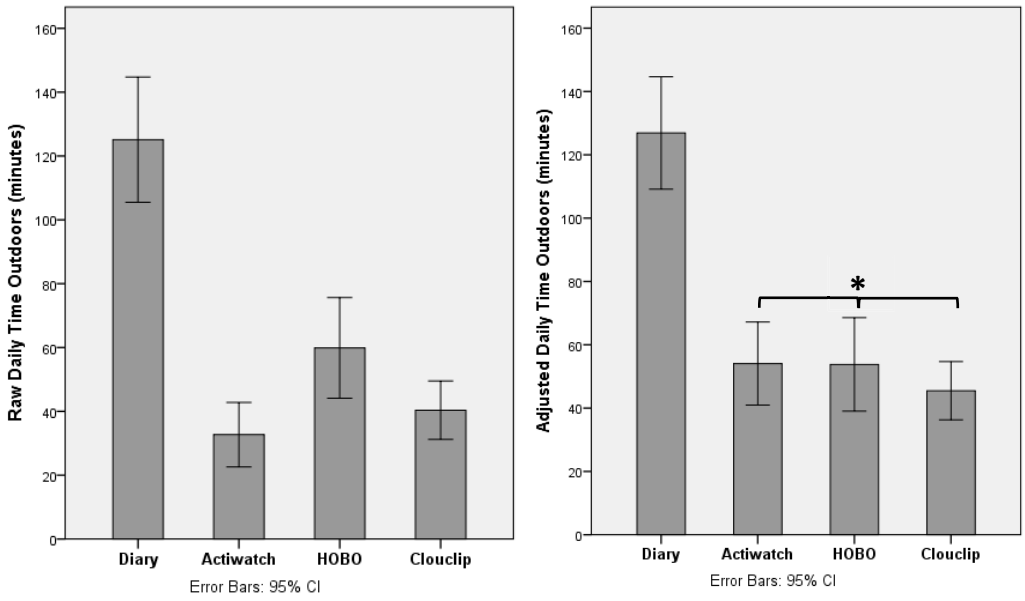


Figure 6.4: Daily time outdoors reported from the diary compared to adjusted LDL measures. Error bars represent 95% CI for mean daily outdoor times. *P ≥ 0.05

6.4.4.2 Outdoor light intensity

Mean outdoor light intensity recorded during the daily measurement window were significantly positively correlated between all LDL devices (all $P < 0.05$). Moderately strong correlations were seen between the Actiwatch and HOBO LDLs ($r = 0.522$), while mean light intensity between the Clouclip and HOBO LDLs ($r = 0.456$) as well as between the Actiwatch and Clouclip LDLs ($r = 0.343$) were poorly correlated. Mean outdoor light intensities recorded by the HOBO LDL were significantly higher than from both the Actiwatch and Clouclip LDLs (both $P < 0.001$) (Table 6.2). Meanwhile, mean outdoor light intensity recorded between the Actiwatch and Clouclip LDLs were similar ($P = 0.086$). Using adjusted values, mean outdoor light intensities calculated were all significantly different between LDLs (Figure 6.5).

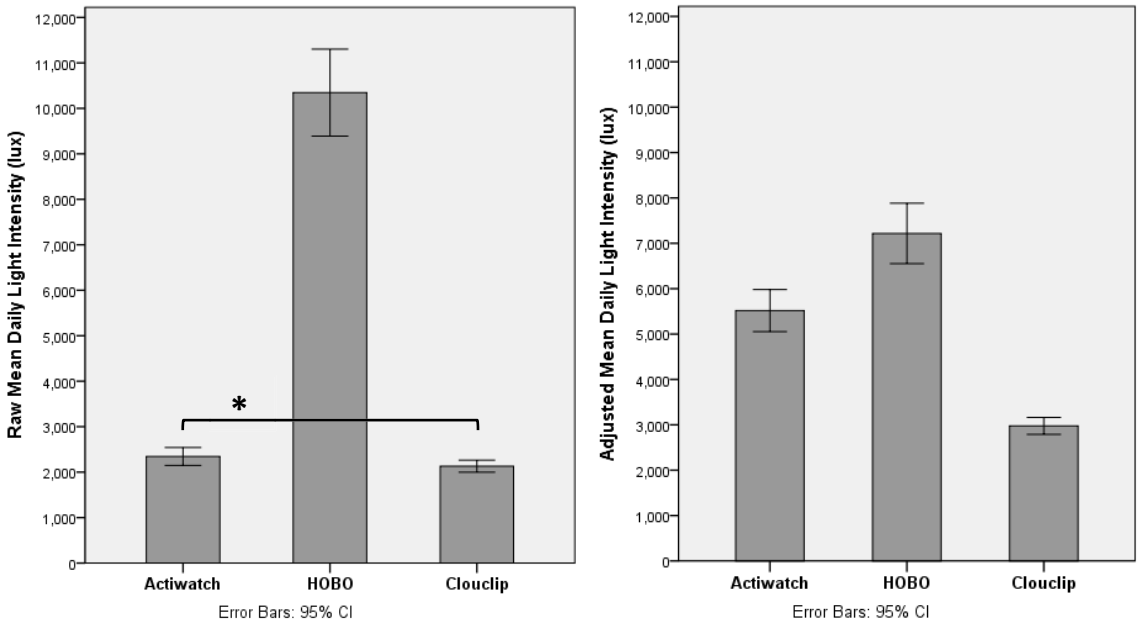


Figure 6.5: Comparison of mean daily light intensity using adjusted LDL measures. Error bars represent 95% CI for mean daily outdoor times. *P ≥ 0.05

6.4.4.3 Daily outdoor frequency

Daily outdoor frequency between all the devices and the diary were significantly correlated with each other (all $P < 0.05$). Among the LDL devices, the Actiwatch and Clouclips were moderately correlated ($r = 0.532$), whereas the Clouclip and HOBO as well as the Actiwatch and HOBO were poorly correlated ($r = 0.438$ & $r = 0.405$ respectively). Outdoor frequency reported from the diary was poorly correlated with all LDL estimates ($r = 0.263$, 0.268 & 0.243, for Actiwatch, HOBO and Clouclip's respectively). Outdoor frequency reported from the diary was similar to Actiwatch estimates ($P = 0.501$), whereas outdoor frequency determined by the Clouclip's and HOBO LDLs were similar ($P = 0.137$) (Table 6.2).

Table 6.2: Daily time outdoors, mean outdoor light intensity and outdoor frequency captured between LDL devices and the outdoor activity diary.

	Diary	Actiwatch	HOBO	Clouclip	Adjusted Actiwatch	Adjusted HOBO	Adjusted Clouclip
Time outdoors, minutes (SD)	125.11 (99.45)	32.69 (51.13)	59.88 (79.96)	40.36 (46.33)	54.07 (68.88)	53.80 (77.40)	45.48 (48.20)
Mean outdoor light intensity, lux (SD)	-	4,317.76 (3,305.0)	10,977.95 (10,167.9)	3,663.73 (2,372.6)	5,517.17 (12,423.9)	7,216.89 (17,861.4)	2,975.86 (4,959.2)
Outdoor frequency, intervals (SD)	1.95 (1.09)	2.11 (1.66)	3.12 (2.08)	2.94 (1.95)	-	-	-

= $P \geq 0.05$

6.4.5 Comparison of subjectively and objectively determined weekly outdoor time

There was a moderate correlation in self-reported weekly outdoor time between the baseline outdoor activity questionnaire and diary (r = 0.541, P = 0.01), with weekly outdoor time calculated from the diaries significantly lower than questionnaire estimates (Table 6.3). Weekly outdoor time from all LDLs were not correlated with questionnaire measures (all P > 0.05), however, measures from both the Clouclip and Actiwatch LDLs had significant correlations compared to self-reported diary estimates (r = 0.395 & 0.340, P = 0.019 & 0.045 for Clouclip and Actiwatches respectively), whereas no correlation was seen for measures from the HOBO LDL. Weekly outdoor time differed significantly between all measures (all P < 0.01). This remained unchanged when weekday and weekend estimates were separated, except between the questionnaire and diary estimates, which were similar on weekdays (P = 0.313). Using adjusted LDL measures, average time outdoors were similar between all LDL devices, but remained significantly lower than both questionnaire and diary measures (Figure 6.6).

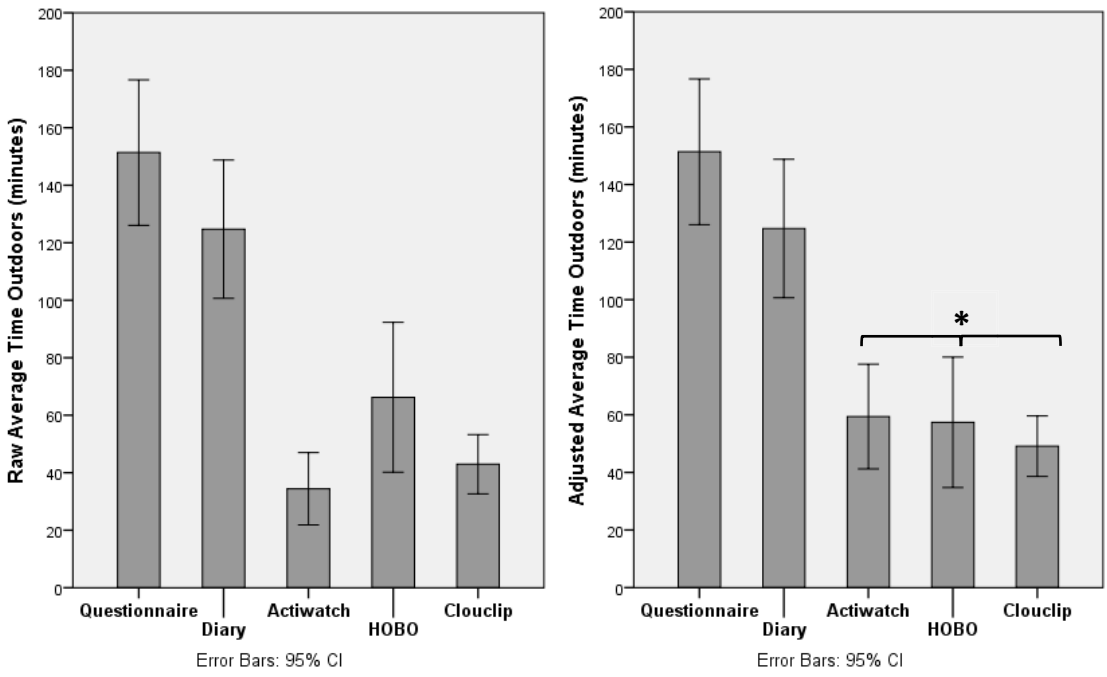


Figure 6.6: Daily time outdoors reported from the diary compared to adjusted LDL measures. Error bars represent 95% CI for mean daily outdoor times. *P ≥ 0.05

Table 6.3: Average time outdoors determined from the LDL devices, outdoor activity questionnaire and the outdoor activity diary.

	Questionnaire	Diary	Actiwatch	HOBO	Clouclip	Actiwatch	HOBO	Clouclip
Average daily time outdoors, minutes (SD)	151.37 (73.72)	124.69 (70.00)	34.42 (36.63)	66.23 (64.68)	42.96 (30.06)	59.41 (53.0)	57.42 (65. 9)	49.09 (30.6)
Average weekday time outdoors, minutes (SD)	144.03* (78.43)	132.29* (78.15)	34.63 (40.61)	63.43 (72.50)	43.54 (37.49)	55.80 (48.8)	53.23 (60.6)	10.63 (38.1)
Average weekend time outdoors, minutes (SD)	169.71 (123.90)	108.94 (84.08)	33.91 (53.18)	73.23 (93.53)	41.49 (45.81)	65.28 (87.0)	59.57 (87.1)	45.80 (56.6)

└─┘ = P ≥ 0.05

6.4.6 Comparison of subjectively and objectively determined near work time

Average weekly near work time determined from Clouclip measures of working distance ≤ 60 cm was not correlated with self-reported near work time from the questionnaire (r = 0.237, P = 0.171) (Figure 6.7). Stratifying the data by weekdays and weekend days, did not improve the correlation between the Clouclip measures and questionnaire estimates (r = 0.231 & 0.109, P = 0.183 & 0.582, weekday & weekends respectively). Average weekly near work time reported using the questionnaire was significantly higher than the objectively determined near work time (419.39 vs 107.63 minutes, P < 0.001).

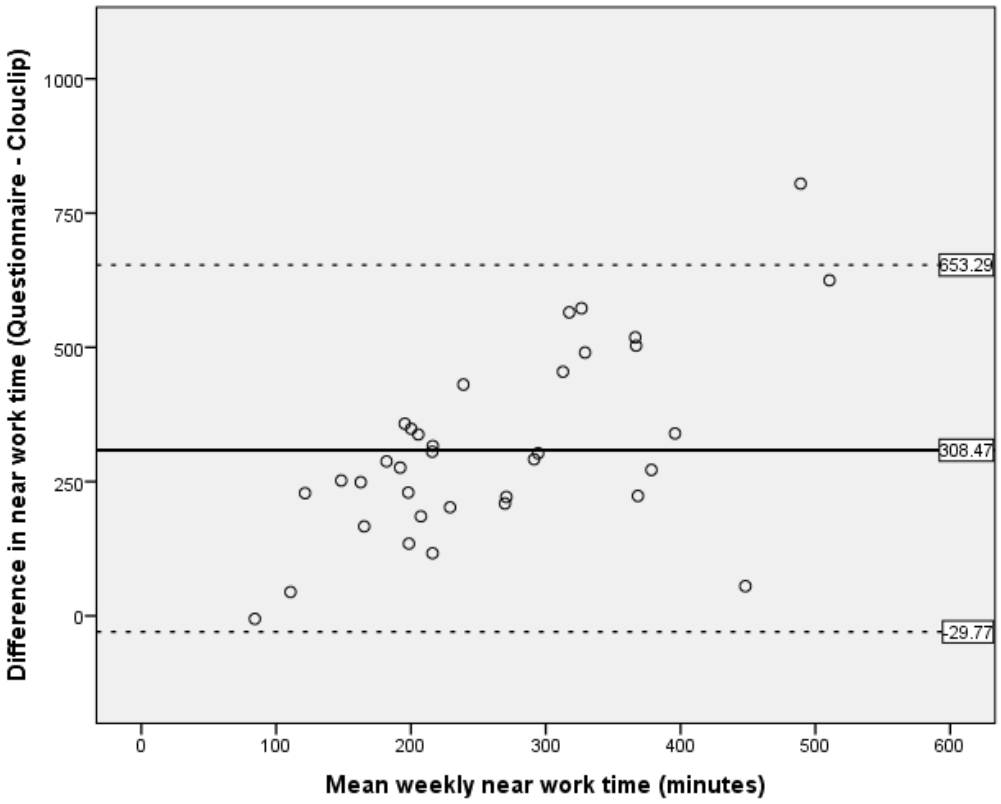


Figure 6.7: Bland-Altman plot comparing the agreement in estimated weekly near work time between the Clouclip LDL and the questionnaire. Dotted lines represent the 95% limits of agreement, solid line represent the mean difference between the two measures.

6.4.7 Outdoor and near work parameters between myopic and non-myopic participants

Table 6.4 presents demographic and biometric data for myopic and non-myopic subjects who had complete data available from all three LDL devices. Myopic subjects were similar in age and had a similar gender distribution to non-myopic subjects (all $P > 0.05$). Myopes were more likely to be 'East Asian' and less likely to be of 'Other' ethnicity than non-myopes ($P = 0.001$). Myopic subjects also tended to have at least one parent with myopia, whereas non-myopic subjects mostly had no parents with myopia. Myopic subjects also tended to have longer axial lengths and higher AL/CR values than non-myopes (both $P < 0.001$). Corneal radius did not significantly differ between myopic and non-myopic subjects ($P = 0.528$).

There were no significant differences in the outdoor exposure variables: daily outdoor time, average outdoor light intensity and daily outdoor frequency, between myopic and non-myopic subjects from both subjective and objective measures (all $P \geq 0.05$) (Table 6.5). These relationships also did not change in significance when analysed between weekdays and weekend days separately (all $P \geq 0.05$).

For near work time, while differences were also not significant (Table 5), myopic subjects reported to spend more time performing near work in the questionnaire and subsequently recorded more time in near work through the Clouclip device than non-myopic subjects ($P = 0.083$ & 0.093 respectively). For questionnaire measures, these differences reached borderline significance during weekdays, (460.88 vs 357.14 minutes, $P = 0.056$). Meanwhile, near work time on weekends were not significantly different between myopic and non-myopic subjects from both measures (both $P \geq 0.05$).

Table 6.4: Characteristics of myopic and non-myopic study participants.

		Myopes	Non-myopes	P-value
N		21	14	-
Age (mean, SD)		23.48 (2.62)	22.79 (2.55)	0.445
Female (n, %)		11 (52)	7 (50)	0.894
Ethnicity	***Caucasian***	3 (14.3)	2 (14.3)	0.001
(n, %)	***East Asian***	14 (66.7)	8 (57.1)	
	Other	4 (19.0)	4 (28.6)	
Parental	***0***	7 (33.3)	11 (78.6)	0.04
myopia	***1***	10 (47.6)	1 (7.1)	
(n, %)	***2***	4 (19.0)	2 (14.3)	
Axial length (mm, SD)		24.96 (0.64)	23.80 (0.56)	<0.001
Corneal radius (mm, SD)		7.83 (0.24)	7.77 (0.26)	0.528
AL/CR		3.19 (0.09)	3.05 (0.09)	<0.001

Table 6.5: Outdoor exposures and near work times between myopic and non-myopic subjects.

Variable	Measure	Myopes (mean, SD)	Non-myopes (mean, SD)	P-value
Daily outdoor time	***Questionnaire***	163.20 (85.93)	133.62 (63.80)	0.061
(minutes)	***Diary***	118.06 (58.95)	134.64 (85.38)	0.881
	Actiwatch	29.16 (32.97)	42.33 (41.55)	0.164
	HOBO	73.67 (94.63)	55.07 (32.47)	0.803
	Clouclip	39.20 (22.81)	48.58 (38.81)	0.654
Average outdoor	***Actiwatch***	3,642.39 (1,736.61)	4,929.15 (2,460.11)	0.112
light intensity	***HOBO***	9,050.72 (5,310.09)	9,998.41 (5,059.94)	0.538
(lux)	***Clouclip***	3,605.96 (1,733.03)	3,786.63 (1,024.38)	0.342
Average daily	***Diary***	2.17 (0.80)	2.04 (1.15)	0.907
outdoor frequency	***Actiwatch***	2.22 (1.37)	2.38 (1.04)	0.654
(n)	***HOBO***	3.10 (1.04)	3.64 (1.54)	0.414
	Clouclip	3.22 (1.39)	2.93 (1.23)	0.630
Average near work	***Questionnaire***	460.88 (187.55)	357.14 (132.73)	0.127
time **(minutes)**	***Clouclip***	127.41 (98.52)	77.94 (50.30)	0.118
Weekday near	***Questionnaire***	470.00 (214.73)	338.57 (140.43)	0.056
work time **(minutes)**	***Clouclip***	135.52 (113.60)	78.14 (57.44)	0.154
Weekend near	***Questionnaire***	438.10 (214.61)	403.57 (185.62)	0.778
work time **(minutes)**	***Clouclip***	98.94 (80.03)	75.17 (45.56)	0.568

6.4.8 Impact of the COVID-19 pandemic on outdoor exposures and near work

Subjects who participated in the study after the global pandemic had a significantly lower frequency of outdoor light exposure determined by the Clouclip than those who participated before (2.4 vs 3.6 intervals respectively, P = 0.007). This difference remained significant for weekdays but not weekend days. Daily outdoor time, average outdoor light intensity and near work times did not significantly differ between subjects who participated prior to the impact of COVID-19 in Australia (all P ≥ 0.05).

6.4.9 Thematic analysis of focus group data

There were four predominant themes raised by participants in response to the questions asked during the focus group discussion.

6.4.9.1 Theme 1: Device wearability & compliance

Most of the points raised during the focus group discussions were in reference to inconveniences encountered during device wear. As each of the devices were worn in a separate fashion, comments made in regards to device wearability were directed to individual devices.

The Actiwatch device appeared to be well received by study participants as it had the least number of targeted comments. The main factor contributing to this was the fact that the wrist-worn nature of Actiwatch was a familiar form factor for participants. In one particular group, a study participant said that the Actiwatch was "*easy to put on and use because I'm used to wearing a watch every day*" with another participant adding that "*it was similar to my Fitbit*".

In contrast, comments made towards the HOBO and Clouclip devices were more negative. For the HOBO pendant, several participants made complaints about the requirement of the device to be placed in an armband, such as: *"The armband was too bulky"* and *"The armband was too annoying".* In a more detailed comment, one participant said "*On colder days, it was uncomfortable to wear the armband of the HOBO device around my outermost layer of clothing*", to which another participant replied with *"I had the opposite experience. Since I didn't want to make the band too tight, when*

wearing t-shirts the band would slide up and down when I moved, so that was definitely also uncomfortable". In another session, a participant commented that "*the HOBO device seemed the least appropriate during work compared to the other two which were more minimal".* These issues were also indirectly raised by a number of participants who stated *"What if you wore it around your neck?"* and *"It would have been nice to have had the option to wear it as a necklace*", suggesting that the traditional method of using the HOBO devices would have been preferred and that the larger form factor provided by the armband was the major issue.

Meanwhile, the most common comments made about the Clouclip suggests that there were issues on a deeper psychological level. Rather than issues with device function, participants made several comments raising concerns on external perceptions during device wear. Examples of these comments were: *"I was just worried that when I was walking around people would think I was blind or had a recording device", "I think the clip drew a bit of attention, so a lot of people would question whether it was a camera or not"* and *"I was beginning to feel a bit self-conscious, thinking if people were looking at me or if they were going to approach me to ask what I was wearing".* These statements were made across several groups and were met with a unanimous agreement by fellow participants. Aside from this issue, some predominantly emmetropic participants experienced discomfort from wearing plano-lensed frames: *"The frames I picked felt ok when I first wore them but I didn't notice the small discomforts until I wore them a bit longer".* In contrast, regular spectacle wearers made more positive comments such as *"I felt that this was the easiest thing to use, especially since I wear glasses all the time anyways, I would eventually forget about it until night-time when I would take it off"* and *"Initially I felt it slightly annoying as I could see it in my peripheral vision, but I got used to it after about a day*".

6.4.9.2 Theme 2: Factors influencing LDL accuracy, reliability and agreement

Comments made by participants on their experience during the study period highlighted several potential sources for the inconsistencies seen between device measures. In general, several

participants mentioned that they felt the devices were not equally exposed to light while travelling. Such comments were: *"During travel on trains and in the car, there may have been differences depending on which side I was sitting on as the devices were on one side of me"* and *"Whenever I was in a car, my non-dominant arm would be in the shaded area of the car, whereas I would be looking outdoors and my clip would be orientated that way too".*

In addition comments were also made identifying issues with individual devices. For the Actiwatch, it was universally noted that the sensor was regularly obstructed by certain articles of clothing: *"As it's approaching winter time I started wearing jumpers, the wrist device would often get covered by my sleeves. Although I would try to pull them up I think the wrist device may not have captured information for some of those times".* Meanwhile for the Clouclip, some participants with longer hair (usually female) noticed that the sensor would sometimes become obstructed in various head positions: *"I have longer hair so when looking down the clip would get covered by my hair".*

6.4.9.3 Theme 3: Factors influencing diary accuracy, reliability and agreement

Similarly, comments made by participants on their experiences when filling in the outdoor activity diary highlighted a variety potential sources of inconsistencies between diary estimates of outdoor time and the objectively derived estimates. The most common issue raised across the various groups was that certain activities (in particular travelling) was not discretely completely characterised as either indoors or outdoors. *"It was hard for me to consider whether travelling was considered indoor or outdoor, especially on public transport and in cars" "I felt that while travelling, that the light was inconsistent so it would not always be considered being outdoors, for example while walking through the city to class I would briefly go through tunnels or through buildings".* Another source of inconsistency contained with the diary measure was the fact that diary records were not always completed in real-time, as one participant commented *"I would usually fill the diary at the end of the day and found it hard to remember the specific time that I did certain activities".*

6.4.9.4 Theme 4: Factors influencing questionnaire accuracy & reliability

The final theme involved factors which influenced the estimates provided by participants in the outdoor activity questionnaire. Many participants felt they were unable to provide an accurate estimate of their behaviour, with comments such as *"I don't really have a set routine, so it was hard to estimate average times for things I would do on a typical single day"* and *"Trying to estimate how much time I spend outdoors and studying per day was difficult, because every day is different".* One source of this inaccuracy likely comes from estimates of activities which are performed multiple times per day or in combination with each other, as one participant saying *"I don't do a lot of activities mentioned continuously, such as studying or computer use, so it was hard to provide an accurate total of how much time was spent*".

6.4.10 Rank analysis of LDL wearability and invasiveness

There was a statistically significant difference in wearability and invasiveness amongst LDL devices ($P < 0.001$). In terms of wearability, the Actiwatch was ranked first, followed by the Clouclip device and then the HOBO device. For invasiveness the opposite occurred, with the HOBO device ranked first, followed by the Clouclip then Actiwatch respectively.

6.5 Discussion

This study directly compared light intensity outputs between three portable light data logging devices during real world use. Light intensity captured at the same time between different portable LDLs were poorly correlated and significantly different. This was most apparent with the HOBO devices, which tended to record higher levels of lux and had larger variability when compared to both the Actiwatch and Clouclip devices. This corresponds with our earlier findings in Chapter 5, where the sensors from HOBO devices showed a tendency to overestimate light intensity in controlled outdoor settings. While there was a significant level of proportional bias occurring between the Actiwatch and Clouclip, differences in light intensity between these devices centred on a mean difference close to zero, indicating that there was not a significant tendency for one device to record higher or lower lux than the other. As previously concluded, this observation is likely due to the fact that the light sensor contained within the HOBO captures a broader wavelength spectrum (150–1,200 nm) and has a higher peak sensitivity (900 vs 570 nm) than the Actiwatch, which has sensor profile closer to the visible light spectrum (400–900 nm). Sensor profile for the Clouclip device has not been publically reported, though this suggests similarity to the Actiwatch.

Similar differences in agreement have been seen among the limited studies of real-world comparisons of LDLs. Jardim et al,[683] compared ambient light exposures within an indoor hospital environment (post-operative inpatient ward) captured between the wrist-worn Actiwatch device and a Daysimeter LDL mounted at an eye level. Although the ranges of light exposure within their study were solely obtained within indoor environments, they found that light exposures captured from the Actiwatch devices were lower than the Daysimeter devices. In particular they noted an increase in mean difference between devices at higher light levels (> 5,000 lux), which is in agreement with our findings of proportional bias occurring between LDL devices. They also noticed that there were instances where instead, the Actiwatch devices recorded higher lux than the Daysimeter. They attributed this to differences in the directionality of the devices, with Actiwatches

sometimes oriented upwards compared to the eye-level monitor, which faced perpendicularly to the person. In our study, there was potential for directionality effects to occur, as each LDL was positioned differently during real world use. This was demonstrated in Experiment 2 of Chapter 5, where despite being exposed to the same light source at the same time, LDLs orientated in different directions recorded significantly different light intensity levels. In this study, further evidence for directionality in the results can be seen in the scatterplots between LDLs, as there were multiple instances where outdoor light (> 1,000 lux) was captured by one device but not all (Figure 3), and in the reduction in strength of correlation between pairs of different LDLs occurring between our experimental comparisons (Experiment 1, Chapter 5) and during real world use. Bhandari and Ostrin, have measured the diameter of the infra-red beam used in the Clouclip for detection of near distance, to be 25.6 ± 2.2°.[690] However, operating ranges for the light sensor contained within the Clouclip and other wearable LDLs have not been investigated nor reported by their respective manufacturers. Nevertheless, our findings indicate that wearable LDLs are subject to directionality effects. Given that the release of retinal dopamine in response to light occurs at a local level,[687] light exposures must be captured as close to the eye as possible, which only spectacle mounted devices can currently do.

Further discrepancies between LDL measures have been seen in myopia-focussed studies. Read et al,[636] who saw that the HOBO had a tendency to overestimate light intensity compared to Actiwatch during their pilot experiment. Mean differences of 9,760 lux seen between these devices in outdoor environments (≥ 1,000 lux), were consistent and similar in magnitude to our findings. In an experimental setting, Howell et al,[670] reported higher mean differences in light intensity between the Actiwatch to the Clouclip against a standard photometer. Conversely, in a real world study, Bhandari et al,[689] reported that Clouclip tended to read slightly higher mean daily light intensity than the Actiwatch (mean difference: 126 lux) though in the context of myopia studies this difference would not be significant. The inconsistences between these studies are likely from the influence of directionality, rather than the differences in sensor capabilities.

While it appears that light intensity obtained from different portable LDLs are not directly comparable, estimates of daily time outdoors, mean light intensity and outdoor frequency determined from LDLs in this study remained in correlation with each other and were correlated with self-reported diary measures. However, absolute differences remained in these variables, suggesting that they are not directly comparable in terms of accuracy. Only two other studies have examined differences in time outdoors between different LDLs. In their pilot study, Read et al,[636] reported that the HOBO recorded slightly higher mean outdoor time compared to Actiwatch (mean difference: 0.4 ± 1.1 minutes). Though there was a 1-hour recording period, it was not reported how much of this time was spent outside, therefore the level of proportional error was unclear. More detailed comparisons were provided by Bhandari et al, who compared time outdoors between Actiwatch and Clouclip over one week in 25 participants.[689] Mean daily time outdoors was significantly higher from Clouclip than Actiwatch (22.2%), which was similar to the degree of overestimation seen in our study (23.5%).

Despite these differences between LDLs, we found that the use of adjustment factors, determined from our previous experimental study, were able to account for these differences in determining time outdoors. While this was able to unite LDL measures across LDLs, estimates of daily outdoor time remained significantly lower than subjectively derived estimates reported by diary and questionnaire. A portion of this discrepancy likely comes from human error through recall bias, as there may be a tendency to overestimate exposures which are thought to lead to positive outcomes. This can be seen by the differences between questionnaire estimates of outdoor time to outdoor exposure times logged from the diaries (Table 6.3). However, the larger differences found in the LDL estimates of time outdoors, suggest that recall bias is not the only contributor. Another major contributor is that while outdoor environments provide a consistent source of high light intensity and the observer notes this as consistent, not all of the light gets uniformly captured the LDLs, depending on their orientation. This was noticed when we examined individual light intensity logs to investigate outdoor frequency, where it was not uncommon for light intensity to fluctuate below

1000 lux between intervals (Figure 6.1). This would cause outdoor transition frequency to appear higher, whilst conversely reducing the estimated time outdoors.

Several other studies have compared single LDL devices to subjective reports of outdoor time and have reported similar findings, with time outdoors from LDLs consistently lower than questionnaire or diary measures.[639-641, 643, 659, 689, 691] From this, it would appear that subjective estimates of outdoor time, represent the maximum potential time for outdoor light exposure in individuals, however in reality, as light exposure in the real world is experienced intermittently rather than constantly, the net duration of exposure captured over various parts of the body including the eye, is often much lower than this limit. This would also suggest that locating LDLs as close to the eye as possible will give a more accurate measure of the light entering the eye, the target of myopia research.

Although estimates of time outdoors differs between LDLs, we found that similarities in mean daily light intensity between Actiwatch and Clouclip. As this variable was overestimated by the HOBO, these similarities likely reflect the sensor properties of each device. While our adjustment factor was able to unite measures of time outdoors, mean light intensities from different LDLs were not comparable, despite adjustment using proportions. This was likely due to the fact that larger magnitudes of errors are experienced at higher lux levels, whereas the investigation of time outdoors is only concerned with light intensity above 1,000 lux. As earlier described, Bhandari et al,[689] reported that mean daily light intensity differed between Actiwatch and Clouclip. Their study considered all levels of light intensity for mean daily lux. This can potentially mask sensor performances at higher light levels, since only a relatively small fraction of the day was spent outdoors. As we only compared light intensities > 1,000 lux, our results suggests that in outdoor environments, mean light exposure can be compared between LDLs with similar sensor characteristics.

Meanwhile, average daily frequencies of exposures to outdoor light exposure have not been investigated as a myopic risk factor as frequently as average daily outdoor time and average daily

light intensity. Questionnaires, one of the primary tools used in large epidemiological studies are not geared to investigate frequency of outdoor exposure. Diaries are designed to capture this data, however, participants may not note brief periods outdoors and if filled in at the end of the day, will also suffer from recall bias. No studies to date have compared LDL readings to subjective diary reports and we found consistent differences in this parameter between methods of capture. Also, unlike mean outdoor time, objective devices; in particular the HOBO and Clouclip tended to detect higher daily outdoor transition frequency. This is likely a by-product of LDL's sensitivity to directionality, as these two devices also record higher outdoor time than the Actiwatch, meaning that there are more data intervals available.

Comparison of near work time derived from the Clouclip and questionnaire suggests that subjective methods again may overestimate near work time. These findings are in contrary to a study in Chinese myopic children by Zhuo et al[659] who found that near-work time derived from Clouclip measurements were higher than both parental and self-reported daily near work time determined by questionnaire. It is possible that all the near work activity captured objectively are likely to include play activities that both parents and children may not designate as near work. In contrast, Bhandari et al,[689] found in adults similarities in daily near work hours between questionnaire and Clouclip data. Our finding of overestimation by questionnaire may have been affected by the limited window during the day (6am-8pm) that objective measures of near work were captured. Thus apparent overestimation of near work time in the questionnaire data may come from these additional hours at night. However, while it is not out of the ordinary for university students to spend time studying at later hours in the day, the large difference we saw between the two measures (~5 hours) suggests that this is unlikely to completely account for all of the differences captured. More comparisons of near work measures are needed for confirmation.

Despite using a variety of both objective and subjective tools, we found that light exposure and near work behaviours did not differ between myopic and non-myopic individuals. Similar findings were

seen in early cross-sectional reports, with one study in children (average age 8 years) not finding a significant difference in outdoor exposure between myopic and non-myopic groups.[633] It is, however, to be noted that the children in Singapore were measured by the HOBO as doing less than 1.4 hours a day outdoors, which could be considered as sub-threshold for myopia protection. A second study of a similar age group to our study,[641] also failed to find differences between emmetropic and myopic individuals in objectively derived outdoor time using the Actiwatch. These and our findings were likely related to the small and older age samples, given that incidence rates of myopia are low in young adults compared to young children, it is unlikely that these current exposures contribute greatly to myopia status. It is also difficult to determine whether current outdoor and near work behaviours recorded in our study are reflective of the patterns of behaviour exhibited during or before the development of myopia.

In contrast, several reports both cross-sectional and longitudinal in nature, do indicate that myopic children spend less time in bright light than non-myopic children,[638, 668] and that lower light exposures are associated with greater myopic shifts and axial elongation.[374, 635] These studies have used a range of LDLs including HOBO and Actiwatch as well as the Clouclip. While these later studies were promising, a recent study using the newly developed FitSight watch was unable to find associations between several outdoor parameters (time spent ≥ 1000 lux, average light intensity and time, and frequency of high light exposure) with myopia status, refraction or axial length in children; despite having a large sample size.[640] Although the FitSight functions similarly to Actiwatch, comparisons have not been made between FitSight measures to other devices nor to subjective methods. Given our primary findings, these differences may have occurred as the result of device variations. Validation of this device alongside standardisation of exposure parameters and measurement techniques is needed in future studies to allow robust comparisons between studies.

This study was conducted during the advent of the COVID-19 global pandemic. While the pandemic changed the delivery of tertiary education in Australia to incorporate more online activities and less

opportunities for face-to-face meetings, this only appeared to impact the frequency of outdoor light exposure and not mean light intensity, daily outdoor or near work time. In the absence of lockdowns, our university adopted a hybrid delivery system, with lectures remaining digital while face-to-face workshops and tutorials resumed on campus. The reduction in weekday outdoor frequency by approximately 1 interval appears to reflect this change in behaviour as students would not be provided with an additional break period between classes. Recently there have been several observations of an increase in myopia progression rate in school-aged children following the global pandemic.[692, 693] Whether or not this is a direct result of behavioural changes following the global pandemic is uncertain, and though there are also reports that indicate myopigenic changes in outdoor time and near work occurred,[694-696] these have used subjective methods and additional data containing objective measures of light exposure and near work would be useful to confirm this association.

This study appears to be the first to qualitatively compare the utility of portable LDLs. While quantitative analysis allows the comparison of device function and captures hardware differences (such as sensor characteristics) that influence exposure measurements, qualitative analysis of LDL wear allows the identification of external factors that may also play a role in determining the comparability of devices during real world use. These factors have the potential to reduce the validity of exposure measures by influencing compliance, modification of individual behaviour or direct obstruction of device sensors.

We found that the most significant element that influenced the wearability of the LDLs was their form factor. The HOBO appeared to be the least favourable as it was relatively larger and less discrete than the Actiwatch and Clouclip. The decision to mount the HOBO pendant using an armband appeared to be the main factor influencing its lower wearability rating, suggesting that the increase in internal consistency provided by securing it to an arm as opposed to being worn as a necklace; was accompanied by a decrease in comfort and the potential for non-compliance.

However, prior pilot studies in Singapore and Sydney using it as a pendant, found that rotation of the device obstructing the sensor, was common (personal communication). For the Clouclip, self-consciousness during wear may lead to alterations in natural behaviours. In sub-sets of users, wearability issues may be expected in those who are not regular spectacle wearers and sensor obstructions may occur in participants with longer hairstyles, suggesting that gender and refractive status may influence device feasibility and reliability. The Actiwatch has a familiar and acceptable form factor for most individuals, however, they were generally prone to sensor obstructions from long sleeved clothing worn in colder climates. This would suggest that seasonal differences in exposure data may be potentially influenced by this limitation. Consideration of device limitations with respect to population characteristics will allow the selection of the optimal tools for light exposure capture in future studies.

The major strength of this study is that it provides a real-world comparison of tools commonly used in myopia studies. This includes several individually validated subjective measures and portable devices which capture light intensity and one that also captures near work. After excluding intervals unable to be validated, there remained a large sample of valid intervals available for analysis. The comparisons of light intensity ≥ 1,000 lux used in this study allows for a more accurate comparison of light exposures in outdoor environments, which is the primary concern for protection against myopia. Since our study did not consider light intensity levels during indoor states for the comparison of agreement, there was no direct data on the comparability of LDLs in low light settings. Although one study has suggested that there may be a relationship between mesopic light exposures and incident myopia,[634] and increases in indoor light intensity has been reported to potentially reduce the incidence of myopia in school-children,[375] LDL sensors still remain sensitive to directional changes, thus we would also expect a high level of discordance when directly comparing light intensity between various devices in indoor settings also.

In terms of limitations, there was potential for bias in the analysis of individual exposure parameters, due to the small sample size of participants, which remains relatively large in comparison to previously conducted validation studies. This limitation would have mainly influenced the validity of total exposures (average daily light intensity, duration and frequency) as well as sub-group analyses between refractive error categories, as there may not have been a large amount of inter-individual variation in exposure and behavioural characteristics. However, it should be acknowledged that the primary aim of this Chapter was not to investigate the relationship between light exposure and refractive error, but rather to perform direct comparisons of light exposure measures between LDLs. For this purpose, the sample size can be considered to be the number of data points where three LDLs were simultaneously recording light intensity (n = 2760).

Another limitation contained within our sub-analyses was that refractive errors were not captured via the gold-standard method, cycloplegic refraction. However, we chose to categorically determine myopia in order to minimise the errors introduced by non-cycloplegic refraction. Self-reported determination of refractive error has been shown to be reliable in categorising refractive errors, particularly myopia in adults with sensitivities ranging from 83–89% and specificities of 83–98%.[697, 698] This reliability is likely to increase when combined with using a VA threshold of 6/9.5; which has been demonstrated to identify myopia with even higher levels of sensitivity (97.8%) and specificity (97.1%) in children;[46] alongside spectacle/lens prescription data (which reflects non-cycloplegic refraction) to confirm myopia status. Additionally out of all myopic participants, none were classified by using a VA definition alone, meaning that they had all been previously prescribed a myopic refractive correction by an independent optician. A final limitation was that all participants did not wear devices at the same time, therefore light exposure measurements between individuals may be affected by differences in weather patterns e.g. on cloudy vs sunny days. This would have mostly affected intensity measurements rather than outdoor time and frequency estimates (> 1,000 lux) as outdoor light commonly exceeds 1,000 lux even on cloudy days.

6.5.1 Impact of the 2019 global coronavirus pandemic on chapter outcomes

The largest effects of the global pandemic were seen during the data collection phase of Chapter 5. The extended closure of university campuses, transition to virtual learning and community stay-at-home orders resulted in a reduction in the participation rate of this study. Of the total sample, over half (n = 28) participated in the study prior to the advent of the pandemic in 2019. In the following year, the study recruited 10 extra participants before restrictions took effect. It was not until these restrictions were eased in early 2021 that recruitment could resume. This continued until June 2021, when the restrictions were once again enforced due to a second wave of containing the delta variant of the virus. As a result, the level of detail in the data collected was less than originally intended for the study. This was set at 100 participants, which had 80% power to detect a 25% difference in daily outdoor time among individuals who spend approximately 80 minutes (SD: 50) of time outdoors.

Alongside limitations in sample size, potential changes in population demographics have occurred from the pandemic. Restrictions on inter-state and international travel meant that the intake of tertiary students; particularly for younger cohorts; has changed, with reductions in rural, interstate and international students. This may have reduced the heterogeneity of the sample population examined post-Covid. Finally, significant changes in educational delivery has occurred in the post-Covid era, with lectures and theoretical learning shifting to virtual forms (e-learning). Despite easing of travel restrictions, many faculties have continued virtual delivery of education or adopt a hybrid mode of delivery. These changes would have undoubtedly altered the natural behaviours of participants in our study and resultant changes in their light exposure and near work scores. Potentially, this may have also affected the accuracy of questionnaire derived exposure measures, as participants may not have formed consistent patterns of behaviour following Covid or based their responses on pre-Covid habits. Again as the primary objective of the study was to perform validation by making inter-device comparisons, differences in exposures between individuals would not have significantly altered this aspect of the findings.

6.5.2 Summary

In summary, this study identifies differences in agreement between three LDLs during real world use. This suggests that light exposure varies significantly across different areas of the body and/or highlights that sensors contained within LDL devices have a limited directionality or "field of view". Whatever the case may be, this means that light exposures relevant for investigating myopia should be captured as close to the eye as possible and directed along the line of sight. In theory, the Clouclip and other upcoming spectacle mounted devices such as the RangeLife and Akeso, should provide more accurate measures of ocular light exposure relevant to myopia development and progression, compared to the other LDLs and traditionally used tools such as questionnaires and diaries. Yet these other tools should not be completely disregarded as they each have their own advantages and utilities that may lead to more consistent, valid results and increased participant retention, as long as their limitations are understood. Understanding the dynamics between measures of outdoor exposure and near work obtained using different tools allows investigators to design more effective and efficient myopia studies and allows the comparison of findings from a range of studies using different tools to capture light exposure.

Chapter 7: The Axial Length to Corneal Radius Ratio as a Determinant of Refractive Error and its Progression

7.1 Abstract

Purpose: To examine the relationship between AL/CR, spherical equivalent refraction (SER) and myopia progression.

Methods: Ocular biometry and cycloplegic autorefraction was measured in 845 six year old and 1,115 twelve year old schoolchildren, with 5-6 year follow-up. Crystalline lens power (LP) was calculated using Bennet and Rabbett's formula. AL/CR and SER relationships were modelled using linear and piecewise regression analysis.

Results: AL/CR changes strongly correlated with SER changes (r = -0.875 & -0.815, younger and older cohort respectively) and were best described by a tri-phasic linear model. In low hyperopes (> 0.75 D to ≤ 2.00 D), a unit increase in AL/CR produced less myopic shift in SER compared to all other refractive groups (all $P < 0.001$). LP changes were negatively correlated with AL/CR changes (all $P < 0.01$), but not in myopes or those with high AL/CR. Myopes displayed the strongest relationships between AL/CR change and SER change ($r^2 = 0.880$ and 0.853, younger and older cohort respectively). Within baseline myopes of the older cohort, AL/CR changes determined 95% of SER changes within ± 0.66 D of actual SER.

Conclusion: AL/CR correlates highly with cycloplegic refraction, although the relationship is not strictly linear. Reductions in crystalline lens power limit the myopic shifts expected from axial elongation, keeping eyes in a state of low hyperopia. Myopia progression can be indirectly monitored through changes in AL/CR with a reasonable level of accuracy.

7.2 Introduction

The development and incorporation of portable objective measurement devices, such as wearable light meters, has allowed for precise and continuous monitoring of environmental risk factors for myopia. However, one issue generated with the detailed investigation of risk factors is that they now need to be accompanied by frequent and accurate measures of refraction. As shown in Chapters 4 & 6, human light exposure is a dynamic variable, with significant temporal variations occurring across days and weeks. The extent to which these variations influence refraction in humans has not been confirmed, however the observed seasonal differences in myopia progression suggests that it is possible for shorter term variations in eye growth to be occurring in response temporal differences in risk factor exposures to sunlight and possibly near work. To examine and confirm this, measurements of refraction in longitudinal studies need to be obtained on a more frequent basis, while cycloplegic measures have been typically performed on an annual or bi-annual basis at best and more usually at baseline and conclusion of a study.

There is no doubt that cycloplegia is a necessity to accurately determine refractive errors. However, the use of effective and consistent cycloplegia carries a number of inconveniences, especially when gathering large volumes of refractive data, such as when sampling large populations for screening purposes, or repeatedly assessing for refractive changes to examine seasonal effects associated with myopia progression or simply to monitor myopia progression closely during treatment. In some of these cases, the use of visual acuity and non-cycloplegic refraction to categorise refractive errors has been used instead, which may be appropriate in a school screening setting, where the aim is to detect children with uncorrected myopia. Much research is now being devoted to improve the efficacy of non-cycloplegic refraction screening by attempting to exclude false positives (known as pseudo-myopes) by adjusting the cut-off for myopia, or by applying a further visual acuity criterion. However, while it may arguably be possible to establish reasonable prevalence rates of myopia using non-cycloplegic refraction by increasing the refractive thresholds to compensate for overestimations

from pseudo-myopes, it becomes difficult to accurately assess refractive categories, as individuals with low myopia will potentially be frequently misdiagnosed. Additionally, without cycloplegia, some low hyperopes may become misdiagnosed, as the distribution of refractive errors shifts towards myopia. As an alternative, indirect non-invasive methods of determining refraction have been explored.

As refractive errors are the most common cause of vision impairment,[699] visual acuity (VA) has been explored as a determinant of refraction. Surveys within Taiwan[12] and China[45] have already used VA to estimate population prevalence's of myopia. Several school-based vision screening programs have also used VA as a primary determinant of refractive error such as the Statewide Eyesight Preschooler Screening (StEPS) program in New South Wales, Australia.[700] However, whether or not this is the most efficient method is open to question. While VA has been shown to be a reliable method of categorising myopia, where a cut-off of 6/9.5 can be used to detect myopia of -1.00 D or more with high sensitivity (97.8%) and specificity (97.1%),[73] it is unable to consistently identify hyperopia or astigmatism to the same level of effectiveness.[73] In addition, VA thresholds alone, inherently capture other ocular conditions, leading to errors through false positives in the absence of further examinations.

Another approach is to consider the biometric components of the eye. Given that differences in ocular component measures underlie the presence of refractive errors, rather than reductions in VA which are the result of refractive errors, then the measurement of ocular biometrics may potentially provide a more reliable method of indirectly determining refraction. Studies comparing the correlation between individual ocular component measures and refraction find that axial length (AL) has the strongest correlation with spherical equivalent refraction (SER),[20, 21] suggesting that AL is the primary determinant of refractive errors. Though true to some extent, in reality some myopes have relatively short eyes, some hyperopes have relatively long eyes, and those considered to be

emmetropic appear to have a relatively broad AL range.[402] This suggests that other component variables have significant contributions and need to be considered.

The axial length to corneal radius ratio (AL/CR) is a proposed unit that attempts to account for these differences. Grosvenor and Scott first investigated AL/CR and found that 84% of the variance in SER could be explained by variances in AL/CR.[48] Unlike measures of individual ocular components which are normally distributed, ALCR has a leptokurtic distribution curve similar to that of refraction, suggesting it may be more closely related to overall refraction. This relationship has been confirmed by several studies that consistently find stronger correlations between AL/CR and SER compared to AL alone.[19-23] As a result, rather than looking at individual biometric units, refraction can potentially be indirectly determined from AL/CR by applying a simple scaling factor obtained from regression analysis. However, the utility of this technique has not been explored in detail, perhaps due to a number of inconsistencies found in the relationship between AL/CR and refraction in existing studies. This has been detailed in Section 1.3.2.2.2 of Chapter 1.

This chapter aims to use data from a population-based longitudinal study of refraction and biometric components to:

- Describe the relationship between AL/CR and refraction and identify variables which may influence its relationship
- Determine the role and utility of AL/CR as an indirect measure of refraction and as a measure for refractive progression

7.3 Methods

Detailed methodology has been described in Chapter 2.

7.3.1 Population

The Sydney Myopia Study (SMS) was a population-based cross-sectional which examined schoolchildren in two age samples, 6 and 12 years, across the Sydney metropolitan area. The Sydney Adolescent Vascular and Eye Study (SAVES) was a 5- to 6-year longitudinal follow-up study of the SMS cohort. Of the original SMS sample, 2103 children were re-examined in SAVES: 892 (50.5%) from the younger cohort and 1,211 (51.5%) from the older cohort. The mean time between baseline and follow-up examinations was 6.1 years for the younger cohort and 4.6 years for the older cohort.

7.3.2 Eye examination

All children completed a comprehensive eye examination at both baseline (SMS) and follow-up (SAVES) that included cycloplegic autorefraction; using the Canon RK-F1 (Canon, Tokyo, Japan); and measures of ocular biometry [axial length (AL), anterior chamber depth (ACD), corneal radius (CR)]; using the IOLMaster TM (Carl Zeiss, Meditec AG Jena, Germany). Cycloplegia was induced by 1 drop each of cyclopentolate 1% and tropicamide 1% administered in 2 cycles, 5 minutes apart, following corneal anesthesia with amethocaine hydrochloride 1%. Crystalline lens power (LP) was calculated using the Bennet and Rabbetts formula.[701, 702] The AL/CR ratio was calculated from individual AL and CR measures. Refractive errors were categorised using the following definitions: hyperopia (> 2.00 D), low hyperopia (≤ 2.00 D to > 0.75 D), pre-myopia (≤ 0.75 D to > -0.50 D) and myopia (≤ -0.50 D). Questionnaires were completed by parents of participating children to assign gender and ethnicity.

7.3.3 Data analysis

Pearson's correlations were obtained between all optical component measures (AL, CR, ACD, LP), AL/CR and SER for both cohorts. Correlations between longitudinal changes in optical component measures, AL/CR and SER were also assessed via Pearson's correlation. The relationship between AL/CR and SER was visualised via scatterplots and analysed via linear regression and LOESS modelling. Piecewise-linear regression using a 3-segment model was also performed to obtain optimised gradient co-efficients and breakpoints, using visual estimates derived from bends seen on LOESS models. Correlations between AL/CR changes and refractive progression were examined via Pearson's correlation. Homogeneity of regression was examined between linear regression lines after stratifying for age cohort and baseline refractive error category.

Statistical significance was determined by an alpha level of 5%. All statistical analyses were performed using the statistical package SPSS Statistics for Windows (version 23.0; IBM Corp., Armonk, NY) with the exception of the tri-phasic linear regression modelling which was performed using Statgraphics (version 19; Statgraphics Technologies, Inc., The Plains, VA).

7.4 Results

7.4.1 Sample population characteristics

In total, 1,960 children with complete follow-up data for all ocular biometric measures were included (845 in younger cohort and 1,115 in the older cohort). Data was analysed and presented for only right eyes, as values for SER, AL and CR were all statistically similar and highly correlated between right and left eyes at baseline and follow-up (all $P < 0.05$). Tables 7.1 and 7.2 contain demographic and biometric characteristics of the younger and older cohorts respectively at baseline and follow-up. In the younger cohort, mean age was 6.7 years at baseline and 12.7 years at follow-up, while in the older cohort, mean age was 12.7 years at baseline and 17.3 years at follow-up. Female subjects made up of 48.2% of the younger cohort and 49.5% of the older cohort. Both cohorts were predominately European Caucasian (67.3% in younger cohort and 56.9% in the older cohort), followed by those of East Asian ethnicity (16.1% in younger cohort and 19.9% in the older cohort).

Table 7.1: Demographic and biometric characteristics of the younger cohort at baseline and at follow-up.

Characteristics (SD)	Baseline	Follow-up	P value
N	845		-
Age	6.65 (0.44)	12.73 (0.99)	-
Gender			
Male	438 (51.8%)		-
Female	407 (48.2%)		-
Ethnicity			
Caucasian	565 (67.3%)		-
East Asian	135 (16.1%)		-
Other	145 (16.7%)		-
Refractive status			
Hyperopia	91 (10.8%)	38 (4.5%)	-
Low Hyperopia	632 (74.8%)	335 (39.6%)	-
Pre-Myopia	109 (12.9%)	386 (45.7%)	-
Myopia	13 (1.5%)	88 (10.4%)	-
SER, D	1.31 (0.83)	0.59 (1.20)	<0.001
AL, mm	22.61 (0.67)	23.41 (0.79)	<0.001
ACD, mm	3.33 (0.23)	3.59 (3.99)	<0.001
CR, mm	7.79 (0.26)	7.83 (0.26)	<0.001
AL/CR	2.90 (0.07)	2.99 (0.08)	<0.001
LP, D	23.90 (1.39)	22.44 (1.64)	<0.001

Table 7.2: Demographic and biometric characteristics of the older cohort at baseline and at follow-up.

Characteristics (SD)	Baseline	Follow-up	P value
N	1115		-
Age	12.74 (0.43)	17.28 (0.49)	-
Gender			
Male	563 (50.5%)		-
Female	552 (49.5%)		-
Ethnicity			
Caucasian	633 (56.9%)		-
East Asian	221 (19.9%)		-
Other	261 (23.3%)		-
Refractive status			
Hyperopia	30 (2.7%)	27 (2.4%)	-
Low Hyperopia	405 (36.3%)	315 (28.3%)	-
Pre-Myopia	526 (47.2%)	545 (48.9%)	-
Myopia	154 (13.8%)	228 (20.4%)	-
SER, D	0.37 (1.36)	0.08 (1.62)	<0.001
AL, mm	23.41 (0.88)	23.66 (0.97)	<0.001
ACD, mm	3.53 (0.27)	3.67 (0.34)	<0.001
CR, mm	7.77 (0.26)	7.79 (0.27)	<0.001
AL/CR	3.01 (0.09)	3.04 (0.11)	<0.001
LP, D	22.14 (1.45)	22.03 (1.52)	<0.001

7.4.2 Correlations between refraction and ocular component measures

Both cohorts displayed similar correlation patterns between SER and individual biometric components, with AL correlating most strongly with SER (Tables 7.3 and 7.4). The rest of the components were poorly correlated (CR, ACD and LP), with CR not significantly correlated with SER in the older cohort. In both cohorts, AL/CR provided the strongest correlation with SER compared to any individual ocular component measure. In comparison to SER, correlations between AL/CR and the spherical component of refraction were weaker in both cohorts at both time points (Table 7.5).

Table 7.3: Cross-tabulation of Pearson's correlation coefficients between ocular component measures and SER in the younger cohort at A) baseline and B) follow-up.

	A) Baseline (6 years old)						B) Follow-up (12 years old)				
	AL	**CR**	**AL/CR**	**ACD**	**LP**		**AL**	**CR**	**AL/CR**	**ACD**	**LP**
SER	-.364*	.099*	-.617*	-.226*	.002	**SER**	-.526*	.150*	-.774*	-.113*	.117*
AL	-	.739*	.231*	.352*	-.642*	**AL**	-	.609*	.464*	.259*	-.574*
CR	-	-	-.484*	-.060	-.216*	**CR**	-	-	-.419*	.046	-.110*
AL/CR	-	-	-	.544*	-.521*	**AL/CR**	-	-	-	.244*	-.532*
ACD	-	-	-	-	-.294*	**ACD**	-	-	-	-	.128*

*P < 0.01

Table 7.4: Cross-tabulation of Pearson's correlation coefficients between ocular component measures and SER in the older cohort at A) baseline and B) follow-up.

	A) Baseline (12 years old)						B) Follow-up (17 years old)				
	AL	**CR**	**AL/CR**	**ACD**	**LP**		**AL**	**CR**	**AL/CR**	**ACD**	**LP**
SER	-.635*	.045	-.810*	-.204*	.135*	**SER**	-.696*	.044	-.855*	-.107*	.172*
AL	-	.616*	.540*	.347*	-.587*	**AL**	-	.569*	.624*	.240*	-.575*
CR	-	-	-.329*	-.010	-.166*	**CR**	-	-	-.286*	-.021	-.182*
AL/CR	-	-	-	.427*	-.528*	**AL/CR**	-	-	-	.299*	-.498*
ACD	-	-	-	-	-.263*	**ACD**	-	-	-	-	-.060*

*P < 0.01

Table 7.5: Pearson's correlation coefficients between AL/CR and the spherical component of refraction as well as SER.

			Sphere	**SER**
ALCR	**Younger cohort**	**Baseline**	-.607	-.617
		Follow-up	-.763	-.774
	Older cohort	**Baseline**	-.793	-.810
		Follow-up	-.841	-.855

Between study visits, the correlation between AL and SER was stronger at follow-up compared to baseline. This was seen in both the younger (r = -0.526 vs -0.364, follow-up vs baseline respectively) and in the older (r = -0.696 vs -0.635, follow-up vs baseline respectively) cohorts. Similarly, the correlation between AL/CR and SER was also stronger at follow-up compared to baseline, seen in both the younger (r = -0.774 vs -0.617, follow-up vs baseline respectively) and older (r = -0.855 vs -0.810, follow-up vs baseline respectively) cohorts.

Between cohorts, the correlation between AL and SER was stronger in the older cohort compared to the younger cohort. This was seen both at baseline (r = -0.635 vs -0.364, older vs younger cohort respectively) and at follow-up (r = -0.696 vs -0.526, older vs younger cohort respectively). Similarly, the correlation between AL/CR and SER was also stronger in the older cohort compared to the younger cohort, seen both at baseline (r = -0.810 vs -0.617 older vs younger cohort respectively) and at follow-up (r = -0.855 vs -0.774, older vs younger cohort respectively)

7.4.3 Correlations between changes in refraction and changes in ocular component measures

Longitudinal correlations between changes in AL/CR were also most strongly correlated with changes in SER than changes in any individual parameter (r = -0.875 & -0.815, younger and older cohort respectively) (Table 7.6).

Table 7.6: Cross-tabulation of Pearson's correlation coefficients between changes in ocular component measures and changes SER in A) the younger cohort and B) the older cohort.

	A) Younger cohort						B) Older cohort				
	ΔAL	**ΔCR**	**ΔAL/CR**	**ΔACD**	**ΔLP**		**ΔAL**	**ΔCR**	**ΔAL/CR**	**ΔACD**	**ΔLP**
ΔSER	-.823**	.071*	-.875**	-.055	.176**	**ΔSER**	-.806**	.227**	-.815**	-.033	-.072*
ΔAL	-	.243**	.926**	.120**	-.475**	**ΔAL**	-	-.015	.878**	.054	-.258**
ΔCR	-	-	-.137**	.096**	-.021	**ΔCR**	-	-	-.489**	.013	.227**
ΔAL/CR	-	-	-	.079*	-.479**	**ΔAL/CR**	-	-	-	.040	-.331**
ΔACD	-	-	-	-	.612**	**ΔACD**	-	-	-	-	.691**

*P < 0.05, **P < 0.01

7.4.4 Relationship between AL/CR and SER

Figure 7.1 shows the relationship between SER and AL/CR using linear regression modelling. In both cohorts at baseline and at follow-up, the relationship between AL/CR and SER appeared non-linear, as there was an underestimation in the degree of both hyperopia and myopia at lower and higher tails of the line of best fit. Re-modelling with LOESS smoothing curves indicated that the relationship between AL/CR and SER remained linear in nature, with three distinct phases (Figure 7.2). Piecewise linear regression performed for each group using 3 segments (Figure 7.3) displayed higher coefficient of determination (R^2) values compared to simple linear regression, indicating that the tri-phasic model was a more appropriate representation of the AL/CR vs SER relationship, with improvements in R^2 between 7-10% (Table 7.7). This is further confirmed, as asymptotic 95% CI's were all statistically significant for each slope change, indicating that each phase was defined by a distinct beta-coefficient. Optimised breakpoints and gradient coefficients for each phase are shown in Table 7.8.

Initial and final slopes for both cohorts, were all statistically similar within each phase (β between -18.05 and -20.8, all $P > 0.05$) (Table 7.8), despite two exceptions from groups which had larger gradient coefficients: the initial slope of the older cohort during SMS (β = -36.09), and the final slope of the younger cohort during SMS (β =-43.49). For the middle slope of the younger cohort, there was a significant reduction in gradient coefficient from age 6 to 12 (β = -4.17 to -5.43, $P = 0.044$), whilst in the older cohort, the gradient coefficient remained effectively unchanged between age 12 to 17 (β = -6.21 to -5.88, $P = 0.235$).

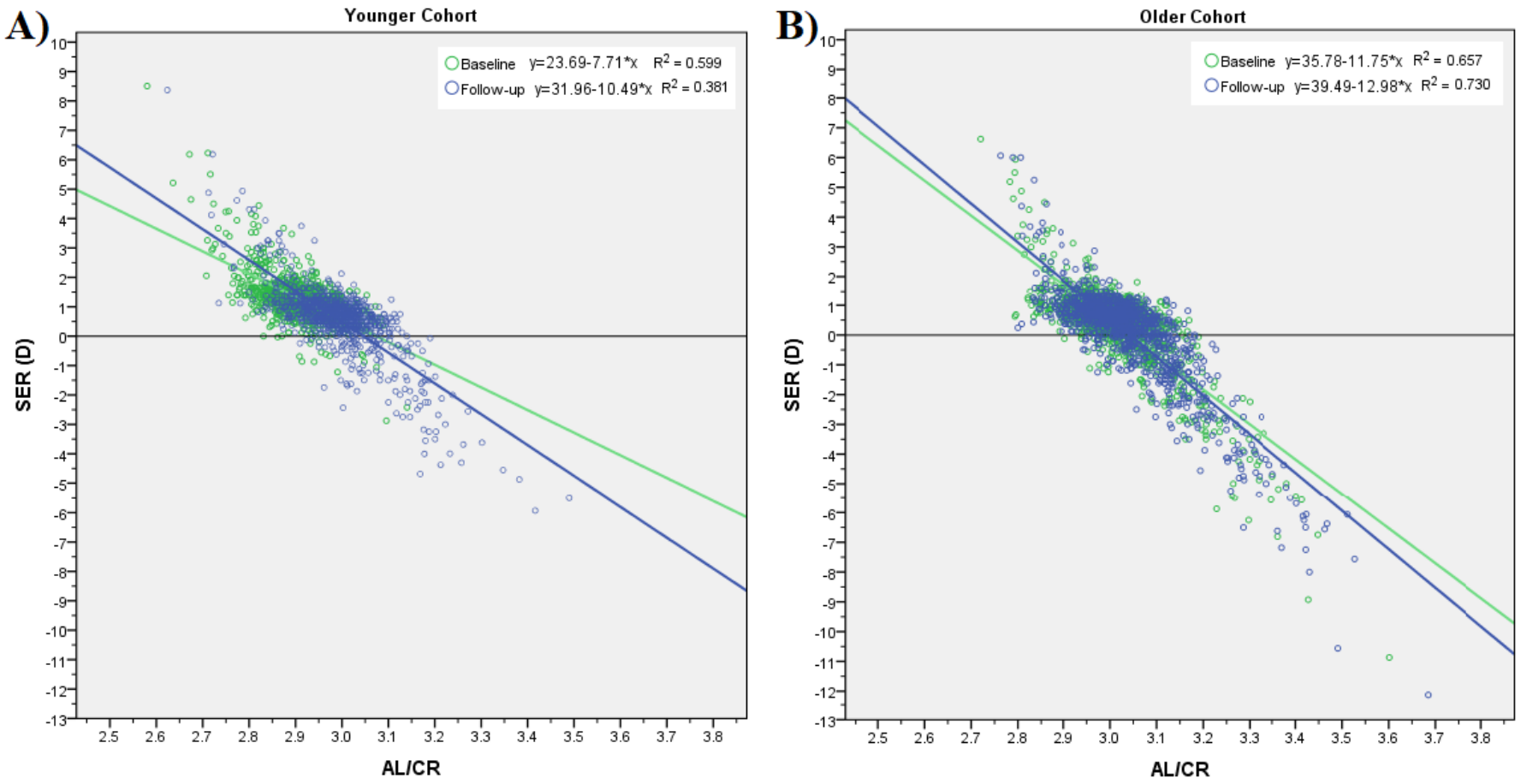


Figure 7.1: Scatter plots with linear regression fit lines for AL/CR vs SER during SMS and SAVES for the A) younger cohort and B) older cohort.

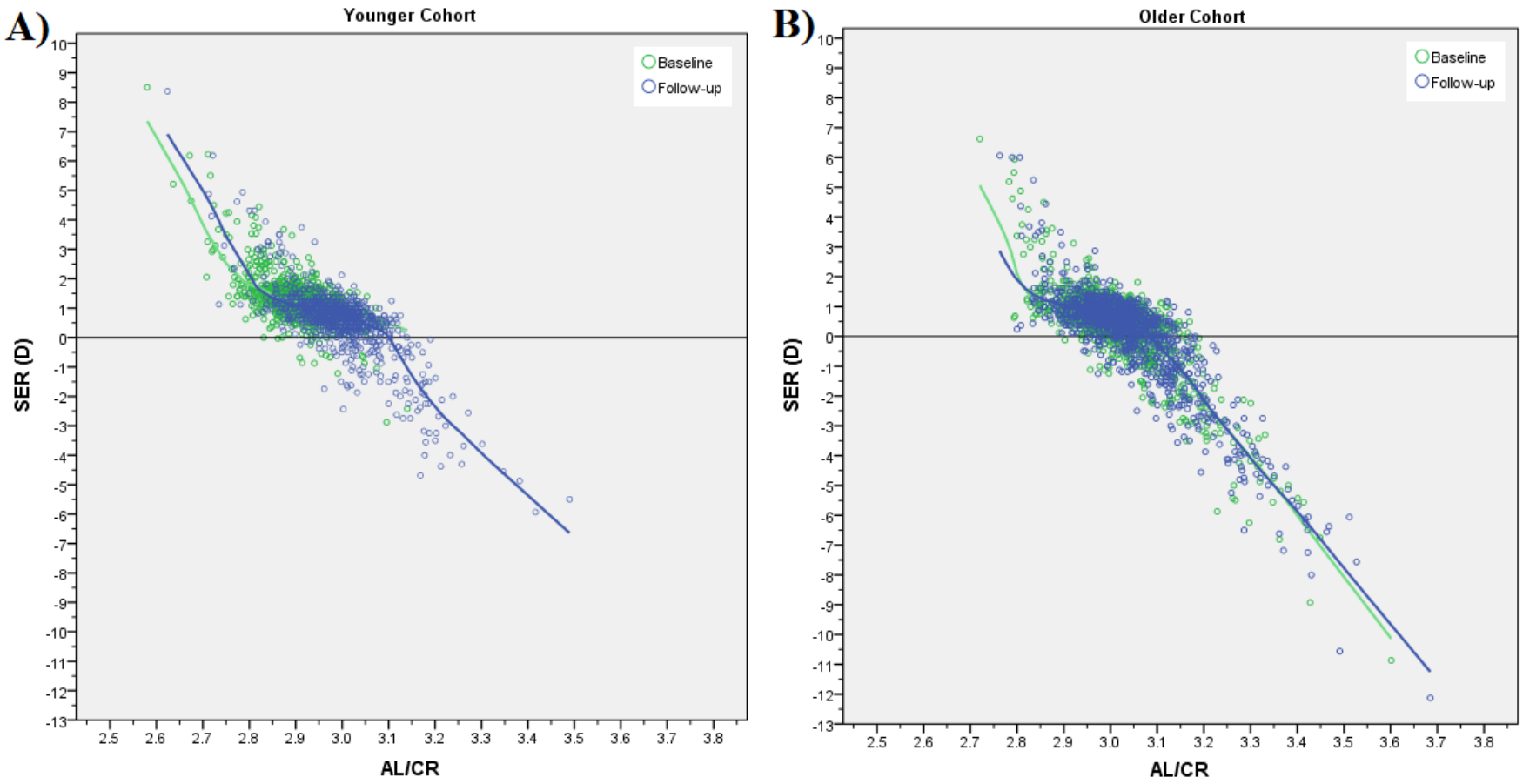


Figure 7.2: Scatter plots with LOESS smoothing curves for AL/CR vs SER during SMS and SAVES for the A) younger cohort and B) older cohort.

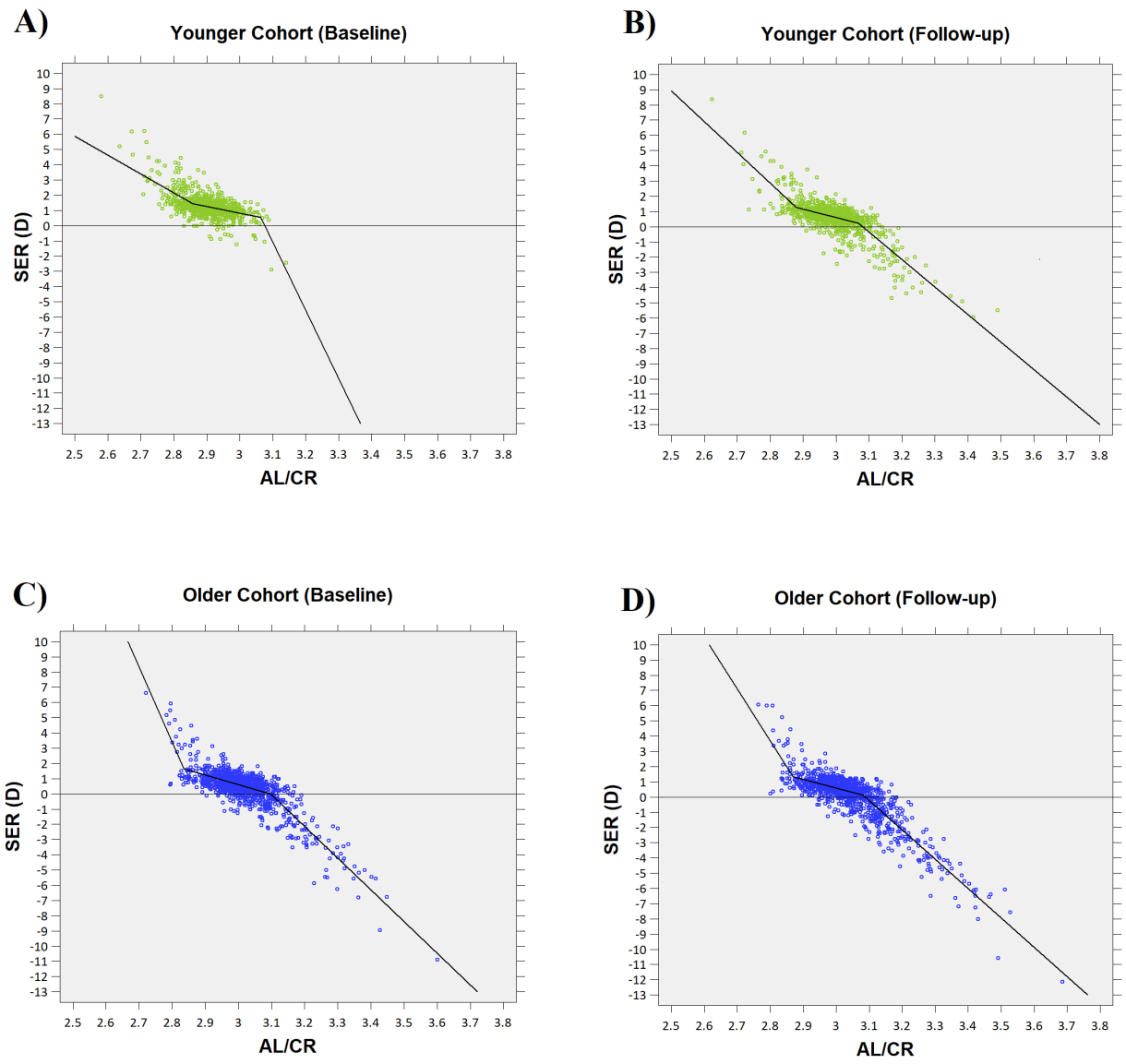


Figure 7.3: Piecewise linear regression plots for the A) younger cohort at baseline, B) younger cohort at follow-up, C) older cohort at baseline and D) older cohort at follow-up.

Table 7.7: Comparison of coefficients of determination (R^2) for AL/CR vs SER between linear and tri-phasic linear models.

	Linear model (%)	Tri-phasic model (%)
Younger cohort (baseline)	38.1	48.4
Younger cohort (follow-up)	59.9	67.2
Older cohort (baseline)	65.7	75.3
Older cohort (follow-up)	73.0	80.1

Table 7.8: Optimised values from piecewise linear regression analysis for gradients and breakpoints of a tri-phasic curve.

	Younger Cohort			Older Cohort		
	Baseline 6 y/o	**Follow-up 12 y/o**	**P value**	**Baseline 12 y/o**	**Follow-up 17 y/o**	**P value**
Initial slope (low AL/CR)	-19.11	-20.18	0.809	-36.09	-20.30	0.118
AL/CR breakpoint 1	2.84	2.88	-	2.85	2.89	-
Middle slope (middle AL/CR)	-4.17	-5.43	0.044	-6.21	-5.88	0.235
AL/CR breakpoint 2	3.06	3.07	-	3.09	3.08	-
Final slope (high AL/CR)	-43.49	-18.05	0.125	-20.80	-19.25	0.159

7.4.5 Relationship between crystalline lens power and AL/CR

The relationship between the calculated crystalline lens power (LP) and AL/CR differed across different phases of AL/CR (Tables 7.9 and 7.10). A moderate negative association between AL/CR and LP was consistently seen for individuals within the middle AL/CR phase. No significant associations between AL/CR and LP were seen for other groups except in the older cohort in the low AL/CR phase at baseline where a moderate positive association was seen. Moderate negative associations between AL/CR and LP changes in ALCR were seen across refractive categories, except in baseline myopes (Table 7.11).

Table 7.9: Pearson's correlation coefficients between AL/CR and LP, stratified by baseline AL/CR sub-group.

		Correlation AL/CR vs LP		
		AL/CR below breakpoint 1	**AL/CR between breakpoint 1 and 2**	**AL/CR above breakpoint 2**
Younger cohort	***Baseline***	-0.150	-0.460**	0.147
	Follow-up	-0.137	-0.480**	-0.007
Older cohort	***Baseline***	0.404**	-0.507**	0.019
	Follow-up	0.141	-0.467**	-0.081

**P < 0.01

Table 7.10: Pearson's correlation coefficients between changes in AL/CR and changes in SER, stratified by baseline AL/CR sub-group.

	Correlation ΔAL/CR vs ΔLP		
	AL/CR below breakpoint 1	**AL/CR between breakpoint 1 and 2**	**AL/CR above breakpoint 2**
Younger cohort	-0.523**	-0.472**	-0.591
Older cohort	-0.873**	-0.363**	-0.159*

*P < 0.05 **P < 0.01

Table 7.11: Pearson's correlation coefficients between changes in AL/CR and changes in SER, stratified by baseline refractive error category.

	Correlation ΔAL/CR vs ΔLP			
	Hyperopia	**Low Hyperopia**	**Pre-myopia**	**Myopia**
Younger cohort	-0.410**	-0.486**	-0.446**	-0.221
Older cohort	-0.466**	-0.513**	-0.329**	-0.167*

*P < 0.05 **P < 0.01

7.5 Relationship between AL/CR change and SER progression

There was a strong negative linear relationship seen between changes in AL/CR and SER progression (R^2: 0.765 & 0.664 for younger and older cohorts respectively) (Figure 7.4). Gradient coefficients between younger and older cohorts were not significantly different (P = 0.840).

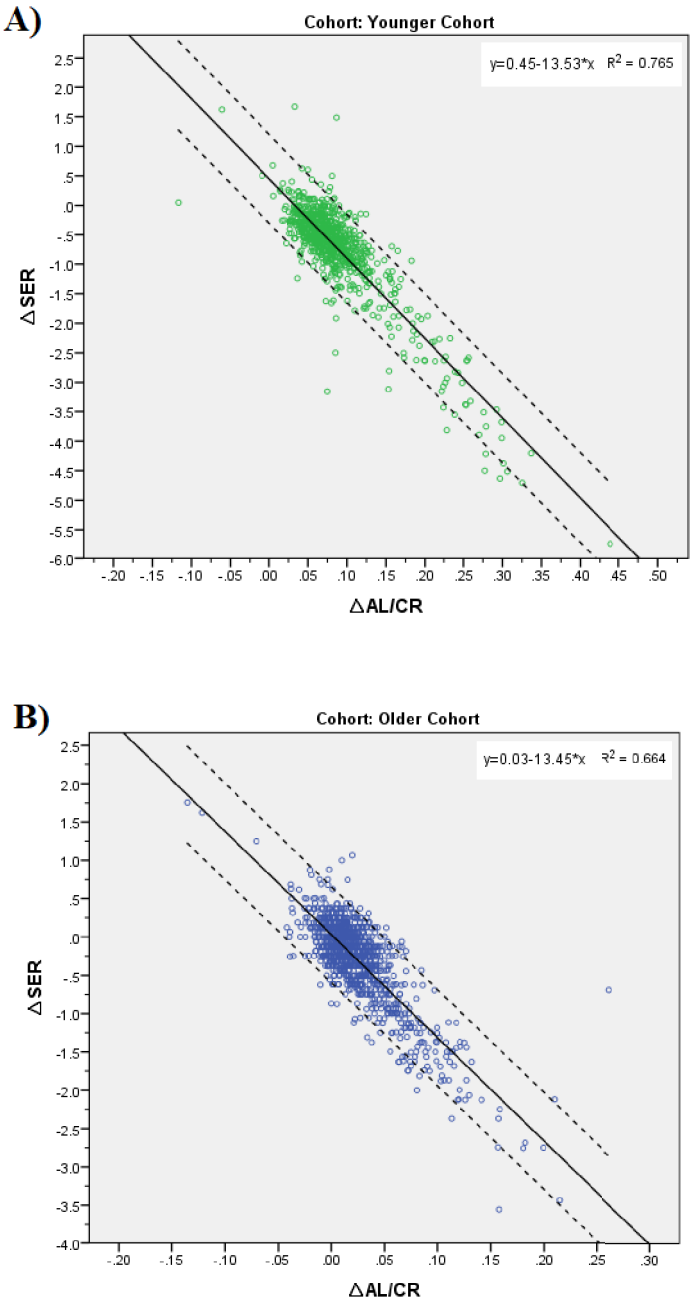
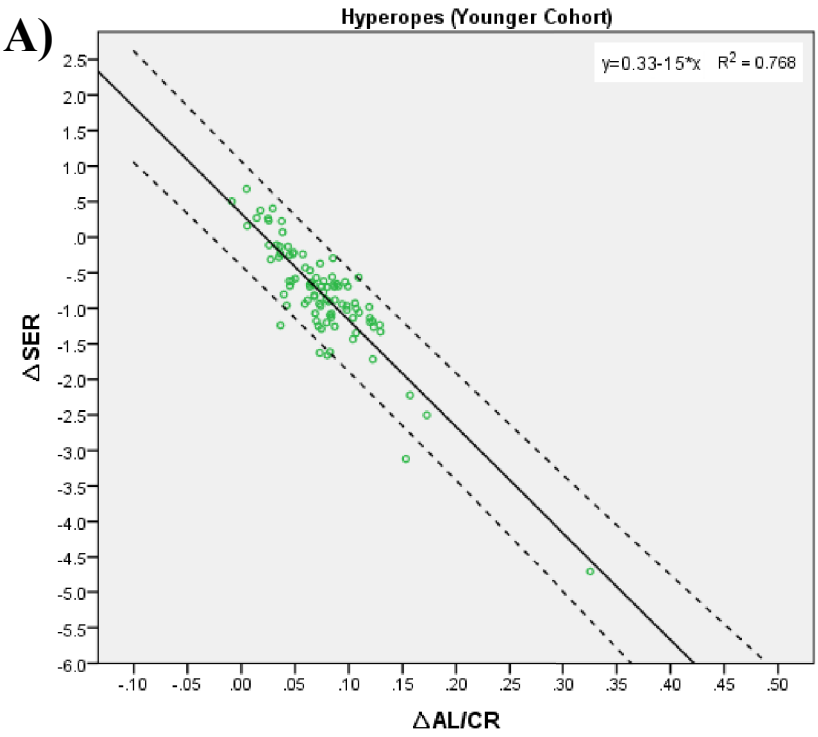


Figure 7.4: Scatter plot of AL/CR change vs SER change with linear regression (solid) and 95% confidence interval (dotted) lines drawn for the A) younger and B) older cohort.

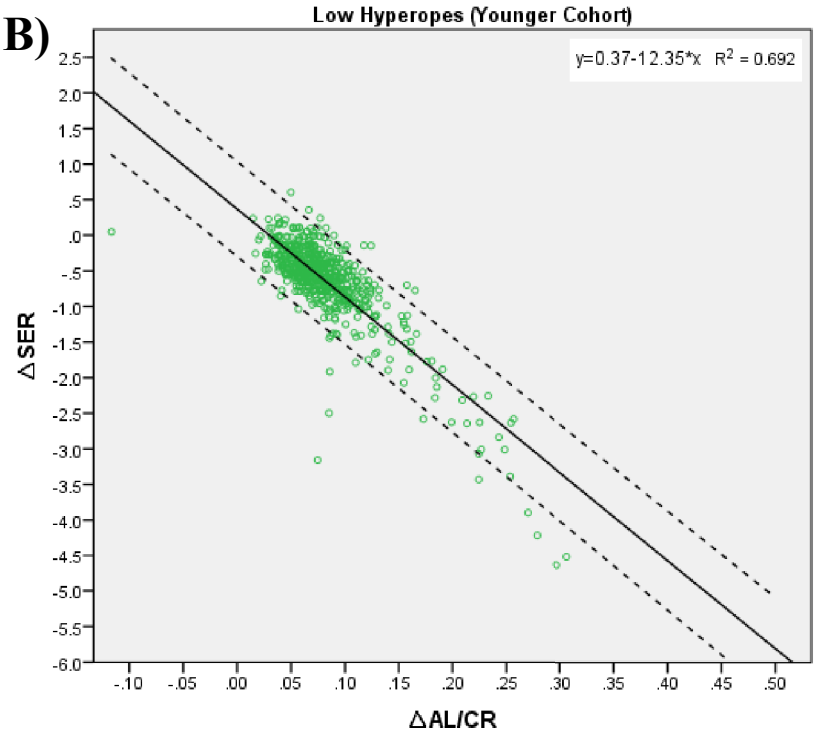
7.5.1 Influence of baseline refractive group on AL/CR change vs SER progression

Figures 7.5 and 7.6 show the relationship between AL/CR change and SER change stratified by baseline refractive group in the younger and older cohorts. In both cohorts, strong negative linear relationships are seen between changes in AL/CR and changes in SER, except for those classified as low hyperopes at baseline who displayed lowest R^2 values. Gradient co-efficients between baseline refractive groups were significantly different in both age cohorts (both $P < 0.001$). After exclusion of low hyperopes, gradient coefficients were similar between the remaining refractive groups ($P = 0.085$ & 0.164, younger and older cohorts respectively). In both age groups, baseline myopes displayed the strongest linear relationships between changes in AL/CR and changes in SER ($R^2 = 0.880$ and 0.853, younger and older cohort respectively). Within baseline myopes of the younger cohort, the linear regression model using AL/CR changes determined that 95% of predicted SER changes were within ± 1.855 D of actual SER (Figure 7.5D). Meanwhile in baseline myopes of the older cohort, the linear regression model using AL/CR changes was able to determine that 95% of SER changes were within ± 0.660 D of actual SER (Figure 7.6D).

A)


Hyperopes (Younger Cohort)
y=0.33-15*x R² = 0.768
ΔSER
ΔAL/CR

B)


Low Hyperopes (Younger Cohort)
y=0.37-12.35*x R² = 0.692
ΔSER
ΔAL/CR

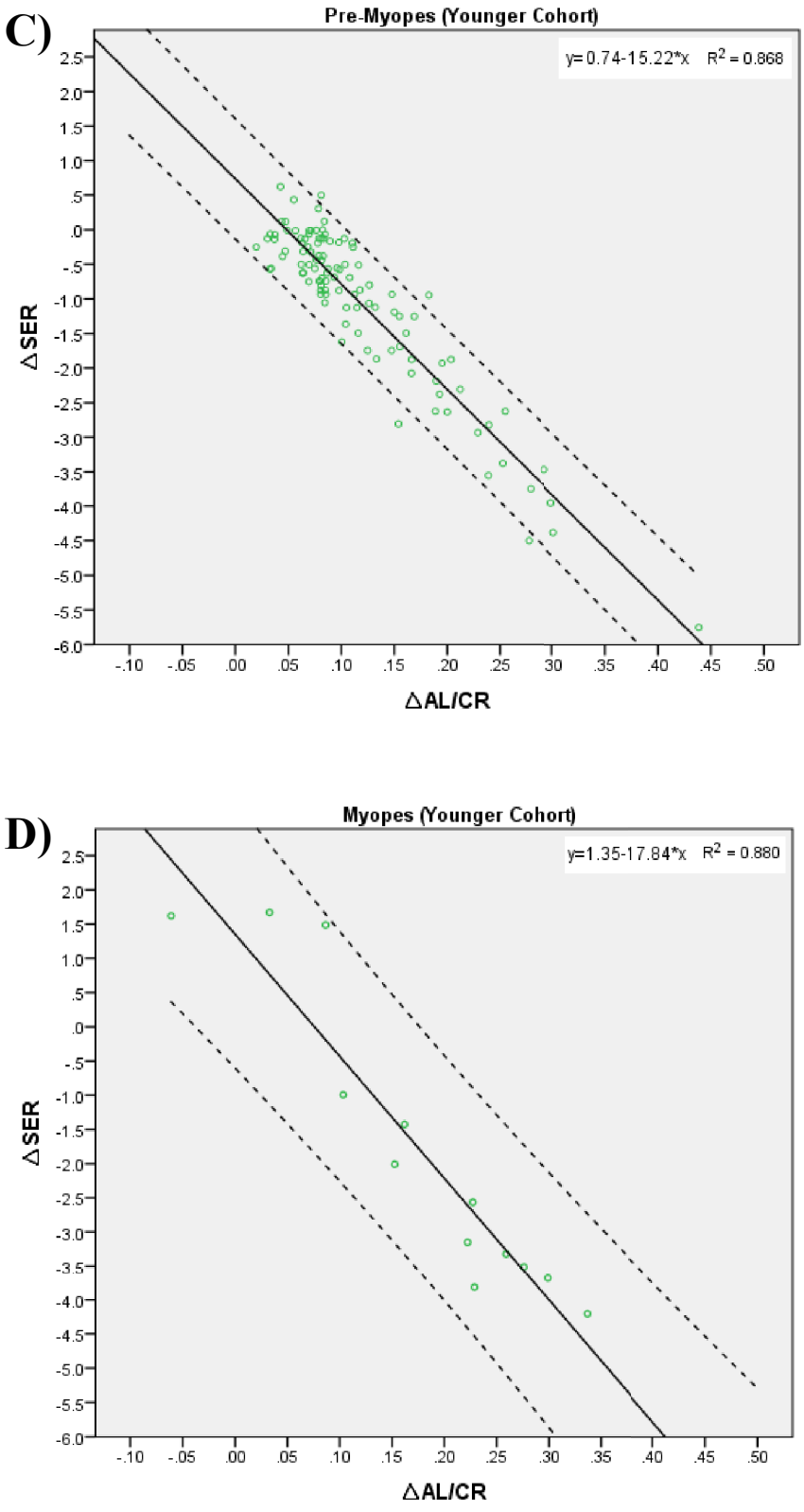
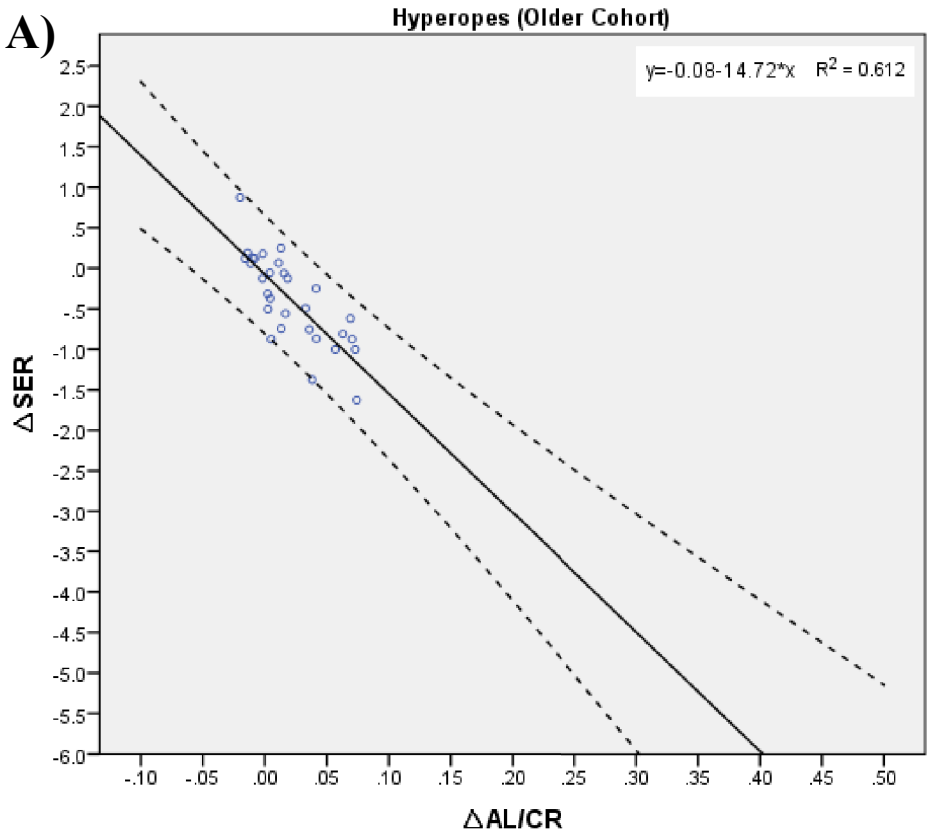
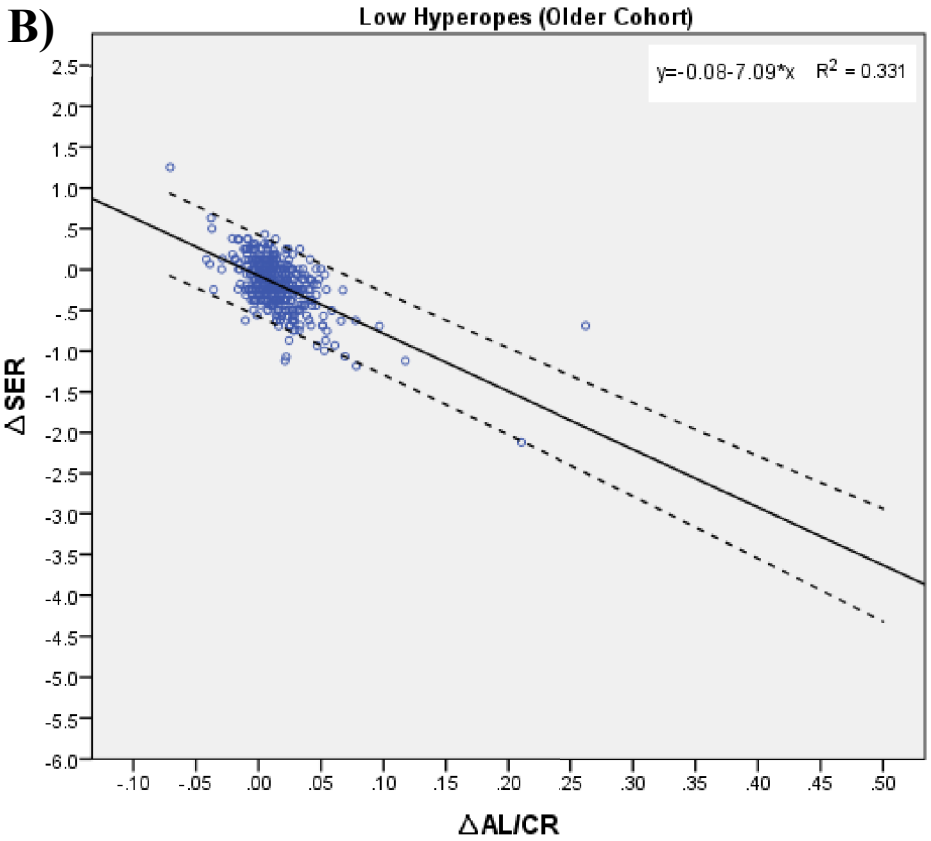


Figure 7.5: Scatter plot of AL/CR change vs SER change with linear regression (solid) and 95% confidence interval (dotted) lines drawn for baseline refractive groups in the younger cohort: A) hyperopia B) low hyperopia C) pre-myopia and D) myopia.


A)
Hyperopes (Older Cohort)
y=-0.08-14.72*x R² = 0.612
ΔSER
ΔAL/CR


B)
Low Hyperopes (Older Cohort)
y=-0.08-7.09*x R² = 0.331
ΔSER
ΔAL/CR

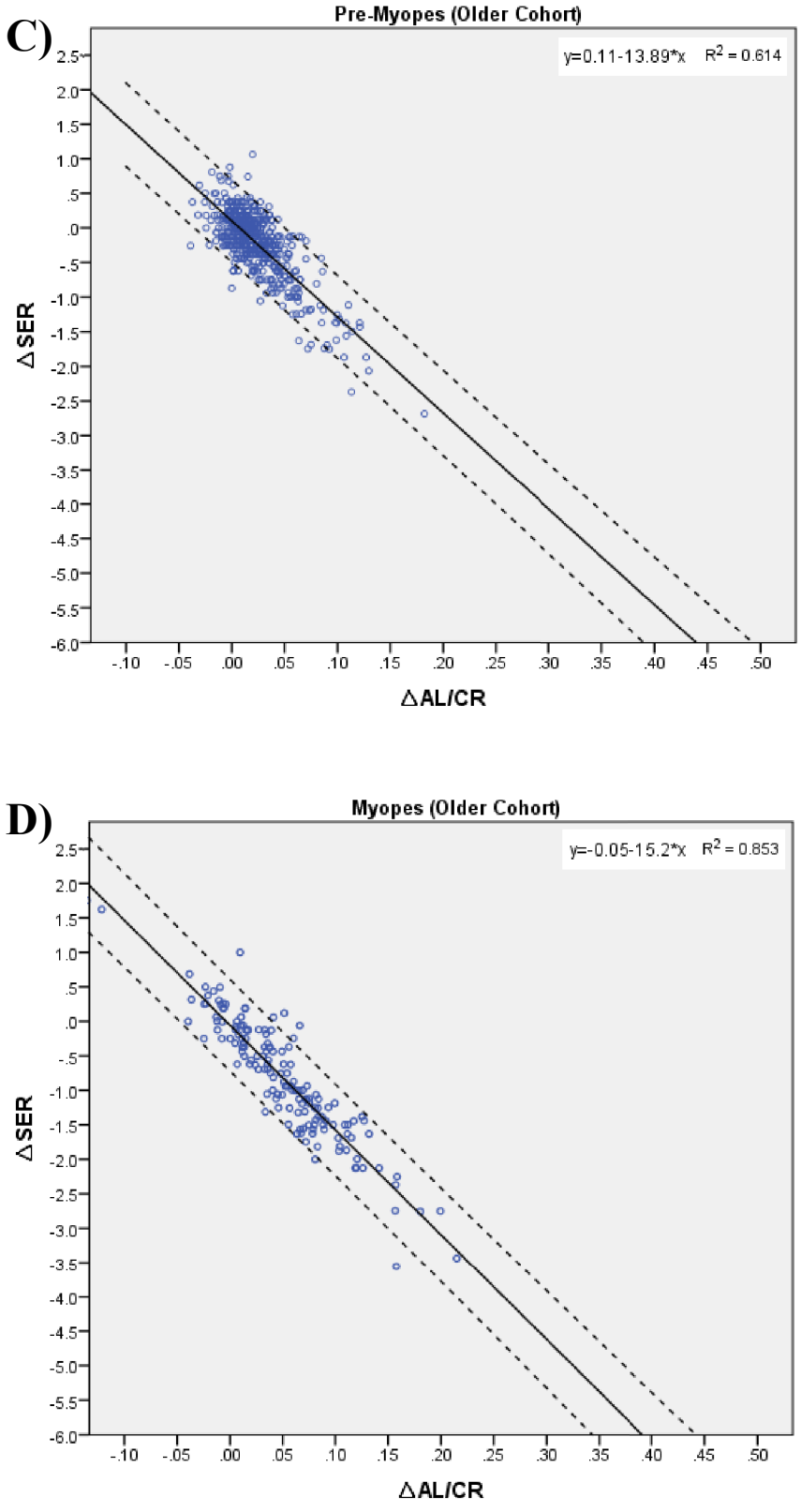


Figure 7.6: Scatter plot of AL/CR change vs SER change with linear regression (solid) and 95% confidence interval (dotted) lines drawn for baseline refractive groups in the older cohort: A) hyperopia B) low hyperopia C) pre-myopia and D) myopia

7.6 Discussion

This study finds that the combination of two biometric parameters; axial length and corneal radius, into a single variable (AL/CR), was more closely related to spherical equivalent refraction than any single optical component measure. AL/CR was also more closely related to the spherical equivalent refraction rather than the purely spherical component of refraction. Though the strength of the relationship between AL/CR and SER has been well-established from the existing literature using linear regression,[19-23] we find that this relationship occurs via a segmented tri-phasic linear relationship rather than a strictly linear pattern.

While this pattern has appeared in previous studies,[23, 49, 50, 52] only two studies have described a non-linear relationship occurring between these two variables. Jong et al,[50] found that this relationship was best described via an inverse quadratic model, indicating that the slopes/beta coefficients for determining SER increased with increasing levels of AL/CR. Meanwhile, Tao et al,[52] recognized that the relationship between AL/CR and SER was not a simple linear relationship, due to differences in correlation coefficients and slopes between non-myopes, where there was no linearity, and myopes who displayed linear associations. Differences in models obtained between these two studies and our findings are likely due to the fact that both studies were performed in cohorts with high levels of prevalent myopia, thus limited data on the nature of the relationship in individuals with hyperopia. More specifically in Jong's model, the internal differences found within their myopic groups may be due to the use of two independent population samples to compare low and high myopic groups, and despite statistical adjustment, age-related interactions with AL/CR may have contributed to the discrepancy.

Our analysis also finds that the relationship between AL/CR and SER may be influenced by a number of factors. Most significantly, the tri-phasic nature of the AL/CR-SER relationship suggests that variation occurs across different states of refraction, as also indicated by a number of previous studies, which find differences in levels of correlation and slope gradients across ametropic

groups.[22, 23, 48, 50-52] However, our data suggests that these variations are tied to levels of AL/CR rather than traditional refractive categories, as the location of the points of slope changes for each of the three phases do not necessarily correspond with conventional SER thresholds for refractive errors (e.g. hyperopia, emmetropia and myopia).

However, the slope changes were consistent at similar AL/CR points for both cohorts examined at both baseline and follow-up; between 2.84–2.89 for the first point and between 3.06–3.09 for the second point (Table 8). Converting the AL/CR breakpoints into SER values place their location at mildly hyperopic values centered around +1.00 D (Figure 7.3). This is likely related to the view that distributions of refractive errors in a population without a high prevalence of myopia, does not centre on a spherical equivalent refraction of zero, but more so in a significantly hyperopic area,[66] indicative of where the ideal state of refraction may be. Between the two breakpoints of the tri-phasic regression line, SER is distributed tightly among individuals with different AL/CR values, compared to those in the higher and lower tails of the AL/CR spectrum, where larger differences in SER are seen.

As the AL/CR variable does not take into account influences from the crystalline lens, differences in lens powers between individuals of different AL/CR levels are likely acting to minimise or offset the large shifts in refraction that could be expected from the increases in AL/CR, keeping the eye in a state of mild hyperopia.[113] This was shown through significant negative correlations between crystalline lens power and AL/CR that only occurred for individuals with AL/CR values between the two breakpoints (Table 7.9). This is consistent with a number of emerging reports documenting crystalline lens power reductions in low hyperopes.[54, 703, 704] This effect has been said to diminish with age, due to age-related reductions in rates of lens thinning. Our results, however, suggest this also occurs in older children, given by the shape of the AL/CR vs SER relationship in the older cohort Figures 7.2 and 7.6, who were 12 years old at baseline. There is, however, an indication of a reduction in lens compensation seen through the increases in the gradient co-efficient between

baseline and follow-up for the younger cohort (Table 7.8), coupled with the larger reductions in lens power seen in the younger cohort compared to the older cohort (Tables 7.1 and 7.2). While there was not enough data to perform meaningful analyses across subgroups of AL/CR to examine other influences such as ethnicity and lifestyle, the established relationship between AL/CR and SER, suggests that apparent differences in the strength of association between AL/CR and SER seen may be confounded by refraction. For example with ethnicity, the stronger correlation between AL/CR and SER among East Asian children compared to European Caucasian children seen by Ip et al,[57] was likely due to the higher prevalence of myopia in the East Asian population.

In terms of longitudinal effects, individual changes in AL/CR and SER progression initially appeared to be linearly related, with 76.5% and 66.4% of the variance in SER changes within the younger and older cohort accounted for by changes in AL/CR. This was also supported by the fact that gradient co-efficients between changes in AL/CR vs SER were identical between the younger and older cohort. This suggests that changes in AL/CR results in constant changes in SER despite differences in baseline refraction. However, this would have been paradoxical with what was seen cross-sectionally in the AL/CR vs SER relationship.

Subsequently, stratifying by baseline refractive error group (Figures 7.5 and 7.6), identified differences in the AL/CR vs SER relationship, distinctly in the low hyperope group, where an increase in AL/CR over time produced significantly less myopic shifts in refraction than all other groups. The overall association between the two variables was also weaker (indicated by lower r^2 values) in low hyperopes than all other refractive groups. Significant negative correlations also occurred between changes in lens power and changes in SER, which diminishes in myopes (Table 7.11) and at high levels of AL/CR (Table 7.10). Similar findings have been reported by Xiong et al,[703] who also found significant negative correlations between changes in axial elongation and lens power in non myopes and new-onset myopes but not in existing myopes. In another study by Ma et al,[704] hyperopic shifts in refraction occurred more commonly in those with refractions ≤ 1.00 D with significant associations

between changes in lens power and baseline refraction also seen, explaining this phenomenon. All together, these findings indicate that lenticular changes in optical power are involved in maintaining an ideal state of refraction (low hyperopia) in the face of eye growth, particularly increased axial elongation and increasing AL/CR.

Naturally, when this process fails to be sufficient, either from natural reductions in the rate of lens thinning and associated loss of power or through excessive axial elongation, then stronger linear associations between increases in axial length and myopic shifts can be expected, as was seen in our study in baseline myopes who displayed the strongest correlations between AL/CR changes and SER change (Figures 7.5 and 7.6). Though this could only be reliably determined in the older cohort, due to a limited number of baseline myopes in the younger cohort. In this group, the linear model was able to determine SER within ± 0.660 D of its cycloplegic value in 95% of existing myopes, a result comparable to the uncertainty expected from conventional direct methods of refraction (± 0.6 D).[705]

Only one other study has longitudinally compared changes between AL/CR and SER progression with less consistent findings. While appearing linear, Jong et al,[50] reported that changes in AL/CR were not strongly related to SER progression (r^2 = 0.45) and that AL/CR explained less of the variance in refractive progression compared to changes in AL alone (45% vs 52% respectively).[50] This resulted the 95% predictive intervals between changes in SER and changes in AL/CR to be larger than compared to our study. Differences in these strengths of association are likely due to statistical effects from differences in study durations and sample size. Our study had a longer follow-up interval and hence there was a larger range of refractive progression seen in our participants. We also had larger sample sizes in our two groups, thus correlations would naturally be higher. Despite this, the older cohort of our study still showed a comparably high level of correlation, yet had rates of refractive progression that were much lower than the younger cohort and comparable to the degree of progression seen in the one year of Jong's study. As their population contained only

myopic participants, refractive progression would most likely be predominantly axially driven, thus explaining their stronger association seen between AL and SER.

The major strength of this study is that it is a longitudinal study into AL/CR, containing detailed measurements of cycloplegic refraction and biometry from ethnically diverse participants. Included are two age groups where significant refractive development occurs, allowing the examination of age-related trends. On the other hand, a limitation of this study is that a large number of initial participants were lost to follow-up (~50%) due to the 5–6 year follow-up period. Another limitation may have come from the fact that crystalline lens power was indirectly calculated without input from phakometry/lens thickness measures. However, given that biometric measurements remained consistent throughout the study, relative differences in lens power between individuals could still be examined using the Bennet and Rabbett's formula.

In conclusion, the measurement of ocular biometry to capture the axial length to corneal radius ratio provides a simple, non-invasive method to potentially quantify refractive errors and to monitor for its progression. Our findings suggests that AL/CR cannot be solely used to determine the magnitude of an individual's spherical equivalent refraction, as the interaction between these variables is more complicated than a simple linear relationship due to lenticular changes being involved. However, as linearity exists in the absence of lenticular involvement, particularly in existing myopes, AL/CR can potentially be incorporated as a supplementary measure alongside cycloplegic refraction to provide additional information on an individual's refractive trajectory. By capturing changes in the AL/CR value in myopes, a simple linear regression formula was able to determine changes in cycloplegic refraction at a level of precision comparable to conventional methods of refraction. This non-invasive method provides the opportunity for more frequent analysis of refractive changes within longitudinal studies and clinical trials and allows the examination of seasonal variations in myopia progression that may be missed with annual captures of cycloplegic refraction.

Chapter 8: Ocular Biometric Changes during Childhood Refractive Development and the Role of the Axial Length to Corneal Radius Ratio in Predicting Myopia Onset

8.1 Abstract

Purpose: To describe longitudinal changes in ocular biometrics and investigate their predictive roles for determining incident myopia in Australian schoolchildren.

Methods: Ocular biometry and cycloplegic autorefraction was measured in 1,960 children from two age cohorts (6 and 12 year olds) and repeated 5–6 years later as part of a longitudinal follow-up. Children not myopic at baseline and who became myopic at follow-up [defined as a right spherical equivalent refraction (SER) of ≤ -0.50 D] were classified as having incident myopia. Axial length to corneal radius (AL/CR) ratio and crystalline lens power were calculated. Changes in ocular biometric components were compared between refractive groups. Logistic regression and ROC analysis were performed to predictively model the relationship between biometric variables and incident myopia.

Results: Significant changes in all biometric components occurred in both age cohorts (all $P < 0.001$). These changes decreased in magnitude in the older cohort (all $P < 0.001$). Children who became myopic and those with existing myopia exhibited significant differences in axial elongation rates and AL/CR changes that were greater in magnitude than all other refractive groups. Baseline AL/CR was a stronger predictor of incident myopia (AUC, younger: 0.629, older cohort: 0.781) than any individual biometric measure. However, SER remained the strongest predictor for myopia (AUC, younger: 0.844, older cohort: 0.916). Children in the younger cohort with an AL/CR ≥ 2.95 and children in the older cohort with an AL/CR ≥ 3.00 were more likely to develop myopia than those with a lower AL/CR measure.

Conclusion: An individual's AL/CR is highly predictive of incident myopia, and may prove to be an alternative to cycloplegic refraction. In combination with other known risk factors, young children at risk of developing myopia may be more readily identified.

8.2 Introduction

Myopia is a growing health concern, following its rapid increase in prevalence over the past decades in younger populations.[706] This has been most severe in urban areas within East Asia, where approximately 85% of high-school leavers are now myopic.[123] Though the visual symptoms of myopia can be corrected with spectacles, contact lenses or refractive surgery, early onset myopia is associated with a greater likelihood of developing high myopia later in life,[707] and therefore increased risk of potentially blinding pathological complications such as retinal detachment and myopic maculopathy.[708] These issues can be expected to become more severe in the near future, with projections estimating ongoing rises in both myopia and high myopia through to the year 2050.[2]

Fortunately, several interventions are available that have demonstrated they are able to slow the progression of myopia,[709] such as low-dose atropine and specialised lens designs.[315, 319, 364] But what has been ground-breaking is the discovery that myopia can be prevented through environmental modifications that increase time spent outdoors,[371-374, 487, 645] allowing alternative public health strategies for myopia control. In countries where there are already high levels of myopia, it may be more effective to focus on reducing progression in those already myopic while implementing broad public health programmes and educational reforms. However, populations which currently have lower prevalence rates of myopia may find it more effective to selectively target intervention strategies to high risk individuals. If this is the case, reliable methods of predicting myopia are needed.

Currently there are several known risk factors that may influence an individual's risk of developing myopia, such as lifestyle and environmental exposures, ethnicity and parental myopia status.[682] Another major risk associated with myopia are ocular biometric measures and refraction during development. Of these variables, several longitudinal studies have found spherical equivalent refraction (SER) to be the strongest risk factor for myopia development,[69, 555, 710, 711] with a lower SER associated with an increased risk of incident myopia, particularly at a young age.

The axial length to corneal radius ratio (AL/CR) is a unit derived from two individual ocular components that are closely related to SER. [19-23, 48] Its role as a risk factor for myopia was first described in 1988 by Theodore Grosvenor,[712] who stated that "an eye having a high AL/CR ratio is at risk for the development of myopia, and that such an eye has maintained its state of emmetropia by virtue of a compensatory flattening of the crystalline lens". However despite over 20 years since this proposal, the role of AL/CR in determining myopia risk remains unclear, with conflicting outcomes reported between two longitudinal studies. Following a 14-year prospective study of children 6–12 years old (COMET), Scheiman et al reported that baseline AL/CR was not a risk factor for myopia progression.[53] More recently, Tao et al reported that a higher baseline AL/CR was a weak risk factor for developing myopia after 1.5 years in children aged between 6 and 15 years old.[52]

Previously in Chapter 7, we identified that the nature of the relationship between refraction and ocular biometry varies across different levels of AL/CR. More specifically, this occurs via a tri-phasic linear pattern, where low hyperopes, with AL/CR levels lying in the plateau between the two breakpoints of the three linear phases, exhibit less myopic shifts in response to increases in AL/CR. This effect was attributed to crystalline lens changes that are believed to act in order to maintain refractive errors in a state of low hyperopia despite increases in ocular globe size. As a consequence, at AL/CR levels after the second breakpoint away from the plateau towards myopic measures, increases in axial length have significant linear effects on SER progression. As this breakpoint occurs during low hyperopia, well before individuals are defined as myopic, it suggests that the AL/CR value may be implicated as a risk factor/predictor for myopia. As biometric measures can be more readily obtained compared to cycloplegic refraction, the consideration of AL/CR values provide an additional non-invasive metric to perform frequent myopia risk assessments, such as in childhood population screening programs.

This chapter aims to use data from a population-based longitudinal study of refraction and biometric components to compare differences in changes in refraction and ocular biometrics among refractive groups and to examine biometric predictors associated with myopia development.

8.3 Methods

Detailed methodology has been described in Chapter 2.

8.3.1 Population

The Sydney Myopia Study (SMS) was a population-based cross-sectional cluster study that examined schoolchildren in two age samples, 6 and 12 years, from schools across the Sydney metropolitan area. The Sydney Adolescent Vascular and Eye Study (SAVES) was 5- to 6-year longitudinal follow-up study of the SMS cohort. Of the original SMS sample, 2103 children were re-examined in SAVES: 892 (50.5%) from the younger cohort and 1,211 (51.5%) from the older cohort. The mean time between baseline and follow-up examinations was 6.1 years for the younger cohort and 4.6 years for the older cohort.

8.3.2 Eye examination

All children completed a comprehensive eye examination at both baseline (SMS) and follow-up (SAVES) that included cycloplegic autorefraction; using the Canon RK-F1 (Canon, Tokyo, Japan); and measures of ocular biometry [axial length (AL), anterior chamber depth (ACD), corneal radius (CR)]; using the IOLMaster TM (Carl Zeiss, Meditec AG Jena, Germany). Cycloplegia was induced by 1 drop each of cyclopentolate 1% and tropicamide 1% administered in 2 cycles, 5 minutes apart, following corneal anesthesia with amethocaine hydrochloride 1%. Crystalline lens power (LP) was calculated using the Bennet and Rabbetts formula.[701, 702] The axial length to corneal radius (AL/CR) ratio was calculated from individual AL and CR measures. Refractive errors were categorised using the following definitions: hyperopia (> 2.00 D), low hyperopia (> 0.75 D to ≤ 2.00 D), pre-myopia (> -0.50 D to ≤ 0.75 D) and myopia (≤ -0.50 D). Questionnaires were completed by parents of participating children to determine gender and ethnicity (for further detail see Chapter 2).

8.3.3 Data analysis

Paired t-tests were used to compare ocular component values between baseline and follow-up, while independent samples t-tests were used to compare ocular component values between the younger and older cohort. Participants were classified into the following refractive groups depending on their refractive status at baseline and follow-up: persistent hyperopes, emmetropising hyperopes, persistent emmetropes, became myopes, remained myopes and those who underwent a hyperopic shift in refractive status. Differences in baseline ocular component values and their changes between baseline and follow-up were assessed by one-way ANOVA's. The relationship between baseline AL/CR and refractive progression was examined using Pearson's correlation. Among non-myopic participants, univariate and multi-variate logistic regression analysis was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs), for incident myopia using the ocular component values as covariates and adjusting for sex and ethnicity. Receiver operating characteristic (ROC) analysis was conducted on variables found significant from multi-variate analysis to obtain the area under the curve (AUC) values for determining the predictive ability of each variable.

Statistical significance was determined by an alpha level of 5%. All statistical analyses were performed using the statistical package SPSS Statistics for Windows (version 23.0; IBM Corp., Armonk, NY).

8.4 Results

8.4.1 Sample population characteristics

Characteristics of the sample population has been previously described in Chapter 7, Section 7.3.1.

8.4.2 Longitudinal changes in refraction and optical component measures

In the younger cohort at baseline, most children were low hyperopes (74.8%), followed by pre-myopes (12.9%), hyperopes (10.8%) and then myopes (1.5%). By the follow-up, prevalence rates of hyperopes and low hyperopes had decreased (prevalence rate: 4.5% and 39.6% respectively), while prevalence rates of pre-myopia and myopia increased (prevalence rate: 45.7% and 10.4% respectively). All biometric components were statistically significantly different at follow-up compared to baseline (all $P < 0.001$). Mean SER decreased by 0.72 D (95% CI: 0.67–0.78), mean AL increased by 0.80 mm (95% CI: 0.78–0.83), mean CR increased by 0.04 mm (95% CI: 0.04–0.05), mean ACD increased by 0.26 mm (95% CI: 0.24–0.28), mean AL/CR increased by 0.09 (95% CI: 0.08–0.09) and mean LP decreased by 1.54 D (95% CI: 1.47–1.62).

In the older cohort at baseline at age 12, most were pre-myopes (47.2%), followed by low hyperopes (36.3%), myopes (13.8%) and then hyperopes (2.7%). By the follow-up, prevalence rates of hyperopes and low hyperopes had decreased (prevalence rate: 2.4% and 28.3% respectively), while prevalence rates of pre-myopia and myopia increased (prevalence rate: 48.9% and 20.4% respectively). All biometric components were statistically significantly different at follow-up compared to baseline (all $P < 0.001$). Mean SER decreased by 0.29 D (95% CI: 0.26–0.32), mean AL increased by 0.25 mm (95% CI: 0.24–0.26), mean CR increased by 0.02 mm (95% CI: 0.02–0.02), mean ACD increased by 0.15 mm (95% CI: 0.13–0.16), mean AL/CR increased by 0.02 (95% CI: 0.02–0.03) and mean LP decreased by 0.11 D (95% CI: 0.07–0.16).

8.4.3 Longitudinal changes in refraction and optical component measures between cohorts

Rates of change for myopic shift, axial elongation, corneal radius flattening, anterior depth deepening, lens power thinning and AL/CR increases between baseline and follow-up were all significantly lower in the older cohort compared to the younger cohort (all P < 0.001) (Table 8.1).

Table 8.1: Comparison of changes in spherical equivalent refraction and optical component values across baseline to follow-up between the younger and older cohort.

	Cohort	Mean change (Follow-up - Baseline)	Std. Deviation	Mean Difference	P value
ΔSER (D)	***Younger***	-0.723	0.79	-0.433	<0.001
	Older	-0.291	0.55		
ΔAL (mm)	***Younger***	0.803	0.40	0.553	<0.001
	Older	0.250	0.23		
ΔCR (mm)	***Younger***	0.043	0.05	0.022	<0.001
	Older	0.021	0.04		
ΔACD (mm)	***Younger***	0.260	0.36	0.115	<0.001
	Older	0.145	0.29		
ΔLP (D)	***Younger***	-1.545	1.07	-1.433	<0.001
	Older	-0.111	0.79		
ΔALCR	***Younger***	0.087	0.05	0.063	<0.001
	Older	0.024	0.03		

8.4.4 Biometric changes between refractive groups

Tables 8.2 and 8.3 compare changes in biometric optical component measures between baseline refractive groups. In the younger cohort, significant differences in myopic shifts, axial elongation, crystalline lens power reduction and AL/CR increases were seen between refractive groups. Post-hoc testing found similar changes in all components between hyperopes and low hyperopes. Pre-myopes exhibited similar changes in SER to hyperopes and low hyperopes, however, exhibited larger increases in AL and AL/CR. LP reduction in pre-myopes was greater than in hyperopes, but the not low-hyperopes. Myopes showed the largest changes in SER, AL, LP and AL/CR than all other groups.

In the older cohort, significant differences in myopic shifts, axial elongation, corneal radius increases, crystalline lens power reduction and AL/CR increases were seen between refractive groups. Post-hoc testing found that low hyperopes had smaller myopic shifts than hyperopes, but exhibited similar changes in all biometric measures. Pre-myopes exhibited similar changes to both hyperopes and low-hyperopes, except they had lower LP changes to the hyperopes. Again those with myopia showed the largest changes in SER, AL and AL/CR yet had similar LP changes to the low hyperopes and pre-myopia groups.

Table 8.2: Longitudinal changes in biometric optical component measures between baseline refractive groups in the younger cohort.

Younger Cohort	Baseline Refractive Group			
	Hyperopia (> 2.00D)	**Low Hyperopia (> 0.75D to ≤ 2.00D)**	**Pre-Myopia (> -0.50D to ≤ 0.75D)**	**Myopia (≤ -0.50D)**
n	91	632	109	13
ΔSER*	-.805	-.637	-1.026	-1.839
ΔAL*	.727	.759	1.034	1.572
ΔCR	.047	.041	.046	.069
ΔACD	.237	.263	.272	.202
ΔLP*	-1.272	-1.490	-1.946	-2.734
ΔAL/CR*	.076	.081	.116	.179

***P < 0.05 between groups, ⌊____⌋ = P ≥ 0.05**

Table 8.3: Longitudinal changes in biometric optical component measures between baseline refractive groups in the older cohort.

Older Cohort	Baseline Refractive Group			
	Hyperopia (> 2.00D)	**Low Hyperopia (> 0.75D to ≤ 2.00D)**	**Pre-Myopia (> -0.50D to ≤ 0.75D)**	**Myopia (≤ -0.50D)**
n	30	405	526	154
ΔSER*	-.381	-.184	-.215	-.815
ΔAL*	.233	.172	.243	.484
ΔCR*	.025	.018	.021	.030
ΔACD	.251	.155	.142	.110
ΔLP*	.271	.021	-.225	-.149
ΔAL/CR*	.021	.015	.023	.050

***P < 0.05 between groups, ⌊____⌋ = P ≥ 0.05**

8.4.5 Biometric changes during the development of refractive errors

In Tables 8.4 and 8.5, changes in optical component measures between baseline hyperopes who either remained hyperopic, became low hyperopes or became either pre-myopic or myopic are compared. In both cohorts, baseline hyperopes who stayed hyperopic exhibited similar changes in optical component measures to those who became low hyperopes. In the younger cohort, only two children became either pre-myopic or myopic, and they exhibited significantly larger axial elongation, greater LP reductions and larger AL/CR increases than the remaining groups.

Changes in optical component measures between low hyperopes at baseline who either remained as low hyperopes, became pre-myopic or became myopic are compared in Tables 8.6 and 8.7. Apart from changes in SER, baseline low hyperopes who became pre-myopic exhibited similar optical component changes to those who remained as low hyperopes. Meanwhile in the younger cohort, low hyperopes who became myopic, exhibited larger AL and AL/CR increases than the remaining groups.

In Tables 8.8 and 8.9, changes in optical component measures for children who remained pre-myopic is compared to those pre-myopes who became myopic, existing myopes and those who experienced hyperopic shifts in refractive category. Pre-myopes who became myopic exhibited similar changes in optical components to those baseline myopes who stayed myopic, except for lower AL/CR increases in the younger cohort. Both pre-myopes who became myopic and children who were originally myopic, exhibited higher increases in AL and AL/CR than children who remained as pre-myopes. Children who had a hyperopic shift in refractive category exhibited less AL and AL/CR increases than pre-myopes, pre-myopes who became myopic and existing myopes but had similar LP changes.

Table 8.4: Longitudinal changes in optical component measures between baseline hyperopes of the younger cohort who either remained hyperopic, became low-hyperopes or became either pre-myopic or myopic.

Younger Cohort	Baseline Hyperopes		
	Stayed Hyperopic	**Became Low Hyperope**	**Became Pre-Myopic or Myopic**
n	36	53	2
ΔSER*	-.390	-.986	-3.465
ΔAL	.569	.782	2.112
ΔCR	.053	.042	.079
ΔACD	.223	.235	.554
ΔLP*	-1.227	-1.247	-2.713
ΔAL/CR*	.054	.085	.241

***P < 0.05 between groups, ⌊___⌋ = P ≥ 0.05**

Table 8.5: Longitudinal changes in optical component measures between baseline hyperopes of the older cohort who either remained hyperopic, became low-hyperopes or became either pre-myopic or myopic.

Older Cohort	Baseline Hyperopes		
	Stayed Hyperopic	**Became Low Hyperope**	**Became Pre-Myopic or Myopic**
n	23	7	0
ΔSER*	-.238	-.849	-
ΔAL	.194	.360	-
ΔCR	.025	.024	-
ΔACD	.249	.261	-
ΔLP	.216	.449	-
ΔAL/CR	.016	.037	-

***P < 0.05 between groups, ⌊___⌋ = P ≥ 0.05**

Table 8.6: Longitudinal changes in optical component measures between baseline low hyperopes of the younger cohort who either remained low-hyperopes, became pre-myopic or became myopic.

Younger Cohort	Baseline Low Hyperopes		
	Stayed Low Hyperope	**Became Pre-myopic**	**Became Myopic**
n	278	318	36
ΔSER*	-.340	-.683	-2.523
ΔAL*	.618	.784	1.624
ΔCR	.044	.040	.033
ΔACD	.255	.253	.404
ΔLP	-1.342	-1.554	-2.079
ΔAL/CR	.062	.085	.196

***P < 0.05 between groups, ⌊___⌋ = P ≥ 0.05**

Table 8.7: Longitudinal changes in optical component measures between baseline low hyperopes of the older cohort who either remained low-hyperopes, became pre-myopic or became myopic.

Older Cohort	Baseline Low Hyperopes		
	Stayed Low Hyperope	**Became Pre-myopic**	**Became Myopic**
n	264	136	1
ΔSER*	-.076	-.405	-2.12
ΔAL	.145	.234	0.382
ΔCR	.022	.013	-0.384
ΔACD	.143	.178	.294
ΔLP	-.016	.095	-1.44
ΔAL/CR	.010	.025	.210

***P < 0.05 between groups, ⌊___⌋ = P ≥ 0.05**

Table 8.8: Longitudinal changes in optical component measures in the younger cohort between children who stayed as pre-myopes, pre-myopes who became myopic, existing myopes and those who experienced hyperopic shifts in refractive category.

Younger Cohort	Stayed Pre-myopic	Pre-myopic → Myopic	Stayed Myopic	Any Hyperopic Shift
n	66	41	10	5
ΔSER*	-.352	-2.175	-2.869	1.066
ΔAL*	.736	1.542	1.831	.618
ΔCR	.042	.053	.035	.124
ΔACD	.228	.341	.153	.350
ΔLP	-1.855	-2.109	-2.586	-2.579
ΔAL/CR*	.079	.179	.227	.032

***P < 0.05 between groups, ⌊——⌋ = P ≥ 0.05**

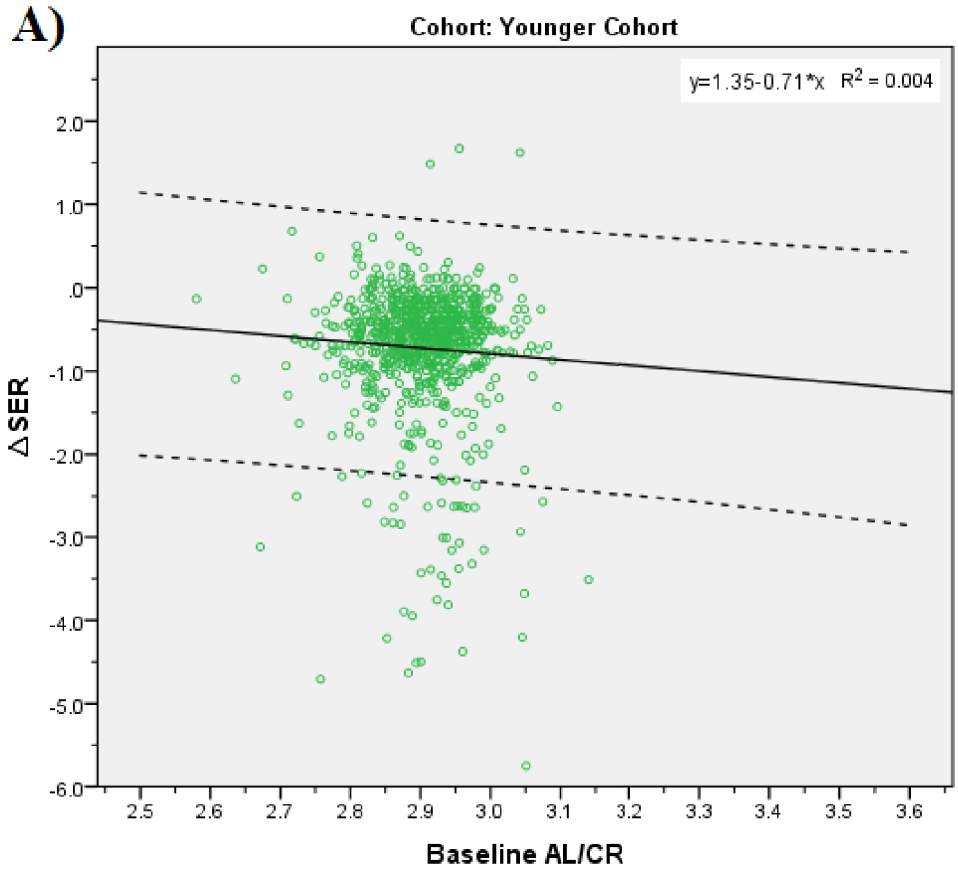
Table 8.9: Longitudinal changes in optical component measures in the older cohort between children who stayed as pre-myopes, pre-myopes who became myopic, existing myopes and those who experienced hyperopic shifts in refractive category.

Older Cohort	Stayed Pre-myopic	Pre-myopic → Myopic	Stayed Myopic	Any Hyperopic Shift
n	403	79	148	54
ΔSER*	-.116	-1.020	-.864	.361
ΔAL*	.201	.526	.501	.088
ΔCR	.021	.016	.029	.030
ΔACD	.152	.134	.106	.081
ΔLP	-.180	-.224	-.151	-.500
ΔAL/CR*	.018	.061	.052	.000

***P < 0.05 between groups, ⌊——⌋ = P ≥ 0.05**

8.4.6 Baseline AL/CR and SER progression

Figure 8.1 shows the relationship between changes in SER related to an individual's baseline AL/CR. For the younger cohort, there was no significant association between initial AL/CR and SER progression over the follow-up interval (r = -0.060, P = 0.082) (Figure 8.1A). However, for individuals in the older cohort, there was a weak negative association between baseline AL/CR and SER progression (r = -0.294, P < 0.001) (Figure 8.1B).



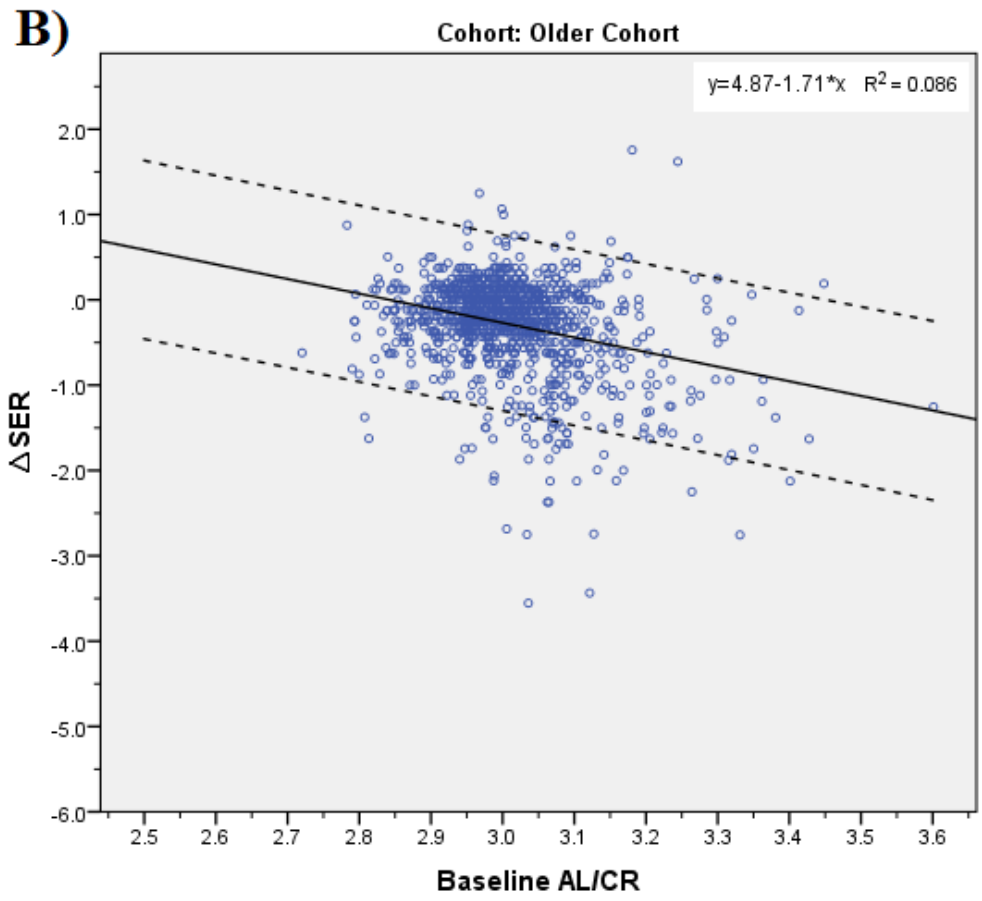


Figure 8.1: Baseline AL/CR vs SER progression over the 5-6 year interval for the A) younger cohort and B) older cohort.

8.4.7 Predictors of incident myopia

Baseline variables significantly associated with incident myopia through univariate logistic regression analysis were SER, CR, LP and AL/CR in the younger cohort, and SER, AL, ACD and AL/CR in the older cohort (Table 8.10). In the younger cohort, only SER and AL/CR remained significantly associated after multivariate analysis, with AUC values of 0.830 and 0.591 respectively. Meanwhile in the older cohort, only ACD and AL/CR remained significantly associated, with AUC values of 0.669 and 0.680 respectively. Figure 8.2 compares AUC values of AL/CR to previously established environmental predictors of myopia. The addition of AL/CR in combination with SER into a single model did not significantly increase the predictive power of determining incident myopia compared to SER alone (Figure 8.3), with an AUC of 0.849 in the younger cohort and 0.920 in the older cohort.

Table 8.10: Logistic regression for predicting the development of myopia in the A) younger cohort and B) older cohort.

A)	Univariate		Multivariate*		AUC
	P value	OR (95% CI)	P value	OR (95% CI)	
SER	<0.001	0.044 (0.023 to 0.085)	<0.001	0.323 (0.188 to 0.554)	0.830
AL	0.671	1.079 (0.761 to 1.530)			
CR	0.021	0.332 (0.130 to 0.844)	0.307	0.517 (0.146 to 1.835)	
ACD	0.989	1.007 (0.369 to 2.750)			
LP	0.033	1.204 (1.015 to 1.428)	0.746	1.044 (0.806 to 1.352)	
AL/CR**	<0.001	2.283 (1.527 to 3.413)	0.009	2.026 (1.189 to 3.449)	0.591

B)	Univariate		MULTIVARIATE*		AUC
	P value	OR (95% CI)	P value	OR (95% CI)	
SER	<0.001	0.011 (0.005 to 0.025)	0.108	0.848 (0.693 to 1.037)	
AL	<0.001	1.967 (1.412 to 2.740)	0.381	1.141 (0.840 to 1.577)	
CR	0.054	0.409 (0.165 to 1.014)			
ACD	<0.001	16.135 (5.947 to 43.779)	<0.001	12.436 (4.052 to 38.171)	0.669
LP	0.074	0.865 (0.737 to 1.014)			
AL/CR**	<0.001	5.535 (3.639 to 8.419)	0.007	1.479 (1.116 to 1.961)	0.680

*Multivariate adjusted for sex, ethnicity, time outdoors, near work and parental myopia status. **OR for a 0.1 increase in AL/CR

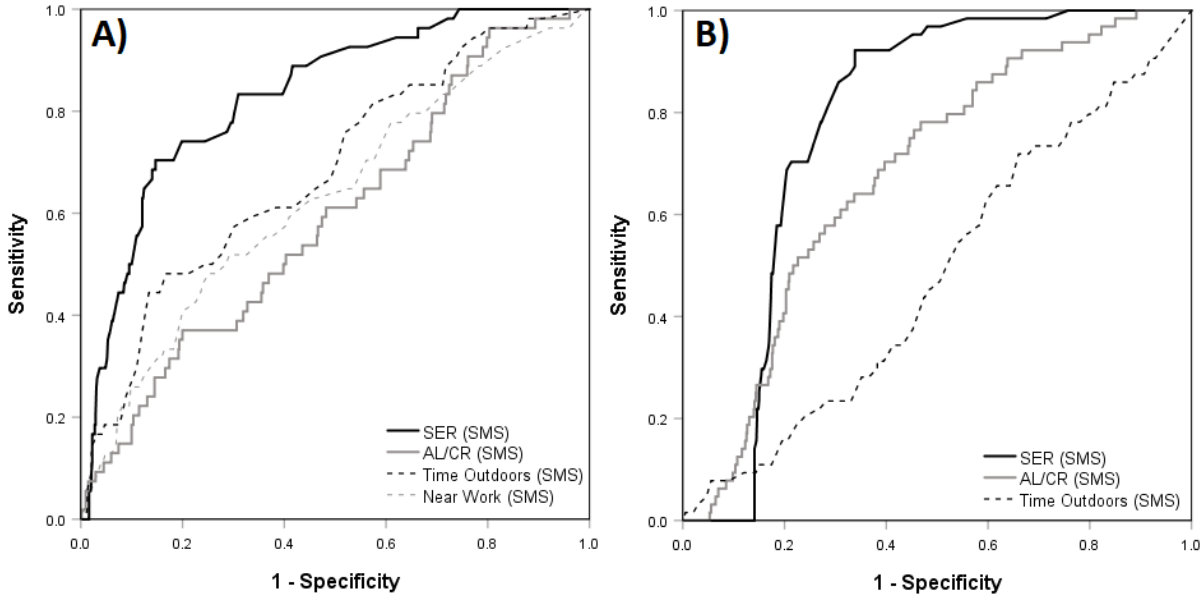


Figure 8.2: Receiver operating characteristic curves for predicting incident myopia using baseline SER, AL/CR, time outdoors and near work time in the A) younger cohort (age 6 years at baseline) B) older cohort (age 12 years at baseline).

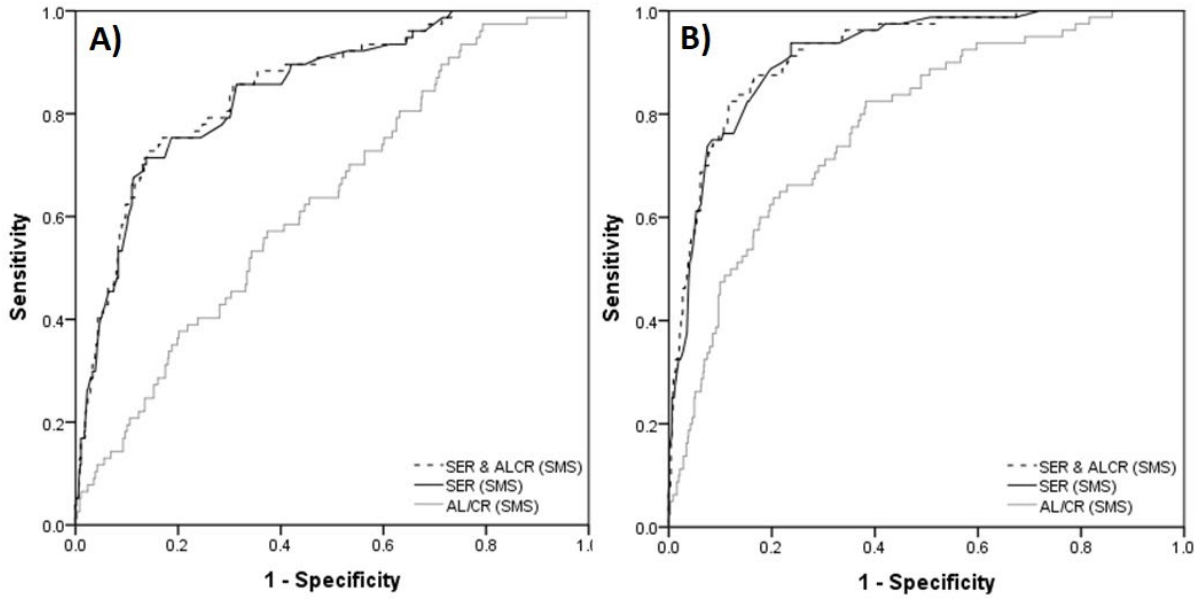
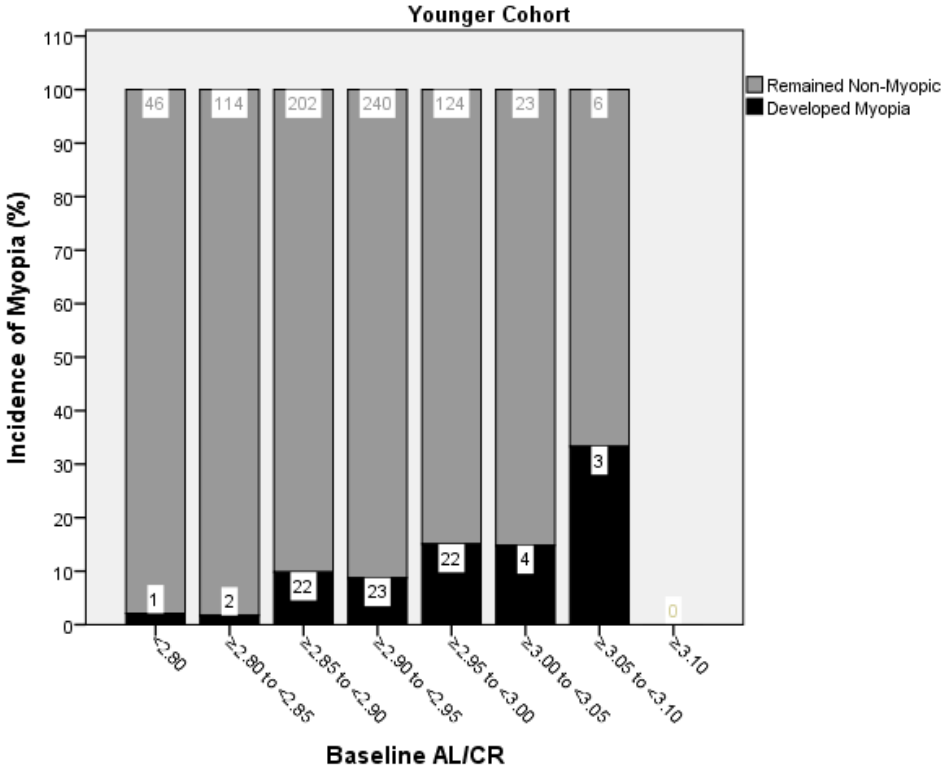


Figure 8.3: Receiver operating characteristic curves for predicting incident myopia using both baseline SER and AL/CR in the A) younger cohort (age 6 years at baseline) B) older cohort (age 12 years at baseline).

Figure 8.4 presents the proportion of children with incident myopia according to levels of baseline AL/CR. For both cohorts, increasing proportions of children with incident myopia were seen those children in higher sub-groups of baseline AL/CR. In the younger cohort, compared to children in the lowest sub-group of AL/CR (< 2.80), significantly higher odds for incident myopia were seen in those with a baseline AL/CR of ≥ 2.95 to < 3.00 (OR: 8.16, 95% CI: 1.07–62.29, P = 0.017), of ≥ 3.00 to < 3.05 (OR: 8.00, 95% CI: 0.85–75.73, P = 0.036) and in those of AL/CR ≥ 3.05 to < 3.10 (OR: 23.00, 95% CI: 2.05–258.08, P = 0.001). Compared to the mean AL/CR group of the younger cohort (≥ 2.90 to < 2.95), children with AL/CR ≥ 2.95 to < 3.00 were more likely to develop incident myopia (OR: 1.85, 95% CI: 0.99–3.45, P = 0.05).

In the older cohort, subgroups of individuals with AL/CR <2.90 were pooled as a reference group, as there were no incident cases of myopia in the lower levels of AL/CR. Compared to children with baseline AL/CR < 2.90, significantly higher odds for incident myopia were seen in those with a baseline AL/CR of ≥ 3.00 to < 3.05 (OR: 18.95, 95% CI: 1.14–314.63, P = 0.04), of ≥ 3.05 to < 3.10 (OR: 51.24, 95% CI: 3.07–853.94, P = 0.006) and in those of AL/CR ≥ 3.10 (OR: 74.31, 95% CI: 4.33–1,275.23, P = 0.003). Compared to the mean AL/CR group of the older cohort (≥ 3.00 to < 3.05), children with AL/CR ≥ 3.05 to < 3.10 were more likely to develop incident myopia (OR: 2.72, 95% CI: 1.49–4.95, P = 0.01).

A)



B)

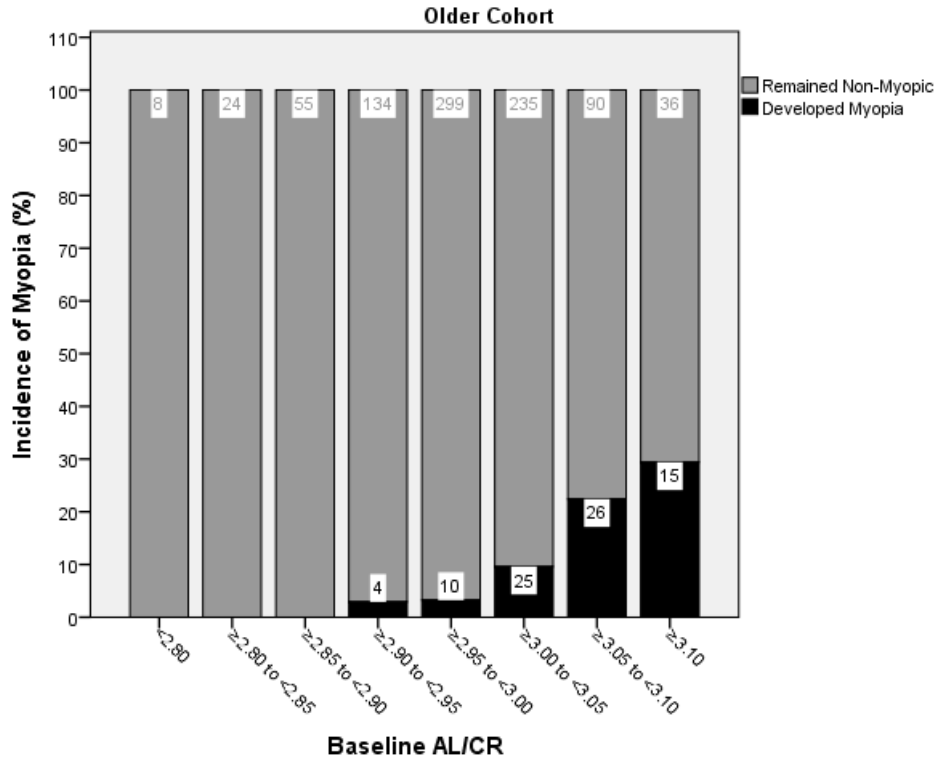


Figure 8.4: The proportion of children with incident myopia and the proportion who remained non-myopic according to baseline AL/CR in the A) younger cohort and B) older cohort.

8.5 Discussion

This study investigates 5–6 year longitudinal changes in refraction and biometric component measures in two cohorts of Australian school-children (initially aged 6 and 12 years old). All ocular components underwent statistically significant changes over time. This was characterised by relatively large increases in AL (particularly in the posterior segment) and minimal increases in CR. This created myopic shifts in SER alongside an increase in AL/CR. Indirect determination of crystalline lens power indicates a reduction in LP over time, which has been attributed to lens thinning in early childhood.[713] While the patterns of change were similar between cohorts, differences in change rates were seen for all components, with reductions in magnitude of each biometric component with increasing age. The biggest difference was seen in LP reduction, which had a > 10-fold difference between age groups. All of these changes have been previously documented from several other longitudinal studies and represent the expected growth curves of refractive development during childhood school years.[108-110, 714] CR change, which typically remains stable throughout childhood, while our findings found statistically significant changes, the absolute changes were minimal, with the mean difference of 0.022 mm translating into an equivalent power difference of -0.074 D between the older and younger cohort.

When comparing changes in component data between children with different refractive trajectories, we saw two distinct growth pathways that appear to be separated by the development of myopia. On one hand, changes in all individual ocular biometric components appear largely similar among children who remain non-myopic, regardless of their initial refractive category. This was most evident when comparing hyperopes who remained hyperopic to those who became low hyperopes (Tables 8.4 and 8.5), and comparing low hyperopes who maintained low hyperopia to those who became pre-myopes (Tables 8.6 and 8.7). Meanwhile, children who developed myopia as well as existing myopes, consistently exhibited distinct differences in one main component, AL change. As a by-product, AL/CR was also significantly higher compared to those who remained non-myopic

despite a lack of difference in CR change between refractive groups. These patterns in existing myopes and developed-myopes are similar to previous reports from both the Orinda Longitudinal Study of Myopia (OLSM)[108] and the Singapore Cohort Study of the Risk Factors for Myopia (SCORM),[109] and has been described as a 'decoupling' of posterior segment growth, due to excessive axial elongation.[112]

From Chapter 7, it appeared that additional crystalline lens power reductions were acting to compensate for myopic shifts expected from increases in AL/CR. However, in this investigation, comparison of LP changes between refractive groups found no major differences. Similar findings have been reported from the Guangzhou Twin Registry,[70] as no significant changes in annual crystalline LP reduction were observed from four years prior to myopia onset to three years after onset in 7–15 year old children. In contrast, several prior studies have found significant changes in crystalline LP during the onset of myopia, suggesting that differences in LP changes are indeed involved in refractive error development.

Garner et al,[714] reported that children who developed myopia had thicker initial crystalline lenses and greater rates of thinning compared to children who remained non-myopic. In Singapore, Irribarren et al, also reported that newly-developed myopes had larger LP losses,[68] with LP in existing myopes lower than non-myopes. From the Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error (CLEERE) study, Mutti et al,[112] found that a low LP preceded the development of myopia in became-myopic children and that LP reduction ceased and began to increase upon the development of myopia. A recent analysis of the SCORM data added support to the changes seen in the CLEERE study, with accelerated LP reduction seen prior to the development of myopia.[715] As these myopia-related LP changes seem to occur within ± 1 year of myopia onset,[112, 715] the difference found in our study may have resulted from its longer follow-up period (~6–7 years), with natural age-related reductions in crystalline LP occurring across the longer follow-up period may have masked the relative changes in LP reduction seen during the brief transition between low-hyperopia

into pre-myopia and from pre-myopia to myopia. More frequent ocular component measures would be required to determine this.

In determining whether biometric variables could predict the onset of myopia, we found that the AL/CR variable was a stronger predictor of myopia development in comparison to any single biometric measure. Non-myopic children with higher levels of AL/CR at baseline were more likely to develop myopia than those with lower AL/CR levels. This level of risk appears to be age-dependent, as increased myopia risk in the younger cohort occurred at AL/CR levels of 2.95 and above, whilst for the older cohort significant increases to myopia risk occurred at AL/CR levels of 3.00. Our findings are consistent with several previous studies investigating the association between AL/CR and incident myopia. Tao et al,[52] found in school-children aged 6–14 years, that the likelihood of myopia development after 1.5 years was higher in those with higher levels of initial AL/CR (OR: 1.096). Similar predictive abilities were also reported by Tideman et al,[405] who found that children with higher AL/CR at age 6 were more likely to have developed myopia by age 9 (OR: 1.21 per 0.01 increase). Eyes in the highest quartile of AL/CR demonstrated stronger relationships between environmental risk factors with AL elongation and incident myopia, suggesting that AL/CR could be used to identify at-risk individuals. Meanwhile, Liu et al, found in 6 year old children that those the highest quartile for AL/CR (> 2.85) were more likely (HR: 2.979) to develop either pre-myopia or myopia compared to those in the lowest quartile (< 2.77) after two years.[716] Altogether, while the strength of its predictive ability remains below that of SER, given that AL/CR can be determined non-invasively, it may be feasible as a marker for in large population screening programmes. In addition, using AL/CR to monitor for changes in myopia risk, may be a more sensitive marker for risk progression, since the distribution of AL/CR values do not tightly cluster in a low hyperopic region, unlike SER (demonstrated in Chapter 7).

Conversely, although AL/CR was a risk factor for incident myopia, we found that AL/CR was not a strong indicator of general refractive progression, particularly in the younger cohort. Only one other

study by Scheiman et al,[53] has examined the relationship between AL/CR and refractive progression. Their findings were similar to those presented here, with no association found between baseline AL/CR and 5-year myopia progression in a similar age group of children (6–12 years old) from the Correction of Myopia Evaluation Trial. From these findings, it is likely that refractive progression is not inherently determined by baseline ocular biometric status, and that external factors; such as time outdoors, near work and parental myopia; play a key role as previously demonstrated in an earlier analysis of this cohort.[555] This may also suggest that in the absence of external influences for myopia, larger eyes with axial myopia do not tend to grow any further, thus highlighting the key role of modifiable risk factors in myopia management.

The major strength of this study is that it is a large longitudinal study, containing detailed measurements of cycloplegic refraction and biometry. Included are two age groups where significant refractive development occurs, allowing the broad examination of age-related trends. On the other hand, a limitation of this study was that a large number of initial participants were lost to follow-up (~50%) due to the 5–6 year follow-up period. Participants retained in the study were slightly more myopic, had more exposure to myopigenic risk factors (parental myopia), and were more likely to be of East Asian ethnicity in the older cohort.[555] As previously described, natural age-related biometric changes occurring in the longer follow-up interval may have also masked short term changes seen between refractive groups. Similar to Chapter 7, another limitation was that LP was not directly measured and was calculated without knowledge of lens thickness. However, given that biometric measurements remained consistent throughout the study, relative differences in LP between individuals could still be examined using the Bennet and Rabbetts formula.

In conclusion, this study finds that children with a high AL/CR are at greater risk of developing myopia. Since the AL/CR unit can be easily captured by non-invasive methods, it can be valuable as an alternative determinant of myopia risk when cycloplegic refractive data is not available or not feasible to obtain. As myopia is a complex heterogeneous condition, a multivariate approach which

combines both an individual's biometric status and external risk factors such as time outdoors, near work and parental myopia is needed to accurately and reliably identify at-risk individuals.

Chapter 9: Summary of Findings, Conclusions and Future Directions

9.1 Summary of findings

In summary, the main findings of this thesis are that:

1. There are several tools available to capture/measure near work and time outdoors as risk factors for myopia, each with specific limitations that may influence the efficiency of study design, as well as the accuracy and reliability of data collected. These differences need to be taken into account when interpreting results.
2. Wearable LDLs give proportional measures with increasing light intensity, but the devices give different absolute measures and may require calibration using an adjustment factor to compare results. In outdoor environments, light intensity measurements from HOBO Pendant UA-002-64 are overestimates, while those from Actiwatch 2 and Clouclip M2 LDLs are underestimates, when compared to true illuminance levels.
3. Light intensity measurements from wearable LDLs are dependent on sensor orientation and positioning. From this perspective, the Clouclip, that collects light along the line of sight, has considerable advantages.
4. During real world use, light intensity measures as well as estimates of daily time outdoors and daily outdoor frequency are not comparable between different LDLs without a calibration/correction factor. This suggests that normal light exposures encountered outdoors can be consistently low enough for inter-device variances to fall below the 1,000 lux threshold used to define time outdoors and thus frequency, leading to discrepancies in these parameters.
5. In young adult university students, objective and subjective estimates of near work time do not correlate, with subjective measures being higher than those obtained objectively. This may indicate that students assess near work time as the total time spent on the task, whereas this time may actually include periods in which they are not focused on the written material, but thinking while gazing at other objects, or even looking out the window.

6. Humans now only spend a minor portion of their day outdoors, with the majority of outdoor time spent between 1,000 and 5,000 lux, and only limited time in high light intensity levels (> 10,000 lux). The limited exposures observed do not parallel the protective measures obtained in animal experiments, which in general require longer exposures of several hours and higher intensities of at least 10,000 Lux. This could possibly be explained by the fact that myopigenic exposures are constant in animal experiments, but are likely to be intermittent in human situations, and thus are more readily overcome with limited exposure.
7. The university student subjects in this thesis showed relatively minor variations in light exposures as measured by intensity and duration. Greater variations in frequency of light exposures were observed. This may be because all tertiary students studying the same course are constrained by the same timetable, with only minor variations possible, in which some students take more advantage of the limited opportunities to get outdoors than others. It is possible that similar "standardisation" effects may be seen with students at primary and secondary schooling levels. Whether these differences are associated with different refractive outcomes is still to be established.
8. AL/CR correlates highly with cycloplegic refraction (SER), although the relationship is not strictly linear but is best represented by three linear segments (tri-phasic). Within the middle phase there is a plateau in the gradient between AL/CR and SER, as reductions in crystalline lens power limit the myopic shifts expected from axial elongation. This would tend to keep eyes in a state of low hyperopia.
9. Additionally, AL/CR correlates more highly with SER than any other biometric parameter, and is thus the best surrogate measure to use if cycloplegic refraction cannot be measured.
10. Since the middle phase occurs in a hyperopic SER region and ends before myopia, AL/CR could be used to predict incident myopia. Non-myopic children with high AL/CR values (≥ 2.95 in 6 year olds and ≥ 3.00 in 12 year olds) were at increased risk of developing myopia.

11. Myopia progression can be indirectly monitored through increases in AL/CR with a reasonable level of accuracy as the offset of change in refraction via reduction in crystalline lens power, no longer appears effective within the third and final phase of AL/CR.

9.2 Conclusions & future directions

These findings stated above address a number of major questions currently posed in myopia research and gives rise to several avenues for further research. Firstly, the introduction of wearable devices to objectively capture exposures of time spent outdoors and time in near work is driven by a need to provide more accurate and reliable measures of myopic risk factors. However, it was not known how useful these novel methods truly were, or whether the measurements that were provided, accurately reflected exposures on an ocular level.

In terms of capturing time outdoors, it is clear that the measurement of light intensity is the most appropriate variable to consider, given that there exists a proven biological pathway linking light exposure to myopia development through the light-dopamine hypothesis.[14-16] Wearable LDLs, which can automatically capture light intensity over set periods of time, have been the main tool used to date. This thesis has identified substantial inter-device variations occurring between the currently used LDLs, which indicates that device selection needs to be considered more critically in the future. Fundamentally, these devices show subtle differences occurring at a sensor level, as light intensities are not directly comparable from the different wearable LDLs, due to variation in spectral response characteristics. Further, differences found between wearable LDLs to a standard calibrated industrial illuminometer (Yokogawa 51012), suggests that absolute light intensity from these devices does not accurately reflect what is experienced by the human eye. However, given a high reliability, relative comparisons can still be made between wearable LDLs, with the use of adjustment/calibration factors.

Aside from internal differences, a crucial issue determining the viability of LDLs is that light exposure measures are affected a high level of directionality within the real world environment. This means

that device orientation needs to be a major consideration, given that the goal is to capture intraocular light exposures. Different wearable LDLs can be mounted across different areas of the body and are also orientated in different directions. As a result, they are unable to capture the same exposures in the same environment, leading to further discrepancies between measures during real world use. Therefore it is clear that spectacle-mounted devices (such as the Clouclip and the less well studied Akeso spectacles) provide the best representation of light entering the eye as they are directed along the line of sight and move in unison with head tilt. While risk-factor analyses using spectacle mounted LDLs in children have been limited so far, they have all identified significant associations between light exposure and myopia,[638, 639] which provides some confirmation that measures at an eye level are relevant and that further investigations using the Clouclip or similar validated devices mounted at eye level are warranted.

A consequence of this directionality effect is that true ocular light exposures remain poorly defined, as only a few studies have characterized and performed risk factor analysis using spectacle-mounted LDLs.[638, 639, 688] So far estimates using objective measures has suggested that natural human exposures to high light environments are considerably lower than what would be expected from the conditions required in animal studies to prevent myopia; which often requires continuous exposure to light intensity levels > 10,000 lux for several hours. Considering the variance in light exposures occurring from directionality and angular effects that exist, it would not be surprising that ocular light exposures are even lower than what has been previously captured and maximally available in outdoor environments. This is because natural viewing angles mostly occur at the horizontal plane and below, even in outdoor environments with some exceptions (such as flying a kite, or playing badminton, basketball and netball outdoors). The disconnect between exposures within these two settings (animal and human) is complicated by the fact that it is clear that protective effects are occurring in human populations, demonstrated by the consistent associations found between time outdoors and myopia. This can be easily explained by the fact that stimuli for myopia in the real world does not occur continuously unlike in animal myopia models. For example, educational load is

not present across the whole day unlike diffuser and lens-wear under FDM/LIM. Additionally, near work is also not constantly occurring within time in education, as children may be looking up at boards, out of windows, engaging in study breaks and participating in sporting activities. This was shown in the Sydney Myopia Study as the requirements for protection from time outdoors varied based upon near work time.[487] The specific light exposure requirements for protection from myopia by time outdoors therefore remain undefined. One way to investigate this would be to compare ocular light exposures between two populations with significantly different levels of myopia such as between Australia and Singapore/China. The first critical element of this investigation is that representative samples from cohorts are required. Ideally, this would be primary school students in grades 4–6 (around the ages of 9–11 years old) as they are undergoing refractive development and susceptible to environmental influences for myopia, with children of this age already being very myopic in East Asia, while minimally myopic in Australia.

The second element is that methods of risk factor capture need to be standardized across populations and studies in order to accurately and reliably capture exposures. Previous work suggests the optimal parameters to be a sampling frequency of at least 2-minute intervals for duration of at least one week.[671] Additionally, samples should be repeated at least bi-annually in longitudinal studies to capture seasonal variations. Though with more frequent sampling periods, there is the potential for logistical issues occurring from the use of objective measures as they typically produce large volumes of data. Particularly, with spectacle mounted LDLs, there may be issues in non-myopic children who would be required to wear empty spectacles to mount the devices, potentially leading to poor compliance and data loss. Here the continued use of subjective methods is viable to supplement objective measures, as they are able to efficiently capture relative differences in myopia risk across large sample sizes over broad periods of time. However, a thorough understanding of the relationship between these methods is needed to interpret these measures. To subjectively assess risk factors, diary sampling or experience sampling would be appropriate in longitudinal studies, as it is subject to less design variation and recall bias than questionnaires.

However, if questionnaires are to be used, validated multi-item surveys to quantify the duration of time outdoors, such as those derived from the SMS and WHO, are preferred.

Lastly, data provided from objective measures needs to be compared appropriately. The transformation of light intensity measurements into an estimate of time outdoors (using the 1,000 lux threshold) has been the main parameter of focus, which has naturally followed from the consistent associations demonstrated between outdoor time and myopia via questionnaire data. However, using objective measures, a more comprehensive analysis is possible by also considering the absolute intensity and duration of relevant light exposures experienced, as well as temporal frequency patterns of exposure. There is a definite role for light intensity as indicated by experimental studies of myopia in animal models.[14, 573] However, light exposure frequency has not been as thoroughly examined so far but also has shown potential value in animal studies.[572, 575] On one hand, there is the suggestion that high frequency light exposure can provide enhanced protective effects against myopia,[575] but these approach frequencies levels that may not be realistically experienced within the natural environment when only indoor-outdoor transitions are considered. However, large fluctuations in light can be occurring within outdoor environments due just to the directionality of light into the eye. On the other hand, the fact that brief periods of light exposure can produce long-lasting protective effects against myopigenic stimuli,[507] suggests that there may be limited additive benefit within such a short periods of light exposure and that frequency of light exposure may not be as significant. While further investigation is warranted, it is logical that the triad of light exposure factors (duration, intensity and frequency) must be considered to comprehensively investigate the myopigenic role of time outdoors.

In terms of near work, it must be considered together with time outdoors for a comprehensive analysis of environmental risk, as both factors can occur independently.[487, 555] Conveniently, spectacle mounted devices can also objectively determine near viewing distance. However, unlike for the measurement of time outdoors, less is known about how to effectively capture near work as

a risk factor for myopia. The main issue is that is it not clear what aspect of near work needs to be captured or is relevant as a risk factor for myopia development and progression. This is complicated by the fact that a mechanism behind the myopigenic effects of near work has not been confirmed, though it is likely to involve either accommodative exertions or defocus on the retina. However, there is some evidence to suggest that continuous reading periods and closer absolute reading distances may be the key variables.[468, 648, 717] If the effect is related to time, the disconnect between these subjectively measured near work variables to what can be obtained via objectively measured near viewing distance, lies in the fact that subjectively reported "near work time" does not strictly indicate that subjects are continuously orientating their eyes to their nearest surface throughout the duration of that particular activity. For example, class study time in schools may be deemed as near work time for the entire period but may in fact comprise time spent by students looking down at a desk and up at a whiteboard or out of a window. Inherently, subjective measures will then tend to provide higher values compared to objective measures. By extension, near work time derived from near viewing distance also assumes that the plane of focus of the individual is always at the nearest surface, which will also inflate true near work aspects, whatever they may be. Alternatively, if it is also absolute distance which is important, using a specific cut-off distance to quantify "near work" may not be an appropriate reflection of the workings of the eye, as accommodative requirements increase linearly over a relatively broad distance, rather than by an "on–off" relationship, which using a cut-off definition imposes. Additionally, there will be a significant level of confounding from uncorrected refractive error, which can dramatically alter near viewing distances when looking at text or other small detail and objects.

Further validation studies are required to definitively understand what is happening between subjective near work time, objectively measured near viewing distances and actual near work experience. Video analysis can be a powerful tool to unify these variables, with subjective reports of/from children wearing spectacle-mounted LDLs compared to objectively provided near work parameters from the device and then confirmed by investigators against what behaviours were

occurring and if children were paying attention to that task at any given point in time. This will allow more accurate and reliable captures of the myopigenic elements underpinning near work and perhaps education as well.

Lastly, precise risk factor measures need to be accompanied by accurate measures of refraction. There is no doubt that cycloplegia is a necessity to accurately determine refractive errors. However, the use of effective and consistent cycloplegia carries a number of inconveniences, especially when gathering large volumes of refractive data, such as when sampling large populations for screening purposes, or repeatedly assessing for refractive changes to examine seasonal effects associated with myopia progression or simply to monitor myopia progression closely during treatment. In some of these cases, the use of visual acuity and non-cycloplegic refraction to categorise refractive errors has been used instead, which may be appropriate in a school screening setting, where the aim is to detect children with uncorrected myopia. Much research is now being devoted to improve the efficacy of non-cycloplegic refraction screening by attempting to exclude false positives (known as pseudo-myopes) by adjusting the cut-off for myopia, or by applying a further visual acuity criterion. While these approaches seem to more accurately define the prevalence, it has not been established that they do this by excluding pseudo-myopes, without generating false negatives among genuine cycloplegic myopes, which is essential for scientific purposes such as risk factor analysis.

In this thesis, the AL/CR variable was investigated for its role as a determinant of refraction, given that variations in biometric component measures are ultimately what underlies refractive errors. The AL/CR variable is clearly highly correlated with cycloplegic SER,[19-23, 48] but little has been done to investigate its clinical utility. Findings within this thesis confirm that AL/CR and changes in AL/CR were strongly correlated with SER, as well as changes in refractive progression. However, instead of being strictly linearly related, the relationship between AL/CR and SER is best characterised by a tri-phasic linear model. In population-based samples from the Sydney Myopia Study, most students were located in the plateau/middle phase of the tri-phasic linear curve between AL/CR and SER.

Over this range, myopic shifts expected from axial elongation are minimised by parallel losses of crystalline lens power. This plateau effect appears to be centred on an area of SER that seems to coincide with where the 'natural' endpoint of refractive development occurs, low hyperopia. Eventually, lens power loss declines and the change in refraction per unit of axial elongation increases, which is likely to explain the rapid declines in SER seen just prior to the onset of myopia, and most particularly the steeper slope of the third phase of the curve. The hyperopic end of the curve, requires further exploration of the interplay between the rate of axial elongation and the reduction in crystalline lens power for those children who remain hyperopic over time, compared to those who experience a reduction in their hyperopic refractive state with age.

Fundamentally, the study of risk factors still requires measurement of cycloplegic refraction, as there will never be an alternative which is devoid of any measurement error. Improving the measurement of exposures will not change this requirement. However, given an absence of significant lens change relative to axial elongation in myopes, changes in the AL/CR variable can potentially be used as an indicator for myopia progression. This was demonstrated in baseline myopes of the older cohort, where AL/CR changes determined 95% of SER changes within ± 0.66 D of actual SER. Future longitudinal studies examining myopia progression should consider investigating seasonal variations using biometric measures alongside annual cycloplegic refractive measures.

Potential clinical applications also exist with these findings. In the context of myopia treatment, shorter term changes in refraction could also be determined through AL/CR given that axial length is already considered a primary outcome. Meanwhile, there has been recent interest to apply more targeted intervention approaches for myopia control. A pre-myopia concept has been established using a refractive definition,[65] however, this requires the use of cycloplegic measures. Given that AL/CR has been demonstrated to be associated with incident myopia and can be non-invasively obtained, it can be incorporated as an indicator in large screening programs, possibly alongside measurement of known risk factors. Some clinical prediction tools have recently been developed,

which contain a variety of measures including AL/CR.[716, 718] However, these need to be independently evaluated and validated to find the optimum set of risk factor variables for prediction. What is needed are large population-based studies in children with both cycloplegic and non-cycloplegic refraction, with AL and CR, and enough biometric measures such as lens thickness, to more accurately calculate lens power.

9.3 Closing statement

In closing, epidemiological studies in the field of myopia have been pivotal in advancing the understanding of myopia and its aetiology. This has now reached a point where current methods of capturing risk factors are not sufficient to provide the statistical power needed to perform more detailed analysis, such as investigating their relationship with myopia progression. Through a series of experiments and validation studies, the research presented in this thesis provides new insight into ways to more accurately and reliably collect risk factors for myopia; in particular time outdoors and near work. In addition to this, investigation into the relationship between ocular biometric measures and refraction, provides an alternative non-invasive method to monitor myopia progression frequently, as well as assess myopia risk in children.

References

1. Morgan IG, French AN, Ashby RS, et al. The epidemics of myopia: aetiology and prevention. *Progress in retinal and eye research*. 2018;62:134-149.
2. Holden BA, Fricke TR, Wilson DA, et al. Global prevalence of myopia and high myopia and temporal trends from 2000 through 2050. *Ophthalmology*. 2016;123(5):1036-1042.
3. Ohno-Matsui K, Lai TY, Lai C-C, Cheung CMG. Updates of pathologic myopia. *Progress in retinal and eye research*. 2016;52:156-187.
4. Haarman AE, Enthoven CA, Tideman JWL, Tedja MS, Verhoeven VJ, Klaver CC. The complications of myopia: a review and meta-analysis. *Investigative ophthalmology & visual science*. 2020;61(4):49-49.
5. Li T, Zhou X. Causes and five-year proportion of new irreversible visual impairment in Jinshan District, Shanghai, from 2009–2018. *Journal of ophthalmology*. 2021;2021
6. Xia F, Wu L, Weng C, Zhou X. Causes and three-year incidence of irreversible visual impairment in Jing-an district, Shanghai, China from 2010-2015. *BMC ophthalmology*. 2017;17(1):1-7.
7. Iwase A, Araie M, Tomidokoro A, et al. Prevalence and causes of low vision and blindness in a Japanese adult population: the Tajimi Study. *Ophthalmology*. 2006;113(8):1354-1362. e1.
8. Xu L, Wang Y, Li Y, et al. Causes of blindness and visual impairment in urban and rural areas in Beijing: the Beijing Eye Study. *Ophthalmology*. 2006;113(7):1134. e1-1134. e11.
9. Wong TY, Ferreira A, Hughes R, Carter G, Mitchell P. Epidemiology and Disease Burden of Pathologic Myopia and Myopic Choroidal Neovascularization: An Evidence-Based Systematic Review. *American Journal of Ophthalmology*. 2014/01/01/ 2014;157(1):9-25.e12. doi:https://doi.org/10.1016/j.ajo.2013.08.010
10. Wong Y-L, Sabanayagam C, Ding Y, et al. Prevalence, Risk Factors, and Impact of Myopic Macular Degeneration on Visual Impairment and Functioning Among Adults in Singapore. *Investigative Ophthalmology & Visual Science*. 2018;59(11):4603-4613. doi:10.1167/iovs.18-24032
11. Jan C, Li L, Keay L, Stafford RS, Congdon N, Morgan I. Prevention of myopia, China. *Bull World Health Organ*. Jun 1 2020;98(6):435-437. doi:10.2471/blt.19.240903
12. Wu P-C, Chen C-T, Chang L-C, et al. Increased time outdoors is followed by reversal of the long-term trend to reduced visual acuity in Taiwan primary school students. *Ophthalmology*. 2020;127(11):1462-1469.
13. Yang Y-C, Hsu N-W, Wang C-Y, Shyong M-P, Tsai D-C. Prevalence trend of myopia after promoting eye care in preschoolers: a serial survey in Taiwan before and during the coronavirus disease 2019 pandemic. *Ophthalmology*. 2022;129(2):181-190.
14. Karouta C, Ashby RS. Correlation Between Light Levels and the Development of Deprivation MyopiaCorrelation Between Light Levels and FDM. *Investigative Ophthalmology & Visual Science*. 2015;56(1):299-309. doi:10.1167/iovs.14-15499
15. Chen S, Zhi Z, Ruan Q, et al. Bright light suppresses form-deprivation myopia development with activation of dopamine D1 receptor signaling in the ON pathway in retina. *Investigative ophthalmology & visual science*. 2017;58(4):2306-2316.
16. Smith EL, Hung L-F, Huang J. Protective effects of high ambient lighting on the development of form-deprivation myopia in rhesus monkeys. *Investigative ophthalmology & visual science*. 2012;53(1):421-428.
17. Morgan IG, Iribarren R, Fotouhi A, Grzybowski A. Cycloplegic refraction is the gold standard for epidemiological studies. *Acta ophthalmologica*. 2015;93(6):581-585.
18. Donovan L, Sankaridurg P, Ho A, et al. Myopia progression in Chinese children is slower in summer than in winter. *Optometry and vision science: official publication of the American Academy of Optometry*. 2012;89(8):1196.

19. Iyamu E, Iyamu J, Obiakor CI. The role of axial length-corneal radius of curvature ratio in refractive state categorization in a Nigerian population. *International Scholarly Research Notices*. 2011;2011
20. Mallen EA, Gammoh Y, Al-Bdour M, Sayegh FN. Refractive error and ocular biometry in Jordanian adults. *Ophthalmic and Physiological Optics*. 2005;25(4):302-309.
21. Ojaimi E, Rose KA, Morgan IG, et al. Distribution of ocular biometric parameters and refraction in a population-based study of Australian children. *Invest Ophthalmol Vis Sci*. Aug 2005;46(8):2748-54. doi:10.1167/iovs.04-1324
22. Foo VHX, Verkicharla PK, Ikram MK, et al. Axial length/corneal radius of curvature ratio and myopia in 3-year-old children. *Translational vision science & technology*. 2016;5(1):5-5.
23. He X, Zou H, Lu L, et al. Axial length/corneal radius ratio: association with refractive state and role on myopia detection combined with visual acuity in Chinese schoolchildren. *PLoS One*. 2015;10(2):e0111766.
24. Zhao J, Mao J, Luo R, Li F, Pokharel GP, Ellwein LB. Accuracy of noncycloplegic autorefraction in school-age children in China. *Optometry and vision science*. 2004;81(1):49-55.
25. Choong Y-F, Chen A-H, Goh P-P. A Comparison of Autorefraction and Subjective Refraction With and Without Cycloplegia in Primary School Children. *American Journal of Ophthalmology*. 2006/07/01/ 2006;142(1):68-74.e1. doi:https://doi.org/10.1016/j.ajo.2006.01.084
26. Fotedar R, Rochtchina E, Morgan I, Wang JJ, Mitchell P, Rose KA. Necessity of cycloplegia for assessing refractive error in 12-year-old children: a population-based study. *American journal of ophthalmology*. 2007;144(2):307-309.
27. Yeotikar NS, Chandra Bakaraju R, Roopa Reddy PS, Prasad K. Cycloplegic refraction and non-cycloplegic refraction using contralateral fogging: a comparative study. *Journal of Modern Optics*. 2007/06/15 2007;54(9):1317-1324. doi:10.1080/09500340600855346
28. Jorge J, Queiros A, González-Méijome J, Fernandes P, Almeida JB, Parafita MA. The influence of cycloplegia in objective refraction. *Ophthalmic and Physiological Optics*. 2005;25(4):340-345.
29. Hopkins S, Sampson GP, Hendicott P, Lacherez P, Wood JM. Refraction in children: a comparison of two methods of accommodation control. *Optom Vis Sci*. Dec 2012;89(12):1734-9. doi:10.1097/OPX.0b013e318277182c
30. Mimouni M, Zoller L, Horowitz J, Wygnanski-Jaffe T, Morad Y, Mezer E. Cycloplegic autorefraction in young adults: is it mandatory? *Graefe's Archive for Clinical and Experimental Ophthalmology*. 2016;254(2):395-398.
31. Sun Y-Y, Wei S-F, Li S-M, et al. Cycloplegic refraction by 1% cyclopentolate in young adults: is it the gold standard? The Anyang University Students Eye Study (AUSES). *British Journal of Ophthalmology*. 2019;103(5):654-658.
32. Fotouhi A, Morgan IG, Iribarren R, Khabazkhoob M, Hashemi H. Validity of noncycloplegic refraction in the assessment of refractive errors: the Tehran Eye Study. *Acta Ophthalmologica*. 2012;90(4):380-386. doi:doi:10.1111/j.1755-3768.2010.01983.x
33. Schallhorn JM, Schallhorn CS, Schallhorn SC. The Utility of Cycloplegic Refraction: Differences Between Manifest and Cycloplegic Refractions in a Large Population. *Investigative Ophthalmology & Visual Science*. 2014;55(13):2734-2734.
34. Ostrin LA, Glasser A. Accommodation measurements in a prepresbyopic and presbyopic population. *Journal of Cataract & Refractive Surgery*. 2004;30(7):1435-1444.
35. Hamasaki D, Ong J, Marg E. The amplitude of accommodation in presbyopia. *American journal of optometry and archives of American Academy of Optometry*. 1956;33(1):3-14.
36. Koretz JF, Kaufman PL, Neider MW, Goeckner PA. Accommodation and presbyopia in the human eye—aging of the anterior segment. *Vision Research*. 1989;29(12):1685-1692.
37. Wold JE, Hu A, Chen S, Glasser A. Subjective and objective measurement of human accommodative amplitude. *Journal of Cataract & Refractive Surgery*. 2003;29(10):1878-1888.
38. Stolovitch C, Loewenstein A, Nemmet P, Lazar M. Atropine cycloplegia: how many instillations does one need? *Journal of pediatric ophthalmology and strabismus*. 1992;29(3):175-176.

39. Yazdani N, Sadeghi R, Momeni-Moghaddam H, Zarifmahmoudi L, Ehsaei A. Comparison of cyclopentolate versus tropicamide cycloplegia: A systematic review and meta-analysis. *Journal of optometry*. Jul-Sep 2018;11(3):135-143. doi:10.1016/j.optom.2017.09.001
40. Bagheri A, Givrad S, Yazdani S, Mohebbi MR. Optimal dosage of cyclopentolate 1% for complete cycloplegia: a randomized clinical trial. *European journal of ophthalmology*. 2007;17(3):294-300.
41. Emiru V. Response to mydriatics in the African. *The British journal of ophthalmology*. 1971;55(8):538.
42. Miranda MN. Residual accommodation: A comparison between cyclopentolate 1% and a combination of cyclopentolate 1% and tropicamide 1%. *Archives of Ophthalmology*. 1972;87(5):515-517. doi:10.1001/archopht.1972.01000020517004
43. Lan W, Zhao F, Lin L, et al. Refractive errors in 3–6 year-old Chinese children: a very low prevalence of myopia? *PLoS One*. 2013;8(10):e78003.
44. Eong KA, Tay T, Lim M. Education and myopia in 110,236 young Singaporean males. *Singapore Med J*. 1993;34(6):489-492.
45. Xiang S, Zhao S, Li X, et al. The prevalence of reduced visual acuity in children from an urban district in China from 2002 to 2018. *Eye*. 2020:1-6.
46. Leone J, Mitchell P, Morgan I, Kifley A, Rose K. Use of visual acuity to screen for significant refractive errors in adolescents: Is it reliable? *Archives of Ophthalmology*. 2010;128(7):894-899. doi:10.1001/archophthalmol.2010.134
47. O'Donoghue L, Rudnicka AR, McClelland JF, Logan NS, Saunders KJ. Visual acuity measures do not reliably detect childhood refractive error-an epidemiological study. *PloS one*. 2012;7(3):e34441.
48. Grosvenor T, Scott R. Role of the axial length/corneal radius ratio in determining the refractive state of the eye. *Optometry and vision science*. 1994;71(9):573-579.
49. Hashemi H, Khabazkhoob M, Miraftab M, et al. Axial length to corneal radius of curvature ratio and refractive errors. *Journal of ophthalmic & vision research*. 2013;8(3):220.
50. Jong M, Sankaridurg P, Naduvilath TJ, Li W, He M. The relationship between progression in axial length/corneal radius of curvature ratio and spherical equivalent refractive error in myopia. *Optometry and Vision Science*. 2018;95(10):921-929.
51. Yebra-Pimentel E, Giraldez M, Glez J-M, Cerviño A, García-Resúa C, Parafita M. Changes in axial length/corneal radius ratio (AL/CR) according to refractive state of the eye. Relationship with ocular components. *Archivos de la Sociedad Espanola de Oftalmologia*. 2004;79(7):317-324.
52. Tao Z, Deng H, Zhong H, et al. A longitudinal study of the effect of ocular biometrics measures on myopia onset. *Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie*. Nov 17 2020;doi:10.1007/s00417-020-05010-1
53. Scheiman M, Gwiazda J, Zhang Q, et al. Longitudinal changes in corneal curvature and its relationship to axial length in the Correction of Myopia Evaluation Trial (COMET) cohort. *Journal of optometry*. 2016;9(1):13-21.
54. Guo X, Fu M, Ding X, Morgan IG, Zeng Y, He M. Significant axial elongation with minimal change in refraction in 3-to 6-year-old Chinese preschoolers: the Shenzhen Kindergarten Eye Study. *Ophthalmology*. 2017;124(12):1826-1838.
55. Jongenelen S, Rozema JJ, Tassignon M-J. Distribution of the crystalline lens power in vivo as a function of age. *Investigative ophthalmology & visual science*. 2015;56(12):7029-7035.
56. Garner LF, Meng CK, Grosvenor TP, Mohidin N. Ocular dimensions and refractive power in Malay and Melanesian children. *Ophthalmic and Physiological Optics*. 1990;10(3):234-238.
57. Ip JM, Huynh SC, Kifley A, et al. Variation of the contribution from axial length and other oculometric parameters to refraction by age and ethnicity. *Investigative ophthalmology & visual science*. 2007;48(10):4846-4853.

58. Kimura S, Hasebe S, Miyata M, Hamasaki I, Ohtsuki H. Axial length measurement using partial coherence interferometry in myopic children: repeatability of the measurement and comparison with refractive components. *Jpn J Ophthalmol*. Mar-Apr 2007;51(2):105-10. doi:10.1007/s10384-006-0410-5
59. Karunakar B, Rajlingam R, Reddy L, Murthy S, Srikanth S. Axial length, corneal curvature and their association with the refractive status of the eye. *Journal of Evolution of Medical and Dental Sciences*. 02/04 2016;5:422-426. doi:10.14260/jemds/2016/97
60. Elmadina A. The axial length and corneal radius of curvature ratio in Sudanese adult myopes. 09/17 2019;
61. Badmus SA, Ajaiyeoba AI, Adegbehingbe BO, Onakpoya OH, Adeoye AO. Axial length/corneal radius of curvature ratio and refractive status in an adult Nigerian population. *Nigerian journal of clinical practice*. Oct 2017;20(10):1328-1334. doi:10.4103/njcp.njcp_183_16
62. Luo HD, Gazzard G, Liang Y, Shankar A, Tan DTH, Saw SM. Defining myopia using refractive error and uncorrected logMAR visual acuity >0.3 from 1334 Singapore school children ages 7-9 years. *The British journal of ophthalmology*. 2006;90(3):362-366. doi:10.1136/bjo.2005.079657
63. Goss DA, Grosvenor T. Reliability of refraction - a literature review. *Journal of the American Optometric Association*. 1996;67(10):619-630.
64. Vongphanit J, Mitchell P, Wang JJ. Prevalence and progression of myopic retinopathy in an older population. *Ophthalmology*. 2002;109(4):704-711.
65. Flitcroft DI, He M, Jonas JB, et al. IMI – Defining and Classifying Myopia: A Proposed Set of Standards for Clinical and Epidemiologic StudiesIMI – Defining and Classifying Myopia. *Investigative Ophthalmology & Visual Science*. 2019;60(3):M20-M30. doi:10.1167/iovs.18-25957
66. Morgan IG, Rose KA, Ellwein LB, Group RESiCS. Is emmetropia the natural endpoint for human refractive development? An analysis of population-based data from the refractive error study in children (RESC). *Acta ophthalmologica*. 2010;88(8):877-884.
67. Thorn F, Gwiazda J, Held R. Myopia progression is specified by a double exponential growth function. *Optometry and vision science*. 2005;82(4):E286.
68. Iribarren R, Morgan IG, Chan YH, Lin X, Saw S-M. Changes in lens power in Singapore Chinese children during refractive development. *Investigative ophthalmology & visual science*. 2012;53(9):5124-5130.
69. Mutti DO, Hayes JR, Mitchell GL, et al. Refractive error, axial length, and relative peripheral refractive error before and after the onset of myopia. *Investigative ophthalmology & visual science*. 2007;48(6):2510-2519.
70. Xiang F, He M, Morgan IG. Annual changes in refractive errors and ocular components before and after the onset of myopia in Chinese children. *Ophthalmology*. 2012;119(7):1478-1484.
71. Verhoeven VJM, Wong KT, Buitendijk GHS, Hofman A, Vingerling JR, Klaver CCW. Visual Consequences of Refractive Errors in the General Population. *Ophthalmology*. 2015/01/01/ 2015;122(1):101-109. doi:https://doi.org/10.1016/j.ophtha.2014.07.030
72. Xiao O, Guo X, Wang D, et al. Distribution and severity of myopic maculopathy among highly myopic eyes. *Investigative ophthalmology & visual science*. 2018;59(12):4880-4885.
73. Leone JF, Mitchell P, Morgan IG, Kifley A, Rose KA. Use of visual acuity to screen for significant refractive errors in adolescents: is it reliable? *Archives of ophthalmology*. 2010;128(7):894-899.
74. Cook RC, Glasscock RE. Refractive and Ocular Findings in the Newborn. *American Journal of Ophthalmology*. 1951;34(10):1407-1413. doi:10.1016/0002-9394(51)90481-3
75. Goldschidt E. Refraction in the Newborn. *Acta Ophthalmologica*. 1969;47(3):570-578. doi:doi:10.1111/j.1755-3768.1969.tb08143.x
76. Mutti DO, Mitchell GL, Jones LA, et al. Axial Growth and Changes in Lenticular and Corneal Power during Emmetropization in Infants. *Investigative Ophthalmology & Visual Science*. 2005;46(9):3074-3080. doi:10.1167/iovs.04-1040
77. Zonis S, Miller B. Refractions in the Israeli newborn. SLACK Incorporated Thorofare, NJ; 1974.

78. Mayer DL, Hansen RM, Moore BD, Kim S, Fulton AB. Cycloplegic refractions in healthy children aged 1 through 48 months. *Archives of Ophthalmology*. 2001;119(11):1625-1628.
79. Wildsoet C. Active emmetropization—evidence for its existence and ramifications for clinical practice. *Ophthalmic and Physiological Optics*. 1997;17(4):279-290.
80. Edwards M. The refractive status of Hong Kong Chinese infants. *Ophthalmic and Physiological Optics*. 1991;11(4):297-303.
81. Saunders KJ, Woodhouse JM, Westall CA. Emmetropisation in human infancy: rate of change is related to initial refractive error. *Vision research*. 1995;35(9):1325-1328.
82. Wood I, Hodi S, Morgan L. Longitudinal change of refractive error in infants during the first year of life. *Eye*. 1995;9(5):551-557.
83. Pennie FC, Wood IC, Olsen C, White S, Charman WN. A longitudinal study of the biometric and refractive changes in full-term infants during the first year of life. *Vision research*. 2001;41(21):2799-2810.
84. Schaeffel F, Glasser A, Howland HC. Accommodation, refractive error and eye growth in chickens. *Vision Research*. 1988/01/01/ 1988;28(5):639-657. doi:https://doi.org/10.1016/0042-6989(88)90113-7
85. Irving E, Callender M, Sivak J. Inducing myopia, hyperopia, and astigmatism in chicks. *Optometry and vision science: official publication of the American Academy of Optometry*. 1991;68(5):364-368.
86. Shaikh AW, Siegwart Jr JT, Norton TT. Effect of interrupted lens wear on compensation for a minus lens in tree shrews. *Optometry and vision science: official publication of the American Academy of Optometry*. 1999;76(5):308-315.
87. Hung L-F, Crawford ML, Smith EL. Spectacle lenses alter eye growth and the refractive status of young monkeys. *Nature medicine*. 1995;1(8):761.
88. Siegwart Jr JT, Norton TT. Binocular lens treatment in tree shrews: Effect of age and comparison of plus lens wear with recovery from minus lens-induced myopia. *Experimental eye research*. 2010;91(5):660-669.
89. Smith III EL, Hung L-F. The role of optical defocus in regulating refractive development in infant monkeys. *Vision research*. 1999;39(8):1415-1435.
90. Irving E, Sivak J, Callender M. Refractive plasticity of the developing chick eye. *Ophthalmic and Physiological Optics*. 1992;12(4):448-456.
91. Miller-Meeks MJ, Bennett SR, Keech RV, Blodi CF. Myopia induced by vitreous hemorrhage. *American journal of ophthalmology*. 1990;109(2):199-203.
92. Weiss AH, Ross EA. Axial myopia in eyes with optic nerve hypoplasia. *Graefe's archive for clinical and experimental ophthalmology*. 1992;230(4):372-377.
93. Twomey J, Gilvarry A, Restori M, Kirkness C, Moore A, Holden A. Ocular enlargement following infantile corneal opacification. *Eye*. 1990;4(3):497-503.
94. von Noorden GK, Lewis RA. Ocular axial length in unilateral congenital cataracts and blepharoptosis. *Investigative ophthalmology & visual science*. 1987;28(4):750-752.
95. Johnson CA, Post RB, Chalupa LM, Lee TJ. Monocular deprivation in humans: a study of identical twins. *Investigative ophthalmology & visual science*. 1982;23(1):135-138.
96. Hoyt CS, Stone RD, Fromer C, Billson FA. Monocular axial myopia associated with neonatal eyelid closure in human infants. *American journal of ophthalmology*. 1981;91(2):197-200.
97. Gusek-Schneider G-C, Martus P. Stimulus deprivation myopia in human congenital ptosis: a study of 95 patients. Slack Incorporated Thorofare, NJ; 2001.
98. Ingram R, Barr A. Changes in refraction between the ages of 1 and 3 1/2 years. *British Journal of Ophthalmology*. 1979;63(5):339-342.
99. Sorsby A, Sheridan M, Leary GA, Benjamin B. Vision, visual acuity, and ocular refraction of young men. *British Medical Journal*. 1960;1(5183):1394.
100. Hashemi H, Fotouhi A, Mohammad K. The age-and gender-specific prevalences of refractive errors in Tehran: the Tehran Eye Study. *Ophthalmic epidemiology*. 2004;11(3):213-225.

101. Mutti DO, Sinnott LT, Mitchell GL, et al. Ocular component development during infancy and early childhood. *Optometry and vision science: official publication of the American Academy of Optometry*. 2018;95(11):976.
102. Qiao-Grider Y, Hung L-F, Kee C-s, Ramamirtham R, Smith EL. Normal ocular development in young rhesus monkeys (Macaca mulatta). *Vision Research*. 2007/05/01/ 2007;47(11):1424-1444. doi:https://doi.org/10.1016/j.visres.2007.01.025
103. Sorsby A. Refraction and its components during the growth of the eye from the age of three. *Medical Research Council*. 1991;301:1-67.
104. Sorsby A, Leary G. A longitudinal study of refraction and its components during growth. *Special Report Series (Medical Research Council (Great Britain))*. 1969;309:1-41.
105. French AN, Morgan IG, Burlutsky G, Mitchell P, Rose KA. Prevalence and 5-to 6-year incidence and progression of myopia and hyperopia in Australian schoolchildren. *Ophthalmology*. 2013;120(7):1482-1491.
106. Zadnik K. Myopia development in childhood. *Optometry and Vision Science*. 1997;74(8):603-608.
107. Zadnik K, Manny RE, Yu JA, et al. Ocular component data in schoolchildren as a function of age and gender. *Optometry and Vision Science*. 2003;80(3):226-236.
108. Jones LA, Mitchell GL, Mutti DO, Hayes JR, Moeschberger ML, Zadnik K. Comparison of ocular component growth curves among refractive error groups in children. *Investigative ophthalmology & visual science*. 2005;46(7):2317-2327.
109. Wong H-B, Machin D, Tan S-B, Wong T-Y, Saw S-M. Ocular component growth curves among Singaporean children with different refractive error status. *Investigative ophthalmology & visual science*. 2010;51(3):1341-1347.
110. Momeni-Moghaddam H, Hashemi H, Zarei-Ghanavati S, Ostadimoghaddam H, Yekta A, Khabazkhoob M. Four-year change in ocular biometric components and refraction in schoolchildren: A cohort study. *Journal of current ophthalmology*. 2019;31(2):206-213.
111. Mutti DO, Zadnik K, Fusaro RE, Friedman NE, Sholtz RI, Adams AJ. Optical and structural development of the crystalline lens in childhood. *Investigative ophthalmology & visual science*. 1998;39(1):120-133.
112. Mutti DO, Mitchell GL, Sinnott LT, et al. Corneal and crystalline lens dimensions before and after myopia onset. *Optometry and Vision Science*. 2012;89(3):251.
113. Iribarren R. Crystalline lens and refractive development. *Progress in retinal and eye research*. 2015;47:86-106.
114. Ooi CS, Grosvenor T. Mechanisms of emmetropization in the aging eye. *Optometry and vision science: official publication of the American Academy of Optometry*. 1995;72(2):60-66.
115. Dubbelman M, Van der Heijde GL. The shape of the aging human lens: curvature, equivalent refractive index and the lens paradox. *Vision Research*. 2001/06/01/ 2001;41(14):1867-1877. doi:https://doi.org/10.1016/S0042-6989(01)00057-8
116. Lee KE, Klein BE, Klein R, Wong TY. Changes in refraction over 10 years in an adult population: the Beaver Dam Eye study. *Investigative ophthalmology & visual science*. 2002;43(8):2566-2571.
117. Guzowski M, Wang JJ, Rochtchina E, Rose KA, Mitchell P. Five-year refractive changes in an older population: the Blue Mountains Eye Study. *Ophthalmology*. 2003;110(7):1364-1370.
118. Wu S-Y, Yoo YJ, Nemesure B, Hennis A, Leske MC. Nine-year refractive changes in the Barbados Eye Studies. *Investigative ophthalmology & visual science*. 2005;46(11):4032-4039.
119. Fotedar R, Mitchell P, Burlutsky G, Wang JJ. Relationship of 10-year change in refraction to nuclear cataract and axial length: findings from an older population. *Ophthalmology*. 2008;115(8):1273-1278. e1.
120. Young FA, Leary GA. The inheritance of ocular components. *Optometry and Vision Science*. 1972;49(7):546-555.

121. Morgan R, Munro M. Refractive problems in northern natives. *Canadian journal of ophthalmology Journal canadien d'ophtalmologie*. 1973;8(2):226-228.
122. Morgan R, Speakman J, Grimshaw S. Inuit myopia: an environmentally induced" epidemic"? *Canadian Medical Association Journal*. 1975;112(5):575.
123. Lin L, Shih Y, Hsiao C, Chen C. Prevalence of myopia in Taiwanese schoolchildren: 1983 to 2000. *Annals-Academy of Medicine Singapore*. 2004;33(1):27-33.
124. Tsai T-H, Liu Y-L, Ma I-H, et al. Evolution of the prevalence of myopia among Taiwanese schoolchildren: a review of survey data from 1983 through 2017. *Ophthalmology*. 2021;128(2):290-301.
125. Wang T, Chiang T, Wang T, Lin LL, Shih Y. Changes of the ocular refraction among freshmen in National Taiwan University between 1988 and 2005. *Eye*. 2009;23(5):1168-1169.
126. Koh V, Yang A, Saw SM, et al. Differences in prevalence of refractive errors in young Asian males in Singapore between 1996–1997 and 2009–2010. *Ophthalmic epidemiology*. 2014;21(4):247-255.
127. Chew S, Chia S, Lee L. The pattern of myopia in young Singaporean men. *MALAY*. 1988;1:12.10.
128. Matsumura H, Hirai H. Prevalence of myopia and refractive changes in students from 3 to 17 years of age. *Survey of ophthalmology*. 1999;44:S109-S115.
129. Zhao J, Pan X, Sui R, Munoz SR, Sperduto RD, Ellwein LB. Refractive Error Study in Children: results from Shunyi District, China. *Am J Ophthalmol*. Apr 2000;129(4):427-35. doi:10.1016/s0002-9394(99)00452-3
130. He M, Zeng J, Liu Y, Xu J, Pokharel GP, Ellwein LB. Refractive error and visual impairment in urban children in southern china. *Invest Ophthalmol Vis Sci*. Mar 2004;45(3):793-9. doi:10.1167/iovs.03-1051
131. Xiang F, He M, Zeng Y, Mai J, Rose KA, Morgan I. Increases in the prevalence of reduced visual acuity and myopia in Chinese children in Guangzhou over the past 20 years. *Eye*. 2013;27(12):1353-1358.
132. Li Y, Liu J, Qi P. The increasing prevalence of myopia in junior high school students in the Haidian District of Beijing, China: a 10-year population-based survey. *BMC ophthalmology*. Jun 12 2017;17(1):88. doi:10.1186/s12886-017-0483-6
133. Chen M, Wu A, Zhang L, et al. The increasing prevalence of myopia and high myopia among high school students in Fenghua city, eastern China: a 15-year population-based survey. *BMC ophthalmology*. Jul 3 2018;18(1):159. doi:10.1186/s12886-018-0829-8
134. Wu MM-m, Edwards MH. The effect of having myopic parents: an analysis of myopia in three generations. *Optometry and vision science: official publication of the American Academy of Optometry*. 1999;76(6):387-392.
135. Vitale S, Sperduto RD, Ferris FL. Increased prevalence of myopia in the United States between 1971-1972 and 1999-2004. *Archives of ophthalmology*. 2009;127(12):1632-1639.
136. Vitale S, Ellwein L, Cotch MF, Ferris FL, III, Sperduto R. Prevalence of Refractive Error in the United States, 1999-2004. *Archives of Ophthalmology*. 2008;126(8):1111-1119. doi:10.1001/archopht.126.8.1111
137. Dayan YB, Levin A, Morad Y, et al. The changing prevalence of myopia in young adults: a 13-year series of population-based prevalence surveys. *Investigative ophthalmology & visual science*. 2005;46(8):2760-2765.
138. Pärssinen O. The increased prevalence of myopia in Finland. *Acta ophthalmologica*. 2012;90(6):497-502.
139. Williams KM, Bertelsen G, Cumberland P, et al. Increasing prevalence of myopia in Europe and the impact of education. *Ophthalmology*. 2015;122(7):1489-1497.
140. Hagen LA, Gjelle JV, Arnegard S, Pedersen HR, Gilson SJ, Baraas RC. Prevalence and possible factors of myopia in Norwegian adolescents. *Scientific reports*. 2018;8(1):1-10.

141. Mackey DA, Lingham G, Lee SS-Y, et al. Change in the prevalence of myopia in Australian middle-aged adults across 20 years. *Clinical & experimental ophthalmology*. 2021;49(9):1039-1047. doi:https://doi.org/10.1111/ceo.13980
142. Jacobsen N, Jensen H, Goldschmidt E. Prevalence of myopia in Danish conscripts. *Acta ophthalmologica Scandinavica*. 2007;85(2):165-170.
143. Lam CSY, Lam CH, Cheng SCK, Chan LYL. Prevalence of myopia among Hong Kong Chinese schoolchildren: changes over two decades. *Ophthalmic and Physiological Optics*. 2012;32(1):17-24.
144. Lam CS, Goh WS. The incidence of refractive errors among school children in Hong Kong and its relationship with the optical components. *Clinical and Experimental Optometry*. 1991;74(3):97-103.
145. Yam JC, Tang SM, Kam KW, et al. High prevalence of myopia in children and their parents in Hong Kong Chinese Population: the Hong Kong Children Eye Study. *Acta Ophthalmologica*. 2020;98(5):e639-e648. doi:https://doi.org/10.1111/aos.14350
146. Fan DS, Lam DS, Lam RF, et al. Prevalence, incidence, and progression of myopia of school children in Hong Kong. *Invest Ophthalmol Vis Sci*. Apr 2004;45(4):1071-5. doi:10.1167/iovs.03-1151
147. Dirani M, Chan YH, Gazzard G, et al. Prevalence of refractive error in Singaporean Chinese children: the strabismus, amblyopia, and refractive error in young Singaporean Children (STARS) study. *Invest Ophthalmol Vis Sci*. Mar 2010;51(3):1348-55. doi:10.1167/iovs.09-3587
148. Giordano L, Friedman DS, Repka MX, et al. Prevalence of refractive error among preschool children in an urban population: the Baltimore Pediatric Eye Disease Study. *Ophthalmology*. Apr 2009;116(4):739-46, 746.e1-4. doi:10.1016/j.ophtha.2008.12.030
149. Prevalence of myopia and hyperopia in 6- to 72-month-old african american and Hispanic children: the multi-ethnic pediatric eye disease study. *Ophthalmology*. Jan 2010;117(1):140-147.e3. doi:10.1016/j.ophtha.2009.06.009
150. Borchert MS, Varma R, Cotter SA, et al. Risk factors for hyperopia and myopia in preschool children the multi-ethnic pediatric eye disease and Baltimore pediatric eye disease studies. *Ophthalmology*. Oct 2011;118(10):1966-73. doi:10.1016/j.ophtha.2011.06.030
151. Wen G, Tarczy-Hornoch K, McKean-Cowdin R, et al. Prevalence of myopia, hyperopia, and astigmatism in non-Hispanic white and Asian children: multi-ethnic pediatric eye disease study. *Ophthalmology*. Oct 2013;120(10):2109-16. doi:10.1016/j.ophtha.2013.06.039
152. Pai AS, Wang JJ, Samarawickrama C, et al. Prevalence and risk factors for visual impairment in preschool children the sydney paediatric eye disease study. *Ophthalmology*. Aug 2011;118(8):1495-500. doi:10.1016/j.ophtha.2011.01.027
153. Fan DS, Lai C, Lau HH, Cheung EY, Lam DS. Change in vision disorders among Hong Kong preschoolers in 10 years. *Clinical & experimental ophthalmology*. Jul 2011;39(5):398-403. doi:10.1111/j.1442-9071.2010.02470.x
154. Lai YH, Hsu HT, Wang HZ, Chang SJ, Wu WC. The visual status of children ages 3 to 6 years in the vision screening program in Taiwan. *Journal of AAPOS : the official publication of the American Association for Pediatric Ophthalmology and Strabismus*. Feb 2009;13(1):58-62. doi:10.1016/j.jaapos.2008.07.006
155. Lan W, Zhao F, Lin L, et al. Refractive errors in 3-6 year-old Chinese children: a very low prevalence of myopia? *PLoS One*. 2013;8(10):e78003. doi:10.1371/journal.pone.0078003
156. Ma Y, Qu X, Zhu X, et al. Age-Specific Prevalence of Visual Impairment and Refractive Error in Children Aged 3-10 Years in Shanghai, China. *Invest Ophthalmol Vis Sci*. Nov 1 2016;57(14):6188-6196. doi:10.1167/iovs.16-20243
157. Wang X, Liu D, Feng R, Zhao H, Wang Q. Refractive error among urban preschool children in Xuzhou, China. *International journal of clinical and experimental pathology*. 2014;7(12):8922-8.
158. Hsu CC, Huang N, Lin PY, et al. Prevalence and risk factors for myopia in second-grade primary school children in Taipei: A population-based study. *Journal of the Chinese Medical Association : JCMA*. Nov 2016;79(11):625-632. doi:10.1016/j.jcma.2016.02.011

159. Zhang M-Z, Saw S-M, Hong R-Z, et al. Refractive errors in Singapore and Xiamen, China—a comparative study in school children aged 6 to 7 years. *Optometry and vision science*. 2000;77(6):302-308.
160. Pi LH, Chen L, Liu Q, et al. Prevalence of eye diseases and causes of visual impairment in school-aged children in Western China. *Journal of epidemiology*. 2012;22(1):37-44. doi:10.2188/jea.je20110063
161. Li Z, Xu K, Wu S, et al. Population-based survey of refractive error among school-aged children in rural northern China: the Heilongjiang eye study. *Clinical & experimental ophthalmology*. May-Jun 2014;42(4):379-84. doi:10.1111/ceo.12198
162. Lin Z, Gao TY, Vasudevan B, et al. Generational difference of refractive error and risk factors in the Handan Offspring Myopia Study. *Invest Ophthalmol Vis Sci*. Aug 5 2014;55(9):5711-7. doi:10.1167/iovs.13-13693
163. Pan C-W, Wu R-K, Li J, Zhong H. Low prevalence of myopia among school children in rural China. *BMC ophthalmology*. 2018/06/11 2018;18(1):140. doi:10.1186/s12886-018-0808-0
164. He M, Huang W, Zheng Y, Huang L, Ellwein LB. Refractive error and visual impairment in school children in rural southern China. *Ophthalmology*. Feb 2007;114(2):374-82. doi:10.1016/j.ophtha.2006.08.020
165. Guo K, Wang Y, Yang XR, et al. Prevalence of myopia in schoolchildren in Ejina: the Gobi Desert Children Eye Study. *Invest Ophthalmol Vis Sci*. Jan 27 2015;56(3):1769-74. doi:10.1167/iovs.14-15737
166. Tideman JWL, Polling JR, Hofman A, Jaddoe VW, Mackenbach JP, Klaver CC. Environmental factors explain socioeconomic prevalence differences in myopia in 6-year-old children. *Br J Ophthalmol*. Feb 2018;102(2):243-247. doi:10.1136/bjophthalmol-2017-310292
167. Logan NS, Shah P, Rudnicka AR, Gilmartin B, Owen CG. Childhood ethnic differences in ametropia and ocular biometry: the Aston Eye Study. *Ophthalmic & physiological optics : the journal of the British College of Ophthalmic Opticians (Optometrists)*. Sep 2011;31(5):550-8. doi:10.1111/j.1475-1313.2011.00862.x
168. O'Donoghue L, McClelland JF, Logan NS, Rudnicka AR, Owen CG, Saunders KJ. Refractive error and visual impairment in school children in Northern Ireland. *Br J Ophthalmol*. Sep 2010;94(9):1155-9. doi:10.1136/bjo.2009.176040
169. Harrington SC, Stack J, Saunders K, O'Dwyer V. Refractive error and visual impairment in Ireland schoolchildren. *British Journal of Ophthalmology*. 2019;103(8):1112-1118.
170. Kleinstein RN, Jones LA, Hullett S, et al. Refractive error and ethnicity in children. *Archives of ophthalmology (Chicago, Ill : 1960)*. Aug 2003;121(8):1141-7. doi:10.1001/archopht.121.8.1141
171. Czepita D, Zejmo M, Mojsa A. Prevalence of myopia and hyperopia in a population of Polish schoolchildren. *Ophthalmic & physiological optics : the journal of the British College of Ophthalmic Opticians (Optometrists)*. Jan 2007;27(1):60-5. doi:10.1111/j.1475-1313.2006.00419.x
172. Villarreal MG, Ohlsson J, Abrahamsson M, Sjöstrom A, Sjöstrand J. Myopisation: the refractive tendency in teenagers. Prevalence of myopia among young teenagers in Sweden. *Acta Ophthalmol Scand*. Apr 2000;78(2):177-81. doi:10.1034/j.1600-0420.2000.078002177.x
173. Anera RG, Soler M, De La Cruz Cardona J, Salas C, Ortiz C. Prevalence of refractive errors in school-age children in Morocco. *Clinical & experimental ophthalmology*. 2009;37(2):191-196. doi:https://doi.org/10.1111/j.1442-9071.2009.02001.x
174. Alrasheed SH, Naidoo KS, Clarke-Farr PC. Prevalence of visual impairment and refractive error in school-aged children in South Darfur State of Sudan. *African Vision and Eye Health*. 2016;75(1):1-9.
175. Assem AS, Tegegne MM, Fekadu SA. Prevalence and associated factors of myopia among school children in Bahir Dar city, Northwest Ethiopia, 2019. *PloS one*. 2021;16(3):e0248936.
176. Atowa UC, Wajuihian SO, Munsamy AJ. Prevalence and risk factors for myopia among school children in Aba, Nigeria. *African Vision and Eye Health*. 2017;76(1):1-5.

177. Ovenseri-Ogbomo G, Omuemu V. Prevalence of refractive error among school children in the Cape Coast Municipality, Ghana. *Clin Optom*. 2010;2:59-66.
178. Soler M, Anera RG, Castro JJ, Jiménez R, Jiménez JR. Prevalence of refractive errors in children in Equatorial Guinea. *Optometry and Vision Science*. 2015;92(1):53-58.
179. Yamamah GAN, Talaat Abdel Alim AA, Mostafa YSED, Ahmed RAAS, Mahmoud AM. Prevalence of visual impairment and refractive errors in children of South Sinai, Egypt. *Ophthalmic epidemiology*. 2015;22(4):246-252.
180. Naidoo KS, Raghunandan A, Mashige KP, et al. Refractive error and visual impairment in African children in South Africa. *Invest Ophthalmol Vis Sci*. Sep 2003;44(9):3764-70. doi:10.1167/iovs.03-0283
181. Ovenseri-Ogbomo G, Osuagwu UL, Ekpenyong BN, et al. Systematic review and meta-analysis of myopia prevalence in African school children. *PLOS ONE*. 2022;17(2):e0263335. doi:10.1371/journal.pone.0263335
182. Kumah BD, Ebri A, Abdul-Kabir M, et al. Refractive error and visual impairment in private school children in Ghana. *Optom Vis Sci*. Dec 2013;90(12):1456-61. doi:10.1097/opx.0000000000000099
183. Maul E, Barroso S, Munoz SR, Sperduto RD, Ellwein LB. Refractive Error Study in Children: results from La Florida, Chile. *Am J Ophthalmol*. Apr 2000;129(4):445-54. doi:10.1016/s0002-9394(99)00454-7
184. Lira RP, Arieta CE, Passos TH, et al. Distribution of Ocular Component Measures and Refraction in Brazilian School Children. *Ophthalmic Epidemiol*. Feb 2017;24(1):29-35. doi:10.1080/09286586.2016.1254249
185. Jamali P, Fotouhi A, Hashemi H, Younesian M, Jafari A. Refractive errors and amblyopia in children entering school: Shahrood, Iran. *Optom Vis Sci*. Apr 2009;86(4):364-9. doi:10.1097/OPX.0b013e3181993f42
186. Hashemi H, Yekta A, Nabovati P, Khoshhal F, Riazi A, Khabazkhoob M. The prevalence of refractive errors in 5-15 year-old population of two underserved rural areas of Iran. *J Curr Ophthalmol*. Sep 2018;30(3):250-254. doi:10.1016/j.joco.2017.05.004
187. Yekta A, Fotouhi A, Hashemi H, et al. Prevalence of refractive errors among schoolchildren in Shiraz, Iran. *Clinical & experimental ophthalmology*. Apr 2010;38(3):242-8. doi:10.1111/j.1442-9071.2010.02247.x
188. Ostadimoghaddam H, Fotouhi A, Hashemi H, et al. Prevalence of the refractive errors by age and gender: the Mashhad eye study of Iran. *Clinical & experimental ophthalmology*. Nov 2011;39(8):743-51. doi:10.1111/j.1442-9071.2011.02584.x
189. Rezvan F, Khabazkhoob M, Fotouhi A, et al. Prevalence of refractive errors among school children in Northeastern Iran. *Ophthalmic & physiological optics : the journal of the British College of Ophthalmic Opticians (Optometrists)*. Jan 2012;32(1):25-30. doi:10.1111/j.1475-1313.2011.00879.x
190. Saw SM, Tong L, Chua WH, et al. Incidence and progression of myopia in Singaporean school children. *Invest Ophthalmol Vis Sci*. Jan 2005;46(1):51-7. doi:10.1167/iovs.04-0565
191. Goh PP, Abqariyah Y, Pokharel GP, Ellwein LB. Refractive error and visual impairment in school-age children in Gombak District, Malaysia. *Ophthalmology*. Apr 2005;112(4):678-85. doi:10.1016/j.ophtha.2004.10.048
192. Yingyong P. Refractive errors survey in primary school children (6-12 year old) in 2 provinces: Bangkok and Nakhonpathom (one year result). *Journal of the Medical Association of Thailand = Chotmaihet thangphaet*. Oct 2010;93(10):1205-10.
193. Murthy GV, Gupta SK, Ellwein LB, et al. Refractive error in children in an urban population in New Delhi. *Invest Ophthalmol Vis Sci*. Mar 2002;43(3):623-31.
194. Dandona R, Dandona L, Srinivas M, et al. Refractive error in children in a rural population in India. *Invest Ophthalmol Vis Sci*. Mar 2002;43(3):615-22.

195. Pokharel GP, Negrel AD, Munoz SR, Ellwein LB. Refractive Error Study in Children: results from Mechi Zone, Nepal. *Am J Ophthalmol*. Apr 2000;129(4):436-44. doi:10.1016/s0002-9394(99)00453-5
196. Sapkota YD, Adhikari BN, Pokharel GP, Poudyal BK, Ellwein LB. The prevalence of visual impairment in school children of upper-middle socioeconomic status in Kathmandu. *Ophthalmic Epidemiol*. Jan-Feb 2008;15(1):17-23. doi:10.1080/09286580701772011
197. Ip JM, Huynh SC, Robaei D, et al. Ethnic differences in refraction and ocular biometry in a population-based sample of 11-15-year-old Australian children. *Eye (London, England)*. May 2008;22(5):649-56. doi:10.1038/sj.eye.6702701
198. Fotouhi A, Hashemi H, Khabazkhoob M, Mohammad K. The prevalence of refractive errors among schoolchildren in Dezful, Iran. *Br J Ophthalmol*. Mar 2007;91(3):287-92. doi:10.1136/bjo.2006.099937
199. Jung S-K, Lee JH, Kakizaki H, Jee D. Prevalence of myopia and its association with body stature and educational level in 19-year-old male conscripts in seoul, South Korea. *Invest Ophthalmol Vis Sci*. Aug 15 2012;53(9):5579-83. doi:10.1167/iovs.12-10106
200. Lee JH, Jee D, Kwon JW, Lee WK. Prevalence and risk factors for myopia in a rural Korean population. *Invest Ophthalmol Vis Sci*. Aug 13 2013;54(8):5466-71. doi:10.1167/iovs.13-12478
201. Lee YY, Lo CT, Sheu SJ, Lin JL. What factors are associated with myopia in young adults? A survey study in Taiwan Military Conscripts. *Invest Ophthalmol Vis Sci*. Feb 5 2013;54(2):1026-33. doi:10.1167/iovs.12-10480
202. Sun J, Zhou J, Zhao P, et al. High prevalence of myopia and high myopia in 5060 Chinese university students in Shanghai. *Invest Ophthalmol Vis Sci*. Nov 1 2012;53(12):7504-9. doi:10.1167/iovs.11-8343
203. Shin H-M, Shin H-U, Jung J-H. Prevalence of Refractive Error in Adults in Phnom Penh, Cambodia. *J Korean Ophthalmic Opt Soc*. 2018;23(4):301-307.
204. Saw SM, Gazzard G, Koh D, et al. Prevalence rates of refractive errors in Sumatra, Indonesia. *Invest Ophthalmol Vis Sci*. Oct 2002;43(10):3174-80.
205. McKnight CM, Sherwin JC, Yazar S, et al. Myopia in young adults is inversely related to an objective marker of ocular sun exposure: the Western Australian Raine cohort study. *Am J Ophthalmol*. Nov 2014;158(5):1079-85. doi:10.1016/j.ajo.2014.07.033
206. Sperduto RD, Seigel D, Roberts J, Rowland M. Prevalence of myopia in the United States. *Archives of ophthalmology (Chicago, Ill : 1960)*. Mar 1983;101(3):405-7. doi:10.1001/archopht.1983.01040010405011
207. Midelfart A, Kinge B, Midelfart S, Lydersen S. Prevalence of refractive errors in young and middle-aged adults in Norway. *Acta Ophthalmol Scand*. Oct 2002;80(5):501-5. doi:10.1034/j.1600-0420.2002.800508.x
208. Xu L, Li J, Cui T, et al. Refractive error in urban and rural adult Chinese in Beijing. *Ophthalmology*. 2005;112(10):1676-1683.
209. He M, Huang W, Li Y, Zheng Y, Yin Q, Foster PJ. Refractive error and biometry in older Chinese adults: the Liwan eye study. *Investigative ophthalmology & visual science*. 2009;50(11):5130-5136.
210. Liang YB, Wong TY, Sun LP, et al. Refractive errors in a rural Chinese adult population: the Handan eye study. *Ophthalmology*. 2009;116(11):2119-2127.
211. Wickremasinghe S, Foster PJ, Uranchimeg D, et al. Ocular biometry and refraction in Mongolian adults. *Investigative ophthalmology & visual science*. 2004;45(3):776-783.
212. Sawada A, Tomidokoro A, Araie M, Iwase A, Yamamoto T, Group TS. Refractive errors in an elderly Japanese population: the Tajimi study. *Ophthalmology*. 2008;115(2):363-370. e3.
213. Nakamura Y, Nakamura Y, Higa A, et al. Refractive errors in an elderly rural Japanese population: the Kumejima study. *Plos one*. 2018;13(11):e0207180.

214. Cheng C-Y, Hsu W-M, Liu J-H, Tsai S-Y, Chou P. Refractive errors in an elderly Chinese population in Taiwan: the Shihpai Eye Study. *Investigative ophthalmology & visual science*. 2003;44(11):4630-4638.
215. Han SB, Jang J, Yang HK, Hwang J-M, Park SK. Prevalence and risk factors of myopia in adult Korean population: Korea national health and nutrition examination survey 2013-2014 (KNHANES VI). *PloS one*. 2019;14(1):e0211204.
216. Yoo Y, Kim J, Park K, Kim C, Kim T. Refractive errors in a rural Korean adult population: the Namil Study. *Eye*. 2013;27(12):1368-1375.
217. Wong TY, Foster PJ, Hee J, et al. Prevalence and risk factors for refractive errors in adult Chinese in Singapore. *Investigative ophthalmology & visual science*. 2000;41(9):2486-2494.
218. Saw S-M, Chan Y-H, Wong W-L, et al. Prevalence and risk factors for refractive errors in the Singapore Malay Eye Survey. *Ophthalmology*. 2008;115(10):1713-1719.
219. Pan C-W, Wong T-Y, Lavanya R, et al. Prevalence and risk factors for refractive errors in Indians: the Singapore Indian Eye Study (SINDI). *Investigative ophthalmology & visual science*. 2011;52(6):3166-3173.
220. Saw S-M, Gazzard G, Koh D, et al. Prevalence rates of refractive errors in Sumatra, Indonesia. *Investigative ophthalmology & visual science*. 2002;43(10):3174-3180.
221. Bourne RR, Dineen BP, Ali SM, Huq DMN, Johnson GJ. Prevalence of refractive error in Bangladeshi adults: results of the National Blindness and Low Vision Survey of Bangladesh. *Ophthalmology*. 2004;111(6):1150-1160.
222. Shah SP, Jadoon MZ, Dineen B, et al. Refractive errors in the adult Pakistani population: the national blindness and visual impairment survey. *Ophthalmic Epidemiology*. 2008;15(3):183-190.
223. Krishnaiah S, Srinivas M, Khanna RC, Rao GN. Prevalence and risk factors for refractive errors in the South Indian adult population: The Andhra Pradesh Eye disease study. *Clinical ophthalmology (Auckland, NZ)*. 2009;3:17.
224. Raju P, Ramesh SV, Arvind H, et al. Prevalence of refractive errors in a rural South Indian population. *Investigative ophthalmology & visual science*. 2004;45(12):4268-4272.
225. Hashemi H, Khabazkhoob M, Jafarzadehpur E, et al. High prevalence of myopia in an adult population, Shahroud, Iran. *Optometry and Vision Science*. 2012;89(7):993-999.
226. Hashemi H, Rezvan F, Ostadimoghaddam H, Abdollahi M, Hashemi M, Khabazkhoob M. High prevalence of refractive errors in a rural population:'N ooravaran S alamat'M obile E ye C linic experience. *Clinical & experimental ophthalmology*. 2013;41(7):635-643.
227. Ziaei H, Katibeh M, Solaimanizad R, et al. Prevalence of refractive errors; the yazd eye study. *Journal of ophthalmic & vision research*. 2013;8(3):227.
228. Hashemi H, Nabovati P, Yekta A, Shokrollahzadeh F, Khabazkhoob M. The prevalence of refractive errors among adult rural populations in Iran. *Clinical and Experimental Optometry*. 2018;101(1):84-89.
229. Williams KM, Verhoeven VJ, Cumberland P, et al. Prevalence of refractive error in Europe: the European eye epidemiology (E 3) consortium. *European journal of epidemiology*. 2015;30(4):305-315.
230. Sherwin JC, Khawaja AP, Broadway D, et al. Uncorrected refractive error in older British adults: the EPIC-Norfolk Eye Study. *British journal of ophthalmology*. 2012;96(7):991-996.
231. Rahi JS, Cumberland PM, Peckham CS. Myopia over the lifecourse: prevalence and early life influences in the 1958 British birth cohort. *Ophthalmology*. 2011;118(5):797-804.
232. Cumberland PM, Bao Y, Hysi PG, et al. Frequency and distribution of refractive error in adult life: methodology and findings of the UK Biobank Study. *PloS one*. 2015;10(10):e0139780.
233. Wolfram C, Höhn R, Kottler U, et al. Prevalence of refractive errors in the European adult population: the Gutenberg Health Study (GHS). *British Journal of Ophthalmology*. 2014;98(7):857-861.
234. Katz J, Tielsch JM, Sommer A. Prevalence and risk factors for refractive errors in an adult inner city population. *Investigative ophthalmology & visual science*. 1997;38(2):334-340.

235. Wu S-Y, Nemesure B, Leske MC. Refractive errors in a black adult population: the Barbados Eye Study. *Investigative ophthalmology & visual science*. 1999;40(10):2179-2184.
236. Tarczy-Hornoch K, Ying-Lai M, Varma R. Myopic refractive error in adult Latinos: the Los Angeles Latino eye study. *Investigative ophthalmology & visual science*. 2006;47(5):1845-1852.
237. Varma R, Torres M, McKean-Cowdin R, et al. Prevalence and risk factors for refractive error in adult Chinese Americans: the Chinese American Eye Study. *American journal of ophthalmology*. 2017;175:201-212.
238. Attebo K, Ivers RQ, Mitchell P. Refractive errors in an older population: the Blue Mountains Eye Study. *Ophthalmology*. 1999;106(6):1066-1072.
239. Wensor M, McCarty CA, Taylor HR. Prevalence and risk factors of myopia in Victoria, Australia. *Archives of ophthalmology*. 1999;117(5):658-663.
240. Ezelum C, Razavi H, Sivasubramaniam S, et al. Refractive error in Nigerian adults: prevalence, type, and spectacle coverage. *Investigative ophthalmology & visual science*. 2011;52(8):5449-5456.
241. Mashige KP, Jaggernath J, Ramson P, Martin C, Chinanayi FS, Naidoo KS. Prevalence of refractive errors in the INK area, Durban, South Africa. *Optometry and Vision Science*. 2016;93(3):243-250.
242. Galvis V, Tello A, Otero J, et al. Prevalence of refractive errors in Colombia: MIOPUR study. *British Journal of Ophthalmology*. 2018;102(10):1320-1323.
243. Hashemi H, Fotouhi A, Yekta A, Pakzad R, Ostadimoghaddam H, Khabazkhoob M. Global and regional estimates of prevalence of refractive errors: systematic review and meta-analysis. *Journal of current ophthalmology*. 2018;30(1):3-22.
244. Mitchell P, Hourihan F, Sandbach J, Wang JJ. The relationship between glaucoma and myopia: the Blue Mountains Eye Study. *Ophthalmology*. 1999;106(10):2010-2015.
245. Xu L, Wang Y, Wang S, Wang Y, Jonas JB. High myopia and glaucoma susceptibility: the Beijing Eye Study. *Ophthalmology*. 2007;114(2):216-220.
246. Leske MC, Connell A, Wu S-Y, Hyman LG, Schachat AP. Risk factors for open-angle glaucoma: the Barbados Eye Study. *Archives of ophthalmology*. 1995;113(7):918-924.
247. Wong TY, Klein BE, Klein R, Knudtson M, Lee KE. Refractive errors, intraocular pressure, and glaucoma in a white population. *Ophthalmology*. 2003;110(1):211-217.
248. Suzuki Y, Iwase A, Araie M, et al. Risk factors for open-angle glaucoma in a Japanese population: the Tajimi Study. *Ophthalmology*. 2006;113(9):1613-1617.
249. Pan C-W, Cheung CY, Aung T, et al. Differential associations of myopia with major age-related eye diseases: the Singapore Indian Eye Study. *Ophthalmology*. 2013;120(2):284-291.
250. Grødum K, Heijl A, Bengtsson B. Refractive error and glaucoma. *Acta ophthalmologica Scandinavica*. 2001;79(6):560-566.
251. Marcus MW, de Vries MM, Montolio FGJ, Jansonius NM. Myopia as a risk factor for open-angle glaucoma: a systematic review and meta-analysis. *Ophthalmology*. 2011;118(10):1989-1994. e2.
252. Lim R, Mitchell P, Cumming RG. Refractive associations with cataract: the blue mountains eye study. *Investigative ophthalmology & visual science*. 1999;40(12):3021-3026.
253. Dandona R, Dandona L, Naduvilath TJ, Srinivas M, McCarty CA, Rao GN. Refractive errors in an urban population in southern India: the Andhra Pradesh Eye Disease Study. *Investigative ophthalmology & visual science*. 1999;40(12):2810-2818.
254. Hashemi H, KhabazKhoob M, Miraftab M, Mohammad K, Fotouhi A. The association between refractive errors and cataract: the tehran eye study. *Middle East African journal of ophthalmology*. 2011;18(2):154.
255. Mukesh BN, Le A, Dimitrov PN, Ahmed S, Taylor HR, McCarty CA. Development of cataract and associated risk factors: the Visual Impairment Project. *Archives of ophthalmology*. 2006;124(1):79-85.

256. Kanthan GL, Mitchell P, Rochtchina E, Cumming RG, Wang JJ. Myopia and the long-term incidence of cataract and cataract surgery: the B lue M ountains E ye S tudy. *Clinical & experimental ophthalmology*. 2014;42(4):347-353.
257. Chen DZ, Koh V, Tan M, et al. Peripheral retinal changes in highly myopic young Asian eyes. *Acta ophthalmologica*. 2018;96(7):e846-e851.
258. Group EDC-CS. Risk factors for idiopathic rhegmatogenous retinal detachment. *American Journal of Epidemiology*. 1993;137(7):749-757.
259. Zou H, Zhang X, Xu X, Wang X, Liu K, Ho P. Epidemiology survey of rhegmatogenous retinal detachment in Beixinjing District, Shanghai, China. *Retina*. 2002;22(3):294-299.
260. Chou S, Yang C, Lee C, et al. Characteristics of primary rhegmatogenous retinal detachment in Taiwan. *Eye*. 2007;21(8):1056-1061.
261. Ogawa A, Tanaka M. The relationship between refractive errors and retinal detachment--analysis of 1,166 retinal detachment cases. *Japanese journal of ophthalmology*. 1988;32(3):310-315.
262. Ross WH, Stockl FA. Visual recovery after retinal detachment. *Current opinion in ophthalmology*. 2000;11(3):191-194.
263. Salicone A, Smiddy WE, Venkatraman A, Feuer W. Visual recovery after scleral buckling procedure for retinal detachment. *Ophthalmology*. 2006;113(10):1734-1742.
264. Törnquist R, Törnquist P. Retinal detachment: A study of a population-based patient material in Sweden 1971–1981 III Surgical results. *Acta Ophthalmologica*. 1988;66(6):630-636.
265. Arias L, Caminal JM, Rubio MJ, et al. Autofluorescence and axial length as prognostic factors for outcomes of macular hole retinal detachment surgery in high myopia. *Retina*. 2015;35(3):423-428.
266. Sharma T, Challa JK, Ravishankar K, Murugesan R. Scleral buckling for retinal detachment. Predictors for anatomic failure. *Retina (Philadelphia, Pa)*. 1994;14(4):338-343.
267. Grizzard WS, Hilton GF, Hammer ME, Taren D. A multivariate analysis of anatomic success of retinal detachments treated with scleral buckling. *Graefe's archive for clinical and experimental ophthalmology*. 1994;232(1):1-7.
268. Neelam K, Cheung CMG, Ohno-Matsui K, Lai TY, Wong TY. Choroidal neovascularization in pathological myopia. *Progress in retinal and eye research*. 2012;31(5):495-525.
269. Asakuma T, Yasuda M, Ninomiya T, et al. Prevalence and risk factors for myopic retinopathy in a Japanese population: the Hisayama Study. *Ophthalmology*. 2012;119(9):1760-1765.
270. Gao LQ, Liu W, Liang YB, et al. Prevalence and characteristics of myopic retinopathy in a rural Chinese adult population: the Handan Eye Study. *Archives of Ophthalmology*. 2011;129(9):1199-1204.
271. Liu HH, Xu L, Wang YX, Wang S, You QS, Jonas JB. Prevalence and progression of myopic retinopathy in Chinese adults: the Beijing Eye Study. *Ophthalmology*. 2010;117(9):1763-1768.
272. Wong Y-L, Sabanayagam C, Ding Y, et al. Prevalence, risk factors, and impact of myopic macular degeneration on visual impairment and functioning among adults in Singapore. *Investigative ophthalmology & visual science*. 2018;59(11):4603-4613.
273. Shih Y-F, Ho T-C, Hsiao CK, Lin LL. Visual outcomes for high myopic patients with or without myopic maculopathy: a 10 year follow up study. *British journal of ophthalmology*. 2006;90(5):546-550.
274. Fricke TR, Jong M, Naidoo KS, et al. Global prevalence of visual impairment associated with myopic macular degeneration and temporal trends from 2000 through 2050: systematic review, meta-analysis and modelling. *British Journal of Ophthalmology*. 2018;102(7):855-862.
275. Taylor H, Pezzullo M, Keeffe J. The economic impact and cost of visual impairment in Australia. *British Journal of Ophthalmology*. 2006;90(3):272-275.
276. Zheng Y-F, Pan C-W, Chay J, Wong TY, Finkelstein E, Saw S-M. The economic cost of myopia in adults aged over 40 years in Singapore. *Investigative ophthalmology & visual science*. 2013;54(12):7532-7537.

277. Lim M, Gazzard G, Sim E, Tong L, Saw S. Direct costs of myopia in Singapore. *Eye*. 2009;23(5):1086-1089.
278. Vitale S, Cotch MF, Sperduto R, Ellwein L. Costs of refractive correction of distance vision impairment in the United States, 1999–2002. *Ophthalmology*. 2006;113(12):2163-2170.
279. Naidoo KS, Fricke TR, Frick KD, et al. Potential lost productivity resulting from the global burden of myopia: systematic review, meta-analysis, and modeling. *Ophthalmology*. 2019;126(3):338-346.
280. Fricke T, Holden B, Wilson D, et al. Global cost of correcting vision impairment from uncorrected refractive error. *Bulletin of the World Health Organization*. 2012;90:728-738.
281. Wong H-B, Machin D, Tan S-B, Wong T-Y, Saw S-M. Visual impairment and its impact on health-related quality of life in adolescents. *American journal of ophthalmology*. 2009;147(3):505-511. e1.
282. Rose K, Harper R, Tromans C, et al. Quality of life in myopia. *British journal of ophthalmology*. 2000;84(9):1031-1034.
283. Chen CY, Keeffe JE, Garoufalis P, et al. Vision-related quality of life comparison for emmetropes, myopes after refractive surgery, and myopes wearing spectacles or contact lenses. Slack Incorporated Thorofare, NJ; 2007.
284. Takashima T, Yokoyama T, Futagami S, et al. The quality of life in patients with pathologic myopia. *Japanese journal of ophthalmology*. 2001;45(1):84-92.
285. Wiesel TN, Raviola E. Myopia and eye enlargement after neonatal lid fusion in monkeys. *Nature*. 1977;266(5597):66-68.
286. Sherman SM, Norton T, Casagrande V. Myopia in the lid-sutured tree shrew (Tupaia glis). *Brain research*. 1977;124(1):154-157.
287. Wallman J, Turkel J, Trachtman J. Extreme myopia produced by modest change in early visual experience. *Science*. 1978;201(4362):1249-1251.
288. Barathi V, Boopathi V, Yap EP, Beuerman RW. Two models of experimental myopia in the mouse. *Vision research*. 2008;48(7):904-916.
289. Shen W, Vijayan M, Sivak JG. Inducing form-deprivation myopia in fish. *Investigative ophthalmology & visual science*. 2005;46(5):1797-1803.
290. Howlett MH, McFadden SA. Form-deprivation myopia in the guinea pig (Cavia porcellus). *Vision research*. 2006;46(1-2):267-283.
291. Verolino M, Nastri G, Sellitti L, Costagliola C. Axial length increase in lid-sutured rabbits. *Survey of ophthalmology*. 1999;44:S103-S108.
292. Andison ME, Sivak J, Bird D. The refractive development of the eye of the American kestrel (Falco sparverius): a new avian model. *Journal of Comparative Physiology A*. 1992;170(5):565-574.
293. Graham B, Judge S. The effects of spectacle wear in infancy on eye growth and refractive error in the marmoset (Callithrix jacchus). *Vision research*. 1999;39(2):189-206.
294. Howlett MH, McFadden SA. Spectacle lens compensation in the pigmented guinea pig. *Vision research*. 2009;49(2):219-227.
295. Metlapally S, McBrien NA. The effect of positive lens defocus on ocular growth and emmetropization in the tree shrew. *Journal of vision*. 2008;8(3):1-1.
296. Shen W, Sivak JG. Eyes of a lower vertebrate are susceptible to the visual environment. *Investigative ophthalmology & visual science*. 2007;48(10):4829-4837.
297. Siatkowski RM, Cotter S, Miller JM, Scher CA, Crockett RS, Novack GD. Safety and efficacy of 2% pirenzepine ophthalmic gel in children with myopia: a 1-year, multicenter, double-masked, placebo-controlled parallel study. *Archives of ophthalmology (Chicago, Ill : 1960)*. Nov 2004;122(11):1667-74. doi:10.1001/archopht.122.11.1667
298. Siatkowski RM, Cotter SA, Crockett RS, Miller JM, Novack GD, Zadnik K. Two-year multicenter, randomized, double-masked, placebo-controlled, parallel safety and efficacy study of 2%pirenzepineophthalmicgelinchildrenwithmyopia. *Journal of American Association for Pediatric*

Ophthalmology and Strabismus. 2008/08/01/ 2008;12(4):332-339. doi:https://doi.org/10.1016/j.jaapos.2007.10.014
299. Tan DTH, Lam DS, Chua WH, Shu-Ping DF, Crockett RS. One-year multicenter, double-masked, placebo-controlled, parallel safety and efficacy study of 2% pirenzepine ophthalmic gel in children with myopia. *Ophthalmology*. 2005/01/01/ 2005;112(1):84-91. doi:https://doi.org/10.1016/j.ophtha.2004.06.038
300. Trier K, Munk Ribel-Madsen S, Cui D, Brøgger Christensen S. Systemic 7-methylxanthine in retarding axial eye growth and myopia progression: a 36-month pilot study. *Journal of Ocular Biology, Diseases, and Informatics*. 2008/11/04 2008;1(2):85. doi:10.1007/s12177-008-9013-3
301. Donders FC, Moore WD. On the Anomalies of Accommodation and Refraction of the Eye. London: The New Sydenham Society; 1864.
302. Bedrossian RH. The Effect of Atropine on Myopia. *Ophthalmology*. 1979/05/01/ 1979;86(5):713-717. doi:https://doi.org/10.1016/S0161-6420(79)35455-0
303. Chou AC, Shih YF, Ho TC, Lin LL. The effectiveness of 0.5% atropine in controlling high myopia in children. *Journal of ocular pharmacology and therapeutics : the official journal of the Association for Ocular Pharmacology and Therapeutics*. Feb 1997;13(1):61-7. doi:10.1089/jop.1997.13.61
304. Shih YF, Chen CH, Chou AC, Ho TC, Lin LL, Hung PT. Effects of different concentrations of atropine on controlling myopia in myopic children. *Journal of ocular pharmacology and therapeutics : the official journal of the Association for Ocular Pharmacology and Therapeutics*. Feb 1999;15(1):85-90. doi:10.1089/jop.1999.15.85
305. Brodstein RS, Brodstein DE, Olson RJ, Hunt SC, Williams RR. The treatment of myopia with atropine and bifocals. A long-term prospective study. *Ophthalmology*. Nov 1984;91(11):1373-9. doi:10.1016/s0161-6420(84)34138-0
306. Yen MY, Liu JH, Kao SC, Shiao CH. Comparison of the effect of atropine and cyclopentolate on myopia. *Annals of ophthalmology*. May 1989;21(5):180-2, 187.
307. Rosenfield M, Gilmartin B. Accommodative error, adaptation and myopia. *Ophthalmic & physiological optics : the journal of the British College of Ophthalmic Opticians (Optometrists)*. Mar 1999;19(2):159-64. doi:10.1046/j.1475-1313.1999.00419.x
308. McBrien NA, Moghaddam HO, Reeder AP. Atropine reduces experimental myopia and eye enlargement via a nonaccommodative mechanism. *Invest Ophthalmol Vis Sci*. Jan 1993;34(1):205-15.
309. Upadhyay A, Beuerman RW. Biological Mechanisms of Atropine Control of Myopia. *Eye & contact lens*. May 2020;46(3):129-135. doi:10.1097/icl.0000000000000677
310. McBrien NA, Stell WK, Carr B. How does atropine exert its anti-myopia effects? *Ophthalmic & physiological optics : the journal of the British College of Ophthalmic Opticians (Optometrists)*. May 2013;33(3):373-8. doi:10.1111/opo.12052
311. Chua W-H, Balakrishnan V, Chan Y-H, et al. Atropine for the Treatment of Childhood Myopia. *Ophthalmology*. 2006/12/01/ 2006;113(12):2285-2291. doi:https://doi.org/10.1016/j.ophtha.2006.05.062
312. Chia A, Chua W-H, Cheung Y-B, et al. Atropine for the Treatment of Childhood Myopia: Safety and Efficacy of 0.5%, 0.1%, and 0.01% Doses (Atropine for the Treatment of Myopia 2). *Ophthalmology*. 2012/02/01/ 2012;119(2):347-354. doi:https://doi.org/10.1016/j.ophtha.2011.07.031
313. Tong L, Huang XL, Koh ALT, Zhang X, Tan DTH, Chua W-H. Atropine for the Treatment of Childhood Myopia: Effect on Myopia Progression after Cessation of Atropine. *Ophthalmology*. 2009/03/01/ 2009;116(3):572-579. doi:https://doi.org/10.1016/j.ophtha.2008.10.020
314. Chia A, Chua W-H, Wen L, Fong A, Goon YY, Tan D. Atropine for the treatment of childhood myopia: changes after stopping atropine 0.01%, 0.1% and 0.5%. *American journal of ophthalmology*. 2014;157(2):451-457. e1.
315. Chia A, Lu Q-S, Tan D. Five-Year Clinical Trial on Atropine for the Treatment of Myopia 2: Myopia Control with Atropine 0.01% Eyedrops. *Ophthalmology*. 2016;123(2):391-399. doi:10.1016/j.ophtha.2015.07.004

316. Yi S, Huang Y, Yu S-Z, Chen X-J, Yi H, Zeng X-L. Therapeutic effect of atropine 1% in children with low myopia. *Journal of American Association for Pediatric Ophthalmology and Strabismus*. 2015/10/01/ 2015;19(5):426-429. doi:https://doi.org/10.1016/j.jaapos.2015.04.006
317. Wang YR, Bian HL, Wang Q. Atropine 0.5% eyedrops for the treatment of children with low myopia: A randomized controlled trial. *Medicine*. Jul 2017;96(27):e7371. doi:10.1097/md.0000000000007371
318. Yam JC, Jiang Y, Tang SM, et al. Low-Concentration Atropine for Myopia Progression (LAMP) Study: A Randomized, Double-Blinded, Placebo-Controlled Trial of 0.05%, 0.025%, and 0.01% Atropine Eye Drops in Myopia Control. *Ophthalmology*. Jan 2019;126(1):113-124. doi:10.1016/j.ophtha.2018.05.029
319. Yam JC, Zhang XJ, Zhang Y, et al. Three-Year clinical trial of low-concentration atropine for myopia progression (lamp) study: continued versus washout: phase 3 report. *Ophthalmology*. 2022;129(3):308-321.
320. Yam JC, Li FF, Zhang X, et al. Two-Year Clinical Trial of the Low-concentration Atropine for Myopia Progression (LAMP) Study: Phase 2 Report. *Ophthalmology*. 2019/12/21/ 2019;doi:https://doi.org/10.1016/j.ophtha.2019.12.011
321. Lin Z, Martinez A, Chen X, et al. Peripheral defocus with single-vision spectacle lenses in myopic children. *Optometry and Vision Science*. 2010;87(1):4-9.
322. Backhouse S, Fox S, Ibrahim B, Phillips JR. Peripheral refraction in myopia corrected with spectacles versus contact lenses. *Ophthalmic & physiological optics : the journal of the British College of Ophthalmic Opticians (Optometrists)*. Jul 2012;32(4):294-303. doi:10.1111/j.1475-1313.2012.00912.x
323. Tokoro T. Treatment of the myopia and the changes in optical components. Report 2. Full-or under-correction of myopia by glasses. *Acta Soc Ophthalmol Jpn*. 1965;69:140-144.
324. Ong E, Grice K, Held R, Thorn F, Gwiazda J. Effects of spectacle intervention on the progression of myopia in children. *Optometry and vision science: official publication of the American Academy of Optometry*. 1999;76(6):363-369.
325. Adler D, Millodot M. The possible effect of undercorrection on myopic progression in children. *Clinical and Experimental Optometry*. 2006;89(5):315-321.
326. Chung K, Mohidin N, O'Leary DJ. Undercorrection of myopia enhances rather than inhibits myopia progression. *Vision research*. 2002;42(22):2555-2559.
327. Sun Y-Y, Li S-M, Li S-Y, et al. Effect of uncorrection versus full correction on myopia progression in 12-year-old children. *Graefe's Archive for Clinical and Experimental Ophthalmology*. 2017;255(1):189-195.
328. Koomson NY, Amedo AO, Opoku-Baah C, Ampeh PB, Ankamah E, Bonsu K. Relationship between reduced accommodative lag and myopia progression. *Optometry and Vision Science*. 2016;93(7):683-691.
329. Li SY, Li S-M, Zhou YH, et al. Effect of undercorrection on myopia progression in 12-year-old children. *Graefe's Archive for Clinical and Experimental Ophthalmology*. 2015;253(8):1363-1368.
330. Berntsen DA, Barr CD, Mutti DO, Zadnik K. Peripheral defocus and myopia progression in myopic children randomly assigned to wear single vision and progressive addition lenses. *Investigative ophthalmology & visual science*. 2013;54(8):5761-5770.
331. Goss DA. Effect of bifocal lenses on the rate of childhood myopia progression. *American journal of optometry and physiological optics*. 1986;63(2):135-141.
332. Grosvenor T, Perrigin DM, Perrigin J, Maslovitz B. Houston Myopia Control Study: a randomized clinical trial. Part II. Final report by the patient care team. *American journal of optometry and physiological optics*. 1987;64(7):482-498.
333. Pärssinen O, Hemminki E, Klemetti A. Effect of spectacle use and accommodation on myopic progression: final results of a three-year randomised clinical trial among schoolchildren. *British Journal of Ophthalmology*. 1989;73(7):547-551. doi:10.1136/bjo.73.7.547

334. Fulk GW, Cyert LA, Parker DE. A randomized trial of the effect of single-vision vs. bifocal lenses on myopia progression in children with esophoria. *Optometry and vision science*. 2000;77(8):395-401.
335. Cheng D, Woo GC, Drobe B, Schmid KL. Effect of bifocal and prismatic bifocal spectacles on myopia progression in children: three-year results of a randomized clinical trial. *JAMA ophthalmology*. 2014;132(3):258-264.
336. Leung J, Brown B. Progression of myopia in Hong Kong Chinese schoolchildren is slowed by wearing progressive lenses. *Optometry and vision science: official publication of the American Academy of Optometry*. 1999;76(6):346-354.
337. Gwiazda J, Hyman L, Hussein M, et al. A randomized clinical trial of progressive addition lenses versus single vision lenses on the progression of myopia in children. *Investigative ophthalmology & visual science*. 2003;44(4):1492-1500.
338. Hasebe S, Ohtsuki H, Nonaka T, et al. Effect of progressive addition lenses on myopia progression in Japanese children: a prospective, randomized, double-masked, crossover trial. *Investigative ophthalmology & visual science*. 2008;49(7):2781-2789.
339. Yang Z, Lan W, Ge J, et al. The effectiveness of progressive addition lenses on the progression of myopia in Chinese children. *Ophthalmic and Physiological Optics*. 2009;29(1):41-48.
340. Group CoMETSGftPEDI. Progressive-addition lenses versus single-vision lenses for slowing progression of myopia in children with high accommodative lag and near esophoria. *Investigative ophthalmology & visual science*. 2011;52(5):2749.
341. Walline JJ, Jones LA, Mutti DO, Zadnik K. A Randomized Trial of the Effects of Rigid Contact Lenses on MyopiaProgression. *Archives of ophthalmology*. 2004;122(12):1760-1766.
342. Katz J, Schein OD, Levy B, et al. A randomized trial of rigid gas permeable contact lenses to reduce progression of children's myopia. *Am J Ophthalmol*. Jul 2003;136(1):82-90. doi:10.1016/s0002-9394(03)00106-5
343. Walline JJ, Jones LA, Sinnott L, et al. A Randomized Trial of the Effect of Soft Contact Lenses on Myopia Progression in Children. *Investigative Ophthalmology & Visual Science*. 2008;49(11):4702-4706. doi:10.1167/iovs.08-2067
344. Marsh-Tootle WL, Dong LM, Hyman L, et al. Myopia Progression in Children Wearing Spectacles vs. Switching to Contact Lenses. *Optom Vis Sci*. 2009;86(6):741-747. doi:10.1097/OPX.0b013e3181a6a250
345. Fulk GW, Cyert LA, Parker DE, West RW. The effect of changing from glasses to soft contact lenses on myopia progression in adolescents. *Ophthalmic and Physiological Optics*. 2003;23(1):71-77.
346. Horner DG, Soni PS, Salmon TO, Swartz TS. Myopia progression in adolescent wearers of soft contact lenses and spectacles. *Optometry and vision science: official publication of the American Academy of Optometry*. 1999;76(7):474-479.
347. Queirós A, Amorim-de-Sousa A, Lopes-Ferreira D, Villa-Collar C, Gutiérrez ÁR, González-Méijome JM. Relative peripheral refraction across 4 meridians after orthokeratology and LASIK surgery. *Eye Vis (Lond)*. 2018;5:12-12. doi:10.1186/s40662-018-0106-1
348. Cho P, Cheung SW. Retardation of myopia in Orthokeratology (ROMIO) study: a 2-year randomized clinical trial. *Invest Ophthalmol Vis Sci*. Oct 11 2012;53(11):7077-85. doi:10.1167/iovs.12-10565
349. Charm J, Cho P. High myopia-partial reduction orthokeratology (HM-PRO): study design. *Contact lens & anterior eye : the journal of the British Contact Lens Association*. Aug 2013;36(4):164-70. doi:10.1016/j.clae.2013.02.012
350. Swarbrick HA, Alharbi A, Watt K, Lum E, Kang P. Myopia control during orthokeratology lens wear in children using a novel study design. *Ophthalmology*. Mar 2015;122(3):620-30. doi:10.1016/j.ophtha.2014.09.028
351. Jakobsen TM, Møller F. Control of myopia using orthokeratology lenses in Scandinavian children aged 6 to 12 years. Eighteen-month data from the Danish Randomized Study: Clinical study

Of Near-sightedness; TReatment with Orthokeratology Lenses (CONTROL study). *Acta Ophthalmologica*. 2022;100(2):175-182. doi:https://doi.org/10.1111/aos.14911
352. Sankaridurg P, Holden B, Smith E, 3rd, et al. Decrease in rate of myopia progression with a contact lens designed to reduce relative peripheral hyperopia: one-year results. *Invest Ophthalmol Vis Sci*. Dec 9 2011;52(13):9362-7. doi:10.1167/iovs.11-7260
353. Walline JJ, Greiner KL, McVey ME, Jones-Jordan LA. Multifocal Contact Lens Myopia Control. *Optometry and Vision Science*. 2013;90(11):1207-1214. doi:10.1097/opx.0000000000000036
354. Paune J, Morales H, Armengol J, et al. Myopia Control with a Novel Peripheral Gradient Soft Lens and Orthokeratology: A 2-Year Clinical Trial. *BioMed Research International*. 2015;2015:10. 507572. doi:10.1155/2015/507572
355. Fujikado T, Ninomiya S, Kobayashi T, Suzaki A, Nakada M, Nishida K. Effect of low-addition soft contact lenses with decentered optical design on myopia progression in children: a pilot study. *Clin Ophthalmol*. 2014;8:1947-1956. doi:10.2147/OPTH.S66884
356. Anstice NS, Phillips JR. Effect of Dual-Focus Soft Contact Lens Wear on Axial Myopia Progression in Children. *Ophthalmology*. 2011;118(6):1152-1161. doi:10.1016/j.ophtha.2010.10.035
357. Lam CSY, Tang WC, Tse DY-Y, Tang YY, To CH. Defocus Incorporated Soft Contact (DISC) lens slows myopia progression in Hong Kong Chinese schoolchildren: a 2-year randomised clinical trial. *British Journal of Ophthalmology*. 2014;98(1):40-45. doi:10.1136/bjophthalmol-2013-303914
358. Aller TA, Liu M, Wildsoet CF. Myopia Control with Bifocal Contact Lenses: A Randomized Clinical Trial. *Optom Vis Sci*. Apr 2016;93(4):344-52. doi:10.1097/opx.0000000000000808
359. Ruiz-Pomeda A, Perez-Sanchez B, Valls I, Prieto-Garrido FL, Gutierrez-Ortega R, Villa-Collar C. MiSight Assessment Study Spain (MASS). A 2-year randomized clinical trial. *Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie*. May 2018;256(5):1011-1021. doi:10.1007/s00417-018-3906-z
360. Chamberlain P, Back A, Lazon P, et al. 3 year effectiveness of a dual-focus 1 day soft contact lens for myopia control. *Contact Lens and Anterior Eye*. 06/01 2018;41:S71-S72. doi:10.1016/j.clae.2018.03.097
361. Ruiz-Pomeda A, Prieto-Garrido FL, Hernández Verdejo JL, Villa-Collar C. Rebound effect in the misight assessment Study Spain (Mass). *Current eye research*. 2021:1-4.
362. Sankaridurg P, Donovan L, Varnas S, et al. Spectacle Lenses Designed to Reduce Progression of Myopia: 12-Month Results. *Optometry and Vision Science*. 2010;87(9):631-641. doi:10.1097/OPX.0b013e3181ea19c7
363. Kanda H, Oshika T, Hiraoka T, et al. Effect of spectacle lenses designed to reduce relative peripheral hyperopia on myopia progression in Japanese children: a 2-year multicenter randomized controlled trial. *Jpn J Ophthalmol*. Sep 2018;62(5):537-543. doi:10.1007/s10384-018-0616-3
364. Lam CSY, Tang WC, Tse DY-y, et al. Defocus Incorporated Multiple Segments (DIMS) spectacle lenses slow myopia progression: a 2-year randomised clinical trial. *British Journal of Ophthalmology*. 2019:bjophthalmol-2018-313739. doi:10.1136/bjophthalmol-2018-313739
365. Lam CS, Tang WC, Lee PH, et al. Myopia control effect of defocus incorporated multiple segments (DIMS) spectacle lens in Chinese children: results of a 3-year follow-up study. *British Journal of Ophthalmology*. 2021;
366. Bao J, Huang Y, Li X, et al. Spectacle Lenses With Aspherical Lenslets for Myopia Control vs Single-Vision Spectacle Lenses: A Randomized Clinical Trial. *JAMA Ophthalmology*. 2022;140(5):472-478. doi:10.1001/jamaophthalmol.2022.0401
367. Cheng X, Xu J, Chehab K, Exford J, Brennan N. Soft contact lenses with positive spherical aberration for myopia control. *Optometry and Vision Science*. 2016;93(4):353-366.
368. Chamberlain P, Peixoto-de-Matos SC, Logan NS, Ngo C, Jones D, Young G. A 3-year randomized clinical trial of MiSight lenses for myopia control. *Optometry and Vision Science*. 2019;96(8):556-567.

369. Rose KA, Ip J, Robaei D, et al. Near–Work and Outdoor Activities and the Prevalence of Myopia in Australian School Students Aged 12–13 Years: The Sydney Myopia Study. *Investigative Ophthalmology & Visual Science*. 2006;47(13):5453-5453.
370. Jones LA, Sinnott LT, Mutti DO, Mitchell GL, Moeschberger ML, Zadnik K. Parental history of myopia, sports and outdoor activities, and future myopia. *Investigative ophthalmology & visual science*. 2007;48(8):3524-3532.
371. Wu P-C, Tsai C-L, Wu H-L, Yang Y-H, Kuo H-K. Outdoor Activity during Class Recess Reduces Myopia Onset and Progression in School Children. *Ophthalmology*. 2013/05/01/ 2013;120(5):1080-1085. doi:https://doi.org/10.1016/j.ophtha.2012.11.009
372. He M, Xiang F, Zeng Y, et al. Effect of Time Spent Outdoors at School on the Development of Myopia Among Children in China: A Randomized Clinical Trial. *Jama*. 2015;314(11):1142-1148. doi:10.1001/jama.2015.10803
373. Jin J-X, Hua W-J, Jiang X, et al. Effect of outdoor activity on myopia onset and progression in school-aged children in northeast china: the sujiatun eye care study. *BMC ophthalmology*. 2015/07/09 2015;15(1):73. doi:10.1186/s12886-015-0052-9
374. Wu P-C, Chen C-T, Lin K-K, et al. Myopia prevention and outdoor light intensity in a school-based cluster randomized trial. *Ophthalmology*. 2018;125(8):1239-1250.
375. Hua WJ, Jin JX, Wu XY, et al. Elevated light levels in schools have a protective effect on myopia. *Ophthalmic and Physiological Optics*. 2015;35(3):252-262.
376. Zhou Z, Chen T, Wang M, et al. Pilot study of a novel classroom designed to prevent myopia by increasing children's exposure to outdoor light. *PLoS One*. 2017;12(7):e0181772.
377. Jiang Y, Zhu Z, Tan X, et al. Effect of repeated low-level red-light therapy for myopia control in children: a multicenter randomized controlled trial. *Ophthalmology*. 2022;129(5):509-519.
378. Summers JA. The choroid as a sclera growth regulator. *Experimental eye research*. 2013;114:120-127.
379. Wallman J, Wildsoet C, Xu A, et al. Moving the retina: choroidal modulation of refractive state. *Vision research*. 1995;35(1):37-50.
380. Xiong F, Mao T, Liao H, et al. Orthokeratology and low-intensity laser therapy for slowing the progression of myopia in children. *BioMed Research International*. 2021;2021
381. Kinoshita N, Konno Y, Hamada N, Kanda Y, Shimmura-Tomita M, Kakehashi A. Additive effects of orthokeratology and atropine 0.01% ophthalmic solution in slowing axial elongation in children with myopia: first year results. *Japanese journal of ophthalmology*. 2018;62(5):544-553.
382. Tan Q, Ng AL, Choy BN, Cheng GP, Woo VC, Cho P. One-year results of 0.01% atropine with orthokeratology (AOK) study: a randomised clinical trial. *Ophthalmic and Physiological Optics*. 2020;40(5):557-566.
383. Huang J, Mutti DO, Jones-Jordan LA, Walline JJ. Bifocal & Atropine in Myopia (BAM) Study: Baseline Data and Methods. *Optometry and vision science: official publication of the American Academy of Optometry*. 2019;96(5):335.
384. Kepler J. Ad vitellionem paralipomena, quibus astronomiae pars optica traditur... de modo visionis, & humorum oculi usu, contra opticos & anatomicos. *Frankfurt: C Marnius & Heirs of J Aubrius*. 1604;
385. Cohn H, Cohn HL. *The hygiene of the eye in schools*. Simpkin, Marshall; 1886.
386. Young FA, Leary GA, Baldwin WR, et al. The transmission of refractive errors within eskimo families. *American Journal of Optometry and Archives of American Academy of Optometry*. 1969;46(9):676-685.
387. Sorsby A, Young F. Transmission of refractive errors within Eskimo families. *American Journal of Optometry and Archives of American Academy of Optometry*. 1970;47(3):244-249.
388. Sorsby A, Sheridan M, Leary G. Refraction and its components in twins. Medical Research Council, Special Report Series No. 303. London: Her Majesty's Stationery Office; 1962.
389. Morgan IG, Ohno-Matsui K, Saw S-M. Myopia. *The Lancet*. 2012;379(9827):1739-1748.

390. Morgan IG, Rose KA. Myopia: is the nature-nurture debate finally over? *Clinical and Experimental Optometry*. 2019;102(1):3-17.
391. Sorsby A, Fraser G. Statistical note on the components of ocular refraction in twins. *Journal of medical genetics*. 1964;1(1):47.
392. Dirani M, Chamberlain M, Shekar SN, et al. Heritability of refractive error and ocular biometrics: the Genes in Myopia (GEM) twin study. *Investigative ophthalmology & visual science*. 2006;47(11):4756-4761.
393. Hammond CJ, Snieder H, Gilbert CE, Spector TD. Genes and environment in refractive error: the twin eye study. *Investigative ophthalmology & visual science*. 2001;42(6):1232-1236.
394. Knobloch WH, Leavenworth NM, Bouchard TJ, Eckert ED. Eye findings in twins reared apart. *Ophthalmic paediatrics and genetics*. 1985;5(1-2):59-66.
395. Teikari J, Koskenvuo M, Kaprio J, O'Donnell J. Study of gene-environment effects on development of hyperopia: a study of 191 adult twin pairs from the Finnish Twin Cohort Study. *Acta geneticae medicae et gemellologiae: twin research*. 1990;39(1):133-136.
396. Teikari J, O'Donnell J, Kaprio J, Koskenvuo M. Impact of heredity in myopia. *Human heredity*. 1991;41(3):151-156.
397. Teikari JM, Kaprio J, Koskenvuo MK, Vannas A, Rao D. Heritability estimate for refractive errors—a population-based sample of adult twins. *Genetic epidemiology*. 1988;5(3):171-181.
398. He M, Hur Y-M, Zhang J, Ding X, Huang W, Wang D. Shared genetic determinant of axial length, anterior chamber depth, and angle opening distance: the Guangzhou Twin Eye Study. *Investigative ophthalmology & visual science*. 2008;49(11):4790-4794.
399. Kim MH, Zhao D, Kim W, et al. Heritability of myopia and ocular biometrics in Koreans: the healthy twin study. *Investigative ophthalmology & visual science*. 2013;54(5):3644-3649.
400. Klein AP, Suktitipat B, Duggal P, et al. Heritability analysis of spherical equivalent, axial length, corneal curvature, and anterior chamber depth in the Beaver Dam Eye Study. *Archives of ophthalmology*. 2009;127(5):649-655.
401. Lyhne N, Sjølie AK, Kyvik KO, Green A. The importance of genes and environment for ocular refraction and its determiners: a population based study among 20–45 year old twins. *British Journal of Ophthalmology*. 2001;85(12):1470-1476.
402. Ip JM, Huynh SC, Robaei D, et al. Ethnic differences in the impact of parental myopia: findings from a population-based study of 12-year-old Australian children. *Investigative ophthalmology & visual science*. 2007;48(6):2520-2528.
403. Lim LT, Gong Y, Ah-Kee EY, Xiao G, Zhang X, Yu S. Impact of parental history of myopia on the development of myopia in mainland China school-aged children. *Ophthalmology and eye diseases*. 2014;6:OED. S16031.
404. Mutti DO, Mitchell GL, Moeschberger ML, Jones LA, Zadnik K. Parental myopia, near work, school achievement, and children's refractive error. *Investigative ophthalmology & visual science*. 2002;43(12):3633-3640.
405. Tideman JWL, Polling JR, Jaddoe VW, Vingerling JR, Klaver CC. Environmental risk factors can reduce axial length elongation and myopia incidence in 6-to 9-year-old children. *Ophthalmology*. 2019;126(1):127-136.
406. Jones-Jordan LA, Sinnott LT, Graham ND, et al. The contributions of near work and outdoor activity to the correlation between siblings in the Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error (CLEERE) Study. *Investigative ophthalmology & visual science*. 2014;55(10):6333-6339.
407. Ghorbani Mojarrad N, Williams C, Guggenheim JA. A genetic risk score and number of myopic parents independently predict myopia. *Ophthalmic and Physiological Optics*. 2018;38(5):492-502.
408. Metlapally R, Li Y-J, Tran-Viet K-N, et al. COL1A1 and COL2A1 genes and myopia susceptibility: evidence of association and suggestive linkage to the COL2A1 locus. *Investigative ophthalmology & visual science*. 2009;50(9):4080-4086.

409. Mutti DO, Cooper ME, O'Brien S, et al. Candidate gene and locus analysis of myopia. *Molecular vision*. 2007;13:1012.
410. Lam CY, Tam PO, Fan DS, et al. A genome-wide scan maps a novel high myopia locus to 5p15. *Investigative ophthalmology & visual science*. 2008;49(9):3768-3778.
411. Naiglin L, Gazagne C, Dallongeville F, et al. A genome wide scan for familial high myopia suggests a novel locus on chromosome 7q36. *Journal of medical genetics*. 2002;39(2):118-124.
412. Nallasamy S, Paluru PC, Devoto M, Wasserman NF, Zhou J, Young TL. Genetic linkage study of high-grade myopia in a Hutterite population from South Dakota. *Molecular vision*. 2007;13:229.
413. Paluru P, Ronan SM, Heon E, et al. New locus for autosomal dominant high myopia maps to the long arm of chromosome 17. *Investigative ophthalmology & visual science*. 2003;44(5):1830-1836.
414. Young TL, Ronan SM, Alvear AB, et al. A second locus for familial high myopia maps to chromosome 12q. *The American Journal of Human Genetics*. 1998;63(5):1419-1424.
415. Zhang Q, Guo X, Xiao X, Jia X, Li S, Hejtmancik JF. A new locus for autosomal dominant high myopia maps to 4q22-q27 between D4S1578 and D4S1612. *Mol Vis*. 2005;11(64-65):554-60.
416. Lu B, Jiang D, Wang P, et al. Replication study supports CTNND2 as a susceptibility gene for high myopia. *Investigative ophthalmology & visual science*. 2011;52(11):8258-8261.
417. Metlapally R, Ki C-S, Li Y-J, et al. Genetic association of insulin-like growth factor-1 polymorphisms with high-grade myopia in an international family cohort. *Investigative ophthalmology & visual science*. 2010;51(9):4476-4479.
418. Shi Y, Qu J, Zhang D, et al. Genetic variants at 13q12. 12 are associated with high myopia in the Han Chinese population. *The American Journal of Human Genetics*. 2011;88(6):805-813.
419. Baird PN, Schäche M, Dirani M. The GEnes in Myopia (GEM) study in understanding the aetiology of refractive errors. *Progress in retinal and eye research*. 2010;29(6):520-542.
420. Young TL, Ronan SM, Drahozal LA, et al. Evidence that a locus for familial high myopia maps to chromosome 18p. *The American Journal of Human Genetics*. 1998;63(1):109-119.
421. Nakanishi H, Yamada R, Gotoh N, et al. A genome-wide association analysis identified a novel susceptible locus for pathological myopia at 11q24. 1. *PLoS genetics*. 2009;5(9):e1000660.
422. Liu J, Zhang H-x. Polymorphism in the 11q24. 1 genomic region is associated with myopia: a comprehensive genetic study in Chinese and Japanese populations. *Molecular vision*. 2014;20:352.
423. Wang Q, Gao Y, Wang P, et al. Replication study of significant single nucleotide polymorphisms associated with myopia from two genome-wide association studies. *Molecular vision*. 2011;17:3290.
424. Ku CS, Loy EY, Pawitan Y, Chia KS. The pursuit of genome-wide association studies: where are we now? *Journal of human genetics*. 2010;55(4):195-206.
425. Kraft P, Zeggini E, Ioannidis JP. Replication in genome-wide association studies. *Statistical science: a review journal of the Institute of Mathematical Statistics*. 2009;24(4):561.
426. Solouki AM, Verhoeven VJ, Van Duijn CM, et al. A genome-wide association study identifies a susceptibility locus for refractive errors and myopia at 15q14. *Nature genetics*. 2010;42(10):897-901.
427. Hysi PG, Young TL, Mackey DA, et al. A genome-wide association study for myopia and refractive error identifies a susceptibility locus at 15q25. *Nature genetics*. 2010;42(10):902-905.
428. Schache M, Richardson AJ, Mitchell P, et al. Genetic association of refractive error and axial length with 15q14 but not 15q25 in the Blue Mountains Eye Study cohort. *Ophthalmology*. 2013;120(2):292-297.
429. Verhoeven VJ, Hysi PG, Saw S-M, et al. Large scale international replication and meta-analysis study confirms association of the 15q14 locus with myopia. The CREAM consortium. *Human genetics*. 2012;131(9):1467-1480.
430. Verhoeven VJ, Hysi PG, Wojciechowski R, et al. Genome-wide meta-analyses of multiancestry cohorts identify multiple new susceptibility loci for refractive error and myopia. *Nature genetics*. 2013;45(3):314-318.

431. Kiefer AK, Tung JY, Do CB, et al. Genome-wide analysis points to roles for extracellular matrix remodeling, the visual cycle, and neuronal development in myopia. *PLoS genetics*. 2013;9(2):e1003299.
432. Cheng C-Y, Schache M, Ikram MK, et al. Nine loci for ocular axial length identified through genome-wide association studies, including shared loci with refractive error. *The American Journal of Human Genetics*. 2013;93(2):264-277.
433. Liao X, Yap MK, Leung KH, Kao PY, Liu LQ, Yip SP. Genetic association study of KCNQ5 polymorphisms with high myopia. *BioMed research international*. 2017;2017
434. Oishi M, Yamashiro K, Miyake M, et al. Association between ZIC2, RASGRF1, and SHISA6 genes and high myopia in Japanese subjects. *Investigative ophthalmology & visual science*. 2013;54(12):7492-7497.
435. Simpson CL, Wojciechowski R, Oexle K, et al. Genome-wide meta-analysis of myopia and hyperopia provides evidence for replication of 11 loci. *PloS one*. 2014;9(9):e107110.
436. Tideman JWL, Fan Q, Polling JR, et al. When do myopia genes have their effect? Comparison of genetic risks between children and adults. *Genetic epidemiology*. 2016;40(8):756-766.
437. Yoshikawa M, Yamashiro K, Miyake M, et al. Comprehensive replication of the relationship between myopia-related genes and refractive errors in a large Japanese cohort. *Investigative ophthalmology & visual science*. 2014;55(11):7343-7354.
438. Tedja MS, Wojciechowski R, Hysi PG, et al. Genome-wide association meta-analysis highlights light-induced signaling as a driver for refractive error. *Nature genetics*. 2018;50(6):834-848.
439. Hysi PG, Choquet H, Khawaja AP, et al. Meta-analysis of 542,934 subjects of European ancestry identifies new genes and mechanisms predisposing to refractive error and myopia. *Nature genetics*. 2020;52(4):401-407.
440. Goldschmidt E. On the etiology of myopia, An epidemiologic study. *Acta Ophtalmol*. 1968;98:1-72.
441. Teasdale T, Fuchs J, Goldschmidt E. Degree of myopia in relation to intelligence and educational level. *Lancet (London, England)*. 1988;2(8624):1351-1354.
442. Rosner M, Belkin M. Intelligence, education, and myopia in males. *Archives of ophthalmology*. 1987;105(11):1508-1511.
443. Tay M, KG AE, Ng C, Lim M. Myopia and educational attainment in 421,116 young Singaporean males. *Annals of the Academy of Medicine, Singapore*. 1992;21(6):785-791.
444. Wu H-M, Seet B, Yap EP-H, Saw S-M, Lim T-H, Chia K-S. Does education explain ethnic differences in myopia prevalence? A population-based study of young adult males in Singapore. *Optometry and vision science*. 2001;78(4):234-239.
445. Saw S-M, Wu H-M, Seet B, et al. Academic achievement, close up work parameters, and myopia in Singapore military conscripts. *British journal of ophthalmology*. 2001;85(7):855-860.
446. Konstantopoulos A, Yadegarfar G, Elgohary M. Near work, education, family history, and myopia in Greek conscripts. *Eye*. 2008;22(4):542-546.
447. Al-Bdour M, Odat T, Tahat A. Myopia and level of education. *European journal of ophthalmology*. 2001;11(1):1-5.
448. Kim EC, Morgan IG, Kakizaki H, Kang S, Jee D. Prevalence and risk factors for refractive errors: Korean National Health and Nutrition Examination Survey 2008-2011. *PloS one*. 2013;8(11):e80361.
449. Mirshahi A, Ponto KA, Hoehn R, et al. Myopia and level of education: results from the Gutenberg Health Study. *Ophthalmology*. 2014;121(10):2047-2052.
450. Shimizu N, Nomura H, Ando F, Niino N, Miyake Y, Shimokata H. Refractive errors and factors associated with myopia in an adult Japanese population. *Japanese journal of ophthalmology*. 2003;47(1):6-12.

451. Wong L, Coggon D, Cruddas M, Hwang C. Education, reading, and familial tendency as risk factors for myopia in Hong Kong fishermen. *Journal of Epidemiology & Community Health*. 1993;47(1):50-53.
452. Wong T, Foster P, Johnson G, Seah S. Education, socioeconomic status, and ocular dimensions in Chinese adults: the Tanjong Pagar Survey. *British Journal of Ophthalmology*. 2002;86(9):963-968.
453. Nickels S, Hopf S, Pfeiffer N, Schuster AK. Myopia is associated with education: results from NHANES 1999-2008. *PloS one*. 2019;14(1):e0211196.
454. Grosvenor T. Refractive state, intelligence test scores, and academic ability. *American Journal of Optometry & Archives of American Academy of Optometry*. 1970;
455. Nadell M, Hirsch M. The relationship between intelligence and the refractive state in a selected high school sample. *American journal of optometry and archives of American Academy of Optometry*. 1958;35(6):321-326.
456. Hirsch M. The relationship between refractive state of the eye and intelligence test scores. *American journal of optometry and archives of American Academy of Optometry*. 1959;36(1):12-21.
457. Williams SM, Sanderson GF, Share DL, Silva PA. Refractive error, IQ and reading ability: A longitudinal study from age seven to 11. *Developmental Medicine & Child Neurology*. 1988;30(6):735-742.
458. Douglas J, Ross J, Simpson H. The ability and attainment of short-sighted pupils. *Journal of the Royal Statistical Society: Series A (General)*. 1967;130(4):479-493.
459. Peckham CS, Gardiner PA, Goldstein H. Acquired myopia in 11-year-old children. *Br Med J*. 1977;1(6060):542-545.
460. Saw SM, Cheng A, Fong A, Gazzard G, Tan DT, Morgan I. School grades and myopia. *Ophthalmic and Physiological Optics*. 2007;27(2):126-129.
461. Saw S-M, Tan S-B, Fung D, et al. IQ and the association with myopia in children. *Investigative ophthalmology & visual science*. 2004;45(9):2943-2948.
462. Williams C, Miller L, Gazzard G, Saw S-M. A comparison of measures of reading and intelligence as risk factors for the development of myopia in a UK cohort of children. *British journal of ophthalmology*. 2008;92(8):1117-1121.
463. Quek TP, Chua CG, Chong CS, et al. Prevalence of refractive errors in teenage high school students in Singapore. *Ophthalmic and Physiological Optics*. 2004;24(1):47-55.
464. Ku P-W, Steptoe A, Lai Y-J, et al. The associations between near visual activity and incident myopia in children: a nationwide 4-year follow-up study. *Ophthalmology*. 2019;126(2):214-220.
465. Zylbermann R, Landau D, Berson D. The influence of study habits on myopia in Jewish teenagers. SLACK Incorporated Thorofare, NJ; 1993.
466. Saw S-M, Chua W-H, Hong C-Y, et al. Nearwork in early-onset myopia. *Investigative ophthalmology & visual science*. 2002;43(2):332-339.
467. Pi L-H, Chen L, Liu Q, et al. Refractive status and prevalence of refractive errors in suburban school-age children. *International journal of medical sciences*. 2010;7(6):342.
468. Ip JM, Saw S-M, Rose KA, et al. Role of near work in myopia: findings in a sample of Australian school children. *Investigative ophthalmology & visual science*. 2008;49(7):2903-2910.
469. O'Donoghue L, Kapetanankis VV, McClelland JF, et al. Risk factors for childhood myopia: findings from the NICER study. *Investigative ophthalmology & visual science*. 2015;56(3):1524-1530.
470. Morgan IG, Rose KA. Myopia and international educational performance. *Ophthalmic and Physiological Optics*. 2013;33(3):329-338.
471. Casson RJ, Kahawita S, Kong A, Muecke J, Sisaleumsak S, Visonnavong V. Exceptionally low prevalence of refractive error and visual impairment in schoolchildren from Lao People's Democratic Republic. *Ophthalmology*. 2012;119(10):2021-2027.
472. Gao Z, Meng N, Muecke J, et al. Refractive error in school children in an urban and rural setting in Cambodia. *Ophthalmic epidemiology*. 2012;19(1):16-22.

473. Skeller E. *Anthropological and ophthalmological studies on the Angmagssalik Eskimos*. CA Reitzel; 1954.
474. Cuellar-Partida G, Lu Y, Kho PF, et al. Assessing the genetic predisposition of education on myopia: a mendelian randomization study. *Genetic epidemiology*. 2016;40(1):66-72.
475. Mountjoy E, Davies NM, Plotnikov D, et al. Education and myopia: assessing the direction of causality by mendelian randomisation. *bmj*. 2018;361
476. Verhoeven VJ, Buitendijk GH, Rivadeneira F, et al. Education influences the role of genetics in myopia. *European journal of epidemiology*. 2013;28(12):973-980.
477. Fan Q, Wojciechowski R, Kamran Ikram M, et al. Education influences the association between genetic variants and refractive error: a meta-analysis of five Singapore studies. *Human molecular genetics*. 2014;23(2):546-554.
478. Angle J, Wissmann DA. The epidemiology of myopia. *Am J Epidemiol*. Feb 1980;111(2):220-8. doi:10.1093/oxfordjournals.aje.a112889
479. Richler A, Bear JC. Refraction, nearwork and education. A population study in Newfoundland. *Acta Ophthalmol (Copenh)*. Jun 1980;58(3):468-78. doi:10.1111/j.1755-3768.1980.tb05748.x
480. Bear JC, Richler A, Burke G. Nearwork and familial resemblances in ocular refraction: a population study in Newfoundland. *Clinical genetics*. Jun 1981;19(6):462-72. doi:10.1111/j.1399-0004.1981.tb02065.x
481. Huang H-M, Chang DS-T, Wu P-C. The association between near work activities and myopia in children—a systematic review and meta-analysis. *PloS one*. 2015;10(10):e0140419.
482. Lin Z, Vasudevan B, Jhanji V, et al. Near work, outdoor activity, and their association with refractive error. *Optometry and Vision Science*. 2014;91(4):376-382.
483. Saw S-M, Nieto FJ, Katz J, Chew S-J. Estimating the magnitude of close-up work in school-age children: a comparison of questionnaire and diary instruments. *Ophthalmic epidemiology*. 1999;6(4):291-301.
484. Saw S-M, Hong R-Z, Zhang M-Z, et al. Near-work activity and myopia in rural and urban schoolchildren in China. Slack Incorporated Thorofare, NJ; 2001.
485. Saw S-M, Zhang M-Z, Hong R-Z, Fu Z-F, Pang M-H, Tan DT. Near-work activity, night-lights, and myopia in the Singapore-China study. *Archives of Ophthalmology*. 2002;120(5):620-627.
486. Saw S-M, Carkeet A, Chia K-S, Stone RA, Tan DT. Component dependent risk factors for ocular parameters in Singapore Chinese children. *Ophthalmology*. 2002;109(11):2065-2071.
487. Rose KA, Morgan IG, Ip J, et al. Outdoor activity reduces the prevalence of myopia in children. *Ophthalmology*. 2008;115(8):1279-1285.
488. Saxena R, Vashist P, Tandon R, et al. Prevalence of myopia and its risk factors in urban school children in Delhi: the North India Myopia Study (NIM Study). *PloS one*. 2015;10(2):e0117349.
489. Guo L, Yang J, Mai J, et al. Prevalence and associated factors of myopia among primary and middle school-aged students: a school-based study in Guangzhou. *Eye*. 2016;30(6):796-804.
490. Saw S-M, Shankar A, Tan S-B, et al. A cohort study of incident myopia in Singaporean children. *Investigative ophthalmology & visual science*. 2006;47(5):1839-1844.
491. Jones-Jordan LA, Sinnott LT, Cotter SA, et al. Time outdoors, visual activity, and myopia progression in juvenile-onset myopes. *Investigative ophthalmology & visual science*. 2012;53(11):7169-7175.
492. Lin Z, Vasudevan B, Mao GY, et al. The influence of near work on myopic refractive change in urban students in Beijing: a three-year follow-up report. *Graefe's Archive for Clinical and Experimental Ophthalmology*. 2016;254(11):2247-2255.
493. Pärssinen O, Lyyra A-L. Myopia and myopic progression among schoolchildren: a three-year follow-up study. *Investigative ophthalmology & visual science*. 1993;34(9):2794-2802.
494. Hsu C-C, Huang N, Lin P-Y, et al. Risk factors for myopia progression in second-grade primary school children in Taipei: a population-based cohort study. *British Journal of Ophthalmology*. 2017;101(12):1611-1617.

495. Saxena R, Vashist P, Tandon R, et al. Incidence and progression of myopia and associated factors in urban school children in Delhi: The North India Myopia Study (NIM Study). *PloS one*. 2017;12(12):e0189774.
496. Schaeffel F, Troilo D, Wallman J, Howland HC. Developing eyes that lack accommodation grow to compensate for imposed defocus. *Visual neuroscience*. 1990;4(2):177-183.
497. McBrien NA, Moghaddam H, New R, Williams L. Experimental myopia in a diurnal mammal (Sciurus carolinensis) with no accommodative ability. *The Journal of physiology*. 1993;469(1):427-441.
498. Stone RA, Lin T, Laties AM. Muscarinic antagonist effects on experimental chick myopia. *Experimental eye research*. 1991;52(6):755-758.
499. Donders FC, Moore WD. *On the anomalies of accommodation and refraction of the eye*. vol 22. New Sydenham Society; 1864.
500. Van Alphen G. On emmetropia and ametropia. 1961;
501. Young FA. The development and control of myopia in human and subhuman primates. 1975;
502. David R, Zangwill LM, Tessler Z, Yassur Y. The correlation between intraocular pressure and refractive status. *Archives of ophthalmology*. 1985;103(12):1812-1815.
503. Quinn GE, Berlin JA, Young TL, Ziylan S, Stone RA. Association of intraocular pressure and myopia in children. *Ophthalmology*. 1995;102(2):180-185.
504. Jensen H. Myopia progression in young school children. A prospective study of myopia progression and the effect of a trial with bifocal lenses and beta blocker eye drops. *Acta Ophthalmol*. 1991;200:1-79.
505. Schmid KL, Abbott M, Humphries M, Pyne K, Wildsoet CF. Timolol lowers intraocular pressure but does not inhibit the development of experimental myopia in chick. *Experimental eye research*. 2000;70(5):659-666.
506. Napper GA, Brennan NA, Barrington M, Squires MA, Vessey GA, Vingrys AJ. The duration of normal visual exposure necessary to prevent form deprivation myopia in chicks. *Vision Research*. 1995;35(9):1337-1344.
507. Smith EL, Hung L-F, Kee C-s, Qiao Y. Effects of brief periods of unrestricted vision on the development of form-deprivation myopia in monkeys. *Investigative ophthalmology & visual science*. 2002;43(2):291-299.
508. Abbott ML, Schmid KL, Strang NC. Differences in the accommodation stimulus response curves of adult myopes and emmetropes. *Ophthalmic and Physiological Optics*. 1998;18(1):13-20.
509. Bullimore MA, Gilmartin B, Royston JM. Steady-state accommodation and ocular biometry in late-onset myopia. *Documenta ophthalmologica*. 1992;80(2):143-155.
510. Goss DA. Clinical accommodation and heterophoria findings preceding juvenile onset of myopia. *Optometry and vision science: official publication of the American Academy of Optometry*. 1991;68(2):110-116.
511. Gwiazda J, Thorn F, Bauer J, Held R. Myopic children show insufficient accommodative response to blur. *Investigative ophthalmology & visual science*. 1993;34(3):690-694.
512. McBrien NA, Millodot M. The effect of refractive error on the accommodative response gradient. *Ophthalmic and Physiological Optics*. 1986;6(2):145-149.
513. Nakatsuka C, Hasebe S, Nonaka F, Ohtsuki H. Accommodative lag under habitual seeing conditions: comparison between myopic and emmetropic children. *Japanese journal of ophthalmology*. 2005;49(3):189-194.
514. Yeo C, Kang KK, Tang W. Accommodative stimulus response curve of emmetropes and myopes. *Annals-Academy of Medicine Singapore*. 2006;35(12):868.
515. Gwiazda J, Thorn F, Held R. Accommodation, accommodative convergence, and response AC/A ratios before and at the onset of myopia in children. *Optometry and Vision Science*. 2005;82(4):273-278.
516. Mutti DO, Mitchell GL, Hayes JR, et al. Accommodative lag before and after the onset of myopia. *Investigative ophthalmology & visual science*. 2006;47(3):837-846.

517. Berntsen DA, Sinnott LT, Mutti DO, Zadnik K, Group CS. Accommodative lag and juvenile-onset myopia progression in children wearing refractive correction. *Vision research*. 2011;51(9):1039-1046.
518. Weizhong L, Zhikuan Y, Wen L, Xiang C, Jian G. A longitudinal study on the relationship between myopia development and near accommodation lag in myopic children. *Ophthalmic and Physiological Optics*. 2008;28(1):57-61.
519. Hoogerheide J, Rempt F, Hoogenboom W. Acquired myopia in young pilots. *Ophthalmologica*. 1971;163(4):209-215.
520. Ehsaei A, Mallen EA, Chisholm CM, Pacey IE. Cross-sectional sample of peripheral refraction in four meridians in myopes and emmetropes. *Investigative ophthalmology & visual science*. 2011;52(10):7574-7585.
521. Mutti DO, Sholtz RI, Friedman NE, Zadnik K. Peripheral refraction and ocular shape in children. *Investigative ophthalmology & visual science*. 2000;41(5):1022-1030.
522. Seidemann A, Schaeffel F, Guirao A, Lopez-Gil N, Artal P. Peripheral refractive errors in myopic, emmetropic, and hyperopic young subjects. *JOSA A*. 2002;19(12):2363-2373.
523. Atchison DA, Li S-M, Li H, et al. Relative peripheral hyperopia does not predict development and progression of myopia in children. *Investigative ophthalmology & visual science*. 2015;56(10):6162-6170.
524. Lee TT, Cho P. Relative peripheral refraction in children: twelve-month changes in eyes with different ametropias. *Ophthalmic and Physiological Optics*. 2013;33(3):283-293.
525. Mutti DO, Sinnott LT, Mitchell GL, et al. Relative peripheral refractive error and the risk of onset and progression of myopia in children. *Investigative ophthalmology & visual science*. 2011;52(1):199-205.
526. Sng CC, Lin X-Y, Gazzard G, et al. Change in peripheral refraction over time in Singapore Chinese children. *Investigative ophthalmology & visual science*. 2011;52(11):7880-7887.
527. Williams KM, Kraphol E, Yonova-Doing E, Hysi PG, Plomin R, Hammond CJ. Early life factors for myopia in the British Twins Early Development Study. *British Journal of Ophthalmology*. 2019;103(8):1078-1084.
528. Huang L, Kawasaki H, Liu Y, Wang Z. The prevalence of myopia and the factors associated with it among university students in Nanjing: A cross-sectional study. *Medicine*. 2019;98(10)
529. McCrann S, Loughman J, Butler JS, Paudel N, Flitcroft DI. Smartphone use as a possible risk factor for myopia. *Clinical and Experimental Optometry*. 2021;104(1):35-41.
530. Enthoven CA, Polling JR, Verzijden T, et al. Smartphone use associated with refractive error in teenagers; the Myopia app Study. *Ophthalmology*. 2021;
531. Lanca C, Saw S-M. The association between digital screen time and myopia: A systematic review. *Ophthalmic and Physiological Optics*. 2020;40(2):216-229. doi:https://doi.org/10.1111/opo.12657
532. Foreman J, Salim AT, Praveen A, et al. Association between digital smart device use and myopia: a systematic review and meta-analysis. *The Lancet Digital Health*. 2021/12/01/ 2021;3(12):e806-e818. doi:https://doi.org/10.1016/S2589-7500(21)00135-7
533. Khader Y, Batayha W, Abdul Aziz S, Al Shiekh Khalil M. Prevalence and risk indicators of myopia among schoolchildren in Amman, Jordan. *EMHJ-Eastern Mediterranean Health Journal, 12 (3-4), 434-439, 2006*. 2006;
534. Jacobsen N, Jensen H, Goldschmidt E. Does the level of physical activity in university students influence development and progression of myopia?—a 2-year prospective cohort study. *Investigative ophthalmology & visual science*. 2008;49(4):1322-1327.
535. Onal S, Toker E, Akingol Z, et al. Refractive errors of medical students in Turkey: one year follow-up of refraction and biometry. *Optometry and vision science*. 2007;84(3):175-180.
536. Stone RA, Lin T, Laties AM, Iuvone PM. Retinal dopamine and form-deprivation myopia. *Proceedings of the National Academy of Sciences*. 1989;86(2):704-706.

537. McCarthy C, Megaw P, Devadas M, Morgan I. Dopaminergic agents affect the ability of brief periods of normal vision to prevent form-deprivation myopia. *Experimental eye research*. 2007;84(1):100-107.
538. Dirani M, Tong L, Gazzard G, et al. Outdoor activity and myopia in Singapore teenage children. *British Journal of Ophthalmology*. 2009;93(8):997-1000.
539. Deng L, Gwiazda J, Thorn F. Children's refractions and visual activities in the school year and summer. *Optometry and Vision Science*. 2010;87(6):406.
540. Guo Y, Liu LJ, Xu L, et al. Outdoor activity and myopia among primary students in rural and urban regions of Beijing. *Ophthalmology*. 2013;120(2):277-283.
541. Lee Y-Y, Lo C-T, Sheu S-J, Yin L-T. Risk factors for and progression of myopia in young Taiwanese men. *Ophthalmic epidemiology*. 2015;22(1):66-73.
542. Pan C-W, Chen Q, Sheng X, et al. Ethnic variations in myopia and ocular biometry among adults in a rural community in China: the Yunnan minority eye studies. *Investigative ophthalmology & visual science*. 2015;56(5):3235-3241.
543. Wu LJ, You QS, Duan JL, et al. Prevalence and associated factors of myopia in high-school students in Beijing. *PLoS One*. 2015;10(3):e0120764.
544. Wu P-C, Tsai C-L, Hu C-H, Yang Y-H. Effects of outdoor activities on myopia among rural school children in Taiwan. *Ophthalmic epidemiology*. 2010;17(5):338-342.
545. Zhou Z, Morgan IG, Chen Q, Jin L, He M, Congdon N. Disordered sleep and myopia risk among Chinese children. *PloS one*. 2015;10(3):e0121796.
546. Ramessur R, Williams KM, Hammond CJ. Risk factors for myopia in a discordant monozygotic twin study. *Ophthalmic and Physiological Optics*. 2015;35(6):643-651.
547. Guggenheim JA, Northstone K, McMahon G, et al. Time outdoors and physical activity as predictors of incident myopia in childhood: a prospective cohort study. *Investigative ophthalmology & visual science*. 2012;53(6):2856-2865.
548. Lundberg K, Suhr Thykjær A, Søgaard Hansen R, et al. Physical activity and myopia in Danish children—the CHAMPS eye study. *Acta ophthalmologica*. 2018;96(2):134-141.
549. Wu L-J, Wang Y-X, You Q-S, et al. Risk factors of myopic shift among primary school children in Beijing, China: a prospective study. *International journal of medical sciences*. 2015;12(8):633.
550. Chua SYL, Ikram MK, Tan CS, et al. Relative contribution of risk factors for early-onset myopia in young Asian children. *Investigative ophthalmology & visual science*. 2015;56(13):8101-8107.
551. Low W, Dirani M, Gazzard G, et al. Family history, near work, outdoor activity, and myopia in Singapore Chinese preschool children. *British Journal of Ophthalmology*. 2010;94(8):1012-1016.
552. Lu B, Congdon N, Liu X, et al. Associations between near work, outdoor activity, and myopia among adolescent students in rural China: the Xichang Pediatric Refractive Error Study report no. 2. *Archives of ophthalmology*. 2009;127(6):769-775.
553. Rose KA, Morgan IG, Smith W, Burlutsky G, Mitchell P, Saw S-M. Myopia, lifestyle, and schooling in students of Chinese ethnicity in Singapore and Sydney. *Archives of ophthalmology*. 2008;126(4):527-530.
554. Jones-Jordan LA, Mitchell GL, Cotter SA, et al. Visual activity before and after the onset of juvenile myopia. *Investigative ophthalmology & visual science*. 2011;52(3):1841-1850.
555. French AN, Morgan IG, Mitchell P, Rose KA. Risk factors for incident myopia in Australian schoolchildren: the Sydney adolescent vascular and eye study. *Ophthalmology*. 2013;120(10):2100-2108.
556. Yao L, Qi L-s, Wang X-f, et al. Refractive change and incidence of myopia among a group of highly selected senior high school students in China: a prospective study in an aviation cadet prerecruitment class. *Investigative ophthalmology & visual science*. 2019;60(5):1344-1352.
557. Li S-M, Li H, Li S-Y, et al. Time outdoors and myopia progression over 2 years in Chinese children: the Anyang Childhood Eye Study. *Investigative ophthalmology & visual science*. 2015;56(8):4734-4740.

558. Öner V, Bulut A, Oruç Y, Özgür G. Influence of indoor and outdoor activities on progression of myopia during puberty. *International ophthalmology*. 2016;36(1):121-125.
559. Fulk GW, Cyert LA, Parker DA. Seasonal variation in myopia progression and ocular elongation. *Optometry and Vision Science*. 2002;79(1):46-51.
560. Gwiazda J, Deng L, Manny R, Norton TT. Seasonal variations in the progression of myopia in children enrolled in the correction of myopia evaluation trial. *Investigative ophthalmology & visual science*. 2014;55(2):752-758.
561. Goss DA, Rainey BB. Relation of childhood myopia progression rates to time of year. *Journal of the American Optometric Association*. 1998;69(4):262-266.
562. Jiang Bc, Schatz S, Seger K. Myopic progression and dark focus variation in optometric students during the first academic year. *Clinical and Experimental Optometry*. 2005;88(3):153-159.
563. Sherwin JC, Reacher MH, Keogh RH, Khawaja AP, Mackey DA, Foster PJ. The association between time spent outdoors and myopia in children and adolescents: a systematic review and meta-analysis. *Ophthalmology*. 2012;119(10):2141-2151.
564. Xiong S, Sankaridurg P, Naduvilath T, et al. Time spent in outdoor activities in relation to myopia prevention and control: a meta-analysis and systematic review. *Acta ophthalmologica*. 2017;95(6):551-566.
565. Fitzgerald ME, Wildsoet CF, Reiner A. Temporal relationship of choroidal blood flow and thickness changes during recovery from form deprivation myopia in chicks. *Experimental eye research*. 2002;74(5):561-570.
566. Read SA, Collins MJ, Vincent SJ. Light exposure and physical activity in myopic and emmetropic children. *Optometry and vision science*. 2014;91(3):330-341.
567. Ashby R, Ohlendorf A, Schaeffel F. The effect of ambient illuminance on the development of deprivation myopia in chicks. *Investigative ophthalmology & visual science*. 2009;50(11):5348-5354.
568. Ashby RS, Schaeffel F. The effect of bright light on lens compensation in chicks. *Investigative ophthalmology & visual science*. 2010;51(10):5247-5253.
569. Siegwart Jr JT, Ward AH, Norton TT. Moderately elevated fluorescent light levels slow form deprivation and minus lens-induced myopia development in tree shrews. *Investigative ophthalmology & visual science*. 2012;53(14):3457-3457.
570. Stone RA, Cohen Y, McGlinn AM, et al. Development of experimental myopia in chicks in a natural environment. *Investigative ophthalmology & visual science*. 2016;57(11):4779-4789.
571. Smith EL, Hung L-F, Arumugam B, Huang J. Negative lens–induced myopia in infant monkeys: effects of high ambient lighting. *Investigative ophthalmology & visual science*. 2013;54(4):2959-2969.
572. Backhouse S, Collins AV, Phillips JR. Influence of periodic vs continuous daily bright light exposure on development of experimental myopia in the chick. *Ophthalmic and Physiological Optics*. 2013;33(5):563-572.
573. Cohen Y, Belkin M, Yehezkel O, Solomon AS, Polat U. Dependency between light intensity and refractive development under light–dark cycles. *Experimental eye research*. 2011;92(1):40-46.
574. Sarfare S, Yang J, Nickla DL. The effects of brief high intensity light on ocular growth in chicks developing myopia vary with time of day. *Experimental eye research*. 2020;195:108039.
575. Lan W, Feldkaemper M, Schaeffel F. Intermittent episodes of bright light suppress myopia in the chicken more than continuous bright light. *PloS one*. 2014;9(10):e110906.
576. Kirsch M, Wagner H-J. Release pattern of endogenous dopamine in teleost retinae during light adaptation and pharmacological stimulation. *Vision research*. 1989;29(2):147-154.
577. Umino O, Lee Y, Dowling JE. Effects of light stimuli on the release of dopamine from interplexiform cells in the white perch retina. *Visual neuroscience*. 1991;7(5):451-458.
578. Brainard GC, Morgan WW. Light-induced stimulation of retinal dopamine: a dose-response relationship. *Brain research*. 1987;424(1):199-203.
579. Cohen Y, Peleg E, Belkin M, Polat U, Solomon AS. Ambient illuminance, retinal dopamine release and refractive development in chicks. *Experimental eye research*. 2012;103:33-40.

580. Connaughton VP, Wetzell B, Arneson LS, DeLucia V, L. Riley A. Elevated dopamine concentration in light-adapted zebrafish retinas is correlated with increased dopamine synthesis and metabolism. *Journal of neurochemistry*. 2015;135(1):101-108.
581. Iuvone PM, Galli C, Garrison-Gund C, Neff NH. Light stimulates tyrosine hydroxylase activity and dopamine synthesis in retinal amacrine neurons. *Science*. 1978;202(4370):901-902.
582. Proll MA, Kamp CW, Morgan WW. Use of liquid chromatography with electrochemistry to measure effects of varying intensities of white light on DOPA accumulation in rat retinas. *Life sciences*. 1982;30(1):11-19.
583. Megaw P, Morgan I, Boelen M. Vitreal dihydroxyphenylacetic acid (DOPAC) as an index of retinal dopamine release. *Journal of neurochemistry*. 2001;76(6):1636-1644.
584. Ohngemach S, Hagel G, Schaeffel F. Concentrations of biogenic amines in fundal layers in chickens with normal visual experience, deprivation, and after reserpine application. *Visual neuroscience*. 1997;14(3):493-505.
585. Iuvone PM, Tigges M, Fernandes A, Tigges J. Dopamine synthesis and metabolism in rhesus monkey retina: development, aging, and the effects of monocular visual deprivation. *Visual neuroscience*. 1989;2(5):465-471.
586. Ashby R, McCarthy CS, Maleszka R, Megaw P, Morgan IG. A muscarinic cholinergic antagonist and a dopamine agonist rapidly increase ZENK mRNA expression in the form-deprived chicken retina. *Experimental eye research*. 2007;85(1):15-22.
587. McBrien NA, Cottriall CL, Annies R. Retinal acetylcholine content in normal and myopic eyes: a role in ocular growth control? *Visual neuroscience*. 2001;18(4):571-580.
588. Nickla DL, Totonelly K, Dhillon B. Dopaminergic agonists that result in ocular growth inhibition also elicit transient increases in choroidal thickness in chicks. *Experimental eye research*. 2010;91(5):715-720.
589. Thomson K, Karouta C, Morgan I, Kelly T, Ashby R. Effectiveness and safety of topical levodopa in a chick model of myopia. *Scientific reports*. 2019;9(1):1-17.
590. Gao Q, Liu Q, Ma P, Zhong X, Wu J, Ge J. Effects of direct intravitreal dopamine injections on the development of lid-suture induced myopia in rabbits. *Graefe's archive for clinical and experimental ophthalmology*. 2006;244(10):1329-1335.
591. Lin Z, Chen X, Ge J, et al. Effects of direct intravitreal dopamine injection on sclera and retina in form-deprived myopic rabbits. *Journal of ocular pharmacology and therapeutics*. 2008;24(6):543-550.
592. Junfeng M, Shuangzhen L, Wenjuan Q, Fengyun L, Xiaoying W, Qian T. Levodopa inhibits the development of form-deprivation myopia in guinea pigs. *Optometry and Vision Science*. 2010;87(1):53-60.
593. Dong F, Zhi Z, Pan M, et al. Inhibition of experimental myopia by a dopamine agonist: different effectiveness between form deprivation and hyperopic defocus in guinea pigs. *Molecular vision*. 2011;17:2824.
594. Chakraborty R, na Park H, Aung MH, et al. Comparison of refractive development and retinal dopamine in OFF pathway mutant and C57BL/6J wild-type mice. *Molecular vision*. 2014;20:1318.
595. Huang F, Zhang L, Wang Q, et al. Dopamine D1 receptors contribute critically to the apomorphine-induced inhibition of form-deprivation myopia in mice. *Investigative ophthalmology & visual science*. 2018;59(6):2623-2634.
596. Landis E, Chrenek M, Chakraborty R, et al. Increased endogenous dopamine prevents myopia in mice. *Experimental eye research*. 2020;193:107956.
597. Wu X-H, Li Y-Y, Zhang P-P, et al. Unaltered retinal dopamine levels in a C57BL/6 mouse model of form-deprivation myopia. *Investigative ophthalmology & visual science*. 2015;56(2):967-977.
598. Yan T, Xiong W, Huang F, et al. Daily injection but not continuous infusion of apomorphine inhibits form-deprivation myopia in mice. *Investigative ophthalmology & visual science*. 2015;56(4):2475-2485.

599. Bartmann M, Schaeffel F, Hagel G, Zrenner E. Constant light affects retinal dopamine levels and blocks deprivation myopia but not lens-induced refractive errors in chickens. *Visual neuroscience*. 1994;11(2):199-208.
600. Guo S, Sivak J, Callender M, Diehl-Jones B. Retinal dopamine and lens-induced refractive errors in chicks. *Current eye research*. 1995;14(5):385-389.
601. Nickla DL, Totonelly K. Dopamine antagonists and brief vision distinguish lens-induced-and form-deprivation-induced myopia. *Experimental eye research*. 2011;93(5):782-785.
602. Thomson K, Morgan I, Karouta C, Ashby R. Levodopa inhibits the development of lens-induced myopia in chicks. *Scientific Reports*. 2020;10(1):1-12.
603. Foulds WS, Barathi VA, Luu CD. Progressive myopia or hyperopia can be induced in chicks and reversed by manipulation of the chromaticity of ambient light. *Investigative ophthalmology & visual science*. 2013;54(13):8004-8012.
604. Rucker FJ, Wallman J. Cone signals for spectacle-lens compensation: differential responses to short and long wavelengths. *Vision research*. 2008;48(19):1980-1991.
605. Seidemann A, Schaeffel F. Effects of longitudinal chromatic aberration on accommodation and emmetropization. *Vision research*. 2002;42(21):2409-2417.
606. Wang M, Schaeffel F, Jiang B, Feldkaemper M. Effects of light of different spectral composition on refractive development and retinal dopamine in chicks. *Investigative ophthalmology & visual science*. 2018;59(11):4413-4424.
607. Jiang L, Zhang S, Schaeffel F, et al. Interactions of chromatic and lens-induced defocus during visual control of eye growth in guinea pigs (Cavia porcellus). *Vision research*. 2014;94:24-32.
608. Gawne TJ, Ward AH, Norton TT. Long-wavelength (red) light produces hyperopia in juvenile and adolescent tree shrews. *Vision research*. 2017;140:55-65.
609. Gawne TJ, Ward AH, Norton TT. Juvenile tree shrews do not maintain emmetropia in narrow-band blue light. *Optometry and vision science: official publication of the American Academy of Optometry*. 2018;95(10):911.
610. Ward AH, Norton TT, Huisingh CE, Gawne TJ. The hyperopic effect of narrow-band long-wavelength light in tree shrews increases non-linearly with duration. *Vision research*. 2018;146:9-17.
611. Hung L-F, Arumugam B, She Z, Ostrin L, Smith III EL. Narrow-band, long-wavelength lighting promotes hyperopia and retards vision-induced myopia in infant rhesus monkeys. *Experimental eye research*. 2018;176:147-160.
612. Smith EL, Hung L-F, Arumugam B, Holden BA, Neitz M, Neitz J. Effects of long-wavelength lighting on refractive development in infant rhesus monkeys. *Investigative ophthalmology & visual science*. 2015;56(11):6490-6500.
613. Artigas JM, Felipe A, Navea A, Fandino A, Artigas C. Spectral transmission of the human crystalline lens in adult and elderly persons: color and total transmission of visible light. *Investigative ophthalmology & visual science*. 2012;53(7):4076-4084.
614. Choi JA, Han K, Park Y-M, La TY. Low serum 25-hydroxyvitamin D is associated with myopia in Korean adolescents. *Investigative ophthalmology & visual science*. 2014;55(4):2041-2047.
615. Jung BJ, Jee D. Association between serum 25-hydroxyvitamin D levels and myopia in general Korean adults. *Indian journal of ophthalmology*. 2020;68(1):15.
616. Mutti DO, Marks AR. Blood levels of vitamin D in teens and young adults with myopia. *Optometry and vision science: official publication of the American Academy of Optometry*. 2011;88(3):377.
617. Tideman JWL, Polling JR, Voortman T, et al. Low serum vitamin D is associated with axial length and risk of myopia in young children. *European journal of epidemiology*. 2016;31(5):491-499.
618. Tang SM, Lau T, Rong SS, et al. Vitamin D and its pathway genes in myopia: systematic review and meta-analysis. *British Journal of Ophthalmology*. 2019;103(1):8-17.
619. Guggenheim JA, Williams C, Northstone K, et al. Does vitamin D mediate the protective effects of time outdoors on myopia? Findings from a prospective birth cohort. *Investigative ophthalmology & visual science*. 2014;55(12):8550-8558.

620. Cuellar-Partida G, Williams KM, Yazar S, et al. Genetically low vitamin D concentrations and myopic refractive error: a Mendelian randomization study. *International journal of epidemiology*. 2017;46(6):1882-1890.
621. Brown JS, Flitcroft DI, Ying G-s, et al. In vivo human choroidal thickness measurements: evidence for diurnal fluctuations. *Investigative ophthalmology & visual science*. 2009;50(1):5-12.
622. Chakraborty R, Read SA, Collins MJ. Diurnal variations in axial length, choroidal thickness, intraocular pressure, and ocular biometrics. *Investigative ophthalmology & visual science*. 2011;52(8):5121-5129.
623. Nickla DL. The phase relationships between the diurnal rhythms in axial length and choroidal thickness and the association with ocular growth rate in chicks. *Journal of Comparative Physiology A*. 2006;192(4):399-407.
624. Nickla DL, Wildsoet C, Wallman J. Visual influences on diurnal rhythms in ocular length and choroidal thickness in chick eyes. *Experimental eye research*. 1998;66(2):163-181.
625. Papastergiou GI, Schmid GF, Riva CE, Mendel MJ, Stone RA, Laties AM. Ocular axial length and choroidal thickness in newly hatched chicks and one-year-old chickens fluctuate in a diurnal pattern that is influenced by visual experience and intraocular pressure changes. *Experimental eye research*. 1998;66(2):195-205.
626. Chakraborty R, Read SA, Collins MJ. Monocular myopic defocus and daily changes in axial length and choroidal thickness of human eyes. *Experimental eye research*. 2012;103:47-54.
627. Burfield HJ, Carkeet A, Ostrin LA. Ocular and systemic diurnal rhythms in emmetropic and myopic adults. *Investigative ophthalmology & visual science*. 2019;60(6):2237-2247.
628. Stone RA, Quinn GE, Francis EL, et al. Diurnal axial length fluctuations in human eyes. *Investigative ophthalmology & visual science*. 2004;45(1):63-70.
629. Kearney S, O'Donoghue L, Pourshahidi LK, Cobice D, Saunders KJ. Myopes have significantly higher serum melatonin concentrations than non-myopes. *Ophthalmic and Physiological Optics*. 2017;37(5):557-567.
630. Abbott KS, Queener HM, Ostrin LA. The ipRGC-Driven Pupil Response with Light Exposure, Refractive Error and Sleep. *Optometry and vision science: official publication of the American Academy of Optometry*. 2018;95(4):323.
631. Ayaki M, Torii H, Tsubota K, Negishi K. Decreased sleep quality in high myopia children. *Scientific reports*. 2016;6(1):1-9.
632. Jee D, Morgan IG, Kim EC. Inverse relationship between sleep duration and myopia. *Acta ophthalmologica*. 2016;94(3):e204-e210.
633. Dharani R, Lee C-F, Theng ZX, et al. Comparison of measurements of time outdoors and light levels as risk factors for myopia in young Singapore children. *Eye*. 2012;26(7):911-918.
634. Landis EG, Yang V, Brown DM, Pardue MT, Read SA. Dim light exposure and myopia in children. *Investigative ophthalmology & visual science*. 2018;59(12):4804-4811.
635. Read SA, Collins MJ, Vincent SJ. Light exposure and eye growth in childhood. *Investigative ophthalmology & visual science*. 2015;56(11):6779-6787.
636. Read SA, Vincent SJ, Tan C-S, Ngo C, Collins MJ, Saw S-M. Patterns of daily outdoor light exposure in Australian and Singaporean children. *Translational vision science & technology*. 2018;7(3):8-8.
637. Ostrin LA, Sajjadi A, Benoit JS. Objectively measured light exposure during school and summer in children. *Optometry and vision science: official publication of the American Academy of Optometry*. 2018;95(4):332.
638. Wen L, Cao Y, Cheng Q, et al. Objectively measured near work, outdoor exposure and myopia in children. *British Journal of Ophthalmology*. 2020;104(11):1542-1547.
639. Bhandari KR, Shukla D, Mirhajianmoghadam H, Ostrin LA. Objective Measures of Near Viewing and Light Exposure in Schoolchildren during COVID-19. *Optom Vis Sci*. Mar 1 2022;99(3):241-252. doi:10.1097/opx.0000000000001871

640. Li M, Lanca C, Tan C-S, et al. Association of time outdoors and patterns of light exposure with myopia in children. *British Journal of Ophthalmology*. 2021;
641. Schmid KL, Leyden K, Chiu Y-h, et al. Assessment of daily light and ultraviolet exposure in young adults. *Optometry and Vision Science*. 2013;90(2):148-155.
642. Ulaganathan S, Read SA, Collins MJ, Vincent SJ. Influence of seasons upon personal light exposure and longitudinal axial length changes in young adults. *Acta ophthalmologica*. 2019;97(2):e256-e265.
643. Alvarez AA, Wildsoet CF. Quantifying light exposure patterns in young adult students. *Journal of modern optics*. 2013;60(14):1200-1208.
644. Rose KA, French AN, Morgan IG. Environmental factors and myopia: paradoxes and prospects for prevention. *The Asia-Pacific Journal of Ophthalmology*. 2016;5(6):403-410.
645. French AN, Ashby RS, Morgan IG, Rose KA. Time outdoors and the prevention of myopia. *Experimental eye research*. 2013;114:58-68.
646. Cao K, Wan Y, Yusufu M, Wang N. Significance of Outdoor Time for Myopia Prevention: A Systematic Review and Meta-Analysis Based on Randomized Controlled Trials. *Ophthalmic research*. 2020;63(2):97-105. doi:10.1159/000501937
647. Saw S-M, Lam DS, Rajan U, Katz J, Chew S-J. Development of instruments to measure near work in myopia studies. *Myopia Updates*. Springer; 1998:58-62.
648. Li S-M, Li S-Y, Kang M-T, et al. Near work related parameters and myopia in Chinese children: the Anyang Childhood Eye Study. *PloS one*. 2015;10(8):e0134514.
649. Harrington SC, Stack J, O'Dwyer V. Risk factors associated with myopia in schoolchildren in Ireland. *British Journal of Ophthalmology*. 2019;103(12):1803-1809.
650. Edwards P, Roberts I, Clarke M, et al. Increasing response rates to postal questionnaires: systematic review. *Bmj*. 2002;324(7347):1183.
651. Tan NW, Saw S-M, Lam DS, Cheng H-M, Rajan U, Chew S-J. Temporal variations in myopia progression in Singaporean children within an academic year. *Optometry and Vision Science*. 2000;77(9):465-472.
652. Scheiman M, Zhang Q, Gwiazda J, et al. Visual activity and its association with myopia stabilisation. *Ophthalmic and Physiological Optics*. 2014;34(3):353-361.
653. Ngo CS, Pan CW, Finkelstein EA, et al. A cluster randomised controlled trial evaluating an incentive-based outdoor physical activity programme to increase outdoor time and prevent myopia in children. *Ophthalmic and Physiological Optics*. 2014;34(3):362-368.
654. Rah MJ, Walline JJ, Lynn Mitchell G, Zadnik K. Comparison of the experience sampling method and questionnaires to assess visual activities in pre-teen and adolescent children. *Ophthalmic and Physiological Optics*. 2006;26(5):483-489.
655. Rah MJ, Mitchell GL, Mutti DO, Zadnik K. Levels of agreement between parents' and children's reports of near work. *Ophthalmic epidemiology*. 2002;9(3):191-203.
656. Sun JT, An M, Yan XB, Li GH, Wang DB. Prevalence and related factors for myopia in school-aged children in Qingdao. *Journal of ophthalmology*. 2018;2018
657. Leung Tw, Flitcroft DI, Wallman J, et al. A novel instrument for logging nearwork distance. *Ophthalmic and Physiological Optics*. 2011;31(2):137-144.
658. Williams R, Bakshi S, Ostrin EJ, Ostrin LA. Continuous objective assessment of near work. *Scientific reports*. 2019;9(1):1-10.
659. Zhuo Z, Wang Y, Yang X, et al. Investigation of Time Duration Spent on Near Work and Outdoor Activities in Children: Perception versus Real-time Measurements. *Investigative Ophthalmology & Visual Science*. 2018;59(9):3401-3401.
660. Salmerón-Campillo RM, Jaskulski M, Lara-Cánovas S, González-Méijome JM, Lopez-Gil N. Novel method of remotely monitoring the face-device distance and face illuminance using mobile devices: A pilot study. *Journal of ophthalmology*. 2019;2019
661. Jaskulski MT, Liu Y, Lopez-Gil N. Measuring face illumination and near work distance using personal mobile devices. *Investigative Ophthalmology & Visual Science*. 2018;59(9):2152-2152.

662. Adarsh S, Kaleemuddin SM, Bose D, Ramachandran K. Performance comparison of Infrared and Ultrasonic sensors for obstacles of different materials in vehicle/robot navigation applications. IOP publishing; 2016:012141.
663. Wen L, Lan W, Huang Y, Wu Y, Li X, Yang Z. A novel device to record the behavior related to myopia development—preliminary results in the lab. *Investigative Ophthalmology & Visual Science*. 2016;57(12):2491-2491.
664. DeCusatis C. *Handbook of applied photometry*. American Inst. of Physics; 1997.
665. Scheuermaier K, Laffan AM, Duffy JF. Light exposure patterns in healthy older and young adults. *J Biol Rhythms*. 2010;25(2):113-122. doi:10.1177/0748730410361916
666. Verkicharla PK, Ramamurthy D, Nguyen QD, et al. Development of the FitSight fitness tracker to increase time outdoors to prevent myopia. *Translational vision science & technology*. 2017;6(3):20-20.
667. Fan Y, Liao J, Liu S, et al. Effect of Time Outdoors and Near-viewing Time on Myopia Progression in 9-to 11-year-old Children in Chongqing. *Optometry and Vision Science*. 2022;99(6):489-495.
668. Mirhajianmoghadam H, Piña A, Ostrin LA. Objective and Subjective Behavioral Measures in Myopic and Non-Myopic Children During the COVID-19 Pandemic. *Translational vision science & technology*. 2021;10(11):4-4.
669. Bhandari KR, Mirhajianmoghadam H, Ostrin LA. Objectively Measured Near Work and Light Exposure in Adults. *Investigative Ophthalmology & Visual Science*. 2021;62(8):2328-2328.
670. Howell CM, McCullough SJ, Doyle L, Murphy MH, Saunders KJ. Reliability and validity of the Actiwatch and Clouclip for measuring illumination in real-world conditions. *Ophthalmic and Physiological Optics*. 2021;
671. Ulaganathan S, Read SA, Collins MJ, Vincent SJ. Measurement duration and frequency impact objective light exposure measures. *Optometry and Vision Science*. 2017;94(5):588-597.
672. Sherwin JC, McKnight CM, Hewitt AW, Griffiths LR, Coroneo MT, Mackey DA. Reliability and validity of conjunctival ultraviolet autofluorescence measurement. *British journal of ophthalmology*. 2012;96(6):801-805.
673. Chodick G, Kleinerman RA, Linet MS, et al. Agreement between diary records of time spent outdoors and personal ultraviolet radiation dose measurements. *Photochemistry and photobiology*. 2008;84(3):713-718.
674. Mutti DO, Mulvihill SP. Estimation of Time Spent Outdoors Using Personal UV and Visible Light Dosimetry. *Investigative Ophthalmology & Visual Science*. 2014;55(13):3641-3641.
675. Cooper AR, Page AS, Wheeler BW, Hillsdon M, Griew P, Jago R. Patterns of GPS measured time outdoors after school and objective physical activity in English children: the PEACH project. *International Journal of Behavioral Nutrition and Physical Activity*. 2010;7(1):1-9.
676. Tandon PS, Saelens BE, Zhou C, Kerr J, Christakis DA. Indoor versus outdoor time in preschoolers at child care. *American journal of preventive medicine*. 2013;44(1):85-88.
677. Lin LL-K, Shih Y-F, Hsiao CK, Chen C. Prevalence of myopia in Taiwanese schoolchildren: 1983 to 2000. *Annals Academy of Medicine Singapore*. 2004;33(1):27-33.
678. Yazar S, Hewitt AW, Black LJ, et al. Myopia Is Associated With Lower Vitamin D Status in Young Adults. *Investigative Ophthalmology & Visual Science*. 2014;55(7):4552-4559. doi:10.1167/iovs.14-14589
679. Espiritu RC, Kripke DF, Ancoli-Israel S, et al. Low illumination experienced by San Diego adults: association with atypical depressive symptoms. *Biological psychiatry*. Mar 15 1994;35(6):403-7. doi:10.1016/0006-3223(94)90007-8
680. Savides TJ, Messin S, Senger C, Kripke DF. Natural light exposure of young adults. *Physiology & Behavior*. 1986/10/01/ 1986;38(4):571-574. doi:https://doi.org/10.1016/0031-9384(86)90427-0
681. Morgan I, Rose K. How genetic is school myopia? *Prog Retin Eye Res*. Jan 2005;24(1):1-38. doi:10.1016/j.preteyeres.2004.06.004

682. Morgan IG, Wu P-C, Ostrin LA, et al. IMI risk factors for myopia. *Investigative ophthalmology & visual science*. 2021;62(5):3-3.
683. Jardim AC, Pawley MD, Cheeseman JF, Guesgen MJ, Steele CT, Warman GR. Validating the use of wrist-level light monitoring for in-hospital circadian studies. *Chronobiology international*. 2011;28(9):834-840.
684. Joyce DS, Zele AJ, Feigl B, Adhikari P. The accuracy of artificial and natural light measurements by actigraphs. *Journal of sleep research*. 2020;29(5):e12963.
685. Lin LI. A concordance correlation coefficient to evaluate reproducibility. *Biometrics*. Mar 1989;45(1):255-68.
686. Dixon E. Spectral distribution of Australian daylight. *JOSA*. 1978;68(4):437-450.
687. Feldkaemper M, Schaeffel F. An updated view on the role of dopamine in myopia. *Experimental eye research*. 2013;114:106-119.
688. Wen L, Cheng Q, Lan W, et al. An objective comparison of light intensity and near-visual tasks between rural and urban school children in China by a wearable device Clouclip. *Translational vision science & technology*. 2019;8(6):15-15.
689. Bhandari KR, Mirhajianmoghadam H, Ostrin LA. Wearable Sensors for Measurement of Viewing Behavior, Light Exposure, and Sleep. *Sensors*. 2021;21(21):7096.
690. Bhandari KR, Ostrin LA. Validation of the Clouclip and utility in measuring viewing distance in adults. *Ophthalmic & physiological optics : the journal of the British College of Ophthalmic Opticians (Optometrists)*. 2020;40(6):801-814. doi:10.1111/opo.12735
691. Ostrin LA. Objectively measured light exposure in emmetropic and myopic adults. *Optometry and Vision Science*. 2017;94(2):229-238.
692. Hu Y, Zhao F, Ding X, et al. Rates of Myopia Development in Young Chinese Schoolchildren During the Outbreak of COVID-19. *JAMA ophthalmology*. 2021;
693. Wang J, Li Y, Musch DC, et al. Progression of myopia in school-aged children after COVID-19 home confinement. *JAMA ophthalmology*. 2021;139(3):293-300.
694. Ma D, Wei S, Li S-M, et al. Progression of myopia in a natural cohort of Chinese children during COVID-19 pandemic. *Graefe's Archive for Clinical and Experimental Ophthalmology*. 2021:1-8.
695. Ma M, Xiong S, Zhao S, Zheng Z, Sun T, Li C. COVID-19 Home Quarantine Accelerated the Progression of Myopia in Children Aged 7 to 12 Years in China. *Investigative Ophthalmology & Visual Science*. 2021;62(10):37-37.
696. Zhang X, Cheung SS, Chan H-N, et al. Myopia incidence and lifestyle changes among school children during the COVID-19 pandemic: a population-based prospective study. *British Journal of Ophthalmology*. 2021;
697. Breslin KM, O'Donoghue L, Saunders KJ. An investigation into the validity of self-reported classification of refractive error. *Ophthalmic and Physiological Optics*. 2014;34(3):346-352.
698. Cumberland PM, Chianca A, Rahi JS. Accuracy and utility of self-report of refractive error. *JAMA ophthalmology*. 2016;134(7):794-801.
699. Naidoo KS, Leasher J, Bourne RR, et al. Global vision impairment and blindness due to uncorrected refractive error, 1990–2010. *Optometry and Vision Science*. 2016;93(3):227-234.
700. Blows SJ, Murphy EP, Martin FJ, Davies RM. Vision screening in preschoolers: The new south wales statewide eyesight preschooler screening program. *Medical Journal of Australia*. 2014;200(4):222-225.
701. Bennett AG, Rabbetts RB. *Bennett and Rabbetts' clinical visual optics*. Elsevier Health Sciences; 1998.
702. Rozema JJ, Atchison DA, Tassignon M-J. Comparing methods to estimate the human lens power. *Investigative ophthalmology & visual science*. 2011;52(11):7937-7942.
703. Xiong S, He X, Sankaridurg P, et al. Accelerated loss of crystalline lens power initiating from emmetropia among young school children: a 2-year longitudinal study. *Acta Ophthalmologica*. 2021;
704. Ma Y, Lin S, Morgan IG, et al. Eyes grow towards mild hyperopia rather than emmetropia in Chinese preschool children. *Acta Ophthalmologica*. 2021;99(8):e1274-e1280.

705. Smith G. Refraction and visual acuity measurements: what are their measurement uncertainties? *Clinical and Experimental Optometry*. 2006;89(2):66-72.
706. Dolgin E. The myopia boom. *Nature News*. 2015;519(7543):276.
707. Hu Y, Ding X, Guo X, Chen Y, Zhang J, He M. Association of age at myopia onset with risk of high myopia in adulthood in a 12-year follow-up of a Chinese cohort. *JAMA ophthalmology*. 2020;138(11):1129-1134.
708. Saw SM, Gazzard G, Shih-Yen EC, Chua WH. Myopia and associated pathological complications. *Ophthalmic and Physiological Optics*. 2005;25(5):381-391.
709. Jonas JB, Ang M, Cho P, et al. IMI prevention of myopia and its progression. *Investigative ophthalmology & visual science*. 2021;62(5):6-6.
710. Zadnik K, Sinnott LT, Cotter SA, et al. Prediction of juvenile-onset myopia. *JAMA ophthalmology*. 2015;133(6):683-689.
711. Zadnik K, Mutti DO, Friedman NE, et al. Ocular predictors of the onset of juvenile myopia. *Investigative ophthalmology & visual science*. 1999;40(9):1936-1943.
712. Grosvenor T. High axial length/corneal radius ratio as a risk factor in the development of myopia. *American journal of optometry and physiological optics*. 1988/09// 1988;65(9):689-696. doi:10.1097/00006324-198809000-00001
713. Zadnik K, Mutti DO, Fusaro RE, Adams AJ. Longitudinal evidence of crystalline lens thinning in children. *Invest Ophthalmol Vis Sci*. Jul 1995;36(8):1581-7.
714. Garner LF, Stewart AW, Owens H, Kinnear RF, Frith MJ. The Nepal Longitudinal Study: biometric characteristics of developing eyes. *Optometry and vision science*. 2006;83(5):274-280.
715. Rozema J, Dankert S, Iribarren R, Lanca C, Saw S-M. Axial growth and lens power loss at myopia onset in Singaporean children. *Investigative ophthalmology & visual science*. 2019;60(8):3091-3099.
716. Liu L, Li R, Huang D, et al. Prediction of premyopia and myopia in Chinese preschool children: a longitudinal cohort. *BMC ophthalmology*. 2021/07/21 2021;21(1):283. doi:10.1186/s12886-021-02045-8
717. You X, Wang L, Tan H, et al. Near Work Related Behaviors Associated with Myopic Shifts among Primary School Students in the Jiading District of Shanghai: A School-Based One-Year Cohort Study. *PLOS ONE*. 2016;11(5):e0154671. doi:10.1371/journal.pone.0154671
718. Guo C, Ye Y, Yuan Y, et al. Development and validation of a novel nomogram for predicting the occurrence of myopia in schoolchildren: a prospective cohort study. *American Journal of Ophthalmology*. 2022;

Appendix 1

Published Authored Paper – “Predictors of Visual Acuity after Treatment of Neovascular Age-Related Macular Degeneration – Current Perspectives”

Clinical Ophthalmology

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

Predictors of Visual Acuity After Treatment of Neovascular Age-Related Macular Degeneration – Current Perspectives

Long T Phan[1,2]
Geoffrey K Broadhead[1,3]
Thomas H Hong[1]
Andrew A Chang[1,3]

[1]Sydney Retina, Sydney, New South Wales, Australia; [2]Discipline of Orthoptics, University of Technology Sydney, Sydney, New South Wales, Australia; [3]Save Sight Institute, The University of Sydney, Sydney, New South Wales, Australia

Abstract: Visual acuity is a key outcome measure in the treatment of neovascular age-related macular degeneration (nAMD) using anti-vascular endothelial growth factor agents. Large variations in visual responses between individuals within clinical trials and real-world studies may relate to underlying differences in patient and treatment factors. Most notably, a better baseline visual acuity, younger age and smaller choroidal neovascularization lesion size have been strongly associated with achieving better visual outcomes. In addition, there is emerging evidence for other roles including genetic factors and anatomical variables such as fluid status. Apart from patient-related factors, treatments that favor a higher number of injections tend to provide better visual outcomes. Overall, the identification of predictive factors does not currently play an essential role in the clinical management of patients with nAMD. However, they have allowed for the understanding that early detection, timely management and close monitoring of the disease are required to achieve optimal visual outcomes. Further investigation into predictive factors alongside the development of novel therapeutic agents may one day provide a means to accurately predict patient outcomes. Treatment regimens that offer flexible dosing patterns such as the treat-and-extend strategy currently provide a degree of personalization during treatment.

Keywords: age-related macular degeneration, anti-VEGF, visual acuity, demographic, genetic, anatomic

Introduction

Age-related macular degeneration (AMD) is a chronic disease of the eye which is the leading cause of irreversible vision impairment in developed countries.[1] Prevalence rates of AMD for individuals aged between 45 and 85 years range between 7% and 18% across Asian and Western countries.[2] Neovascular age-related macular degeneration (nAMD) or "wet" AMD, is an advanced form of AMD characterized by choroidal neovascularization (CNV), where newly formed blood vessels leak into the retina, causing distortion and rapid loss of vision. nAMD occurs in approximately 10% of individuals with AMD, however it is responsible for up to 90% of vision loss.[2,3] The burden of AMD is expected to increase, as current prevalence rates are estimated to rise by approximately 50% over the next two decades.[2]

While the exact cause of CNV is unconfirmed, it is believed to be triggered by local retinal ischemia/hypoxia, caused by the buildup of abnormal extracellular deposits located between the retinal pigment epithelium (RPE) and Bruch's

Correspondence: Andrew A Chang
Sydney Retina, Level 13, Park House, 187 Macquarie Street, Sydney, 2000, New South Wales, Australia
Tel +61 2 9221 3755
Fax +61 2 9221 1637
Email achang@sydneyretina.com.au

Received: 9 July 2021
Accepted: 28 July 2021
Published: 11 August 2021

membrane. The overexpression of vascular endothelial growth factor (VEGF) in response to retinal hypoxia has been identified as the main mediator behind the development of CNV.[4–6] These findings have led to a paradigm shift in the treatment of nAMD through the introduction of anti-VEGF medication given intravitreally into the eye. Anti-VEGF agents primarily target and block VEGF-A isoforms, preventing further vision loss caused by angiogenesis, fluid leakage and subsequent scar formation. The improvement and stabilization of vision through fluid reduction is the primary goal of treatment, which also improves vision-related quality of life.[7] As a result, visual acuity (VA) has been considered one of the primary markers for treatment success within several pivotal Phase 3 clinical trials; namely the MARINA[8] and ANCHOR[9] trials for ranibizumab (Lucentis; Genentech, South San Francisco, California), the VIEW1 & VIEW2 studies[10,11] for aflibercept (Eylea; Regeneron, Tarrytown, New York) and more recently in the HAWK and HARRIER trials[12] for brolucizumab (Beovu; Novartis, Basel, Switzerland). In addition to these agents which have been FDA approved for ocular use, bevacizumab (Avastin; Regeneron) has been used off-label, and its non-inferiority to ranibizumab has been demonstrated in the CATT studies.[13,14] In each of their landmark studies, over 90% of patients maintained VA levels within 15 Early Treatment Diabetic Retinopathy Study (ETDRS) letters over the course of treatment. Remarkably also, 30–40% of patients demonstrated visual improvements beyond the 15 letter threshold, demonstrating superiority over previously used photodynamic therapy and laser photocoagulation treatment, which rarely saw VA improvement.[15,16]

However, while the introduction of anti-VEGF therapy has been revolutionary in reducing rates of legal blindness associated with AMD,[17] not all patients respond positively, with a small remainder of patients (~5–10%) experiencing significant reductions in vision. These variations are also seen in the real world, with post-marketing trials and clinical studies finding larger proportions of patients who lose vision compared to the control trials.[18–20] In addition to these early responses, further treatment variation occurs in the longer term past the first 1–2 years of treatment, with some patients experiencing gradual declines in visual acuity despite continuous intensive treatment and a good initial response.[21–23]

It currently remains unclear as to why such heterogeneity in treatment response exists. Though several retrospective analyses have identified several functional, demographic, genetic and anatomic factors associated with various visual outcomes. The identification of prognostic factors allows the provision of personalized medicine, as physicians can provide patients with a more accurate expectation for their visual prognosis. This review investigates factors which may have a predictive value in determining visual response after anti-VEGF treatment among patients with nAMD and assesses the current roles of predictive markers in treatment decision-making.

Literature Search Method

Articles up until January 2021 were initially searched using PubMed by 2 independent authors (LP & GB) using a combination of the terms “Macular degeneration”, “Neovascular”, “Predictive factors”, “Predictors”, “Visual acuity” and “Visual outcomes”. From 190 identified articles, 101 non-relevant articles and 9 non-English articles were excluded after screening through abstracts. The remaining articles were reviewed to generate a list of relevant predictors for further investigation. Sixty-two further studies were identified following manual searching of secondary analyses from major randomized clinical trials of anti-VEGF and separate searches that included additional terms specific for sub-categories of predictors including “smoking”, “pharmacogenetics”, “polymorphisms”, “CFH”, “ARMS2”, “HTRA1”, “VEGF-A”, “VEGFR-2”, “GWAS”, “Optical coherence tomography”, “Atrophy” and “Hemorrhage”. There was a focus on post-hoc analyses of clinical trials and large retrospective studies which used multivariate analysis. Smaller studies or those which used univariate analyses were also included if they demonstrated a significant novel finding. This excluded 48 articles, leaving 94 studies which were included in this review.

Variations in Outcome Reporting and Risk Factor Analyses

Different measures of efficacy have been used throughout the literature. Most studies report visual outcomes as a continuous variable either in terms of visual gain (either in ETDRS letters or using a logMAR equivalent), or as absolute levels of VA achieved by the end of the observational period. On the other hand, outcomes have also been evaluated categorically, through the grouping of participants via their visual response. Though the thresholds for these categories vary between studies, a loss of ≥15 letters

for poor responders has been the most popular definition. Alongside these variations in outcome measures, there have been differences in study designs and statistical analyses and reporting of the various risk factors within the literature. As such meta-analyses have not been previously possible[24,25] and will not be attempted in this exploration for the same reason.

Functional Variables

Visual Acuity

Baseline VA has been the most thoroughly investigated variable and its relationship with visual response following treatment has been well established as the most significant predictor of visual outcome in both clinical trials (Table 1) and real-world studies (Table 2).

VA changes following treatment are heavily influenced by ceiling effects, where patients with better VA at presentation have a reduced capacity or "ceiling" for VA gains compared to those who present with lower baseline VA levels. Post-hoc analysis of the MARINA study found a 1.2–1.6 letter reduction in VA gains for every 5-letter increase in baseline VA.[26] Meanwhile in the VIEW studies, VA gains were +0.65 letters higher for every 1 letter reduction in baseline VA.[27] However, the presence of intraretinal fluid (IRF) at baseline reduced the expected letter gain to +0.22.[27]

While it appears that anti-VEGF treatment is more effective in eyes with poorer VA, patients presenting with better initial VA are more likely to have better final VA. A large retrospective analysis from the Moorfields Eye Hospital (MEH) database reported a 43% increase in likelihood for achieving and maintaining a VA of 20/40 for every 5-letter increase in VA at baseline.[28] Meanwhile, data from the Swedish Macular Register revealed that eyes with initial VA >60 letters (20/63) had only a 20% risk of having low VA (≤60 letters) after 1 or 2 years of treatment, compared to 60% in eyes with low initial VA.[29] This relationship has also been observed in several long-term studies,[30–35] suggesting that the larger visual gains in those with worse initial VA are not enough to overcome a good starting VA despite continuous treatment. As those with worse initial VA are also more likely to respond negatively to treatment, low baseline VA may be an indicator for worse disease severity as there may be underlying pathology not treatable by anti-VEGF, such as atrophy, scarring or other anatomical changes not controlled for in multivariate analysis. van Asten et al,[36] found that those with worse baseline VA were more likely to be non-responders (defined by loss of more than 30% initial letters) after the first 3 months of treatment (OR: 3.3, VA 20/63-20/200 vs >20/63). Similarly, analysis of data from the Fight Retinal Blindness! (FRB) registry found that eyes with VA better than 20/40 were 39% less likely to experience a ≥30 letter loss than those with worse baseline VA after 5 years of treatment.[37]

Although baseline VA is consistently associated with visual outcomes, one's early response may be a better predictor of their visual trajectory.[38–40] The CATT studies found that an individual's VA gain at week 12 of treatment was a stronger predictor of their long-term visual gains than the combination of all their significant baseline predictors including initial VA (R^2 for 2 year VA gains: 0.30 vs 0.13).[40] Similar findings have also been found from the FRB registry,[39] where those who achieved good vision (≥70 letters) by their 4th injection were more likely to maintain good vision after 3 years of treatment than those who did not (OR: 9.8, VA ≥70 vs <70 letters).

As anti-VEGF therapy does not cure nAMD, the nature of the relationship between presenting VA and its response to treatment suggests that individuals should be treated earlier in the disease course. Studies which find that a shorter duration between symptom occurrence and treatment initiation is also associated with better visual outcomes support this notion.[41–44]

Patient Characteristics

Age

Similar to VA, strong relationships between age and visual outcomes were identified in the early clinical studies, with less VA gain seen in older patients (Table 1).[26,40,45–47] In the MARINA study,[26] a 13.6 year difference in age at disease diagnosis was associated a 5-letter reduction in VA gains in the older patient. Meanwhile in the ANCHOR study,[45] an 18.8 year difference in age was associated with a 5-letter reduction in VA gain. In the HARBOR study,[48] patients aged ≤73 years at baseline gained 4.5 letters more than those aged >73 after ranibizumab treatment. The VIEW studies found that older age was also associated with negative treatment outcomes, with older patients more likely to lose VA over their first year of aflibercept treatment (OR for >1 letter loss: 2.1, ages 80–89 vs 46–69 years).[47] Over the first 2 years of CATT,[40,46] older age was associated with less VA gains, worse final VA levels and a decreased likelihood for a ≥15

Table 1 Summary of Clinical Trials Investigating Predictors of Visual Outcomes in Anti-VEGF Treated Patients

Study	Treatment	Duration (Years)	Findings and Significant Factors	Non-Significant Factors
ANCHOR[45]	RBZ 0.3/0.5mg, q1m or PDT prn	1	• RBZ treated arms gained more VA than the PDT group • Lower baseline VA, smaller baseline CNV lesion size and younger age associated with better VA gains	• Gender • CNV type • Duration between diagnosis and treatment
MARINA[26]	RBZ 0.3/0.5mg vs sham	2	• Lower baseline VA, smaller baseline CNV lesion size and younger age associated with better VA gains	• Gender • CNV type • Duration between diagnosis and treatment
MARINA & ANCHOR[122]	RBZ	1	• Fellow eye visual acuity was not predictive of study eye response	• Fellow eye visual acuity
PrONTO[123]	RBZ prn	2	• Larger reductions in CRT after 1 month associated with better VA gains	• # of injections
PIER[124]	RBZ 0.3/0.5mg q3m	2	• Lesion inactivity determined by FFA at 3 months associated with better 1 year VA gains • Lesion inactivity on determined by OCT at 5 or 8 months associated with better 2 year VA gains	• RBZ dose
CATT[46,67]	RBZ or BVZ, prn or q1m	1	• Factors associated with worse final VA were older age, worse baseline VA, larger CNV size, predominantly or minimally classic lesions, presence of GA, thicker foveal thickness and the presence of RPE elevation • Factors associated with less VA gains were older age, better baseline VA (≥20/40), larger CNV size, absence of RAP lesions and presence of RPE elevation • Factors associated with a decreased likelihood of VA gains ≥15 letters were better baseline VA, worse VA in the fellow eye, larger CNV size, absence of RAP lesions, thinner foveal thickness and the presence of RPE elevation • PRN treatment group was less likely to gain ≥15 letters compared to fixed monthly dosing	• SNPs of CFH, ARMS2, HTRA1 & C3 • No interactions between treatment groups and predictors
CATT[40,106]	RBZ or BVZ, prn or q1m	2	• Older age, baseline VA of 20/40 or better, larger CNV area, presence of GA in the study eye, thicker (≥425 μm) or thinner (≤325 μm) CRT, and presence of RPE elevation were associated with less VA gain • VA gains at 12 months (R^2=0.30) more predictive of 2 year VA gains than baseline VA (R^2=0.13) • Baseline non-foveal GA (OR: 2.86), larger CNV area (OR: 3.91, 4 DA vs ≤1 DA), and BVZ treatment (OR: 1.83) were associated with a VA loss of 15 or more letters by weeks 88 and 104 • Scars, GA, persistent IRF and SRHM were more common in eyes with VA loss	• Treatment group • # of treatments or visits
CATT[49]	RBZ or BVZ, prn or q1m	5	• Better baseline VA associated with better final VA but less VA gains • Smaller CNV lesion size presence of SRF associated with better final VA and better VA gains • Absence of RPE elevation (OR: 3.85), female gender (OR: 1.79) and BVZ use during first 2 years of treatment (OR: 1.62) more likely to gain ≥3 lines • Current (OR: 2.61) and former smokers (OR: 1.21) more likely to have final VA 20/200 or worse	• Various SNPs • Hypertension, diabetes • Treatment group • IRF • Various RT measures
HARBOR[48]	RBZ 0.5/2mg, prn or q1m	1	• Baseline predictors of better VA gains and/or percentage of 3-line gainers included lower VA, younger age, smaller CNV leakage area, smaller area of occult CNV, and presence of SRF • Baseline predictors of final VA better than 20/40 included higher VA, smaller CNV leakage area, and presence of SRF	• Gender, ethnicity, smoking status • Treatment regimen • CNV type • Other baseline morphologies

(*Continued*)

Table 1 (Continued).

Study	Treatment	Duration (Years)	Findings and Significant Factors	Non-Significant Factors
HARBOR[125,126]	RBZ 0.5/2mg, prn or q1m	2	• Those in the lowest quartile for BCVA-LLVA gap at baseline (≤ 17 letters) gained more VA than those in the highest quartile (≥ 33 letters) and were more likely to gain ≥ 15 letters as well as lose ≥15 letters • Patients who achieved peak BCVA after 6 months of treatment, had better VA gains and final VA than those who peaked during the first 6 months	• Treatment group • Baseline morphology
VIEW[47,97]	RBZ q4w, AFL q4w/q8w	1	• Younger age, lower VA and smaller CNV size more likely to have ≥15 letter VA gains • Older age, larger CNV size and pre-dominantly classic CNV lesions likely to lose ≥1 and ≥15 letter VA • Younger age, better baseline VA and smaller CNV size more likely to have final VA better than 20/40 • Older age, lower baseline VA, larger CNV size and predominantly classic CNV lesions more likely to have final VA worse than 20/200 • Higher baseline VA associated with less VA gain (−0.25 letters per letter increase) • IRF and PED at baseline associated with less VA gains (−2.77 and −1.88 letters respectively) • SRF at baseline associated with better VA gains (+2.11 letters)	• Gender • Ethnicity • Lesion location
EXCITE[99]	RBZ 0.3mg q1m or 0.3/ 0.5mg q3m	1	• Baseline IRF and infrequent treatment associated with less VA gains (−3.6 and −4.4 letters respectively) • PVD and SRF at baseline associated with better VA gains (+3.5 and +2.8 letters respectively) • Interaction between SRF, PVD and treatment frequency, where those without SRF and/or PVD at baseline requiring frequent dosing for better VA gains	• CRT, PED • RBZ dose
OSPREY[102]	Brolucizumab or AFL	1	• Decreased SHRM correlated with better VA gains • Improved ellipsoid zone integrity was associated with better VA gains	• Sub RPE volume
AREDS[111]	Any anti-VEGF	2	• Patients with final VA of 20/200 or worse were more likely to be non-White, have lower baseline VA, have macular atrophy or macular hemorrhage at baseline and fewer anti-VEGF injections in total	-

Abbreviations: AFL, aflibercept; RBZ, ranibizumab; BVZ, bevacizumab; PRN, pro re nata; VA, visual acuity; BCVA, best-corrected visual acuity; LLVA, low-luminance visual acuity; PDT, photodynamic therapy; CNV, choroidal neovascularization; RT, retinal thickness CRT, central retinal thickness; FFA, fundus fluorescein angiography; OCT, optical coherence tomography; GA, geographic atrophy; RPE, retinal pigment epithelium; RAP, retinal anomalous proliferation; SNP, single nucleotide polymorphism; IRF, intraretinal fluid; SRF, subretinal fluid; SHRM, subretinal hyper-reflective material; PED, pigment epithelial detachment; PVD, posterior vitreous detachment.

letter VA increases, however this was no longer significant at the 5-year follow-up[49] suggesting that age does not influence long-term outcomes. In real world studies, the relationship between age and visual outcome is not as consistent (Table 2). Though associations are found in larger observational cohorts,[28,29,50] suggesting this is due to smaller sample sizes and larger patient variations in combination with its relatively small effect size.

The effect of age may be influenced by other factors, with Yamashiro et al.[51] finding that age was associated with 12-month VA changes in typical nAMD patients, but not for those presenting with the polypoidal choroidal vasculopathy (PCV) variant of AMD. As age is a major risk factor for advanced AMD, its relationship with visual outcomes likely represents part of the natural history of the disease. These individuals should be considered more carefully during treatment.

Gender

There have been some associations between prevalent AMD and gender which may suggest that the course of treatment may differ between men and women.[52] However, despite gender being regularly included in risk factor analyses in clinical trials and retrospective studies, no significant associations have been found between gender and the visual response to anti-VEGF treatment in

Table 2 Summary from Major Real-World Studies Investigating Predictors of Visual Outcomes in Anti-VEGF Treated Patients

Author (Year)	Study	N (Eyes)	Treatment	Duration (Years)	Findings and Significant Factors	Non-Significant Factors
Holz (2016)[50]	AURA	1184	RBZ	2	• Higher baseline VA (−0.42 per letter) and older age (−0.28 per year) associated with less VA gains • Higher # of ophthalmoscopies and OCT's (+0.13 per observation) and higher total injections (+0.32 per injection) associated with better VA gains • Age, baseline VA and # of ophthalmoscopies and OCT associated with VA maintenance (<15 letters) • Age, baseline VA and # of injections associated with ≥15 letter gains	-
Fasler (2019)[118]	MEH	3357	AFL or RBZ	2	• Younger age, lower baseline VA and more injections were associated with higher VA gains	• Gender
Nguyen V (2019)[39]	FRB	2051	Any anti-VEGF	3	• Eyes with VA >70 letters by the 4th injection were more likely to have final VA >70 letters (OR: 9.8) • VA change at 4th injection correlated more strongly with final VA (R^2=0.37) than baseline VA (R^2=0.20)	-
Nguyen CL (2019)[37]	FRB	856	Any anti-VEGF	5	• Older age (OR: 1.33, >80 vs ≤80 years), lower total number of injections (OR: 0.97 per injection) and a higher proportion of visits with active CNV (OR: 1.97 upper vs lower quartile) were associated with sustained ≥15 letter VA loss • Older age (OR: 1.64, >80 vs ≤80 years), lower baseline VA (OR: 1.64, ≤70 vs > 70 letters), lower total number of injections (OR: 0.96 per injection) and a higher proportion of visits with active CNV (OR: 2.22 upper vs lower quartile) were associated with sustained ≥30 letter VA loss • Eyes with sustained VA loss were more likely to have haemorrhage, RPE tears, GA and subretinal fibrosis	• Lesion type • GLD
Fu (2020)[28]	MEH	7802	AFL or RBZ	~19 months	• Better baseline VA associated with an increased likelihood of achieving 20/40 (HR: 1.43 per 5 letters) • Higher # of injections associated with an increased likelihood of achieving 20/40 (HR: 1.12 per injection) • Older patients were less likely to achieve 20/40 (HR: 0.88 per 5 years) • Baseline VA, injection # and age also associated with the ability to maintain 20/40 or better • Those who had an incomplete loading phase less likely to achieve 20/40 (HR: 0.87) and more likely to have final VA 20/400 or worse • Those on RBZ more likely to have final VA 20/400 or worse	• Drug choice (for good visual outcomes) • Sex • Ethnicity
Ho (2020)[32]	IRIS	162,902	Any anti-VEGF	2	• Eyes with worse baseline VA had larger VA gains but worse final VA	-
Schroeder (2020)[127]	SMR	6142	Any anti-VEGF	2	• Those with worse baseline VA, worse-seeing eye treated, older age, larger CNV lesion size at baseline and treated by RBZ or BVZ monotherapy were more likely to have final VA of ≤ 35 letters	• Sex • Lesion type and location • Symptom duration

Abbreviations: AFL, aflibercept; RBZ, ranibizumab; BVZ, bevacizumab; VEGF, vascular endothelial growth factor; CNV, choroidal neovascularization; OCT, optical coherence tomography; GLD, greatest linear dimension; RPE, retinal pigment epithelium; GA, geographic atrophy; VA, visual acuity.

AMD, except in the 5 year follow-up of the CATT study,[49] where females were more likely to ≥15 letter VA gains than males (OR: 1.79).

Ethnicity

The influence of ethnicity is inconclusive as few studies have been performed in diverse populations, however most large studies have found no direct relationship between ethnicity and visual outcome.[28,48] Outcomes related to ethnic background may be tied to CNV lesion sub-type due to the higher prevalence of PCV seen within Black and Asian populations compared to Caucasian populations.[53–55] PCV has been found to be associated with poor anatomic responses to ranibizumab treatment[54,56] and is likely to result in worse visual outcomes in the longer term. Differences in genetic susceptibilities may underlie ethnic differences in treatment outcomes.

Systemic Disease and Social Habits

There are several well-known systemic diseases and behavioral risk factors for AMD such as cardiovascular disease, smoking and nutrition.[57] van Asten et al[36] found that patients with a history of diabetes mellitus were 2.1x more likely to have a non-response to treatment, however no associations were found for cardiovascular disease, smoking status or body mass index. Piermarocchi et al.[58] reported that those with hypertension as well as current and former smokers gained less VA (−3.86 and −4 letters respectively) over 1 year of ranibizumab treatment. Similarly, Lee et al.[59] found that current smokers were more likely have poor VA improvement (VA gain below group median) after ranibizumab treatment (OR: 7.5). Meanwhile, the 5-year follow-up of CATT found that those who were current smokers at baseline were more likely to have worse final VA (OR for VA <20/200: 2.61),[49] suggesting that smoking may exert long-term detrimental effects on VA. In contrast to these findings, a larger majority of studies have failed to find associations.[48,60–66] However, while their role in determining treatment response is unclear, these risk factors remain as strong modifiable risk factors for disease prevention and the improvement of general health.

Genetics

Like other patient factors, genetic polymorphisms that have been strongly associated with the development of nAMD have also been investigated for their role in determining treatment response. Initial investigations were done into AMD risk alleles such as single nucleotide polymorphisms (SNPs) involving the CFH & ARMS2 genes. Analysis of data from the CATT clinical trials was unable to find any associations between SNPs of CFH, ARMS2, HTRA1 and C3 with treatment response across drugs or dosing regimens.[67] Similar results were obtained from analyzing data from the IVAN trials,[68] which also could not find associations in SNPs of CFH, FZD4, ARMS2 and HTRA1. However for the CFH gene, two meta-analyses which have included the CATT and IVAN studies,[69,70] have confirmed that the Y402H polymorphism of CFH was in fact associated with treatment response, with those carrying the minor allele having reduced VA gains. This may be linked to ethnic variations, with subgroup analyses in both papers finding the relationship occurring in Caucasian populations and not East Asians, however it may be due to the significantly lower incidence rates of CFH polymorphisms in Asians and the limited number of Asian studies included. On the other hand, two meta-analyses of studies investigating polymorphisms of ARMS2 have found that the minor allele of A69S was associated better treatment responses to anti-VEGF among East Asians;[71,72] though not all studies included used visual acuity to define treatment response. For HTRA1 gene, a meta-analysis of five studies found no associations between its polymorphisms and treatment response.[73]

Attention has also turned to investigate SNPS involving VEGF, such as VEGF-A & VEGFR2/KDR polymorphisms. However, there have been many conflicting results with large studies failing to find associations.[74,75] For VEGF-A, Lazzeri et al[76] found that SNP rs699947 was related to an early visual response following 3 months of RBZ treatment, with patients carrying the minor allele experiencing positive VA gains (+6.3–7.4 letters) compared to those without, who lost VA following treatment (−1.8 letters). However, Park et al[77] and Cruz-Gonzalez et al78 have both found that the minor allele of rs699947 to be associated with worse visual outcomes after 5 and 12 months respectively. Individuals carrying the minor allele of rs833061 were also more likely to gain VA (≥5 letters) after 1 year of RBZ treatment (OR: 1.62).[78] For VEGFR-2, Hermann et al64 found that SNPs rs4576072 and rs6828477 were independent predictors for VA gains, with carriers of three minor alleles experiencing positive VA gains (~13 letters) compared to those without any minor alleles after 1 year of RBZ treatment. However, the larger CATT and IVAN studies failed to find

associations between SNPS of VEGF-A and VEGFR-2 and VA response.[74,79]

In 2017, 8 polymorphisms of VEGF-A (rs699947, rs699946, rs833069, rs833061, rs2146323, rs1413711, rs2010963 and rs1570360) and 1 polymorphism of VEGFR-2 (rs2071559) were investigated by Wu et al,[80] in a meta-analysis of 8 studies, which found anti-VEGF treatment to be more effective in patients homozygous for the minor allele of VEGF-A rs833061. While this meta-analysis also included studies which assessed anatomic outcomes, sub-analysis of studies describing purely visual outcomes found stronger associations, with OR's for a positive visual response ranging from 2.6 to 3.8 across the genotypic models.

VEGF isoform and receptor polymorphisms have the potential to result in differences in treatment responses between anti-VEGF medications, as aflibercept has additional binding capabilities to PGF and VEGF-B compared to bevacizumab and ranibizumab which only target isoforms of VEGF-A. A Phase 4 trial of aflibercept[81] found strong associations with polymorphisms of VEGF-B (rs12366035) and C5 (rs25681), with those homozygous for their minor alleles more likely to have ≥15 letter gains (OR: 217 and 19.7, respectively). Smaller associations were also found for polymorphisms within CX3CR1, CETP, IL6 and CCL2. These results are promising as it suggests that responses to different anti-VEGF agents may be tied to separate gene polymorphisms.

Apart from selected targeted studies, broader approaches using genome-wide association studies have the allowed identification of other candidate genes associated with treatment response such as CTGF,[82] OR52B4,[83] and CCT3,[84] however a lack of association with previously investigated genes have also raised further uncertainty.

While the role of pharmacogenomics is promising, the prevalence of predictive genes must be common enough and their effects must be strong enough to warrant routine genetic testing in a clinical setting. Despite the availability of several meta-analyses, more individual studies are required in order to further investigate the effects of less commonly assessed SNPs, treatment-related effects and ethnic contributions. Furthermore, external clinical validation of the effects of identified SNPs are required through prospective trials to confirm their roles.

Anatomic Factors

Given the expanded role of imaging in the diagnosis and management of nAMD, considerable efforts have been made to identify potential anatomic characteristics that may predict visual outcomes. Although initially predominantly examination or angiographically based, the expanded role of OCT has meant that many of these factors are now predominantly assessed via OCT imaging. Broadly speaking, factors can be predictive from baseline or during treatment, and both are discussed below.

Lesion Type and Lesion Size

In terms of VA gains, no significant difference has been found between the responsiveness of classic or occult lesions to anti-VEGF agents in large RCTs (Table 1). However, CATT did show that those with classic lesions had lower final VA at 1 year compared to occult lesions (64.2 vs 70.4 letters) yet were more likely to gain ≥15 letters on univariate analysis,[46] and VIEW 1/2 showed that those with classic lesions were more likely to have a final VA worse than 20/200 at 1 year but were more likely to lose ≥15 letters instead.[47] Since those with classic lesions more commonly present with worse VA in these studies, we would expect this to translate into better overall VA gains due to the effects of baseline VA. However, the lack of differences suggests that apart from a small group of good responders, those with classic lesions perform relatively worse compared to other subtypes.

Retinal Angiomatous Proliferation (RAP) lesions have also been associated with increased VA gains after anti-VEGF therapy compared to other lesion types in both the CATT and VIEW trials.[79] These benefits are most pronounced early in therapy (during the 1st year), with differences in visual outcomes between RAP lesions and other angiographic lesion types becoming non-significant after 2 years of therapy.[85] However, RAP lesions have also been linked to higher rates of geographic atrophy (GA), notably in the CATT study,[85] and it remains to be seen if this has any effect on RAP lesions as a predictor of vision with even longer follow-up times, given the role of atrophy in long-term visual decline, as discussed below.

Larger baseline lesion size has been consistently associated with worse VA gain in multiple large RCT's, including the MARINA,[26] ANCHOR,[86] CATT[46,87] and VIEW studies.[88] In the CATT, compared to those with a lesion size ≤2.54 mm^2, patients with a lesion size >10.2 mm^2 experienced less VA gain (+4.2 vs +8.7 letters), had a lower

proportion of ≥15 letter gainers (23.8% vs 30.1%) and had worse final VA (64.5 vs 69.9 letters) after 1 year of treatment.[46]

Retinal Thickness

OCT measured retinal thickness (RT) is a commonly assessed clinical trial outcome and has been used as a criteria for treatment in some trials including HAWK/HARRIER,[89] and it is important to determine in each instance what is meant by retinal RT. Frequently used terms such as central retinal thickness (CRT) or central macular thickness (CMT) in some publications may also include subretinal fluid (SRF) in this measurement, and in some case also include pigment epithelial detachment (PED) height, although here we refer to thickness of the retina alone, excluding SRF or PED. In the CATT, thinner (<120μm, 57.7 letters) or thicker (>212, 64.0 letters) retinal thickness (not including SRF or PED) had worse final VA than those between those two ranges (12–212μm, 72.0 letters) after 2 years of therapy.[90] Similarly, the PrONTO study also found a correlation between change in RT and VA change at 3 and 12 months,[91] suggesting improved retinal thickness is a predictor of greater VA gain.

There is also recent evidence that fluctuations in RT may be a poor prognostic factor. Retrospective analysis of pooled data from the CATT and IVAN trials showed that greater fluctuations in RT were associated with worse VA gains after 2 years, with individuals in the highest quartile for RT variations experiencing and average of 6.27 less letter gain than those who had the least variation in RT (95% CI: −8.45 to −4.0). Individuals with higher variations in RT were also more likely to develop fibrosis and/or GA.[92]

Retinal Exudation – Intraretinal Fluid (IRF), Subretinal Fluid (SRF) and Subretinal Hyperreflective Material (SHRM)

Both IRF and SRF have been studied extensively as markers of disease activity. The presence of IRF has been demonstrated to be associated with worse vision both at baseline and during treatment in large clinical trials including both CATT and VIEW,[27,90] as well as at baseline in the EXCITE study.[93] In VIEW,[44] those with IRF gained 3.85 less letters after 1 year of aflibercept treatment. Recent analysis has also suggested that the volume of IRF is of importance, with increased IRF volume associated with progressively worse BCVA change in post-hoc analysis of the HARBOR trial,[94] as well as in post-hoc analysis of the FLUID trial.[95] Location of IRF was also important in the FLUID analysis, with IRF in the central 1mm significantly associated with reduced VA gain, but IRF in the surrounding 1–6mm not associated with VA change.[95]

The role of SRF, in contrast, is less clear. Analysis of CATT, VIEW and HARBOR has shown that SRF at baseline may be predictive of better visual outcomes,[48,90,94,96,97] and that residual SRF may be associated with larger VA improvement at 24 months in the HARBOR trial. Both the EXCITE and FLUID trials have shown that individuals with SRF could tolerate extended treatment intervals without adversely affecting visual outcomes.[98,99] However, post-hoc analysis of the FLUID trial has shown that increasing SRF volume within the central 1–6mm (but not the central 1mm) of the retina is associated with increasingly reduced VA (−0.2 letters per 100nL).[95] Similarly, post-hoc analysis of the HAWK and HARRIER trials showed that eyes with greater SRF volume at the end of dose loading (12 weeks) had lower VA gain from weeks 12 to 96 than those with lower SRF volume, suggesting that the effect of SRF as a prognostic factor may in part be dependent on the volume of SRF present.[100]

SHRM is an OCT-detectable form of exudation that manifests as hyperreflectivity between the RPE and the retina. The presence of SHRM, particularly at the foveal center, has been associated with significantly worse VA in the CATT study at year 2 (73.5 vs 63.9 letters),[101] as well as being a predictor of poor final VA at year 5.[87] Decreased SHRM volume correlated with improved vision in post-hoc sub-analysis of the OSPREY trial,[102] suggesting that SHRM is an important marker of outcomes in neovascular AMD.

The effect of changes in retinal exudation volume highlights the importance of ongoing monitoring and comparison of retinal imaging across the course of nAMD treatment, as worsening of exudation volumes may result in worse visual outcomes. This may require alterations to management to more effectively control.

Pigment Epithelial Detachments

The presence of PED has been associated with worse baseline vision in nAMD, as well as reduced VA gain in some series such as the CATT study,[46] although this was not seen in the HARBOR study.[103] Response of a PED to therapy has not been associated with visual outcomes in multiple studies,

including retrospective analysis of the HARBOR and VIEW trials,[97,103,104] although post-hoc analysis of the VIEW study showed that patients with a PED at baseline who developed IRF during follow up had the lowest VA gains of any combination of anatomic parameters.[27]

Based on these findings, treatment aimed at eliminating or reducing the size of a PED is currently not recommended,[105] although ongoing monitoring and treatment of any signs of retinal exudation, particularly IRF, is encouraged, given the poorer prognosis of IRF in combination with PED.

RPE Atrophy

Long-term follow-up of a number of clinical trial cohorts has shown that atrophy development is a major cause of long-term visual decline. Five-year outcomes of the CATT cohort showed that the development of atrophy was a significant reason for visual decline in this cohort (mean final VA 62 letters for no foveal pathology vs 53 for GA),[87] and foveal GA at year 2 was associated with worse vision at year 5. The presence of nonfoveal GA at baseline was a risk factor for visual acuity loss at 2 years in the CATT,[106] suggesting that GA progression is an important reason for vision loss even during the first few years of anti-VEGF therapy. Similarly, post-hoc analysis of the subset of the Age-Related Eye Diseases Study 2 (AREDS2) cohort who had neovascular AMD identified atrophy as being the cause of 60% of cases of poor vision (<20/200).[106] Pooled analysis of the ANCHOR, MARINA and HORZION studies also showed that macular atrophy progression was the major cause of visual decline 7 years after commencing treatment,[107] implying that increasing central atrophy is a poor prognostic factor.

Hemorrhage and Subretinal Fibrosis

The presence of clinical hemorrhage by itself has not been associated with worse visual outcomes, with the CATT study showing that lesions composed of >50% hemorrhage had similar VA gains at 2 years compared to those that were not.[108] Hemorrhage, however, needs to be clearly defined, as the presence of sub-retinal hemorrhage can significantly impair vision, particularly those of larger sizes (>1DD) and those located directly below the fovea, and large, foveal sub-macular hemorrhage is associated with poor visual outcomes, particularly if left untreated.[109]

The presence of scar has also been associated with worse visual outcomes in trials, notably the CATT.[87,90] Interestingly, larger hemorrhage (>1DD) was a risk factor for scar development in post-hoc analysis of the CATT, suggesting that part of the poor visual prognosis of these large hemorrhagic lesions may relate to the risk of scarring.[110] Post-hoc analysis of the AREDS2 cohort treated for neovascular AMD also identified fibrosis as being responsible for 40% of the cases of poor vision (<20/200),[111] implying that preventing scar formation remains an important goal in preserving vision.

Treatment Regime and Visual Outcomes

In combination with patient-related factors, decisions made upon and throughout the course of treatment may also influence visual outcomes. Initially, anti-VEGF was approved for fixed dosing every 4 weeks, and this was later extended to 8 weeks as new anti-VEGF molecules with higher binding affinity were discovered.[10,11] In combination with the CATT[14] and IVAN[112] studies, which demonstrated that dosing via a pro re nata (PRN) regimen provided similar visual outcomes, more flexible dosing regimens have been adopted by treating practitioners which has also included the treat and extend (TREX) regime. Under a PRN regimen, patients typically are followed on a monthly basis however at each interval, the decision to treat is guided by disease activity, determined by the presence or absence of exudation. Meanwhile, the TREX regime is considered a proactive approach whereby patients who achieve an exudative-free status on monthly dosing, have their review and treatment interval extended, typically in either 1- or 2-week increments. Upon the presence of exudation, treatment intervals are then reduced, with the goal of maintaining an exudative-free status under the longest possible dosing interval. By design, TREX offers patients with better anatomical outcomes (as there is less recurrence of exudation) and a higher level of individualization, whilst reducing the burden associated with frequent clinical visits. Both the TREX-AMD[113] and CANTREAT[114] studies demonstrated that the TREX regime provided similar visual outcomes to fixed monthly dosing while requiring less injections.

Between PRN and TREX dosing, a systematic review of 70 studies found TREX to provide larger VA gains compared to PRN over a 12-month period (+10.4 vs +5.4 letters respectively), though they received a higher number of injections (8.1 vs 5.6 injections).[115] In the third year of the TREX-AMD randomized trial, those who spent the first 2 years on TREX and switched to PRN for the final year, had significantly worse visual

outcomes compared to those who remained on a TREX regime for the remainder of the study.[116] In a 4-year study, Spooner et al compared progression rates of macular atrophy among 264 eyes treated with anti-VEGF using either PRN or TREX regimes.[117] They found that VA gains among the TREX group were higher compared to the PRN group after 1 year of treatment (+2.7 vs +0.3 letters respectively), however these gains were lost after 4 years (+0.9 vs −0.5 letters, respectively). More long-term prospective data is needed between these two regimes. As data from real-world studies suggest that patients receive fewer injections than those studied in clinical trials, the benefit seen from a TREX regime likely comes from its proactive nature, as a higher number of injections are also associated with better visual outcomes.[28,37,50,118]

Table 3 Summary of Predictive Factors, Their Effects on Visual Outcomes Following Anti-VEGF Treatment and the Level of Supporting Evidence Within the Literature

Baseline Factors	Level of Evidence (Strong, Insufficient or Mixed)	Relationship with VA After Anti-VEGF Treatment
Functional		
Visual acuity	Strong	• Patients presenting with lower VA gain more VA during treatment but are more likely to respond poorly • Those with good initial VA are more likely to maintain good final VA in both the short and long term
Demographic		
Gender	Insufficient	-
Age	Strong	• Older age is associated with worse visual outcomes
Ethnicity	Insufficient	-
Systemic disease	Insufficient	-
Social habits	Mixed	• Current and previous smoking status may be associated with worse visual outcomes
Genetics	Mixed	• The presence of certain AMD risk alleles (CFH & ARMS2) and VEGF polymorphisms may influence visual response
Anatomic		
CNV lesion type	Mixed	• Classic & pre-dominantly classic lesions may be associated with worse visual outcomes due to worse presenting VA.
CNV lesion size	Strong	• A larger lesion size is associated with lower VA gains
Retinal thickness	Mixed	• Markedly thinner or thicker retinas associated with worse VA gain • Fluctuations in thickness are associated with less VA gain and higher risk of atrophy
Retinal exudation	Mixed	• IRF (particularly sub-foveal) associated with worse visual outcomes • SRF at baseline associated with better VA gains, residual SRF associated with poorer outcomes
Pigment epithelial detachments	Mixed	• Presence of PED at baseline associated with worse visual outcomes • Response of PED not associated with VA gain
Atrophy	Mixed	• Presence of macular atrophy associated with worse long-term VA gain
Hemorrhage	Mixed	• Sub-retinal hemorrhage may lead to worse visual outcomes through scar formation

Abbreviations: AMD, age-related macular degeneration; VA, visual acuity; VEGF, vascular endothelial growth factor; IRF, intraretinal fluid; SRF, subretinal fluid; PED, pigment epithelial detachment.

Multivariate Predictive Modelling

Using a combination of OCT biomarkers and VA over the first 3 months of treatment from HARBOR, Schmidt-Erfurth et al[119] used machine learning algorithms to predict 1 year VA outcomes with an accuracy of 71% and an error margin of 8.6 letters. A similar attempt using both VA and OCT data from electronic medical records by Rohm et al,[120] provided comparable levels of accuracy, with errors of 5.5 and 8 letters for predicting 3 and 12 month VA respectively. The incorporation of more predictive variables such as genetic data as well as the examination of larger datasets may provide more precise models in the future. However, because preserving vision is the primary goal of anti-VEGF therapy, rather than quantifying vision, it may be more valuable to develop models which identify non-responders, as this could trigger the earlier consideration of alternative treatment routes such as the switching of anti-VEGF drugs or additional therapy.

Conclusion

Several factors have been found to influence a patient's visual outcome during nAMD treatment (Table 3). However, they play a limited role in the current scope of practice as they do not have the precision in determining whether an individual will respond favorably or not to treatment, nor is there sufficient evidence to guide treatment choices based on individual factors, as the effects of these factors are not associated with certain treatment agents or regimens.

Nevertheless, there are several clinical aspects that can be drawn from these findings. Considering that AMD is a disease of senescence, the strong associations seen for VA, age and lesion size suggests that early detection and timely management is required to achieve optimal visual outcomes. Alongside treatment, exacerbating factors; notably smoking; should also be reduced or ceased if possible, given their possible association with worse visual outcomes, and with AMD progression in general.

Currently, individualized treatment is achieved by using flexible dosing strategies such as PRN or TREX. While these strategies do not necessarily offer superior visual outcomes, they may indirectly improve patient's quality of life and reduce their disease burden through economic relief. These OCT-guided approaches may be further optimized from knowledge of anatomical predictors, as it is suggested that the presence of IRF should be more aggressively controlled in comparison to SRF. While this provides room for further flexibility and individualization during treatment, it is essential that patients remain closely monitored for anatomical changes which may subsequently affect their visual trajectory. Proactive approaches such as TREX appear to be an effective middle-ground.

In the current treatment landscape, currently available agents have been compared based on non-inferiority of visual outcomes. With emerging anti-VEGF agents such as brolucizumab offering longer treatment intervals and greater anatomic outcomes,[121] the consideration of additional markers of efficacy may also be required during treatment decision making. The release of newer therapeutics in combination with further knowledge into predictive factors one day may allow the personalization of more effective treatments for individuals with specific baseline characteristics, disease subtypes or genetic susceptibilities.

Disclosure

A. Chang is a consultant for Allergan, Bayer, Novartis, and Roche. The authors report no other conflicts of interest in this work.

References

1. Flaxman SR, Bourne RR, Resnikoff S, et al. Global causes of blindness and distance vision impairment 1990–2020: a systematic review and meta-analysis. *Lancet Global Health*. 2017;5(12):e1221.
2. Wong WL, Su X, Li X, et al. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. *Lancet Global Health*. 2014;2(2):e106. doi:10.1016/S2214-109X(13)70145-1
3. Ferris FL, Fine SL, Hyman L. Age-related macular degeneration and blindness due to neovascular maculopathy. *Arch Ophthalmol*. 1984;102(11):1640–1642. doi:10.1001/archopht.1984.01040031330019
4. Kvanta A, Algvere P, Berglin L, Seregard S. Subfoveal fibrovascular membranes in age-related macular degeneration express vascular endothelial growth factor. *Invest Ophthalmol Vis Sci*. 1996;37(9):1929–1934.
5. Shweiki D, Itin A, Soffer D, Keshet E. Vascular endothelial growth factor induced by hypoxia may mediate hypoxia-initiated angiogenesis. *Nature*. 1992;359(6398):843–845. doi:10.1038/359843a0
6. Spilsbury K, Garrett KL, Shen W-Y, Constable IJ, Rakoczy PE. Overexpression of vascular endothelial growth factor (VEGF) in the retinal pigment epithelium leads to the development of choroidal neovascularization. *Am J Pathol*. 2000;157(1):135–144. doi:10.1016/S0002-9440(10)64525-7
7. Finger RP, Guymer RH, Gillies MC, Keeffe JE. The impact of anti–vascular endothelial growth factor treatment on quality of life in neovascular age-related macular degeneration. *Ophthalmology*. 2014;121(6):1246–1251. doi:10.1016/j.ophtha.2013.12.032
8. Rosenfeld PJ, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration. *N Eng J Med*. 2006;355(14):1419–1431. doi:10.1056/NEJMoa054481
9. Brown DM, Kaiser PK, Michels M, et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Eng J Med*. 2006;355(14):1432–1444. doi:10.1056/NEJMoa062655
10. Heier JS, Brown DM, Chong V, et al. Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. *Ophthalmology*. 2012;119(12):2537–2548. doi:10.1016/j.ophtha.2012.09.006

11. Schmidt-Erfurth U, Kaiser PK, Korobelnik J-F, et al. Intravitreal aflibercept injection for neovascular age-related macular degeneration: ninety-six–week results of the VIEW studies. *Ophthalmology*. 2014;121(1):193–201. doi:10.1016/j.ophtha.2013.08.011
12. Dugel PU, Koh A, Ogura Y, et al. HAWK and HARRIER: phase 3, multicenter, randomized, double-masked trials of brolucizumab for neovascular age-related macular degeneration. *Ophthalmology*. 2020;127(1):72–84. doi:10.1016/j.ophtha.2019.04.017
13. Martin DF, Maguire MG, Fine SL, et al. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. *Ophthalmology*. 2012;119(7):1388–1398. doi:10.1016/j.ophtha.2012.03.053
14. Group CR. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. *N Eng j Med*. 2011;364(20):1897–1908. doi:10.1056/NEJMoa1102673
15. Group ToA-RMDwPTS. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin. One-year results of 2 randomized clinical trials-TAP report 1. *Arch Ophthalmol*. 1999;117:1329–1345. doi:10.1001/archopht.117.10.1329
16. Group MPS. Laser photocoagulation of subfoveal neovascular lesions of age-related macular degeneration. Updated findings from two clinical trials. *Arch Ophthalmol*. 1993;111:1200–1209. doi:10.1001/archopht.1993.01090090052019
17. Bloch SB, Larsen M, Munch IC. Incidence of legal blindness from age-related macular degeneration in Denmark: year 2000 to 2010. *Am J Ophthalmol*. 2012;153(2):209–213. doi:10.1016/j.ajo.2011.10.016
18. Zarranz-Ventura J, Liew G, Johnston RL, et al. The neovascular age-related macular degeneration database: report 2: incidence, management, and visual outcomes of second treated eyes. *Ophthalmology*. 2014;121(10):1966–1975. doi:10.1016/j.ophtha.2014.04.026
19. Chong V. Ranibizumab for the treatment of wet AMD: a summary of real-world studies. *Eye*. 2016;30(2):270–286. doi:10.1038/eye.2015.217
20. Holz FG, Figueroa MS, Bandello F, et al. Ranibizumab treatment in treatment-naive neovascular age-related macular degeneration: results from LUMINOUS, a global real-world study. *Retina*. 2020;40(9):1673. doi:10.1097/IAE.0000000000002670
21. Rofagha S, Bhisitkul RB, Boyer DS, Sadda SR, Zhang K, Group S-US. Seven-year outcomes in ranibizumab-treated patients in ANCHOR, MARINA, and HORIZON: a multicenter cohort study (SEVEN-UP). *Ophthalmology*. 2013;120(11):2292–2299. doi:10.1016/j.ophtha.2013.03.046
22. Maguire MG, Martin DF, Ying G-S, et al. Five-year outcomes with anti–vascular endothelial growth factor treatment of neovascular age-related macular degeneration: the comparison of age-related macular degeneration treatments trials. *Ophthalmology*. 2016;123(8):1751–1761. doi:10.1016/j.ophtha.2016.03.045
23. Chandra S, Arpa C, Menon D, et al. Ten-year outcomes of antivascular endothelial growth factor therapy in neovascular age-related macular degeneration. *Eye*. 2020;34(10):1888–1896. doi:10.1038/s41433-020-0764-9
24. Finger RP, Wickremasinghe SS, Baird PN, Guymer RH. Predictors of anti-VEGF treatment response in neovascular age-related macular degeneration. *Surv Ophthalmol*. 2014;59(1):1–18. doi:10.1016/j.survophthal.2013.03.009
25. Gill CR, Hewitt CE, Lightfoot T, Gale RP. Demographic and clinical factors that influence the visual response to anti-vascular endothelial growth factor therapy in patients with neovascular age-related macular degeneration: a systematic review. *Ophthalmol Ther*. 2020;9(4):725–737. doi:10.1007/s40123-020-00288-0
26. Boyer DS, Antoszyk AN, Awh CC, et al. Subgroup analysis of the MARINA study of ranibizumab in neovascular age-related macular degeneration. *Ophthalmology*. 2007;114(2):246–252. doi:10.1016/j.ophtha.2006.10.045
27. Schmidt-Erfurth U, Waldstein SM, Deak -G-G, Kundi M, Simader C. Pigment epithelial detachment followed by retinal cystoid degeneration leads to vision loss in treatment of neovascular age-related macular degeneration. *Ophthalmology*. 2015;122(4):822–832. doi:10.1016/j.ophtha.2014.11.017
28. Fu DJ, Keenan TD, Faes L, et al. Insights from survival analyses during 12 years of anti-vascular endothelial growth factor therapy for neovascular age-related macular degeneration. *JAMA Ophthalmol*. 2020;139:57.
29. Westborg I, Albrecht S, Rosso A. Risk for low visual acuity after 1 and 2 years of treatment with ranibizumab or bevacizumab for patients with neovascular age-related macular degeneration. *Retina*. 2017;37(11):2035–2046. doi:10.1097/IAE.0000000000001431
30. Gillies M, Arnold J, Bhandari S, et al. Ten-year treatment outcomes of neovascular age-related macular degeneration from two regions. *Am J Ophthalmol*. 2020;210:116–124. doi:10.1016/j.ajo.2019.10.007
31. Pedrosa AC, Sousa T, Pinheiro-Costa J, et al. Treatment of neovascular age-related macular degeneration with anti-VEGF agents: predictive factors of long-term visual outcomes. *J Ophthalmol*. 2017;2017:4263017. doi:10.1155/2017/4263017
32. Ho AC, Kleinman DM, Lum FC, et al. Baseline visual acuity at wet AMD diagnosis predicts long-term vision outcomes: an analysis of the iris registry. *Ophthalmic Surg Lasers Imaging Retina*. 2020;51(11):633–639. doi:10.3928/23258160-20201104-05
33. Brynskov T, Munch IC, Larsen TM, Erngaard L, Sørensen TL. Real-world 10-year experiences with intravitreal treatment with ranibizumab and aflibercept for neovascular age-related macular degeneration. *Acta Ophthalmol*. 2020;98(2):132–138. doi:10.1111/aos.14183
34. Arpa C, Khalid H, Chandra S. et al. Ten-year survival trends of neovascular age-related macular degeneration at first presentation. *Br J Ophthalmol*;2020. bjophthalmol-2020-317161. doi:10.1136/bjophthalmol-2020-317161
35. Spooner K, Fraser-Bell S, Hong T, Phan L, Wong JG, Chang A. Long-term anti–vascular endothelial growth factor treatment for neovascular age-related macular degeneration: the LATAR study: report 1: ten-year, real-world outcomes. *Ophthalmol Retina*. 2020;5:511.
36. van Asten F, Rovers MM, Lechanteur YT, et al. Predicting non-response to ranibizumab in patients with neovascular age-related macular degeneration. *Ophthalmic Epidemiol*. 2014;21(6):347–355. doi:10.3109/09286586.2014.949010
37. Nguyen CL, Gillies MC, Nguyen V, et al. Characterization of poor visual outcomes of neovascular age-related macular degeneration treated with anti–vascular endothelial growth factor agents. *Ophthalmology*. 2019;126(5):735–742. doi:10.1016/j.ophtha.2018.11.036
38. Fulcher C, Hazel CA, Pacey I, Ali H, Ghanchi FD. Predicting visual outcomes in patients treated with aflibercept for neovascular age-related macular degeneration: data from a real-world clinical setting. *Eur J Ophthalmol*. 2020;30(3):543–549. doi:10.1177/1120672119839299
39. Nguyen V, Daien V, Guymer R, et al. Projection of long-term visual acuity outcomes based on initial treatment response in neovascular age-related macular degeneration. *Ophthalmology*. 2019;126(1):64–74. doi:10.1016/j.ophtha.2018.08.023
40. Ying GS, Maguire MG, Daniel E, et al. Association of baseline characteristics and early vision response with 2-year vision outcomes in the comparison of AMD treatments trials (CATT). *Ophthalmology*. 2015;122(12):2523–2531.e2521. doi:10.1016/j.ophtha.2015.08.015

41. Canan H, Sızmaz S, Altan-Yaycıoğlu R, Sarıtürk C, Yılmaz G. Visual outcome of intravitreal ranibizumab for exudative age-related macular degeneration: timing and prognosis. *Clin Interv Aging*. 2014;9:141–145. doi:10.2147/CIA.S56863
42. Lim JH, Wickremasinghe SS, Xie J, et al. Delay to treatment and visual outcomes in patients treated with anti-vascular endothelial growth factor for age-related macular degeneration. *Am J Ophthalmol*. 2012;153(4):678–686. doi:10.1016/j.ajo.2011.09.013
43. Fang K, Tian J, Qing X, et al. Predictors of visual response to intravitreal bevacizumab for treatment of neovascular age-related macular degeneration. *J Ophthalmol*. 2013;2013:1–9. doi:10.1155/2013/676049
44. Kim JH, Chang YS, Kim JW, Kim CG, Yoo SJ, Cho HJ. Intravitreal anti-vascular endothelial growth factor for submacular hemorrhage from choroidal neovascularization. *Ophthalmology*. 2014;121(4):926–935. doi:10.1016/j.ophtha.2013.11.004
45. Kaiser PK, Brown DM, Zhang K, et al. Ranibizumab for predominantly classic neovascular age-related macular degeneration: subgroup analysis of first-year ANCHOR results. *Am J Ophthalmol*. 2007;144(6):850–857. doi:10.1016/j.ajo.2007.08.012
46. Ying G-S, Huang J, Maguire MG, et al. Baseline predictors for one-year visual outcomes with ranibizumab or bevacizumab for neovascular age-related macular degeneration. *Ophthalmology*. 2013;120(1):122–129. doi:10.1016/j.ophtha.2012.07.042
47. Lanzetta P, Cruess AF, Cohen SY, et al. Predictors of visual outcomes in patients with neovascular age-related macular degeneration treated with anti-vascular endothelial growth factor therapy: post hoc analysis of the VIEW studies. *Acta Ophthalmol*. 2018;96(8):e911. doi:10.1111/aos.13751
48. Regillo CD, Busbee BG, Ho AC, Ding B, Haskova Z. Baseline predictors of 12-month treatment response to ranibizumab in patients with wet age-related macular degeneration. *Am J Ophthalmol*. 2015;160(5):1014–1023.e1012. doi:10.1016/j.ajo.2015.07.034
49. Ying G-S, Maguire MG, Pan W, et al. Baseline predictors for five-year visual acuity outcomes in the comparison of AMD treatment trials. *Ophthalmol Retina*. 2018;2(6):525–530. doi:10.1016/j.oret.2017.10.003
50. Holz FG, Tadayoni R, Beatty S, et al. Key drivers of visual acuity gains in neovascular age-related macular degeneration in real life: findings from the AURA study. *Br J Ophthalmol*. 2016;100(12):1623–1628. doi:10.1136/bjophthalmol-2015-308166
51. Yamashiro K, Tomita K, Tsujikawa A, et al. Factors associated with the response of age-related macular degeneration to intravitreal ranibizumab treatment. *Am J Ophthalmol*. 2012;154(1):125–136. doi:10.1016/j.ajo.2012.01.010
52. Kawasaki R, Yasuda M, Song SJ, et al. The prevalence of age-related macular degeneration in Asians: a systematic review and meta-analysis. *Ophthalmology*. 2010;117(5):921–927. doi:10.1016/j.ophtha.2009.10.007
53. Kwok A, Lai T, Chan C, Neoh E, Lam D. Polypoidal choroidal vasculopathy in Chinese patients. *Br J Ophthalmol*. 2002;86(8):892–897. doi:10.1136/bjo.86.8.892
54. Kokame GT, deCarlo TE, Kaneko KN, Omizo JN, Lian R. Anti–vascular endothelial growth factor resistance in exudative macular degeneration and polypoidal choroidal vasculopathy. *Ophthalmol Retina*. 2019;3(9):744–752. doi:10.1016/j.oret.2019.04.018
55. Lorentzen TD, Subhi Y, Sørensen TL. Prevalence of polypoidal choroidal vasculopathy in white patients with exudative age-related macular degeneration: systematic review and meta-analysis. *Retina*. 2018;38(12):2363–2371. doi:10.1097/IAE.0000000000001872
56. Hatz K, Prünte C. Polypoidal choroidal vasculopathy in Caucasian patients with presumed neovascular age-related macular degeneration and poor ranibizumab response. *Br J Ophthalmol*. 2014;98(2):188–194. doi:10.1136/bjophthalmol-2013-303444
57. Lim LS, Mitchell P, Seddon JM, Holz FG, Wong TY. Age-related macular degeneration. *Lancet*. 2012;379(9827):1728–1738. doi:10.1016/S0140-6736(12)60282-7
58. Piermarocchi S, Miotto S, Colavito D, Leon A, Segato T. Combined effects of genetic and non-genetic risk factors affect response to ranibizumab in exudative age-related macular degeneration. *Acta Ophthalmol*. 2015;93(6):e451. doi:10.1111/aos.12587
59. Lee S, Song SJ, Yu HG. Current smoking is associated with a poor visual acuity improvement after intravitreal ranibizumab therapy in patients with exudative age-related macular degeneration. *J Korean Med Sci*. 2013;28(5):769. doi:10.3346/jkms.2013.28.5.769
60. Kang S, Roh YJ. One-year results of intravitreal ranibizumab for neovascular age-related macular degeneration and clinical responses of various subgroups. *Jpn J Ophthalmol*. 2009;53(4):389–395. doi:10.1007/s10384-009-0670-y
61. Singh RP, Fu EX, Smith SD, Williams DR, Kaiser PK. Predictive factors of visual and anatomical outcome after intravitreal bevacizumab treatment of neovascular age-related macular degeneration: an optical coherence tomography study. *Br J Ophthalmol*. 2009;93(10):1353–1358. doi:10.1136/bjo.2008.141879
62. Abedi F, Wickremasinghe S, Richardson AJ, et al. Variants in the VEGFA gene and treatment outcome after anti-VEGF treatment for neovascular age-related macular degeneration. *Ophthalmology*. 2013;120(1):115–121. doi:10.1016/j.ophtha.2012.10.006
63. Byun YJ, Lee SJ, Koh HJ. Predictors of response after intravitreal bevacizumab injection for neovascular age-related macular degeneration. *Jpn J Ophthalmol*. 2010;54(6):571–577. doi:10.1007/s10384-010-0866-1
64. Hermann MM, van Asten F, Muether PS, et al. Polymorphisms in vascular endothelial growth factor receptor 2 are associated with better response rates to ranibizumab treatment in age-related macular degeneration. *Ophthalmology*. 2014;121(4):905–910. doi:10.1016/j.ophtha.2013.10.047
65. Jakobsen DB, Torp TL, Stefansson E, Peto T, Grauslund J. Retinal metabolic and structural alterations in response to aflibercept treatment in neovascular age-related macular degeneration. *Acta Ophthalmol*. 2019;97(5):525–531. doi:10.1111/aos.13996
66. Lee H, Ji B, Chung H, Kim HC. Correlation between optical coherence tomographic hyperreflective foci and visual outcomes after anti-vegf treatment in neovascular age-related macular degeneration and polypoidal choroidal vasculopathy. *Retina*. 2016;36(3):465–475. doi:10.1097/IAE.0000000000000645
67. Hagstrom SA, Ying GS, Pauer GJT, et al. Pharmacogenetics for genes associated with age-related macular degeneration in the Comparison of AMD Treatments Trials (CATT). *Ophthalmology*. 2013;120(3):593–599. doi:10.1016/j.ophtha.2012.11.037
68. Lotery AJ, Gibson J, Cree AJ, et al. Pharmacogenetic associations with vascular endothelial growth factor inhibition in participants with neovascular age-related macular degeneration in the IVAN Study. *Ophthalmology*. 2013;120(12):2637–2643. doi:10.1016/j.ophtha.2013.07.046
69. Chen G, Tzekov R, Li W, Jiang F, Mao S, Tong Y. Pharmacogenetics of complement factor H Y402H polymorphism and treatment of neovascular AMD with anti-VEGF agents: a meta-analysis. *Sci Rep*. 2015;5(1):1–9.
70. Hong N, Shen Y, Yu CY, Wang SQ, Tong JP. Association of the polymorphism Y402H in the CFH gene with response to anti-VEGF treatment in age-related macular degeneration: a systematic review and meta-analysis. *Acta Ophthalmol*. 2016;94(4):334–345. doi:10.1111/aos.13049
71. Hu Z, Xie P, Ding Y, Yuan D, Liu Q. Association between variants A69S in ARMS2 gene and response to treatment of exudative AMD: a meta-analysis. *Br J Ophthalmol*. 2015;99(5):593–598. doi:10.1136/bjophthalmol-2014-305488

72. Zhang J, Liu Z, Hu S, Qi J. Meta-analysis of the pharmacogenetics of ARMS2 A69S polymorphism and the response to advanced age-related macular degeneration. *Ophthalmic Res*. 2021;64(2):192–204.
73. Zhou Y-L, Chen C-L, Wang Y-X, et al. Association between polymorphism rs11200638 in the HTRA1 gene and the response to anti-VEGF treatment of exudative AMD: a meta-analysis. *BMC Ophthalmol*. 2017;17(1):1–9. doi:10.1186/s12886-017-0487-2
74. Hagstrom SA, Ying G-S, Pauer GJ, et al. Vegfa and vegfr2 gene polymorphisms and response to anti–vascular endothelial growth factor therapy: comparison of age-related macular degeneration treatments trials (CATT). *JAMA Ophthalmol*. 2014;132(5):521–527. doi:10.1001/jamaophthalmol.2014.109
75. Boltz A, Ruiß M, Jonas JB, et al. Role of vascular endothelial growth factor polymorphisms in the treatment success in patients with wet age-related macular degeneration. *Ophthalmology*. 2012;119(8):1615–1620. doi:10.1016/j.ophtha.2012.02.001
76. Lazzeri S, Figus M, Orlandi P, et al. VEGF-A polymorphisms predict short-term functional response to intravitreal ranibizumab in exudative age-related macular degeneration. *Pharmacogenomics*. 2013;14(6):623–630. doi:10.2217/pgs.13.43
77. Park UC, Shin JY, Kim SJ, et al. Genetic factors associated with response to intravitreal ranibizumab in Korean patients with neovascular age-related macular degeneration. *Retina*. 2014;34(2):288–297. doi:10.1097/IAE.0b013e3182979e1e
78. Cruz-Gonzalez F, Cabrillo-Estévez L, López-Valverde G, Cieza-Borrella C, Hernández-Galilea E, González-Sarmiento R. Predictive value of VEGF A and VEGFR2 polymorphisms in the response to intravitreal ranibizumab treatment for wet AMD. *Graefes Arch Clin Exp Ophthalmol*. 2014;252(3):469–475. doi:10.1007/s00417-014-2585-7
79. Hagstrom SA, Ying G-S, Maguire MG, et al. VEGFR2 gene polymorphisms and response to anti–vascular endothelial growth factor therapy in age-related macular degeneration. *Ophthalmology*. 2015;122(8):1563–1568. doi:10.1016/j.ophtha.2015.04.024
80. Wu M, Xiong H, Xu Y, et al. Association between VEGF-A and VEGFR-2 polymorphisms and response to treatment of neovascular AMD with anti-VEGF agents: a meta-analysis. *Br J Ophthalmol*. 2017;101(7):976–984. doi:10.1136/bjophthalmol-2016-309418
81. Jelstrup AB, Pomares E, Navarro R, Group BS. Relationship between aflibercept efficacy and genetic variants of genes associated with neovascular age-related macular degeneration: the BIOIMAGE trial. *Ophthalmologica*. 2020;243(6):461–470. doi:10.1159/000508902
82. Francis PJ. The influence of genetics on response to treatment with ranibizumab (Lucentis) for age-related macular degeneration: the Lucentis Genotype Study (an American Ophthalmological Society thesis). *Trans Am Ophthalmol Soc*. 2011;109:115.
83. Riaz M, Lorés-Motta L, Richardson AJ, et al. GWAS study using DNA pooling strategy identifies association of variant rs4910623 in OR52B4 gene with anti-VEGF treatment response in age-related macular degeneration. *Sci Rep*. 2016;6(1):1–10. doi:10.1038/srep37924
84. Lorés-Motta L, Riaz M, Grunin M, et al. Association of genetic variants with response to anti–vascular endothelial growth factor therapy in age-related macular degeneration. *JAMA Ophthalmol*. 2018;136(8):875–884. doi:10.1001/jamaophthalmol.2018.2019
85. Daniel E, Shaffer J, Ying G-S, et al. Outcomes in eyes with retinal angiomatous proliferation in the comparison of age-related macular degeneration treatments trials (CATT). *Ophthalmology*. 2016;123(3):609–616. doi:10.1016/j.ophtha.2015.10.034
86. Rosenfeld PJ, Shapiro H, Tuomi L, Webster M, Elledge J, Blodi B. Characteristics of patients losing vision after 2 years of monthly dosing in the Phase III ranibizumab clinical trials. *Ophthalmology*. 2011;118(3):523–530. doi:10.1016/j.ophtha.2010.07.011
87. Jaffe GJ, Ying G-S, Toth CA, et al. Macular morphology and visual acuity in year five of the comparison of age-related macular degeneration treatments trials. *Ophthalmology*. 2019;126(2):252–260. doi:10.1016/j.ophtha.2018.08.035
88. Steinle NC, Du W, Gibson A, Saroj N. Outcomes by baseline choroidal neovascularization features in age-related macular degeneration: a post hoc analysis of the VIEW Studies. *Ophthalmol Retina*. 2021;5(2):141–150. doi:10.1016/j.oret.2020.07.003
89. Dugel PU, Singh RP, Koh A, et al. HAWK and HARRIER: ninety-six-week outcomes from the phase 3 trials of brolucizumab for neovascular age-related macular degeneration. *Ophthalmology*. 2021;128(1):89–99. doi:10.1016/j.ophtha.2020.06.028
90. Sharma S, Toth CA, Daniel E, et al. Macular morphology and visual acuity in the second year of the comparison of age-related macular degeneration treatments trials. *Ophthalmology*. 2016;123(4):865–875. doi:10.1016/j.ophtha.2015.12.002
91. Fung AE, Lalwani GA, Rosenfeld PJ, et al. An optical coherence tomography-guided, variable dosing regimen with intravitreal ranibizumab (Lucentis) for neovascular age-related macular degeneration. *Am J Ophthalmol*. 2007;143(4):566–583. doi:10.1016/j.ajo.2007.01.028
92. Evans RN, Reeves BC, Maguire MG, et al. Associations of variation in retinal thickness with visual acuity and anatomic outcomes in eyes with neovascular age-related macular degeneration lesions treated with anti–vascular endothelial growth factor agents. *JAMA Ophthalmol*. 2020;138(10):1043–1051. doi:10.1001/jamaophthalmol.2020.3001
93. Simader C, Ritter M, Bolz M, et al. Morphologic parameters relevant for visual outcome during anti-angiogenic therapy of neovascular age-related macular degeneration. *Ophthalmology*. 2014;121(6):1237–1245. doi:10.1016/j.ophtha.2013.12.029
94. Schmidt-Erfurth U, Vogl W-D, Jampol LM, Bogunović H. Application of automated quantification of fluid volumes to Anti–VEGF therapy of neovascular age-related macular degeneration. *Ophthalmology*. 2020;127(9):1211–1219. doi:10.1016/j.ophtha.2020.03.010
95. Reiter GS, Grechenig C, Vogl W-D, et al. Analysis of fluid volume and its impact on visual acuity in the fluid study as quantified with deep learning. *Retina*. 2021;41(6):1318–1328.
96. Busbee BG, Ho AC, Brown DM, et al. Twelve-month efficacy and safety of 0.5 mg or 2.0 mg ranibizumab in patients with subfoveal neovascular age-related macular degeneration. *Ophthalmology*. 2013;120(5):1046–1056. doi:10.1016/j.ophtha.2012.10.014
97. Waldstein SM, Simader C, Staurenghi G, et al. Morphology and visual acuity in aflibercept and ranibizumab therapy for neovascular age-related macular degeneration in the VIEW trials. *Ophthalmology*. 2016;123(7):1521–1529. doi:10.1016/j.ophtha.2016.03.037
98. Guymer RH, Markey CM, McAllister IL, et al. Tolerating subretinal fluid in neovascular age-related macular degeneration treated with ranibizumab using a treat-and-extend regimen: FLUID study 24-month results. *Ophthalmology*. 2019;126(5):723–734. doi:10.1016/j.ophtha.2018.11.025
99. Waldstein SM, Wright J, Warburton J, Margaron P, Simader C, Predictive S-EU. Value of retinal morphology for visual acuity outcomes of different ranibizumab treatment regimens for neovascular AMD. *Ophthalmology*. 2016;123(1):60–69. doi:10.1016/j.ophtha.2015.09.013
100. Jhaveri CD Visual and anatomical outcomes for brolucizumab and aflibercept in patients with nAMD: 96-week data from HAWK and HARRIER. Paper presented at: American Society of Retina Specialists; July 2019; Chicago, IL.

101. Willoughby AS, Ying G-S, Toth CA, et al. Subretinal hyperreflective material in the comparison of age-related macular degeneration treatments trials. *Ophthalmology*. 2015;122(9):1846–1853.
102. Ehlers JP, Zahid R, Kaiser PK, et al. Longitudinal assessment of ellipsoid zone integrity, subretinal hyperreflective material, and subretinal pigment epithelium disease in neovascular age-related macular degeneration. *Ophthalmol Retina*. 2021. doi:10.1016/j.oret.2021.02.012
103. Sarraf D, London NJ, Khurana RN, et al. Ranibizumab treatment for pigment epithelial detachment secondary to neovascular age-related macular degeneration: post hoc analysis of the HARBOR study. *Ophthalmology*. 2016;123(10):2213–2224. doi:10.1016/j.ophtha.2016.07.007
104. Javaheri M, Hill L, Ghanekar A, Stoilov I. Changes in treatment-naive pigment epithelial detachments associated with the initial anti–vascular endothelial growth factor injection: a post hoc analysis from the HARBOR Trial. *JAMA Ophthalmol*. 2021;139(2):219–223. doi:10.1001/jamaophthalmol.2020.5130
105. Khanani AM, Eichenbaum D, Schlottmann PG, Tuomi L, Sarraf D. Optimal management of pigment epithelial detachments in eyes with neovascular age-related macular degeneration. *Retina*. 2018;38(11):2103. doi:10.1097/IAE.0000000000002195
106. Ying G-S, Kim BJ, Maguire MG, et al. Sustained visual acuity loss in the comparison of age-related macular degeneration treatments trials. *JAMA Ophthalmol*. 2014;132(8):915–921. doi:10.1001/jamaophthalmol.2014.1019
107. Bhisitkul RB, Mendes TS, Rofagha S, et al. Macular atrophy progression and 7-year vision outcomes in subjects from the ANCHOR, MARINA, and HORIZON studies: the SEVEN-UP study. *Am J Ophthalmol*. 2015;159(5):915–924. doi:10.1016/j.ajo.2015.01.032
108. Altaweel MM, Daniel E, Martin DF, et al. Outcomes of eyes with lesions composed of> 50% blood in the comparison of age-related macular degeneration treatments trials (CATT). *Ophthalmology*. 2015;122(2):391–398.
109. Stanescu-Segall D, Balta F, Jackson TL. Submacular hemorrhage in neovascular age-related macular degeneration: a synthesis of the literature. *Surv Ophthalmol*. 2016;61(1):18–32. doi:10.1016/j.survophthal.2015.04.004
110. Daniel E, Pan W, Ying G-S, et al. Development and course of scars in the comparison of age-related macular degeneration treatments trials. *Ophthalmology*. 2018;125(7):1037–1046. doi:10.1016/j.ophtha.2018.01.004
111. Okeagu CU, Agrón E, Vitale S, et al. Principal cause of poor visual acuity after neovascular age-related macular degeneration: age-related eye disease study 2 report number 23. *Ophthalmol Retina*. 2021;5(1):23–31. doi:10.1016/j.oret.2020.09.025
112. Chakravarthy U, Harding SP, Rogers CA, et al. A randomised controlled trial to assess the clinical effectiveness and cost-effectiveness of alternative treatments to Inhibit VEGF in Age-related choroidal Neovascularisation (IVAN). *Health Tech Assessment*. 2015;19(78):1. doi:10.3310/hta19780
113. Wykoff CC, Ou WC, Brown DM, et al. Randomized trial of treat-and-extend versus monthly dosing for neovascular age-related macular degeneration: 2-year results of the TREX-AMD study. *Ophthalmol Retina*. 2017;1(4):314–321. doi:10.1016/j.oret.2016.12.004
114. Kertes PJ, Galic IJ, Greve M, et al. Efficacy of a treat-and-extend regimen with ranibizumab in patients with neovascular age-related macular disease: a randomized clinical trial. *JAMA Ophthalmol*. 2020;138(3):244–250. doi:10.1001/jamaophthalmol.2019.5540
115. Chin-Yee D, Eck T, Fowler S, Hardi A, Apte RS. A systematic review of as needed versus treat and extend ranibizumab or bevacizumab treatment regimens for neovascular age-related macular degeneration. *Br J Ophthalmol*. 2016;100(7):914–917. doi:10.1136/bjophthalmol-2015-306987
116. Wykoff CC, Ou WC, Croft DE, et al. Neovascular age-related macular degeneration management in the third year: final results from the TREX-AMD randomised trial. *Br J Ophthalmol*. 2018;102(4):460–464. doi:10.1136/bjophthalmol-2017-310822
117. Spooner KL, Fraser-Bell S, Cozzi M, et al. Macular atrophy incidence and progression in eyes with neovascular age-related macular degeneration treated with vascular endothelial growth factor inhibitors using a treat-and-extend or a pro re nata regimen: four-year results of the MANEX Study. *Ophthalmology*. 2020;127(12):1663–1673. doi:10.1016/j.ophtha.2020.06.019
118. Fasler K, Moraes G, Wagner S, et al. One- and two-year visual outcomes from the Moorfields age-related macular degeneration database: a retrospective cohort study and an open science resource. *BMJ Open*. 2019;9(6):e027441. doi:10.1136/bmjopen-2018-027441
119. Schmidt-Erfurth U, Bogunovic H, Sadeghipour A, et al. Machine learning to analyze the prognostic value of current imaging biomarkers in neovascular age-related macular degeneration. *Ophthalmol Retina*. 2018;2(1):24–30. doi:10.1016/j.oret.2017.03.015
120. Rohm M, Tresp V, Müller M, et al. Predicting visual acuity by using machine learning in patients treated for neovascular age-related macular degeneration. *Ophthalmology*. 2018;125(7):1028–1036. doi:10.1016/j.ophtha.2017.12.034
121. Singh RP, Wykoff CC, Tadayoni R, et al. Visual and expanded anatomical outcomes for brolucizumab versus aflibercept in patients with neovascular AMD: 96-week data from HAWK and HARRIER. *Invest Ophthalmol Vis Sci*. 2019;60(9):5194.
122. Zweifel SA, Saroj N, Shapiro H, Freund KB. The effect of fellow eye visual acuity on visual acuity of study eyes receiving ranibizumab for age-related macular degeneration. *Retina*. 2012;32(7):1243–1249. doi:10.1097/IAE.0b013e3182469064
123. Lalwani GA, Rosenfeld PJ, Fung AE, et al. A variable-dosing regimen with intravitreal ranibizumab for neovascular age-related macular degeneration: year 2 of the PrONTO Study. *Am J Ophthalmol*. 2009;148(1):43–58. doi:10.1016/j.ajo.2009.01.024
124. Brown DM, Tuomi L, Shapiro H, Group PS. Anatomical measures as predictors of visual outcomes in ranibizumab-treated eyes with neovascular age-related macular degeneration. *Retina*. 2013;33(1):23–34. doi:10.1097/IAE.0b013e318263cedf
125. Frenkel RE, Shapiro H, Stoilov I. Predicting vision gains with anti-VEGF therapy in neovascular age-related macular degeneration patients by using low-luminance vision. *Br J Ophthalmol*. 2016;100(8):1052–1057. doi:10.1136/bjophthalmol-2015-307575
126. Khurana RN, Chang L, Day BM, Ghanekar A, Stoilov I. Timing of peak vision gains in patients with neovascular age-related macular degeneration treated with ranibizumab. *Ophthalmol Retina*. 2020;4(8):760–766. doi:10.1016/j.oret.2020.02.011
127. Schroeder M, Westborg I, Lövestam Adrian M. Twelve per cent of 6142 eyes treated for neovascular age-related macular degeneration (nAMD) presented with low visual outcome within 2 years. Analysis from the Swedish macula registry (SMR). *Acta Ophthalmol*. 2020;98(3):274–278. doi:10.1111/aos.14239

Appendix 2

Published Co-authored Paper – “Comparison between two multimodal imaging platforms: Nidek Mirante and Heidelberg Spectralis ”

Graefe's Archive for Clinical and Experimental Ophthalmology (2021) 259:1791–1802
https://doi.org/10.1007/s00417-020-05050-7

RETINAL DISORDERS

Comparison between two multimodal imaging platforms: Nidek Mirante and Heidelberg Spectralis

Kimberly Spooner[1] · Long Phan[1,2] · Mariano Cozzi[3] · Thomas Hong[1] · Giovanni Staurenghi[3] · Eugenia Chu[1] · Andrew A Chang[1,4]

Received: 13 September 2020 / Revised: 4 December 2020 / Accepted: 11 December 2020 / Published online: 6 January 2021

Abstract

Purpose To investigate the reliability and comparability of retinal measurements obtained with spectral-domain optical coherence tomography (OCT), optical coherence tomography angiography (OCTA), confocal scanning laser ophthalmoscopy (cSLO) colour images, and fundus autofluorescence (FAF) between two multimodal imaging platforms in eyes with macular pathology and normal, healthy volunteers.

Methods This cross-sectional, multi-centre, instrument validation study recruited 94 consecutive subjects. All participants underwent a dilated examination and were scanned consecutively on the Heidelberg Spectralis (Heidelberg Engineering, Heidelberg, Germany) and Nidek Mirante (Nidek Co. Ltd., Gamagori, Japan) devices. Agreement between device images were evaluated from measures of the central retinal thickness (CRT), presence of segmentation and fixation imaging artefacts (IA), foveal avascular zone (FAZ) measurements; as well as sensitivity and specificity values from the detection of atrophy on fundus autofluorescence (FAF), drusen, subretinal drusenoid deposits, geographic atrophy, epiretinal membrane, fibrosis and haemorrhage on multicolour imaging, and agreement between devices and groups.

Results Compared with reference clinical examination, sensitivity values for the identification of retinal features using sole device images ranged from 100% for epiretinal membranes to 66.7% for subretinal drusenoid deposits (SSD). Mean absolute difference for CRT between OCT devices was 3.78 μm (95% confidence interval [CI]: −21.39 to 28.95, $P = 0.809$). Differences in the superficial and deep capillary plexus FAZ area on OCTA between devices were not statistically significant ($P = 0.881$ and $P = 0.595$, respectively). IAs were significantly increased in the presence of macular pathology.

Conclusion Comparison of retinal measurements between the OCT devices did not differ significantly. Common ultrastructural biomarkers of multiple macular pathologies were identified with high sensitivities and specificities, with good agreement between graders, indicating that they can be identified with comparable confidence in retinal imaging between the two devices.

✉ Andrew A Chang
achang@sydneyretina.com.au

[1] Sydney Retina, Level 13, Park House, 187 Macquarie Street, Sydney, NSW 2000, Australia

[2] Graduate School of Health, University of Technology, Sydney, New South Wales, Australia

[3] Department of Biomedical and Clinical Science "Luigi Sacco", Eye Clinic, Sacco Hospital, University of Milan, Milan, Italy

[4] The Save Sight Institute, Discipline of Ophthalmology, Sydney Medical School, The University of Sydney, Sydney, New South Wales, Australia

Key messages:

- There are several commercially available optical coherence tomography devices. Until recently, there was only one multimodal imaging platform; the Heidelberg Spectralis, able to obtain images from SD-OCT, OCTA, and cSLO. This allowed it to become the most widely-used comprehensive imaging device forophthalmic practice and clinical trial purposes
- This paper presents the comparability of retinal measurements between two multimodal imaging platforms: Heidelberg Spectralis and Nidek Mirante undertaken across 2 retinal practices.

Keywords Optical coherence tomography (OCT) · Fundus autofluorescence (FAF) · Multicolour (MC) · Spectralis · Mirante

Introduction

The development of optical coherence tomography (OCT) over recent decades has revolutionized ophthalmic management [1]. OCT is a quick and non-invasive tool providing both quantitative and qualitative measurements of the retina with a relatively high level of reliability and reproducibility and is considered essential in clinical practice and research. However, several factors; including media opacities, scan resolution, capture speed, auto-segmentation, and patient cooperation; can cause errors in the evaluation of data and may affect the accuracy of OCT measurements [2, 3]. Spectral-domain OCT (SD-OCT) is currently the gold standard and most widely utilized ocular imaging technology [4, 5].

Presently, there are several OCT devices available from various manufacturers. These all use a variety of proprietary algorithms for analysis, thereby yielding a potential for significant variability in retinal measurements and hence the interpretation of results [6–8]. Software algorithms for auto-segmentation from these devices have now evolved to the extent that they can now segment the retina's microstructures and provide quantitative thickness data [9]. In retinal diseases, where specific pathologies can obscure underlying retinal areas, the auto-segmentation may be affected, impairing the reliability of measurements. Other studies have reported varying levels of repeatability in measurements of inner retinal thickness in retinal diseases using SD-OCT [6, 10, 11]. These differences have posed challenges for inter-relating data collected in clinical trials and clinical practice.

Optical coherence tomography angiography (OCTA) is a more recent innovative imaging modality that allows visualization of retinal and choroidal vasculature structures in vivo [12, 13]. This technology enables assessment for the presence of a variety of retinal diseases, reducing the use of dye-based approaches such as fluorescein angiography (FA) [12]. Similar to differences in thickness measurement algorithms, different companies have proposed multiple processing algorithms for each device [14]. Although each module's device software generates similar and clinically comparable images [15], it has been observed that images produced from different algorithms are not equivalent in terms of quantitative morphologic features; such as vessel density, fractal dimension, and foveal avascular zone (FAZ) [14].

Confocal scanning laser ophthalmoscopy (cSLO) has dramatically improved the quality of the fundus images, providing higher contrast and resolution compared with standard flash-based fundus cameras [16]. Moreover, this particular technology has facilitated the introduction of monochromatic laser light sources to capture reflectance images [17]. A combination of simultaneous acquisition-based off multiple wavelengths generates a colour image of the fundus [17] A further step forward, driven by the development of cSLO, has been the introduction of fundus autofluorescence (FAF) more than two decades ago [18]. This technology allows for the documentation of the presence of lipofuscin within the retinal pigment epithelium (RPE) cells [19]. Nowadays, FAF can be captured using either blue light (excitation 486 nm, emission 500–700 nm) or green light wavelength (excitation 514 nm, emission 500–700 nm) [20]. Concerning the latter, the conventional flash-based camera is also able to perform it.

The need for multimodal imaging is proving to be more critical in the management of retinal conditions than ever. However, this often requires multiple machines with significant financial investment, as well as the allowance of physical space. Until recently, there was only one multimodal imaging platform; the Heidelberg Spectralis, able to obtain images from SD-OCT, OCTA, and cSLO. This allowed it to become the most widely-used comprehensive imaging device for ophthalmic practice and clinical trial purposes. Recently, Nidek introduced an innovative SD-OCT, the Mirante, which can also obtain a wide range of imaging modalities on one device.

The present study aims to evaluate the comparability of retinal measurements and accuracy of auto-segmentation in healthy eyes and eyes with various macular pathologies

between two multimodal imaging platforms; Nidek Mirante (Nidek Co., Ltd., Gamagori, Japan) and the widely-used Heidelberg Spectralis (Heidelberg Engineering, Heidelberg, Germany). Moreover, we evaluated the sensitivity and specificity of detecting macular biomarkers using either cSLO colour and FAF images.

Materials and methods

Design and participants

This cross-sectional, comparative instrument validation study was conducted to evaluate the agreement between two multimodal imaging platforms. Healthy volunteers over 18-years of age with no history of eye disease, as well as eyes with common macular pathology including age-related macular degeneration (AMD), diabetic macular oedema (DMO), and retinal vein occlusion (RVO), were recruited. One eye per patient was included. If both eyes qualified for the study, one eye was chosen at random by the OCT technician. Participants were recruited from two tertiary retinal clinics (Eye Clinic Luigi Sacco Hospital, University of Milan and Sydney Retina Clinic) between December 2019 and January 2020. Institutional approval was obtained from the University of Sydney Ethics Committee [2019/1006], and the study adhered to the tenets of the Declaration of Helsinki. Informed written consent was obtained from all participants.

The normal, healthy group was age-matched and included subjects of at least 18 years of age with a normal fundus and an intraocular pressure < 21 mmHg. These participants were often accompanying patients at routine appointments. Participants were excluded if they had a spherical equivalent of ± 6 dioptres. All participants had a best-corrected visual acuity (BCVA) of 55 Early Treatment in Diabetic Retinopathy Score (ETDRS) letters or better to ensure they could fixate on the device generated targets. All participants underwent comprehensive ophthalmological examination and imaging following pupillary dilation with tropicamide 1%.

Imaging protocol

All OCT scans and imaging were performed by four technicians with previous clinical trial imaging experience (KS, MC, TH, EC). All participants underwent imaging with both SD-OCT devices: Heidelberg Spectralis (Heidelberg Engineering, Heidelberg, Germany) and the Nidek Mirante (Nidek Co. Ltd., Gamagori, Japan). Internal fixation targets were used across both OCT devices for consistency. There was a 10-min interval between examinations using the two devices. Unacceptable images, such as those with poor scan quality obtained by either device, were excluded.

The OCT acquisition protocol consisted of a 6 × 6 millimetre (mm) three-dimensional vertical scan centred on the fovea comprising 512 × 128 scans for the Nidek Mirante and 512 × 97 for Heidelberg Spectralis. Each B-scan was averaged nine times in both the OCT patterns.

OCTA consisted of a 3 × 3 mm volume scan centred on the fovea. Pre-selected scan patterns were used consisting of 256/256 (HS mode) averaged five times for the Heidelberg Spectralis, and 256/256 scans averaged four times for the Nidek Mirante.

Three channels form colour cSLO captured with the Heidelberg Spectralis multicolour (MC) system (infrared: 815 nm, green: 518 nm; blue:486 nm) captured simultaneously with a single detector. The built-in software generates a 30 × 30 degree colour fundus image with a resolution of 768X768 pixels. Nidek Mirante colour images have a field of view of 45° and a resolution of 768X768 pixels. The colour images are obtained by combining three different laser wavelengths: red (670 nm), green (532 nm) and blue (488 nm), coupled to a specifically dedicated sensor for each wavelength. Fundus autofluorescence (FAF) is obtained through a blue light excitation wavelength of 486 nm (emission 500–700 nm) for Heidelberg Spectralis and with an excitation wavelength of 488 nm (emission > 500 nm) with Nidek Mirante (Fig. 1). Finally, all the topographic images were acquired, averaging up to 30 frames per image. The characteristics of the two imaging platforms are listed in Table 1.

Data analysis

Following image acquisition, central retinal thickness (CRT) and FAZ metrics were measured, and a number of retinal features were identified from a pre-determined list. The ETDRS chart in the macula map was used to measure the retinal thickness. The FAZ area of the superficial capillary plexus (SCP) and the deep capillary plexus (DCP) were determined from macular OCTA scans. The FAZ was defined as the area encompassing the central fovea, where there are no vessels [21]. A centralized scan area measuring 3 × 3 mm was selected in the superficial and deep layer, and OCTA images of this area were generated automatically. Imaging processing was performed using ImageJ software (National Institutes of Health, Maryland, USA). Graders independently manually segmented and outlined the SCP and DCP FAZ. The surface area was measured in square pixels and was converted to square millimetres [22]. Measurement of CRT was defined as the mean thickness from Bruch's membrane to the inner retinal border within the central 1-mm circle of the ETDRS grid [23]. The prevalence of imaging artefacts (IA) was classified as either the presence or absence of segmentation and/or fixation errors. Segmentation artefacts were due to inaccurate automated segmentation of retinal layers resulting in incorrect retinal thickness measurements, while fixation artefacts were associated with inappropriate identification of the fovea or patient motion.

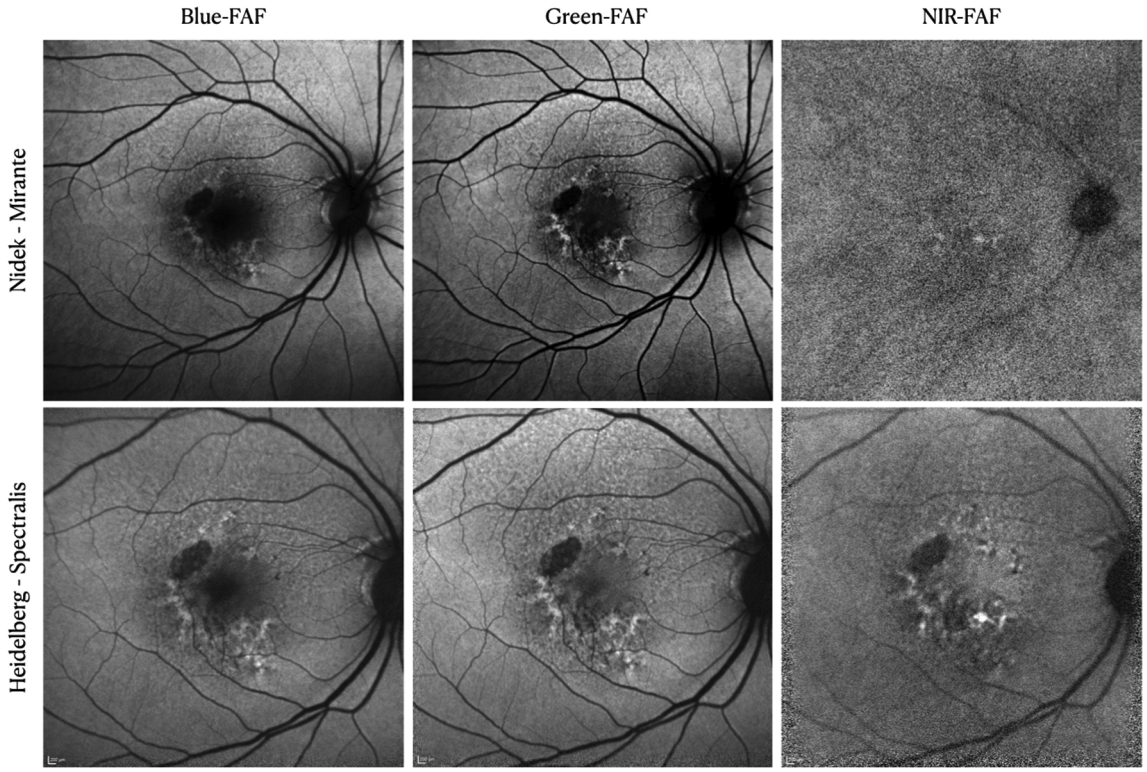


Fig. 1 Examples of the fundus autofluorescence (FAF) capabilities of both devices. FAF is obtained through a blue light excitation wavelength of 486 nm (emission 500–700 nm) for Heidelberg Spectralis and with an excitation wavelength of 488 nm (emission > 500 nm) with Nidek Mirante. Green-FAF is obtained through excitation wavelength of 518 nm for Heidelberg Spectralis and 432 nm with Nidek Mirante. Near infrared-FAF is obtained with excitation wavelength of 788 nm for Heidelberg Spectralis and 490 nm with Nidek Mirante

Multicolour and fundus autofluorescence images were used to assess retinal features using Heidelberg Eye Explorer (version 1.9.13.0) and Mirante Navis (version 1.9.0.8). Six retinal features including subretinal fibrosis, drusen, atrophy, epiretinal membrane (ERM), subretinal drusenoid deposits (SDDs), and haemorrhages were selected for assessment and defined as the test characteristics on cSLO colour imaging, while atrophy and SDDs were test characteristics on FAF. All grading and data analyses was performed by three (KS, LP, and MC) experienced graders using a structured data extraction template. Subsequently, all images were reviewed by the senior expert clinician (AC). The agreement of manual measurements and data analysis between graders was assessed using intraclass correlation coefficient (ICC). All grading was conducted with screen settings standardized to the highest available resolution (1440 × 900). All image graders were masked to ophthalmic and medical history information. The expert subjective assessment was used as the reference for the evaluation for the objective measure of scan quality. The objective image/scan quality limits were appraised in terms of the graders ability to discriminate between good, fair, and poor image/scan qualities. The agreement of the objective parameters and subjective assessment results were analysed using the kappa statistic. The grader recorded "cannot grade" when inadequate image quality or media opacity prevented determining the presence of a characteristic being graded.

Statistical analysis

Results were analysed using IBM SPSS (version 24; SPSS, Chicago, IL). Disease status was determined by using the reference standard, dilated fundoscopy findings of the senior expert physician (AC) and Heidelberg Spectralis. Quantitative variables were expressed as mean and standard deviation (SD), and qualitative variables as percentages. Sample size was calculated with power set at 0.95 and α error 0.05. The calculated sample size was 85 subjects. The Shapiro-Wilk test was used to check whether the sample came from a normally distributed population. According to the normality test results, the Mann-Whitney U test or Student t test was used to compare the independent and paired samples.

The non-parametric Kruskal-Wallis or parametric ANOVA test was used to compare groups. Pearson's chi-square test used to analyse the gender distribution among the age groups. Participants were stratified into healthy, normal eyes or eyes with retinal pathology. In the total study population, the correlations of the age, central retinal thickness (CRT), FAZ area were analysed using the

Table 1 Multimodal imaging platforms characteristics

	Heidelberg Spectralis	Nidek Mirante
Field of view (degrees)	8° (HMM lens), 30° or 55°	45°
Ultra-widefield module (degrees)	102°	110°
Resolution (pixels)	From 384 × 384 (HS) up to 1536 × 1536 (HR)	From 512 × 512 up to 4096 × 4096
Eye tracking	With SLO frame rate	From 1,4 to 25 fps
Image averaging	Up to 100 frames	Up to 120 frames
MPOD measurements	Excitation, 486 nm and 518 nm; barrier, 500+ nm (research module)	Not available
Infrared-reflectance wavelength (nm)	815	790
cSLO colour wavelengths (nm)	815	670
	518	532
	486	488
Blue-FAF excitation wavelength (nm)	486	488
Green-FAF excitation wavelength (nm)	518 (research module)	532
Near infrared-FAF excitation wavelength (nm)	788	790
SD-OCT (A-scans/second)	85,000 A-Scans/Second	85,000 A-scans/second
OCTA algorithm	Full spectrum Probabilistic approach	CODAA (complex OCT-signal difference analysis angiography)
Fluorescein angiography excitation–barrier filter (nm)	486–500+	488–500+
Indocyanine green angiography–excitation–barrier filter (nm)	788–800+	790–800+

HMM, high magnification lens; *HS*, high speed; *HR*, high resolution; *SLO*, scanning laser ophthalmoscope; *fps*, frames per second; *MPOD*, macular pigment optical density; *cSLO*, confocal scanning laser ophthalmoscope; *FAF*, fundus autofluorescence; *SD-OCT*, spectral-domain optical coherence tomography; *OCTA*, optical coherence tomography angiography

Field of view is reported as maximum image size displayed on the image plane, expressed as the angle subtended at the exit pupil of the eye by the maximum dimension 2*r* (ISO 10940)

Pearson correlation test. For sensitivity and specificity to detect macular pathology, it was estimated with a 95% Wilson confidence interval. For each imaging modality, Interobserver agreement was calculated using a kappa statistic [24]. The frequency of IA and the effect on the agreement between devices and groups were assessed using the chi-square test and independent *t* test. All data was inputted to Microsoft Excel version 14.0 (Microsoft Corporation, Redmond, WA) and SPSS for analysis. A *P* value of less than 0.5 was considered statistically significant.

Results

Study population

Ninety-four eyes of 94 patients were included in the study, with 96% being Caucasian participants. Forty-eight (51%) of the study subjects were female. The overall mean age was 71.2 ± 12.2 years (range: 34–91). There were 70 eyes in the retinal disease group and 24 healthy eyes in the control group. According to the reference standard clinical evaluation, there were 42 eyes with age-related macular degeneration (AMD), 20 with diabetic retinopathy (DR), and 8 with retinal vein occlusion (RVO). The baseline characteristics of the entire cohort are summarized in Table 2.

Structural OCT analyses

The overall mean difference in CRT between the two devices was 4.3 μm (95%CI: − 20.8 to 29.5 μm, $P = 0.734$) (Fig. 2a). In the control group, the Spectralis showed the lowest mean retinal thickness, with a mean difference in CRT between Spectralis and Mirante of 4.9 μm (95%CI: − 25.7 to 15.8 μm, $P = 0.635$). In the retinal disease group, the Mirante showed the lowest retinal thickness with a mean difference in CRT of 7.8 μm (95%CI: − 26.7 to 42.2 μm, $P = 0.655$). Figure 3 shows examples of structural OCT's obtained using both devices.

OCTA analyses

The mean and standard deviations of the FAZ area of SCP and DCP are shown in Table 2 for all participants. The FAZ of the SCP and DCP were significantly different between the control and retinal disease groups ($P = 0.024$ and $P = 0.016$, respectively). There was no significant difference between the two OCT devices for both the SCP (mean difference, − 0.018 mm^2 (95% CI: − 0.035 to − 0.002, $P = 0.881$) and DCP (MD, − 0.004 mm^2 (95%CI: − 0.015 to − 0.018, $P = 0.595$) (Fig. 2).

The coefficients of variation (COV) for FAZ and CRT measurements were calculated for both the Spectralis and Mirante devices. The coefficients of variation for the SCP and DCP FAZ were 55% and 64% for Spectralis, and 59% and 61% for Mirante. The coefficients of variation for superficial plexus were statistically similar; however, there was more variability for the deep plexus. There was less variation of CRT measurements on both devices with 30% COV on Spectralis and 28% on Mirante.

Colour images and FAF analyses

Compared to the reference standard, the sensitivity and specificity of pre-specified retinal features on cSLO colour imaging on Spectralis and Mirante devices were comparable among all variables (Table 3). Compared with fundoscopy findings, sensitivity and specificity values of detection on MC imaging ranged from 100% for epiretinal membranes to 73.2% for atrophy. The sensitivity and specificity of atrophy were higher on FAF imaging compared to cSLO colour imaging, but no significant difference was seen between the two devices (Table 4) (Fig. 4).

Table 2 Baseline characteristics of study population

Characteristics	Control group	Retinal pathology group	*P* value
Eyes (*n*)	24	70	
Age (mean years (SD))	63.3 (14.5)	74.3 (9.6)	0.04
Spectralis OCT			
CMT μm (mean (SD))	288.4 (36.6)	292.5 (36.0)	0.51
FAZ (SCP mm^2)	0.29 (0.19)	0.27 (0.15)	0.37
FAZ (DCP mm^2)	0.29 (0.21)	0.32 (0.21)	0.32
Mirante OCT			
CMT μm (mean (SD))	304.5 (104.2)	296.7 (95.6)	0.28
FAZ (SCP mm^2)	0.26 (0.18)	0.33 (0.21)	0.17
FAZ (DCP mm^2)	0.26 (0.16)	0.32 (0.21)	0.21

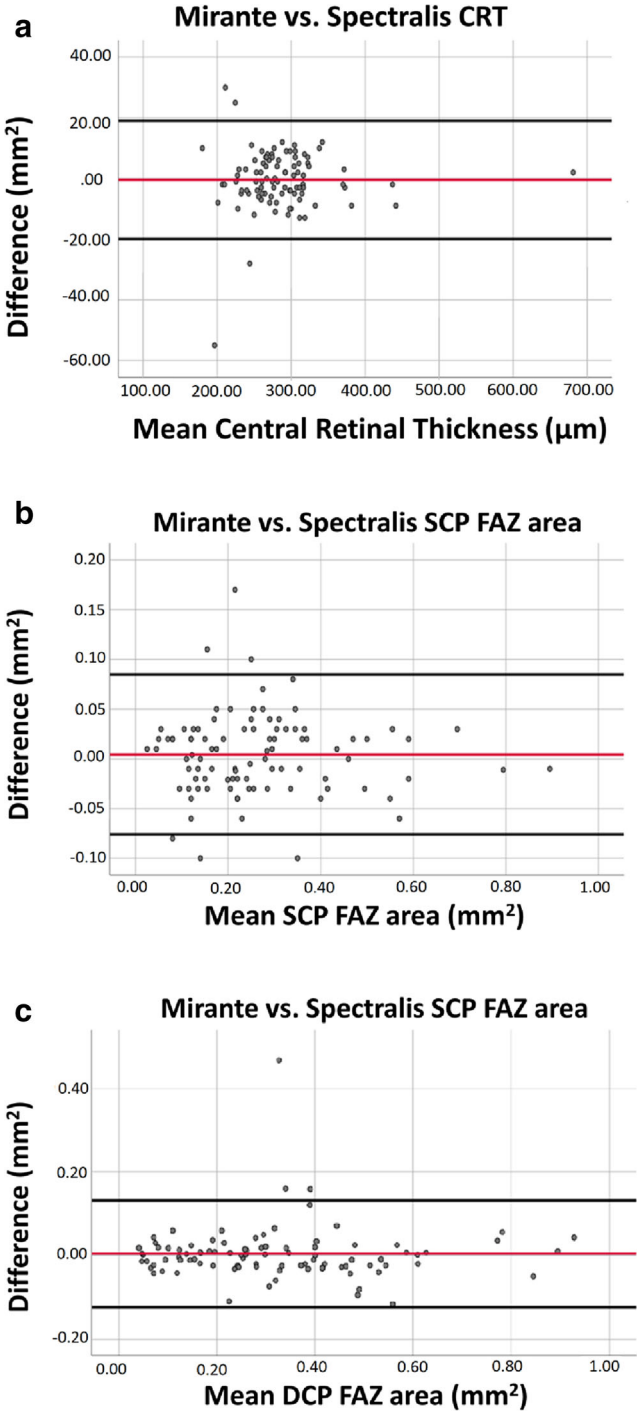


Fig. 2 Bland-Altman plot showing agreement between the two OCT devices for measurement of (a) central retinal thickness (CRT); (b) superficial capillary plexus FAZ area; and (c) deep capillary plexus FAZ area

Imaging artefacts and segmentation errors

There was a low occurrence of imaging artefacts (IA) in the control group (5% and 3% in the Mirante and Spectralis, respectively). The highest rates of IA occurred in the DR group. When comparing devices, IA prevalence was 3% lower on the Spectralis compared to Mirante ($P = 0.62$). The IA prevalence was otherwise similar between the control group and the retinal disease group across both devices. A total of 6 FAF images were ungradable due to motion artefacts.

No significant segmentation errors were found in the Spectralis or Mirante in control eyes, with automatic segmentation being accurate in all healthy subjects. However, in 6 of 94 eyes (6%) of Spectralis and 4 of 94 (4%), Mirante scans, moderate segmentation errors were detected ($P > 0.05$). In most cases, the segmentation errors were caused by incorrect identification of Bruch's membrane due to severe oedema or pigment epithelial detachment (PED), particularly in eyes with diabetic macular oedema (DMO) and macular neovascularization (MNV) (Fig. 3).

Non-significant differences were seen in CRT and FAZ measurements across both devices among the entire cohort and in each subgroup. The CRT and mean FAZ measurements consistently measured highest in Mirante, showing high agreement between devices ($P = 0.617$). These differences were less evident after the manual segmentation of scans to correct for IA.

Interobserver reliability

Overall, the Interobserver reliability between the two image graders was moderately high (ICC = 0.998). The agreement was consistently high for both the Heidelberg Spectralis and Nidek Mirante for all image modalities. Both graders classified more images as "ungradable" among the Nidek Mirante (Proportion of ungradable images: 2.1–3.2%) compared to the Heidelberg Spectralis (1.9–2.7%; $P = 0.06$). However, this was not significant. Simultaneously, a high proportion of images were classified as excellent among both devices (92.9–94.7%) on the Mirante and (89.9–93.4%) on the Spectralis. Interobserver reliability of OCTA measurements is included in Table 5.

Discussion

In the present study, multiple imaging variables measured with two different multimodal imaging platforms devices were comparable among healthy eyes and those with retinal disease. Both devices were able to detect common pathology with imaging artefacts having similar effects on automated measurements, and with high sensitivity and specificity.

To our knowledge, this is the first comparative clinical study analysing the Nidek Mirante with the Heidelberg Spectralis, and there are likely variances across the devices owing to the various segmentation algorithms inherent in each device [23, 25]. In both devices, segmentation errors occurred more frequently and were more pronounced in areas affected by macular disease.

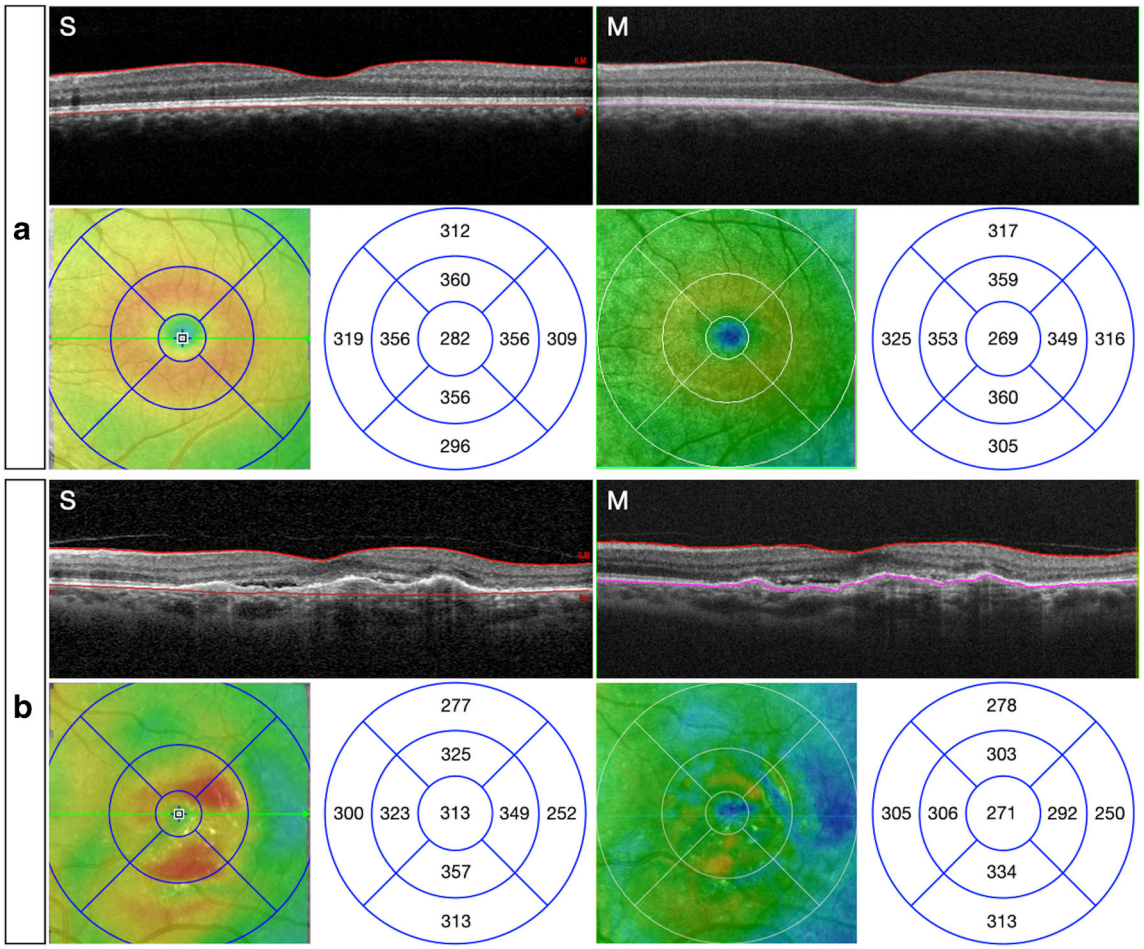


Fig. 3 Structural OCT of a healthy subject (A) and a patient affected by macular neovascularization (MNV) in neovascular AMD (B). A 6 × 6 ml macular volume scan was obtained with both Heidelberg Spectralis (S) and Nidek Mirante (M). Colour code thickness maps and ETDRS grids are presented. Concerning the latter (B), the CRT values are more deviated in the area affected by the MNV since the RPE is split from the underling Bruch's membrane. AMD, age-related macular degeneration; OCT, optical coherence tomography; ETDRS, Early treatment diabetic retinopathy study; CRT, Central retinal thickness; MNV, Macular neovascularization; RPE, retinal pigment epithelium

Segmentation errors also increased with the level of macular oedema or PED and were mainly caused by incorrect identification of RPE/Bruch's complex. Regarding CRT measurements, our results are similar to those of previous studies, which describe comparable baseline values in normal, healthy eyes, and eyes with retinal pathology, assessed by a single OCT device [7, 26–28]. Therefore, we assert that the population of our study group is representative of their respective pathologies.

In previous studies, there has been limited interchangeability between the Heidelberg Spectralis and Zeiss Cirrus devices [29–33]. The apparent difference in macula thickness between

Table 3 Sensitivity and specificity summaries of each retinal feature compared through cSLO colour imaging

Retinal feature	Spectralis		Mirante	
	Sensitivity	Specificity	Sensitivity	Specificity
Subretinal fibrosis % (95% CI)	80.0 (75.7–83.6)	96.9 (91.5–98.4)	85.7 (81.7–88.6)	97.9 (95.6–98.8)
Drusen % (95% CI)	76.7 (75.7–78.9)	95.7 (91.9–98.9)	74.7 (73.1–77.4)	97.4 (94.9–99.8)
Atrophy % (95% CI)	73.6 (70.1–75.9)	88.2 (85.6–91.5)	73.1 (71.3–76.1)	89.8 (87.1–93.5)
Epiretinal membrane % (95% CI)	100.0 (95.5–100)	92.9 (88.8–95.4)	85.71 (82.6–89.1)	98.9 (97.7–99.6)
Subretinal drusenoid deposits % (95% CI)	85.7 (81.8–88.7)	95.2 (91.1–97.6)	76.2 (75.7–78.9)	88.9 (86.3–91.4)
Haemorrhage % (95% CI)	85.7 (82.1–87.6)	93.7 (90.7–96.6)	86.2 (84.9–88.9)	98.4 (97.4–99.6)

Table 4 Sensitivity and specificity summaries of each retinal feature compared on FAF

Retinal feature	Spectralis		Mirante	
	Sensitivity	Specificity	Sensitivity	Specificity
Atrophy % (95% CI)	76.2 (75.7–78.9)	93.5 (91.2–96.4)	73.2 (70.6–75.5)	92.2 (89.1–94.7)
Subretinal drusenoid deposits % (95% CI)	76.7 (74.3–79.2)	94.4 (90.7–98.7)	88.2 (85.3–91.4)	94.4 (93.8–98.6)

OCTs could be explained by analysing the specific retina boundaries established by each manufacturer. While the inner border is always the vitreoretinal interface, the outer retinal boundary varies between manufacturers. For Spectralis, the outer perimeter corresponds to the level of Bruch's membrane (even if this layer is not distinguishable to RPE in the healthy retina), while in Mirante device the inner boundary is the internal limiting membrane (ILM) while the outer border is the base of the RPE (RPE/BM). As the inner and outer boundaries are at the same level among both devices, then comparability between both imaging modalities can be achieved.

As the total macula thickness boundaries can be manually corrected in both Spectralis and Mirante output, correction of errors in individual layer segmentation is possible. We did not observe a significant difference in total macula thickness means before and after manual revision of inner and outer retinal boundaries in both devices. No segmentation errors were detected in the healthy subjects, demonstrating the incidence of retinal pathology indicates a more significant influence involving accurate segmentation. Segmentation errors involving the ILM were predominately due to subjects with ERM, which were more frequent in individuals with hyper-reflective ERMs. Segmentation errors of BM were also more pronounced in cases of macular oedema; as the slab thickness does not alter even though the thickness of the retinal layers expands substantially due to the oedema [34]; and were more prevalent due to the intensity discontinuity and inconsistencies in the retinal layers [3].

Remarkably, the discrimination of the FAZ borders did not differ significantly between devices, although the SCP was better visualized than the DCP across both devices. The variability of FAZ measurements has been documented in studies [35–37], perhaps the lack of inter-individual disparity in the present study may be due to the use of the whole retinal slab [38].

The Nidek Mirante has previously been studied to detect drusen by Cozzi et al. (2020) [39]. However, this study was the first to compare to the Heidelberg

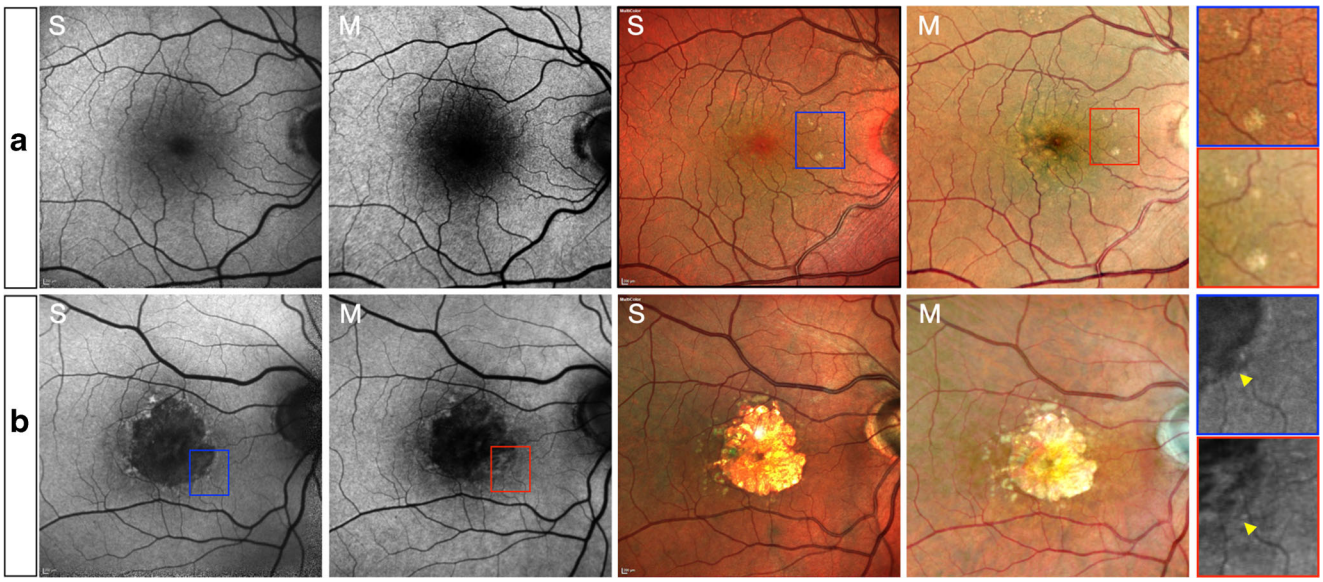


Fig. 4 Fundus autofluorescence and cSLO colour imaging of a patient affected by intermediate AMD (A) and geographic atrophy (B). The first row shows the multimodal imaging obtained with Heidelberg Spectralis (S) and Nidek Mirante (M) in a case of intermediate AMD. The magnified cSLO colour images clearly reveal the presence of multiple drusen with similar aspects between the two devices. The second row (B) represents multimodal imaging obtained with Heidelberg Spectralis (S) and Nidek Mirante (M) in a case of geographic atrophy. Magnified views of FAF exhibit a slightly different autofluorescence pattern in the inferior-nasal sector of the atrophic lesion (yellow arrow heads). Despite this subtle difference, the atrophic lesion appears visible and clear between both devices. cSLO, confocal scanning laser ophthalmoscopy; AMD, age-related macular degeneration; FAF, fundus autofluorescence

Table 5 Interobserver reproducibility of FAZ area measurements of the SCP and DCP OCTA for both devices

	SCP ICC (95%CI)	DCP ICC (95%CI)
Spectralis	0.995 (0.988–0.998)	0.976 (0.971–0.989)
Mirante	0.994 (0.986–0.998)	0.972 (0.965–0.979)

Spectralis. Those authors included 100 eyes with early or intermediate AMD and concluded the Mirante had excellent sensitivity and specificity for characterizing different types of drusen. These findings, along with the results of the present study, emphasize Mirante's exceptional ability to identify specific retinal pathology. The comparison of imaging quality and reliability between the two multimodal devices will be of high interest in the development of future retinal imaging studies, especially inclusion of multiple sites who have different imaging devices.

In our study, we used the standard Heidelberg Spectralis and clinical fundoscopy to assess the sensitivity of the Mirante and its ability to detect even finite pathology. We report high sensitivity for detecting several predefined retinal pathologies using the Mirante Navis software used on images obtained with the Mirante. This was comparable to the high sensitivity of the Spectralis, which showed high sensitivity and specificity in the present study compared to conventional clinical fundoscopy. However, the high sensitivity and specificity benefit from the exclusion of ungradable images. Presumably, the sensitivity and specificity scores would have been lower if the ungradable images were included.

This study's strengths include the use of standardized imaging protocols to obtain the OCT scans and trained graders to define the choroidoscleral boundaries. The reliability of manual grading is demonstrated by the high ICC (0.998). The OCT scans on different devices were performed consecutively, within a few minutes of each other, to eliminate the potential effects of diurnal variation [40, 41]. The prospective recruitment of healthy volunteers with no retinal disease minimizes any possible confounding factors from eyes with retinal diseases.

The study's limitations include lower ICC in the retinal disease group than in the healthy group in our study. This may be due to the low mean visual acuity, unstable gaze, or auto-segmentation errors due to the change in macular contour—secondly, the small sample size, which increases the risk for type 1 errors due to the number of statistical comparisons made in the study. Further prospective studies in more significant numbers of patients are needed to confirm our present findings. Lastly, the retinal diseases included in this study were heterogeneous. In practice, segmentation errors are more likely to be more influenced by specific retinal layer abnormalities than CRT [10, 42]. For example, ERM can cause inner retinal segmentation errors [43], while AMD can cause outer retinal segmentation errors [10].

In summary, we have demonstrated good comparability in central retinal thickness and FAZ measurements and detection of retinal biomarkers on FAF and colour images obtained from 2 multimodal imaging platforms. This may allow images from either image acquisition protocol to be directly compared, allowing direct comparisons in multi-centre clinical trials and individual clinical practice.

Compliance with ethical standards

Conflict of interest A. Chang is a consultant for Allergan, Bayer, Novartis and Roche. G. Staurenghi is a consultant for Heidelberg Engineering, Quantel Medical, Centervue, Carl Zeiss Meditec, Alcon, Allergan, Bayer, Boheringer, Genentech, GSK, Novartis, and Roche and has received grant support from Optos, Optovue, and Centervue. M. Cozzi has received speaker fees from Heidelberg Engineering and Nidek. G. Staurenghi is consultant for Heidelberg Engineering and Nidek. All other authors declare no conflict of interests.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Ethics Committee of the University of Sydney [2019/1006].

Informed consent All subjects from this research read, signed, and gave the researcher their informed consent prior to their inclusion in the study. The authors affirm that human research participants provided informed consent for publication of the images in Figs. 2 and 3.

References

1. Meyer CH, Saxena S, Sadda SR (2017) Spectral domain optical coherence tomography in macular diseases. Springer, New York. https://doi.org/10.1007/978-81-322-3610-8
2. Spaide RF (2012) Questioning optical coherence tomography. Ophthalmology 119 (11):2203-2204.e2201. doi:https://doi.org/10.1016/j.ophtha.2012.09.009
3. Lauermann JL, Woetzel AK, Treder M, Alnawaiseh M, Clemens CR, Eter N, Alten F (2018) Prevalences of segmentation errors and motion artifacts in OCT-angiography differ among retinal diseases. Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie 256(10):1807–1816. https://doi.org/10.1007/s00417-018-4053-2
4. Rosenfeld PJ (2016) Optical coherence tomography and the development of antiangiogenic therapies in neovascular age-related macular degeneration. Investigative ophthalmology & visual science 57 (9):Oct14-26. doi:https://doi.org/10.1167/iovs.16-19969
5. Bogunovic H, Venhuizen F, Klimscha S, Apostolopoulos S, Bab-Hadiashar A, Bagci U, Beg MF, Bekalo L, Chen Q, Ciller C, Gopinath K, Gostar AK, Jeon K, Ji Z, Kang SH, Koozekanani DD, Lu D, Morley D, Parhi KK, Park HS, Rashno A, Sarunic M, Shaikh S, Sivaswamy J, Tennakoon R, Yadav S, De Zanet S, Waldstein SM, Gerendas BS, Klaver C, Sanchez CI, Schmidt-Erfurth U (2019) RETOUCH: the retinal OCT fluid detection and

segmentation benchmark and challenge. IEEE Trans Med Imaging 38(8):1858–1874. https://doi.org/10.1109/tmi.2019.2901398
6. Grover S, Murthy RK, Brar VS, Chalam KV (2010) Comparison of retinal thickness in normal eyes using Stratus and Spectralis optical coherence tomography. Invest Ophthalmol Vis Sci 51(5):2644–2647. https://doi.org/10.1167/iovs.09-4774
7. Carpineto P, Nubile M, Toto L, Aharrh Gnama A, Marcucci L, Mastropasqua L, Ciancaglini M (2010) Correlation in foveal thickness measurements between spectral-domain and time-domain optical coherence tomography in normal individuals. Eye (London, England) 24(2):251–258. https://doi.org/10.1038/eye.2009.76
8. Taban M, Sharma S, Williams DR, Waheed N, Kaiser PK (2009) Comparing retinal thickness measurements using automated fast macular thickness map versus six-radial line scans with manual measurements. Ophthalmology 116(5):964–970. https://doi.org/10.1016/j.ophtha.2008.12.033
9. Ghasia FF, El-Dairi M, Freedman SF, Rajani A, Asrani S (2015) Reproducibility of spectral-domain optical coherence tomography measurements in adult and pediatric glaucoma. J Glaucoma 24(1):55–63. https://doi.org/10.1097/IJG.0b013e31829521db
10. Bhende M, Shetty S, Parthasarathy MK, Ramya S (2018) Optical coherence tomography: a guide to interpretation of common macular diseases. Indian J Ophthalmol 66(1):20–35. https://doi.org/10.4103/ijo.IJO_902_17
11. Murthy RK, Haji S, Sambhav K, Grover S, Chalam KV (2016) Clinical applications of spectral domain optical coherence tomography in retinal diseases. Biom J 39(2):107–120. https://doi.org/10.1016/j.bj.2016.04.003
12. Spaide RF, Klancnik JM Jr, Cooney MJ (2015) Retinal vascular layers imaged by fluorescein angiography and optical coherence tomography angiography. JAMA ophthalmology 133(1):45–50. https://doi.org/10.1001/jamaophthalmol.2014.3616
13. Matsunaga D, Yi J, Puliafito CA, Kashani AH (2014) OCT angiography in healthy human subjects. Ophthalmic surgery, lasers & imaging retina 45(6):510–515. https://doi.org/10.3928/23258160-20141118-04
14. Corvi F, Pellegrini M, Erba S, Cozzi M, Staurenghi G, Giani A (2018) Reproducibility of vessel density, fractal dimension, and foveal avascular zone using 7 different optical coherence tomography angiography devices. Am J Ophthalmol 186:25–31. https://doi.org/10.1016/j.ajo.2017.11.011
15. Rabiolo A, Gelormini F, Marchese A, Cicinelli MV, Triolo G, Sacconi R, Querques L, Bandello F, Querques G (2018) Macular perfusion parameters in different angiocube sizes: does the size matter in quantitative optical coherence tomography angiography? Invest Ophthalmol Vis Sci 59(1):231–237. https://doi.org/10.1167/iovs.17-22359
16. Sharp PF, Manivannan A, Xu H, Forrester JV (2004) The scanning laser ophthalmoscope–a review of its role in bioscience and medicine. Phys Med Biol 49(7):1085–1096. https://doi.org/10.1088/0031-9155/49/7/001
17. Aumann S, Donner S, Fischer J, Müller F (2019) Optical coherence tomography (OCT): principle and technical realization. In: Bille JF (ed) High resolution imaging in microscopy and ophthalmology: new frontiers in biomedical optics. Springer Copyright 2019, The Author(s). Cham (CH), pp 59-85. doi:https://doi.org/10.1007/978-3-030-16638-0_3
18. Schmitz-Valckenberg S, Holz FG, Bird AC, Spaide RF (2008) Fundus autofluorescence imaging: review and perspectives. Retina (Philadelphia, Pa) 28(3):385–409. https://doi.org/10.1097/IAE.0b013e318164a907
19. Sepah YJ, Akhtar A, Sadiq MA, Hafeez Y, Nasir H, Perez B, Mawji N, Dean DJ, Ferraz D, Nguyen QD (2014) Fundus autofluorescence imaging: fundamentals and clinical relevance. Saudi journal of ophthalmology : official journal of the Saudi Ophthalmological Society 28(2):111–116. https://doi.org/10.1016/j.sjopt.2014.03.008
20. Müller PL, Pfau M, Mauschitz MM, Möller PT, Birtel J, Chang P, Gliem M, Schmitz-Valckenberg S, Fleckenstein M, Holz FG, Herrmann P (2018) Comparison of green versus blue fundus autofluorescence in ABCA4-related retinopathy. Translational vision science & technology 7(5):13. https://doi.org/10.1167/tvst.7.5.13
21. Shiihara H, Terasaki H, Sonoda S, Kakiuchi N, Shinohara Y, Tomita M, Sakamoto T (2018) Objective evaluation of size and shape of superficial foveal avascular zone in normal subjects by optical coherence tomography angiography. Sci Rep 8(1):10143. https://doi.org/10.1038/s41598-018-28530-7
22. Battaglia Parodi M, Romano F, Cicinelli MV, Rabiolo A, Arrigo A, Pierro L, Iacono P, Bandello F (2018) Retinal vascular impairment in best vitelliform macular dystrophy assessed by means of optical coherence tomography angiography. Am J Ophthalmol 187:61–70. https://doi.org/10.1016/j.ajo.2017.12.013
23. Chiang TT, Keenan TD, Agrón E, Liao J, Klein B, Chew EY, Cukras CA, Wong WT (2020) Macular thickness in intermediate age-related macular degeneration is influenced by disease severity and subretinal drusenoid deposit presence. Invest Ophthalmol Vis Sci 61(6):59. https://doi.org/10.1167/iovs.61.6.59
24. Viera AJ, Garrett JM (2005) Understanding interobserver agreement: the kappa statistic. Fam Med 37(5):360–363
25. Lu Y, Wang JC, Zeng R, Katz R, Vavvas DG, Miller JW, Miller JB (2019) Quantitative comparison of microvascular metrics on three optical coherence tomography angiography devices in chorioretinal disease. Clinical ophthalmology (Auckland, NZ) 13:2063-2069. doi:https://doi.org/10.2147/opth.S215322
26. Falavarjani KG, Shenazandi H, Naseri D, Anvari P, Kazemi P, Aghamohammadi F, Alissmail F, Alemzadeh SA (2018) Foveal avascular zone and vessel density in healthy subjects: an optical coherence tomography angiography study. Journal of ophthalmic & vision research 13(3):260–265. https://doi.org/10.4103/jovr.jovr_173_17
27. Mo S, Krawitz B, Efstathiadis E, Geyman L, Weitz R, Chui TY, Carroll J, Dubra A, Rosen RB (2016) Imaging foveal microvasculature: optical coherence tomography angiography versus adaptive optics scanning light ophthalmoscope fluorescein angiography. Investigative ophthalmology & visual science 57 (9):Oct130-140. doi:https://doi.org/10.1167/iovs.15-18932
28. Wylegala A, Teper S, Dobrowolski D, Wylegala E (2016) Optical coherence angiography: a review. Medicine 95(41):e4907. https://doi.org/10.1097/md.0000000000004907
29. Chin EK, Sedeek RW, Li Y, Beckett L, Redenbo E, Chandra K, Park SS (2012) Reproducibility of macular thickness measurement among five OCT instruments: effects of image resolution, image registration, and eye tracking. Ophthalmic surgery, lasers & imaging : the official journal of the International Society for Imaging in the Eye 43(2):97–108. https://doi.org/10.3928/15428877-20111222-02
30. Heussen FM, Ouyang Y, McDonnell EC, Narala R, Ruiz-Garcia H, Walsh AC, Sadda SR (2012) Comparison of manually corrected retinal thickness measurements from multiple spectral-domain optical coherence tomography instruments. Br J Ophthalmol 96(3):380–385. https://doi.org/10.1136/bjo.2010.201111
31. Major JC Jr, Wykoff CC, Mariani AF, Chen E, Croft DE, Brown DM (2014) Comparison of spectral-domain and time-domain optical coherence tomography in the detection of neovascular age-related macular degeneration activity. Retina (Philadelphia, Pa) 34(1):48–54. https://doi.org/10.1097/IAE.0b013e3182965743
32. Smretschnig E, Krebs I, Moussa S, Ansari-Shahrezaei S, Ansari-Shahrezarei S, Binder S (2010) Cirrus OCT versus Spectralis OCT: differences in segmentation in fibrovascular pigment epithelial detachment. Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie 248. doi:https://doi.org/10.1007/s00417-010-1415-9

33. Willoughby AS, Chiu SJ, Silverman RK, Farsiu S, Bailey C, Wiley HE, Ferris FL 3rd, Jaffe GJ (2017) Platform-independent cirrus and Spectralis thickness measurements in eyes with diabetic macular edema using fully automated software. Translational vision science & technology 6(1):9. https://doi.org/10.1167/tvst.6.1.9
34. Spaide RF (2016) Volume-rendered optical coherence tomography of retinal vein occlusion pilot study. Am J Ophthalmol 165:133–144. https://doi.org/10.1016/j.ajo.2016.02.037
35. Munk MR, Giannakaki-Zimmermann H, Berger L, Huf W, Ebneter A, Wolf S, Zinkernagel MS (2017) OCT-angiography: a qualitative and quantitative comparison of 4 OCT-A devices. PLoS One 12(5): e0177059. https://doi.org/10.1371/journal.pone.0177059
36. Trachsler S, Baston AE, Menke M (2019) Intra- and interdevice deviation of optical coherence tomography angiography. Klinische Monatsblatter fur Augenheilkunde 236(4):551–554. https://doi.org/10.1055/a-0747-5333
37. Anegondi N, Kshirsagar A, Mochi TB, Sinha Roy A (2018) Quantitative comparison of retinal vascular features in optical coherence tomography angiography images from three different devices. Ophthalmic surgery, lasers & imaging retina 49(7):488–496. https://doi.org/10.3928/23258160-20180628-04
38. Campbell JP, Zhang M, Hwang TS, Bailey ST, Wilson DJ, Jia Y, Huang D (2017) Detailed vascular anatomy of the human retina by projection-resolved optical coherence tomography angiography. Sci Rep 7:42201. https://doi.org/10.1038/srep42201
39. Cozzi M (2020) Sensitivity and specificity of multimodal imaging in characterising drusen. Ophthalmology retina 4(10):987–995. https://doi.org/10.1016/j.oret.2020.04.013
40. Sarwar S, Hassan M, Soliman MK, Halim MS, Sadiq MA, Afridi R, Agarwal A, Do DV, Nguyen QD, Sepah YJ (2018) Diurnal variation of choriocapillaris vessel flow density in normal subjects measured using optical coherence tomography angiography. Int J Retina Vitreous 4:37. https://doi.org/10.1186/s40942-018-0140-0
41. Munk MR, Kiss CG, Ekmekcioglu C, Huf W, Sulzbacher F, Gerendas B, Simader C, Schmidt-Erfurth U (2014) Influence of orthostasis and daytime on retinal thickness in uveitis-associated cystoid macular edema. Curr Eye Res 39(4):395–402. https://doi.org/10.3109/02713683.2013.845227
42. Alshareef RA, Dumpala S, Rapole S, Januwada M, Goud A, Peguda HK, Chhablani J (2016) Prevalence and distribution of segmentation errors in macular ganglion cell analysis of healthy eyes using cirrus HD-OCT. PLoS One 11(5):e0155319. https://doi.org/10.1371/journal.pone.0155319
43. Kim JM, Kim KN, Kim WJ, Kim CS (2019) Influence of epiretinal membranes on the retinal nerve fiber layer thickness measured by spectral domain optical coherence tomography in glaucoma. Korean journal of ophthalmology : KJO 33(5):422–429. https://doi.org/10.3341/kjo.2018.0105

Appendix 3

Published Co-authored Paper – “Long-term Anti-Vascular Endothelial Growth Factor Treatment for Neovascular Age-Related Macular Degeneration: The LATAR Study: Report 1: Ten-Year, Real-World Outcomes.”

AMERICAN ACADEMY OF OPHTHALMOLOGY®

Long-term Anti–Vascular Endothelial Growth Factor Treatment for Neovascular Age-Related Macular Degeneration: The LATAR Study

Report 1: Ten-Year, Real-World Outcomes

Kimberly Spooner, MMedHum, PhD,[1] Samantha Fraser-Bell, MBBS, PhD,[2] Thomas Hong, PhD,[1] Long Phan, MOrth,[1,3] James G. Wong, MBBS,[2,4] Andrew Chang, MBBS, PhD[1,2]

Purpose: To report the 10-year outcomes of eyes with neovascular age-related macular degeneration (nAMD) treated with vascular endothelial growth factor (VEGF) inhibitors.

Design: Ten-year, retrospective cohort study.

Participants: A total of 1046 patients who commenced treatment with anti-VEGF for nAMD.

Methods: Anti-VEGF–naïve eyes diagnosed with nAMD that commenced treatment between November 2006 and December 2009 were identified. Data collected included the baseline demographics, visual acuity (VA), and number of intravitreal injections. Baseline fundus fluorescein angiograms and OCT images were graded for choroidal neovascularization type. OCT images were graded for central macular thickness (CMT) and the presence of fluid over the 10 years.

Main Outcome Measures: Change in vision at 10 years. Secondary outcomes included the proportion of eyes with 20/40 vision or better and 20/200 or worse, the proportion of eyes that were dry on OCT imaging, and the number of injections.

Results: Of 1046 eligible eyes, 10-year data were available for 293 (28%), which were included in the analyses. Eyes received 58.1 (standard deviation [SD], 33.6) injections during the 10 years. The mean CMT decreased from 355.5 μm (SD, 107.8 μm) to 264.2 (SD, 79.5) μm ($P < 0.001$). The median baseline VA was 60 (interquartile range [IQR], 45–70) letters, which improved by 9 (IQR, 1–14) letters after the first year of treatment ($P < 0.001$). Over the 10-year period, these initial gains were lost over time with a final VA change of +3 letters (IQR, 8–10 letters, $P = 0.162$). However, the proportion of eyes with VA 20/40 or better increased from 29% at baseline to 35% at 10 years ($P < 0.001$). The proportion of eyes at baseline with VA 20/200 or worse was 14% and 17% at 10 years.

Conclusions: On average, eyes with nAMD maintained starting VA when treated with VEGF inhibitors for 10 years. With ongoing regular treatment, a greater proportion of eyes achieved VA of 20/40 or better at 10 years than at presentation. *Ophthalmology Retina 2021;5:511-518 © 2020 by the American Academy of Ophthalmology*

Neovascular age-related macular degeneration (nAMD) is a progressive, degenerative disease of the retina that causes significant vision loss and irreversible blindness in the elderly population.[1] The development of intravitreally injected vascular endothelial growth factor (VEGF) inhibitors has revolutionized the treatment outcomes of this disabling disease, and they are now considered the gold standard.[2,3]

Many studies have demonstrated the ability of intravitreally injected VEGF inhibitors to prevent severe vision loss in the first 2 years of treatment.[3-6] However, relatively few investigators have addressed outcomes after 5 years or more[7,8] despite the widely accepted recommendation that patients continue ongoing treatment well beyond that.[9,10]

The present study aims to assess the outcomes of eyes with nAMD treated with the licensed VEGF inhibitors ranibizumab (Lucentis: Genentech, San Francisco, CA) and aflibercept (Eylea: Regeneron, Tarrytown, NY) for 10 years in routine clinical practice.

Methods

This was a retrospective chart review of all consecutive patients in a private retina practice diagnosed with nAMD who initiated

https://doi.org/10.1016/j.oret.2020.09.019
ISSN 2468-6530/20

treatment with intravitreal therapy between November 2006 and December 2009.

Patients were identified through a search of the electronic pharmacy database. Exclusion criteria included prior anti-VEGF therapy, other macular diseases such as diabetic retinopathy or retinal vein occlusion, and fewer than 3 injections in the first 12 months of treatment. The sample was derived from a pool of patients of 4 practitioners from a single tertiary referral center. Generally, between 2006 and 2008, patients were treated as per local label instructions (i.e., monthly). Then, from late 2008, patients were converted over time to a modified treat-and-extend regimen according to the treating physician. Being routine clinical practice, the extension did not follow specific rules, and earlier on, physicians were more cautious at extending the interval between injections. By 2010, treat-and-extend became more accepted, and the treating physicians followed a more typical approach, that is, extending the interval by 1 to 2 weeks to a maximum of 12 weeks, in eyes without fluid or hemorrhage and stable VA. Although the treating physicians did not typically extend treatment past 12 weeks, in routine clinical practice, patients could receive injections less often than 12 weeks. Upon recurrent signs of active disease, the injection frequency was shortened by at least 2 weeks (to a minimum of 4-week intervals).

Institutional Review Board approval was obtained from the University of Sydney (Approval No: 2019/997). The study adhered to the tenets of the Declaration of Helsinki. Informed consent was waived for this study.

Demographic and clinical features were obtained from the medical records, including age at baseline, sex, and visual acuity (VA). Fundus fluorescein and indocyanine green angiograms and OCT images were graded by masked graders to classify the lesion types (types 1, 2, and 3 or polypoidal choroidal vasculopathy).

Ranibizumab was administered in all patients because it was the sole licensed VEGF inhibitor available through the government insurance scheme (Australian Pharmaceutical Benefits Scheme), which became available in February 2007, with some patients accessing earlier treatment in November 2006 by patient familiarization schemes. Aflibercept was subsidized later in March 2012.

Visual acuity was determined at every clinical visit using a standard Snellen chart at 6 m with the patient's regular correction/spectacles and supplemented with pinhole correction. This highest number was used. Lower VAs such as counting fingers and hand movements were converted using the method described by Lange et al.[11] Snellen acuity was converted to ETDRS letters for analysis.[12] Yearly data were defined as the examination at each year closest to the month at which treatment had been initiated. If there were 2 visits equidistant (before and after the month), then the later one was used for analysis. Futility was determined by the treating physician after assessment and discussion with the patient. Treatment was considered futile if the visual prognosis was poor because of extensive atrophy or fibrosis and would be unlikely to improve with treatment. This decision was made on an individualized basis with no firm defined criteria. A patient who was legally blind (in both eyes) may have continued to receive anti-VEGF treatment to his/her better eye to maintain vision, whereas a patient with excellent vision in his/her better-seeing eye may have been more likely to cease treatment in the poorer-seeing eye.

Outcomes

The primary outcome was the difference in VA 10 years after starting treatment. Secondary outcomes included the number of injections, proportion of eyes with VA 20/40 or better, proportion of eyes with VA 20/200 or worse, and proportion of eyes that were dry on OCT imaging at 10 years.

Central macular thickness (CMT) was measured using OCT as the average thickness of the 1-mm thickness map measurement area. Macular atrophy (MA) was also examined whether MA occurred 10 years after treatment using OCT and multimodal imaging. Initially, all patients' OCT scans were captured using the Zeiss Cirrus OCT (Oberkochen, Germany) and later converted to Heidelberg Spectralis (Heidelberg, Germany).

Statistical Analysis

Statistical analyses were performed using SPSS version 24.0 (IBM Corp, New York, NY). Data were first analyzed for normality using the Shapiro–Wilk test. Continuous variables are expressed as means (standard deviation [SD]), median (first and third quartiles), or percentages where applicable. Categoric variables are expressed as numbers and percentages. To compare 2 dependent variables, repeated-measures t test was used. Generalized estimating equations were used to account for the inclusion of 2 eyes from the same patient. Univariate and multivariate analyses with logistic regression were used to determine variables associated with the final VA, including age, sex, baseline VA, number of injections, and fluid status. A P value < 0.05 was considered statistically significant.

Results

The initial search yielded 1202 eyes, which started ranibizumab injections between November 2006 and December 2009. The mean age at initiation of therapy was 74.5 (SD, 8.9) years with a median VA of 60 (interquartile range [IQR], 45–70) letters. Seventy-three eyes did not receive at least 3 injections in the first year, and 83 eyes underwent prior PDT therapy and were thus excluded from the analyses. Of the remaining 1046 eyes, 10-year data were available for 293 eyes (28%). Data from both eyes of 43 patients were analyzed. The baseline characteristics of eyes for which there are 10-year data and those lost to follow-up are summarized in Table 1.

Eyes Lost to Follow-up

The median baseline VA of eyes lost to follow-up was similar to that of included eyes (60 [IQR, 44–70] letters in eyes lost to follow-up vs. 60 [IQR, 45–70] letters in included eyes; $P = 0.679$). Patients who did not complete 10 years of follow-up were 7.5 years older than those who did (81.7 [SD, 7.9] vs. 74.5 [SD, 8.9] years, respectively; $P < 0.001$). The first 2 years of treatment had the most substantial proportion of eyes discontinuing treatment, with 272 eyes (26%) that initiated treatment not returning for further treatment. A further 136 eyes (13%) were lost between the second and third year of treatment. The proportion of eyes lost to follow-up in the remaining years are presented in Figure 1. Noncompleters had a significantly lower VA change in the first year of treatment (1 [IQR, 1–3] vs. 8 [IQR, 0–14] letters, $P < 0.001$), despite receiving a similar number of injections (7.6 vs. 7.7, $P = 0.9$) (Fig 2). Noncompleters continued to have significantly lower VA gains at the year of dropout (Fig 2), with similar injection frequency to those that completed 10 years ($P < 0.001$), except for the final year in which VA was similar (56 [IQR, 40–70] vs. 56 [IQR, 42–76], $P = 0.54$).

A total of 753 eyes did not complete 10 years of follow-up; 417 of 753 patients (55%) were deceased, 288 of 753 patients (38%) relocated and transferred to a specialist closer to home, 14 patients (2%) discontinued treatment because of futility, and the reason was unknown for 107 patients (14%).

Table 1. Baseline Characteristics of Eyes with Neovascular Age-Related Macular Degeneration with 10-Year Data Compared with Those Lost to Follow-Up

Characteristic	Eyes with 10-Year Data (n = 293)	Eyes Lost to Follow-up (n = 753)	*P* Value
Age (yrs), mean (SD)	74.5 (8.9)	81.7 (7.9)	<0.001
Female, n (%)	154 (62)	473 (63)	0.87
VA, letter score, median (IQR)	60 (45−70)	60 (44−70)	0.89
Baseline MA, n (%)	63 (22)	188 (25)	0.43
Baseline CMT, μm (SD)	355.5 (107.8)	341.7 (82.4)	0.12
Lens status			0.03
Phakic, n (%)	167 (57)	527 (70)	
Underwent cataract surgery during study, n (%)	68 (41)	45 (20)	0.05
Hypertension, n (%)	152 (52)	414 (55)	0.56
Diabetes mellitus, n (%)	32 (11)	68 (9)	0.63
Choroidal neovascularization classification, n (%)			0.23
Type 1	132 (45)	324 (43)	
Type 2	120 (41)	309 (41)	
Type 3 (retinal angiomatous proliferation)	19 (6)	58 (8)	
Polypoidal choroidal vasculopathy	22 (8)	63 (8)	

CMT = central macular thickness; IQR = interquartile range; MA = macular atrophy; SD = standard deviation; VA = visual acuity.

Ten-Year Outcomes

The mean age of patients with 10-year follow-up data (n = 293 eyes) was 74.5 (SD, 8.9) years at the initiation of therapy, 154 (62%) were women, and 275 (94%) were White (Table 1). The mean follow-up time for all included patients was 11.5 (SD, 0.7) years after initiating therapy.

Visual Acuity Changes

The median baseline VA of eyes with 10-year follow-up was 60 (IQR, 45−70) letters (mean 55.9 letters [SD, 16.2], Snellen acuity 20/80). By evaluating the change in VA over time, there was a significant gain in median VA 1 year after starting treatment by 9 (IQR, 1−14) letters ($P < 0.001$) and then a gradual decline in VA began at the year 2 visit that continued to decline over time. The final VA of all eyes was maintained at 60 (IQR, 40−76) ($P = 0.16$) (mean, 56.8 [SD, 19.8] letters) (Fig 3).

The proportion of eyes with VA ≥70 letters (Snellen 20/40 or better) at baseline was 29% (n = 84), with this proportion increasing to 35% (n = 104) at 10 years. The proportion of eyes with VA ≤35 letters (Snellen acuity, 20/200) or worse was 14% (40 eyes) at baseline and increased to 17% (51 eyes) at year 10. At the 10-year visit, the proportion of eyes that gained ≥15 letters was 46 eyes (16%), and 181 eyes (62%) had maintained or gained vision (≥0 letters improvement in VA). The proportion of eyes losing ≥15 letters at year 10 was 17% (n = 49) (Table 2).

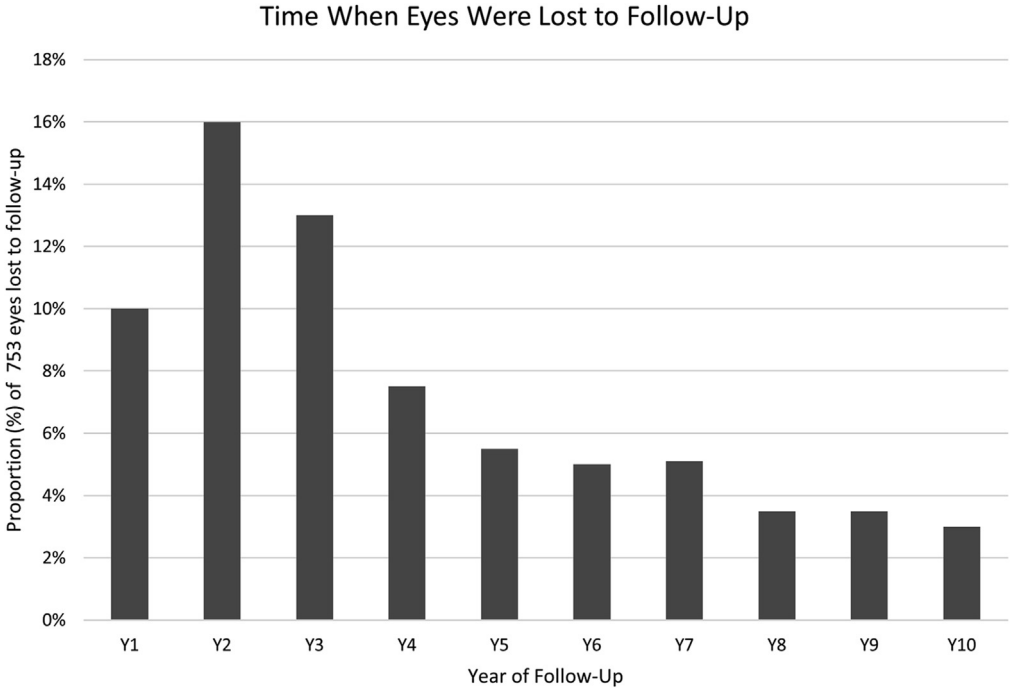


Figure 1. Proportion of patients lost to follow-up by year.

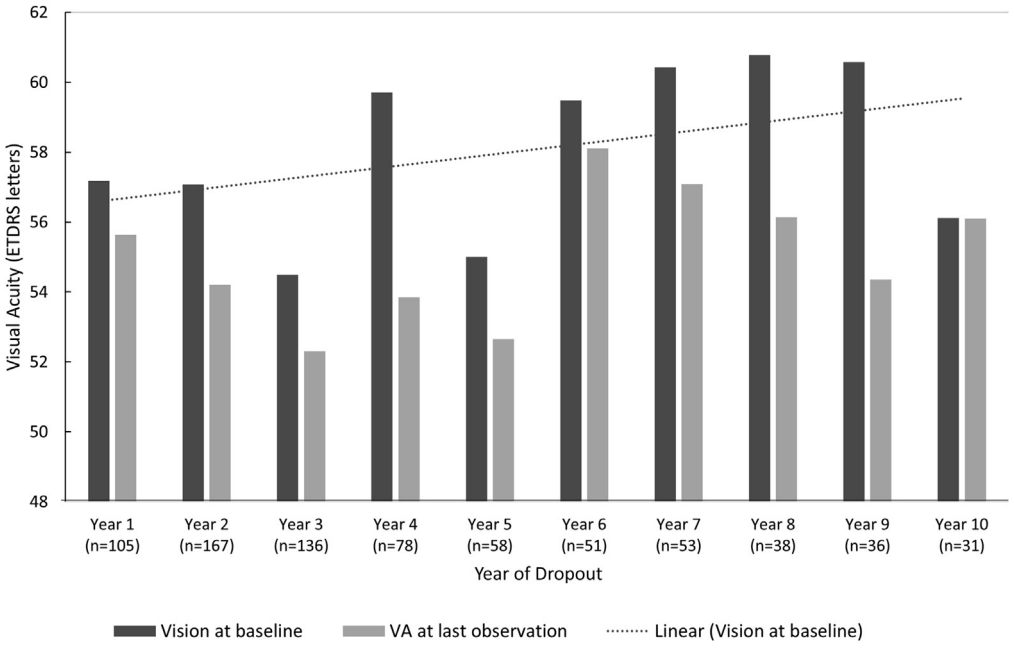


Figure 2. The number of eyes that discontinued treatment over time and compares their mean visual acuity (VA) from baseline with the last observation before they discontinued.

The mean VA of eyes with baseline VA ≥70 letters was maintained over the 10 years of follow-up with a median final VA of 76 letters (IQR, 60−82). The eyes with initial poor VA (≤35 letters at baseline) gained a median of 5 (IQR, 0−10) letters (mean 10.3 letters) for a final VA of 35 (IQR, 34−40) letters (Fig 3).

Univariate analysis demonstrated that eyes with poorer baseline VA (≤35 letters) were more likely to have higher gains in VA at 10 years, but had a poorer chance of attaining VA of 20/40 or better ($P < 0.0001$) (Fig 3). Younger age ($P = 0.045$) and a greater number of injections ($P = 0.017$) were also associated with greater VA improvement. There was no association among sex ($P = 0.6$), baseline CMT ($P = 0.06$), and change in VA.

Anatomic Outcomes

The mean CMT decreased significantly from 355.5 μm (SD, 107.8) at baseline to 276 μm at 1 year ($P < 0.001$), when it stabilized. The final mean CMT was 264.2 μm (SD, 79.5). The most significant mean difference in CMT was among the eyes with a lower initial VA

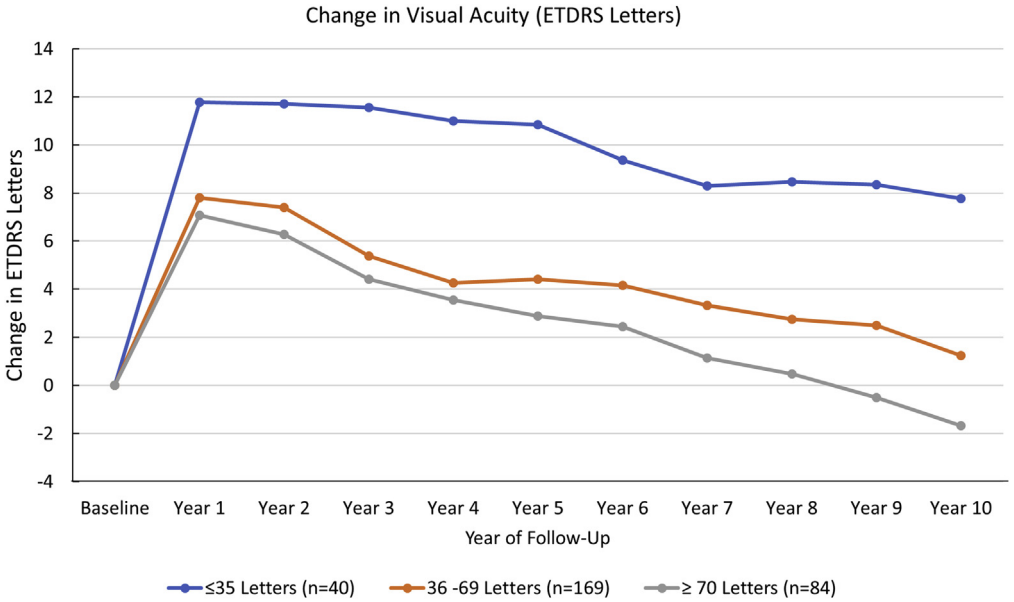


Figure 3. Change in VA over time of 293 eyes with neovascular age-related macular degeneration (nAMD) treated with anti−vascular endothelial growth factor (VEGF) agents with 10-year follow-up stratified by baseline VA **(gray line)** ≥70 letters, **(orange line)** >35 to <70 letters, and **(blue line)** ≤35 letters.

Table 2. Clinical Characteristics of Eyes with Neovascular Age-Related Macular Degeneration after 10 Years of Anti–Vascular Endothelial Growth Factor Therapy

Characteristic	Eyes with 10-Year Data (n = 293)
Mean change in VA, letter score (SD)	1.3 (16.0)
Mean change in CMT, μm (SD)	−90.4 (120.5)
MA at 10 yrs, n (%)	174 (59)
Subfoveal atrophy	62 (21)
Nonsubfoveal atrophy	112 (79)
Fibrosis at 10 yrs, n (%)	126 (43)
Proportion eyes achieving ≥20/40, n (%)	104 (35)
Proportion eyes ≤20/200, n (%)	51 (17)
Proportion eyes gaining ≥15 letters, n (%)	46 (16)
Proportion eyes losing ≥15 letters, n (%)	49 (17)
No. of injections, n (%)	58.1 (33.6)

CMT = central macular thickness; MA = macular atrophy; SD = standard deviation; VA = visual acuity.

with a mean reduction of 112.1 μm (SD, 159.8) over the 10 years of follow-up. The eyes with the better initial VA demonstrated the least mean reduction in final CMT of 72.2 μm (SD, 88.7). However, the eyes with the poorer initial VA had a higher baseline CMT compared with those with better initial VA (389.7 vs. 329.1 μm, $P = 0.03$). The treatment effect demonstrated a continuous decline for up to 10 years ($R^2 = -0.7$, $P = 0.05$) (Fig 4).

All eyes had fluid on OCT imaging at baseline. At the final visit, 104 eyes (35%) still had OCT evidence of fluid (30 eyes with SRF and 90 eyes with intraretinal fluid). Macular atrophy had developed in 174 eyes (59%) and subretinal fibrosis in 125 eyes (43%) (Table 2). Macular atrophy was more likely to occur in type 2 and 3 choroidal neovascularization than the other types ($P = 0.03$ and 0.04, respectively). Intraretinal fluid was associated with MA at year 10 (R = 0.72, $P < 0.001$), but SRF was not (R = −0.31, $P = 0.45$). There was no association between the number of injections and the development of MA at year 10 (R = 0.04, $P = 0.96$). Baseline variables associated with development of subfoveal MA included age (R = 0.491, $P = 0.011$), intraretinal fluid (R = 0.511, $P = 0.001$), SRF (R = −0.591, $P = 0.004$), and reticular pseudodrusen (R = 0.530, $P = 0.037$).

During the 10 years of follow-up, 5 eyes developed retinal pigment epithelium tears (1.7%) and 9 eyes (3%) developed disciform scarring. Eyes that developed retinal pigment epithelium tears had low initial VA of 44.0 letters (SD, 19.4), lost a mean 10.1 letters (SD, 19.1) by the final visit ($P < 0.001$), and had an initial CMT of 360.0 μm (SD, 182.3). The mean CMT reduction at year 10 was 37.2 μm (SD, 206.4) ($P < 0.001$). Retinal pigment epithelium tears were more likely to occur in the first 5 years of treatment. Three eyes (0.008%) developed a submacular hemorrhage during the study. For 2 of 3 eyes, vision remained poor (VA <20/200), and 1 eye recovered vision to 57 letters (Snellen equivalent 20/80).

Multivariable analysis revealed that the baseline presence of intraretinal fluid ($P = 0.022$) and fibrosis ($P = 0.002$) were independent risk factors for poorer final VA. The baseline presence of subretinal hyperreflective material ($P = 0.043$) and reticular pseudodrusen ($P = 0.043$) were associated with a lower CMT reduction.

In 43 patients, fellow eyes developed nAMD during the time studied and were included in the analyses. The second eyes had a median VA of 65 (IQR, 44–70) letters when they developed nAMD and 62 letters (IQR, 40–78) at 10 years after starting treatment. There was no difference in change in vision in the first versus the second eye at 10 years ($P = 0.27$).

A total of 68 phakic patients (41%) underwent cataract surgery during the 10 years of the study. The mean time of surgery was 6.6 ± 2.7 years. The vision at the year before surgery was a median of 65 (IQR, 45–75) letters, and vision after surgery was 68 (IQR, 50–79) letters.

Injections

The mean number of injections received by eyes with 10 years of follow-up was 58.1 (SD, 33.6) (median 63 [IQR, 27–87]) intravitreal injections, and the mean number of visits was 65.5 (SD, 25.6). The mean number of injections per year ranged from 1 to 13 injections (IQR, 4–7) (Fig 5). Eyes with better initial VA (70 letters) underwent approximately double the number of injections compared with those with poor initial VA (60.6 vs. 37.9; $P < 0.001$).

In this group, a total of 17 018 injections were administered over the 10 years of follow-up. There were 2 cases of endophthalmitis (0.007%), with 1 of the 2 eyes having permanent vision loss. The causative pathogen was unknown at the time of data collection. Thirty-one eyes (11%) had suspended injection therapy for at least 6 months and resumed treatment during the study.

Discussion

The approval of ranibizumab in 2006 transformed the management of nAMD. Effective treatment of this formerly blinding disease has allowed many older individuals to maintain functional vision and independence. The results of this retrospective study demonstrate the long-term effectiveness of anti-VEGF therapy in treating nAMD. The assessment of patients treated with anti-VEGF revealed that 3 monthly injections, followed by an individualized regimen, resulted in significant improvement in vision by the end of the first year. However, VA showed a continuous decline to a level comparable to baseline over the subsequent years of follow-up.

The vision improved significantly from baseline during the first year, with a mean maximum increase of 8.1 letters achieved at year 1. Subsequently, there was a continuous decline in vision, with a final VA of 60 letters, reflecting a gain of just 3 (IQR, −8 to 10) letters compared with baseline. The Fight Retinal Blindness! project demonstrated similar vision maintenance at 10 years,[13] and the Moorfields group showed a loss of 2.1 letters from baseline.[14]

A higher proportion of eyes at 10 years achieved a vision of 20/40 or better than at baseline (29% at baseline vs. 35% at 10 years). This vision level has been used as an indicator of functional vision and is the minimum vision required to hold a driver's license in many countries. Similar proportions were demonstrated in the Fight Retinal Blindness! study,[13] in which 36% of eyes had VA ≥20/40 at baseline, which increased to 42% at 10 years and a 10-year study by Starr et al,[15] in which the proportion at baseline was 23.8%,

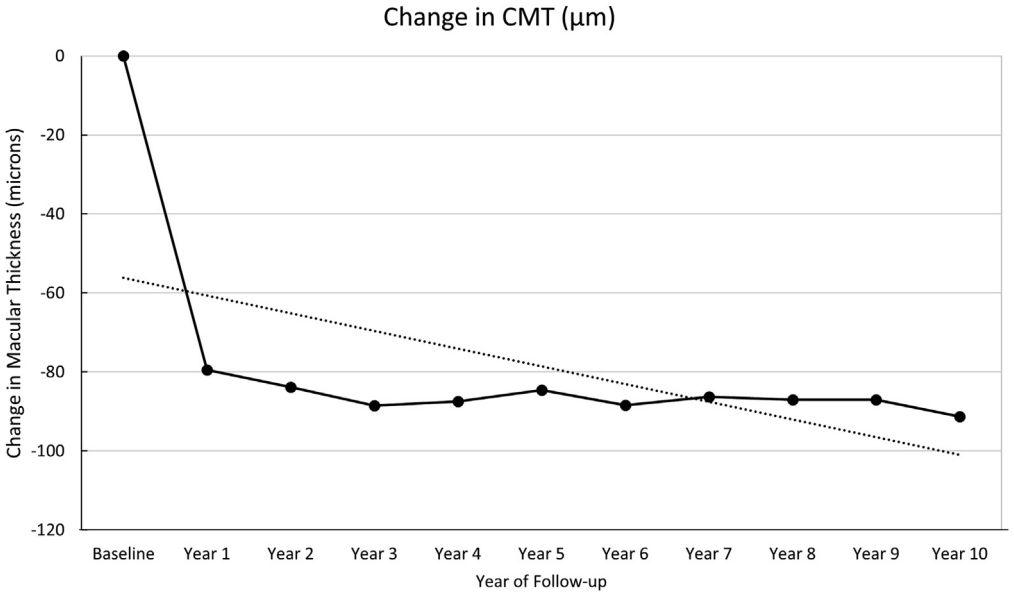


Figure 4. Change in central macular thickness (CMT) over time of 293 eyes with nAMD treated with anti-VEGF agents with 10-year follow-up.

increasing to 26.2% at 10 years. Conversely, the Moorfields study[14] demonstrated a decline in the proportion of eyes with VA ≥20/40 (39% at baseline vs. 33.5% at 10 years). This is significant considering the natural history of nAMD in which the majority of eyes would be legally blind without treatment after a few years with the disease.[1] An initial increase in mean VA followed by a gradual decline is often reported in intravitreal studies and has been proposed to be a result of atrophy formation from age-related macular degeneration[16,17] and undertreatment, often seen in routine clinical practice.

Although a direct comparison with other studies is difficult because of differences in baseline characteristics and injection protocol, 5-year outcomes in the CATT study revealed a decrease in mean BCVA with 3 letters below the baseline.[8] The SEVEN-UP study demonstrated a decline of 8.6 letters from baseline after 7.3 years of treatment and a mean of 1.6 injections per year.[10] A recent similar study of

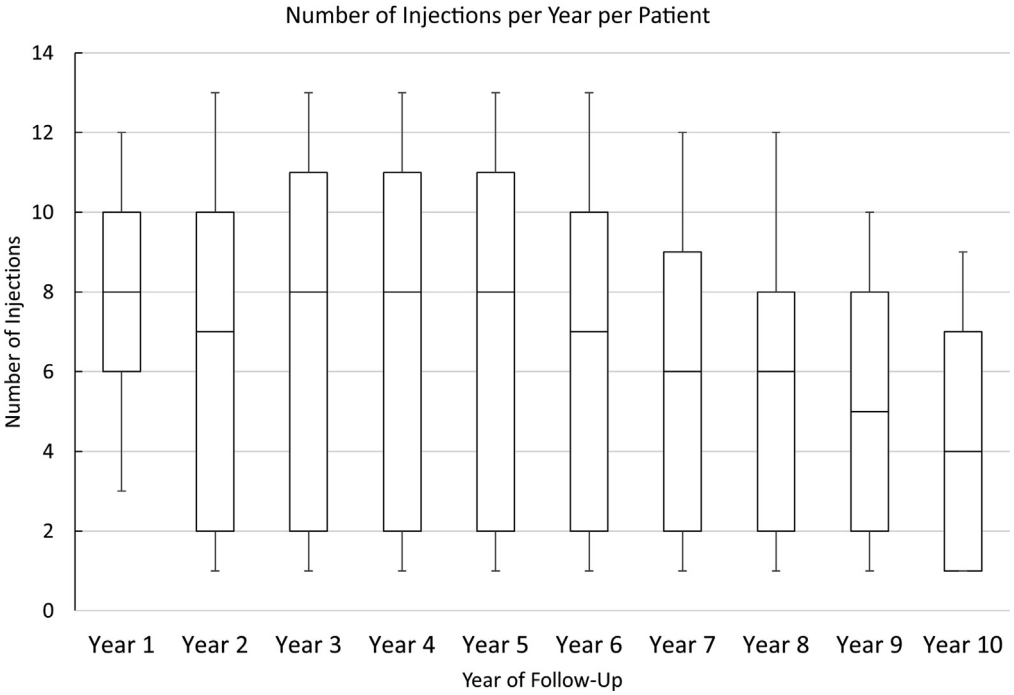


Figure 5. Box plot of the number of injections per patient per year. Median number represented by line inside the box. Lower and upper box boundaries represent 25th and 75th percentiles, respectively.

130 eyes by Starr et al[15] demonstrated a loss of 13.5 letters from baseline after 10 years of anti-VEGF treatment and a mean of 45.1 injections. It is likely the undertreatment seen in these studies or development of atrophy may be the reason for the significant loss in vision. However, recent 10-year findings from the Fight Retinal Blindness! project[13] and a study from Moorfields[14] showed similar maintenance of baseline vision to the present study with more than 50 injections given over 10 years, likely due to the higher injection rates seen in a treat-and-extend regimen commonly used in Australia and the universal reimbursement of licensed anti-VEGF agents.[18] Peden et al[19] described VA gains of +12.1 letters after 7 years of fixed-interval dosing, where patients received a mean of 10.5 injections each year, further likening the higher the frequency of injections, the more significant gains in vision seen.

Although major clinical trials undertake subanalyses by presenting vision, most trials exclude patients with vision less than 23 letters and greater than 73 letters. In the present study, we included all VA ranges. Our findings demonstrated that those with poor initial VA did undergo significant improvements in VA. Although these eyes may have significant structural damage, even a small increase in vision may push these eyes to a higher category of vision and shift the balance toward maintaining independence and reducing reliance on caregivers. The results in the present study and similar long-term studies have shown that vision typically decreases after 2 to 3 years despite treatment. It is worth recalling that maintenance of baseline vision is still significantly better than the natural history of the disease, and patients would continue to have functional vision to perform activities of daily living. Likewise, we included eyes with good vision with reduced capacity to improve vision but greater potential to keep good vision.

Our patients were elderly at presentation, and a considerable proportion of the discontinued patients in our study died during the 10-year follow-up period. High dropout rates are typical in long-term observational studies. A Danish study reported a 4-year mortality rate of 5.6% per year.[20] Another Danish study found after 4 years of treatment, the reasons for ceasing treatment were inactive disease (45%), intractable disease (28%), and unwilling to proceed with treatment (9%).[21] Those who ceased treatment lost a mean of 3.4 letters compared with baseline, compared with 0.9 letters gained by those who completed 10 years of follow-up ($P < 0.001$).

Study Strengths and Limitations

The present study has several strengths. First, the nAMD diagnosis was confirmed using fluorescein or indocyanine green angiography, minimizing the risk of misdiagnosis. Second, all patients, regardless of baseline vision and presence of morbidities, were included, thereby reducing selection bias and presenting real-world clinical data. Third, our study represents a significant and long evaluation of continuous anti-VEGF treatment.

There are also significant limitations. First, the present study was retrospective in nature. Those with less benefit from treatment were more likely to cease treatment. It is not comparable to randomized controlled trials because the concomitant systemic disease was not a reason to exclude patients. However, many real-world studies are conducted in a similar manner, are reflective of real clinical practice, and may prove useful for future nAMD treatment strategies. Second, we did not restrict vision criteria, and VA was not performed in a standardized fashion with protocol-subjective refraction. Third, treatment schedules after the initial loading phase, which might have influenced long-term outcomes, were at the discretion of the treating ophthalmologist and patient, although most underwent a treat-and-extend regimen.

Conclusions

Although ranibizumab and aflibercept have been shown to be effective in several extensive clinical studies, long-term data are limited. In the present study, we showed after an initial improvement in vision, this gradually decreased over the 10 years of follow-up to mean baseline levels. However, with ongoing frequent intravitreal injections, there is an incentive to continue treatment as a significant proportion of patients were able to preserve a functional vision of 20/40 or better.

Acknowledgments. The authors thank Shaun Jackson for providing electronic dispensing data and Eugenia Chu for collecting data.

Footnotes and Disclosures

Originally received: May 27, 2020.
Final revision: August 27, 2020.
Accepted: September 17, 2020.
Available online: September 29, 2020.

[1] Sydney Retina, Sydney, New South Wales, Australia.

[2] The University of Sydney, The Save Sight Institute, Discipline of Ophthalmology, Sydney Medical School, Sydney, New South Wales, Australia.

[3] The University of Technology, Sydney, New South Wales, Australia.

[4] Strathfield Retina Clinic, Sydney, New South Wales, Australia.

Disclosure(s):
All authors have completed and submitted the ICMJE disclosures form.
The author(s) have made the following disclosure(s): A.F.: Consultant — Allergan, Bayer, Novartis, Roche.
S.F-B.: Consultant — Allergan, Bayer, Novartis.
Author Contributions:
Conception and design: Spooner, Fraser-Bell
Data collection: Spooner, Fraser-Bell, Phan, Wong, Chang
Analysis and interpretation: Spooner, Fraser-Bell, Hong, Phan, Wong, Chang
Obtained funding: N/A

Overall responsibility: Spooner, Fraser-Bell, Hong, Phan, Wong, Chang

HUMAN SUBJECTS: Human subjects were included in this study. The human ethics committees at the University of Sydney approved the study. All research adhered to the tenets of the Declaration of Helsinki. Informed consent was waived for this study.

No animal subjects were used in this study.

Abbreviations and Acronyms:
CMT = central macular thickness; **IQR** = interquartile range; **MA** = macular atrophy; **nAMD** = neovascular age-related macular degeneration; **SD** = standard deviation; **VA** = visual acuity; **VEGF** = vascular endothelial growth factor.

Keywords:
anti-VEGF, macular degeneration, neovascular, long-term.

Correspondence:
Andrew Chang, MBBS, PhD, Sydney Retina, Level 13, Park House, 187 Macquarie St., Sydney 2000, NSW, Australia. E-mail: achang@sydneyretina.com.au.

References

1. Wong TY, Chakravarthy U, Klein R, et al. The natural history and prognosis of neovascular age-related macular degeneration: a systematic review of the literature and meta-analysis. *Ophthalmology*. 2008;115:116−126.
2. Rosenfeld PJ, Brown DM, Heier JS. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med*. 2006;355.
3. Martin DF, Maguire MG, Fine SL, et al. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. *Ophthalmology*. 2012;119:1388−1398.
4. Martin DF, Maguire MG, Ying GS, et al. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. *N Engl J Med*. 2011;364:1897−1908.
5. Schmidt-Erfurth U, Kaiser PK, Korobelnik JF, et al. Intravitreal aflibercept injection for neovascular age-related macular degeneration: ninety-six-week results of the VIEW studies. *Ophthalmology*. 2014;121:193−201.
6. Rosenfeld PJ, Rich RM, Lalwani GA. Ranibizumab: Phase III clinical trial results. *Ophthalmol Clin North Am*. 2006;19:361−372.
7. Bhisitkul RB, Desai SJ, Boyer DS, et al. Fellow eye comparisons for 7-year outcomes in ranibizumab-treated AMD subjects from ANCHOR, MARINA, and HORIZON (SEVEN-UP Study). *Ophthalmology*. 2016;123:1269−1277.
8. Maguire MG, Martin DF, Ying GS, et al. Five-year outcomes with anti-vascular endothelial growth factor treatment of neovascular age-related macular degeneration: the Comparison of Age-Related Macular Degeneration Treatments Trials. *Ophthalmology*. 2016;123:1751−1761.
9. Gerding H. Long-term results of intravitreal anti-VEGF injections in wet AMD: a meta-analysis. *Klinische Monatsblatter fur Augenheilkunde*. 2016;233:471−474.
10. Rofagha S, Bhisitkul RB, Boyer DS, et al. Seven-year outcomes in ranibizumab-treated patients in ANCHOR, MARINA, and HORIZON: a multicenter cohort study (SEVEN-UP). *Ophthalmology*. 2013;120:2292−2299.
11. Lange C, Feltgen N, Junker B, et al. Resolving the clinical acuity categories "hand motion" and "counting fingers" using the Freiburg Visual Acuity Test (FrACT). *Graefes Arch Clin Exp Ophthalmol*. 2009;247:137−142.
12. Gregori NZ, Feuer W, Rosenfeld PJ. *Novel method for analyzing Snellen visual acuity measurements*30. Philadelphia, Pa: Retina; 2010:1046−1050.
13. Gillies M, Arnold J, Bhandari S, et al. Ten-year treatment outcomes of neovascular age-related macular degeneration from two regions. *Am J Ophthalmol*. 2020;210:116−124.
14. Chandra S, Arpa C, Menon D, et al. Ten-year outcomes of anti-vascular endothelial growth factor therapy in neovascular age-related macular degeneration. *Eye (Lond)*. 2020;34:1888−1896.
15. Starr MR, Kung FF, Mejia CA, et al. Ten-year follow-up of patients with exudative age-related macular degeneration treated with intravitreal anti-vascular endothelial growth factor injections. *Retina*. 2020;40:1665−1672.
16. Munk MR, Ceklic L, Ebneter A, et al. Macular atrophy in patients with long-term anti-VEGF treatment for neovascular age-related macular degeneration. *Acta Ophthalmologica*. 2016;94:e757−e764.
17. Grunwald JE, Daniel E, Huang J, et al. risk of geographic atrophy in the comparison of age-related macular degeneration treatments trials. *Ophthalmology*. 2014;121:150−161.
18. Adrean SD, Chaili S, Ramkumar H, et al. Consistent long-term therapy of neovascular age-related macular degeneration managed by 50 or more anti-VEGF injections using a treat-extend-stop protocol. *Ophthalmology*. 2018;125:1047−1053.
19. Peden MC, Suñer IJ, Hammer ME, Grizzard WS. Long-term outcomes in eyes receiving fixed-interval dosing of anti-vascular endothelial growth factor agents for wet age-related macular degeneration. *Ophthalmology*. 2015;122:803−808.
20. Rasmussen A, Bloch SB, Fuchs J, et al. A 4-year longitudinal study of 555 patients treated with ranibizumab for neovascular age-related macular degeneration. *Ophthalmology*. 2013;120:2630−2636.
21. Brynskov T, Munch IC, Larsen TM, et al. Real-world 10-year experiences with intravitreal treatment with ranibizumab and aflibercept for neovascular age-related macular degeneration. *Acta Ophthalmol*. 2020;98:132−138.

Appendix 4

Outdoor Activity Diary

4-day Activity Diary

Study ID No.: ----------

Start Date: ----------

Office (DD /MM /YYYY)

Instructions

An important part of our research is to find out how you spend your time during weekdays and on the weekends. The 4-day Diary tells us about what you do each day and where.

- Please fill out the diary for the whole **24-hour** time period for **all 4 days which include the two weekend days.** List your first activity of the day, your second activity of the day, and on to your last activity of the day.
- **There should be no gaps in time**. The end time for one activity should match the start time for the next activity.
- Use **one line** for each activity. For each activity, **code the activity type** using the codes at the top of each page and its **start & end time**
- For each activity, please record whether you are outdoors (outside any building) or indoors (inside any building or structure)
- It works best to fill out the diary as the day goes by, so that you will remember what you did and it will be accurate.
- This **4-day Diary is completely confidential.** Only you and the research team will see it. Please be as exact as possible.

If you have any enquiries, please contact us

at

9514 7238 between 9.00 am to 5.00 pm on weekdays

(Monday to Friday)

Today is Saturday, Sunday, Monday, Tuesday, Wednesday, Thursday, Friday
please circle the correct day

Activity codes

1. Sleep

2. Travelling (car, bus and/or train)

3. University/ additional out of university classes

4. Workplace/ Clinical placement

5. Physical activity (sport, gym, riding bike, walking etc.)

6. Computer, watching TV, video-games

7. Studying, completing assignments, reading books

8. iPad/ tablet, smart phone or other hand-held electronic device

9. Other indoor activity (cooking, playing instruments etc.)

10. Other (specify)

Did you wear the light meters today? (please tick) **YES** ☐ **NO** ☐

Start time of activity	End time of activity	Name & code of the activity	Outdoor/ Indoor activity (please tick)
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02

Activity codes

1. Sleep

2. Travelling (car, bus and/or train)

3. University/ additional out of university classes

4. Workplace/ Clinical placement

5. Physical activity (sport, gym, riding bike, walking etc.)

6. Computer, watching TV, video-games

7. Studying, completing assignments, reading books

8. iPad/ tablet, smart phone or other hand-held electronic device

9. Other indoor activity (cooking, playing instruments etc.)

10. Other (specify)

Start time of activity	End time of activity	Name & code of the activity	Outdoor/ Indoor activity (please tick)
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02

Today is Saturday, Sunday, Monday, Tuesday, Wednesday, Thursday, Friday
please circle the correct day

Activity codes

1. Sleep

2. Travelling (car, bus and/or train)

3. University/ additional out of university classes

4. Workplace/ Clinical placement

5. Physical activity (sport, gym, riding bike, walking etc.)

6. Computer, watching TV, video-games

7. Studying, completing assignments, reading books

8. iPad/ tablet, smart phone or other hand-held electronic device

9. Other indoor activity (cooking, playing instruments etc.)

10. Other (specify)

Did you wear the light meters today? (please tick) **YES** ☐ **NO** ☐

Start time of activity	End time of activity	Name & code of the activity	Outdoor/ Indoor activity (please tick)
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02

Activity codes

1. Sleep

2. Travelling (car, bus and/or train)

3. University/ additional out of university classes

4. Workplace/ Clinical placement

5. Physical activity (sport, gym, riding bike, walking etc.)

6. Computer, watching TV, video-games

7. Studying, completing assignments, reading books

8. iPad/ tablet, smart phone or other hand-held electronic device

9. Other indoor activity (cooking, playing instruments etc.)

10. Other (specify)

Start time of activity	**End time of activity**	**Name & code of the activity**	**Outdoor/ Indoor activity (please tick)**
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02

Today is Saturday, Sunday, Monday, Tuesday, Wednesday, Thursday, Friday
please circle the correct day

Activity codes

1. Sleep

2. Travelling (car, bus and/or train)

3. University/ additional out of university classes

4. Workplace/ Clinical placement

5. Physical activity (sport, gym, riding bike, walking etc.)

6. Computer, watching TV, video-games

7. Studying, completing assignments, reading books

8. iPad/ tablet, smart phone or other hand-held electronic device

9. Other indoor activity (cooking, playing instruments etc.)

10. Other (specify)

Did you wear the light meters today? (please tick) **YES** ☐ **NO** ☐

Start time of activity	End time of activity	Name & code of the activity	Outdoor/ Indoor activity (please tick)
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02

Activity codes

1. Sleep

2. Travelling (car, bus and/or train)

3. University/ additional out of university classes

4. Workplace/ Clinical placement

5. Physical activity (sport, gym, riding bike, walking etc.)

6. Computer, watching TV, video-games

7. Studying, completing assignments, reading books

8. iPad/ tablet, smart phone or other hand-held electronic device

9. Other indoor activity (cooking, playing instruments etc.)

10. Other (specify)

Start time of activity	**End time of activity**	**Name & code of the activity**	**Outdoor/ Indoor activity (please tick)**
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02

Today is Saturday, Sunday, Monday, Tuesday, Wednesday, Thursday, Friday
please circle the correct day

Activity codes

1. Sleep

2. Travelling (car, bus and/or train)

3. University/ additional out of university classes

4. Workplace/ Clinical placement

5. Physical activity (sport, gym, riding bike, walking etc.)

6. Computer, watching TV, video-games

7. Studying, completing assignments, reading books

8. iPad/ tablet, smart phone or other hand-held electronic device

9. Other indoor activity (cooking, playing instruments etc.)

10. Other (specify)

Did you wear the light meters today? (please tick) **YES** ☐ **NO** ☐

Start time of activity	End time of activity	Name & code of the activity	Outdoor/ Indoor activity (please tick)
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02

Activity codes

1. Sleep

2. Travelling (car, bus and/or train)

3. University/ additional out of university classes

4. Workplace/ Clinical placement

5. Physical activity (sport, gym, riding bike, walking etc.)

6. Computer, watching TV, video-games

7. Studying, completing assignments, reading books

8. iPad/ tablet, smart phone or other hand-held electronic device

9. Other indoor activity (cooking, playing instruments etc.)

10. Other (specify)

Start time of activity	End time of activity	Name & code of the activity	Outdoor/ Indoor activity (please tick)
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02

Today is Saturday, Sunday, Monday, Tuesday, Wednesday, Thursday, Friday
please circle the correct day

Activity codes

1. Sleep

2. Travelling (car, bus and/or train)

3. University/ additional out of university classes

4. Workplace/ Clinical placement

5. Physical activity (sport, gym, riding bike, walking etc.)

6. Computer, watching TV, video-games

7. Studying, completing assignments, reading books

8. iPad/ tablet, smart phone or other hand-held electronic device

9. Other indoor activity (cooking, playing instruments etc.)

10. Other (specify)

Did you wear the light meters today? (please tick) **YES** ☐ **NO** ☐

Start time of activity	End time of activity	Name & code of the activity	Outdoor/ Indoor activity (please tick)
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02

Activity codes

1. Sleep

2. Travelling (car, bus and/or train)

3. University/ additional out of university classes

4. Workplace/ Clinical placement

5. Physical activity (sport, gym, riding bike, walking etc.)

6. Computer, watching TV, video-games

7. Studying, completing assignments, reading books

8. iPad/ tablet, smart phone or other hand-held electronic device

9. Other indoor activity (cooking, playing instruments etc.)

10. Other (specify)

Start time of activity	End time of activity	Name & code of the activity	Outdoor/ Indoor activity (please tick)
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02

Today is Saturday, Sunday, Monday, Tuesday, Wednesday, Thursday, Friday
please circle the correct day

Activity codes

1. Sleep

2. Travelling (car, bus and/or train)

3. University/ additional out of university classes

4. Workplace/ Clinical placement

5. Physical activity (sport, gym, riding bike, walking etc.)

6. Computer, watching TV, video-games

7. Studying, completing assignments, reading books

8. iPad/ tablet, smart phone or other hand-held electronic device

9. Other indoor activity (cooking, playing instruments etc.)

10. Other (specify)

Did you wear the light meters today? (please tick) **YES** ☐ **NO** ☐

Start time of activity	End time of activity	Name & code of the activity	Outdoor/ Indoor activity (please tick)
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify……………………….	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify……………………….	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify……………………….	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify……………………….	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify……………………….	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify……………………….	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify……………………….	Indoors ☐ 01 Outdoors ☐ 02

Activity codes

1. Sleep

2. Travelling (car, bus and/or train)

3. University/ additional out of university classes

4. Workplace/ Clinical placement

5. Physical activity (sport, gym, riding bike, walking etc.)

6. Computer, watching TV, video-games

7. Studying, completing assignments, reading books

8. iPad/ tablet, smart phone or other hand-held electronic device

9. Other indoor activity (cooking, playing instruments etc.)

10. Other (specify)

Start time of activity	End time of activity	Name & code of the activity	Outdoor/ Indoor activity (please tick)
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02

Today is Saturday, Sunday, Monday, Tuesday, Wednesday, Thursday, Friday
please circle the correct day

Activity codes

1. Sleep

2. Travelling (car, bus and/or train)

3. University/ additional out of university classes

4. Workplace/ Clinical placement

5. Physical activity (sport, gym, riding bike, walking etc.)

6. Computer, watching TV, video-games

7. Studying, completing assignments, reading books

8. iPad/ tablet, smart phone or other hand-held electronic device

9. Other indoor activity (cooking, playing instruments etc.)

10. Other (specify)

Did you wear the light meters today? (please tick) **YES** ☐ **NO** ☐

Start time of activity	End time of activity	Name & code of the activity	Outdoor/ Indoor activity (please tick)
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify……………………….	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify……………………….	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify……………………….	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify……………………….	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify……………………….	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify……………………….	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify……………………….	Indoors ☐ 01 Outdoors ☐ 02

Activity codes

1. Sleep

2. Travelling (car, bus and/or train)

3. University/ additional out of university classes

4. Workplace/ Clinical placement

5. Physical activity (sport, gym, riding bike, walking etc.)

6. Computer, watching TV, video-games

7. Studying, completing assignments, reading books

8. iPad/ tablet, smart phone or other hand-held electronic device

9. Other indoor activity (cooking, playing instruments etc.)

10. Other (specify)

Start time of activity	End time of activity	Name & code of the activity	Outdoor/ Indoor activity (please tick)
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02
- - : - - (am/pm)	- - : - - (am/pm)	Code of the activity ☐ Other, specify………………………..	Indoors ☐ 01 Outdoors ☐ 02

Appendix 5

Real World LDL Comparison Study – Recruitment Poster

Help prevent short-sightedness!

UTS HREC REF NO. ETH20-4870

Myopia (short-sightedness) is a type of refractive error.

Though usually corrected by wearing glasses, higher degrees can lead to uncorrectable visual impairment and potential blindness.

Not spending enough time outdoors and performing high amounts of near work is associated with becoming short-sighted

How can you help?

- Researchers in the Discipline of Orthoptics at the UTS Graduate School of Health are conducting a study to validate a device that measures these risk factors. This can help us understand how and why myopia develops.
- We are in need of student volunteers to help us test this device

For more information or if you are interested in participating, please contact: **Long.Phan@uts.edu.au**

Long.Phan@uts.edu.au
Long.Phan@uts.edu.au
Long.Phan@uts.edu.au
Long.Phan@uts.edu.au
Long.Phan@uts.edu.au
Long.Phan@uts.edu.au
Long.Phan@uts.edu.au
Long.Phan@uts.edu.au
Long.Phan@uts.edu.au
Long.Phan@uts.edu.au
Long.Phan@uts.edu.au

Appendix 6

Real World LDL Comparison Study – Outdoor Activity Questionnaire

Validation of the Clouclip for measuring Light Intensity and Near work

Pre-study questionnaire

Study Research ID: | | | | |

Background questions

1) What is your **sex**?

- ☐ Male
- ☐ Female
- ☐ Other (please specify) _____

2) What is your **age**?

☐☐ *(years old)*

Questions about your refractive error

The following questions will be used to collect information about any potential refractive error you may have and your background surrounding refractive error.

1) Are you currently required to wear **glasses or contact lenses**?

- ☐ Yes
- ☐ No

If YES go to Q1a). If NO, skip to Q2)

1a) At what age were you first required to wear glasses/contact lenses? ☐☐ *(years old)*

1b) Are you aware of what refractive error it is prescribed for?

- ☐ Short-sightedness (myopia)
- ☐ Long-sightedness (hyperopia)
- ☐ Astigmatism (irregularly shaped cornea / “football-shaped” eye)
- ☐ Short-sightedness (myopia) + astigmatism
- ☐ Long-sightedness (hyperopia) + astigmatism
- ☐ Unsure

2) Are you currently using **orthokeratology lenses**? (nightly contact lenses)

- ☐ Yes
- ☐ No

3) Have you had **refractive surgery** (laser or otherwise e.g. “LASIK”, “PRK”) in the past?

- ☐ Yes
- ☐ No

4) How many **biological parents** (mother/father) do you have with **short-sightedness** (myopia)?

- ☐ Both parents (mother and father)
- ☐ 1 parent (only mother/father)
- ☐ 0 parents (neither mother or father)

5) Please provide an estimate of your **reading distance** during study i.e. the approximate distance between your eyes and the pages of a book/screen while you study.

☐☐ *(Centimeters)*

The following questions will be used to collect information about your environmental behaviors across various days of the week. Your responses will be used solely in order to estimate the amount of time you spend both indoors and outdoors on both weekdays and weekends.

While activities between days may vary significantly, please answer each of the questions based on a typical day.

Questions about how you spend a TYPICAL UNIVERSITY/WORK DAY

1) **UNIVERSITY:** How many days per week do you attend university or work ☐ *(days)*

2) **SLEEP:** What time do you usually go to sleep on these days? *(at night)* ☐☐.☐☐ *(hour) (minute)*

3) **SLEEP:** What time do you usually wake up in the morning? ☐☐.☐☐ *(hour) (minute)*

4) **BEFORE YOU LEAVE FOR UNIVERSITY:** After you wake up in the morning and before you leave, do you spend any time outside?

- ☐ Not at all
- ☐ less than an hour
- More than one hour (please specify) ☐☐ *(hours)*

5) **TRAVEL:** What time do you leave home to go to university? ☐☐.☐☐ *(hour) (minute)*

6) **TRAVEL:** How do you travel to university and how long does it take? If you go by both a vehicle and walking, tick both boxes & note how much time is spent in each mode

- ☐ Car, bus, train or tram
- ☐ Walking, bicycle or motorbike

☐☐ ☐☐ *(minutes)*

7) **UNIVERSITY:** After arriving at university, do you spend any time outside before it starts?

- ☐ Not at all
- ☐ less than an hour
- More than one hour (please specify) ☐☐ *(hours)*

8) **UNIVERSITY:** What time do you usually start university ☐☐.☐☐
(hour) (minute)

9) **UNIVERSITY:** In your university day, do you spend any time outside?

☐ Not at all

☐ less than an hour

More than one hour (please specify) ☐☐
(hours)

10) **UNIVERSITY:** What time do you usually finish university ☐☐.☐☐
(hour) (minute)

11) **UNIVERSITY:** After university finishes, do you spend any time outside before leaving to go home/work?

☐ Not at all

☐ less than an hour

More than one hour (please specify) ☐☐
(hours)

12) **TRAVEL:** What time do you leave to go to home/work? ☐☐.☐☐
(hour) (minute)

13) **TRAVEL:** Do you travel to home/work the same way you traveled in the morning?

☐ Yes

☐ No, *if so how do you travel?* ☐ Car, bus, train or tram

☐ Walking, bicycle or motorbike ☐☐
☐☐
(minutes)

*We would now like to ask you about how you spend your time when you are not in university or asleep. We need to know how long you are indoors or outdoors and what kinds of activities you do. We will start with indoor activities. Remember **do not** include university or sleep time.*

14) Before and after a TYPICAL UNIVERSITY DAY, **WHILE YOU ARE INDOORS**, how long (per day) do you do the following activities:

14a) Read printed material for pleasure, for example reading a magazine or novel?

☐ Not at all

☐ less than an hour

More than one hour (please specify) ☐☐
(hours)

14b) Doing homework/study or attending additional classes outside university?

☐ Not at all

☐ less than an hour

More than one hour (please specify) ☐☐
(hours)

14c) Use computers for study/pleasure?

☐ Not at all

☐ less than an hour

More than one hour (please specify) ☐☐
(hours)

14d) Watch television/go to the movies?

☐ Not at all

☐ less than an hour

More than one hour (please specify) ☐☐ *(hours)*

14e) Play indoor sports or exercise indoors?

☐ Not at all

☐ less than an hour

More than one hour (please specify) ☐☐ *(hours)*

14f) Are there any other indoor activities that you would do for **more than 2 hours** in a typical day?

☐ Not at all

☐ Yes 1. ☐☐ *(hours)* Please specify the activity *(optional)* _____

2. ☐☐ *(hours)* Please specify the activity *(optional)* _____

3. ☐☐ *(hours)* Please specify the activity *(optional)* _____

15) **OUTDOORS:** Before and after a TYPICAL UNIVERSITY DAY, how many hours do you spend outdoors

DO NOT *include hours during university* ☐☐ *(hours)*

15a) Play sports or exercise outdoors?

☐ Not at all

☐ less than an hour

More than one hour (please specify) ☐☐ *(hours)*

15b) Are there any other outdoor activities that you would do often for **more than 2 hours in** a typical day, for example sitting, walking, gardening or shopping outside?

☐ Not at all

question continues on next page

☐ Yes ☐☐ *(hours)* Please specify the activity *(optional)* _____

☐ Another? ☐☐ *(hours)* Please specify *(optional)* _____

QUESTIONS ABOUT HOW YOU SPEND A TYPICAL WEEKEND

16) **INDOOR CLASSES:** Do you attend any academic tuition classes, for example mathematics or language or music classes on the weekend?

☐ Not at all

☐ less than an hour

More than one hour (please specify) ☐☐ *(hours)*

17) **SLEEP:** When do you usually go to sleep at night? ☐☐.☐☐ *(hour) (minute)*

18) **SLEEP:** What time do you usually wake up in the morning? ☐☐.☐☐ *(hour) (minute)*

19) **INDOORS:** How many hours do you spend indoors in a day ☐☐ ***DO NOT*** *include sleep or academic tuition classes* *(hours)*

20) On a typical non- university day, **WHILE YOU ARE INDOORS**, for how long (per day) do you do the following activities:

21a) Read printed material for pleasure, for example a magazine or novel?

☐ Not at all

☐ less than an hour

More than one hour (please specify) ☐☐ *(hours)*

21b) Read printed material or do handwriting for study?

☐ Not at all

☐ less than an hour

question continues on next page

More than one hour (please specify) ☐☐ *(hours)*

21c) Use computers for study/pleasure?

☐ Not at all

☐ less than an hour

More than one hour (please specify) ☐☐ *(hours)*

21d) Watch television/go to the movies?

☐ Not at all

☐ less than an hour

More than one hour (please specify) ☐☐ *(hours)*

21e) Play sports or exercise indoors?

☐ Not at all

☐ less than an hour

More than one hour (please specify) ☐☐ *(hours)*

21f) Are there any other indoor activities that you would do for **more than 2 hours** in a typical day?

☐ Not at all

☐ Yes 1. ☐☐ *(hours)* Please specify the activity *(optional)* _____

2. ☐☐ *(hours)* Please specify the activity *(optional)* _____

3. ☐☐ *(hours)* Please specify the activity *(optional)* _____

21) **OUTDOORS:** How many hours do you spend outdoors in a day ☐☐ *(hours)*
DO NOT *include university/sleep*

22) On a typical non-university day, **WHILE YOU ARE OUTDOORS**, for how long (per day) do you do the following activities:

22a) While you are outdoors, do you do any close work activities such as; reading for pleasure or study, use computers or watch television?

☐ No *(if answered no, proceed to question 25b)*

☐ Yes ☐☐ *(hours)* Please specify the activity *(optional)* _____

☐ Another? ☐☐ *(hours)* Please specify *(optional)* _____

22b) Play sports or exercise outdoors?

☐ Not at all

☐ less than an hour

More than one hour (please specify) ☐☐ *(hours)*

22c) Are there any other outdoor activities that you would do for **more than 2 hours** in a typical day, for example walking, gardening or shopping outside?

☐ Not at all

☐ Yes ☐☐ *(hours)* Please specify the activity *(optional)* _____

☐ Another? ☐☐ *(hours)* Please specify *(optional)* _____

Comments: _____

_____

_____

_____

Appendix 7

Real World LDL Comparison Study – Focus Group Structured Questions

FOCUS GROUP QUESTIONS

- Is there anything we could have done to make it easier to wear the light data loggers?

- Were you able to remember to wear the light data loggers each day and what do you think might have made it easier to remember?

- Did the Clouclip specifically cause any inconvenience or discomfort? How do you think this could be improved?

- Did you note any time when you felt that the Clouclip may not be recording the same information as the other light loggers or what you were recording in your diary and can you remember what was happening?

- Was there anything you found difficult to code in the diary?

- How easy or hard was it to complete the questionnaire and diary and how do you think it could be improved?

- Was there any time when filling out the questionnaire and diary that you felt you could not accurately reflect what you were doing in the options provided, can you think of any examples?

- Is there anything we have forgotten to ask or any other comments you might like to make?

Appendix 8

Real World LDL Comparison Study – Post-study Questionnaire

Validation of the Clouclip for measuring Light Intensity and Near work

Post-study questionnaire

Study Research ID:				

Questions about the light meters.

The following questions will be used to collect information about your experience while wearing the light meter devices.

Please rank the three devices from 1-3 (1 being most relevant, 3 being least relevant) for the following criteria:

1) **Wearability** (which device was the **most comfortable** to wear)

- ☐ Clouclip
- ☐ Actiwatch
- ☐ HOBO meter

2) **Invasiveness** (which device **interfered most** with your daily activities)

- ☐ Clouclip
- ☐ Actiwatch
- ☐ HOBO meter

Comments: _____

_____

_____

_____

Appendix 9

Real World LDL Comparison Study – Ethical Approval

30 June 2020

Dear Dr French and Team,

Re: UTS HREC REF NO. ETH20-4870– "Validation of the Cloudclip for Measuring Light Intensity and Nearwork"

Thank you for submitting your research project ethics approval and the additional information for consideration by the GSH AD-R Local Research Office Ethics Panel which has delegated approval by the UTS Human Research Ethics Review Committee to review low risk research within the Graduate School of Health.

The Panel has considered your request and resolved to approve your application. In considering the application, the Panel made a suggestion that your advertisement flyer should have information that the research is open to those who wear and those who don't wear glasses. In addition, you may want to specify on the flyer that the minimum participation age is 18.

Your approval number is UTS HREC REF NO. ETH20-4870.

Please note that the ethical conduct of research is an on-going process. The National Statement on Ethical Conduct in Research Involving Humans requires us to obtain a report about the progress of the research, and in particular about any changes to the research which may have ethical implications. This report form must be completed at least annually, and at the end of the project (if it takes more than a year).

I also refer you to the AVCC guidelines relating to the storage of data, which require that data be kept for a minimum of 5 years after publication of research. However, in NSW, longer retention requirements are required for research on human subjects with potential long-term effects, research with long-term environmental effects, or research considered of national or international significance, importance, or controversy. If the data from this research project falls into one of these categories, contact University Records for advice on long-term retention.

To access this application, please follow the URLs below:
* if accessing within the UTS network: https://rm.uts.edu.au
* if accessing outside of UTS network: https://vpn.uts.edu.au , and click on " RM7 – Production " after logging in.

If you have any queries about your ethics approval, or require any amendments to your research in the future, please do not hesitate to contact me.

Yours sincerely,

Production Note:
Signature removed
prior to publication.

Eddy Dharmadji
GSH Local Research Office
University of Technology Sydney

Appendix 10

Real World LDL Comparison Study – Consent Form

UTS UNIVERSITY OF TECHNOLOGY SYDNEY

PARTICIPANT INFORMATION SHEET
Validation of the Clouclip for measuring Light Intensity and Near Work

UTS HREC REF NO. ETH20-4870

WHO IS DOING THE RESEARCH?

My name is Long Phan (Long.Phan@student.uts.edu.au) and I am a research student within the Discipline of Orthoptics at UTS. My supervisors are Professor Kathryn Rose (Kathryn.Rose@uts.edu.au) and Dr Amanda French (Amanda.French@uts.edu.au).

WHAT IS THIS RESEARCH ABOUT?

This research is to validate a new device called the Clouclip. This device measures light exposure and the amount of time you spend doing near work. This is because studies have found that when children spend too little time outdoors and too much time on near work, they are more likely to develop myopia (short-sightedness). This important finding indicates that educational programs to promote a healthy lifestyle including increasing the time that children time spend outdoors, may help prevent myopia from developing in some children. However, before such prevention programs can be implemented we need more accurate and non-invasive ways to measure light exposure over periods of time. Once validated, the Clouclip device will provide objective measures of risk factors (time outdoors and near work) and may fulfil this purpose.

FUNDING

This project is not directly funded by any external industry or governmental sources. Clouclip devices for investigational use have been provided by collaborating researchers at the Aier Institute of Optometry and Vision Science (Aier Eye Hospital Group, China). Plano (zero-powered) spectacles, have been previously donated to the Discipline of Orthoptics by the optical company Specsavers Pty Ltd for teaching and research purposes. All other devices and investigational equipment used are as part of existing equipment as part of the Discipline of Orthoptics.

WHY HAVE I BEEN ASKED?

You have been invited to participate in this study because we are looking to first validate the Clouclip device in comparison to previously used portable light meter devices in a broad group of adolescent university students. Selected participants are required to be of at least 18 years of age and studying full-time at university.

IF I SAY YES, WHAT WILL IT INVOLVE?

If you agree to participate in this study, we will invite you to attend a baseline study session held in one of the orthoptic clinical rooms located on level 8 of UTS Building 20.

You will first be asked to complete two questionnaires asking about the normal amount of time you spend outdoors throughout the week. This should take no longer than 15 minutes.

You will then have some measurements taken of your eyes. First a test of visual acuity (the ability to read small text at a distance) and secondly, measurements of eye shape via a non-contact machine. These measurements involve looking into a machine which takes a number of scans using a variety of lights. This may cause minimal discomfort however, there will be no direct contact of your eyes and no eye drops are required.

Following this, you will be asked to wear three light meter devices during waking hours over a 4 day period. The Clouclip is a small device approximately 2cm long which attaches to the arm of a pair of glasses. If you already wear glasses, the Clouclip can be attached to your normal glasses. If you don't normally wear glasses you will be provided with some glasses (without any prescription in the lenses) to wear with the device. The Actiwatch2 is a watch-like device, similar to a Fitbit or Apple Watch that also measures light exposure, which you will be asked to wear on your wrist. Finally, the HOBO light meter is a small (58 x 33 x 23mm) lightweight (18g) device which is attached to your outer layer of clothing via a

fitness band. While wearing the light measuring devices, over the 4 day period, you will be asked to simultaneously complete a diary of your daily activities.

At the conclusion of this period, a short post-study questionnaire will be conducted. Then a focus group will be conducted with you and up to 10 other participants in the study. The study researchers will conduct the focus group where the group will be asked various questions relating to the wearing the light meters and filling out the diary. This session will be audio recorded for transcription of responses. Responses will be transcribed anonymously and will reflect feedback from the group as a whole.

ARE THERE ANY RISKS/INCONVENIENCE?

There are no particular risks for this study. However, wearing the light meters and completing the diary may cause inconvenience over the days.

Existing spectacle wearers may experience some discomfort, from the Clouclip device (though small and light). It may also potentially interfere with your peripheral vision (side vision).

If you are provided with glasses to wear over the course of the research study, these will not have any power/a prescription and they will not cause any disruption to your vision while wearing them or following the study conclusion. There may however, be some slight discomfort from the constant wearing of spectacles throughout the day. This will be minimised as we have a range of different sized spectacles which you can select. You will also be provided with a cleaning cloth to maintain clarity of vision through the glasses.

DO I HAVE TO SAY YES?

Participation in this study is voluntary. It is completely up to you whether or not you decide to take part.

WHAT WILL HAPPEN IF I SAY NO?

Participation in this study is entirely voluntary. It is completely up to you whether or not you decide to take part. If you decide not to participate, it will not affect your relationship with the researchers or the University of Technology Sydney.

If you choose to participate, you can withdraw at any time without having to give a reason. If you wish to withdraw from the study you can do so by contacting Dr Amanda French or Long Phan (contact details below). However, it may not be possible to withdraw your data from the study results if these have already had your identifying details removed. If you take part in a focus group and wish to withdraw, as this is a group discussion it will not be possible to exclude individual data once the session has commenced. Whatever your decision, please be assured that it will not affect your relationship with the University of Technology Sydney. If you decide to leave the research project, we will not collect additional personal information from you, although personal information already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law. You should be aware that data collected up to the time you withdraw will form part of the research project results.

CONFIDENTIALITY

By signing the consent form you consent to the research team collecting and using personal information about you for the research project. All this information will be treated confidentially and only the researchers named above will have access to it.

For the study, you will be assigned an ID number for the purpose of de-identification and any documents used during the study will use this ID number for collation. Data collected via machines will also use this ID number and will be destroyed by erasure once transcribed into the study documents. Written data will be stored in a locked filing cabinet, within in a locked office at UTS. Electronic data arising from the study will be stored on a password protected computer, in a locked office at UTS. Your information will only be used for the purpose of this research project. We would like to store your information for future use in research projects that may arise as an extension of this research project. In all instances your information will be treated confidentially.

The study results may be presented at a conference or in a scientific publication. In any publication or presentation, information will be provided in such a way that you cannot be identified as all information will be disseminated as a whole and not from any individual participant.

WHAT IF I HAVE CONCERNS OR A COMPLAINT?

When you have read this information, we will discuss the study with you and answer any questions you may have. If you would like to know more information at any stage or you have any concerns that you think we can help you with, please feel free to contact Long Phan at Long.Phan@student.uts.edu.au or Dr Amanda French on 9514 7238 or Amanda.French@uts.edu.au.

You will be given a copy of this form to keep.

NOTE:
This study has been approved by the University of Technology Sydney Human Research Ethics Committee [UTS HREC]. If you have any concerns or complaints about any aspect of the conduct of this research, please contact the Ethics Secretariat on ph.: +61 2 9514 2478 or email: Research.Ethics@uts.edu.au], and quote the UTS HREC reference number. Any matter raised will be treated confidentially, investigated and you will be informed of the outcome.

UTS UNIVERSITY OF TECHNOLOGY SYDNEY

CONSENT FORM

Validation of the Clouclip for measuring Light Intensity and Near work

UTS HREC REF NO. ETH20-4870.

I _____ agree to participate in the research project, Validation of the Clouclip for measuring Light Intensity and Near work (ETH20-4870) being conducted by researchers from the Discipline of Orthoptics, Graduate School of Health.

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research as described in the Participant Information Sheet.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project as described and understand that I am free to withdraw at any time without affecting my relationship with the researchers or the University of Technology Sydney.

I understand that I will be given a signed copy of this document to keep.

I agree to be:
☐ Audio recorded

I agree that the research data gathered from this project may be published in a form that:
☐ Does not identify me in any way
☐ May be used for future research purposes

I am aware that I can contact Long Phan (Long.Phan@student.uts.edu.au) or Dr Amanda French (Amanda.French@uts.edu.au) if I have any concerns about the research.

_____ ____/____/____
Name and Signature [participant] Date

_____ ____/____/____
Name and Signature [researcher or delegate] Date