NOVELTY OPTIMISATION TECHNIQUES FOR MYOPIA ASSESSMENT & MANAGEMENT

NIKOLAY BOZHIDAROV BOYCHEV

Doctor of Philosophy (PhD)

ASTON UNIVERSITY

March, 2021

©Nikolay Boychev, 2021
Nikolay Boychev asserts his moral right to be identified as the author of this thesis

This copy of the thesis has been supplied on condition that anyone who consults it is understood to recognise that its copyright belongs to its author and that no quotation from the thesis and no information derived from it may be published without appropriate permission or acknowledgement.

Thesis Summary

Aston University

Novelty Optimisation Techniques for Myopia Assessment & Management

Nikolay Bozhidarov Boychev

Doctor of Philosophy (PhD)

2021

This thesis hoped to inform the practice of future individual myopia management. All myopia risk factors across global ethnic regions must be considered, instead of relying on the most widely used averaged parameters, towards the development of growth model tools. There could be possible crucial cut points of near phoria development at specified age ranges, earlier and later in life, suggesting this myopia risk factor should be measured alongside other primary outcome parameters important for treatment efficacy. Other notable human lifespan findings included: emmetropic and female patients attended eye examinations more frequently; females exhibited higher levels of near phoria and myopia; myopes were more esophoric than emmetropes, progressive myopes were more esophoric than both myopes and emmetropes, and were less likely to increase in exophoria with age. The presumed design optimisation, regarding daily CE-marked optical myopia control strategies, was based on the possible mechanism behind myopic retinal defocus (blur) and accommodative lag in myopia development and progression. Contact lens designs could have an inherent characteristic for their treatment effect in the temporal retina at 30° and J0 astigmatic component. Multifocal contact lenses for myopia control significantly impacted glare, but did not affect contrast sensivitiy differently than standard lenses, and would offer equally acceptable treatment compliance and qualifty of life expectations. Specialty instrumentation for measuring primary outcomes (refraction and axial length) should be used interchangeably for myopia control studies. This was confirmed between the gold standard biometers, IOLMaster 700 and IOLMaster 500, for the key parameters of axial length, anterior chamber depth and corneal topography, where discrepancies in white-to-white corneal diameter values, following MiSight and NaturalVue contact lens wear, were minimal and clinically irrelevant. Further novel discoveries proved myopia control contact lenses were viable non-invasive sampling vehicles for human dopamine detection. Thus, the thesis probed the viability of novelty applications of such “labelled” and/or gold standard medical devices and instrumentations towards treating individual myopic patients and highlighted that appropriate global myopia management and standardisation remain poor.

Keywords: (practice guidelines, growth models, risk factors, optical control strategies and instrumentation, mechanisms)

Dedication

For my mother Mariela, father Karol, grandmother Stefka, and uncle Plamen.

Acknowledgements

Special thanks to my supervisors James Wolffsohn, Nicola Logan, and Raquel Gil-Cazorla, and the entire School of Optometry.

List of Contents

Title Page (p.1)

Thesis Summary (p.2)

Dedication (p.3)

Acknowledgements (p.4)

List of Contents (p.5-7)

List of Tables (p.8-10)

List of Figures (p.11-14)

Chapter 1 Introduction (p.15-16)

1.1 Emmetropisation & Eye Growth Overview
1.1.1 Paediatric Development (p.16-19)
1.1.2 Uncorrected Refractive Error Prevalence & Economic Burden (p.19)

1.2 Myopia (p.17-45)
1.2.1 Definition & Classification (p.19-22)
1.2.2 Developmental (relative peripheral refraction; eye growth; refractive ametropia; age; binocular vision) Risk Factors & Progression (p.22-25)
1.2.3 Genetic (family history; ethnicity) & Visual Environment (near work; time outdoors; education) Risk Factors & Progression (p.25-29)
1.2.4 Worldwide Myopia Prevalence (p.29-30)
1.2.5 Economic Burden of the Myopia Epidemic (p.30)
1.2.6 Modes of Myopia Treatment (p.30-34)
1.2.6.1 Spectacles (p.34)
1.2.6.2 Soft Multifocal Contact Lenses (p.34-36)
1.2.6.3 Orthokeratology (p.36-38)
1.2.6.4 Pharmaceuticals (p.38-40)
1.2.7 The Problem with Myopia Treatment (p.40-41)
1.2.8 Developments in myopia assessment & prediction technology (p.41-42)
1.2.8.1 Axial Length & Refractive Error (p.42-44)
1.2.8.2 Models of Growth (p.44-45)
1.2.8.3 Machine Learning & Artificial Intelligence (p.45-46)
1.2.8.4 App & Device Tools (p.46-47)
1.2.8.5 Summary (p.47)

Chapter 2 Global trends in myopia management attitudes and strategies in clinical practice – 2019 update

2.1 Introduction (p.48-49)
2.2 Method (p.49-50)
2.3 Results (p.50-64)
2.4 Discussion (p.64-67)
2.5 Conclusion (p.67)

Chapter 3 Clinical myopia-related near phoria magnitude and variability across the human lifespan among Canadians

3.1 Introduction (p.68-70)

3.2 Methods (p.70-71)
3.3 Results (p.71-79)
3.4 Discussion (p.80-81)

Chapter 4 Impact of blur from a dual focus and an extended depth of focus contact lens

4.1 Introduction (p.82-84)
4.2 Methods (p.84)
4.2.1 Participants (p.84)
4.2.2 Contact Lenses (p.84-85)
4.2.3 Study Design (p.85-87)
4.2.4 Statistical Analyses (p.87-88)
4.3 Results (p.88)
4.3.1 Cyclo-Autorefraction (p.88-90)
4.3.2 Accommodative Lag (p.90-91)
4.3.3 Contrast Sensitivity (p.91-93)
4.3.4 Dysphotopsia (Glare) (p.93-96)
4.4 Discussion (p.96)
4.4.1 Peripheral Refraction (p.96-98)
4.4.2 Accommodative Lag (p.98)
4.4.3 Visual Quality (p.98-99)
4.5 Conclusion (p.99)

Chapter 5 IOLMaster agreement evaluation in healthy adults, comparing ocular biometry measurements, after immediate soft contact lens wear for myopia control

5.1 Introduction (p.100-102)
5.2 Methods (p.102)
5.2.1 Participants (p.102)
5.2.2 Study Lenses (p.102)
5.2.3 Study Design (p.102-103)
5.2.4 Statistical Analyses (p.103)
5.3 Results (p.104)
5.3.1 Agreement (p.104-111)
5.4 Discussion (p.112-115)

Chapter 6 Are soft contact lenses a viable source for human dopamine levels measurement using the ELISA dopamine kit?

6.1 Introduction (p.116-118)
6.2 Methods (p.118)
6.2.1 Participants (p.118)
6.2.2 Study Lenses (p.118)
6.2.3 Study Design (p.118)
6.2.4 Measurement of tear dopamine (p.119)
6.2.5 Statistical Analyses (p.119)
6.3 Results (p.119)
6.3.1 Tear dopamine levels (p.119-120)
6.4 Discussion (p.120-121)

Chapter 7 Conclusions (p.122-123)

7.1 Limitations & Future Direction
7.1.2 Global trends in myopia management attitudes and strategies in clinical practice – 2019 update (p.123)
7.1.3 Clinical myopia-related near phoria magnitude and variability across the human lifespan among Canadians (p.123-124)
7.1.4 Impact of blur from a dual focus and an extended depth of focus contact lens (p.124)
7.1.5 IOLMaster agreement evaluation in healthy adults, comparing ocular biometry measurements, after immediate soft contact lens wear for myopia control (p.124)
7.1.6 Are soft contact lenses a viable source for human dopamine levels measurement using the ELISA dopamine kit? (p.125)

List of References (p.126-152)

Appendices

Appendix 1: Study Protocol (p.153-162)
Appendix 2: Study Participant Information Sheet (p.163-168)
Appendix 3: Study Consent Form (p.169)

List of Tables

Chapter 1 Introduction

Table 1.1 The recommended consensus on qualitative and quantitative myopia terms and definitions for global adaptation, as adapted and quoted from the IMI – Defining and Classifying Myopia: A Proposed Set of Standards for Clinical and Epidemiological Studies white paper report (Flitcroft *et al*., 2019).

Table 1.2 The recommended consensus on myopia structural complications terms and definitions for global adaptation, as adapted and quoted from the IMI – Defining and Classifying Myopia: A Proposed Set of Standards for Clinical and Epidemiological Studies white paper report (Flitcroft *et al*., 2019).

Table 1.3 Listed are the 27 currently known Online Mendelian Inheritance in Man (OMIM) secondary syndromic myopias associated with ocular abnormalities, as adapted and recreated from the IMI – Myopia Genetics Report (Tedja *et al*., 2019).

Table 1.4 Listed are the 7 risk factor categories associated with myopia, along with the currently accepted relationship of each specific factor and its confounding issues, as adapted and recreated from the IMI – Risk Factors for Myopia Report white paper (Morgan *et al*., 2021).

Table 1.5 The reported efficacy of atropine, soft multifocal contact lenses, and orthokeratology to reduce myopia by various controlled studies, after the review by Smith & Walline (2015).

Table 1.6 A summary of reported CARE for different myopia control strategies, across the literature, as adapted and recreated from Brennan *et al*. (2020a), where abbreviations are as follows: Devices (Opt – optical interferometric biometry; US - ultrasound); Rand. (whether the study was randomised); N = (T, C) indicating the sample size in treated and control groups.

Chapter 2 Global trends in myopia management attitudes and strategies in clinical practice – 2019 update

Table 2.1 Perceived effectiveness (defined as the expected level of reduction in childhood myopia progression in percent) of myopia control options by practitioners in different continents. Data are expressed as mean ± S.D.

Table 2.2 Frequency of prescribing myopia correction options for progressing / young myopes by practitioners in different continents for progressing / young myopes. Data are expressed as mean ± S.D.

Table 2.3 Minimum patient age considered necessary by practitioners (from different continents who prescribed these options for different myopia correction options. Data are expressed as mean ± S.D years (% that would not prescribe this refractive modality).

Table 2.4 Minimum level of patient myopia (in dioptres) before myopia correction options would be considered by practitioners from different continents who prescribed these options. Data are expressed as mean ± S.D.

Chapter 3 Clinical myopia-related near phoria magnitude and variability across the human lifespan among Canadians

Table 3.1 Percentile near phoria chart showing sex differences (female-male) over the human lifespan, where esophoric and exophoric deviations are represented by the (-) negative and (+) positive values.

Table 3.2 Percentile near phoria chart showing refraction group differences (myope-emmetrope) over the human lifespan, where esophoric and exophoric deviations are represented by the (-) negative and (+) positive values.

Table 3.3 Percentile near phoria chart showing refraction group differences (progressive myope-emmetrope) over the human lifespan, where esophoric and exophoric deviations are represented by the (-) negative and (+) positive values.

Table 3.4 Percentile near phoria chart showing refraction group differences (progressive myope-myope) over the human lifespan, where esophoric and exophoric deviations are represented by the (-) negative and (+) positive values.

Table 3.5 Percentile near phoria chart showing refraction group differences (female-male progressive myope) over the human lifespan, where esophoric and exophoric deviations are represented by the (-) negative and (+) positive values.

Chapter 4 Impact of blur from a dual focus and an extended depth of focus contact lens

Table 4.1 Central (on-axis) and peripheral (at 30° temporally and nasally in the horizontal meridian) cyclo-Autorefraction measured after 8 hours of contact lens wear; values are means ± SD, where values denoted * were considered significant (p<0.05).

Table 4.2 Contact lens group (Proclear [Group A], MiSight [Group B], NaturalVue [Group C]) comparison of temporal (at 30° in the horizontal meridian) cyclo-Autorefraction for the J0 sphero-cylindrical power vector, where * represented a significant (p<0.05) difference.

Table 4.3 Accommodative Lag measured after 8 hours of contact lens wear; values are means ± SD, where values denoted * were considered significant (p<0.05).

Table 4.4 Contact lens group (Proclear [Group A], MiSight [Group B], NaturalVue [Group C]) comparison of Accommodative Lag, where * represented a significant (p<0.05) difference.

Table 4.5 Contrast Sensitivity measured after 8 hours of contact lens wear; values are means, where values denoted * were considered significant (p<0.05).

Table 4.6 Dysphotopsia (Glare) measured after 8 hours of contact lens wear; values are means, where values denoted * were considered significant (p<0.05).

Table 4.7 Contact lens group (Proclear [Group A], MiSight [Group B], NaturalVue [Group C]) comparison of Dysphotopsia (Glare) at 0°, where * represented a significant (p<0.05) difference.

Table 4.8 Contact lens group (Proclear [Group A], MiSight [Group B], NaturalVue [Group C]) comparison of Dysphotopsia (Glare) at 225°, where * represented a significant (p<0.05) difference.

Chapter 5 IOLMaster agreement evaluation in healthy adults, comparing ocular biometry measurements, after immediate soft contact lens wear for myopia control

Table 5.1 The reported post-wear Proclear lens mean difference and standard deviation, two tailed *t* test for the differences and their significance, and 95% confidence interval of lower and upper limits of agreement based on ± 1.96 SD between the IOLMaster 500 and IOLMaster 700; AL = axial length; Km = mean keratometry; ACD = anterior chamber depth; WTW = horizontal (white-to-white) corneal diameter.

Table 5.2 The reported post-wear MiSight lens mean difference and standard deviation, two tailed *t* test for the differences and their significance, and 95% confidence interval of lower and upper limits of agreement based on ± 1.96 SD between the IOLMaster 500 and IOLMaster 700; AL = axial length; Km = mean keratometry; ACD = anterior chamber depth; WTW = horizontal (white-to-white) corneal diameter; * = p<0.05.

Table 5.3 The reported post-wear NaturalVue lens mean difference and standard deviation, two tailed *t* test for the differences and their significance, and 95% confidence interval of lower and upper limits of agreement based on ± 1.96 SD between the IOLMaster 500 and IOLMaster 700; AL = axial length; Km = mean keratometry; ACD = anterior chamber depth; WTW = horizontal (white-to-white) corneal diameter; * = p<0.05.

Chapter 6 Are soft contact lenses a viable source for human dopamine levels measurement using the ELISA dopamine kit?

Table 6.1 Comparison of tear DA levels (pg/ml), as well as comparative Schirmer strip and capillary tube values from Sharma *et al*. (2019).

Table 6.2 Comparison of tear DA levels (pg/ml) between the different contact lenses extracted from Plates 2 & 3.

List of Figures

Chapter 1 Introduction

Figure 1.1 Vision-dependent/retinal defocus feedback mechanisms and associated functional/structural ocular anatomical changes, regulating emmetropisation and eye growth during paediatric development as adapted and copied from the IMI – Report on Experimental Models of Emmetropization and Myopia white paper (Troilo *et al*., 2019).

Figure 1.2 The reported efficacy (%) of atropine, soft multifocal contact lenses, and orthokeratology to reduce myopia by various controlled studies adapted from Smith & Walline (2015).

Chapter 2 Global trends in myopia management attitudes and strategies in clinical practice – 2019 update

Figure 2.1 Level of practitioner concern (rated from 0-10) regarding the perceived increasing frequency of paediatric myopia in their practice for practitioners located in different continents. N=1,336. Box = 1 SD, line = median and whiskers 95% confidence interval.

Figure 2.2 Perceived level of clinical activity in the area of myopia control for practitioners located in different continents. N=1,336. Box = 1 SD, line = median and whiskers 95% confidence interval.

Figure 2.3 Minimum annual amount of patient myopia progression, in dioptres per year (D/year), that practitioners located in different continents considered to necessitate a myopia control approach. N=1,336.

Figure 2.4 Use of single-vision distance under-correction as a strategy to slow myopia progression by practitioners located in different continents. N=1,336.

Figure 2.5 Factors preventing practitioners located in different continents from prescribing a myopia control approach. N=1,336.

Chapter 3 Clinical myopia-related near phoria magnitude and variability across the human lifespan among Canadians

Figure 3.1 Near phoria changes over the human lifespan, as a function of age for the right eye of 86 patients, where esophoric and exophoric deviations are represented by the (-) negative and (+) positive values on the y-axis.

Figure 3.2 Percentile near phoria curves over the human lifespan, where esophoric and exophoric deviations are represented by the (-) negative and (+) positive values on the y-axis.

Figure 3.3 Percentile near phoria curves over the male human lifespan, where esophoric and exophoric deviations are represented by the (-) negative and (+) positive values on the y-axis.

Figure 3.4 Percentile near phoria curves over the female human lifespan, where esophoric and exophoric deviations are represented by the (-) negative and (+) positive values on the y-axis.

Figure 3.5 Percentile near phoria curves over the emmetrope human lifespan, where esophoric and exophoric deviations are represented by the (-) negative and (+) positive values on the y-axis.

Figure 3.6 Percentile near phoria curves over the myope human lifespan, where esophoric and exophoric deviations are represented by the (-) negative and (+) positive values on the y-axis.

Figure 3.7 Percentile near phoria curves over the progressive myope human lifespan, where esophoric and exophoric deviations are represented by the (-) negative and (+) positive values on the y-axis.

Figure 3.8 Percentile near phoria curves over the male progressive myope human lifespan, where esophoric and exophoric deviations are represented by the (-) negative and (+) positive values on the y-axis.

Figure 3.9 Percentile near phoria curves over the female progressive myope human lifespan, where esophoric and exophoric deviations are represented by the (-) negative and (+) positive values on the y-axis.

Figure 3.10 Clinical patient visit differences over the human lifespan for 70 patients.

Chapter 4 Impact of blur from a dual focus and an extended depth of focus contact lens

Figure 4.1 The Aston Contrast Sensitivity Near App, adopted from Kingsnorth *et al*. (2016).

Figure 4.2 The Aston Halometer and Tablet App, adopted from Buckhurst *et al*. (2015).

Figure 4.3 Contact lens group (Proclear [Group A], MiSight [Group B], NaturalVue [Group C]) comparison of temporal (at 30° in the horizontal meridian) cyclo-Autorefraction mean values for the J0 sphero-cylindrical power vector, where * represented a significant (p<0.05) difference.

Figure 4.4 Contact lens group (Proclear [Group A], MiSight [Group B], NaturalVue [Group C]) comparison of Accommodative Lag mean values, where * represented a significant (p<0.05) difference.

Figure 4.5 Contact lens comparison of Contrast Sensitivity across the sample population.

Figure 4.6 Contact lens comparison of Dysphotopsia (Glare) across the sample population.

Figure 4.7 Contact lens group (Proclear [Group A], MiSight [Group B], NaturalVue [Group C]) comparison of Dysphotopsia (Glare) at 0° mean values, where * represented a significant (p<0.05) difference.

Figure 4.8 Contact lens group (Proclear [Group A], MiSight [Group B], NaturalVue [Group C]) comparison of Dysphotopsia (Glare) at 225° mean values, where * represented a significant (p<0.05) difference.

Chapter 5 IOLMaster agreement evaluation in healthy adults, comparing ocular biometry measurements, after immediate soft contact lens wear for myopia control

Figure 5.1 Bland-Altman plots for axial length comparison between the IOLMaster 500 and IOLMaster 700 with the post-wear Proclear lens. The mean difference is designated by the solid line. The 95% confidence interval of the upper and lower limits of agreement based on ± 1.96 SD are designated by the dotted lines.

Figure 5.2 Bland-Altman plots for mean keratometry comparison between the IOLMaster 500 and IOLMaster 700 with the post-wear Proclear lens. The mean difference is designated by the solid line. The 95% confidence interval of the upper and lower limits of agreement based on ± 1.96 SD are designated by the dotted lines.

Figure 5.3 Bland-Altman plots for anterior chamber depth comparison between the IOLMaster 500 and IOLMaster 700 with the post-wear Proclear lens. The mean difference is designated by the solid line. The 95% confidence interval of the upper and lower limits of agreement based on ± 1.96 SD are designated by the dotted lines.

Figure 5.4 Bland-Altman plots for the horizontal (white-to-white) corneal diameter comparison between the IOLMaster 500 and IOL Master700 with the post-wear Proclear lens. The mean difference is designated by the solid line. The 95% confidence interval of the upper and lower limits of agreement based on ± 1.96 SD are designated by the dotted lines.

Figure 5.5 Bland-Altman plots for axial length comparison between the IOLMaster 500 and IOLMaster 700 with the post-wear MiSight lens. The mean difference is designated by the solid line. The 95% confidence interval of the upper and lower limits of agreement based on ± 1.96 SD are designated by the dotted lines.

Figure 5.6 Bland-Altman plots for mean keratometry comparison between the IOLMaster 500 and IOLMaster 700 with the post-wear MiSight lens. The mean difference is designated by the solid line. The 95% confidence interval of the upper and lower limits of agreement based on ± 1.96 SD are designated by the dotted lines.

Figure 5.7 Bland-Altman plots for anterior chamber depth comparison between the IOLMaster 500 and IOLMaster 700 with the post-wear MiSight lens. The mean difference is designated by the solid line. The 95% confidence interval of the upper and lower limits of agreement based on ± 1.96 SD are designated by the dotted lines.

Figure 5.8 Bland-Altman plots for the horizontal (white-to-white) corneal diameter comparison between the IOLMaster 500 and IOLMaster 700 with the post-wear MiSight lens. The mean difference is designated by the solid line. The 95% confidence interval of the upper and lower limits of agreement based on ± 1.96 SD are designated by the dotted lines.

Figure 5.9 Bland-Altman plots for axial length comparison between the IOLMaster 500 and IOLMaster 700 with the post-wear NaturalVue lens. The mean difference is

designated by the solid line. The 95% confidence interval of the upper and lower limits of agreement based on ± 1.96 SD are designated by the dotted lines.

Figure 5.10 Bland-Altman plots for mean keratometry comparison between the IOLMaster 500 and IOLMaster 700 with the post-wear NaturalVue lens. The mean difference is designated by the solid line. The 95% confidence interval of the upper and lower limits of agreement based on ± 1.96 SD are designated by the dotted lines.

Figure 5.11 Bland-Altman plots for anterior chamber depth comparison between the IOLMaster 500 and IOLMaster 700 with the post-wear NaturalVue lens. The mean difference is designated by the solid line. The 95% confidence interval of the upper and lower limits of agreement based on ± 1.96 SD are designated by the dotted lines.

Figure 5.12 Bland-Altman plots for the horizontal (white-to-white) corneal diameter comparison between the IOLMaster 500 and IOLMaster 700 with the post-wear NaturalVue lens. The mean difference is designated by the solid line. The 95% confidence interval of the upper and lower limits of agreement based on ± 1.96 SD are designated by the dotted lines.

Chapter 1 Introduction

Myopia has become a global public health issue (Vitale *et al*., 2008; Morgan *et al.*, 2010; Holden *et al*. 2016). Uncorrected myopia is the most common visual condition encountered and has been described as an epidemic with its increasingly early onset and high progression rates worldwide (Bourne *et al*., 2013; Holden *et al*. 2016; Fricke *et al*., 2018). Myopia progression during childhood even at low levels increases the risk of sight-threatening ocular diseases in adult life, as a result of abnormal eye growth (Vongphanit *et al*., 2002; Younan *et al*., 2002; Wong *et al*., 2003; Saw *et al*., 2005; Flitcroft, 2012). Previous animal research has shown that ocular growth is associated with peripheral hyperopic defocus (Smith *et al*., 2007; Smith *et al*., 2009a; Smith *et al*., 2012). Treatment modes such as specialty spectacles and soft contact lenses, orthokeratology or OK (corneal reshaping/refractive therapy or reverse geometry rigid gas-permeable contact lenses), and pharmaceuticals have been shown to control myopia progression in addition to correcting visual acuity (Walline *et al.*, 2011; Smith & Walline, 2015; Gonzalez-Meijome *et al*., 2016).

The scientific community has been developing various interventions to control myopia, including the general undercorrection of myopic refraction (Chung *et al*., 2002; Adler & Millodot, 2006; Vasudevan *et al*., 2014), multifocal spectacles (Gwiazda *et al*., 2003; Berntsen *et al*., 2012; Cheng *et al*., 2014), contact lenses; [multifocal soft contact lenses or MFSCLs (Anstice & Phillips, 2011; Sankaridurg *et al*., 2011; Walline *et al*., 2013), rigid gas-permeable (Khoo *et al*., 1999; Katz *et al*., 2003; Walline *et al*., 2004), and orthokeratology (Kakita *et al*., 2011; Hiraoka *et al*., 2012; Swarbrick *et al*., 2015)], topical pharmaceuticals; [low-dose atropine of 0.5%, 0.1%, and 0.01% (Lee *et al*., 2006; Chia *et al*., 2012; Chia *et al*., 2014) and pirenzepine (Siatkowski *et al*., 2004; Tan *et al*., 2005; Siatkowski *et al*., 2008)], and lifestyle changes (Guggenheim *et al*., 2012; Jones-Jordan *et al*., 2012; Lin *et al*., 2014), but a standardized clinical protocol only continues in development. Additionally, these strategies are mostly off-label treatments (not approved specifically for myopia control), and low dose atropine and pirenzepine in particular are not commercially available (Smith & Walline, 2015). Other techniques such as scleral reinforcement surgery (Hu *et al*., 2018) and cross-linking (Zhang *et al*., 2015) have postulated scleral strengthening and thickening, but lack human reproducibility/repeatability (Ward, 2013).

Despite evidence-based research, management challenges persist due to cost (Flitcroft, 2012), safety (Liu & Xie, 2016), inadequate information (Santodomingo-Rubido *et al*., 2012), and outcome unpredictability (Wolffsohn *et al*., 2016), whilst myopia often continues to be wrongfully

treated with conventional remedies (undercorrection, single vision spectacles and contact lenses) only capable of correcting visual acuity. Rigid orthokeratology and soft multifocal contact lenses currently remain the most promising tools available to clinicians (Smith & Walline, 2015; Gonzalez-Meijome *et al*., 2016; Wolffsohn *et al*., 2016). However, studies have not directly investigated the myopia management efficacy of different MFSCL designs. The optimisation of all methods, including "labelled" and gold standard instrumentation techniques and clinical guidelines, must be challenged to aid the quest towards universal myopia management standardisation. Moreover, this thesis will also explore novel applications of these treatment strategies, such as predictive technology, and other avenues including MFSCLs acting as viable dopamine vehicles, which may possibly lead to improved individual patient care.

1.1 Emmetropisation & Eye Growth Overview

1.1.1 Paediatric Development

Refractive error, or ametropia, reflects the mismatch between the power of the eye's optical system (corneal and lens shape/size/position) and its length. Ametropia is mainly described by the following terms: myopia (nearsightedness); hyperopia (farsightedness); astigmatism (error from irregular corneal or lens curvature and anterior chamber development; changes as the corneal curvature increases horizontally with age and typically occurs in conjunction with myopia and hyperopia); and presbyopia (age-related vision impairment at near distance, due to the natural loss of accommodation-the crystalline lens' elastic ability to adjust light focus at various distances). Mutti *et al*. (2005) noted that whilst eye growth may continue until puberty, the increase in corneal curvature occurs in the first few months, whilst lens power decreases during early childhood. The average newborn infant is hyperopic (Mutti *et al*., 2005) and astigmatic (Gwiazda *et al*., 1984) with a decline between six months and six years of age. This reduction in refractive error, or emmetropisation, during the first years of life is based on the eye's ability to focus light and corresponding retinal image quality dictated by optical power (spherical and astigmatic defocus) and visual optics (higher-order monochromatic aberrations-mainly positive spherical aberrations, coma, trefoil, and astigmatism) respectively (Troilo *et al*., 2019). Emmetropisation is regulated via the balance of increase in axial length (AL) leading to myopia and radius increases in the cornea or crystalline lens causing hyperopia by decreasing the lens power (Wildsoet, 1997; Ip *et al*., 2008). Although the impact is much lower, emmetropisation is further influenced by higher-order aberrations affecting luminance and chromatic contrast, due to additional corneal and lens refractive index and thickness changes during infantile development with previous studies reporting approximately 20-50% more

aberrations exhibited by children than adults (Brunette *et al*., 2003; Wang & Candy, 2005); as well as astigmatism (Fulton *et al*., 1982; Gwiazda *et al*., 2000). Overall, refractive status depends on an infant's visual experience within sensitive periods of development, which is determined by genetics and the environment (Mutti *et al*., 2002; Farbrother *et al*., 2004).

The IMI (International Myopia Institute) – Report on Experimental Models of Emmetropization and Myopia white paper by Troilo *et al*. (2019), summarized in full the current understanding on emmetropisation, myopia development and treatments for its progression from research with experimental animal models. This compendium also attributed axial and refractive changes triggered by form-deprivation/optical defocus, optical image quality (higher-order monochromatic aberrations and astigmatism), lighting (luminance and chromatic contrast signals), as well as circadian rhythms to both genetic and environmental vision-dependent factors – regulated signal cascade pathways locally restricted to the retina and decreased exerted magnitude with eccentricity, without brain input. Moreover, ocular anatomic changes caused by independent visual regulation during experimentally induced refractive errors were particularly related to the posterior segment (scleral and vitreous chamber shape and size) and not the programmed growth changes in the anterior segment (corneal curvature, anterior chamber depth, accommodation with increased intraocular pressure) (Bailey *et al*., 2008; Pucker *et al*., 2013, 2015). The report has further reviewed the literature surrounding the involved molecular mechanisms and significant drug interactions in eye growth and refractive error relative to defocus, as well as including the following notably identified biochemical compounds: neurotransmitter (retinal dopamine, vasoactive intestinal peptide), growth factor (retinoic acid, glucagon, insulin), and gene expression (nitric oxide, melanopsin) visual signals in the retina, retinal pigment epithelium, choroid, and sclera; all depicted by **Figure 1.1** below (Troilo *et al*., 2019). Choroidal thickness is especially considered a major determinant of ocular growth and emmetropisation potentially via accommodation (Guggenheim *et al*., 2011); whilst atropine is consistently accepted to be effective in myopia prevention possibly via muscarinic/non-muscarinic mechanisms inhibiting smooth muscle contraction and resultant choroidal thinning, but not involving ciliary muscles or accommodation (Stone *et al*., 1991; Tigges *et al*., 1999; Barathi *et al*., 2009).

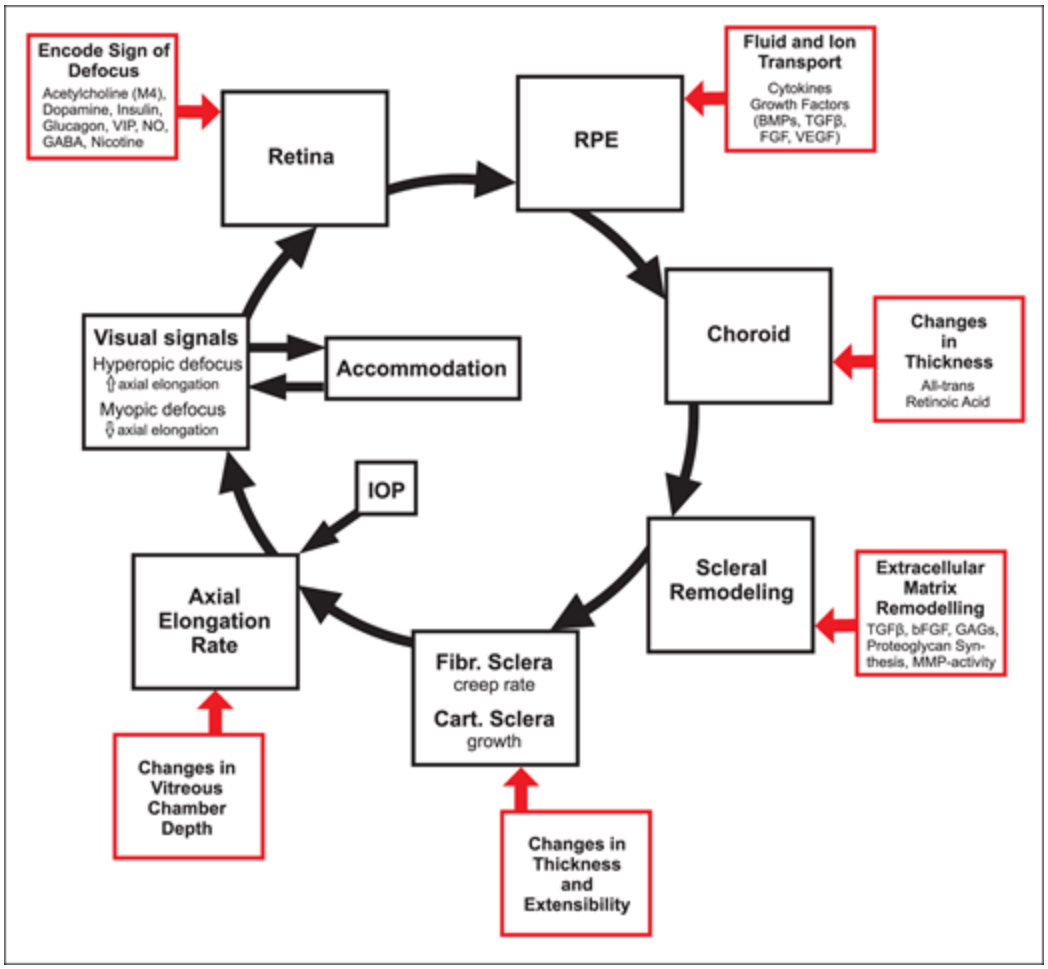

Figure 1.1: Vision-dependent/retinal defocus feedback mechanisms and associated functional/structural ocular anatomical changes, regulating emmetropisation and eye growth during paediatric development, as adapted and copied from the IMI – Report on Experimental Models of Emmetropization and Myopia white paper (Troilo *et al*., 2019).

Human (Rabin *et al*., 1981; Huo *et al*., 2012) and animal (Gottlieb *et al*., 1987; Norton & Siegwart, 1995) studies have suggested shared mechanisms in form-deprivation myopia such as increased axial elongation rate (especially increased vitreous chamber depth and elongation) with thinned fibrous sclera and choroid at normal intraocular pressure. Likewise, human axial elongation rate and choroidal thickness compensation for optically-imposed defocus in the retina (along with gene expression changes) was shown to be bidirectional, respective of the encoded lens sign (Read *et al*., 2010; Chakraborty *et al*., 2012, 2013; Wang *et al*., 2016). Zhu *et al*. (2005) had stated choroidal thinning by as much as ~50 µm is possible in just an hour. Increased eye growth due to defocus also causes retinal pigment epithelium enlargement from

blocked ionic fluid transport between the vitreous chamber and choroid, resulting in swelling and thinning respectively (Liang *et al*., 2014; Jonas *et al*., 2017a, 2017b). Historically, the choroid (van Alphen, 1986), but especially the sclera (Curtin *et al*., 1979), are both considered to dictate human eye size and shape. Scleral remodeling caused by myopia results from thinning via loss of its extracellular matrix mainly at the posterior pole (Norton & Rada, 1995; Gentle *et al*., 2003), coupled with increased extensibility/viscoelasticity or decreased stiffness due to higher fibrous tissue creep rate (Siegwart & Norton, 1999; Phillips *et al*., 2000) and cartilage growth (Grytz & Siegwart, 2015).

1.1.2 Uncorrected Refractive Error Prevalence & Economic Burden

Refractive error prevalence varies with age (the most important factor), sex, ethnicity and socioeconomic status. Uncorrected refractive error is the primary cause of visual impairment (visual acuity <6/18) with a reported estimate of 108 million in 2010 and the second leading cause of blindness (visual acuity <3/60) worldwide (Bourne *et al*., 2013). In 2007, the global burden of uncorrected refractive error was conservatively estimated to be $268.8 billion (Smith *et al*., 2009). This is a global public health issue due to its effect on individual visual performance and quality of life, as well as economic productivity loss regarding subsequent care and disability. Since levels of hyperopia are typically low, human clinical studies have not been implemented to investigate control strategies. In contrast, myopia is now considered an epidemic by the World Health Organization (WHO) and is the commonest refractive error among children and young adults (Morgan *et al.*, 2010).

1.2 Myopia

1.2.1 Definition & Classification

Due to the excessive classifications and associated terms of myopia in the existing literature, simpler and internationally agreed evidence-based standards are necessary. In their IMI – Defining and Classifying Myopia: A Proposed Set of Standards for Clinical and Epidemiological Studies white paper report, (Flitcroft *et al*., 2019) recommended the descriptive terminology to be consolidated into myopia, axial myopia, refractive myopia, secondary myopia, and pathological myopia; standardized quantitative myopia thresholds for children were proposed as pre-myopia (≤ +0.75 D and > -0.50 D), myopia (≤ -0.50 D), low myopia (≤ -0.50 D and > -6.00 D), and high myopia (≤ -6.00 D). This comes after discovering significant myopia threshold variations among epidemiologic studies from conducted meta-analysis, reporting: 87.7% of 138 studies used < -0.50 D or ≤ -0.50 D for myopia; 35.6% and 61% of 59 studies used < -5.00 D or

≤ -5.00 D and < -6.00 D or ≤ -6.00 D for high myopia respectively (Flitcroft *et al*., 2019). In order to prevent inconsistency, over-simplification, and misleading for true myopia study and management, **Tables 1.1** & **1.2** below include this IMI committee's recommended consensus on terms and definitions for global adaptation; based on myopia "optics, etiology (if known), diagnostic thresholds, progression, and structural complications" (Flitcroft *et al*., 2019).

Term	Definition
Qualitative definitions	
Myopia	"A refractive error in which rays of light entering the eye parallel to the optic axis are brought to a focus in front of the retina when ocular accommodation is relaxed. This usually results from the eyeball being too long from front to back, but can be caused by an overly curved cornea and/or a lens with increased optical power. It also is called nearsightedness."
Axial myopia	"A myopic refractive state primarily resulting from a greater than normal axial length."
Refractive myopia	"A myopic refractive state that can be attributed to changes in the structure or location of the image forming structures of the eye, i.e. the cornea and lens."
Secondary myopia	"A myopic refractive state for which a single, specific cause (e.g., drug, corneal disease or systemic clinical syndrome) can be identified that is not a recognized population risk factor for myopia development."
Quantitative definitions	
Myopia	"A condition in which the spherical equivalent refractive error of an eye is ≤ -0.50 D when ocular accommodation is relaxed."
Low myopia	"A condition in which the spherical equivalent refractive error of an eye is ≤ -0.50 and > -6.00 D when ocular accommodation is relaxed."
High myopia	"A condition in which the spherical equivalent refractive error of an eye is ≤ -6.00 D when ocular accommodation is relaxed."
Pre-myopia	"A refractive state of an eye of ≤ +0.75 D and > -0.50 D in children where a combination of baseline refraction, age, and other quantifiable risk factors provide a sufficient likelihood of the future development of myopia to merit preventative interventions."

Table 1.1: The recommended consensus on qualitative and quantitative myopia terms and definitions for global adaptation, as adapted and quoted from the IMI – Defining and Classifying Myopia: A Proposed Set of Standards for Clinical and Epidemiological Studies white paper report (Flitcroft *et al*., 2019).

Term	Definition
Descriptive definitions	
Pathologic myopia	"Excessive axial elongation associated with myopia that leads to structural changes in the posterior segment of the eye (including posterior staphyloma, myopic maculopathy, and high myopia-associated optic neuropathy) and that can lead to loss of best-corrected visual acuity."
Myopic macular degeneration (MMD)	"A vision-threatening condition occurring in people with myopia, usually high myopia that comprises diffuse or patchy macular atrophy with or without lacquer cracks, macular Bruch's membrane defects, CNV and Fuchs spot."
Diagnostic subdivisions of MMD	
Myopic maculopathy	"Category 0: no myopic retinal degenerative lesion. Category 1: tessellated fundus. Category 2: diffuse chorioretinal atrophy. Category 3: patchy chorioretinal atrophy. Category 4: macular atrophy. ''Plus'' features (can be applied to any category): lacquer cracks, myopic choroidal neovascularization, and Fuchs spot."
Presumed myopic macular degeneration	"A person who has vision impairment and vision acuity that is not improved by pinhole, which cannot be attributed to other causes, and: • The direct ophthalmoscopy records a supplementary lens < -5.00 D and shows changes such as ''patchy atrophy'' in the retina or, • The direct ophthalmoscopy records a supplementary lens < -10.00 D."
Specific clinical conditions characteristic of pathologic myopia	
Myopic traction maculopathy (MTM)	"A combination of macular retinoschisis, lamellar macula hole and/or foveal retinal detachment (FRD) in eyes with high myopic attributable to traction forces arising from adherent vitreous cortex, epiretinal membrane, internal limiting membrane, retinal vessels,

	and posterior staphyloma."
Myopia-associated glaucoma-like optic neuropathy	"Optic neuropathy characterized by a loss of neuroretinal rim and enlargement of the optic cup, occurring in eyes with high myopia eyes with a secondary macrodisc or peripapillary delta zone at a normal IOP."

Table 1.2: The recommended consensus on myopia structural complications terms and definitions for global adaptation, as adapted and quoted from the IMI – Defining and Classifying Myopia: A Proposed Set of Standards for Clinical and Epidemiological Studies white paper report (Flitcroft *et al*., 2019).

Moreover, the committee has also submitted these updated, as well as collectively agreed to be more accurate, myopia definitions to WHO's International Classification of Disease (ICD).

1.2.2 Developmental (relative peripheral refraction; eye growth; refractive ametropia; age; binocular vision) Risk Factors & Progression

Animal studies have associated vision-dependent peripheral refraction (Smith *et al*., 2007, 2009; Zhu *et al*., 2013; Benavente-Perez *et al*., 2014), as well as vision-independent higher-order aberrations (Coletta *et al*., 2003; Garcia de la Cera *et al*., 2006; Ramamirtham *et al*., 2007; Coletta *et al*., 2010) and astigmatism (Kee *et al*., 2003; Kee, 2013; Chu & Kee 2015) with myopia development and progression, but these may not be principal causes in humans. Several human studies demonstrated myopes had higher higher-order aberrations (Collins *et al*., 1995; He *et al*., 2002; Paquin *et al*., 2002; Llorente *et al*., 2004); and peripheral hyperopia relative to the central refractive error, which was even maintained through five years regardless of the increasing eye elongation since the myopia onset (Mutti *et al*., 2007); whereas emmetropes and hyperopes had relative peripheral myopia (Chen *et al*., 2010; Ehsaei *et al*., 2011; Sng *et al*., 2011). However, other human studies have particularly considered relative peripheral refraction (Lee & Cho, 2013; Atchison *et al*., 2015) and higher-order aberrations (Carkeet *et al*., 2002; Cheng *et al*., 2003) only as possible risk factors or consequences of myopia development and progression, instead of having a causal relationship.

Myopia is caused by an increase in eye length or vitreous depth (axial ametropia, where every 0.09-0.10 mm increase translates to 0.25 D in higher myopia), and/or corneal curvature and crystalline lens power (refractive ametropia); axial ametropia has the largest effect on refractive error as it may progress into the third decade of life (Hashemi *et al*., 2004). Since light is focused in front of the retina, distance vision is blurry, whilst close objects remain clear. Childhood myopia assumes onset around age eight and continues to develop during

adolescence between ages 15-16 (Goss & Cox, 1985; Thorn *et al*., 2005), after which is termed as late-onset (McBrien & Millodot, 1987; Jiang, 1995). However, the Correction of Myopia Evaluation Trial (COMET) stated that although myopia stabilised at an average age of 15.6 ± 4 years, 95% stabilised by age 24 (COMET, 2013). The age to end treatment may be currently unspecified, but the need for early intervention is certainly indicated; the prospective Northern Ireland Childhood Errors of Refraction (NICER) and multi-center Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error (CLEERE) key studies showed younger children 6-10 years of age experienced axial growth faster (Breslin *et al*., 2013) with notable increases three years pre- and five years post- onset, as well as reduced hyperopia four years pre-onset (Mutti *et al*., 2007), respectively. Emmetropic axial length may range between 22-24.5 mm, whilst ALs >25 mm are considered myopic (Tideman *et al*., 2016b). Furthermore, annual AL increases of 0.1 mm vs. 0.2-0.3 mm are thought as emmetropic and myopic respectively (Mutti *et al*., 2007). In one study on Hong Kong Chinese high myopes of age 12-18, an AL >26 mm was considered significant for developing peripheral retinal pathologies (Cheng *et al*., 2013). Zadnik *et al*. (2015) additionally stated children at age six are of particular risk to develop myopia if they have hyperopia <0.75 D. This is further supported by Morgan *et al*. (2010), who stated that hyperopia is the natural endpoint for refractive development, in order to reduce the risk of myopia progression in children. A child's binocular vision state is another possible association with myopia. Studies have reported higher levels of esophoria or inward eye deviation and unstable/insufficient accommodative responses or higher accommodative lag (Gwiazda *et al*., 1995; Nakatsuka *et al*., 2005; Allen & O'Leary, 2006), higher accommodative convergence or AC/A ratio (Gwiazda *et al*., 1999; Gwiazda *et al*., 2005), as well as lower accommodative facility (Allen & O'Leary, 2006; Pandian *et al*., 2006) at near distances among nearsighted children and young adults compared to their emmetropic counterparts. These outcomes are thought to be involved in triggering eye growth by causing relative peripheral retinal blur; however, both lower (Rosenfield *et al*., 2002; Berntsen *et al*., 2012) and higher (Gwiazda *et al*., 2003; Allen & O'Leary, 2006) accommodative lags have been shown among myopic and emmetropic subjects. For instance, better efficacy was achieved in children having higher esophoria and accommodative lag in the five-year COMET randomised clinical trial by spectacles fitted with progressive addition lenses (PALs) (Gwiazda *et al*., 2004); lower accommodative lag of <1.01 D by the three-year randomised clinical trial regarding prismatic bifocal spectacles (Cheng *et al*., 2014); lower accommodative amplitude with orthokeratology (Zhu *et al*., 2014), at near. These studies, including randomized clinical trials, suggest that binocular vision aspects also do not consistently indicate a causal relationship with myopia,

whilst remain important when designing control strategies and selecting management options for patients.

Myopia progression refers to the uncontrolled growth of the eye via axial length elongation, which results in a change of refractive error (in the minus dioptric direction) and retinal/scleral thinning (Saw *et al*., 2005). Moreover, various studies have stated an average rate of progression in Caucasians per year of 0.50 D (Fulk *et al*., 2000; Gwiazda *et al*., 2003; Walline *et al.,* 2004, 2009), whereas an earlier study on Singaporean children by Saw *et al*. (2000) considered annual progression of >0.50 D to indicate a faster rate. Although myopia progression is a multifactorial problem remaining misunderstood, previous studies in individual children have recognized earlier onset as the primary factor to its faster rate, regardless of genetic and environmental risks (Price *et al*., 2013; Sankaridurg & Holden, 2014; Chua *et al*., 2016); with higher baseline myopia (Hsu *et al*., 2017) and seasonal changes such as during winter possibly due to reduced time outdoors coupled with more time in school (Gwiazda *et al*., 2014) also considered. A population cohort meta-analysis of 20 myopia control investigations confirmed a similar average annual rate of progression in Caucasian and Asian nearsighted children of 0.50-1.00 D, with greater rates among younger female Asians (Donovan *et al*., 2012). Even at low and moderate levels of myopia, nearsighted people are more prone to cataracts (Wong *et al*., 2001; Younan *et al*., 2002; Flitcroft, 2012), glaucoma (Yoshida *et al*., 2001; Wong *et al*., 2003; Flitcroft, 2012), macular degeneration, retinal detachments/holes/tears, choroidal/peripapillary atrophy, tilted disc, staphyloma, and reduced cone photoreceptor density, whilst high myopia (>5.00-6.00 D) may ultimately lead to blindness (Pierro *et al*., 1992; Vongphanit *et al*., 2002; Saw *et al*., 2005; Flitcroft, 2012; Chang *et al*., 2013; Smith & Walline, 2015). The risks for developing these ocular conditions are comparable to those of smoking and hypertension to cardiovascular health (Flitcroft, 2012). Even children with high myopia aged ≤10 years had retinal pathologies in a retrospective review (Bansal & Hubbard, 2010). These conditions further solidify myopia's status as an epidemic, being a primary contributor to global visual impairment and blindness, as described in the popular review by Holden *et al*. (2016), as well as more recently in a key systemic review and meta-analysis by Fricke *et al*. (2018). Although some of the risk factors associated with myopia are lower juvenile hyperopia (Zadnik *et al*., 2015), peripheral refraction (Mutti *et al*., 2007; Downie & Lowe, 2013), and binocular vision (Mutti *et al*., 2006; Felipe-Marquez *et al*., 2015), the type of visual environment has been shown to specifically dictate its onset, progression and cessation (Aller, 2014). Diet also may be a possible contributor, where Lim *et al*. (2010) noted that healthy Asian children with diets

consisting of higher saturated fat and cholesterol, but lower fruit, vegetable, and whole grain intakes had longer axial lengths, whilst Trier *et al*. (2008) identified caffeine (oral 7-methylxanthine or 7-MX is approved as myopia control medication in Denmark) to reduce axial length via a scleral mechanism over three years; however, the 10-year Blue Mountains Eye Study deemed nutritional evidence as inconclusive (Hong *et al*., 2014). Other studies have also drawn an association between increased eye growth and human circadian rhythms, due to low sleep quality (Ayaki *et al*., 2016; Jee *et al*., 2016; Abbott *et al*., 2018) and higher serum melatonin (Kearney *et al*., 2017), but such lifestyle research is still limited. Although the exact physiological effects are unknown, this further stems from animal research associating diurnal light cycles (Li *et al*., 2000) and ocular circadian rhythms (Nickla, 2013) with myopic eye growth and emmetropisation based on axial length, choroidal thickness, or intraocular pressure daily fluctuations (Nickla *et al*., 2002) and scleral proteoglycan synthesis rate (Nickla *et al*., 1999); form-deprivation/defocus-related anterior chamber depth and corneal curvature changes resulting from circadian rhythm systems' response to light duration, intensity, and level (Norton & Siegwart, 2013; Ashby, 2016); as well as the circadian rhythms and hormone roles of the spectral composition of light, chromatic signals, and wavelength-dependent defocus in luminance contrast (with specific oscillations in axial length, choroidal thickness, and vitreous chamber depth) (Rucker, 2013).

1.2.3 Genetic (family history; ethnicity) & Visual Environment (near work; time outdoors; education) Risk Factors & Progression

Rose *et al*. (2002) had already attributed genetics to the magnitude of myopia, especially the ocular biometry heritability of corneal curvature and axial length (Meng *et al*., 2011), whilst environmental factors are deemed responsible for the sudden worldwide increase in myopia prevalence (Morgan & Rose, 2005; Morgan *et al*., 2012; Dolgin, 2015). The IMI – Myopia Genetics Report (Tedja *et al*., 2019) confirmed refractive error and myopia predisposition is due to both genetics and environmental risk factors (near work and outdoor exposure; specifically education holding most prominence), as well as a light-processing retina-to-sclera molecular mechanism for common myopia development. The summarized literature on genome-wide association studies (GWAS) by the Consortium for Refractive Error and Myopia (CREAM) and 23andMe, as well as genome-environment-wide interaction studies (GEWIS) has identified nearly 200 genetic loci for refractive error (spherical equivalent), high myopia, or eye growth (corneal curvature and axial length), and nine loci for the association between high education and high myopia susceptibility respectively (Tedja *et al*., 2019). In particular, more than half of

the loci were discovered during this decade and the report estimated myopia heritability in the range of 60-80%. Two GWAS meta-analyses also have found numerous retinal and other ocular tissue gene expression changes from animal studies to overlap with human myopia quantitative trait loci (QTL) (Verhoeven *et al*., 2013; Riddell & Crewther, 2017). Although all retinal cells and layers are considered sites of gene expression, a candidate gene meta-analysis validated only the PAX6 gene (Chen *et al*., 2012) for ocular development to be associated with high myopia (Tang *et al*., 2014). A GWAS meta-analysis specifically linked vasoactive intestinal peptide receptor 2 (VIPR2) with high myopia among Chinese people (Yiu *et al*., 2013). Likewise, secondary syndromic myopias (myopia with systemic or ocular conditions, as well as mental retardation and connective tissue disorders) have been uniquely associated to single causal genes (Li & Zhang, 2017) and only two such genes, the collagen type II alpha 1 chain or COL2A1 (Mutti *et al*., 2007; Metlapally *et al*., 2009) and fibrilin 1 or FBN1 (Fan *et al*., 2016; Tedja *et al*., 2018), have been linked to common myopia (Tedja *et al*., 2019). **Table 1.3** below outlines the currently 27 secondary syndromic myopias associated with ocular abnormalities. Moreover, a combined GWAS meta-analysis by CREAM and 23andMe emphasized the TGF-beta pathway and specific gene sets (“abnormal photoreceptor inner segment morphology”, “thin retinal outer nuclear layer”, “detection of light stimulus”, “nonmotile primary cilium”, “abnormal anterior-eye segment morphology”) as key myopia drivers (Tedja *et al*., 2018). Other methods, such as myopia epigenetics research considering noncoding RNAs, particularly microRNAs (miRNAs), have the potential for both prevention and treatment of associated retinal pathology (Liang *et al*., 2011; Chen *et al*., 2012; Jiang *et al*., 2017).

Achromatopsia; Aland Island eye disease; Anterior-segment dysgenesis; Bietti crystalline corneoretinal dystrophy; Blue cone monochromacy; Brittle cornea syndrome; Cataract; Colobomatous macrophthalmia with microcornea; Cone dystrophy; Cone rod dystrophy; Congenital microcoria; Congenital stationary night blindness; Ectopia lentis et pupillae; High myopia with cataract and vitreoretinal degeneration; Keratoconus; Leber congenital amaurosis; Microcornea, myopic chorioretinal atrophy, and telecanthus; Microspherophakia and/or megalocornea, with ectopia lentis and/or secondary glaucoma; Ocular albinism; Primary open angle glaucoma; Retinal cone dystrophy; Retinal dystrophy; Retinitis pigmentosa; Sveinsson chorioretinal atrophy; Vitreoretinopathy; Wagner vitreoretinopathy; Weill-Marchesani syndrome

Table 1.3: Listed are the 27 currently known Online Mendelian Inheritance in Man (OMIM) secondary syndromic myopias associated with ocular abnormalities, as adapted and recreated from the IMI – Myopia Genetics Report white paper (Tedja *et al*., 2019).

Both Hammond *et al*. (2001) and Lyhne *et al*. (2001) attributed the variability of refractive error to genetic over environmental factors, due to the wide array of candidate genes and loci (Ciner

et al., 2009; Wojciechowski *et al*., 2009; Schache *et al*., 2013). In this regard, past familial and twin studies have reported a widely variable myopic spherical equivalent heritability in the range of 10%-98% (Angi *et al*., 1993; Lyhne *et al*., 2001; Sanfilippo *et al*., 2010). Similar studies have highlighted the high heritability of ocular biometry (Klein *et al*., 2009; Kim *et al*., 2013), and Guggenheim *et al*. (2013) especially stated a 64% correlation between measures of corneal curvature and axial length. Also, a family history correlation between increased genetic predisposition for myopia and the number of myopic parents has been demonstrated (Saw *et al*., 2006), with various studies highlighting an increased heritability risk of ≥3x when both parents are myopic (Mutti *et al*., 2002; Farbrother *et al*., 2004; Jones-Jordan *et al*., 2014; Wu *et al*., 2015). Jones-Jordan *et al.* (2010) particularly stated the risk of becoming nearsighted is five to six times greater when both parents are nearsighted, especially for children between 6-14 years of age. The study additionally noted that the children of nearsighted parents spent less time outside, whilst engaged more in near work activities compared to children of parents without a refractive error.

The IMI – Risk Factors for Myopia report (Morgan *et al*., 2021) recently stated education and time outdoors to be the leading risk factors for school myopia; **Table 1.4** below shows the complete summary of factors associated with myopia, as outlined in this white paper. Studies also have considered ethnicity (Voo *et al*., 1998; Kleinstein *et al*., 2003; Ip *et al*., 2007, 2008; Rudnicka *et al*., 2010) to be an important determinant, since myopia onset, as well as its progression rate and duration differ worldwide, where Asians in particular have been worse off relative to other groups (Donovan *et al*., 2012; Morgan *et al*., 2018). East Asian children in Australia between 11-15 years of age were eight times more susceptible to become nearsighted compared to Caucasian children in the same age group (Ip *et al*., 2008). Similar ethnic myopia prevalence differences were given by the Child Heart and Health Study in England (CHASE) for South Asian children in Britain relative to their Caucasian European counterparts (Rudnicka *et al*., 2010). Rose *et al*. (2008) found that the duration of near tasks has ethnic variations, where East Asian children spent 20% more time than their Caucasian counterparts, whilst children from myopic parents were longer engaged with reading and less outside overall. However, environmental factors such as reduced time outdoors and sunlight exposure, as well as increased engagement in near tasks (especially using portable devices and reading at close distances of <20 cm for >45 minutes) with reduced lighting are considered the primary risks for developing myopia regardless of ethnicity (Ip *et al*. 2008; Li *et al*., 2015). Moreover, Ip *et al*. (2008) emphasized prolonged and intensive near tasks among highly pressured educational

systems as a contributing factor towards childhood myopia, just as found among Asian nations exhibiting the highest prevalence (Dolgin, 2015; Rose *et al*., 2016). Studies have approximated double the myopia prevalence among those entering higher education relative to groups at the level of primary education (Morgan & Rose, 2013; Mirshahi *et al*., 2013; Ramessur *et al*., 2015). Gene-environment (GxE) interaction studies with Mendelian randomization (MR) of GWAS meta-analysed cohorts have confirmed the causal relationship between education and myopia, reporting effects of 0.27 D myopic shift per year of education (Mountjoy *et al*., 2018) and estimated 0.92 D for two years of education (Cuellar-Partida *et al*., 2016). Although Jones-Jordan *et al*. (2012) did not report a strong correlation between near work and myopia onset or progression, other studies have shown increased time outdoors to prevent myopia onset (Guggenheim *et al*., 2012; Jones-Jordan *et al*., 2014; Lin *et al*., 2014), but that is not an effective myopia control strategy (Jones-Jordan *et al*., 2012; Wu *et al*., 2013).

Factor	Evidence/Causal Relationship	Confounding Issues
Major factors		
Education	Strong and causal	Time outdoors
Time outdoors	Strong and causal	Role of light (intensity, duration, spectrum)
Screen time	Equivocal	Nearwork
Basic birth factors		
Sex	Weak	Social factors
Ethnicity	Inconsistent	Cultural attitudes or genetics
Parental myopia	Strong	Genetics or myopiagenic environments
Birth order	Weak	Years of education
Birth season	Weak	Years of education
Other personal factors		
Height	Weak	Social factors
Intelligence	Moderate	Education, time outdoors
Physical activity	Moderate	Time outdoors
Sleep	Weak	Educational pressures
Family characteristics		
Socio-economic status	Moderate	Education
Smoking	Weak	Education, SES
Diet	Weak	Education, SES
Environment		
Urban/rural	Moderate	Education, SES, time outdoors
Pollution	Weak	SES
Housing	Weak	Education, SES
Circadian rhythms	Weak	Dopamine
Night light	Negative	
Light spectrum	Weak	Limited data

Miscellaneous factors		
Allergic conjunctivitis, hay fever, Kawasaki disease, febrile diseases	Weak	Limited data, time outdoors
Fertility treatment	Weak	Limited data
Common beliefs		
Reading in dim light, under bed-clothes or in transport	Weak	Limited data
Posture in reading/writing and holding pen, font size in book	Weak	Limited data

Table 1.4: Listed are the 7 risk factor categories associated with myopia, along with the currently accepted relationship of each specific factor and its confounding issues, as adapted and recreated from the IMI – Risk Factors for Myopia Report white paper (Morgan *et al*., 2021).

Indeed, a more recent key meta-analysis and systemic review by Xiong *et al*. (2017) confirmed increased time outdoors to be effective in preventing myopia onset and slowing the myopic shift, but not in controlling progression. Various studies have recommended at least 8-15 hours of weekly outdoor time (Rose *et al*., 2008; Guggenheim *et al*., 2012; Jones-Jordan *et al*., 2012; He *et al*., 2015; Read *et al*., 2015). French *et al*. (2013) have suggested that the preventative mechanism of increased outdoor activity is related to reduced accommodative demand, bigger depth of focus, improved contrast, higher levels of Vitamin D (Mutti & Marks, 2011; Choi *et al*., 2014; Tideman *et al*., 2016a) and retinal dopamine acting against form-deprivation myopia. However, only minimal myopia causality via MR has been attributed to Vitamin D concentration (Tedja *et al*., 2019). Other studies have inconclusively contemplated the brightness (Dharani *et al*., 2012; Read *et al*., 2014; Read *et al*., 2015; Hua *et al*., 2015), as well as the elevated ultraviolet radiation and short-wavelength (blue light of wavelength <400 nm) transmission (Torii *et al*., 2017; Williams *et al*., 2017) associated with outdoor light exposure.

1.2.4 Worldwide Myopia Prevalence

In a recent publication, Holden *et al*. (2016) approximated global myopia prevalence at 1.4 billion people and 163 million with high myopia (≥6.00 D) in the year 2000; but predicted these values to reach nearly 5 (~50% of the world population) and 1 billion respectively by 2050, even from the overall current estimate of ~30%. Moreover, the same review showed that myopia distribution by 2050 will spread between ages 10-79, when previously compared to ages 10-39 in 2000, implying that this increased global myopic population will also be older. Whilst myopia in the U.S. has increased from 25% to 42% in the past 30 years (Vitale *et al*., 2008), prevalence varies widely from 3% in Nepalese children (Garner *et al*., 1999) to 90% in Taiwanese university

students (Want *et al*., 2009). The literature is inconclusive whether males or females exhibit higher myopia prevalence (Katz *et al*., 1997; Attebo *et al*., 1999; Junghans & Crewther, 2003), although some studies have suggested females to hold greater representation (Dandona *et al*., 2002; Hashemi *et al*., 2004; Bar Dayan *et al*., 2005; He *et al*., 2007). However, the samples of these studies largely varied in age groups and ethnicities. Overall, myopia prevalence is highest among children of Asian ethnicities (Voo *et al*., 1998; Kleinstein *et al*., 2003; Ip *et al*., 2007, 2008), followed by Hispanic, African-American, and Caucasian backgrounds (Voo *et al*., 1998; Kleinstein *et al*., 2003).

1.2.5 Economic Burden of the Myopia Epidemic

Myopia carries a heavy socioeconomic burden. The cost of correcting myopia in Singapore, only for ages between 12-17 has been estimated to be $37.5 million (Lim et al., 2009), while the approximate individual cost for adults of age ≥ 40 was $709 annually (Zheng et al., 2013). In the United States, an approximate annual cost between $3.9-7.2 billion was reported (Vitale et al., 2006).

1.2.6 Modes of Myopia Treatment

From the currently implemented myopia control strategies, only multifocal soft contact lenses (MFSCLs), orthokeratology (OK), and topical pharmaceuticals are considered clinically significant (the ability to reduce myopia progression by approximately 50%); **Figure 1.2** (Smith & Walline, 2015) and **Table 1.5**, below. Myopic undercorrection (Chung *et al*., 2002; Adler & Millodot, 2006), as well as conventional single vision spectacles or contact lenses increase its progression in nearsighted children between 0.50-1.00 D annually (Donovan *et al*., 2012). However, multifocal spectacles and those with progressive addition lenses (PALs) can produce an efficacy of 20-50% in some cohorts (Gwiazda *et al*., 2003; Cheng *et al*., 2014) and with minimal safety concerns. Orthokeratology efficacy has been reported in the range of 30-60% by various studies (Walline *et al*., 2009; Hiraoka *et al*., 2012; Santodomingo-Rubido *et al*., 2012), including the longitudinal randomised Retardation of Myopia in Orthokeratology (ROMIO) clinical trial (Cho & Cheung, 2012). Reported treatment efficacy for OK may vary with study location and subject ethnicity, unless a range of ethnicities were present (Jones *et al*., 2019). Similar efficacy of 30-50% or higher can be achieved by MFSCLs depending on the design (Anstice & Phillips, 2011; Sankaridurg *et al*., 2011; Lam *et al*., 2014; Aller *et al*., 2016; Cooper *et al*., 2018). The efficacy with atropine extends to 30-80% (Chua *et al*., 2006; Tong *et al*., 2009; Chia *et al*., 2012), but unlike OK (Santodomingo-Rubido *et al*., 2017) and MFSCLs (Walline *et*

al., 2013), atropine (Pineles *et al*., 2017) is contraindicated for long-term application exceeding two years. Children have not been deemed anymore prone to either OK (Bullimore *et al*., 2013; Liu & Xie, 2016) or MFSCL (Chalmers *et al*., 2011; Bullimore, 2017) complications than adults. However, it is important to highlight the effects of myopia control lenses on contrast sensitivity and the accommodation response. Recent notable works by Sanchez *et al*. (2018) and Przekoracka *et al*. (2020) have stressed the role of multifocal contact lens design in distinctly limiting visual performance by inflicting halos, reduced contrast sensitivity and visual acuity. Furthermore, Ruiz-Pomeda *et al*. (2018) and Cheng *et al*. (2019) suggested that the contact lens optical design may have a crucial role in myopic children by influencing the binocular and accommodative function in utilising positive spherical aberration. Novel use of combination therapy between optical and pharmaceutical treatments is also possible, but research in this area is still very limited (Verzhanskaya & Tarutta, 2017; Tan *et al*., 2020).

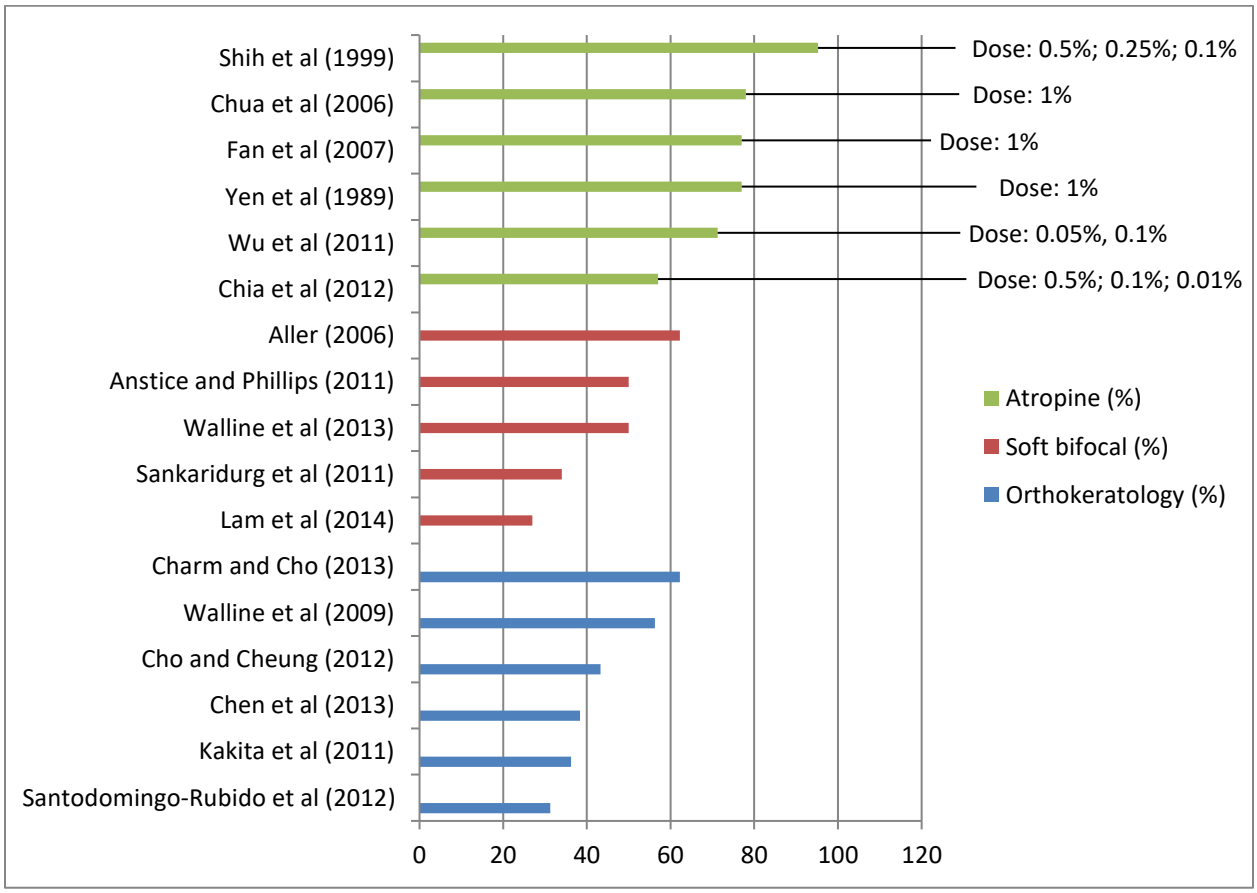

Figure 1.2 The reported efficacy (%) of atropine, soft multifocal contact lenses, and orthokeratology to reduce myopia by various controlled studies adapted from Smith & Walline (2015).

Treatment	Study	Efficacy in slowing myopia progression	Efficacy in slowing axial elongation
Soft multifocal contact lenses	Paune *et al*. (2015) Aller *et al*. (2016) Cheng *et al*. (2016) Ruiz-Pomeda *et al*. (2018)	42.9% 77.2% 20.6% 39.32%	26.9% 79.2% 38.9% 36.04%
Orthokeratology	Paune *et al*. (2015)		38%
Atropine			
1%	Yi *et al*. (2015)	138%	109%
0.5%	Chia *et al*. (2016)	75%	0.27 mm
0.1%		67%	0.28 mm
0.01%		58%	0.41 mm
0.5%	Wang *et al*. (2017)	160%	300%
0.05%	Yam *et al*. (2018)	-0.27 D	0.20 mm
0.025%		-0.46 D	0.29 mm
0.01%		-0.59 D	0.36 mm

Table 1.5 The reported efficacy of atropine, soft multifocal contact lenses, and orthokeratology to reduce myopia by various controlled studies, after the review by Smith & Walline (2015).

Due to persistent variability in efficacy and mechanism understanding of the current optical, pharmacological, environmental, and surgical treatment strategies, the committee on Interventions for Myopia Onset and Progression (Wildsoet *et al*., 2019) maintains that no therapy yet exists for all patients able to fully prevent, delay, or control myopia. This IMI white paper extensively summarizes the variable optical treatment efficacies as such: single vision spectacles (14%); bifocal and progressive addition spectacles (6-51%); off-label soft multifocal contact lenses (38%); and orthokeratology (30-55%). Also, studies have shown myopia progression to be clinically similar between full correction single vision spectacles and soft contact lenses (Horner *et al*., 1999; Fulk *et al*., 2003; Marsh-Tootle *et al*., 2009), whilst undercorrection in some randomized controlled trials (RCTs) either holds no significant clinical effect or further increases myopia progression (Chung *et al*., 2002; Koomson *et al*., 2016; Adler & Millodot, 2006). Although pharmacological control of myopia has consisted of atropine (non-selective antimuscarinic antagonist), pirenzepine (M1-selective muscarinic antagonist), oral 7-methylxanthine (adenosine antagonist), and topical timolol (non-selective beta-adrenergic antagonist), the report mentions only topical atropine has been widely used in both trials and practice with ranging myopia control efficacy of 60-80% for the 1% dose (Yen *et al*., 1989; Shih *et al*., 1999; Chua *et al*., 2006) and 42-58% for the lower 0.01% dose (Shih *et al*., 1999; Chia *et al*., 2014; Chia *et al*., 2016) resulting in reduced rebound and side-effects. Studies on environmental strategies have associated outdoor time efficacy with myopia prevention and not its control (Donovan *et al*., 2012; Gwiazda *et al*., 2014; Li *et al*., 2015); noted a missing

correlation between near work and outdoor time (Guggenheim *et al*., 2012; Lin *et al*., 2014; Li *et al*., 2015); and missing support for a causal relationship between lower serum vitamin D levels and myopia (Guggenheim *et al*., 2014; Cuellar-Partida *et al*., 2017). Moreover, the meta-analysis by Sherwin *et al*. (2012) linked every extra hour spent outdoors per week with a 2% reduction in myopia development among children and adolescents. The committe has mentioned that the only surgical interventions for mypia control in the literature involve scleral reinforcement including posterior scleral reinforcement (PSR), injection-based scleral strengthening (SSI), and collage cross-linking scleral strengthening (CCL); where both clinical application and research has been limited to PSR and only in China, Eastern Europe, and Russia.

Although complete understanding remains elusive, the potential mechanisms of these treatments consist of peripheral refraction, positive spherical aberration, and accommodation; whilst the extended efficacy, safety, and rebound effects in the current literature only spans up to five years. For instance, Berntsen *et al*. (2013) linked PAL efficacy with peripheral myopic defocus restricted to the superior retina, whilst Smith (2013) attributed the greater efficacy with OK and MFSCLs to their ability for induced simultaneous peripheral myopic defocus over all or most of the retina. The randomized clinical trial by Walline *et al*. (2004) on standard rigid gas-permeable contact lenses reported only a temporary significantly reduced myopia progression, due to changes in corneal curvature, but no effect on axial elongation. Indeed, AL changes by contact lenses are well-correlated with myopia control, where many studies have mentioned mean efficacy of 41%, as well as corresponding increased average elongation over two-years of 0.33 mm and 0.55 mm in the experimental and control groups respectively (Walline *et al*., 2009; Kakita *et al*., 2011; Cho & Cheung, 2012; Santodomingo-Rubido *et al*., 2012b; Charm & Cho, 2013; Cheung & Cho, 2013; Walline *et al*., 2013; Lam *et al*., 2014; Back *et al*., 2017; Jones *et al*., 2019). There are various designs of orthokeratology lenses, all producing similar levels of myopia control, which are significantly more effective than traditional means (undercorrection, single vision spectacles and contact lenses). Centre distance progressive contact lenses are also effective and have started to emerge commercially (Kollbaum *et al*., 2013). Although visual acuity may be compromised depending on the design, the primary goal is controlling myopia progression. For instance, contact lens use particularly with preserved cleaning solutions and potential wear discomfort (Fonn, 2009; Chalmers, 2014; Mizoguchi *et al*., 2017), as well as topical atropine preserved with benzalkonium chloride toxic to the cornea (Baudouin *et al*.,

2010; Datta *et al*., 2017), have been generally linked with dry eye disease, especially in younger groups (Mizoguchi *et al*., 2017; Wu *et al*., 2017).

1.2.6.1 Spectacles

Multifocal spectacles correct distance vision through the upper half portion of the lenses and were perceived to be able to slow myopia by relaxing accommodation via the bottom half (Mutti *et al*., 2006). Randomised clinical trials, including COMET 1 & 2 and the Study of Theories about Myopia Progression (STAMP), have incorporated bifocals and PALs with +1.50 or +2.00 Adds (Hyman *et al*., 2001; Edwards *et al*., 2002; Gwiazda *et al*., 2003; Berntsen *et al*., 2010; Cheng *et al*., 2010; COMET 2, 2011), but new designs exerting relative peripheral defocus are being developed (Sankaridurg *et al*., 2010; Lam *et al*., 2017). Although a longitudinal randomised three-year clinical trial by Cheng *et al*. (2014) did report myopia control of 51% in Chinese-Canadian children of age 8-13, both large (Li *et al*., 2011; Cheng *et al*., 2014) and small (Sankaridurg *et al*., 2010; Hasebe *et al*., 2014) efficacy by multifocal spectacles has been reported. Various studies noted the ability of multifocal spectacles to control myopia in comparison to single vision lenses, especially in nearsighted children with faster progression, lower baseline myopia, binocular errors (near esophoria or high accommodative lag) and reduced reading distance, but the effect was generally not clinically significant and did not last for more than a year (Cheng *et al*., 2010; COMET 2, 2011; Berntsen *et al*., 2013; Smith & Walline, 2015). The randomised trial by Berntsen *et al*. (2012) also showed no rebound effect post-PAL treatment in children after one year of wear. However, Hasebe *et al*. (2005) have reported that nearsighted children wearing multifocal spectacles misuse the near zone within the lens profile by not fixating correctly and require regular frame adjustments. Overall, due to their unconvincing efficacy, as well as lack of wear compliance from reduced esthetics and useful field of view with visual distortion, spectacles for myopia management should be considered second-tier options for patients unideal to be fitted with contact lens treatments or those in remote geographical regions (Gifford *et al*., 2019; Jones *et al*., 2019).

1.2.6.2 Soft Multifocal Contact Lenses

Soft multifocal contact lenses that are normally used to correct presbyopia are also promising for myopia control (Anstice & Phillips, 2011; Sankaridurg *et al*., 2011; Berntsen & Kramer, 2013; Kang *et al*., 2013; Ticak & Walline, 2013; Walline *et al*., 2013; Fujikado *et al*., 2014; Lam *et al*., 2014; Cheng *et al*., 2016; Gifford & Gifford, 2016; Sankaridurg, 2017). This treatment mode allows for flexible wear (Lam *et al*., 2014) and even better self-esteem among children relative

to spectacles (Rah *et al*., 2010). As with the different spectacle lens designs, although no rebound effect was found post-MFSCL treatment after one-two years of wear, Cheng *et al*. (2016) reported efficacy only during the initial six months. The two main designs of MFSCLs, usually utilised with a +2.00 to +2.50 D power Add, include: concentric dual-focus or bifocal with alternating distance plus power for refractive error correction and myopic defocus treatment; and aspheric progressive power or peripheral add having a central zone correcting distance refractive error with gradual increase in relative peripheral plus power for myopia defocus (Gifford *et al*., 2019). In 2011, Anstice & Phillips carried out a 20-month crossover study comparing a dual-focus center-distance concentric soft multifocal lens in one eye with a conventional single vision soft lens for distance correction in the other eye, which were exchanged after a 10-month interval. The researchers reported ≥30% reduction in myopia progression with the dual-focus lens. In a two-year study, Cheng *et al.* (2013) showed that the myopia control mechanism with aspheric soft multifocal contact lenses is based on inducing the most positive spherical aberration, whilst Anstice & Phillips (2011) did not report significant difference in visual acuity and contrast sensitivity using a concentric design. However, Kollbaum *et al*. (2013) found reduced visual performance (decreased acuity by one line) and contrast sensitivity when they compared a dual-focus center-distance multifocal (MiSight, CooperVision) and center-near bifocal (Proclear Multifocal, CooperVision) two-zone concentric soft designs with +2.00 D power Add to conventional spectacle-corrected performance in young adults age 18-25, whilst no difference resulted when only the multifocal lenses were compared. In a two-year study on myopic children of age 8-11 wearing aspheric center-distance soft multifocal lenses (Proclear Multifocal, CooperVision) with +2.00 D power Add, Walline *et al*. (2013) reported a maintained 50% and 29% reduction in myopic refraction and eye elongation respectively, when compared to a conventional single vision soft lens.

The three-year Bifocal Lenses in Nearsighted Kids (BLINK) study (Walline *et al*., 2020) on approximately 300 children age 7-11, also the first randomised clinical trial comparing center-distance multifocal soft lenses of +1.50 D and +2.50 D Adds, found that bifocal contact lenses, especially those of high-add, slowed myopia progression by 43% and reduce axial length by 0.23 mm, when compared to standard single-vision contact lenses. Walline *et al*. (2017) earlier noted that even if myopia control is the primary concern, children must be able to tolerate lens wear. This comes after Lopes-Ferreira *et al*. (2011) earlier concluded only center-distance MFSCLs with +3.00 D and +4.00 D power Adds can induce significant relative peripheral myopic defocus, but Adds >2.50 D may not be visually acceptable by children (Bickle & Walline,

2013). A study by Sankaridurg *et al*. (2011), where Chinese children age 7-14 were fitted with an aspheric, peripheral progressive plus-powered (center-distance) soft contact lens (Lotrafilcon B, CIBA Vision) for one year, resulted in 34% and 33% reduction in myopic refraction and axial elongation respectively, when compared to the nearly two-fold reduced myopia control effectivity of the flat optical profile in spectacle lens wearers within the same age group. Although new developments are constantly made, the literature suggests that the current majority of contact lens designs for myopia control correct the distance refractive error within their central optical diameter, whilst control myopia progression by reducing the relative peripheral hyperopia (Gifford & Gifford, 2016). The study by Sankaridurg *et al*. (2011) showed that the use of conventional soft single vision contact lenses for myopia control is ineffective, since their optical profile only exerts relative peripheral hyperopia, instead of creating peripheral myopic defocus. Additionally, in their two-year randomised clinical trial among nearsighted Hong Kong Chinese children, Lam *et al*. (2014) proposed a positive correlation between Defocus Incorporated Soft Contact (DISC) lens wearing time and corresponding efficacy, suggesting a daily modality of ≥5 hours. Studies have been inconclusive regarding the efficacy influence of inducing a relative peripheral myopia refraction profile with varying add powers and visual field treatment extent, as well as the impact on accommodation, all requiring further research (Smith, 2013; Walline *et al*., 2017). To better understand such differences in retinal peripheral refraction with different lens designs and powers, recent studies have visualised the power profiles of the many used MFSCLs (Kim *et al*., 2017; Nti *et al*., 2021).

1.2.6.3 Orthokeratology

Orthokeratology has been implemented since the 1960s, but only in the last two decades has it generated significant attention (Mountford, 1997; Lui *et al*., 2000; Mountford, 2004). This is largely attributed to the worldwide increased prevalence of myopia (Vitale *et al*., 2008; Williams *et al*., 2015; Holden *et al*., 2016), coupled with improvements in lens materials, designs, and instrumentation (Coon, 1984; Wlodyga & Bryla, 1989; Mountford, 1997). Overnight OK is a temporary, reversible, and non-invasive treatment option that can provide natural daytime clear vision, without the need of a corrective appliance (Swarbrick, 2006; Walline *et al*., 2009; Cho & Cheung, 2012). Such a clinical option offers ground-breaking independence with subsequent quality of life improvements for many myopes, as well as ease for parental involvement and oversight (Lipson *et al*., 2005; Smith *et al*., 2009b; Santodomingo-Rubido *et al*., 2013). Although the exact mechanism of orthokeratology remains inconclusive, the literature suggests that the redistribution of epithelial cells increases the power of the mid-periphery to reduce eye

elongation (Alharbi & Swarbrick, 2003; Nieto-Bona *et al*., 2011a; Nieto-Bona *et al*., 2011b; Qian *et al*., 2013). These corneal changes of flattening and steepening represent the central and peripheral transition zones respectively, while the area of corneal flattening is referred to as the treatment zone (Mountford, 2004; Swarbrick, 2006; Lu *et al*., 2007). Studies have speculated that the treatment zone size of orthokeratology lenses is responsible for the treatment effect in myopia control (Owens *et al*., 2004; Lu *et al*., 2007; Gifford & Swarbrick, 2009), but existing research in this area is scarce.

Orthokeratology is particularly effective in comparison to other optical myopia control strategies, due to its ability to treat moderate and high nearsightedness (3.00-6.00 D), as well as being less susceptible to eye movement and blinking than soft contact lens correction (Smith, 2013). Efficacy for correcting high myopia >6.00 D in conjunction with single vision spectacles has also been demonstrated over a two-year randomised study (Charm & Cho, 2013). The treatment zone is the site for corneal reshaping, where the cornea changes from prolate to a spherical shape (Mountford *et al*., 2004; Swarbrick, 2006; Chan *et al*., 2008). Success has been linked to the treatment zone size (Alharbi & Swarbrick, 2003) in relation to corneal epithelial thinning and refractive surgery concepts surrounding Munnerlyn's formula, where the expected orthokeratology change in refractive error is based on corneal thickness or sagittal height changes (Swarbrick *et al*., 1998); higher myopia requires a wider treatment zone and deeper corneal flattening, which may increase the risk for corneal abrasion (Chan *et al*., 2008). Furthermore, higher myopic refractive error imposes an increased risk of lens decentration and corneal staining (Lu *et al*., 2007). Thus, the application of orthokeratology towards correcting myopia beyond 4.00 D is usually restricted to smaller optical treatment zones, in order to limit flattening into the corneal stromal tissue (Owens *et al*., 2004) and account for pupil size changes under dim illumination (Swarbrick *et al*., 1998). Optical zone diameters of four- and five-zone orthokeratology lenses typically range between 5.50-6.50 mm, with 6.00 mm being the most common; however, for corrections between 1.00-3.00 D and 3.50-6.00 D, it is possible to have a zone of 6.00-6.50 mm and 4.00-5.00 mm respectively (Mountford *et al*., 2004). Moreover, both studies by Owens *et al*. (2004) and Lu *et al*. (2007) found that longer orthokeratology lens wear (over four weeks) leads to an increasing treatment zone size, which has been associated with better visual acuity, increased optical aberrations, and improved subjective visual quality. A more recent study by Kang *et al*. (2013) investigated the effects on peripheral refraction, corneal topography, and aberrations and did not find significant differences after changing orthokeratology lens parameters (5.00 mm and 6.00 mm optic zone diameters) in

myopic (1.00 D to 4.00 D) young adults over a two-week period. Although statistically insignificant, the authors reported that the 6.00 mm orthokeratology lens seemingly achieved greater peripheral myopic defocus via steepening of the corneal midperiphery. Thus, the relationship between corneal reshaping, treatment zone sizes, optical aberrations, and quality of life measures warrants further research.

Orthokeratology predominantly exists as an overnight modality based on many advantages: it eliminates adaptation problems associated with a blink reflex since lens movement and lid interaction are reduced in a closed eye, it lowers the risk of foreign bodies and corneal staining, offers a stable environment leading to a potentially higher compliance, and has higher overall efficacy (Mountford, 1997; Swarbrick, 2006; Cho *et al*., 2008). Also, the lenses never leave one's home and parents may be involved with every aspect of their use in cases of children wearers (Santodomingo-Rubido *et al*., 2013). In addition to myopia control, overnight orthokeratology provides the same convenience and cosmetic appeal as laser surgery by providing quality unaided daytime vision, with the further advantages of being reversible, non-invasive, and allowing patients to take a break from lens wear (Soni *et al*., 2004; Wu *et al*., 2009; Chen *et al*., 2010). Orthokeratology can also be used to correct refractive error regression and restore corneal regularity due to complications arising from refractive surgeries (Ozkurt *et al*., 2012). Furthermore, dry eye prevalence in ages ≥40 was reported to be 54.3% (Shah & Jani, 2015), whilst tear evaporation has been found to be significantly higher in ages ≥45 (Guillon & Maissa, 2010), especially in females, as the lipid layer in the tear film becomes thinner and less efficient with age. Dry eye symptoms experienced by presbyopic contact lens users can be avoided with overnight orthokeratology wear, since rigid lenses allow for less tear evaporation in a closed eye (Muntz *et al*., 2014).

1.2.6.4 Pharmaceuticals

The literature has shown that topical cycloplegic therapy (low-dose atropine of 0.01% or pirenzepine antimuscarinic drugs) most commonly applied to young children between ages 3-11 is a highly effective myopia control strategy (Tan *et al*., 2005; Siatkowski *et al*., 2008; Tong *et al*., 2009; Chia *et al*., 2016). Cycloplegic drugs are already used to slow myopia progression in East Asia and success rates are between 32%-72% (Chia *et al*., 2014, 2016). However, atropine is not often clinically prescribed due to its side effects (temporary and reversible light-sensitivity, blurry vision at close distance, stinging/burning, and allergic conjunctivitis) via pupil dilation and lowered accommodation, whilst pirenzepine is not commercially available (Chua *et*

al., 2006; Tong *et al*., 2009; Chia *et al*., 2012; Smith & Walline, 2015). Unlike atropine, pirenzepine is a selective muscarinic receptor and may exert reduced side effects (Siatkowski *et al*., 2008). Tan *et al*. (2005) reported 50% (0.35 D) myopia reduction and deemed the application of 2% pirenzepine gel in Asian myopic children of age 6-12 over a one-year period as safe (one case of abdominal pain, two cases of treatment withdrawal due to accommodative relaxation and pupil dilation, and 8% withdrawal due to allergic reactions). In a two-year longitudinal study on the application of 2% pirenzepine gel among myopic children of age 8-12, Siatkowski *et al*. (2008) showed myopia control (myopia progression of 0.26 D and 0.58 D at years one and two respectively compared to the control group) and patient safety to be maintained. However, the use of pirenzepine is limited due to its unknown mechanism, initial age to commence application, treatment length, and long-term efficacy.

Atropine is particularly a potent drug only available in 0.5% and 1% doses in the UK as ointment and drops. Other concentrations of ≤0.5% are not commercially available and unlicensed by the Medicines & Healthcare Products Regulatory Agency (MHRA). According to the Medicines Act 1968, atropine is classified as a prescription only medicine (POM) available to UK practitioners with a minimum of additional supply training and is mainly used in hospital eye services (HES) for mydriasis or cycloplegia. In another two-year longitudinal study on myopic Asian children of age 6-12, Tong *et al.* (2009) showed that the cycloplegic effect of 1% atropine drops was reduced within six months and a lower myopia progression was observed in the following six months. Like the different orthokeratology lens designs, there is a rebound effect after atropine cessation, but long-term investigation on myopia control and post-treatment stabilisation with variable atropine concentrations also has not been performed yet. Debate continues regarding the optimum concentration necessary, in order to minimize the associated adverse reactions, whilst maintaining effectiveness and preventing rebound. The two-year longitudinal study on Asian myopic children of age 6-12 by Chia *et al*. (2012) demonstrated that lower atropine concentrations (0.5%, 0.1%, and 0.01%) had comparable efficacy and safety results. The 0.01% dose was especially shown to be the safest and with lower rebound effect (Chia *et al*., 2012; Loughman & Flitcroft, 2016), as well as reducing accommodative amplitude only by 2-3 D (Chia *et al*., 2016). The Atropine for the Treatment of Myopia (ATOM) studies (Chua *et al*., 2006; Chia *et al*., 2016) confirmed these outcomes, but over a five-year clinical trial. Although atropine's action may be based on reduced accommodation and changes of the crystalline lens curvatures (Chua *et al*., 2006; Chia *et al*., 2014), or eye growth receptor interaction associated with circadian rhythms (Stone *et al*., 2013; Bullimore & Berntsen, 2018), the exact mechanism

remains unknown. One meta-analysis has also considered ethnicity, stipulating improved atropine efficacy in Asian children over their Caucasian counterparts (Li *et al*., 2014).

1.2.7 The Problem with Myopia Treatment

Although clinicians are aware of the available myopia control strategies, as well as the sufficient and accepted research evidence behind their efficacy and safety (Wolffsohn *et al*., 2016), the lack of global standardization in treatment protocol persists. In a review by Wolffsohn *et al*. (2016), important trends among current clinical practice regarding myopia control were noted: undercorrection continues to be employed as a control strategy particularly in India, Spain, Portugal, and South America despite its myopia inducing effects, pharmaceutical efficacy was reported to be underestimated, while the efficacy of increased outdoor activity was overestimated, and >68% of nearsighted children were still prescribed with single vision spectacles or contact lenses. In addition to clinical standardization, further clinical trials are still necessary to confirm the mechanism, efficacy, safety, predictability, and economic feasibility of these optical treatments, in order to gain clinical acceptance worldwide (Polse *et al*., 1983a and b; Santodomingo-Rubido *et al*., 2012).

Myopia control treatments are mainly off-label/unlicensed prescriptions, and the relevant legal, regulatory, and professional stance is country-specific, varying worldwide. An exception is the recently approved European certification standard or CE marking for the MFSCLs dailies MiSight (CooperVision) and NaturalVue (Visioneering Technologies), which is also recognised in Canada, Australia/New Zealand, and sporadically in Asia. Increased practitioner training and patient education are additionally required to stagnate the myopia crisis. The IMI – Industry Guidelines and Ethical Considerations for Myopia Control Report (Jones *et al*., 2019) discussed extensively the ethical and regulatory responsibilities shared by stakeholders (governmental and regulatory bodies, manufacturers, academics, health and eye care practitioners, patients) regarding myopia control products, since these are mainly off-label/unlicensed treatments and devices directed at vulnerable patients. Off-label/unlicensed prescribing must be thoroughly understood, as listed reasons for and against off-label promotion, as well as permitted FDA sources of related use information in the United States may be found in the white paper report, as adapted from Ventola (2009). Its reported use by an early study was both common and frequent, for instance, accounting for about 21% of all prescriptions and possibly reaching 83% in some therapeutic specialties or patient populations in the United States (Radley *et al*., 2006).

The IMI – Clinical Management Guidelines Report (Gifford *et al*., 2019) has provided an evidence-based best practice framework to identify risk factors and environment interventions; lay terminology to discuss myopia, its risks and treatment options, including off-label strategies; standard procedure for baseline examination, as well as additional evaluation and exploratory tests; regulations for clinical advice and care; and advise for future research and clinician professional development. Further key conclusions from the white paper report include: a myopia range of at least 0.50-0.75 D is necessary before considering treatment; myopia correction is to be worn full time and undercorrection as a control strategy should be abandoned; near work should not be prevented, but coupled with time spent outdoors for the minimally recommended 8-15 hours/week; the efficacy and safety of treatments should be monitored on 6-month intervals.

Futhermore, the IMI – Clinical Myopia Control Trials and Instrumentation Report (Wolffsohn *et al*., 2019) highlighted the following: clinical trials should span a minimum of three years (two years with treatment and the final year without treatment to assess possible rebound effects); a control group is mandatory; a standardised adverse event reporting system and dilated fundus examinations should be inplace; dysphotopsia should be investigated at baseline and throughout the study; classification of outcome measures is to consist of primary (refractive error or axial length), secondary (patient/guardian reported outcomes via a questionnaire and treatment compliance in real time), and exploratory (peripheral refraction, changes in accommodative lag and dynamics, ocular alignment, pupil size, outdoor activity and lighting levels, anterior and posterior segment anatomical changes particularly related to choroidal thickness, and scleral and corneal biomechanics) results.

1.2.8 Developments in myopia assessment & prediction technology

The global myopia epidemic has prompted the development of clinical models to predict and monitor its onset, progression, and control. Such predictive methods of assessment and technology have taken various forms from the use of growth models (Tideman *et al*., 2018; Diez *et al*., 2019; Jagadeesh *et al*., 2020), electronic medical record (EMR) systems into machine learning (Kaya *et al*., 2018; Lin *et al*., 2018; Xu *et al*., 2018; Yang *et al*., 2020), as well as mobile apps and devices (the Brien Holden Vision Institute [BHVI] Myopia Calculator; Plano; FitSight; Myopia Master; MYAH). Epidemiological research has identified many risk factors for childhood and adolescent myopia (Pan *et al*., 2012; Kim *et al*., 2013; Stambolian, 2013), but predictive

models have grouped these into optical, structural, genetic and environmental classifications. These categories have also assigned myopia-specific measurement parameters, such as uncorrected refractive error (including parental history), corneal curvature, crystalline lens power, accommodative lag, axial length (AL), age, ethnicity, sex, education and time spent with outdoor and near-vision tasks (He *et al*., 2015; Medina, 2015; Zadnik *et al*., 2015) towards the application of specialty devices. Furthermore, in the recent Singapore Cohort Study of the Risk Factors for Myopia (SCORM) among 674 children of age 7-10, Brennan *et al*. (2020) noted that although annual and subsequent annual progression were strongly correlated (1 D increase = 0.35 D increase respectively), annual progression alone was a poor model for predicting long-term myopia development. The authors concluded that practitioners must additionally consider past progression rates, if known, as well as the age of onset (especially early onset considered to be younger than age 12) and parental history, before commencing a myopia control treatment. Bullimore & Richdale (2020) added that multiple criteria for progression, investigated by standardised measurement methods, must be applied towards obtaining accurate myopia rate predictions.

The present feasibility to predict true individual myopia progression rates is low (Hernandez *et al*., 2018). Thus, there is strong interest in non-invasive, predictive prevention and treatment strategies, particularly targeting at-risk potential high myopes, which will further equip policymakers, parents, and eye care professionals in successfully managing myopia. The scope corresponds to the proposed Package of Eye Care Interventions (PECI) and Integrated People-Centred Eye Care (IPCEC) approaches, outlined in the latest World Health Organization report on vision (WHO, 2019), which should be considered by all involved in eye care. This is thought to be the first review of its kind on myopia predictive technology.

1.2.8.1 Axial Length & Refractive Error

Gordon & Donzis (1985) noted that AL and corneal diameter changes were the most significant factors in the first two years of life that determined human refractive development during childhood. Axial length measurement is long recommended as the gold standard in monitoring pediatric myopia progression (Meng *et al*., 2011), where ocular disease risk increases with each *millimeter* of elongation (Haarman *et al*., 2020), high myopia (≥6.00 D) has been linked with excessive AL (≥26 mm) (Tideman *et al*., 2016), and the associated higher risk of visual impairment evidenced by some of the latest randomised myopia control clinical trials (Chamberlain *et al*., 2019; Walline *et al*., 2020). However, the International Myopia Institute (IMI) has suggested the use of both AL and refractive error to predict myopia onset, due to their

variable correlation, particularly in early childhood, as well as the lack of global standardised AL criteria for individual patients (Gifford *et al*., 2019; Wolffsohn *et al*., 2019).

A recent meta-analysis also highlighted significant ethnical differences in AL, where Asian children had 40% greater length than their Caucasian counterparts (Brennan *et al*., 2018) for the same refractive error. Brennan *et al*. (2020a) have additionally suggested the use of the Cumulative Absolute Reduction in Axial Elongation (CARE) factor for assessing myopia control efficacy, stating a maximum CARE of 0.44 mm (~1 D) over a period of 2-3 years for currently available treatments, as illustrated by **Table 1.6**. This is especially relevant, as Bullimore & Brennan (2019) previously analysed the data of 21,000 patients across five population-based studies, showing that a 1 D myopia increase and 0.44 mm reduction in axial length corresponded to a 67% increase and 40% decrease in myopic maculopathy, respectively. Further clinical research is needed to validate whether AL, refractive error, or their combination is the most reliable predictor for individual myopia progression rates within all population cohorts.

Study	Treatment	CARE (mm)	Study design details			
			Time (y)	Device	Rand.	N= (T, C)
Santodomingo-Rubido et al. (2017)	OK	0.44	6+	Opt	N	14, 16
Hiraoka et al. (2012)	OK	0.42	5	Opt	N	22, 21
Leung & Brown (1999)	Specs	0.41	1.5	US	N	14, 32
Chua et al. (2006)	Atr 1.0%	0.40	2	US	Y	166,190
Zhu et al. (2014)	OK	0.36	2	Opt	N	65, 63
Chen et al. (2013)	OK	0.33	2	Opt	N	35, 23
Charm & Cho (2013)	OK	0.32	2	Opt	Y	12, 16
Walline et al. (2009)	OK	0.32	2	US	N	28, 28
Lam et al. (2019)	Specs	0.31	2	Opt	Y	79, 81
Chamberlain et al. (2019)	SMCLs	0.28	3	Opt	Y	48, 51
Cho et al. (2005)	OK	0.28	2	US	N	35, 35
Cheng et al. (2014)	Specs	0.28	3	US	Y	46, 50
Cho et al. (2012)	OK	0.27	2	Opt	Y	37, 41

Table 1.6 A summary of reported CARE for different myopia control strategies, across the literature, as adapted and recreated from Brennan *et al*. (2020a), where abbreviations are as follows: Devices (Opt – optical interferometric biometry; US - ultrasound); Rand. (whether the study was randomised); N = (T, C) indicating the sample size in treated and control groups.

1.2.8.2 Models of Growth

Research efforts have validated longitudinal population- and age- specific growth percentile charts referencing the visual development (refractive error and ocular biometry) of children and adolescents using large epidemiological cohorts, in order to estimate abnormally distributed clinical myopia relative to normative data. Early (Jones *et al*., 2005) and later (Rozema *et al*., 2019) studies have also shown that myopia onset occurs at around a similar AL between future myopes and children who remained emmetropic, where boys and future myopes had a greater axial elongation rate than girls and persistent emmetropes, respectively. The study by Jones *et al*. (2005) tested 247 Californian myopic children of age 6-14 between 1989-2001 and produced differing myopic and persistent emmetropic growth curves for corneal power, axial length, as well as anterior and vitreous chamber depth. Furthermore, Rozema *et al*. (2019) added from their longitudinal SCORM data that future myopes had higher lenticular power loss than persistent emmetropes, before myopia onset. The Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error (CLEERE) Study, which tested 1854 nonmyopic children, highlighted the relatively low sensitivity and specificity of first grade refractive error and the number of myopic parents alone for predicting myopia onset between grades two and eight, being 62.5% and 81.9%, respectively (Jones-Jordan *et al*., 2010). These results suggested that a multitude of myopia predictors must be combined to produce models with greater accuracy. Zadnik *et al*. (2015) also used CLEERE data, based on 4512 nonmyopic children from grades one to eight of diverse ethnicities between 1989 and 2010. The authors investigated 13 possible risk factors for their predictive ability of myopia onset and stated spherical equivalent refractive error as the best factor for estimation, particularly six years old children of <0.75 D. Zhang *et al*. (2011) validated a three-year predictive myopia model from two different population cohorts (236 and 1979 Chinese children from mixed urban-rural Xiamen and Singapore, respectively) by using measures of visual acuity, refractive error, biometry, height, and weight. The authors reported similar sensitivity and specificity to Jones-Jordan *et al*. (2010), but additionally mentioned that children of the Singaporean cohort had more myopia, longer mean axial length, and were taller and heavier.

Chen *et al*. (2016) compared the Guangzhou Refractive Error Study in Children (RESC) cross-section data of 4218 children aged 5-15 and the Guangzhou Twin Eye Study (GTES) longitudinal data between 2006-2012 of 354 children, in order to validate reference centile refraction curves for predicting the high myopia onset and scaled severity that may be representative of the South Chinese school-aged urban population. The authors noted the efficacy of this age-specific tool and particularly the lower percentiles, where the 5th centile was the best overall diagnostic test (92.9% sensitivity; 97.9% specificity; 65% positive predictive value). Other studies have focused on AL growth. Tideman *et al*. (2018) provided normative eye growth values for myopia prevention and control, representative of European children; the study sample of 12,386, combined the AL and corneal curvature data from the Dutch Generation R and Rotterdam Study III (RS-III), and British Avon Longitudinal Study of Parents and Children (ALSPAC) studies, but was limited to only Dutch refractive error data. The authors reported AL growth predicted future myopia at a 50% rate. Diez *et al*. (2019) produced similar AL percentile growth curves from 12,554 Chinese children aged 6-15 and offered a comparison. The Chinese and European populations had similar percentiles for AL at age 6, but Chinese children showed higher percentile AL values at the ages of 9 and 15, and females always exhibited lower ALs than their male counterparts. More recently, Jagadeesh *et al*. (2020) analyzed the myopia-associated structural changes from multiple optic disc and retinal features (ODRFs) on 2851 Chinese children aged 6-9. The authors suggested such data may additionally be used in predicting myopia incidence and AL progression, having planned for an upcoming validation study of this model.

1.2.8.3 Machine Learning & Artificial Intelligence

Prognostic algorithms based on large-scale EMRs, or big data, and integration with cloud technology remain an untapped, but potentially may be the ultimate future clinical tool in medicine. As Obermeyer & Emanuel (2016) reported, the ability of such methods to compile seemingly infinite, complex volumes of clinical parameters and predictors is still based on correlation principles, which are prone to overestimate biased real-world data and still cannot provide knowledge of causation. The current research is promising, but independent clinical validation databases from unique population and time clusters are limited. Lin *et al*. (2018) combined the refraction data of Chinese school-aged children from EMRs spanning eight independent centres and two longitudinal population-based cohorts (>half a million ophthalmic records between 2005-2015), in order to validate a predictive random forest (RF) algorithm for high myopia in adulthood. By using the age of examination, spherical equivalent, and annual

progression rate predictors, the authors concluded that their model was clinically accurate in predicting high myopia over 10 years, which may be used as a targeted myopia progression monitoring and control intervention tool representative of Chinese school-aged populations. A more recent study by Yang *et al*. (2020) for instance, applied a Gradient Boosting Regression Tree (GBRT) machine learning method based on correlation analysis and found their predictive Support Vector Machine (SVM) model to be accurate. Other works have analysed Electrooculogram (EOG) data by various data mining techniques (Logistic Regression [LR]; Naive Bayes [NB]; RF; REP Tree [RT]) to categorise individual ametropia (Kaya *et al*., 2018), whilst Multiple Kernel Learning (MKL) frameworks have been utilised to predict ocular pathology (Xu *et al*., 2018). Thus, validated prospective models originating from the analysis and synthesis of longitudinal myopia progression datasets may hold the most promise towards solving the global myopia prediction problem.

1.2.8.4 App & Device Tools

Additional methods of predicting and tracking myopia progression exist. The Myopia Calculator by the BHVI combines patient history (age, ethnicity, refractive error) with the available evidence-based myopia control strategies to estimate an individual's future myopia outlook using average data. The calculator is based on BHVI statistical datasets and the meta-analysis by Donovan *et al*. (2012) of myopia progression rates among urban Asian and European children corrected with single-vision spectacles from 20 studies, all spanning 1-3 years. Its effectiveness has been compared to the Northern Ireland Childhood Errors of Refraction (NICER) longitudinal data, where McCullough *et al*. (2016) evaluated the six-year refractive error change in UK Caucasian children and adolescents (aged 6-19) relative to an Australian cohort of European Caucasian children, as well as retrospective UK data of 50 years. Overall, the literature suggests accuracy of the BHVI calculator to improve with age (>12) and higher baseline refractive error, whereas myopia progression rates are prone to overestimation in younger Caucasian children; for instance, the BHVI Myopia Calculator overestimated myopia progression for groups aged 9-10 and 12-13 by 1 D and 0.75 D, respectively, than the NICER model. The Myappia Calculator, created by Thomas Aller in 2016, is another digital tool utilising peer-reviewed growth curves from large population cohorts, but also states it incorporates other myopia risk factors into its progression estimates aimed for a range of 10 years. The EndMyopia Calculator is one other, but different calculator, which has inputs for a patient's current spherical prescription (D) and blur-distance or edge of blur (cm), in order to provide a true myopia value (D) result, according to the developers. This tool could eventually be used as an alternative

customisable monitoring option for parents and their children next to other recent smartphone application technologies, such as Plano of the Singapore National Eye Centre by Mo Dirani in 2017, which tracks a child's digital device habits and behaviour. The smartphone/smartwatch wearable FitSight tracker evaluating time spent outdoors patterns and associated levels of light illumination follows the same concept (Verkicharla *et al*., 2017). Although more validation is necessary, these options together could aid global myopia screening efforts by adding more longitudinal databases and consequentially enhance the ability to predict myopia.

The combined advancement of the mentioned science and technology in this review has also allowed for the development of specialty instrumentation tailored to assessing and predicting myopia. These include the very new Myopia Master (2019) from OCULUS and MYAH (2020) by Topcon. OCULUS stated that the Myopia Master is the first device to apply the licensed predictive refractive error algorithms by the BHVI, alongside a documenting software for myopia-specific risk factors (ethnicity, number of nearsighted parents, time spent with outdoor and near-vision tasks) and measurement parameters (refraction, AL, keratometry); in order to compare an individual patient's values to a large built-in age-related normative database, providing growth curves for refraction and AL. According to Topcon, MYAH assesses corneal topography coupled with aberration summary and support for specialty myopia contact lens fitting, dynamic pupillometry, AL by optical low coherence interferometry, myopia progression relative to treatment efficacy and provided initial baseline, as well as comprehensive dry eye analysis. Since these instruments are brand new, no peer-reviewed validation yet exists.

1.2.8.5 Summary

The predicting and tracking of myopia are multifactorial. Research involving large datasets of bespoke associated risk factors for individual patients across unique ethnic regions is still necessary to explain discrepancies in progression rates of similar cohorts. Moreover, these datasets must be perpetually updated to precisely reflect global epidemiological shifts. Axial length changes alone are insufficient to predict future myopia and should be considered alongside the other optical, structural, genetic, and environmental patterns discussed, in order to create true comparative emmetropic and myopic growth models. This may lead to greater specificity for predicting and tracking clinical myopia, as well as the efficacy of any correspondingly applied control treatments. Although various developments in these assessments exist, further validation is required to expand success outside of averaging the highly myopic and at-risk children.

Chapter 2 Global trends in myopia management attitudes and strategies in clinical practice – 2019 update

2.1 Introduction

Due to the uncontrolled global myopia growth, perpetual improvement in the evidence-based understanding of its vision risks and associated management remains essential. Holden *et al*. (2016) projected myopia to affect half of the world's inhabitants by 2050 and its propensity to become the leading cause for irreversible blindness. Deeming it a public health concern worldwide, The International Myopia Institute (IMI) released white papers (available online: https://www.myopiainstitute.org/imi-white-papers.html) compounding the latest and complete knowledge surrounding myopia across seven expert committees, including: Myopia Control Reports Overview and Introduction (Wolffsohn et al., 2019); Defining and Classifying Myopia (Flitcroft et al., 2019); Experimental Models of Emmetropization and Myopia (Troilo et al., 2019); Myopia Genetics (Tedja et al., 2019); Interventions for Myopia Onset and Progression (Wildsoet et al., 2019); Clinical Myopia Control Trials and Instrumentation (Wolffsohn et al., 2019); Industry Guidelines and Ethical Considerations for Myopia Control (Jones et al., 2019); Clinical Myopia Management Guidelines (Gifford et al., 2019). This is a major milestone among many, as the field has always continued to expand and develop: the biennial International Myopia Conference, since 1964; the National Committee on Myopia, since 1990s; joint global myopia scientific meeting by the World Health Organization and the Brien Holden Vision Institute (2015); FDA interdisciplinary public workshop on myopia clinical trial design (2016).

During the past two decades, research in the field of myopia has extrapolated, but global agreement of an optimum and standardized treatment guidance is still limited. Similarly, reported practitioner perception in the literature is scarce. A survey by Jung *et al*. (2011) noted that most Korean ophthalmologists preferred to prescribe full cycloplegic spectacle refraction for childhood myopia control, followed by orthokeratology and spectacle undercorrection, whilst atropine was mostly considered ineffective. An international perspective (Zloto *et al*., 2018), but also solely focused on the prescribing trends of pediatric ophthalmologists, reported: 57% of the total 940 respondents routinely engaged in myopia control, but a lack of consensus remained on when to initiate treatment; the main precursor for treatment was myopia progression of ≥ 1 D/year; 70% prescribed eye drops of which atropine 0.01% accounted for 63.4%; 86% recommended increased time spent outdoors, whilst 60.2% and 63.9% advised less screen viewing and smartphone use respectively. From the survey conducted in 2015, Wolffsohn *et al*. (2016) reported that despite the high concern and activity over myopia progression and control

respectively, most eye care practitioners worldwide prescribed single vision spectacles and contact lenses. This paper provides an update of these attitudes and trends toward myopia management strategies in clinical practice four years later.

2.2 Method

A self-administrated, internet-based cross-sectional survey in Chinese, English, French, German, Italian, Portuguese, Russian and Spanish was distributed using software SurveyMonkey (Palo Alto, California, USA) through various professional bodies across the world to reach eye care professionals (optometrists, dispensing opticians, ophthalmologists and others) globally. The survey matched the 2015 version (Wolffsohn *et al*., 2016) comprising of nine questions relating to the self-reported clinical management behaviours of practitioners for progressive myopia and practitioner's current opinions on myopia related clinical care including:

- level of concern about the increasing frequency of paediatric myopia in their clinical practice (rated as 'Not at all,' to 'extremely,' on a 10 point scale)
- perceived effectiveness, defined as the expected level of reduction in childhood myopia progression of a range of myopia control options (rated as a percentage from 0 to 100%)
- how active they would consider their clinical practice in the area of myopia control (rated as 'Not at all,' to 'fully,' on a 10 point scale)
- frequency of prescribing different myopia correction options for progressive / young myopes during a typical month
- minimum age a patient would need to be for them to consider myopia refractive correction options (assuming average handling skills and child/parent motivation)
- minimum amount of myopia that would need to be present to consider myopia refractive correction options (specified in half dioptre steps)
- minimum level of myopia progression that would prompt a practitioner to specifically adopt a myopia control approach (specified in quarter dioptre steps)
- frequency of adopting single vision under-correction as a strategy to slow myopia progression (reported as 'no,' 'sometimes,' or 'always')?
- if they had only ever fitted single vision spectacles/contact lenses for myopic patients, what had prevented them (multiple options could be selected) from prescribing alternative refractive correction methods; options consisted of:
    - They don't believe that these are any more effective
    - The outcome is not predictable
    - Safety concerns

- Cost to the patient makes them uneconomical
- Additional chair time required
- Inadequate information / knowledge
- Benefit / risk ratio
- Other

There was an option to add further comments to each of the questions and the topic as a whole. Voluntary participation in the survey, following an explanation of the research, was anonymous, however, respondents were asked to provide basic demographic information about themselves (highest qualification, years of being qualified and everyday working environment). The data was collected between October 2018 and April 2019.

Statistical Analysis

Statistical analysis was conducted with SPSS (v21 IBM, New York, USA). Only complete surveys were analysed. Median, mean and standard deviations were calculated for each question response, with the results grouped by continent (Asia, Australasia, Europe, North America and South America) and countries within a continent where response rate allowed ($n \geq 30$), with Kruskal-Wallis tests applied to determine statistical difference (taken as $p < 0.05$) between them. For conciseness, only significant comparisons have been reported.

2.3 Results

Responses

The total number of 1,336 complete survey responses were received, with the distribution by continent being: Africa 13 (not included in further analysis), Asia 202, Australasia 79; Europe 717; Middle East 5 (not included in further analysis), North America 147; and South America 173. Country specific responses could be extracted from:

- Europe: Germany (n=68), Italy (n = 102), Netherlands (n = 40) Portugal (n = 76), Russia (n=78), Spain (n = 173) and UK/EIRE (n = 78)
- Asia: China (n = 37), Hong Kong (n = 59) and India (n = 30)
- North America; Canada (n = 47) and USA (n = 90)

Of the study participants, 72.5% (n=968) were optometrists, 19.6% (n = 262) were ophthalmologists, 6.7% (n = 90) were contact lens opticians and 1.2% (n = 16) were other types of eye care specialists. The principal working environment for 90.7% was in clinical practice (n = 1,212), 5.1% worked in academia (n = 68), 2.1% worked within industry (n = 29) and 2.1% (n =

29) worked in other environments. However, all study participants were registered eye care practitioners. The median number of years qualified was the 11-20 category, with a normal distribution.

Self-reported concern about the increasing frequency of paediatric myopia (Figure 2.1)

Practitioners' concern about the increasing frequency of paediatric myopia in their practices was highest (9.0 ± 1.6; $p < 0.001$) in Asia and lowest (7.6 ± 2.2; $p < 0.001$) in Australasia among the surveyed continents, with similar levels across Europe (8.0 ± 2.2; $p < 0.001$), North (7.9 ± 2.1; $p < 0.001$) and South America (8.5 ± 2.2; $p < 0.001$). In Asia, Chinese practitioners were more concerned (9.5 ± 1.2; $p < 0.001$) than those in Hong Kong (8.7 ± 1.4; $p < 0.001$) or India (8.9 ± 1.3; $p < 0.001$). In Europe, practitioners from Russia (8.7 ± 1.9; $p < 0.001$), Portugal (8.7 ± 2.0; $p < 0.001$) and Spain (8.5 ± 1.9; $p < 0.001$) were most concerned, followed by Italy (7.8 ± 2.2; $p < 0.001$) and the UK/EIRE (7.5 ± 2.5; $p < 0.001$), with lowest concern in the Netherlands (7.1 ± 2.3; $p < 0.001$) and Germany (6.4 ± 2.3; $p < 0.001$). In North America, practitioners from the USA (8.1 ± 2.0; $p < 0.001$) were more concerned than their Canadian (7.5 ± 2.2; $p < 0.001$) neighbours.

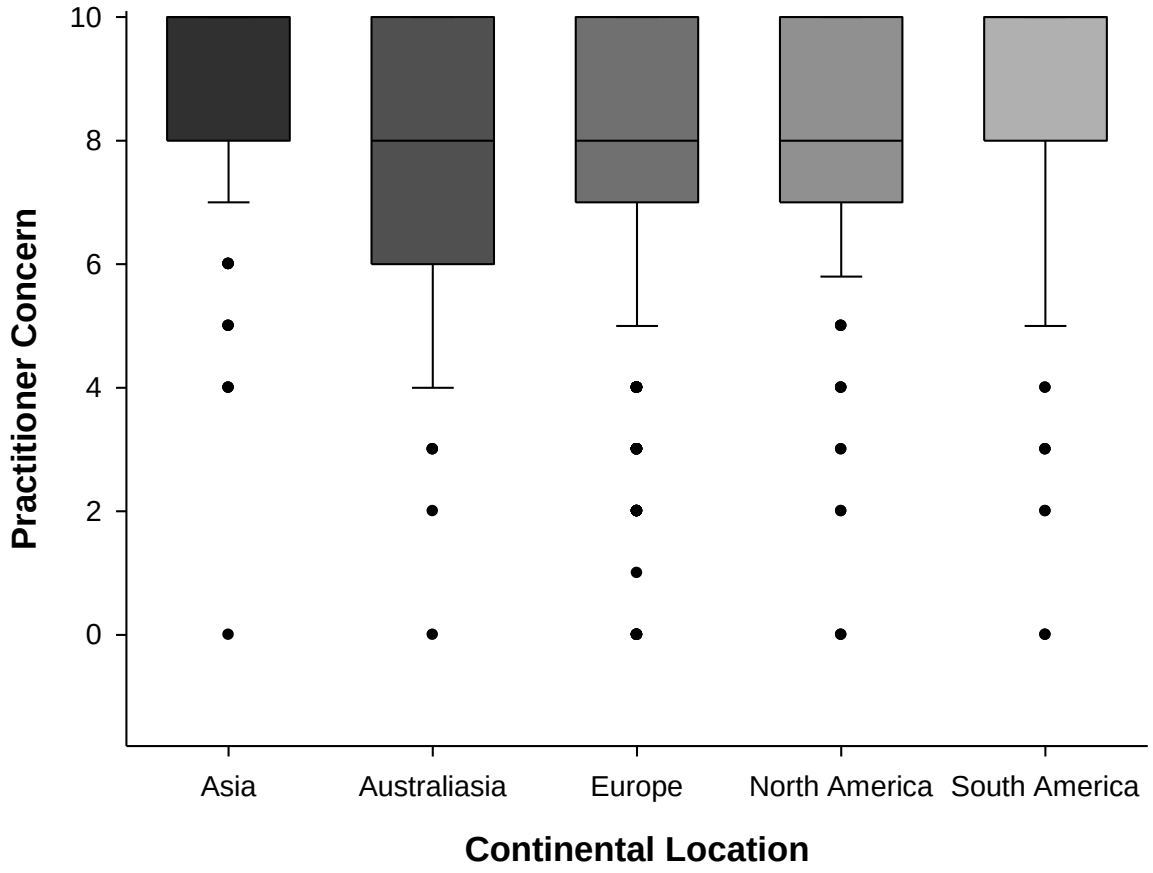

Figure 2.1: Level of practitioner concern (rated from 0-10) regarding the perceived increasing frequency of paediatric myopia in their practice for practitioners located in different continents. N=1,336. Box = 1 SD, line = median and whiskers 95% confidence interval.

Perceived effectiveness of myopia control options (Table 2.1)

Overall, orthokeratology was perceived by practitioners to be the most effective method of myopia control, followed by pharmaceutical approaches and approved myopia control soft contact lenses. The least effective perceived methods were single vision distance under-correction and single vision spectacles, as well as single vision soft contact lenses and refractive surgery options. These findings were largely consistent across all continents with some variations: practitioners from South America held the lowest relative consideration regarding the most effective perceived methods, whilst practitioners from Asia, Europe, and South America held the highest relative consideration for the least effective perceived methods ($p < 0.001$). Moreover, the single vision spectacles modality was considered the 7th least effective out of the 12 survey choices in South America ($p < 0.001$). Practitioners from Asia

considered bifocals and progressive addition (PALs) lenses to be relatively more effective for reducing childhood myopia progression compared with practitioners from all other continents ($p < 0.001$). Practitioners from Australasia and North America perceived single vision distance under-correction, single vision spectacles, rigid gas permeable (RGP) and single vision soft contact lenses, refractive surgery, and increased time outdoors as less effective than practitioners from other continents ($p < 0.001$).

Within Asia, Chinese practitioners generally held the highest relative consideration for most myopia control options, whereas practitioners from Hong Kong held the least overall perceived effectiveness for most myopia control options ($p < 0.001$). Similar effectiveness among practitioners from China, Hong Kong, and India was perceived for multifocal and approved myopia control soft contact lenses, as well as orthokeratology and pharmaceutical modalities ($p < 0.001$). Within Europe, the Netherlands generally held the lowest relative consideration for most myopia control options, whereas practitioners from Portugal, Russia, and Spain held the highest overall perceived effectiveness for most myopia control options ($p < 0.001$). Spanish practitioners perceived approved myopia control soft contact lenses and orthokeratology as more effective than their European colleagues, while Portuguese practitioners did so regarding refractive surgery ($p < 0.001$). Russian practitioners perceived pharmaceutical methods as less effective than other European practitioners, while Italian practitioners and those from the UK/EIRE did so regarding increased time spent outdoors ($p < 0.001$). Within North America, practitioners from the USA perceived rigid gas permeable (RGP) and multifocal soft contact lenses, as well as orthokeratology and pharmaceutical options as more effective than their Canadian counterparts ($p < 0.001$).

Technique \ Continent		Asia	Australasia	Europe	North America	South America
Spectacles	Under-correction	11.6 ± 21.6	-0.2 ± 6.6	6.9 ± 17.6	1.4 ± 4.6	14.9 ± 21.9
	Single Vision	17.6 ± 24.9	1.2 ± 3.8	13.4 ± 24.7	1.2 ± 3.7	21.3 ± 32.9
	Bifocals	33.0 ± 22.7	25.4 ± 17.4	19.4 ± 20.5	16.7 ± 15.1	16.0 ± 22.2
	Progressive Addition (PALs)	32.9 ± 23.0	22.4 ± 15.2	20.9 ± 21.4	16.5 ± 14.9	18.2 ± 24.6
Contact Lenses	Rigid Gas Permeable (RGP)	25.0 ± 27.8	8.4 ± 16.3	16.8 ± 24.1	6.8 ± 12.7	15.0 ± 25.1
	Single Vision Soft	18.1 ± 24.6	3.1 ± 10.3	13.1 ± 21.9	1.7 ± 4.5	16.3 ± 27.1
	Multifocal Soft	31.9 ± 23.6	35.7 ± 18.0	26.6 ± 22.5	31.4 ± 19.0	21.9 ± 26.6
	Approved Myopia Control Soft	45.4 ± 24.0	45.6 ± 18.2	44.1 ± 24.4	42.9 ± 20.0	29.0 ± 29.4
	Orthokeratology	60.7 ± 21.9	52.5 ± 21.2	52.1 ± 24.7	48.3 ± 22.0	34.8 ± 31.1
Pharmaceutical		54.5 ± 23.6	52.1 ± 20.9	43.1 ± 26.9	45.6 ± 21.3	43.0 ± 29.8
Refractive Surgery		20.6 ± 33.0	7.7 ± 21.3	13.9 ± 25.6	8.1 ± 22.2	13.9 ± 24.8
Increased Time Outdoors		43.6 ± 27.8	20.4 ± 20.5	37.1 ± 27.7	22.4 ± 20.1	40.2 ± 31.8

Table 2.1: Perceived effectiveness (defined as the expected level of reduction in childhood myopia progression in percent) of myopia control options by practitioners in different continents. Data are expressed as mean ± S.D.

Perceived level of clinical activity in the area of myopia control (Figure 2.2)

Practitioners from Asia considered their clinical practice of myopia control to be the most active (7.7 ± 2.3; $p < 0.001$) among the surveyed continents, with similar levels for Australasia (7.3 ± 2.5; $p < 0.001$) and Europe (7.0 ± 4.2; $p < 0.001$), and least by practitioners from North America (6.3 ± 2.9; $p < 0.001$) and South America (6.4 ± 3.2; $p < 0.001$). North American practitioners perceived themselves to be the least active in this area of practice ($p < 0.001$). Within Europe, practitioners from Russia (8.5 ± 9.8; $p < 0.001$) reported the highest perceived level of clinical activity in myopia control and the lowest was reported by those from the UK/EIRE (6.1 ± 3.5; $p < 0.001$), with similar responses by Spain (7.0 ± 2.6; $p < 0.001$), Italy (7.0 ± 2.3; $p < 0.001$), Portugal (6.6 ± 2.5; $p < 0.001$), the Netherlands (6.6 ± 2.6; $p < 0.001$), and Germany (6.6 ± 3.0; $p < 0.001$). Within Asia, Indian practitioners (6.3 ± 2.6; $p < 0.001$) considered themselves relatively less active than their counterparts in China (8.4 ± 2.2; $p < 0.001$) or Hong Kong (8.1 ±

2.0; p < 0.001). Within North America, Canadian practitioners (5.7 ± 3.0; p < 0.001) considered themselves less active than those from the USA (6.6 ± 2.8; p < 0.001).

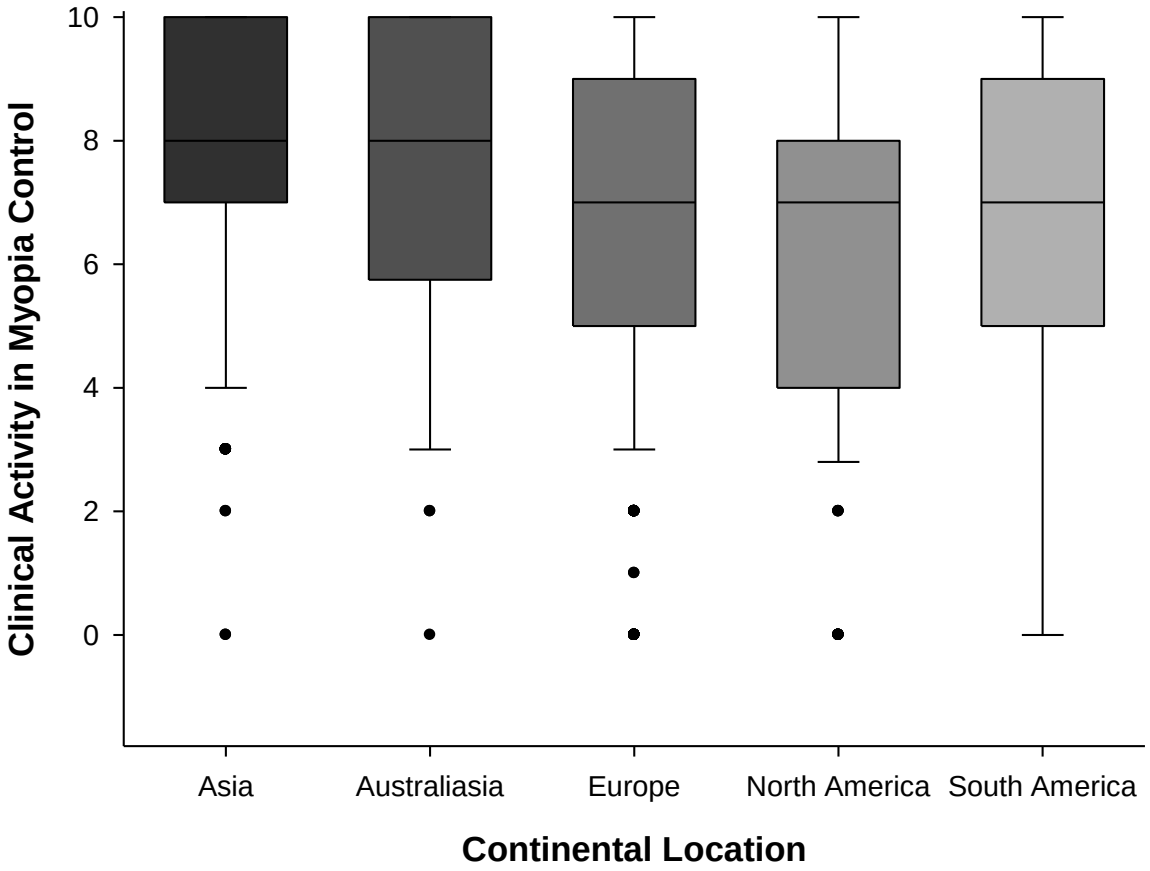

Figure 2.2: Perceived level of clinical activity in the area of myopia control for practitioners located in different continents. N=1,336. Box = 1 SD, line = median and whiskers 95% confidence interval.

Frequency of prescribing different myopia correction options for progressing / young myopes (Table 2.2)

The majority of progressing / young myopes were being prescribed single vision (full correction) spectacles (39.3 ± 30.0%), followed by single vision soft contact lenses (12.3 ± 15.5%) and orthokeratology (12.0 ± 20.0%). The least frequently prescribed myopia correction option was refractive surgery (0.8 ± 4.1%), followed by rigid gas permeable (RGP) contact lenses (2.1 ± 6.6%) and bifocal spectacles (2.4 ± 6.2%). Progressive addition (PALs) spectacles (8.8 ± 14.5%), multifocal soft contact lenses (6.8 ± 13.9%), approved myopia control soft contact lenses (7.3 ± 13.0%), and pharmaceutical (8.2 ± 16.3%) options were prescribed at a similar frequency. These findings were largely consistent across all continents with some variations.

Practitioners from Asia indicated prescribing single vision (full correction) spectacles most frequently, whereas those from Australasia prescribed them least often ($p < 0.001$). Also, practitioners from Asia indicated prescribing bifocal spectacles most frequently for progressing / young myopes, whereas those from South America prescribed them least often ($p < 0.001$). Practitioners from Australasia, and to a lesser degree, practitioners from Asia, prescribed progressive addition (PALs) spectacles more frequently than those from other continents, while the option was prescribed least often by South America ($p < 0.001$). South American practitioners prescribed rigid gas permeable (RGP) contact lenses most frequently to these patients, while was done least often by their counterparts in Australasia ($p < 0.001$). Practitioners from North America and Australasia prescribed more single vision and multifocal soft contact lenses respectively, while Asian practitioners prescribed these options less often than other regions ($p < 0.001$). Approved myopia control soft contact lenses are being prescribed most in Australasia, Europe, and North America, while notably less in Asia and South America ($p < 0.001$). Practitioners from Australasia, and to a lesser degree, practitioners from Europe, prescribed orthokeratology more frequently than their counterparts, while the option was prescribed least frequently by South American practitioners ($p < 0.001$). South American practitioners indicated utilising pharmaceutical options notably most frequently for progressing / young myopes, while those from Asia and Europe did so the least ($p < 0.001$). South American practitioners also recommended refractive surgery more than other continents for these patients, but the prescribing frequency was still low ($p < 0.001$).

Within Asia, practitioners from India prescribed single vision spectacles, rigid gas permeable (RGP), single vision, multifocal, and approved myopia control soft contact lenses, as well as pharmaceutical myopia correction options most frequently ($p < 0.001$). Chinese practitioners prescribed progressive addition (PALs) spectacles the most frequently and orthokeratology the least in comparison to Hong Kong and India ($p < 0.001$). Within Europe, practitioners from Russia and Spain prescribed single vision spectacles and soft contact lenses most frequently, whereas practitioners from the Netherlands prescribed these options the least ($p < 0.001$). Russian practitioners also prescribed bifocal and progressive addition (PALs) spectacles the most, whereas their colleagues from the Netherlands and Portugal did so the least ($p < 0.001$). German practitioners prescribed rigid gas permeable (RGP) and multifocal soft contact lenses most frequently, whereas those from the UK/EIRE and Portugal prescribed these options the least respectively ($p < 0.001$). Spanish practitioners demonstrated the highest frequency of prescribing approved myopia control soft contact lenses ($p < 0.001$). Orthokeratology was

prescribed the most in Italy and the Netherlands, and the least by Portuguese practitioners ($p < 0.001$). Russian practitioners had the highest frequency of prescribing pharmaceutical and refractive surgery options ($p < 0.001$). Within North America, practitioners from the USA prescribed single vision spectacles and soft contact lenses more frequently than their Canadian colleagues ($p < 0.001$).

Technique \ Continent		Asia	Australasia	Europe	North America	South America
Spectacles	Single Vision	54.7 ± 31.9	18.8 ± 22.3	37.3 ± 29.3	36.5 ± 30.5	49.3 ± 35.8
	Bifocals	3.4 ± 7.7	2.8 ± 6.2	2.0 ± 7.5	2.6 ± 5.7	1.1 ± 4.0
	Progressive Addition (PALs)	11.0 ± 15.5	19.4 ± 20.3	4.5 ± 10.5	5.6 ± 14.3	3.7 ± 11.9
Contact Lenses	Rigid Gas Permeable (RGP)	1.8 ± 4.7	0.3 ± 1.1	2.9 ± 9.6	1.1 ± 9.1	4.5 ± 8.4
	Single Vision Soft	7.2 ± 13.0	9.6 ± 13.3	15.6 ± 17.3	16.6 ± 19.0	12.4 ± 14.8
	Multifocal Soft	1.7 ± 5.1	13.0 ± 18.5	5.5 ± 13.7	8.2 ± 15.5	5.6 ± 16.7
	Approved Myopia Control Soft	3.6 ± 8.7	10.5 ± 14.9	10.5 ± 16.9	9.6 ± 16.4	2.2 ± 8.3
	Orthokeratology	11.5 ± 20.4	16.8 ± 22.0	15.9 ± 24.4	12.3 ± 19.4	3.3 ± 11.8
Pharmaceutical		4.1 ± 11.9	8.7 ± 11.7	4.7 ± 15.0	7.2 ± 12.1	16.3 ± 30.7
Refractive Surgery		0.9 ± 4.1	0.1 ± 0.6	1.0 ± 6.7	0.4 ± 2.9	1.7 ± 6.3

Table 2.2: Frequency of prescribing myopia correction options for progressing / young myopes by practitioners in different continents for progressing / young myopes. Data are expressed as mean ± S.D.

Minimum patient age that practitioners consider myopia correction options (Table 2.3)

Overall, single vision spectacles were prescribed from the youngest age (6.8 ± 4.2 years), whereas rigid gas permeable (RGP) contact lenses were reserved for older children (13.3 ± 5.3). Bifocal spectacles (8.9 ± 5.7), progressive addition (PALs) spectacles (8.9 ± 6.0), single vision soft contact lenses (9.0 ± 4.8), multifocal soft contact lenses (10.2 ± 4.9), specific myopia

control soft contact lenses (8.9 ± 4.0), orthokeratology (9.7 ± 4.8), and pharmaceutical (9.6 ± 6.0) options were all prescribed for a similar minimum patient age range. Practitioners from all regions did not recommend refractive surgery to patients under 18 years of age (19.6 ± 1.6). Practitioners from Asia, Australasia, and North America were more conservative in their minimum fitting age of rigid gas permeable (RGP) contact lenses than European and South American practitioners ($p < 0.001$). Practitioners from Asia were most conservative in their minimum patient age for prescribing single vision, multifocal, and specific myopia control soft contact lenses ($p < 0.001$). South American practitioners tended to be least conservative towards most myopia correction options relative to their colleagues ($p < 0.001$).

Within Asia, practitioners from Hong Kong were the most conservative in their minimum age for fitting rigid gas permeable (RGP), single vision and multifocal soft contact lenses, as well as pharmaceuticals ($p < 0.001$). Practitioners from India were the most conservative in fitting bifocal and progressive addition (PALs) spectacles, as well as orthokeratology ($p < 0.001$). Chinese practitioners were least conservative in prescribing bifocal spectacles, multifocal soft contact lenses, and pharmaceutical options ($p < 0.001$). Within Europe, practitioners from the Netherlands were the most conservative in their minimum age for fitting most of the myopia correction options, followed by the UK/EIRE, particularly for bifocal and progressive addition (PALs) spectacles, rigid gas permeable (RGP) contact lenses, as well as orthokeratology, pharmaceutical, and refractive surgery ($p < 0.001$). Within North America, Canadian practitioners were more conservative regarding bifocal spectacles and orthokeratology than their USA colleagues ($p < 0.001$).

Technique \ Continent		Asia	Australasia	Europe	North America	South America
Spectacles	Single Vision	7.0 ± 4.4 (1)	8.0 ± 6.0	6.0 ± 3.2 (10)	7.7 ± 5.9	5.5 ± 1.7 (12)
	Bifocals	10.4 ± 6.5 (13)	9.5 ± 6.9	9.0 ± 6.1 (30)	9.6 ± 7.0	5.9 ± 2.1 (44)
	Progressive Addition (PALs)	9.4 ± 4.9 (7)	7.6 ± 5.1	9.4 ± 5.7 (27)	10.4 ± 7.0	7.5 ± 3.6 (48)
Contact Lenses	Rigid Gas Permeable (RGP)	15.2 ± 5.6 (8)	15.4 ± 6.2	10.8 ± 4.8 (28)	14.2 ± 6.2	10.9 ± 3.9 (45)
	Single Vision Soft	13.2 ± 5.2 (10)	11.1 ± 5.8	9.0 ± 3.9 (9)	10.4 ± 5.3	10.2 ± 3.9 (22)
	Multifocal Soft	13.8 ± 5.9 (16)	9.9 ± 5.2	9.3 ± 4.5 (26)	9.4 ± 4.9	8.8 ± 4.1 (52)
	Specific Myopia Control Soft	10.8 ± 4.8 (11)	8.5 ± 3.9	7.8 ± 3.2 (4)	8.3 ± 3.9	9.2 ± 4.2 (30)
	Orthokeratology	9.8 ± 5.1 (10)	9.6 ± 5.0	9.3 ± 4.0 (8)	10.7 ± 6.1	9.1 ± 4.2 (35)
Pharmaceutical		13.0 ± 7.6 (13)	8.5 ± 5.8	10.6 ± 6.9 (51)	9.5 ± 6.5	6.5 ± 3.2 (16)
Refractive Surgery		19.9 ± 2.1 (23)	20.4 ± 1.2	19.3 ± 2.7 (55)	20.4 ± 1.2	18.2 ± 0.9 (46)

Table 2.3: Minimum patient age considered necessary by practitioners (from different continents who prescribed these options for different myopia correction options. Data are expressed as mean ± S.D years (% that would not prescribe this refractive modality).

Minimum degree of myopia that needs to be present for practitioners to consider myopia control options (Table 2.4)

Overall, practitioners indicated that myopia would be corrected with single vision spectacles at the lowest degree of myopia (-0.82 ± 0.58 D), whereas it would be corrected with refractive surgery at the highest degree (-2.80 ± 1.72 D). All other myopia control options would be considered at approximately -1.50 D, except for rigid gas permeable (RGP) contact lenses that were considered at -2.50 D. Australasian and North American practitioners were willing to fit most modalities at a lower level of myopia than Asian, European or South American clinicians ($p < 0.001$). South American practitioners required a higher level of myopic refractive error before they would consider bifocal spectacles, multifocal soft contact lenses, and orthokeratology than all other regions ($p < 0.001$). Asian practitioners prescribed rigid gas permeable (RGP) and single vision soft contact lenses, as well as refractive surgery to children with higher degree of myopia than others ($p < 0.001$). However, North American practitioners considered rigid gas permeable (RGP) contact lenses at a lower level of myopia than in other continents ($p < 0.001$). Practitioners from Asia and South America recommended approved myopia control soft contact lenses and pharmaceutical options at higher levels of myopia ($p < 0.001$).

Within Asia, Indian practitioners required a higher level of refractive error before they would consider bifocal and progressive addition (PALs) spectacles, as well as orthokeratology, pharmaceutical and refractive surgery options ($p < 0.001$) than practitioners from China or Hong Kong. Within Europe, Portuguese practitioners considered single vision, bifocal and progressive addition (PALs) spectacles, rigid gas permeable (RGP) and approved myopia control soft contact lenses, orthokeratology, pharmaceutical, and refractive surgery options for a higher myopia level than other countries in the continent ($p < 0.001$). Spanish practitioners also required a higher level of myopia for approved myopia control soft contact lenses and pharmaceuticals, as well as multifocal soft contact lenses ($p < 0.001$). Italian practitioners required high myopia levels when considering refractive surgery ($p < 0.001$). Practitioners from Russia required a higher level of myopia before utilising single vision soft contact lenses, but lower levels for pharmaceuticals relative to their European colleagues ($p < 0.001$). Practitioners from the UK/EIRE considered single vision, bifocal and progressive addition (PALs) spectacles, single vision, multifocal and approved myopia control soft contact lenses, and refractive surgery options for a lower myopia level than others in the continent ($p < 0.001$). German practitioners also required a lower level of myopia for single vision, bifocal and progressive addition (PALs) spectacles, as well as rigid gas permeable (RGP) and single vision soft contact lenses ($p < 0.001$). The same was reported by practitioners from the Netherlands regarding single vision and bifocal spectacles, and rigid gas permeable (RGP) and single vision soft contact lenses ($p <$

0.001). The only difference across North America was that Canadian practitioners required a higher level of myopia before they would consider rigid gas permeable (RGP) contact lenses than those from the USA ($p < 0.001$).

Technique \ Continent		Asia	Australasia	Europe	North America	South America
Spectacles	Single Vision	-1.0 ± 0.9	-0.6 ± 0.2	-0.9 ± 0.7	-0.7 ± 0.4	-0.9 ± 0.7
	Bifocals	-1.8 ± 1.4	-0.9 ± 0.4	-1.8 ± 1.3	-1.2 ± 1.0	-2.3 ± 1.7
	Progressive Addition (PALs)	-1.7 ± 1.2	-0.8 ± 0.3	-1.8 ± 1.3	-1.2 ± 1.1	-2.0 ± 1.6
Contact Lenses	Rigid Gas Permeable (RGP)	-2.9 ± 2.0	-2.5 ± 2.1	-2.4 ± 2.0	-2.0 ± 1.6	-2.7 ± 2.1
	Single Vision Soft	-1.8 ± 1.4	-1.0 ± 0.4	-1.3 ± 0.9	-1.0 ± 0.5	-1.5 ± 1.2
	Multifocal Soft	-1.7 ± 1.2	-1.0 ± 0.4	-1.6 ± 1.3	-1.2 ± 0.7	-1.9 ± 1.6
	Approved Myopia Control Soft	-1.8 ± 1.5	-1.0 ± 0.4	-1.5 ± 1.1	-1.2 ± 0.7	-1.9 ± 1.6
	Orthokeratology	-1.7 ± 1.3	-1.3 ± 0.7	-1.6 ± 1.0	-1.3 ± 0.7	-2.1 ± 1.6
Pharmaceutical		-1.9 ± 1.8	-1.2 ± 0.5	-1.5 ± 1.3	-1.3 ± 1.0	-1.9 ± 1.2
Refractive Surgery		-3.8 ± 2.4	-2.2 ± 1.0	-3.3 ± 2.3	-2.0 ± 1.2	-2.7 ± 1.7

Table 2.4: Minimum level of patient myopia (in dioptres) before myopia correction options would be considered by practitioners from different continents who prescribed these options. Data are expressed as mean ± S.D.

Minimum annual amount of patient myopia progression that would prompt a practitioner to specifically adopted a myopia control approach (Figure 2.3)

The minimum myopia progression rate that practitioners considered warranted a myopia control approach was 0.51 to 0.75 D/year for the majority of respondents (36.7%), with 82% indicating a level between 0.25 and 1.00 D/year. Practitioners from Australasia indicated they would adopt myopia control strategies for the lowest level of myopia progression, followed by Europe and North America ($p < 0.001$). Highest rates of progression were required in South America, followed by Asia ($p < 0.001$). Practitioners from Australasia, Europe, and North America

particularly indicated a range between 0.26 and 0.75 D/year of patient myopia progression that would prompt the adaptation of a myopia control approach. In comparison, the range increased to between 0.26 and 1.00 D/year for Asian practitioners and spread further between 0.26 and > 1.00 D/year among South American practitioners ($p < 0.001$). Other factors influencing practitioners' management decisions, as identified from the free text responses, included ethnicity (1 respondent), absolute degree of refractive error at the time (2 respondents), environmental factors/lifestyle (2 respondents), lighting exposure (2 respondents), parental decisions (2 respondents), ocular biometry (3 respondents), family history of myopia (6 respondents), and age of myopia onset (10 respondents).

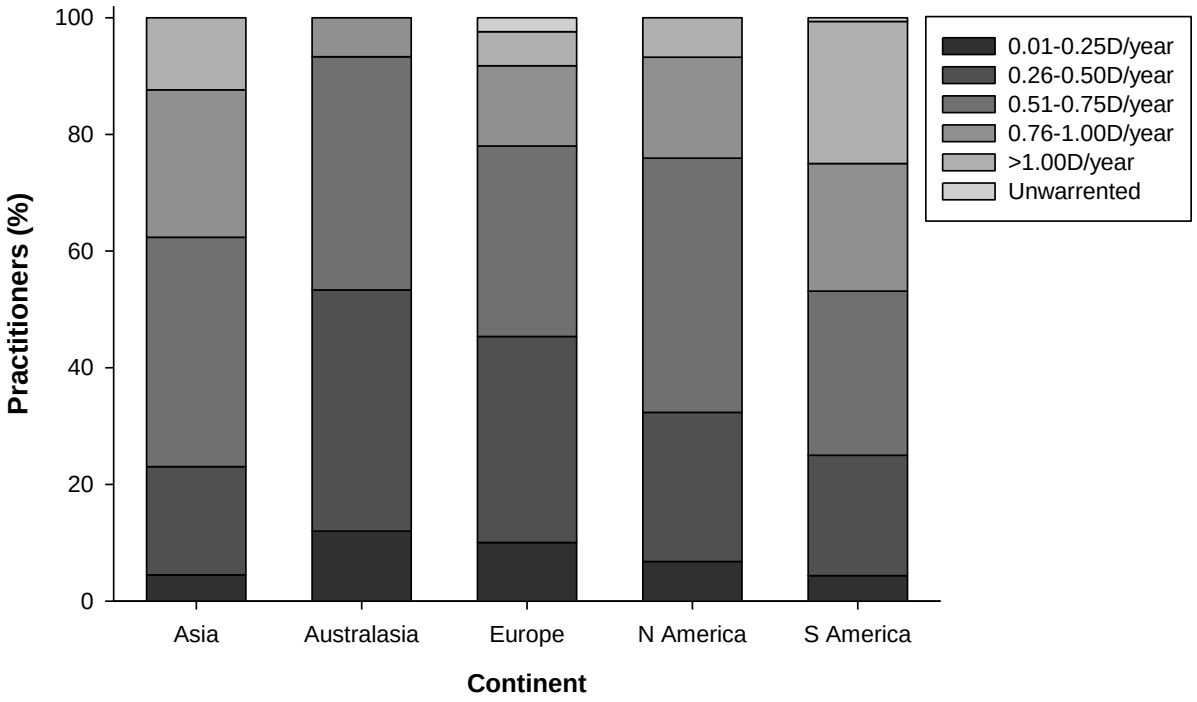

Figure 2.3: Minimum annual amount of patient myopia progression, in dioptres per year (D/year), that practitioners located in different continents considered to necessitate a myopia control approach. N=1,336

Use of single-vision under-correction as a strategy to slow myopia progression (Figure 2.4)

Overall, most practitioners did not consider single-vision distance under-correction to be an effective strategy for attenuating myopia progression (79.6%). South American practitioners used this strategy relatively more than all other regions ($p < 0.001$). Within Asia, Indian practitioners utilised under-correction more than those from China or Hong Kong ($p < 0.001$). Within Europe, practitioners from Portugal, Russia, and Spain indicated using under-correction

as a strategy to control myopia more than their counterparts ($p < 0.001$). Within North America, there was no difference in the use of under-correction between Canada and the USA ($p < 0.001$).

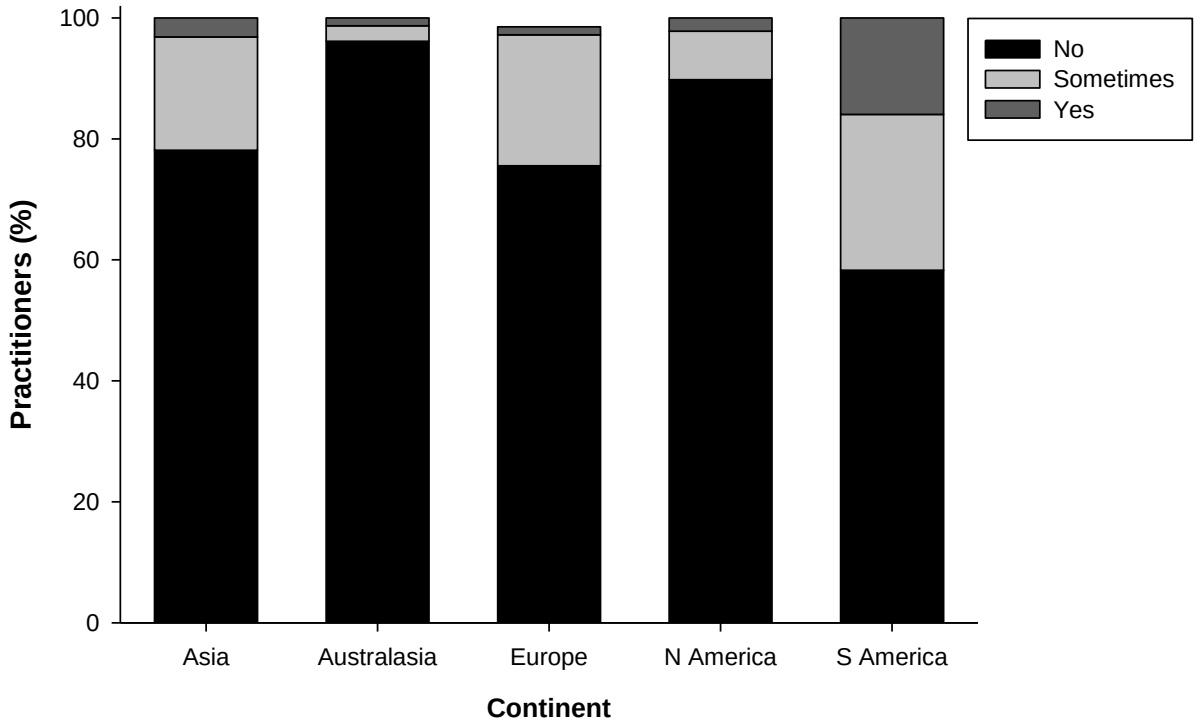

Figure 2.4: Use of single-vision distance under-correction as a strategy to slow myopia progression by practitioners located in different continents. N=1,336.

Factors preventing the prescription of a myopia control approach (Figure 2.5)

The most common reasons practitioners gave for not adopting myopia control strategies were: they were felt to be uneconomical (20.6%); they considered there to be inadequate information about the modalities (17.6%); they viewed the outcomes to be unpredictable (9.6%); concerns about safety (8.5%); they perceived them to be ineffective for reducing myopia progression (7.9%); the benefit to risk ratio was too low (7.0%); and additional chair time (3.1%). There was no significant difference in the distribution of these factors between or within continents ($p > 0.05$). Free text comments identified other factors affecting the prescription of these strategies to relate to the relative availability of the myopia control treatments and the instrumentation necessary to prescribe them, and the need for consistent regulations and informational materials.

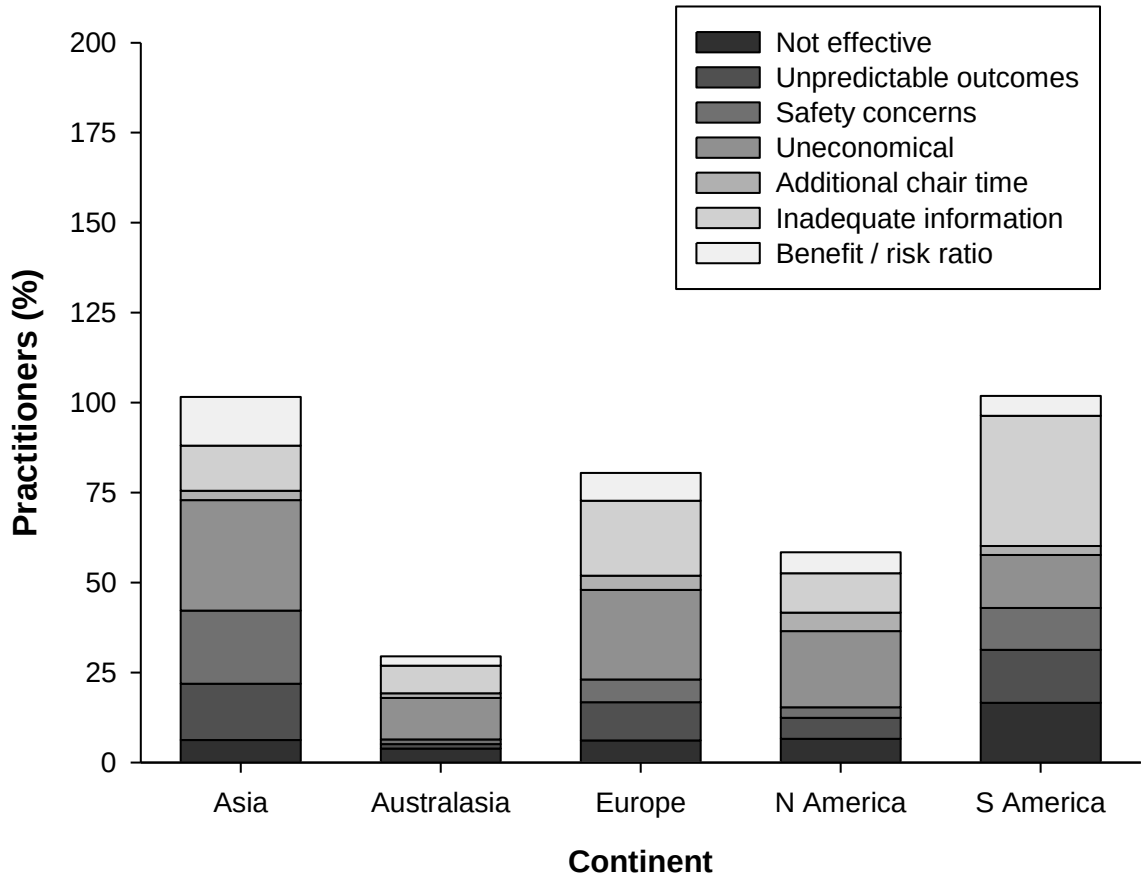

Figure 2.5: Factors preventing practitioners located in different continents from prescribing a myopia control approach. N=1,336.

2.4 Discussion

This is the updated follow-up study to examine the self-reported attitudes and practices of eye care practitioners towards myopia control approaches across the globe. More than one thousand practitioners responded, principally spread over five continents. The exact response rate is not known, as maximum coverage was promoted by involving professional bodies whose members may not all be practicing eye care practitioners. However, it may be presumed that questionnaires are completed both by people cynical and enthusiastic to the issue being examined, balancing the average response. In addition, the recruitment approach across nations was the same, allowing cross-national comparisons. The majority of the respondents (92.1%) were again optometrists and ophthalmologists, reflecting those professions legally allowed to prescribe vision care correction and, in many regions, pharmaceuticals as well.

Once again, as one might expect from the high prevalence rates of myopia in Asia, Asian practitioners, especially those practicing in China, were more concerned about the increasing prevalence of paediatric myopia in their practices than clinicians in any of the other continents. A similar pattern existed in relation to how active they considered their clinical practice in the area of myopia control. Myopia prevalence is approximately 30% in 30-35 year olds in Spain (Montes-Mico et al., 2000) and may be increasing in Portugal (Jorge et al., 2007), but is as high as 58% in Italian university students, and as low as 23% in 12-13 year olds in the UK (McCullough *et al*., 2016) and 28% in Dutch school children (Hendricks et al., 2009); hence it is unclear why the former country's practitioners are more concerned than the latter. The prevalence of myopia in the USA is around 42% in 12-54 year olds (Vitale *et al*., 2009). Despite their lower concern, the myopia occurrence is not documented in Canada; neither in Russia or Germany to warrant their higher and lower concern in Europe respectively.

Overall, orthokeratology was again perceived by practitioners to be the most effective method of myopia control. However, in this survey update, eye care practitioners correctly perceived pharmaceutical approaches and approved myopia control soft contact lenses to be similarly effective, in accordance with the mentioned IMI white paper by Wildsoet *et al*. (2019). While single vision distance under-correction has been shown fairly conclusively to increase, rather than decrease, the rate of myopia progression in children (Chung et al., 2002; Adler et al., 2006), there were still practitioners who consider the converse to be true; this was confirmed by a question later in the survey, with under-correction still practiced as a method of myopia control particularly by practitioners from South America, Portugal, Russia and Spain within Europe and India within Asia; however the reported use of undercorrection as a strategy for myopia control has decreased from the original survey (Wolffsohn et al., 2016).

Despite the self-perceived activity of practitioners in the area of myopia control, still over half of progressing and/or young myopes were being prescribed single vision spectacles or contact lenses (52%), with continental and national differences in the adoption of refractive correction options known to reduce myopia progression. However, this is an improvement in comparison to the reported 68% from the original study four years ago (Wolffsohn *et al*., 2016). Approximately one third of practitioners not adopting myopia control approaches felt them to be uneconomical and/or that there was inadequate information about them; about another one third of respondents suggested that outcomes were unpredictable, the relative safety of these strategies was concerning, myopia control methods were ineffective and/or that the benefit to risk ratio

was too low; with some also mentioning the involved additional chair time. Further comments raised the issue of availability of some myopia control options, presumably of novel myopia control lenses, as current approaches are off-label, highlighting the need for regulatory oversight and guidance (Jones et al., 2019). Limited access to necessary instrumentation was also raised as a potential barrier, as more advanced contact lens fitting, such as orthokeratology, require the use of corneal topography (Gifford et al., 2019). Attempts to specifically manipulate peripheral retinal focus may also require instrumentation to rapidly and robustly assess peripheral retinal shape and/or refraction with myopia control ophthalmic medical devices (Wolffsohn et al., 2019). However, this strategy might not 'translate' well from animal studies to human trials (Mutti et al., 2011; Atchison et al., 2015).

Spherical equivalent refractive error (measured under cycloplegia) is currently the single best predictive measure of juvenile myopia development, with children aged six years with less than +0.75D of hyperopia being at increased risk of developing myopia [108]. Most practitioners were again comfortable fitting single vision spectacles to myopic patients of this age, but in this update tended to wait until a child was older for single vision soft contact lenses and pharmaceuticals in addition to the more complex designs such as PALs, novel myopia control soft contact lenses and RGPs (including orthokeratology). Interestingly, one potential advantage of orthokeratology is that the parents or carer can manage lens application, removal and lens care, along with the lenses not having to leave the home, which can make this modality a popular option for parents or carers with younger myopic children. This is exemplified by Hong Kong, an early adopter of orthokeratology, where its use is considered at an earlier age than other countries in the region.

Research suggests that lower levels of hypermetropia at a young age is a strong risk factor for myopia development, so it would seem that practitioners remain too conservative in waiting until mild-moderate levels of myopia (approximately -1.50 D for most interventions) are present before control approaches are considered (Mutti et al., 2011; Zadnik et al., 2015). However, this is an improvement in comparison to the reported -2.00 D minimum degree of myopia from the original study four years ago (Wolffsohn *et al*., 2016). Myopia progresses at much faster rates in children in comparison to teenagers, thus supporting the need for earlier intervention (Dong et al., 2013). There may be also a "window of opportunity" for myopia treatment according to the age of onset, rate of progression and myopia magnitude (Thorn et al., 2005). More research is needed on the relative benefits of myopia control strategies in adolescents and even young

adults. Interestingly, Australasian and North American practitioners, but not those from Asia this time, considered most myopia control approaches at a lower level of myopia than other continents. This is evidence for the worldwide leap in success over recent years in the field, as demonstrated by the IMI and its white paper compendium (Wolffsohn et al., 2019). Chinese practitioners still considered prescribing pharmaceutical modalities at a younger age, and at a much lower level of myopia, compared with practitioners from other countries in the region. This may be due to different countries having different regulations and practitioners with different backgrounds (for example training, education and scope of practice), which can affect local practice, apart from the prevalence of myopia and need for correction or retardation. The rate of patient refractive progression that triggered practitioners to prescribe a myopia control approach generally mirrored the prevalence rate of myopia in each region; the higher the prevalence of myopia, usually the higher the level of myopia developed in individuals and the higher the risk of ocular pathology (Saw et al., 2005). Practitioners understandably also identified several other factors that, combined with the degree of myopic progression, influenced their decision to prescribe myopia control approaches; these included ethnicity, absolute degree of refractive error at the time, environmental factors/lifestyle, lighting exposure, parental decisions, ocular biometry, family history of myopia, and the age of myopia onset.

2.5 Conclusion

This updated global survey of current trends in eye care practitioner myopia management attitudes and strategies in clinical practice has identified that, despite growing evidence of the negative impact of even low levels of myopia on health economics, and moderate levels of practitioner concern and perceived activity (particularly where the prevalence of myopia is highest) uptake of appropriate techniques has improved, but remains generally poor. Furthermore, myopia control techniques are not being applied early enough in a child's ocular development to elicit their optimum effect. Adequate education of practitioners is lacking, along with access to appropriately regulated myopia control 'labelled' products with efficacy and safety data. A guide, such as the IMI white papers, has been developed to inform practitioners of economically viable models of eye care, including the development of instrumentation to enhance management selection, which address the myopia epidemic to reduce the growing health burden.

Chapter 3 Clinical myopia-related near phoria magnitude and variability across the human lifespan among Canadians

3.1 Introduction

The recent review by Bullimore & Richdale (2020) suggested that the ability to decide when to implement myopia control treatment, but more importantly, to predict and prevent myopia progression cannot be based on a single factor; where, age, ethnicity, familial refractive history, as well as the measurement methods, separately influenced an individual patient's management. The recent survey of paediatric ophthalmologists worldwide by Leshno *et al*. (2020) stated a progression rate of 1.10 D/year^{-1} in children, as the basis for treatment initiation. Notable publications pointed to baseline age as the primary criterion for myopia progression (Donovan *et al*., 2012) and axial elongation (Brennan *et al*., 2018), where ethnicity was a significant contributor, as both studies mentioned Asian children had 50% faster rates, respectively; specific axial elongation rates of 0.3 mm/year^{-1} (age 8) and 0.2 mm/year^{-1} (age 11) in White children, compared to 0.4 mm/year^{-1} (age 9) and 0.3 mm/year^{-1} (age 11) in Asian children were reported by Brennan *et al*. (2018). The effects of parental myopia history are scarcely documented and no recent literature exists: Saw *et al*. (2001) found rates of 0.63 D/year^{-1} in children with myopic parents, compared to 0.42 D/year^{-1} in children without myopic parents, irrespective if one or both parents were myopic; whilst Kurtz *et al*. (2007) had rates of 0.78 D/year^{-1} and 0.55 D/year^{-1} among children with two myopic parents and with one or none, respectively. Despite these well-established mean rates, Hernandez *et al*. (2018) highlighted that past rates of averaged fast progression were able to aid in predicting future individual rates by only 2%. The effect of measurement methods on the clinical trial primary outcomes of refractive error and axial length must also be considered. Twelker & Mutti (2001) and Sankaridurg *et al*. (2017) reported that refractions without cycloplegia were more myopic in infants and children, respectively. Furthermore, studies have demonstrated that the cycloplegic drug of choice has an impact, where tropicamide led to higher myopic outcomes than cyclopentolate (Egashira *et al*., 1993; Mutti *et al*., 1994; Yazdani *et al*., 2018). Instrument myopia must also be accounted, as Moore & Berntsen (2014) noted an autorefraction repeatability of ~±0.21 D. Regarding axial length, Chakraborty *et al*. (2011) emphasised the importance of limiting diurnal variations, whilst Wolffsohn *et al*. (2019) have discussed in detail the ultrasound and optical biometry instrumentation techniques.

The literature also differed on myopia progression across the human lifespan with reports of up to age 18 (Cooper *et al*., 2012); early 20s (Irving *et al*., 2009); 10% into late 30s (Fernandez-Montero *et al*., 2015); 35% in ages 20-25, 20% in ages 25-30, 14% in ages 30-35, and 10% in

ages 35-40 (Buillmore *et al*., 2002); as well as that 40% of non-myopes becoming myopic by age 25 (National Research Council, 1989). Furthermore, Goss & Winkler (1983) showed myopia stabilised in females at ages 14.5-15.5 and males at ages 15-16.5, and Kurtz *et al*. (2007) later reported a similar mean age of 15.5, but this estimate was irrespective of parental myopia or sex differences. Regarding axial length, Hou *et al*. (2018) found the mean age of stabilisation to be at 16.5, slightly after refractive myopia. Bullimore & Richdale (2020) already summarised from these studies that axial length stabilisation was correlated with the patient's sex and parental myopia history, but not ethnicity, whereas none of these factors were associated with myopia stabilisation. Longitudinal and population-based research has focused on prevalence distributions such as those outlined above, but studies investigating severity or magnitude changes over the human lifespan are limited; especially examinations of individual ocular changes with age (Strenk *et al*., 2006; Atchison *et al*., 2008; Richdale *et al*., 2013), refractive error (Atchison *et al*., 2004; Irving *et al*., 2019)), accommodation (Strenk *et al*., 2006; Richdale *et al*., 2013), and all three (Richdale *et al*., 2016); as well as those concerning binocular vision and near phoria (Palomo *et al*., 2006; Leat *et al*., 2013). Irving & Machan (2012) also previously noted distance phoria to trend towards orthophoria and remain stable over time. Furthermore, the Study of Progression of Adult Nearsightedness (SPAN) by Bullimore *et al*. (2006) stated that near work was the greatest risk factor for myopia progression and stabilisation in adults and teens, respectively. Previous research has also suggested a significant link of higher near esophoria among myopes (Gwiazda *et al*., 1995; Nakatsuka *et al*., 2005; Allen & O'Leary, 2006); with variable prevalence rates in pre-presbyopic populations, due to differences in inclusion criteria: 10% (Hokoda, 1985); 15.5% (Porcar & Martinez-Palomera, 1997); 22% (Montes-Mico, 2001). In adult populations, Yekta *et al*. (1989) and Pickwell *et al*. (1991) found higher near exophoria up to age 65 and among those aged 40+, respectively. Leat *et al*. (2013) further showed the prevalence of binocular vision disorders was lower for all age groups 10 years younger corresponding to the age groups 60-69, 70-79, and 80+, overall. Overall, Jones *et al*. (2005) compared various ocular component growth curves in refractive error groups among children and noted progression differences exist between emmetropes and myopes, but not relative to hyperopes.

Thus, it remains unknown whether binocular vision errors are a component of myopia or directly cause its state. The literature above has investigated longitudinal population and individual changes, but not regarding near phoria, or the possible associated differences in sex and

among progressive myopes. This added investigation was intended to contribute further clues and aid to forming more appropriate myopia management guidelines.

3.2 Methods

Retrospective cross-sectional clinical data of 86 patient files were taken from the Waterloo Eye Study (WatES) database, consisting of 1400+ assessment dates and an average of 16 patient visits. The selected patients were drawn from a pool of 118 files, all seen between 1968 and 2010 and for at least 27 years, having full and complete records for all measured parameters analysed in this study, and without a history of health conditions or treatments, whether medical or ocular in nature, as justified by the literature described below. This study focused on the following data: age, sex, and near phoria (measured by alternate cover test). The study was also approved by the University of Waterloo's Office of Research Ethics and followed the Declaration of Helsinki. It is important to note the limitations of near phoria measures, as reported in the prospective, randomised study by Anstice *et al*. (2021). Specific to the alternate cover test data used in the present study, the authors noted that this method had the lowest variability for near heterophoria measures, indicating a stable accommodative response during clinical testing.

Machan *et al*. (2011) previously confirmed the quality of the WatES database and that it was representative of Canadian patients. The database was used by Irving *et al*. (2011) and Irving & Machan (2012) in investigating the overall longitudinal prevalence changes of human refractive error and near vergence across the human lifespan, respectively, whilst Irving *et al*. (2019) and Leat *et al*. (2013) further applied those methodologies in examining the severity behind those parameters, respectively. These studies have also confirmed the similarity in systematic variations between longitudinal and cross-sectional clinical data. The current study followed these works by examining such changes in separate groups to explore individual differences in age (across the human lifespan), sex (males and females), and refraction (emmetropes, myopes and progressive myopes). Participants were defined by spherical equivalent refraction (SER; sum of sphere and ½ cylinder) as emmetropes (-0.50 D<SER<1.00 D), myopes (SER ≤-0.50 D), and progressive myopes (rate of ≥-0.50 D (Parssinen *et al*., 2014; Afanasyeva, 2020)), all who remained in the respective groups, throughout the period.

Statistical analyses (Microsoft Excel; Microsoft Corp.) from the right eye data included: means and standard deviations; ANOVA *t*-tests and Bonferroni post hoc tests (where $P < 0.05$ represented statistical significance); regression mixed model linear functions, as well as

percentile (3rd, 50th, and 97th [Chen *et al*., 2016]) generated reference curves and charts over time for near phoria age distribution and direct group (sex and refraction) comparisons based on binned individual patients of the same parameters. Percentile growth curves and charts have been a recent application within the vision sciences used to predict the risk and severity of myopia and its development (Chen *et al*., 2016; Tideman *et al*., 2018; Diez *et al*., 2019). These studies have all highlighted the specific relevance of the 3rd, 50th, and 97th percentiles, where the 3rd centile was particularly noteworthy for magnitude differences, the 50th centile was indicative of variation differences, and the 97th centile was best for representing changes between groups.

3.3 Results

The 70 analysed patients consisted of the following demographics: 43 women and 27 men (emmetropes [11 female and 10 male]; myopes [16 female and 11 male]; progressive myopes [16 female and 6 male]); mean age of 48.1 ± 18.0 years (range 2.7 to 91.3 years); mean SER of -1.19 ± 2.61 D, $p<0.001$ (Males -0.92 ± 2.53 D; Females -1.64 ± 2.38 D; $p<0.001$). The remaining 16 patients of the total 86 were hyperopes (13 females and 3 males), which were only accounted for to construct a complete near phoria (**Figure 3.1**) representations for the human lifespan, as well as to compare this Canadian sample with earlier works.

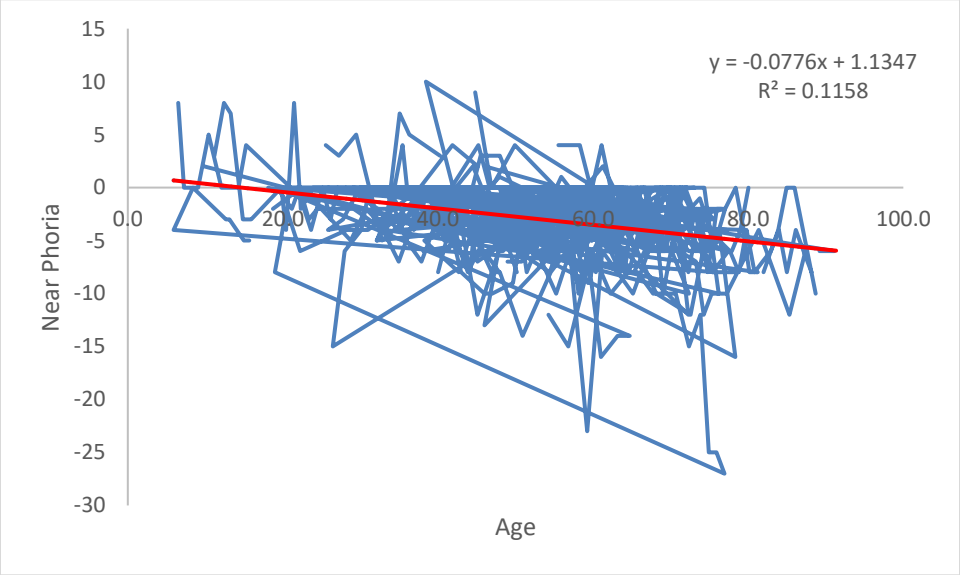

Figure 3.1. Near phoria changes over the human lifespan, as a function of age for the right eye of 86 patients, where esophoric and exophoric deviations are represented by the (-) negative and (+) positive values on the y-axis.

The mean for near phoria (-3.00 ± 3.75; p<0.001) had statistical significance over the human lifespan in this population sample. There were statistically significant sex differences for mean near phoria (Males -2.53 ± 3.57; Females -3.28 ± 3.85; p=0.002), as well as within progressive myopes for near phoria (Males -1.54 ± 2.65; Females -3.46 ± 4.49; p=0.0007). Overall, females exhibited higher levels of near phoria and myopia.

Percentile Growth Charts & Curves for Near Phoria

Figures 3.2-3.4 and **Table 3.1** show percentile (3rd, 50th, and 97th) generated reference curves and charts, respectively, over time for near phoria age (across the human lifespan) distribution, as well as associated sex differences; **Figures 3.5-3.9** and **Tables 3.2-3.5** provide the same for refraction (emmetropes, myopes and progressive myopes) group comparisons.

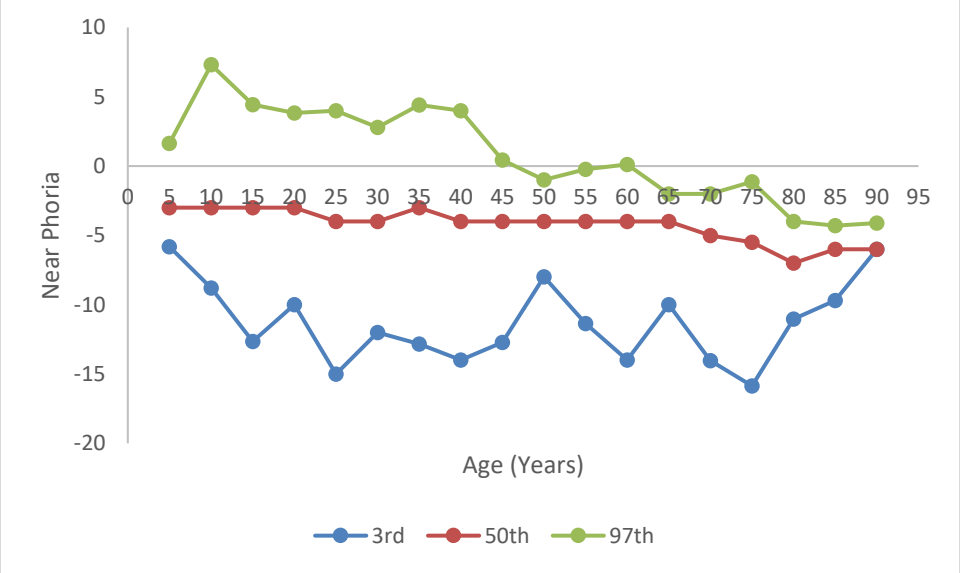

Figure 3.2. Percentile near phoria curves over the human lifespan, where esophoric and exophoric deviations are represented by the (-) negative and (+) positive values on the y-axis.

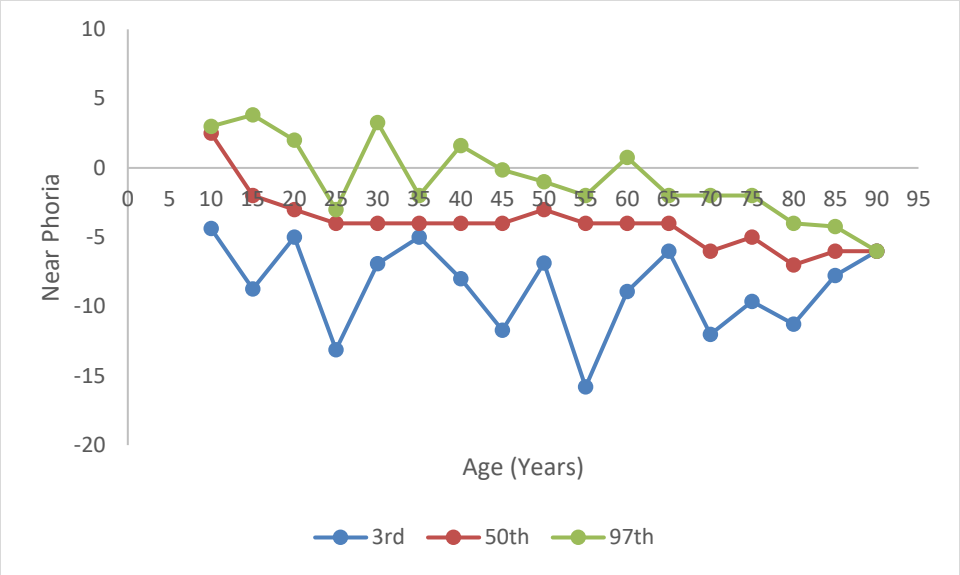

Figure 3.3. Percentile near phoria curves over the male human lifespan, where esophoric and exophoric deviations are represented by the (-) negative and (+) positive values on the y-axis.

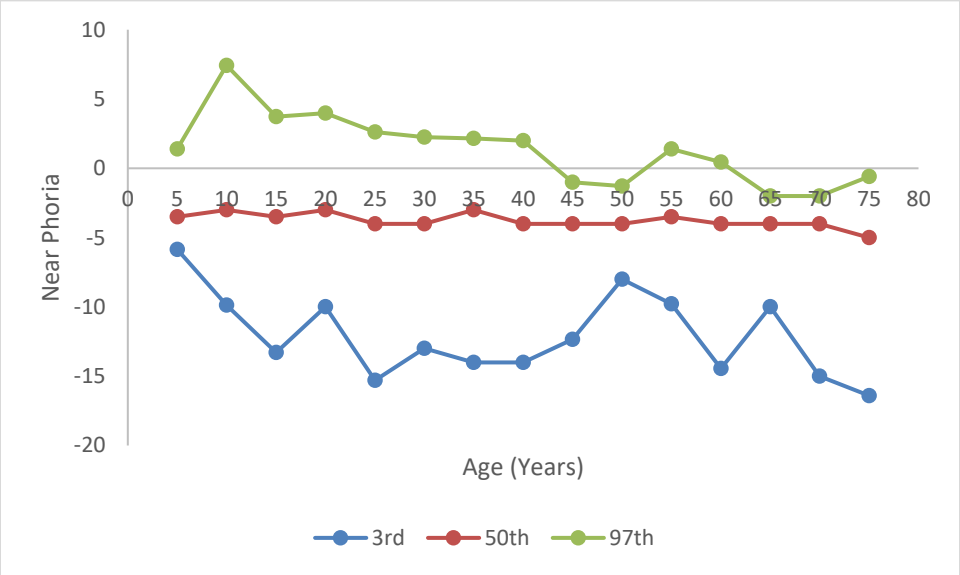

Figure 3.4. Percentile near phoria curves over the female human lifespan, where esophoric and exophoric deviations are represented by the (-) negative and (+) positive values on the y-axis.

Age (Years)	3rd	50th	97th
10	-5.5	-5.5	4.43
15	-4.55	-1.5	-0.1
20	-5	0	1.98
25	-2.2	0	5.62
30	-6.08	0	-1.03
35	-9	1	4.16
40	-6	0	0.4
45	-0.63	0	-0.86
50	-1.14	-1	-0.29
55	6.02	0.5	3.39
60	-5.52	0	-0.32
65	-4	0	0
70	-3	2	0
75	-6.76	0	1.4

Table 3.1. Percentile near phoria chart showing sex differences (female-male) over the human lifespan, where esophoric and exophoric deviations are represented by the (-) negative and (+) positive values.

Percentile growth charts showed all three centiles were of different variation between the sexes. The female 3rd centile was more esophoric for all available age groups, spanning ages 10-79. The 50th centile was similar for both sexes, except where females were more esophoric for ages 10-19 and 50-54. The 97th centile showed exophoric and esophoric changes, but differences were more similar to the 50th centile.

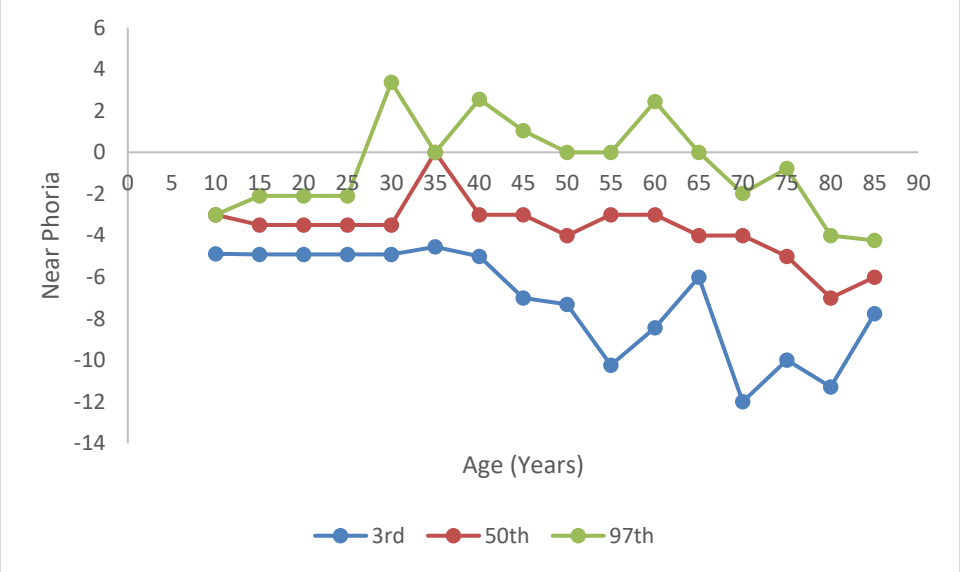

Figure 3.5. Percentile near phoria curves over the emmetrope human lifespan, where esophoric and exophoric deviations are represented by the (-) negative and (+) positive values on the y-axis.

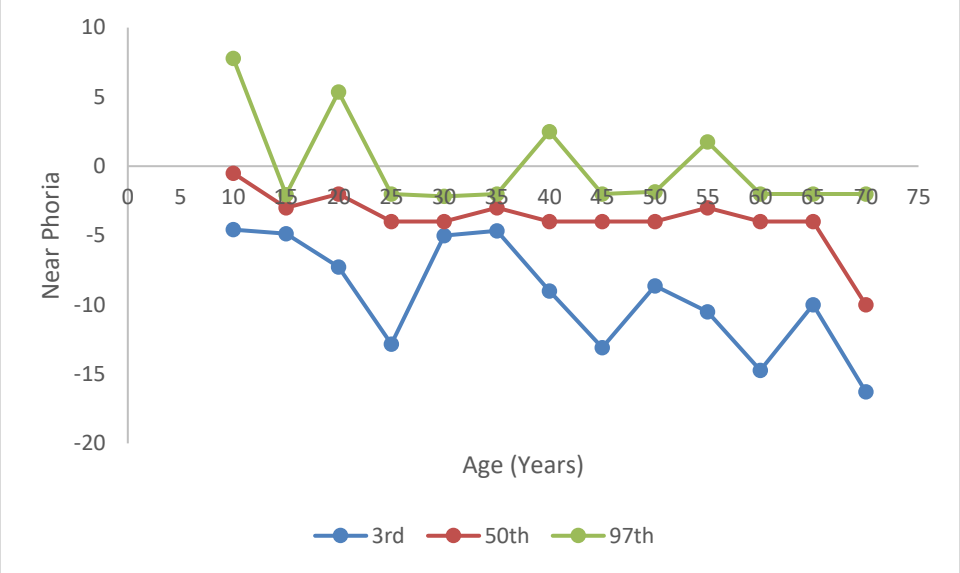

Figure 3.6. Percentile near phoria curves over the myope human lifespan, where esophoric and exophoric deviations are represented by the (-) negative and (+) positive values on the y-axis.

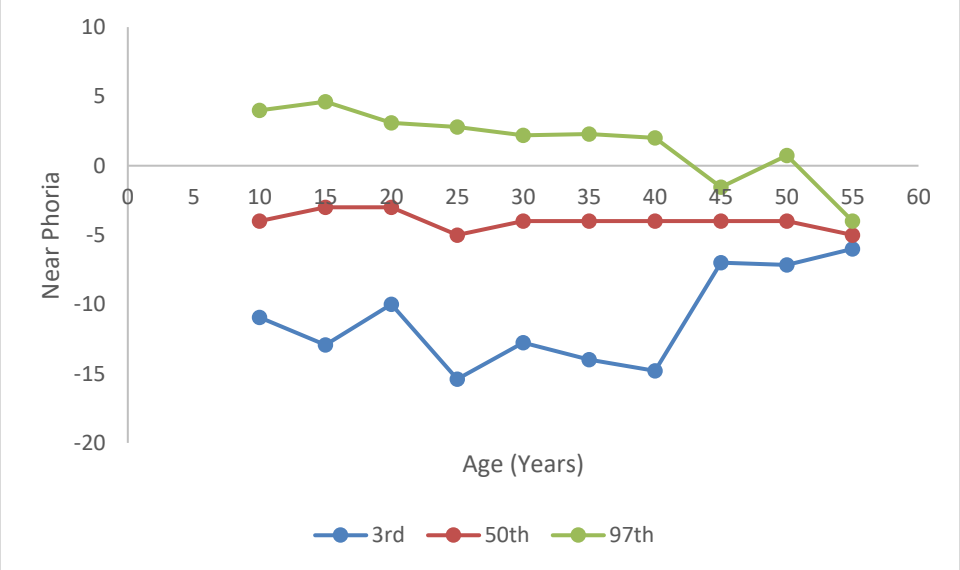

Figure 3.7. Percentile near phoria curves over the progressive myope human lifespan, where esophoric and exophoric deviations are represented by the (-) negative and (+) positive values on the y-axis.

Age (Years)	3rd	50th	97th
10	0.3	2.5	10.79
15	0.03	0.5	0.03
20	-2.37	1.5	7.45
25	-7.93	-0.5	0.09
30	-0.09	-0.5	-5.55
35	-0.12	-3	-2
40	-4	-1	-0.06
45	-6.1	-1	-3.04
50	-1.33	0	-1.84
55	-0.26	0	1.75
60	-6.3	-1	-4.44
65	-4	0	-2
70	-4.28	-6	-0.02

Table 3.2. Percentile near phoria chart showing refraction group differences (myope-emmetrope) over the human lifespan, where esophoric and exophoric deviations are represented by the (-) negative and (+) positive values.

All three centiles were of similar variation between myopes and emmetropes, but progressively differed with age commencement. The myope 3rd centile was more esophoric for all available age groups, spanning ages 20-74. The 50th centile was similar for both refraction groups, except where myopes were more esophoric from age 25. The 97th centile showed exophoric and esophoric changes, except where myopes were more esophoric from age 30.

Age (Years)	3rd	50th	97th
10	-6.07	-1	4.52
15	-8.02	0.5	6.09
20	-5.09	0.5	6.71
25	-10.49	-1.5	5.19
30	-7.85	-0.5	-0.57
35	-9.45	-4	2.19
40	-9.8	-1	-0.28
45	0	-1	0.96
50	0.15	0	-1.54
55	4.24	-2	0.74

Table 3.3. Percentile near phoria chart showing refraction group differences (progressive myope-emmetrope) over the human lifespan, where esophoric and exophoric deviations are represented by the (-) negative and (+) positive values.

All three centiles were of different variation between progressive myopes and emmetropes. The progressive myope 3rd centile was more esophoric for all available age groups, spanning ages 10-44. The 50th centile was similar for both refraction groups, except where progressive myopes were more exophoric for ages 15-24 and 50-54. The 97th centile showed a reversed trend, compared to the other centiles.

Age (Years)	3rd	50th	97th
10	-6.37	-3.5	-3.79
15	-8.05	0	6.68
20	-2.72	-1	-2.26
25	-2.56	-1	4.8
30	-7.76	0	4.37
35	-9.33	-1	4.28
40	-5.8	0	-0.5
45	6.1	0	0.46
50	1.48	0	2.58
55	4.5	-2	-5.75

Table 3.4. Percentile near phoria chart showing refraction group differences (progressive myope-myope) over the human lifespan, where esophoric and exophoric deviations are represented by the (-) negative and (+) positive values.

All three centiles were of different variation between progressive myopes and myopes. The progressive myope 3rd centile was more esophoric for all available age groups, spanning ages 10-44. The 50th centile was similar for both refraction groups, except where progressive myopes were more esophoric for ages 10-14, 20-29, 35-39, and 55-59. The 97th centile showed exophoric and esophoric changes, but differences were more similar to the 50th centile.

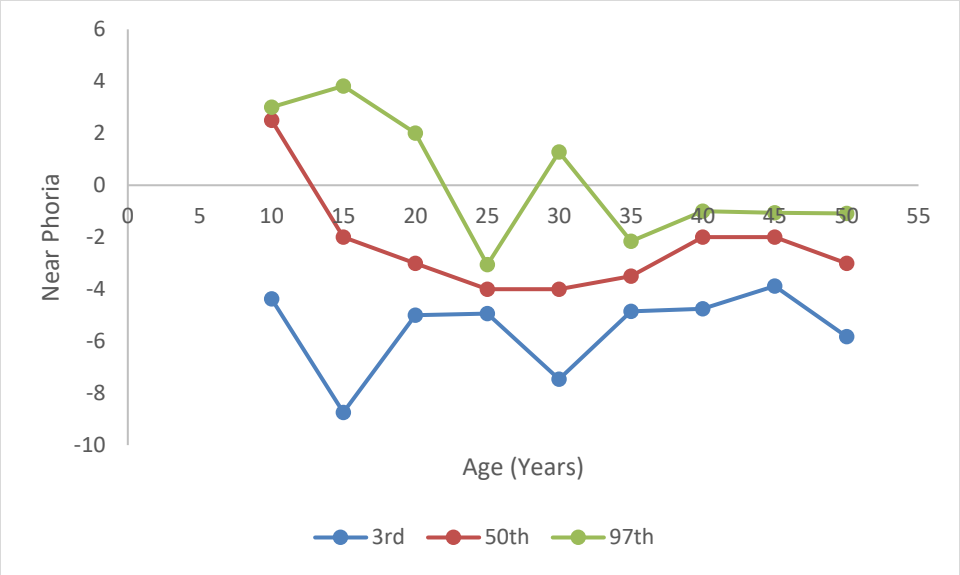

Figure 3.8. Percentile near phoria curves over the male progressive myope human lifespan, where esophoric and exophoric deviations are represented by the (-) negative and (+) positive values on the y-axis.

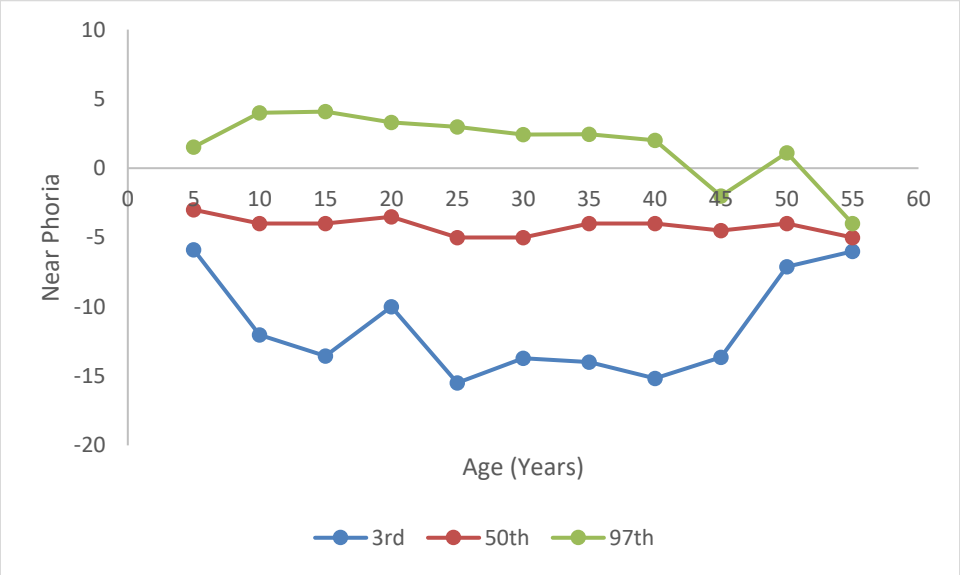

Figure 3.9. Percentile near phoria curves over the female progressive myope human lifespan, where esophoric and exophoric deviations are represented by the (-) negative and (+) positive values on the y-axis.

Age (Years)	3rd	50th	97th
10	-7.66	-6.5	1
15	-4.82	-2	0.26
20	-5	-0.5	1.31
25	-10.55	-1	6.04
30	-6.26	-1	1.15
35	-9.15	-0.5	4.61
40	-10.4	-2	3
45	-9.77	-2.5	-0.94
50	-1.28	-1	2.19

Table 3.5. Percentile near phoria chart showing refraction group differences (female-male progressive myope) over the human lifespan, where esophoric and exophoric deviations are represented by the (-) negative and (+) positive values.

The female progressive myope 3rd and 50th centiles were both more esophoric for all available age groups, spanning ages 10-54. The 97th centile showed a reversed trend, compared to the other centiles, except where female progressive myopes were more esophoric for ages 45-49.

Clinical Patient Visits

Investigation of patient visit (**Figure 3.10**) differences only across the emmetrope, myope, and progressive myope groups showed emmetropic and female patients were examined more frequently.

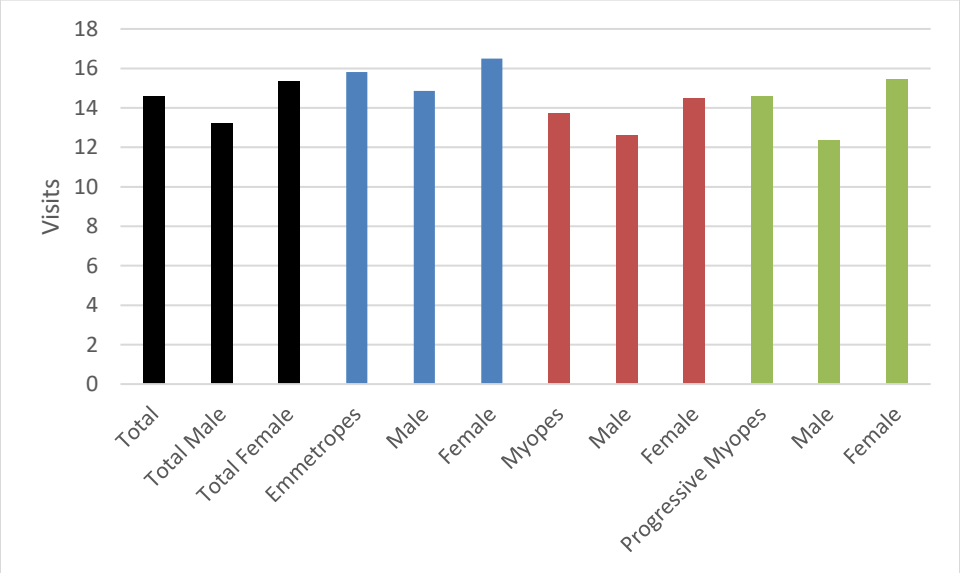

Figure 3.10. Clinical patient visit differences over the human lifespan for 70 patients.

3.4 Discussion

The mean for near phoria (-3.00 ± 3.75 Δ) over the human lifespan in this sample was similar to the results (mean near phoria of -2.03 ± 4.00 Δ analysed at the first visit, relative to that of -4.49 ± 4.56 Δ at the final visit) reported by Irving & Machan (2012) of the same larger population, both using the WatES database. This reliability was then applied towards additional individual patient analysis to investigate the age-dependent distribution of near phoria severity. However, no previous such study exists for further comparisons of the reported differences in sex, progressive myopes, as well as percentile growth charts and curves for near phoria spanning at least 27 years.

Overall for the current study, emmetropic and female patients were examined more frequently; females and female progressive myopes exhibited higher levels of near phoria and myopia; myopes were more esophoric than emmetropes, progressive myopes were more esophoric than both myopes and emmetropes, and were less likely to increase in exophoria with age. These findings are important, since previous literature has reported on the constant and gradual increase of near exophoria with age in both pre-presbyopes and presbyopes, irrespective of a reading addition (Yekta *et al*., 1989; Hrynchak *et al*., 2011; Irving & Machan, 2012; Leat *et al*., 2013).

In this population sample, the 3rd centile was particularly noteworthy for differences in the near phoria magnitude, whereas the 50th centile was more indicative of the variation in near phoria onset, and the 97th centile was best for representing esophoric and exophoric changes among the sex and refraction groups, across the human lifespan. This agreed with Chen *et al*. (2016), who reported younger Chinese children with refractive centiles below lower percentiles, especially those below the 5th percentile having the highest predictive accuracy and age-related cut points, were expected to have high myopia later in life. In-between refractive group comparisons showed the most interesting changes. Myopes and emmetropes differed by esophoria onset, occurring earlier among myopes and 5 years later in each subsequent centile: ages 20-24 for the 3rd centile; 25-29 for the 50th, and 30-34 for the 97th. This is interesting relative to the study by Jones *et al*. (2005), who noted the growth differences between emmetropic and myopic eyes, whereas the respective investigated changes between these refraction groups remained similar at baseline. The present study also supported the notion of a short opportunistic interval for prediction and intervention prior myopia onset, as well as that myopes and emmetropes differed by growth. Moreover, the 3rd centile of the percentile growth curves in this study showed near phoria severity peaks occurred at the following: for the overall

sample population at ages 15-19, 25-29, 40-44, and 60-64, where this happened at 15-19, 25-29, 45-49, 55-59 and 15-19, 25-29 for males and females, respectively; for emmetropes at ages 45-49 and 55-59, for myopes at ages 25-29, 45-49, and 60-64, and for progressive myopes at ages 15-19, 25-29, and 40-44. The 50th centile from the percentile growth chart results included: relative to emmetropes, myopes were esophoric at ages 25-29, whilst progressive myopes were exophoric for ages 15-24 and 50-54; relative to myopes, progressive myopes were esophoric for ages 10-14, 20-29, and 55-59. Also relative to myopes, progressive myopes were esophoric for ages 10-14 and exophoric for ages 15-19 at the 97th centile of that percentile growth chart. These findings agreed with Rozema *et al*. (2019), noting the increased growth changes surrounding onset, followed by a gradual dip among progressive myopes. Likewise, the findings here supported the statement by Irving *et al*. (2019), who discovered the myopes in that population were the cause for the greater longitudinal refractive error variability and change over human life. The results suggested possible crucial cut points of near phoria development at the age ranges of 10-29 and 40-64, particularly 15-19, 25-29, and 40-49, earlier and later in life, respectively. This was emphasised by Diez *et al*. (2019), who suggested the age of 9 to be vital for Chinese children, after reporting that axial length centiles there, above the 50th percentile were expected to develop high myopia. Similar findings were observed by Tideman *et al*. (2018) in a European population. Thus, there may be a clinically manifesting myopia-related near phoria control target across the human lifespan, which was observed to be greater and occurred later in males and male progressive myopes.

Although these findings reflected the age-, sex-, and refraction-specific near phoria distribution in Canadians, the study (known to be the first of its kind) intended to inform future research towards better understanding myopia prediction, its progression over human life, the way individuals might benefit from intervention, as well as suggesting that the near phoria risk factor should be measured alongside other primary outcome parameters important for treatment efficacy. This study may also be added towards the implementation of individual monitoring standards relative to a population, which would be beneficial for myopia assessment and prediction technologies.

Chapter 4 Impact of blur from a dual focus and an extended depth of focus contact lens

4.1 Introduction

Since Holden *et al*. (2016) projected half of the world to become myopic by the year 2050, efforts towards myopia control and prevention have increased. In a meta-analysis of thirty randomized controlled trials (RCTs) with a minimum of one year treatment duration, Huang *et al*. (2016) noted that a range of interventions are effective against myopia progression in children relative to single vision spectacles or no intervention at all. However, due to persistent variability in efficacy and mechanism understanding of the current optical, pharmacological, environmental, and surgical myopia treatment strategies, the International Myopia Institute (IMI) committee on Interventions for Myopia Onset and Progression (Wildsoet *et al*., 2019) maintained that no therapy yet exists for all patients that is able to fully prevent, delay, or control myopia. Also, many myopia control treatments are currently off-label/unlicensed prescriptions, and the relevant legal, regulatory, and professional stance is country-specific, varying worldwide. An exception is the approved European certification standard or CE marking for the multifocal soft contact lenses MFSCLs MiSight (CooperVision), NaturalVue (Visioneering Technologies), and MYLO (Mark'ennovy in collaboration with the Brien Holden Vision Institute), of which only MiSight is additionally Food and Drug Administration (FDA)-approved and recognised in the US, Canada, Australia, New Zealand, Hong Kong, and Singapore for controlling myopia progression. MYLO is a monthly silicone hydrogel contact lens with extended depth of focus (EDOF) optics and higher water content, whilst MiSight and NaturalVue are both daily hydrogel lenses of similar water content, but MiSight has a dual focus optical design, whereas NaturalVue also incorporates EDOF. Since these options currently stand as the most accessible to eye care practitioners, it is of vital importance to understand the associated "real world" clinical applications.

Wildsoet *et al*. (2019) outlined the variable optical treatment efficacies (reduction in myopia over time, compared to a simultaenous control group) such as: single vision spectacles (14%) [where the literature is adamant that any effect is unsustained and this treatment strategy is ultimately ineffective in slowing myopia]; bifocal and progressive addition spectacles (6-51%); MFSCLs (38%); and orthokeratology (30-55%). Despite these results, animal studies have consistently suggested that myopia developement and progression is driven by standard spherical optical treatments causing relative peripheral hyperopic defocus (Smith *et al*., 2007; Smith, 2010; Cooper *et al*., 2012). On the other hand, orthorokeratology options have been of concern regarding adverse effecs (Lang & Rah, 2004; Liu & Xie, 2016) and limitations for correcting low

and high myopia, as well as older patients (Fu *et al*., 2016; Want *et al*., 2017). A meta-analysis and systemic review by Bullimore (2017) on the safety of soft contact lenses in children, for example, asserted the risk of infiltrative complications was shown to be lower for ages 8-12 relative to older groups, which also matches the typical commencement range for myopia control implementation. Thus, MFSCLs with centre-distance concentric ring or progressive power designs have been increasingly used as an attractive optical paediatric myopia intervention and are well accepted by both clinicians and their patients.

Chamberlain *et al*. (2019) and Wildsoet *et al*. (2019) have recently summarised the majority of published MFSCLs trials, but without inclusion of the lone NaturalVue (Cooper *et al*., 2018) and MYLO (Sankaridurg *et al*., 2019) investigations, and only a few of these studies used country-dependent commercially available lenses (Anstice & Phillips, 2011; Walline *et al*., 2011; Ruiz-Pomeda *et al*., 2018; Chamberlain *et al*., 2019; Sankaridurg *et al*., 2019). NaturalVue also has a presently on-going clinical study performed by Thomas Aller and Visioneering Technologies, Inc. with an estimated completion by mid-2022. Wildsoet *et al*. (2019) highlighted that MFSCLs of concentric ring designs were more effective in slowing axial elongation. Furthermore, only Sankaridurg *et al*. (2011) and Fujikado *et al*. (2014) with MFSCLs, and Paune *et al*. (2015) with orthokeratology contact lenses, have examined the role of corrected peripheral refraction. The contact lenses in these studies have been termed concentric (Anstice & Phillips, 2011; Aller *et al*., 2016) or peripheral gradient (Sankaridurg *et al*., 2011; Fujikado *et al*., 2014; Paune *et al*., 2015) lenses. The literature is definitive in that contact lenses are superior to spectacles in correcting peripheral refraction, as they move with the eye and are on the cornea. MFSCLs in particular have been shown to reduce myopia significantly more than progressive addition spectacles, due to their ablitity for exerting more extensive peripheral myopic defocus (Smith, 2013).

In addition to refractive error, axial length (AL), and relative peripheral defocus, there are other well established outcome measures from myopia control trials that should be adopted on the quest to solving the unanswered efficacy and mechanism questions (Wolffsohn *et al*., 2019). Early research has reported higher near accommodative lag and associated errors among myopes (Gwiazda *et al*., 1995; Nakatsuka *et al*., 2005; Allen & O'Leary, 2006), which are importantly linked to the induced retinal blur by MFSCLs (Anstice & Phillips, 2011; Paune *et al*., 2016; Gong *et al*., 2017). The report by the IMI committee on Clinical Myopia Control Trials and Instrumentation (Wolffsohn *et al*., 2019) has stressed the examination of treatment compliance and qualifty of life impact by the effect of dysphotopsia and contrast sensitivity with myopia

control strategies. However, only single studies have reported some of these measures with 0.01% atropine (Loughman & Flitcroft, 2016) and the MiSight and NaturalVue MFSCLs (Ghorbani-Mojarrad *et al*., 2021). MFSCLs, in particular, have previously been shown to significantly impact these measures in presbyopes, due to the alternating zones of optical powers (Rajagopalan *et al*., 2007; Kolbaum *et al*., 2012; García-Lazaro *et al*., 2015; Wahl *et al*., 2018), but myopia control use is aimed at children and young adults.

In order to address the above gaps in knowledge, this study evaluated the clinical impact (peripheral refractive defocus, accommodative lag, contrast sensitivity, and dysphotopsia) of the commercially available and CE-marked for myopia control MiSight and NaturalVue MFSCLs, compared with a standard single vision Proclear lens, after daily wear. This is considered the first such study, comparing these lenses and parameters, aimed at better understanding the possible mechanisms surrounding optical myopia control options, as well as how effectiveness may vary for individual patient or combine with other therapies.

4.2 Methods

4.2.1 Participants

The study (single-centre, prospective, randomised, and double-masked) was conducted at the Aston University Ophthalmic Research Clinics, where 18 participants with myopia in good overall general and ocular health were recruited. This sample size was enough to obtain 80% statistical power for a significance level of $\alpha = 0.05$ with a confidence level of 95%, based on an effect size of 0.8 for the statistical analyses used in this study, published literature, and priori power analysis (G*Power 3.1, University of Dusseldorf). All participants gave informed written consent. All procedures followed the Declaration of Helsinki and the protocol was approved by the Aston University Research Ethics Committee.

4.2.2 Contact Lenses

Three different daily soft contact lenses (standard single vision Proclear® 1-Day [omafilcon A; hydrophilic; CooperVision, Inc.] for the control group, as well as specialty multifocal MiSight® 1-Day [omafilcon A; hydrophilic, water content 60%; refractive index 1.40; center thickness of 0.08 mm at -3.00 D; CooperVision, Inc.] and NaturalVue® 1-Day [etafilcon A; hydrophilic, water content 58%; refractive index 1.40; center thickness of 0.08 mm at -3.00 D; Visioneering Technologies, Inc.] designed for myopia control for the test groups) were compared. The optical

design technology of the MiSight and NaturalVue lenses has already been described in detail by Chamberlain *et al*. (2019) and Cooper *et al*. (2018), respectively.

4.2.3 Study Design

Eligible participants visited on alternating days and in the same week, in order to implement a test group washout period in between, and so that each participant can be fitted with all lenses. Participants were asked to attend for a morning visit (8:30 AM – 11:30 AM) and 8 hours later in the afternoon to allow for an adaptation period, mimic a typical work-day interval, and consistency in diurnal variation. The visits were each conducted by two separate investigators, where the first investigator fitted the randomised contact lenses via coded letter (A, B, C) assignment, known only by the principal investigator, whilst the second investigator performed the measurements. The participants were unaware as to which lens and in which eye they were fitted during the visit.

During the morning visit, Investigator 1 provided a copy of the informed consent and participant information sheet; confirmed eligibility (age range 18-35; prescription range -0.75 D to -4.50 D with astigmatism ≤1 D; spectacle, contact lens, and myopia control intervention history; as well as no relevant contraindication; and medical and ocular health history, including medications); and performed autorefraction (3 measurements were taken from each eye, whilst the participant viewed a distant non-accommodative target [Grand Seiko WAM-5500; Grand Seiko Co., Hiroshima, Japan]), best-corrected distance visual acuity (logMAR letter chart), slit-lamp biomicroscopy anterior eye examination, and randomised contact lens fitting according to manufacturers' criteria.

In order to investigate differences in materials and designs, peripheral refractive defocus, accommodative lag, contrast sensitivity, and dysphotopsia were measured by also accounting for diurnal variations.

During the afternoon visit, Investigator 2 measured the following:

Accommodative Lag: 3 measurements were taken from each contact lens-corrected eye with the opposite eye being occluded and the lights turned off; the participant viewed a distant non-accommodative target, followed by near readings at -3 D/33 cm and fixating the centre of a near Maltese cross target in free space attached to the mounted adjustable apparatus [Grand Seiko WAM-5500; Grand Seiko Co., Hiroshima, Japan].

Contrast Sensitivity and Dysphotopsia (Glare): Contrast Sensitivity was measured with the Aston Contrast Sensitivity Near App and Dysphotopsia (disability glare) was measured with the

Aston Halometer and Tablet App; both monocularly from each contact lens-corrected eye and using an iPad4. The validation and repeatability completed previously on these techniques have been assessed by Kingsnorth *et al*. (2016) and Buckhurst *et al*. (2015; 2017), respectively, where the measurement protocol followed the recommendations in those studies. These tests were selected for their objectivity towards such normally subjective reported data.

Contrast Sensitivity was measured at 40 cm, as participants traced the boundary of contrast grating detection using their finger on the touch screen (**Figure 4.1**).

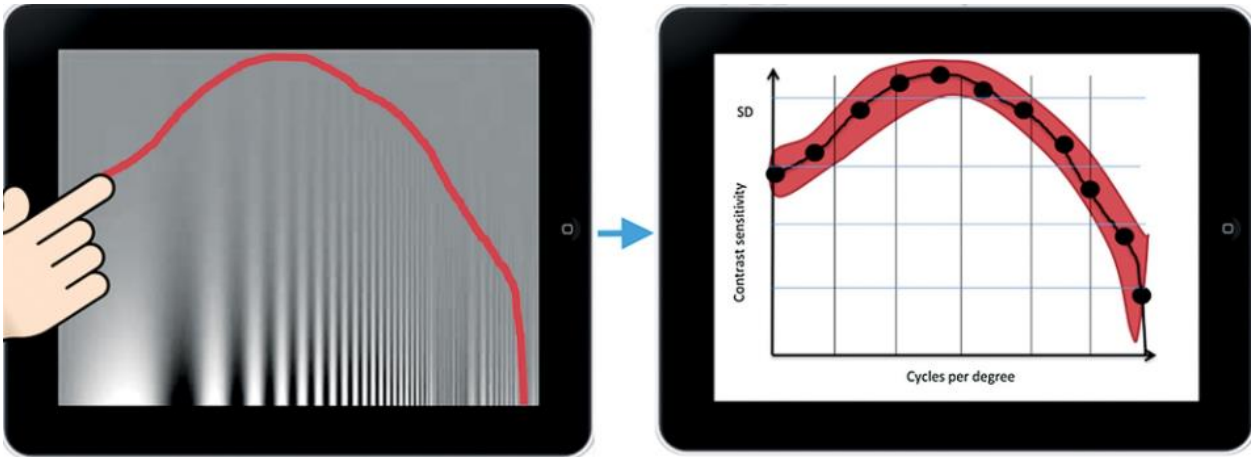

Figure 4.1. The Aston Contrast Sensitivity Near App, adopted from Kingsnorth *et al*. (2016).

Dysphotopsia was measured at 2 m with the lights turned off. The Halometer is a light-emitting-diode (LED) glare source centrally positioned on the iPad. The investigator manually moved randomised letters subtending 0.21° centrifugally from the LED in 0.05° steps in all 8 directions of gaze. Photopic scotoma size was measured, once participant responses were recorded at all orientations, where each letter response had to be correct in at least 2 out of 3 presentations (**Figure 4.2**).

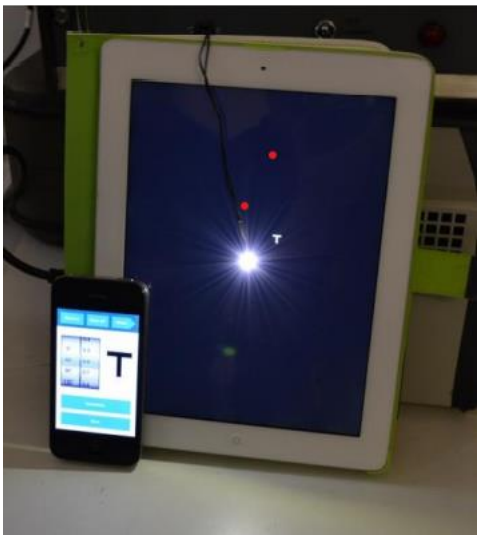

Figure 4.2. The Aston Halometer and Tablet App, adopted from Buckhurst *et al*. (2015).

Cyclo-Autorefraction: 3 measurements were taken from each eye with the opposite eye being occluded and the lights turned off; central (on-axis) refractive error was measured with the participant viewing a distant target 1 line larger than best VA; peripheral refraction was measured at 30° in the horizontal meridian with the participant viewing a distant Maltese cross on a wall and the nasal/temporal sides randomised by head turning (Wolffsohn *et al*., 2019) [Grand Seiko WAM-5500; Grand Seiko Co., Hiroshima, Japan].

Cycloplegia: complete details of the drops were provided along with official College of Optometrists leaflet; the British National Formulary (BNF) number, expiration date, and time of instillation were recorded [1% Tropicamide; 1 drop/eye; minimum 20-minute waiting period].

Visual acuity (logMAR letter scoring) and anterior eye health (slit-lamp biomicroscopy with fluorescein) were also examined, and the study concluded with a verbal debrief. Visual acuity (distance at 4 m [2000 Series Revised ETDRS Chart; Precision Vision] and near at 40 cm [Near Point Flip Charts; Precision Vision]) was assessed monocularly from each contact lens-corrected eye, until missing ≥3 letters on a line.

4.2.4 Statistical Analyses

The normality of the data distributions was confirmed using the Kolmogorov-Smirnov test ($P>0.05$). ANOVA *t*-tests and Bonferroni post hoc tests were carried out in Microsoft Excel for Office 365 ProPlus (Microsoft Corp.); values are means ± SD, where values denoted * were

considered significant (p<0.05). Statistical significance (P<0.05) between groups (contact lenses Proclear [Group A], MiSight [Group B], NaturalVue [Group C]) is denoted *.

An accommodative response ≥1.00 D was considered as lag of accommodation (Manny *et al*., 2009), which was calculated as the average refraction difference between distance and near readings (Wolffsohn *et al*., 2019).

Sphero-cylindrical refraction data was converted into power vector components M, J0, and J45 using the standard formulas (Thibos *et al*., 1997) below:

$$\text{Spherical equivalent } M = \text{sphere} + (\text{cylinder}/2)$$

$$J0 = -(\text{cyl}/2) \times \cos(2 \times \text{axis})$$

$$J45 = -(\text{cyl}/2) \times \sin(2 \times \text{axis})$$

4.3 Results

From the 18 subjects included in the study, the pool consisted of the following demographics: 15 female and 3 male (12 British Asian and 6 white European); mean age of 22.8 years ± 4.1 (range 18 to 35 years); mean spherical equivalent refraction (SER) of -2.4 ± 1.3 D (range -0.75 to -4.50 D); there were no adverse events.

4.3.1 Cyclo-Autorefraction

Central and peripheral refractive error results measured by cyclo-Autorefraction are summarised in **Table 4.1**. Temporal (at 30° in the horizontal meridian) refraction for the J0 sphero-cylindrical power vector was found to be significant (p=0.019*), after 8 hours of contact lens wear. The result was followed by individual group comparisons in **Table 4.2**, where temporal peripheral defocus for the J0 vector exerted by the NaturalVue MFSCLs test group was significant (p=0.011*) relative to the Proclear single vision contact lens control group. This was not the case for the other MiSight MFSCLs test group, as well as there was no significant difference between test groups. These contact lens group differences are further illustrated by **Figure 4.3**.

	Proclear	MiSight	NaturalVue	*p*
Central Refraction (D)				
M	-2.08 ± 1.41	-1.99 ± 1.47	-2.19 ± 1.46	0.921912
J0	0.003 ± 0.19	-0.01 ± 1.47	0.05 ± 0.22	0.666939
J45	0.03 ± 0.24	0.04 ± 0.22	-0.01 ± 0.21	0.741804
Temporal Refraction (D)				
M	0.5 ± 3.25	0.93 ± 2.29	0.80 ± 1.95	0.875083
J0	-0.67 ± 1.20	0.001 ± 0.90	0.27 ± 0.87	0.019611 *
J45	-0.26 ± 1.03	0.03 ± 0.90	-0.16 ± 0.69	0.73341
Nasal Refraction (D)				
M	1.20 ± 2.83	0.68 ± 2.46	0.18 ± 2.57	0.533038
J0	0.28 ± 0.74	0.16 ± 0.95	0.09 ± 0.80	0.793238
J45	0.07 ± 0.72	-0.01 ± 0.86	-0.28 ± 0.58	0.32894

Table 4.1. Central (on-axis) and peripheral (at 30° temporally and nasally in the horizontal meridian) cyclo-Autorefraction measured after 8 hours of contact lens wear; values are means ± SD, where values denoted * were considered significant (p<0.05).

	J0 Temporal Refraction (D)
Group A vs. Group B *P*	0.064925
Group A vs. Group C *P*	0.010582 *
Group B vs. Group C *P*	0.368238

Table 4.2. Contact lens group (Proclear [Group A], MiSight [Group B], NaturalVue [Group C]) comparison of temporal (at 30° in the horizontal meridian) cyclo-Autorefraction for the J0 sphero-cylindrical power vector, where * represented a significant (p<0.05) difference.

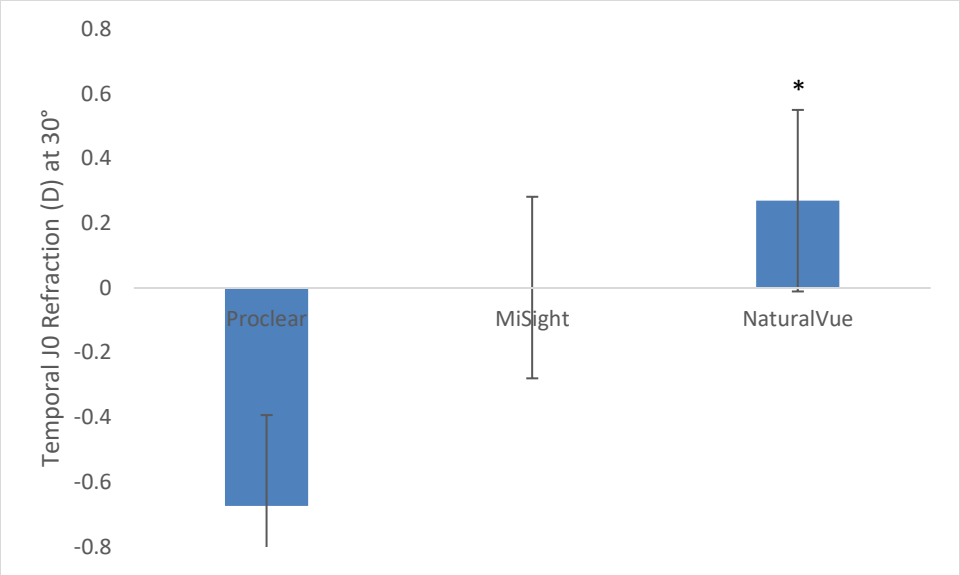

Figure 4.3. Contact lens group (Proclear [Group A], MiSight [Group B], NaturalVue [Group C]) comparison of temporal (at 30° in the horizontal meridian) cyclo-Autorefraction mean values for the J0 sphero-cylindrical power vector, where * represented a significant (p<0.05) difference.

4.3.2 Accommodative Lag

The type of contact lens had a significant (p=0.006*) effect on accommodative lag, after 8 hours of wear (**Table 4.3**). The result was followed by individual group comparisons in **Table 4.4**, where Accommodative Lag exerted by the NaturalVue MFSCLs test group was significant (p=0.002*) relative to the Proclear single vision contact lens control group. This was not the case for the other MiSight MFSCLs test group, as well as there was no significant difference between test groups. These contact lens group differences are further illustrated by **Figure 4.4**.

	Proclear	**MiSight**	**NaturalVue**	***p***
Accommodative Lag (D)	1.88 ± 0.65	1.39 ± 1.04	0.73 ± 1.28	0.006019 *

Table 4.3. Accommodative Lag measured after 8 hours of contact lens wear; values are means ± SD, where values denoted * were considered significant (p<0.05).

	Accommodative Lag (D)
Group A vs. Group B *P*	0.102538
Group A vs. Group C *P*	0.001833 *
Group B vs. Group C *P*	0.099409

Table 4.4. Contact lens group (Proclear [Group A], MiSight [Group B], NaturalVue [Group C]) comparison of Accommodative Lag, where * represented a significant (p<0.05) difference.

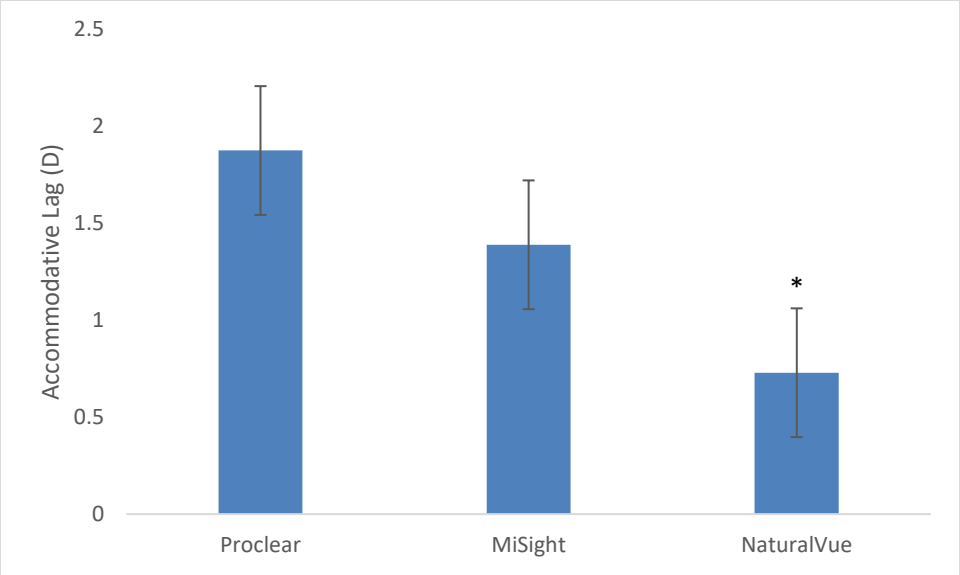

Figure 4.4. Contact lens group (Proclear [Group A], MiSight [Group B], NaturalVue [Group C]) comparison of Accommodative Lag mean values, where * represented a significant (p<0.05) difference.

4.3.3 Contrast Sensitivity

Results for Contrast Sensitivity are summarised in **Table 4.5**. Although no significant differences were found, after 8 hours of contact lens wear, **Figure 4.5** further illustrates the contact lens comparison of Contrast Sensitivity across the sample population.

	Proclear	MiSight	NaturalVue	*p*
CS at -1 Frequency (cpd)	0.06	-0.02	-0.003	0.66733
CS at -0.84 Frequency (cpd)	0.60	0.53	0.43	0.632625
CS at -0.68 Frequency (cpd)	1.04	0.93	0.80	0.386645
CS at -0.53 Frequency (cpd)	1.33	1.25	1.17	0.699912
CS at -0.37 Frequency (cpd)	1.60	1.54	1.49	0.868029
CS at -0.21 Frequency (cpd)	1.85	1.80	1.78	0.934923
CS at -0.06 Frequency (cpd)	2.05	2.00	1.98	0.943056
CS at 0.1 Frequency (cpd)	2.20	2.14	2.12	0.922987
CS at 0.26 Frequency (cpd)	2.29	2.22	2.20	0.896381
CS at 0.41 Frequency (cpd)	2.33	2.23	2.21	0.797075
CS at 0.57 Frequency (cpd)	2.30	2.19	2.14	0.628749
CS at 0.72 Frequency (cpd)	2.19	2.08	1.99	0.429189
CS at 0.88 Frequency (cpd)	2.01	1.91	1.78	0.303972
CS at 1.04 Frequency (cpd)	1.78	1.70	1.55	0.212765
CS at 1.19 Frequency (cpd)	1.53	1.47	1.33	0.275027
CS at 1.35 Frequency (cpd)	1.29	1.19	1.12	0.496834

Table 4.5. Contrast Sensitivity measured after 8 hours of contact lens wear; values are means, where values denoted * were considered significant (p<0.05).

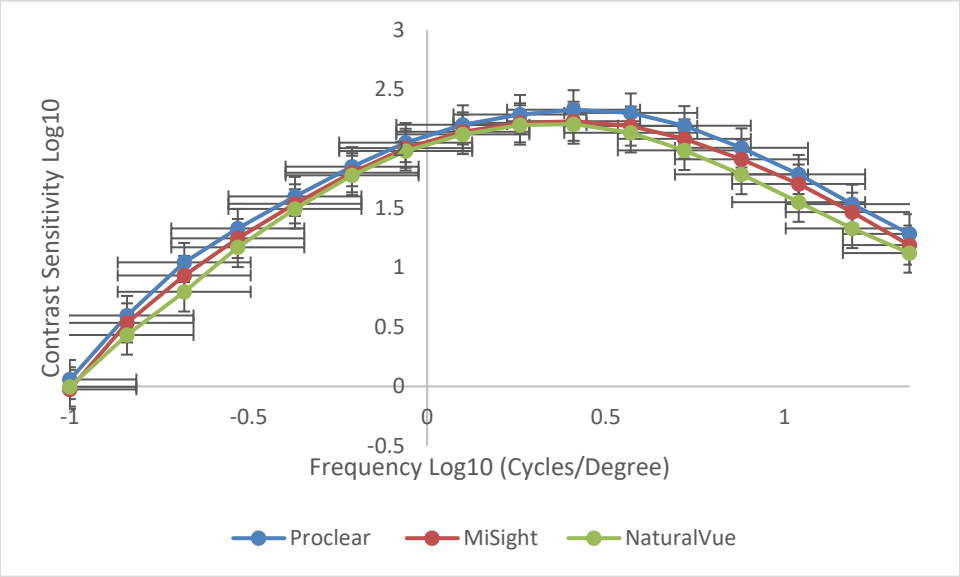

Figure 4.5. Contact lens comparison of Contrast Sensitivity across the sample population.

4.3.4 Dysphotopsia (Glare)

Results for Dysphotopsia (Glare) are summarised in **Table 4.6**. Glare at 0° and 225° was found to be significant (p=0.015901* and p=0.024147*, respectively), after 8 hours of contact lens wear. **Figure 4.6** further illustrates the contact lens comparison of Glare across the sample population. The result was followed by individual group comparisons in **Table 4.7** and **Table 4.8**, representing Glare at 0° and 225°, respectively. Glare at 0° exerted by the NaturalVue MFSCLs test group was significant (p=0.015548*) relative to the Proclear single vision contact lens control group. This was not the case for the other MiSight MFSCLs test group, but there was a significant difference between test groups (p=0.02591*). Additionally, Glare at 225° exerted by both the NaturalVue and MiSight MFSCLs test groups was significant (p=0.007196* and p=0.016713*, respectively) relative to the Proclear single vision contact lens control group. There was no significant difference between test groups. These contact lens group differences are further illustrated by **Figure 4.7** and **Figure 4.8**, representing Glare at 0° and 225°, respectively.

	Proclear	MiSight	NaturalVue	*p*
Radii (DOV°) at 0°	1.31	1.35	1.62	0.015901 *
Radii (DOV°) at 45°	1.42	1.22	1.47	0.051771
Radii (DOV°) at 90°	1.24	1.26	1.39	0.144891
Radii (DOV°) at 135°	1.27	1.39	1.40	0.323785
Radii (DOV°) at 180°	1.32	1.44	1.40	0.557052
Radii (DOV°) at 225°	1.26	1.56	1.48	0.024147 *
Radii (DOV°) at 270°	1.32	1.38	1.36	0.766676
Radii (DOV°) at 315°	1.35	1.33	1.38	0.971743

Table 4.6. Dysphotopsia (Glare) measured after 8 hours of contact lens wear; values are means, where values denoted * were considered significant (p<0.05).

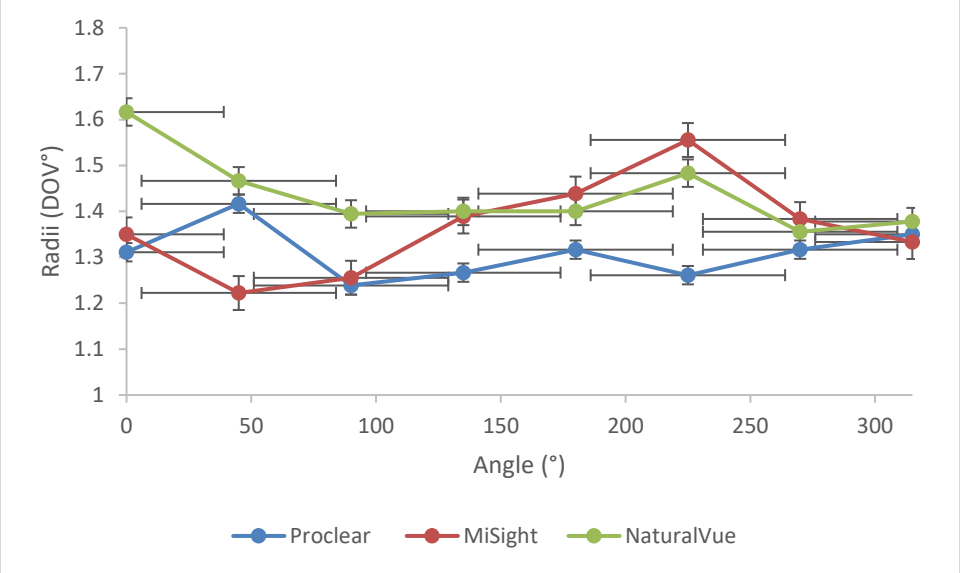

Figure 4.6. Contact lens comparison of Dysphotopsia (Glare) across the sample population.

	Glare at 0° [Radii (DOV°)]
Group A vs. Group B *P*	0.691174
Group A vs. Group C *P*	0.015548 *
Group B vs. Group C *P*	0.02591 *

Table 4.7. Contact lens group (Proclear [Group A], MiSight [Group B], NaturalVue [Group C]) comparison of Dysphotopsia (Glare) at 0°, where * represented a significant (p<0.05) difference.

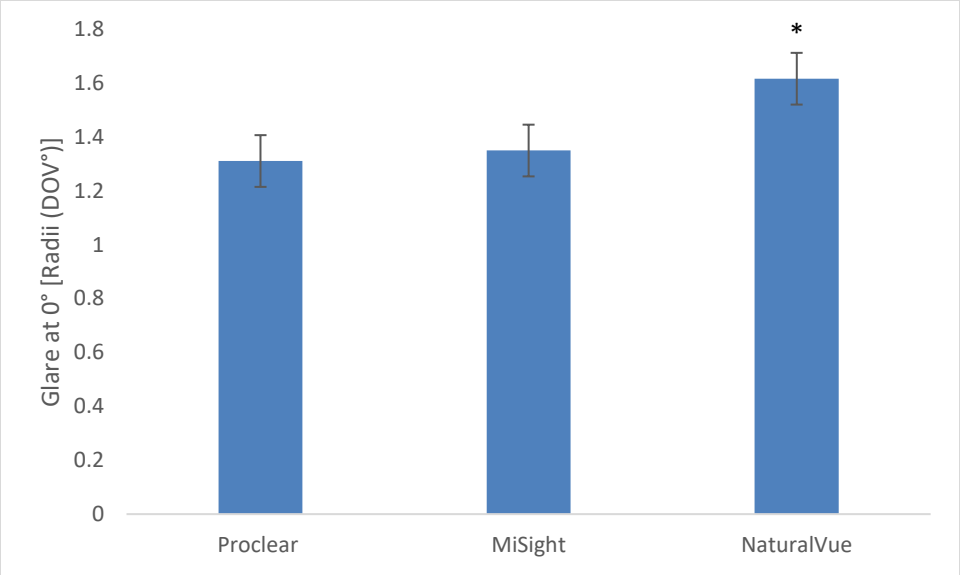

Figure 4.7. Contact lens group (Proclear [Group A], MiSight [Group B], NaturalVue [Group C]) comparison of Dysphotopsia (Glare) at 0° mean values, where * represented a significant (p<0.05) difference.

	Glare at 225° [Radii (DOV°)]
Group A vs. Group B *P*	0.016713 *
Group A vs. Group C *P*	0.007196 *
Group B vs. Group C *P*	0.565933

Table 4.8. Contact lens group (Proclear [Group A], MiSight [Group B], NaturalVue [Group C]) comparison of Dysphotopsia (Glare) at 225°, where * represented a significant (p<0.05) difference.

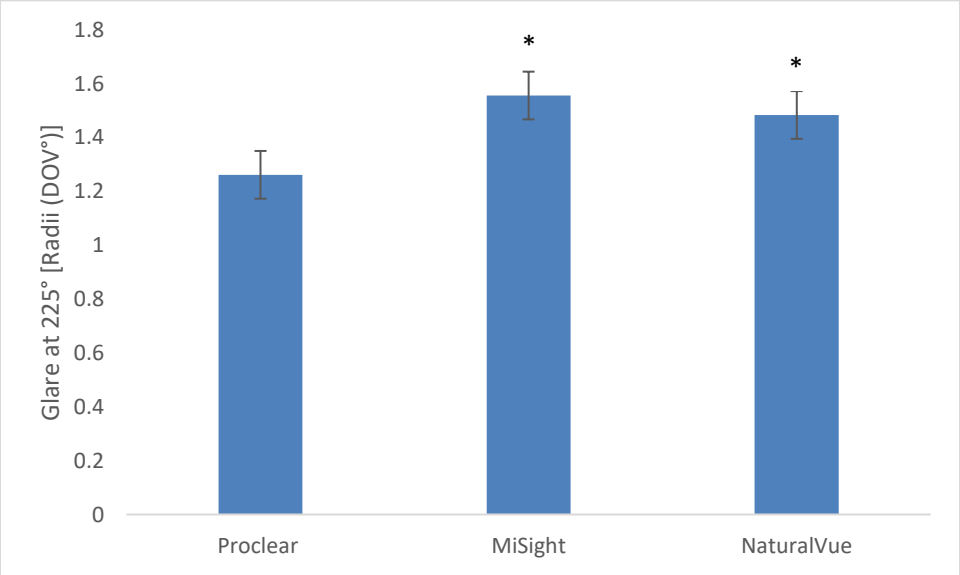

Figure 4.8. Contact lens group (Proclear [Group A], MiSight [Group B], NaturalVue [Group C]) comparison of Dysphotopsia (Glare) at 225° mean values, where * represented a significant (p<0.05) difference.

4.4 Discussion

The successful contact lens efficacy in slowing refractive myopia progression and axial elongation is well established, but the surrounding mechanisms and associated clinical impact remain inconclusive. Although Ghorbani-Mojarrad *et al*. (2021) recently assessed accommodative lag and contrast sensitivity based on patient experience, their analyses were exploratory and did not test a hypothesis. The present study is considered the first to additionally measure corrected peripheral defocus and dysphotopsia with the MiSight and NaturalVue MFSCLs (the only daily CE-marked myopia control options). This study is further unique in its used cohort (British Asian and European myopic adults) and control group (commercially available single vision contact lenses) for the comparisons, after 8 hours of contact lens wear.

4.4.1 Peripheral Refraction

Gifford *et al*. (2019) and Wolffsohn *et al*. (2019) have summarised the research surrounding peripheral refraction, concluding that its mechanism in myopia control and progression remains unknown, whilst clinically significant standardised criteria does not yet exist. However, studies have consistently showed that myopes have greater relative peripheral hyperopia, compared to emmetropes and hyperopes, and vice-versa for myopic relative peripheral refraction (Ehsaei *et al*., 2011; Sng *et al*., 2011; Lundstrom & Rosen, 2017). Based on the compiled findings for significant patterns in uncorrected relative peripheral refraction measurements across the literature, Wolffsohn *et al*. (2019) stated differences between 0.50-1.00 D in the 30° temporal visual field may be used as a reference. As mentioned above, only Sankaridurg *et al*. (2011) and Fujikado *et al*. (2014) have previously measured corrected peripheral defocus during MFSCLs wear, using single vision spectacle and contact lenses as controls, respectively. Moreover, the studies were performed on Chinese myopic children of ages 7-14 and Japanese myopic children of ages 10-16, respectively.

Sankaridurg *et al*. (2011) measured peripheral refraction horizontally (both nasal and temporal directions) at 20°, 30°, and 40°, with and without correction, after 12 months. The authors reported no differences in relative hyperopia magnitude and/or eccentricity, without correction; expected increases with increased eccentricity, but particularly higher hyperopia magnitude

nasally for both spectacle and contact lens groups; however, spectacles lenses equally increased the relative peripheral hyperopia, whereas, contact lenses showed reductions, especially nasally, presumed to be a result of the nasal centering on the corneal geometric axis during wear. This study stated that increased relative peripheral hyperopia at 30° and 40° nasally, as well as 40° temporally were ultimately correlated with greater myopia progression. Fujikado *et al*. (2014) expanded the above findings in a randomised study with MFSCLs of nasally decentered optical design and lower add (0.50 D), after 12 and 24 months. However, no significant difference in reduced relative peripheral hyperopic blur between the naked eye and either contact lens type, regardless of eccentricity, was reported. In comparison to Sankaridurg *et al*. (2011), the authors attributed this discrepancy to that study's use of higher addition (2.00 D) MFSCLs, but concluded that the efficacy in AL reduction was similar, possibly due to the reduced near accommodation, which neither study investigated.

Although interesting changes in central and peripheral (nasal and temporal) refractive blur were observed, where individual contact lens results supported indications by the literature, the present study also consistently found the temporal horizontal meridian at 30° for the J0 sphero-cylindrical power vector to be of practical significance, particularly with the NaturalVue MFSCLs of EDOF optical design achieving the highest level of blur. No previous similar data exists for direct comparison, but Paune *et al*. (2015) did report a lack of significant correlations for the horizontal (J0) and oblique (J45) astigmatic components with multifocal orthokeratology contact lenses when tested on Caucasian myopic children of ages 9-16. A more recent study by Moore *et al*. (2018) investigated the effect of peripheral retinal defocus with four commercially available spherical soft contact lenses (Biofinity, Acuvue2, PureVision2, and Air Optix Night & Day) on myopic young adults at 20°, 30°, and 40°. The study stated that all lenses significantly reduced relative peripheral hyperopic defocus on the temporal retina when compared to the uncorrected eye, except PureVision2, but magnitudes differed with eccentricities: J0 was significant for the same three lenses at 40° temporally, as well as at 30° temporally and 40° nasally for Air Optix; J45 was significant only for Air Optix at 40° temporally. The authors noted that Air Optix was the only contact lens to decenter nasally, as well as that a more negative contact lens power overall (which is the opposite mechanism to spectacles [Lin *et al*., 2010]), and the optic zone size significantly accounted for differences between eccentricities; results confirmed to be similar to the summarised literature based on previous such studies. These insights further support the results in the current study, emphasising the essential importance of the optical design

characteristics in contact lenses, where: the treatment zones of the MiSight optic zone incorporate 2.00 D of defocus, whilst NaturalVue has a universal addition power up to 3.00 D.

4.4.2 Accommodative Lag

The significant results of reduced near accommodative lag, especially with the NaturalVue MFSCLs achieving the lowest level of lag, corresponded to the outcome in induced peripheral defocus. Although there are no previous data, but similar findings were reported in studies on myopic children evaluating changes in accommodative lag with MFSCLs (Paune *et al*., 2016; Gong *et al*., 2017); whereas, Anstice & Phillips (2011) and Berntsen *et al*. (2010) did not discover an impact on the accommodative lag with dual-focus soft contact lenses (which are of similar design to the MiSight lenses with 2.00 D treatment zones) and progressive addition lenses (2.00 D add), respectively. An early longitudinal study also stated a lack of significant link in childhood myopia progression with near accommodative lag (Weizhong *et al*., 2008). Moreover, Anstice & Phillips (2011) suggested the myopia control mechanism of the dual-focus contact lenses was based on sustained and simultaneous myopic defocus at both distance and near, where the lenses did not seem to be used as multifocal and relax accommodation, which can be attributed to the MiSight findings in the current study. The authors also noted this design with 2.00 D treatment zones and overall parameters may not be optimal.

4.4.3 Visual Quality

The effect on glare at 0° and 225° was significantly impacted by the contact lenses, especially for MiSight and NaturalVue achieving the highest level of glare at 225° and 0°, respectively. There were no significant differences in contrast sensitivity. Some studies in children have reported reduced contrast sensitivity with MFSCLs, particularly at the lower spatial frequencies (Paune *et al*., 2016; Gong *et al*., 2017; Sankaridurg *et al*., 2019), whilst others have not (Collins *et al*., 1989; Anstice & Phillips, 2011). The study by Wahl *et al*. (2018), which investigated contrast sensitivity (with and without glare) and disability glare influenced by centre-near and centre-distance MFSCLs with single vision spectacle and contact lenses as controls in myopic young adults, is the most similar to the present study for comparisons. The authors reported significant reductions in contrast sensitivity with the centre-distance MFSCLs, but only under the glare condition; disability glare was significant for all lenses and highest at low and medium contrast, but greatest for the centre-distance MFSCLs, whilst all other types had similar levels. Furthermore, van Den Berg *et al*. (2010) and Wahl *et al*. (2018) stated that visual acuity is not linked to glare, due to its minimal impact on contrast sensitivity relative to corrected blur with

MFSCLs. Gifford *et al*. (2013) and Loughman & Flitcroft (2016) also offered agreeable insights with overnight orthokeratology and 0.01% atropine, respectively. These findings support the observations in the current study and highlight the importance of including these visual performance parameters in myopia control research utilising various optical designs.

4.5 Conclusion

The presumed design optimisation, regarding the only daily CE-marked optical myopia control strategies, was based on the possible mechanism behind peripheral refraction and accommodative lag in myopia development and progression. MiSight and NaturalVue MFSCLs achieved myopic retinal defocus differently; MiSight reduced hyperopic blur by sustained and simultaneous myopic defocus, whilst reduced lag was not only associated with the treatment effect for NaturalVue in reducing hyperopic blur, but this novel EDOF lens design could have an inherent characteristic for doing so in the temporal retina at 30° and J0 astigmatic component, which potentially may also be used as a predictive factor for success. These findings may be extended to comparisons of all concentric and peripheral gradient contact lens types, suggesting that except for the possibility of a causal effect by these factors with NaturalVue, reduced hyperopic blur (temporally at 30° for the J0 sphero-cylindrical power vector) and accommodative lag appeared only to be byproducts of the optical design in other contact lenses influencing myopia progression. The optical design of multifocal contact lenses also directly influenced visual quality. Both myopia control strategies significantly impacted glare, but did not effect contrast sensivitiy differently than standard lenses, and would offer equally acceptable treatment compliance and qualifty of life expectactions.

Chapter 5 IOLMaster agreement evaluation in healthy adults, comparing ocular biometry measurements, after immediate soft contact lens wear for myopia control

5.1 Introduction

Optical biometry instrumentation is a critical tool for eye care practitioners in assessing keratometry (K), central corneal thickness (CCT), horizontal white-to-white (WTW) corneal diameter measurements, lens thickness (LT), anterior chamber depth (ACD), and axial length (AL); especially in relation to cataract and refractive surgery optical power planning (Rohrer *et al*., 2009; Akman *et al*., 2016; Young *et al*., 2018), glaucoma screening (Hashemi *et al*., 2005; Rosa *et al*., 2006; Dinc *et al*., 2010), specialty contact lens fitting and corneal shape analysis (Cho *et al*., 2002; Kamiya *et al*., 2014; Lloyd *et al*., 2014), and following myopia progression and control (Smith, 2013; Walline *et al*., 2017; Gifford *et al*., 2019). Although the IOLMaster 500's (Carl Zeiss Meditec, Germany) partial coherence interferometry (PCI) technology has been established as the gold standard (Vogel *et al*., 2001), the newer swept-source optical coherence tomography (SS-OCT) approach, such as that used by the IOLMaster 700 (Carl Zeiss Meditec, Germany), has been shown to have many advantages, including faster analysis, the ability to measure CCT, LT, and both anterior and posterior structural curvatures, as well as higher accuracy performance with complicated patients (Tonn *et al*., 2014; Young *et al*., 2018; Haddad *et al*., 2020). Several studies have already reported on the excellent interchangeability, repeatability, and reproducibility of the IOLMaster 700 relative to the IOLMaster 500 in cataract patients (Srivannaboon *et al*., 2015; Akman *et al*., 2016; Kunert *et al*., 2016; Shammas *et al*., 2016; Yoo *et al*., 2017; Lee & Kim, 2018; Bullimore *et al*., 2019; Moshirfar *et al*., 2019; Wang *et al*., 2019), but only one also included healthy children and adult groups (Huang *et al*., 2020).

The report by the International Myopia Institute (IMI) committee on Clinical Myopia Control Trials and Instrumentation (Wolffsohn *et al*., 2019) provided best practice guidelines to assess myopia control intervention efficacy and mechanisms, as well as treatment and instrumentation development. Refractive error and axial length were classified as primary outcome measures. The literature has already established the strong correlation between increased axial length and myopia progression (Atchison *et al*., 2004; Saw *et al*., 2005; Richter *et al*., 2017), where diurnal variations (Stone *et al*., 2004; Read *et al*., 2008; Chakraborty *et al*., 2011), intraocular pressure (Leydolt *et al*., 2008; Read *et al*., 2011), and accommodation changes (Drexler *et al*, 1998; Read *et al*., 2010) must be accounted for during measurements. This is especially important, since a 0.1 mm change in axial length leads to a refractive change of ~0.3 D (Findl *et al*., 2003). In comparison to early axial biometry via ultrasound instrumentation limited to a resolution of

~0.30 D (Santodomingo-Rubido *et al*., 2002), accuracy of ~0.1 mm (Olsen, 1989), and repeatability of 95% limits of agreement (LoA) between 60.2 to 60.3 mm (Rudnicka *et al*., 1992; Chan *et al*., 2006; Hussin *et al*., 2006), current commercial optical biometers offer resolution of ~0.03 D (Santodomingo-Rubido *et al*., 2002; Buckhurst *et al*., 2009), precision of ~0.01 mm (Drexler *et al*., 1998; Haigis *et al*., 2000; Santodomingo-Rubido *et al*., 2002), and repeatability of 95% LoA of 60.04 mm (Chan *et al*., 2006; Hussin *et al*., 2006). Furthermore, some relevant exploratory measures indentified by this IMI white paper included anterior segment anatomical changes and biomechanics. Axial elongation is well correlated with a flatter corneal curvature (Chang *et al*., 2001; Fledelius & Goldschmidt, 2010; Park *et al*., 2010), whilst various studies have reported a deeper ACD in myopic populations (Hosny *et al*., 2000; Ucakhan *et al*., 2008; Park *et al*., 2010), as well as greater vitreous chamber volume (Orucoglu *et al*., 2015; Kasahara *et al*., 2017; Zong *et al*., 2017). Also, an association between axial elongation and weakened biomechanical properties of the posterior sclera (Saka *et al*., 2013) has been reported.

Despite it being considered advantageous to be able to keep myopia control lenses in-situ, whilst performing measurements, in order to fully assess their demonstrated efficacy in exerting AL reduction (Walline et al., 2013; Lam et al., 2014; Chamberlain et al., 2019), studies by Lewis et al. 2008 (IOLMaster PCI; AL and K; undilated) and Ferrer-Blasco et al. 2019 (IOLMaster SS-OCT; AL, CCT, ACD, and K; undilated) noted clinically significant changes with biometry through CLs compared to the naked eye. Hence CLs need to be removed to assess ocular biometry. The only study to examine the effect of prior soft CL wear on (undilated) ocular biometry (Goudie et al. 2018), immediately after removing contact lenses and then after 2, 4 and 7 days of no contact lens use, concluding that any change in corneal shape did not significantly alter AL and K parameters. However, these were spherical lenses and lenses for myopia control have a more complex surface profile which could impact corneal topography and possibly axial length. Hence, this study investigated possible causes of these differences that may be attributed to the mentioned varying biometry technology, as well as the specialty optical dual focus and extended depth of focus designs (concentric ring design with alternating optical correction and treatment zones, simultaneously correcting the distance central myopia and exerting peripheral myopic defocus) of myopia control soft contact lenses (Ruiz-Pomeda *et al*., 2018; Chamberlain *et al*., 2019).

Thus, the clinical reliability of optical biometry instrumentation impacted by the post-wear of myopia control indicated soft contact lenses among healthy adults has not been previously investigated and warrants consideration towards improving myopia progression monitoring. The

purpose of this study was to evaluate the agreement between the IOLMaster 700 and IOLMaster 500 measurements in myopic eyes for axial length (AL), mean keratometry (Km), anterior chamber depth (ACD), and horizontal white-to-white (WTW) corneal diameter, after immediate MiSight and NaturalVue daily soft contact lens wear for myopia control, compared with a standard single vision Proclear lens.

5.2 Methods

5.2.1 Participants

The study (single-centre, prospective, randomised, and double-masked) was conducted at the Aston University Ophthalmic Research Clinics, where 18 participants with myopia in good overall general and ocular health were recruited. This sample size was enough to obtain 80% statistical power for a significance level of $\alpha = 0.05$ with a confidence level of 95%, based on an effect size of 0.8 for the statistical analyses used in this study, published literature, and priori power analysis (G*Power 3.1, University of Dusseldorf). All participants gave informed written consent. All procedures followed the Declaration of Helsinki and the protocol was approved by the Aston University Research Ethics Committee.

5.2.2 Study Lenses

Two investigators compared the interchangeability between the IOLMaster 700 and IOLMaster 500 for four measurement parameters (AL, Km, ACD, and WTW), after cycloplegia, and immediately following the removal of three different daily soft contact lenses (standard single vision Proclear® 1-Day [omafilcon A; hydrophilic; CooperVision, Inc.] for the control group, as well as MiSight® 1-Day [omafilcon A; hydrophilic, water content 60%; refractive index 1.40; CooperVision, Inc.; with center thickness of 0.08 mm at -3.00 D] and NaturalVue® 1-Day [etafilcon A; hydrophilic, water content 58%; refractive index 1.40; Visioneering Technologies, Inc.; with center thickness of 0.08 mm at -3.00 D] designed for myopia control for the test groups) via randomised coded letter (A, B, C) assignment (only the principal investigator had access to the lens assignments).

5.2.3 Study Design

Eligible participants visited twice on alternating days and in the same week, in order to implement a test group washout period in between, and so that each participant can be fitted with all three lenses. Participants were asked to attend for a morning visit (8:30 AM – 11:30 AM) and 8 hours later in the afternoon to allow for an adaptation period, mimic a typical work-day interval, and

consistency in diurnal variation. The two visits were each conducted by separate investigators, where the first investigator fitted the randomised contact lenses, whilst the second investigator performed the biometry measurements. The participants were unaware as to which lens and in which eye they were fitted during the visit.

During the morning visit, Investigator 1 provided a copy of the informed consent and participant information sheet; confirmed eligibility (age range 18-35; prescription range -0.75 D to -4.50 D with astigmatism ≤ 1 D; spectacle, contact lens, and myopia control intervention history; as well as no relevant contraindication; and medical and ocular health history, including medications); and performed autorefraction (3 measurements were taken from each eye, whilst the participant viewed a distance non-accommodative target [Grand Seiko WAM-5500; Grand Seiko Co., Hiroshima, Japan]), best-corrected distance visual acuity (logMAR letter chart), slit-lamp biomicroscopy anterior eye examination, and randomised contact lens fitting. During the afternoon visit, Investigator 2 verified the distance visual acuity (logMAR letter chart); removed the contact lenses; applied cycloplegia (complete details of the drops were provided along with official College of Optometrists leaflet; the British National Formulary (BNF) number, expiration date, and time of instillation were recorded [1% Tropicamide; 1 drop/eye; minimum 20-minute waiting period]); performed cycloplegic-IOLMaster 500 (Carl Zeiss Meditec, Germany) and -IOLMaster 700 (Carl Zeiss Meditec, Germany) measurements for AL, Km, ACD, and WTW (>2.0 signal:noise or SNR), slit-lamp biomicroscopy anterior eye examination with fluorescein assessment; and concluded with a verbal debrief.

5.2.4 Statistical Analyses

The IOLMaster 700 and IOLMaster 500 agreement was evaluated by using Bland-Altman plots, where analyses were made with two tailed *t* tests (AL, Km, ACD, and WTW values with $p<0.05$ were considered statistically significant) and 95% limits of agreement (LoA) as the mean difference ± 1.96 SD (narrow LoA was indicative of strong instrument interchangeability) in Microsoft Excel for Office 365 ProPlus (Microsoft Corp.). A Bland-Altman difference plot is a routinely used, standardised method of agreement analyses between quantitative measurements through the application of LoA. The normality of the data distributions was confirmed using the Kolmogorov-Smirnov test ($P>0.05$), enabling parametric statistical analyses.

5.3 Results

From the 18 subjects included in the study, the pool consisted of the following demographics: 15 women and 3 men (12 British Asian and 6 white European); mean age of 22.8 years ± 4.1 (range 18 to 35 years); mean spherical equivalent refraction (SER) of -2.4 ± 1.3 D (range -0.75 to -4.50 D); there were no adverse events.

5.3.1 Agreement

The mean difference and standard deviation, two tailed *t* test for the differences and their significance, and 95% confidence interval of lower and upper LoA based on ± 1.96 SD between the IOLMaster 700 and IOLMaster 500 for 4 parameters (AL = axial length; Km = mean keratometry; ACD = anterior chamber depth; WTW = horizontal [white-to-white] corneal diameter) are represented by **Tables 5.1-5.3** for a post-wear Proclear, MiSight, and NaturalVue lens. The mean difference ± SD WTW (mm) values taken by the newer IOLMaster 700 were statistically significant and had wide 95% LoA, when measured from the post-wear MiSight (-0.21 ± 0.23; -0.66. 0.24) and NaturalVue (-0.19 ± 0.41; -1.00. 0.62) daily soft contact lenses for myopia control test groups, compared with the IOLMaster 500 and post-wear standard single vision Proclear (-0.07 ± 0.49; -1.02. 0.89) lens control group. Bland-Altman plots (**Figures 5.1-5.12**) implied good comparison agreement for all other parameters between the two instruments (where those mean differences were not significantly different from zero and with narrow 95% confidence interval of limits of agreement) and may be used interchangeably. This study evaluated clinical / “real world” correlations and comparisons of agreement via *t* tests, *p* values, 95% LoA, and Bland-Altman plots, instead of assessing repeatability and reproducibility.

Parameter	**Mean Difference ± SD**	***P* Value***	**95% LoA**
AL (mm)	-0.004 ± 0.06	.25	-0.13. 0.12
Km (mm)	-0.01 ± 0.02	.78	-0.05. 0.03
ACD (mm)	-0.07 ± 0.05	0.13	-0.17. 0.03
WTW (mm)	-0.07 ± 0.49	0.12	-1.02. 0.89

Table 5.1. The reported post-wear Proclear lens mean difference and standard deviation, two tailed *t* test for the differences and their significance, and 95% confidence interval of lower and upper limits of agreement based on ± 1.96 SD between the IOLMaster 500 and IOLMaster 700; AL = axial length; Km = mean keratometry; ACD = anterior chamber depth; WTW = horizontal (white-to-white) corneal diameter.

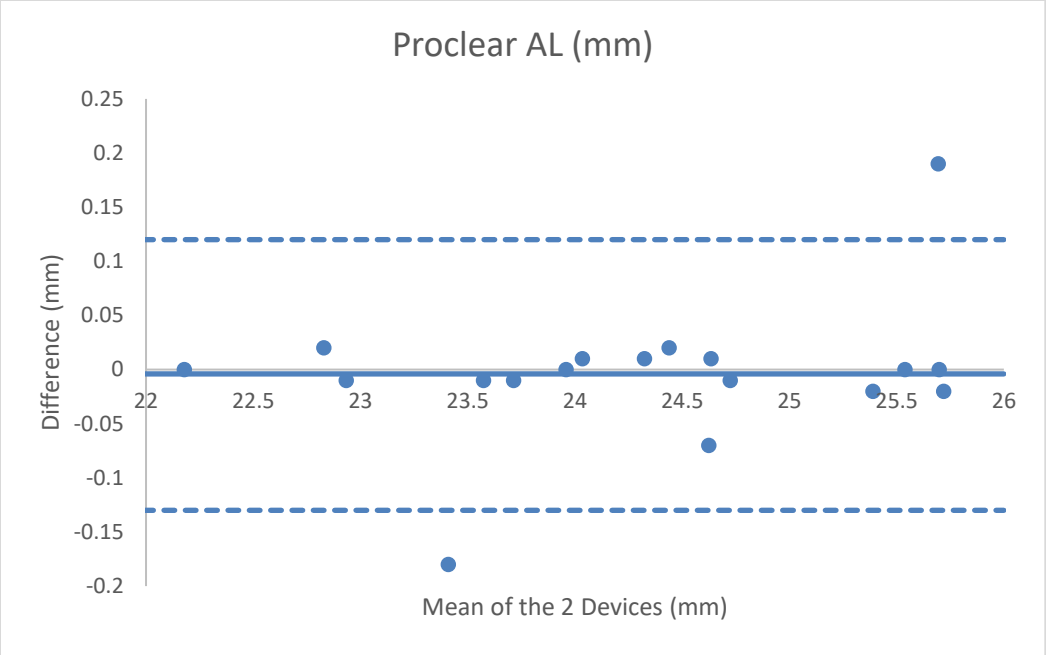

Figure 5.1. Bland-Altman plots for axial length comparison between the IOLMaster 500 and IOLMaster 700 with the post-wear Proclear lens. The mean difference is designated by the solid line. The 95% confidence interval of the upper and lower limits of agreement based on ± 1.96 SD are designated by the dotted lines.

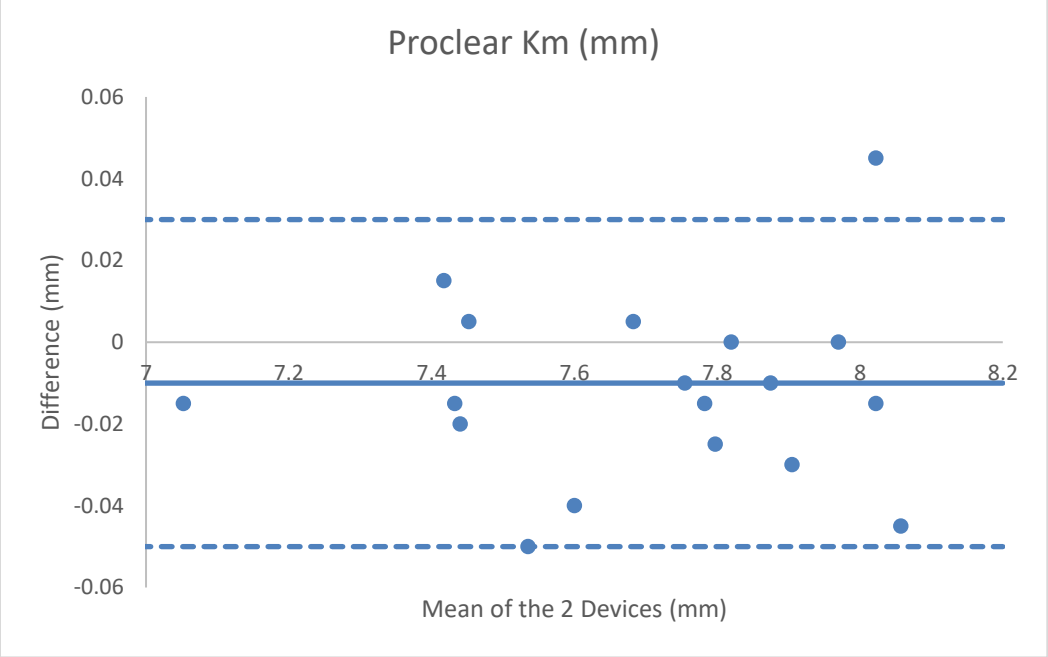

Figure 5.2. Bland-Altman plots for mean keratometry comparison between the IOLMaster 500 and IOLMaster 700 with the post-wear Proclear lens. The mean difference is designated by the solid line. The 95% confidence interval of the upper and lower limits of agreement based on ± 1.96 SD are designated by the dotted lines.

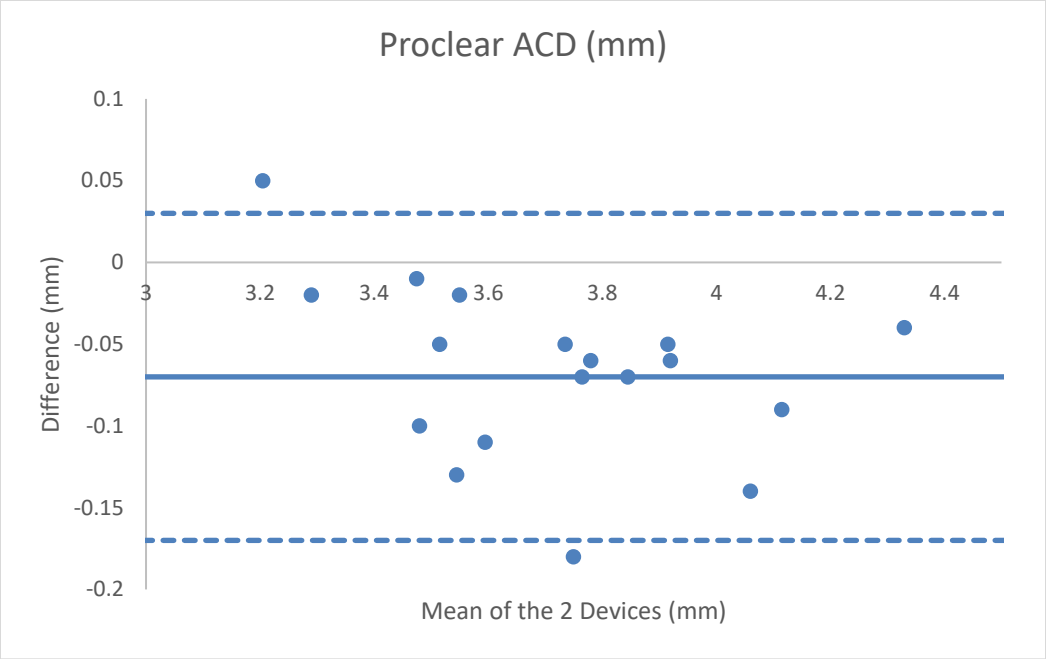

Figure 5.3. Bland-Altman plots for anterior chamber depth comparison between the IOLMaster 500 and IOLMaster 700 with the post-wear Proclear lens. The mean difference is designated by the solid line. The 95% confidence interval of the upper and lower limits of agreement based on ± 1.96 SD are designated by the dotted lines.

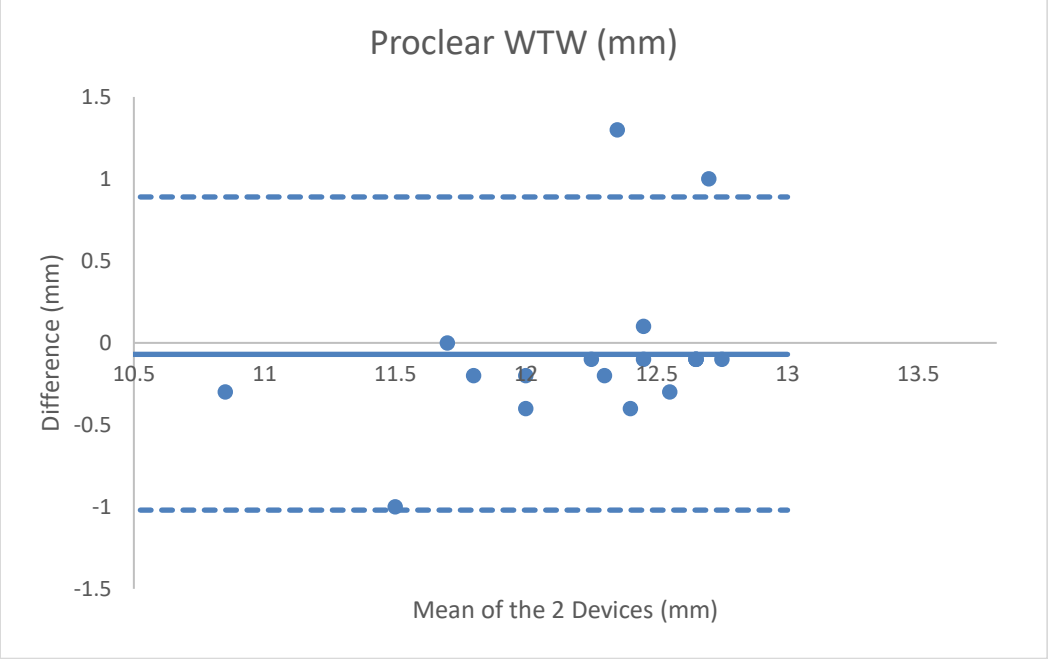

Figure 5.4. Bland-Altman plots for the horizontal (white-to-white) corneal diameter comparison between the IOLMaster 500 and IOL Master700 with the post-wear Proclear lens. The mean difference is designated by the solid line. The 95% confidence interval of the upper and lower limits of agreement based on ± 1.96 SD are designated by the dotted lines.

Parameter	Mean Difference ± SD	*P* Value	95% LoA
AL (mm)	-0.002 ± 0.02	.58	-0.05. 0.04
Km (mm)	-0.01 ± 0.02	.77	-0.05. 0.03
ACD (mm)	-0.07 ± 0.07	0.33	-0.2. 0.07
WTW (mm)	-0.21 ± 0.23	0.02*	-0.66. 0.24

Table 6.2. The reported post-wear MiSight lens mean difference and standard deviation, two tailed *t* test for the differences and their significance, and 95% confidence interval of lower and upper limits of agreement based on ± 1.96 SD between the IOLMaster 500 and IOLMaster 700; AL = axial length; Km = mean keratometry; ACD = anterior chamber depth; WTW = horizontal (white-to-white) corneal diameter; * = $p<0.05$.

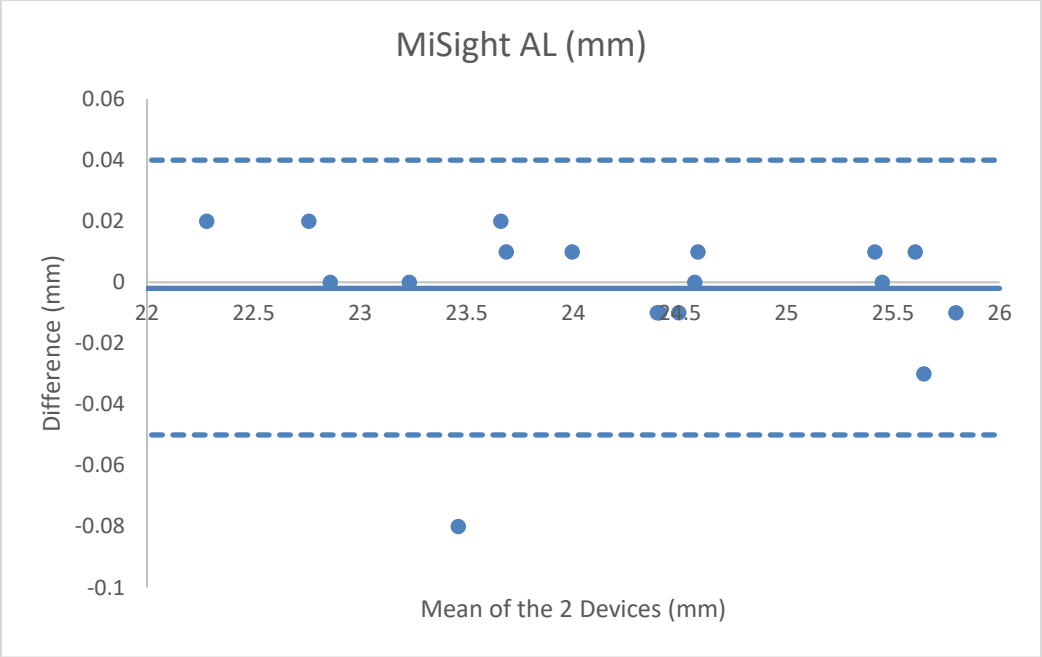

Figure 5.5. Bland-Altman plots for axial length comparison between the IOLMaster 500 and IOLMaster 700 with the post-wear MiSight lens. The mean difference is designated by the solid line. The 95% confidence interval of the upper and lower limits of agreement based on ± 1.96 SD are designated by the dotted lines.

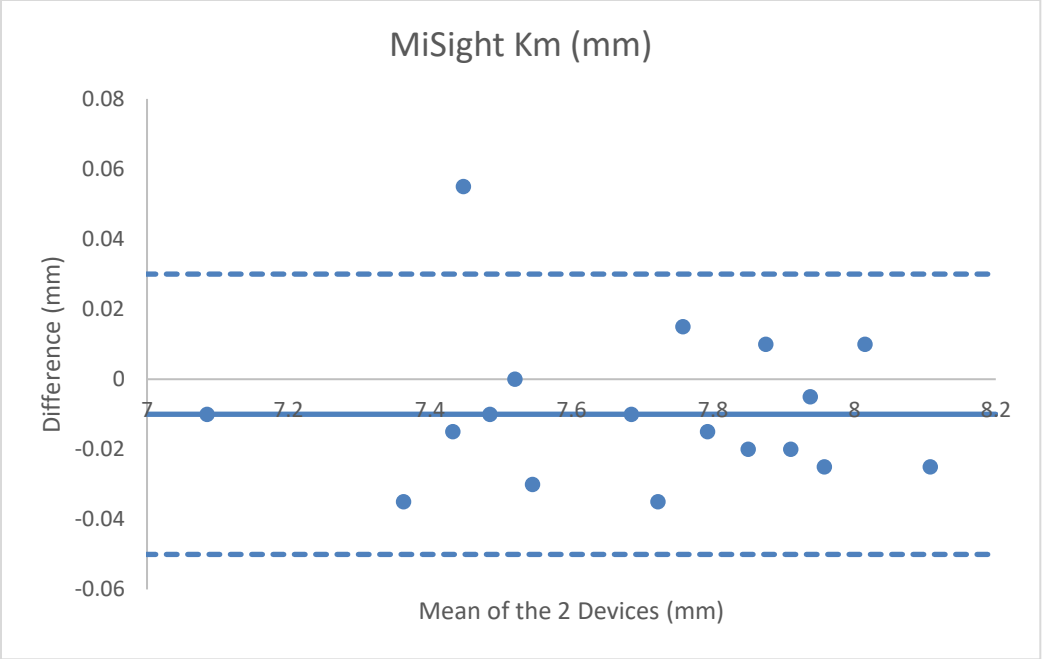

Figure 5.6. Bland-Altman plots for mean keratometry comparison between the IOLMaster 500 and IOLMaster 700 with the post-wear MiSight lens. The mean difference is designated by the solid line. The 95% confidence interval of the upper and lower limits of agreement based on ± 1.96 SD are designated by the dotted lines.

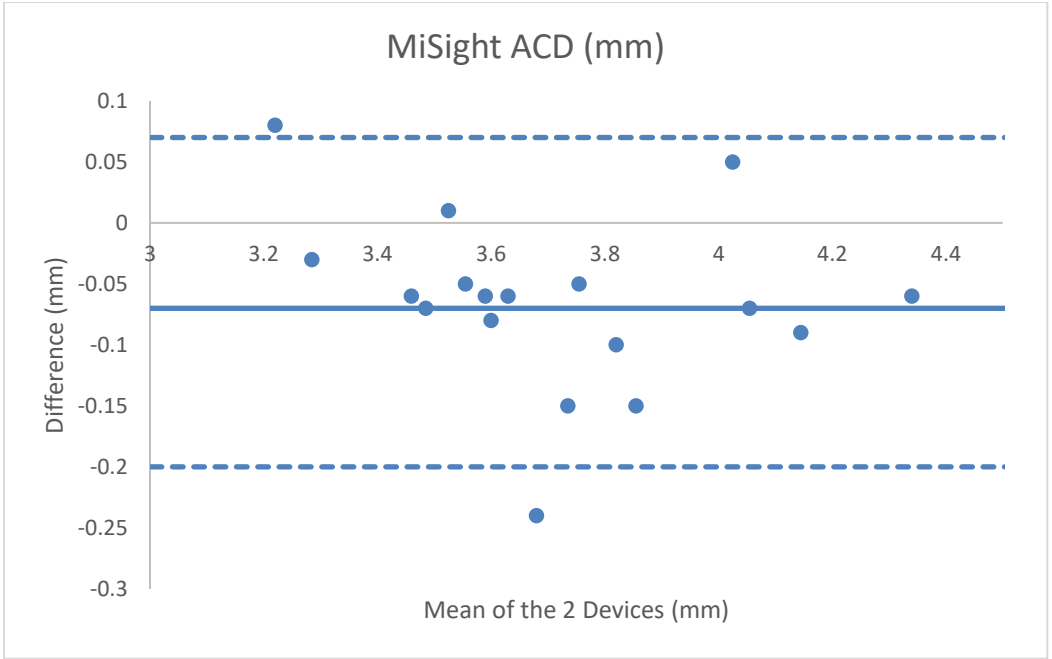

Figure 5.7. Bland-Altman plots for anterior chamber depth comparison between the IOLMaster 500 and IOLMaster 700 with the post-wear MiSight lens. The mean difference is designated by the solid line. The 95% confidence interval of the upper and lower limits of agreement based on ± 1.96 SD are designated by the dotted lines.

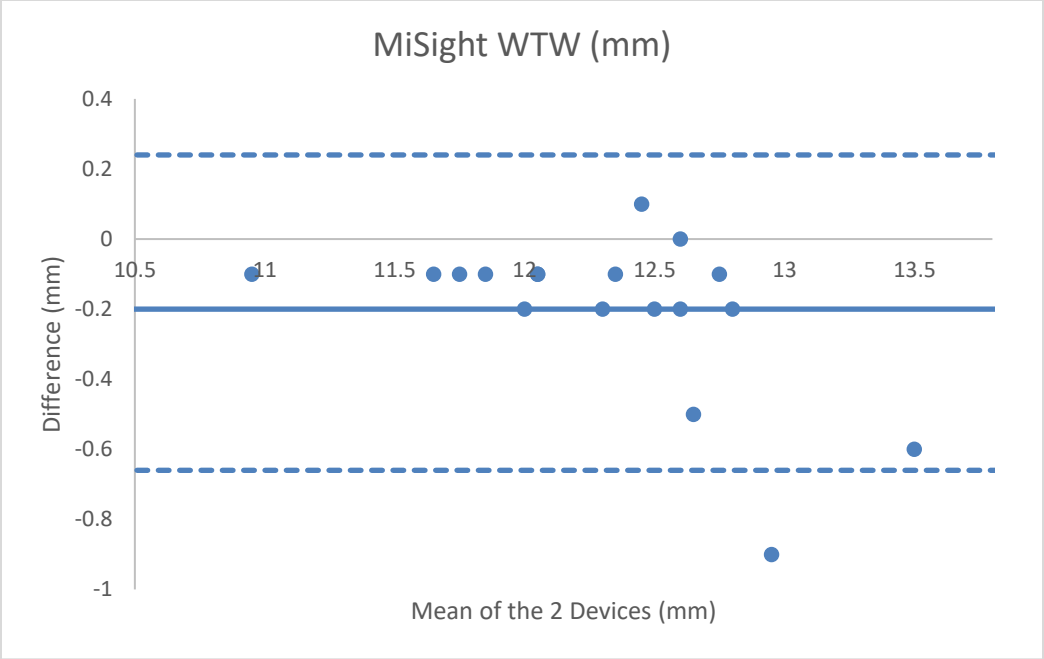

Figure 5.8. Bland-Altman plots for the horizontal (white-to-white) corneal diameter comparison between the IOLMaster 500 and IOLMaster 700 with the post-wear MiSight lens. The mean difference is designated by the solid line. The 95% confidence interval of the upper and lower limits of agreement based on ± 1.96 SD are designated by the dotted lines.

Parameter	Mean Difference ± SD	*P* Value	95% LoA
AL (mm)	0.004 ± 0.01	.09	-0.02. 0.02
Km (mm)	-0.02 ± 0.01	.39	-0.05. 0.01
ACD (mm)	-0.04 ± 0.06	0.06	-0.16. 0.08
WTW (mm)	-0.19 ± 0.41	0.01*	-1.00. 0.62

Table 5.3. The reported post-wear NaturalVue lens mean difference and standard deviation, two tailed *t* test for the differences and their significance, and 95% confidence interval of lower and upper limits of agreement based on ± 1.96 SD between the IOLMaster 500 and IOLMaster 700; AL = axial length; Km = mean keratometry; ACD = anterior chamber depth; WTW = horizontal (white-to-white) corneal diameter; * = $p<0.05$.

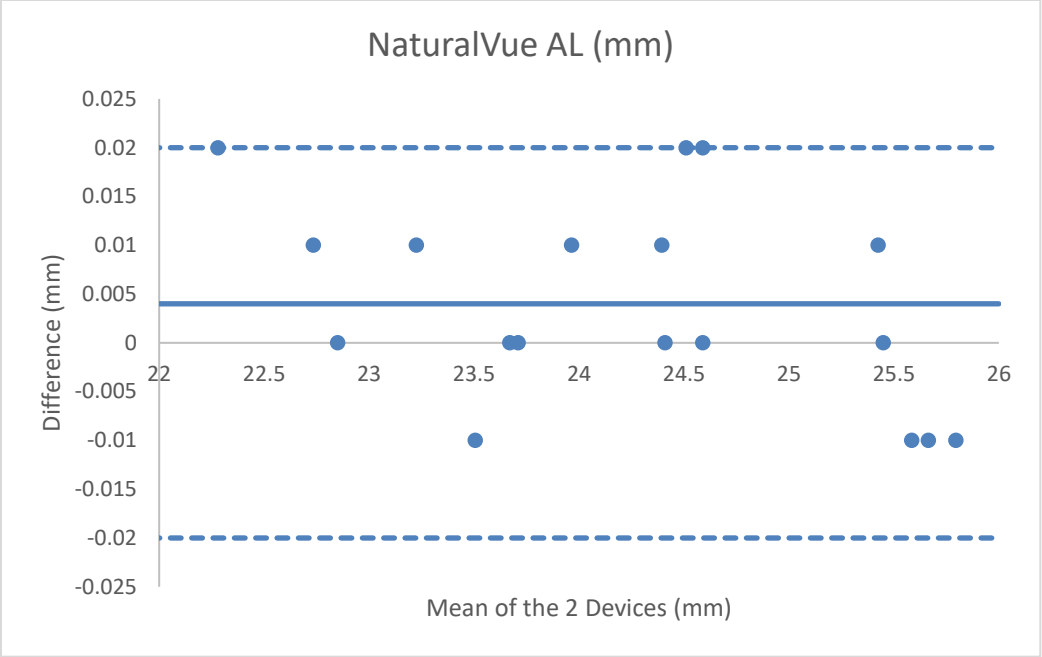

Figure 5.9. Bland-Altman plots for axial length comparison between the IOLMaster 500 and IOLMaster 700 with the post-wear NaturalVue lens. The mean difference is designated by the solid line. The 95% confidence interval of the upper and lower limits of agreement based on ± 1.96 SD are designated by the dotted lines.

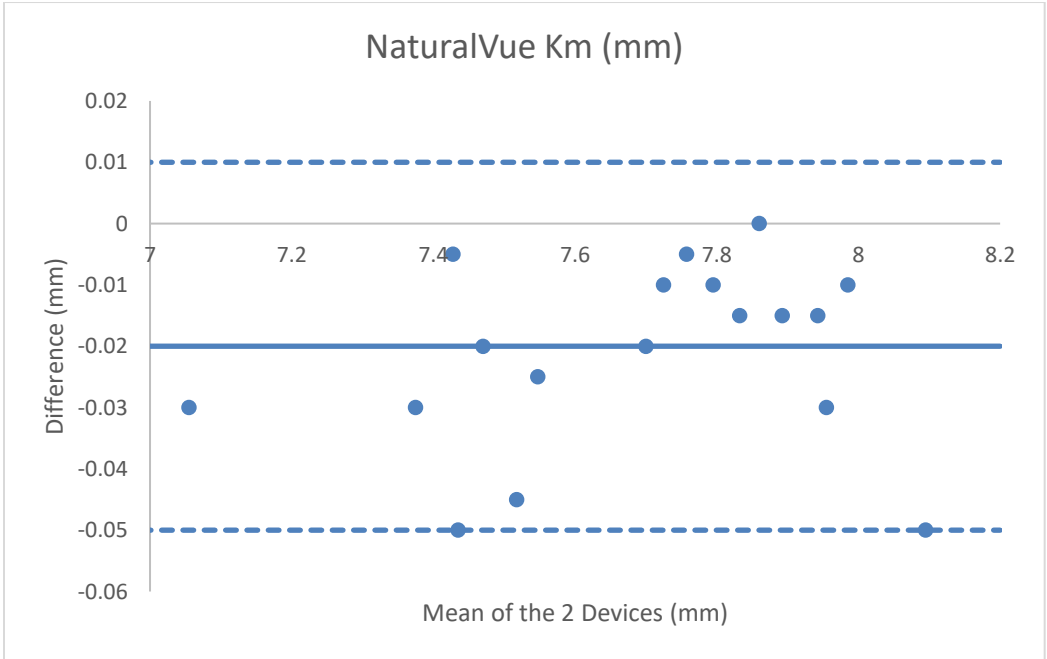

Figure 5.10. Bland-Altman plots for mean keratometry comparison between the IOLMaster 500 and IOLMaster 700 with the post-wear NaturalVue lens. The mean difference is designated by the solid line. The 95% confidence interval of the upper and lower limits of agreement based on ± 1.96 SD are designated by the dotted lines.

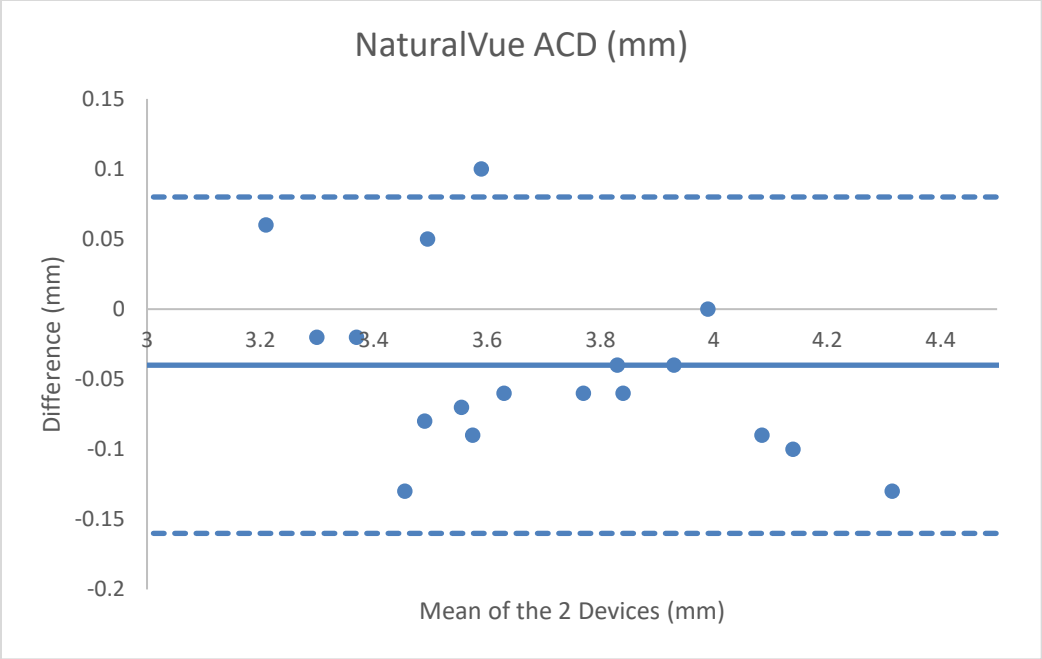

Figure 5.11. Bland-Altman plots for anterior chamber depth comparison between the IOLMaster 500 and IOLMaster 700 with the post-wear NaturalVue lens. The mean difference is designated by the solid line. The 95% confidence interval of the upper and lower limits of agreement based on ± 1.96 SD are designated by the dotted lines.

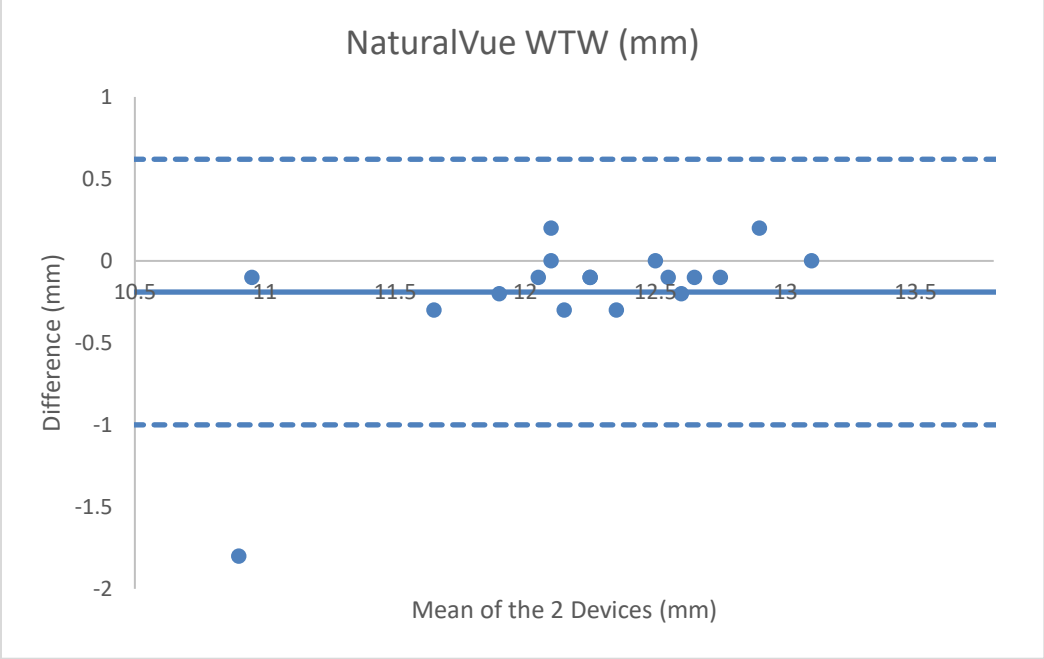

Figure 5.12. Bland-Altman plots for the horizontal (white-to-white) corneal diameter comparison between the IOLMaster 500 and IOLMaster 700 with the post-wear NaturalVue lens. The mean difference is designated by the solid line. The 95% confidence interval of the upper and lower limits of agreement based on ± 1.96 SD are designated by the dotted lines.

5.4 Discussion

This study evaluated the agreement between the IOLMaster 700 and IOLMaster 500 measurements in myopic eyes for axial length (AL), mean keratometry (Km), anterior chamber depth (ACD), and horizontal white-to-white (WTW) corneal diameter, after cycloplegia, immediately following the removal of three different daily soft contact lenses; standard single vision Proclear® 1-Day, as well as MiSight® 1-Day and NaturalVue® 1-Day designed for myopia control. This is considered the first study to investigate optical biometer instrument validation impacted by the post-wear of myopia control indicated soft contact lenses and specifically focused on the relative parameters.

The mean difference ± SD WTW (mm) values taken by the IOLMaster 700 with its SS-OCT technology were statistically significant and had wide 95% LoA, when measured from the post-wear MiSight (-0.21 ± 0.23; -0.66. 0.24) and NaturalVue (-0.19 ± 0.41; -1.00. 0.62) contact lenses, compared with the IOLMaster 500 and post-wear standard Proclear lens (-0.07 ± 0.49; -1.02. 0.89). However, the discrepancy in WTW values between the IOLMaster 700 and IOLMaster 500 with the post-wear MiSight and NaturalVue contact lenses alone were minimal and clinically irrelevant, implying agreement. Bland-Altman plots suggested good comparison agreement for all other parameters (AL, Km, ACD) between the two instruments, across all post-wear contact lenses used, and may be used interchangeably. These WTW differences may be attributed to the overall varying technology in measurement, as previously suggested by Cho *et al*. (2018) in their comparison of the IOLMaster 700 with the Galilei G4 from cataract eyes, or the PCI with the Tomey OA-2000 using SS-OCT in healthy adults (Huang *et al*., 2017; Hua *et al*., 2018) and the AL-Scan in cataract eyes (Huang *et al*., 2014), stating the impact of grey-scale image processing discrepancies and limbus detection sensitivity by any imposed darkness (device / eyelash / nose shadow), as possible causes. In addition to cataract patients, the only other evaluation of confirmed biometric measurement reliability with the IOLMaster 700 using SS-OCT, relative to the IOLMaster 500, as well as also including healthy adults and the WTW parameter is by Huang *et al*. (2020). The authors consistently noted excellent repeatability and reproducibility between the two devices for all parameters (AL, Km, ACD) in all three groups, besides WTW values among cataract patients (corneal arcus was reported to result in dimmer central boundaries).

Lewis *et al*. (2008) previously validated the IOLMaster's PCI repeatability and reliability for AL and Km in healthy myopic eyes fitted with soft contact lenses of -0.50 D (cast-molded So*f*Lens38 [polymacon; hydrophilic, water content 38%; refractive index 1.43; Bausch & Lomb;

with center thickness of 0.035 mm] and the soft-molded Acuvue2 [etafilcon A; hydrophilic, water content 58%; refractive index 1.40; Johnson & Johnson; with center thickness of 0.119 mm]), relative to the naked eye. The study was interested in the possible coupling of soft contact lenses (as ideal optical interfaces) with PCI biometry in patients with corneal irregularities, inadequate fixation, and severe cataracts, before and after cataract surgery and Descemet's stripping with endothelial keratoplasty (DSEK), which otherwise leads to unpredictable measurements. The authors noted the corresponding increased AL measures, as well as associated change in precorneal tear layer and central corneal thicknesses (which were correlated with the K differences), with the contact lens manufacturing method, thickness and higher water-content attributes. A different and more recent study by Goudie *et al*. (2018) investigated the effect of the specific cessation duration of soft contact lenses on IOLMaster biometry, concluding that any change in corneal shape did not significantly alter AL and K parameters. The only evaluation of confirmed biometric measurement reliability with the IOLMaster 700 using SS-OCT on eyes with soft contact lenses (hilafilcon B; hydrophilic, water content 59%; refractive index 1.40) was by Ferrer-Blasco *et al*. (2019), performed only on eight subjects with healthy eyes. This study was interested in the interaction of soft contact lenses with OCT biometry measurements, as a prelude to the use of specialty therapeutic (ocular drug delivery) or bandage (corneal epithelial healing) contact lenses, when not removed for assessments. Although there was no reported LT difference between soft contact lens wear and the naked eye (where contact lenses of varying optical powers may impose specific accommodation requirements in eyes without cycloplegia and possibly result in LT differences), increased changes in AL, CCT, ACD, and K were statistically significant, which the authors attributed to the individual contact lens thickness and optical design discrepancies, as described earlier by Lewis *et al*. (2008). This study is of particular interest regarding any future biometry evaluation with myopia control indicated soft contact lenses in-situ and assessing the possible impact on the crystalline lens, considering MiSight and NaturalVue are of similar material, water content, and refractive index.

Previous studies involving IOLMaster validation have noted the following: a significantly flatter Km from the RK-F1 AutoRef-Keratometer in children of age 6 (Huynh *et al*., 2006) and the Lenstar OLCR assessed on cataract eyes (Chen *et al*., 2011) relative to the IOLMaster; interchangeable agreement in K and ACD values between the Lenstar OLCR, IOLMaster, and an A-scan ultrasonographer (Salouti *et al*., 2011); high repeatability, reproducibility, and agreement for corneal power from a comprehensive assessment of 8 devices (Wang *et al*.,

2012), as well as when comparing the Keratograph 4, Pentacam HR, and IOLMaster (Mao *et al*., 2013), and the OphthaTOP, Pentacam HR, and IOLMaster (Huang *et al*., 2015) in normal eyes, without clinically significant differences. Mehravaran *et al*. (2014) compared the keratometry repeatability and agreement of the previous gold standard manual Javal keratometer with the IOLMaster, Pentacam, Topcon, and EyeSys instruments, stating that the IOLMaster had the best repeatability for minimum and maximum keratometry measurements. Other studies have further noted the IOLMaster's accuracy and reliability for IOL power calculation in regular cataract patients (Olsen, 2007; Hsieh & Wang, 2012), as well as those also having high myopia (Roessler *et al*., 2012), although difficulty with abnormal eyes has been previously reported (Freeman & Pesudovs, 2005; McAlinden *et al*., 2015). Moreover, a comprehensive literature review by Dominguez-Vicent *et al*. (2016), specified device interchangeability for measuring ACD and WTW in healthy eyes among the following: A-scan ultrasound, Orbscan and Orbscan II, Pentacam and Pentacam HR, Galilei, Visante OCT, IOLMaster, and Lenstar LS 900.

Regarding studies specifically investigating the interchangeability, repeatability, and reproducibility of the IOLMaster 700 and IOLMaster 500, Akman *et al*. (2016) did so by comparing AL, ACD, K, and failure rate measurements on cataract eyes, reporting excellent agreement, but significantly higher acquisition rate via the IOLMaster 700's SS-OCT technology; which was able to overcome the IOLMaster 500's PCI limitations, particularly in groups with advanced cataracts. In a prospective, multi-centre study on elderly patients undergoing cataract surgery, Kunert et al. (2016) noted a high repeatability between the IOLMaster 700 and IOLMaster 500 for AL, ACD, and spherical equivalent (SE), and for CCT and LT with the Lenstar OLCR. Cho *et al*. (2018) evaluated the agreement in cataract eyes between the IOLMaster 700 and IOLMaster 500, A-scan for AL; and Galilei G4, A-scan for ACD; and Galilei G4 for WTW; and Galilei G4, manual keratometer, automated refractor for Km. The study also concluded a higher acquisition rate over the IOLMaster 500, as well as outstanding agreement for AL and Km; for ACD between the IOLMaster 700 and Galilei G4, but poor correlation for the A-scan with either instrument; and no interchangeability with the Galilei G4 for WTW. However, Yang *et al*. (2017) found a longer AL from the IOLMaster 700 compared to the IOLMaster 500 in myopic eyes, emphasising its greater precision in patients with posterior staphyloma of good fixation status. The overall literature comparing the IOLMaster 700 and IOLMaster 500 is limited, particularly outside of cataract populations, but these authors suggested AL

discrepancies may be due to fixation loss, which is not necessarily evaluated by the IOLMaster 500.

Therefore, this study's firstly comparative evaluation also confirmed good clinical agreement between the IOLMaster 700 and IOLMaster 500 for AL, Km, ACD, and WTW measured on the myopic eyes of healthy adults, following daily soft contact lens (standard and specialty for myopia control) post-wear, with separate results consistent with the previous relative literature.

Chapter 6 Are soft contact lenses a viable source for human dopamine levels measurement using the ELISA dopamine kit?

6.1 Introduction

Myopia has been well established as a worldwide epidemic and high myopia (≥6 D or axial length ≥26 mm) is one of the leading causes of global blindness (Holden *et al*., 2016). Although optical myopia may be corrected by optical and surgical interventions, high myopia still is not completely preventable or treatable (Bosch-Morell *et al*., 2015). The International Myopia Institute (IMI) – Myopia Genetics Report (Tedja *et al*., 2019) confirmed refractive error and myopia predisposition is due to both genetics and environmental risk factors (near work and outdoor exposure; specifically education holding most prominence), as well as a light-processing retina-to-sclera molecular mechanism for common myopia development. A key meta-analysis and systemic review by Xiong *et al*. (2017), also noted increased time outdoors to be effective in preventing myopia onset and slowing the myopic shift, but not in controlling progression. French *et al*. (2013) previously suggested that the preventative mechanism of increased outdoor activity is related to reduced accommodative demand, bigger depth of focus, improved contrast, higher levels of Vitamin D (Mutti & Marks, 2011; Choi *et al*., 2014; Tideman *et al*., 2016a) and retinal dopamine acting against form-deprivation myopia. However, the mechanisms behind these protective effects remain unresolved, which may be vital to slowing childhood myopia progression and lead to more proficient clinical management.

The dopamine (DA) retinal neurotransmitter is part of the signalling cascade that regulates eye growth (Feldkaemper & Schaeffel, 2013), where its increased levels during the day and with higher light intensity have been shown to inhibit axial elongation upon emmetropisation (Nebbioso *et al*., 2014), and has been recognised to be critical for light adaptation and preventing myopia (Teves *et al*., 2014). Although human DA levels could be measured from biological fluids such as blood plasma, cerebrospinal fluid (CSF) and urine (Suominen *et al*., 2013), tear fluid sample extraction through the commonly used Schirmer strips and capillary tubes (Dumortier & Chaumeil, 2004; Shetty *et al*., 2016; Shetty *et al*., 2017) has been preferred for its non-invasive nature (Sharma *et al*., 2019). This is especially beneficial to longitudinal studies with pediatric patients, where compliance is of paramount importance. However, comparative investigation of the non-invasive Schirmer strip and capillary tube sampling techniques for human tear fluid has been mixed. Capillary tube collection was perceived as less invasive, since Schirmer strips have been reported to induce irritation and further reflex tear secretion (Choy *et al*., 2001), as well as damage conjunctival cells (van Setten *et al*., 1990), which may all affect the true tear concentrations. On the other hand, the Schirmer strip

technique was reported to be quick, simple, and precise (Small *et al*., 2000), whilst the capillary tube extraction was more aggressive and irritable, posing a higher injury risk. More recently, Posa *et al*. (2012) concluded that the difference of tears from Schirmer strips containing higher protein composition was minimal, and although both methods were efficient and suitable for non-invasive human tear fluid analysis, Schirmer strips were quicker, simpler, and perceived as having a more pleasant sensation by patients.

The proteins found in human tear fluid have long been identified as non-invasive biomarkers for numerous conditions (Hagan *et al*., 2016), including cancers (Evans *et al*., 2001) and diabetes (Herber *et al*., 2001), as well as eye-specific pathologies (blepharitis [Koo *et al*., 2005]; allergic conjunctivitis [Li *et al*., 2010]; keratoconus [Acera *et al*., 2011]; and pterygium [Zhou *et al*., 2009] among others). Likewise, abnormal DA levels have been linked to Parkinson's (Dirkx *et al*., 2017); Alzheimer's (Yates *et al*., 1979); schizophrenia (Brisch *et al*., 2014); epilepsy (Starr, 1996); and various ocular diseases (myopia [Feldkaemper & Schaeffel, 2013]; glaucoma [Bucolo *et al*., 2018]; and dry eye [Lemon & Shah, 2013]. Research on DA detection from human tears is scarce (Van Haeringen, 1981; Trope & Rumley, 1984; Sharma *et al*., 2019) and only that by Sharma *et al*. (2019) has evaluated the use of the direct competitive chemiluminescent enzyme-linked immunosorbent assay (ELISA; [Cloud Clone Corp, TX, USA]) dopamine kit, as an alternative quantification method. Soft multifocal contact lenses have been successful to reduce myopia and axial length progression in children and young adults via peripheral defocus (Walline *et al*., 2013; Lam *et al*., 2014; Chamberlain *et al*., 2019). Willcox (2019) summarised the literature showing the many tear film proteins adsorbing on contact lenses, which varied with the material (Saville *et al*., 2010; Babaei *et al*., 2011; Brown *et al*., 2013), patient (Omali *et al*., 2013), modality (Willcox *et al*., 2002), as well as whether a disinfectant was used or if there were other proteins (Chao *et al*., 2019). Moreover, Willcox (2019) noted that besides fibronectin, phospholipids, secretory immunoglobulin A, and cholesterol, tear film biochemistry was not affected by contact lens wear.

Thus, the purpose of this study was to (1) assess the viability of daily soft contact lenses (MiSight and NaturalVue for myopia control, as well as a standard single vision Proclear lens) to be used as a non-invasive vehicle for DA measurements in human tears and (2) optimise the ELISA-based dopamine kit methodology for ex vivo lenses and future applications, since the effect of other tear components on the DA assay has yet to be determined. This exploratory/pilot study is considered the first of its kind – investigating the potential for an additional non-

invasive, efficient, and reliable tool to monitor local DA status, which may become an integral early diagnostic clinical component in the fight against myopia.

6.2 Methods

6.2.1 Participants

This exploratory/pilot study (single-centre, prospective, randomised, and double-masked) was conducted at the Aston University Ophthalmic Research Clinics, where 18 participants with myopia in good overall general and ocular health were recruited. This sample size was enough to obtain 80% statistical power for a significance level of $\alpha = 0.05$ with a confidence level of 95%, based on an effect size of 0.8 for the statistical analyses used in this study, published literature, and priori power analysis (G*Power 3.1, University of Dusseldorf). All participants gave informed written consent. All procedures followed the Declaration of Helsinki and the protocol was approved by the Aston University Research Ethics Committee.

6.2.2 Study Lenses

The three different daily soft contact lenses used in this study were: standard single vision Proclear® 1-Day (CooperVision, Inc.), as well as MiSight® 1-Day (CooperVision, Inc.) and NaturalVue® 1-Day (Visioneering Technologies, Inc.) designed for myopia control. These lenses were randomised via coded letter (A, B, C) assignment (only the principal investigator had access to the lens assignments). Equal unworn number of these lenses were used as the control sample group.

6.2.3 Study Design

Eligible participants were asked to attend for a morning visit (8:30 AM – 11:30 AM) and 8 hours later in the afternoon to allow for an adaptation period, mimic a typical work-day interval, and consistency in diurnal variation. The first investigator fitted the randomised contact lenses in the morning and removed these 8 hours later. The lenses were then stored in random order, in a beaker that was either dry, or instilled with a saline solution just fully covering the lens. The beakers were sealed, labelled, and transferred to the Biomaterials Research Unit (BRU) within 48 hours for tear sample analysis by a second investigator; the fluid envelop and ocular species associated with each lens on removal allows analysis of tear proteins and lipids, without tear fluid stimulation. The participants were unaware as to which lens and in which eye they were fitted during the visit.

6.2.4 Measurement of tear dopamine

Total dopamine levels in the tear fluid from the lenses were quantified using a direct competitive chemiluminescent enzyme-linked immunosorbent assay (ELISA) dopamine kit.

The methodology sequence was: (1) lens removed from eye; (2) tear fluid (envelop) extracted into phosphate-buffered saline (PBS) solution in a sterile 1.5 ml microcentrifuge tube at 4°C for 1.5 hours; (3) the tear extract in saline was quantified using an ELISA dopamine kit (ENZO Life Sciences) where positive results were shown as blue colouration (each plate has 96 wells, where the first 16 are used to create the standard curve); (4) plate read in spectrometer (SpectraMax 2; Molecular Devices Corp., CA, USA), where each sample was run in duplicate with each well read 9 times; (5) averaged absorbance values for the samples converted to concentrations using the standard curve (This study used 3 plates in total).

6.2.5 Statistical Analyses

The data was reported as means and standard deviations, or as median with the corresponding range. $P<0.05$ was considered of statistical significance.

6.3 Results

From the 18 subjects included in the study, the pool consisted of the following demographics: 15 women and 3 men (12 British Asian and 6 white European); mean age of 22.8 years ± 4.1 (range 18 to 35 years); mean spherical equivalent refraction (SER) of -2.4 ± 1.3 D (range -0.75 to -4.50 D); there were no adverse events.

6.3.1 Tear dopamine levels

The tear DA level (**Table 6.1**) extracted from Plate 1 was 354.1 ± 49.3 pg/ml (mean ± SEM) with a value range of 268.9 and 484.8 pg/ml (median, 333.3 pg/ml). In comparison, this was lower than Plates 2 & 3 with a DA level of 485.8 ± 44.6 pg/ml (mean ± SEM), and a value range of 415 and 569.1 pg/ml (median, 477 pg/ml). Thus, **Table 6.1** showed the collection variation between the three plates, prior continued standardisation, where collections for Plates 2 & 3 were better controlled, despite being comparative to previous studies using Schirmer strips and capillary tubes.

			Literature values	
	Initial Set (Plate 1)	**Subsequent Set (Standardised Plates 2 & 3)**	**Schirmer**	**Capillary**
Mean	354.1	485.8	279	470.4
Min	268.9	415	152	254.7
Max	484.8	569.1	519.1	845.0
Median	333.3	477	273.2	428.4
SD	± 49.3	± 44.6	± 14.8	± 37.6

Table 6.1. Comparison of tear DA levels (pg/ml), as well as comparative Schirmer strip and capillary tube values from Sharma *et al*. (2019).

Table 6.2 showed the differences between the daily soft contact lenses used in the current study, reflecting the results obtained only from the standardised set (Plates 2 & 3). Proclear DA was 491.5 ± 48.1 pg/ml (mean ± SEM) with a value range of 415 and 569.2 pg/ml (median, 479.2 pg/ml); MiSight DA was 482.5 ± 47.2 pg/ml (mean ± SEM) with a value range of 415.2 and 547.4 pg/ml (median, 470.2 pg/ml); NaturalVue DA was 488.5 ± 42.9 pg/ml (mean ± SEM) with a value range of 405.5 and 556.9 pg/ml (median, 486.4 pg/ml). Thus, similar DA levels were obtained, irrespective of the contact lens type, suggesting lens material was not a factor.

	Proclear	**MiSight**	**NaturalVue**
Mean	491.5	482.5	488.5
Min	415	415.2	405.5
Max	569.2	547.4	556.9
Median	479.2	470.2	486.4
SD	± 48.1	± 47.2	± 42.9

Table 6.2. Comparison of tear DA levels (pg/ml) between the different contact lenses extracted from Plates 2 & 3.

6.4 Discussion

Although the DA values were within the range reported by the only other recent study (Sharma *et al*., 2019) with human tears DA values using ELISA, the recovery rate from the Schirmer strips was less, emphasising one of the indications for contact lenses being used as a probe to remove the tear envelope. Sharma *et al*. (2019) further noted that the tear DA level from both Schirmer strips and capillary tubes was significantly higher relative to plasma fluids, specifically stated as 3.9 ± 0.84 (mean ± SEM) and 6.2 ± 0.85 (mean ± SEM) fold higher respectively.

Additionally, the authors showed 80% of the subjects had >1.2 fold higher tear DA levels from the capillary tubes, relative to the Schirmer strips.

DA measured from plasma and urine has been originally implemented by high-performance liquid chromatography (HPLC) with fluorescence (Peaston & Weinkove, 2004; Tsunoda, 2006; Pussard *et al*., 2009). A study by Nichkova *et al*. (2013) on the validation of a competitive ELISA for urinary DA samples did report high specificity, good precision, reliability and efficiency for the analysis and monitoring of a pathological DA system such as Parkinson's disease, which was well-correlated to liquid chromatography tandem mass spectrometry (LC-MS/MS; the more recently preferred method [Kushnir *et al*., 2002; de Jong *et al*., 2011; Moriarty *et al*., 2011]). Although immunoassays have been considered being more efficient than LC-MS/MS, research has reported on associated drawbacks when applied to biological fluids, such as an oxidising tendency, specific antibody requirement, and low physiological concentrations (Peaston & Weinkove, 2004; Kim *et al*., 2008, 2010). Furthermore, You *et al*. (2015) compared the quantification of human tear lactoferrin between ELISA and multiple reaction monitoring (MRM) mass spectrometry in prostate cancer patients, noting that despite tear fluid analysis being limited by the small available tear volumes of ≤10 µl, the amounts of lactoferrin were comparable to the published literature. A previous study examining the tear film in patients with keratoconus with a capillary tube and specific ELISAs concluded that the differences in tear proteomics had no correlation with age, gender, or contact lens wear (Balasubramanian *et al*., 2012).

Therefore, data from this exploratory/pilot study informed the following: (1) daily soft contact lenses proved to be viable non-invasive tear envelope sampling vehicles for human DA detection; (2) lens type was not a factor, as the detected DA levels were well correlated for all contact lenses used in this study; (3) ELISA successfully detected DA; (4) values were similar to those reported previously from tears obtained with Schirmer's strips and capillary tubes, but throughout the wear period.

Chapter 7 Conclusions

This thesis explored novelty utilization methods of some of the latest myopia control strategies available with a scope on assessing and managing the individual short-sighted patient.

Despite the negative worldwide myopia outlook, as well as the notable escalation of practitioner concern and treatment activity, the global trends survey showed that appropriate management and standardisation remain poor. Moreover, treatment is not implemented early enough, whilst practitioner education and access to regulated myopia control options are still inadequate. The following research chapters probed the viability of such “labelled” and/or gold standard medical device and instrumentation options towards their application in individual patient treatment.

For instance, percentile growth curves and charts demonstrated that there may be a clinically manifesting myopia-related near phoria control target across the human lifespan, including possible associated differences in sex and within progressive myopes. This study intended to better understand myopia prediction and its progression by suggesting that the near phoria risk factor should be measured alongside other primary outcome parameters important for individual treatment efficacy.

In studying the only daily CE-marked optical myopia control strategies, it was evident that MiSight and NaturalVue MFSCLs achieved myopic retinal defocus differently. These findings may be extended to comparisons of all concentric and peripheral gradient contact lens types, suggesting that except for the possibility of a causal effect by these factors with NaturalVue, reduced hyperopic blur and accommodative lag appeared only to be byproducts of the optical design in other contact lenses influencing myopia progression. The optical design of multifocal contact lenses also directly influenced visual quality and although glare was significantly impacted, contrast sensitivity, treatment compliance and quality of life expectations were undeterred.

The evaluation of the agreement between the gold standard optical biometers investigated the impact by the post-wear of myopia control indicated soft contact lenses, after cycloplegia. Findings reported good interchangeability for all other parameters (AL, Km, ACD) between the two instruments, where WTW differences were attributed to the overall varying technology in measurement, as well as the impact of grey-scale image processing discrepancies and limbus detection sensitivity by any imposed darkness. The overall literature comparing the IOLMaster

700 and IOLMaster 500 is limited in myopic populations. Thus, this study should be of particular interest regarding any future biometry evaluation with myopia control indicated soft contact lenses in-situ and assessing the possible impact on the crystalline lens.

The exploratory/pilot study informed that daily soft contact lenses are viable non-invasive tear envelope sampling vehicles for human DA detection. This suggested that practitioners may have an additional tool to monitor local DA status, which may become an integral early diagnostic clinical component in the fight against myopia.

This thesis intended to contribute to the growing innovative developments in the field of myopia. The IMI white papers should be used in conjunction by all professionals interested in this topic. The global myopia problem is not going anywhere and such efforts at dissecting the individual utility potential by each control strategy must be pursued.

7.1 Limitations & Future Direction

7.1.2 Global trends in myopia management attitudes and strategies in clinical practice – 2019 update

Future similar studies should note the many strengths (cheap, practical, quick, simple, scalable, standardised, anonymous, valid, reliable) and limitations (room for dishonesty, allows user interpretation, accessibility constraints, response fatigue) of online questionnaires, as a methodology.

7.1.3 Clinical myopia-related near phoria magnitude and variability across the human lifespan among Canadians

Like Chen *et al*. (2016), the attributes in this exploratory study were specific to the examined cross-sectional WatES database. Future efforts should implement equal sample sizes for all groups; ethnicity and prevalence levels towards international validation and translation; data for ages before 10; further centiles (2nd, 5th, 10th, 25th, 75th, 90th, 95th, and 98th); receiver operating characteristic (ROC) analysis for model validation by including sensitivity and specificity, as well as positive predictive value (PPV) diagnostic testing of the near phoria percentile curves. Additional consideration of risk factors such as optical biometry (Jones *et al*., 2005; Tideman *et al*., 2018; Diez *et al*., 2019; Rozema *et al*., 2019), near work activity (Rose *et al*., 2008; French *et al*., 2013), genetics (parental myopic history [Negrel *et al*., 2000; Baird *et al*. 2010]) and environmental (Rose *et al*., 2008; Morgan *et al*., 2018) into the model is also

warranted. It would be of value to make future comparisons to the myopic SER reversal in the late 20s reported by various studies (Irving *et al*., 2019).

7.1.4 Impact of blur from a dual focus and an extended depth of focus contact lens

Limitations from this study, regarding the measure of peripheral refraction and accommodative lag stem from the cohort (young adults and not children) and the use of the Grand Seiko WAM-5500, which is affected by the contact lens optical design. Future studies should consider the following: other lens designs and of different powers; peripheral defocus effects in other retinal locations; disability glare and dysphotopsia under further conditions; varying contact lens wear periods to understand the natural time course of such parameter changes; richer demographics for a better balance between the sexes, ethnicities, age groups, and eyes of varying complexity and severity; inclusion of subjects with binocular vision ailments; adding fixation status, ocular alignment, or lens decentration as stand-alone parameters; the implementation of a multi-centre, longitudinal clinical trial.

7.1.5 IOLMaster agreement evaluation in healthy adults, comparing ocular biometry measurements, after immediate soft contact lens wear for myopia control

Sources of analysis variability consisted of the following: the timing of post-lens wear measurements was not standardised and future studies should measure exactly the time between lens removal and parameter measurement.

Future instrument validation studies on the IOLMaster 700 may consider the following: a follow-up study with peripheral off-axis measurements and the plausible inquiry into the effect of varying contact lens cessation periods; study the comparison with myopia control soft contact lenses in-situ to assess the possible impact on off-axis measurements, crystalline lens, or post-lens tear film and associated refractive index changes of similar and different contact lens materials; investigate the repeatability and reproducibility for other specialty contact lenses such as orthokeratology and sclerals, considering appropriate timespans across the set of visits; implement different optical powers and richer demographics to incorporate a better balance between the sexes, as well as additional ethnicities, age groups, and eyes of varying complexity and severity; inclusion of lens status, but especially fixation status as a stand-alone parameter; astigmatism and vector analysis relative to toric IOL; the implementation of a multi-centre trial.

7.1.6 Are soft contact lenses a viable source for human dopamine levels measurement using the ELISA dopamine kit?

Sources of analysis variability consisted of the following: some data was incomplete, since lenses stored in saline solution were in variable volumes and too large for the detection limit, hence, dry lens collection is recommended; although stored at the same temperature (-80°C degrees), the storage time interval between lens collection and analysis was longer for plate 1 than plates 2 and 3, therefore, lenses should be placed directly into the extraction (where volume of 300 µl is recommended) microtube of an ELISA plate to reduce degradation.

Future studies should explore the following: whether there is a significant drop in dopamine if contact lenses were to be worn only for a shorter daytime period and/or in the evening/overnight to note any diurnal variations; the application of a microcuvette to enable direct use of a 300 µl dopamine extract and other ocular biomarkers via ELISA, without following ex vivo lens extraction and possibly make the analysis more sensitive to lower dopamine levels; collect tear fluid using Schirmer's strips and capillary tubes on the same visit for alternative sampling technique control comparison; include a richer patient demographic and larger cohort, in order to enable monitoring.

List of References

Abbott, K.S., Queener, H.M., Ostrin, L.A. 2018. The ipRGC Driven pupil response with light exposure, refractive error, and sleep. *Optom Vis Sci*, 95, 323-331.

Abdalla, Y. F., Elsahn, A. F., Hammersmith, K. M. & Cohen, E. J. 2010. Synergeyes lenses for keratoconus. *Cornea*, 29, 5-8.

Abraham, L. M., Kuriakose, T., Sivanandam, V., et al. 2005. Amplitude ofaccommodation and its relation to refractive errors. *Indian JOphthalmol*, 53, 105-108.

Acera, A., Vecino, E., Rodriguez-Agirretxe, I., et al. 2011. Changes in tear protein profile in keratoconus disease. *Eye*, 25, 1225-1233.

Adler, D. & Millodot, M. 2006. The possible effect of undercorrection on myopic progression in children. *Clin. Exp. Optom*., 89, 315-321.

Afanasyeva, D. 2020. Effectiveness of 0.01% atropine sulfate solution in controlling of myopia progression in children. ClinicalTrials.gov Identifier: NCT04338373.

Akman, A., Asena, L., Gungor, S.G. 2016. Evaluation and comparison of the new swept source OCT-based IOLMaster 700 with the IOLMaster 500. *Br J Ophthalmol*, 100, 1201–1205.

Allen, P. M. & O'Leary, D. J. 2006. Accommodation functions: co-dependency and relationship to refractive error. *Vision Res*, 46, 491-505.

Aller, T. A. 2014. Clinical management of progressive myopia. *Eye,* 28**,** 147-153.

Aller, T.A., Liu, M., Wildsoet, C.F. 2016. Myopia control with bifocal contact lenses: a randomized clinical trial. *Optom Vis Sci*, 93, 344-352.

Angi, M.R., Clementi, M., Sardei, C., Piattelli, E., Bisantis, C. 1993. Heritability of myopic refractive errors in identical and fraternal twins. *Graefes Arch Clin Exp Ophthalmol*, 231, 580-585.

Anstice, N. S. & Phillips, J. R. 2011. Effect of dual-focus soft contact lens wear on axial myopia progression in children. *Ophthalmology*,118, 1152-1161.

Anstice, N. S., Davidson, B., Field, B, et al. 2021. The repeatability and reproducibility of four techniques for measuring horizontal heterophoria: Implications for clinical practice. *J Optom*, 14, 275-281.

Ariza-Gracia, M. A., Zurita, J. F., Pinero, D. P., Rodriquez-Matas, J. F. & Calvo, B. 2015. Coupled Biomechanical Response of the Cornea Assessed by Non-Contact Tonometry. A Simulation Study. *Plos One,* 10**,** 15.

Ashby, R. 2016. Animal studies and the mechanism of myopia – protection by light? *Optom Vis Sci*, 93, 1052-1054.

Atchison, D.A., Jones, C.E., Schmid, K.L., et al. 2004. Eye shape in emmetropia and myopia. *Invest Ophthalmol Vis Sci*, 45, 3380–3386.

Atchison, D.A., Li, S.-M., Li, H., et al. 2015. Relative Peripheral Hyperopia Does Not Predict Development and Progression of Myopia in Children. *Invest. Ophthalmol. Vis. Sci.*, 56, 6162-6170.

Atchison, D.A., Markwell, E.L., Kasthurirangan, S., et al. 2008. Age-related changes in optical and biometric characteristics of emmetropic eyes. *J Vis*, 8, 1-0.

Attebo, K., Ivers, R. Q. & Mitchell, P. 1999. Refractive errors in an older population: the Blue Mountains Eye Study. *Ophthalmology*, 106, 1066-1072.

AV, S. D. 2009. The Ocular Respnse Analyzer. *Journal of Current Glaucoma Practice*, 3, 24-27.

Ayaki, M., Torii, H., Tsubota, K., Negishi, K. 2016. Decreased sleep quality in high myopia children. *Sci Rep*, 6, 33902.

Babaei, O.N., Zhu, H., Zhao, Z., et al. 2011. Effect of cholesterol deposition on bacterial adhesion to contact lenses. *Optom Vis Sci*, 88, 950-958.

Back, A., Chamberlain, P., Logan, N., et al. 2017. Clinical evaluation of a dual-focus myopia control 1 day soft contact lens—2-year results. *Optom Vis Sci*, e-abstract 160035.

Baird, P.N., Schache, M., Dirani, M. 2010. The GEnes in Myopia (GEM) study in understanding the aetiology of refractive errors. *Prog Retin Eye Res*, 29, 520-542.
Bailey, M.D, Sinnott, L.T., Mutti, D.O. 2008. Ciliary body thickness and refractive error in children. *Invest Ophthalmol Vis Sci*, 49, 4353-4360.
Balasubramanian, S.A., Pye, D.C., Willcox, M.D. 2012. Levels of lactoferrin, secretory IgA and serum albumin in the tear film of people with keratoconus. *Exp Eye Res*, 96, 132-137.
Bansal, A.S. & Hubbard, G.B III. 2010. Peripheral retinal findings in highly myopic children < or ¼10 years of age. *Retina*, 30, 15-19.
Bar Dayan, Y., Levin, A., Morad, Y., et al. 2005. The changing prevalence of myopia in young adults: a 13-year series of population-based prevalence surveys. *Invest Ophthalmol Vis Sci*, 46, 2760-2765.
Barathi, V.A., Beuerman, R.W., Schaeffel, F. 2009. Effects of unilateral topical atropine on binocular pupil responses and eye growth in mice. *Vision Res*, 49, 383-387.
Baudouin, C., Labbe, A., Liang, H., et al. 2010. Preservatives in eyedrops: the good, the bad and the ugly. *Prog Retin Eye Res*, 29, 312-334.
Benavente-Perez, A., Nour, A., Troilo, D. 2014. Axial eye growth and refractive error development can be modified by exposing the peripheral retina to relative myopic or hyperopic defocus. *Invest Ophthalmol Vis Sci*, 55, 6765-6773.
Bennett, E. S. 2008. Contact lens correction of presbyopia. *Clin Exp Optom*, 91, 265-278.
Berntsen, D.A. & Kramer, C.E. 2013. Peripheral defocus with spherical and multifocal soft contact lenses. *Optom Vis Sci*, 90, 1215-1224.
Berntsen, D.A., Barr, C.D., Mutti, D.O., Zadnik, K. 2013. Peripheral defocus and myopia progression in myopic children randomly assigned to wear single vision and progressive addition lenses. *Invest Ophthalmol Vis Sci*, 54, 5761-5770.
Berntsen, D.A., Mutti, D.O., Zadnik, K. 2010. Study of Theories about Myopia Progression (STAMP) design and baseline data. *Optom Vis Sci*, 87, 823-832.
Berntsen, D. A., Sinnott, L. T., Mutti, D. O. & Zadnik, K. 2012. A randomized trial using progressive addition lenses to evaluate theories of myopia progression in children with a high lag of accommodation. *Invest Ophthalmol Vis Sci*, 53, 640-649.
Bickle, K. & Walline, J. 2013. Bifocal Lenses in Nearsighted Kids (BLINK) study. *Optom Vis Sci*, 90, Abstract 130789.
Bosch-Morell, F., Merida, S., and Navea, A. 2015. Oxidative Stress in Myopia. *Oxid Med Cell Longey*: 750637.
Bourne, R. R., Stevens, G. A., White, R. A., et al. 2013. Causes of vision loss worldwide, 1990-2010: a systematic analysis. *The Lancet Global Health*, 1, 339-49.
Brennnan, N.A., Cheng, X., Toubouti, Y., et al. 2018. Influence of age and race on axial elongation in myopic children. *Optom Vis Sci*, 95:e180072.
Brennan, N., Matsumara, S., Htoon, H., et al. 2020. Annual myopia progression and subsequent year progression in Singaporean children. *Investigative Ophthalmology & Visual Science*, 61: ARVO Annual Meeting Abstract.
Brennan, N., Toubouti, Y., Cheng, X., and Bullimore, M. 2020a. Efficacy in myopia control. *Progress in Retinal and Eye Research*, 100923.
Breslin, K.M., O'Donoghue, L., Saunders, K.J. 2013. A prospective study of spherical refractive error and ocular components among Northern Irish schoolchildren (the NICER study). *Invest Ophthalmol Vis Sci*, 54, 4843-4850.
Brisch, R., Saniotis, A., Wolf, R., et al. 2014. The role of dopamine in schizophrenia from a neurobiological and evolutionary perspective: Old fashioned, but still in vogue. *Front Psychiatry*, 5, 47.
Brown, S.H., Huxtable, L.H., Willcox, M.D., et al. 2013. Automated surface sampling of lipids from worn contact lenses coupled with tandem mass spectrometry. *Analyst*, 138, 1316-1320.

Brunette, I., Bueno, J.M., Parent, M., et al. 2003. Monochromatic aberrations as a function of age, from childhood to. *Invest Ophthalmol Vis Sci*, 44, 5438-5446.
Buckhurst, P., Naroo, S., Davies, L., et al. 2015. Tablet App Aston Halometer for the assessment of Dysphotopsia. *Elsevier*: Licensed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International.
Buckhurst, P., Naroo, S., Davies, L., et al. 2017. Assessment of dysphotopsia in pseudophakic subjects with multifocal intraocular lens. *BMJ Open Ophth*, 1:e000064.
Buckhurst, P.J., Wolffsohn, J.S., Shah, S., et al. 2009. A new optical low coherence reflectometry device for ocular biometry in cataract patients. *Br J Ophthalmol*, 93, 949–953.
Bucolo, C., Platania, C.B.M., Drago, F., et al. 2018. Novel therapeutics in glaucoma management. *Curr Neuropharmacol*, 16, 978-92.
Bullimore, M.A. 2017. The safety of soft contact lenses in children. *Optom Vis Sci*, 94, 638-646.
Bullimore, M.A., et al. 2006. The Study of Progression of Adult Nearsightedness (SPAN): design and baseline characteristics. *Optometry and vision science,* 83, 594-604.
Bullimore, M.A. & Berntsen, D.A. 2018. Low Dose atropine for myopia control: considering all the data. *JAMA Ophthalmol*, 136-303.
Bullimore, M.A. & Brennan, N.A. 2019. Myopia Control: Why Each Diopter Matters. *Optom Vis Sci*, 96, 463-465.
Bullimore, M., Jones, L.A., Moeschberger, M.L., et al. 2002. A retrospective study of myopia progression in adult contact lens wearers. *Invest Ophthalmol Vis Sci*, 43, 2110-2113.
Bullimore, M. & Richdale, K. 2020. Myopia Control 2020: Where are we and where are we heading? *Ophthalmic and Physiological Optics*, 40, 254-270.
Bullimore, M.A., Slade, S., Yoo, P., Otani, T. 2019. An Evaluation of the IOLMaster 700. *Eye & Contact Lens*, 45, 117-123.
Carkeet, A., Luo, H.D., Tong, L., et al. 2002. Refractive error and monochromatic aberrations in Singaporean children. *Vision Res*, 42, 1809-1824.
Chakraborty, R., Read, S.A., Collins, M.J. 2011. Diurnal variations in axial length, choroidal thickness, intraocular pressure, and ocular biometrics. *Invest Ophthalmol Vis Sci*, 52, 5121–5129.
Chakraborty, R., Read, S.A., Collins, M.J. 2012. Monocular myopic defocus and daily changes in axial length and choroidal thickness of human eyes. *Exp Eye Res*, 103, 47-54.
Chakraborty, R., Read, S.A., Collins, M.J. 2013. Hyperopic defocus and diurnal changes in human choroid and axial length. *Optom Vis Sci*, 90, 1187-1198.
Chalmers, R. 2014. Overview of factors that affect comfort with modern soft contact lenses. *Cont Lens Anterior Eye*, 37, 65-76.
Chamberlain, P., Peixoto-de-Matos, S.C., Logan, N.S., et al. 2019. A 3-year Randomized Clinical Trial of MiSight Lenses for Myopia Control. *Optometry and Vision Science*, 96, 556–567.
Chan, B., Cho, P., Cheung, S.W. 2006. Repeatability and agreement of two A-scan ultrasonic biometers and IOLMaster in nonorthokeratology participants and post-orthokeratology children. *Clin Exp Optom*, 89, 160–168.
Chang, L., Pan, C.W., Ohno-Matsui, K., et al. 2013. Myopia-related fundus changes in Singapore adults with high myopia. *Am J Ophthalmol*, 155, 991-999.
Chang, S.W., Tsai, I.L., Hu, F.R., et al. 2001. The cornea in young myopic adults. *Br J Ophthalmol*, 85, 916–920.
Chao, C., Richdale, K., Willcox, M. 2019. The absorption and extraction of inflammatory mediators from contact lens materials. *Eye Contact Lens,* 45, 340-345.
Charm, J. & Cho, P. 2013. High myopia-partial reduction ortho-k: a 2- year randomized study. *Optom Vis Sci*, 90, 530-539.

Charman, W. N. 2014. Developments in the correction of presbyopia I: spectacle and contact lenses. *Ophthalmic and Physiological Optics,* 34**,** 8-29.
Charman, W. N. & Radhakrishnan, H. 2010. Peripheral refraction and the development of refractive error: a review. *Ophthalmic and Physiological Optics,* 30**,** 321-338.
Chen, D., Lam, A. K. & Cho, P. 2009. A pilot study on the corneal biomechanical changes in short-term orthokeratology. *Ophthalmic and Physiological Optics,* 29**,** 464-71.
Chen, K.C., His, E., Hu, C.Y., Chou, W.W., et al. 2012. MicroRNA-328 may influence myopia development by mediating the PAX6 gene. *Invest Ophthalmol Vis Sci*, 53, 2732-2739.
Chen, Y.A., Hirnschall, N., Findl, O. 2011. Evaluation of 2 new optical biometry devices and comparison with the current gold standard biometer. *J Catarct Refract Surg*, 37, 513–517.
Chen, Y., Zhang, J., Morgan, I.G., and He, M. 2016. Identifying Children at Risk of High Myopia Using Population Centile Curves of Refraction. *PLoS One*, 11: e0167642.
Cheng, D., Schmid, K.L., Woo, G.C., Drobe, B. 2010. Randomized trial of effect of bifocal and prismatic bifocal spectacles on myopic progression: two-year results. *Arch Ophthalmol*, 128, 12-19.
Cheng, D., Woo, G.C., Drobe, B., Schmid, K.L. 2014. Effect of bifocal and prismatic bifocal spectacles on myopia progression in children: three-year results of a randomized clinical trial. *JAMA Ophthalmol*, 132, 258-264.
Cheng, S.C., Lam, C.S., Yap, M.K. 2013. Prevalence of myopia-related retinal changes among 12-18 year old Hong Kong Chinese high myopes. *Ophthalmic Physiol Opt*, 33, 652-660.
Cheng, X., Bradley, A., Hong, X., Thibos, L. 2003. Relationship between refractive error and monochromatic aberrations of the eye. *Optom Vis Sci*, 80, 43-49.
Cheng, X., Chehab, K., Brennan, N. A. & Xu, J. 2013. Controlling myopia progression with positive spherical aberration in soft contact lenses. *Optom Vis Sci*, 90, 130-252.
Cheng, X., Xu, J., Brennan, N. A. 2019. Accommodation and its role in myopia progression and control with soft contact lenses. *Ophthalmic and Physiological Optics*, 39, 162-171.
Cheng, X., Xu, J., Chehab, K., et al. 2016. Soft contact lenses with positive spherical aberration for myopia control. *Optom Vis Sci*, 93, 353-366.
Cheung, S.W. & Cho, P. 2013. Validity of axial length measurements for monitoring myopic progression in orthokeratology. *Invest Ophthalmol Vis Sci*, 54, 1613-1615.
Chia, A., Chua, W. H., Cheung, Y. B., Wong, W. L., et al. 2012. 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,* 119**,** 347-354.
Chia, A., Chua, W. H., Wen, L., Fong, A., Goon, Y. Y. & Tan, D. 2014. Atropine for the treatment of childhood myopia: changes after stopping atropine 0.01%, 0.1% and 0.5%. *Am J Ophthalmol*, 157, 451-457.
Chia, A., Lu, Q. S. & Tan, D. 2016. Five-Year Clinical Trial on Atropine for the Treatment of Myopia 2 Myopia Control with Atropine 0.01% Eyedrops. *Ophthalmology,*123**,** 391-399.
Cho, P., Cheung, S. W., Mountford, J. & White, P. 2008. Good clinical practice in ortho-k. *Contact Lens Anterior Eye*, 31, 17-28.
Cho, P., Lam, A.K., Mountford, J., et al. 2002. The performance of four different corneal topographers on normal human corneas and its impact on orthokeratology lens fitting. *Optom Vis Sci,* 79, 175–183.
Cho, Y.J., Lim, T.H., Choi, K.Y., et al. 2018. Comparison of Ocular Biometry Using New Swept-source Optical Coherence Tomography-based Optical Biometer with Other Devices. *Korean J Ophthalmol*, 32, 257–264.
Choi, J.A., Han, K., Park, Y.M., La, T.Y. 2014. Low serum 25- hydroxyvitamin D is associated with myopia in Korean adolescents. *Invest Ophthalmol Vis Sci*, 55, 2041-2047.
Choy, C.K., Cho, P., Chung, W.Y., et al. 2001. Water-soluble antioxidants in human tears: effect of the collection method. *Invest. Ophthalmol. Vis. Sci*, 42, 3130-3134.

Chu, C.H. & Kee, C.S. 2015. Effects of optically imposed astigmatism on early eye growth in chicks. *PLoS One*, 10, e0117729.
Chua, W.H., Balakrishnan, V., Chan, Y.H., et al. 2006. Atropine for the treatment of childhood myopia. *Ophthalmology*, 113, 2285-2291.
Chua, S.Y., Sabanayagam, C., Cheung, Y.B., et al. 2016. Age of onset of myopia predicts risk of high myopia in later childhood in myopic Singapore children. *Ophthalmic Physiol Opt*, 36, 388-394.
Chung, K., Mohidin, N. & O'Leary, D.J. 2002. Undercorrection of myopia enhances rather than inhibits myopia progression. *Vision Res*, 42, 2555-2559.
Ciner, E., Ibay, G., Wojciechowski, R., et al. 2009. Genome-wide scan of African-American and white families for linkage to myopia. *Am J Ophthalmol*, 147, 512-517.
Coletta, N.J., Marcos, S., Troilo, D. 2010. Ocular wavefront aberrations in the common marmoset Callithrix jacchus: effects of age and refractive error. *Vision Res*, 50, 2515-2529.
Coletta, N.J., Marcos, S., Wildsoet, C., Troilo, D. 2003. Double-pass measurement of retinal image quality in the chicken eye. *Optom Vis Sci*, 80, 50-57.
Collins, M.J., Brown, B., Bowman, K.J.. 1989. Contrast sensitivity with contact lens corrections for presbyopia. *Ophthalmic Physiol. Opt.*, 9, 133-138.
Collins, M.J., Wildsoet, C.F., Atchison, D.A. 1995. Monochromatic aberrations and myopia. *Vision Res*, 35, 1157-1163.
COMET, Group. 2013. Myopia stabilization and associated factors among participants in the Correction of Myopia Evaluation Trial (COMET). *Invest. Ophthalmol. Vis. Sci*, 54, 7871-7884.
COMET 2 Study Group for the Pediatric Eye Disease Investigator Group. 2011. Progressive-addition lenses versus single-vision lenses for slowing progression of myopia in children with high accommodative lag and near esophoria. *Invest Ophthalmol Vis Sci*, 52, 2749-2757.
Coon, L. J. 1984. Orthokeratology. Part II: Evaluating the Tabb method. *Journal of the American Optometric Association,* 55**,** 409-18.
Cooper, J., O'Connor, B., Watanabe, R., et al. 2018. Case Series Analysis of Myopic Progression Control With a Unique Extended Depth of Focus Multifocal Contact Lens. *Eye & Contact Lens*, 44, 16-24.
Cooper, J., Schulman, E., Jamal, N. 2012. Current status on the development and treatment of myopia. *Optometry*, 83, 179-199.
Cuellar-Partida, G., Lu, Y., Kho, P.F., et al. 2016. Assessing the genetic predisposition of education on myopia: a Mendelian Randomization Study. *Genet Epidemiol*, 40, 66-72.
Cuellar-Partida, G., Williams, K.M., Yazar, S., et al. 2017. Genetically low vitamin D concentrations and myopic refractive error: a Mendelian randomization study. *Intl J Epidemiol*., 46, 1882-1890.
Curtin, B.J., Iwamoto, T., Renaldo, D.P. 1979. Normal and staphylomatous sclera in high myopia. *Arch Ophthalmol*, 97, 912-921.
Dandona, R., Dandona, L., Srinivas, M., et al. 2002. Refractive error in children in a rural population in India. *Invest Ophthalmol Vis Sci*, 43, 615-622.
Datta, S., Baudouin, C., Brignole-Baudouin, F., et al. 2017. The eye drop preservative benzalkonium chloride potently induces mitochondrial dysfunction and preferentially affects LHON mutant cells. *Invest Ophthalmol Vis Sci*, 58, 2406-2412.
Dharani, R., Lee, C.F., Theng, Z.X., et al. 2012. Comparison of measurements of time outdoors and light levels as risk factors for myopia in young Singapore children. *Eye*, 26, 911-918.
Diez, P., Yang, L., Lu, M., et al. 2019. Growth curves of myopia-related parameters to clinically monitor the refractive development in Chinese schoolchildren. *Graefes Arch Clin Exp Ophthalmol*, 257, 1045-1053.

Dinc, U., Gorgun, E., Oncel, B., et al. 2010. Assessment of anterior chamber depth using Visante optical coherence tomography, slitlamp optical coherence tomography, IOL Master, Pentacam and Orbscan IIz. Ophthalmologica, 224, 341–346.
Dirkx, M.F., den Ouden, H.E., Aarts, E., et al. 2017. Dopamine controls parkinson's tremor by inhibiting the cerebellar thalamus. *Brain*, 140, 721-34.
Dolgin, E. 2015. The myopia boom. *Nature*, 519, 276-278.
Dominguez-Vicent, A., Perez-Vives, C., Ferrer-Blasco, T., et al. 2016. Device interchangeability on anterior chamber depth and white-to-white measurements: a thorough literature review. *Int J Ophthalmol*, 9, 1057–1065.
Dong, L.M., Fazzari, M., Gwiazda, J., et al. 2013. Myopia Stabilization and Associated Factors Among Participants in the Correction of Myopia Evaluation Trial (COMET). *Invest. Ophthalmol. Vis. Sci.*, 54, 7871-7883.
Donovan, L., Sankaridurg, P., Ho, A., et al. 2012. Myopia progression rates in urban children wearing single-vision spectacles. *Optom Vis Sci*, 89, 27-32.
Downie, L. 2013. Predictive Value of Corneal Topography for ClearKone Hybrid Contact Lenses. *Optometry and Vision Science*, 90, 191-197.
Drexler, W., Findl, O., Menapace, R., et al. 1998. Partial coherence interferometry: a novel approach to biometry in cataract surgery. *Am J Ophthalmol*, 126, 524–534.
Drexler, W., Findl, O., Schmetterer, L., et al. 1998. Eye elongation during accommodation in humans: differences between emmetropes and myopes. *Invest Ophthalmol Vis Sci*, 39, 2140–2147.
Dumortier, G. & Chaumeil, J.C. 2004. Lachrymal determinations: Methods and updates on biopharmaceutical and clinical applications. *Ophthalmic Res*, 36, 183-94.
Edwards, M.H., Li, RW-H., Lam, CS-Y., et al. 2002. The Hong Kong progressive lens myopia control study: study design and main findings. *Invest Ophthalmol Vis Sci*, 43, 2852-2858.
Efron, N., Morgan, P. B., Woods, C. A. & International Contact Lens Prescribing Consortium. 2011. Survey of contact lens prescribing to infants, children, and teenagers. *Optom Vis Sci*, 88, 461-468.
Efron, N., Morgan, P. B., Woods, C. A. & Int Contact Lens Prescribing, S. 2013. International Survey of Rigid Contact Lens Fitting. *Optometry and Vision Science,* 90**,** 113-118.
Egashira, S.M., Kish, L.L., Twelker, J.D., et al. 1993. Comparison of cyclopentolate versus tropicamide cycloplegia in children. *Optom Vis Sci.*, 70, 1019-1026.
Ehsaei, A., Mallen, E.A., Chisholm, C.M., et al. 2011. Cross-sectional sample of peripheral refraction in four meridians in myopes and emmetropes. *Invest Ophthalmol Vis Sci*, 52, 7574- 7585.
Evans, V., Vockler, C., Friedlander, M., et al. 2001. Lacryglobin in human tears, a potential marker for cancer. *Clin. Exp. Ophthalmol.*, 29, 161-163.
Fan, Q., Verhoeven, V.J.M., Wojciechowski, R., et al. 2016. Meta-analysis of gene-environment-wide association scans accounting for education level identifies additional loci for refractive error. *Nat Commun*, 7, 1000-1008.
Farbrother, J.E., Kirov, G., Owen, M.J., Guggenheim, J.A. 2004. Family aggregation of high myopia: estimation of the sibling recurrence risk ratio. *Invest Ophthalmol Vis Sci*, 45, 2873-2878.
Feldkaemper, M. & Schaeffel F. 2013. An updated view on the role of dopamine in myopia. *Experimental Eye Research*, 114, 106-119.
Fernandez-Montero, A., Olmo-Jimenez, J.M., Olmo, N., et al. 2015. The impact of computer use in myopia progression: A cohort study in Spain. *Prev Med*, 71, 67-71.
Fernandez-Velazquez, F.J. 2011. Severe epithelial edema in Clearkone SynergEyes contact lens wear for keratoconus. *Eye Contact Lens*, 37, 381-385.

Ferrer-Blasco, T., Esteve-Taboada, J.J., Dominquez-Vicent, A., et al., 2019. Effect of contact lenses on ocular biometric measurements based on swept-source optical coherence tomography. *Arq. Bras. Oftalmol.*, 82, 129–135.
Findl, O., Kriechbaum, K., Sacu, S., et al. 2003. Influence of operator experience on the performance of ultrasound biometry compared to optical biometry before cataract surgery. *J Cataract Refract Surg*, 29, 1950–1955.
Fledelius, H.C. & Goldschmidt, E. 2010. Oculometry findings in high myopia at adult age: considerations based on oculometric follow-up data over 28 years in a cohort-based Danish highmyopia series. *Acta Ophthalmol*, 88, 472–478.
Flitcroft, D.I. 2012. The complex interactions of retinal, optical, and environmental factors in myopia aetiology. *Prog Retin Eye Res*, 31, 622-660.
Flitcroft, D.I., He, M., Jonas, J.B., et al., 2019. IMI – Defining and classifying myopia: a proposed set of standards for clinical and epidemiologic studies. *Invest Ophthalmol Vis Sci*, 60, 20-30.
Fonn, D. 2009. Dryness with contact lenses and dry eye: are they the same or different? *Eye Contact Lens*, 35, 219.
Freeman, G. & Pesudovs, K. 2005. The impact of cataract severity on measurement acquisition with the IOLMaster. *Acta Ophthalmol Scand*, 83, 439–42.
French, A.N., Ashby, R.S., Morgan, I. G. & Rose, K.A. 2013. Time outdoors and the prevention of myopia. *Exp Eye Res*, 114, 58-68.
French, A.N., Morgan, I.G., Mitchell, P., Rose, K.A. 2013. Patterns of myopigenic activities with age, gender and ethnicity in Sydney schoolchildren. *Ophthalmic Physiol Opt*, 33, 318-328.
Fricke, T.R., Jong, M., Naidoo, K.S., et al. 2018. Global prevalence of visual impairment associated with myopic macular degeneration and temporal trends from 2000 through 2050: systematic review, meta-analysis and modelling. *Br J Ophthalmol*, 102, 855-862.
Fu, A.C., Chen, X.L., Lv, Y., et al. 2016. Higher spherical equivalent refractive errors is associated with slower axial elongation wearing orthokeratology. *Cont Lens Anterior Eye*, 39, 62-66.
Fujikado, T., Ninomiya, S., Kobayashi, T., et al. 2014. Effect of low-addition soft contact lenses with decentered optical design on myopia progression in children: a pilot study. *Clin Ophthalmol*, 8, 1947-1956.
Fulk, G.W., Cyert, L.A. & Parker, D.E. 2000. A randomized trial of the effect of single-vision vs bifocal lenses on myopia progression in children with esophoria. *Optom Vis Sci*, 77, 395-401.
Fulk, G.W., Cyert, L.A., Parker, D.E., et al. 2003. The effect of changing from glasses to soft contact lenses on myopia progression in adolescents. *Ophthalmic Physiol Opt*, 23, 71-77.
Fulton, A.B., Hansen, R.M., Petersen, R.A. 1982. The relation of myopia and astigmatism in developing eyes. *Ophthalmology*, 89, 298-302.
Garcia de la Cera, E., Rodriguez, G., Marcos, S. 2006. Longitudinal changes of optical aberrations in normal and form-deprived myopic chick eyes. *Vision Res*, 46, 579-589.
García-Lazaro, S., Ferrer-Blasco, T., Madrid-Costa, D., et al. 2015. Visual performance of four simultaneous-image multifocal contact lenses under dim and glare conditions. *Eye Contact Lens Sci. Clin. Pract*., 41, 19-24.
Garner, L. F., Owens, H., Kinnear, R. F. & Frith, M. J. 1999. Prevalence of myopia in Sherpa and Tibetan children in Nepal. *Optom Vis Sci*, 76, 282–285.
Gentle, A., Liu, Y.Y., Martin, J.E., et al. 2003. Collagen gene expression and the altered accumulation of scleral collagen during the development of high myopia. *J Biol Chem*, 278, 16587-16594.

Ghorbani-Mojarrad, N., Cargill, C., Collard, S., et al. 2021. Patient experience and physiological response to two commercially available daily disposable myopia control contact lenses. *Contact Lens and Anterior Eye*, In Press.
Gifford, P. & Gifford, K. L. 2016. The Future of Myopia Control Contact Lenses. *Optometry and Vision Science,* 93**,** 336-343.
Gifford, K., Gifford, P., Hendicott, P.L., Schmid, K.L. 2017. Near binocular visual function in young adult orthokeratology versus soft contact lens wearers. *Cont Lens Anterior Eye*, 40, 184-189.
Gifford, K.L., Richdale, K., Kang, P., et al. 2019. IMI – Clinical Management Guidelines Report. *Invest Ophthalmol Vis Sci*, 60, 184-203.
Gifford, P. & Swarbrick, H. A. 2009. The effect of treatment zone diameter in hyperopic orthokeratology. *Ophthalmic Physiol Opt*, 29, 584-592.
Gifford, P. & Swarbrick, H. A. 2013. Refractive changes from hyperopic orthokeratology monovision in presbyopes. *Optometry and Vision Science,* 90**,** 306-13.
Gil-Cazorla, R., Shah, S. and Naroo, S.A. 2015. A review of the surgical options for the correction of presbyopia. *British Journal of Ophthalmology*.
Gong CR, Troilo D, Richdale K. 2017. Accommodation and phoria in children wearing multifocal contact lenses. *Optom Vision Sci*, 94, 353-360.
Gonzalez-Meijome, J. M., Peixoto-De-Maots, S. C., Faria-Ribeiro, M., et al. 2016. Strategies to Regulate Myopia Progression With Contact Lenses: A Review. *Eye & Contact Lens-Science and Clinical Practice,* 42**,** 24-34.
Gonzalez-Meijome, J. M., Villa-Collar, C., Queiros, A., Jorge, J. & Parafita, M. A. 2008. Pilot study on the influence of corneal biomechanical properties over the short term in response to corneal refractive therapy for myopia. *Cornea,* 27**,** 421-6.
Gordon, R.A. & Donzis, P.B. 1985. Refractive development of the human eye. *Arch Ophthalmol*, 103, 785-789.
Goss, D. A. & Cox, V. D. 1985. Trends in the change of clinical refractive error in myopes. *J Am Optom Assoc*, 56, 608-613.
Goss, D.A. & Winkler, R.L. 1983. Progression of myopia in youth: age of cessation. *Am J Optom Physiol Opt*, 60, 651-658.
Gottlieb, M.D., Fugate-Wentzek, L.A., Wallman, J. 1987. Different visual deprivations produce different ametropias and different eye shapes. *Invest Ophthalmol Vis Sci*, 28, 1225-1235.
Goudie, C., Tatham, A., Davies, R., et al. 2018. The effect of the timing of the cessation of contact lens use on the results of biometry. *Eye (Lond)*, 32, 1048–1054.
Group, C. 2013. Myopia stabilization and associated factors among participants in the Correction of Myopia Evaluation Trial (COMET). *Invest Ophthalmol Vis Sci*, 54, 7871-7884.
Grytz, R. & Siegwart, J.T Jr. 2015. Changing material properties of the tree shrew sclera during minus lens compensation and recovery. *Invest Ophthalmol Vis Sci*, 56, 2065-2078.
Guggenheim, J.A., Chen, Y.P., Yip, E., et al. 2011. Pre-treatment choroidal thickness is not predictive of susceptibility to form-deprivation myopia in chickens. *Ophthalmic Physiol Opt*, 31, 516-528.
Guggenheim, J. A., Northstone, K., McMahon, G., et al. 2012. Time outdoors and physical activity as predictors of incident myopia in childhood: a prospective cohort study. *Invest Ophthalmol Vis Sci*, 53, 2856-2865.
Guggenheim, J.A., Williams, C., Northstone, K., et al. 2014. Does vitamin D mediate the protective effects of time outdoors on myopia? Findings from a prospective birth cohort. *Invest Ophthalmol Vis Sci*., 55, 8550-8558.

Guggenheim, J.A., Zhou, X., Evans, D.M., et al. 2013. Coordinated genetic scaling of the human eye: shared determination of axial eye length and corneal curvature. *Invest Ophthalmol Vis Sci*, 54, 1715-1721.
Guillon, M. & Maïssa, C. 2010. Tear film evaporation – effect of age and gender. *Cont Lens Anterior Eye*, 33, 171-175.
Gwiazda, J., Bauer, J., Thorn, F., Held, R. 1995. A dynamic relationship between myopia and blur Driven accommodation in schoolaged children. *Vision Res*, 35, 1299-1304.
Gwiazda, J., Deng, L., Manny, R., Norton, T.T. 2014. Seasonal variations in the progression of myopia in children enrolled in the correction of myopia evaluation trial. *Invest Ophthalmol Vis Sci*, 55, 752-758.
Gwiazda, J., Grice, K., Held, R., et al. 2000. Astigmatism and the development of myopia in children. *Vision Res*, 40, 1019-1026.
Gwiazda, J., Grice, K., Thorn, F. 1999. Response AC/A ratios are elevated in myopic children. *Ophthalmic Physiol Opt*, 19, 173-179.
Gwiazda, J., Hyman, L., Hussein, M., et al. 2003. A randomized clinical trial of progressive addition lenses versus single vision lenses on the progression of myopia in children. *Invest Ophthalmol Vis Sci*, 44, 1492-1500.
Gwiazda, J.E., Hyman, L., Norton, T.T., et al. 2004. Accommodation and related risk factors associated with myopia progression and their interaction with treatment in COMET children. *Invest Ophthalmol Vis Sci*, 45, 2143-2151.
Gwiazda, J., Scheiman, M., Mohindra, I., Held, R. 1984. Astigmatism in children: changes in axis and amount from birth to six years. *Invest Ophthalmol Vis Sci*, 25, 88-92.
Gwiazda, J., Thorn, F., Held, R. 2005. Accommodation, accommodative convergence, and response AC/A ratios before and at the onset of myopia in children. *Optom Vis Sci*, 82, 273- 278.
Haarman, A.E., Enthoven, C.A., Tideman, J.W.L., et al. 2020. The Complications of Myopia: A Review and Meta-Analysis. *Investigative Ophthalmology & Visual Science*, *61*, 49-49.
Haddad, J.S., Barnwell, E., Rocha, K.M., et al. 2020. Comparison of Biometry Measurements Using Standard Partial Coherence Interferometry versus New Scheimpflug Tomography with Integrated Axial Length Capability. *Clin Ophthalmol*, 14, 353-358.
Hagan, S., Martin, E., Enríquez-de-Salamanca, A. 2016. Tear fluid biomarkers in ocular and systemic disease: Potential use for predictive, preventive and personalised medicine. *EPMA J*, 7, 15.
Haigis, W., Lege, B., Miller, N., et al. 2000. Comparison of immersion ultrasound biometry and partial coherence interferometry for intraocular lens calculation according to Haigis. *Graefes Arch Clin Exp Ophthalmol*, 238, 765–773.
Hammond, C. J., Snieder, H., Gilbert, C. E. & Spector, T. D. 2001. Genes and environment in refractive error: the twin eye study. *Invest Ophthalmol Vis Sci*, 42, 1232–1236.
Hasebe, S., Jun, J., Varnas, S.R. 2014. Myopia control with positively aspherized progressive addition lenses: a 2-year, multicenter, randomized, controlled trial. *Invest Ophthalmol Vis Sci*, 55, 7177-7188.
Hasebe, S., Nakatsuka, C., Hamasaki, I. & Ohtsuki, H. 2005. Downward deviation of progressive addition lenses in a myopia control trial. *Ophthalmic Physiol Opt*, 25, 310–314.
Hashemi, H., Fotouhi, A. and Mohammad, K. 2004. The age- and gender-specific prevalences of refractive errors in Tehran: the Tehran Eye Study. *Ophthalmic Epidemiol*, 11,213-225.
Hashemi, H., Shaygan, N., Asgari, S., Rezvan, F. & Asgari, S. 2014. ClearKone-Synergeyes or rigid gas-permeable contact lens in keratoconic patients: a clinical decision. *Eye Contact Lens*, 40, 95-98.
Hashemi, H., Yazdani, K., Mehravaran, S., et al. 2005. Anterior chamber depth measurement with a-scan ultrasonography, Orbscan II, and IOLMaster. *Optom Vis Sci*, 82, 900–904.

He, J.C., Sun, P., Held, R., et al. 2002. Wavefront aberrations in eyes of emmetropic and moderately myopic school children and young adults. *Vision Res*, 42, 1063-1070.
He, M., Huang, W., Zheng, Y., Huang, L., Ellwein, L. B. 2007. Refractive error and visual impairment in school children in rural southern China. *Ophthalmology*, 114, 374-382.
He, M., Xiang, F., Zeng, Y., et al. 2015. Effect of time spent outdoors at school on the development of myopia among children in China: a randomized clinical trial. *JAMA Ophthalmol*, 314, 1142-1148.
He, X., Zou, H., Lu, L., et al. 2015. Axial length/corneal radius ratio: association with refractive state and role on myopia detection combined with visual acuity in Chinese schoolchildren. *PLoS One*, 10: e0111766.
Hendricks, T.J.W., De Brabander, J., Vankan-Hendricks, M.H.P. 2009. Prevalence of habitual refractive errors and anisometropia among Dutch schoolchildren and hospital employees. *Acta Ophthalmol*., 87, 538-543.
Herber, S., Grus, F.H., Sabuncuo, P. 2001. Two-dimensional analysis of tear protein patterns of diabetic patients. *Electrophoresis*, 22, 1838-1844.
Hernandez, J., Sinnott, L.T., Brennan, N.A., et al. 2018. Analysis of CLEERE data to test the feasibility of identifying future fast myopic progressors. *Invest Ophthalmol Vis Sci*, 59:e3388.
Hiraoka, T., Kakita, T., Okamoto, F., Takahashi, H. & Oshika, T. 2012. Long-term effect of overnight orthokeratology on axial length elongation in childhood myopia: a 5-year follow-up study. *Invest Ophthalmol Vis Sci*, 53, 3913-3919.
Hiraoka, T., Kotsuka, J., Kakita, T., et al. 2017. Relationship between higher-order wavefront aberrations and natural progression of myopia in schoolchildren. *Sci Rep*, 7, 7876.
Hokoda, S.C. 1985. General binocular dysfunctions in an urban optometric population. *J Am Optom Assoc*, 56, 560-562.
Holden, B. A., et al. 2016. Global Prevalence of Myopia and High Myopia and Temporal Trends from 2000 through 2050. *American Academy of Ophthalmology*, 123, 1036-1042.
Holden, B. A., Fricke, T. R., Ho, S. M., Wong, R., et al. 2008. Global vision impairment due to uncorrected presbyopia. *Archives of Ophthalmology*, 126, 1731-1739.
Holden, B. A., et al. 2016. Global Prevalence of Myopia and High Myopia and Temporal Trends from 2000 through 2050. American Academy of Ophthalmology, 123, 1036-1042.
Hong, T., Flood, V., Rochtchina, E., et al. 2014. Adherence to dietary guidelines and the 10-year cumulative incidence of visual impairment: the Blue Mountains Eye Study. *Am J Ophthalmol*, 158, 302-308.
Horner, D.G., Soni, P.S., Salmon, T.O., et al. 1999. Myopia progression in adolescent wearers of soft contact lenses and spectacles. *Optom Vis Sci*, 76, 474-479.
Hosny, M., Alio, J.L., Claramonte, P., et al. 2000. Relationship between anterior chamber depth, refractive state, corneal diameter, and axial length. *J Refract Surg*, 16, 336–340.
Hou, W., Norton, T.T., Hyman, L., et al. 2018. Axial elongation in myopic children and its association with myopia progression in the Correction of Myopia Evaluation Trial. *Eye Contact Lens*, 44, 248-259.
Hrynchak, P., Machan, C., Mittelstaedt, A., Irving, E. 2011. Near phoria and strabismus as a function of age in a clinical population. *American Academy of Optometry*: 115820.
Hsieh, Y.T. & Wang, I.J. 2012. Intraocular lens power measured by partial coherence interferometry. *Optom Vis Sci*, 89, 1697–701.
Hsu, C.C., Huang, N., Lin, P.Y., et al. 2017. Risk factors for myopia progression in second-grade primary school children in Taipei: a population-based cohort study. *Br J Ophthalmol*, 101, 1611-1617.
Hu, H., Zhao, G., Wu, R., et al. 2018. Axial length/corneal radius of curvature ratio assessment of posterior sclera reinforcement for pathologic myopia. *Ophthalmologica*, 239, 128-132.

Hua, Y., Qiu, W., Xiao, Q., et al. 2018. Precision (repeatability and reproducibility) of ocular parameters obtained by the Tomey OA-2000 biometer compared to the IOLMaster in healthy eyes. *PloS one*, 13, e0193023.
Hua, W.J., Jin, J.X., Wu, X.Y., et al. 2015. Elevated light levels in schools have a protective effect on myopia. *Ophthalmic Physiol Opt*, 35, 252-262.
Huang, J., Savini, G., Hoffer, K. J., et al. 2017. Repeatability and interobserver reproducibility of a new optical biometer based on swept-source optical coherence tomography and comparison with IOLMaster. *The British journal of ophthalmology*, 101, 493–498.
Huang, J., Savini, G., Li, J., et al. 2014. Evaluation of a new optical biometry device for measurements of ocular components and its comparison with IOLMaster. *The British journal of ophthalmology*, 98, 1277–1281.
Huang, J., Wed, D., Wang, Q., et al. 2016. Efficacy comparison of 16 interventions for myopia control in children. *Ophthalmology*, 123, 697-708.
Huang, J., Zhao, Y., Savini, G., et al. 2020. Reliability of a New Swept-Source Optical Coherence Tomography Biometer in Healthy Children, Adults, and Cataract Patients. *Journal of ophthalmology*, 8946364.
Huo, L., Cui, D., Yang, X., et al. 2012. A restrospective study: formdeprivation myopia in unilateral congenital ptosis. *Clin Exp Optom*, 95, 404-409.
Hussin, H.M., Spry, P.G., Majid, M.A., et al. 2006. Reliability and validity of the partial coherence interferometry for measurement of ocular axial length in children. *Eye (Lond)*, 20, 1021–1024.
Huynh, S.C., Mai, T.Q., Kifley, A., et al. 2006. An evaluation of keratometry in 6-yearold children. *Cornea*, 25, 383–387.
Hyman, L., Gwiazda, J., Marsh-Tootle, W.L., et al. 2001. The Correction of Myopia Evaluation Trial (COMET): design and general baseline characteristics. *Control Clin Trials*, 22, 573-592.
Ip, J. M., Huynh, S. C., Robaei, D., et al. 2007. Ethnic differences in the impact of parental myopia: findings from a population-based study of 12-year-old Australian children. *Invest Ophthalmol Vis Sci*, 48, 2520-2528.
Ip, J. M., Huynh, S.C., Robaei, D., Kifley, A., Rose, K. A., et al. 2008. Ethnic differences in refraction and ocular biometry in a population-based sample of 11-15-year-old Australian children. *Eye (Lond)*, 22, 649-656.
Ip, J. M., Saw, S. M., Rose, K. A., Morgan, I. G., Kifley, A., Wang, J.J. & Mitchell, P. 2008. Role of near work in myopia: findings in a sample of Australian school children. *Invest Ophthalmol Vis Sci*, 49, 2903-2910.
Irving, E.L. & Machan, C.M. 2012. Longitudinal Study of Age Changes in Vergence Posture. ARVO Abstract, 53, 1785.
Irving, E.L., Machan, C.M., Hrynchak, P.K. 2009. Lifespan refractive change in an optometric clinic population. *Invest Ophthalmol Vis Sci*, 50:e3949.
Irving, E.L., Machan, C.M., Lam, S., et al. 2019. Refractive error magnitude and variability: relation to age. *Journal of Optometry*, 12, 55-63.
Irving, E.L., Machan, C.M., and Simpson T. 2011. Longitudinal Changes in Human Refractive Error. ARVO Abstract, 52, 2823.
Jagadeesh, D., Weng, R., He, X., et al. 2020. Predictive models for the incidence and progression of myopia in children. ARVO Annual Meeting Abstract. *Investigative Ophthalmology & Visual Science*, 61, 856.
Jee, D., Morgan, I.G., Kim, E.C. 2016. Inverse relationship between sleep duration and myopia. *Acta Ophthalmol*, 94, 204-210.
Jiang, B.C. 1995. Parameters of accommodative and vergence systems and the development of late-onset myopia. *Invest Ophthalmol Vis Sci*, 36, 1737-1742.

Jiang, B., Huo, Y., Gu, Y., Wang, J. 2017. The role of microRNAs in myopia. *Graefes Arch Clin Exp Ophthalmol*, 255, 7-13.
Jonas, J.B., Ohno-Matsui, K., Holbach, L., Panda-Jonas, S. 2017a. Retinal pigment epithelium cell density in relationship to axial length in human eyes. *Acta Ophthalmol*, 95, 22-28.
Jonas, J.B., Ohno-Matsui, K., Jiang, W.J., Panda-Jonas, S. 2017b. Bruch's membrane and the mchanism of myopization: a new theory. *Retina*, 37, 1428-1440.
Jones, L.A., et al. 2005. Comparison of Ocular Component Growth Curves among Refractive Error Groups in Children. *Invest Ophthalmol Vis Sci*, 46, 2317-2327.
Jones, L., Drobe, B., Gonzalez-Meijome, J.M., et al. 2019. IMI – Industry Guidelines and Ethical Considerations for Myopia Control Report. *Invest Ophthalmol Vis Sci*, 60, 161-183.
Jones-Jordan, L. A., Sinnott, L. T., Cotter, S. A., et al. 2012. Time outdoors, visual activity, and myopia progression in juvenile-onset myopes. *Invest Ophthalmol Vis Sci*, 53, 7169–7175.
Jones-Jordan, L. A., Sinnott, L. T., Graham, N. D., et al. 2014. 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. *Invest Ophthalmol Vis Sci*, 55, 6333-6339.
Jones-Jordan, L. A., Sinnott, L. T., Manny, R. E., Cotter, S. A., et al. 2010. Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error (CLEERE) Study Group. Early childhood refractive error and parental history of myopia as predictors of myopia. *Invest Ophthalmol Vis Sci*, 51, 115-121.
de Jong, W.H., de Vries, E.G., and Kema, I.P. 2011. Current status and future developments of LC-MS/MS in clinical chemistry for quantification of biogenic amines. *Clin. Biochem*, 44, 95-103.
Jorge, J., Almeida, J.B., Parafita, M.A. 2007. Refractive, biometric and topographic changes among Portuguese university science students: a 3-year longitudinal study. *Ophthalmic Physiol. Opt*., 27, 287-294.
Jung, J.J., Lim, E.H., Baek, S.H., et al. 2011. Attempts to reduce the progression of myopia and spectacle prescriptions during childhood: a survey of eye specialists. *Korean J Ophthalmol*., 25, 417-420.
Junghans, B. M. & Crewther, S. G. 2003. Prevalence of myopia among primary school children in eastern Sydney. *Clin Exp Optom*, 86, 339-345.
Kamiya, K., Ishii, R., Shimizu, K., et al. 2014. Evaluation of corneal elevation, pachymetry and keratometry in keratoconic eyes with respect to the stage of Amsler-Krumeich classification. *Br J Ophthalmol*.
Kang, P., Fan, Y., Oh, K., et al. 2013. The effect of multifocal soft contact lenses on peripheral refraction. *Optom Vis Sci*, 90, 658-666.
Kang, P. & Swarbrick, H. 2016. The Influence of Different OK Lens Designs on Peripheral Refraction. *Optometry and Vision Science,* 93**,** 1112-1119.
Kasahara, K., Maeda, N., Fujikado, T., et al. 2017. Characteristics of higher-order aberrations and anterior segment tomography in patients with pathologic myopia. *Int Ophthalmol*, 37, 1279–1288.
Katz, J., Schein, O. D., Levy, B., et al. 2003. A randomized trial of rigid gas permeable contact lenses to reduce progression of children's myopia. *Am J Ophthalmol*,136, 82-90.
Katz, J., Tielsch, J. M. & Sommer, A. 1997. Prevalence and risk factors for refractive errors in an adult inner city population. *Invest Ophthalmol Vis Sci*, 38, 334-340.
Kaya, C., Erkaymaz, O., Ayar, O., Ozer, M. 2018. Classification of refractive disorders from electrooculogram (EOG) signals by using data mining techniques. *In Proceedings of the 26th Signal Processing and Communications Applications Conference (SIU)*, 1-4.

Kearney, S., O'Donoghue, L., Pourshahidi, L.K., et al. 2017. Myopes have significantly higher serum melatonin concentrations than non-myopes. *Ophthalmic Physiol Opt*, 37, 557-567.
Kee, C.S. 2013. Astigmatism and its role in emmetropization. *Exp Eye Res*, 114, 89-95.
Kee, C.S., Hung, L.F., Qiao, Y., Smith, E.L III. 2003. Astigmatism in infant monkeys reared with cylindrical lenses. *Vision Res*, 43, 2721-2739.
Khoo, C. Y., Chong, J. & Rajan, U. 1999. A 3-year study on the effect of RGP contact lenses on myopic children. *Singapore Med J*, 40, 230-237.
Kim, E., Bakaraju, R.C., Ehrmann, K. 2017. Power profiles of commercial multifocal soft contact lenses. *Optometry and Vision Science*, 94, 183-196.
Kim, E.C., Morgan, I.G., Kakizaki, H., et al. 2013. Prevalence and risk factors for refractive errors: Korean National Health and nutrition examination survey 2008-2011. *PLoS One*, 8: e80361.
Kim, J., Jeon, M., Paeng, K., et al. 2008. Competitive enzymelinked immunosorbent assay for determination of catecholamine, dopamine in serum. *Anal. Chim. Acta*, 619, 87-93.
Kim, J., Park, H., Ryu, J., et al. 2010. Competitive enzyme-linked immunosorbent assay for a selective and sensitive determination of dopamine in the presence of ascorbic acid and uric acid. *J. Immunoassay Immunochem*, 31, 33-44.
Kim, M.H., Zhao, D., Kim, W., et al. 2013. Heritability of myopia and ocular biometrics in Koreans: the healthy twin study. *Invest Ophthalmol Vis Sci*, 54, 3644-3649.
Kingsnorth, A., Drew, T., Grewal, B., et al. 2016. Mobile app Aston contrast sensitivity test. *Clinical and Experimental Optometry*, 99, 350-355.
Klein, A.P., Suktitipat, B., Duggal, P., et al. 2009. Heritability analysis of spherical equivalent, axial length, corneal curvature, and anterior chamber depth in the Beaver Dam Eye Study. *Arch Ophthalmol*, 127, 649-655.
Kleinstein, R. N., Jones, L. A., Hullett, S., et al. 2003. Refractive error and ethnicity in children. *Arch Ophthalmol*, 121, 1141-1147.
Kollbaum, P.S., Dietmeier, B.M., Jansen, M.E., et al. 2012. Quantification of ghosting produced with presbyopic contact lens correction, eye contact lens sci. *Clin. Pract*., 38, 252-259.
Kollbaum, P. S., Jansen, M. E., Tan, J., Meyer, D. M. & Rickert, M.E. 2013. Vision performance with a contact lens designed to slow myopia progression. *Optom Vis Sci*, 90, 205-214.
Koomson, N.Y., Amedo, A.O., Opoku-Baah, C., et al. 2016. Relationship between reduced accommodative lag and myopia progression. *Optom Vis Sci*., 93, 683-691.
Kotecha, A., Russell, R. A., Sinapis, A., Pourjavan, S., et al. 2014. Biomechanical parameters of the cornea measured with the Ocular Response Analyzer in normal eyes. *Bmc Ophthalmology,* 14**,** 7.
Koo, B.S., Lee, D.Y., Ha, H.S., et al. 2005. Comparative analysis of the tear protein expression in blepharitis patients using two-dimensional electrophoresis. *J. Proteome Res.*, 4, 719-724.
Kunert, K.S., Peter, M., Blum, M., et al. 2016. Repeatability and agreement in optical biometry of a new swept-source optical coherence tomography-based biometer versus partial coherence interferometry and optical low-coherence reflectometry. *J Cataract Refract Surg*, 42, 76-83.
Kurtz, D., Hyman, L., Gwiazda, J.E., et al. 2007. Role of parental myopia in the progression of myopia and its interaction with treatment in COMET children. *Invest Ophthalmol Vis Sci*, 48, 562-570.
Kushnir, M., Urry, F., Frank, E. 2002. Analysis of catecholamines by positive-ion electrospray tandem mass spectrometry. *Clin. Chem*, 48, 323-331.
Lam, CS-Y., Tang, W.C., Lee, R.P., et al. 2017. Myopia control with multi-segment myopic defocus (MSMD) spectacle lens: a randomised clinical trial. *Ophthal Physiol Opt*, 37, O017.

Lam, C.S., Tang, W.C., Tse, D.Y., et al. 2014. Defocus Incorporated Soft Contact (DISC) lens slows myopia progression in Hong Kong Chinese schoolchildren: a 2-year randomised clinical trial. *Br J Ophthalmol*, 98, 40-5.
Lang, J. & Rah, M.J. 2004. Adverse corneal events associated with corneal reshaping: A case series. *Eye Contact Lens*, 30, 231-233.
Leat, S., Chan, L., Maharaj, P., et al. 2013. Binocular Vision and Eye Movement Disorders in Older Adults. *Invest. Ophthalmol. Vis. Sci.*, 54, 3798-3805.
Lee, H.K. & Kim, M.K. 2018. Comparison of a new swept-source optical biometer with a partial coherence interferometry. *BMC Ophthalmology*, 18.
Lee, J. J., Fang, P. C., Yang, I. H., et al. 2006 Prevention of myopia progression with 0.05% atropine solution. *J Ocul Pharmacol Ther*, 22, 41-46.
Lee, T.T. & Cho, P. 2013. Relative peripheral refraction in children: twelve-month changes in eyes with different ametropias. *Ophthalmic Physiol Opt*, 33, 283-293.
Lee, W. B. & Gotay, A. 2010. Bilateral Acanthamoeba Keratitis in Synergeyes Contact Lens Wear: Clinical and Confocal Microscopy Findings. *Eye & Contact Lens-Science and Clinical Practice,* 36**,** 164-169.
Legerton, J. A., Merz, D., Collins, J. & Chen, B. 2007. Hybrid contact lens system and method of fitting. Google Patents, patent number US20060250576 A1.
Lemon, T.I. & Shah, R.D. 2013. Relationship between interblink interval and dopamine. *Clin Ophthalmol*, 7, 793-4.
Leshno, A., Farzavandi, S.K., Gomez-de-Liano, R., et al. 2020. Practice patterns to decrease myopia progression differ among paediatric ophthalmologists around the world. *Br J Ophthalmol*, 104, 535-540.
Lewis, J.R., Knellinger, A.E., Mahmoud, A.M., et al. 2008. Effect of Soft Contact Lenses on Optical Measurements of Axial Length and Keratometry for Biometry in Eyes with Corneal Irregularities. *Invest. Ophthalmol. Vis. Sci.*, 49, 3371-3378.
Leydolt, C., Findl, O., Drexler, W. 2008. Effects of change in intraocular pressure on axial eye length and lens position. *Eye (Lond)*, 22, 657–661.
Li, J. & Zhang, Q. 2017. Insight into the molecular genetics of myopia. *Mol Vis*, 23, 1048-1080.
Sanfilippo, P.G., Hewitt, A.W., Hammond, C.J., Mackey, D.A. 2010. The heritability of ocular traits. *Surv Ophthalmol*, 55, 561-583.
Li, K., Liu, X., Chen, Z., et al. 2010. Quantification of tear proteins and sPLA2-IIa alteration in patients with allergic conjunctivitis. *Mol. Vis.*, 16, 2084-2091.
Li, S.M., Ji, Y.Z., Wu, S.S., et al. 2011. Multifocal versus single vision lenses intervention to slow progression of myopia in schoolage children: a meta-analysis. *Surv Ophthalmol*, 56, 451-460.
Li, S.M., Li, S.Y., Kang, M.T., et al. 2015. Near work related parameters and myopia in Chinese children: the Anyang Childhood Eye Study. *PLoS One*, 10, e0134514.
Li, S.M., Wu, S.S., Kang, M.T., et al. 2014. Atropine slows myopia progression more in Asian than white children by meta-analysis. *Optom Vis Sci*, 91, 342-350.
Li, T., Troilo, D., Howland, H.C. 2000. Diurnal illumination patterns affect the development of the chick eye. *Vision Res*, 40, 2387-2393.
Liang, C.L., His, E., Chen, K.C., Pan, Y.R., Wang, Y.S., Juo, S.H.H. 2011. A functional polymorphism at 30 UTR of the PAX6 gene may confer risk for extreme myopia in the Chinese. *Invest Ophthalmol Vis Sci*, 52, 3500-3505.
Liang, H., Crewther, S.G., Crewther, D.P., Junghans, B.M. 2004. Structural and elemental evidence for edema in the retina, retinal pigment epithelium, and choroid during recovery from experimentally induced myopia. *Invest Ophthalmol Vis Sci*, 45, 2463-2474.
Lim, L. S., Gazzard, G., Low, Y. L., Choo, R., et al. 2010. Dietary factors, myopia, and axial dimensions in children. Ophthalmology, 117, 993-997.
Lim, M. C., Gazzard, G., Sim, E. L, et al. 2009. Direct costs of myopia in Singapore.

Eye (Lond), 23, 1086-1089.
Lin, H., Long, E., Ding, X., et al. 2018. Prediction of myopia development among Chinese school-aged children using refraction data from electronic medical records: A retrospective, multicentre machine learning study. *PLoS Med*, 15: e1002674.
Lin, L. L., Shih, Y. F., Lee, Y. C., Hung, P. T. & Hou, P. K. 1996. Changes in ocular refraction and its components among medical students – A 5-year longitudinal study. *Optom Vis Sci*, 73, 495-498.
Lin, Z., Martinez, A., Chen, X., et al. 2010. Peripheral defocus with single-vision spectacle lenses in myopic children. *Optom Vis Sci,* 87, 4-9.
Lin, Z., Vasudevan, B., Jhanji, V., et al. 2014. Near work, outdoor activity, and their association with refractive error. *Optom Vis Sci*, 91, 376–382.
Llorente, L., Barbero, S., Cano, D., et al. 2004. Myopic versus hyperopic eyes: axial length, corneal shape and optical aberrations. *J Vis*, 4, 288-298.
Lloyd, M.A., O'Dwyer, V., Simo, M.L. 2014. The influence of soft contact lens wear and two weeks cessation of lens wear on corneal curvature. *Cont Lens Anterior Eye*, 37, 31–37.
Lopes-Ferreira, D., Ribeiro, C., Maia, R., et al. 2011. Peripheral myopization using a dominant design multifocal contact lens. *J Optom*, 4, 14-32.
Loughman, J. & Flitcroft, D.I. 2016. The acceptability and visual impact of 0.01% atropine in a Caucasian population. *Br J Ophthalmol*, 100, 1525-1529.
Lu, F., Simpson, T., Sorbara, L. and Fonn, D. 2007. The relationship between the treatment zone diameter and visual, optical and subjective performance in Corneal Refractive Therapy lens wearers. *Ophthal. Physiol. Opt*, 27, 568-578.
Lui, W., Edwards, M. H. and Cho, P. 2000. Contact lenses in myopia reduction – from orthofocus to accelerated Orthokeratology. *Cont. Lens Anterior Eye*, 23, 68-76.
Lundstrom, L. & Rosen, R. 2017. Peripheral aberrations. In: ´ Handbook of Visual Optics. Fundamentals and Eye Optics. Vol. 1. London: CRC Press; 313-335.
Lyhne, N., Sjolie, A. K., Kyvik, K. O. & Green, A. 2001. The importance of genes and environment for ocular refraction and its determiners: a population based study among 20–45 year old twins. *Br J Ophthalmol*, 85, 1470-1476.
Machan, C., Hrynchak, P., and Irving, E. 2011. Waterloo Eye Study: Data Abstraction and Population Representation. *Optometry and Vision Science*, 88, 613-620.
McAlinden, C., Wang, Q., Pesudovs, K., et al. 2015. Axial length measurement failure rates with the IOLMaster and Lenstar LS 900 in eyes with cataract. *PLoS ONE*, 10, 128–929.
McBrien, N.A. & Millodot, M. 1987. A biometric investigation of late onset myopic eyes. *Acta Ophthalmologica*, 65, 461-468.
McCullough, S. J., O'Donoghue, L., & Saunders, K. J. 2016. Six Year Refractive Change among White Children and Young Adults: Evidence for Significant Increase in Myopia among White UK Children. *PloS one*, 11, e0146332.
Manny, R.E., Chandler, D.L., Scheiman, M.M., et al (Correction of Myopia Evaluation Trial 2 Study Group for the Pediatric Eye Disease Investigator Group). 2009. Accommodative lag by autorefraction and two dynamic retinoscopy methods. *Optometry and Vision Science*, 86, 233-243.
Mao, X., Savini, G., Zhuo, Z., et al. 2013. Repeatability, reproducibility, and agreement of corneal power measurements obtained with a new corneal topographer. *J Cataract Refract Surg*, 39, 1561–1569.
Marsh-Tootle, W.L., Dong, L.M., Hyman, L., et al. 2009. Myopia progression in children wearing spectacles vs. switching to contact lenses. *Optom Vis Sci*, 86, 741-747.
Medina, A. 2015. The progression of corrected myopia. *Graefes Arch Clin Exp Ophthalmol*, 253, 1273-1277.
Mehravaran, S., Asgari, S., Bigdeli, S., et al. 2014. Keratometry with five different techniques: a study of device repeatability and inter-device agreement. *Int Ophthalmol*, 34, 869–875.

Meng, W., Butterworth, J., Malecaze, F., & Calvas, P. 2011. Axial length of myopia: a review of current research. *Ophthalmologica*, *225*, 127-134.
Metlapally, R., Li, Y.J., Tran-Viet, K.N., et al. 2009. COL1A1 and COL2A1 genes and myopia susceptibility: evidence of association and suggestive linkage to the COL2A1 locus. *Invest Ophthalmol Vis Sci*, 50, 4080-4086.
Mirshahi, A., Ponto, K.A., Hoehn, R., et al. 2014. Myopia and level of education: results from the Gutenberg Health Study. *Ophthalmology*, 121, 2047-2052.
Mizoguchi, T., Arita, R., Fukuoka, S., Morishige, N. 2017. Morphology and function of meibomian glands and other tear film parameters in junior high school students. *Cornea*, 36, 922-926.
Montes-Mico, R. 2001. Prevalence of general dysfunctions in binocular vision. *Ann Ophthalmol*, 33, 205-208.
Montes-Mico, R. & Ferrer-Blasco, T. 2000. Distribution of refractive errors in Spain. *Doc. Ophthalmol*., 101, 25-33.
Moore, K.E., Benoit, J.S., & Berntsen, D.A. 2017. Spherical Soft Contact Lens Designs and Peripheral Defocus in Myopic Eyes. *Optometry and vision science*, 94, 370-379.
Moore, K.E. & Berntsen, D.A. 2014. Central and peripheral autorefraction repeatability in normal eyes. *Optom Vis Sci.*, 91, 1106-1112.
Morgan, P. B., Efron, N. and Woods, C. A. 2011. An international survey of contact lens prescribing for presbyopia. International Contact Lens Prescribing Survey Consortium. *Clin Exp Optom*, 94, 87-92.
Morgan, I.G., French, A.N., Ashby, R.S., et al. 2018. The epidemics of myopia: aetiology and prevention. *Prog Retin Eye Res*, 62, 134–149.
Morgan, I.G., Ohno-Matsui, K. & Saw, S.M. 2012. Myopia. *Lancet*, 379, 1739-1748.
Morgan, I. & Rose, K. 2005. How genetic is school myopia?. *Prog Retin Eye Res*, 24, 1-38.
Morgan, I.G. & Rose, K.A. 2013. Myopia and international educational performance. *Ophthalmic Physiol Opt*, 33, 329-338.
Morgan, I. G., Rose, K. A. & Ellwein, L. B. 2010. Refractive Error Study in Children Survey Group. Is emmetropia the natural endpoint for human refractive development? An analysis of population-based data from the Refractive Error Study in Children (RESC). *Acta Ophthalmol,* 88, 877-884.
Morgan, I.G., Wu, P-C., Ostrin, L.A., et al. 2021. IMI Risk factors for myopia. *Invest Ophthalmol Vis Sci*, 62:3.
Moriarty, M., Lee, A., O'Connell, B. 2011. Development of an LC-MS/MS method for the analysis of serotonin and related compounds in urine and the identification of a potential biomarker for attention deficit hyperactivity/hyperkinetic disorder. *Anal. Bioanal. Chem*, 401, 2481-2493.
Moshirfar, M., Buckner, B., Ronquillo, Y.C., et al. 2019. Biometry in cataract surgery: a review of the current literature. *Curr Opin Ophthalmol*, 30, 9-12.
Mountjoy, E., Davies, N.M., Plotnikov, D., et al. 2018. Education and myopia: assessing the direction of causality by mendelian randomisation. *BMJ*, 361, k2022.
Muntz, A., Subbaraman, L. N., Sorbara, L. and Jones, L. 2014. Tear exchange and contact lenses: A review. *Journal of Optometry*, 8, 2-11.
Mutti, D.O., Cooper, M.E., O'Brien, S., et al. 2007. Candidate gene and locus analysis of myopia. *Mol Vis*, 13, 1012-1019.
Mutti, D. O., Hayes, J. R., Mitchell, G. L., et al; for the CLEERE Study Group. 2007. Refractive error, axial length, and relative peripheral refractive error before and after the onset of myopia. *Invest Ophthalmol Vis Sci*, 48, 2510-2519.
Mutti, D.O. & Marks, A.R. 2011. Blood levels of vitamin D in teens and young adults with myopia. *Optom Vis Sci*, 88, 377-382.

Mutti, D. O., Mitchell, G. L., Hayes, J. R., et al. 2006. Accommodative lag before and after the onset of myopia. *Invest Ophthalmol Vis Sci*, 47, 837-846.
Mutti, D. O., Mitchell, G. L., Jones, L. A., Friedman, N. E., et al. 2005. Axial Growth and Changes in Lenticular and Corneal Power during Emmetropization in Infants. *Investigative Ophthalmology & Visual Science*, 46, 3074-3080.
Mutti, D. O., Mitchell, G. L., Moeschberger, M. L., Jones, L. A. & Zadnik, K. 2002. Parental myopia, near work, school achievement, and children's refractive error. *Invest Ophthalmol Vis Sci*, 43, 3633-3640.
Mutti, D.O., Sinnott, L.T., Mitchell, G.L. et al. 2011. Relative peripheral refractive error and the risk of onset and progression of myopia in children. *Invest. Ophthalmol. Vis. Sci.*, 52, 199.
Mutti, D.O., Zadnik, K., Egashira, S., et al. 1994. The effect of cycloplegia on measurement of the ocular components. *Invest Ophthalmol Vis Sci.*, 35, 515-527.
Nakatsuka, C., Hasebe, S., Nonaka, F., et al. 2005. Accommodative lag under habitual seeing conditions: comparison between myopic and emmetropic children. *Jap J Ophthalmol*, 49, 189-194.
National Research Council. Working Group on Myopia Prevalence and Progression. Myopia: Prevalence and Progression. Washington, DC, National Academy Press, 1989.
Nebbioso, M., Plateroti, A.M., Pucci, B. 2014. Role of the dopaminergic system in the development of myopia in children and adolescents. *Journal of Child Neurology*, 29, 1739-1746.
Negrel, A.D., Maul, E., Pokharel, G.P., et al.2000. Refractive Error Study in Children: sampling and measurement methods for a multi-country survey. *Am J Ophthalmol*, 129, 421-426.
Nichkova, M., Wynveen, P.M., Marc, D.T., et al., 2013. Validation of an ELISA for urinary dopamine: applications in monitoring treatment of dopamine-related disorders. *Journal of Neurochemistry*, 125, 724-735.
Nickla, D.L. 2013. Ocular diurnal rhythms and eye growth regulation: where we are 50 years after Lauber. *Exp Eye Res*, 114, 25-34.
Nickla, D.L., Rada, J.A., Wallman, J. 1999. Isolated chick sclera shows a circadian rhythm in proteoglycan synthesis perhaps associated with the rhythm in ocular elongation. *J Comp Physiol A Neuroethol Sens Neural Behav Physiol*, 185, 81-90.
Nickla, D.L., Wildsoet, C.F., Troilo, D. 2002. Diurnal rhythms in intraocular pressure, axial length, and choroidal thickness in a primate model of eye growth, the common marmoset. *Invest Ophthalmol Vis Sci*, 43, 2519-2528.
Nieto-Bona, A., Gonzalez-Mesa, A., Nieto-Bona, M. P., Villa-Collar, C. & Lorente-Velazquez, A. 2011a. Long-term changes in corneal morphology induced by overnight orthokeratology. *Current eye research,* 36**,** 895-904.
Nieto-Bona, A., Gonzalez-Mesa, A., Nieto-Bona, M. P., Villa-Collar, C. & Lorente-Velazquez, A. 2011b. Short-term effects of overnight orthokeratology on corneal cell morphology and corneal thickness. *Cornea,* 30**,** 646-654.
Norton, T.T. & Rada, J.A. 1995. Reduced extracellular matrix in mammalian sclera with induced myopia. *Vision Res*, 35, 1271-1282.
Norton, T.T. & Siegwart, J.T. 1995. Animal models of emmetropization: matching axial length to the focal plane. *Basic Sci*, 66, 405-414.
Norton, T.T. & Siegwart, J.T Jr. 2013. Light levels, refractive development, and myopia – a speculative review. *Exp Eye Res*, 114, 48-57.
Nti, A.N., Ritchey, E.R., & Berntsen, D.A. 2021. Power profiles of centre-distance multifocal soft contact lenses. *Ophthalmic & physiological optics*, 41, 393-400.
Obermeyer, Z. & Emanuel, E.J. 2016. Predicting the Future – Big Data, Machine Learning, and Clinical Medicine. *N Engl J Med*, 375, 1216-1219.

Olsen, T. 1989. The accuracy of ultrasonic determination of axial length in pseudophakic eyes. *Acta ophthalmologica*, 67, 141–144.
Olsen, T. 2007. Improved accuracy of intraocular lens power calculation with the Zeiss IOLMaster. *Acta Ophthalmol Scand*, 85, 84–7.
Omali, N.B., Zhao, Z., Zhu, H., et al. 2013. Quantification of individual proteins in silicone hydrogel contact lens deposits. *Mol Vis*, 19, 390-399.
Orucoglu, F., Akman, M., Onal, S. 2015. Analysis of age, refractive error and gender related changes of the cornea and the anterior segment of the eye with Scheimpflug imaging. *Cont Lens Anterior Eye*, 38, 345–350.
Ozkurt, Y., Atakan, M. et al. 2012. Contact lens visual rehabilitation in keratoconus and corneal keratoplasty. *J Ophthalmol*.
Palomo, C., Puell, M., Sanchez-Ramos, C., et al. 2006. Normal values of distance heterophoria and fusional vergence ranges and effects of age. *Graefes Arch Clin Exp Ophthalmol*, 244, 821-824.
Pan, C.W., Ramamurthy, D., Saw, S.M. 2012. Worldwide prevalence and risk factors for myopia. *Ophthalmic Physiol Opt*, 32, 3-16.
Pandian, A., Sankaridurg, P.R., Naduvilath, T., et al. 2006. Accommodative facility in eyes with and without myopia. *Invest Ophthalmol Vis Sci*, 47, 4725-4731.
Paquin, M-P., Hamam, H., Simonet, P. 2002. Objective measurement of optical aberrations in myopic eyes. *Optom Vis Sci*, 79, 285-291.
Park, S.H., Park, K.H., Kim, J.M., et al. 2010. Relation between axial length and ocular parameters. *Ophthalmologica*, 224, 188–193.
Parssinen, O., Kauppinen, M., Viljanen, A. 2014. The Progression of Myopia From Its Onset at Age 8-12 to Adulthood and the Influence of Heredity and External Factors on Myopic Progression. A 23-year Follow-Up Study. *Acta Ophthalmol*, 92, 730-739.
Paune, J., Morales, H., Armengol, J., et al. 2015. Myopia control with a novel peripheral gradient soft lens and orthokeratology: a 2-year clinical trial. *Biomed Res Int*: 507572.
Paune, J., Thivent, S., Armengol, J., et al. 2016. Changes in Peripheral Refraction, Higher-Order Aberrations, and Accommodative Lag With a Radial Refractive Gradient Contact Lens in Young Myopes. *Eye & Contact Lens: Science & Clinical Practice,* 42, 380-387.
Peaston, R. & Weinkove, C. 2004. Measurement of catecholamines and their metabolites. *Ann. Clin. Biochem*, 41, 17-38.
Phillips, J.R., Khalaj, M., McBrien, N.A. 2000. Induced myopia associated with increased scleral creep in chick and tree shrew eyes. *Invest Ophthalmol Vis Sci*, 41, 2028-2034.
Pickwell, L.D., Kayet, N.A., Jenkins, T.C.A. 1991. Distance and near readings of associated heterophoria taken on 500 patients. *Ophthalmic Physiol Opt*, 11, 291-296.
Pierro, L., Camesasca, F. I., Mischi, M. & Brancato, R. 1992. Peripheral retinal changes and axial myopia. *Retina*, 12, 12-17.
Pilskalns, B., Fink, B. A. & Hill, R. M. 2007. Oxygen demands with hybrid contact lenses. *Optometry and Vision Science,* 84**,** 334-342.
Pineles, S.L., Kraker, R.T., VanderVeen, D.K., et al. 2017. Atropine for the prevention of myopia progression in children: a report by the American Academy of Ophthalmology. *Ophthalmol*, 124, 1857-1866.
Pinero, D. P., Carracedo, G., Ruiz-Fortes, P. & Perez-Cambrodi, R. J. 2015. Comparative analysis of the visual performance and aberrometric outcomes with a new hybrid and two silicone hydrogel multifocal contact lenses: a pilot study. *Clinical and Experimental Optometry,* 98**,** 451-458.
Pointer, J. S. 2002. Gender-related optical aspects of the onset of presbyopia. *Ophthalmic Physiol Opt*, 22, 126-129.

Polse, K. A., Brand, R. J., Schwalbe, J. S., Vastine, D. W. & Keener, R. J. 1983a. The Berkeley Orthokeratology Study, part II: efficacy and duration. *Am J Optom Physiol Opt*, 60, 187-198.
Polse, K. A., Brand, R. J., Keener, R. J., Schwalbe, J. S. & Vastine, D. W. 1983b. The Berkeley Orthokeratology Study, part III: safety. *Am J Optom Physiol Opt*, 60, 321-328.
Porcar, E. & Martinez-Palomera, A. 1997. Prevalence of general binocular dysfunctions in a population of university students. *Optom Vis Sci*,74, 111-113.
Posa, A., Bräuer, L., Schicht, M., et al. 2012. Schirmer strip vs. capillary tube method: Non-invasive methods of obtaining proteins from tear fluid. *Annals of Anatomy*, 195, 137-142.
Price, H., Allen, P.M., Radhakrishnan, H., et al. 2013. The Cambridge Anti-myopia Study: variables associated with myopia progression. *Optom Vis Sci*, 90, 1274-1283.
Przekoracka, K., Michalak, K., Olszewski, J., et al., 2020. Contrast sensitivity and visual acuity in subjects wearing multifocal contact lenses with high additions designed for myopia progression control. *Contact Lens and Anterior Eye*, 43, 33-39.
Pucker, A.D., Jackson, A.R., Morris, H.J., et al. 2015. Ciliary muscle cell changes during guinea pig development. *Invest Ophthalmol Vis Sci*, 56, 7691-7696.
Pucker, A.D., Sinnott, L.T., Kao, C.Y., Bailey, M.D. 2013. Region-specific relationship between refractive error and ciliary muscle thickness in children. *Invest Ophthalmol Vis Sci*, 54, 4710-4716.
Pussard, E., Neveux, M., Guigueno, N. 2009. Reference intervals for urinary catecholamines and metabolites from birth to adulthood. *Clin. Biochem*, 42, 536-539.
Qian, Y., Xue, F., Huang, J., Qu, X., Zhou, X. & Van Lanen-Wanek, D. 2014. Pachymetry Map of Corneal Epithelium in Children Wearing Orthokeratology Contact Lenses. *Current Eye Research,* 39**,** 263-270.
Rabin, J., Van Sluyters, R.C., Malach, R. 1981. Emmetropization: a vision-dependent phenomenon. *Invest Ophthalmol Vis Sci*, 20, 561-564.
Radley, D.C., Finkelstein, S.N., Stafford, R.S. 2006. Off-label prescribing among office-based physicians. *Arch Intern Med*, 166, 1021-1026.
Rah, M.J., Walline, J.J., Jones-Jordan, L.A., et al. 2010. Vision specific quality of life of pediatric contact lens wearers. *Optom Vis Sci*, 87, 560-566.
Rajagopalan, A.S., Bennett, E.S., Lakshminarayanan, V. 2007. Contrast sensitivity with presbyopic contact lenses. *J. Mod. Opt.*, 54, 1325-1332.
Ramamirtham, R., Kee, C.S., Hung, L.F., et al. 2007. Wave aberrations in rhesus monkeys with vision-induced ametropias. *Vision Res*, 47, 2751-2766.
Ramessur, R., Williams, K.M., Hammond, C.J. 2015. Risk factors for myopia in a discordant monozygotic twin study. *Ophthalmic Physiol Opt*, 35, 643-651.
Read, S.A., Collins, M.J., Annis-Brown, T., et al. 2011. The short-term influence of elevated intraocular pressure on axial length. *Ophthalmic Physiol Opt*, 31, 398–403.
Read, S.A., Collins, M.J., Iskander, D.R. 2008. Diurnal variation of axial length, intraocular pressure, and anterior eye biometrics. *Invest Ophthalmol Vis Sci*, 49, 2911–2918.
Read, S.A., Collins, M.J., Sander, B.P. 2010. Human optical axial length and defocus. *Invest Ophthalmol Vis Sci*, 51, 6262-6269.
Read, S.A., Collins, M.J., Vincent, S.J. 2014. Light exposure and physical activity in myopic and emmetropic children. *Optom Vis Sci*, 91, 330-341.
Read, S.A., Collins, M.J., Vincent, S.J. 2015. Light exposure and eye growth in childhood. *Invest Ophthalmol Vis Sci*, 56, 6779-6787.
Read, S.A., Collins, M.J., Woodman, E.C., et al. 2010. Axial length changes during accommodation in myopes and emmetropes. *Optom Vis Sci*, 87, 656–662.
Renna, A., Alió, J.L. and Vejarano, L.F. 2017. Pharmacological treatments of presbyopia: a review of modern perspectives. *Eye and Vision*, *4*, 3.

Richdale, K., Bullimore, M., and Zadnik, K. 2016. The effect of age, accommodation and refractive error on the adult human eye. *Optom Vis Sci*, 93, 3-11.
Richdale, K., Sinnott, L.T., Bullimore, M.A., et al. 2013. Quantification of age-related and per diopter accommodative changes of the lens and ciliary muscle in the emmetropic human eye. *Invest Ophthalmol Vis Sci.*, 54, 1095-1105.
Richter, G.M., Wang, M., Jiang, X., et al. 2017. Ocular determinants of refractive error and its age- and sex-related variations in the Chinese American eye study. *JAMA Ophthalmol*, 135, 724–732.
Riddell, N. & Crewther, S.G. 2017. Novel evidence for complement system activation in chick myopia and hyperopia models: a meta-analysis of transcriptome datasets. *Sci Rep*, 7, 9719.
Roessler, G.F., Dietlein, T.S., Plange, N., et al. 2012. Accuracy of intraocular lens power calculation using partial coherence interferometry in patients with high myopia. *Ophthalmic Physiol Opt*, 32, 228–33.
Rohrer, K., Frueh, B.E., Wälti, R., et al. 2009. Comparison and evaluation of ocular biometry using a new noncontact optical low-coherence reflectometer. *Ophthalmology*, 116, 2087–92.
Rosa, N., Lanza, M., Capasso, L., et al. 2006. Anterior chamber depth measurement before and after photorefractive keratectomy: comparison between IOL master and Orbscan II. *Ophthalmology*, 113, 962–969.
Rose, K.A., French, A.N., Morgan, I.G. 2016. Environmental factors and myopia: paradoxes and prospects for prevention. *Asia Pac J Ophthalmol (Phila)*, 5, 403-410.
Rose, K.A., Morgan, I.G., Ip, J., et al. .2008. Outdoor activity reduces the prevalence of myopia in children. *Ophthalmology*, 115. 1279-1285.
Rose, K.A., Morgan, I.G., Smith, W., et al. 2008. Myopia, lifestyle, and schooling in students of Chinese ethnicity in Singapore and Sydney. *Arch Ophthalmol*, 126, 527-530.
Rose, K.A., Morgan, I.G., Smith, W., Mitchell, P. 2002. High heritability of myopia does not preclude rapid changes in prevalence. *Clin Experiment Ophthalmol*, 30, 168-172.
Rosenfield, M., Desai, R. & Portello, J. K. 2002. Do progressing myopes show reduced accommodative responses? *Optom Vis Sci,* 79, 268-273.
Rozema, J., Dankert, S., Iribarren, R., et al. 2019. Axial Growth and Lens Power Loss at Myopia Onset in Singaporean Children. *Invest Ophthalmol Vis Sci*, 60, 3091-3099.
Rucker, F.J. 2013. The role of luminance and chromatic cues in emmetropisation. *Ophthalmic Physiol Opt*, 33, 196-214.
Rudnicka, A.R., Owen, C.G., Nightingale, C.M., et al. 2010. Ethnic differences in the prevalence of myopia and ocular biometry in 10- and 11-year-old children: the Child Heart and Health Study in England (CHASE). *Invest Ophthalmol Vis Sci*, 51, 6270-6276.
Rudnicka, A.R., Steele, C.F., Crabb, D.P., et al. 1992. Repeatability, reproducibility and intersession variability of the Allergan Humphrey ultrasonic biometer. *Acta Ophthalmol*, 70, 327–334.
Ruiz-Pomeda, A., Perez-Sanchez, B., Canadas, P., et al. 2019. Binocular and accommodative function in the controlled randomized clinical trial MiSight Assessment Study Spain (MASS). *Graefe's Archive for Clinical and Experimental Ophthalmology*, 257, 207-215.
Ruiz-Pomeda, A., Perez-Sanchez, B., Valls, I., et al. 2018. MiSight Assessment Study Spain (MASS). A 2-year randomized clinical trial. *Graefe's Archive for Clinical and Experimental Ophthalmology*, 256, 1011–1021.
Saka, N., Moriyama, M., Shimada, N., et al. 2013. Changes of axial length measured by IOL master during 2 years in eyes of adults with pathologic myopia. *Graefes Arch Clin Exp Ophthalmol*, 251, 495–499.

Salouti, R., Nowroozzadeh, M. H., Zamani, M., et al. 2011. Comparison of the ultrasonographic method with 2 partial coherence interferometry methods for intraocular lens power calculation. *Optometry*, 82, 140–147.
Sanchez, I., Ortiz-Toquero, S., Blanco, M., Martin, R. 2018. A new method to analyse the effect of multifocal contact lenses on visual function. *Contact Lens and Anterior Eye*, 41, 169-174.
Sankaridurg, P. 2017. Contact lenses to slow progression of myopia. *Clin Exp Optom*, 100, 432-437.
Sankaridurg, P., Bakaraju, R.C., Naduvilath, T., et al. 2019. Myopia control with novel central and peripheral plus contact lenses and extended depth of focus contact lenses: 2 year results from a randomised clinical trial. *Ophthalmic & physiological optics*, 39, 294-307.
Sankaridurg, P., Donovan, L., Varnas, S., et al. 2010. Spectacle lenses designed to reduce progression of myopia: 12-month results. *Optom Vis Sci*, 87, 631-641.
Sankaridurg, P., He, X., Naduvilath, T., et al. 2017. Comparison of noncycloplegic and cycloplegic autorefraction in categorizing refractive error data in children. *Acta Ophthalmol*, 95, 633-640.
Sankaridurg, P.R. & Holden, B.A. 2014. Practical applications to modify and control the development of ametropia. *Eye*, 28, 134-141.
Sankaridurg, P., Holden, B., Smith, E 3rd., et al. 2011. Decrease in rate of myopia progression with a contact lens designed to reduce relative peripheral hyperopia: one-year results. *Invest Ophthalmol Vis Sci*, 52, 9362-9367.
Santodomingo-Rubido, J., Mallen, E.A., Gilmartin, B., et al. 2002. A new non-contact optical device for ocular biometry. *Br J Ophthalmol*, 86, 458–462.
Santodomingo-Rubido, J., Villa-Collar, C., Gilmartin, B., Gutierrez-Ortega, R. 2012b. Myopia control with orthokeratology contact lenses in Spain: refractive and biometric changes. *Invest Ophthalmol Vis Sci*, 53, 5060-5065.
Santodomingo-Rubido, J., Villa-Collar, C., Gilmartin, B., et al. 2017. Long-term efficacy of orthokeratology contact lens wear in controlling the progression of childhood myopia. *Curr Eye Res*, 42, 713-720.
Saville, J.T., Zhao, Z., Willcox, M.D., et al. 2010. Detection and quantification of tear phospholipids and cholesterol in contact lens deposits: the effect of contact lens material and lens care solution. *Invest Ophthalmol Vis Sci*, 51, 2843-2851.
Saw, S.M., Chua, W.H., Gazzard, G., et al. 2005. Eye growth changes in myopic children in Singapore. *Br J Ophthalmol*, 89, 1489–1494.
Saw, S.M., Gazzard, G., Shih-Yen, E.C., et al. 2005. Myopia and associated pathological complications. *Ophthalmic Physiol. Opt.*, 25, 381-391.
Saw, S.M., Nieto, F.J., Katz, J., et al. 2000. Factors related to the progression of myopia in singaporean children. *Optom Vis Sci*, 77, 549-554.
Saw, S.M., Nieto, F.J., Katz, J., et al. 2001. Familial clustering and myopia progression in Singapore school children. *Ophthalmic Epidemiol*, 8, 227-236.
Schachar, R. 2000. Theoretical basis for the scleral expansion band procedure for surgical reversal of presbyopia (SRP). *Annals of Ophthalmology*, 32, 271-278.
Schache, M., Richardson, A. J., Mitchell, P., et al. 2013. Genetic association of refractive error and axial length with 15q14 but not 15q25 in the Blue Mountains Eye Study cohort. *Ophthalmology*, 120, 292-297.
Shah, S. & Jani, H. 2015. Prevalence and associated factors of dry eye: Our experience in patients above 40 years of age at a Tertiary Care Center. *Oman Journal of Ophthalmology*, 8, 151-156.
Shammas, H.J., Ortiz, S., Shammas, M.C., et al. 2016. Biometry measurements using a new large-coherence-length swept-source optical coherence tomographer. *J Cataract Refract Surg*, 42, 50-61.

Sharma, N.S., Acharya, S.K., Nair, A.P., et al. 2019. Dopamine levels in human tear fluid. *Indian journal of ophthalmology*, *67*, 38-41.
Sherwin, J.C., Reacher, M.H., Keogh, R.H., et al. 2012. The association between time spent outdoors and myopia in children and adolescents: a systematic review and meta-analysis. *Ophthalmology*., 119, 2141-2151.
Shetty, R., Deshmukh, R., Ghosh, A., et al. 2017. Altered tear inflammatory profile in indian keratoconus patients-the 2015 col rangachari award paper. *Indian J Ophthalmol*, 65, 1105-8.
Shetty, R., Sethu, S., Chevour, P., et al. 2016. Lower Vitamin D level and distinct tear cytokine profile were observed in patients with mild dry eye signs but exaggerated symptoms. *Transl Vis Sci Technol*, 5, 16.
Shih, Y.F., Chen, C.H., Chou, A.C., et al. 1999. Effects of different concentrations of atropine on controlling myopia in myopic children. *J Ocul Pharmacol Ther*., 15, 85-90.
Siatkowski, R. M., Cotter, S., Miller, J. M., et al. 2004. Safety and efficacy of 2% pirenzepine ophthalmic gel in children with myopia: a 1-year, multicenter, double-masked, placebo-controlled parallel study. *Arch Ophthalmol*, 122, 1667-1674.
Siatkowski, R. M., Cotter, S. A., Crockett, R. S., Miller, J. M., et al. 2008. Two-year multicenter, randomized, double-masked, placebo-controlled, parallel safety and efficacy study, of 2% pirenzepine ophthalmic gel in children with myopia. *Journal of Aapos,* 12**,** 332-339.
Siegwart, J.T. & Norton, T.T. 1999. Regulation of the mechanical properties of tree shrew sclera by the visual environment. *Vision Res*, 39, 387-407.
Small, D., Hevy, J., Tang-Liu, D. 2000. Comparison of tear sampling techniques for pharmacokinetics analysis: ofloxacin concentrations in rabbit tears after sampling with Schirmer tear strips, capillary tubes, or surgical sponges. *J. Ocul. Pharmacol. Ther*, 16, 439-446.
Smith, E.L. 2010. A case for peripheral optical treatment strategies for myopia. *Optom Vis Sci*, 88, 1029-1044.
Smith, E. L., III. 2013. Optical treatment strategies to slow myopia progression: Effects of the visual extent of the optical treatment zone. *Experimental Eye Research,* 114**,** 77-88.
Smith, E. L. 3rd., Hung, L. F. & Huang, J. 2009. Relative peripheral hyperopic defocus alters central refractive development in infant monkeys. *Vision Res*, 49, 2386-2392.
Smith, E. L., Hung, L.-F. & Huang, J. 2012. Protective effects of high ambient lighting on the development of form-deprivation myopia in rhesus monkeys. *Investigative ophthalmology & visual science,* 53**,** 421.
Smith, E. L. 3rd., Ramamirtham, R., et al. 2007. Effects of foveal ablation on emmetropization and form-deprivation myopia. *Invest Ophthalmol Vis Sci*, 48, 3914-3922.
Smith, M. J. & Walline, J. J. 2015. Controlling myopia progression in children and adolescents. *Adolescent health, medicine and therapeutics,* 6**,** 133-40.
Smith, T., Frick, K., Holden, B., et al. 2009b. Potential lost productivity resulting from the global burden of uncorrected refractive error. *Bull World Health Org*, 87, 431-437.
Sng, C.C., Lin, X.Y., Gazzard, G., et al. 2011. Peripheral refraction and refractive error in singapore chinese children. *Invest Ophthalmol Vis Sci*, 52, 1181-1190.
Srivannaboon, S., Chirapapaisan, C., Chonpimai, P., et al. 2015. Clinical comparison of a new swept-source optical coherence tomography-based optical biometer and a time-domain optical coherence tomography-based optical biometer. *J Cataract Refract Surg*, 41, 2224–32.
Stambolian, D. 2013. Genetic susceptibility and mechanisms for refractive error. *Clin Genet*, 84, 102-108.
Starr, M.S. 1996. The role of dopamine in epilepsy. *Synapse*, 22, 159-94.
Stone, R.A., Lin, T., Laties, A.M. 1991. Muscarinic antagonist effects on experimental chick myopia. *Exp Eye Res*, 52, 755-758.

Stone, R.A., Pardue, M.T., Iuvone, P.M., Khurana, T.S. 2013. Pharmacology of myopia and potential role for intrinsic retinal circadian rhythms. *Exp Eye Res*, 114, 35-47.
Stone, R.A., Quinn, G.E., Francis, E.L., et al. 2004. Diurnal axial length fluctuations in human eyes. *Invest Ophthalmol Vis Sci*, 45, 63–70.
Strenk, S.A., Strenk, L.M., Guo, S. 2006. Magnetic resonance imaging of aging, accommodating, phakic, and pseudophakic ciliary muscle diameters. *J Cataract Refract Surg*, 32, 1792-1798.
Suominen, T., Uutela, P., Ketola, R.A., et al. 2013. Determination of serotonin and dopamine metabolites in human brain microdialysis and cerebrospinal fluid samples by UPLC-MS/MS: Discovery of intact glucuronide and sulfate conjugates. *PLoS One*, 8, e68007.
Swarbrick, H. A., Wong, G. and O'Leary, D. J. 1998. Corneal response to orthokeratology. *Optometry and Vision Science*, 75, 791-799.
Tan, D. T. H., Lam, D. S., Chua, W. H., et al. 2005. One-year multicenter, double-masked, placebo-controlled, parallel safety and efficacy study of 2% pirenzepine ophthalmic gel in children with myopia. *Ophthalmology*, 112, 84-91.
Tan, Q., Ng, A.L.K., Choy, B.N.K., et al. 2020. One-year results of 0.01% atropine with orthokeratology (AOK) study: a randomised clinical trial. *Ophthalmic Physiol Opt*, 40, 557-566.
Tang, S.M., Rong, S.S., Young, A.L., et al. 2014. PAX6 gene associated with high myopia: a meta-analysis. *Optom Vis Sci*, 91, 419-429.
Tedja, M.S., Haarman, A.E.G., Meester-Smoor, M.A., et al. 2019. for the CREAM Consortium, IMI – Myopia Genetics Report. *Invest Ophthalmol Vis Sci*, 60, 89-105.
Tedja, M.S., Wojciechowski, R., Hysi, P.G., et al. 2018. Genome-wide association meta-analysis highlights light-induced signaling as a driver for refractive error. *Nat Genet*, 50, 834-848
Teves, M., Shi, Q., Stell, W.K. 2014. The role of cell-cell coupling in myopia development and light adaptation. *Investigative Ophthalmology & Visual Science*, 55, 3036.
Thibos, L.N., Wheeler, W., Horner, D. 1997. Power vectors: an application of Fourier analysis to the description and statistical analysis of refractive error. *Optom Vis Sci*., 74, 367-375.
Thorn, F., Gwiazda, J. & Held, R. 2005. Myopia progression is specified by a double exponential growth function. *Optom Vis Sci*, 82, 286–297.
Ticak, A. & Walline, J.J. 2013. Peripheral optics with bifocal soft and corneal reshaping contact lenses. *Optom Vis Sci*, 90, 3-8.
Tideman, J.W.L., Polling, J.R., Voortman, T., et al. 2016a. Low serum vitamin D is associated with axial length and risk of myopia in young children. *Eur J Epidemiol*, 31, 491-499.
Tideman, J.W.L., Polling, J.R., Vingerling, J.R., et al. 2018. Axial length growth and the risk of developing myopia in European children. *Acta Ophthalmologica*, 96, 301-309.
Tideman, J.W.L., Snabel, M.C., Tedja, M.S., et al. 2016. Association of axial length with risk of uncorrectable visual impairment for Europeans with myopia. *JAMA ophthalmology*, *134*, 1355-1363.
Tigges, M., Iuvone, P.M., Fernandes, A., et al. 1999. Effects of muscarinic cholinergic receptor antagonists on postnatal eye growth of rhesus monkeys. *Optom Vis Sci*, 76, 397-407.
Tong, L., Huang, X. L., Koh, A. L., Zhang, X., et al. 2009 Atropine for the treatment of childhood myopia: effect on myopia progression after cessation of atropine. *Ophthalmology*, 116, 572-579.
Tonn, B., Klaproth, OK., Kohnen, T. 2014. Anterior surface-based keratometry compared with Scheimpflug tomography-based total corneal astigmatism. *Invest Ophthalmol Vis Sci*, 56, 291–298.
Torii, H., Ohnuma, K., Kurihara, T., et al. 2017. Violet light transmission is related to myopia progression in adult high myopia. *Sci Rep*, 7, 14523.

Trier, K., Munk, Ribel-Madsen S., Cui, D., Brogger, Christensen S. 2008. Systemic 7-methylxanthine in retarding axial eye growth and myopia progression: a 36-month pilot study. *J Ocular Biol Dis Informat*, 1, 85-93.
Troilo, D., Smith III, E.L., Nickla, D.L., et al. 2019. IMI – Report on Experimental Models of Emmetropization and Myopia. *Invest Ophthalmol Vis Sci*., 60, 31-88.
Trope, G.E. & Rumley, A.G. 1984. Catecholamine concentrations in tears. *Exp Eye Res*, 39, 247-50.
Tsunoda, M. 2006. Recent advances in methods for the analysis of catecholamines and metabolites. *Anal. Bioanal. Chem*, 386, 506-514.
Tung, H. C. 2003. Orthokeratology and bi-focal contact lens. Google Patents, patent number US6652095 B2.
Twelker, J.D. & Mutti, D.O. 2001. Retinoscopy in infants using a near noncycloplegic technique, cycloplegia with tropicamide 1%, and cycloplegia with cyclopentolate 1%. *Optom Vis Sci*, 78, 215-222.
Ucakhan, O.O., Gesoglu, P., Ozkan, M., et al. 2008. Corneal elevation and thickness in relation to the refractive status measured with the Pentacam Scheimpflug system. *J Cataract Refract Surg*, 34, 1900–1905.
van Alphen, GWHM. 1986. Choroidal stress and emmetropization. *Vision Res*, 26, 723-734.
Verzhanskaya, T.Y. & Tarutta, E.P. 2017. Stabilizing effectiveness of orthokeratology and long-term minute-concentration atropine therapy in myopia [in Russian]. *Vestn Oftalmol*, 133, 43-48.
Van Haeringen, N.J. 1981. Clinical biochemistry of tears. *Surv Ophthalmol*, 26, 84-96.
van Setten, G.B., Stephens, R., Tervo, T., et al. 1990. Effects of the Schirmer test on the gibrinolytic system in the tear fluid. *Exp. Eye Res*, 50, 135-141.
van den Berg, T.J.T.P., Franssen, L., Coppens, J.E. 2010. Ocular media clarity and straylight, *Encycl. Eye*, 173-183.
Vasudevan, B., Esposito, C., Peterson, C., et al. 2014. Under-correction of human myopia–Is it myopigenic?: A retrospective analysis of clinical refraction data. *Journal of optometry,* 7**,** 147-152.
Ventola, C.L. 2009. Off-label drug information: regulation, distribution, evaluation, and related controversies. *P T*, 34, 428-440.
Verhoeven, V.J., Hysi, P.G., Wojciechowski, R., et al. 2013. Genomewide meta-analyses of multiancestry cohorts identify multiple new susceptibility loci for refractive error and myopia. *Nat Genet*, 45, 314-318.
Verkicharla, P., Ramamurthy, D., Nguyen, Q., et al. 2017. Development of the FitSight Fitness Tracker to Increase Time Outdoors to Prevent Myopia. *Translational Vision Science & Technology*, 6.
Vitale, S., Cotch, M. F., Sperduto, R., et al. 2006. Costs of refractive correction of distance vision impairment in the United States, 1999-2002. *Ophthalmology*, 113, 2163-2170.
Vitale, S., Ellwein, L., Cotch, M. F., et al. 2008. Prevalence of refractive error in the United States, 1999-2004. *Arch Ophthalmol*, 126, 1111-1119.
Vitale, S., Sperduto, R.D., and Ferris, F.L. 2009. Increased prevalence of myopia in the United States between 1971-1972 and 1999-2004. *Archives of ophthalmology*., 127, 1632-1639.
Vogel, A., Dick, H.B., Krummenauer, F. 2001. Reproducibility of optical biometry using partial coherence interferometry: intraobserver and interobserver reliability. *J Cataract Refract Surg*, 27, 1961–1968.
Vongphanit, J., Mitchell, P. and Wang, J. J. 2002. Prevalence and progression of myopic retinopathy in an older population. *Ophthalmology,* 109**,** 704-711.

Voo, I., Lee, D. A. & Oelrich, F. O. 1998. Prevalences of ocular conditions among Hispanic, white, Asian, and black immigrant students examined by the UCLA Mobile Eye Clinic. *J Am Optom Assoc*, 69, 255–261.
Wahl, S., Fornoff, L., Ochakovski, G.A., et al. 2018. Disability glare in soft multifocal contact lenses. *Contact Lens & Anterior Eye*, 41, 175-179.
Walline, J.J., Gaume Giannoni, A., Sinnott, L.T., et al. 2017. A randomized trial of soft multifocal contact lenses for myopia control: baseline data and methods. *Optom Vis Sci*, 94, 856-866.
Walline, J.J., Greiner, K.L., McVey, M.E., et al. 2013. Multifocal contact lens myopia control. *Optom Vis Sci*, 90, 1207-14.
Walline, J. J., Jones, L. A., et al. 2004. A randomized trial of the effects of rigid contact lenses on myopia progression. *Arch Ophthalmol*, 122, 1760-1766.
Walline, J. J., Jones, L. A., Sinnott, L., et al. 2009b. Randomized trial of the effect of contact lens wear on self-perception in children. *Optom Vis Sci*, 86, 222–232.
Walline, J., Jones-Jordan, L.A., Greiner, K.L., et al. 2011. The effects of soft bifocal contact lenses on myopia progression in children. *Optom Vis Sci*, 88.
Walline, J. J., Lindsley, K., Vedula, S. S., et al. 2011. Interventions to slow progression of myopia in children. *Cochrane Database Syst Rev*, 12, 1-121.
Walline, J.J., Walker, M.K., Mutti, D.O., et al. 2020. Effect of High Add Power, Medium Add Power, or Single-Vision Contact Lenses on Myopia Progression in Children: The BLINK Randomized Clinical Trial. *JAMA*, 324, 571-580.
Wang, J. & Candy, T.R. 2005. Higher order monochromatic aberrations of the human infant eye. *J Vis*, 5, 543-555.
Wang, T. J., Chiang, T. H., Wang, T. H., et al. 2009. Changes of the ocular refraction among freshmen in National Taiwan University between 1988 and 2005. *Eye (Lond)*, 23, 1168–1169.
Wang, D., Chun, R.K., Liu, M., et al. 2016. Optical defocus rapidly changes choroidal thickness in schoolchildren. *PLoS One*, 11, e0161535.
Wang, B., Naidu, R.K., Qu, X. 2017. Factors related to axial length elongation and myopia progression in orthokeratology practice. *PLoS One*, 12:e0175913.
Wang, Q., Savini, G., Hoffer, K.J., et al. 2012. A comprehensive assessment of the precision and agreement of anterior corneal power measurements obtained using 8 different devices. *PLoS One 7*, e45607.
Wang, Y.R., Bian, H.L., Wang, Q. 2017. Atropine 0.5% eyedrops for the treatment of children with low myopia: a randomized controlled trial. *Medicine (Baltimore)*, 96:e7371.
Wang, Z.Y., Yang, W.L., Li, D.J., et al. 2019. [Comparison of biometry with the Pentacam AXL, IOLMaster 700 and IOLMaster 500 in cataract patients]. *Chinese journal of ophthalmology*, 55, 515–521.
Ward, B. 2013. Degenerative myopia: myopic macular schisis and the posterior pole buckle. *Retina*, 33, 224-231.
Weale, R. A. 2003. Epidemiology of refractive errors and presbyopia. *Surv Ophthalmol*, 48, 515-543.
Weizhong, L., Zhikuan, Y., Wen, L., et al. 2008. A longitudinal study on the relationship between myopia development and near accommodation lag in myopic children. *Ophthalmic Physiol Opt*, 28, 57-61.
Whitford, C., Studer, H., Boote, C., et al. 2015. Biomechanical model of the human cornea: considering shear stiffness and regional variation of collagen anisotropy and density. *Journal of the Mechanical Behavior of Biomedical Materials,* 42**,** 76-87.
WHO. 2019. World report on vision. Available at: https://www.who.int/publications/i/item/world-report-on-vision (Accessed: 2 December 2020).

Wildsoet, C.F. 1997. Active emmetropization: evidence for its existence and ramifications for clinical practice. *Ophthalmic Physiol Opt*, 17, 279-290.
Wildsoet, C.F., Chia, A., Cho, P., et al. 2019. IMI – Interventions for Controlling Myopia Onset and Progression Report. *Invest Ophthalmol Vis Sci*., 60, 106-131.
Willcox, M. 2019. Tear film, contact lenses and tear biomarkers. *Clin Exp Optom*, 102, 350-363.
Willcox, M., Pearce, D., Tan, M., et al. 2002. Contact lenses and tear film interactions. *Adv Exp Med Biol*, 506, 879-884.
Williams, K.M., Bentham, G.C., Young, I.S., et al. 2017. Association between myopia, ultraviolet B radiation exposure, serum vitamin D concentrations, and genetic polymorphisms in vitamin D metabolic pathways in a multicountry European study. *JAMA Ophthalmol*, 135, 47-53.
Williams, K. M., Verhoeven, V. J. M., Cumberland, P., et al. 2015. Prevalence of refractive error in Europe: the European Eye Epidemiology (E-3) Consortium. *European Journal of Epidemiology,* 30**,** 305-315.
Winn, B., Whitaker, D., Elliott, D. B. & Phillips, N. J. 1994. Factors affecting light-adapted pupil size in normal human subjects. *Invest. Ophthalmol. Vis. Sci,* 35, 1132-1137.
Wlodyga, R. & Bryla, C. 1989. Corneal molding: the easy way. *Contact Lens Spectrum,* 4**,** 58-65.
Wojciechowski, R., Stambolian, D., Ciner, E., et al. 2009. Genomewide linkage scans for ocular refraction and meta-analysis of four populations in the Myopia Family Study. *Invest Ophthalmol Vis Sci*, 50, 2024-2032.
Wolffsohn, J.S., Calossi, A., Cho, P., et al. 2016. Global trends in myopia management attitudes and strategies in clinical practice. *Cont Lens Anterior Eye*., 39, 106-116.
Wolffsohn, J.S., Flitcroft, D.I., Gifford, K.L., et al. 2019. IMI – Myopia control reports overview and introduction. *Invest Ophthalmol Vis Sci*., 60, M1–M19.
Wolffsohn, J.S., Kollbaum, P.S., Berntsen, D.A., et al. 2019. IMI – Clinical Myopia Control Trials and Instrumentation Report. *Invest Ophthalmol Vis Sci*, 60, 132–160.
Wong, T. Y., Klein, B. E., Klein, R., et al. 2003. Refractive errors, intraocular pressure, and glaucoma in a white population. *Ophthalmology*, 10, 211-217.
Wong, T. Y., Klein, B. E., Klein, R., et al. 2001. Refractive errors and incident cataracts: the Beaver Dam Eye Study. *Invest Ophthalmol Vis Sci*, 42, 1449-1454.
Wu, L.J., Wang, Y.X., You, Q.S., et al. 2015. Risk factors of myopic shift among primary school children in Beijing, China: a prospective study. *Int J Med Sci*, 12, 633-638.
Wu, P.C., Tsai, C. L., Wu, H. L., et al. 2013. Outdoor activity during class recess reduces myopia onset and progression in school children. *Ophthalmology*, 120, 1080-1085.
Wu, Y., Li, H., Tang, Y., Yan, X. 2017. Morphological evaluation of meibomian glands in children and adolescents using noncontact infrared meibography. *J Pediatr Ophthalmol Strabismus*, 54, 78-83.
Xiong, S., Sankaridurg, P., Naduvilath, T., Zang, J., et al. 2017. Time spent in outdoor activities in relation to myopia prevention and control: a meta-analysis and systemic review. *Acta Ophthalmol*, 95, 551-566.
Xu, Y., Duan, L., Fu, H., et al. 2018. Ocular disease detection from multiple informatics domains. *In Proceedings of the IEEE 15th International Symposium on Biomedical Imaging (ISBI)*, 43-47.
Yam, J., Jiang, Y., Tang, S., et al. 2019. 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*, 126, 113-124.
Yang, X., Chen, G., Qian, Y., et al. 2020. Prediction of Myopia in Adolescents through Machine Learning Methods. *Int. J. Environ. Res. Public Health*, 17, 463.

Yang, J.Y., Kim, H.K., Kim, S.S. 2017. Axial length measurements: comparison of a new swept-source optical coherence tomography-based biometer and partial coherence interferometry in myopia. *J Cataract Refract Surg*, 43, 328–332.
Yates, C.M., Allison, Y., Simpson, J., et al. 1979. Dopamine in alzheimer's disease and senile dementia. *Lancet*, 2, 851-2.
Yazdani, N., Sadeghi, R., Momeni-Moghaddam, H., et al. 2018. Comparison of cyclopentolate versus tropicamide cycloplegia: a systematic review and metaanalysis. *J Optom.*, 11, 135-143.
Yekta, A.A., Pickwell, L.D., Jenkins, T.C.A. 1989. Binocular vision, age and symptoms. *Ophthalmic Physiol Opt*, 9, 115-120.
Yen, M.Y., Liu, J.H., Kao, S.C., et al. 1989. Comparison of the effect of atropine and cyclopentolate on myopia. *Ann Ophthalmol*., 21, 180-182, 187.
Yi, S., Huang, Y., Yu, S.Z., et al. 2015. Therapeutic effect of atropine 1% in children with low myopia. *J AAPOS*, 19, 426-429.
Yoo, T.K., Choi, M.J., Lee, H.K., et al. 2017. Comparison of ocular biometry and refractive outcomes using IOL master 700, IOL master 500, and ultrasound. *J Korean Ophthalmol Soc*, 58, 523–9.
Yoshida, M., Okada, E., Mizuki, N., et al. 2001. Age-specific prevalence of open-angle glaucoma and its relationship to refraction among more than 60,000 asymptomatic Japanese subjects. *J Clin Epidemiol*, 54, 1151-1158.
You, J., Willcox, M., Fitzgerald, A., et al. 2015. Absolute quantification of human tear lactoferrin using multiple reaction monitoring technique with stable-isotopic labeling. *Analytical Biochemistry*, 496, 30-34.
Younan, C., Mitchell, P., Cumming, R. G., et al. 2002. Myopia and incident cataract and cataract surgery: the Blue Mountains Eye Study. *Invest Ophthalmol Vis Sci*, 43, 3625-3632.
Young, J.C., Tae, H.M., Kee, Y.C., et al. 2018. Comparison of Ocular Biometry Using New Swept-source Optical Coherence Tomography-based Optical Biometer with Other Devices. *Korean J Ophthalmol*, 32, 257–264.
Zadnik, K., Sinnott, L.T., Cotter, S.A., et al. 2015. Prediction of juvenile-onset myopia. *JAMA Ophthalmol*, 133, 683-689.
Zhang, M., Gazzard, G., Fu, Z., et al. 2011. Validating the Accuracy of a Model to Predict the Onset of Myopia in Children. *Investigative Ophthalmology & Visual Science*, 52, 5836-5841.
Zhang, M., Zou, Y., Zhang, F., et al. 2015. Efficacy of bluelight cross-linking on human scleral reinforcement. *Optom Vis Sci*, 92, 873-878.
Zheng, Y., Pan, C., Chay, J., Wong, T. Y., et al. 2013. The Economic Cost of Myopia in Adults Aged Over 40 Years in Singapore. *Invest. Ophthalmol. Vis. Sci,* 54, 7532-7537.
Zhou, L., Beuerman, R.W., Ang, L.P.K., et al. 2009. Elevation of human α-defensins and S100 calcium-binding proteins A8 and A9 in tear fluid of patients with pterygium. *Invest. Ophthalmol. Vis. Sci.*, 50, 2077-2086.
Zhu, X., McBrien, N.A., Smith, E.L III, et al. 2013. Eyes in various species can shorten to compensate for myopic defocus. *Invest Ophthalmol Vis Sci*, 54, 2634-2644.
Zhu, X., Park, T.W., Winawer, J., Wallman, J. 2005. In a matter of minutes, the eye can know which way to grow. *Invest Ophthalmol Vis Sci*, 46, 2238-2241.
Zloto, O., Wygnanski-Jaffe, T., Farzavandi, S.K., et al. 2018. Current trends among pediatric ophthalmologists to decrease myopia progression-an international perspective. *Graefe's Archive for Clinical and Experimental Ophthalmology*, 256, 2457-2466.
Zong, Y., Xu, Q., Jiang, C., et al. 2017. Measurement of and factors associated with the anterior chamber volume in healthy Chinese adults. *J Ophthalmol*, 6762047.

Appendix 1: Study Protocol

[*How does the eye respond to blur?*]

Protocol Number: [NL0028]

Version [2]

[*26/09/2019*]

Institution: Aston University

Chief Investigator: Dr Nicola Logan

Investigators: Dr Raquel Gil Cazorla, Mr Nikolay Boychev, Ms Noelia Martinez, Mr Daniel Lea, Prof James Wolffsohn

Table of Contents

1. Background and Rationale
    1.1. References
2. Study Objectives and Design
    2.1. Study Objectives
    2.2. Study Design
3. Selection and Withdrawal of Participants
    3.1. Inclusion Criteria
    3.2. Exclusion Criteria
    3.3. Withdrawal of Participants
    3.4. Expected Duration of Study
4. Study Procedures
5. Assessment of Safety
    5.1. Participant Safety
    5.2. Procedures for Reporting Adverse Events
6. Statistics: Analysis
7. Direct Access to Source Data and Documents
8. Ethics and Governance
9. Quality Assurance
10. Data Management
11. Publication
12. Insurance/Indemnity
13. Signatures

1. Background and Rationale

Myopia, and its increasing global prevalence, has been described as a global epidemic; a condition which brings significant socio-economic burden and can lead to sight-threatening ocular complications.[1] While the highest prevalence of myopia is found in East Asian populations, research from the UK demonstrates that myopia constitutes a significant burden in our population; with nearly 20% of white teenagers and 40% of South Asian teenagers being myopic.[2,3] There is an increasing body of evidence to suggest that myopia is influenced by environmental factors. Research points to the protective effects of spending time outdoors,[4,5] more specifically that it could prevent the onset of myopia however the exact mechanism is currently unclear. Evidence for the role of time outdoors as being protective for myopia progression is equivocal. Studies on animals have suggested that manipulating peripheral defocus through an optical means while simultaneously providing correct axial focus can either discourage or encourage axial growth to effectively treat myopia or hyperopia respectively[6]. Recent research has established that progression of myopia and axial growth can be significantly reduced in children and adolescents through the use of bifocal, dual focus, extended depth of focus or multifocal contact lenses[7-10]. The dual focus and extended depth of focus lenses while correcting the distance central myopia impose simultaneous myopic defocus. This intervention relies on active accommodation and the myopia control studies show that children accommodate normally with multifocal contact lenses. Some children in myopia control intervention studies show minimal further progression in their myopia whereas others show greater progression of myopia.[10] Understanding the mechanisms underlying development and progression of myopia is paramount to establishing greater efficacy in myopia control interventions.

The proposed study would explore how blur impacts on ocular parameters and in particular how the eye responds to the simultaneous defocus (blur) it receives from a dual focus contact lens (MiSight) and an extended depth of focus contact lens (NaturalVue).

1.1 References

1. Zheng YF, Pan CW, Chay J, Wng TY, Finkelstein E, Saw SM. The economic cost of myopia in adults aged over 40 years in Singapore. Invest Ophthalmol Vis Sci. 2013;54:7532-7.

2. Logan NS, Shah P, Rudnicka AR, Gilmartin B, Owen CG. Childhood ethnic differences in ametropia and ocular biometry: the Aston Eye Study. Ophthalmic Physiol Opt. 2011;31:550-8.

3. 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. 2010;94:1155-9.

4. French AN. Increasing children's time spent outdoors reduces the incidence of myopia. Evid Based Med. 2016;21:76

5. Ramamurthy D, Lin Chua SY, Saw SM. A review of environmental risk factors for myopia during early life, childhood and adolescence. Clin Exp Optom. 2015;98:497-506

6. Benavente-Pérez A, Nour A, Troilo D. Axial eye growth and refractive error development can be modified by exposing the peripheral retina to relative myopic or hyperopic defocus. Invest Ophthalmol Vis Sci. 2014;55:6765-73.

7. Anstice NS, Phillips JR. Effect of dual-focus soft contact lens wear on axial myopia progression in children. Ophthalmol. 2011;118:1152-61.

8. Lam CS, Tang WC, Tse DY, Tang YY, To CH. Defocus Incorporated Soft Contact (DISC) lens slows myopia progression in Hong Kong Chinese schoolchildren: a 2-year randomised clinical trial. Br J Ophthalmol. 2014;98:40-5.

9. Walline JJ, Greiner KL, McVey ME, Jones-Jordan LA. Multifocal contact lens myopia control. Optom Vis Sci. 2013;90:1207-14.

10. Chamberlain P et al. A Three-Year Randomized Clinical Trial of MiSight® Lenses for Myopia Control. Optom Vis Sci 2019; 96, 556-567.

11. Chakraborty R, Read SA, Collins MJ. Monocular myopic defocus and daily changes in axial length and choroidal thickness of human eyes. Exp Eye Res. 2012;103:47-54

2. Study Objective and Design

2.1 Study Objective

- To explore how the ocular parameters in particular the ciliary muscle and choroid respond when subject to simultaneous blur

2.2 Study Design

Everyone who is able to take part in the study will visit the research centre over a period of 3 within a two week period. Two visits per day for 3 consecutive days. The 2 visits per day is to allow fitting of the contact lenses in the morning and allow an adaption period before measurements are taken in the afternoon. The participants will be randomised to which lens they wear on which day.

Lens conditions:

1) Single vision Proclear daily disposable (DD) contact lens
2) MiSight DD contact lens
3) NaturalVue DD contact lens

The measurement procedures are described below.

At the first visit to the research centre, we will:

• assess spectacle and contact lens wearing history and any history of previous myopia control interventions

• assess suitablility to participate in the study by measuring refractive error with an autorefractor (WAM Grand Seiko. This instrument is used in a number of research studies eg ref #556).

At each visit to the research centre, we will:

• measure visual acuity using a logMAR letter chart. Additionally VA will also be measured using a black and white grating chart both with the participant looking straight ahead and with them looking at 40 degrees to fixation. This is to assess impact of peripheral blur from the contact lens on vision.

• measure the shape of the anterior part of the eye and it's components (lens, anterior chamber and ciliary muscle). This is done using an ocular coherence tomographer (Zeiss Cirrus

5000/ Zeiss Visante). The participant is required to place your chin on a rest and look at a target.

- the thickness of the retina and choroid will also be made using the ocular coherence tomographer.

- measure the length of the eye. This is done using the IOLMaster 500 (Zeiss). It has been used in previous studies ref (#556 #551). The participant places their chin on the machine's chin rest and looks at a spot of light straight ahead and the machine will take several quick measurements of the eye length. Nothing touches the eye.

- Assess lag of accommodation – focussing ability at near to a specific distance of 33cm, this will be assessed with the autorefractor.

At the final visit we will also:

- measure refractive error under cycloplegia using tropicamide 1% with an autorefractor to allow accurate assessment.

Eye drop information: Tropicamide 1.0%

The eye drops used in the study are used to make the pupils larger than normal allowing the investigator to view the inside of the eye more easily and to reduce focusing at near. The drops take about 15 to 30 minutes to work and around 6 hours to wear off, off (in some cases up to 24 hours.) It is very unlikely, but should you experience any unusual symptoms such as severe pain and/ or blood shot around the eye and cloudy vision during this period please contact Dr Nicola Logan (n.s.logan@aston.ac.uk 0121 204 4128) and/ or your optometrist/ GP as you may be experiencing an adverse reaction to the drops.

An adaptation period will be allowed between each set of measurements to allow for any change in lighting level and for change in fixation distance.

Refractive error will be assessed using the Grand Seiko WAM 500 open-field autorefractor. This is a non-contact instrument and involves the participant placing his chin on a chinrest and forehead against a forehead rest. Five measurements will be taken from each eye when the participant is viewing a distance non-accommodative target.

The measurements will take a maximum of 45 minutes to complete including time for adapting to the different conditions. We allow 20 minutes for initial fitting of the contact lens in the morning and 1 hour for the afternoon session.

3. Selection and Withdrawal of Participants

3.1 Inclusion Criteria

- Able to wear contact lenses
- Participants aged 18-30 years
- Myopia range -0.75D to -5.00D
- Astigmatism 1D or less

3.2 Exclusion Criteria

- Amblyopia
- History of ocular surgery or myopia control intervention
- Use of medications known to impact on growth

3.3 Withdrawal of Participants

Participants will be withdrawn from the study in the following circumstances:

- If there are not able to have tropicamide instilled into their eyes
- any serious side effects related to contact lens wear
- If the investigator determines that it is not in the best interest of the participant to continue in the study

3.4 Expected Duration of Study

The study is expected to last one year from July 2019 to July 2020.

4. Study Procedures

- Informed consent
- Visual acuity using logMAR chart at distance and using grating acuity centrally and peripherally
- Lag of accommodation using autorefractor
- Axial length measures using a biometer
- Ciliary body and crystalline lens assessment using optical coherence tomography
- Choroidal thickness measures using OCT
- Cycloplegia using tropicamide

- Refraction undertaken objectively with autorefractor
- Verbal debrief at the end of the study.

5. Assessment of Safety

5.1 Participant Safety

Potential hazards in this study relate to those associated with contact lens wear but are no greater than with normal use. All participants will be experienced contact lens wearers and aware of risks with contact lens wear. The researchers are experienced optometrists (one researcher, Daniel Lea, is a student optometrist who will work under supervision) who are trained to recognise and manage any complications arising from contact lens wear and will closely monitor subjects throughout the study.

Dilation drops are used routinely during the course of optometric practice. All eyes will be checked appropriately prior to instillation of tropicamide.

The instruments used within this study are standard ophthalmic instruments. The risks in this study are considered to be minimal and no greater than those associated with normal contact lens wear or the use of dilation drops in routine practice. A number of measures have been taken to minimise risks:

- Participants will be monitored closely throughout the study
- Eyes will be checked prior to instillation of tropicamide and pre and post contact lens wear.

Participants will be instructed during the consent process that they are free to withdraw at any stage of the study. Leaving the study part way through will not have detrimental consequences.

Confidentiality - records upon which the participant's name appears will be kept strictly confidential within the eye clinic. The information collected throughout the study, which will be used for analysis and publication will have the participant’s details removed and replaced by a code known only to the investigators so that the participant will not be identifiable from it.

Investigators will have completed appropriate training and will be experienced clinicians registered with the General Optical Council

For participants in this study there is no direct benefit, however the findings may be of benefit for intervention for myopia progression in the future.

5.2 Procedures for Reporting Adverse Events

Adverse clinical events associated with the project will be reported through UREC adverse event reporting systems.

Any adverse events associated with the specific procedures will be reported immediately to the Chief Investigator who will formally report them to the Aston University Research Ethics Committee.

6. Statistics

Analysis

Comparison between data taken with single vision (standard) contact lenses will be compared to data taken with MiSight and NaturalVue contact lenses.

7. Direct Access to Source Data and Documents

The investigators will permit UREC review by providing direct access to source data and other documents.

8. Ethics and Governance

The study will be conducted in compliance with principles of the Declaration of Helsinki (1996), the principles of GCP and in accordance with all applicable requirements.

This protocol and related documents will be submitted for review to Aston University Research Ethics Committee. The Chief Investigator will submit a final report to the UREC.

9. Quality Assurance

Monitoring and auditing of this study will be in accordance with the Aston University Monitoring and Auditing Policy for Human Participant Research.

10. Data Management

The Chief Investigator will act as custodian of the study data. The data will be shared with the other study investigators.

The following guidelines will be strictly adhered to:

- Participant data will be anonymized
- All study data will be stored in accordance with University data storage policies for research data

Study data will be archived in accordance with Aston University Archive Policies and Procedures for archiving of clinical research data.

11. Publication

It is intended that the results of the study will be reported in peer reviewed scientific journals.

12. Insurance/Indemnity

Insurance/indemnity will not be provided for non-negligent harm.

Insurance/indemnity for negligent harm will be provided for clinical research procedures undertaken by Aston University staff and research students by the University.

Aston University will provide indemnity/insurance for the design and management of the research.

13. Signature of Chief Investigator

Nicola Logan

---------- 26/09/2019

Chief Investigator **Date**

Dr Nicola Logan

Appendix 2: Study Participant Information Sheet

PARTICIPANT INFORMATION SHEET

How does the eye respond to blur?

You are being invited to take part in a research study. Please take time to read the following information carefully and discuss it with others if you wish. Before you decide whether you want to take part or not, it is important for you to understand why the research is being done and what it will involve. Our team will be available by phone or in person to go through this information leaflet with you, to help you decide whether or not you want to take part and answer any questions you may have. If there is anything that you don't understand, please ask one of the research team to explain this further.

The study is being carried out at Aston University Ophthlamic Research Clinics. We would like 20 short-sighted young adults to take part in our study.

This Participant Information Sheet tells you the purpose of the study and an explanation of what will happen to you during the study if you decide to take part . Please ask if anything is unclear.

Thank you for taking the time to read this Participant Information Sheet.

What is the study about?
Short-sightedness, also called myopia makes objects in the distance, such as the television, look blurred. This is caused by the eye growing too long, something that usually happens during childhood but can continue into young adulthood.

We can make people with myopia see better with glasses or contact lenses, but this doesn't stop their eyes continuing to grow longer and become more myopic.

Children in a study at Aston University have successfully been using a new design of soft contact lens (MiSight) to slow the progression of myopia for over 5 years now, however we do not fully understand how this lens works. The current study is the first of its kind looking at specifically how the eye responds to this type of contact lens. It will allow us to better understand why myopia develops and progresses.

Why have I been chosen?
You have been given information about this study as you are short-sighted. Whether you decide to take part in the study or not, we would like you to continue to go to your own optometrist for regular eye tests and glasses and/or contact lens checks. This study does not replace your routine eye examination.

Do I have to take part?
It is up to you to decide whether you want to take part or not. If you decide now that you wish to take part, you can change your mind in the future and withdraw from the study. You don't have to tell us why and it won't affect your eye care in the future.

We will ask you to sign a form (called an informed consent form) to say that you have agreed to be part of the study. At this time, you will be given a copy of this information sheet and a copy of the form you have signed.

Am I suitable for the study?
If you decide you would like to take part, the first thing we need to do is to check whether you are definitely myopic. We will do this by taking an autorefraction measurement. This takes approximately 2 minutes and is a little like having a photograph taken. It measures the strength of any spectacles you may require. We need to make sure all particpants who take part are short-sighted, are not receiving any other treatments for myopia (apart from glasses or contact lenses), have healthy eyes and are in good general health too.

What will happen to me if I take part?
In this study, we will be comparing how the eye responds when it is corrected with a standard contact lens to how it responds when corrected with the MiSight design of contact lens and with another lens for myopia control called NaturalVue. Everyone who is able to take part in the study will visit the research centre over a period of 2 days. Two visits are required per day. At each visit, we will take some measurements of your eyes and test how well you can see. These measurements are described below.

At the first visit to the research centre, we will:

- ask you about your spectacle and contact lens wearing history and if you have used any myopia control interventions previously
- assess if you are suitable to participate in the study by measuring your level of myopia using an autorefractor. A non-contact instrument where you place your chin on a rest and look at a distant target. The measurement takes seconds.

At each visit to the research centre, we will:

- measure how well you see things far away using letters on a letter chart. We will do this while you are wearing contact lenses. We will also measure your vision using a black and white grating chart
- measure the shape of the anterior part of your eye and it's components (lens, anterior chamber and ciliary muscle). This is done using an ocular coherence tomographer. Nothing touches your eye and you are required to place your chin on a rest and look at a target.
- the thickness of the light-sensitive tissues at the back of your eye (retina and choroid) using a ocular coherence tomographer. Nothing touches your eye and you are required to place your chin on a rest and look at a target.
- measure the length of your eye. This is done using a machine called an ocular biometer. You will place your chin on the machine's chin rest and look at a spot of light straight ahead and the machine will take several quick measurements of the eye length. Nothing touches the eye and all you have to do is look at the light and keep your eyes still.
- assess how well you can focus at near while looking at an image at 33cm.
- measure the effect of glare on your vision. You will look at a letter target while a bright light is near the target
- measure how well you can see letters of different contrast i.e light grey to dark grey
- measure the aberrations in the eye – this involves looking at a fixation target while an instrument takes some readings. It does not touch your eye.

At the final visit we will also:

- measure your level of myopia. To do this accurately, we will put an eye drop into each of your eyes. This eye drop relaxes the muscles in the eyes and allows us to accurately measure the level of short-sightedness. These drops are used routinely by optometrists. After 20 minutes, we will measure the amount of short-sightedness with a machine called an autorefractor. Again you put your chin on the machine's chin rest and look at a picture or letter placed on the other side of the room. Details of the drops are given below. You should not to drive, cycle or operate moving machinery until the drop has worn off.

Eye drop information: Tropicamide 1.0%

The eye drops used in the study are used to make the pupils larger than normal allowing the investigator to view the inside of the eye more easily and to reduce focusing at near. The drops take about 15 to 30 minutes to work and around 6 hours to wear off, (in some cases up to 24 hours.) It is very unlikely, but should you experience any unusual symptoms such as severe pain and/ or blood shot around the eye and cloudy vision during this period please contact Dr Nicola Logan (n.s.logan@aston.ac.uk 0121 204 4128) and/ or your optometrist/ GP as you may be experiencing an adverse reaction to the drops.

How long do the visits last?
The first and last visit to the clinic will last up to one hour. The other visits will take approximately 30 minutes. There will be time for you to rest between measurements if you need to.

What are the possible disadvantages and risks of taking part?

The following side effects are possible from the use of tropicamide.

An increase in pupil size (which may make your vision a little uncomfortable when it is really bright outside, but you can use sunglasses or a hat to help with this) and a reduction in the ability to focus very close up.

What are the possible benefits of taking part?
There are no direct benefits to you for participating in the study.

Your help with the study is valuable because it will help us decide how this new design of contact lenses may work to slow myopia progression.

What happens when the research study stops?
The information we collect will be kept for six years after the study is concluded and may be combined with other research studies. After that, the information we have on computer and on paper will be safely deleted or destroyed.

What if I have a concern about the study?

If you have any concerns about anything to do with this study, please speak to the research team and we will do our best to answer your questions. Contact details can be found at the end of this information sheet.

If the research team are unable to address your concerns or you wish to make a complaint about how it is being conducted then you should contact the Aston University Director of Governance, Mr John Walter, at j.g.walter@aston.ac.uk or telephone 0121 204 4869.

Will my taking part in this study be kept confidential?
We will take great care to ensure that any information we collect is stored safely. In computer files that contain information about you, we will use an identification number rather than their name or any other detail that would allow someone to work out who you are. All information that we collect about your eyes will be kept on a password protected computer or in a locked filing cabinet.

What are the costs and payments for taking part in this study?
You will be given a £30 voucher to thank you for taking part in this study.

What will happen to the results of the research study?
At the end of the study we will tell you what the results of the study were. We hope to do this quite soon after the study ends. We will tell other researchers and the public about what we have found through scientific reports, websites and press releases. Your name won't appear in any of the reports describing the study or its findings.

Who is funding the research?
There is no specific funding for this study.

Who has reviewed the study?
This research has been reviewed by an independent group of people, called a Research Ethics Committee, to protect your safety, rights, wellbeing and dignity. This study has been reviewed and given a favourable opinion by the University Research Ethics Committee.

Contact for Further Information

Principal Investigator

Name: Dr Nicola Logan
Address: Vision Sciences, Aston University, Birmingham, B4 7ET

Investigators

Dr Raquel Gil Cazorla

Mr Nikolay Boychev

Ms Noelia Martinez

Mr Daniel Lea

Thank you for taking time to read this information leaflet

Transparency statement

Aston University takes its obligations under data and privacy law seriously and complies with the General Data Protection Regulation ("GDPR") and the Data Protection Act 2018 ("DPA").

Aston University is the data controller and organizer for this study based in the United Kingdom. We will be using information from you and your child in order to undertake this study. Aston University will process your and your child's personal data in order to register your child as a participant and to manage your child's participation in the study. It will process your child's personal data on the grounds that it is necessary for the performance of a task carried out in the public interest (GDPR Article 6(1)(e). Aston University may process special categories of data about your child which includes details about your child's health. Aston University will process this data on the grounds that it is necessary for statistical or research purposes (GDPR Article 9(2)(j)). Aston University will keep identifiable information about your child for 6 years after the study has finished.

Your rights to access, change or move your child's information are limited, as we need to manage your child's information in specific ways in order for the research to be reliable and accurate. If your child withdraws from the study, we will keep the information about your child that we have already obtained. To safeguard your child's rights, we will use the minimum personally identifiable information possible.

You can find out more about how we use your child's information at www.aston.ac.uk/dataprotection or by contacting our Data Protection Officer at dp_officer@aston.ac.uk.

If you wish to raise a complaint on how we have handled your child's personal data, you can contact our Data Protection Officer who will investigate the matter. If you are not satisfied with our response or believe we are processing your child's personal data in a way that is not lawful you can complain to the Information Commissioner's Office (ICO).

Appendix 3: Study Consent Form

Volunteer Consent Form

Participant Number:_____

Title of Project: How does the eye respond to blur?

Name of Researchers: Dr Nicola Logan, Dr Raquel Gil Cazorla, Mr Nikolay Boychev, Ms Noelia Martinez, Mr Daniel Lea

		Initial box
1	I confirm that I have read and understand the information sheet **(version 3 dated 27/11/19)** for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
2	I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my legal rights being affected.	
3	I agree to take part in the above study.	

_____ _____ _____

Name of volunteer Date Signature

_____ _____ _____

Investigator taking consent Date Signature

2 copies: 1 for participant

1 for investigator