
Doctoral

Science

2021

Big Data: Potential as an Ocular Epidemiology and Public Health Tool

Michael Moore

Technological University Dublin, michael.moore@tudublin.ie

Follow this and additional works at: <https://arrow.tudublin.ie/sciendoc>



Part of the [Optics Commons](#)

Recommended Citation

Moore, M. (2021). Big Data: Potential as an Ocular Epidemiology and Public Health Tool. Technological University Dublin. DOI: 10.21427/26WX-FB96

This Theses, Ph.D is brought to you for free and open access by the Science at ARROW@TU Dublin. It has been accepted for inclusion in Doctoral by an authorized administrator of ARROW@TU Dublin. For more information, please contact arrow.admin@tudublin.ie, aisling.coyne@tudublin.ie, gerard.connolly@tudublin.ie.



This work is licensed under a [Creative Commons Attribution-NonCommercial-Share Alike 4.0 License](#)



Big Data: Potential as an Ocular Epidemiology and Public Health Tool

Michael Moore BSc MSc

PhD Thesis

Technological University Dublin

Supervisors: Prof. James Loughman

Prof. Ian Flitcroft

School of Physics & Clinical & Optometric Sciences

July 2021

Abstract

Refractive error is a significant cause of vision impairment both through the limited access to correction in some areas and the associated ocular diseases for which refractive errors are risk factors. Having timely, regular access to population level estimates of refractive error and vision impairment is necessary to adequately plan public health resources and resource appropriate interventions. A lack of access to current and regularly updated refractive error and vision impairment prevalence data has been identified as a significant limitation in predicting future population trends with many countries lacking any prevalence data or available data being outdated. This project addresses this gap by utilising the untapped potential of Big Data in the form of spectacle lens sales data and optometric electronic medical record data and assesses the potential of these data sources as a public health tool. Chapter 5 contains a review of the application of Big Data and Artificial Intelligence to the field of eyecare and describes the revolutionary potential these new technologies may hold. Chapter 6 describes the data used in this project and the steps taken to acquire and clean the data. Chapter 7 and 8 compare the prevalence of refractive error found using spectacle lens sales data and optometric electronic medical record data to a large population survey of refractive error and demonstrate that with careful analysis an accurate estimation of population distribution of refractive error can be obtained from both types of data. Chapter 8 also estimates the likely level of vision impairment by age 75 given the distribution of myopia in the spectacle lens sales data. Chapter 9 analyses visual acuity data within the optometric electronic medical records which allowed the optimum recall interval and visual acuity threshold for driving licence renewal to be determined. Chapter 10 provides a summary and conclusion on the work, and contains recommendations for future research.


Declaration

I certify that this thesis which I now submit for examination for the award of PhD is entirely my own work and has not been taken from the work of others, save and to the extent that such work has been cited and acknowledged within the text of my work.

This thesis was prepared according to the regulations for graduate study by research of the Technological University Dublin (TU Dublin) and has not been submitted in whole or in part for another award in any other third level institution.

The work reported on in this thesis conforms to the principles and requirements of the TU Dublin's guidelines for ethics in research.

TU Dublin has permission to keep, lend or copy this thesis in whole or in part, on condition that any such use of the material of the thesis be duly acknowledged.

Signature  Date 12/01/2022

Candidate: Michael Moore

Acknowledgements

Foremost, I would like to offer my sincerest gratitude to my supervisors Prof James Loughman and Prof Ian Flitcroft, for taking me on as a student and providing support, motivation, insightful comments and encouragement. Thank you for providing me with this opportunity, it has been my privilege to learn from your knowledge and experience.

Heartfelt thanks go to Dr John Butler for his valuable input and for providing statistical support.

I would like to thank all of the optometrists who kindly agreed to provide data for this research. In particular I would like to thank my collaborators Dr Arne Ohlendorf and Dr Siegfried Wahl. Without your participation and input, the research could not have been successfully conducted.

My sincere thanks to all my colleagues in the Optometry Department and in particular Declan Hovenden and Dr Catriona Barrett who went over and above with help and support throughout this project.

Thank you to my parents, Bernadette and Ciarán, who have given me so many opportunities in life. This achievement is a testament to the privileges I've had, and to your ongoing support, guidance and encouragement. Thank you both.

Thank you to my sister Shauna and her husband Dan for their support and encouragement throughout this project.

Thank you to my son Adam, your mischievous smile always lifts my spirits.

Finally, my biggest thanks go to my beautiful and eternally patient wife Mary. Thank you for living through this process with me. Thank you for always encouraging me to persevere and always being there to pick up the pieces.

Abbreviations List

ACG	Angle Closure Glaucoma
ADD	Addition Lens Group
AES	Aston Eye Study
AI	Artificial intelligence
AMD	Age Related Macular Degeneration
Anti VEGF	Anti-vascular Endothelial Growth Factor
ATR	Against-the-rule
AUC	Area Under the Curve
BD	Big Data
BDA	Big Data Analysis
CVA	Corrected Visual Acuity
CREAM	Consortium on Refractive Error and Myopia
CSV	Comma-separated Values
CZVI	Carl Zeiss Vision International GmbH
D	Dioptres
DALY	Disability Adjusted Life Year
DC	Cylindrical Dioptres
DL	Deep Learning

DMO	Diabetic Macular Oedema
DR	Diabetic Retinopathy
EMR	Electronic Medical Record
E3	European Eye Epidemiology Consortium
GDA	Greater Dublin Area
GDPR	General Data Protection Regulations
GHS	Gutenberg Health Survey
GON	Glaucomatous Optic Neuropathy
GWAS	Genome-wide Association Study
ICD	International Statistical Classification of Diseases and Related Health Problems
IES	Ireland Eye Study
IMI	International Myopia Institute
IOP	Intra-ocular Pressure
IoT	Internet of Things
IRIS	Intelligent Research In Sight
KMS	Kaplan-Meier Survival
KNHANES	Korea National Health and Nutrition Examination Survey
LASIK	Laser-assisted in situ Keratomileusis
ML	Machine Learning

MMD	Myopic Macular Degeneration
MSVI	Moderate to Severe Vision Impairment
NHANES	National Health and Nutrition Examination Survey
NICER	Northern Ireland Childhood Errors of Refraction
NLP	Natural Language Processing
NVI	Near Vision Impairment
OAG	Open Angle Glaucoma
OCT	Optical Coherence Tomography
ONH	Optic Nerve Head
OR	Odds Ratio
QoL	Quality of Life
RAM	Random-access Memory
RCT	Randomised Controlled Trial
RD	Retinal Detachment
RESC	Refractive Error Studies in Children
REVIEWS	Refractive Error and Vision Impairment Estimation With Spectacle data study
RNFL	Retinal Nerve Fibre Layer
ROC	Receiver Operating Characteristic
SER	Spherical Equivalent Refraction

SNP	Single Nucleotide Polymorphism
SV	Single Vision Lens Group
TU Dublin	Technological University Dublin
UCVA	Uncorrected Visual Acuity
VA	Visual Acuity
VLEG	Vision Loss Expert Group
WHO	World Health Organisation
WTR	With-the-rule

Contents

Abstract	2
Declaration	3
Acknowledgements.....	4
Abbreviations List.....	5
List of Tables.....	13
List of Figures	16
List of Equations	24
1 Introduction	25
1.1 Background	25
1.2 Research Aims and Objectives	26
2 Refractive Error	28
2.1 Introduction	28
2.2 Emmetropisation	29
2.3 Myopia	31
2.3.1 Scleral Remodelling.....	31
2.3.2 Education & Near Work	34
2.3.3 Time Spent Outdoors	37
2.3.4 Parental Myopia.....	42
2.3.5 Genetic Studies of Myopia	45
2.4 Hyperopia.....	46
2.5 Astigmatism	49
2.6 Presbyopia.....	51
2.7 Summary	54
3 Prevalence of Refractive Error	56
3.1 Introduction	56
3.2 Interpreting Refractive Error Prevalence Studies	56
3.3 Prevalence of Refractive Error in Adults	62
3.3.1 Myopia	62
3.3.2 Hyperopia.....	68
3.3.3 Astigmatism	69
3.3.4 Presbyopia.....	72
3.4 Refractive Error Prevalence in Children	74
3.4.1 Myopia	75
3.4.2 Hyperopia.....	82

3.4.3	Astigmatism	83
3.5	Evidence for Increasing Myopia	87
3.6	Future Predictions	88
3.7	Summary	90
4	Vision Impairment.....	91
4.1	Introduction	91
4.2	Causes of Vision Impairment	93
4.3	Vision Impairment in Ireland	94
4.3.1	Vision Impairment in Adults.....	94
4.3.2	Vision Impairment in Children	96
4.4	Vision Impairment Due to Refractive Error.....	98
4.4.1	Causes of Vision Impairment in Myopia	98
4.4.2	Causes of Vision Impairment in Hyperopia.....	103
4.4.3	Impact of Myopic Complications	104
4.4.4	Near Vision Impairment	106
4.5	Summary	107
5	Big Data and Artificial Intelligence in Eyecare	109
5.1	Title Page:.....	109
5.2	Abstract:.....	110
5.3	Introduction	111
5.3.1	How Big is Big Data?.....	111
5.3.2	Big Data and Artificial Intelligence	112
5.4	Big Data in Eyecare.....	113
5.4.1	Electronic Medical Records.....	114
5.4.2	Insurance Records.....	115
5.4.3	Image Databases and Biobanks	115
5.4.4	Smart Health Devices	116
5.4.5	Multi-omics	117
5.5	Interpreting Results.....	118
5.6	Applications of Big Data in Eyecare.....	121
5.6.1	Epidemiology.....	122
5.6.2	Disease Screening	123
5.6.2.1	Diabetic Retinopathy.....	124
5.6.2.2	Glaucoma	124
5.6.2.3	Refractive Error	125
5.6.3	Treatment Outcomes	126

5.7	Limitations.....	127
5.8	Conclusion.....	129
	EXPERIMENTAL PROCEDURES, RESULTS & ANALYSIS.....	130
6	Data Collection and Demographics.....	131
6.1	Introduction	131
6.1.1	Hypotheses.....	132
6.2	Methods.....	133
6.2.1	Ethics.....	133
6.2.2	Data Collection.....	133
6.2.3	Data Management	134
6.2.4	Data Protection Compliance and Data Storage	135
6.2.5	Data Description and Demographic Analysis.....	135
6.3	Results.....	136
6.3.1	Data Overview.....	136
6.3.2	Geographic Overview.....	139
6.3.3	Age and Gender Analysis	142
6.4	Discussion.....	143
6.5	Conclusion.....	145
7	Application of Big-Data for Epidemiological Studies of Refractive Error.....	146
7.1	Title Page:.....	146
7.2	Abstract:.....	148
7.3	Introduction:	150
7.4	Methods:.....	152
7.5	Results:.....	155
7.5.1	Spectacle Lens Dispensing and EMR Refractive Error Distribution:	155
7.5.2	Estimating Age Using Reading Addition:.....	158
7.5.3	Comparison with E3:.....	161
7.6	Discussion:.....	166
7.7	Conclusion:.....	171
8	The Refractive Error and Vision Impairment Estimation With Spectacle data (REVIEWS) study.....	173
8.1	Title Page:.....	173
8.2	Abstract.....	175
8.3	Introduction	177
8.4	Methods.....	179
8.5	Results.....	182
8.6	Discussion.....	188

9	Evidence-based Recommendations for Standardised Driver Vision Screening – A Big Data Approach.....	193
9.1	Title Page.....	193
9.2	Abstract:.....	194
9.3	Introduction:	196
9.4	Methods:.....	198
9.5	Results:.....	201
9.5.1	Longitudinal Analysis – Uncorrected Visual Acuity.....	203
9.5.2	Longitudinal Analysis – Corrected Visual Acuity.....	206
9.6	Discussion:.....	211
10	Summary, Conclusions, and Directions for Future Work.....	218
10.1	Summary and Conclusions	218
10.2	Directions for Future Work	220
11	References	224
12	Appendices.....	276
12.1	Appendix 1 – Acuitas Data Extraction Consent Form	276
12.2	Appendix 2 – Practitioner Recruitment Document as Sent to All AOI Member Optometrists.....	278
12.3	Appendix 3 – SQLite Code to Join EMR CSV Files.....	281
12.4	Appendix 4 – R Code to Convert Snellen Acuity to LogMAR.....	283
12.5	Appendix 5 – Poster Presentations.....	284
12.6	Appendix 6 – Application of big-data for epidemiological studies of refractive error. PLoS One publication.....	287
	List of Publications	288
	Oral Presentations.....	288
	Poster Presentations	288
	Structured PhD Programme Modules Completed	290

List of Tables

Table 3.1: Prevalence of myopia and high myopia in adults around the world.	66
Table 3.2: Prevalence of hyperopia and astigmatism in adults around the world.	70
Table 3.3: Prevalence of myopia and high myopia in young children (6 – 10 years old) around the world.	79
Table 3.4: Prevalence of myopia and high myopia in children (11 – 15 years old) around the world.	80
Table 3.5: Prevalence of myopia and high myopia in older children (16 years old and over) around the world.	81
Table 3.6: Prevalence of hyperopia and astigmatism in young children (6 – 10 years old) around the world.	84
Table 3.7: Prevalence of hyperopia and astigmatism in young children (11 – 15 years old) around the world.	85
Table 3.8: Prevalence of hyperopia and astigmatism in older children (16 years old and over) around the world.	86
Table 4.1: Classification of severity of vision impairment based on visual acuity in the better eye. Adapted from the World Health Report on Vision. ²⁴¹	91
Table 6.1: Sample of 10 electronic medical record (EMR) patient visit records following conversion from 14 separate comma-separated values (CSV) files.	137
Table 6.2: Sample of 10 spectacle lens records as supplied by Carl Zeiss Vision International GmbH (CZVI).	137

Table 6.3: Proportion of Carl Zeiss Vision International GmbH (CZVI) spectacle lenses produced in Europe by final destination in global regions.	140
Table 6.4: Top 15 countries for Carl Zeiss Vision International GmbH (CZVI) spectacle lens delivery for the years 2007 – 2015.....	140
Table 7.1: Mean, range and distribution characteristics of spectacle lens and optometric electronic medical record (EMR) data.	157
Table 7.2: Contingency table comparing the frequency of addition prescribing for patients under age 45 and those age 45 and over.....	159
Table 7.3: Descriptive statistics comparing single vision optometric electronic medical record (EMR) prescriptions to younger patients and addition EMR prescriptions to older patients.	159
Table 7.4: Age matched comparison of refractive error rates between the E3 consortium and optometric electronic medical record (EMR) data (mean age = 60.16 ± 12.23 years).....	163
Table 7.5: Age matched comparison of refractive error rates between the E3 consortium and spectacle lenses with an addition (ADD) lens data (mean age = 62.55 ± 8.59 years)	163
Table 8.1: Proportion of refractive error types in each dataset	183
Table 8.2: Refractive distribution within the myopic tail of the SV spectacle lens data and the GHS data, estimated risk of vision impairment at age 75 from equation 1 and 2 and estimated number of individuals with vision impairment at age 75 per 100,000 people with myopia of -2 D or worse for both the SV lens group and GHS.....	188
Table 9.1: Detailed breakdown of data included in analysis showing the number of patient visits in each age group along with the mean, standard deviation and range for uncorrected visual acuity, corrected visual acuity and spherical equivalent refraction (right eye only included).	202

Table 9.2: Reassessment intervals needed in order for a given proportion of the population to still pass the uncorrected visual acuity (UCVA) standard..... 204

Table 9.3: Reassessment intervals required to achieve an approximate 80% survivability rate based on uncorrected visual acuity (top panel) compared to survivability rates for the most commonly used screening intervals used in countries that require regular vision screening (bottom panel)..... 206

Table 9.4: Reassessment intervals needed in order for a given proportion of the population to still pass the corrected visual acuity (CVA) standard 207

List of Figures

Figure 2.1: Comparison of axial length in emmetropia, myopia and hyperopia showing a long axial length in myopia and a short axial length in hyperopia.. Reproduced from Schachar.¹¹ 29

Figure 2.2: Comparison of a normal distribution of spherical equivalent (dashed line) to the distribution of spherical equivalent observed in adults participating in the Gutenberg Health Survey¹⁴ 30

Figure 2.3: Lengthening of the vitreous chamber is the primary cause of myopia development. Higher levels of myopia usually have greater vitreous elongation. Adapted from Baird et al.²⁷ 32

Figure 2.4: Representation of hyperopic and myopic defocus in an eye. In a myopic eye, the relative peripheral hyperopic defocus causes peripheral light to focus behind the retina is thought to drive axial elongation. Reproduced from <https://www.cvs.rochester.edu/yoonlab/research/mpc.html>.... 33

Figure 2.5: A typical educational environment involves time spent indoors with periods of near work. Reproduced from <https://www.irishtimes.com/news/education/middle-class-children-outperform-others-before-starting-school-1.3512956> 35

Figure 2.6: Spending more time outdoors may reduce risk of myopia via multiple means including less hyperopic defocus, bright luminance and different chromatic composition of the light. Reproduced from Lingham et al.⁶⁷ 39

Figure 2.7: Dioptric error maps taking into account of the accommodation response and the point of fixation for both an indoor and outdoor scene showing greater hyperopic defocus for the indoor scene. Reproduced from Flitcroft.²⁹ 42

Figure 2.8: An approximately normal distribution of refractive error centred at +2.00 D SER in 3-month-old babies. This is the typical distribution of refractive error found in young children. Reproduced from Flitcroft.¹² 48

Figure 2.9: As children age the distribution of refractive error becomes more leptokurtotic and less hyperopic. This is seen by the high peak of the distribution and reducing frequency of hyperopia in children by 3 years of age. Reproduced from Flitcroft.¹² 48

Figure 2.10: Astigmatism occurs when two principal points of focus occur due to a difference in the curvature of the anterior cornea, posterior cornea, anterior crystalline lens or posterior crystalline lens. Reproduced from www.mayoclinic.org. 50

Figure 2.11: Corneal topography illustrating with the rule astigmatism (image 1), against the rule astigmatism (image 2) and oblique astigmatism (image 3). Reproduced from www.optometricmanagement.com/issues/2009/february-2009/perfect-the-football-fit 50

Figure 2.12: Presbyopia is thought to occur due to increased rigidity of the crystalline lens causing a reduction of accommodation. This reduction in accommodation results in the inability to focus the image of a near object on the retina. Reproduced from <https://www.news-medical.net/health/Presbyopia-Age-Related-Farsightedness.aspx> 53

Figure 3.1: The effect of changing the refractive error definition. In this distribution of spherical equivalent refraction (SER) the crude prevalence of myopia changes from 33.9% using a definition of ≤ -0.50 D (dashed red line) to 26.4% using a definition of ≤ -1.00 D (dashed blue line) 57

Figure 3.2: An example of an open-field autorefractor, the device recommended by the International Myopia Institute (IMI) to determine refractive error in epidemiological and interventional studies of myopia.¹⁶⁹ Reproduced from Bradley et al.¹⁷³ 60

Figure 3.3: The mean spherical equivalent refraction (SER) for 5-year age groups in a large (n = 649,486) cross sectional electronic medical records (EMR) database. 62

Figure 3.4: Current and projected myopia prevalence in adults around the world. Highest rates are observed in East Asia. Data taken from Holden et al.³ Reproduced from <https://retinatoday.com/articles/2019-sept/myopia-a-global-epidemic> 64

Figure 3.5: Map showing the prevalence of vision impairment resulting from uncorrected presbyopia. The highest prevalence is found in Africa and East Asia while lowest prevalence is observed in Western countries. Reproduced from Fricke et al.²⁰⁷ 73

Figure 3.6: The rate of myopia seen in children based on recent studies. Myopia less than 25% reported in blue, myopia less than 45% reported in green and myopia greater than or equal to 45% reported in red. Adapted from <https://myopiainstitute.org/myopia/>..... 75

Figure 3.7: The prevalence of myopia in among older teenagers is extremely high in some east Asian countries as indicated by the almost universal need for correction in this group of male teenage students. Reproduced from Dolgin.²²⁷ 77

Figure 3.8: Estimated increase in myopia based on analysis by Holden et al.³ 89

Figure 4.1: Geographic variation in vision impairment with highest number of people affected by vision loss found in East and South Asia. Reproduced from the Vision Loss Expert Group Atlas.^{5,256} Available at <https://www.iapb.org/learn/vision-atlas/> 94

Figure 4.2: An example of optic nerve hypoplasia, one of the most common causes of blindness in children in Ireland.^{265,266} Reproduced from <https://webeye.ophth.uiowa.edu/eyeforum/cases/case10.htm>..... 97

Figure 4.3: Normal ocular shape (A), axial elongation in myopia (B) and axial elongation with posterior staphyloma (C). Adapted from Ohno-Matsui.²⁷⁴ 99

Figure 4.4: Progression of MMD from a tessellated fundus (image A) to diffuse chorioretinal atrophy (image B) to patchy chorioretinal atrophy (image C). Adapted from Hayashi et al.²⁷² 100

Figure 4.5: Lattice degeneration confers an increased risk of retinal tears and occurs with greater frequency in myopia. Adapted from <https://www.asrs.org/patients/retinal-diseases/36/lattice-degeneration>..... 101

Figure 4.6: Two optic nerves in highly myopic eyes. Image 1 has been diagnosed with glaucoma while image 2 has no glaucoma. The similarity in appearance of the two optic nerves demonstrates the difficulty in making this diagnosis. Adapted from <https://www.aao.org/eyenet/article/myopia-glaucoma-sorting-out-diagnosis> 102

Figure 5.1: Association between Big Data (BD) and Artificial Intelligence (AI)..... 113

Figure 5.2: Examples of receiver operator characteristic (ROC) curves with levels of accuracy represented by area under the curves (AUC) ranging from perfect (pink line) to random (orange line). 120

Figure 5.3: Results of a Web of Science search for the number of publications per year containing any of the terms “Big Data”, “Artificial Intelligence”, “Machine Learning” or “Deep Learning” in the fields of ophthalmology or optometry 121

Figure 5.4: Comparison of the distribution of myopia in the Gutenberg Health Survey (GHS), a typical population survey of refractive error (n = 13,959) and a Big Data study using spectacle lens manufacturing records (n = 134,280,063). At these higher levels of myopic refractive error there is increased variance in the GHS as the sample size is likely too small to adequately describe the underlying population trend. 123

Figure 6.1: Percentage of electronic medical record (EMR) patient visits in each year. The percentage increases linearly with time ($t = 23.09$, $p < 0.001$, $R^2 = 0.97$) as shown by the linear regression (red line) with 95% confidence intervals (dashed red lines). 138

Figure 6.2: Percentage of spectacle lens sales records in each year. No correlation was found between the year and sales records. 139

Figure 6.3: Geographic distribution of electronic medical record (EMR) patient visits around Ireland. All counties are represented with the highest number of visits occurring in Dublin. Interactive version available at: <https://irelandrefractiveerror.shinyapps.io/PatientDistribution/> 141

Figure 6.4: The mean age of EMR patients increased with exam year as shown by linear regression (red line) with 95% confidence intervals (dashed red lines). 142

Figure 6.5: Gender and age distribution of EMR patients. The gender distribution for the EMR dataset was 52.8% female, 36.1% male and not recorded in 11.1% of cases. The mean age for the total EMR dataset was 47.08 ± 22.20 years. 143

Figure 7.1: Number of spectacle lenses and EMR visits included in analysis 156

Figure 7.2: Distribution of spherical equivalent in each dataset 157

Figure 7.3: Age and the prescribing of an addition are highly correlated 159

Figure 7.4: Predicted age based on the prescribed reading addition with 95% prediction intervals 160

Figure 7.5: Likelihood of needing a reading addition at different ages with 95% prediction intervals 161

Figure 7.6: Comparison of spherical equivalent distribution between E3 and EMR. E3 distribution of refractive error spherical equivalent (dotted line) compared to the gender and age matched EMR distribution of right eye refractive error spherical equivalent (bars). 162

Figure 7.7: Total myopia proportion for EMR (inverted triangle), ADD Lenses (triangle), GHS (circle) and E3 (square) data as a function of age group. The E3 data confidence intervals (dark shaded area) are plotted to illustrate comparison with the other data sets. The EMR data confidence intervals (light shaded area) are plotted to show the overlap with the E3 data. 164

Figure 7.8: Total hyperopia proportion for EMR (inverted triangle), ADD Lenses (triangle), GHS (circle) and E3 (square) data as a function of age group. The E3 data confidence intervals (dark shaded area) are plotted to illustrate comparison with the other data sets. The EMR data confidence intervals (light shaded area) are plotted to show the overlap with the E3 data. 165

Figure 7.9: Total high myopia proportion for EMR (inverted triangle), ADD Lenses (triangle) and E3 (square) data as a function of age group. The E3 data confidence intervals (dark shaded area) are plotted to illustrate comparison with the other data sets. The EMR data confidence intervals (light shaded area) are plotted to show the overlap with the E3 data. GHS not present as high myopia data was unavailable..... 166

Figure 8.1: Spectacle Lens Distribution of refractive error from manufacturer data for single vision (SV) lenses (n = 84,561,994), addition (ADD) lenses (n = 49,709,191) and from the Gutenberg Health Survey (n= 13,959). 183

Figure 8.2: Deviation between bootstrapped confidence intervals and the observed occurrence of refractive error in the Gutenberg Health Survey. The deviation is greatest when starting at zero dioptres spherical equivalent and trends towards zero at higher absolute values of spherical equivalent. 184

Figure 8.3: Bootstrapped myopic mean distribution with 95% confidence intervals for Single Vision lenses (solid line and shaded area) compared to the Gutenberg Health Survey (dotted line). 185

Figure 8.4: Bootstrapped hyperopic mean distribution with 95% confidence intervals for Single Vision lenses (solid line and shaded area) compared to the Gutenberg Health Survey (dotted line). 186

Figure 8.5: Bootstrapped myopic mean distribution with 95% confidence intervals for Addition lenses (solid line and shaded area) compared to the Gutenberg Health Survey (dotted line). 186

Figure 8.6: Bootstrapped hyperopic mean distribution with 95% confidence intervals for Addition lenses (solid line and shaded area) compared to the Gutenberg Health Survey (dotted line). 187

Figure 9.1: Boxplot for right eye uncorrected visual acuity (UCVA) (left panel, n = 154,824) and right eye corrected visual acuity (CVA) (right panel, n = 154,824) for each age category 202

Figure 9.2: Percentage of VA measurements falling into each vision standard category for both uncorrected visual acuity (UCVA) and corrected visual acuity (CVA) 203

Figure 9.3: Kaplan-Meier curves demonstrating the reducing likelihood of passing the standard in a cohort of individuals that initially passed the standard with uncorrected visual acuity (UCVA). Increasing time since the initial vision assessment reduces the likelihood of passing for all age groups. The dotted lines indicate the time interval for each age group by which 80% of individuals will still pass the UCVA standard..... 205

Figure 9.4: Kaplan-Meier curves demonstrating the reducing likelihood of passing the standard in a cohort of myopic (right eye SER ≤ -0.50 D) individuals (n = 9,209) that initially passed the standard with corrected visual acuity (CVA). Increasing time since the initial vision assessment reduces the likelihood of passing for all age groups. The dotted lines indicate the time interval for each age group by which 80% of individuals will still pass the CVA standard if their refractive error correction is not updated..... 208

Figure 9.5: Kaplan-Meier curves demonstrating the reducing likelihood of passing the standard in a cohort of hyperopic (right eye SER $\geq +0.75$ D) individuals (n = 15,155) that initially passed the standard with corrected visual acuity (CVA). Increasing time since the initial vision assessment reduces the likelihood of passing for all age groups. The dotted lines indicate the time interval for

each age group by which 80% of individuals will still pass the CVA standard if their refractive error correction is not updated. 209

Figure 9.6: Time between eye exams for female and male patients with refractive error ($SER \leq -0.50$ D or $SER \geq +0.75$ D). Cumulative percentage shown by dashed line. 210

Figure 9.7: Logistic function demonstrating the age-independent change in percentage of patients that fail the binocular visual acuity standard (even with correction), when the threshold is varied between 0.0 and 1.0 logMAR..... 211

List of Equations

Equation 8.1: Vision Impairment Odds Ratio due to Myopia 181

Equation 8.2: Vision Impairment Risk due to Myopia 181

1 Introduction

1.1 Background

In 1999 the World Health Organisation (WHO) launched “VISION 2020 – The Right to Sight” initiative in order to eliminate avoidable blindness.¹ As part of this initiative refractive error was identified as a priority condition.² In the intervening years, it has become apparent that of all refractive errors, myopia is the most concerning as the prevalence has increased dramatically and is projected to continue on this trajectory.³ This may result in an increasing number of individuals affected by vision impairment both due to uncorrected myopia and the complications of myopia.⁴ One of the recognised barriers to establishing the extent of these problems is the significant lack of population level prevalence data for both refractive error and vision impairment.^{3,5}

Accurate and current prevalence data for refractive error and vision is needed to allow policy makers and relevant stake holders determine the need for public health interventions and to ensure the necessary level of support is in place for those effected. Beyond merely establishing the extent of the problem however there is an ongoing need for this data to assess the impact of any interventions that are put in place. Current population level data on refractive error and vision is also needed to ensure evidence-based decisions can be made by policy makers with regards to any vision standards that may be applied to the public.

In recent years there has been an explosion in the volume of digital data created on a daily basis⁶ with the healthcare domain seeing a particularly large increase in data being generated.⁷ In this new era of “Big Data”, insight to some research questions that previously were difficult or impossible to answer, is now achievable. It may now be possible to bridge the gap that is present in refractive error and vision data using these new techniques.

1.2 Research Aims and Objectives

It has been established that myopia prevalence is increasing dramatically^{8,9} and is projected to continue to increase over the coming years.³ A lack of current refractive error prevalence data has been identified as a potential limitation in these predictions³ and also presents a barrier to assessing the efficacy of possible interventions at a population level. The lack of data is likely as a result of the prohibitive cost and significant amount of time required to conduct a typical epidemiological study of refractive error. Therefore, the primary aim of this research was to examine and validate alternative data sources and methods to determine the distribution of refractive error and vision across the general population and validate these results against pre-existing research. Secondary aims were to use these results to estimate the vision impairment due to myopia in a population and demonstrate how these data sources and methods can be used as a basis for public health policy.

To achieve these aims a large database of refractive error and vision data was created from spectacle lens sales data and optometric electronic medical record (EMR) data. The prevalence of refractive error is reported and detailed comparison of these results with typical epidemiological studies of refractive error is undertaken. Deriving a relationship between age and prescribed reading addition allowed an estimated age for the spectacle lens data to be calculated. This facilitated a comparison of both the spectacle lens data and EMR data across age groups with published data on refractive error prevalence.

In order to validate the use of spectacle lens sales data as a source of refractive error epidemiological data, a novel methodology was investigated which established the range of refractive errors over which spectacle lens sales data can be used to estimate the distribution of refractive error in a population. Having established this range, the potential level of vision impairment due to myopia is reported across the range of myopic refractive errors.

To further demonstrate how this form of data can be used as the basis for public health policy, evidence-based recommendations for standardised driver vision screening were developed.

Determining the variation in visual acuity with age within the population of the EMR data allowed the maximum length of time that could pass between vision screenings for an individual to still pass the driving visual acuity standard to be calculated. The influence of varying the visual acuity standard for driving on the number of individuals expected to meet the standard was also determined.

The long-term aim of this project is to continue data collection creating the most comprehensive, current and easily accessible database on refractive error and vision available. This will provide a foundation upon which public health policy in eyecare can be developed and also allow monitoring of the impact of these policies over time.

2 Refractive Error

2.1 Introduction

Refractive error is a condition in which the eye fails to create a sharp image at the retina resulting in a degradation of visual acuity. Generally, refractive error can be considered as one of four distinct types with all individuals experiencing 1 or more refractive errors over the course of their life.

Myopia (short-sightedness) causes difficulty with viewing distant objects and is usually caused by an eye whose axial length has grown too long (Figure 2.1). Hyperopia (long-sightedness) causes difficulty with viewing near objects and possibly distant objects depending on the degree of hyperopia and age of the individual. Hyperopia is usually caused by an eye whose AL is too short (Figure 2.1). Presbyopia causes difficulty with viewing near objects in older individuals as they lose the ability to accommodate. Astigmatism is caused by a variation in curvature of the cornea or crystalline lens which causes an object to have two points of focus.

Typically, in high income countries, refractive error can be easily addressed by the provision of an optical appliance such as spectacles or contact lenses or through surgical techniques such as laser-assisted in situ keratomileusis (LASIK). Unfortunately, despite the ease with which refractive error can be corrected, it is still the leading cause of moderate to severe vision impairment in older adults and second most common cause of blindness in older adults globally.¹⁰

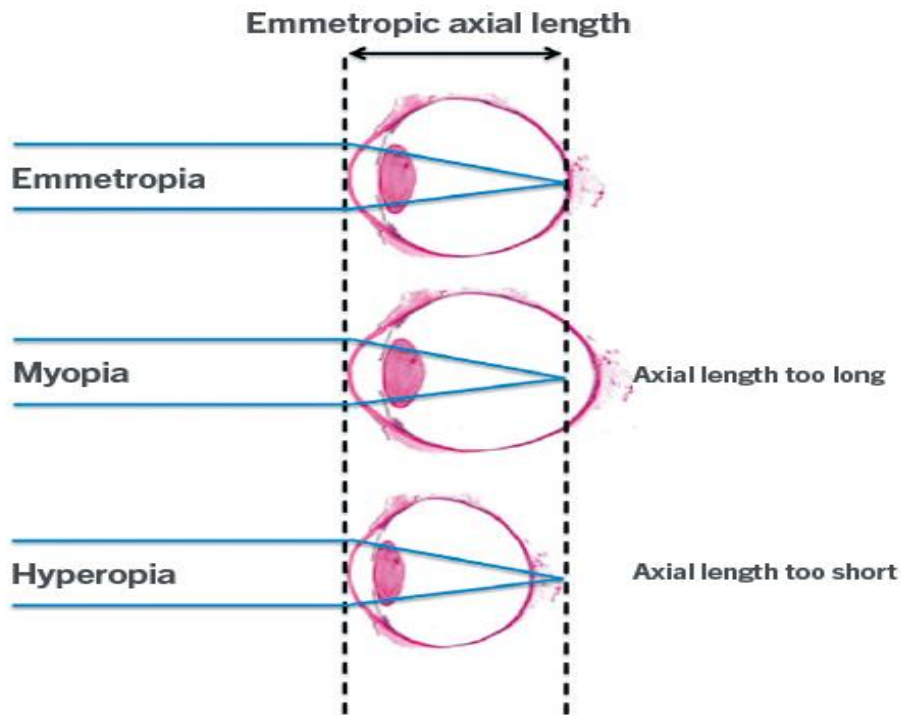


Figure 2.1: Comparison of axial length in emmetropia, myopia and hyperopia showing a long axial length in myopia and a short axial length in hyperopia.. Reproduced from Schachar.¹¹

2.2 Emmetropisation

To understand why refractive error develops, it is necessary to consider how refraction changes in infancy and young childhood through the process of emmetropisation. At birth refractive error is approximately normally distributed within the population.¹² If this situation was to remain unchanged the number of individuals effected by refractive error would be considerably higher than that observed in most studies of refractive error (Figure 2.2). In early childhood, the process by which refractive error reduces in most children is referred to as emmetropisation. The mean refractive error in infants is hyperopic and there is significant variability as seen by relatively large standard deviations.¹³ Over the first year of life, there is a shift to less hyperopic refractive errors with a significant reduction in the variability of refractive errors.¹² This occurs due to a combination of changes in the power of the refractive surfaces of the eye i.e., the cornea and the crystalline lens

and an increase in the axial length of the eye.¹³ At a population level, these changes have the effect of altering the distribution of refractive error away from a normal distribution towards a leptokurtotic distribution (Figure 2.2). This distribution is positively skewed as opposed to the negatively skewed distributions seen in adults but otherwise is more closely aligned to the distributions observed in adults than the approximately normal distribution found at birth.

The majority of the emmetropisation process has occurred within the first year of life¹³ with the process finishing by approximately age 6 with low rates of refractive error in most populations by this age.¹² At this point the persistence of refractive error is likely due to a failure in the emmetropisation process, a large initial refractive error at birth which failed to sufficiently emmetropise or a combination of both. Given the significant number people requiring refractive error correction by adulthood other processes appear to be involved in the development of refractive error.

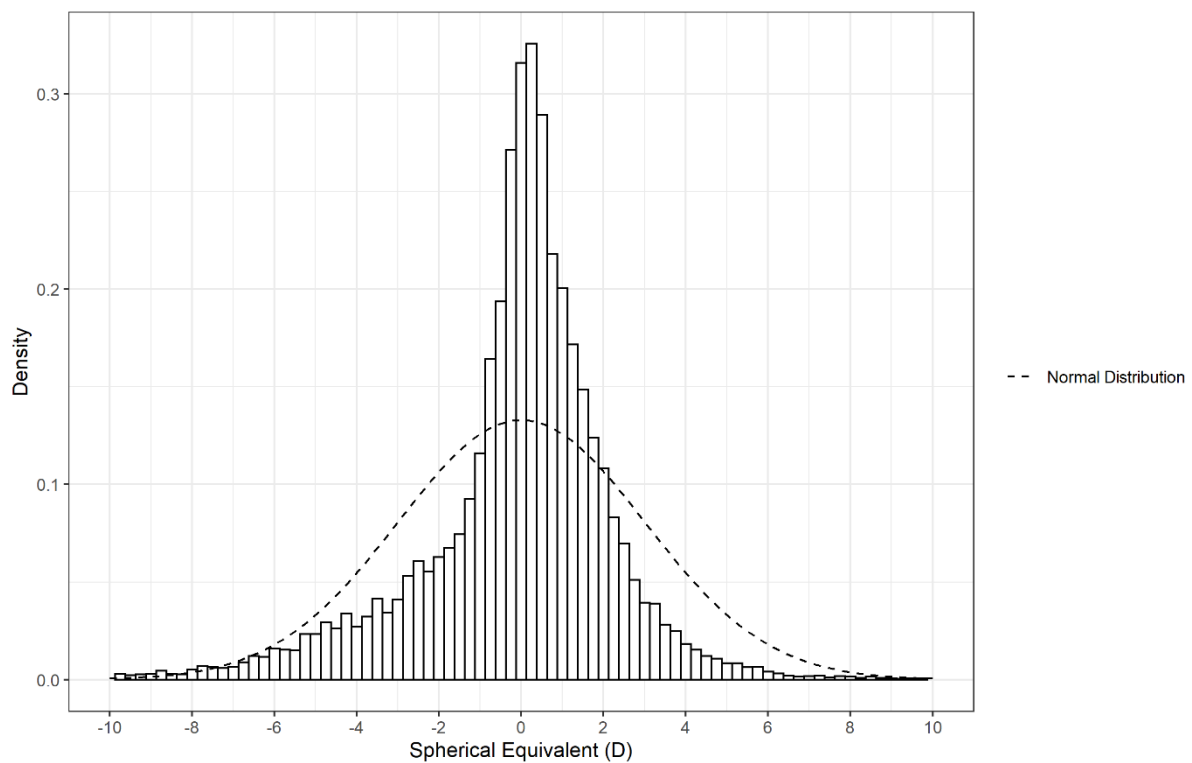


Figure 2.2: Comparison of a normal distribution of spherical equivalent (dashed line) to the distribution of spherical equivalent observed in adults participating in the Gutenberg Health Survey¹⁴

2.3 Myopia

Myopia occurs when there is an imbalance between the refracting surfaces of the eye (the cornea and the crystalline lens) and the axial length of the eye that results in light focusing before it reaches the retina. Although any component of the optical system of the eye can be responsible for myopia, increased axial length is by far the most common cause of myopia.¹⁵⁻¹⁷ Average values of axial length are considered to be approximately 23.5 mm with men usually having a slightly larger axial length than women.¹⁷ High myopia is usually associated with axial lengths greater than 26 mm with axial length rising to above 30 mm in cases of very high myopia.¹⁶

The aetiology of myopia and increasing axial length is complex and not fully understood. There are several mechanisms suggested with both environmental and genetic causes proposed. There is significant debate over the degree to which recognised environmental and genetic risk factors contribute to myopia development although most authors agree both contribute to some extent.^{18,19} The following sections describe the current thinking in the mechanics of how myopia develops and the risk factors for myopia.

2.3.1 Scleral Remodelling

The exact biological mechanism by which the axial length of the eye increases in myopia is not fully described. The increase in axial length is usually as a result of a lengthening of the vitreous chamber during myopia development (Figure 2.3).²⁰ In myopia this change in vitreous chamber size usually results in a prolate ocular shape with the change in vitreous chamber occurring primarily through elongation along the visual axis.²¹ This is supported by animal studies which also demonstrate prolate shapes in myopic chick eyes.²¹ Changes in the biomechanical structure of the sclera is the prevailing theory as to how axial length elongation occurs.²² There is evidence that the sclera is less

rigid in myopic eyes than emmetropic or hyperopic eyes with the sclera being least rigid in the most myopic eyes.²³ The sclera has also been observed to be thinner in myopic eyes^{24,25} with the greatest degree of thinning happening in the most myopic eyes. This thinning appears to occur as a result of the thinning of collagen fibre bundles and reduced collagen fibre diameters.²² There is also evidence from animal studies that demonstrate scleral glycosaminoglycan synthesis is reduced when myopia is developing.²⁶

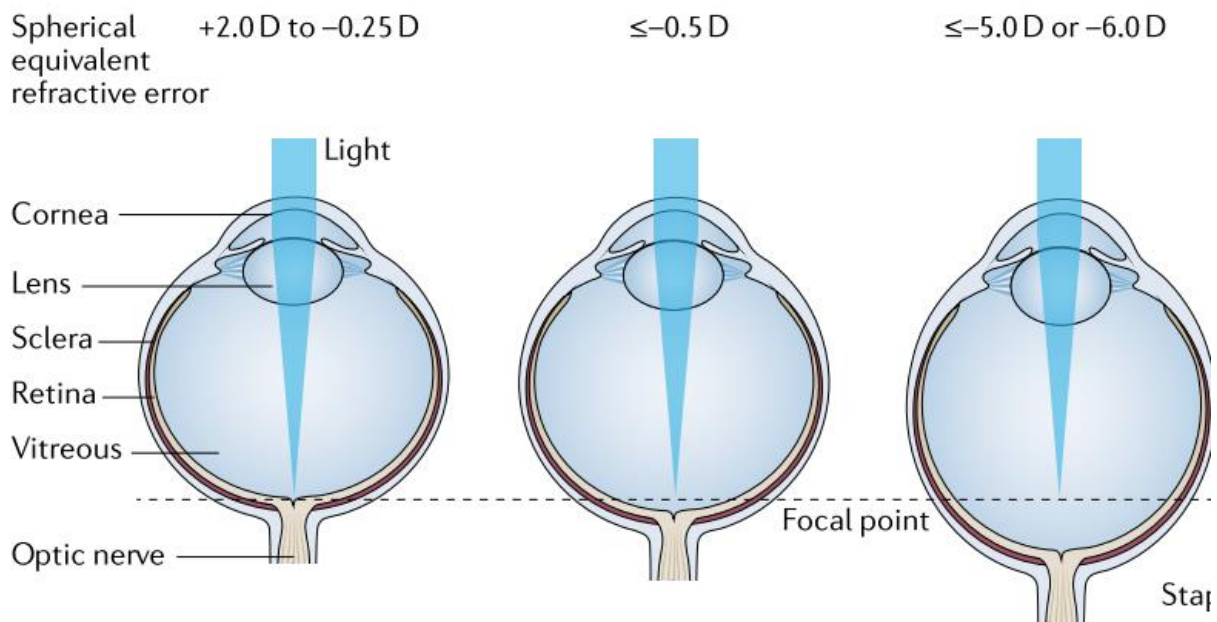


Figure 2.3: Lengthening of the vitreous chamber is the primary cause of myopia development. Higher levels of myopia usually have greater vitreous elongation. Adapted from Baird et al.²⁷

Although there appears to be strong evidence that the observed changes in the scleral structure are responsible for the increase in axial length observed in myopia, several authors^{22,28} have emphasised that this evidence is primarily based on eyes that have been examined after enucleation which has occurred in many cases after the death of the patient. This is likely to have been some time after myopia developed and the changes in scleral structure may actually be in response to the increased

axial length associated with myopia as opposed to having been responsible for the increased axial length.^{22,28}

The exact method by which the sclera is stimulated to grow and cause increased axial length in myopia is poorly understood. Flitcroft explored the most likely causes of eye growth in a detailed summary of the current research.²⁹ There is evidence in both animal and human studies that the retina plays a role in controlling eye growth. Flitcroft suggests the more myopic and skewed distribution of refractive error apparent in those with a retinal dystrophy may be evidence of a failure in the process of emmetropisation due to the retina's dysfunction in controlling eye growth.²⁹ There is also evidence that peripheral retinal defocus may be a key instigator of myopic eye growth with several studies in both animals^{30,31} and humans³²⁻³⁴ finding off-axis hyperopia may signal for an increase in eye growth (Figure 2.4). Interestingly, this seems to be a local effect with several animal studies that used a lens or diffuser to affect only half the visual field demonstrating increased scleral growth only in the affected part of the eye.^{35,36} The pathway by which the retina signals for increased scleral growth is also not fully understood although retinoic acid and dopamine may play a role.²⁹

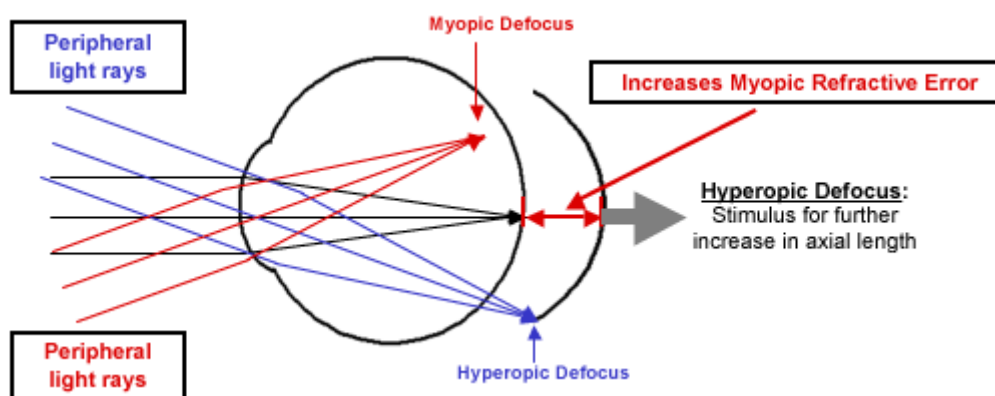


Figure 2.4: Representation of hyperopic and myopic defocus in an eye. In a myopic eye, the relative peripheral hyperopic defocus causes peripheral light to focus behind the retina is thought to drive axial elongation. Reproduced from <https://www.cvs.rochester.edu/yoonlab/research/mpc.html>

2.3.2 Education & Near Work

There appears to be a significant link between education and myopia. Studies have found evidence for education as a risk factor for myopia development in populations of both adults and children. Mirshahi et al³⁷ found a significant effect of number of years spent in education and the risk of becoming myopic in a German adult population. The authors observed a prevalence of myopia of 60.3% in those that had completed at least 13 years of education in comparison to a prevalence of 26.9% in those that had never finished secondary education. This study had a significant strength in that they were able to control for 45 myopia-associated single nucleotide polymorphisms. They observed weak genetic effects in the likelihood of myopia development however these were much smaller than the effect of education.

Williams et al also observed significantly higher prevalence of myopia in those with higher education in an adult European population.³⁸ Myopia prevalence was 36.6% in those completing higher education compared to 25.4% in those completing primary education only. As the authors were comparing participants from different countries with different educational systems, a simplification in the definition of primary (leaving education before 16 years of age), secondary (leaving education up to 19 years of age) and higher education was necessary (leaving education at or after 20 years of age). As the participants were from different generations, this simplification may overlook some variance in education attainment. The authors also used a lower definition for myopia (≤ -0.75 D SE) than the more common definition (≤ -0.50 D SE) used by Mirshahi et al.³⁷ Regardless of the differences between these two studies, both show strong evidence for a higher prevalence of myopia in adults that have spent more years in education.

Studies in children have also observed links between education and myopia development. Saw et al³⁹ observed higher levels of academic performance in Asian children with myopia a finding that was also observed in a cohort of predominately Caucasian children.⁴⁰ Establishing that education specifically is the primary driver of myopia development is difficult due to the number of possible

confounding causes of myopia development. Most education systems involve time spent indoors with periods of near work (Figure 2.5), both of which have been identified as risk factors for myopia development.^{41,42}



Figure 2.5: A typical educational environment involves time spent indoors with periods of near work. Reproduced from <https://www.irishtimes.com/news/education/middle-class-children-outperform-others-before-starting-school-1.3512956>

The effect of near work on myopia in children is unclear with conflicting results observed. Myopic children have been observed to spend more time on near work activities in both Asian and Caucasian populations,^{43,44} however other studies have found that varying amounts of time spent on near work had no association with myopia prevalence in some populations of children.⁴⁵ Some authors have also examined the effect of near work on the development of myopia. Hepsen et al⁴⁶ studied both refractive and biometric changes in two groups of Turkish male students under different educational systems. Children engaged in more near work and study were observed to have more myopic progression and an increase in axial length over a three-year period. Saw et al⁴⁷

observed no association between time spent on near work and myopic progression in group of myopic children. A recent meta-analysis on the effect of near work on myopia found that more hours of near work might increase myopia prevalence although “more longitudinal and randomized controlled trials should be performed to confirm whether near work is a risk factor for the development of myopia”.⁴¹ Developing such a trial would however present significant challenges, not the least of which would be the ethical issues raised by preventing children doing near work.

The conflicting results obtained when assessing the impact of near work on myopia may lead to the conclusion that near work itself is not a risk factor for myopia development and progression but rather the type and intensity of near work with some suggestion that prolonged periods studying small text can drive myopia development.⁴⁸ Morgan and Rose identified the use of after school tutorials in many East Asian countries as possibly being related to the very high levels of myopia found in older adolescents in those countries.⁴⁹ The authors observed that in many East Asian countries there is significant emphasis placed on educational performance with some children taking part in after school tutorials while in primary school. There is less use of after school tutorials in countries with a lower prevalence of myopia⁴⁹ where children may spend more time outdoors.⁵⁰ The conclusion of Morgan and Rose are somewhat supported by evidence from Israel. Male Ultra-Orthodox Jewish communities have been observed to have very high levels of myopia, similar to those found in East Asian young adults.^{48,51,52} Male students from these communities can spend up to 16 hours per day reading and discussing religious texts⁴⁸ which may explain the higher level of myopia even when compared to female students from the same community.^{48,51} These findings are supported by evidence from studies of immigrant communities. These studies have found children from countries with typically low prevalence of myopia that have emigrated to countries with higher prevalence are more likely to become myopic, particularly if they emigrated at a younger age and were thus exposed to a different educational environment from a younger age.⁵³

Despite the evidence supporting education as a risk factor for developing myopia, it is not possible to conclusively determine what environmental aspect of education is resulting in a higher prevalence of myopia due to the difficulty in controlling for confounders. Some areas with very high myopia prevalence have introduced modifications to the school day in an effort to reduce the risk of developing myopia with most increasing mandatory time spent outdoors for school children.^{54,55}

2.3.3 Time Spent Outdoors

Over the last decade, there has been significant research on the protective role time spent outdoors may have with regards to the development or progression of myopia.^{56,57} A meta-analysis observed a small but significant protective effect of increasing time spent outdoors in developing myopia.⁵⁶ The authors found a 2% reduction in odds of myopia for each additional hour spent outdoors per week. There is also good evidence from three RCT studies in both Taiwan⁵⁸ and China^{59,60} that increasing time spent outdoors reduces the risk of developing myopia. All three studies used a similar design with children some schools assigned provided with additional time spent outdoors while those in the control arm of the study continued with the normal school day. In all cases incident myopia was reduced in the intervention schools with the reduction ranging from 4.8%⁵⁹ to 9.2%.⁵⁸ A recent large scale cohort study from Taiwan supports these findings.⁵⁴ The authors reported a 2.34% annual reduction in prevalence of presumed myopia among school children following a government initiative to encourage 2 hours of outdoor activity per day. There are some limitations with this finding as reduced visual acuity (VA) was measured as a surrogate for refractive error with the authors assuming a child with reduced VA suffered with myopia. The authors were also not able to ensure the protocol was followed precisely in each school or control for other risk factors such as parental myopia. Nevertheless, in a country with such high levels of myopia,⁹ this simple intervention has shown promising results.

The protective effect time spent outdoors has on myopia progression for those already myopic is less clear. Two Taiwanese studies found conflicting results with a 2013 study finding no difference in myopia progression between school children encouraged to spend recess outdoors and those allowed to have recess in the classroom.⁵⁸ A 2018 study by the same authors did observe a difference in myopia progression between students spending time outdoors and those spending less time outdoors (0.57 D vs 0.79D) over the course of a year.⁵⁵ The authors point to the students assessed being younger in the later study and concerns about compliance in the initial study as a possible explanation for the discrepancy in the results. Two studies from China also observed lower rates of myopia progression (0.17 D reduction after 1 year⁶⁰ and 0.17 D reduction after 3 years⁵⁹) in children encouraged to participate in more outdoor activities. A meta-analysis including some of the above studies observed no significant protective effect of increasing time spent outdoors on myopia progression.⁶¹ As the overall level of reduction of myopia progression is less than would be typically achieved using other myopia control strategies such as atropine or orthokeratology contact lenses, increased time outdoors is recommended as an adjunct therapy for those already myopic.^{55,62-64}

The exact mechanism by which increased time outdoors may be protective against both developing myopia and progressing myopia is poorly understood and requires further research. There are numerous theories proposed with varying degrees of evidence to support each (Figure 2.6). An initial theory proposed that physical activity was protective against the development and progression of myopia.^{42,65} These studies did not adequately differentiate between physical activity that took place either outdoors or indoors and hence did not control for time spent outdoors. Rose et al⁴⁵ found outdoor activity was similarly related to reduced development of myopia but observed no relationship between indoor sport participation and lower prevalence of myopia. These findings are supported by a recent longitudinal study which found no association between physical activity and myopia.⁶⁶

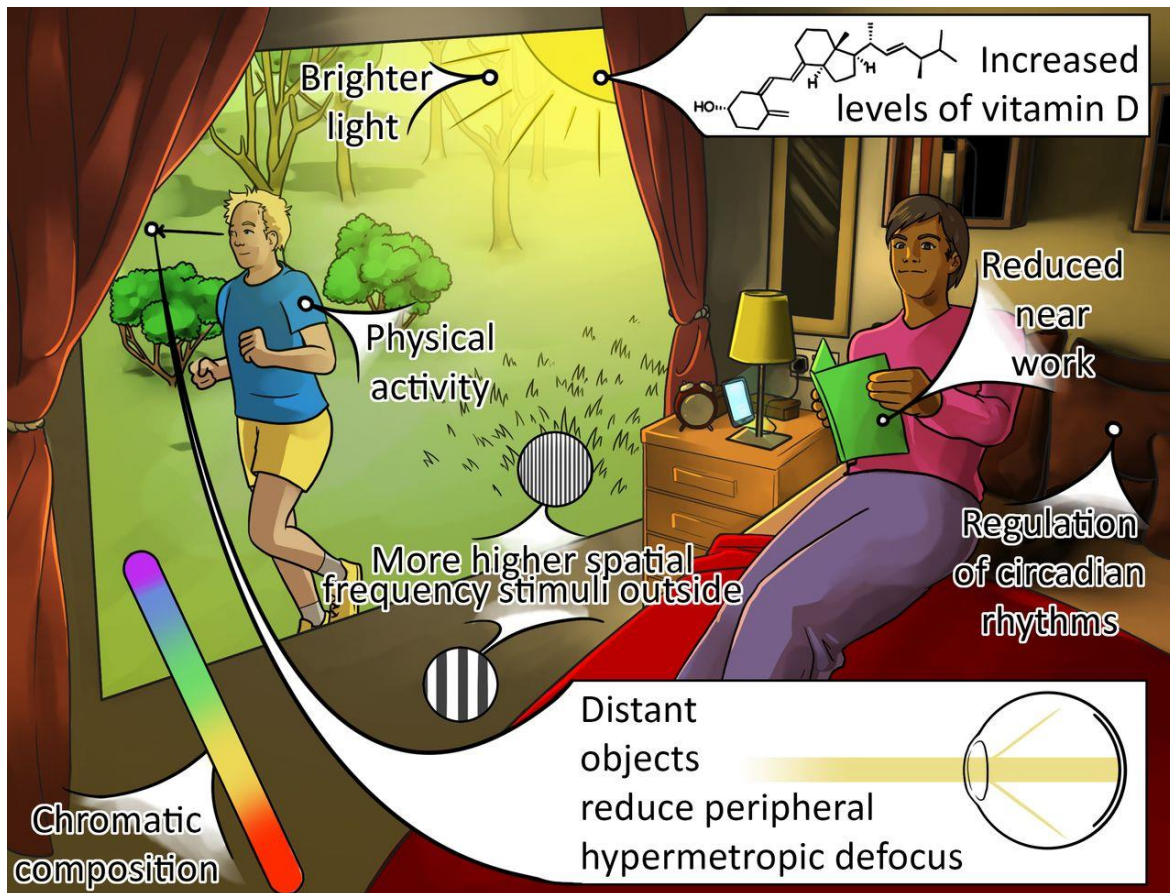


Figure 2.6: Spending more time outdoors may reduce risk of myopia via multiple means including less hyperopic defocus, bright luminance and different chromatic composition of the light. Reproduced from Lingham et al.⁶⁷

A simple explanation by which time outdoors could be protective against myopia development is that children that spend more time outdoors are spending less time partaking in activities that are thought to be myopiagenic such as near work.⁴¹ This does not seem to be case as it has been found that time spent outdoors and time spent reading in children are not correlated.^{42,45} This lack of correlation with near work only extends to reading and it is unknown if it also extends to near work using electronic devices however a recent meta-analysis of the limited data available found no association between screen use and myopia.⁶⁸ It should be noted this lack of correlation is from countries that do not typically have the intensive educational practices that have been observed in countries with very high levels of childhood myopia.⁴⁹ It may not be the case that time spent on near

work and time spent outdoors are not correlated in countries with these type of educational practices.

Serum vitamin D levels have also been suggested to be related to myopia and a possible mechanism by which increased time outdoors may reduce the risk of myopia development.^{69,70} It is theorised the relationship between myopia and vitamin D occurs in one of two ways. Vitamin D is either directly protective against myopia development, which can explain the protective nature of time spent outdoors due to the increase in vitamin D production, or increased vitamin D is merely present due to spending more time outdoors and is not related to myopia development or progression.⁷¹ A recent meta-analysis confirmed the finding that reduced serum vitamin D levels were associated with an increased risk of being myopic.⁷² The authors controlled for time spent outdoors and still found an increased risk of myopia with lower serum vitamin D levels however they expressed concern that time spent outdoors was self-reported by the subjects which led the authors to have less confidence in the result. They felt lower serum vitamin D was in reality just a bio-marker for less time spent outdoors and not actually responsible for the development of myopia. The conclusion that low serum vitamin D is a bio-marker for less time spent outdoors rather than pathognomonic for myopia is supported by a recent study assessing the relationship between genetic variants known to affect vitamin D serum concentration and refractive error.⁷³

In an outdoor environment, there is typically less dioptric variation as most objects are at a distance which results in relatively uniform dioptric values.²⁹ Figure 2.7 demonstrates the dioptric variation that can occur with both indoor and outdoor environments. As a result of the reduced dioptric variation, there is minimal peripheral retinal defocus which has been found to be a driver for myopia development.³²⁻³⁴ This is one possible explanation as to why increased time outdoors can result in lower prevalence of myopia without any significant evidence to the contrary.

Higher levels of illuminance have also been suggested as a possible explanation as to the protective effect time spent outdoors has on developing myopia. The level of illuminance outside can be orders

of magnitude higher than those found indoors. It has been found that longer periods in higher levels of illuminance can be protective against developing myopia.^{55,74} The type of light exposure may also play role in myopia development. Several animal studies have observed increased levels of myopia in animals exposed to red light when compared to controls exposed to white light.^{75,76} Increased levels of hyperopia were observed in animals exposed to blue/violet light indicating this type of light may be protective against myopia development.^{75,76} It should be noted there are conflicting results in this area with some animal species finding the opposite effect of increasing myopia with blue light exposure.⁷⁷ Adjusting the lighting to be of a higher illuminance and more towards the blue end of the spectrum may be an alternative in schools that have difficulty increasing the number of hours spent outdoors for their students. This however is a less desirable strategy than spending time outdoors for several reasons. The added public health benefit of increased activity outdoors for children cannot be understated given concerns over increasing levels of childhood obesity and diabetes in some countries.⁷⁸ There is also a risk that increased use of blue blocking lenses in spectacles and contact lenses could render this benefit minimal in those children already using a refractive error correction.⁷⁹

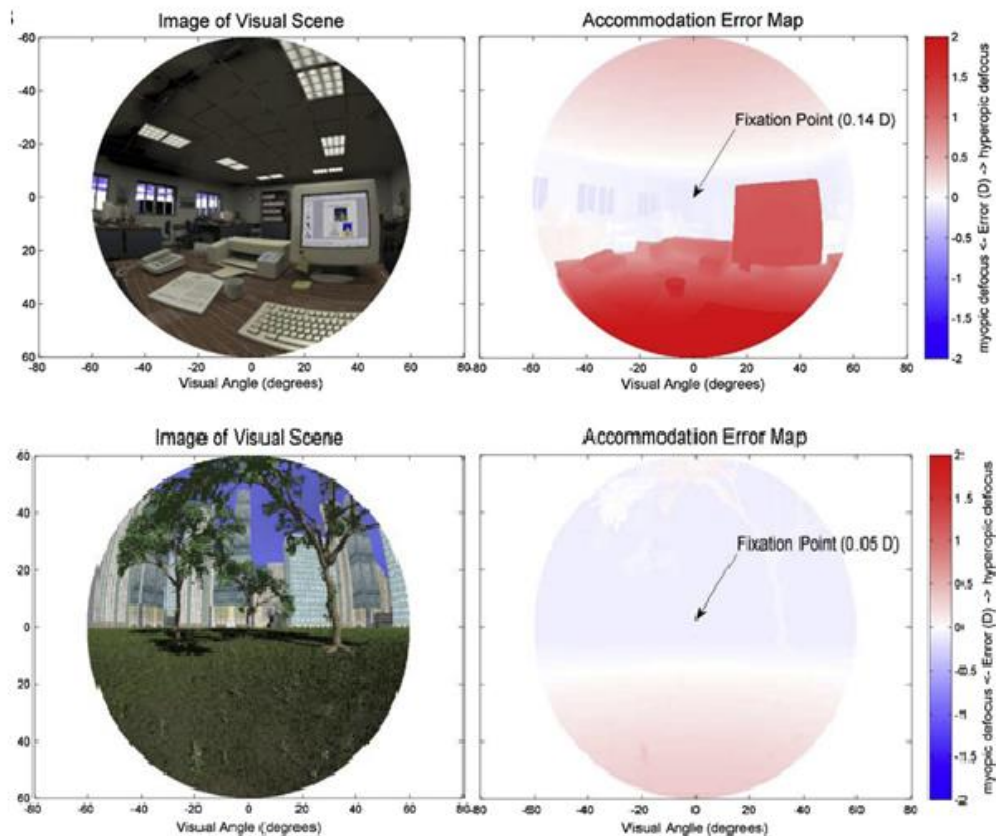


Figure 2.7: Dioptric error maps taking into account of the accommodation response and the point of fixation for both an indoor and outdoor scene showing greater hyperopic defocus for the indoor scene. Reproduced from Flitcroft.²⁹

2.3.4 Parental Myopia

The risk of a child developing myopia when one or both parents is myopic is not fully understood. A recent meta-analysis of the risk of developing myopia in the presence of parental myopia observed varying odds ratios depending on the underlying study design.⁸⁰ Taking the results at their most conservative, the authors observed odds of developing myopia of 1.44 when one parent is myopic and 1.85 when both parents are myopic. The majority of studies used in this meta-analysis demonstrated increased odds of myopia with either one or both parents being myopic. It should be noted there was a wide range of results with higher odds typically found in studies with worse

design and lower statistical power such as the case control design used by Konstantopoulos, Yadegarfar and Elgohary.⁸¹

All studies of the risk of myopia associated with parental myopia are subject to a significant confounder in that children share their environment with their parents. This makes it difficult to establish if the true risk factor is having parents with myopia or living in an environment that may induce myopia. It has been established that education is a risk factor for myopia.^{37,38} In the field of family psychology, a significant link has been observed between the level of education of parents and their expectation of academic achievement in their children.⁸² This results in parents making changes to the home environment in an effort to support their children's academic achievement.⁸² This may include the increased use of after school tuition which was noted to be used to a much greater extent in countries with very high levels of myopia⁴⁹ or encouragement of more time spent on near work.⁸³ It has been observed in one study of the risks associated with myopia development that parents did not influence the near work environment of their children⁴⁰ however this was based on self-reported time spent on near work which has only been found to have fair reliability.⁸⁴

Comparing studies with findings on the effect of parental myopia is difficult for several reasons which mainly relate to the design of each study. Some studies determine parental myopia using refraction^{85,86} while others ask parents to self-identify as myopic through the use of a questionnaire^{83,87-92} with an obvious potential risk of misclassification by using a questionnaire. Xiang et al⁹⁰ investigated this misclassification risk by performing refraction on a subgroup of parents after they had completed their questionnaire. They found a sensitivity of 0.83 and specificity of 0.79 which they determined was sufficient to deem the questionnaire results accurate. The most common misclassification error was that myopic parents did not realise that they were myopic.

Many studies use a varying definition of myopia and most do not identify the degree of parental myopia but merely whether a parent is myopic. The variable definitions of myopia used make direct comparison between studies difficult. Using threshold values of myopia closer to emmetropia can

induce a classification error,⁹³ particularly when there is uncertainty about the measure of refractive error as there is in the case of self-reporting of myopia status. Simply identifying parents in a binary fashion as myopic or non-myopic leads to a lack of nuance when describing the results in many of these studies and leads to further questions. Do highly myopic parents have highly myopic children? In families with both parents being myopic, if one is highly myopic does this increase the odds of myopia in children compared to families with both parents having low myopia? Is there a greater effect of paternal or maternal myopia? A recent study⁸⁵ assessed the refractive status of both parents and their children to determine the risk of myopia based on the level of parental myopia. They identified that the risk of myopia was dose dependent with children of parents with higher myopia more likely to be myopic. When both parents had high myopia, this led to the highest risk of developing myopia. If either parent had low to moderate myopia, this reduced the risk of developing myopia when compared to children with both parents having high myopia. When the authors controlled for possible confounders such as near work and time spent outdoors, it was found the odds of myopia development reduced for children whose parents had low to moderate myopia but increased for children whose parents were highly myopic. The authors suggest this may indicate that high myopia has greater degree of heritability while low to moderate myopia may be more influenced by environmental conditions.

The age of the children assessed is also significant. An individual's highest absolute level of myopia has typically been reached by the late teenage years or in early adulthood.⁹⁴ Many studies of parental myopia assess children of relatively young age^{87,90,92} before the maximal level of myopia will have been reached. This may induce a misclassification error as some non-myopic children may become myopic in the ensuing years. This may cause a misclassification error in two opposing ways. Firstly, if the children of myopic parents have not yet become myopic when the study is conducted this will have the effect of reducing the apparent effect of parental myopia. Secondly, if the children of non-myopic parents develop myopia after the study has been conducted this will have the effect of increasing the apparent effect of parental myopia. There is some evidence for the former as

French et al⁸⁸ assessed risk factors for myopia in both younger and older children. They observed parental myopia was significant in the younger age group but was not significant in the older age group. This may imply that some of the younger participants would have become myopic later and thereby reduce the apparent effect of parental myopia or it may point to increased hereditary in younger onset myopia and increased environmental effect in older onset myopia.

The study location can also contribute to some uncertainty with regards to results. Studies carried out in locations with very high myopia prevalence among both parents and children may find a relationship merely because such a high number of individuals are myopic. Several studies carried out in East Asia have observed a significant effect of parental myopia on the risk of developing myopia in children however relatively few children in some of these studies had no myopic parents^{86,87} with one study having as few as 20% of included children with no myopic parents.⁹²

2.3.5 Genetic Studies of Myopia

It has been recognised for a long time that myopia is to some extent a heritable condition.⁹⁵ Twin studies have been used to estimate the relative contribution of both genetics and the environment to myopia development. This usually involves comparing monozygotic (identical) twins to dizygotic (fraternal) twins. If a condition is entirely genetic monozygotic twins would have a correlation of 1.0 as they have identical genetics while dizygotic twins would have a correlation of 0.5 as they share half their genetics. If the environment shared by the twins were the only source for the condition then both sets of twins would have a correlation 1.0.⁹⁶ In reality most complex conditions such as myopia are a combination of both genetics and the environment. Twin studies have estimated the heritability of myopia as being from approximately 60% up to as high as 98%.^{95,97-99} These findings are somewhat supported by findings that axial length and corneal curvature are also heritable with twin studies showing heritability of both being approximately 60-90%.¹⁰⁰⁻¹⁰²

As a result of increased computing power and reduced costs for genotyping, the number of genetic studies of myopia has grown significantly over the last decade.¹⁰³ Prior to 2009, no genes had been identified for non-syndromic myopia. Within 10 years over 200 gene loci had been identified as a result of increased use of genome-wide association studies (GWAS).¹⁰³⁻¹⁰⁵ Despite this work, the largest such study can only explain 7.8% of the heritability of myopia.¹⁰³ This heritability gap is a common feature of GWAS¹⁰⁶ and may reduce with larger sample studies although not being able to account for gene-environment effects or rare gene variants may always be a limitation preventing full mapping of the heritability of myopia.^{103,106}

Some effort has been made to determine the interaction between genetic risk of myopia and environment. Verhoeven et al¹⁰⁷ determined the genetic risk of 2 large cohorts of Europeans for myopia based on the findings of the Consortium on Refractive Error and Myopia (CREAM).¹⁰⁴ They also assessed the educational level and refractive error of the participants and found a significant synergistic effect between high genetic risk of myopia and high educational attainment. The odds ratio (OR) for myopia was higher with both high genetic risk (OR: 7.2) and higher educational attainment (OR: 6.1) but was substantially higher when a participant had both high genetic risk and higher educational attainment (OR: 51.3) implying the environment associated with higher educational attainment may up-regulate genes conveying a risk of myopia.

2.4 Hyperopia

In many respects hyperopia is a refractive error which is opposite to myopia. Hyperopia occurs when light focuses behind the retina (Figure 2.1). Much like myopia this occurs as a result of an imbalance between the refracting surfaces of the eye and the axial length. In hyperopia the failure to focus light at the retina occurs due to having too short an axial length,¹⁰⁸ refracting surfaces with flatter radii of

curvature^{108,109} or a combination of both. It has been observed that having too short an axial length is the most common cause of hyperopia.^{108,109}

When compared to myopia there is significantly less research carried out in the field of hyperopia. There are several likely reasons for this lack of research. Firstly, myopia is easier to detect without the use of cycloplegia, even if imperfectly, particularly in children.¹¹⁰ This occurs due to the masking of hyperopia by the accommodative system which results in less obvious symptoms. Having less obvious symptoms can also result in the perception that hyperopia has less impact on some aspects of life such as childhood learning which may also explain the lack of research. The impact of uncorrected myopia on childhood learning has been established as significant¹¹¹ however the effect of hyperopia is less clear although some research indicates it also has a significant effect.^{112,113} Another reason for the greater volume of research in myopia is likely due to the significant increases in myopia prevalence³ and associated pathology¹¹⁴ over the last number years which have given researchers more impetus to understand and manage myopia and its associated complications.

Refractive error is approximately normally distributed at birth¹² although the distribution is not centred at 0 dioptres (D) spherical equivalent refraction (SER) but centred at a low hyperopic refraction which has been found to be in the range of approximately +2 to +4 D SER (Figure 2.8).^{13,115-118} The level of hyperopia present at birth appears to be related to birth weight or weeks of gestation with lower levels of hyperopia observed in those children born at earlier weeks of gestation and with lower birth weights.^{117,119} Several studies^{13,116,118} on new-borns have demonstrated that hyperopia reduces through the process of emmetropisation with a low prevalence of significant hyperopia by age 6 (Figure 2.9).¹² Flitcroft describes the persistence of hyperopia beyond this stage as a failure of the process of emmetropisation, an initial refractive error at birth too great to sufficiently emmetropise or a combination of both.¹²

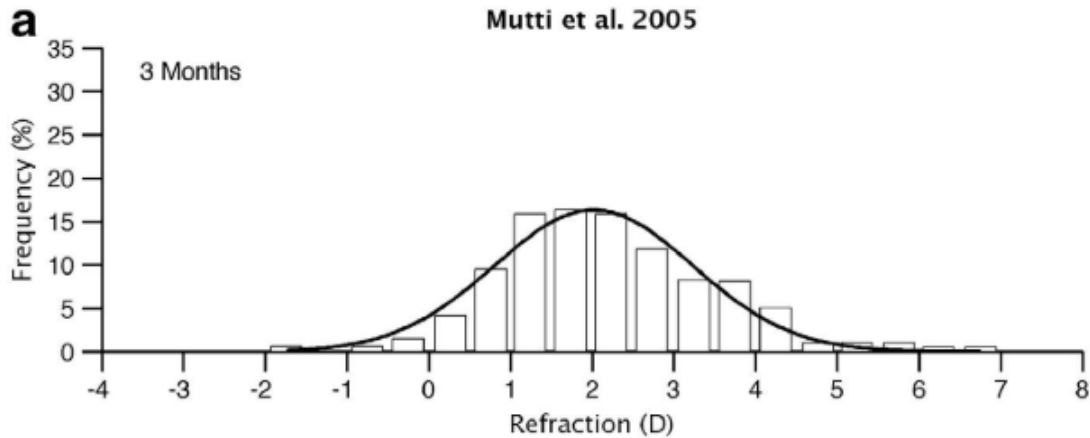


Figure 2.8: An approximately normal distribution of refractive error centred at +2.00 D SER in 3-month-old babies. This is the typical distribution of refractive error found in young children. Reproduced from Flitcroft.¹²

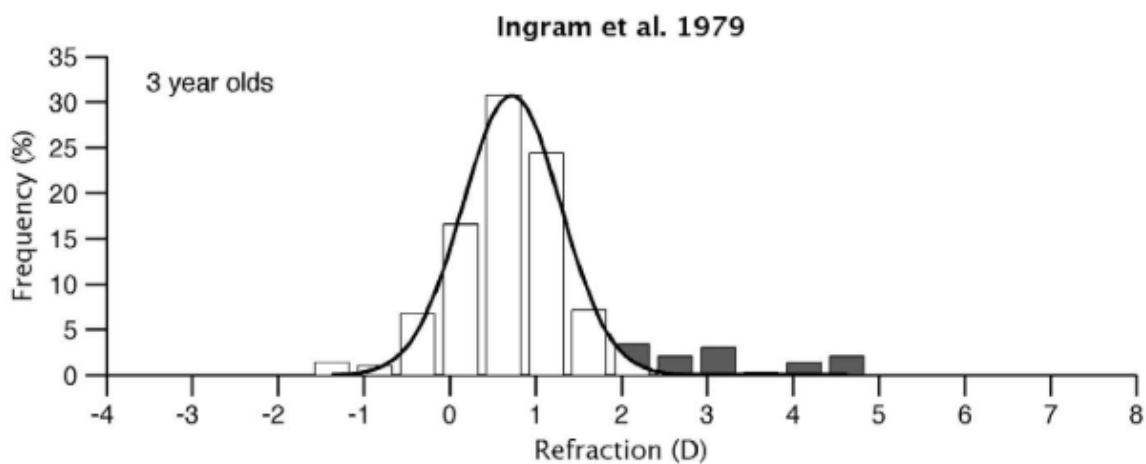


Figure 2.9: As children age the distribution of refractive error becomes more leptokurtotic and less hyperopic. This is seen by the high peak of the distribution and reducing frequency of hyperopia in children by 3 years of age. Reproduced from Flitcroft.¹²

Unlike myopia, there have been no environmental risk factors identified which seem to increase the risk of hyperopia development. Age has however been associated with increasing hyperopia.^{120–122}

Longitudinal studies have observed mean refractive errors increasing in the hyperopic direction in populations aged approximately 50 to 70 years old with the trend reversing in those older than 70.^{120,121} There are several mechanisms proposed by which eyes become more relatively hyperopic with age. The loss of accommodation with age and hence the manifestation of latent hyperopia is

often considered to be the primary cause of hyperopia due to aging amongst clinicians however Hashemi et al¹²² demonstrated that there was very little difference between the longitudinal change of manifest and cycloplegic refractions of their study participants. This indicates the loss of accommodation is unlikely to be the main driver of increasing hyperopia with age. It is also suggested that changes in the parameters of the crystalline lens are responsible for increasing hyperopia with age.¹²² Given most hyperopia occurs due to a reduced axial length, it may be anticipated that axial length might reduce with age and be the cause for increasing hyperopia. Gudmundsdottir et al¹²¹ did observe a reduced axial length in older cohorts but no longitudinal data on axial length was available so this finding may have been a cohort effect and not truly the cause of the increasing hyperopia. Given the significant increases in myopia prevalence in recent decades, it also needs to be acknowledged that the apparent increase in hyperopia with age may just be a cohort effect and what is being observed is merely generational differences in refractive error prevalence. This is an area that requires further research to truly establish the if there is a mechanism which drives an age-related change in refractive error or if this is merely a cohort effect.

2.5 Astigmatism

Astigmatism is a refractive error caused by a variation in the refractive power of the eye along different meridians. This variation can occur due to a difference in the curvature of the anterior cornea, posterior cornea, anterior crystalline lens or posterior crystalline lens (Figure 2.10).

Astigmatism can also occur as a result of the decentration or tilting of the crystalline lens or a combination of any of these factors.¹²³ Astigmatism is usually considered as with-the-rule (WTR), having the strongest power orientated approximately vertically or as against-the-rule (ATR), having the strongest power orientated approximately horizontally.¹²³ Astigmatism that with the strongest power orientated neither vertically or horizontally is referred to as oblique (Figure 2.11).

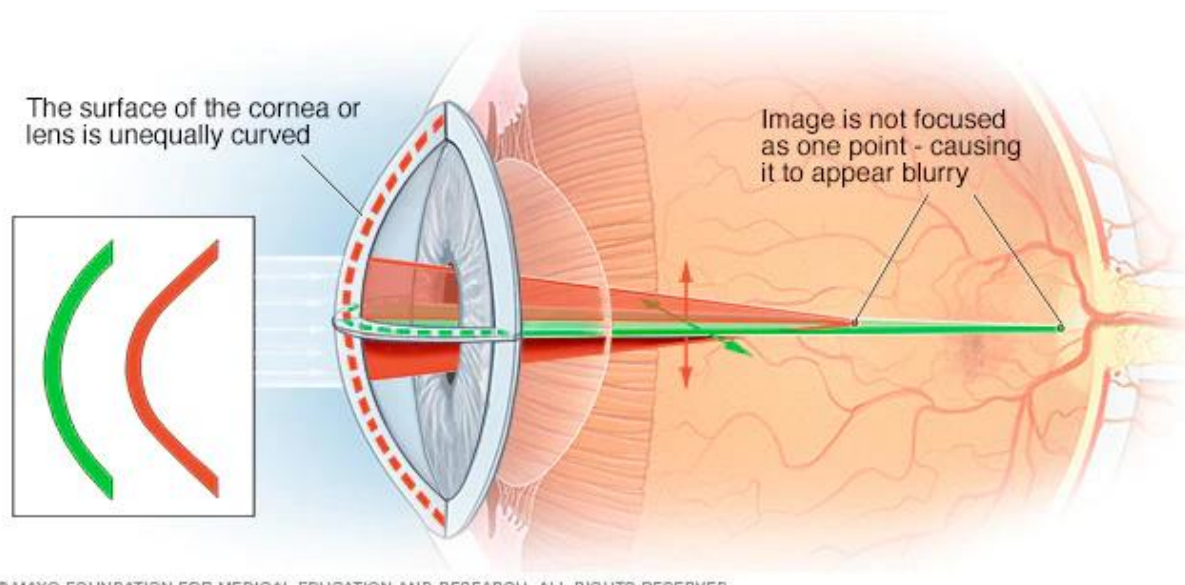


Figure 2.10: Astigmatism occurs when two principal points of focus occur due to a difference in the curvature of the anterior cornea, posterior cornea, anterior crystalline lens or posterior crystalline lens. Reproduced from www.mayoclinic.org.

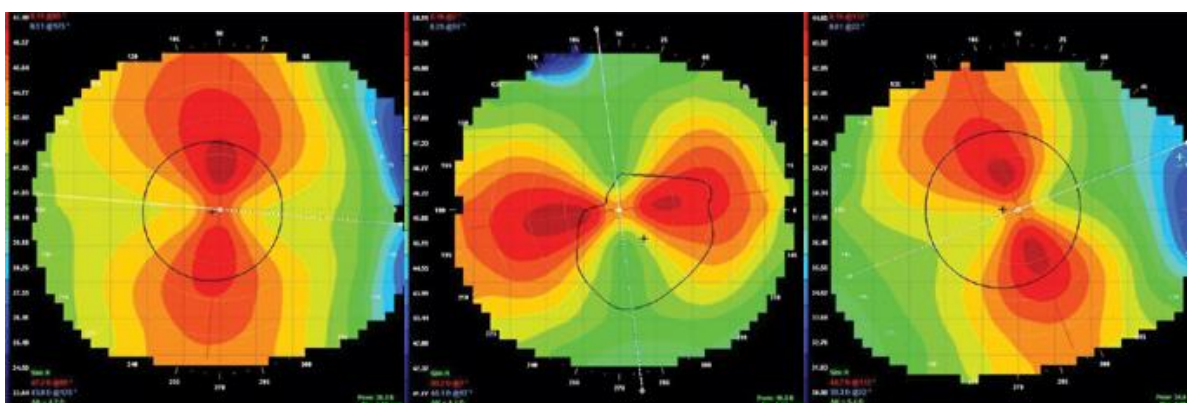


Figure 2.11: Corneal topography illustrating with the rule astigmatism (image 1), against the rule astigmatism (image 2) and oblique astigmatism (image 3). Reproduced from www.optometricmanagement.com/issues/2009/february-2009/perfect-the-football-fit

At birth, higher levels of astigmatism have been found with mean values of approximately 6 DC¹²⁴ which would be considered very high in an adult population.¹²⁵ These high values of astigmatism are related to the very steep corneas present in infants.¹²⁴ As the cornea flattens in the first 6 to 12

months of life a form of emmetropisation takes place that results in a significant reduction in the level of astigmatism present in most infants.^{124,126}

Astigmatism also changes with increasing age.¹²⁵ Low levels of astigmatism are quite common in young adult populations.^{123,125} In later life there is an increase in astigmatism that also changes from the WTR type more commonly found in younger populations to ATR.¹²⁵ This change in orientation of astigmatism is thought to be due to increased lid laxity. It is theorised the lids may be one of the causative factors for astigmatism with the pressure exerted by the lids on the cornea influencing both the orientation¹²⁷ and severity of the astigmatism.¹²⁸ As the lids become less tight with age, this results in decreasing WTR astigmatism and increasing ATR astigmatism.¹²⁵

There is some suggestion that the magnitude¹²⁹ and type^{130,131} of astigmatism is associated with higher spherical refractive error although there are conflicting results with some studies observing no association.¹³² Conflicting results have also been found with regards to the genetics of astigmatism. Twin studies of astigmatism have reported results with evidence both for⁹⁷ and against¹³³ a genetic component to astigmatism.

There is still a significant degree of uncertainty surrounding the potential causes of astigmatism with both environmental and genetic causes implicated.¹²³ There has been significantly less research carried out in the area of astigmatism when compared to myopia and further studies will be required to ascertain the mechanism behind astigmatism development and any potential modifiable risk factors.

2.6 Presbyopia

Presbyopia is a universal condition which will affect all people living to an older age. Despite the universality of this condition, there is a lack of agreement on the definition of presbyopia which may

be due to an incomplete understanding of the aetiology of presbyopia. Wolffshon and Davies¹³⁴ address this point in a recent review of presbyopia and propose the following definition:

“presbyopia occurs when the physiologically normal age-related reduction in the eyes focusing range reaches a point, when optimally corrected for distance vision, that the clarity of vision at near is insufficient to satisfy an individual’s requirements”

In a young eye the process of accommodation allows a dynamic range of focussing power which enables a seamless adjustment from distance to near viewing. Although there is some debate over the exact mechanism of accommodation,¹³⁵ the Helmholtz theory is the most widely supported.¹³⁴ This theory describes accommodation occurring as a result of ciliary body muscle contraction which leads to relaxation of the zonules and the decrease in the radius of curvature of both the anterior and posterior surface of the crystalline lens.¹³⁶ The most commonly accepted physiological cause for presbyopia is an increase in the rigidity of the crystalline lens resulting in a reduction of accommodation (Figure 2.12).^{137,138}

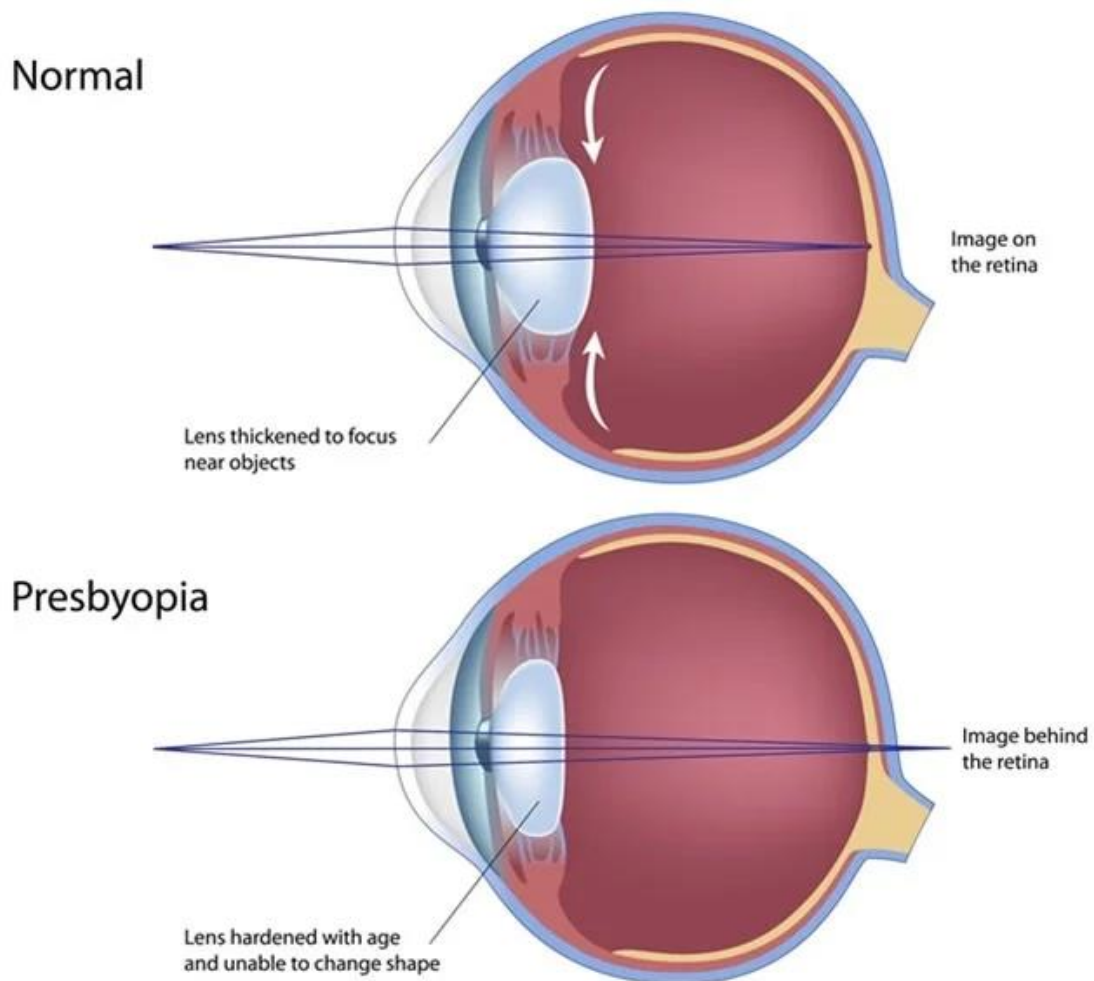


Figure 2.12: Presbyopia is thought to occur due to increased rigidity of the crystalline lens causing a reduction of accommodation. This reduction in accommodation results in the inability to focus the image of a near object on the retina. Reproduced from <https://www.news-medical.net/health/Presbyopia-Age-Related-Farsightedness.aspx>

Presbyopia is typically considered to commence at approximately age 40 although there is significant variation between individuals^{139,140} and taken from a purely mechanistic standpoint, there is evidence of reduced accommodation after the first decade of life.¹⁴¹ The variation in age of onset of presbyopia has been attributed to several causes. Distance refractive error has been observed to affect accommodation with myopes found to have higher accommodation which can delay the onset of presbyopia.^{142,143} Some natural variation in accommodative ability between individuals may result in the symptoms of presbyopia manifesting earlier in some individuals.¹⁴⁴ Climate and geographic location have also been implicated in developing presbyopia symptoms at a younger age with higher

ambient temperature and locations closer to the equator both implicated in an earlier onset of symptoms.^{139,145} Female sex has also been identified as resulting in the onset of symptoms at an earlier age.^{146,147} It has been suggested this may be as a result of women typically having shorter arms and therefore a closer near point of focus which requires a higher accommodative ability.¹⁴⁶ Ethnicity has also been investigated with Caucasians typically found to experience presbyopia symptoms at an older age.^{148–150}

It should be noted that there is significant interplay between all of these risk factors for earlier onset of presbyopia symptoms and it has been argued that there is an inherent risk of bias in most of these studies due to confounding factors.¹⁴⁹ One significant confounder in many of these risk factor is the presence of myopia. The presence of myopia can negate the symptoms of presbyopia as many myopic individuals have good near vision despite their age-related loss of accommodation. As previously established education is strongly associated with myopia.^{37,38} Historically, high levels of education have typically been found in males in Western countries. These are countries which are not close to the equator and are largely Caucasian in ethnicity. This may imply that geographic location, ambient temperature, ethnicity and female sex are in reality surrogates for lower educational attainment and a corresponding lower level of myopia prevalence. Regardless of the exact age at which the symptoms of presbyopia become manifest, this is a universal condition in older eyes.¹³⁴

2.7 Summary

Refractive error is a normal state for the eye after birth. By age 6 the process of emmetropisation should result in the majority of children having minimal refractive error. The development of refractive error beyond this age is usually in the myopic direction. Much research has been carried out into the cause of myopia development with both environmental and genetic risk factors

identified. Education involving long periods indoors and intensive study would appear to be the one of the primary drivers of myopia development. Hyperopia after the age of 6 in children seems to be a failure of the process of emmetropisation. High levels of astigmatism are also found at birth with a similar reduction in the early years of life as is observed with hyperopia. Relatively little research has been carried out on the development of hyperopia and astigmatism beyond young childhood although both appear to be affected by aging. Presbyopia is a universal condition in older life although earlier development of symptoms may be influenced by several factors such as sex, ethnicity and climate.

3 Prevalence of Refractive Error

3.1 Introduction

Establishing the prevalence of refractive error is crucial to ensure adequate public health planning can take place. This information is required to facilitate adequate correction of refractive error and plan for possible additional care needed due to the complications of refractive error. There is also a need to predict the likely changes in refractive error prevalence and put in place appropriate plans to prevent or mitigate against any consequences due to population level changes in refractive error distribution. This chapter explores some of the difficulties in determining refractive error prevalence and the current estimates of refractive error prevalence.

3.2 Interpreting Refractive Error Prevalence Studies

Several difficulties exist when comparing and contrasting published epidemiological studies of refractive error. There is a significant lack of consistency in the reporting of results with variety in the definition of refractive error, the use of cycloplegia and the method of refraction. The lack of consistency with regards to defining the refractive error of interest is one of the most considerable barriers to making comparisons. Most studies of refractive error define the refractive error based on the SER with common definitions of myopia being ≤ -0.25 D,¹⁵¹ ≤ -0.50 D,^{152,153} < -0.50 D,^{14,120} ≤ -0.75 D,^{154,155} < -0.75 D,^{156,157} ≤ -1.00 D^{158,159} and < -1.00 D.^{156,160} There is even less consistency in hyperopia with definitions ranging from $\geq +0.50$ D¹⁵² to $> +3.00$ D.¹⁵⁸ As refractive error is usually found to have a leptokurtotic distribution centred at approximately zero refractive error, changing the definition of a refractive error can have a significant impact on the reported prevalence. This problem is described by the example in Figure 4.1 which represents the distribution of refractive error taken from a large EMR database. The figure demonstrates the typical leptokurtotic distribution of

refractive error in a population. The dashed lines represent two possible definitions for myopia; ≤ -0.50 D (dashed red line) and ≤ -1.00 D (dashed blue line). The crude prevalence of myopia changes in this dataset from 33.9% using a definition of ≤ -0.50 D to 26.4% using a definition of ≤ -1.00 D. Apart from making epidemiological studies of refractive error difficult to compare, varying the definitions of myopia and hyperopia can alter the apparent effect of associated risk factors.^{60,161}

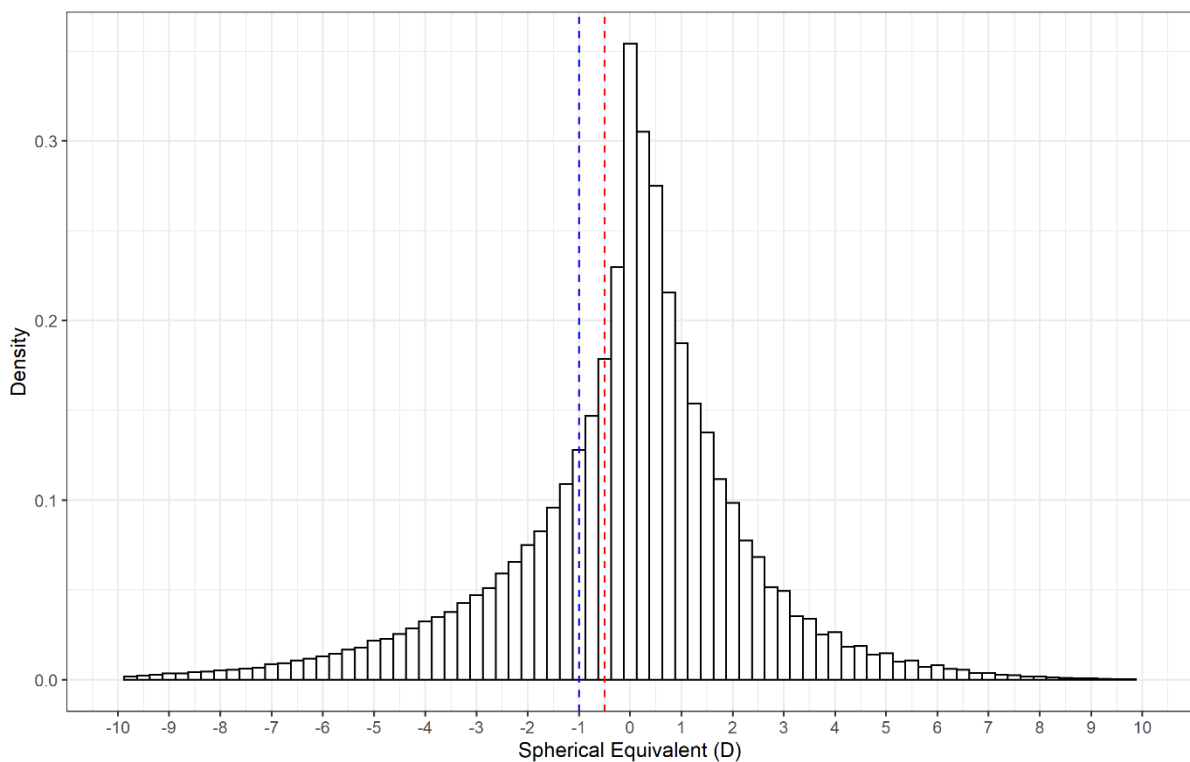


Figure 3.1: The effect of changing the refractive error definition. In this distribution of spherical equivalent refraction (SER) the crude prevalence of myopia changes from 33.9% using a definition of ≤ -0.50 D (dashed red line) to 26.4% using a definition of ≤ -1.00 D (dashed blue line)

The problem of establishing a consistent definition is even more difficult to overcome with astigmatism as this refractive error contains two components; the cylindrical power and axis. The definitions for power usually vary from ≤ -0.50 cylindrical dioptres (DC) to ≤ -1.00 DC^{14,154,158} with the axis type usually described as being WTR, ATR or oblique if described at all.^{125,162} The difficulty in defining presbyopia is explored by Wolffsohn and Davies in their comprehensive review of the

condition.¹³⁴ Having a definition purely focussed on near vision impairment would include many young individuals however presbyopia is an inherently age related condition. Some authors have used an objective definition of requiring an optical correction of $\geq +1.00$ D added to the distance correction to achieve near vision of N8 however this does not account for low myopes that can read N8 with no correction in place but still suffer from the loss of accommodation that causes presbyopia.¹⁶³ It should be noted however that both in terms of effect on the individual and at a population level, having difficulty seeing at near distances is the most significant issue whether this has been caused by presbyopia in an older person or hyperopia in young person.

Some of these issues have been recognised within the research community with a recent consensus paper from the International Myopia Institute (IMI) attempting to resolve the definition of myopia.⁹³ The authors suggest a definition of ≤ -0.50 D SER as this is the most widely used definition of myopia in published literature. The authors acknowledge this threshold is not without limitations and suggest a higher threshold may be more appropriate for intervention trials to avoid false positive and false negative associations. They also suggest a higher threshold may be appropriate if there is a risk of misclassification as may be the case if cycloplegia is not used in younger individuals.

Cycloplegia involves the use of drugs such as tropicamide or cyclopentolate to paralyse the accommodative system. An active accommodation system can significantly affect the results of refraction, particularly in children. Both myopic and hyperopic children's refractions have been found to be more hyperopic when using cycloplegia with the magnitude of effect more pronounced for higher levels of hyperopia and at younger ages.¹⁶⁴ Most significantly, there is a real risk of misclassifying children as myopic when performing non-cycloplegic refraction as it has been found that up to 34% of children found to be myopic when assessed with non-cycloplegic auto-refraction are found to be emmetropic or hyperopic following cycloplegia.¹⁶⁴ Consensus has not yet been reached on the need for cycloplegia in adults.¹⁶⁵⁻¹⁶⁷ The difference between non-cycloplegic and cycloplegic refractions appears to diminish with age.¹⁶⁶ Some authors have found a difference in

young adults that could result in a misclassification error^{166,167} while others have not.¹⁶⁵ This difference has not been found in older adults that have started to experience the effects of presbyopia so cycloplegia is not necessary in this group¹⁶⁶ however the exact age between young adulthood and commencement of presbyopia at which cycloplegia is no longer necessary has not been established.

The pharmaceutical agent used to obtain a cycloplegic effect recommended by the IMI is 2 drops of 1% tropicamide separated by 5 minutes with the refraction measurement taking place 30 minutes after the first drop is instilled. This recommendation is consistent with the published findings comparing pharmaceutical agents for cycloplegia. A recent meta-analysis found no statistically significant difference in the results of cycloplegic refraction using either 1% tropicamide or 1% cyclopentolate.¹⁶⁸ The authors did observe a statistically significant difference for young children and in hyperopes with more hyperopic refractions found in the presence of 1% cyclopentolate however despite reaching statistical significance, the differences were still minimal (0.25 D, CI: 0.10 D, 0.40 D) and unlikely to cause a misclassification error. As 1% tropicamide reaches its maximal effect in a quicker time and causes less side effects, this is the most commonly used and recommended agent for studies of refractive error.¹⁶⁹

The method by which the refraction has been determined also needs to be considered when comparing epidemiological studies of refractive error. Refraction techniques for most studies use either an objective or subjective technique. Objective techniques primarily involve the use of autorefraction while subjective techniques comprise either a full subjective refraction or retinoscopy. The IMI recommends the use of objective techniques in myopia control studies as they are more repeatable and subject to less practitioner bias than subjective techniques.¹⁶⁹ They also recommend the use of an open-field autorefractor (Figure 3.2) to reduce the likelihood of instrument accommodation and instrument myopia.¹⁶⁹ Although subjective refraction is less repeatable than objective techniques the intra and inter examiner repeatability is within ± 0.50 D in

the presence of cycloplegia¹⁷⁰ which is approximately 0.25 D worse than the intra and inter examiner repeatability of autorefractometry.¹⁷¹ This difference is significant for studies examining the effectiveness of a myopia control technique which usually report change of the order of under 1.00 D per year,¹⁷² however for an appropriately powered epidemiological study of refractive error this difference is unlikely to result in a significant level of misclassification.



Figure 3.2: An example of an open-field autorefractor, the device recommended by the International Myopia Institute (IMI) to determine refractive error in epidemiological and interventional studies of myopia.¹⁶⁹ Reproduced from Bradley et al.¹⁷³

The changes that occur in refractive error due to age can also make prevalence figures hard to interpret. In general, most children are born hyperopic becoming less hyperopic over the first

months and years of life.¹² If myopia develops, this usually occurs with increased axial elongation during the teenage years resulting in the maximal level of myopia being reached by early adulthood.¹⁷⁴ There appears to be a tendency for most people to become increasingly hyperopic with increasing age¹²² until later life when an increase in myopia can be observed as a consequence of the development of nuclear sclerotic cataracts.¹⁷⁵ Figure 3.3 demonstrates these changes by showing the mean refractive error at 5-year age groups for a large EMR database. A significant caveat when considering these changes with age is the potential for a cohort effect. There are no longitudinal studies of refractive error over a long period of time that adequately control for a cohort effect so these perceived changes in refractive error may just be changes occurring due to population level changes in refractive error prevalence. This is a particular risk when considering populations that have a significant change in refractive error prevalence over a short period of time such as several Asian countries.³ Nevertheless, these potential changes in refractive error over the life course mean that refractive error prevalence studies need to adequately describe the participants' age to allow appropriate comparisons. This is particularly the case for children where significant changes in refractive error can occur in a relatively short period of time.

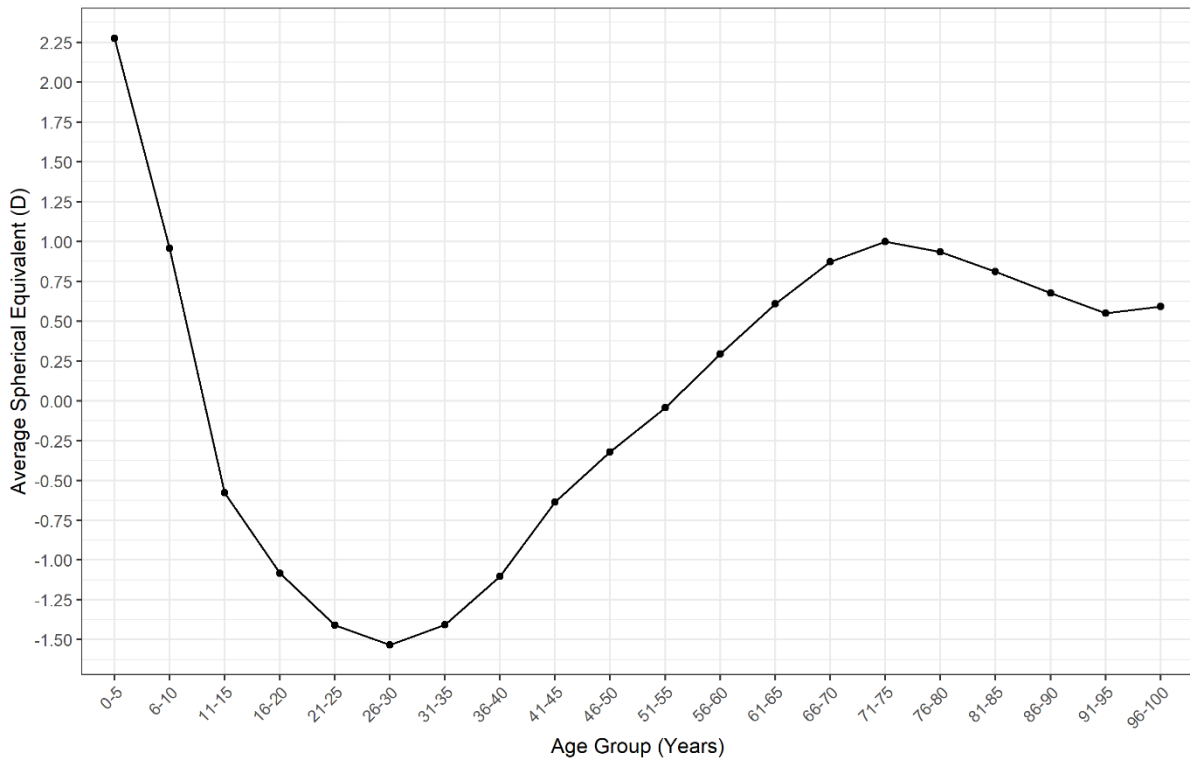


Figure 3.3: The mean spherical equivalent refraction (SER) for 5-year age groups in a large (n = 649,486) cross sectional electronic medical records (EMR) database.

3.3 Prevalence of Refractive Error in Adults

3.3.1 Myopia

When comparing epidemiological studies of myopia, there are obvious geographic trends (Figure 3.4). East Asia has been found to have a significantly higher prevalence of myopia than any other geographic location.³ Many studies of refractive error in this area have observed prevalence rates over 40%¹⁷⁶⁻¹⁷⁸ with some even exceeding 50%^{179,180} (Table 3.1). The Beijing Eye Study found a myopia (<-0.50 D SER) prevalence of 22.9% among 3,251 participants aged over 40 years¹⁸¹ with a prevalence of 2.6% of high myopia (<-6.00 D SER). This study used a combination of non-cycloplegic auto-refractor and subjective refraction to assess refractive error but did not assess refractive error in anyone found to have unaided visual acuity of logMAR 0.0 or better which may have led to an underestimation of myopia prevalence. Much higher rates of myopia have been observed in other

urbanised parts of East Asia. The Korea National Health and Nutrition Examination Survey (KNHANES) found a prevalence of myopia (< -0.50 D SER) of 48.1% in 33,355 participants aged 20 years old and older. They assessed refractive error using non-cycloplegic auto-refractor. Similarly high rates of myopia have been observed in Indonesia,¹⁷⁶ Myanmar¹⁸⁰ and Japan¹⁷⁷ with a recent study in Japan¹⁷⁹ observing a prevalence rate of 50.0% in adults aged 34 – 80. The very high prevalence of myopia observed in some Asian countries has not been seen in all Asian countries. Bangladesh,¹⁸² India^{183,184} and Iran¹⁸⁵ have all reported lower prevalence rates (Table 3.1). Unsurprisingly, countries with higher rates of myopia also tend to have higher rates of high myopia with several East Asian countries having rates in excess of 5%^{179,180,186} although the use of various definitions of high myopia make direct comparisons difficult.

The prevalence of myopia is not typically found to be as high outside Asia. After Asia, the highest prevalence of myopia is usually found in Western countries (Table 3.1). The European Eye Epidemiology Consortium (E3) has produced the largest estimate of refractive error prevalence in Europe¹⁵⁴. Fifteen different studies on refractive error were combined to produce an age-standardised prevalence of myopia in Europe of 30.6% using a definition of myopia as < -0.50 D SER. Refractive error was measured without cycloplegia either by auto-refractor or subjective refraction in all included studies. High myopia was observed in 2.7% of all participants with higher levels in younger age groups. The UK Biobank has recruited 502,682 participants aged from 40 to 69 years old to study health and disease¹⁵⁹. Refractive error was assessed in 107,452 participants using non-cycloplegic auto-refractor making this one of the largest studies of refractive error in Europe. Myopia (≤ -0.50 D SER) was observed in 33.5% of participants while high myopia (≤ -6.00 D SER) was found in 4.0% of participants. In the United States the National Health and Nutrition Examination Survey (NHANES) found a prevalence of myopia (≤ -0.50 D SER) of 44.7% in adults over the age of 20 years old which reduced to 20.5% in adults over the age of 60 years old¹⁵⁸ which is similar to the rates found in European populations. The Blue Mountains Eye Study showed much lower prevalence of myopia than has been observed in other Western populations¹⁸⁷. Refractive error data was collected

from 3,174 Australians aged from 49 to 97 by either subjective refraction or lensometry. The prevalence of myopia was found to be 14.4% overall.

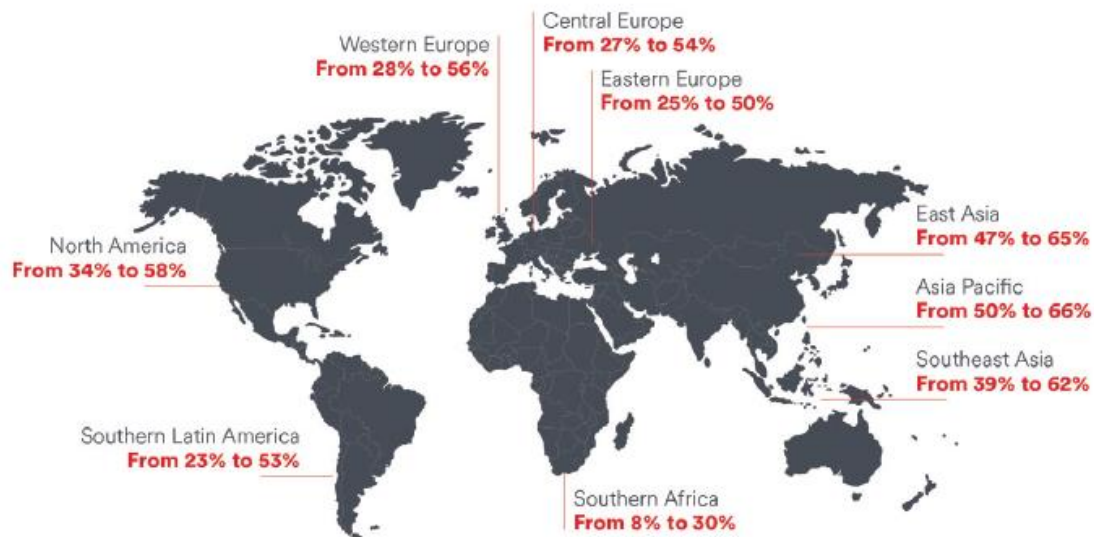


Figure 3.4: Current and projected myopia prevalence in adults around the world. Highest rates are observed in East Asia. Data taken from Holden et al.³ Reproduced from <https://retinatoday.com/articles/2019-sept/myopia-a-global-epidemic>

The prevalence of myopia varies across South America reflecting the different backgrounds and environments of its inhabitants. Myopia (< -0.99 D SER) levels of approximately 7.5% have been found after non-cycloplegic auto-refraction in 1,261 Venezuelan inhabitants of both rural and urban backgrounds¹⁸⁸. Lower levels of myopia (≤ -0.50 D SER) of 4.7% and 5.5% were observed in two communities in Ecuador¹⁸⁹. The lower rates of myopia found in Ecuador may be as the result of using cycloplegic retinoscopy as the method to assess refractive error. Another factor may be the difference in age cohorts with the groups in Ecuador limited to between 18 and 45 while in Venezuela the age ranged from 0 to over 55. Higher levels of myopia (≤ -0.50 D SER) have been observed in some South American communities with a prevalence of 14.4% observed in Columbia¹⁹⁰ and 29.2% found in office workers in Argentina.¹⁹¹

There is relatively little information available on the prevalence of myopia in Africa. Several studies detail the rates of uncorrected refractive error but do not go into detail as to the nature of the refractive error.^{192,193} Some studies do provide information on refractive error status in adults such as a Nigerian study that found myopia (< -0.50 D SER) was observed in 16.2% and high myopia (< -5.00 D SER) was observed in 2.1% of adults over 40 when assessed with either non-cycloplegic auto-refractor or subjective refraction¹⁹⁴. Comparable results were found in Durban, South Africa with a prevalence of myopia (< -0.50 D SER) of 11.4% for a similarly aged group of adults.¹⁹⁵

When comparing the above prevalence studies, it is important to consider the make-up of the study population. Table 3.1 lists a number of studies reporting myopia prevalence with similar age profiles however many studies do not provide detailed breakdowns of the participants by age. As myopia has usually reached its maximum prevalence in the second to third decade,^{154,158,179} studies having more or less younger participants will be biased towards having a higher or lower prevalence rate. The environment of the study participants also needs to be considered. It has been consistently found that urban lifestyles tend to result in a higher prevalence of myopia^{160,196} likely due to experiencing many of the risk factors described in chapter 2. Many of the studies with the lowest prevalence of myopia usually take place in rural environments with low levels of educational attainment^{189,195} while the highest prevalence is usually found in highly urbanised environments with high levels of educational attainment.^{178,179}

Table 3.1: Prevalence of myopia and high myopia in adults around the world.

Author (year)	Country	Sample Size	Age	Cycloplegia	Refraction Method	Myopia Definition	Myopia Prevalence	High Myopia Definition	High Myopia Prevalence
Africa									
Ezelum (2011) ¹⁹⁴	Nigeria	13599	40+	No	Objective	< -0.50 D	16.2%	< -5.00 D	2.1%
Mashige (2016) ¹⁹⁵	South Africa	1939	35 – 90	No	Objective	< -0.50 D	11.4%	NR	NR
Asia									
Saw (2002) ¹⁷⁶	Indonesia	1043	21+	No	Objective	≤ -0.50 D	48.5%	≤ -6.00 D	0.6%
Tan (2011) ¹⁹⁷	Singapore	1835	55+	No	Objective	≤ -0.50 D	30.0%	< -6.00 D	3.1%
Hashemi (2012) ¹⁸⁵	Iran	4864	40 – 64	Yes	Subjective	≤ -0.50 D	30.2%	< -6.00 D	1.9%
Nakao (2020) ¹⁷⁹	Japan	9850	34 – 80	No	Objective	≤ -0.50 D	50.0%	≤ -6.00 D	7.9%
Wong (2000) ¹⁸⁶	Singapore	1113	40 – 79	No	Subjective	< -0.50 D	35.0%	< -5.00 D	6.9%
Bourne (2004) ¹⁸²	Bangladesh	11189	30+	No	Objective	< -0.50 D	22.1%	< -5.00 D	1.8%
Xu (2005) ¹⁸¹	China	4319	40+	No	Subjective	< -0.50 D	22.9%	< -6.00 D	2.6%
Sawada (2008) ¹⁷⁷	Japan	3021	40+	No	Objective	< -0.50 D	41.8%	< -6.00 D	5.5%
Gupta (2008) ¹⁸⁰	Myanmar	2076	40+	No	Objective	< -0.50 D	51.0%	< -6.00 D	6.5%
Liang (2009) ¹⁹⁸	China	6491	30+	No	Subjective	< -0.50 D	21.8%	< -5.00 D	1.7%
Krishnaiah (2009) ¹⁸⁴	India	3642	40 – 95	No	Subjective	< -0.50 D	36.5%	< -5.00 D	4.8%
Nangia (2010) ¹⁸³	India	4619	30+	No	Subjective	< -0.50 D	17.0%	< -6.00 D	0.9%
Kim (2013) ¹⁷⁸	South Korea	23392	20+	No	Objective	< -0.50 D	48.1%	< -6.00 D	4.0%
Yoo (2013) ¹⁹⁹	South Korea	1532	40+	No	Objective	< -0.50 D	20.5%	< -6.00 D	1.0%
Western Countries									
Vitale (2008) ¹⁵⁸	USA	12010	20+	No	Objective	≤ -0.50 D	44.7%	≤ -5.00 D	6.5%
Antón (2009) ¹⁵²	Spain	417	40 – 79	No	Subjective	≤ -0.50 D	25.4%	≤ -5.00 D	3.5%
Nowak (2018) ²⁰⁰	Poland	998	35 – 97	No	Subjective	≤ -0.50 D	24.1%	NR	NR

Sherwin (2012) ²⁰¹	UK	4428	48 – 89	No	Objective	≤ -0.50 D	27.8%	NR	NR
Cumberland (2015) ¹⁵⁹	UK	107452	40 – 69	No	Objective	≤ -0.50 D	33.5%	≤ -6.00 D	4.0%
Wang (1994) ²⁰²	USA	4275	43 – 84	No	Objective	< -0.50 D	26.2%	NR	NR
Attebo (1999) ²⁰³	Australia	3654	49 – 97	No	Subjective	< -0.50 D	15.5%	≤ -4.00 D	3.0%
Hendricks (2009) ²⁰⁴	Netherlands	444	17 – 60	No	Objective	< -0.50 D	29.7%	≤ -5.00 D	4.3%
Wolfram (2014) ¹⁴	Germany	13959	35 – 74	No	Objective	< -0.50 D	35.1%	≤ -6.00 D	3.5%
Varma (2017) ²⁰⁵	USA	4582	50+	No	Objective	< -0.50 D	35.1%	≤ -5.00 D	7.4%
Central and South America									
Jiménez (2004) ¹⁸⁹	Ecuador	1283	18 – 45	Yes	Subjective	≤ -0.50 D	4.7%/5.5%	NR	NR
Cortinez (2008) ¹⁹¹	Argentina	1518	25 – 65	No	Subjective	≤ -0.50 D	29.2%	≤ -6.00 D	1.6%
Galvis (2018) ¹⁹⁰	Columbia	3608	35 – 55	No	Subjective	≤ -0.50 D	14.4%	NR	NR

NR = Not reported.

3.3.2 Hyperopia

The prevalence of hyperopia in adults tends to follow an opposed trend as that described for myopia. The highest prevalence of hyperopia is found in regions with a low prevalence of myopia (Table 3.2). Although relatively few assessments of refractive error in adults have taken place in Africa, those that have, indicate a high prevalence of hyperopia with one Nigerian study finding over 50% of adults aged 40 and older to be hyperopic.¹⁹⁴ Similar results have been found in Central and South America which also typically have lower rates of myopia when compared internationally.¹⁹⁰ Western countries typically have a lower prevalence of hyperopia with the E3 observing a rate of hyperopia ($\geq +1.00$ D SER) of 25.23% in adults aged 25 – 89.¹⁵⁴ The prevalence of hyperopia in Australian adults is high at over 50% when compared to other Western countries although this study used an older age group and lower definition of hyperopia ($> +0.50$ D SER) which may contribute to some of the difference observed.²⁰³ A study with a similar age profile in the UK observed a similar prevalence of hyperopia of 49.4%.²⁰¹ This highlights the need to consider the age of participants when considering hyperopia prevalence in much the same way as is required when considering studies of myopia prevalence. As hyperopia increases with age (Figure 3.2), studies using older participants are likely to find higher rates of hyperopia. This point is further highlighted when comparing two studies of refractive error conducted over the same time period in South Korea. Yoo et al observed a prevalence rate of 41.8% in adults aged 40 and over.¹⁹⁹ Kim et al observed a prevalence rate of 24.2% in adults aged over 20 but they also reported rates for adults aged 40 and over and found a prevalence of 34.8% which is much closer to the finding the by Yoo et al.^{178,199} The remaining difference may be accounted for by the differing environments of the participants with Yoo et al's study focusing on rural inhabitants¹⁹⁹ although as described in chapter 3.2, there is a significant risk of a cohort effect when comparing refractive error prevalence across generations which may also explain this variance. In general, East Asia tends to have the lowest rates of hyperopia (Table 4.2) with a prevalence as low as 13.9% in Indonesia.¹⁷⁶

3.3.3 Astigmatism

The prevalence of astigmatism in adults follows less obvious trends than myopia or hyperopia. High prevalence of astigmatism was found in countries in all geographical regions with participants living in various environments (Table 3.2). High levels of astigmatism were reported in Japan,¹⁷⁷ South Korea,¹⁹⁹ Spain¹⁵² and Nigeria¹⁹⁴ while low levels were observed in Ecuador¹⁸⁹ and Poland.²⁰⁰

The most consistent explanation for higher levels of astigmatism in a population is older age. Many studies reported a relationship between increasing astigmatism and increasing age.^{177,194,199,200,203}

This relationship was consistent across studies with both high and low overall prevalence of astigmatism. This likely indicates a significant level of variation in astigmatism prevalence between studies is due to the age of the study participants. This cannot completely explain the variance however as different prevalence rates of astigmatism have been found even in similarly aged populations.^{182,200}

Some authors have suggested that higher refractive error results in higher levels of astigmatism²⁰³ and thus countries with high prevalence of myopia or hyperopia will also have high levels of astigmatism. There have been conflicting reports on this relationship with some authors finding no relationship between refractive error and astigmatism.¹⁷⁷ Another possible explanation for the differences observed is suggested by Bourne et al.¹⁸² In this study the authors observed a higher rate of astigmatism in those with cataract. It may be the case that areas reporting higher levels of astigmatism in older participants may also be areas with worse access to cataract surgery and the high astigmatism prevalence may indicate a higher prevalence of cataract in the elderly in these countries.

Table 3.2: Prevalence of hyperopia and astigmatism in adults around the world.

Author (year)	Country	Sample Size	Age	Cycloplegia	Refraction Method	Hyperopia Definition	Hyperopia Prevalence	Astigmatism Definition	Astigmatism Prevalence
Africa									
Ezelum (2011) ¹⁹⁴	Nigeria	13599	40+	No	Objective	> +0.50 D	50.7%	> 0.50 D	63.5%
Mashige (2016) ¹⁹⁵	South Africa	1939	35 – 90	No	Objective	> +0.50 D	37.7%	≥ 0.50 D	25.7%
Asia									
Saw (2002) ¹⁷⁶	Indonesia	1043	21+	No	Objective	≥ +0.50 D	13.9%	≥ 0.50 D	44.3%
Wong (2000) ¹⁸⁶	Singapore	1113	40 – 79	No	Subjective	> +0.50 D	28.4%	> 0.50 D	43.9%
Bourne (2004) ¹⁸²	Bangladesh	11189	30+	No	Objective	> +0.50 D	20.6%	> 0.50 D	32.4%
Xu (2005) ¹⁸¹	China	4319	40+	No	Subjective	> +0.50 D	20.0%	NR	NR
Sawada (2008) ¹⁷⁷	Japan	3021	40+	No	Objective	> +0.50 D	27.9%	> 0.50 D	54.0%
Liang (2009) ¹⁹⁸	China	6491	30+	No	Subjective	> +0.50 D	22.0%	> 0.50 D	28.0%
Krishnaiah (2009) ¹⁸⁴	India	3642	40 – 95	No	Subjective	> +0.50 D	18.1%	> 0.50 D	38.2%
Nangia (2010) ¹⁸³	India	4619	30+	No	Subjective	> +0.50 D	18.0%	NR	NR
Hashemi (2012) ^{185,206}	Iran	4864/5020	40 – 64	Yes	Subjective	> +0.50 D	35.6%	> 0.50 D	49.1%
Kim (2013) ¹⁷⁸	South Korea	23392	20+	No	Objective	> +0.50 D	24.2%	> 1.00 D	28.3%
Yoo (2013) ¹⁹⁹	South Korea	1532	40+	No	Objective	> +0.50 D	41.8%	> 0.50 D	63.7%
Tan (2011) ¹⁹⁷	Singapore	1835	55+	No	Objective	≥ +1.00 D	41.5%	≥ 1.00 D	43.5%
Gupta (2008) ¹⁸⁰	Myanmar	2076	40+	No	Objective	> +1.00 D	15.0%	> 1.00 D	30.6%
Western Countries									
Antón (2009) ¹⁵²	Spain	417	40 – 79	No	Subjective	≥ +0.50 D	43.6%	> 0.50 D	53.5%
Sherwin (2012) ²⁰¹	UK	4428	48 – 89	No	Objective	≥ +0.50 D	49.4%	NR	NR
Nowak (2018) ²⁰⁰	Poland	998	35 – 97	No	Subjective	≥ +0.50 D	37.5%	≥ 0.50 D	10.8%

Wang (1994) ²⁰²	USA	4275	43 – 84	No	Objective	> +0.50 D	49.0%	NR	NR
Attebo (1999) ²⁰³	Australia	3654	49 – 97	No	Subjective	> +0.50 D	56.6%	≥ 0.75 D	37.0%
Hendricks (2009) ²⁰⁴	Netherlands	444	17 – 60	No	Objective	> +0.50 D	9.9%	> 0.50 D	23.6%
Varma (2017) ²⁰⁵	USA	4582	50+	No	Objective	> +0.50 D	40.2%	> 0.50 D	45.6%
Wolfram (2014) ¹⁴	Germany	13959	35 – 74	No	Objective	> +0.50 D	31.8%	> 0.50 D	32.3%
Cumberland (2015) ¹⁵⁹	UK	107452	40 – 69	No	Objective	≥ +1.00 D	27.6%	NR	NR
Vitale (2008) ¹⁵⁸	USA	12010	20+	No	Objective	≥ +3.00 D	3.6%	≥ 1.00 D	36.2%
Central and South America									
Cortinez (2008) ¹⁹¹	Argentina	1518	25 – 65	No	Subjective	≥ +0.50 D	18.1%	NR	NR
Galvis (2018) ¹⁹⁰	Columbia	3608	35 – 55	No	Subjective	≥ +0.50 D	42.1%	NR	NR
Jiménez (2004) ¹⁸⁹	Ecuador	1283	18 – 45	Yes	Subjective	≥ +1.00 D	16.1%/11.5%	≥ 0.50 D	9.9%/7.7%

NR = not reported.

3.3.4 Presbyopia

The ambiguity with regards to the definition of presbyopia makes reporting on the prevalence of presbyopia difficult. Taken from a purely mechanistic view point, presbyopia can be considered the loss of accommodative ability through aging in which case every person that lives long enough will eventually be affected by presbyopia.¹³⁴ This should mean that prevalence rates should reach 100% past a certain age however most studies of presbyopia prevalence are more concerned with finding those affected by correctable near vision impairment and establishing the number of people that are uncorrected or undercorrected.²⁰⁷ If this is used as the basis for defining presbyopia, many myopic individuals will not suffer from near vision impairment when they have no correction in place and therefore prevalence rates will not reach 100% and may be much lower in countries with a high prevalence of myopia. There are also relatively few studies describing the prevalence of presbyopia, in a 2008 meta-analysis only 4 studies were found that met the inclusion criteria.¹⁶³ This meta-analysis was repeated in 2018 when more studies had been carried out however there were still only 25 prevalence studies which primarily consisted of studies performed in Africa and Asia.²⁰⁷

The current estimated number of people effected by presbyopia is approximately 1.8 billion which is projected to rise to 2.1 billion by the year 2030.²⁰⁷ This prevalence rate is expected to reduce after the year 2030 due to the compensatory effect caused by the projected increase in myopia.³ Most significantly there are estimated to be 826 million (95% CI: 686 – 960 million) people affected by near vision impairment due to uncorrected and undercorrected presbyopia (Figure 3.5).²⁰⁷ Bourne et al recently estimated near vision impairment due to uncorrected and under corrected presbyopia was lower at 510 million (95% CI: 371 – 667 million) people using a different methodology.⁵ Although there is disagreement between these two studies, the confidence intervals are quite close so the true number of people affected by near vision impairment can likely be estimated as lying between the two values.



Figure 3.5: Map showing the prevalence of vision impairment resulting from uncorrected presbyopia. The highest prevalence is found in Africa and East Asia while lowest prevalence is observed in Western countries. Reproduced from Fricke et al.²⁰⁷

3.4 Refractive Error Prevalence in Children

Many of the difficulties in comparing refractive error prevalence studies in adults are also present in studies of children. This is often magnified due to the significant changes in refractive error that can take place over relatively short periods of time in children.²⁰⁸ The Refractive Error Studies in Children (RESC) suggested a uniform methodology and reporting structure to allow a better estimation of global prevalence of refractive error and vision impairment in children.²⁰⁹ This resulted in a series of studies in a variety of locations which were directly comparable.^{210–214} Several other studies of refractive error in children such as the Northern Ireland Childhood Errors of Refraction (NICER) study²¹⁵ and the Ireland Eye Study (IES)²¹⁶ have also adopted the same reporting methodology allowing for straightforward comparison however studies using the RESC protocol are not available in all locations and in particular are less commonly performed for older children (Table 3.5 and 3.8).

The primary strength of the RESC methodology is the uniformity of reporting and the use of cycloplegic autorefraction as the method of determining refractive error. One of the weaknesses is that, the protocol does not require investigation of refractive error if a child has VA better than 0.625 decimal²⁰⁹ although many authors using this methodology carried out refractive error assessment in all children regardless of VA.^{216,217} For those authors that did not assess refractive error in children with VA better than 0.625 decimal, this will likely result in an underreporting of low levels of myopia.²¹⁸ The use of consistent definitions for refractive errors is another strength of the RESC methodology although there was some variation in the definitions used for astigmatism with investigators using either ≥ 0.75 DC^{210,212,214} or ≥ 1.00 DC.^{216,218}

3.4.1 Myopia

Myopia prevalence in children follows similar trends as those seen in adults. The highest prevalence rates are typically seen in East Asia in urban settings^{208,219} with the lowest rates observed in Africa and rural settings (Figure 3.6).^{220,221} The most significant difference when considering refractive error prevalence in children as opposed to adults, is the rapid changes in refractive error that can occur over a relatively short period of time.²²² This necessitates grouping children in relatively small age cohorts to facilitate appropriate comparison.



Figure 3.6: The rate of myopia seen in children based on recent studies. Myopia less than 25% reported in blue, myopia less than 45% reported in green and myopia greater than or equal to 45% reported in red. Adapted from <https://myopiainstitute.org/myopia/>

For young children under the age of 11, there is a greater level of homogeneity observed in myopia prevalence. This is particularly the case for younger children aged approximately 6 years old (Table

3.3). It is uncommon to observe myopia prevalence above 10% in this age group. One of the highest levels of myopia observed in the approximately 6-year-old age group was 10% in a group of children in Malaysia.²¹⁴ The authors noted that the prevalence varied by ethnicity with prevalence in Chinese children being higher at 20.9%. This level of myopia prevalence at this age has not been found in other studies of Chinese children which are typically under 10%.^{210,223,224} The lowest prevalence rates of myopia of less than 1% at this age have been observed in Australia²²⁵, Brazil²¹⁸ and Ghana.²²⁶ Rates were similarly low in this age cohort in other Western populations^{215,216} apart from those reported in the Aston Eye Study (AES) which observed a prevalence of 9.4% however this study was more ethnically diverse, including a significant cohort of Asian children, which may explain the variation.²²⁴

Myopia prevalence has been found in all locations to consistently increase as children reach the teenage years (Figure 3.7) however the most dramatic changes are typically seen in East Asia (Table 3.4). Two Chinese studies found a prevalence of approximately 50% by age 10 – 11 in an urban setting^{213,223} with relatively high prevalence of 38.8% also found in a rural setting in China.²¹⁰ The prevalence found by the mid teenage years was not as high in some other Asian countries with prevalence's of 10.8% and 32.5% in India²¹² and Malaysia²¹⁴ by age 15 respectively. In Western countries the prevalence of myopia by the early teenage years has also risen but is typically lower than that found in Asia, usually below 20%.^{215,216} As with younger children, Africa, Australia and South America usually have the lowest prevalence rates which are at or below 10% by age 15.^{211,217,225,226}



Figure 3.7: The prevalence of myopia in among older teenagers is extremely high in some east Asian countries as indicated by the almost universal need for correction in this group of male teenage students. Reproduced from Dolgin.²²⁷

There is less consistency in the reporting of myopia prevalence among older teenagers and young adults. Studies using the RESC methodology have not to date recruited children older than 16.^{210,213,214,216,217,225} Most studies of myopia prevalence in older children still make use of the most common definition of myopia of ≤ -0.50 D SER however the method of refraction used and use of cycloplegia is inconsistent (Table 3.5). In this age group the rates of myopia increase dramatically in East Asia (Figure 3.7) with a prevalence above 90% reported in both China²⁰⁸ and South Korea.²¹⁹ The study by Wang et al²⁰⁸ did not use cycloplegia so this very high prevalence may overstate the true prevalence however the study by Jung et al²¹⁹ found a prevalence of 96.5% using cycloplegia and a more conservative definition of myopia of < -0.50 D SER making a misclassification error unlikely. The very high prevalence (over 20%) of high myopia found in both studies is of most concern (see chapter 4.4.3).^{208,219} Elsewhere the rates of myopia in this age cohort are more variable with rates in Western countries varying from 13.4% in Norway²²⁸ to 59.0% in the USA.²²⁹ The study conducted in Norway used cycloplegia with autorefraction and a definition of ≤ -0.50 D SER while the study in the USA used non-cycloplegic subjective refraction with a definition of ≤ -1.00 D SER. The very high rate

observed in the USA may be due to referral bias as this was a retrospective study using EMRs of those accessing eyecare through a private health insurance plan. This may underrepresent the number of emmetropic and hyperopic children in this age group as they are less likely to be symptomatic and access care. A Polish study using a similar methodology to the study conducted in Norway observed a myopia rate of 32.6% however the sample sizes for both studies were relatively small. In Africa, the prevalence of myopia in this age group remained low with two studies finding very similar rates of 4.6% and 4.3% in Rwanda²²⁰ and Ghana²²⁶ respectively. The only study of this age cohort in central and South America reported a myopia prevalence of 15.5%, however, the unusual definitions used for refractive error (myopia \leq -0.10 D SER) make these results hard to interpret.²³⁰

Table 3.3: Prevalence of myopia and high myopia in young children (6 – 10 years old) around the world.

Author (year)	Country	Sample Size	Age	Cycloplegia	Refraction Method	Myopia Definition	Myopia Prevalence	High Myopia Definition	High Myopia Prevalence
Africa									
Naidoo (2003) ²¹⁷	South Africa	458 551	6 10	Yes	Objective	≤ -0.50 D	4.6% 1.9%	NR	NR
Ovenseri-Ogbomo (2010) ²²⁶	Ghana	231 254	5 – 7 8 – 10	Yes	Objective	≤ -0.50 D	0.9% 8.3%	NR	NR
Asia									
Zhao (2000) ²¹⁰	China	1152	5 – 7	Yes	Objective	≤ -0.50 D	1.2%	NR	NR
Murthy (2002) ²¹²	India	494 590	6 10	Yes	Objective	≤ -0.50 D	5.9% 7.0%	NR	NR
He (2004) ²¹³	China	295 415	6 10	Yes	Objective	≤ -0.50 D	5.9% 30.1%	NR	NR
Goh (2005) ²¹⁴	Malaysia	590 589	7 10	Yes	Objective	≤ -0.50 D	10.0% 16.2%	NR	NR
Ma (2016) ²²³	China	1230 962	6 10	Yes	Subjective	≤ -0.50 D	5.2% 52.2%	≤ -6.00 D	0.0% 1.0%
Western Countries									
O'Donoghue (2010) ²¹⁵	UK	392	6 – 7	Yes	Objective	≤ -0.50 D	2.8%	NR	NR
Logan (2011) ²²⁴	UK	359	6 – 7	Yes	Objective	≤ -0.50 D	9.4%	NR	NR
French (2012) ²²⁵	Australia	1105	6 – 7	Yes	Objective	≤ -0.50 D	0.7%	NR	NR
Harrington (2019) ²¹⁶	Ireland	733	6 – 7	Yes	Objective	≤ -0.50 D	3.3%	NR	NR
Central and South America									
Maul (2000) ²¹¹	Chile	1675	5 – 7	Yes	Objective	≤ -0.50 D	3.5%	NR	NR
Moraes Ibrahim (2013) ²¹⁸	Brazil	246	10	Yes	Subjective	≤ -0.50 D	0.8%*	NR	NR

NR = not reported. *Refractive error was not assessed in children with VA ≥ 0.625 decimal.

Table 3.4: Prevalence of myopia and high myopia in children (11 – 15 years old) around the world.

Author (year)	Country	Sample Size	Age	Cycloplegia	Refraction Method	Myopia Definition	Myopia Prevalence	High Myopia Definition	High Myopia Prevalence
Africa									
Naidoo (2003) ²¹⁷	South Africa	476 326	11 15	Yes	Objective	≤ -0.50 D	4.4% 9.6%	NR	NR
Ovenseri-Ogbomo (2010) ²²⁶	Ghana	253 203	11 – 13 14 – 16	Yes	Objective	≤ -0.50 D	9.1% 8.9%	NR	NR
Asia									
Zhao (2000) ²¹⁰	China	905	14 – 15	Yes	Objective	≤ -0.50 D	38.8%	NR	NR
Murthy (2002) ²¹²	India	528 381	11 15	Yes	Objective	≤ -0.50 D	9.7% 10.8%	NR	NR
He (2004) ²¹³	China	427 376	11 15	Yes	Objective	≤ -0.50 D	49.7% 78.4%	NR	NR
Goh (2005) ²¹⁴	Malaysia	701 693	11 15	Yes	Objective	≤ -0.50 D	22.6% 32.5%	NR	NR
Rim (2016) ¹⁵⁶	South Korea	7486 ⁺	12 – 18	No	Objective	< -0.75 D	73.0%	< -6.00 D	9.3%
Western Countries									
O'Donoghue (2010) ²¹⁵	UK	661	12 – 13	Yes	Objective	≤ -0.50 D	15.0%	NR	NR
Logan (2011) ²²⁴	UK	296	12 – 13	Yes	Objective	≤ -0.50 D	29.4%	NR	NR
French (2012) ²²⁵	Australia	1406	12 – 13	Yes	Objective	≤ -0.50 D	4.6%	NR	NR
Harrington (2019) ²¹⁶	Ireland	901	12 – 13	Yes	Objective	≤ -0.50 D	19.9%	NR	NR
Central and South America									
Maul (2000) ²¹¹	Chile	1675	14 – 15	Yes	Objective	≤ -0.50 D	12.5%	NR	NR
Moraes Ibrahim (2013) ²¹⁸	Brazil	340 175	12 15	Yes	Subjective	≤ -0.50 D	2.9%** 3.4%**	NR	NR

*Astigmatism prevalence for entire study population, not reported in age groups. **Refractive error was not assessed in children with VA ≥ 0.625 decimal.

⁺Sample size for ages 5 – 19. NR = not reported.

Table 3.5: Prevalence of myopia and high myopia in older children (16 years old and over) around the world.

Author (year)	Country	Sample Size	Age	Cycloplegia	Refraction Method	Myopia Definition	Myopia Prevalence	High Myopia Definition	High Myopia Prevalence
Africa									
Semanyenzi (2015) ²²⁰	Rwanda	300	17 – 20	Yes	Objective	≤ -0.50 D	4.6%	≤ -6.00 D	0.5%
Mehari (2013) ²²¹	Ghana	814	16 – 18	No	Subjective	≤ -0.50 D	4.3%	NR	NR
Asia									
Wang (2020) ²⁰⁸	China	370	18	No	Objective	≤ -0.50 D	92.7%	≤ -6.00 D	26.0%
Jung (2012) ²¹⁹	South Korea	23616	19	Yes	Objective	< -0.50 D	96.5%	≤ -6.00 D	21.6%
Quek (2004) ²³¹	Singapore	453	15+	No	Objective	≤ -0.50 D	74.2%	≤ -6.00 D	6.8%
Hashemi (2014) ²³²	Iran	434 ⁺	18	No	Subjective	≤ -0.50 D	37.1%	≤ -6.00 D	0.5%*
Western Countries									
Hagen (2018) ²²⁸	Norway	439	16 – 19	Yes	Objective	≤ -0.50 D	13.4%	≤ -6.00 D	0.5%
Shapira (2019) ²³³	Israel	104689	16 – 19	No	Objective	≤ -0.50 D	23.3%	≤ -6.00 D	1.7%
Czepita (2006) ²³⁴	Poland	187	18	Yes	Subjective	≤ -0.50 D	32.6%	NR	NR
Theophanous (2018) ²²⁹	USA	2849	17 – 19	No	Subjective	≤ -1.00 D	59.0%	≤ -6.00 D	4.9%
Central and South America									
De Amorim Garcia (2005) ²³⁰	Brazil	1024	16 – 20	Yes	Subjective	≤ -0.10 D	15.5%	NR	NR

*High myopia prevalence for entire study population. ⁺Sample size for ages 14 – 18. NR = not reported.

3.4.2 Hyperopia

Hyperopia prevalence in children has been found to be highest at younger ages and usually reduces as the prevalence of myopia increases with increasing age. The RESC used a definition for hyperopia of $\geq +2.00$ D SER.²⁰⁹ When compared to adult studies this is an unusually high definition for hyperopia however this was likely chosen as the effects of accommodation in childhood mean a child with a refraction below $+2.00$ D SER is likely to be asymptomatic. The screening strategy employed by the RESC²⁰⁹ and many other studies of refractive error in children contains a significant limitation. Children first had their visual acuity screened and if it was found to be 0.625 decimal or better, they were deemed to be emmetropic with no full refractive error examination. This is particularly problematic for hyperopic children as many hyperopic children can appear to have good distance visual acuity due to the compensatory effect of their accommodation.

The highest prevalence of hyperopia ($\geq +2.00$ D) in young children (6 – 10 years old) has been observed in Europe with two studies finding rates above 25%.^{215,216} A similar rate has been found in Chile²¹¹ although most other countries with prevalence data for young children report rates of approximately 10% or less (Table 3.6). Having higher rates of hyperopia in young children does not necessarily imply the rates of myopia will be lower as the children age. Naidoo et al²¹⁷ found a hyperopia prevalence of 4.6% in South Africa in 6-year-olds which was much lower than the 25.0% observed in 6 – 7-year-olds by Harrington et al²¹⁶ in Ireland however by age 12 – 13 the myopia prevalence observed by Harrington et al²¹⁶ was 19.9% while Naidoo et al²¹⁷ only observed 9.6% myopia prevalence by age 15.

In young teenage children the rates of hyperopia are reduced to below 10% (Table 3.7) with the lowest rates observed in East Asian populations.^{210,213,214} The low rate of hyperopia observed in these populations is likely a consequence of the increasing levels of myopia that become apparent at this age. This trend of reducing hyperopia prevalence continues in older children (Table 3.8) however these studies are more difficult to compare as most authors use a lower definition of hyperopia of \geq

+0.50 D SER. There are also relatively few studies reporting on the prevalence of hyperopic refractive error in older teenagers. The highest levels of hyperopia were observed in Norway²²⁸ and Brazil²³⁰ however the low threshold for hyperopia selected in both studies is the most likely cause for these high prevalence values. The Norwegian study²²⁸ also reported a prevalence of 6.4% at a threshold of $\geq +2.00$ D SER which is still higher than that found in other studies but not as significantly different.

3.4.3 Astigmatism

Establishing trends in astigmatism prevalence in children is more difficult than for myopia and hyperopia. This is primarily due to how astigmatism is reported in the literature. The RESC recommended astigmatism was defined as ≥ 0.75 DC²⁰⁹ however not all authors have used this definition instead using ≥ 1.00 DC.^{216,225} More significantly, most studies using the RESC protocol did not report astigmatism prevalence for each age group but instead reported the prevalence for the entire cohort of children making any age-related patterns difficult to elicit. There are also no obvious geographical trends (Table 3.6 – 3.8) with both high and low prevalence of astigmatism reported in Asia^{210,213} and elsewhere.^{211,215} In China, a higher prevalence of astigmatism was found in children living in an urban environment than those living in a rural environment.^{210,213} This may offer an explanation as to the various prevalence values observed in different studies however these two studies also had significantly different rates of myopia with much higher levels of myopia observed in the urban setting.^{210,213} It has been suggested that astigmatism may be associated with having a refractive error¹²³ in which case the higher prevalence of myopia may be the true reason for the difference in astigmatism prevalence found in these two studies.

Table 3.6: Prevalence of hyperopia and astigmatism in young children (6 – 10 years old) around the world.

Author (year)	Country	Sample Size	Age	Cycloplegia	Refraction Method	Hyperopia Definition	Hyperopia Prevalence	Astigmatism Definition	Astigmatism Prevalence
Africa									
Naidoo (2003) ²¹⁷	South Africa	458 551	6 10	Yes	Objective	≥ +2.00 D	4.6% 1.9%	≥ 0.75 D	14.6%*
Ovenseri-Ogbomo (2010) ²²⁶	Ghana	231 254	5 – 7 8 – 10	Yes	Objective	≥ +2.00 D	0.9% 8.3%	≥ 0.75 D	13.0% 14.2%
Asia									
Zhao (2000) ²¹⁰	China	1152	5 – 7	Yes	Objective	≥ +2.00 D	8.5%	≥ 0.75 D	9.5%*
Murthy (2002) ²¹²	India	494 590	6 10	Yes	Objective	≥ +2.00 D	13.0% 5.3%	≥ 0.75 D	14.6%*
He (2004) ²¹³	China	295 415	6 10	Yes	Objective	≥ +2.00 D	10.7% 4.6%	≥ 0.75 D	42.8%*
Goh (2005) ²¹⁴	Malaysia	590 589	7 10	Yes	Objective	≥ +2.00 D	5.0% 1.4%	≥ 0.75 D	20.3%*
Ma (2016) ²²³	China	1230 962	6 10	Yes	Subjective	≥ +0.50 D	87.3% 30.5%	≥ 1.00 D	21.6% 24.1%
Western Countries									
O'Donoghue (2010) ²¹⁵	UK	392	6 – 7	Yes	Objective	≥ +2.00 D	26.0%	NR	24.3%
Logan (2011) ²²⁴	UK		6 – 7	Yes	Objective	≥ +2.00 D	12.3%	NR	NR
French (2012) ²²⁵	Australia	1105	6 – 7	Yes	Objective	≥ +2.00 D	12.0%	≥ 1.00 D	3.8%
Harrington (2019) ²¹⁶	Ireland	733	6 – 7	Yes	Objective	≥ +2.00 D	25.0%	≥ 1.00 D	19.2%
Central and South America									
Maul (2000) ²¹¹	Chile	1675	5 – 7	Yes	Objective	≥ +2.00 D	21.6%	≥ 0.75 D	26.7%*
Moraes Ibrahim (2013) ²¹⁸	Brazil	246	10	Yes	Subjective	≥ +2.00 D	1.63%**	≥ 1.00 D	1.45%

*Astigmatism prevalence for entire study population, not reported in age groups. **Refractive error was not assessed in children with VA ≥ 0.625 decimal. NR = not reported.

Table 3.7: Prevalence of hyperopia and astigmatism in young children (11 – 15 years old) around the world.

Author (year)	Country	Sample Size	Age	Cycloplegia	Refraction Method	Hyperopia Definition	Hyperopia Prevalence	Astigmatism Definition	Astigmatism Prevalence
Africa									
Naidoo (2003) ²¹⁷	South Africa	476 326	11 15	Yes	Objective	≥ +2.00 D	3.2% 0.7%	≥ 0.75 D	14.6%*
Ovenseri-Ogbomo (2010) ²²⁶	Ghana	253 203	11 – 13 14 – 16	Yes	Objective	≥ +2.00 D	1.6% 3.0%	≥ 0.75 D	13.0% 16.7%
Asia									
Zhao (2000) ²¹⁰	China	905	14 – 15	Yes	Objective	≥ +2.00 D	1.1%	≥ 0.75 D	9.5%*
Murthy (2002) ²¹²	India	528 381	11 15	Yes	Objective	≥ +2.00 D	5.0% 3.9%	≥ 0.75 D	14.6%*
He (2004) ²¹³	China	427 376	11 15	Yes	Objective	≥ +2.00 D	3.5% 0.5%	≥ 0.75 D	42.8%*
Goh (2005) ²¹⁴	Malaysia	701 693	11 15	Yes	Objective	≥ +2.00 D	0.9% 0.9%	≥ 0.75 D	20.3%*
Rim (2016) ¹⁵⁶	South Korea	7486 ⁺	12 – 18	No	Objective	> +0.50 D	2.6%	≥ 1.00 D	34.0%
Western Countries									
O'Donoghue (2010) ²¹⁵	UK	392	12 – 13	Yes	Objective	≥ +2.00 D	11.8%	NR	24.3%
Logan (2011) ²²⁴	UK	296	12 – 13	Yes	Objective	≥ +2.00 D	5.4%	NR	NR
French (2012) ²²⁵	Australia	1105	12 – 13	Yes	Objective	≥ +2.00 D	4.4%	≥ 1.00 D	3.8%
Harrington (2019) ²¹⁶	Ireland	733	12 – 13	Yes	Objective	≥ +2.00 D	8.9%	≥ 1.00 D	15.9%
Central and South America									
Maul (2000) ²¹¹	Chile	1675	5 – 7	Yes	Objective	≥ +2.00 D	7.5%	≥ 0.75 D	26.7%*
Moraes Ibrahim (2013) ²¹⁸	Brazil	340 175	12 15	Yes	Subjective	≥ +2.00 D	0.8%** 1.12%**	≥ 1.00 D	1.45%*

*Astigmatism prevalence for entire study population, not reported in age groups. **Refractive error was not assessed in children with VA ≥ 0.625 decimal.

⁺Sample size for ages 5 – 19. NR = not reported.

Table 3.8: Prevalence of hyperopia and astigmatism in older children (16 years old and over) around the world.

Author (year)	Country	Sample Size	Age	Cycloplegia	Refraction Method	Hyperopia Definition	Hyperopia Prevalence	Astigmatism Definition	Astigmatism Prevalence
Africa									
Semanyenzi (2015) ²²⁰	Rwanda	300	17 – 20	Yes	Objective	≥ +0.50 D	4.3%*	≥ 0.50 D	2.2%
Mehari (2013) ²²¹	Ghana	814	16 – 18	No	Subjective	≥ +2.00 D	0.3%	≥ 0.50 D	2.17%**
Asia									
Quek (2004) ²³¹	Singapore	453	15+	No	Objective	≥ +0.50 D	1.8%	≥ 0.50 D	60.3%
Hashemi (2014) ²³²	Iran	434 ⁺	18	No	Subjective	≥ +0.50 D	22.6%	> 0.50 D	27.4%
Western Countries									
Hagen (2018) ²²⁸	Norway	439	16 – 19	Yes	Objective	≥ +0.50 D	55.4%	≥ 1.00 D	8.9%
Czepita (2006) ²³⁴	Poland	187	18	Yes	Subjective	≥ +1.00 D	3.2%	NR	NR
Central and South America									
De Amorim Garcia (2005) ²³⁰	Brazil	1024	16 – 20	Yes	Subjective	≥ +0.10 D	67.8%	≥ 0.10 D	4.0%

*Hyperopia prevalence for entire study population, not reported in age groups. ** Astigmatism prevalence for entire study population, not reported in age groups ⁺Sample size for ages 14 – 18. NR = not reported.

3.5 Evidence for Increasing Myopia

The evidence above indicates the high levels of myopia present in some locations and also appears to indicate an increased prevalence of myopia in younger generations. Some studies have specifically looked at changes in myopia prevalence that have occurred over longer periods of time within certain populations.

Comparison of the results from the 1999-2004 National Health and Nutrition Examination Survey NHANES with those from 1971-1972 demonstrated a significant increase in the prevalence of myopia⁸ in participants aged 12 to 54 in the United States. Overall myopia prevalence increased from 25.0% to 41.6%. All levels of myopia increased over time with severe myopia (≤ -7.9 D SER) increasing from 0.2% to 1.6%. A similar time span was assessed in Australian Aboriginal communities.²³⁵ In 1977 161 adults aged 20 to 30 had their refractive error measured by cycloplegic subjective refraction with a mean refraction of +0.54 D SER. 128 adults of the same age range were assessed in 2000 and observed to have mean refraction of -0.55 D SER. In 2000 refractive error was assessed by non-cycloplegic auto-refractor. The authors validated the use of non-cycloplegic auto-refractor as showing excellent agreement against cycloplegic subjective refraction but this may have induced a bias for increased myopia.

Bar Dayan et al²³⁶ documented an increase of myopia (≤ -0.50 D SER) in 919,929 young adults (16 to 22) attending for military service in the Israeli army. They observed a change in myopia prevalence from 20.3% to 28.3% from 1990 to 2002. This was based on non-cycloplegic subjective refraction.

A slightly younger age group (18.46 ± 0.69 years) was assessed over a 15-year period by Chen et al in China.²³⁷ 43,858 third-year high school students were assessed with non-cycloplegic autorefraction to determine refractive error. The prevalence of myopia (≤ -0.50 D SER) was found to increase from 79.5% to 87.7% between the years 2001 and 2015. They observed significant increases in moderate myopia (38.8% to 45.7%) and high myopia (7.9% to 16.6%) levels.

Another East Asian study²³⁸ assessed the refractive error difference between parents and their children in an attempt to determine change in myopia (≤ -0.50 D SER) prevalence over time. Refractive error was determined by cycloplegic auto-refractor in children and non-cycloplegic auto-refractor or self-reporting in adults. Children at younger ages were found to be more hyperopic than their parents but by age 16 to 17.9 years 70% of children were more myopic than their parents. The overall estimation indicated the children would eventually be approximately -1.94 D SER more myopic than their parents at age 18.

In Taiwan a study examined children aged 7, 12, 15 and 16 to 18 in 8 different years between 1983 and 2016.⁹ They observed an increase in the prevalence of myopia (≤ -0.25 D SER) across all age categories over the time span with the prevalence of myopia in children aged 7 increasing from 5.8% to 25.4% and the prevalence in those aged 16 to 18 increasing from 74% to 90%. There were also significant increases in the rate of high myopia (< -6.00 D SER) with highest rates seen in those aged 16 to 18 (17% to 24%).

3.6 Future Predictions

Given the apparent increasing myopia prevalence over the last number of decades several authors have attempted to predict the future prevalence of myopia. Holden et al.³ conducted the largest such study and based their predictions on a meta-analysis of 145 epidemiological studies of refractive error. The authors predicted a global prevalence of myopia of 49.8% by 2050 with the highest prevalence in high income Asian countries at 66.4% and the lowest in East Africa at 22.7% (Figure 3.8). Of most concern the authors predict the global prevalence of high myopia will reach 9.8% by 2050. The authors noted several limitations in their predictions including the relative lack of data available in some regions. Similar projections have been made for Chinese²³⁹ and Indian²⁴⁰ children. Dong et al.²³⁹ based their predictions on 22 studies of refractive error in Chinese children

and predicted by 2050 84.3% of Chinese children aged 3 – 18 years would be myopic. This is higher than that predicted by Holden et al.³ however their results did not apply specifically to children. Priscilla and Verkicharla²⁴⁰ used a similar methodology to predict the prevalence of myopia in Indian children by 2050. They based their prediction on a meta-analysis of 8 studies of refractive error. By the 2050 the authors predict 48.2% of Indian children living in urban settings would be myopic. This is less than the 53.0% predicted by Holden et al. and Priscilla and Verkicharla²⁴⁰ suggest the true difference may be even larger as their prediction does not include adults and those living in rural settings that are less likely to be myopic. This variation may be due to the authors using a different statistical model to Holden et al.³ as the data available could not facilitate a similar analysis.

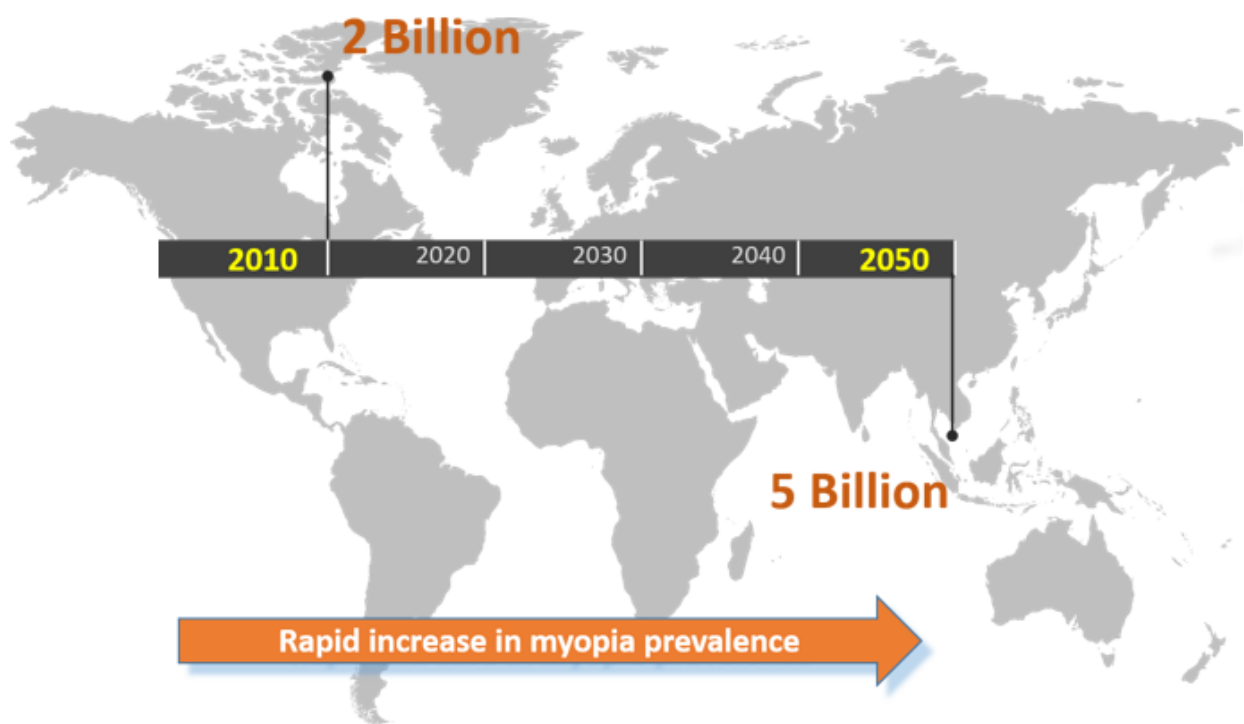


Figure 3.8: Estimated increase in myopia based on analysis by Holden et al.³

3.7 Summary

There are several challenges in establishing the current worldwide prevalence of refractive error however the evidence available indicates some patterns. Myopia is a refractive error of significant concern as the prevalence of myopia has increased significantly in recent decades and is projected to continue to increase over the coming decades if interventions do take place. This is particularly the case in some parts of Asia where myopia prevalence has reached extreme levels. As the prevalence of high myopia increases in tandem with the increases found in myopia in general, the risk of uncorrectable vision loss due to the complications of myopia (see chapter 4) may increase significantly in the coming years. Fewer epidemiological studies of hyperopia and astigmatism have taken place but current evidence indicates the prevalence of hyperopia is reducing as the prevalence of myopia is increasing while the only obvious trend in astigmatism is that the prevalence increases with increasing age. The prevalence of presbyopia is difficult to establish due to a lack of studies and an inconsistent definition for presbyopia. The primary concern with presbyopia is the level of undercorrection of presbyopia resulting in near vision impairment which has been estimated to affect in excess of 500 million people currently.

4 Vision Impairment

4.1 Introduction

The WHO defines vision impairment using categories ranging from mild vision impairment to blind.²⁴¹ This is done using the level of presenting visual acuity according to table 1.

Table 4.1: Classification of severity of vision impairment based on visual acuity in the better eye. Adapted from the World Health Report on Vision.²⁴¹

Category	Visual Acuity in the Better Eye	
	Worse than:	Equal to or better than:
Mild vision impairment	6/12 (0.5)	6/18 (0.33)
Moderate vision impairment	6/18 (0.33)	6/60 (0.1)
Severe vision impairment	6/60 (0.1)	3/60 (0.05)
Blindness	3/60 (0.05)	
Near vision impairment	N6 or M 0.8 at 40 cm	

Classically, vision impairment was not considered based on presenting visual acuity but rather based on best corrected visual acuity.²⁴¹ Both methods of defining vision impairment have advantages and disadvantages. By measuring vision impairment based on presenting visual acuity, the number of people within a population that require eye care is determined as many of these individuals can achieve normal vision with interventions such as refractive error correction or cataract surgery. This is particularly useful in countries with poor access to eyecare. Measuring vision impairment based on best corrected visual acuity more accurately reflects the number of individuals within a population that have uncorrectable vision impairment and allows better resource and support planning for those affected.

Vision impairment may also be defined according to the level visual field restriction, with a visual field less than 20 degrees in the better eye representing vision impairment and a visual field less than 10 degrees representing blindness.²⁴²

Vision impairment has a significant impact on both the individual and society. Many studies have examined the impact of vision impairment on various aspects of an affected individual's quality of life (QoL).²⁴³ A recent review article demonstrated a consistent reduction of QoL in those with vision impairment.²⁴³ It has also been found that QoL measures reduce with worse levels of vision impairment regardless of how long the vision impairment is present.²⁴⁴ It should be noted however that even mild levels of vision impairment are associated with a reduction in QoL.²⁴⁵ The most consistently reported individual impact of vision impairment is on leisure and work, social interactions, household and personal care, mobility and the emotional reaction to vision loss.^{244,246,247} There are also several reports on the potential health impacts of vision impairment. An association with an increased risk of falls and vision impairment has been found in both an Asian²⁴⁵ and a North American²⁴⁸ population. There are mixed reports on the association of vision impairment and depression symptoms. Some investigators have observed an association between symptoms of depression and vision impairment^{249,250} while others have found no association.^{251,252} Frank et al²⁴⁹ suggest that the strongest relationship is found with self-reported vision impairment as opposed to measures of VA which may explain the variation in results. A recent meta-analysis reported on the association between vision impairment and mortality finding an increased risk of mortality in those with vision impairment with the risk of mortality increasing as the level of vision impairment increased.²⁵³

Apart from the individual impact, vision impairment has significant societal impacts. There are significant economic costs associated with vision impairment and blindness with a conservative analysis estimating the global cost of loss of productivity due to undercorrected refractive error at \$121 billion in 2007.²⁵⁴ These estimates have increased in the intervening years with undercorrected myopia alone accounting for \$244 billion in lost productivity in 2015.⁴ In the Republic of Ireland, the estimated direct cost of vision impairment and blindness to the healthcare system in 2020 was €137 million.²⁵⁵ Additional direct costs in the form of lost productivity, informal care and welfare costs

amounted to €312 million giving a total cost to the economy in 2020 of €449 million.²⁵⁵ When adding the indirect cost of disability adjusted life years (DALYs), a measure combining years of life lost due to earlier death and years lost due to disability, the economic cost rises to over €2 billion.²⁵⁵

4.2 Causes of Vision Impairment

The vision loss expert group (VLEG) provides an estimation of the global burden of vision impairment and blindness (Figure 4.1).⁵ They estimated that in 2020 the leading cause of blindness globally was cataract followed by glaucoma with cataract accounting for over 50% of all cases of blindness.²⁵⁶ Cataract was the second leading cause of moderate to severe vision impairment (MSVI) after undercorrected refractive error and together they accounted for 75% of all cases of MSVI.²⁵⁶ The overall global prevalence of vision impairment has increased from 3.92% in 2010 to 4.34% in 2020 and it is predicted that by 2050 895 million people will have some level of distance vision impairment.⁵ Since 2010 there was found to be no change in the overall crude prevalence of total vision impairment in older adults however the overall crude prevalence of blindness had decreased by 14.4% while MSVI had slightly increased by 1.6%.²⁵⁶

There was some variation noted with significant differences in the causes of vision impairment and blindness in different geographic regions. Typically, in higher income regions such as Western Europe, cataract and undercorrected refractive error did not represent as many cases of blindness although they still contributed significantly as a cause of vision impairment.^{10,256} Other causes of blindness such as age related macular degeneration and glaucoma were more common in higher income regions, likely due to the older populations within these regions.^{10,256}

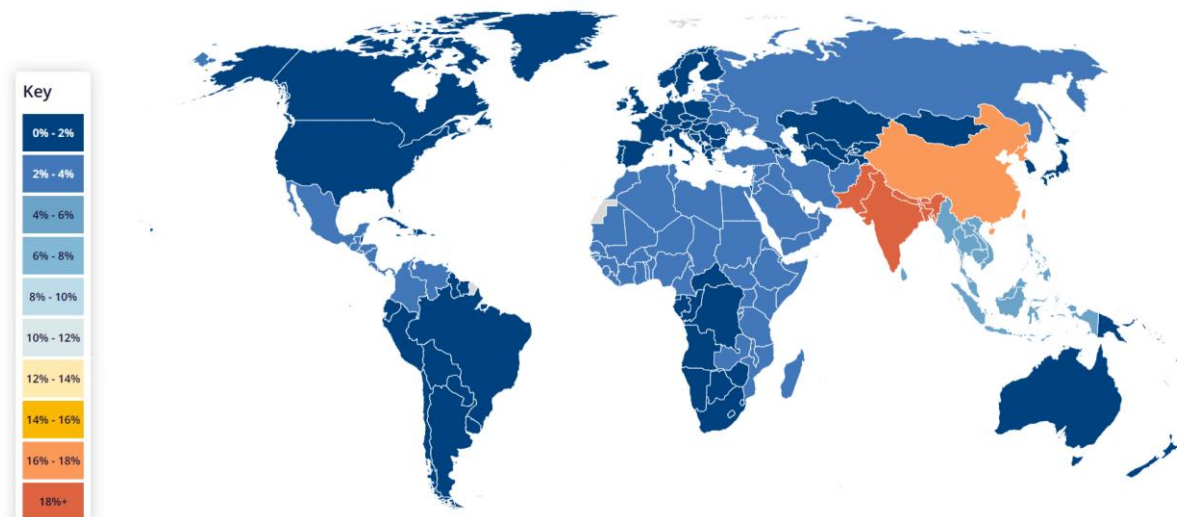


Figure 4.1: Geographic variation in vision impairment with highest number of people affected by vision loss found in East and South Asia. Reproduced from the Vision Loss Expert Group Atlas.^{5,256} Available at <https://www.iapb.org/learn/vision-atlas/>

4.3 Vision Impairment in Ireland

4.3.1 Vision Impairment in Adults

The level of vision impairment within Ireland is estimated by the VLEG to be 5.3% or approximately 270,000 people affected in 2020.^{5,256} Approximately 0.2% of the population of Ireland is estimated to be blind.^{5,256} These figures are projections based on modelling using data from other countries and the level of access to eyecare available within Ireland.^{257,258} VLEG currently have no data on vision impairment in Ireland and have identified a lack of vision impairment data in Western countries as a limitation in their projections.^{5,256}

Although the VLEG have not included any data from Ireland in their analysis, there are a small number of studies on vision impairment in Ireland. The studies that have been conducted typically describe vision impairment and blindness in either children or adults. Most of these studies do not report undercorrected refractive error as a cause of vision impairment or blindness as the most common methodology used is to perform an audit of the Irish blind register which does not allow

registration due to undercorrected refractive error. This methodology also only captures those with more severe vision impairment, typically those that are legally blind,²⁵⁹ resulting in no information on the number of individuals suffering with milder forms of vision impairment.

The most recent study of adult blindness covers the period 1996 – 2003 and estimated the number of blind adults in Ireland.²⁵⁹ This study performed an audit on the Irish blind register and observed a level of 0.23% blind adults in Ireland in 2003. This is very similar to the figure estimated by the VLEG and represented a 37% increase from 1996.^{259,260} The authors of this study noted however that their reported prevalence was likely underestimating the true level of blindness as they observed 57% of patients attending an ophthalmology outpatients clinic that met the criteria for blind registration were not registered. Significantly, 21% of patients attending the clinic had no appropriate reason for not being registered. These results are in line with those found in the UK where over 50% of patients eligible to be registered as blind were not registered.²⁶¹

Among the adult population in Ireland, the most common reason for blind registration in 2003 was age related macular degeneration (AMD) with 25% of those registered blind being due to AMD.²⁵⁹ This was followed by glaucoma (12%), retinitis pigmentosa (7%), myopia (5%) and diabetic retinopathy (5%).²⁵⁹ AMD and diabetic retinopathy (DR) as a cause of blindness had more than doubled since 1996.²⁶⁰ All other causes were relatively stable apart from cataract which had more than halved from 11% to less than 4%.^{259,260} The reduction in blindness due to cataract is almost certainly due to improved access to cataract surgery. The number of people registered as blind due to DR was found to have reduced over the following 10 years however the number of people with vision impairment due to DR had increased over the same time period.²⁶² Given the most recent audit of the blind register was almost 20 years ago, predating the widespread use of effective treatments for neovascular AMD such as anti-vascular endothelial growth factor (anti VEGF) drugs²⁶³ and the existence of the Irish National Diabetic RetinaScreen Programme,²⁶⁴ it would be interesting to determine if these trends had been reversed.

4.3.2 Vision Impairment in Children

There have been 3 studies reporting on vision impairment and blindness in children in Ireland. A 1991 report determined the causes and prevalence of blindness in those aged under 16 by seeking eligible patients for examination from ophthalmologists and social and educational facilities involved in the care of blind children.²⁶⁵ The rate of blindness in children found was 0.02% with most cases of blindness occurring in the prenatal stage with optic nerve hypoplasia (Figure 4.2) the most commonly diagnosed cause of blindness.²⁶⁵ A similar study was performed in 2004 and found a rate of blindness in children of 0.05%.²⁶⁶ The authors suggested the increased rate of blindness was artificial and actually due to better registration of and follow up of blind children enabling the authors to more easily identify those children affected. Most significantly the study showed a changing pattern of blindness in children in Ireland with much lower rates of acquired blindness due to conditions such as retinopathy of prematurity and higher rates of blindness due to cerebrovascular impairment likely due to increased survival rates in preterm infants.²⁶⁶



Figure 4.2: An example of optic nerve hypoplasia, one of the most common causes of blindness in children in Ireland.^{265,266} Reproduced from <https://webeye.ophth.uiowa.edu/eyeforum/cases/case10.htm>

To date only one study has reported on rates of vision impairment including undercorrected refractive error as a potential cause. The IES assessed 1,626 children in 2 age cohorts to determine the prevalence of refractive error and vision impairment.²¹⁶ Unlike other studies of vision impairment or blindness in children in Ireland, the IES was a representative cross sectional study that used random cluster sampling to select schools for participation. Presenting vision impairment was defined as ≥ 0.3 logMAR with spectacles if worn. The prevalence of “better eye” presenting vision impairment was 3.7% in the younger cohort and 3.4% in the older cohort. Higher levels of presenting vision impairment were observed in minority groups and the overall level of presenting vision impairment was significantly higher than that found in similar populations.²¹⁵

4.4 Vision Impairment Due to Refractive Error

It is clear that undercorrected refractive error is a significant cause of vision impairment²⁵⁶ however refractive error is itself a risk factor for uncorrectable vision impairment,²⁶⁷ something for which the general public does not seem to have an awareness.²⁶⁸ It has been demonstrated that increasing refractive error, both myopic and hyperopic are associated with an increased risk of vision impairment however the causes of vision impairment are usually different.²⁶⁷

4.4.1 Causes of Vision Impairment in Myopia

The increasing prevalence of myopia discussed in chapter 3 makes the potential for associated vision impairment very concerning. Myopia can cause a number of complications with the retina frequently involved. These complications are thought to occur in response to the changes in shape of the ocular globe that occurs with increasing axial length.²⁶⁹ A structural change that can occur in those with high myopia is the development of a posterior staphyloma. This is a posterior outpouching of the fundus which has a radius of curvature which is less than the globe²⁸ (Figure 4.3). In eyes with high myopia, those with the posterior staphyloma have been found to be at higher risk of reduced visual acuity and macular complications.²⁸ Macular complications in myopia are usually referred to as myopic macular degeneration (MMD) or myopic maculopathy and represent one of the most common causes of vision impairment in myopia.²⁶⁷ The first description of MMD was given by Curtin and Karlin²⁷⁰ with the authors describing several retinal lesions and their association with axial length. Since then several attempts have been made to create a unified classification system for MMD.^{269,271} Ohno-Matsui et al describe MMD in four stages going from the presence of a tessellated fundus with minimal effect on visual acuity to macular atrophy which can cause severe vision impairment.²⁷¹ The authors also described plus features including Lacquer cracks, Fuch's spot and choroidal neovascularisation all of which confer an increased risk of vision impairment.²⁷¹ Progression through the stages of MMD (Figure 4.4) and the resultant loss of visual acuity appears to

be a function of the level of myopia and axial length combined with the age of the patient.²⁷²

Hayashi et al followed a series of patients having bilateral high myopia and high axial length measurements over a mean follow-up period of 12.7 years to assess the progression of MMD in high myopia over the life course.²⁷² The authors observed progression of MMD in 40.6% of eyes with the development of myopic choroidal neovascularisation having the most significant effect on visual acuity. This level of MMD progression was not observed in another group of highly myopic eyes in Australia, however this may be explained by the much shorter follow-up period of 5 years for all participants and also the sample of eyes with MMD was far less.²⁷³

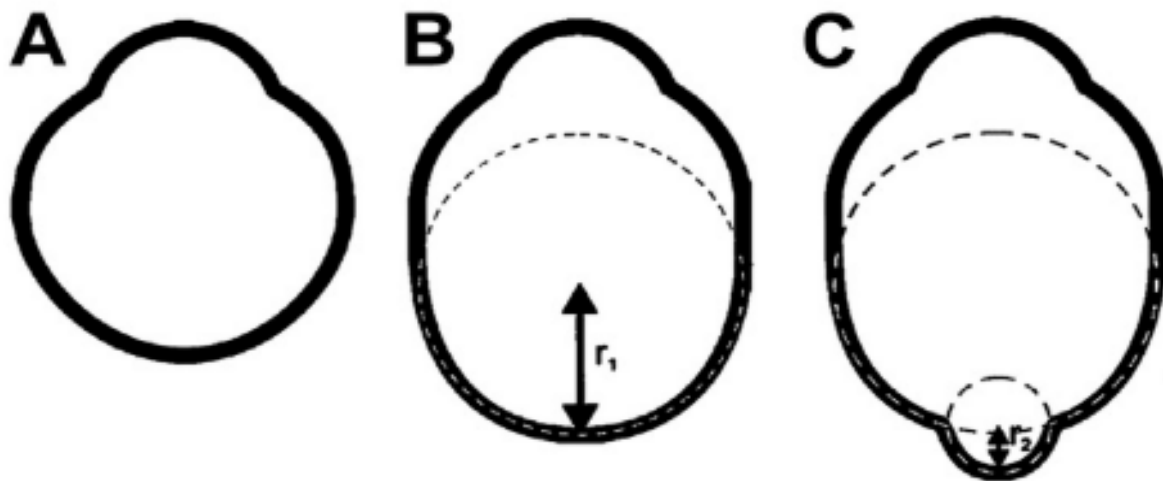


Figure 4.3: Normal ocular shape (A), axial elongation in myopia (B) and axial elongation with posterior staphyloma (C). Adapted from Ohno-Matsui.²⁷⁴

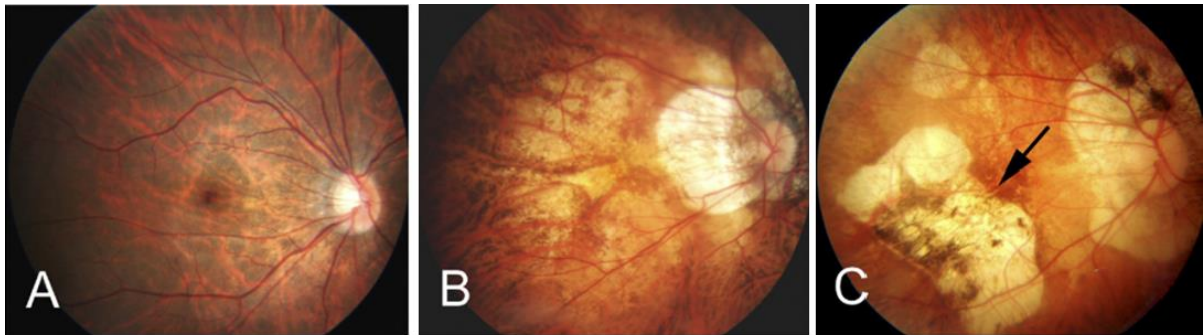


Figure 4.4: Progression of MMD from a tessellated fundus (image A) to diffuse chorioretinal atrophy (image B) to patchy chorioretinal atrophy (image C). Adapted from Hayashi et al.²⁷²

The peripheral retina is not spared in myopia with a higher risk of retinal detachment (RD) with increasing levels of myopia. There is an increased prevalence of peripheral retinal degenerations such as lattice degeneration (Figure 4.5) in myopia which, when combined with the occurrence of posterior vitreous detachment at a younger age in myopia, results in higher rates of RD.²⁷⁵ There is also an increased risk of RD following cataract surgery in myopia when compared to non-myopes.²⁷⁵ There have been several reports describing an increase in RD prevalence over time.^{276,277} It is difficult to establish the exact cause for this population level increase in RD prevalence but some authors point to increasing myopia prevalence as the most likely culprit.^{276,277} The association of RD with cataract surgery makes this conclusion difficult to confirm due to the increasing number of cataract surgeries performed every year however there are also increases in RD prevalence in phakic eyes which likely is associated with myopia prevalence.²⁷⁷ Some authors have also noted an increasing prevalence of RD at younger ages which may be as a result of a generational shift in myopia prevalence given RD prevalence usually increases with age to a maximum prevalence at age 70.²⁷⁸

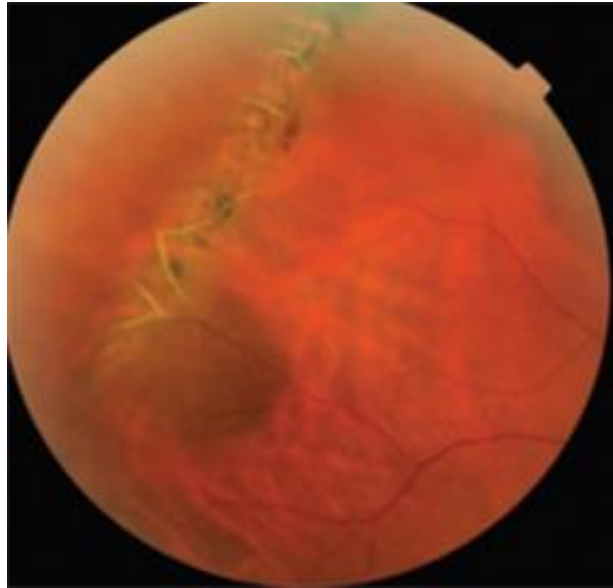


Figure 4.5: Lattice degeneration confers an increased risk of retinal tears and occurs with greater frequency in myopia. Adapted from <https://www.asrs.org/patients/retinal-diseases/36/lattice-degeneration>

The retina is not the only structure affected by myopia with significant alteration of the optic nerve head (ONH) and associated structures occurring in myopia.²⁷⁹ Myopia is considered a risk factor for the development of open angle glaucoma (OAG) with a meta-analysis of 48,161 individuals showing an OR of developing glaucoma of 1.92 for any level of myopia and 2.46 for high myopia (≤ -3.00 D SER).²⁸⁰ There are very few population based longitudinal studies of OAG development in myopia. An Italian study conducted comprehensive exams on 411 participants 12 years apart and found high myopia (< -6.00 D SER) was the highest risk factor for developing OAG.²⁸¹ The exact mechanism by which myopia confers an increased risk of OAG is poorly understood but is thought to involve the stretching of the lamina cribrosa as a result of the axial elongation that takes place in myopia.²⁷⁹ This results in increased strain on retinal ganglion cells making them more susceptible to damage due to higher intra-ocular pressure (IOP).²⁸² One of the difficulties in establishing the link between myopia and OAG, is the difficulty in diagnosing OAG in myopia. Many of the structural changes that take place at the ONH in myopia can simulate glaucomatous optic neuropathy making diagnosis of OAG

challenging (Figure 4.6) which has resulted in the suggestion that the relationship between OAG and myopia may be overstated and may in fact be due to an over-diagnosis of OAG in high myopia.²⁷⁹



Figure 4.6: Two optic nerves in highly myopic eyes. Image 1 has been diagnosed with glaucoma while image 2 has no glaucoma. The similarity in appearance of the two optic nerves demonstrates the difficulty in making this diagnosis. Adapted from <https://www.aaopt.org/eyenet/article/myopia-glaucoma-sorting-out-diagnosis>

Age related cataract has also been associated with myopia however the development of index myopia with nuclear sclerotic cataracts confounds the exact relationship. A meta-analysis found myopia was associated with prevalent nuclear and posterior subcapsular cataract however no longitudinal relationship was found between myopia and any form of cataract.²⁸³ The authors suggested the association with prevalent cataract was likely due to the confounding of index myopia. A borderline significant relationship was observed between incident posterior subcapsular cataract and myopia with the authors suggesting a more significant relationship may be observed with a larger sample size and longer follow-up. To overcome the issue of index myopia some investigators have used the need for distance glasses at a young age as a surrogate for myopia. Using this strategy, myopia was found to be an independent risk factor for posterior subcapsular cataract.²⁸⁴

4.4.2 Causes of Vision Impairment in Hyperopia

The association between vision impairment and hyperopia is less well studied than myopia. The most significant ocular disease associations for hyperopia have been found with AMD and angle closure glaucoma (ACG). A meta-analysis investigated the relationship between hyperopia and AMD increased odds of both incident and prevalent AMD in hyperopes.²⁸⁵ The authors found a 6 – 9% increase in risk of AMD each dioptre increase in hyperopia. They also found that myopia was protective against AMD. The mechanism by which hyperopia increases the risk of AMD has not been established. It has been suggested the increased scleral rigidity in hyperopic eyes when compared to myopic eyes may contribute to the risk of AMD.²⁸⁶ The higher rate of posterior vitreous detachment in myopic eyes has also been suggested as being protective against the development of AMD possibly explaining the comparatively higher rate of AMD in hyperopia.²⁸⁵

Hyperopia is also considered a risk factor for ACG. The first association of hyperopia as a risk factor for ACG was made in 1970.²⁸⁷ Since then, several studies have examined this in differing populations with conflicting results. The Beijing Eye Study found hyperopia was associated with having a shallow anterior chamber which was in turn associated with ACG.²⁸⁸ A study in India also found a relationship between hyperopia and ACG but only in participants living in an urban environment.²⁸⁹ The authors suggested that index myopia due to cataract may have masked underlying hyperopia in the rural participants. Conversely, a Dutch study did not observe the association between hyperopia and ACG.²⁹⁰ All of the above studies did observe having a shorter axial length as a significant risk factor for ACG.²⁸⁸⁻²⁹⁰ These conflicting results may stem from two sources. The true risk factor for ACG is likely having a shorter axial length, for which hyperopia is a surrogate measure however as hyperopia is a balance of the axial length and refracting surface of the eyes, not all eyes that are hyperopic have a shorter axial length. Additionally, hyperopia is treated as a categorical rather than continuous variable in these studies. As an eye with a high level of hyperopia is far more likely to

have a short axial length when compared to an eye with a low level of hyperopia, it is not necessarily correct to consider both eyes the same when analysing the risk of ACG.

4.4.3 Impact of Myopic Complications

In recent times several studies have been carried out to determine the prevalence of complications due to myopia and also the impact these complications have by causing vision impairment. Similar work has not been carried out for hyperopia most likely as the changes in myopia prevalence as described in chapter 3 necessitate more urgent action. The overall risk associated with hyperopia to ocular health is also not as significant as that found for myopia.²⁹

The prevalence of MMD in highly myopic eyes has been studied in both European²⁹¹ and Asian^{292,293} populations. A high prevalence was observed in Asian eyes in one study²⁹² with 22.9% of eyes demonstrating clinically significant MMD. Lower prevalence of MMD of approximately 8 – 9% was observed in both Asian and European populations.^{291,293} The exact distribution of myopia was not fully described in any study making direct comparison difficult but a variation in this distribution may explain the difference in MMD prevalence. All studies observed MMD prevalence increased both with increasing level of myopia and increasing age. Significantly, the increase in MMD prevalence was not linear but increased exponentially with increased level of myopia and age. This highlights a significant limitation of many epidemiological studies of refractive error which often do not report the prevalence of myopia or hyperopia as a distribution. In many cases just the total prevalence is reported which makes accurately estimating the risk of vision impairment due to refractive error impossible as the risk varies as refractive error increases and importantly, the risk does not vary in a linear manner.

Several studies have assessed the risk of vision impairment due to myopia and have also found the risk increases non-linearly with increasing age and level of myopia.^{294,295} Tideman et al²⁹⁴ estimated a

cumulative risk of vision impairment by age 75 or older of over 90% for eyes having an axial length of 30mm or greater. This is supported by a recent French study which observed a rate of vision impairment in 60 years olds having very high myopia (< -10 D SER) of 25.71%. Using these results a recent study²⁹⁶ developed a model to predict the age-related cumulative risk of vision impairment which the authors used to predict lifetime years of vision impairment at various thresholds of myopia. The highest number of estimated years of vision impairment was observed at higher levels of myopia however even lower levels of myopia such as -3 D SER resulted in an estimated 4.4 years of vision impairment.

These estimates are concerning due to the apparent generational shift in myopia prevalence rates described in chapter 3. As these younger myopes age there is likely to be a significant increase in the number of individuals affected by vision impairment due to complications related to myopia. Fricke et al²⁹⁷ estimated that by 2050 over 55 million people worldwide would have some form of vision impairment due to MMD alone, exceeding the current number of people over age 50 estimated to have moderate to severe vision impairment due to AMD, glaucoma and DR combined.²⁵⁶ Fricke et al did not include the fact that low and moderate myopes can also develop MMD in their estimates which may mean these figures are an underestimation however the authors state the likely increase in the use of myopia control and the development of better treatments may offset this underestimation.²⁹⁷ There is relatively little global prevalence data on MMD however the VLEG recently estimated that blindness and MSVI due to MMD had increased in China by 200% and 340% respectively²⁵⁶ which although only representing one county, may support the projections by Fricke et al.²⁹⁷

4.4.4 Near Vision Impairment

Near vision impairment (NVI) is estimated to affect over 500 million people globally and is the most common type of vision impairment.^{5,207} NVI is primarily associated with uncorrected and undercorrected presbyopia and as such primarily affects older individuals however hyperopia can also cause NVI and can be present in both young and old. Establishing trends in NVI is difficult due to a relative lack of epidemiological data for both presbyopia and hyperopia (chapter 3) however changes in the published prevalence over the last decade indicate NVI is increasing as a result of an aging population.^{163,207} The prevalence of NVI due to uncorrected and undercorrected presbyopia is estimated to have increased from 517 million in 2005 to 826 million in 2015,^{163,207} a substantial increase in just 10 years. This increase is not expected to continue due to the increasing prevalence of myopia and the compensatory effect myopia has on NVI due to presbyopia. It is predicted that by 2050 presbyopia prevalence may decrease by as much as 20% due to the predicted increase in myopia prevalence.²⁰⁷ It should be noted however that NVI primarily occurs in low and middle income countries due to a lack of access to refractive error correction^{207,256} so even if NVI reduces due to increasing myopia many of these individuals will have a distance vision impairment due to uncorrected myopia unless refractive error correction becomes more available in these countries.

Apart from the impact on the individual, this level of uncorrected and undercorrected presbyopia has been estimated to have a significant economic impact with an estimated global productivity loss of \$25 billion or 0.037% of global gross domestic product (GDP).²⁹⁸ Some work has been done estimating the effect of the provision of near refractive error correction. Chan et al summarised the published results of near vision correction provision finding several observational studies and one RCT study which demonstrated the improvement in QoL for the individual and improved work life and productivity.²⁹⁹ Significant increases in productivity were seen among 268 textile workers in South Africa that were provided with a near refractive error correction having previously had correctable near vision of 6/9 Snellen or worse.³⁰⁰ Strong evidence of this improvement of

productivity with near vision correction is provided by the only RCT study in this field.³⁰¹ The authors divided Indian tea pickers into intervention and control groups and provided near refractive error correction to the intervention group and the same to the control group 11 weeks later, after the study period had elapsed. They found an increase in productivity of 20% in the intervention group with over 98% of participants finding the glasses useful or very useful 95% saying they would pay to replace them if they were broken.

The provision of near refractive error correction is a simple and inexpensive method to significantly improve QoL and productivity among low- and middle-income country inhabitants. This simple intervention was at least as good and, in many cases, better when compared to other interventions to improve productivity in this type of population.³⁰¹ This intervention also extends to other aspects of life such as the increasing use of smartphones playing an important part of daily communications for people from all over the world, the ability to see well at near distances is likely to become even more important.²⁹⁹

4.5 Summary

Vision impairment has significant individual and societal costs. The rate of blindness has reduced internationally however the rate of vision impairment has increased. There is relatively little data on vision impairment in the Republic of Ireland with the most recent estimation predating significant changes in eyecare such as the widespread use of anti-VEGF treatments that will likely have altered the main cause of vision impairment. Refractive error remains a significant contributor to vision impairment, primarily due to undercorrection. This is particularly an issue with regards to uncorrected presbyopia and NVI as NVI represents the most common reason for vision impairment globally and is likely to increase due to aging populations. The increasing prevalence of myopia is likely to be a significant challenge when addressing global vision impairment, not only due to the

need provide correction for myopia, but also due to substantial increase in risk of uncorrectable vision loss associated with higher levels of myopia.

5 Big Data and Artificial Intelligence in Eyecare

5.1 Title Page:

Title: Big Data and Artificial Intelligence in Eyecare

Authors:

Corresponding Author: Michael Moore¹ (email: michael.moore@tudublin.ie, ORCID ID: 0000-0003-3919-444X)

Daniel I. Flitcroft^{1,2} (ORCID ID: 0000-0002-7004-6026)

James Loughman¹ (ORCID ID: 0000-0003-3130-8991)

Affiliations:

¹Centre for Eye Research Ireland, School of Physics and Clinical and Optometric Sciences, Technological University Dublin, Dublin, Ireland

²Children's University Hospital, Dublin, Ireland

5.2 Abstract:

Big Data and artificial intelligence are technologies that are poised to significantly alter the provision of healthcare in the near future. As a field that generates large volumes of digital clinical data in the form of both electronic medical records and imaging, eyecare is at the forefront of these changes. To date eyecare has already benefited from the use of Big Data and artificial intelligence in the areas of disease epidemiology, disease screening and surveillance and treatment outcomes. In this review, we introduce the concept of Big Data and artificial intelligence and explore their relationship. We also describe the types of Big Data that can be utilised in eyecare, provide examples of the application of Big Data and artificial intelligence in eyecare and describe how to interpret research in this area.

5.3 Introduction

By the end of 2020 it was estimated that the volume of digital information in existence will exceed 44 trillion gigabytes or over 40 times as many bytes as the estimated number of stars in the observable universe.⁶ The pace of data generation is also accelerating rapidly with the amount of data generated daily expected to reach almost 500 billion gigabytes by 2025.⁶ This massive proliferation of data has led to use of the term “Big Data” (BD) in an effort to describe this ever expanding amount of heterogenous data. Harnessing the value within BD may facilitate new knowledge discovery with data being referred to in recent times as a more valuable resource than oil.³⁰²

Healthcare being a field that generates large volumes of data is one which has been shown to benefit from the use of Big Data analytics (BDA).⁷ Subspecialities within healthcare that make increased use of imaging technology may particularly benefit from BDA due to the large data storage requirements needed. The use of imaging is commonplace in the field of eyecare which has resulted in this being the area with the most BDA research taking place in all of healthcare.³⁰³ As a new and rapidly expanding field, BDA in eyecare may be unfamiliar to many practitioners. This review therefore seeks to describe BDA, how it might be applied in eyecare and the tools it may provide practitioners in the future.

5.3.1 How Big is Big Data?

The exact definition of BD is somewhat vague and would appear to vary with domain.³⁰⁴ In the realm of healthcare, the characteristics of BD are usually described using 5 V's; volume, variety, velocity, veracity and value.³⁰⁵ The “Big” in Big Data derives from the volume of data usually associated with this type of analysis. How large the volume of data must be to be considered BD is somewhat disputed. Baro et al suggest the logarithm of the number of individuals multiplied by the number of

variables i.e. $\log(n \cdot p)$ should equal 7 or more to be considered BD, however many published works using the term BD do not meet this criteria.³⁰⁴ The size of the data is not the only characteristic common to BD. Diversity in the type of data collected is another feature with much of the data used in this field collected for other purposes such as insurance billing.³⁰⁶ The increasing use of wearable health sensors allows data to be gathered and analysed in real time³⁰⁷ with this type of BD generation referred to as velocity. BD is often generated in real world settings as opposed to data generated through typical research which is highly controlled. This can lead to concerns over the veracity of the data with appropriate steps necessary to ensure the data is accurate. Lastly, BD needs to have value, simply having a larger sample size does not add value unless this can provide new insights or improve clinical care giving better outcomes for both patients and clinicians.

5.3.2 Big Data and Artificial Intelligence

A number of terms in this field of research are used to describe different methodologies with significant overlap between these methodologies which may lead to confusion for a clinician that is new to this area. Artificial intelligence (AI) is a technique in computer science that allows software to mimic human intelligence. AI is an umbrella term that includes machine learning (ML) and deep learning (DL). Machine learning is a form of AI that is not pre-programmed but instead learns from a training set of data. An example of a training set may be both normal and abnormal retinal images. Based on the training set of retinal images the software will create an algorithm to detect abnormal images. A test set of images will then be assessed using the algorithm which will allow the calculation of the accuracy, sensitivity and specificity of the algorithm. This would be considered an example of supervised ML. Supervised ML is a similar technique however the training set of images will be labelled as normal or abnormal otherwise known as the “ground truth” which can improve the ML algorithm. Deep learning, also known as convolutional neural networks, is a form of ML that utilises multiple layers of algorithms to generate results.

The association between BD and AI techniques is shown in Figure 5.1. Although BDA and AI can be used independently of each other, there is significant overlap. Many ML and DL techniques require huge datasets to appropriately train the underlying algorithm and hence make use of BD. Equally some insights on BD can only be observed using ML or DL.

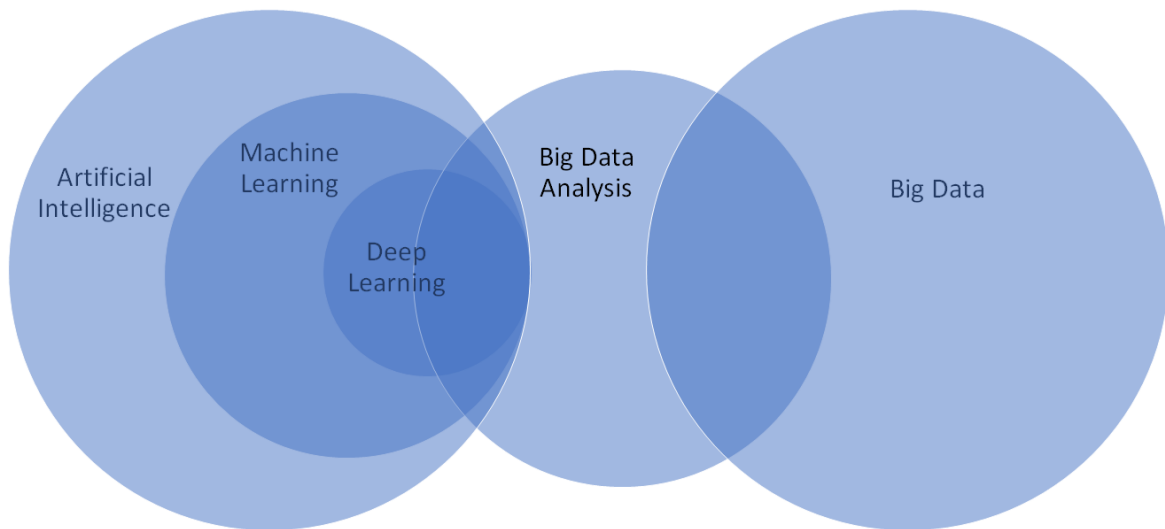


Figure 5.1: Association between Big Data (BD) and Artificial Intelligence (AI)

5.4 Big Data in Eyecare

In the field of eyecare, BD is derived from multiple sources which vary from EMRs and national insurance records containing observations on thousands to millions of individuals to genomic testing which can generate millions of variables for each individual assessed. Each of the various sources of BD present their own opportunities and challenges and often need varying approaches to analysis.

5.4.1 Electronic Medical Records

In most fields of medical care, EMRs have replaced traditional paper based records with up to 95% of primary care physicians reporting they used EMRs in 2012,³⁰⁸ a figure which has likely only increased in the intervening years. EMRs represent a potentially enormous wealth of untapped patient data to be exploited. In recent years, several authors have used EMR data to answer research questions relating to epidemiology of ocular disease,^{295,309–312} treatment efficacy,^{313–315} disease progression prediction^{316–318} and to develop novel screening and disease monitoring systems.^{318,319} Recognising the potential of EMRs, the American Academy of Ophthalmology created the Intelligent Research In Sight (IRIS) registry which allows their members to upload deidentified EMR data which can be made available for research purposes.³²⁰ At the time of writing approximately 350 million visits of 60 million patients have been collated with insights published on glaucoma³²¹ and cataract surgery,³²² amblyopia,³²³ complications of myopia³¹⁰ and treatment outcomes for diabetic macular oedema³²⁴ to name a few.

A challenge present in EMR data is the data format. The data available is often both structured and unstructured in nature. For example, refractive error data will likely be recorded in an easy to analyse numeric format while ocular health information may be recorded using free text. The possible impact of this variation was illustrated nicely by Stein et al³²⁵ who used a combination of International Statistical Classification of Diseases and Related Health Problems (ICD) codes and natural language processing (NLP) of free text notes to determine the prevalence of exfoliation syndrome in a large EMR dataset. The prevalence of exfoliation syndrome found when using ICD codes alone was only 40% of that found when NLP was used indicating the variability of the completeness of the records. Researchers using EMR data need to be cognisant of this when conducting their analysis and ensure the analysis is correctly tailored to the type of data available.

5.4.2 Insurance Records

Some of the earliest forms of BD research in eyecare used insurance claims records as the primary data source.³²⁶ These records represent a readily available source of data on ocular disease and treatment and typically contain information on huge numbers of the population. Insurance claims records are usually more limited in scope than EMRs as they usually contain demographic information and disease and treatment coding for each patient but often do not contain more nuanced information.³²⁷ For example, a patient may be coded as having glaucoma but the record might not provide more accurate coding which indicates if it is closed angle or open angle glaucoma. Even if more accurate coding is present, it is usually not possible to determine the severity of the condition or the effect on the patient.³²⁸ There is also the potential for referral bias as those with mild forms of the disease under consideration may not present for treatment. The most significant limitation with this type of data is the ability to draw population level conclusions. In most cases the relevant insurance may only be accessed by a particular cohort of a population such as those able to afford the insurance or a particular segment of society to whom national insurance schemes may be targeted e.g., the elderly.^{306,329} Conversely, some jurisdictions with universal health insurance coverage can provide findings which are generalisable to the entire population.^{330,331}

5.4.3 Image Databases and Biobanks

One of the most common applications of BD in eyecare is as a data source for AI models. In recent years there has been significant interest in developing AI models to detect ocular disease using images generated by ocular imaging techniques such as fundus photography and optical coherence tomography (OCT) scans.^{332–334} Developing such an AI model requires train, test and validation image datasets. Publicly available image sets have been available for a number of years, many of which have been reviewed by domain experts and have been appropriately labelled to serve as a ground truth for AI models.^{335–338} Most of these datasets consist of images numbering in the hundreds, it is

only in recent times that substantially larger image datasets have become available. Kaggle is a data science education platform and hosts thousands of public datasets including several large retinal image datasets with some numbering close to 100,000 OCT scans.^{339,340}

The UK Biobank is step further than an image dataset and is a prospective large scale population study designed to determine environmental and genetic effects on health outcomes.³⁴¹ A group of 500,000 participants aged 40-69 were assessed between 2006 and 2010 and continue to be followed through repeat assessments and through linkages with other national datasets.³⁴¹ Included within the data collected for each participant are datasets containing refractive error, intraocular pressure, visual acuity and OCT images.³⁴¹ Combining this with each participants health, environment and genetic data has already resulted in many interesting findings that may influence not only disease treatment³⁴² and monitoring^{343,344} in individual patients but also public health decisions.³⁴⁵⁻³⁴⁷

5.4.4 Smart Health Devices

The internet of things (IoT) enables physical devices to collect and report data in real time. The introduction of IoT health devices may allow for near constant monitoring of areas of concern by clinicians, patients and health-conscious members of the public. This constant monitoring generates huge volumes of data which will only increase as the use of these devices becomes more widespread. There are several devices in development and in active use in eyecare that aim to provide ongoing patient monitoring. The Clouclip is a wearable device that was developed for use in children at risk of progressive myopia. The device detects the light intensity of the environment and the distance at which near work³⁴⁸ is being undertaken both of which have been found to increase the risk of progressive myopia.^{41,50} Typically, studies assessing the effect of near work and time spent outdoors on the development or progression of myopia rely on self-reporting by the study participants or their parents^{41,50} which carries a risk of misreporting.³⁴⁹ More objective monitoring of these risk factors using a device such as the Clouclip may help researchers to more fully understand

the relationship between myopia development and these risk factors. This device has also been used to modify behaviour in children and was successful at reducing behaviours that increase the risk of myopia development.³⁵⁰ Intra-ocular pressure measurement is another area that would benefit from constant monitoring. The SENSIMED Triggerfish (Sensimed AG, Lausanne, Switzerland) is a contact lens that infers the diurnal variation in IOP by detecting small changes in ocular circumference when it is worn.³⁵¹ Although this device is only used for a single 24-hour period, it is not difficult to imagine a future device being used by glaucoma patients to self-monitor their IOP in much the same way diabetic patients monitor their blood glucose levels. Devices such as the Clouclip or Triggerfish may potentially provide clinicians with a large volume of real-time health data for their patients which could allow for more individualised health planning and interventions.

5.4.5 Multi-omics

The term “omics” refers to characterization and quantification of biological molecules that are grouped according to their structure and function.³⁵² Just some of the areas of study encapsulated within “omics” include genomics, epigenomics and proteomics with genomics being the first and most widely studied field of “omics”.³⁵² Over the last decade the number of GWAS has increased dramatically since the first GWAS was performed to determine any genetic risk factors for the development of AMD.³⁵³ GWAS are usually designed as observational studies using a case control design with cases recruited for individuals with the disease of interest and controls recruited from individuals without the disease. Each individual is genotyped for approximately one million single nucleotide polymorphisms (SNPs) with odds ratios for the relevant disease calculated for each SNP.³⁵⁴ This results in a huge volume of data for each study participant and requires significant computational resources.

Numerous GWAS have been performed in the field of eyecare since the first study identifying risk factors for AMD.³⁵³ To date GWAS have been carried out which have identified genetic risk factors

for ocular diseases such as glaucoma,^{355,356} DR^{357,358} and AMD^{353,359–362} along with GWAS that have established genetic links to ocular parameters such as refractive error,^{105,363,364} corneal curvature,³⁶⁵ axial length^{365,366} and IOP.^{367,368} As many ocular conditions have a complex aetiology with no single causative agent, the interaction between the genetic risk of a disease and the environment is of particular interest. GWAS can facilitate a better understanding of this interaction such as the significantly increased risk of myopia when both high levels of education and higher genetic risk are present compared to when only one is present.¹⁰⁷

5.5 Interpreting Results

It is important to recognise that although BD can provide answers to questions that were previously impossible to answer, merely having a larger dataset does not negate the potential limitations that are present in all study designs. For example, a GWAS is an observational study and despite the huge volume of data and genetic associations that would previously have been unknown, as an observational study a GWAS can only establish correlation but not causation.³⁶⁹ Care also needs to be taken when reporting statistical significance. Due to the very high number of SNPs (≈ 1 million) for each participant and their relatively small effect size, there is a risk of a type 2 error in a GWAS.^{354,370} To avoid this possibility, the best GWAS have large sample sizes numbering thousands of cases and controls.^{354,370} The very large number of SNPs in each GWAS implies traditional statistical significance values of $p < 0.05$ are far more likely to occur by chance and hence much smaller significance values of the order of $p < 5 \times 10^{-8}$ are to be expected.³⁵⁴ Any BD study of sufficient size will suffer from similar problems and hence the clinical significance of a finding should be considered of greater importance than if an arbitrary statistical significance value of $p < 0.05$ has been reached.

Typically, a well-designed and comprehensively reported study using AI will describe using both a training and testing data set. A BD dataset such as those found in EMRs or from imaging tools is split

in two with approximately 70-80% of the data assigned to the training dataset and 20-30% assigned to the testing dataset. Ideally data for the same patient is not found in both datasets. Studies with the best design will make use of a completely separate dataset for testing which has come from a different population.

Many AI studies quote figures for sensitivity and specificity when describing their results. Most healthcare practitioners will be familiar with these concepts as they apply to the accuracy of different testing techniques with tests with high sensitivity able to correctly identify a patient with a disease and tests with high specificity able to correctly identify patients without a disease.³⁷¹ In the field of AI, these terms are often used to describe the performance of a disease prediction model although the terms recall and precision are sometimes used as alternatives to sensitivity and specificity respectively.³⁷¹ The ideal medical test or disease prediction model will give 100% sensitivity and 100% specificity meaning all diseased patients are detected as having the disease and no healthy patients are detected as having the disease. In reality, this is impossible to achieve but some diagnostic tests can approach these values. This limitation gives rise to designing medical tests to be biased towards greater sensitivity or specificity as both cannot typically be achieved. In AI models the concept of thresholding achieves the same outcome with thresholds selected that will give higher sensitivity or specificity. Disease screening AI models usually have thresholds selected that will give outcomes with higher sensitivity to ensure as few patients with the disease are missed as is possible even if this means some normal patients are incorrectly found to have the disease. As these models are used for screening purposes, any normal patient detected as diseased should be correctly classified at a later stage when reviewed by a domain expert.

The accuracy of any AI model used in eyecare can be described by its ability to correctly classify individuals into subgroups e.g., a disease is present or is not present. The most common method of reporting accuracy is using the receiver operating characteristic (ROC) curve. The unusual name derives from its initial use by operators of radar receivers during World War II.³⁷² The ROC curve

shows sensitivity of the test on the y axis and 1 - specificity of the test on the x axis. This allows the trade-off between sensitivity and specificity to be visualised. Examples of various ROC curves are given in Figure 5.2.

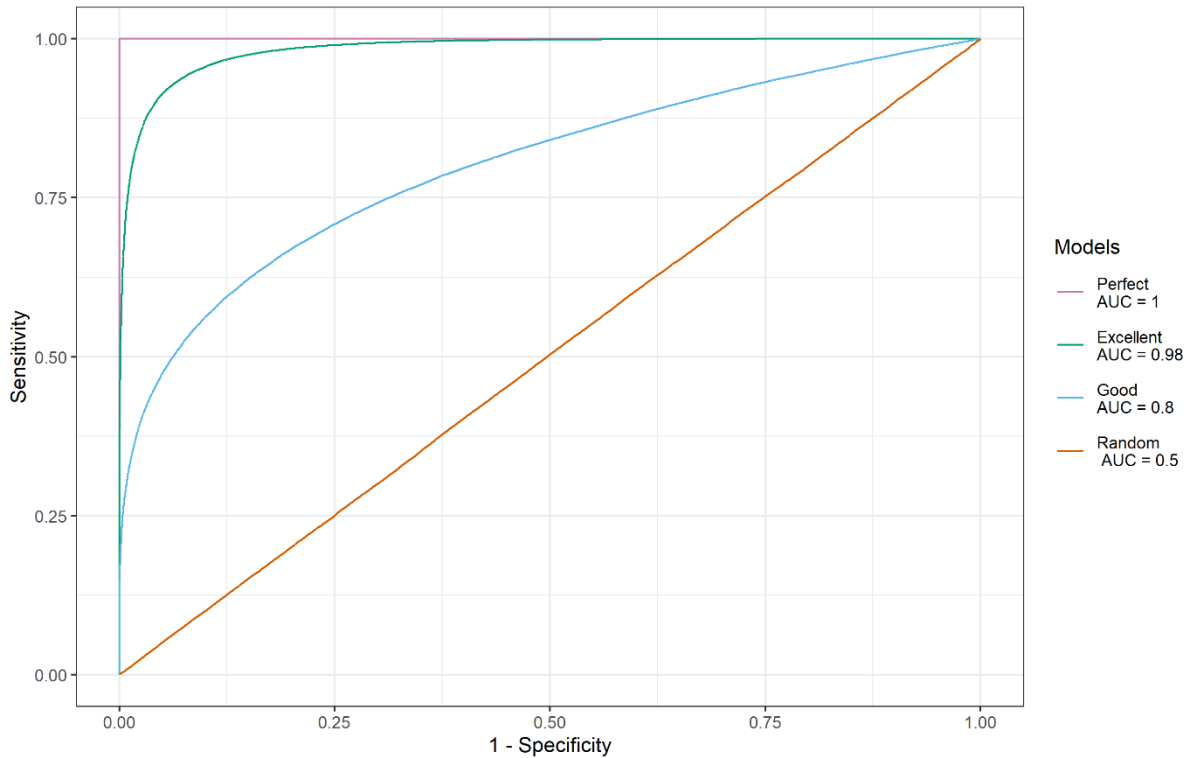


Figure 5.2: Examples of receiver operator characteristic (ROC) curves with levels of accuracy represented by area under the curves (AUC) ranging from perfect (pink line) to random (orange line).

A perfect test that provides 100% sensitivity and 100% specificity and hence perfectly detects all individuals with a disease and all those without a disease will have a ROC curve with a point at (0, 1) represented by the pink line in Figure 5.2. This may also be described as having an area under the curve (AUC) of 1.0. The opposite situation i.e., a useless test, is represented by the orange line going from (0, 0) to (1, 1) in Figure 5.2. This test is as likely to give a true positive result as it is a false positive result and is essentially no different from flipping a coin with an AUC of 0.5. Most AI models

will be somewhere between these two examples with the best models approaching an AUC of 1.0. The use of descriptive terms for AI models such as excellent or poor is somewhat arbitrary and models should ideally be compared to alternatives in the field. A model which provides an AUC of 0.90 may be considered poor when compared to an alternative that achieves an AUC of 0.98 while a model with an AUC of 0.6 may be considered good if no alternative is currently available.

5.6 Applications of Big Data in Eyecare

The value of BD and AI has been increasingly recognised within the research community with a significant increase in the number of publications using these and related terms in their titles in recent years (Figure 5.3). BD has been used to good effect in multiple areas of ocular research including; disease epidemiology, disease screening and treatment outcomes.

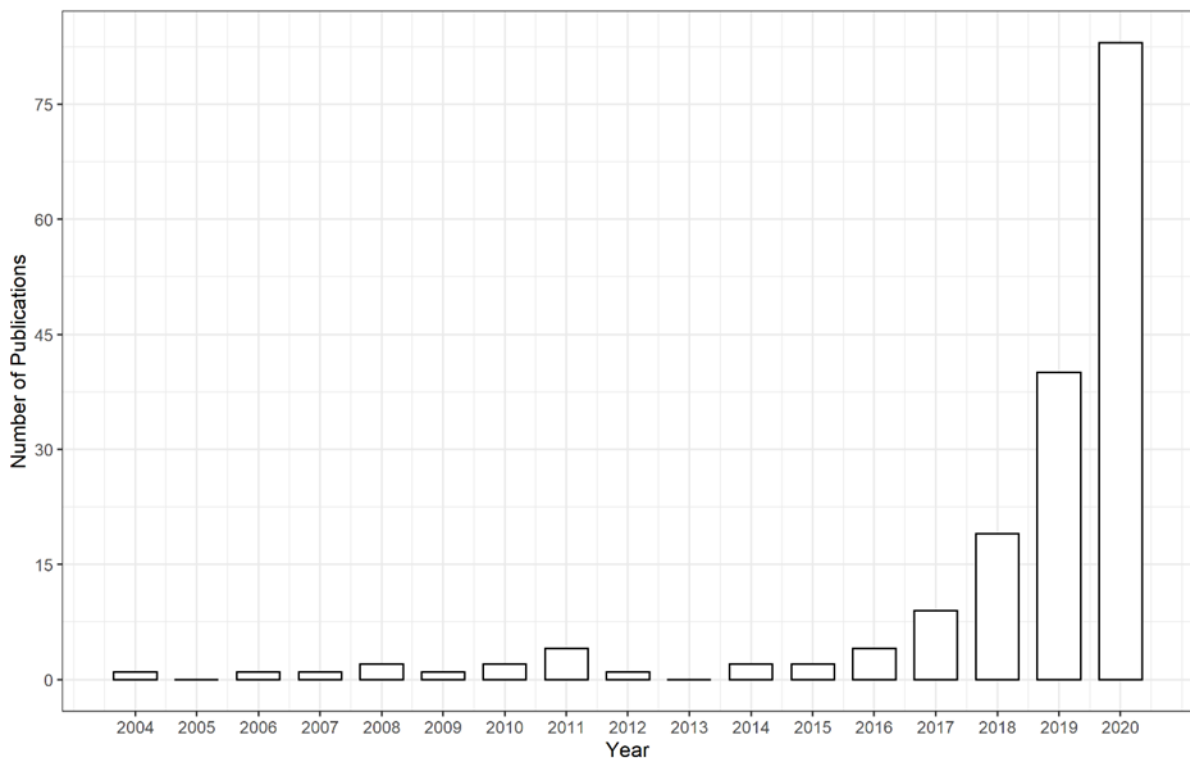


Figure 5.3: Results of a Web of Science search for the number of publications per year containing any of the terms “Big Data”, “Artificial Intelligence”, “Machine Learning” or “Deep Learning” in the fields of ophthalmology or optometry

5.6.1 Epidemiology

One of the most obvious uses of BD in eyecare is in disease epidemiology. Most epidemiological studies of disease examine the disease prevalence at a single point in time with relatively few large-scale longitudinal studies. This is most likely due to the significant time and cost involved in carrying out such studies. This can make accurate public health planning and forecasting difficult if the needed epidemiological data is either outdated or non-existent.³ BD offers an opportunity to exploit readily available longitudinal data which can address this problem with studies on dry eye,³¹¹ uveitis,^{330,331} retinal detachment,²⁷⁶ AMD,³⁷³ diabetic eye disease,³⁷⁴ adult onset strabismus,³⁷⁵ glaucoma,^{376,377} endophthalmitis³⁷⁸ and many others having been conducted using data from EMRs and insurance claims records in recent years.

BD is of particular use in the epidemiology of rare diseases. Accurately determining the prevalence of a rare disease within a population can be very difficult and requires large sample sizes. Figure 5.4 gives an example using refractive error data from a recently published BD study of refractive error.³⁰⁹ The data is taken from spectacle lens manufacturing records (n = 134,280,063) and the Gutenberg Health Survey (GHS),¹⁴ a large (n = 13,959) typical population survey of refractive error. Although refractive error is in no way a rare disease, higher absolute values of refractive error become increasingly rare within a population due to the leptokurtotic population distribution of refractive error. Figure 5.4 shows the number of occurrences for each value of SER for worse levels of myopia. Intuitively, the number of occurrences should reduce uniformly with worsening myopia. The GHS shows increased variability when compared to the spectacle lens data. As both datasets are essentially population samples, this pattern indicates it may be necessary to use much larger sample sizes to accurately determine the occurrence of rare ocular diseases within the population.

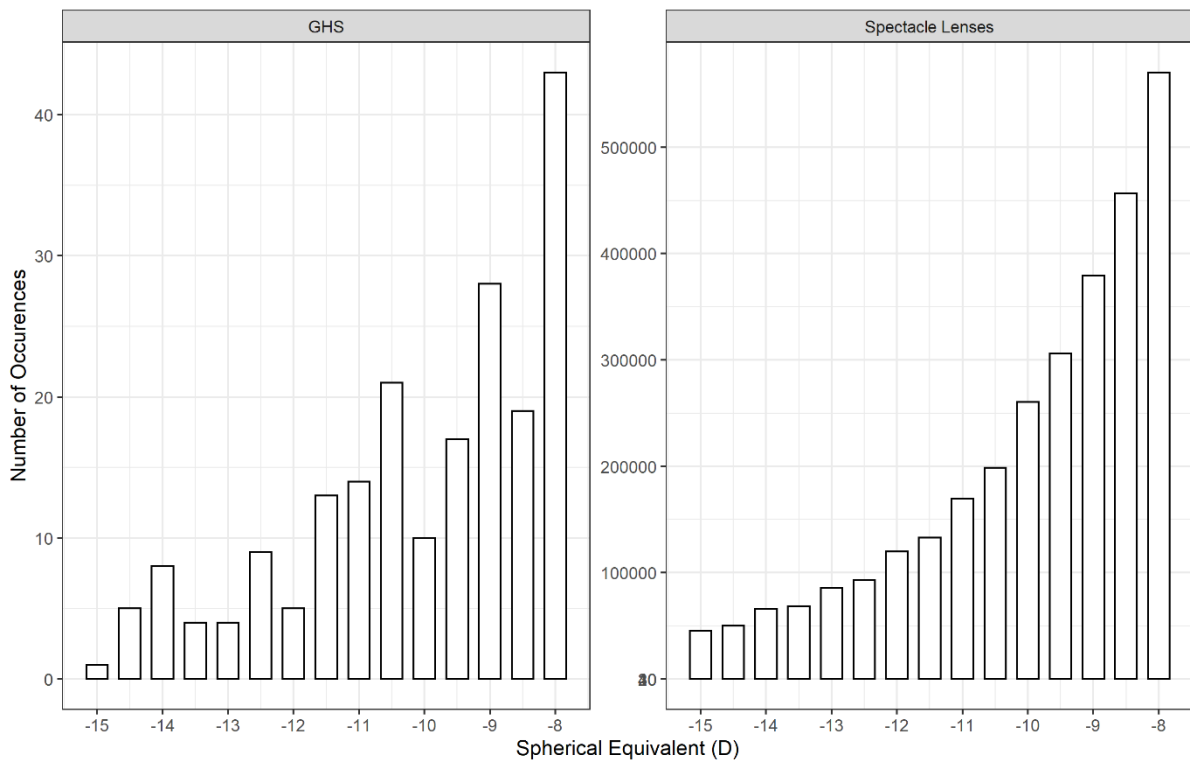


Figure 5.4: Comparison of the distribution of myopia in the Gutenberg Health Survey (GHS), a typical population survey of refractive error ($n = 13,959$) and a Big Data study using spectacle lens manufacturing records ($n = 134,280,063$). At these higher levels of myopic refractive error there is increased variance in the GHS as the sample size is likely too small to adequately describe the underlying population trend.

5.6.2 Disease Screening

The increase in chronic disease associated with an aging population has put increased pressure on the need for disease screening and surveillance. The number of eyecare professionals available to meet this need is not keeping pace with the growing global population.^{5,258} This unmet need may result in increased levels of vision impairment⁵ and is the primary reason that disease screening represents one of the areas of most interest in BD and AI research in eyecare.³³⁴ Outlined below are some of the positive findings and developments from AI for three common ocular conditions; diabetic retinopathy, glaucoma and refractive error.

5.6.2.1 Diabetic Retinopathy

Much of the initial usage of AI and BD in the field of eyecare has centred around diabetic retinopathy (DR) screening. As the rates of diabetes are increasing internationally,³⁷⁹ the need for more DR screening has increased significantly and, in many countries, this exceeds the capacity of the available eyecare services.³⁸⁰ AI which can accurately diagnose the presence of DR to determine if review by an eyecare clinician is necessary would significantly relieve these capacity issues. The first successful AI tool developed for DR screening was described by Gulshan et al.³⁸¹ It used a training dataset of 128,175 retinal images to develop the screening algorithm which was validated against two test datasets comprising 9,963 and 1,748 retinal images. Optimizing the algorithm for high sensitivity, as would be needed for a screening service, the sensitivity and specificity were 97.5% and 93.4% for the first test data set and 96.1% and 93.9% for the second test data set. This model was later tested against both non-physician trained graders of retinal images and retinal specialists to determine the difference in sensitivity and specificity for moderate to severe DR and referable diabetic macular oedema (DMO).³⁸² In all cases the AI algorithm was observed to be as good or better than both the trained graders and retinal specialists at detecting both DR and DMO. When used as a tool to aid in diagnosing DR by ophthalmologists with varying levels of training, the sensitivity of the ophthalmologists was improved by using the AI algorithm demonstrating its usefulness in diagnosis as well as screening.³⁸³

5.6.2.2 Glaucoma

Glaucoma is another condition that has been of significant interest to AI researchers. The majority of AI research in glaucoma has focussed on the diagnosis of glaucomatous optic neuropathy (GON) using OCT scans.³⁸⁴ Multiple approaches have been used with AI models trained to utilise OCT parameters such as retinal nerve fibre layer (RNFL) thickness,^{385,386} en face images,³⁸⁵ b scan

images³⁸⁷ and volumetric scans.³⁸⁸ Several different methodologies have been used when creating AI models to detect GON using OCT data with some observed to be more effective than others. Most AI models achieved a better AUC to detect GON when compared to OCT parameters alone.³⁸⁴

Despite the success that has been achieved using AI and OCT in glaucoma diagnosis, there are some limitations. Most significantly, despite increased adoption of OCT in clinical practice in high income countries, the high purchase price of an OCT will prevent an AI model based solely on OCT parameters from being clinically useful in areas without access to OCT such as low- and middle-income countries. AI models have also been developed which are based on fundus images which are much more widely used and less costly.^{389,390} These models have shown very good sensitivity to detect GON with AUCs of 0.945³⁸⁹ and 0.986³⁹⁰ found in two separate models. These models are, however, built on a ground truth of labelled normal and glaucomatous fundus images which may itself be subject to a misclassification error as the agreement between experts when labelling these images is only slight to fair.³⁹¹ A recent study attempted to overcome this limitation by using an AI model to determine RNFL thickness from fundus images and use these values to detect GON.³⁹² The authors found close agreement between the AI determined RNFL thickness values and those directly measured by OCT.³⁹² This may provide a more objective method to assess fundus images for GON and as such overcome this limitation when developing AI models for GON screening using fundus images.

5.6.2.3 Refractive Error

Refractive error is another area in which useful applications of BD and AI have been developed. The increasing levels of myopia, and in particular high myopia, globally³ are of significant concern due to the associated vision loss in later life.^{114,294} Due to the significant research that has taken place in the area of myopia control we are now entering an era where myopia may be considered a modifiable

risk factor for vision impairment.^{62,393,394} Identifying children at an early age that would most benefit from myopia control is crucial to achieve the best outcomes.³⁹⁴ A recent study utilised BD in the form of electronic medical records of 129,242 children to develop a ML model that could predict the likelihood of a child becoming highly myopic.³¹⁶ When assessed on external test datasets, the model was able to accurately predict the likelihood of high myopia by 18 years old as early as age 10. Use of this model could allow practitioners to identify those most at risk of high myopia at a young age and provide appropriate intervention.

The use of AI to determine refractive error using fundus images only has been recently reported.³⁹⁵ The DL model used was able to predict the refractive error with a mean absolute error of 0.56 dioptres. The exact features that allow the model to predict refractive error are unknown however heat maps showed the fovea was the area that most contributed to the prediction. The anatomical changes of the fundus that take place with myopia are well established²⁷⁰ however no clinician would be able to predict the refractive error associated with those changes with any degree of precision. The accuracy achieved and ease of use of this methodology is no better than autorefraction so this model is unlikely to have any real-world application. However, by identifying associations between retinal appearance and refractive error that human clinicians cannot observe, new insights into the pathophysiology of refractive error may be determined.³⁹⁵

These are just three examples of the disease screening capabilities of AI. Work is progressing on AI powered disease screening in many areas of eyecare with encouraging results observed in detecting cataract,³⁹⁶ AMD,³⁹⁷ retinopathy of prematurity³⁹⁸ and cardiovascular risk.³⁹⁹

5.6.3 Treatment Outcomes

In recent times there is an increasing recognition that although randomised controlled trials (RCTs) represent the gold standard in determining the safety and efficacy of a treatment, the results are not

always replicated in real-world clinical scenarios.⁴⁰⁰ RCTs by their nature require strict inclusion and exclusion criteria which means the results may not be as generalisable to a heterogeneous clinical population. This has given rise to increased use of real-world data in place of and in addition to results from RCTs to optimise patient treatment, a practice that appears to be supported by the literature.⁴⁰¹

One of the most significant examples of real-world data affecting clinical treatment in eyecare is the finding that the use of anti-VEGF drugs for patients with neovascular AMD but still having good visual acuity (> 6/12 Snellen) offered better outcomes when compared to those whose initial treatment was after visual acuity had deteriorated.⁴⁰² The authors' results were determined using a large EMR dataset of patients that had received treatment for neovascular AMD. As the patients involved had good visual acuity to begin, it is unlikely this research question would have been explored using an RCT as there may not have been a perceived benefit in treating patients with good vision. There are several other examples of BD providing information on treatment outcomes that have implications for clinical practice. For rare events such as endophthalmitis following cataract surgery, it is necessary to have sufficient statistical power to determine if the case rate has reduced following a change in practice such as combined surgery or the use of intracameral antibiotics.³¹⁵ Additional studies have also used BD to demonstrate an increased reoperation rate in strabismus surgery with increasing age⁴⁰³ and an indication for earlier use of anti-VEGF drugs in myopic choroidal neovascularisation.³¹⁴

5.7 Limitations

Despite the apparent potential BD and AI hold as both public health and clinical tools, there are some challenges to be overcome before widespread adoption can occur. Accessing data and ensuring the data used is of high quality are issues that still need to be overcome in future

applications of BD and AI in eyecare. In many cases despite the proliferation of medical data, data from EMRs, insurance records and image capture devices is not easily accessible to researchers in BD and AI with the result that some datasets currently in use may lack heterogeneity and as such may not be applicable to all populations.³³⁴ Greater collaboration between data holders and researchers can overcome this issue however issues of data privacy need to be respected to ensure widespread acceptance. Greater collaboration and use of larger datasets can also help with issues of data accuracy, particularly in the case of AI disease screening models. These models use a “ground truth” dataset to make their diagnosis, if this is a small dataset labelled by one or two individuals, the subsequent model may learn the same biases as the clinicians that initially labelled the “ground truth”.⁴⁰⁴ A recent call for researchers to make datasets available publicly in an easily accessible repository may be the first step towards overcoming this issue.⁴⁰⁵

One of the most significant challenges lies in convincing clinicians of the accuracy and reliability of these tools. Many of the AI models developed to date provide little explanation as to how the clinical decision has been made and leave clinicians in a position of trusting a “black box”.^{334,406} To overcome this limitation several models have added heatmaps to their output to allow clinicians understand what part of the image has contributed most to the diagnosis.^{388,395} Heatmaps however have been criticised as being difficult to interpret and can struggle to adequately demonstrate a situation where no disease is present.³³⁴ Further development is ongoing in this area with a recent study using adversarial examples to more clearly highlight how the AI model diagnosis was generated.⁴⁰⁷ Conversely in settings where the tools provided by BD and AI become more commonplace, clinicians are at potential risk of losing their clinical skills and decision-making ability. Automation complacency is a form of bias that can occur in clinicians that make frequent use of automated diagnostic tools.⁴⁰⁸ Clinicians can base their decision solely on the guidance of a machine without attempting seek additional confirmatory evidence.⁴⁰⁶ This has been found to occur most frequently when the case is predicted to be normal⁴⁰⁹ and clinicians are performing multiple tasks.⁴⁰⁸

5.8 Conclusion

The use of BD and AI in the field of eyecare and medicine in general looks set to grow at a rapid pace in the coming years. This changing clinical environment offers the opportunity to gain new insights into disease epidemiology, pathophysiology and treatment. Most significantly, some AI enabled tools may offer the solution to overburdened disease screening and surveillance systems allowing more efficient use of clinician time and achieve better public health outcomes. To make these possibilities a reality, it is vital that clinicians understand what an AI model can and cannot achieve. This will require a willingness to adapt to a changing clinical environment on the part of the clinician but will also require an increased effort on the part of researchers and developers to ensure the tools they develop are easy to use and interpretable.

EXPERIMENTAL PROCEDURES, RESULTS & ANALYSIS

6 Data Collection and Demographics

6.1 Introduction

Chapter 3 describes many of the epidemiological studies of refractive error carried out to date.

Although there is a much-improved understanding of refractive error distribution and the changes that have taken place over the last several decades, there are significant gaps in our knowledge.

Many countries and geographic areas have no published data on refractive error.³ The first survey of refractive error distribution in the Republic of Ireland was only carried out quite recently²¹⁶ and it is unclear if any future surveys will take place.

Traditional methods of reporting refractive error data are by cohort, cross-sectional or longitudinal study. These study designs involve recruiting participants and in the case of longitudinal studies reassessing these same participants at given intervals. The data collection therefore requires significant time and financial resources to acquire which likely explains the lack of data in some areas. Another possible explanation for a lack of refractive error data in some areas may be that increasing myopia prevalence is not perceived as a significant problem by the general public.

McCran et al²⁶⁸ showed that the majority of parents in Ireland did not consider myopia to be a health risk. The authors noted that the number of parents that considered myopia an inconvenience was the same as the number that considered it a health risk. This is despite myopia being as significant a health risk for ocular disease as hypertension is for cardiovascular disease.²⁹ This may not be the case in all locations with more widespread use of myopia control initiatives in Asia indicating greater understanding of the problem among the public.⁵⁴ The findings of McCran et al²⁶⁸ may indicate there is a lack of understanding of the health risks associated with refractive error among the public in some countries making funding and adequate recruitment for epidemiological studies more difficult.

6.1.1 Hypotheses

Alternative sources of refractive error and vision data may provide a unique opportunity to address some of these gaps in the research. EMRs and spectacle lens sales records represent two such sources of data. Therefore, the primary aim of this research was to examine and validate alternative data sources and methods to determine the distribution of refractive error and vision across the general population and validate these results against pre-existing research. Secondary aims were to use these results to estimate the vision impairment due to myopia in a population and demonstrate how these data sources and methods can be used as a basis for public health policy. The following research questions were posed in order to achieve these aims:

- i. Can alternative sources of refractive error data be used as a surrogate for population surveys of refractive error?
- ii. What is the distribution of refractive error in Europe/Ireland using alternative data sources?
- iii. Can the levels of vision impairment due to refractive error be estimated using these techniques?
- iv. Are the current vision screening standards for driving done at appropriate intervals?

This chapter describes the method by which the data was acquired for this project. An overview and analysis of the available demographic information contained within the data is provided.

6.2 Methods

6.2.1 Ethics

Approval for this study was obtained from the Technological University Dublin (TU Dublin) (formerly known as the Dublin Institute of Technology) Research Ethics Committee. The research adhered to the principles of the Declaration of Helsinki.

6.2.2 Data Collection

After consultation between researchers at TU Dublin and Ocuco Limited, an agreement was reached to provide anonymised patient information from private optometry practices. Ocuco provides an EMR system tailored for use in eyecare called Acuitas. This system has been available for over 20 years and is currently used in over 8,000 practices worldwide. Before the data is supplied, the practice owner as the data controller must sign a consent form (Appendix 1) to allow extraction of their patient data. Practices were recruited through word of mouth, through the Association for Optometrists Ireland (Appendix 2) and at educational events around the country. Once consent has been obtained, the data is extracted as 14 separate comma-separated values (CSV) files for each practice with each CSV providing various clinical data such as refraction, VA, IOP, and funduscopy. A new anonymised patient identifier is generated for each patient which allows patients to be tracked across the 14 separate CSV files and across multiple visits. The data can be re-extracted on an as needed basis to allow ongoing monitoring.

A similar agreement was reached with Carl Zeiss Vision International GmbH (CZVI). CZVI is an international manufacturer in the area of optics and optoelectronics. CZVI has a substantial spectacle lens manufacturing business and is usually included among the top producers of spectacle lenses internationally. CZVI agreed to provide data on all spectacle lenses they had shipped from

their European production facility based in Germany. Data was provided in a single large CSV file with accompanying information describing lens codes and delivery locations.

6.2.3 Data Management

To facilitate analysis, the EMR data needed to be converted from the delivered 14 CSV files to one single file containing the required data. This was achieved by creating a database using the SQLite database engine (Hipp, Wyrick & Company, Inc., Charlotte, North Carolina, USA) and performing a series of joins (Appendix 3) to allow a single data file to be extracted.

As CZVI provided data in a single file, pre-processing before analysis was unnecessary however due to the very large data size minimum computing hardware requirements were necessary. The primary computing bottleneck was having sufficient random-access memory (RAM) with local machines requiring at least 64 gigabytes of RAM or the use of cloud computing resources. The data was analysed using the R programming language (R Core Team (2020). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL <https://www.R-project.org/>).

Several refraction values were provided in the EMR dataset. These included auto-refraction, focimetry, retinoscopy, subjective refraction and refraction given. The most consistently recorded value was the refraction given which represents the refraction to be dispensed if the patient was to purchase spectacles. As this was the most consistently recorded refraction this was used for all analysis. Refraction values for both datasets were converted to SER by adding half the cylinder value to the sphere value. The method by which refraction was carried out was not available for the spectacle lens data and whether cycloplegia had been used was not recorded for either dataset.

Visual acuity values within the EMR data when available were typically recorded as Snellen and saved as a string variable. To allow appropriate analysis these values were converted to logMAR

using a custom function written in the R programming language (Appendix 4). Due to the uneven number of letters on each line of a Snellen chart the function first rounds to the nearest achieved line and then converts this to a logMAR value.

6.2.4 Data Protection Compliance and Data Storage

This study is compliant with the general data protection regulations which came into force on the 25th May 2018 (Data Protection Act 2018). The European Union General Data Protection Regulations (GDPR) were implemented in Ireland by the Data Protection Act 2018. Recital 26 of the GDPR discusses anonymisation of data and advises only data which could be used to identify a natural person should be considered personal data and subject to the GDPR. The data used in this study was anonymised before delivery to the researchers in such a way as to remove personally identifying data and to prevent the data from being de-anonymised.

The data used in this study was subject to appropriate data access controls with password protection of all primary and backup data which was stored on secured TU Dublin servers. Consent forms provided by practice owners were also stored on secured TU Dublin servers. Consent forms that were returned as hard copies were scanned so that an electronic copy could be stored on secured TU Dublin servers. The original hard copy was stored in a locked filing cabinet with restricted access.

6.2.5 Data Description and Demographic Analysis

An overview of the data collected to date was generated with any temporal trends in the data assessed using linear regression. Where available, demographic information was presented and compared to publicly available census data.

6.3 Results

6.3.1 Data Overview

At the time of writing, the most recent extract of EMR data took place in July 2020 with the data representing 40 practices around Ireland. At this time the dataset comprised 722,393 visits of 303,727 unique patients which represents approximately 6% of the population of the Republic of Ireland. A sample of the format of 10 patient visit records following conversion to a single data file is given in Table 6.1. Significantly more variables were available for each patient record however the majority of the work carried out as part of this project was confined to analysis of refractive error and visual acuity data as represented in Table 6.1. Patient data is available from 1980 up to the present day although the number of records before 2000 are minimal. From the year 2000 onwards the percentage of patient visits increased every year and could be modelled with a linear regression ($t = 23.09$, $p < 0.001$, $R^2 = 0.97$) as shown in Figure 6.1.

In total there were 141,547,436 spectacle lens sales records ranging from the 1998 to 2016. A sample of the format of 10 spectacle lens sales records is given in Table 6.2. Prior to the year 2001 very few records were available and from the year 2002 onwards there was no statistically significant change ($t = 1.459$, $p = 0.86$) in the percentage of records each year (Figure 6.2).

For both datasets there was very little missing or malformed data with less than 1% of the data for both datasets considered missing or uninterpretable. Missing or uninterpretable data was easily dealt with by confining the analysis to realistic values and excluding unrealistic values. For example, excluding sphere values greater than an absolute value of 30.

Table 6.1: Sample of 10 electronic medical record (EMR) patient visit records following conversion from 14 separate comma-separated values (CSV) files.

	NewPxID	Age	Gender	County	Rx_date	RE_SPH	RE_CYL	RE_AXIS	RE_add	RE_UVA	RE_VA	LE_SPH	LE_CYL	LE_AXIS	LE_add	LE_UVA	LE_VA
1	5919_34359738897	45	Male	Dublin 3	2012-04-17	-2.50	0.00	NA	1.0	6/60	6/3.8	-2.50	0.00	NA	1.0	6/48	6/3.8
2	5919_34359738897	46	Male	Dublin 3	2013-06-07	-2.50	0.00	NA	1.5	6/60	6/3.8	-2.75	-0.50	135	1.5	6/60	6/3.8
3	5919_34359738897	50	Male	Dublin 3	2017-05-10	-2.75	0.00	NA	1.5	NA	6/4.8	-2.75	0.00	NA	1.5	NA	6/4.8
4	5919_34359738898	18	Female	Dublin	2007-02-23	-0.75	0.00	NA	0.0	6/9	6/5-2	-0.75	0.00	NA	0.0	6/9	6/5-2
5	5919_34359738898	19	Female	Dublin	2007-11-19	0.00	0.00	NA	0.0	6/6-2	NA	0.00	0.00	NA	0.0	6/6-2	NA
6	5919_34359738898	19	Female	Dublin	2007-11-26	-0.50	-0.25	118	0.0	6/6-1	6/5+2	-0.50	-0.25	60	0.0	6/6-1	6/5
7	5919_34359738900	11	Male	Wicklow	2007-02-23	0.50	0.00	NA	0.0	6/5	6/4	0.75	-0.25	85	0.0	6/5	6/4-2
8	5919_34359738900	11	Male	Wicklow	2007-03-02	0.50	0.00	NA	0.0	6/4	6/4	0.50	0.00	NA	0.0	6/4	6/4
9	5919_34359738900	12	Male	Wicklow	2008-04-18	0.25	0.00	NA	0.0	6/5-3	6/5	0.25	0.00	NA	0.0	6/5	6/5
10	5919_34359738900	12	Male	Wicklow	2008-10-30	0.00	0.00	NA	0.0	6/5	6/5	0.00	-0.25	15	0.0	6/6	6/5

Table 6.2: Sample of 10 spectacle lens records as supplied by Carl Zeiss Vision International GmbH (CZVI).

	date	Lens-Code	diameter	left_right	sphere	cylinder	axis	addition	add_lens	Commercial Name	Material	Index
1	25.06.2007	DURM	65	R	-100	200	NA	0	NA	NA	NA	NA
2	25.06.2007	DURM	65	L	-50	150	NA	0	NA	NA	NA	NA
3	25.06.2007	DUR	60	R	200	100	NA	0	NA	NA	NA	NA
4	25.06.2007	DUR	60	L	250	150	NA	0	NA	NA	NA	NA
5	25.06.2007	PLAS	70	R	-225	0	NA	0	NA	NA	NA	NA
6	25.06.2007	PLAS	70	L	-75	0	NA	0	NA	NA	NA	NA
7	25.06.2007	S5	70	R	-350	50	5	0	NA	NA	NA	NA
8	25.06.2007	S5	70	L	-550	25	12	0	NA	NA	NA	NA
9	25.06.2007	DURM	65	R	100	150	90	0	NA	NA	NA	NA
10	25.06.2007	DURM	65	L	75	0	NA	0	NA	NA	NA	NA

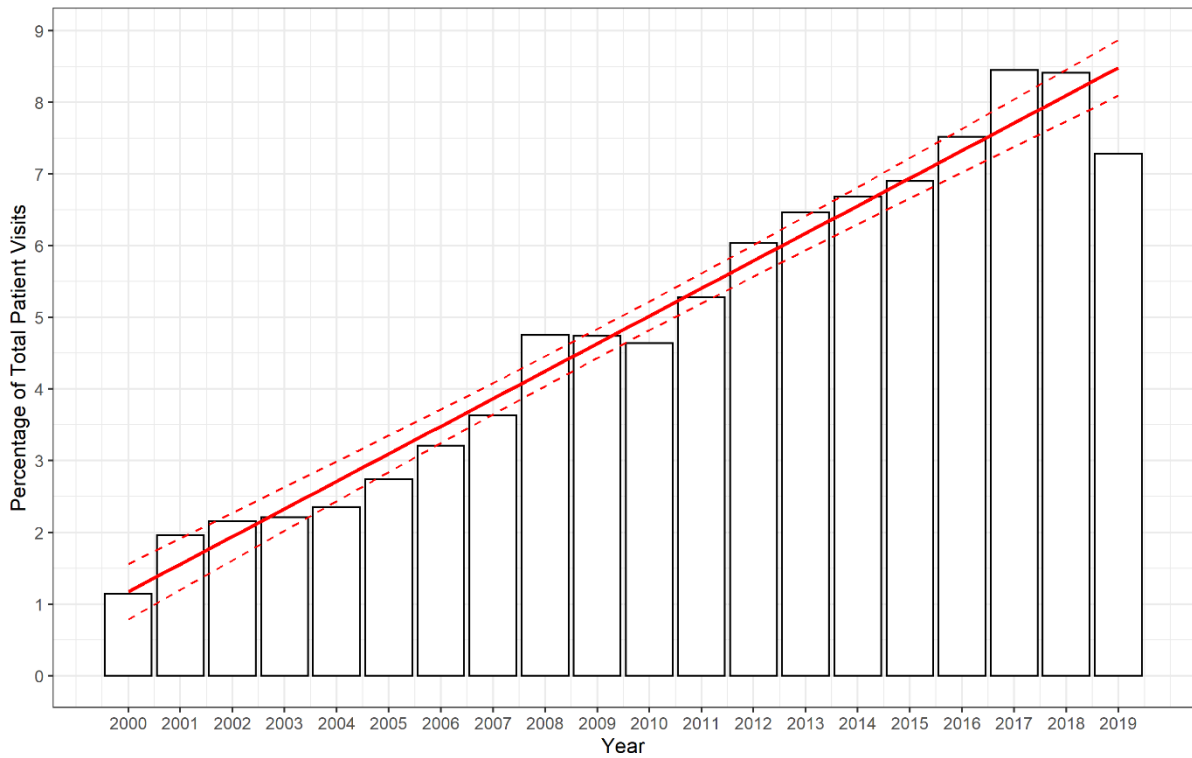


Figure 6.1: Percentage of electronic medical record (EMR) patient visits in each year. The percentage increases linearly with time ($t = 23.09$, $p < 0.001$, $R^2 = 0.97$) as shown by the linear regression (red line) with 95% confidence intervals (dashed red lines).

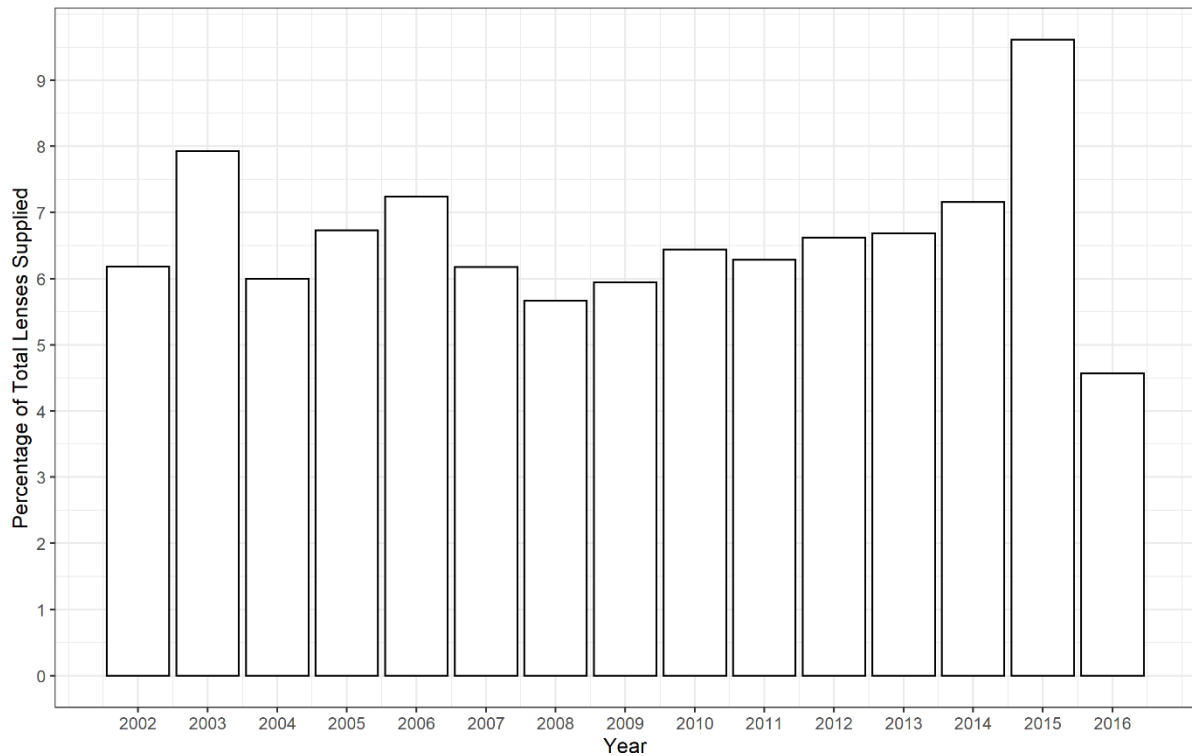


Figure 6.2: Percentage of spectacle lens sales records in each year. No correlation was found between the year and sales records.

6.3.2 Geographic Overview

The significant majority ($\approx 98\%$) of spectacle lenses produced were for delivery in Europe (Table 6.3) with Germany consistently the largest consumer accounting for an average of 48% of all lens deliveries over the period 2007 – 2015 (Table 6.4). The geographic distribution of the EMR data is shown in Figure 6.3 which is a screengrab of an interactive map (available at <https://irelandrefractiveerror.shinyapps.io/PatientDistribution/>). All counties are represented within the dataset however they are not evenly represented with the highest percentage of patient visits occurring in Dublin (25.8%) while several counties have less than 1% of all patient visits.

Table 6.3: Proportion of Carl Zeiss Vision International GmbH (CZVI) spectacle lenses produced in Europe by final destination in global regions.

	2007	2008	2009	2010	2011	2012	2013	2014	2015
Europe	97.4%	98.3%	98.4%	98.6%	98.3%	98.2%	98.1%	97.3%	97.3%
Asia	1.9%	1.3%	1.3%	1.2%	1.2%	1.0%	1.1%	1.0%	1.3%
America	0.4%	0.2%	0.1%	0.1%	0.3%	0.5%	0.3%	0.4%	0.6%
Africa	0.2%	0.1%	0.1%	0.1%	0.1%	0.3%	0.5%	0.4%	0.6%
Oceania	0.2%	0.1%	0.1%	0.0%	0.0%	0.0%	0.1%	0.9%	0.1%

Table 6.4: Top 15 countries for Carl Zeiss Vision International GmbH (CZVI) spectacle lens delivery for the years 2007 – 2015.

Top 15 Countries 2007 - 2015

	2007		2008		2009		2010		2011		2012		2013		2014		2015	
	Country	%	Country	%	Country	%	Country	%	Country	%	Country	%	Country	%	Country	%	Country	%
1	D	57	D	56	D	52	D	48	D	44	D	40	D	42	D	47	D	42
2	ITA	6	GB	6	F	10	F	14	ITA	10	ITA	10	ITA	10	ITA	10	ITA	12
3	GB	5	ITA	6	GB	7	GB	8	GB	9	GB	8	GB	8	F	9	GB	7
4	CH	4	F	5	ITA	6	ITA	6	F	8	F	8	F	6	GB	6	E	4
5	NL	4	NL	4	CH	3	CH	3	E	5	E	5	E	5	E	3	CH	4
6	FIN	3	CH	3	A	2	E	3	NL	4	NL	5	NL	4	B	3	B	4
7	A	3	A	2	NL	2	NL	2	B	3	B	4	B	4	CH	2	F	3
8	F	2	E	2	E	2	A	2	CH	3	CH	3	CH	3	P	2	A	3
9	E	2	B	1	DK	2	B	2	A	2	P	3	P	3	A	2	P	3
10	DK	1	DK	1	P	1	P	2	P	2	A	2	A	2	NL	2	NL	3
11	B	1	P	1	B	1	DK	2	DK	2	DK	2	DK	2	H	2	DK	2
12	S	1	S	1	S	1	S	1	S	1	S	2	S	2	DK	2	S	2
13	P	1	RUS	1	RO	1	N	1	L	1	H	2	H	2	S	2	H	2
14	N	1	L	1	H	1	H	1	H	1	L	1	L	1	AUS	2	IL	1
15	RC	1	N	1	L	1	RC	1	N	1	BRA	1	IL	1	IRL	1	L	1
Σ		93		92		93		94		95		94		94		94		92

D= Germany; ITA = Italy; GB= Great Britain; CH = Switzerland; NL = Netherlands; FIN = Finland; A = Austria; F = France; E = Spain; DK = Denmark, B = Belgium; S = Sweden; P = Portugal; N = Norway; RC = Romania; L = Luxembourg; H = Hungary; BRA = Brazil; IRL = Ireland IL = Israel; AUS= Australia

Geographic Distribution of Patient Visits

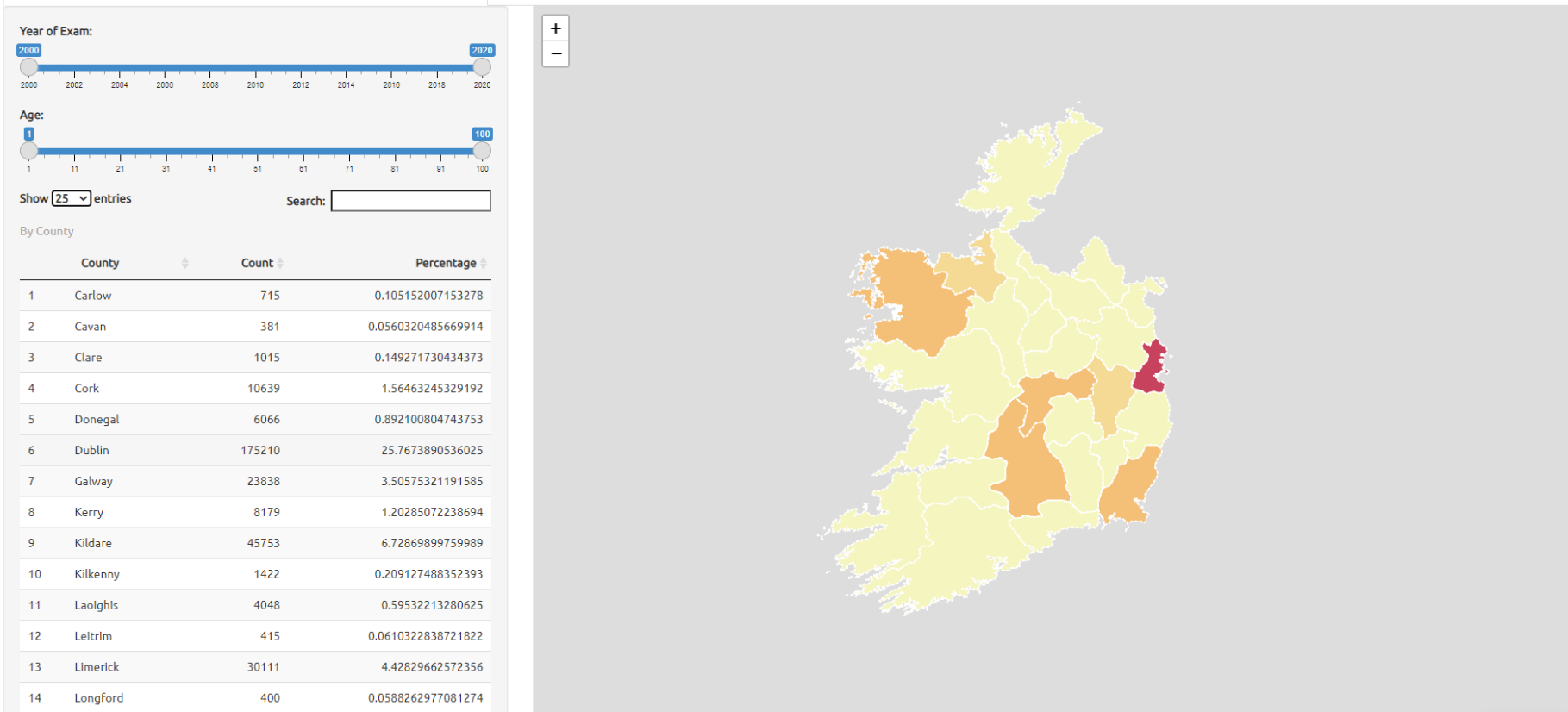


Figure 6.3: Geographic distribution of electronic medical record (EMR) patient visits around Ireland. All counties are represented with the highest number of visits occurring in Dublin. Interactive version available at: <https://irelandrefractiveerror.shinyapps.io/PatientDistribution/>

6.3.3 Age and Gender Analysis

Age and gender information was not available for the spectacle lens sales data. A method for inferring the age of some of the spectacle lens users is described in chapter 7.4. The mean age for the total EMR dataset was 47.08 ± 22.20 years while it was 47.61 ± 21.98 years in females and 47.39 ± 22.72 years in males. The mean age was observed to increase over time and could be accurately modelled with a linear regression ($t = 12.71$, $p < 0.001$, $R^2 = 0.89$) as shown in Figure 6.4.

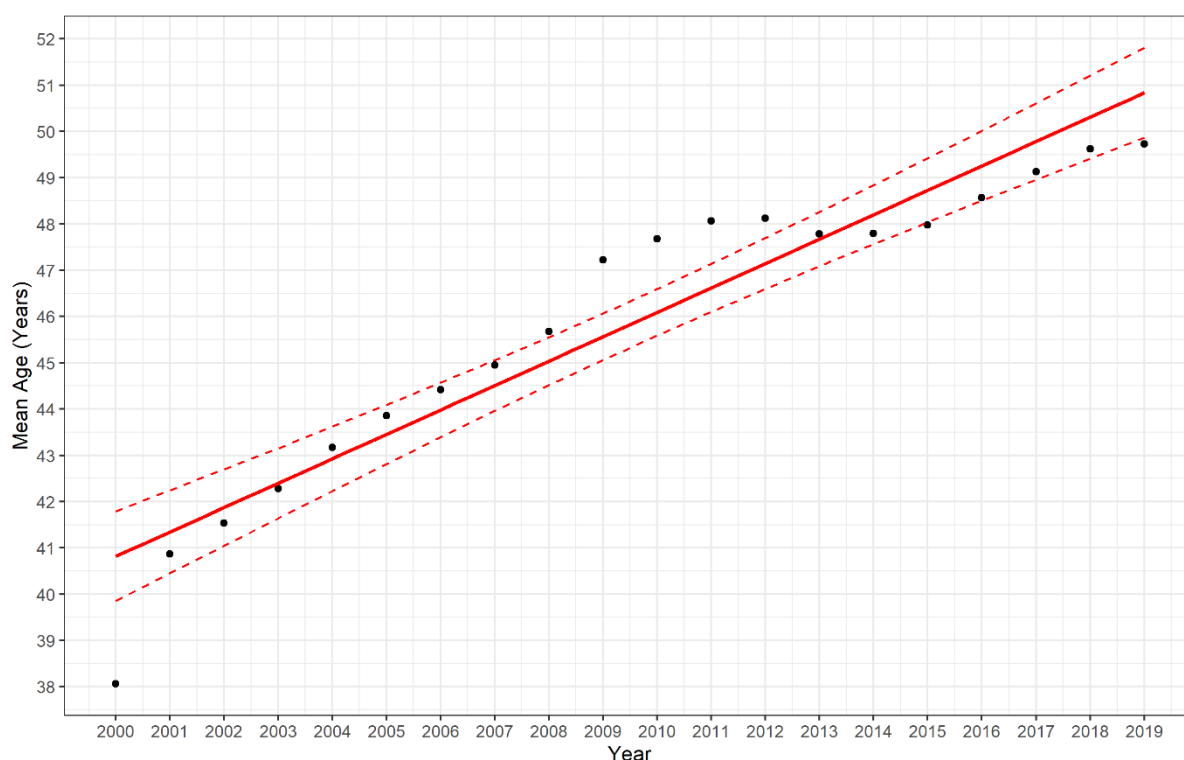


Figure 6.4: The mean age of EMR patients increased with exam year as shown by linear regression (red line) with 95% confidence intervals (dashed red lines).

The gender distribution for the EMR dataset was 52.8% female, 36.1% male and not recorded in 11.1% of cases. This was statistically different (two-sided binomial test, $p < 0.001$) to the most recent census report of 51.1% female.⁴¹⁰ This difference was apparent across all age groups apart from young children (Figure 6.5).

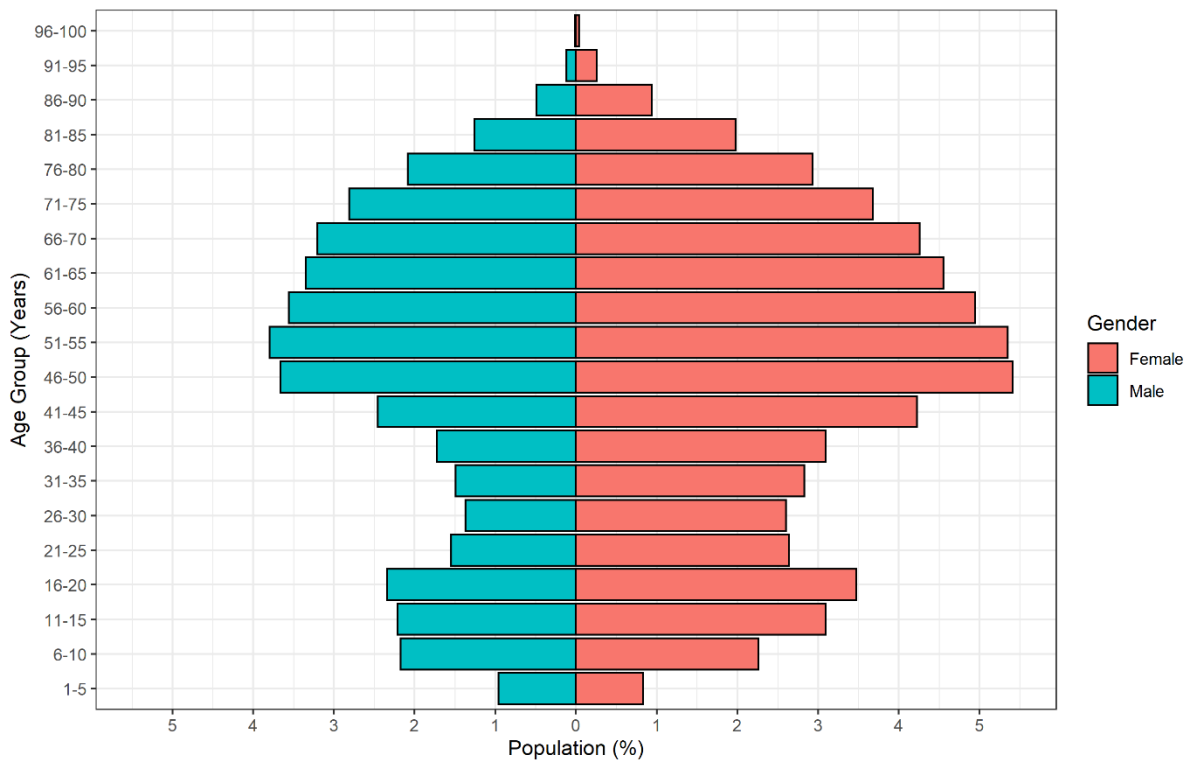


Figure 6.5: Gender and age distribution of EMR patients. The gender distribution for the EMR dataset was 52.8% female, 36.1% male and not recorded in 11.1% of cases. The mean age for the total EMR dataset was 47.08 ± 22.20 years.

6.4 Discussion

The data collected for this study presents a unique opportunity to explore the potential of alternative sources of refractive error and vision data. This is of particular interest given the significant lack of refractive error and vision data available around the world.^{3,5} The level of detail available in both datasets is significantly different allowing a far more nuanced exploration of the EMR data.

The time trends in both the EMR and spectacle lens datasets are interesting even if they are somewhat anticipated. The consistent level of lenses produced from the year 2002 onwards is explained by the complete switch over to electronic ordering of lenses that occurred in CZVI in the early 2000's (Figure 6.4). The relatively static number of lenses produced each year reflects the established position of CZVI in spectacle lens market. The increasing number of records available per

year in the EMR data is also expected due to the increasing use of EMRs among healthcare providers over this time period.⁴¹¹ Although these results are expected further exploration of these trends may provide more useful findings such evidence for or against the theory of seasonal a variation in myopia progression.^{412,413} This might be observed by increased myopic spectacle lens orders during winter months and higher myopia progression rates in children and young adults in the EMR data during winter months.

The geographic trends indicate the population under consideration in both datasets is largely Western European and should compare well with studies of similar populations. The large representation of Germans in the spectacle lens sales data (Figure 6.5) is unsurprising given lens production takes place in Germany. Despite the significant number of lenses that were for delivery in Germany there is still a wide spread of locations in Western Europe so the data should be representative of this population. EMR patient visits are not evenly spread around the country but occur with a much higher density in some counties, particularly Dublin. To some extent this is likely as a result of the population density in Ireland with the highest densities occurring in the Greater Dublin Area (GDA) however other urban areas with high population densities in the Republic of Ireland are not represented to a similar extent. There are two possible explanations for this variation. Firstly, the EMR product from which the data is derived may not have equal market penetration all over the country resulting in a deviation from the population distribution as reported by the census.⁴¹⁴ Secondly, the author is based in Dublin which may have led to increased practice recruitment in the GDA with less recruitment in other parts of the country. Despite the EMR data not reflecting the population distribution in Ireland, all counties are represented with a good spread of data in both urban and rural locations.

The mean age found in the EMR data is older than that found during the most recent census carried out in Ireland.⁴¹⁵ This is likely due to the increased prevalence of ocular disease^{416,417} and the need for presbyopia correction in later life.¹⁴⁴ The overall pattern of population distribution by age is

similar to that found by the most recent census with lower population numbers in young adults and the highest numbers occurring in middle age (Figure 6.8).⁴¹⁰ The proportion of young children aged 1 – 5 years is less than observed by the census.⁴¹⁰ This is likely as a result of the eyecare structures in the Republic of Ireland with children of this age needing eyecare usually seen in a hospital or community ophthalmology setting. The gender distribution observed within the EMR data was more significantly skewed to females than that observed in the most recent census. This is likely due to the established lower attendance of men for healthcare checks.⁴¹⁸

6.5 Conclusion

Alternative sources of data on refractive error and vision provide a unique opportunity to address some of the gaps in scientific research on these topics. Further validation by comparison with published results is necessary to confirm the appropriateness of utilising these alternative data sources for research purposes. A deep understanding of the underlying data and the limitations associated with the data is necessary to ensure accurate conclusions can be drawn.

7 Application of Big-Data for Epidemiological Studies of Refractive Error

7.1 Title Page:

Title: Application of Big-Data for Epidemiological Studies of Refractive Error

Authors:

Corresponding Author: Michael Moore¹ (email: michael.moore@tudublin.ie, ORCID ID: 0000-0003-3919-444X)

James Loughman¹ (ORCID ID: 0000-0003-3130-8991)

John S. Butler^{1,2} (ORCID ID: 0000-0001-5567-8634)

Arne Ohlendorf^{3,4} (ORCID ID: 0000-0002-6373-1420)

Siegfried Wahl^{3,4} (ORCID ID: 0000-0003-3437-6711)

Daniel I. Flitcroft^{1,5} (ORCID ID: 0000-0002-7004-6026)

Affiliations:

¹Centre for Eye Research Ireland, School of Physics and Clinical and Optometric Sciences, Technological University Dublin, Dublin, Ireland

²School of Mathematical Sciences, Technological University Dublin, Dublin, Ireland

³Technology & Innovation, Carl Zeiss Vision International GmbH, Turnstrasse 27, 73430 Aalen, Germany

⁴Institute for Ophthalmic Research, Center for Ophthalmology, Eberhard Karls University of Tübingen, Elfriede-Aulhorn-Straße 7, 72076 Tübingen, Germany

⁵Children's University Hospital, Dublin, Ireland

7.2 Abstract:

Purpose:

To examine whether data sourced from electronic medical records (EMR) and a large industrial spectacle lens manufacturing database can estimate refractive error distribution within large populations as an alternative to typical population surveys of refractive error.

Subjects:

A total of 555,528 patient visits from 28 Irish primary care optometry practices between the years 1980 and 2019 and 141,547,436 spectacle lens sales records from an international European lens manufacturer between the years 1998 and 2016.

Methods:

Anonymized EMR data included demographic, refractive and visual acuity values. Anonymized spectacle lens data included refractive data. Spectacle lens data was separated into lenses containing an addition (ADD) and those without an addition (SV). The proportions of refractive errors from the EMR data and ADD lenses were compared to published results from the European Eye Epidemiology (E3) Consortium and the Gutenberg Health Study (GHS).

Results:

Age and gender matched proportions of refractive error were comparable in the E3 data and the EMR data, with no significant difference in the overall refractive error distribution ($\chi^2=527$, $p=0.29$, $DoF=510$). EMR data provided a closer match to the E3 refractive error distribution by age than the ADD lens data. The ADD lens data, however, provided a closer approximation to the E3 data for total myopia prevalence than the GHS data, up to age 64.

Conclusions:

The prevalence of refractive error within a population can be estimated using EMR data in the absence of population surveys in countries with high levels of access to refractive services. Industry derived sales data can also provide insights on the epidemiology of refractive errors in a population over certain age ranges. EMR and industrial data may therefore provide a fast and cost-effective surrogate measure of refractive error distribution that can be used for future health service planning purposes in countries with good access to optometric and spectacle dispensing services.

7.3 Introduction:

Refractive error occurs when the eye does not correctly focus light at the retina which results in blurred vision. It arises as a result of the eye growing too long (myopia/short sightedness), the eye not growing long enough (hyperopia/long sightedness), uneven focussing due to corneal shape (astigmatism) or a failure to focus at close ranges due to aging (presbyopia). In order to obtain clear vision, correction either through the use of optical aids such as spectacles or contact lenses or refractive surgery is required.

Refractive errors are a leading cause of vision impairment and blindness globally, due to limited access to optical correction in some regions,⁴¹⁹ and the range of ocular diseases for which refractive errors, in particular myopia, are an identified risk factor.^{420,421} There is a growing concern about myopia due to the rapid rise in global prevalence over the last few decades.³ Vitale et al⁸ found an increase in myopia prevalence from 25% in 1971 - 1972 to 41.6% in 1999 –2004 in the United States of America. Similar increases have been observed in Europe, with higher levels of myopia observed in more recent birth cohorts.³⁸ The largest increases in myopia prevalence have been observed in Asia,⁴²² particularly east Asia, with rates reaching 84% in older children.¹⁵¹ The level of myopia prevalence is not as high in South America^{191,423} or Africa,¹⁹⁵ however, it is expected to rise significantly in all parts of the world in the coming years.³ Holden et al³ estimated that almost half of the world's population will be myopic by 2050, with almost 10% set to be highly myopic. The authors extrapolated these myopia rates by using data from published population surveys of refractive error. The primary limitation identified in this study was the significant lack of global epidemiological refractive error data, with many countries having no data whatsoever or significant gaps in data across different regions, age groups and ethnicities. The authors made specific reference to the reduced certainty with regards to their high myopia predictions, with only 48 studies contributing data to these projections.

In order to assess the public health implications of refractive errors, it is essential to have accurate population-based epidemiological data. In light of the observed differences between countries and changing prevalence over time, such data needs to be both representative of a given population and current. In Europe, epidemiological data has been collected over many decades, often from historical cohorts. The largest such study,¹⁵⁴ the European Eye Epidemiology (E3) consortium of 33 groups from 12 European countries, collated data on 124,000 European participants from population cohort and cross-sectional studies on refractive error conducted between 1990 and 2013. While this data does show a trend of increased myopia prevalence for people born in more recent decades, the available data from recent years and on younger population cohorts is relatively sparse.

Gathering comprehensive epidemiological data that can determine global prevalence trends in refractive error over time using this traditional methodology is slow and open to question in terms of cost effectiveness.^{424,425} For this reason, the growing volume of data gathered in healthcare in recent years is of specific interest. Data such as electronic medical records (EMR) and industrial manufacturing or sales records represent a potentially valuable source of secondary data, i.e. data used for a purpose that is different from that for which it was originally collected. The scale of such data is often far larger than conventional research datasets and it is now commonly referred to as Big Data. Big Data is now recognized as an important resource for scientific research, allowing conclusions to be drawn that would otherwise be impossible using traditional scientific techniques^{426,427}.

In the field of eyecare, several studies have demonstrated the usefulness of EMR data for determining disease epidemiology^{310,311} and treatment outcomes.^{314,402} The application of such approaches to myopia genetics research has shown strong correlation with the results obtained using conventional epidemiological research methodologies.^{104,105} National^{330,331} and private insurance claims records have also been used to determine the epidemiology of several ocular diseases, as have hospital records.³²⁹ Big Data sources of this type can be used as an alternative form

of epidemiological data, particularly in the absence of conventional epidemiological studies.

Datasets such as national insurance claims records can be generalised to an entire population while EMR and hospital record data are useful when considering specific population cohorts.

The potential of Big Data as a tool to monitor population trends in refractive error has received little attention. Optometric EMR data provides an obvious example of a rich source of data on refractive error that has yet to be exploited for this purpose. Another novel, but less obvious, source of data is the manufacturing and sales records of companies involved in the supply of optical appliances such as spectacle and contact lenses. This data source is much more limited in terms of the information available, but the ubiquity of these optical appliances indicates such data may still elicit useful insights on refractive error epidemiology.

This study was designed, therefore to examine whether optometric EMR data or spectacle lens data can provide estimates of refractive error distribution that are comparable to traditional population surveys.

7.4 Methods:

Anonymized EMR data was gathered from 28 Irish optometry practices. The data was extracted remotely through the EMR provider following provision of explicit consent from the data (practice) owners during the period of May 2018 to June 2019 for all 28 practices. The data extracted comprised all practice records since first use up to the date of extraction for each practice. The EMR provider removed any personally identifying data and anonymized the data prior to delivery so that the anonymization could not be reversed by the researchers. The data was analysed using the R programming language (R Core Team (2020). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL <https://www.R-project.org/>). At the time of extraction, a new unique identifying number was generated for each subject within the EMR data allowing their data to be tracked across multiple visits. The data

available for each subject included demographic, refractive, visual acuity, binocular vision, contact lens, ocular health and clinical management data. For this analysis only demographic, refractive and visual acuity data were considered with most refractions having been performed as non-cycloplegic subjective refractions.

Anonymized patient spectacle lens sales data was provided by a major European manufacturer. This comprised lenses that had been manufactured and dispatched after an order was received from a practitioner with the majority of lenses for delivery within Europe. The data was collated into histogram data using the SQLite database engine (Hipp, Wyrick & Company, Inc., Charlotte, North Carolina, USA) and analysed using the R statistical programming language. The data provided included the spherical power, cylindrical power and axis of the spectacle prescription. The lens design, diameter, laterality (prescribed for right or left eye) and date of manufacture were also included. For lens designs with an addition, this was also specified. The presence of an addition allowed the lenses to be separated into two groups, the single vision (SV) lens group and the addition (ADD) lens group. The data was validated for missing and malformed data fields and any lenses with incomplete or invalid data were excluded. The spherical equivalent power was calculated for each lens.

Data from the E3 study was extracted by digitizing the published results using Plot Digitiser.⁴²⁸ Data from the GHS study,¹⁴ a population based observational study, was also digitized as an additional comparison. The GHS was chosen as an additional comparison as it took place in Germany, had a similar age range (35-74) and was one of the component studies of the E3 study. In addition, Germany was the largest contributor to the spectacle lens data.

Myopia was defined according to the International Myopia standards,⁹³ with a spherical equivalent refraction (SER) of ≤ -0.50 D being considered myopic, and ≤ -6.00 D SER considered highly myopic. Hyperopia was defined as $\geq +0.75$ D SER and emmetropia defined as > -0.50 D SER and $< +0.75$ D

SER. For comparison with the E3 study, analysis was also performed using the myopia definition used in that study, i.e. ≤ -0.75 D SER.

The E3 study, a meta-analysis on refractive error prevalence in Europe, was chosen as a comparative study for several reasons. Firstly, the manufacturer database reflected almost exclusively European lens sales. Secondly, as the spectacle lens data comprised a substantial proportion of reading addition lenses typically used by older presbyopic adults⁴²⁹ (age ≥ 40 -45 typically),¹⁶³ the adult age profile of the E3 consortium (age 25-89 years) was deemed suitable, and it was assumed that the datasets could be comparable. These age assumptions were also validated using the EMR data. With this more detailed optometric data, both the age and spectacle correction data were available, allowing determination of the age distribution of patients with single vision and reading addition spectacles. The relationship between age and reading addition was determined by fitting a logistic function to the age and right eye reading addition found in the EMR data using the 'drc' extension package for R.⁴³⁰ A logistic function was also created to determine the number of individuals requiring a reading addition at each age from 1 to 100 years old within the EMR data. The base R predict function was then used to generate 95% prediction intervals for both logistic models. Probability density functions were generated for each reading addition value to determine the distribution of age associated with that reading addition. The ADD lens group then had an estimated age assigned for each spectacle lens based on the reading addition value for that lens using the probabilities generated from the EMR data. The EMR data was randomly sampled to provide an age and gender matched population for comparison with the E3 population. The ADD lens data was also age matched with the E3 population using the estimated age for each lens. From the age matched EMR and ADD lens data, the proportion of myopia, high myopia and hyperopia present was calculated in 5-year age brackets to allow comparison with the E3 and GHS data.

This study was approved by our institution's ethics committee and adheres to the tenets of the Declaration of Helsinki. Due to the irreversible nature of the data anonymization patient level consent was not required.

7.5 Results:

7.5.1 Spectacle Lens Dispensing and EMR Refractive Error Distribution:

Initially the spectacle lens dataset comprised 141,547,436 lenses from the manufacturer sales records ranging from the year 1998 to 2016. The acquired EMR dataset included 555,528 patient visits ranging from the year 1980 to 2019. Records with incomplete or missing data were excluded from both datasets and only years with complete data were included in the analysis (Figure 7.1). In total 134,280,063 spectacle lenses were included, comprised of 84,561,994 SV lenses and 49,709,191 ADD lenses. The final EMR dataset was composed of 524,868 patient visits.

Over 97% of spectacle lenses were for delivery within Europe with Germany accounting for the largest proportion ($\approx 48\%$) of all lenses delivered. The EMR data included 244,002 unique patients representing 5.1% of the population of the Republic of Ireland ⁴¹⁵. The gender distribution of EMR patient visits was 51.3% female, 34.9% male and not recorded in 13.8% of records. The 28 optometric practices were located all across the Republic of Ireland representing both rural and urban populations.

The distribution of refractive error within the EMR data and spectacle lens data are presented in Figure 7.2, including the complete datasets and also segregated according to lens type (SV or ADD lens). Table 7.1 summarises the descriptive statistics for each distribution.

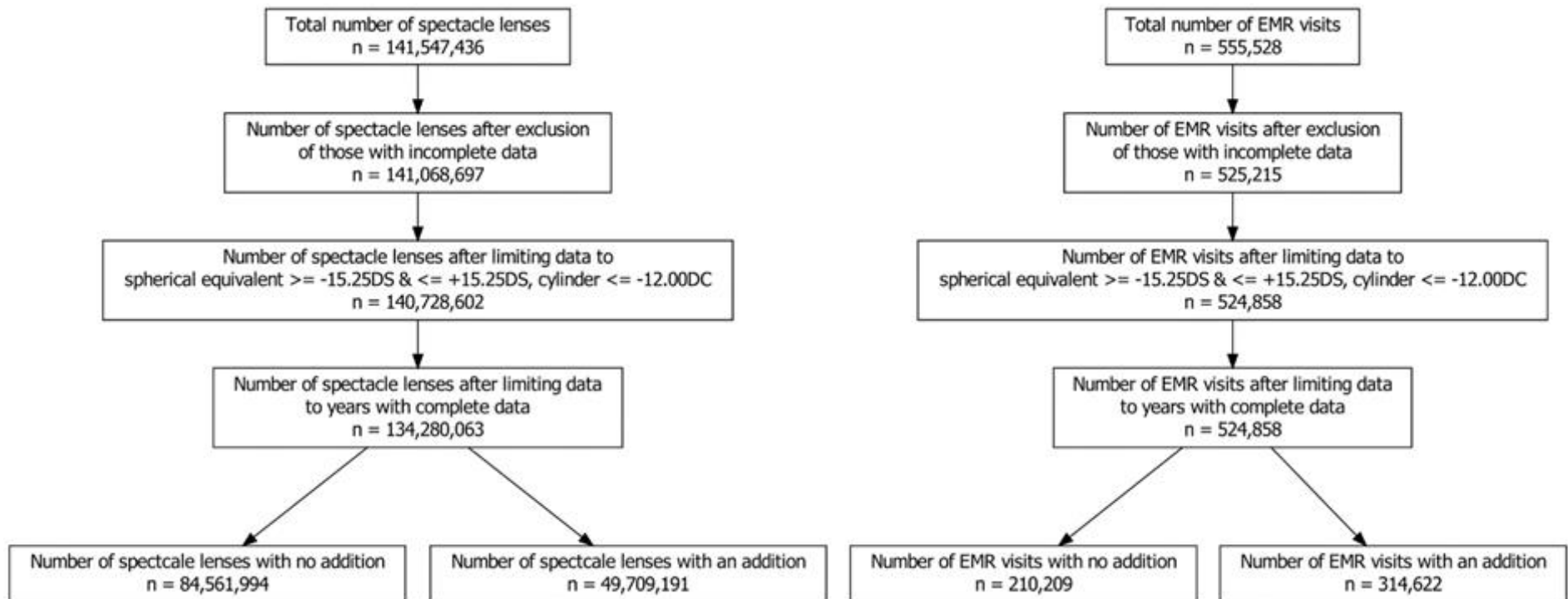


Figure 7.1: Number of spectacle lenses and EMR visits included in analysis

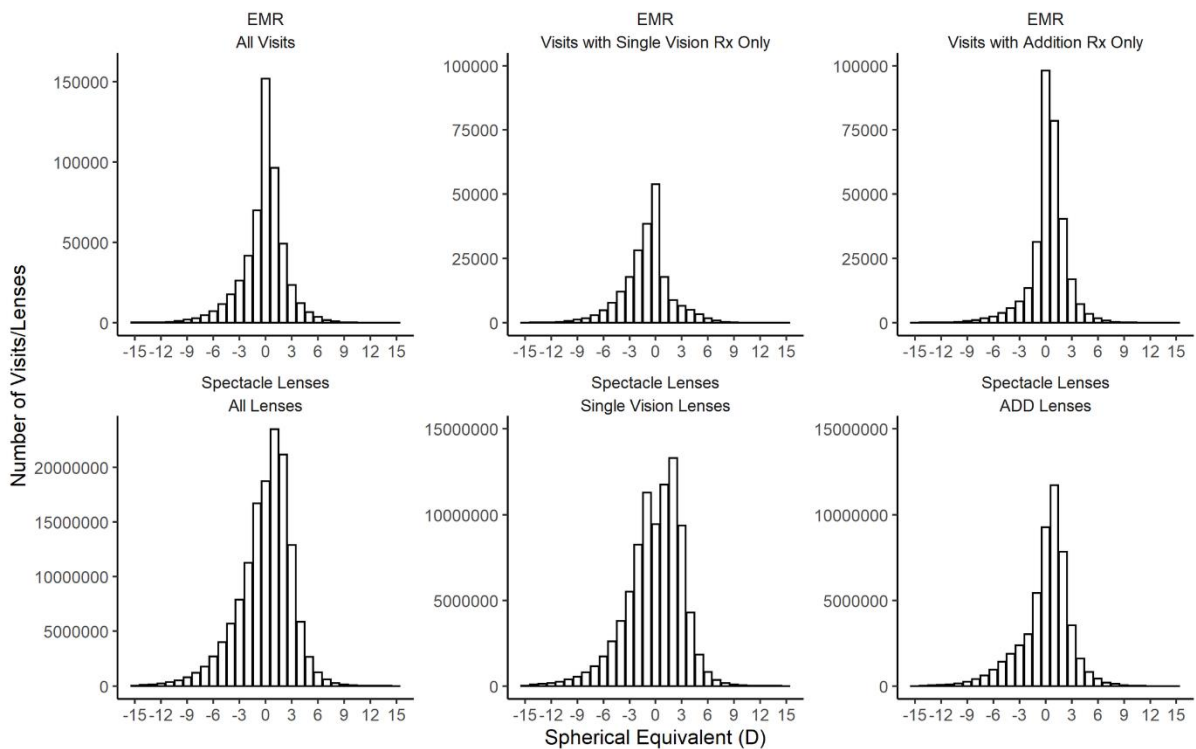


Figure 7.2: Distribution of spherical equivalent in each dataset

Top Panel - EMR from Irish optometry practices right spherical equivalent distribution for all visits ($n = 536,249$), single vision prescriptions ($n = 215,207$) and addition prescriptions ($n = 321,013$).

Bottom Panel - Spectacle Lens Distribution from manufacturer data for all lenses ($n = 134,280,063$), single vision, (SV) lenses ($n = 84,561,994$) and addition, (ADD) lenses ($n = 49,709,191$).

Table 7.1: Mean, range and distribution characteristics of spectacle lens and optometric electronic medical record (EMR) data.

Dataset	Mean SER (D) \pm SD	Skew	Kurtosis
All Spectacle Lenses	+0.02 \pm 3.08	-0.80	1.73
SV Lenses	-0.03 \pm 3.22	-0.74	1.47
ADD Lenses	+0.11 \pm 2.84	-0.89	2.20
All EMR Visits	-0.13 \pm 2.50	-0.74	3.19
Visits with SV Rx	-0.91 \pm 2.74	-0.30	2.09
Visits with Add Rx	+0.39 \pm 2.17	-1.09	5.82

All distributions demonstrate the classic negatively skewed leptokurtotic curve found in most studies of refractive error, with the majority of observations centred close to emmetropia. The only

exception to this pattern was the SV spectacle lenses which were found to have a bimodal distribution with a significant notch apparent at zero spherical equivalent.

7.5.2 Estimating Age Using Reading Addition:

Figure 7.3 shows the relationship between age and the presence of an addition by comparing the EMR distribution of SER for single vision prescriptions with those aged under 45 and the SER distribution of prescriptions with an addition and those aged 45 and over. It can be seen that the distribution of SER for those under age 45 (left panel, histogram bars) is very similar to the distribution of those prescribed a SV lens (left panel, dashed line), while the distribution of SER for those over age 45 (right panel, histogram bars) is very similar to the distribution of those prescribed an ADD lens (right panel, dashed line). The remarkable degree of similarity between being under age 45 and being prescribed single vision ($\chi^2 = 552$, $p = 0.2365$, DoF = 529) and being 45 years or older and being prescribed an addition ($\chi^2 = 899$, $p = 0.2408$, DoF = 870) indicates that age and the prescribing of an addition are highly correlated. Table 7.2 shows the relationship between age and the likelihood of prescribing a reading addition in the form of a contingency table. A summary of the distributions and their statistical relationship is given in Table 7.3.

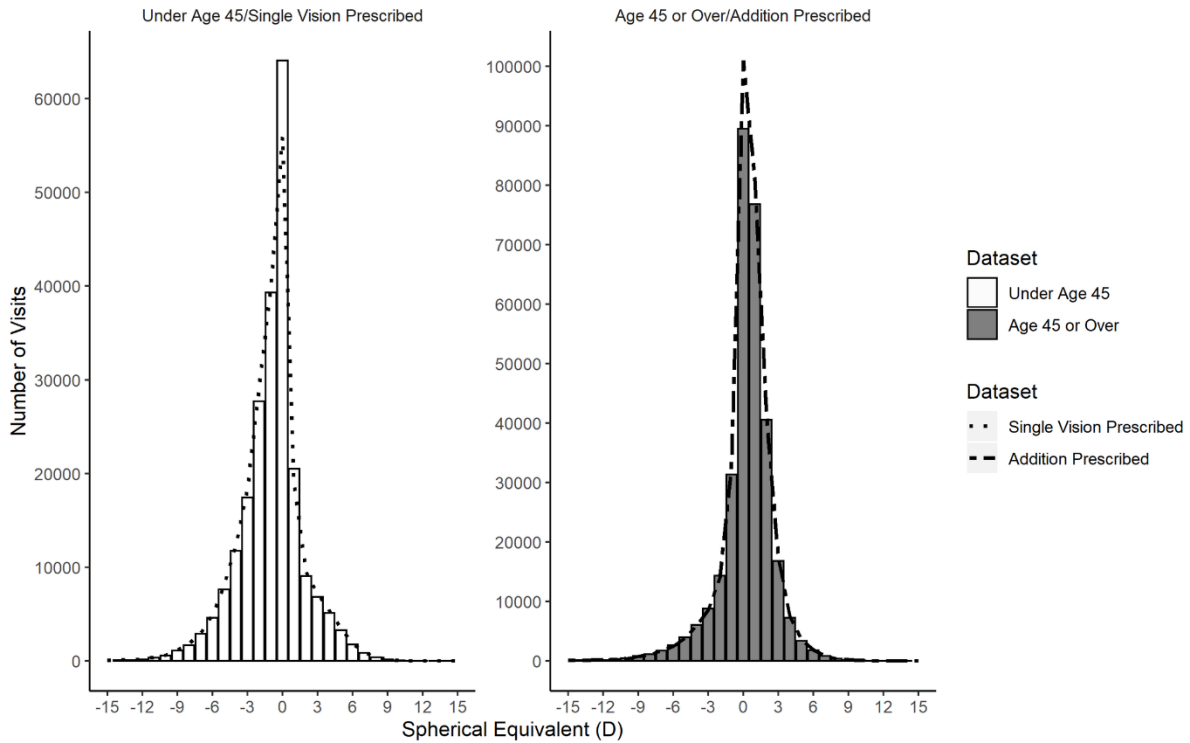


Figure 7.3: Age and the prescribing of an addition are highly correlated

Distribution of spherical equivalent for those under age 45 (left panel bars) and those age 45 and over (right panel bars). The dotted line represents the distribution of spherical equivalent for those given a single vision prescription (left panel) and those given a prescription containing an addition (right panel).

Table 7.2: Contingency table comparing the frequency of addition prescribing for patients under age 45 and those age 45 and over.

	No Addition Prescribed	Addition Prescribed
Under 45	204,027	24,512
Age 45 or Over	13,515	298,807

Table 7.3: Descriptive statistics comparing single vision optometric electronic medical record (EMR) prescriptions to younger patients and addition EMR prescriptions to older patients.

Dataset	Mean SE (D)	Skew	Kurtosis	Chi-Square Test
Single Vision	-0.91 ± 2.74	-0.30	2.09	$\chi^2 = 552, p = 0.2365, \text{DoF} = 529$
Under Age 45	-0.80 ± 2.66	-0.30	2.26	
Addition	$+0.39 \pm 2.17$	-1.09	5.82	$\chi^2 = 899, p = 0.2408, \text{DoF} = 870$
Over Age 45	$+0.36 \pm 2.25$	-1.16	5.58	

The relationship between age and the power of the addition given in glasses for the EMR data is shown in Figure 7.4. This relationship could be accurately fitted to a logistic function with nonlinear regression (estimate = 2.2 D, t = 818.94, p < 0.001). The residual standard error found was 7.56 years.

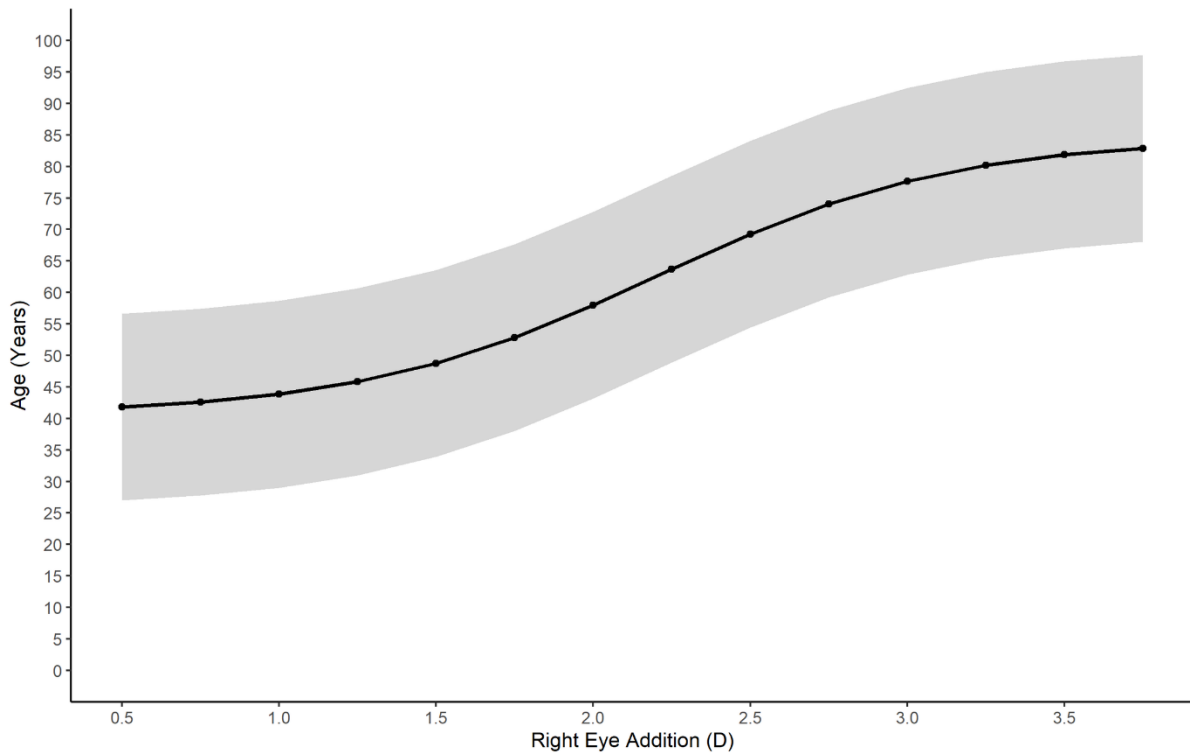


Figure 7.4: Predicted age based on the prescribed reading addition with 95% prediction intervals

Figure 7.4 also shows the 95% prediction limits for estimating age if only the add is known, as is the case with lens dispensing data. A logistic function was also fitted to the relationship between the probability of being prescribed a reading addition and age (estimate = 42.29 years, t = 653.73, p < 0.001). The residual standard error was 1.73%. This allows estimation of the proportion of individuals at each age likely to require a reading addition (Figure 7.5). These relationships were then used to infer ages for the ADD lens data. This allowed the generation of sub-populations of a given age for comparison with the EMR, E3 and GHS data. Using these two functions to determine age

ranges and by generating probability density functions for each value of reading addition in the EMR data, the level of myopia, hyperopia and astigmatism was calculated for age groups from ≥ 45 years to ≤ 80 years for the ADD lens data.

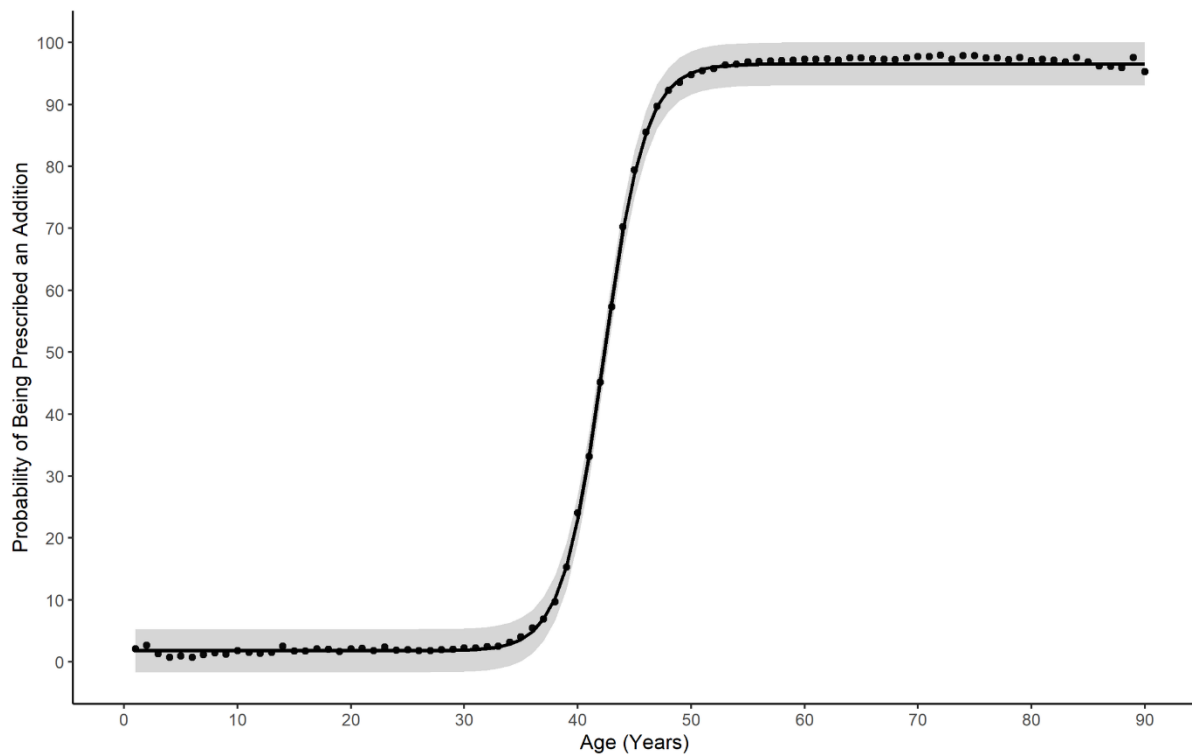


Figure 7.5: Likelihood of needing a reading addition at different ages with 95% prediction intervals

7.5.3 Comparison with E3:

The distributions of spherical equivalent refraction in the E3 study and the age matched EMR data were closely matched ($\chi^2 = 527$, $p = 0.29$, DoF = 510) with both being negatively skewed leptokurtotic distributions (Figure 7.6).

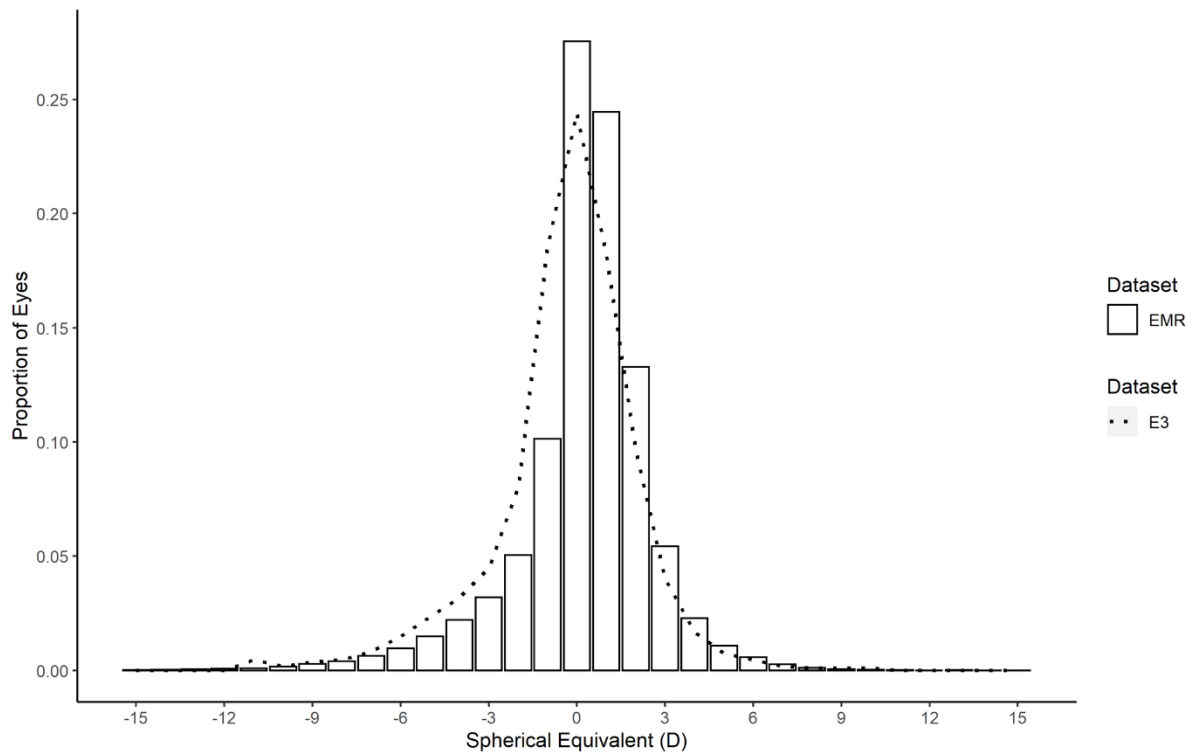


Figure 7.6: Comparison of spherical equivalent distribution between E3 and EMR. E3 distribution of refractive error spherical equivalent (dotted line) compared to the gender and age matched EMR distribution of right eye refractive error spherical equivalent (bars).

Age-matched comparison of the level of myopia, hyperopia and astigmatism for EMR relative to E3 data revealed broadly similar distributions across the refractive error types, albeit that the distribution of myopia was lower and hyperopia higher in the EMR data relative to the E3 data (Table 7.4). The ADD lens data distributions of myopia, hyperopia and astigmatism were all higher but also similar to the age matched E3 data (Table 8.5).

Table 7.4: Age matched comparison of refractive error rates between the E3 consortium and optometric electronic medical record (EMR) data (mean age = 60.16 ± 12.23 years)

Data Set	All Myopia ≤ -0.75	Low Myopia ≤ -0.75 to > -3.00	Moderate Myopia ≤ -3.00 to > -6.00	High Myopia ≤ -6.00	All Hyperopia ≥ +1.00	High Hyperopia ≥ +3.00	Emmetropia > -0.75 to < +1.00	Astigmatism ≥ 1.00
E3 (n = 62,393)	30.60%	19.50%	8.08%	2.71%	25.23%	5.37%	44.17%	23.86%
EMR (n = 200,076)	21.52%	13.56%	5.70%	2.26%	37.89%	7.38%	40.59%	28.38%

Table 7.5: Age matched comparison of refractive error rates between the E3 consortium and spectacle lenses with an addition (ADD) lens data (mean age = 62.55 ± 8.59 years)

Data Set	All Myopia ≤ -0.75	Low Myopia ≤ -0.75 to > -3.00	Moderate Myopia ≤ -3.00 to > -6.00	High Myopia ≤ -6.00	All Hyperopia ≥ +1.00	High Hyperopia ≥ +3.00	Emmetropia > -0.75 to < +1.00	Astigmatism ≥ 1.00
E3 (n = 50,010)	22.44%	14.08%	6.24%	1.93%	37.23%	7.98%	40.33%	26.96%
ADD Lenses (n = 35,720,655)	28.60%	15.12%	9.52%	3.95%	43.02%	9.98%	28.38%	31.45%

The E3 reported levels of myopia, hyperopia and high myopia across various age groups were compared to the EMR, ADD lenses and GHS data across the same age groups (Figure 7.7 – 7.9). These figures show the EMR data is the closest match to the E3 data. Confidence intervals for the EMR data were found to be overlapping with the confidence intervals for E3 data at 7 age points for myopic refractions (Figure 7.7), 6 age points for hyperopic refractions (Figure 7.8) and 12 age points for highly myopic refractions (Figure 7.9). The ADD lens data, however, provides a closer approximation to the E3 data for total myopia compared to the GHS data, particularly up to age 64 (Figure 7.7).

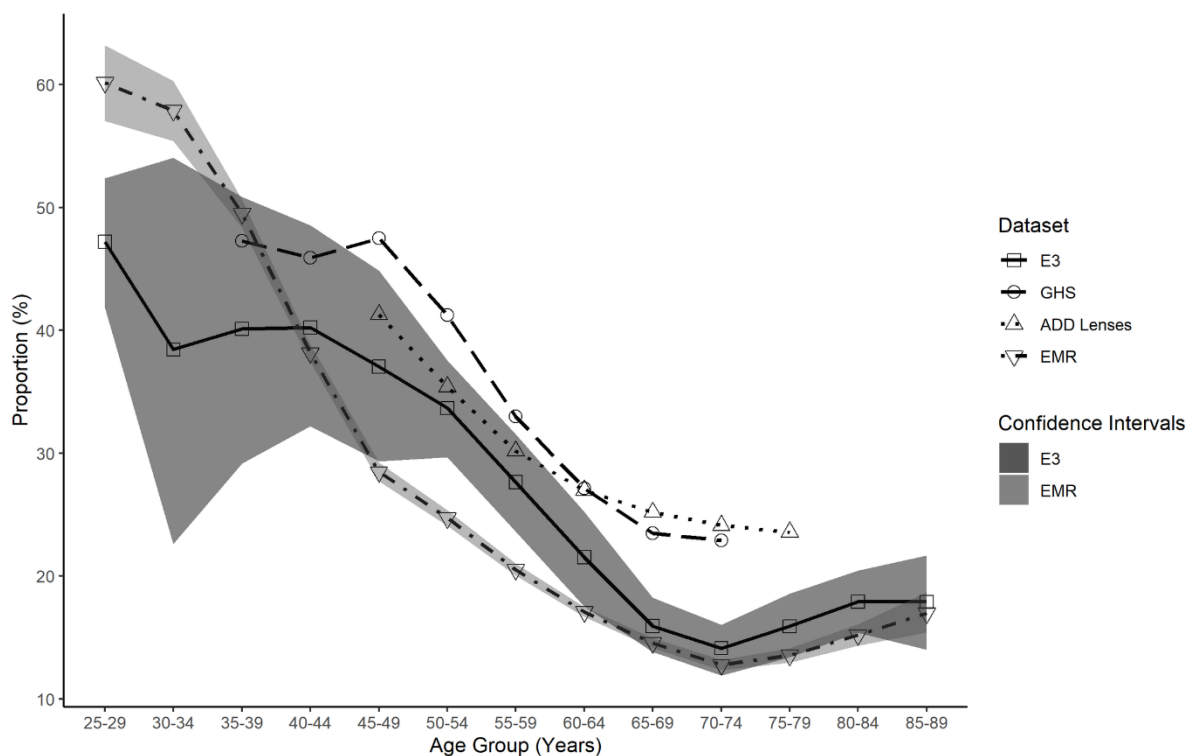


Figure 7.7: Total myopia proportion for EMR (inverted triangle), ADD Lenses (triangle), GHS (circle) and E3 (square) data as a function of age group. The E3 data confidence intervals (dark shaded area) are plotted to illustrate comparison with the other data sets. The EMR data confidence intervals (light shaded area) are plotted to show the overlap with the E3 data.

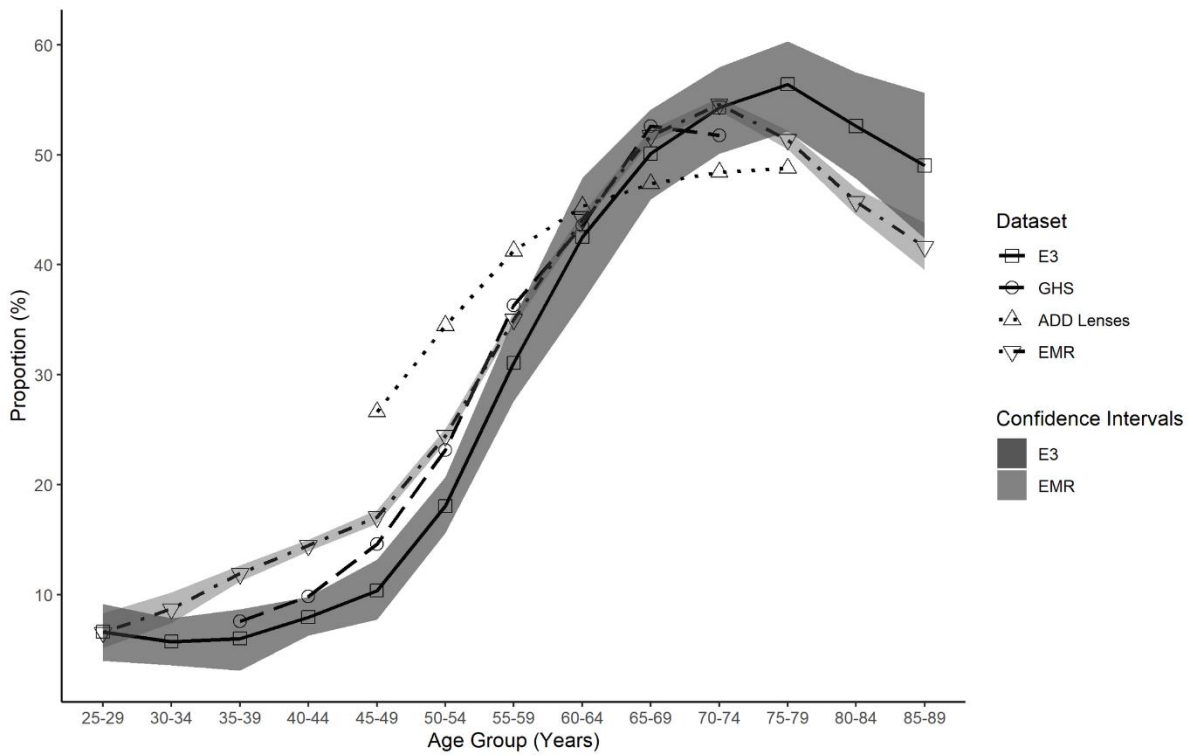


Figure 7.8: Total hyperopia proportion for EMR (inverted triangle), ADD Lenses (triangle), GHS (circle) and E3 (square) data as a function of age group. The E3 data confidence intervals (dark shaded area) are plotted to illustrate comparison with the other data sets. The EMR data confidence intervals (light shaded area) are plotted to show the overlap with the E3 data.

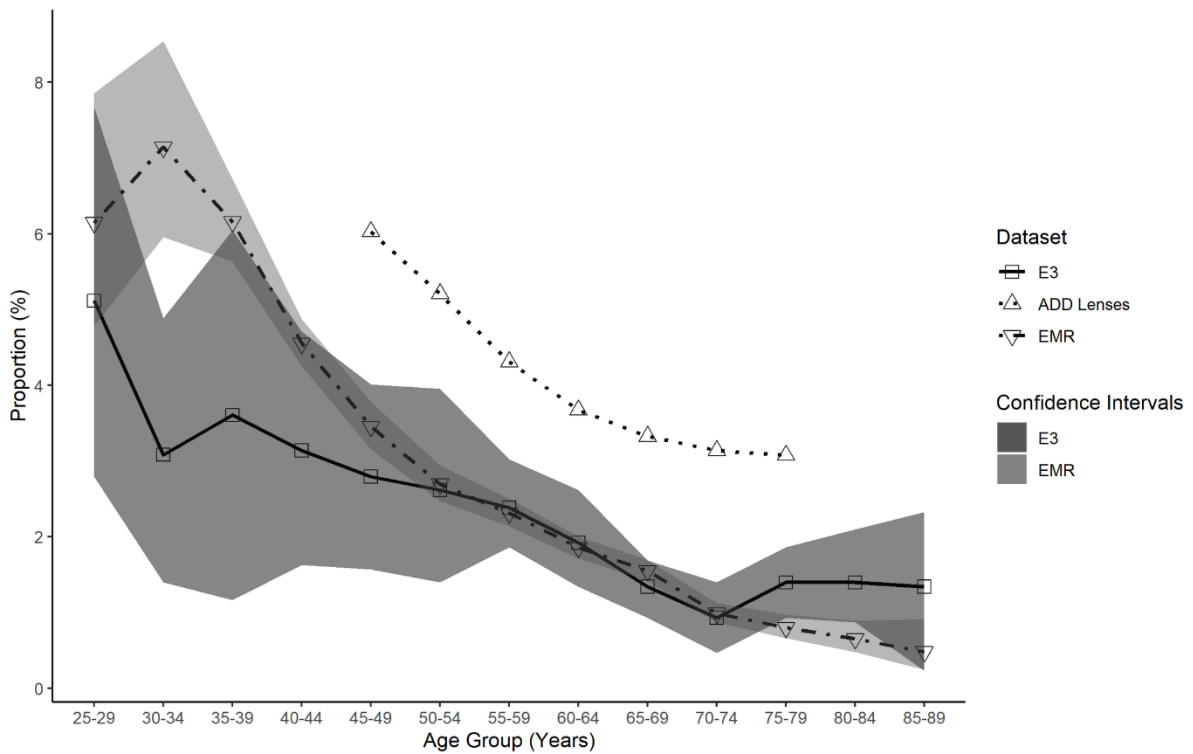


Figure 7.9: Total high myopia proportion for EMR (inverted triangle), ADD Lenses (triangle) and E3 (square) data as a function of age group. The E3 data confidence intervals (dark shaded area) are plotted to illustrate comparison with the other data sets. The EMR data confidence intervals (light shaded area) are plotted to show the overlap with the E3 data. GHS not present as high myopia data was unavailable.

7.6 Discussion:

Our results indicate that EMR data provides a close approximation to refractive error prevalence values found as part of the E3 study. Age related variation in the proportions of myopes and hyperopes are similar across the EMR and E3 data. Although the EMR data falls outside the E3 confidence intervals at some points in both comparisons, this is also true of the GHS data which was a component study of the E3 dataset, with the EMR data providing a closer match to the E3 than the GHS data. As the confidence intervals indicate the likely position of the mean of the study population some fluctuation is expected when comparing different study populations.

It was possible to estimate the likely recipient age for every spectacle lens prescription containing a reading addition by using the EMR data. This was achieved based on the observation that a

significant majority of EMR patient visits below the age of 40 years were not prescribed an addition while the majority of patients visits above the age of 50 years were prescribed an addition. Along with the presence of an addition, the power of the reading addition was also found to provide a means of estimating a patient's age. These inferences allowed an estimated age to be associated with each spectacle lens containing an addition within the spectacle lens sales dataset. The combination of disparate data sources to provide greater insight is a hallmark of Big Data analysis,³⁰⁵ and in this case allowed a deeper understanding of the usefulness of the spectacle lens sales data as a source of epidemiological data of refractive error.

Having accurate and current information on the prevalence of refractive error is vital to allow health services to plan for the increasing need for optical correction and the increased burden due to the ocular comorbidities^{273,276,280,421,431} associated with increasing refractive error. Myopia is of particular concern as it is estimated that up to 49.8% of the global population will be myopic by 2050 and 9.8% of those will be highly myopic.³ The combination of high myopia and increasing age have been found to be a risk factor for vision impairment and blindness.²⁹⁴ A recent meta-analysis found a significantly increased risk of myopic macular degeneration and retinal detachment in high myopes with reduced visual acuity and worse treatment outcomes in eyes with these conditions.¹¹⁴ Assessing any change to the prevalence of high myopia within a population is the area of most concern when considering the ocular comorbidities associated with refractive error. EMR data contains refractive error information and patient demographics including age, which can help to determine the population risk of vision impairment. The EMR data provides a good match to the E3 study for high myopia (Figure 7.9) and as such may be an invaluable method to determine the ongoing risk of vision impairment.

While conventional epidemiological studies remain the gold standard, they have some disadvantages. The most reliable studies have large sample sizes allowing their results to be generalized to the entire population. Such sample sizes require significant investment and time to

conduct the study, which perhaps explains the relative lack of epidemiological studies of refractive error and significant lack of longitudinal studies of refractive error. This paucity of data also contributes to uncertainty with regards to future projections of myopia prevalence.³ Where such data is not available, EMR or industrial data may have a useful role as these are increasingly being collected as a matter of routine and can be collected with greater ease and at more regular intervals.

It is important to acknowledge that all epidemiological studies suffer from various forms of bias. For example, it is well established that most cross sectional studies suffer from volunteer bias, with volunteers usually from higher socio-economic backgrounds with a higher level of education.⁴³²

Longitudinal studies frequently suffer from loss to follow up which may induce a bias in the profile of the remaining study population. It is important, therefore, when designing an epidemiological survey of refractive error to attempt to minimise these biases. Big data studies on refractive error will not suffer with the same biases as the data was not collected for the purpose of determining the population burden of refractive error. This type of epidemiological study will however, have a different set of biases which need to be considered. A frequent criticism of the secondary use of EMR data concerns the lack of access to healthcare of some population cohorts⁴³³ due to a lack of health insurance. As this EMR data has come from a jurisdiction with free access to eyecare which is widely availed of, this should not create a significant bias in our data,^{434,435} although it should be acknowledged some population cohorts do not access healthcare readily, even when provided free of charge, for a myriad of reasons. Results from the UK indicating very high usage of refractive services imply these individuals are likely to represent a very small cohort.⁴³⁶ Less frequent replacement of spectacle lenses from those of lower socio-economic backgrounds may present a more significant issue with regards to the spectacle lens dispensing data and is a very significant limitation in countries where poor access to spectacles is a leading cause of vision impairment.²⁵⁶ Measurement error can exist as a bias in any epidemiological study but may be well controlled in small studies through standardization of equipment and procedures. In a Big Data study of this

nature, this is not possible. Nevertheless, error rates of subjective refraction in adults are typically low at between 1% and 2%, indicating the vast majority of refractions should be accurate to within \pm 0.50 D of the correct refraction.^{437,438}

It should be acknowledged that both EMR and spectacle lens datasets are likely to only be available in countries with good access to eyecare and as such this methodology will have a much more limited application in countries with poor access to refractive services. In those countries with good access to refractive services, for this data to be representative, there needs to be a high level of use of these services. There are no published usage rates for refractive services in Ireland however a 2013 survey from the UK, Ireland's nearest neighbour, indicates very high use of refractive services with 74% of the population using a refractive correction and greater than 96% of the population over the age of 50 using a refractive correction.⁴³⁶

There are several limitations to this study that must be considered. In relation to spectacle lens data, demographic information of the individuals purchasing the spectacle lenses is not typically available in industrial datasets. Geographic information is likely to be available, however, which can provide some useful information. Using the EMR data to infer the age of a cohort of the spectacle lens users enhances the usefulness of this data, but the overall lack of demographic information means that further conclusions on subpopulations cannot be drawn. In this study, the spectacle lens data was supplied by one manufacturer. Economic factors and market penetration may have an effect on the background of the consumer choosing lenses from this manufacturer. Industrial data could be biased, for example, to particular socio-economic, ethnic or other demographic subgroups for reasons such as product cost, geographic location and other factors specific to individual manufacturers. Higher educational attainment is associated with both socio-economic status and myopia,³⁸ for example, so the possibility that the oversampling of individuals from particular backgrounds within individual datasets might influence population estimates of refractive error needs to be considered.

Under sampling of emmetropic patients is a more significant issue for the spectacle lens data as these represent spectacle lens sales. This will tend to produce an apparent increased proportion of hyperopic and myopic refractive errors, especially for younger subjects, as observed in this study. It is unlikely that emmetropic patients are purchasing spectacle lenses in significant numbers. This is particularly evident when considering the SV lenses in Figure 7.3. The notch apparent at zero dioptic power represents the reduction in purchasing of spectacle lenses by this group. It might be expected that the number of zero power lenses would be smaller than was observed, but there are plausible reasons to explain this. In cases of anisometropia one eye may have a zero-power lens when the fellow eye needs correction. In addition, the computation of spherical equivalent may result in zero spherical equivalent power for lenses prescribed to patients with mixed astigmatism. The lack of emmetropes represented within the spectacle lens sales data presents a problem and may explain the poorer match to the E3 study relative to EMR data. This implies that such data may be more representative of the distribution of refractive error within a population above a certain threshold of refractive error. The greatest risk of uncorrectable visual impairment due to refractive error are associated with high levels of myopia,¹¹⁴ and also high levels of hyperopia.⁴²¹ These are both categories likely to seek optical correction due to the significant symptoms associated with each, particularly in countries with easy access to free eyecare such as Ireland. Further analysis and modelling may remove the limitation associated with the under sampling of emmetropes and allow the determination of the risk of vision impairment in those using spectacle lenses to correct higher refractive errors (Chapter 8).

There are fewer limitations applicable to the EMR data due to the increased demographic detail captured in this data. Under sampling of emmetropic patients is likely to be less problematic for the EMR data which includes refraction data found as part of a patient's eye examination. Emmetropic patients are still likely to attend routine eye examinations for the purposes of screening for common ocular pathologies such as glaucoma and cataract.⁴³⁹ Importantly, EMR data is likely to be highly

representative of the older population given the almost universal need for optical correction as presbyopia begins to manifest as a problem, even for emmetropes and low hyperopes who did not previously need correction. This is particularly the case in most countries in Europe where subsidised eye examinations are accessible to the majority of the population.²⁵⁷ The close match of the EMR and E3 data observed herein suggests that the EMR is representative of the population at large. The results indicate that the EMR and E3 data are a close match but the underlying assumption that a European meta-analysis of refractive error is the best comparator to an Irish population is not necessarily true. The most ideal comparator would be an Irish population survey of refractive error; however, none exist. As the E3 study is the largest such study in Europe and the results are similar to other surveys of refractive error of populations similar to Ireland in Western Europe,^{14,154,159} this is the best currently available data with which to draw a comparison.

In this EMR dataset, it was not possible to tell what type of refraction had been performed to reach the refractive error prescribed. Cycloplegic refraction is performed to avoid the errors in refraction that can be induced by accommodation in children and the use of cycloplegia is considered the most appropriate method to assess refractive error for research purposes.¹⁶⁹ Although it is unknown how many of these refractions have been performed with the aid of cycloplegia, a significant number of epidemiological surveys on refractive error have been carried out without the use of cycloplegia.⁴²² It has been found that accommodation mostly affects the determination of refractive error in children and has little impact on adults^{164,165}, particularly older adults.¹⁶⁶ The technique of refraction used, therefore, should have little impact on the primarily adult dataset used herein.

7.7 Conclusion:

The prevalence of refractive error within a population can be estimated using EMR data in the absence of population surveys in countries with high levels of access to refractive services. Results from EMR data also allow age to be inferred from the addition in a spectacle lens. Industry derived

sales can then be used to provide insights on the epidemiology of refractive errors in a population over certain age ranges. EMR and industrial data may therefore provide a fast and cost-effective surrogate measure of refractive error distribution that can be used for future health service planning purposes in countries with good access to optometric and spectacle dispensing services.

8 The Refractive Error and Vision Impairment

Estimation With Spectacle data (REVIEWS) study

8.1 Title Page:

Title: The Refractive Error and Vision Impairment Estimation With Spectacle data (REVIEWS) study

Authors:

Corresponding Author: Michael Moore MSc BSc¹

James Loughman PhD BSc¹

John S. Butler PhD MSc^{1,2}

Arne Ohlendorf PhD^{3,4}

Siegfried Wahl PhD^{3,4}

Daniel I. Flitcroft DPhil MB^{1,5}

¹Centre for Eye Research Ireland, School of Physics and Clinical and Optometric Sciences,
Technological University Dublin, Dublin, Ireland

²School of Mathematical Sciences, Technological University Dublin, Dublin, Ireland

³Technology & Innovation, Carl Zeiss Vision International GmbH, Turnstrasse 27, 73430 Aalen, Germany

⁴Institute for Ophthalmic Research, Center for Ophthalmology, Eberhard Karls University of Tübingen, Elfriede-Aulhorn-Straße 7, 72076 Tübingen, Germany

⁵Children's University Hospital, Dublin, Ireland

Financial Support: None

Conflict of Interest: Arne Ohlendorf and Siegfried Wahl are employees of Carl Zeiss Vision International GmbH

Running Head: The REVIEWS study

8.2 Abstract

Objective:

To investigate whether spectacle lens sales data can be used to estimate the population distribution of refractive error amongst ametropes and hence estimate the current and future risk of vision impairment.

Design:

Cross Sectional Study

Subjects:

A total 141,547,436 spectacle lens sales records from an international European lens manufacturer between the years 1998 and 2016.

Methods:

Anonymized patient spectacle lens sales data including refractive error information was provided by a major European spectacle lens manufacturer. Data from the Gutenberg Health Survey was digitized to allow comparison of a representative, population-based sample to the spectacle lens sales data. A bootstrap analysis was completed to assess the comparability of both datasets. The expected level of vision impairment due to myopia at age 75 was calculated for both datasets using a previously published risk estimation equation combined with a saturation function.

Main Outcome Measures:

Comparability of spectacle lens sales data on refractive error to typical population surveys of refractive error and its potential utility to predict vision impairment due to refractive error.

Results:

Equivalent estimates of the population distribution of spherical equivalent refraction can be provided from spectacle lens data within limits. For myopia, the population distribution was equivalent to the Gutenberg Health Survey ($\leq 5\%$ deviation) for levels ≤ -2.0 dioptres, while for

hyperopia the distribution was equivalent ($\leq 5\%$ deviation) for levels $\geq +3.0$ diopters. The estimated rates of vision impairment due to myopia were not statistically significantly different ($\chi^2 = 182$, DoF = 169, $p = 0.234$) between the spectacle lens data and Gutenberg Health Survey data.

Conclusions:

The distribution of refractive error and hence the risk of vision impairment due to refractive error within a population can be determined using spectacle lens sales data. Pooling this type of data from multiple industry sources could provide a cost effective, timely and globally representative mechanism for monitoring the evolving epidemiology of refractive error and associated vision impairment.

8.3 Introduction

Vision impairment is a huge challenge internationally which is projected to worsen as a consequence of global population aging unless significant effort is made to address the many underlying causes.

Refractive error has been identified as a risk factor for the development of numerous ocular pathologies which can lead to vision impairment. Significant refractive errors, both myopic and hyperopic, are known to be amblyogenic in children.⁴⁴⁰ Higher degrees of hyperopia is a risk factor for the development of age-related macular degeneration (AMD),⁴²¹ while higher levels of myopia are known to increase the risk of glaucoma,⁴⁴¹ cataract,⁴⁴² retinal detachment⁴⁴³ and myopic maculopathy.²⁷²

The individual and societal cost of vision impairment is substantial. Societal costs can be measured by the loss of productivity²⁵⁴ and the need to provide adequate medical care and support to those affected by vision impairment.⁴⁴⁴ Those with vision impairment are more likely to require support in day to day living, suffer from falls and have health or emotional problems interfere with their life.^{245,444} Quality of life is also significantly affected, with vision impairment having a similar impact as stroke, heart attack and diabetes,⁴⁴⁵ and even mild vision impairment associated with reduced quality of life.⁴⁴⁶

Refractive error typically develops in childhood.²⁹ The association between refractive error and vision impairment, however, does not become apparent for many decades and is a function of refractive error type and magnitude as well as increasing age.^{285,294,295} Myopia is the refractive error that is of most concern. It has been demonstrated that there is an increased lifetime risk of vision impairment with all levels of myopia, but particularly at higher levels.²⁹⁴ A recent meta-analysis indicated that one in three high myopes are at risk of bilateral vision impairment within their lifetime and that even low to moderate myopes are at significantly increased risk of ocular disease and disability.¹¹⁴ There is an increasing amount of evidence that the prevalence of myopia within the population has increased over the last number of decades. The most significant increases have been

observed in Asian populations⁴²² with some countries seeing over 90% of children become myopic by the late teenage years.^{153,447} Although ethnicity appears to play a role, there is evidence of increasing prevalence of myopia in many populations around the world.^{8,38,236,448}

It is important to have current and easily accessible refractive error epidemiological data in order to plan appropriate public health resource allocation to meet the need for correction of refractive error and treatment of any associated pathology, particularly in the context of a changing population burden of refractive error. Holden et al.'s landmark paper³ predicted that by 2050 almost 50% of the global population will be myopic, with nearly 10% of the population falling into the highly myopic category (using a threshold of -5 D). This is of great concern given the likelihood of increased levels of vision impairment due to both uncorrected refractive error and the ocular pathology associated with myopia. Holden et al.³ used existing epidemiological studies to make their predictions. They identified the lack of epidemiological data in "many countries and age groups, across representative geographic areas"³ as a significant limitation of their study, with predictions of high myopia prevalence particularly susceptible to the paucity of available evidence. The lack of epidemiological data is not surprising given the time and financial investment required to carry out these studies.

As the risk of vision loss associated with increasing refractive error is non-linear,^{114,294,295} it is not sufficient to merely establish the proportion of the population affected by myopia or hyperopia. It is necessary to determine the number of individuals affected by different levels of refractive error within a population to gain a true insight into the population risk of vision impairment due to refractive error.

Spectacle lens sales data represents a potential source of contemporary refractive error data which, if made accessible, could provide valuable insights into the changing epidemiology of refractive error and associated risks of vision impairment. The value and limitations of spectacle lens sales data as an epidemiological tool to determine refractive error distribution in a population has previously been described.³⁰⁹ Principally, the distribution of refractive error found in spectacle lens sales data does

not follow standard population distributions of refractive error as individuals with no refractive error do not typically purchase spectacles lenses, hence emmetropes and near-emmetropes are under-represented in such data. The symptomatic nature of higher levels of refractive error implies that the majority of the population affected are likely to use spectacles, particularly in high income countries where the visual demands associated with education and employment are high and where subsidised access to eyecare is available.²⁵⁷ Most studies of refractive error epidemiology report their distributions across the entire range of refractive error. By concentrating analysis on the myopic and hyperopic ends or tails of the distribution, rather than the central emmetropic range of the distribution it may be possible to use spectacle lens sales data as an epidemiological tool.

The aim of this paper, therefore, was to investigate whether spectacle lens sales data can be used to estimate the population distribution of refractive error amongst ametropes and hence estimate the current and future impact of refractive errors on the risk of vision impairment.

8.4 Methods

Anonymized patient spectacle lens sales data were provided by a major European spectacle lens manufacturer. This dataset (n=141,547,436) comprised lenses that had been manufactured and dispatched after an order was received from an eye care practitioner, with the majority (> 98%) of lenses for delivery within Europe. The data was collated into histogram data using the SQLite database engine (Hipp, Wyrick & Company, Inc., Charlotte, North Carolina, USA) and analyzed using the R statistical programming language (R Core Team (2021). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL <https://www.R-project.org/>). The Technological University Dublin Research Ethics Committee approved this study and which adhered to the tenets of the Declaration of Helsinki. The data provided included the spherical power, cylindrical power and axis of the spectacle prescription, lens design, diameter, laterality (prescribed for right or left eye) and date of manufacture. For lens designs with a addition,

this was also specified. The presence of an addition allowed the lenses to be separated into two groups, the single vision (SV) lens group and the addition (ADD) lens group. The data was validated for missing and malformed data fields and any lenses with incomplete or invalid data were excluded. The spherical equivalent power was calculated for each lens.

Data from the Gutenberg Health Study¹⁴ (GHS) study was extracted by digitizing the published results using Plot Digitiser (<http://plotdigitizer.sourceforge.net/>). The GHS was chosen as a comparison for several reasons. Firstly, the GHS took place in Mainz, Germany and the manufacturer database reflected almost exclusively European lens sales, with Germany the largest contributor (\approx 48%). Secondly, as the spectacle lens data comprised a substantial proportion of reading addition lenses typically used by older presbyopic adults⁴²⁹ (age \geq 40-45 typically),¹⁶³ the adult age profile of the GHS (age 35-74 years) was comparable.

Myopia and hyperopia were analyzed using the definitions given by the GHS i.e., a spherical equivalent (SE) refractive error of < -0.50 D being considered myopic and a SE refractive error of > 0.75 D being considered hyperopic. High myopia was defined as $SE \leq -6.00$ D. The International Myopia Institute recommends the adoption of an agreed standard for myopia of ≤ -0.50 D⁹³ so results using this criterion are also reported.

To determine confidence intervals of the estimates, a bootstrapping technique was used to generate 1,000 new distributions of refractive error from the SV and ADD lens data, with each new distribution comprising the same original sample size as the GHS ($n = 13,959$). Bootstrapping is a statistical technique which involves constructing many samples by randomly drawing sets of observations from a dataset.^{449,450} These multiple samples can then be used to calculate test statistics and confidence intervals.^{449,450} The new distributions were constructed using the 'infer' extension package for R. With this technique, the mean number of cases for each 1 D bin value of spherical equivalent was calculated along with 95% confidence intervals. This was repeated for both

the myopic and hyperopic tails of the distributions and the results were compared to the GHS distribution of refractive error.

In order to determine the range of refractive error values over which the bootstrap analysis should take place, the analysis was repeated with different spherical equivalent starting values, starting at 0 D spherical equivalent and changing in 1 D steps for both the myopic and hyperopic tails of the distribution. This allowed the deviance between the calculated 95% confidence intervals and the GHS distribution to be determined.

The final fitted bootstrapped distributions were generated which allowed comparison with the GHS. The proportion of each diopter value of myopia and hyperopia was calculated within the range that was found to match the GHS well. The odds ratio of vision impairment due to myopia at each diopter value of myopia was determined using equation 1 as described by Bullimore et al.²⁹⁶ and was modelled on published data and models that relate refractive error and age to vision impairment risk.^{294,295} Vision impairment was defined as 20/67 (0.3 decimal visual acuity equivalent) or worse, the same definition used by Bullimore et al.²⁹⁶ The odds ratio was converted into vision impairment risk percentage using equation 2. This allowed the expected level of vision impairment by age 75 for a sample of 100,000 SV spectacle lens users to be calculated. This was compared to the expected level of vision impairment at age 75 over the same range of myopia for participants in the GHS.

$$\mathbf{Vision\ Impairment\ Odds\ Ratio} = 1.26 \times 10^{(0.057 \times Age - 0.122 \times SE - 4.03)}$$

Equation 8.1: Vision Impairment Odds Ratio due to Myopia

$$\mathbf{Vision\ Impairment\ Risk} = \left(\frac{\mathbf{Odds\ Ratio}}{(1 - 1.26) + (1.26 + Odds\ Ratio)} \right) \times 1.26 \times 100$$

Equation 8.2: Vision Impairment Risk due to Myopia

8.5 Results

The spectacle lens dataset comprised 141.5 million lenses from the manufacturer sales records ranging from the year 1998 to 2016. Records with incomplete or missing data were excluded, and only years with complete data were included in the analysis. In total 134.3 million spectacle lenses were included, comprised of 84.6 million SV lenses and 49.7 million ADD lenses.

The distribution of refractive error for the SV, ADD lenses and the GHS are shown in Figure 8.1. All distributions demonstrate the classic negatively skewed leptokurtotic curve found in most studies of refractive error, with the majority of observations centred close to emmetropia. The only exception to this pattern was the SV spectacle lenses which were found to have a bimodal distribution with a significant notch apparent at zero spherical equivalent. Table 8.1 shows the proportion of myopia and hyperopia found in each dataset. The most significant difference observed was in the proportion of emmetropia present, with much lower levels in all spectacle lens datasets.

Repeating the bootstrapping technique for both the myopic and hyperopic tails of each distribution, it was found that the deviation between the actual occurrence of each 1 D value of spherical equivalent for the GHS and all of the spectacle lens data sets was greatest (over 50%) at 0 D spherical equivalent. The deviation reduced to 5% or less between -2 D and -15 D for the myopic end of the distributions and between +3 D and +15 D for the hyperopic end of the distributions (Figure 2).

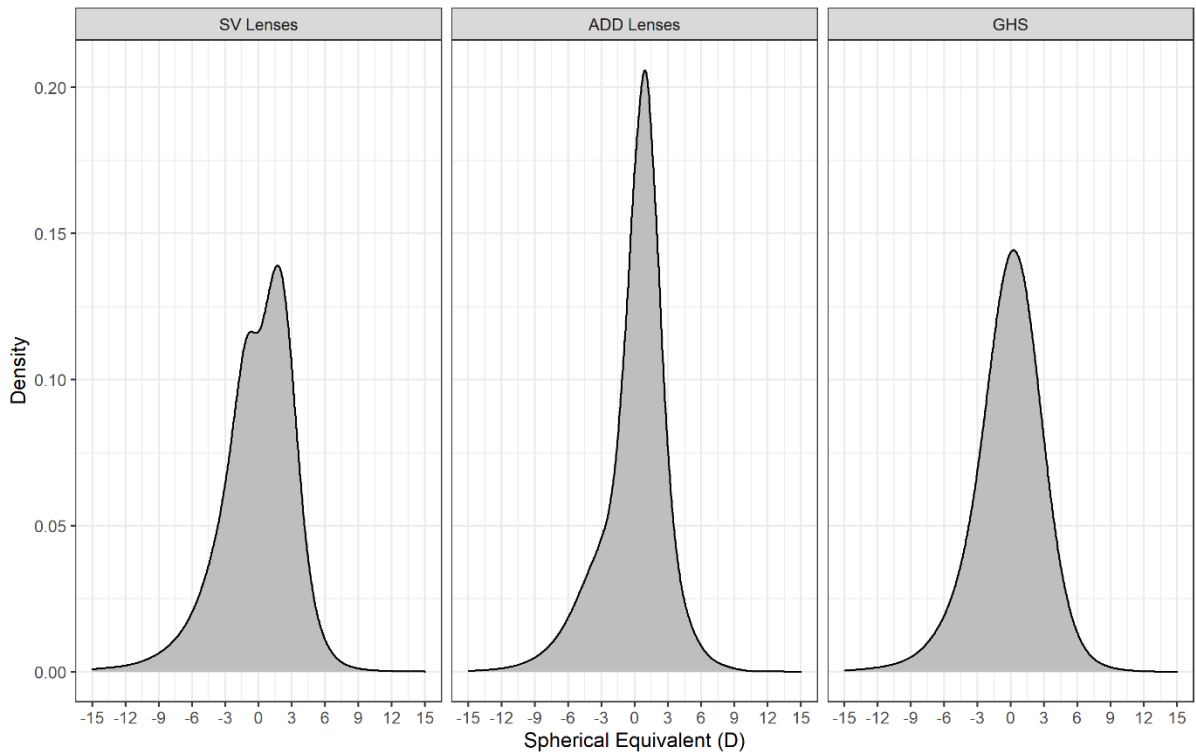


Figure 8.1: Spectacle Lens Distribution of refractive error from manufacturer data for single vision (SV) lenses ($n = 84,561,994$), addition (ADD) lenses ($n = 49,709,191$) and from the Gutenberg Health Survey ($n = 13,959$).

Table 8.1: Proportion of refractive error types in each dataset

	Total Emmetropia (SE ≥ -0.50 D and $\leq +0.75$ D)	Total Hyperopia (SE $> +0.75$ D)	Total Myopia (SE < -0.50 D)	Total Myopia (SE ≤ -0.50 D)	High Myopia (SE ≤ -6.00 D)
All Spectacle Lenses	19.1%	44.9%	36.0%	38.0%	4.8%
SV Lenses	15.5%	44.9%	39.6%	41.7%	5.3%
ADD Lenses	25.0%	45.1%	29.9%	31.9%	4.0%
GHS	35.1%	29.8%	35.1%	39.9%	3.5%

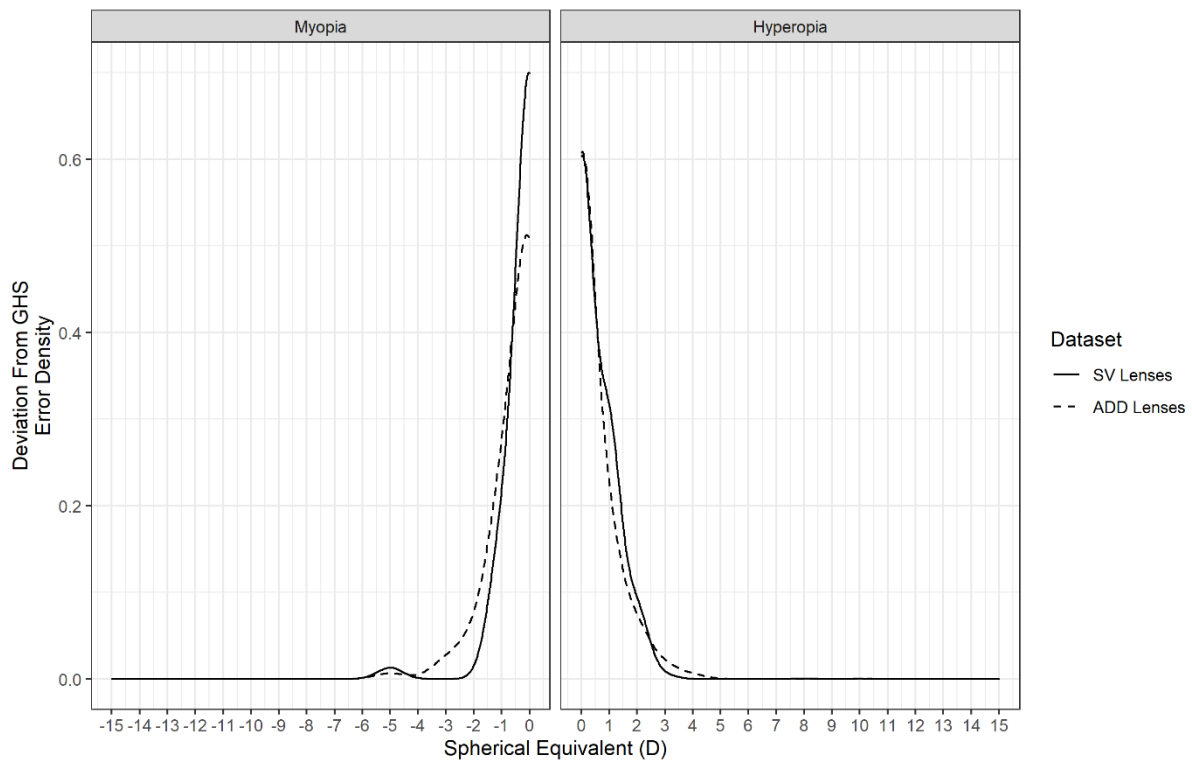


Figure 8.2: Deviation between bootstrapped confidence intervals and the observed occurrence of refractive error in the Gutenberg Health Survey. The deviation is greatest when starting at zero dioptres spherical equivalent and trends towards zero at higher absolute values of spherical equivalent.

Figures 8.3 and 8.4 show the mean number of lenses with 95% confidence intervals for each 1 D from all 1,000 generated distributions for the myopic and hyperopic tails of the SV lens distribution over the range of refractive error where the deviation was less than 5%. Figures 8.5 and 8.6 show the mean number of lenses with 95% confidence intervals for the myopic and hyperopic tails of the ADD lens distribution. These are compared with the GHS over the same range of refractive error. The GHS was found to be statistically indistinguishable from the 1,000 generated distributions as it mostly sat within the 95% confidence intervals.

As the tails of the spectacle lens distributions were found to match the GHS between -2 D to -15D and +3 D to +15D, it was possible to determine the estimated risk of vision impairment at age 75 among myopic SV spectacle lens wearers (Table 8.2). Using the spectacle lens data, it was estimated that 8.18% of myopic spectacle lens wearers ($n = 8,179$ cases per 100,000 population) will be visually

impaired by age 75. Over the same range of myopia in the GHS, 7.72% of myopic individuals (n = 7,720 cases per 100,000 population) were estimated to be vision impaired by age 75. The estimated rates of vision impairment were not statistically significantly different ($\chi^2 = 182$, DoF = 169, p = 0.234).

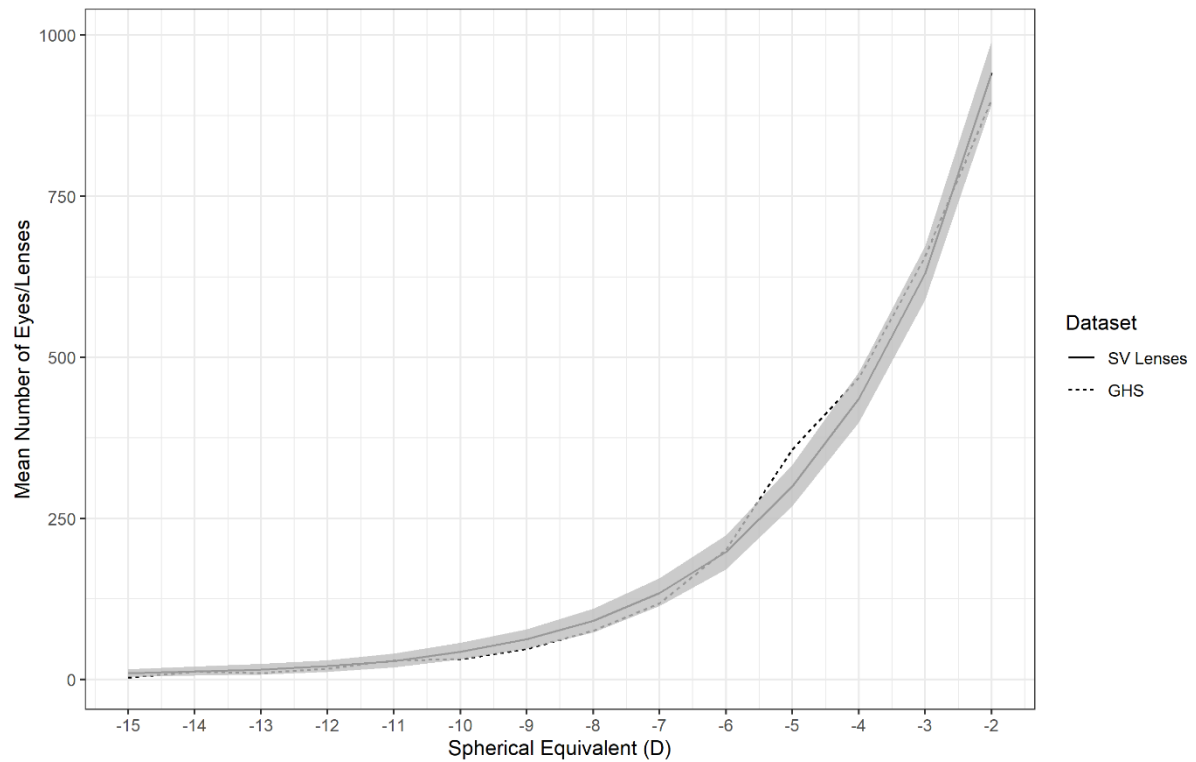


Figure 8.3: Bootstrapped myopic mean distribution with 95% confidence intervals for Single Vision lenses (solid line and shaded area) compared to the Gutenberg Health Survey (dotted line).

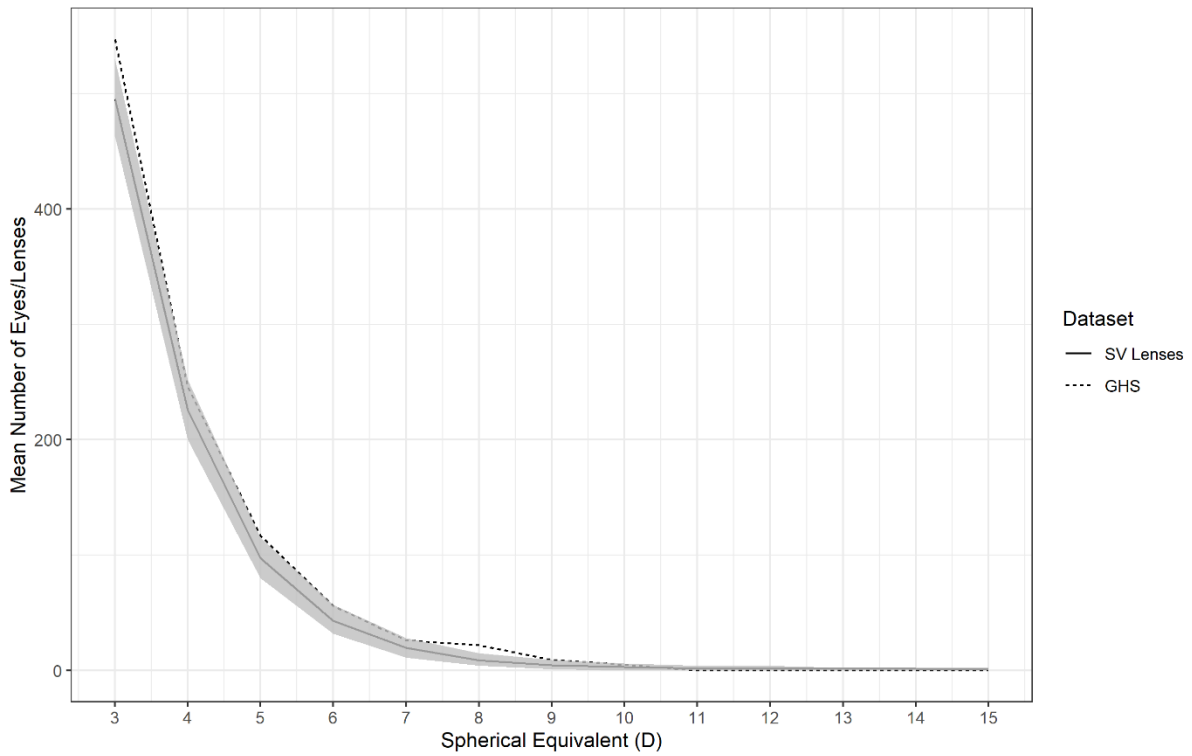


Figure 8.4: Bootstrapped hyperopic mean distribution with 95% confidence intervals for Single Vision lenses (solid line and shaded area) compared to the Gutenberg Health Survey (dotted line).

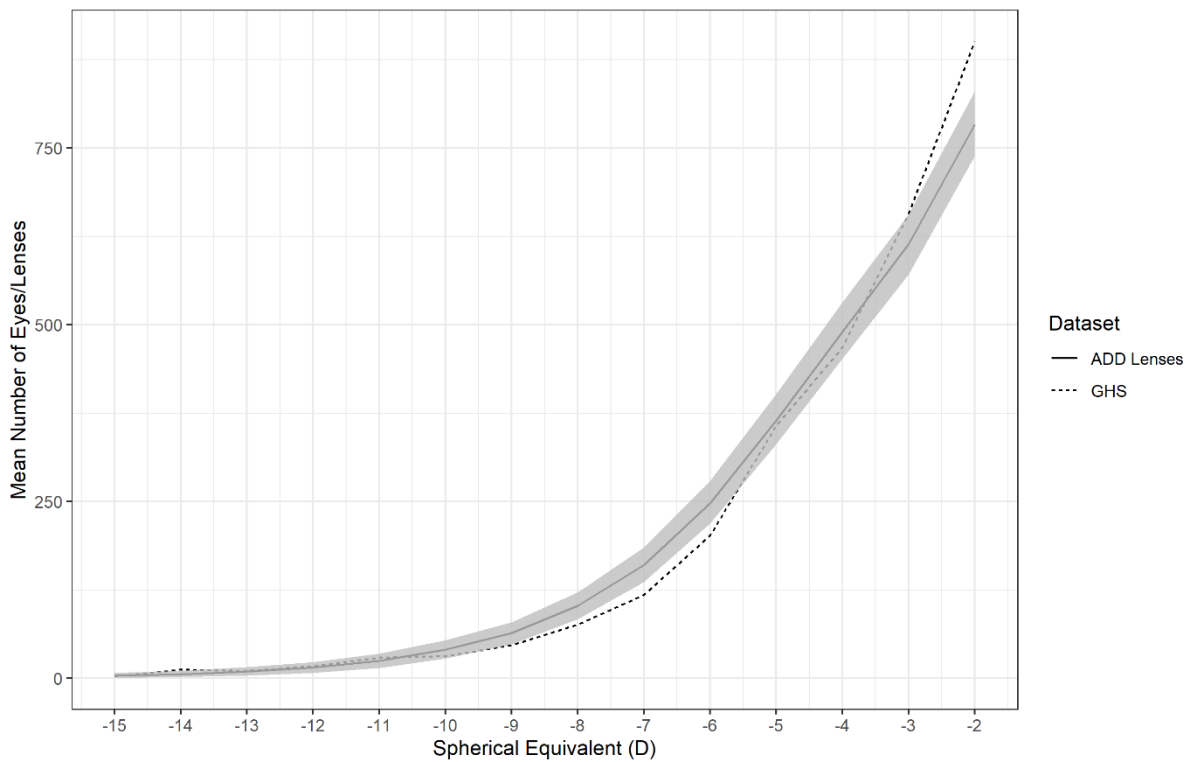


Figure 8.5: Bootstrapped myopic mean distribution with 95% confidence intervals for Addition lenses (solid line and shaded area) compared to the Gutenberg Health Survey (dotted line).

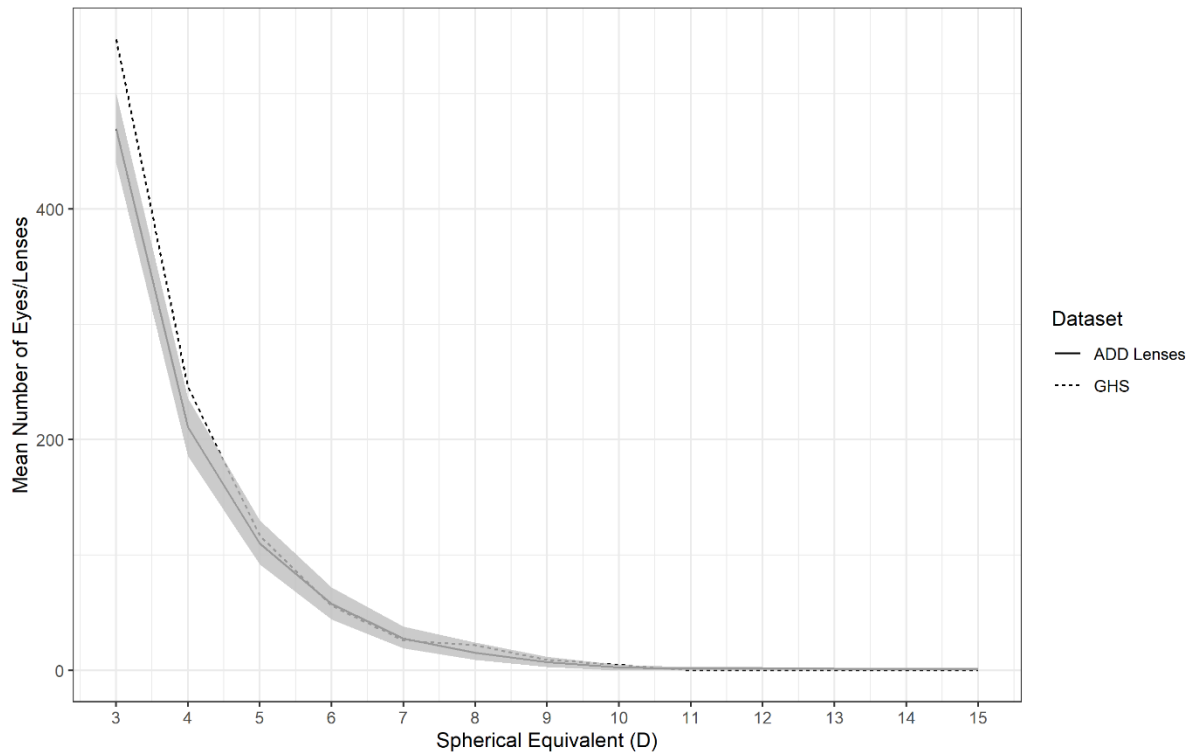


Figure 8.6: Bootstrapped hyperopic mean distribution with 95% confidence intervals for Addition lenses (solid line and shaded area) compared to the Gutenberg Health Survey (dotted line).

Table 8.2: Refractive distribution within the myopic tail of the SV spectacle lens data and the GHS data, estimated risk of vision impairment at age 75 from equation 1 and 2 and estimated number of individuals with vision impairment at age 75 per 100,000 people with myopia of -2 D or worse for both the SV lens group and GHS

Spherical Equivalent (D)	Proportion of myopia in SV lenses	Proportion of myopia in GHS	Risk of Vision Impairment at Age 75	Estimated number of cases of vision impairment due to myopia per 100,000 population at age 75 (spectacle lens data)	Estimated number of cases of vision impairment due to myopia per 100,000 population at age 75 (GHS data)
-2	0.322	0.307	4%	1,219	1,164
-3	0.215	0.224	5%	1,067	1,112
-4	0.149	0.160	6%	962	1,032
-5	0.102	0.122	8%	854	1,021
-6	0.068	0.069	11%	733	745
-7	0.046	0.040	14%	634	557
-8	0.031	0.026	18%	548	455
-9	0.022	0.016	22%	472	352
-10	0.015	0.011	27%	402	287
-11	0.010	0.010	33%	330	327
-12	0.007	0.006	40%	285	229
-13	0.005	0.003	46%	248	158
-14	0.004	0.004	53%	225	219
-15	0.003	0.001	60%	200	62
Total estimated vision impairment cases per 100,000 population at age 75 due to myopia \leq -2.00D				8,179	7,720

8.6 Discussion

This study describes a new method to estimate refractive error distribution. For spherical equivalent refractive errors exceeding +3 D for hyperopia and -2 D for myopia, spectacle lens sales data can provide equivalent estimates of the distribution of refractive error to those determined by conventional population surveys of refractive error. Furthermore, by accurately estimating the shape of the hyperopic and myopic tails of the distribution outside these threshold levels, this approach can provide useful estimates of future population risks of vision impairment.

There are some limitations with the use of spectacle lens sales data. Ametropes may not be corrected with spectacle lenses for numerous reasons, including, for example, lack of access to

correction, a leading cause of preventable vision impairment in some parts of the world,²⁵⁶ or the use of alternative forms of correction such as contact lenses. A recent study from the USA indicated the majority of contact lens wearers also make use of spectacles, however, with only approximately 15% of contact lens wearers reporting they did not own any spectacles and over 75% reporting their spectacle prescription provided clear vision indicating it was up to date.⁴⁵¹ It is not certain that European contact lens wearers have the same habits as those in the USA however given the widespread availability of spectacles and contact lenses in both jurisdictions it would be surprising if there were significant differences in spectacle usage among contact lens wearers. It is also not possible to account for individuals who may have had refractive or cataract surgery in the current dataset. The literature indicates, however, that although the rates of surgery have increased they still represent less than 1% of all individuals.^{452,453} Conversely, some individuals may purchase multiple sets of spectacles however given the very large sample size exploited herein, it is unlikely that these factors would have a significant impact on the results. This is supported by the similar levels of vision impairment predicted using both the spectacle lens data and GHS data. By utilising multiple datasets, it may be possible to better account for individuals not captured within spectacle lens data. In Europe, statistics are published on the number of surgical procedures performed,⁴⁵⁴ with similar data available for most countries,⁴⁵⁵ which may account for those undergoing cataract and refractive surgery. Applying the same methodology to contact lens sales data can account for patients that only use contact lenses for refractive error correction.

Other limitations also apply to the use of industrial type datasets. Drawing conclusions on subpopulations, for example, can be more difficult as spectacle lens manufacturers and other industry suppliers do not typically record data on their customers gender, ethnicity or age. If this data was to be captured by manufacturers in the future it could facilitate subpopulation analysis. It has, however, previously been demonstrated that lenses with a reading addition can be used to estimate a customer's age.³⁰⁹ As the relationship between increasing age and increasing refractive

error is the primary driver for vision impairment due to refractive error,^{294,295,421} accurate forecasting for the population risk of vision impairment using this methodology should be possible.

Emmetropes are also not well represented within this data. This is not surprising as it is unlikely that individuals with minimal or no refractive error purchase spectacle lenses in any significant quantities. This can be observed by the atypical distribution of refractive error for the SV lenses in Figure 8.1. Another contributing factor to this atypical distribution may be the use of low plus SV lenses as a reading correction by emmetropic presbyopes. It was expected that the ADD lens data would provide a closer match to the GHS in the emmetropic range due to the similar age profile to the GHS and the near universality of presbyopia over the age of 50.³⁰⁹ A likely explanation for the deviation of the ADD lens data at emmetropia in Figure 8.2 is the wide availability of over the counter reading glasses that can be used by emmetropes and low hyperopes and the ability of low myopes to read comfortably when no correction is in place, meaning those in this range of SE are less likely to purchase progressive addition spectacle lenses. The lack of representation of those with approximately emmetropic refractive errors in our data is a significant limitation, but epidemiological studies are best placed to establish baseline vision impairment risks for emmetropes/near emmetropes. In the GHS, the percentage of individuals estimated to be vision impaired by age 75 increases by 1.2% to 8.92% if those with myopia > -2.00 D SE are included in the calculations, which translates to approximately 9.38% if extrapolated to the SV spectacle lens wearers. Further modelling of the spectacle lens data may allow for more accurate estimates of the proportion of individuals in this low myopia group which in turn could allow a full population estimate of vision impairment due to myopia to be calculated. From a public health perspective, obtaining the current population burden of those with higher absolute refractive errors, especially myopia, is of particular importance as we are entering an era where myopia can reasonably be considered as a modifiable risk factor for vision impairment. These represent the individuals most at

risk of vision impairment due to refractive error and estimating the number of people affected by higher refractive error can allow better public health planning.²⁶⁹

Due to the nature of the data, it is impossible to state how the refraction for each individual was carried out. Ideally all refractions would be carried out under cycloplegia in order to avoid the effects of accommodation, particularly for myopic refractions.¹⁶⁹ It has been shown that the assessment of refractive error in adults is not significantly affected by the use of cycloplegia,¹⁶⁵ particularly in older adults,¹⁶⁶ those most at risk of vision impairment. The data used in this study likely represents predominantly adult populations, particularly the ADD lens data from which approximate ages can be calculated,³⁰⁹ so the probable lack of cycloplegia should have minimal effect on the refractive error and vision impairment estimations. It should also be noted that many well regarded population surveys of refractive error do not make use of cycloplegia^{156,158} including the main comparison study used herein.¹⁴ Additionally, the probable lack of cycloplegia in this study is unlikely to be significant as the higher myopic threshold should reduce the risk of a misclassification error and is the approach suggested by the International Myopia Institute when this risk may apply.⁹³

The comparability of the results obtained from spectacle lens data and a conventional epidemiological study demonstrates the utility of industrial datasets as a public health tool in refractive error and vision impairment. The use of industrial data can potentially address the paucity of epidemiological data available for both refractive error³ and vision impairment.⁵ Manufacturers with large market share for spectacle lens sales may have refractive error data which can accurately determine the number of ametropes in a population and hence the risk of vision impairment due to refractive error, myopia in particular.

How this methodology could be best exploited to produce ongoing estimates of the population burden of refractive error and consequential vision impairment needs to be determined. The most significant challenge is gaining access to commercial data for public health purposes. One possible solution would involve the creation of an international consortium of industry, academic,

professional, intergovernmental and non-governmental organisations and other key stakeholder bodies. This could provide a forum for international collaboration in the form of a Big Data coalition and lead to a Global Myopia Observatory of data analytic and data visualisation resources which could be used for public health planning, research, commercial and other uses. In providing the platform to gather and merge disparate sources of industry data, this consortium could provide a readily accessible, current and globally representative body of resources to monitor the changing epidemiology of refractive error and associated eye disease and the impact of new treatments and public health interventions essentially in real time. Furthermore, these resources would inform health planning decisions, drive clinical practice reform, stimulate industrial innovation and ultimately lead to better population health.

In conclusion, the distribution of refractive error within a population over a large range of refractive error can be determined using spectacle lens sales data. This provides a good alternative when population level data on refractive error is either absent or outdated. This is a particularly useful methodology to determine the population burden of higher absolute levels of refractive error which represents the population cohort most at risk of vision impairment due to refractive error. An estimation of the future risk of vision impairment due to myopia can also be calculated from such data.

9 Evidence-based Recommendations for Standardised Driver Vision Screening – A Big Data Approach

9.1 Title Page

Title: Evidence-based recommendations for standardised driver vision screening – a Big Data approach

Authors:

Corresponding Author: Michael Moore MSc BSc¹

John S. Butler PhD MSc^{1,2}

Daniel I. Flitcroft DPhil MB^{1,3}

James Loughman PhD BSc¹

¹Centre for Eye Research Ireland, School of Physics and Clinical and Optometric Sciences, Technological University Dublin, Dublin, Ireland

²School of Mathematical Sciences, Technological University Dublin, Dublin, Ireland

³Children's University Hospital, Dublin, Ireland

Financial Support: None

Conflict of Interest: None

Running Head: Driver Vision Screening Standards with Big Data

9.2 Abstract:

Purpose:

Visual acuity assessment is the most commonly performed vision screening method for drivers. The standards and repeat assessment intervals used, however, are arbitrary, lack an evidence base and are highly variable across different countries. This study utilises the power of Big Data to provide evidence-based recommendations for standardised driver vision screening.

Methods:

Anonymised electronic medical record data was gathered from 40 Irish optometry practices comprising 81,184 unique patients. A Kaplan-Meier Survival (KMS) analysis was used to determine the effect of increasing age and time since screening on the likelihood of passing the visual acuity standard for driving. A logistic function was fit to assess the effect of varying the minimum visual acuity standard required to drive on the screening pass rate within the population.

Results:

The likelihood of failing repeat screening increased as a function of time since initial screening for all age groups ($\chi^2=1447$, $df=6$, $p<0.001$), with older patients most affected. Rescreening intervals for individuals who initially met the vision standard unaided reduced as a function of age. Using an 80% survivability threshold, intervals ranged from every eight years for drivers under 50, reducing to every two years for those aged over 80. Rescreening intervals for drivers requiring optical correction to meet the standard, also decreased with age. Approximately 1% of individuals are excluded from driving using a 0.3 logMAR visual acuity standard with correction.

Conclusion:

Visual acuity-based screening should take place at regular intervals for all drivers, not just those over 70. Re-screening intervals should be based on age, with shorter intervals for older drivers due to the

combined effect of age and time on the likelihood of passing the driving visual acuity standards. The most commonly used standard of 0.3 logMAR results in a minimal number of potential drivers being excluded from driving.

9.3 Introduction:

The ability to drive safely is complex, involving detailed sensory, cognitive and motor factors which have to be integrated and enacted within a limited timeframe.⁴⁵⁶ Vision provides the most important sensory input when driving and several studies have linked various forms of reduced vision with increased traffic collisions.^{457,458} Vision loss has also been associated with decreased cognition in older adults,⁴⁵⁹ itself a factor for road traffic crashes.⁴⁶⁰ There is conflicting evidence, however, regarding the influence of commonly tested aspects of vision such as visual acuity (VA) and visual field on driving performance.^{461,462} Furthermore, there is a distinct paucity of high quality evidence exploring the relationship between mandatory vision screening and driver safety.⁴⁶³ Nevertheless, most countries require evidence that vision meets a pre-defined standard in order to be legally permitted to drive.

The vision screening standards used for driving vary widely across different countries, including in Europe. The European regulatory directives on driving licences (EC Directives 2006/126/EC and 2009/113/EC)⁴⁶⁴ required harmonisation of driving licence vision screening standards by 2013, however this has not taken place. A wide spectrum of vision standards persists, therefore, varying from licence plate figure recognition tests carried out by non-qualified driving test employees in some countries, to a full vision and ocular health assessment carried out by an ophthalmologist in others. Currently the primary method by which vision is assessed to determine suitability for driving is by measuring visual acuity, but the level required to be eligible to drive is country specific. The most common minimum standard with or without optical correction required in Europe is binocular acuity of 0.5 decimal (0.3 logMAR, 6/12 (20/40) Snellen), although this varies from 0.0 logMAR in Italy and Turkey to identifying figures on a licence plate at a specified distance in countries such as the Netherlands and the United Kingdom,⁴⁶⁵ an approach which does not compare favourably to the use of vision charts.⁴⁶⁶ The use of licence plates may encourage self-assessment however it has been found many drivers do not recall the correct distances at which to conduct this self-assessment.⁴⁶⁷

Many countries have a standard for visual field assessment, with the most common requirement that the field extends to 120 degrees horizontally,⁴⁶⁵ while others also require additional vision assessments such as colour vision, contrast sensitivity and glare recovery although it is unclear how frequently these additional assessments are performed.⁴⁶⁵ Another significant source of variance in standards across countries relates to the frequency of repeat screening. Some jurisdictions require repeat screening every 10 years up to age 70 (and more frequently thereafter), while others place the responsibility on the driver themselves to self-report any changes in their vision, with no mandatory screening after the initial assessment until age 70.⁴⁶⁵

Driver vision screening standards have been criticised as lacking an adequate evidence base,^{468,469} a view that appears justified by the apparent lack of consensus demonstrated between countries. Irrespective of whether visual acuity is a good indicator of driver safety, the clinical implications of the substantial variation in existing standards merits investigation. In Ireland, mandatory vision screening takes place when initially applying for a licence (minimum age 16 for motorcycles; 17 for cars). No further screening is required until the driver reaches the age of 70, after which vision is assessed at 3-year intervals at each licence renewal. Screening is conducted by registered optometrists or medical doctors, with applicants needing to meet the most common standard for visual acuity of 0.3 logMAR, either with or without correction.

This study was designed to examine the suitability of driver vision screening standards as currently used in Ireland and many other European countries to determine fitness to drive. Specifically, EMR data derived from optometric practices involved in the routine measurement of visual acuity (e.g. as part of routine driver vision screening and refractive error management) was initially used to assess how uncorrected and corrected visual acuity vary as a function of age within the population. Subsequently, the EMR data was analysed using a machine learning approach to examine: (i) what effect does variation in the legal visual acuity threshold have on the probability of failing the vision standard even with correction; and (ii) how does age and the length of time between vision tests

influence the probability of meeting the required vision standard for driving at a subsequent vision test, after initially meeting the standard either with or without correction. These analyses were used to develop evidence-based recommendations regarding the frequency of driver vision screening and threshold acuity level required to be legally permitted to drive.

9.4 Methods:

Anonymised EMR data was gathered from 40 Irish optometry practices. The data was extracted remotely through the EMR provider following provision of explicit consent from the data (practice) owners during the period of May 2018 to June 2020 for all 40 practices. The data extracted comprised all practice records since first use up to the date of extraction for each practice. The EMR provider removed any personally identifying data and anonymised the data prior to delivery so that the anonymisation could not be reversed by the researchers. The data was provided in multiple CSV files which were combined using the SQLite database engine V 3.30.00 (Hipp, Wyrick & Company, Inc., Charlotte, North Carolina, USA) with further analysis carried out using the R programming language (R Core Team (2020). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. <https://www.R-project.org/>). At the time of extraction, a new unique identifying number was generated within the EMR data allowing individual subject data to be tracked across multiple visits. The data available for each individual clinical practice patient included demographic, refractive, visual acuity, binocular vision, contact lens, ocular health and clinical management data. For this analysis, only demographic, refractive and visual acuity data were considered. This study was approved by the Research Ethics Committee of the Technological University of Dublin and adheres to the tenets of the Declaration of Helsinki.

A custom function was written to remove erroneous visual acuity values and convert all Snellen and decimal uncorrected visual acuity (UCVA) and corrected visual acuity (CVA) values to logMAR

notation. All patient records without complete and interpretable visual acuity data for both UCVA and CVA were excluded from the analysis. Patient visits under the age of 21 were also excluded from the analysis to specifically capture individuals most likely to drive. Patient visits were grouped in 10-year age intervals up to age 80, with all those aged over 80 grouped together due to the smaller number of patient visits. The average level of UCVA and CVA for each age group was calculated. The effect of age group on both UCVA and CVA was also assessed using the Kruskal-Wallis rank sum test. Given the most widely adopted standard for visual acuity as it applies to driving is 0.3 logMAR, this was used as a reference to categorise measured UCVA and CVA according to vision standards criteria. A visual acuity of ≤ 0.2 logMAR in either eye was considered a pass, a visual acuity of > 0.2 logMAR and ≤ 0.4 logMAR in both eyes considered borderline and a visual acuity of > 0.4 logMAR in both eyes considered a fail. The proportion of visual acuity measurements in each visual acuity category and age group was determined for both CVA and UCVA. Subsequent analyses relating to vision standards were conducted separately for those without visually significant refractive error who passed based on their initial presenting UCVA and for those with refractive error who required optical correction to meet the standards based on CVA.

A Kaplan-Meier survival (KMS) analysis was used to determine the survival time before patients that initially passed the UCVA standard (≥ 0.3 logMAR in either eye) would fail the standard in a subgroup of patients that attended for multiple visits at least six months apart and were observed to pass the UCVA standard at their first visit. Patients were categorised into age groups according to their age at the initial visit. Right censoring was used in order to account for patients that never failed the UCVA standard over their observation period. The log-rank test was used to compare the survival curves for each age group.

To determine the effect of changes in refractive error on the likelihood of passing the standard in those using optical correction, the KMS analysis was repeated for a subgroup of patients that were found to: (i) be myopic (right eye spherical equivalent refraction (SER) ≤ -0.50 D) or hyperopic (right

eye SER $\geq +0.75$ D) at their first and subsequent visits (without regression towards emmetropia at subsequent visits); (ii) failed the standard based on UCVA, but passed the standard based on CVA with correction; and (iii) had multiple visits at least six months apart. Progression of refractive error was analysed in these patients over time, and the calculated progression was used to provide an estimate of change in visual acuity, with a deterioration of 0.3 D SER assumed to be equivalent to a 0.1 logMAR deterioration in CVA if the original optical correction used to pass the initial vision screening was not updated.⁴⁷⁰ These patients were considered to have failed the standard when their estimated change in visual acuity resulted in a new estimated CVA greater than 0.3 logMAR (necessarily assuming that spectacle correction was not updated). For the purposes of this analysis, accommodation effects were ignored. The log-rank test was used to compare the survival curves for each age group.

The KMS analysis was also used to determine optimised repeat vision screening intervals for both the UCVA and CVA standards. This involved determining vision screening intervals as a function of the proportion of the population expected to still pass the UCVA or CVA standard. The time between visits was assessed for those with refractive error to determine if the frequency of repeat eye exams was less than the KMS analysis recommended repeat vision screening intervals for the UCVA standard.

To determine an appropriate visual acuity standard, the number of patients that would pass at different acuity threshold levels with and without correction were assessed. The thresholds used followed the typical Snellen chart letter size progression (the most commonly used chart type in clinical practice). A logistic function was fit to the percentage of patients passing at each acuity standard.

9.5 Results:

The original data set comprised of 697,098 practice visits of 288,777 unique patients, representing 5.9% of the population of the Republic of Ireland.⁴¹⁵ The 40 participating optometric practices were located all across the Republic of Ireland comprising both rural and urban populations. After excluding patients under age 21 and with incomplete data, 154,824 practice visits of 81,184 unique patients remained. The absence of either UCVA or CVA values was the primary reason for exclusion, accounting for 96.7% of records removed. The gender distribution was 54.7% female, 37.9% male and unrecorded in 7.4% of records. The mean age was 49.6 ± 21.1 years.

The mean right eye UCVA was 0.35 ± 0.36 logMAR while the mean right eye CVA was 0.01 ± 0.15 logMAR (females: UCVA 0.35 ± 0.36 , CVA 0.01 ± 0.15 ; males: UCVA 0.33 ± 0.36 , CVA 0.01 ± 0.16). Gender was found to have a statistically significant effect on both UCVA ($t = -11.55$, $df = 167051$, p -value < 0.001) and CVA ($t = -4.89$, $df = 167051$, p -value < 0.001), however this was likely due to the large sample size as the difference in the means were not considered clinically significant. There was higher variability of UCVA when compared to CVA across all age groups, a likely reflection of the range of refractive errors that affect individuals of all ages (Figure 9.1). Additionally, both UCVA and CVA deteriorated with increasing age, with an obvious reduction in CVA from the seventh decade onwards (Table 9.1). The effect of age group was statistically significant for both UCVA ($\chi^2 = 8225$, $df = 6$, p -value < 0.001) and CVA ($\chi^2 = 18241$, $df = 6$, p -value < 0.001). Pairwise comparisons using Dunn's test indicated significant differences between every age group ($p < 0.001$ for all).

Table 9.1: Detailed breakdown of data included in analysis showing the number of patient visits in each age group along with the mean, standard deviation and range for uncorrected visual acuity, corrected visual acuity and spherical equivalent refraction (right eye only included).

Age Group (years)	Number of patient visits	Mean \pm SD (range) UCVA (logMAR)	Mean \pm SD (range) CVA (logMAR)	Mean \pm SD (range) SER (D)
21-30	14504	0.36 \pm 0.41 (-0.30 – 2.18)	-0.03 \pm 0.12 (-0.30 – 1.38)	-0.94 \pm 2.05 (-16.63 – +9.00)
31-40	15874	0.33 \pm 0.40 (-0.20 – 2.08)	-0.02 \pm 0.13 (-0.30 – 1.60)	-0.73 \pm 2.05 (-18.38 – +14.75)
41-50	28714	0.26 \pm 0.36 (-0.30 – 2.08)	-0.02 \pm 0.13 (-0.30 – 1.60)	-0.13 \pm 1.76 (-19.75 – +10.00)
51-60	33610	0.32 \pm 0.34 (-0.30 – 1.78)	-0.01 \pm 0.14 (-0.30 – 1.48)	+0.30 \pm 1.68 (-16.13 – +12.25)
61-70	30351	0.39 \pm 0.33 (-0.30 – 2.08)	0.02 \pm 0.15 (-0.30 – 1.78)	+0.74 \pm 1.67 (-20.00 – +15.25)
71-80	22449	0.44 \pm 0.33 (-0.20 – 1.82)	0.08 \pm 0.17 (-0.20 – 1.82)	+0.85 \pm 1.61 (-14.38 – +11.00)
Over 80	9322	0.47 \pm 0.33 (-0.18 – 2.08)	0.14 \pm 0.22 (-0.18 – 2.08)	+0.64 \pm 1.61 (-14.50 – +11.25)

Abbreviations: CVA, corrected visual acuity; D, dioptres; SER, spherical equivalent refraction; SD, standard deviation; UCVA, uncorrected visual acuity

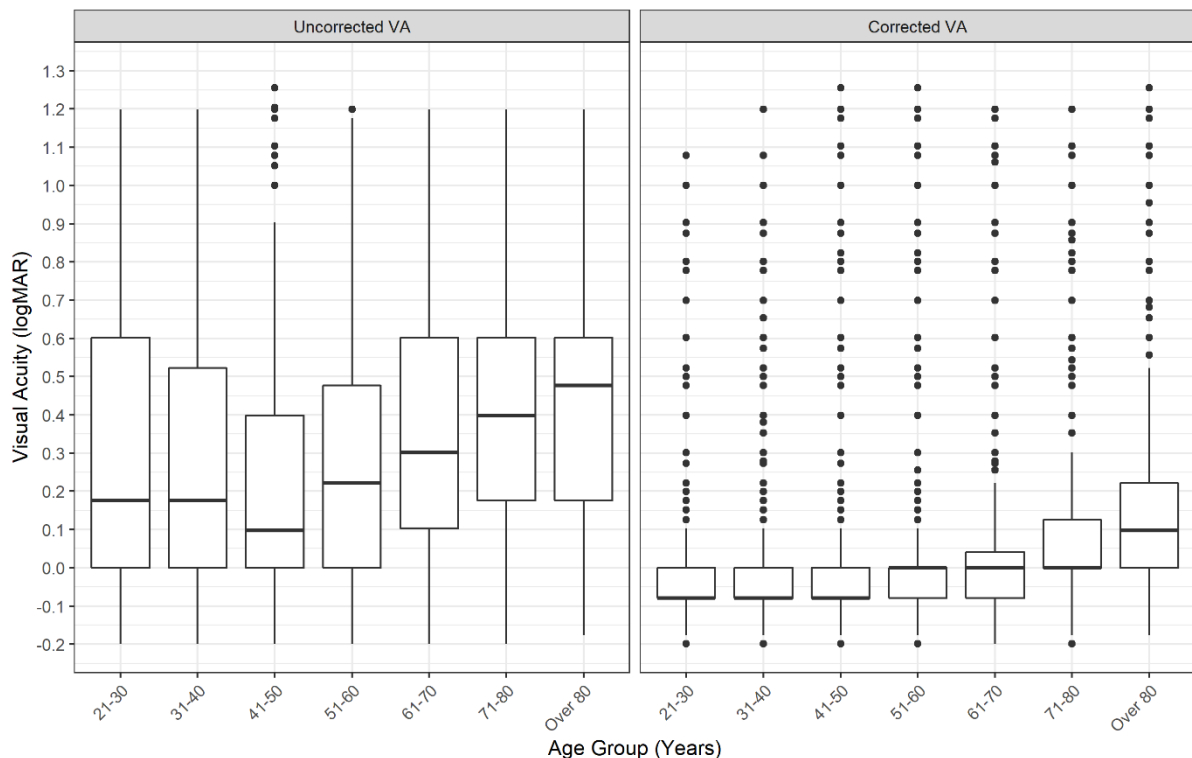


Figure 9.1: Boxplot for right eye uncorrected visual acuity (UCVA) (left panel, n = 154,824) and right eye corrected visual acuity (CVA) (right panel, n = 154,824) for each age category

The relative proportions of VA measurements falling into each vision standard category (pass, borderline and fail) were observed to vary as a function of age for both UCVA ($\chi^2 = 4555$, $df = 2$, p -value < 0.001) and CVA ($\chi^2 = 2349$, $df = 2$, p -value < 0.001). An increasing percentage of measurements fell into the borderline and fail categories with increasing age, particularly for UCVA (Figure 9.2). Over 40% of VA measurements were categorised as failing or borderline according to UCVA, while less than 2% of VA measurements were similarly categorised for CVA, primarily among older drivers aged over 70.

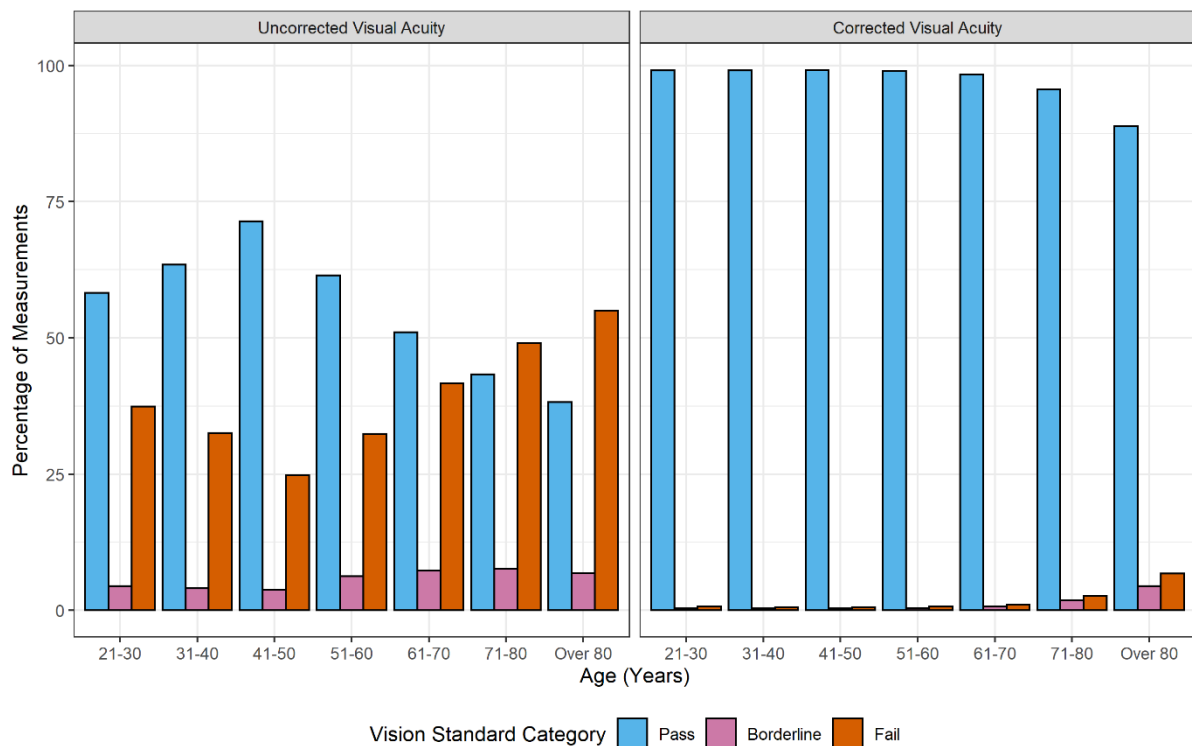


Figure 9.2: Percentage of VA measurements falling into each vision standard category for both uncorrected visual acuity (UCVA) and corrected visual acuity (CVA)

9.5.1 Longitudinal Analysis – Uncorrected Visual Acuity

In total, 23,393 patients who initially passed the vision standard with UCVA were eligible for inclusion in the longitudinal analysis. The mean time between visits was 1.86 ± 2.12 years, with a mean total follow up time of 3.62 ± 3.76 years. For patients with longitudinal data, the mean

annualised change in UCVA and CVA was 0.022 ± 0.531 logMAR per year and 0.003 ± 0.157 logMAR per year respectively.

The KMS analysis revealed that increasing time since the initial visit was found to negatively affect the likelihood of passing at subsequent visits. Older initial age was also found to negatively affect the likelihood of passing at subsequent visits ($\chi^2 = 1447$, $df = 6$, $p\text{-value} < 0.001$). Reassessment intervals determined using the KMS analysis were observed to vary according to different survivability threshold levels across each age group (Table 9.2), with lower threshold values (e.g. 50% survivability where just half the population will be expected to still meet the standard) resulting in long reassessment intervals for all age groups, and high thresholds (e.g., 90% survivability where most of the population will be expected to still meet the standard) requiring frequent reassessment intervals for all.

Table 9.2: Reassessment intervals needed in order for a given proportion of the population to still pass the uncorrected visual acuity (UCVA) standard

Age Group (years)	RI for 90% Pass Rate (years)	RI for 80% Pass Rate (years)	RI for 75% Pass Rate (years)	RI for 70% Pass Rate (years)	RI for 50% Pass Rate (years)
21-30	3.6	7.0	8.5	10.5	16.2
31-40	5.1	8.1	9.5	10.7	18.3
41-50	4.0	7.1	8.5	9.6	13.1
51-60	3.4	5.9	7.1	8.0	11.6
61-70	2.3	4.3	5.4	6.2	10.0
71-80	2.1	3.1	3.8	4.4	7.7
Over 80	1.5	2.1	2.5	2.9	4.6

Abbreviations: RI, Reassessment Interval

Figure 9.3 illustrates the relationship between initial age and time since first visit on the likelihood of passing. All age groups were negatively affected by increasing time since first visit. Using a survivability threshold of 80% (i.e., 80% of individuals still pass the standard), survival time reduced as a function of age, with older age groups exceeding the threshold at progressively shorter intervals, dropping from an expected survival time of 8 years for patients in their 30s, to just over 2

years for those aged over 80.

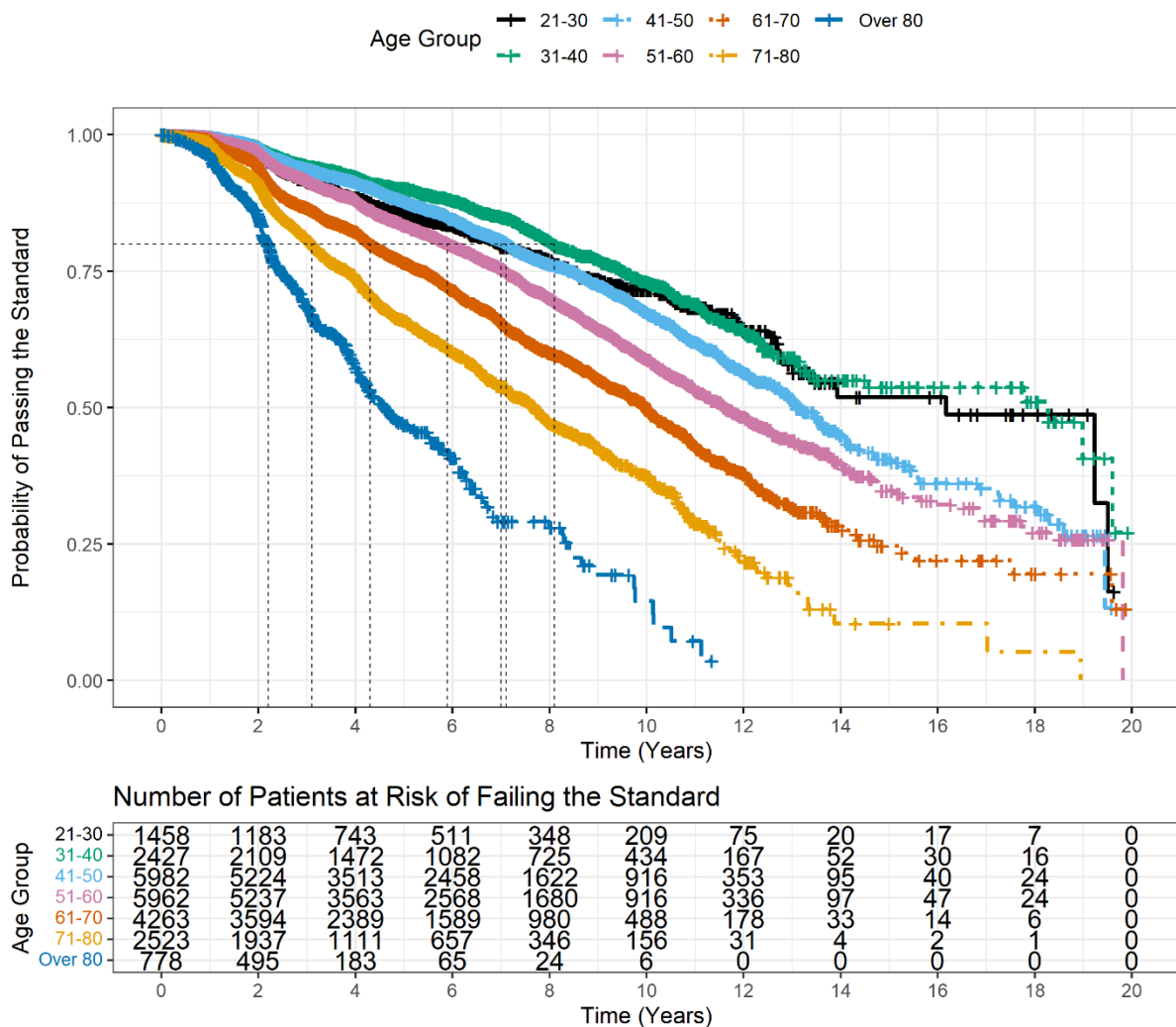


Figure 9.3: Kaplan-Meier curves demonstrating the reducing likelihood of passing the standard in a cohort of individuals that initially passed the standard with uncorrected visual acuity (UCVA). Increasing time since the initial vision assessment reduces the likelihood of passing for all age groups. The dotted lines indicate the time interval for each age group by which 80% of individuals will still pass the UCVA standard.

Reassessment intervals to achieve an approximate 80% survivability are provided in Table 9.3, which also illustrates the expected survivability rates for the most common re-screening criteria currently used in countries where periodic rescreening is required (rescreening every 10 years until age 70). This analysis demonstrates a progressive age-related decrease in survivability from 71% among the youngest drivers to just 50% after 10 years among those aged 61-70. For the youngest drivers, just

17% are expected survive after 20 years (the longest period available for analysis within this data), long before the most common mandatory rescreening at age 70.

Table 9.3: Reassessment intervals required to achieve an approximate 80% survivability rate based on uncorrected visual acuity (top panel) compared to survivability rates for the most commonly used screening intervals used in countries that require regular vision screening (bottom panel).

Reassessment Intervals Based on 80% Survivability		
Age Group (years)	Reassessment Interval (years)	Percentage Expected to Pass
21-30	8	77%
31-40	8	80%
41-50	8	76%
51-60	6	80%
61-70	4	82%
71-80	3	81%
Over 80	2	86%
Common Reassessment Intervals		
Age Group (years)	Reassessment Interval (years)	Percentage Expected to Pass
21-30	10	71%
31-40	10	73%
41-50	10	67%
51-60	10	59%
61-70	10	50%
71-80	3	81%
Over 80	3	68%

9.5.2 Longitudinal Analysis – Corrected Visual Acuity

There were 9,209 myopic patients and 15,155 hyperopic patients that met the inclusion criteria for longitudinal analysis. For the myopic subgroup, the mean time between visits was 2.89 ± 2.15 years, with a mean total follow up duration of 5.02 ± 3.32 years. For the hyperopic subgroup, the mean time between visits was 2.79 ± 2.03 years, with a mean total follow up duration of 5.37 ± 3.42 years. Reassessment intervals were observed to vary according to different survivability threshold levels across each age group for the myopic and hyperopic cohorts in a similar way to the uncorrected cohort, with low survivability thresholds requiring longer reassessment intervals and high survivability thresholds requiring shorter reassessment intervals (Table 9.4).

Table 9.4: Reassessment intervals needed in order for a given proportion of the population to still pass the corrected visual acuity (CVA) standard

Age Group (years)	RI for 90% Pass Rate (years)	RI for 80% Pass Rate (years)	RI for 75% Pass Rate (years)	RI for 70% Pass Rate (years)	RI for 50% Pass Rate (years)
Myopia (SER ≤ -0.50 D)					
21-30	3.2	4.1	4.4	4.6	6.2
31-40	3.8	4.6	5.1	5.9	8.6
41-50	3.8	4.8	5.4	6.1	8.3
51-60	3.6	4.6	4.9	5.7	8.0
61-70	2.9	4.1	4.7	5.2	7.8
71-80	2.2	3.5	4.1	4.5	7.7
Over 80	2.1	3.2	3.8	4.5	7.5
Hyperopia (SER ≥ +0.75 D)					
21-30	2.3	3.5	3.8	3.9	5.6
31-40	3.3	4.5	5.3	5.7	7.6
41-50	3.3	4.2	4.5	4.9	7.0
51-60	3.6	4.6	5.1	5.7	8.0
61-70	3.5	4.4	4.8	5.4	7.8
71-80	2.8	3.8	4.1	4.5	6.5
Over 80	2.1	3.2	3.7	4.2	6.8

Abbreviations: RI, Reassessment Interval; SER, Spherical equivalent refraction; D, dioptre

The mean reassessment interval for both the myopic and hyperopic cohorts to achieve 80% survivability was 4.1 years. Figures 9.4 (myopic subgroup) and 9.5 (hyperopic subgroup) demonstrate the relationship between initial age and time since first visit on the likelihood of continuing to pass the standard. All age groups were negatively affected by increasing time since first visit. For the myopic subgroup, there was a statistically significant difference in the risk of failing between all age groups ($\chi^2 = 159$, $df = 6$, $p\text{-value} < 0.001$). This was also the case for the hyperopic subgroup ($\chi^2 = 51.2$, $df = 6$, $p\text{-value} < 0.001$). Older age groups were likely to fail the standard in the shortest time, although the difference between age groups was not as great as that found for the UCVA group.

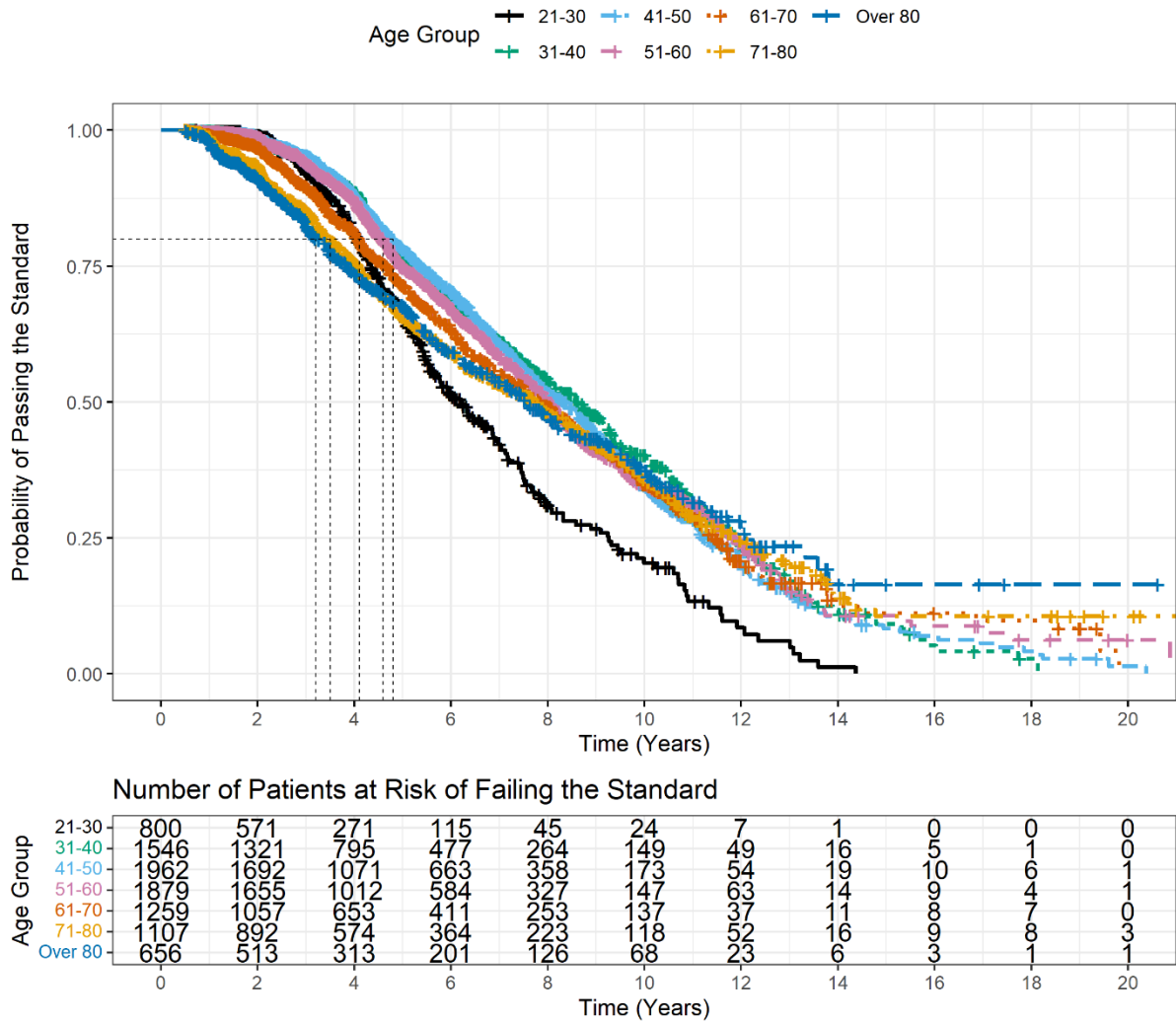


Figure 9.4: Kaplan-Meier curves demonstrating the reducing likelihood of passing the standard in a cohort of myopic (right eye SER ≤ -0.50 D) individuals ($n = 9,209$) that initially passed the standard with corrected visual acuity (CVA). Increasing time since the initial vision assessment reduces the likelihood of passing for all age groups. The dotted lines indicate the time interval for each age group by which 80% of individuals will still pass the CVA standard if their refractive error correction is not updated.

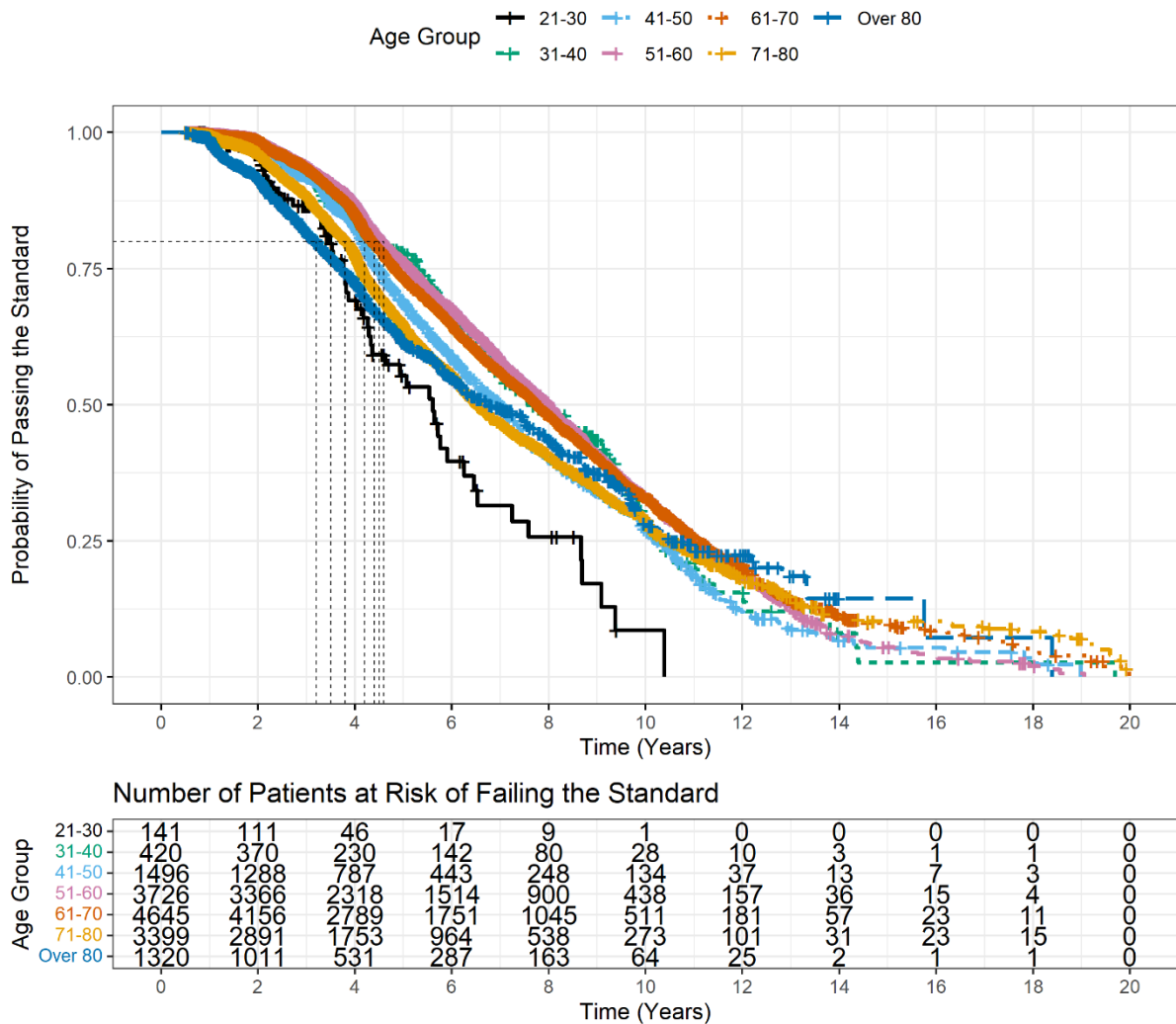


Figure 9.5: Kaplan-Meier curves demonstrating the reducing likelihood of passing the standard in a cohort of hyperopic (right eye SER $\geq +0.75$ D) individuals ($n = 15,155$) that initially passed the standard with corrected visual acuity (CVA). Increasing time since the initial vision assessment reduces the likelihood of passing for all age groups. The dotted lines indicate the time interval for each age group by which 80% of individuals will still pass the CVA standard if their refractive error correction is not updated.

Figure 9.6 shows the time between eye exam visits for both male and female patients in the myopic and hyperopic groups. The significant majority of visits occurred within 1-3 years of the previous visit, with just 16.4% of visits occurring at intervals greater than the respective 80% survivability

threshold intervals across all age groups. There was no statistically significant difference in the time between visits for female and male patients (Wilcoxon signed-rank test; $W = 62674901$, $p = 0.52$).

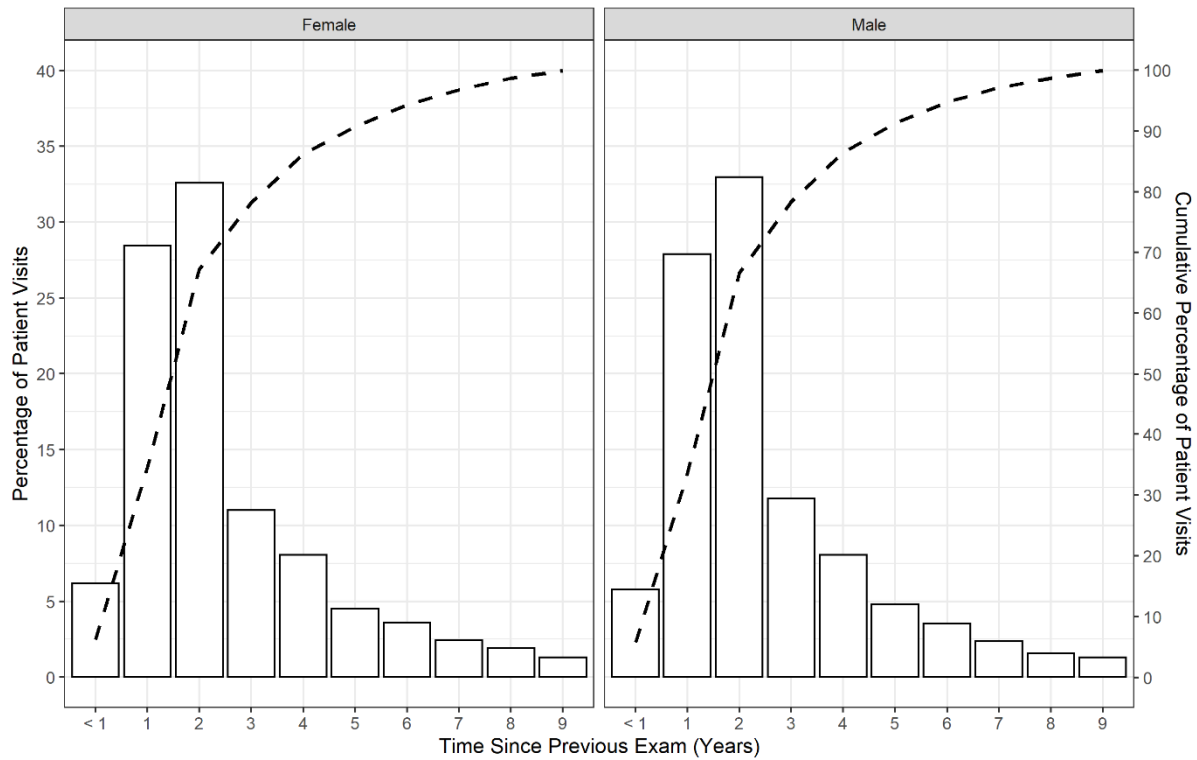


Figure 9.6: Time between eye exams for female and male patients with refractive error ($SER \leq -0.50$ D or $SER \geq +0.75$ D). Cumulative percentage shown by dashed line.

Figure 9.7 shows the percentage of patients that would pass at various thresholds for the binocular CVA standard. At a low CVA threshold of 1.0 logMAR (6/60 Snellen), almost 100% of patients pass the standard, irrespective of age. The proportion of patients passing reduces only marginally ($\approx 1\%$) when the threshold is increased to the most commonly used standard of 0.3 logMAR (6/12 Snellen). Increasing the threshold further results in a more significant number of patients failing the standard, with 12% failing at the 0.0 logMAR (6/6 Snellen) standard (estimate = -1.6, $t = -9.0$, $p < 0.001$).

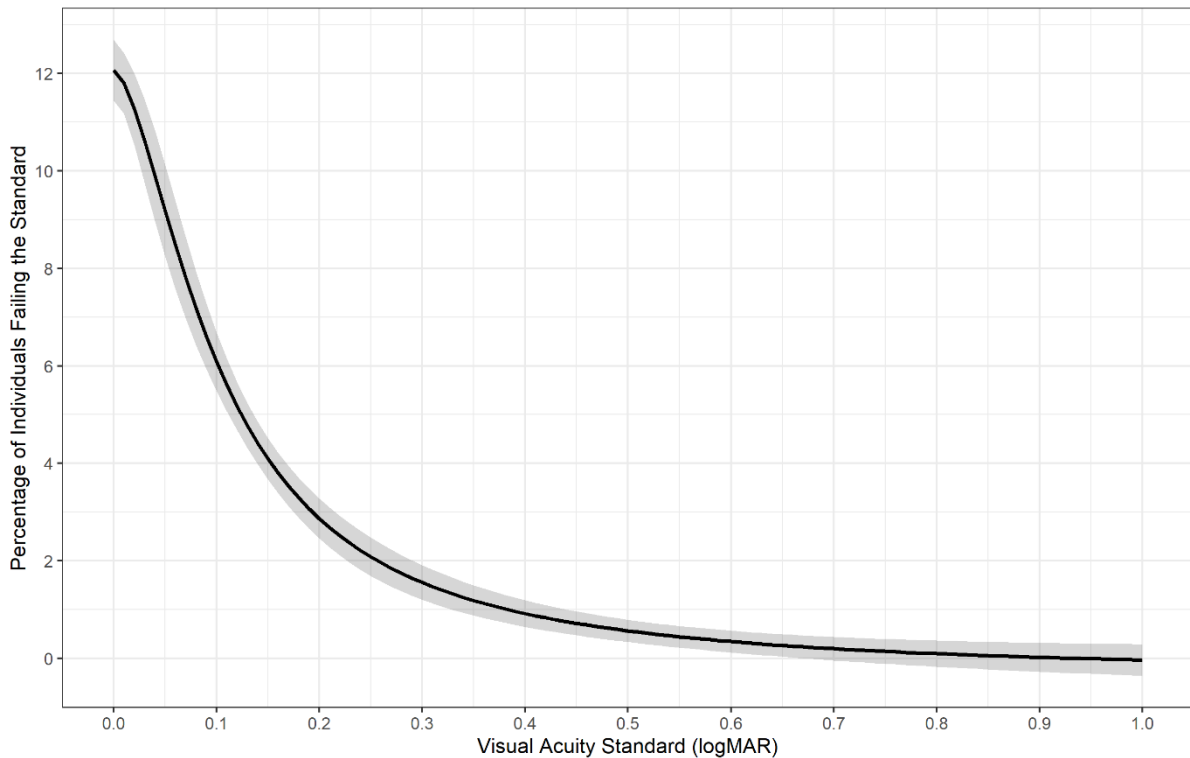


Figure 9.7: Logistic function demonstrating the age-independent change in percentage of patients that fail the binocular visual acuity standard (even with correction), when the threshold is varied between 0.0 and 1.0 logMAR

9.6 Discussion:

This study exploited a sizeable EMR dataset containing detailed cross sectional and longitudinal UCVA and CVA data for the purposes of evaluating visual acuity thresholds as a legal driving standard. The finding that the most commonly used visual acuity threshold (0.3 logMAR (6/12 Snellen)) excludes just a small minority of potential drivers is important for a number of reasons. It is well established that the cessation of driving in older drivers is associated with increased rates of depression^{471,472} through loss of independence and steeper declines in general health.⁴⁷³ Given that older drivers are most likely to experience reducing visual acuity, it is important to set standards at a level which does not unfairly bias screening against older drivers. This must, however, be weighed against the increased risk potentially posed to other road users by those with reduced vision.⁴⁷⁴ The available evidence pertaining to the relationship between visual acuity and driver safety is

somewhat conflicting, with some studies suggesting no relationship,^{475,476} while others have found a small but statistically significant relationship.^{461,477} A recent meta-analysis of vision function and traffic safety outcomes in low and middle income countries observed a 46% increased risk of traffic crash in those with visual acuity of $\leq 6/18$ Snellen (≥ 0.48 logMAR),⁴⁷⁸ adding to the evidence base that reduced visual acuity contributes to an increased risk of traffic crashes. The lack of definitive evidence is not surprising given that concomitant reductions in other aspects of visual function such as contrast sensitivity, visual field and useful field of view may also impact driver safety and are not necessarily captured by visual acuity measures.^{479,480} It is important to have a measure of visual performance, however, as diminishing visual function has been shown to negatively impact both driver safety and driver performance.⁴⁷⁹

Irrespective of whether visual acuity provides the best index of driver safety or performance, several factors dictate that visual acuity standards are likely to persist as a core component of driver vision screening. It does capture certain visual requirements for driving such as road sign recognition and hazard avoidance.⁴⁸¹ Additionally, visual acuity screening is the most commonly performed and widely understood method for assessing vision, requires relatively little specialist equipment or training, and is widely enshrined in policy and legislation as an accepted means of classifying vision (e.g. legal classification of a patient as vision impaired or blind). Setting the standard at 0.3 logMAR ensures that up to 99% of potential drivers can comfortably be expected to pass this commonly used visual acuity standard for driving. This is the standard currently used in Norway and Sweden, which have some of the lowest road deaths per vehicle distance travelled in Europe.⁴⁸² Other countries with more stringent visual acuity standards (which would prevent a higher percentage of people from driving) have substantially poorer road death statistics,⁴⁸² suggesting that other factors may be more important determinants of driver safety. Uncertainty regarding the importance of visual acuity for driver performance^{481,483} and safety,⁴⁷⁹ coupled with the established association⁴⁷⁹ between driving cessation and poor health outcomes, suggests there is limited value in setting the standard at a

threshold value which might unnecessarily exclude a significant percentage of people from driving without any supporting safety evidence. A 0.3 logMAR standard, therefore, appears a balanced and fair threshold which virtually all ($\approx 99\%$) drivers will meet either with or without correction in the absence of significant ocular disease or other cause of reduced CVA.

Another key finding from this Big Data analysis is that the frequency of driver vision screening assessments appears to be inappropriately long for younger drivers in Ireland and many other European countries. Exploring the relationship between time since initial screening, age and the likelihood of passing the standard for individuals who originally met the standard unaided revealed that the likelihood of passing reduced with time for all age groups, not just for elderly drivers. With an average reduction in UCVA of $+0.022$ logMAR per year, a driver who initially passed the standard unaided would lose approximately 2-3 lines of visual acuity over a 10-year licence renewal period, which could result in an individual changing from the comfortably passing category to the borderline or fail category without correction. Furthermore, in the myopic subgroup, the youngest drivers included herein (age 21-30) were found to have the fastest reduction of UCVA of all potential drivers, likely due to increased myopic progression in this age cohort.⁴⁸⁴ The current standards adopted in many countries, where repeat visual function assessments are only required when individuals reach a certain age, usually over the age of 70,⁴⁶⁵ would fail to detect such drivers and instead have to rely on driver discretion with respect to their ability to see sufficiently well to drive in all conditions. In such countries, drivers are expected to self-regulate, recognise and report changes in their vision. This raises the possibility of lengthy gaps between vision screening assessments, particularly for drivers who do not wear optical correction and therefore do not routinely attend an eye care practitioner. This is contrary to public preference, with a 2014 study finding that 87% of those surveyed thought drivers should have to provide evidence of meeting the vision standard when renewing their licence.⁴⁸⁵

The age-related decrease in CVA and sizeable reductions in likelihood of passing the vision standard observed among older individuals herein suggests that more frequent vision screening in older drivers is justified. In most countries, older drivers, usually over the age of 70, are already required to undertake regular vision screening at each licence renewal.⁴⁶⁵ There is little evidence to support the idea that targeting elderly individuals for vision screening reduces the risk of motor vehicle crashes.⁴⁶³ Increased frequency of screening of this age cohort seems sensible, however, given that the prevalence of many of the major causes of vision impairment and blindness such as cataract, glaucoma and age-related macular degeneration is highly age-dependent.^{256,416,417} Both UCVA and CVA were observed to deteriorate with increasing age and over time herein, evidenced by the increasing proportion of older individuals falling into the borderline and failing vision standard categories. Among individuals that initially met the standard without correction, the likelihood of passing a future vision screening unaided therefore reduced over time. These findings are not unexpected as it is well established that visual function diminishes with age,⁴⁸⁶ but they provide solid evidence to support a requirement that screening protocol should be age-specific.

Our analyses suggest that separate vision screening protocol should be considered for those who meet the standard unaided and those who require optical correction to drive. Rescreening intervals were notably shorter at every survivability threshold for those requiring refractive error correction, particularly among younger drivers under the age of 50 who would have to be screened every 4-5 years to meet an 80% survivability criterion. Drivers who initially meet vision standards unaided may subsequently fail due to pathology, or more likely due to the development of new refractive error or loss of acuity over time due to the progressive manifestation of latent hyperopia. Based on our observations herein, this gradual decline in UCVA appears to be slower than the change in CVA affecting drivers who require optical correction to meet the standard. It is likely that the reduction in CVA is due to progression of existing refractive error in most cases, which may lead individuals to fall below the standard more quickly if their correction is not updated routinely. Such individuals,

however, are typically under the care of an eyecare practitioner and likely to attend for regular review eye exams.⁴⁸⁷ The majority of individuals with refractive error requiring optical correction in our dataset attended for repeat visits within the recommended rescreening interval for their respective age group, so any deterioration in CVA is likely to be addressed for most drivers before CVA falls below the legal standard. Although the survivability data suggests the need for separate protocol, it seems reasonable to consider that a single protocol could be implemented. This would avoid the necessity to implement different screening protocol based on whether refractive correction is required to drive or not as long as specific provisions are incorporated to address the issue of poorer survivability among those who require correction to pass the CVA standard. The use of a single protocol would be a more realistically achievable approach given the apparent difficulties involved in implementing a single harmonised policy across Europe.

Rescreening intervals varied according to the selected survivability threshold. For those who initially meet the standard unaided, selecting a survivability threshold of 90% would require approximately biennial testing across many age cohorts. This would have huge resource implications and is unlikely to be a sustainable model. Lower thresholds at the level of 50% would require far less frequent screening, with the oldest drivers only requiring rescreening at 5-year intervals, which would lead to a scenario where half the population of drivers would no longer meet the vision standards by the time they are re-screened, which is certainly not desirable. Aligning re-screening intervals with driving licence renewals might make practical sense, and would certainly represent an improvement in countries like Ireland. A survivability threshold around 75 to 80% would appear to provide a reasonable compromise, with an interval between screening that remains relatively close to standard 10-year licence renewal periods up to age 50, but requires more frequent screening thereafter.

This study provides the most comprehensive analysis of driver vision standards completed to date. Particular strengths of the study include the large sample size and longitudinal nature of the data.

The refraction and visual acuity data were acquired by highly trained optometrists which should represent high quality clinical data. Limitations of the study include the retrospective nature of the study. The data analysed was not captured specifically for this purpose, although it is unlikely that a prospective study of a similar scale would be feasible to conduct. It is unknown what proportion of the data in this study represents actual drivers or what proportion of patient examinations involved actual driver vision screening. However, over 75% of all adults in Ireland hold a valid driving licence,⁴⁸⁸ and the data is certainly representative of adults eligible to undertake driver vision screening. Selection bias might be considered as a limitation given the clinical nature of the data analysed, as it is unknown what proportion of examinations were for the purpose of driver vision screening. This is unlikely to be a major concern herein, however, as most driver vision screening is conducted by optometrists in Ireland, so our dataset naturally contains a subset of such data. The large number of individuals with longitudinal data that maintained good UCVA for long periods of time (≥ 10 years) should mean the survival analysis is also representative of those with stable good UCVA. The dataset analysed also contained more female than male participants. This is not surprising as it has been found elsewhere that female patients are more likely to attend optometric services likely as a result of attitudinal differences on seeking health services between men and women.⁴⁸⁹ Despite this difference the very large number of both female and male participants should ensure these results can be applied to both the adult male and female populations. All of the data analysed is specific to the Republic of Ireland which may be perceived to limit generalisability, but it is unlikely there are significant population differences in terms of change in UCVA or CVA over time across Europe. Refractive error has been found to vary with ethnicity, with much higher rates of myopia and faster progression observed in Asia.³ This may mean the reassessment intervals calculated for CVA are not applicable in all parts of the world. These analyses also do not include a specific assessment of changes in visual field, an important parameter for fitness to drive, or other affects ocular pathology may have on the eye. The survival analyses conducted herein are influenced by individuals with conditions that affect vision, but the data was not available to evaluate their

precise impact on vision over time. In high income countries such as Ireland with good access to eyecare, most patients in these categories will be under more regular review, however, this may not be the case in all countries. These results also apply to the most commonly used visual acuity criteria for driving of 0.3 logMAR which is the standard typically used for cars and motorcycles.⁴⁶⁵ The standard for heavy goods vehicles and buses is usually more stringent, with more frequent reassessment required. This analysis does not apply to this cohort who represent a small proportion of drivers, accounting for less than 2% of the 200+ million total drivers in the European Union and for whom, stricter standards are already in place.⁴⁹⁰ Lastly, the analyses contained herein represent an evaluation of the technical suitability of current visual acuity based driver vision screening standards. The findings do not relate in any way to driver safety, which would require a more significant body of prospective research to identify which battery of vision screening tools might provide the best indicator of individual fitness to drive. Indeed, a recent Cochrane review failed to find any suitably designed study which could evaluate the general efficacy of vision screening in reducing crashes,⁴⁶³ so it is simply not possible, at present, to implement an evidence-based vision screening strategy based on safety data.

This Big Data powered analysis confirms that the commonly used 0.3 logMAR standard seems an appropriate threshold from an inclusionary perspective, and that regular visual acuity screening should be extended to include all drivers at age-appropriate intervals. To develop these findings into a harmonised protocol, key decisions would need to be made in relation to the chosen survivability threshold and in relation to the treatment of drivers who require optical correction, particularly if a single protocol was to be prioritised. Electronic medical record data derived from ophthalmic clinical practice has previously been validated as a useful epidemiological tool for refractive error.³⁰⁹ This type of data represents an ideal resource to develop evidence-based recommendations for acuity-based driver vision screening standards, which might perhaps lead to a harmonised Europe-wide standard for driver vision screening.

10 Summary, Conclusions, and Directions for Future Work

10.1 Summary and Conclusions

This work was designed to investigate the use of Big Data as an epidemiological and public health tool in eyecare with a particular focus on refractive error and vision. The findings reported are based on two sources of data; a large dataset of spectacles lenses manufactured for delivery in Europe and anonymised EMRs of 40 optometric practices in the Republic of Ireland. The findings of the research presented in this thesis (i) demonstrates the viability of EMR data as a population level source of refractive error information, (ii) describes a method to use spectacle lens sales data to determine refractive error distribution in a population and (iii) provides an example of how this data can be used as evidence to influence public health policy.

Our initial analysis (chapter 7) of both the EMR data and spectacle lens data revealed the EMR data closely matched the distribution of refractive error found as part of a meta-analysis of refractive error prevalence in Europe. The EMR data was also a closer match to the prevalence of hyperopia, myopia and high myopia by age to the meta-analysis than one of the component studies of the meta-analysis. The spectacle lens data did not offer as close a match, likely due to the effect of underrepresentation of those that are approximately emmetropic. Interestingly, by combining information from both datasets it was possible to gain more insight into the spectacle lens data and estimate the age of those using an addition which allowed an age matched comparison.

Further analysis of the spectacle lens data revealed that outside the approximately emmetropic range of refractive error, the distribution of refractive error for spectacle lenses closely matched the that found in population surveys of refractive error (chapter 8). This is not surprising, as due to the symptomatic nature of refractive error, it can be expected most individuals will seek correction if it is available. By using previously described work²⁹⁶ it was possible to estimate the likelihood of vision

impairment due to myopia by age 75 among spectacle lens wearers with myopia worse than -2.00 D SER. This was found not to be statistically different to the likelihood of vision impairment due to myopia over the same range of refractive error as estimated from a typical population survey of refractive error. Significantly, it was estimated by age 75, over 9% of myopes will be vision impaired. High myopes had a higher risk of vision impairment however the overall number of those estimated to become vision impaired also contained a significant cohort of low to moderate myopes due to their large numbers within the population despite their lower risk.

Our analysis of visual acuity in a large number of Irish adults (chapter 9) showed the current driver vision reassessment intervals are inappropriately long, particularly in young individuals. Although there is some debate over the relationship between visual acuity and driver safety,^{461,475-477} it is visual acuity is likely to remain a core part of driver vision screening and as such the reassessment intervals should be evidence based. We also observed an exponential increase in the number of individuals potentially excluded from driving as the visual acuity standard is made more stringent than the most commonly used standard of 0.3 logMAR.

There are several recommendations to emerge from this work. The current driver vision reassessment intervals need to be re-evaluated with key decisions made around the proportion of drivers expected to still meet the standard at reassessment and how reassessment intervals should be handled for those with refractive error. A sensible approach may be to align reassessment intervals with licence renewal (typically every 10 years) for drivers aged 50 and younger with progressively shorter intervals for older drivers. A single protocol for drivers with and without refractive error is more practical to have in place and is supported by the finding that the significant majority ($\approx 84\%$) of those with refractive error will reattend their optometrist before the required reassessment interval. Given the uncertainty over the relationship between visual acuity and driver safety, countries that currently enforce a more stringent standard than 0.3 logMAR should consider

lowering their standard to 0.3 logMAR to avoid the unnecessary exclusion of older individuals from driving.

Both EMR and spectacle lens data provide a unique solution to the documented³ lack of available population level refractive error data. The ability to acquire the data with relative ease and on an as needed basis may allow for almost real time monitoring of the population burden of refractive error and associated risk of vision impairment. This level of representative and current information can facilitate public health policy and provide an evidence base upon which to base key decisions. The burgeoning myopia epidemic will require accurate and current data to encourage widespread use of myopia control and ongoing monitoring will be needed to assess the effectiveness of these interventions on a population level. With an aging population, the burden of vision impairment is likely to increase. Current estimates of vision impairment in the Republic of Ireland are outdated and likely do not capture the true prevalence.²⁵⁹ The work described as part of this project may provide an additional way to capture vision impairment risk and plan appropriate resources for those affected. Some public health policies currently in place, such as the driver vision rescreening intervals, are not evidence based. This data can provide evidence on which to base these policies to improve outcomes for the public.

10.2 Directions for Future Work

This project has evolved into a much larger piece of work than was originally envisioned. Data collection is still ongoing with new data sources becoming available while multiple additional analyses are taking place. The spectacle lens data supplied by CZVI is due to be updated to reflect lens delivery to the current year. An additional spectacle lens data source has been acquired representing over 3 million lens sales in North America. Ocuco Ltd, the developer of the EMR software used in this project has customers in several countries in Europe and North America, it is

hoped in the future that data may be acquired from these countries to create a more global dataset and facilitate comparisons between countries.

Two key next steps should take place to most fully realise the potential of the spectacle lens data as described in chapter 7 and 8. In chapter 8, we suggest the development of an international consortium of lens manufacturers, research intuitions and public health bodies. The spectacle lens data used as part of this study was almost wholly for delivery in Europe and sourced from one manufacturer. The creation of this consortium would allow the methodology described in chapter 8 to be applied on a global basis and overcome the limitations associated with using data from one manufacturer supplying one geographic region. Additionally, temporal trends in the spectacle lens data collected to date require investigation to determine if the prevalence of refractive error has changed in Europe over time, particularly over the range of refractive error determined in chapter 8 to match population distributions of refractive error.

Additional work using the EMR data acquired is currently ongoing. Establishing the baseline prevalence of refractive error in this population and historical changes in prevalence will provide useful insights which may indicate the overall population burden of refractive error in Ireland, particularly in the current circumstances, in which no other population level data is available.

Current work indicates an overall prevalence of myopia (≤ -0.50 D SER) of 33% with highest rates observed in the 20 – 30 age cohort. Confining analysis to the presbyopic age group that are more likely to be representative of the population, a much higher proportion of myopia is evident in younger age groups. More in-depth analysis is required using higher threshold values of myopia to confirm these findings.

Having established a baseline level of refractive error prevalence, the ongoing collection of EMR data will allow continued monitoring of refractive error trends over time. Taking inspiration from the VLEG International Agency for the Prevention of Blindness Atlas,^{5,256} work has commenced on the development of a number of visualisation tools in order to follow trends in refractive error

prevalence over time and to allow easy to access information policy makers and other stakeholders.

An early-stage example can be found at:

<https://irelandrefractiveerror.shinyapps.io/RefractiveError/>.

Investigation of vision impairment has also commenced with a total level of vision impairment (< 0.3 logMAR) of 1.04% (<https://irelandrefractiveerror.shinyapps.io/VisionImpairment/>). Determining the cause of vision impairment will require further investigation and likely need to employ natural language processing techniques but will provide very useful data on vision impairment in the Republic of Ireland and indicate directions for public health intervention.

Aside from using this data as a population monitoring tool, it can also be used in clinical applications. Recognising the children that would benefit most from myopia control and encouraging the use of myopia control is key to prevent the predicted global increase in myopia and associated vision impairment.^{3,4} Work is ongoing to develop a refractive error centile progression tool based on this real world data which may become a valuable tool to aid clinicians and parents when deciding to commence myopia control.⁴⁹¹ Centile growth charts offer the possibility of predicting the development of high myopia however an alternative strategy using AI may be another avenue to explore in predicting high myopia. A recent study in China described good results using a ML model for this purpose.³¹⁶ This model may not be applicable to European children given the differences in myopia development and prevalence discussed in chapter 3. The EMR data gathered as part of our project may offer the opportunity to develop a similar model based on European children.

This data also provides the opportunity to explore some of the theories suggested for refractive error development. It may be possible to investigate the association between month of birth and the development of myopia. It has previously been suggested that individuals born during the summer months are more likely to develop myopia.⁴⁹² Our EMR data can explore this trend and see if it is consistent in across years. This would provide another risk factor for clinicians to consider when examining children. Another area that may be explored is the theory that the degree and axis of

astigmatism varies as a function of spherical refractive error with higher and more oblique astigmatism thought to be associated with higher spherical refractive error.¹²³ Early work carried out in this area seems to confirm this association (Appendix 5) but further research is needed.

11 References

1. Pararajasegaram R. VISION 2020-the right to sight: from strategies to action. *Am J Ophthalmol.* 1999;128(3):359-360.
2. Pizzarello L. VISION 2020: The Right to Sight. *Arch Ophthalmol.* 2004;122(4):615.
3. Holden BA, Fricke TR, Wilson DA, et al. Global Prevalence of Myopia and High Myopia and Temporal Trends from 2000 through 2050. *Ophthalmology.* 2016;123(5):1036-1042.
4. Naidoo KS, Fricke TR, Frick KD, et al. Potential Lost Productivity Resulting from the Global Burden of Myopia: Systematic Review, Meta-analysis, and Modeling. *Ophthalmology.* 2019;126(3):338-346.
5. Bourne R, Steinmetz JD, Flaxman S, et al. Trends in prevalence of blindness and distance and near vision impairment over 30 years: an analysis for the Global Burden of Disease Study. *Lancet Glob Heal.* 2021;9(2):e130-e143.
6. Reinsel D, Gantz J, Rydning J. *Data Age 2025: The Digitization of the World From Edge to Core.*; 2018.
7. White S. A review of big data in health care: challenges and opportunities. *Open Access Bioinformatics.* 2014;(November):13.
8. Vitale S, Sperduto RD, Ferris FL. Increased prevalence of myopia in the United States between 1971-1972 and 1999-2004. *Arch Ophthalmol (Chicago, Ill 1960).* 2009;127(12):1632-1639.
9. Tsai TH, Liu YL, Ma IH, et al. Evolution of the Prevalence of Myopia among Taiwanese Schoolchildren: A Review of Survey Data from 1983 through 2017. *Ophthalmology.* Published online 2020.
10. Flaxman SR, Bourne RRA, Resnikoff S, et al. Global causes of blindness and distance vision

- impairment 1990–2020: a systematic review and meta-analysis. *Lancet Glob Heal*. 2017;5(12):e1221-e1234.
11. Schachar RA. The Early Signs Symptoms of Presbyopia. *Points Vue*. 2014;(70):12-15.
 12. Flitcroft DI. Emmetropisation and the aetiology of refractive errors. *Eye*. 2014;28(2):169-179.
 13. Mutti DO, Mitchell GL, Jones LA, et al. Axial growth and changes in lenticular and corneal power during emmetropization in infants. *Investig Ophthalmol Vis Sci*. 2005;46(9):3074-3080.
 14. Wolfram C, Höhn R, Kottler U, et al. Prevalence of refractive errors in the European adult population: the Gutenberg Health Study (GHS). *Br J Ophthalmol*. 2014;98(7):857-861.
 15. Morgan IG, Ohno-Matsui K, Saw S. Myopia. *Lancet*. 2012;379(9827):1739-1748.
 16. Lee MW, Lee S, Lim H, Kim J. Longitudinal changes in axial length in high myopia: a 4-year prospective study. *Br J Ophthalmol*. 2020;104(5):600-603.
 17. Fotedar R, Wang JJ, Burlutsky G, et al. Distribution of Axial Length and Ocular Biometry Measured Using Partial Coherence Laser Interferometry (IOL Master) in an Older White Population. *Ophthalmology*. 2010;117(3):417-423.
 18. Foster PJ, Jiang Y. Epidemiology of myopia. *Eye (Lond)*. 2014;28(2):202-208.
 19. Morgan IG, Rose KA. Myopia: is the nature-nurture debate finally over? *Clin Exp Optom*. 2019;102(1):3-17.
 20. Tong L, Wong EH, Chan YH, Balakrishnan V. A multiple regression approach to study optical components of myopia in Singapore school children. *Ophthalmic Physiol Opt*. 2002;22(1):32-37.
 21. Stone RA, Flitcroft DI. Ocular Shape and Myopia. *Ann Acad Med Singapore*. 2004;33(1):7-15.

22. Summers Rada JA, Shelton S, Norton TT. The sclera and myopia. *Exp Eye Res.* 2006;82(2):185-200.
23. Sergienko NM, Shargorogska I. The scleral rigidity of eyes with different refractions. *Graefe's Arch Clin Exp Ophthalmol.* 2012;250(7):1009-1012.
24. Shen L, You QS, Xu X, et al. Scleral thickness in Chinese eyes. *Investig Ophthalmol Vis Sci.* 2015;56(4):2720-2727.
25. Vurgese S, Panda-Jonas S, Jonas JB. Scleral thickness in human eyes. *PLoS One.* 2012;7(1).
26. McBrien NA, Lawlor P, Gentle A. Scleral remodeling during the development of and recovery from axial myopia in the tree shrew. *Invest Ophthalmol Vis Sci.* 2000;41(12):3713-3719.
27. Baird PN, Saw SM, Lanca C, et al. Myopia. *Nat Rev Dis Prim.* 2020;6(1).
28. Ohno-Matsui K, Jonas JB. Posterior staphyloma in pathologic myopia. *Prog Retin Eye Res.* 2019;70:99-109.
29. Flitcroft DI. The complex interactions of retinal, optical and environmental factors in myopia aetiology. *Prog Retin Eye Res.* 2012;31(6):622-660.
30. Smith EL, Ramamirtham R, Qiao-Grider Y, et al. Effects of foveal ablation on emmetropization and form-deprivation myopia. *Investig Ophthalmol Vis Sci.* 2007;48(9):3914-3922.
31. Smith EL, Kee C, Ramamirtham R, Qiao-Grider Y, Hung L-F. Peripheral Vision Can Influence Eye Growth and Refractive Development in Infant Monkeys. *Investig Ophthalmology Vis Sci.* 2005;46(11):3965.
32. Mutti DO, Sholtz RI, Friedman NE, Zadnik K. Peripheral refraction and ocular shape in children. *Invest Ophthalmol Vis Sci.* 2000;41(5):1022-1030.
33. Kang P, Gifford P, McNamara P, et al. Peripheral refraction in different ethnicities. *Investig*

- Ophthalmol Vis Sci.* 2010;51(11):6059-6065.
34. Atchison DA, Pritchard N, Schmid KL. Peripheral refraction along the horizontal and vertical visual fields in myopia. *Vision Res.* 2006;46(8-9):1450-1458.
 35. Hodos W, Kuenzel WJ. Retinal-image degradation produces ocular enlargement in chicks. *Investig Ophthalmol Vis Sci.* 1984;25(6):652-659.
 36. Diether S, Schaeffel F. Local changes in eye growth induced by imposed local refractive error despite active accommodation. *Vision Res.* 1997;37(6):659-668.
 37. Mirshahi A, Ponto KA, Hoehn R, et al. Myopia and level of education: Results from the gutenberg health study. *Ophthalmology.* 2014;121(10):2047-2052.
 38. Williams KM, Bertelsen G, Cumberland P, et al. Increasing Prevalence of Myopia in Europe and the Impact of Education. *Ophthalmology.* 2015;122(7):1489-1497.
 39. Saw SM, Cheng A, Fong A, Gazzard G, Tan DTH, Morgan I. School grades and myopia. *Ophthalmic Physiol Opt.* 2007;27(2):126-129.
 40. Mutti DO, Mitchell GL, Moeschberger ML, Jones LA, Zadnik K. Parental myopia, near work, school achievement, and children's refractive error. *Invest Ophthalmol Vis Sci.* 2002;43(12):3633-3640.
 41. Huang HM, Chang DST, Wu PC. The association between near work activities and myopia in children - A systematic review and meta-analysis. *PLoS One.* 2015;10(10):1-15.
 42. Jones LA, Sinnott LT, Mutti DO, Mitchell GL, Moeschberger ML, Zadnik K. Parental history of myopia, sports and outdoor activities, and future myopia. *Investig Ophthalmol Vis Sci.* 2007;48(8):3524-3532.
 43. Saw SM, Chua WH, Hong CY, et al. Nearwork in early-onset myopia. *Investig Ophthalmol Vis*

- Sci.* 2002;43(2):332-339.
44. Mavracanas TA, Mandalos A, Peios D, et al. Prevalence of myopia in a sample of Greek students. *Acta Ophthalmol Scand.* 2000;78(6):656-659.
 45. Rose KA, Morgan IG, Ip J, et al. Outdoor Activity Reduces the Prevalence of Myopia in Children. *Ophthalmology.* 2008;115(8):1279-1285.
 46. Hepsen IF, Evereklioglu C, Bayramlar H. The effect of reading and near-work on the development of myopia in emmetropic boys: A prospective, controlled, three-year follow-up study. *Vision Res.* 2001;41(19):2511-2520.
 47. Saw SM, Nieto FJ, Katz J, Schein OD, Levy B, Chew SJ. Factors related to the progression of myopia in Singaporean children. *Optom Vis Sci.* 2000;77(10):549-554.
 48. Zylbermann R, Landau D, Berson D. The influence of study habits on myopia in Jewish teenagers. *J Pediatr Ophthalmol Strabismus.* 1993;30(5):319-322.
 49. Morgan IG, Rose KA. Myopia and international educational performance. *Ophthalmic Physiol Opt.* 2013;33(3):329-338.
 50. Rose KA, Morgan IG, Smith W, Burlutsky G, Mitchell P, Saw SM. Myopia, lifestyle, and schooling in students of Chinese ethnicity in Singapore and Sydney. *Arch Ophthalmol.* 2008;126(4):527-530.
 51. Ben-Simon GJ, Peiss M, Anis E, Nakra T, Luski A, Spierer A. Spectacle use and reduced unaided vision in third grade students: A comparative study in different educational settings. *Clin Exp Optom.* 2004;87(3):175-179.
 52. Bez D, Megreli J, Bez M, Avramovich E, Barak A, Levine H. Association between Type of Educational System and Prevalence and Severity of Myopia among Male Adolescents in Israel.

- JAMA Ophthalmol.* 2019;137(8):887-893.
53. Peled A, Afek A, Twig G, et al. Myopia and Childhood Migration: A Study of 607 862 Adolescents. *Ophthalmology.* 2020;127(6):713-723.
 54. Wu PC, Chen CT, Chang LC, et al. Increased Time Outdoors Is Followed by Reversal of the Long-Term Trend to Reduced Visual Acuity in Taiwan Primary School Students. *Ophthalmology.* 2020;127(11):1462-1469.
 55. Wu PC, Chen CT, Lin KK, et al. Myopia Prevention and Outdoor Light Intensity in a School-Based Cluster Randomized Trial. *Ophthalmology.* 2018;125(8):1239-1250.
 56. Sherwin JC, Reacher MH, Keogh RH, Khawaja AP, MacKey DA, Foster PJ. The association between time spent outdoors and myopia in children and adolescents: A systematic review and meta-analysis. *Ophthalmology.* 2012;119(10):2141-2151.
 57. French AN, Ashby RS, Morgan IG, Rose KA. Time outdoors and the prevention of myopia. *Exp Eye Res.* 2013;114:58-68.
 58. Wu PC, Tsai CL, Wu HL, Yang YH, Kuo HK. Outdoor activity during class recess reduces myopia onset and progression in school children. *Ophthalmology.* 2013;120(5):1080-1085.
 59. Jin JX, Hua WJ, Jiang X, et al. Effect of outdoor activity on myopia onset and progression in school-aged children in northeast china: The sujiatun eye care study. *BMC Ophthalmol.* 2015;15(1):1-11.
 60. He M, Xiang F, Zeng Y, et al. Effect of time spent outdoors at school on the development of myopia among children in China a randomized clinical trial. *JAMA - J Am Med Assoc.* 2015;314(11):1142-1148.
 61. Xiong S, Sankaridurg P, Naduvilath T, et al. Time spent in outdoor activities in relation to

- myopia prevention and control: a meta-analysis and systematic review. *Acta Ophthalmol.* 2017;95(6):551-566.
62. Bullimore MA, Richdale K. Myopia Control 2020: Where are we and where are we heading? *Ophthalmic Physiol Opt.* 2020;40(3):254-270.
 63. Wildsoet CF, Chia A, Cho P, et al. IMI – Interventions for Controlling Myopia Onset and Progression Report. *Investig Ophthalmology Vis Sci.* 2019;60(3):M106.
 64. Jong M, Jonas JB, Wolfssohn JS, et al. IMI 2021 yearly digest. *Investig Ophthalmol Vis Sci.* 2021;62(5):1-3.
 65. Jacobsen N, Jensen H, Goldschmidt E. Does the level of physical activity in university students influence development and progression of myopia?-A 2-year prospective cohort study. *Investig Ophthalmol Vis Sci.* 2008;49(4):1322-1327.
 66. Lundberg K, Suhr Thykjær A, Sjøgaard Hansen R, et al. Physical activity and myopia in Danish children—The CHAMPS Eye Study. *Acta Ophthalmol.* 2018;96(2):134-141.
 67. Lingham G, MacKey DA, Lucas R, Yazar S. How does spending time outdoors protect against myopia? A review. *Br J Ophthalmol.* 2020;104(5):593-599.
 68. Lanca C, Saw SM. The association between digital screen time and myopia: A systematic review. *Ophthalmic Physiol Opt.* 2020;40(2):216-229.
 69. Yazar S, Hewitt AW, Black LJ, et al. Myopia Is Associated With Lower Vitamin D Status in Young Adults. *Investig Ophthalmology Vis Sci.* 2014;55(7):4552.
 70. Choi JA, Han K, Park Y, La TY. Low Serum 25-Hydroxyvitamin D Is Associated With Myopia in Korean Adolescents. Published online 2014.
 71. Guggenheim JA, Williams C, Northstone K, et al. Does vitamin D mediate the protective

- effects of time outdoors on myopia? Findings from a prospective birth cohort. *Investig Ophthalmol Vis Sci*. 2014;55(12):8550-8558.
72. Tang SM, Lau T, Rong SS, et al. Vitamin D and its pathway genes in myopia: systematic review and meta-analysis. *Br J Ophthalmol*. 2019;103(1):8-17.
73. Cuellar-Partida G, Williams KM, Yazar S, et al. Genetically low vitamin D concentrations and myopic refractive error: a Mendelian randomization study. *Int J Epidemiol*. 2017;46(6):1882-1890.
74. Read SA, Collins MJ, Vincent SJ. Light exposure and eye growth in childhood. *Investig Ophthalmol Vis Sci*. 2015;56(11):6779-6787.
75. Foulds WS, Barathi VA, Luu CD. Progressive myopia or hyperopia can be induced in chicks and reversed by manipulation of the chromaticity of ambient light. *Investig Ophthalmol Vis Sci*. 2013;54(13):8004-8012.
76. Wang M, Schaeffel F, Jiang B, Feldkaemper M. Effects of light of different spectral composition on refractive development and retinal dopamine in chicks. *Investig Ophthalmol Vis Sci*. 2018;59(11):4413-4424.
77. Gawne TJ, Ward AH, Norton TT. Juvenile Tree Shrews Do Not Maintain Emmetropia in Narrow-band Blue Light. *Optom Vis Sci*. 2018;95(10):911-920.
78. Han JC, Lawlor DA, Kimm SY. Childhood obesity. *Lancet*. 2010;375(9727):1737-1748.
79. Lawrenson JG, Hull CC, Downie LE. The effect of blue-light blocking spectacle lenses on visual performance, macular health and the sleep-wake cycle: a systematic review of the literature. *Ophthalmic Physiol Opt*. 2017;37(6):644-654.
80. Zhang X, Qu X, Zhou X. Association between parental myopia and the risk of myopia in a child.

- Exp Ther Med.* 2015;9(6):2420-2428.
81. Konstantopoulos A, Yadegarfar G, Elgohary M. Near work, education, family history, and myopia in Greek conscripts. *Eye.* 2008;22(4):542-546.
 82. Davis-Kean PE. The influence of parent education and family income on child achievement: The indirect role of parental expectations and the home environment. *J Fam Psychol.* 2005;19(2):294-304.
 83. Williams C, Miller LL, Gazzard G, Saw SM. A comparison of measures of reading and intelligence as risk factors for the development of myopia in a UK cohort of children. *Br J Ophthalmol.* 2008;92(8):1117-1121.
 84. Rah MJ, Mitchell GL, Mutti DO, Zadnik K. Levels of agreement between parents' and children's reports of near work. *Ophthalmic Epidemiol.* 2002;9(3):191-203.
 85. Tang SM, Kam KW, French AN, et al. Independent Influence of Parental Myopia on Childhood Myopia in a Dose-Related Manner in 2,055 Trios: The Hong Kong Children Eye Study. *Am J Ophthalmol.* 2020;218:199-207.
 86. Lim DH, Han J, Chung T-Y, Kang S, Yim HW. The high prevalence of myopia in Korean children with influence of parental refractive errors: The 2008-2012 Korean National Health and Nutrition Examination Survey. *PLoS One.* 2018;13(12):e0209876.
 87. Saw S, Shankar A, Tan S-B, et al. A Cohort Study of Incident Myopia in Singaporean Children. *Investig Ophthalmology Vis Sci.* 2006;47(5):1839.
 88. French AN, Morgan IG, Mitchell P, Rose KA. Risk factors for incident myopia in Australian schoolchildren: The Sydney Adolescent Vascular and Eye Study. *Ophthalmology.* 2013;120(10):2100-2108.

89. Low W, Dirani M, Gazzard G, et al. Family history, near work, outdoor activity, and myopia in Singapore Chinese preschool children. *Br J Ophthalmol*. 2010;94(8):1012-1016.
90. Xiang F, He M, Morgan IG. The impact of parental myopia on myopia in Chinese children: Population-based evidence. *Optom Vis Sci*. 2012;89(10):1487-1496.
91. Wu MMM, Edwards MH. The effect of having myopic parents: An analysis of myopia in three generations. *Optom Vis Sci*. 1999;76(6):387-392.
92. Jiang D, Lin H, Li C, et al. Longitudinal association between myopia and parental myopia and outdoor time among students in Wenzhou: a 2.5-year longitudinal cohort study. *BMC Ophthalmol*. 2021;21(1):1-8.
93. Flitcroft DI, He M, Jonas JB, et al. IMI – Defining and Classifying Myopia: A Proposed Set of Standards for Clinical and Epidemiologic Studies. *Investig Ophthalmology Vis Sci*. 2019;60(3):M20.
94. Hardy R, Hillis A, Mutti D, et al. Myopia stabilization and associated factors among participants in the correction of myopia evaluation trial (COMET). *Investig Ophthalmol Vis Sci*. 2013;54(13):7871-7883.
95. Wojciechowski R, Congdon N, Bowie H, Munoz B, Gilbert D, West SK. Heritability of Refractive Error and Familial Aggregation of Myopia in an Elderly American Population. *Investig Ophthalmology Vis Sci*. 2005;46(5):1588.
96. Grasby KL, Verweij KJH, Mosing MA, Zietsch BP, Medland SE. Estimating heritability from twin studies. *Methods Mol Biol*. 2017;1666:171-194.
97. Hammond CJ, Snieder H, Gilbert CE, Spector TD. Genes and environment in refractive error: The twin eye study. *Investig Ophthalmol Vis Sci*. 2001;42(6):1232-1236.

98. Lin LL, Chen C -J. A twin study on myopia in Chinese school children. *Acta Ophthalmol.* 1988;66(185 S):51-53.
99. Teikari JM, Kaprio J, Koskenvuo MK, Vannas A. Heritability estimate for refractive errors—a population-based sample of adult twins. *Genet Epidemiol.* 1988;5(3):171-181.
100. Klein AP, Suktitipat B, Duggal P, et al. Heritability analysis of spherical equivalent, axial length, corneal curvature, and anterior chamber depth in the Beaver Dam Eye Study. *Arch Ophthalmol (Chicago, Ill 1960).* 2009;127(5):649-655.
101. Guggenheim JA, Zhou X, Evans DM, et al. Coordinated genetic scaling of the human eye: Shared determination of axial eye length and corneal curvature. *Investig Ophthalmol Vis Sci.* 2013;54(3):1715-1721.
102. Kim MH, Zhao D, Kim W, et al. Heritability of myopia and ocular biometrics in Koreans: the healthy twin study. *Invest Ophthalmol Vis Sci.* 2013;54(5):3644-3649.
103. Tedja MS, Haarman AEG, Meester-Smoor MA, et al. IMI – Myopia genetics report. *Investig Ophthalmol Vis Sci.* 2019;60(3):M89-M105.
104. Verhoeven VJM, Hysi PG, Wojciechowski R, et al. Genome-wide meta-analyses of multiancestry cohorts identify multiple new susceptibility loci for refractive error and myopia. *Nat Genet.* 2013;45(3):314-318.
105. Kiefer AK, Tung JY, Do CB, et al. Genome-Wide Analysis Points to Roles for Extracellular Matrix Remodeling, the Visual Cycle, and Neuronal Development in Myopia. *PLoS Genet.* 2013;9(2).
106. Manolio TA, Collins FS, Cox NJ, et al. Finding the missing heritability of complex diseases. *Nature.* 2009;461(7265):747-753.

107. Verhoeven VJM, Buitendijk GHS, Rivadeneira F, et al. Education influences the role of genetics in myopia. *Eur J Epidemiol.* 2013;28(12):973-980.
108. Strang NC, Schmid KL, Carney LG. Hyperopia is predominantly axial in nature. *Curr Eye Res.* 1998;17(4):380-383.
109. Llorente L, Barbero S, Cano D, Dorronsoro C, Marcos S. Myopic versus hyperopic eyes: Axial length, corneal shape and optical aberrations. *J Vis.* 2004;4(4):288-298.
110. Choong YF, Chen AH, Goh PP. A Comparison of Autorefractometry and Subjective Refraction With and Without Cycloplegia in Primary School Children. *Am J Ophthalmol.* 2006;142(1).
111. Congdon N, Burnett A, Frick K. The impact of uncorrected myopia on individuals and society. *Community Eye Heal J.* 2019;32(105):7-8.
112. Harrington S, Davison PA, O'Dwyer V. School performance and undetected and untreated visual problems in schoolchildren in Ireland; a population-based cross-sectional study. *Irish Educ Stud.* 2021;0(0):1-22.
113. Kulp MT, Ciner E, Maguire M, et al. Uncorrected hyperopia and preschool early literacy: Results of the Vision in Preschoolers-Hyperopia in Preschoolers (VIP-HIP) study. *Ophthalmology.* 2016;123(4):681-689.
114. Haarman AEG, Enthoven CA, Tideman JWL, Tedja MS, Verhoeven VJM, Klaver CCW. The Complications of Myopia: A Review and Meta-Analysis. *Invest Ophthalmol Vis Sci.* 2020;61(4):49.
115. Saunders KJ. Early refractive development in humans. *Surv Ophthalmol.* 1995;40(3):207-216.
116. Mayer DL, Hansen RM, Moore BD, Kim S, Fulton AB. Cycloplegic refractions in healthy children aged 1 through 48 months. *Arch Ophthalmol.* 2001;119(11):1625-1628.

117. Varghese RM, Sreenivas V, Puliyeel JM, Varughese S. Refractive status at birth: Its relation to newborn physical parameters at birth and gestational age. *PLoS One*. 2009;4(2):1-6.
118. Semeraro F, Forbice E, Nascimbeni G, et al. Ocular Refraction at Birth and Its Development During the First Year of Life in a Large Cohort of Babies in a Single Center in Northern Italy. *Front Pediatr*. 2020;7(January):1-6.
119. Saunders KJ, McCulloch DL, Shepherd AJ, Wilkinson AG. Emmetropisation following preterm birth. *Br J Ophthalmol*. 2002;86(9):1035-1040.
120. Guzowski M, Wang JJ, Rochtchina E, Rose KA, Mitchell P. Five-year refractive changes in an older population: The Blue Mountains Eye Study. *Ophthalmology*. 2003;110(7):1364-1370.
121. Gudmundsdottir E, Arnarsson A, Jonasson F. Five-year refractive changes in an adult population: Reykjavik eye study. *Ophthalmology*. 2005;112(4):672-677.
122. Hashemi H, Iribarren R, Morgan IG, Khabazkhoob M, Mohammad K, Fotouhi A. Increased hyperopia with ageing based on cycloplegic refractions in adults: The Tehran Eye Study. *Br J Ophthalmol*. 2010;94(1):20-23.
123. Read SA, Collins MJ, Carney LG. A review of astigmatism and its possible genesis: Invited review. *Clin Exp Optom*. 2007;90(1):5-19.
124. Isenberg SJ, Del Signore M, Chen A, Wei J, Christenson PD. Corneal topography of neonates and infants. *Arch Ophthalmol*. 2004;122(12):1767-1771.
125. Rozema JJ, Hershko S, Tassignon MJ, et al. The components of adult astigmatism and their age-related changes. *Ophthalmic Physiol Opt*. 2019;39(3):183-193.
126. Mutti DO, Mitchell GL, Jones LA, et al. Refractive astigmatism and the toricity of ocular components in human infants. *Optom Vis Sci*. 2004;81(10):753-761.

127. Read SA, Collins MJ, Carney LG. The influence of eyelid morphology on normal corneal shape. *Investig Ophthalmol Vis Sci.* 2007;48(1):112-119.
128. Wilson G, Bell C, Chotai S. The effect of lifting the lids on corneal astigmatism. *Optom Vis Sci.* 1982;59(8):670-674.
129. Heidary G, Ying GS, Maguire MG, Young TL. The association of astigmatism and spherical refractive error in a high myopia cohort. *Optom Vis Sci.* 2005;82(4):244-247.
130. Tong L, Saw SM, Carkeet A, Chan WY, Wu HM, Tan D. Prevalence rates and epidemiological risk factors for astigmatism in Singapore school children. *Optom Vis Sci.* 2002;79(9):606-613.
131. Farbrother JE, Welsby JW, Guggenheim JA. Astigmatic Axis is Related to the Level of Spherical Ametropia. *Optom Vis Sci.* 2004;81(1):18-26.
132. Pärssinen O. Astigmatism and school myopia. *Acta Ophthalmol.* 1991;69(6):786-790.
133. Valluri S, Minkovitz JB, Budak K, et al. Comparative corneal topography and refractive variables in monozygotic and dizygotic twins. *Am J Ophthalmol.* 1999;127(2):158-163.
134. Wolffsohn JS, Davies LN. Presbyopia: Effectiveness of correction strategies. *Prog Retin Eye Res.* 2019;68:124-143.
135. Schachar RA. The Mechanism of Accommodation and Presbyopia. *Int Ophthalmol Clin.* 2006;46(3):39-61.
136. Charman WN. Virtual Issue Editorial: Presbyopia – grappling with an age-old problem. *Ophthalmic Physiol Opt.* 2017;37(6):655-660.
137. Sheppard AL, John Evans C, Singh KD, Wolffsohn JS, Dunne MCM, Davies LN. Three-dimensional magnetic resonance imaging of the phakic crystalline lens during accommodation. *Investig Ophthalmol Vis Sci.* 2011;52(6):3689-3697.

138. Laughton DS, Sheppard AL, Mallen EAH, Read SA, Davies LN. Does transient increase in axial length during accommodation attenuate with age? *Clin Exp Optom*. 2017;100(6):676-682.
139. Miranda MN. The geographic factor in the onset of presbyopia. *Trans Am Ophthalmol Soc*. 1979;VOL. 77:603-621.
140. Patel I, West SK. Presbyopia: prevalence, impact, and interventions. *Community eye Heal*. 2007;20(63):40-41.
141. Heys KR, Cram SL, Truscott RJW. Massive increase in the stiffness of the human lens nucleus with age: The basis for presbyopia? *Mol Vis*. 2004;10(June):956-963.
142. Pointer JS. The presbyopic add. III. Influence of the distance refractive type. *Ophthalmic Physiol Opt*. 1995;15(4):249-253.
143. Abraham LM, Kuriakose T, Sivanandam V, Venkatesan N, Thomas R, Muliylil J. Amplitude of accommodation and its relation to refractive errors. *Indian J Ophthalmol*. 2005;53(2):105-108.
144. Spierer A, Shalev B. Presbyopia among normal individuals. *Graefe's Arch Clin Exp Ophthalmol*. 2003;241(2):101-105.
145. Weale RA. Human ocular aging and ambient temperature. *Br J Ophthalmol*. 1981;65(12):869-870.
146. Pointer JS. Gender-related optical aspects of the onset of presbyopia. *Ophthalmic Physiol Opt*. 2002;22(2):126-129.
147. Pointer JS. The presbyopic add. II. Age-related trend and a gender difference. *Ophthalmic Physiol Opt*. 1995;15(4):241-248.
148. Edwards MH, Law LF, Lee CM, Leung KM, Lui WO. Clinical norms for amplitude of

- accommodation in Chinese. *Ophthalmic Physiol Opt.* 1993;13(2):199-204.
149. Carnevali T, Southaphanh P. A retrospective study on presbyopia onset and progression in a Hispanic population. *Optometry.* 2005;76(1):37-46.
150. Weale RA. Epidemiology of refractive errors and presbyopia. *Surv Ophthalmol.* 2003;48(5):515-543.
151. Lin LLK, Shih YF, Hsiao CK, Chen CJ. Prevalence of myopia in Taiwanese schoolchildren: 1983 to 2000. *Ann Acad Med Singapore.* 2004;33(1):27-33.
152. Anton A, Andrada M, Mayo A, Portela J, Merayo J. Epidemiology of Refractive Errors in an Adult European Population: The Segovia Study. *Ophthalmic Epidemiol.* 2009;16(4):231-237.
153. Yotsukura E, Torii H, Inokuchi M, et al. Current Prevalence of Myopia and Association of Myopia with Environmental Factors among Schoolchildren in Japan. *JAMA Ophthalmol.* 2019;137(11):1233-1239.
154. Williams KM, Verhoeven VJM, Cumberland P, et al. Prevalence of refractive error in Europe: the European Eye Epidemiology (E3) Consortium. *Eur J Epidemiol.* 2015;30(4):305-315.
155. Rahi JS, Cumberland PM, Peckham CS. Myopia over the lifecourse: prevalence and early life influences in the 1958 British birth cohort. *Ophthalmology.* 2011;118(5):797-804.
156. Rim TH, Kim S-H, Lim KH, Choi M, Kim HY, Baek S-H. Refractive Errors in Koreans: The Korea National Health and Nutrition Examination Survey 2008-2012. *Korean J Ophthalmol.* 2016;30(3):214.
157. Yoon K, Mun G, Kim S-D, et al. Prevalence of Eye Diseases in South Korea: Data from the Korea National Health and Nutrition Examination Survey 2008-2009. *Korean J Ophthalmol.* 2011;25(6):421.

158. Vitale S, Ellwein L, Cotch MF, Ferris FL, Sperduto R. Prevalence of refractive error in the United States, 1999-2004. *Arch Ophthalmol (Chicago, Ill 1960)*. 2008;126(8):1111-1119.
159. Cumberland PM, Bao Y, Hysi PG, et al. Frequency and Distribution of Refractive Error in Adult Life: Methodology and Findings of the UK Biobank Study. Pan C-W, ed. *PLoS One*. 2015;10(10):e0139780.
160. Jonas JB, Xu L, Wang YX. The Beijing Eye Study. *Acta Ophthalmol*. 2009;87(3):247-261.
161. Cumberland PM, Bountziouka V, Rahi JS. Impact of varying the definition of myopia on estimates of prevalence and associations with risk factors: time for an approach that serves research, practice and policy. *Br J Ophthalmol*. 2018;102(10):1407-1412.
162. Young G, Sulley A, Hunt C. Prevalence of Astigmatism in Relation to Soft Contact Lens Fitting. *Eye Contact Lens Sci Clin Pract*. 2011;37(1):20-25.
163. Holden BA, Fricke TR, Ho SM, et al. Global vision impairment due to uncorrected presbyopia. *Arch Ophthalmol (Chicago, Ill 1960)*. 2008;126(12):1731-1739.
164. Hu YY, Wu JF, Lu TL, et al. Effect of cycloplegia on the refractive status of children: The shandong children eye study. *PLoS One*. 2015;10(2):1-10.
165. Sanfilippo PG, Chu BS, Bigault O, et al. What is the appropriate age cut-off for cycloplegia in refraction? *Acta Ophthalmol*. 2014;92(6):458-462.
166. Morgan IG, Iribarren R, Fotouhi A, Grzybowski A. Cycloplegic refraction is the gold standard for epidemiological studies. *Acta Ophthalmol*. 2015;93(6):581-585.
167. Mimouni M, Zoller L, Horowitz J, Wygnanski-Jaffe T, Morad Y, Mezer E. Cycloplegic autorefraction in young adults: is it mandatory? *Graefe's Arch Clin Exp Ophthalmol*. 2016;254(2):395-398.

168. Yazdani N, Sadeghi R, Momeni-Moghaddam H, Zarifmahmoudi L, Ehsaei A. Comparison of cyclopentolate versus tropicamide cycloplegia: A systematic review and meta-analysis. *J Optom.* 2018;11(3):135-143.
169. Wolffsohn JS, Kollbaum PS, Berntsen DA, et al. IMI – Clinical Myopia Control Trials and Instrumentation Report. *Investig Ophthalmology Vis Sci.* 2019;60(3):M132.
170. McCullough SJ, Doyle L, Saunders KJ. Intra- and inter- examiner repeatability of cycloplegic retinoscopy among young children. *Ophthalmic Physiol Opt.* 2017;37(1):16-23.
171. Pesudovs K, Parker KE, Cheng H, Applegate RA. The precision of wavefront refraction compared to subjective refraction and autorefractometry. *Optom Vis Sci.* 2007;84(5):387-392.
172. Walline JJ. Myopia control: A review. *Eye Contact Lens.* 2016;42(1):3-8.
173. Bradley JC, Cohn CD, Wu PW, Brown SM. Comparison of a monocular pupillometer and the pupillometry function of a binocular free-viewing autorefractor. *J Cataract Refract Surg.* 2011;37(7):1257-1262.
174. Donovan L, Sankaridurg P, Ho A, Naduvilath T, Smith EL, A. Holden B. Myopia Progression Rates in Urban Children Wearing Single-Vision Spectacles. *Optom Vis Sci.* 2012;89(1):27-32.
175. Brown NAP, Hill AR. Cataract: the relation between myopia and cataract morphology. *Br J Ophthalmol.* 1987;71(6):405-414.
176. Saw SM, Gazzard G, Koh D, et al. Prevalence rates of refractive errors in Sumatra, Indonesia. *Investig Ophthalmol Vis Sci.* 2002;43(10):3174-3180.
177. Sawada A, Tomidokoro A, Araie M, Iwase A, Yamamoto T. Refractive Errors in an Elderly Japanese Population. *Ophthalmology.* 2008;115(2):363-370.e3.
178. Kim EC, Morgan IG, Kakizaki H, Kang S, Jee D. Prevalence and risk factors for refractive errors:

- Korean National Health and Nutrition Examination Survey 2008-2011. *PLoS One*. 2013;8(11):11-15.
179. Nakao S ya, Miyake M, Hosoda Y, et al. Myopia Prevalence and Ocular Biometry Features in a General Japanese Population: The Nagahama Study. *Ophthalmology*. Published online 2020:1-10.
180. Gupta A, Casson RJ, Newland HS, et al. Prevalence of Refractive Error in Rural Myanmar. The Meiktila Eye Study. *Ophthalmology*. 2008;115(1):26-34.
181. Xu L, Li J, Cui T, et al. Refractive error in urban and rural adult Chinese in Beijing. *Ophthalmology*. 2005;112(10):1676-1683.
182. Bourne RRA, Dineen BP, Ali SM, Noorul Huq DM, Johnson GJ. Prevalence of refractive error in Bangladeshi adults: Results of the national blindness and low vision survey of Bangladesh. *Ophthalmology*. 2004;111(6):1150-1160.
183. Nangia V, Jonas JB, Sinha A, Matin A, Kulkarni M. Refractive Error in Central India. The Central India Eye and Medical Study. *Ophthalmology*. 2010;117(4):693-699.
184. Krishnaiah S, Srinivas M, Khanna RC, Rao GN. Prevalence and risk factors for refractive errors in the South Indian adult population: The Andhra Pradesh Eye disease study. *Clin Ophthalmol*. 2009;3:17-27.
185. Hashemi H, Khabazkhoob M, Jafarzadehpur E, et al. High prevalence of myopia in an adult population, Shahroud, Iran. *Optom Vis Sci*. 2012;89(7):993-999.
186. Wong TY, Foster PJ, Hee J, et al. Prevalence and risk factors for refractive errors in adult Chinese in Singapore. *Invest Ophthalmol Vis Sci*. 2000;41(9):2486-2494.
187. Attebo K, Ivers R, Mitchell P. Refractive Errors in an Older Population - The Blue Mountains

- Study. *Ophthalmology*. 1999;106(6):1066-1072.
188. Mitchell JP, Williams N, Martin R, et al. The Venezuela Eye Evaluation Study. *J Natl Med Assoc*. 2008;100(4):435-438.
 189. Jiménez JR, Bermúdez J, Rubiño M, Gómez L, Anera RG. Prevalence of myopia in an adult population of two different ethnic groups in the Ecuadorian Amazon. *Jpn J Ophthalmol*. 2004;48(2):163-165.
 190. Galvis V, Tello A, Otero J, et al. Prevalence of refractive errors in Colombia: Miopur study. *Br J Ophthalmol*. 2018;102(10):1320-1323.
 191. Cortinez MF, Chiappe JP, Iribarren R. Prevalence of Refractive Errors in a Population of Office-Workers in Buenos Aires, Argentina. *Ophthalmic Epidemiol*. 2008;15(1):10-16.
 192. Chan VF, Mebrahtu G, Ramson P, Wepo M, Naidoo KS. Prevalence of Refractive Error and Spectacle Coverage in Zoba Ma'ekel Eritrea: A Rapid Assessment of Refractive Error. *Ophthalmic Epidemiol*. 2013;20(3):131-137.
 193. Bright T, Kuper H, Macleod D, Musendo D, Irunga P, Yip JLY. Population need for primary eye care in Rwanda: A national survey. Tsai D-C, ed. *PLoS One*. 2018;13(5):e0193817.
 194. Ezelum C, Razavi H, Sivasubramaniam S, et al. Refractive Error in Nigerian Adults: Prevalence, Type, and Spectacle Coverage. *Investig Ophthalmology Vis Sci*. 2011;52(8):5449.
 195. Mashige KP, Jaggernath J, Ramson P, Martin C, Chinanayi FS, Naidoo KS. Prevalence of Refractive Errors in the INK Area, Durban, South Africa. *Optom Vis Sci*. 2016;93(3):243-250.
 196. He M, Zheng Y, Xiang F. Prevalence of myopia in urban and rural children in mainland China. *Optom Vis Sci*. 2009;86(1):40-44.
 197. Tan CSH, Chan YH, Wong TY, et al. Prevalence and risk factors for refractive errors and ocular

- biometry parameters in an elderly Asian population: The Singapore Longitudinal Aging Study (SLAS). *Eye*. 2011;25(10):1294-1301.
198. Liang YB, Wong TY, Sun LP, et al. Refractive Errors in a Rural Chinese Adult Population. The Handan Eye Study. *Ophthalmology*. 2009;116(11):2119-2127.
199. Yoo YC, Kim JM, Park KH, Kim CY, Kim TW. Refractive errors in a rural Korean adult population: The Namil Study. *Eye*. 2013;27(12):1368-1375.
200. Nowak MS, Jurowski P, Grzybowski A, Smigielski J. Characteristics of Refractive Errors in a Population of Adults in the Central Region of Poland. *Int J Environ Res Public Health*. 2018;15(1):10-14.
201. Sherwin JC, Khawaja AP, Broadway D, et al. Uncorrected refractive error in older British adults: The EPIC-Norfolk eye study. *Br J Ophthalmol*. 2012;96(7):991-996.
202. Wang Q, Klein BEK, Klein R, Moss SE. Refractive status in the Beaver Dam eye study. *Investig Ophthalmol Vis Sci*. 1994;35(13):4344-4347.
203. Attebo K, Ivers RQ, Mitchell P. Refractive errors in an older population: the Blue Mountains Eye Study. *Ophthalmology*. 1999;106(6):1066-1072.
204. Hendricks TJW, de Brabander J, Vankan-Hendricks MHP, van der Horst FG, Hendrikse F, Knottnerus JA. Prevalence of habitual refractive errors and anisometropia among Dutch schoolchildren and hospital employees. *Acta Ophthalmol*. 2009;87(5):538-543.
205. Varma R, Torres M, McKean-Cowdin R, et al. Prevalence and Risk Factors for Refractive Error in Adult Chinese Americans: The Chinese American Eye Study. *Am J Ophthalmol*. 2017;175:201-212.
206. Hashemi H, Khabazkhoob M, Yekta A, et al. High prevalence of astigmatism in the 40- to 64-

- year-old population of Shahroud, Iran. *Clin Exp Ophthalmol*. 2012;40(3):247-254.
207. Fricke TR, Tahhan N, Resnikoff S, et al. Global Prevalence of Presbyopia and Vision Impairment from Uncorrected Presbyopia: Systematic Review, Meta-analysis, and Modelling. *Ophthalmology*. 2018;125(10):1492-1499.
208. Wang J, Ying GS, Fu X, et al. Prevalence of myopia and vision impairment in school students in Eastern China. *BMC Ophthalmol*. 2020;20(1):1-10.
209. Negrel AD, Maul E, Pokharel GP, Zhao J, Ellwein LB. Refractive error study in children: Sampling and measurement methods for a multi-country survey. *Am J Ophthalmol*. 2000;129(4):421-426.
210. Zhao J, Pan X, Sui R, Munoz SR, Sperduto RD, Ellwein LB. Refractive error study in children: Results from Shunyi District, China. *Am J Ophthalmol*. 2000;129(4):427-435.
211. Maul E, Barroso S, Munoz SR, Sperduto RD, Ellwein LB. Refractive Error Study in Children: results from La Florida, Chile. *Am J Ophthalmol*. 2000;129(4):445-454.
212. Murthy GVS, Gupta SK, Ellwein LB, et al. Refractive error in children in an urban population in New Delhi. *Investig Ophthalmol Vis Sci*. 2002;43(3):623-631.
213. He M, Zeng J, Liu Y, Xu J, Pokharel GP, Ellwein LB. Refractive Error and Visual Impairment in Urban Children in Southern China. *Investig Ophthalmology Vis Sci*. 2004;45(3):793.
214. Goh PP, Abqariyah Y, Pokharel GP, Ellwein LB. Refractive error and visual impairment in school-age children in Gombak District, Malaysia. *Ophthalmology*. 2005;112(4):678-685.
215. 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(9):1155-1159.

216. Harrington SC, Stack J, Saunders K, O'Dwyer V. Refractive error and visual impairment in Ireland schoolchildren. *Br J Ophthalmol*. 2019;103(8):1112-1118.
217. Naidoo KS, Raghunandan A, Mashige KP, et al. Refractive error and visual impairment in African children in South Africa. *Investig Ophthalmol Vis Sci*. 2003;44(9):3764-3770.
218. Moraes Ibrahim F, Moraes Ibrahim M, Pompeio de Camargo JR, Veronese Rodrigues M de L, Scott IU, Silva Paula J. Visual impairment and myopia in Brazilian children: a population-based study. *Optom Vis Sci*. 2013;90(3):223-227.
219. Jung S, Lee JH, Kakizaki H, Jee D. Prevalence of Myopia and its Association with Body Stature and Educational Level in 19-Year-Old Male Conscripts in Seoul, South Korea. *Investig Ophthalmology Vis Sci*. 2012;53(9):5579.
220. Semanyenzi SE, Karimurio J, Nzayirambaho M. Prevalence and pattern of refractive errors in high schools of Nyarugenge district. *Rwanda Med J*. 2015;72(3):8-13.
221. Mehari ZA, Yimer AW. Prevalence of refractive errors among schoolchildren in rural central Ethiopia. *Clin Exp Optom*. 2013;96(1):65-69.
222. Zhou W, Zhang Y, Li H, et al. Five-Year Progression of Refractive Errors and Incidence of Myopia in School-Aged Children in Western China. *J Epidemiol*. 2016;26(7):386-395.
223. Ma Y, Qu X, Zhu X, et al. Age-specific prevalence of visual impairment and refractive error in children aged 3–10 years in Shanghai, China. *Investig Ophthalmol Vis Sci*. 2016;57(14):6188-6196.
224. 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(5):550-558.

225. French AN, O'Donoghue L, Morgan IG, Saunders KJ, Mitchell P, Rose KA. Comparison of Refraction and Ocular Biometry in European Caucasian Children Living in Northern Ireland and Sydney, Australia. *Investig Ophthalmology Vis Sci*. 2012;53(7):4021.
226. Ovenseri-Ogbomo G, Dr V Omuemu. Prevalence of refractive error among school children in the Cape Coast Municipality, Ghana. *Clin Optom*. Published online 2010:59.
227. Dolgin E. The myopia boom. *Nature*. 2015;519(7543):276-278.
228. Hagen LA, Gjelle JVB, Arnegard S, Pedersen HR, Gilson SJ, Baraas RC. Prevalence and Possible Factors of Myopia in Norwegian Adolescents. *Sci Rep*. 2018;8(1):1-10.
229. Theophanous C, Modjtahedi BS, Batech M, Marlin DS, Luong TQ, Fong DS. Myopia prevalence and risk factors in children. *Clin Ophthalmol*. 2018;12:1581-1587.
230. De Amorim Garcia CA, Oréface F, Dutra Nobre GF, De Brito Souza D, Ramalho Rocha ML, Garrido Vianna RN. Prevalence of refractive errors in students in Northeastern Brazil. *Arq Bras Oftalmol*. 2005;68(3):321-325.
231. Quek TPL, Chua CG, Chong CS, et al. Prevalence of refractive errors in teenage high school students in Singapore. *Ophthalmic Physiol Opt*. 2004;24(1):47-55.
232. Hashemi H, Rezvan F, Beiranvand A, et al. Prevalence of Refractive Errors among High School Students in Western Iran. *J Ophthalmic Vis Res*. 2014;9(2):232-239.
233. Shapira Y, Mimouni M, Machluf Y, Chaiter Y, Saab H, Mezer E. The Increasing Burden of Myopia in Israel among Young Adults over a Generation: Analysis of Predisposing Factors. *Ophthalmology*. 2019;126(12):1617-1626.
234. Czepita D, Żejmo M, Mojsa A. Prevalence of myopia and hyperopia in a population of Polish schoolchildren. *Ophthalmic Physiol Opt*. 2006;27(1):60-65.

235. Taylor HR, Robin TA, Lansingh VC, Weih LM, Keeffe JE. A myopic shift in Australian Aboriginals: 1977-2000. *Trans Am Ophthalmol Soc.* 2003;101:107-110; discussion 110-2.
236. Bar Dayan Y, Levin A, Morad Y, et al. The changing prevalence of myopia in young adults: a 13-year series of population-based prevalence surveys. *Invest Ophthalmol Vis Sci.* 2005;46(8):2760-2765.
237. Chen M, Wu A, Zhang L, et al. The increasing prevalence of myopia and high myopia among high school students in Fenghua city, eastern China: a 15-year population-based survey. *BMC Ophthalmol.* 2018;18(1):159.
238. Liang YB, Lin Z, Vasudevan B, et al. Generational difference of refractive error in the baseline study of the Beijing Myopia Progression Study. *Br J Ophthalmol.* 2013;97(6):765-769.
239. Dong L, Kang YK, Li Y, Wei W Bin, Jonas JB. PREVALENCE AND TIME TRENDS OF MYOPIA IN CHILDREN AND ADOLESCENTS IN CHINA. *Retina.* 2020;40(3):399-411.
240. Priscilla JJ, Verkicharla PK. Time trends on the prevalence of myopia in India – A prediction model for 2050. *Ophthalmic Physiol Opt.* 2021;41(3):466-474.
241. WHO. World report on vision. *World Heal Organ.* 2019;214(14):1-160.
242. Resnikoff S, Pascolini D, Etya'ale D, et al. Global data on visual impairment in the year 2002. *Bull World Health Organ.* 2004;82(11):844-851.
243. Tseng YC, Liu SHY, Lou MF, Huang GS. Quality of life in older adults with sensory impairments: a systematic review. *Qual Life Res.* 2018;27(8):1957-1971.
244. Hassell JB, Lamoureux EL, Keeffe JE. Impact of age related macular degeneration on quality of life. *Br J Ophthalmol.* 2006;90(5):593-596.
245. Lamoureux EL, Chong E, Wang JJ, et al. Visual impairment, causes of vision loss, and falls: The

- singapore malay eye study. *Investig Ophthalmol Vis Sci*. 2008;49(2):528-533.
246. Lamoureux EL, Hassell JB, Keeffe JE. The Impact of Diabetic Retinopathy on Participation in Daily Living. *Arch Ophthalmol*. 2004;122(1):84-88.
247. West SK, Munoz B, Rubin GS, et al. Function and visual impairment in a population-based study of older adults: The SEE project. *Investig Ophthalmol Vis Sci*. 1997;38(1):72-82.
248. Klein BEK, Klein R, Lee KE, Cruickshanks KJ. Performance-based and self-assessed measures of visual function as related to history of falls, hip fractures, and measured gait time: The Beaver Dam Eye Study. *Ophthalmology*. 1998;105(1):160-164.
249. Frank CR, Xiang X, Stagg BC, Ehrlich JR. Longitudinal Associations of Self-reported Vision Impairment with Symptoms of Anxiety and Depression among Older Adults in the United States. *JAMA Ophthalmol*. 2019;137(7):793-800.
250. Rovner BW, Ganguli M. Depression and disability associated with impaired vision: The moVIES project. *J Am Geriatr Soc*. 1998;46(5):617-619.
251. Evans JR, Fletcher AE, Wormald RPL. Depression and Anxiety in Visually Impaired Older People. *Ophthalmology*. 2007;114(2):283-288.
252. Cosh S, von Hanno T, Helmer C, Bertelsen G, Delcourt C, Schirmer H. The association amongst visual, hearing, and dual sensory loss with depression and anxiety over 6 years: The Tromsø Study. *Int J Geriatr Psychiatry*. 2018;33(4):598-605.
253. Ehrlich JR, Ramke J, Macleod D, et al. Association between vision impairment and mortality: a systematic review and meta-analysis. *Lancet Glob Heal*. 2021;9(4):e418-e430.
254. Smith TST, Frick KD, Holden BA, Fricke TR, Naidoo KS. Potential lost productivity resulting from the global burden of uncorrected refractive error. *Bull World Health Organ*.

- 2009;87(6):431-437.
255. Deloitte Access Economics. The Cost of Sight Loss: The Economic Impact of Vision Impairment and Blindness in the Republic of Ireland. *Deloitte Access Econ.* 2011;(May).
256. Steinmetz JD, Bourne RRA, Briant PS, et al. Causes of blindness and vision impairment in 2020 and trends over 30 years, and prevalence of avoidable blindness in relation to VISION 2020: the Right to Sight: an analysis for the Global Burden of Disease Study. *Lancet Glob Heal.* 2021;9(2):e144-e160.
257. European Council of Optometry and Optics. *Blue Book 2020 Trends in Optics and Optometry - Comparative European Data.*; 2020.
258. Resnikoff S, Lansingh VC, Washburn L, et al. Estimated number of ophthalmologists worldwide (International Council of Ophthalmology update): Will we meet the needs? *Br J Ophthalmol.* 2020;104(4):588-592.
259. Kelliher C, Kenny D, O'Brien C. Trends in blind registration in the adult population of the Republic of Ireland 1996-2003. *Br J Ophthalmol.* 2006;90(3):367-371.
260. Munier A, Gunning T, Kenny D, O'Keefe M. Causes of blindness in the adult population of the Republic of Ireland. *Br J Ophthalmol.* 1998;82(6):630-633.
261. Robinson R, Deutsch J, Jones HS, et al. Unrecognised and unregistered visual impairment. *Br J Ophthalmol.* 1994;78(10):736-740.
262. Tracey ML, McHugh SM, Fitzgerald AP, Buckley CM, Canavan RJ, Kearney PM. Trends in blindness due to diabetic retinopathy among adults aged 18–69 years over a decade in Ireland. *Diabetes Res Clin Pract.* 2016;121:1-8.
263. Solomon SD, Lindsley K, Vedula SS, Krzystolik MG, Hawkins BS. Anti-vascular endothelial

- growth factor for neovascular age-related macular degeneration. *Cochrane Database Syst Rev.* 2014;35(10):1957-1963.
264. Pandey R, Morgan MM, Murphy C, et al. Irish National Diabetic RetinaScreen Programme: Report on five rounds of retinopathy screening and screen-positive referrals. (INDEAR study report no. 1). *Br J Ophthalmol.* 2020;(1):1-6.
265. Goggin M, O'Keefe M. Childhood blindness in the Republic of Ireland: A national survey. *Br J Ophthalmol.* 1991;75(7):425-429.
266. Khan RI, O'Keefe M, Nolan L, Kenny D. Changing pattern of childhood blindness. *Ir Med J.* 2007;100(5):82-85.
267. Verhoeven VJM, Wong KT, Buitendijk GHS, Hofman A, Vingerling JR, Klaver CCW. Visual consequences of refractive errors in the general population. *Ophthalmology.* 2015;122(1):101-109.
268. McCrann S, Flitcroft I, Lalor K, Butler J, Bush A, Loughman J. Parental attitudes to myopia: a key agent of change for myopia control? *Ophthalmic Physiol Opt.* 2018;38(3):298-308.
269. Ruiz-Medrano J, Montero JA, Flores-Moreno I, Arias L, García-Layana A, Ruiz-Moreno JM. Myopic maculopathy: Current status and proposal for a new classification and grading system (ATN). *Prog Retin Eye Res.* 2019;69(November 2018):80-115.
270. Curtin BJ, Karlin DB. Axial length measurements and fundus changes of the myopic eye. I. The posterior fundus. *Trans Am Ophthalmol Soc.* 1970;68:312-334.
271. Ohno-Matsui K, Kawasaki R, Jonas JB, et al. International photographic classification and grading system for myopic maculopathy. *Am J Ophthalmol.* 2015;159(5):877-883.e7.
272. Hayashi K, Ohno-Matsui K, Shimada N, et al. Long-term pattern of progression of myopic

- maculopathy: A natural history study. *Ophthalmology*. 2010;117(8):1595-1611.e4.
273. Vongphanit J, Mitchell P, Wang JJ. Prevalence and progression of myopic retinopathy in an older population. *Ophthalmology*. 2002;109(4):704-711.
274. Ohno-Matsui K. Proposed classification of posterior staphylomas based on analyses of eye shape by three-dimensional magnetic resonance imaging and wide-field fundus imaging. *Ophthalmology*. 2014;121(9):1798-1809.
275. Ikuno Y. Overview of the complications of high myopia. *Retina*. 2017;37(12):2347-2351.
276. Mitry D, Chalmers J, Anderson K, et al. Temporal trends in retinal detachment incidence in Scotland between 1987 and 2006. *Br J Ophthalmol*. 2011;95(3):365-369.
277. Van Leeuwen R, Haarman AEG, Van De Put MAJ, Klaver CCW, Los LI. Association of Rhegmatogenous Retinal Detachment Incidence with Myopia Prevalence in the Netherlands. *JAMA Ophthalmol*. 2021;139(1):85-92.
278. Park SJ, Choi NK, Park KH, Woo SJ. Five year nationwide incidence of rhegmatogenous retinal detachment requiring surgery in Korea. *PLoS One*. 2013;8(11).
279. Tan NYQ, Sng CCA, Jonas JB, Wong TY, Jansonius NM, Ang M. Glaucoma in myopia: Diagnostic dilemmas. *Br J Ophthalmol*. 2019;103(10):1347-1355.
280. Marcus MW, De Vries MM, Junoy Montolio FG, Jansonius NM. Myopia as a risk factor for open-angle glaucoma: A systematic review and meta-analysis. *Ophthalmology*. 2011;118(10):1989-1994.e2.
281. Cedrone C, Mancino R, Ricci F, Cerulli A, Culasso F, Nucci C. The 12-year incidence of glaucoma and glaucoma-related visual field loss in Italy: The Ponza eye study. *J Glaucoma*. 2012;21(1):1-6.

282. Hsu CH, Chen RI, Lin SC. Myopia and glaucoma: Sorting out the difference. *Curr Opin Ophthalmol*. 2015;26(2):90-95.
283. Pan CW, Cheng CY, Saw SM, Wang JJ, Wong TY. Myopia and age-related cataract: A systematic review and meta-analysis. *Am J Ophthalmol*. 2013;156(5):1021-1033.e1.
284. Lim R, Mitchell P, Cumming RG. Refractive associations with cataract: the Blue Mountains Eye Study. *Invest Ophthalmol Vis Sci*. 1999;40(12):3021-3026.
285. Pan CW, Ikram MK, Cheung CY, et al. Refractive errors and age-related macular degeneration: A systematic review and meta-analysis. *Ophthalmology*. 2013;120(10):2058-2065.
286. Pallikaris IG, Kymionis GD, Ginis HS, Kounis GA, Christodoulakis E, Tsilimbaris MK. Ocular rigidity in patients with age-related macular degeneration. *Am J Ophthalmol*. 2006;141(4).
287. Lowe RF. Aetiology of the anatomical basis for primary angle-closure glaucoma. Biometrical comparisons between normal eyes and eyes with primary angle-closure glaucoma. *Br J Ophthalmol*. 1970;54(3):161-169.
288. Xu L, Cao WF, Wang YX, Chen CX, Jonas JB. Anterior Chamber Depth and Chamber Angle and Their Associations with Ocular and General Parameters: The Beijing Eye Study. *Am J Ophthalmol*. 2008;145(5).
289. Vijaya L, George R, Arvind H, et al. Prevalence of Primary Angle-Closure Disease in an Urban South Indian Population and Comparison with a Rural Population. The Chennai Glaucoma Study. *Ophthalmology*. 2008;115(4):655-661.
290. Van Romunde SHM, Thepass G, Lemij HG. Is hyperopia an important risk factor for PACG in the dutch population? - A case control study. *J Ophthalmol*. 2013;2013.
291. Hopf S, Korb C, Nickels S, et al. Prevalence of myopic maculopathy in the German population:

- Results from the Gutenberg health study. *Br J Ophthalmol*. 2020;104(9):1254-1259.
292. Xiao O, Guo X, Wang D, et al. Distribution and severity of myopic maculopathy among highly myopic eyes. *Investig Ophthalmol Vis Sci*. 2018;59(12):4880-4885.
293. Koh V, Tan C, Tan PT, et al. Myopic Maculopathy and Optic Disc Changes in Highly Myopic Young Asian Eyes and Impact on Visual Acuity. *Am J Ophthalmol*. 2016;164:69-79.
294. Tideman JW, Snabel MC, Tedja MS, et al. Association of axial length with risk of uncorrectable visual impairment for Europeans with myopia. *JAMA Ophthalmol*. 2016;134(12):1355-1363.
295. Leveziel N, Marillet S, Dufour Q, et al. Prevalence of macular complications related to myopia – Results of a multicenter evaluation of myopic patients in eye clinics in France. *Acta Ophthalmol*. 2020;98(2):e245-e251.
296. Bullimore MA, Ritchey ER, Shah S, Leveziel N, Bourne RRA, Flitcroft DI. The Risks and Benefits of Myopia Control. *Ophthalmology*. 2021;128(11):1561-1579.
297. Fricke TR, Jong M, Naidoo KS, et al. Global prevalence of visual impairment associated with myopic macular degeneration and temporal trends from 2000 through 2050: Systematic review, meta-analysis and modelling. *Br J Ophthalmol*. 2018;102(7):855-862.
298. Frick KD, Joy SM, Wilson DA, Naidoo KS, Holden BA. The Global Burden of Potential Productivity Loss from Uncorrected Presbyopia. *Ophthalmology*. 2015;122(8):1706-1710.
299. Chan VF, MacKenzie GE, Kassalow J, Gudwin E, Congdon N. Impact of presbyopia and its correction in low- And middle-income countries. *Asia-Pacific J Ophthalmol*. 2018;7(6):370-374.
300. Naidoo KS, Jaggernath J, Chinanayi FS, Chan VF. Near vision correction and work productivity

- among textile workers. *African Vis Eye Heal.* 2016;75(1):1-6.
301. Reddy PA, Congdon N, MacKenzie G, et al. Effect of providing near glasses on productivity among rural Indian tea workers with presbyopia (PROSPER): a randomised trial. *Lancet Glob Heal.* 2018;6(9):e1019-e1027.
302. The Economist. The world's most valuable resource is no longer oil, but data. *Econ.* 2017;423:5-8.
303. Scheetz J, He M, van Wijngaarden P. Ophthalmology and the emergence of artificial intelligence. *Med J Aust.* 2021;214(4):155-157.e1.
304. Baro E, Degoul S, Beuscart R, Chazard E. Toward a literature-driven definition of big data in healthcare. *Biomed Res Int.* 2015;2015.
305. Andreu-Perez J, Poon CCY, Merrifield RD, Wong STC, Yang GZ. Big Data for Health. *IEEE J Biomed Heal Informatics.* 2015;19(4):1193-1208.
306. Reeves SW, Sloan FA, Lee PP, Jaffe GJ. Uveitis in the elderly: Epidemiological data from the National Long-term Care Survey medicare cohort. *Ophthalmology.* 2006;113(2):302-308.
307. Liu Y, Wang H, Zhao W, Zhang M, Qin H, Xie Y. Flexible, stretchable sensors for wearable health monitoring: Sensing mechanisms, materials, fabrication strategies and features. *Sensors (Switzerland).* 2018;18(2).
308. Schoen C, Osborn R, Squires D, et al. A Survey Of Primary Care Doctors In Ten Countries Shows Progress In Use Of Health Information Technology, Less In Other Areas. *Health Aff.* 2012;31(12):2805-2816.
309. Moore M, Loughman J, Butler JS, Ohlendorf A, Wahl S, Flitcroft DI. Application of big-data for epidemiological studies of refractive error. Mimouni M, ed. *PLoS One.* 2021;16(4):e0250468.

310. Willis JR, Vitale S, Morse L, et al. The Prevalence of Myopic Choroidal Neovascularization in the United States: Analysis of the IRIS®Data Registry and NHANES. *Ophthalmology*. 2016;123(8):1771-1782.
311. Donthineni PR, Kammari P, Shanbhag SS, Singh V, Das AV, Basu S. Incidence, demographics, types and risk factors of dry eye disease in India: Electronic medical records driven big data analytics report I. *Ocul Surf*. 2019;17(2):250-256.
312. Das AV, Donthineni PR, Sai Prashanthi G, Basu S. Allergic eye disease in children and adolescents seeking eye care in India: Electronic medical records driven big data analytics report II. *Ocul Surf*. 2019;17(4):683-689.
313. Johnston RL, Lee AY, Buckle M, et al. UK Age-Related Macular Degeneration Electronic Medical Record System (AMD EMR) Users Group Report IV: Incidence of Blindness and Sight Impairment in Ranibizumab-Treated Patients. *Ophthalmology*. 2016;123(11):2386-2392.
314. Willis J, Morse L, Vitale S, et al. Treatment Patterns for Myopic Choroidal Neovascularization in the United States: Analysis of the IRIS Registry. *Ophthalmology*. 2017;124(7):935-943.
315. Coleman AL. How Big Data Informs Us about Cataract Surgery: The LXXII Edward Jackson Memorial Lecture. *Am J Ophthalmol*. 2015;160(6):1091-1103.e3.
316. Lin H, Long E, Ding X, et al. Prediction of myopia development among Chinese school-aged children using refraction data from electronic medical records: A retrospective, multicentre machine learning study. *PLoS Med*. 2018;15(11):1-17.
317. Shuldiner SR, Boland M V, Ramulu PY, et al. Predicting eyes at risk for rapid glaucoma progression based on an initial visual field test using machine learning. Le KNQ, ed. *PLoS One*. 2021;16(4):e0249856.
318. Bommakanti NK, Zhou Y, Ehrlich JR, et al. Application of the Sight Outcomes Research

- Collaborative Ophthalmology Data Repository for Triaging Patients with Glaucoma and Clinic Appointments during Pandemics Such as COVID-19. *JAMA Ophthalmol.* 2020;138(9):974-980.
319. Jones L, Bryan SR, Miranda MA, Crabb DP, Kotecha A. Example of monitoring measurements in a virtual eye clinic using “big data.” *Br J Ophthalmol.* 2018;102(7):911-915.
320. Parke DW, Rich WL, Sommer A, Lum F. The American Academy of Ophthalmology’s IRIS[®] Registry (Intelligent Research in Sight Clinical Data): A Look Back and a Look to the Future. *Ophthalmology.* 2017;124(11):1572-1574.
321. Vanner EA, Sun CQ, McSoley MJ, et al. Tube Versus Trabeculectomy IRIS registry 1-Year Composite Outcome Analysis with Comparisons to the Randomized Controlled Trial. *Am J Ophthalmol.* 2021;227:87-99.
322. Pershing S, Lum F, Hsu S, et al. Endophthalmitis after Cataract Surgery in the United States: A Report from the Intelligent Research in Sight Registry, 2013–2017. *Ophthalmology.* 2020;127(2):151-158.
323. Repka MX. Amblyopia Outcomes Through Clinical Trials and Practice Measurement: Room for Improvement: The LXXVII Edward Jackson Memorial Lecture. *Am J Ophthalmol.* 2020;219:A1-A26.
324. Cantrell RA, Lum F, Chia Y, et al. Treatment Patterns for Diabetic Macular Edema: An Intelligent Research in Sight (IRIS[®]) Registry Analysis. *Ophthalmology.* 2020;127(3):427-429.
325. Stein JD, Rahman M, Andrews C, et al. Evaluation of an Algorithm for Identifying Ocular Conditions in Electronic Health Record Data. *JAMA Ophthalmol.* 2019;137(5):491-497.
326. Javitt JC, Vitale S, Canner JK, et al. National Outcomes of Cataract Extraction: Endophthalmitis Following Inpatient Surgery. *Arch Ophthalmol.* 1991;109(8):1085-1089.

327. Clark A, Ng JQ, Morlet N, Semmens JB. Big data and ophthalmic research. *Surv Ophthalmol*. 2016;61(4):443-465.
328. Cassard SD, Quigley HA, Gower EW, Friedman DS, Ramulu PY, Jampel HD. Regional variations and trends in the prevalence of diagnosed glaucoma in the medicare population. *Ophthalmology*. 2012;119(7):1342-1351.
329. Gritz DC, Wong IG. Incidence and prevalence of uveitis in Northern California: The Northern California Epidemiology of Uveitis Study. *Ophthalmology*. 2004;111(3):491-500.
330. Rim TH, Kim SS, Ham D II, Yu SY, Chung EJ, Lee SC. Incidence and prevalence of uveitis in South Korea: A nationwide cohort study. *Br J Ophthalmol*. Published online 2017:1-5.
331. Hwang DK, Chou YJ, Pu CY, Chou P. Epidemiology of uveitis among the Chinese population in Taiwan: A population-based study. *Ophthalmology*. 2012;119(11):2371-2376.
332. Dahrouj M, Miller JB. Artificial Intelligence (AI) and Retinal Optical Coherence Tomography (OCT). *Semin Ophthalmol*. 2021;00(00):1-5.
333. Ting DSW, Peng L, Varadarajan A V., et al. Deep learning in ophthalmology: The technical and clinical considerations. *Prog Retin Eye Res*. 2019;72(December 2018):100759.
334. Ting DSW, Pasquale LR, Peng L, et al. Artificial intelligence and deep learning in ophthalmology. *Br J Ophthalmol*. 2019;103(2):167-175.
335. Budai A, Bock R, Maier A, Hornegger J, Michelson G. Robust vessel segmentation in fundus images. *Int J Biomed Imaging*. 2013;2013.
336. Carmona EJ, Rincón M, García-Feijó J, Martínez-de-la-Casa JM. Identification of the optic nerve head with genetic algorithms. *Artif Intell Med*. 2008;43(3):243-259.
337. Kauppi T, Kämäräinen J-K, Lensu L, et al. Constructing Benchmark Databases and Protocols for

- Medical Image Analysis: Diabetic Retinopathy. *Comput Math Methods Med.* 2013;2013:1-15.
338. Abràmoff MD, Folk JC, Han DP, et al. Automated Analysis of Retinal Images for Detection of Referable Diabetic Retinopathy. *JAMA Ophthalmol.* 2013;131(3):351.
339. Farsiu S, Chiu SJ, O'Connell R V., et al. Quantitative classification of eyes with and without intermediate age-related macular degeneration using optical coherence tomography. *Ophthalmology.* 2014;121(1):162-172.
340. Kermany DS, Goldbaum M, Cai W, et al. Identifying Medical Diagnoses and Treatable Diseases by Image-Based Deep Learning. *Cell.* 2018;172(5):1122-1131.e9.
341. Sudlow C, Gallacher J, Allen N, et al. UK Biobank: An Open Access Resource for Identifying the Causes of a Wide Range of Complex Diseases of Middle and Old Age. *PLoS Med.* 2015;12(3):1-10.
342. McKibbin M, Farragher T, Shickle D. Vitreoretinal interface abnormalities in middle-aged adults with visual impairment in the UK Biobank study: Prevalence, impact on visual acuity and associations. *BMJ Open Ophthalmol.* 2017;1(1).
343. Chan MPY, Grossi CM, Khawaja AP, et al. Associations with intraocular pressure in a large cohort: Results from the UK Biobank. *Ophthalmology.* 2016;123(4):771-782.
344. Patel PJ, Foster PJ, Grossi CM, et al. Spectral-domain optical coherence tomography imaging in 67 321 adults: Associations with macular thickness in the UK biobank study. *Ophthalmology.* 2016;123(4):829-840.
345. Plotnikov D, Williams C, Atan D, Davies NM, Mojarrad NG, Guggenheim JA. Effect of education on myopia: Evidence from the United Kingdom ROSLA 1972 Reform. *Investig Ophthalmol Vis Sci.* 2020;61(11).

346. Chua SYL, Warwick A, Peto T, et al. Association of ambient air pollution with age-related macular degeneration and retinal thickness in UK Biobank. *Br J Ophthalmol*. Published online 2021:1-7.
347. Cumberland PM, Rahi JS. Visual function, social position, and health and life chances the UK Biobank study. *JAMA Ophthalmol*. 2016;134(9):959-966.
348. Wen L, Cheng Q, Lan W, et al. An objective comparison of light intensity and near-visual tasks between rural and urban school children in China by a wearable device clouclip. *Transl Vis Sci Technol*. 2019;8(6).
349. Wen L, Cheng Q, Cao Y, et al. The Clouclip, a wearable device for measuring near-work and outdoor time: validation and comparison of objective measures with questionnaire estimates. *Acta Ophthalmol*. Published online 2021:1-14.
350. Cao Y, Lan W, Wen L, et al. An effectiveness study of a wearable device (Clouclip) intervention in unhealthy visual behaviors among school-age children: A pilot study. *Med (United States)*. 2020;99(2).
351. Mansouri K. The road ahead to continuous 24-hour intraocular pressure monitoring in glaucoma. *J Ophthalmic Vis Res*. 2014;9(2):260-268.
352. Perakakis N, Yazdani A, Karniadakis GE, Mantzoros C. Omics, big data and machine learning as tools to propel understanding of biological mechanisms and to discover novel diagnostics and therapeutics. *Metabolism*. 2018;87:A1-A9.
353. Haines JL, Hauser MA, Schmidt S, et al. Complement factor H variant increases the risk of age-related macular degeneration. *Science (80-)*. 2005;308(5720):419-421.
354. Corvin A, Craddock N, Sullivan PF. Genome-wide association studies: A primer. *Psychol Med*. 2010;40(7):1063-1077.

355. Choquet H, Paylakhi S, Kneeland SC, et al. A multiethnic genome-wide association study of primary open-angle glaucoma identifies novel risk loci. *Nat Commun.* 2018;9(1).
356. Wiggs JL, Pasquale LR. Genetics of glaucoma. *Hum Mol Genet.* 2017;26(R1):R21-R27.
357. Graham PS, Kaidonis G, Abhary S, et al. Genome-wide association studies for diabetic macular edema and proliferative diabetic retinopathy. *BMC Med Genet.* 2018;19(1):1-8.
358. Huang YC, Lin JM, Lin HJ, et al. Genome-wide association study of diabetic retinopathy in a Taiwanese population. *Ophthalmology.* 2011;118(4):642-648.
359. Fritsche LG, Igl W, Bailey JNC, et al. A large genome-wide association study of age-related macular degeneration highlights contributions of rare and common variants. *Nat Genet.* 2016;48(2):134-143.
360. Holliday EG, Smith A V., Cornes BK, et al. Insights into the Genetic Architecture of Early Stage Age-Related Macular Degeneration: A Genome-Wide Association Study Meta-Analysis. *PLoS One.* 2013;8(1).
361. Chen W, Stambolian D, Edwards AO, et al. Genetic variants near TIMP3 and high-density lipoprotein-associated loci influence susceptibility to age-related macular degeneration. *Proc Natl Acad Sci U S A.* 2010;107(16):7401-7406.
362. Verhoeven VJM, Hysi PG, Saw SM, et al. Large scale international replication and meta-analysis study confirms association of the 15q14 locus with myopia. The CREAM consortium. *Hum Genet.* 2012;131(9):1467-1480.
363. Hysi PG, Young TL, MacKey DA, et al. A genome-wide association study for myopia and refractive error identifies a susceptibility locus at 15q25. *Nat Genet.* 2010;42(10):902-905.
364. Hysi PG, Mahroo OA, Cumberland P, et al. Common mechanisms underlying refractive error

- identified in functional analysis of gene lists from genome-wide association study results in 2 European British cohorts. *JAMA Ophthalmol.* 2014;132(1):50-56.
365. Guggenheim JA, McMahon G, Kemp JP, et al. A genome-wide association study for corneal curvature identifies the platelet-derived growth factor receptor alpha gene as a quantitative trait locus for eye size in white Europeans. *Mol Vis.* 2013;19(February):243-253.
366. Cheng CY, Schache M, Ikram MK, et al. Nine loci for ocular axial length identified through genome-wide association studies, including shared loci with refractive error. *Am J Hum Genet.* 2013;93(2):264-277.
367. Ozel AB, Moroi SE, Reed DM, et al. Genome-wide association study and meta-analysis of intraocular pressure. *Hum Genet.* 2014;133(1):41-57.
368. MacGregor S, Ong JS, An J, et al. Genome-wide association study of intraocular pressure uncovers new pathways to glaucoma. *Nat Genet.* 2018;50(8):1067-1071.
369. Sedgwick P. Bias in observational study designs: Prospective cohort studies. *BMJ.* 2014;349(December):1-3.
370. MacKey DA, Hewitt AW. Genome-wide association study success in ophthalmology. *Curr Opin Ophthalmol.* 2014;25(5):386-393.
371. Swift A, Heale R, Twycross A. What are sensitivity and specificity? *Evid Based Nurs.* 2020;23(1):2019-2021.
372. Streiner DL, Cairney J. What's under the ROC? An Introduction to Receiver Operating Characteristics Curves. *Can J Psychiatry.* 2007;52(2):121-128.
373. Ganley JP. Longitudinal prevalence of major eye diseases. *Evidence-Based Eye Care.* 2004;5(1).

374. Sloan FA, Belsky D, Ruiz D, Lee P. Changes in incidence of diabetes mellitus-related eye disease among US elderly persons, 1994-2005. *Arch Ophthalmol*. 2008;126(11):1548-1553.
375. Martinez-Thompson JM, Diehl NN, Holmes JM, Mohny BG. Incidence, types, and lifetime risk of adult-onset strabismus. *Ophthalmology*. 2014;121(4):877-882.
376. Stein JD, Kim DS, Niziol LM, et al. Differences in rates of glaucoma among Asian Americans and other racial groups, and among various Asian ethnic groups. *Ophthalmology*. 2011;118(6):1031-1037.
377. Jammal AA, Thompson AC, Mariottoni EB, et al. Rates of Glaucomatous Structural and Functional Change From a Large Clinical Population: The Duke Glaucoma Registry Study. *Am J Ophthalmol*. 2021;222:238-247.
378. Cedrone C, Ricci F, Regine F, Cerulli A, Palma S, Culasso F. Nationwide incidence of endophthalmitis among the general population and the subjects at risk of endophthalmitis in Italy. *Ophthalmic Epidemiol*. 2008;15(6):366-371.
379. Sarah Wild, Gojka Roglic, Anders Green, Richard Sicree HK. Estimates for the year 2000 and projections for 2030. *World Health*. 2004;27(5):1047-1053.
380. Beede E, Baylor E, Hersch F, et al. A Human-Centered Evaluation of a Deep Learning System Deployed in Clinics for the Detection of Diabetic Retinopathy. *Conf Hum Factors Comput Syst - Proc*. Published online 2020:1-12.
381. Gulshan V, Peng L, Coram M, et al. Development and validation of a deep learning algorithm for detection of diabetic retinopathy in retinal fundus photographs. *JAMA - J Am Med Assoc*. 2016;316(22):2402-2410.
382. Gulshan V, Rajan RP, Widner K, et al. Performance of a Deep-Learning Algorithm vs Manual Grading for Detecting Diabetic Retinopathy in India. *JAMA Ophthalmol*. 2019;137(9):987-993.

383. Sayres R, Taly A, Rahimy E, et al. Using a Deep Learning Algorithm and Integrated Gradients Explanation to Assist Grading for Diabetic Retinopathy. *Ophthalmology*. 2019;126(4):552-564.
384. Ran AR, Tham CC, Chan PP, et al. Deep learning in glaucoma with optical coherence tomography: a review. *Eye*. 2021;35(1):188-201.
385. Muhammad H, Fuchs TJ, De Cuir N, et al. Hybrid Deep Learning on Single Wide-field Optical Coherence tomography Scans Accurately Classifies Glaucoma Suspects. *J Glaucoma*. 2017;26(12):1086-1094.
386. Lee J, Kim YK, Park KH, Jeoung JW. Diagnosing Glaucoma with Spectral-domain Optical Coherence Tomography Using Deep Learning Classifier. *J Glaucoma*. 2020;29(4):287-294.
387. Thompson AC, Jammal AA, Berchuck SI, Mariottoni EB, Medeiros FA. Assessment of a Segmentation-Free Deep Learning Algorithm for Diagnosing Glaucoma from Optical Coherence Tomography Scans. *JAMA Ophthalmol*. 2020;138(4):333-339.
388. Ran AR, Cheung CY, Wang X, et al. Detection of glaucomatous optic neuropathy with spectral-domain optical coherence tomography: a retrospective training and validation deep-learning analysis. *Lancet Digit Heal*. 2019;1(4):e172-e182.
389. Thompson AC, Jammal AA, Medeiros FA. A Deep Learning Algorithm to Quantify Neuroretinal Rim Loss From Optic Disc Photographs. *Am J Ophthalmol*. 2019;201:9-18.
390. Li Z, He Y, Keel S, Meng W, Chang RT, He M. Efficacy of a Deep Learning System for Detecting Glaucomatous Optic Neuropathy Based on Color Fundus Photographs. *Ophthalmology*. 2018;125(8):1199-1206.
391. Jampel HD, Friedman D, Quigley H, et al. Agreement Among Glaucoma Specialists in Assessing Progressive Disc Changes From Photographs in Open-Angle Glaucoma Patients. *Am J Ophthalmol*. 2009;147(1):39-44.

392. Medeiros FA, Jammal AA, Mariottoni EB. Detection of Progressive Glaucomatous Optic Nerve Damage on Fundus Photographs with Deep Learning. *Ophthalmology*. 2021;128(3):383-392.
393. Bullimore MA, Brennan NA. Myopia Control: Why Each Diopter Matters. *Optom Vis Sci*. 2019;96(6):463-465.
394. Brennan NA, Toubouti YM, Cheng X, Bullimore MA. Efficacy in myopia control. *Prog Retin Eye Res*. 2020;(xxxx):100923.
395. Varadarajan A V., Poplin R, Blumer K, et al. Deep Learning for Predicting Refractive Error From Retinal Fundus Images. *Investig Ophthalmology Vis Sci*. 2018;59(7):2861.
396. Goh JHL, Lim ZW, Fang X, et al. Artificial intelligence for cataract detection and management. *Asia-Pacific J Ophthalmol*. 2020;9(2):88-95.
397. Pead E, Megaw R, Cameron J, et al. Automated detection of age-related macular degeneration in color fundus photography: a systematic review. *Surv Ophthalmol*. 2019;64(4):498-511.
398. Scruggs BA, Paulchan R V., Kalpathy-Cramer J, Chiang MF, Peter Campbell J. Artificial intelligence in retinopathy of prematurity diagnosis. *Transl Vis Sci Technol*. 2020;9(2):1-10.
399. Poplin R, Varadarajan A V., Blumer K, et al. Prediction of cardiovascular risk factors from retinal fundus photographs via deep learning. *Nat Biomed Eng*. 2018;2(3):158-164.
400. Blonde L, Khunti K, Harris SB, Meizinger C, Skolnik NS. Interpretation and Impact of Real-World Clinical Data for the Practicing Clinician. *Adv Ther*. 2018;35(11):1763-1774.
401. Anglemyer A, Horvath HT, Bero L. Healthcare outcomes assessed with observational study designs compared with those assessed in randomized trials. *Cochrane Database Syst Rev*. 2014;2014(4).

402. Lee AY, Lee CS, Butt T, et al. UK AMD EMR Users Group Report V: Benefits of initiating ranibizumab therapy for neovascular AMD in eyes with vision better than 6/12. *Br J Ophthalmol*. 2015;99(8):1045-1050.
403. Repka MX, Lum F, Burugapalli B. Strabismus, Strabismus Surgery, and Reoperation Rate in the United States: Analysis from the IRIS Registry. *Ophthalmology*. 2018;125(10):1646-1653.
404. Ting DSW, Lee AY, Wong TY. An Ophthalmologist's Guide to Deciphering Studies in Artificial Intelligence. *Ophthalmology*. 2019;126(11):1475-1479.
405. Zarbin MA, Lee AY, Keane PA, Chiang MF. Data Science in Translational Vision Science and Technology. *Transl Vis Sci Technol*. 2021;10(8):20.
406. Challen R, Denny J, Pitt M, Gompels L, Edwards T, Tsaneva-Atanasova K. Artificial intelligence, bias and clinical safety. *BMJ Qual Saf*. 2019;28(3):231-237.
407. Chang J, Lee J, Ha A, et al. Explaining the Rationale of Deep Learning Glaucoma Decisions with Adversarial Examples. *Ophthalmology*. 2021;128(1):78-88.
408. Parasuraman R, Manzey DH. Complacency and bias in human use of automation: An attentional integration. *Hum Factors*. 2010;52(3):381-410.
409. Tahvildari M, Singh RB, Saeed HN. Application of Artificial Intelligence in the Diagnosis and Management of Corneal Diseases. *Semin Ophthalmol*. 2021;00(00):1-8.
410. Central Statistics Office Ireland. Age and sex composition. *Census 2016 Rep*. 2016;Chapter 3:19-25.
411. Nguyen L, Bellucci E, Nguyen LT. Electronic health records implementation: An evaluation of information system impact and contingency factors. *Int J Med Inform*. 2014;83(11):779-796.
412. Fujiwara M, Hasebe S, Nakanishi R, Tanigawa K, Ohtsuki H. Seasonal variation in myopia

- progression and axial elongation: An evaluation of Japanese children participating in a myopia control trial. *Jpn J Ophthalmol*. 2012;56(4):401-406.
413. Gwiazda J, Deng L, Manny R, et al. Seasonal variations in the progression of myopia in children enrolled in the correction of myopia evaluation trial. *Investig Ophthalmol Vis Sci*. 2014;55(2):752-758.
414. Central Statistics Office Ireland. Geographical Distribution. *Census 2016 Rep*. 2016;Chapter 2:5.
415. Central Statistics Office Ireland. *Census 2016 Summary Results.*; 2017.
416. Smith W, Assink J, Klein R, et al. Risk factors for age-related macular degeneration. *Ophthalmology*. 2001;108(4):697-704.
417. Coleman AL, Miglior S. Risk Factors for Glaucoma Onset and Progression. *Surv Ophthalmol*. 2008;53(6 SUPPL.):3-10.
418. Cook EJ, Sharp C, Randhawa G, Guppy A, Gangotra R, Cox J. Who uses NHS health checks? Investigating the impact of ethnicity and gender and method of invitation on uptake of NHS health checks. *Int J Equity Health*. 2016;15(1):1-11.
419. Bourne RRA, Stevens GA, White RA, et al. Causes of vision loss worldwide, 1990–2010: a systematic analysis. *Lancet Glob Heal*. 2013;1(6):e339-e349.
420. Xu L, Wang Y, Li Y, et al. Causes of Blindness and Visual Impairment in Urban and Rural Areas in Beijing. The Beijing Eye Study. *Ophthalmology*. 2006;113(7):1134.e1-1134.e11.
421. Lavanya R, Kawasaki R, Tay WT, et al. Hyperopic refractive error and shorter axial length are associated with age-related macular degeneration: The Singapore Malay eye study. *Investig Ophthalmol Vis Sci*. 2010;51(12):6247-6252.

422. Pan C, Ramamurthy D, Saw S. Worldwide prevalence and risk factors for myopia. *Ophthalmic Physiol Opt.* 2012;32(1):3-16.
423. Ferraz FH, Corrente JE, Opromolla P, Padovani CR, Schellini SA. Refractive errors in a Brazilian population: age and sex distribution. *Ophthalmic Physiol Opt.* 2015;35(1):19-27.
424. Claxton K, Posnett J. An economic approach to clinical trial design and research priority-setting. *Health Econ.* 1996;5(6):513-524.
425. Phillips C V. The economics of “more research is needed.” *Int J Epidemiol.* 2001;30(4):771-776.
426. Mooney SJ, Westreich DJ, El-Sayed AM. Epidemiology in the era of big data. *Epidemiology.* 2015;26(3):390-394.
427. US Food and Drug Administration. Examining the Impact of Real-World Evidence on Medical Product Development. *Natl Acad Sci Eng Med.* 2018;(February).
428. Huwaldt J. Plot Digitizer.
429. Sullivan CM, Fowler CW. Analysis of a progressive addition lens population. *Ophthalmic Physiol Opt.* 1989;9(2):163-170.
430. Ritz C, Baty F, Streibig JC, Gerhard D. Dose-response analysis using R. *PLoS One.* 2015;10(12):1-13.
431. Grossniklaus H, Green W. Pathologic Findings in Pathologic Myopia. *Retina.* 1992;12(2):127-133.
432. Sedgwick P. Bias in observational study designs: Cross sectional studies. *BMJ.* 2015;350(March):2-3.
433. Kaplan RM, Chambers DA, Glasgow RE. Big data and large sample size: A cautionary note on

- the potential for bias. *Clin Transl Sci.* 2014;7(4):342-346.
434. Department of Employment Affairs and Social Protection. Almost 1.2 Million Claims for PRSI Treatment Benefit Supports. Published online 2020:1-5.
435. Health Service Executive. PCRS Optical Report. *PCRS Opt Rep.* Published online 2018:1-2.
436. The College of Optometrists. *Britain's Eye Health in Focus. A Snapshot of Consumer Attitudes and Behaviour towards Eye Health.*; 2013.
437. Hrynychak P. Prescribing spectacles: Reasons for failure of spectacle lens acceptance. *Ophthalmic Physiol Opt.* 2006;26(1):111-115.
438. Freeman CE, Evans BJW. Investigation of the causes of non-tolerance to optometric prescriptions for spectacles. *Ophthalmic Physiol Opt.* 2010;30(1):1-11.
439. Attebo K, Mitchell P, Cumming R, Smith W. Knowledge and beliefs about common eye diseases. *Aust N Z J Ophthalmol.* 1997;25(4):283-287.
440. Pascual M, Huang J, Maguire MG, et al. Risk factors for amblyopia in the vision in preschoolers study. *Ophthalmology.* 2014;121(3):622-629.e1.
441. Wong TY, Klein BEK, Klein R, Knudtson M, Lee KE. Refractive errors, intraocular pressure, and glaucoma in a white population. *Ophthalmology.* 2003;110(1):211-217.
442. Kanthan GL, Mitchell P, Rochtchina E, Cumming RG, Wang JJ. Myopia and the long-term incidence of cataract and cataract surgery: The Blue Mountains Eye Study. *Clin Exp Ophthalmol.* 2014;42(4):347-353.
443. Yannuzzi L. Risk Factors for Idiopathic Rhegmatogenous Retinal Detachment. *Am J Epidemiol.* 1993;137(7):749-757.
444. Vu HTV, Keeffe JE, McCarty CA, Taylor HR. Impact of unilateral and bilateral vision loss on

- quality of life. *Br J Ophthalmol*. 2005;89(3):360-363.
445. Chia EM, Wang JJ, Rochtchina E, Smith W, Cumming RR, Mitchell P. Impact of Bilateral Visual Impairment on Health-Related Quality of Life: The Blue Mountains Eye Study. *Investig Ophthalmol Vis Sci*. 2004;45(1):71-76.
446. Finger RP, Fenwick E, Marella M, et al. The impact of vision impairment on vision-specific quality of life in Germany. *Investig Ophthalmol Vis Sci*. 2011;52(6):3613-3619.
447. Chen M, Wu A, Zhang L, et al. The increasing prevalence of myopia and high myopia among high school students in Fenghua city, eastern China: A 15-year population-based survey. *BMC Ophthalmol*. 2018;18(1):1-10.
448. Hrynchak PK, Mittelstaedt A, Machan CM, Bunn C, Irving EL. Increase in Myopia Prevalence in Clinic-Based Populations Across a Century. *Optom Vis Sci*. 2013;90(11):1331-1341.
449. Bland JM, Altman DG. Statistics Notes: Bootstrap resampling methods. *BMJ*. 2015;350(jun02 13):h2622-h2622.
450. Carpenter J, Bithell J. Bootstrap confidence intervals: When, which, what? A practical guide for medical statisticians. *Stat Med*. 2000;19(9):1141-1164.
451. Chalmers RL, Wagner H, Kinoshita B, et al. Is purchasing lenses from the prescriber associated with better habits among soft contact lens wearers? *Contact Lens Anterior Eye*. 2016;39(6):435-441.
452. Gollogly HE, Hodge DO, St. Sauver JL, Erie JC. Increasing incidence of cataract surgery: Population-based study. *J Cataract Refract Surg*. 2013;39(9):1383-1389.
453. Daien V, Le Pape A, Heve D, Carriere I, Villain M. Incidence and Characteristics of Cataract Surgery in France from 2009 to 2012: A National Population Study. *Ophthalmology*.

- 2015;122(8):1633-1638.
454. Eurostat. Surgical operations and procedures performed in hospitals by ICD-9-CM Source of data. Eurostat Database. Published 2021. Accessed April 28, 2021.
<https://appsso.eurostat.ec.europa.eu/nui/submitViewTableAction.do>
455. Wang W, Yan W, Fotis K, et al. Cataract surgical rate and socioeconomics: A global study. *Investig Ophthalmol Vis Sci*. 2016;57(14):5872-5881.
456. Anstey KJ, Wood J, Lord S, Walker JG. Cognitive, sensory and physical factors enabling driving safety in older adults. *Clin Psychol Rev*. 2005;25(1):45-65.
457. Gresset JA, Meyer FM. Risk of accidents among elderly car drivers with visual acuity equal to 6/12 or 6/15 and lack of binocular vision. *Ophthalmic Physiol Opt*. 1994;14(1):33-37.
458. Owsley C, Ball K, McGwin G, et al. Visual processing impairment and risk of motor vehicle crash among older adults. *J Am Med Assoc*. 1998;279(14):1083-1088.
459. Chen SP, Bhattacharya J, Pershing S. Association of vision loss with cognition in older adults. *JAMA Ophthalmol*. 2017;135(9):963-970.
460. Reger MA, Welsh RK, Watson GS, Cholerton B, Baker LD, Craft S. The Relationship between Neuropsychological Functioning and Driving Ability in Dementia: A Meta-Analysis. *Neuropsychology*. 2004;18(1):85-93.
461. Ivers RQ, Mitchell P, Cumming RG. Sensory impairment and driving: The Blue Mountains Eye Study. *Am J Public Health*. 1999;89(1):85-87.
462. Margolis KL, Kerani RP, McGovern P, Songer T, Cauley JA, Ensrud KE. Risk factors for motor vehicle crashes in older women. *Journals Gerontol - Ser A Biol Sci Med Sci*. 2002;57(3):M186-M191.

463. Desapriya E, Harjee R, Brubacher J, et al. Vision screening of older drivers for preventing road traffic injuries and fatalities. *Cochrane Database Syst Rev.* 2014;2014(2).
464. European Commission. *Commission Directive 2009/113/EC Amending Directive 2006/126/EC;* 2009:31-35.
465. ECOO Working Group on Vision and Driving. *Visual Standards for Driving in Europe.*; 2017.
466. Latham K, Katsou MF, Rae S. Advising patients on visual fitness to drive: Implications of revised DVLA regulations. *Br J Ophthalmol.* 2015;99(4):545-548.
467. Pointer JS. Poor recognition of the UK minimum driving vision standard by motorists attending optometric practice. *Ophthalmic Physiol Opt.* 2007;27(3):238-244.
468. O'Neill D. Medical screening of older drivers is not evidence based. *BMJ.* 2012;345(September):6371.
469. Desapriya E, Ranatunga Y, Pike I. We need evidence based tools to identify medically at risk drivers. *BMJ.* 2012;345(7880):7087.
470. Smith G. Relation between Spherical Refractive Error and Visual Acuity. *Optom Vis Sci.* 1991;68(8):591-598.
471. Chihuri S, Mielenz TJ, Dimaggio CJ, et al. Driving cessation and health outcomes in older adults. *J Am Geriatr Soc.* 2016;64(2):332-341.
472. Ragland DR, Satariano WA, MacLeod KE. Driving cessation and increased depressive symptoms. *Journals Gerontol - Ser A Biol Sci Med Sci.* 2005;60(3):399-403.
473. Edwards JD, Lunsman M, Perkins M, Rebok GW, Roth DL. Driving cessation and health trajectories in older adults. *Journals Gerontol - Ser A Biol Sci Med Sci.* 2009;64(12):1290-1295.
474. Wood JM, Tyrrell RA, Chaparro A, Marszalek RP, Carberry TP, Chu BS. Even moderate visual

- impairments degrade drivers' ability to see pedestrians at night. *Investig Ophthalmol Vis Sci*. 2012;53(6):2586-2592.
475. Rubin GS, Ng ESW, Bandeen-Roche K, et al. A prospective, population-based study of the role of visual impairment in motor vehicle crashes among older drivers: The SEE study. *Investig Ophthalmol Vis Sci*. 2007;48(4):1483-1491.
476. Cross JM, McGwin G, Rubin GS, et al. Visual and medical risk factors for motor vehicle collision involvement among older drivers. *Br J Ophthalmol*. 2009;93(3):400-404.
477. Marottoli RA, Richardson ED, Stowe MH, et al. Development of a test battery to identify older drivers at risk for self-reported adverse driving events. *J Am Geriatr Soc*. 1998;46(5):562-568.
478. Piyasena P, Olvera-Herrera VO, Chan VF, et al. Vision impairment and traffic safety outcomes in low-income and middle-income countries: a systematic review and meta-analysis. *Lancet Glob Heal*. 2021;9(10):e1411-e1422.
479. Owsley C, McGwin G. Vision and driving. *Vision Res*. 2010;50(23):2348-2361.
480. Freeman EE, Muñoz B, Turano KA, West SK. Measures of visual function and their association with driving modification in older adults. *Investig Ophthalmol Vis Sci*. 2006;47(2):514-520.
481. Higgins KE, Wood JM. Predicting components of closed road driving performance from vision tests. *Optom Vis Sci*. 2005;82(8):647-656.
482. European Transport Safety Council. *Ranking EU Progress on Road Safety 14th Road Safety Performance Index Report.*; 2020.
483. Patoine A, Mikula L, Mejía-Romero S, et al. Increased visual and cognitive demands emphasize the importance of meeting visual needs at all distances while driving. Chen F, ed. *PLoS One*. 2021;16(3):e0247254.

484. Polling JR, Klaver C, Tideman JW. Myopia progression from wearing first glasses to adult age: The DREAM Study. *Br J Ophthalmol*. Published online 2021:1-5.
485. Brake. *Driver Eyesight Survey 2014.*; 2014.
486. Johnson MA, Choy D. On the definition of age-related norms for visual function testing. *Appl Opt*. 1987;26(8):1449.
487. Wright DM, O'Reilly D, Azuara-Blanco A, Curran R, McMullan M, Hogg RE. Delayed attendance at routine eye examinations is associated with increased probability of general practitioner referral: a record linkage study in Northern Ireland. *Ophthalmic Physiol Opt*. 2020;40(3):365-375.
488. Central Statistics Office Ireland. *National Travel Survey 2019.*; 2019.
489. Harris B, Sampson G. Gender differences in the utilisation of optometric services in Victoria. *Clin Exp Optom*. 2005;88(2):109-112.
490. Eurostat. Majority of transport jobs held by men. European Statistical System. Published 2020. Accessed July 22, 2021. <https://ec.europa.eu/eurostat/web/products-eurostat-news/-/ddn-20200421-1>
491. Loughman J, Moore M, Flitcroft DI. Myopia Progression Centiles from Real World Data: An Ecologically Valid Tool for Myopia Treatment Efficacy Monitoring? *Investig Ophthalmol Vis Sci*. 2020;7(June):2019-2021.
492. Williams KM, Krapohl E, Yonova-Doing E, Hysi PG, Plomin R, Hammond CJ. Early life factors for myopia in the British Twins Early Development Study. *Br J Ophthalmol*. 2019;103(8):1078-1084.

12 Appendices

12.1 Appendix 1 – Acuitas Data Extraction Consent Form

Consent to Extraction and Secondary Use of Data from Acuitas

I, _____ (Print Name) confirm that I am the data controller for _____ (Practice/Company Name). I consent to the anonymised use of data from my electronic patient record system (Acuitas) by Michael Moore, Ian Flitcroft and James Loughman for research purposes in accordance with:

1. the best practice guidelines on research in the health sector from the Data Protection Commissioner ¹
2. the approval of the research ethics committee at Technological University Dublin.

The purpose of the use of the extracted data has been explained to me.

I understand that the data extracted will be limited to the dataset outlined in the table below and will exclude patient names and identification numbers.

I also hereby authorise Ocuco to access my system remotely for the purposes of installing the data extraction process and allowing it to be run when required for the purposes of the defined research.

Data Category	Data Elements
Demographic Data	<ul style="list-style-type: none"> • Gender • Age at exam date • County of residence • Race
Visit Data	<ul style="list-style-type: none"> • Date of exam
Clinical data	<ul style="list-style-type: none"> • Retinoscopy (sphere & cyl) Right + Left eyes (R+L) • Autorefractor sphere & cyl (R+L) • Subjective refraction sphere & cyl (R+L) • Prescribed refractive correction sphere & cyl i.e. Rx Given (R+L) • Refraction Spherical Equivalent R+L (calculated during extraction) • Unaided vision R+L • Corrected Visual Acuity R+L • Keratometry • IOP • Pathology • History

--	--

Signed: _____

Date: _____ (Data Owner)



Signed: _____

Date: 04/12/16 _____ (Researcher)

¹ http://www.dataprotection.ie/documents/guidance/Health_research.pdf

12.2 Appendix 2 – Practitioner Recruitment Document as Sent to All

AOI Member Optometrists



Centre for Eye Research Ireland
Environmental Sustainability & Health Institute (ESHI)
The Greenway Hub, DIT Grangegorman, Dublin 7, Ireland

Dear Practitioner,

Prof. James Loughman and Prof. Ian Flitcroft are leading an international series of trials to explore myopia development and its control at the Centre for Eye Research Ireland in the new DIT Grangegorman campus. This will include an upcoming clinical trial involving the use of atropine to slow down myopia progression. As part of the MOSAIC (Myopia Outcome Study of Atropine In Children) trial we are seeking additional data through practitioners currently using the Acuitas patient management system. We are working with Ocuco with the aim of creating a large set of vision and ocular related data. There is currently very limited data available on the distribution of refractive error in Europe. We hope to create a database using pre-existing data to establish any change in distribution of refractive error over the past number of years, specifically, any change in the level of myopia present. We also want to assess if the age of onset of myopia has any bearing on the final level of myopia. Such data will help us to inform future myopia control strategies and is, therefore, a potentially valuable resource.

Ocuco can remotely extract the relevant data from your Acuitas system. As a data controller we need your permission to pull this data. No patient identifiers will be taken so all patient data will be completely anonymous. As all patient data is kept anonymous there is no need to inform your patients. This is in accordance with the current data protection legislation relating to research. This method of data collection has a significant advantage over other forms of research such as longitudinal studies, which are expensive and time consuming.

As the data will be extracted remotely by Ocuco staff, this requires no input from the practitioner for data to be collected other than signed permission.

The data we are interested in acquiring includes:

- Gender
- Age at exam date
- County of residence
- Race
- Date of exam
- Retinoscopy sphere & cyl (R+L)
- Autorefractor sphere & cyl (R+L)
- Subjective refraction sphere & cyl (R+L)
- Prescribed refractive correction
- Refraction Spherical Equivalent R+L (calculated during extraction)
- Unaided vision R+L
- Corrected Visual Acuity R+L
- Keratometry
- IOP
- Pathology
- History
- Management

If you are willing to participate in this study or require further information please feel free to contact me by email at michael.moore@dit.ie. The attached consent form can be signed, scanned and emailed to me directly, or sent in hard copy to:

Michael Moore

Department of Optometry

Dublin Institute of Technology

Kevin Street

Dublin 8

Regards,

Michael Moore Prof. Ian Flitcroft Prof. James Loughman



12.3 Appendix 3 – SQLite Code to Join EMR CSV Files

```
CREATE TABLE Extract(  
Customer_number    INT,  
PX_ID             INT,  
Gender            STRING,  
County           STRING,  
Rx_date          STRING,  
Age              INT,  
RE_SPH           INT,  
RE_CYL           INT,  
RE_AXIS          INT,  
LE_SPH           INT,  
LE_CYL           INT,  
LE_AXIS          INT,  
RE_add           INT,  
LE_add           INT,  
RE_UVA           STRING,  
LE_UVA           STRING,  
RE_VA           STRING,  
LE_VA           STRING,  
Glasses_sold     STRING,  
Contacts_sold    STRING);  
  
/*Get data into extract table, repeat for each DB*/  
  
/*NOC*/  
Insert INTO Exports.Extract  
SELECT  
NOC.Rx_Given.Customer AS Customer_number,  
NOC.Patients.Patient_ID AS PX_ID,  
NOC.Patients.Gender,  
NOC.Patients.County,  
strftime ( '%Y-%m-%d',datetime (substr(NOC.Rx_Given.Rx_Date, 7, 4) || '-'  
|| substr (NOC.Rx_Given.Rx_Date, 4, 2) || '-' ||  
substr(NOC.Rx_Given.Rx_Date, 1, 2))) AS Rx_Date,  
NOC.Rx_Given.Age,  
NOC.Rx_Given.RE_Distance_Sphere AS RE_SPH,  
NOC.Rx_Given.RE_Distance_Cylinder AS RE_CYL,  
NOC.Rx_Given.RE_Distance_Axis AS RE_AXIS,  
NOC.Rx_Given.LE_Distance_Sphere AS LE_SPH,  
NOC.Rx_Given.LE_Distance_Cylinder AS LE_CYL,  
NOC.Rx_Given.LE_Distance_Axis AS LE_AXIS,  
NOC.Rx_Given.RE_near_add AS RE_add,  
NOC.Rx_Given.LE_near_add AS LE_add,  
NOC.Subjective.RE_distance_unaided_VA AS RE_UVA,  
NOC.Subjective.LE_distance_unaided_VA AS LE_UVA,
```

```
NOC.Rx_Given.RE_distance_aided_VA AS RE_VA,  
NOC.Rx_Given.LE_distance_aided_VA AS LE_VA,  
NOC.Visits.Glasses_sold AS Glasses_sold,  
NOC.Visits.Contacts_sold AS Contacts_sold  
FROM NOC.Rx_Given  
LEFT JOIN NOC.Patients ON NOC.Rx_Given.Patient_ID =  
NOC.Patients.Patient_ID  
LEFT JOIN NOC.Subjective ON NOC.Rx_Given.Visit_ID =  
NOC.Subjective.Visit_ID  
LEFT JOIN NOC.Visits ON NOC.Rx_Given.Visit_ID = NOC.Visits.Visit_ID;
```

12.4 Appendix 4 – R Code to Convert Snellen Acuity to LogMAR

```
VA_conv <- function(VA){  
  inter <- sub("\\-.*", "", VA)  
  inter2 <- sub("\\+.*", "", inter)  
  dec <- sapply(inter2, function(x) eval(parse(text = x)))  
  logMAR <- ((log10(dec) * -1))  
  return(logMAR)}  
}
```

12.5 Appendix 5 – Poster Presentations

The Potential value of Big-Data for Epidemiological Studies of Refractive Error

Moore, Michael¹; Loughman, James¹; Wahl, Siegfried^{2, 3}; Ohlendorf, Arne^{2, 3}; Flitcroft, Daniel I.^{1,4} 2397

1. Centre for Eye Research Ireland, Dublin Institute of Technology, Dublin, Ireland. 2. ZEISS Vision Science Lab, University Tuebingen, Tuebingen, Germany. 3. Carl Zeiss Vision International GmbH, Tuebingen, Germany. 4. Children's University Hospital Temple Street, Dublin, Ireland.

Introduction

Big-Data, as it relates to epidemiology, can be considered in terms of variety, volume and velocity (Mooney SJ et al. 2015). The variety aspect of Big-Data refers to the practice of combining data collected for alternative purposes for analysis. In Europe, epidemiological data on refractive error is relatively sparse: the European Eye Epidemiology (E3) consortium, a consortium of 29 groups from 12 European countries, has collated data on 170,000 European study participants. Our study, based on 134 million spectacle lens prescriptions between 2001 and 2015, was conducted to examine if such large industrial databases could be used as a surrogate means to determine a shift in refractive error over time.

Methods

Anonymised patient lens data was provided by a major European manufacturer. The data included the full spherocylindrical correction and whether the dispensed lens included a reading addition (ADD). This data was separated into single vision (SV) lenses (n = 84 million) and lenses that included a reading ADD (n = 50million). Anonymised data on prescribed refractions was also collected from Irish optometry practices (n = 79,359). The manufacturing data was compared with the practice data to demonstrate the likely age of ADD versus SV lens users. The manufacturing data was also compared with existing population-based studies of refractive error distribution to evaluate agreement in distribution of refractive error over time.

Results

Overall, lens power showed a bimodal distribution with a central minimum corresponding to emmetropia (Fig. 1). This bimodal distribution

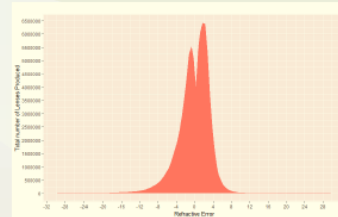


Figure 1 Single Vision Lenses Produced 2000-2015 (n = 84,856,381)

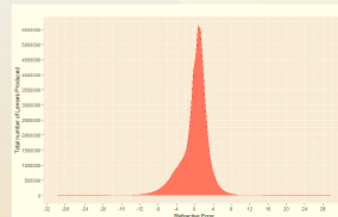


Figure 2 ADD Lenses Produced 2000-2015 (n = 49,742,737)

was most apparent in SV lenses. In contrast, ADD lenses showed a classic uni-modal, negatively skewed and leptokurtotic distribution typical of adult refractive error distributions (Fig. 2). The ADD lens subgroup should predominantly represent older adults. Using practice data the average age of patients prescribed a reading addition was found to be 58.1 years with a standard deviation of 18.3 years (n = 79,359) (Fig. 3). When separated out for myopes (Fig. 4) and hyperopes (Fig. 5) the mean age was 55.4 and 59 years respectively. This supports our supposition that the ADD lens subgroup predominately represents

older adults. Comparison population survey data of older adults from the Gutenberg Health Study (GHS) has recently been published from Germany (Wolfram et al. 2014). The GHS assessed participants aged 35-74 which is similar to our suggested age group for the ADD lenses. The proportion of myopia estimated from the ADD lens group closely mirrors the GHS data suggesting that this lens type may have value as a valid estimator of adult refractive errors in a population.

Myopia Threshold	All Lens Types	SV Lenses	ADD Lenses	Gutenberg (for comparison)
< -1 D	31.7%	35.1%	25.8%	26.2%
< -3 D	15.3%	16.4%	13.4%	11.8%
< -6 D	5.8%	6.3%	4.0%	3.5%
< -9 D	1.5%	1.8%	1.2%	1.0%

Conclusions

Large lens manufacturing databases manufacturing activity can provide useful epidemiological data. Lenses with a reading addition most closely match distributions reported in the GHS likely due to similar age groups for both populations. Such data may allow collection of far more information on global refractive error distribution than is currently available from orthodox epidemiological surveys and may also be done at a significantly lower cost.

References

Mooney SJ, Westreich DJ and El-Sayed AM. Epidemiology in the Era of Big Data. *Epidemiology*. 2015 May ; 26(3): 390-394.
 Williams KM et al. Prevalence of refractive error in Europe: the European Eye Epidemiology (E3) Consortium. *Eye J Epidemiol* (2015) 30:305-315.
 Wolfram C, Höhn R, Kottler U, et al. Prevalence of refractive errors in the European adult population: the Gutenberg Health Study (GHS). *Br J Ophthalmol* 2014;98:857-861.

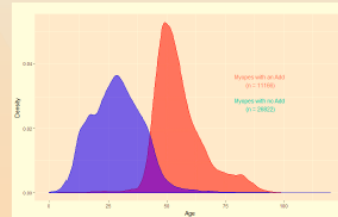


Figure 4 Distribution of Age for Myopes With or Without a Reading Addition

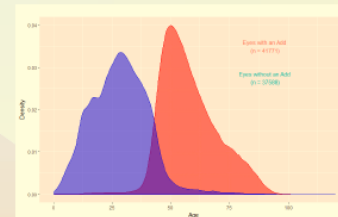


Figure 3 Distribution of Age With or Without a Reading Addition



Figure 5 Distribution of Age for Hyperopes With or Without a Reading Addition



Big Data and Driving: Using pooled practice data to guide health policy

Moore, Michael^a; Loughman, James^a; Flitcroft, D. Ian^{a,b}

^aCentre for Eye Research Ireland, Dublin Institute of Technology, Dublin, Ireland; ^bChildren's University Hospital Temple Street, Dublin, Ireland.



Introduction

A core concept of Big-Data [refers to] is the practice of re-analysing large amounts of data for new purposes.¹ In this case we have attempted to determine the appropriateness of the ages at which visual acuity is screened for driving from a large, anonymized sample (n=115,778) of optometry practice data, pooled across 20 individual sites. Currently to be licensed to drive in the European Union and in most states in the United States, an individual must achieve a visual acuity of 20/40 either with or without an optical appliance. It is a requirement to have a vision assessment when first applying for a driving licence and when renewing a driving licence from the age of 70 and over in Ireland.² As most people will apply for their first licence in their late teens or early twenties, there is a significant period of approximately 50 years during which it is possible to continue holding a driving licence without further vision assessment. Such a significant time period between required vision assessments does not seem appropriate, particularly, given the myopia epidemic affecting young people up to their late twenties and the well established increasing levels of hyperopia in later life.

Results

Figure 1 shows the distribution of all of the patients by age. The mean age was 47 ± 21 years. The distribution peaks in the 46-50 age group.

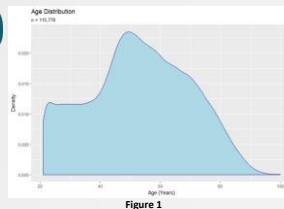


Figure 1

Figure 2 shows the distribution of unaided visual acuity at different ages when categorised as comfortably passing, borderline passing or failing the driving standard.

The mean unaided visual acuity (expressed as a decimal) was 0.61 ± 0.38. Overall the number of individuals comfortably passing the standard reduces with age while the number failing the standard increases with age. Interestingly the proportion of those in the borderline category is fairly static until the fifth decade when this also begins to increase with age.

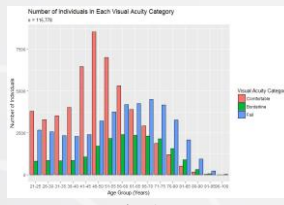


Figure 2

Figure 3 shows the total number of people in the borderline (blue) and fail (green) categories. The increase in the number of individuals falling into this category is more obvious in this figure with a dramatic increase during the fourth and fifth decades that starts to fall in the seventh decade.

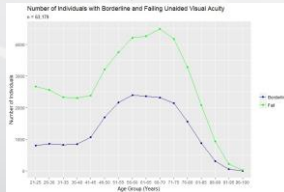


Figure 3

Figure 4 shows the average refractive error for individuals in the borderline category

The change in refractive error with age shown in Figure 4 indicates that this is most likely due to increasing levels of hyperopia as the increasing hyperopia observed in Figure 4 appears to coincide with the increasing number of individuals falling into the borderline category

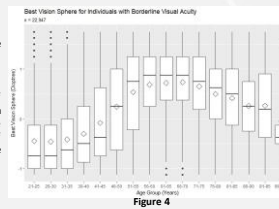


Figure 4

Figure 5 shows the proportion of individuals in the borderline category that will be detected if a vision assessment is required at different ages. At the current requirement of over 70 years old, 24.4% of individuals in the borderline category are detected. If the requirement for a vision assessment was from the age of 50, 69.9% of all individuals in the borderline category would be detected.

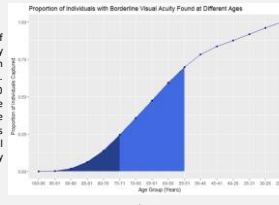


Figure 5

Figure 6 shows the detection levels for those who fall into the failing category. 25% of individuals are detected if assessed from 70 on while 64% are detected if assessed from age 50 onwards.

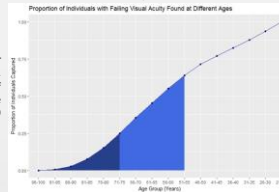


Figure 6

Methods

Anonymized electronic medical records [EMR] were provided by a large software developer. This data set comprised of 363,457 refractions of 152,164 unique patients and included the date of the visit, subject age, vision and full sphere-cylindrical refraction. There were 137,294 patients with complete data. Patients under the age of 21 were excluded from the analysis as the majority of these are not eligible to apply for a driving licence. This left 115,778 unique patients that were included in the analysis. Unaided visual acuity for the right eye was converted to decimal format and categorized as comfortably passing the required standard (> 0.6), as failing the standard (< 0.4) or as being borderline (>= 0.4 & <= 0.6). The subjects were grouped according to age in 5-year intervals from 20 years to 100 years. The data was collated into histogram data using the SQLite database engine and analyzed using the R programming language.

Country	VA requirement	Vision assessment at renewal	Renewal interval	Number of failing individuals detected at current screening age	Number of borderline individuals detected at current screening age
EU	20/40	Over 70s only	Every 3 years	25%	24.4%
UK	20/40	Not required - Over 70s must confirm they meet vision requirement but no evidence required		0%	0%
USA (State dependent)	20/40 - varies from state to state	Variable - Some states require vision assessment at every renewal while some never require vision assessment	Variable 2-8 years	0-100%	0-100%
Australia	20/40	Over 80s only	Every year	7.8%	6.2%

Discussion

There is some small variability internationally on the level of visual acuity required to drive safely but most jurisdictions require visual acuity of approximately 20/40 (or 0.5 in decimal). The frequency with which a vision assessment is required to renew a driving licence is highly variable. Some jurisdictions such as Indiana require a vision assessment at every renewal while other states such as Iowa only require it when a licence is first issued³. This research indicates that with increasing age more and more drivers fall below the required legal visual acuity limits due to increasing levels of hyperopia. A relationship between reduced visual acuity and the ability to recognise pedestrians at night has recently been reported⁴ giving rise to safety concerns for those with even mildly reduced acuity. This indicates a possible need for a change in vision assessment policy in many jurisdictions.

Conclusions

A significant number of licensed drivers may develop a vision impairment over time that constitutes a safety risk for driving if undetected. Policy makers should introduce more frequent vision assessment, ideally when drivers renew their licence. If vision is not to be assessed at every licence renewal, it should be regularly assessed from the fifth decade onwards when increasing levels of hyperopia combined with presbyopia cause reducing levels of unaided visual acuity.

References

- Andreu-Perez J, Poon CY, Merrifield RD, Wong STC, Yang G-Z. Big Data for Health. IEEE J Biomed Health Informatics. 2015;19(4):1193-1208.
- Irish Road Safety Authority. Sáinte agus Tiomsint Medical Fitness to Drive Guidelines (Group 1 and 2 Drivers). 2016; (April).
- US Department of Transportation. Physician's Guide to Assessing and Counseling Older Drivers. 2010; (March).
- Wood JM, Tyrrell BA, Chaparro A, Marszalek RP, Carberry TP, Chu BS. Even Moderate Visual Impairments Degrade Drivers' Ability to See Pedestrians at Night. Investigative Ophthalmology & Visual Science. 2012;53(6): 2586-2592.

Michael Moore

Centre for Eye Research Ireland

michael.moore@dit.ie

www.ceri.ie



The distribution and characteristics of astigmatic refractive error in European populations determined using a Big-Data approach

Moore, Michael¹; Loughman, James¹; Wahl, Siegfried^{2,3}; Ohlendorf, Arne^{2,3}; Flitcroft, D. Ian^{1,4}

1. Centre for Eye Research Ireland, Dublin Institute of Technology, Dublin, Ireland. 2. ZEISS Vision Science Lab, University Tuebingen, Tuebingen, Germany. 3. Carl Zeiss Vision International GmbH, Tuebingen, Germany. 4. Children's University Hospital Temple Street, Dublin, Ireland.



Introduction

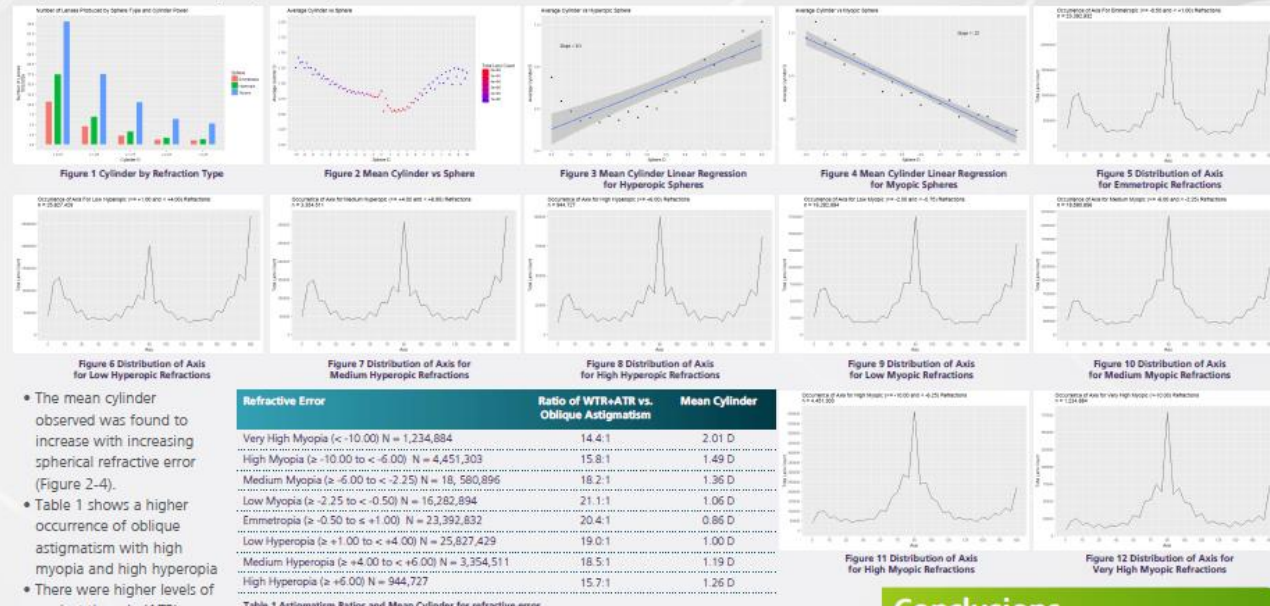
Big-Data, as it relates to epidemiology, can be considered in terms of variety, volume and velocity (Mooney SJ et al, 2015). The variety aspect of Big-Data refers to the practice of combining data collected for alternative purposes for analysis. In Europe, epidemiological data on refractive error is relatively sparse, particularly on astigmatic refractive error (Read SA et al, 2007). Our study, based on 141 million spectacle lens prescriptions issued between 2001 and 2015, was conducted to examine if such large industrial databases could be used as a surrogate means to determine the distribution and characteristics of astigmatic refractive error in European populations.

Methods

Anonymised patient lens data was provided by a major European manufacturer. The data included the full spherocylindrical correction and whether the dispensed lens included a reading add. The total data set with complete refractive data comprised 141,547,436 spectacle lenses. 98% of these lenses were for European delivery, with Germany being the largest single country (>40% of total). The data was collated into histogram data using the SQLite database engine.

Results

- 66.5% (94,069,558) of lenses had a cylindrical component
- 37.2% (52,627,656) of lenses in this data set had a cylindrical component of at least 0.75D
- Figure 1 shows a breakdown of cylinder by refraction type
- Astigmatic correction was present in myopic lenses 1.74 times more often than hyperopic lenses



- The mean cylinder observed was found to increase with increasing spherical refractive error (Figure 2-4).
- Table 1 shows a higher occurrence of oblique astigmatism with high myopia and high hyperopia
- There were higher levels of against the rule (ATR) astigmatism across all refractions except very high myopic refractions (Figure 5-12)
- There appeared to be a trend of increasing with the rule (WTR) astigmatism with increasing myopia (Figure 10-12) which was not seen with increasing hyperopia

Discussion

The occurrence of astigmatism in this dataset is within the range found and reported in previous studies (Young G et al, 2011). The increasing amount of astigmatic

error with increasing spherical error is similar to that observed in animal models (Kee CS et al, 2005). The difference in the rate of increasing astigmatic error for increasing levels of myopia and hyperopia may suggest different underlying mechanisms for the development of astigmatism in myopia and hyperopia. These results also show an increasing amount of oblique astigmatism with increasing spherical refractive error. Similar findings have also been observed in animal models (Kee CS et al, 2005) which may suggest a similar mechanism for the development of oblique astigmatism in humans.

Conclusions

The results of this big data analysis broadly agree with previously published epidemiological data, and exhibits similar trends to those observed in animal studies. Large lens manufacturing databases manufacturing activity can provide useful epidemiological data.

References

Mooney SJ, Westreich DJ and El-Sayed AM. Epidemiology in the Era of Big Data. *Epidemiology*. 2015 May; 26(3): 390-394.
 Read SA, Collins MJ and Carney LG. A Review of Astigmatism and its Possible Genesis. *Clin Exp Optom* 2007; 90(1): 5-19.
 Young G, Sully A and Hunt C. Eye & Contact Lens. Prevalence of Astigmatism in Relation to Soft Contact Lens Fitting 2011; 37: 20-25.
 Kee CS, Hung LF, Qiao-Gilder Y, Ramamirtham R and Smith EL. Astigmatism in Monkeys with Experimentally Induced Myopia or Hyperopia. *Optom Vis Sci*. 2005 April; 82(4): 248-260.

Disclosures: Siegfried Wahl and Arne Ohlendorf are employees of Carl Zeiss Vision International GmbH



12.6 Appendix 6 – Application of big-data for epidemiological studies of refractive error. PLoS One publication.

RESEARCH ARTICLE

Application of big-data for epidemiological studies of refractive error

Michael Moore^{1*}, James Loughman¹, John S. Butler^{1,2}, Arne Ohlendorf^{3,4}, Siegfried Wahl^{3,4}, Daniel L. Filtcroft^{1,5}

1 Centre for Eye Research Ireland, School of Physics and Clinical and Optometric Sciences, Technological University Dublin, Dublin, Ireland, 2 School of Mathematical Sciences, Technological University Dublin, Dublin, Ireland, 3 Technology & Innovation, Carl Zeiss Vision International GmbH, Turnstrasse, Aalen, Germany, 4 Institute for Ophthalmic Research, Center for Ophthalmology, Eberhard Karls University of Tübingen, Elfriede-Aulhorn-Strasse, Tübingen, Germany, 5 Children's University Hospital, Dublin, Ireland

* michael.moore@tudublin.ie



Abstract

Purpose

To examine whether data sourced from electronic medical records (EMR) and a large industrial spectacle lens manufacturing database can estimate refractive error distribution within large populations as an alternative to typical population surveys of refractive error.

Subjects

A total of 555,528 patient visits from 28 Irish primary care optometry practices between the years 1980 and 2019 and 141,547,436 spectacle lens sales records from an international European lens manufacturer between the years 1998 and 2016.

Methods

Anonymized EMR data included demographic, refractive and visual acuity values. Anonymized spectacle lens data included refractive data. Spectacle lens data was separated into lenses containing an addition (ADD) and those without an addition (SV). The proportions of refractive errors from the EMR data and ADD lenses were compared to published results from the European Eye Epidemiology (E3) Consortium and the Gutenberg Health Study (GHS).

Results

Age and gender matched proportions of refractive error were comparable in the E3 data and the EMR data, with no significant difference in the overall refractive error distribution ($\chi^2 = 527$, $p = 0.29$, $DoF = 510$). EMR data provided a closer match to the E3 refractive error distribution by age than the ADD lens data. The ADD lens data, however, provided a closer approximation to the E3 data for total myopia prevalence than the GHS data, up to age 64.

OPEN ACCESS

Citation: Moore M, Loughman J, Butler JS, Ohlendorf A, Wahl S, Filtcroft DL (2021) Application of big-data for epidemiological studies of refractive error. PLoS ONE 16(4): e0250468. <https://doi.org/10.1371/journal.pone.0250468>

Editor: Michael Mimouni, University of Toronto, CANADA

Received: December 22, 2020

Accepted: April 6, 2021

Published: April 23, 2021

Peer Review History: PLOS recognizes the benefits of transparency in the peer review process; therefore, we enable the publication of all of the content of peer review and author responses alongside final, published articles. The editorial history of this article is available here: <https://doi.org/10.1371/journal.pone.0250468>

Copyright: © 2021 Moore et al. This is an open access article distributed under the terms of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Data Availability Statement: The data from this study is available on request. This data contains potentially identifying and sensitive patient data such as date of birth, date of exam and county of residence. The TU Dublin Research and Ethics

List of Publications

Moore M, Loughman J, Butler JS, Ohlendorf A, Wahl S, Flitcroft DI. (2021). Application of big-data for epidemiological studies of refractive error. PLoS One. (Appendix 6)

Moore M, Loughman J, Butler JS, Ohlendorf A, Wahl S, Flitcroft DI. (In Press). The Refractive Error and Vision Impairment Estimation With Spectacle data (REVIEWS) study. Ophthalmology Science.

Moore M, Butler JS, Flitcroft DI, Loughman J. (2021). Evidence-based recommendations for standardised driver vision screening – a Big Data approach. Manuscript Submitted.

Oral Presentations

“Myopia and Vision Loss: Can Electronic Medical Records Help to Quantify the Problem?” Ocuco Virtual Webinar. May 2020.

“Application of Big-Data for Epidemiological Studies of Refractive Error.” The International Myopia Conference. Tokyo Medical and Dental University, Tokyo, Japan, September 2019.

“Epidemiology of Refractive Error and Vision.” Association of Optometrists Ireland Continuing Education Event. Athlone, Ireland, February 2019.

Poster Presentations

“Big Data and Driving: Using pooled practice data to guide health policy.” America Academy of Optometry Annual Meeting. San Antonio, Texas, USA, November 2018. (Refer to appendix 5 for poster presented)

“The distribution and characteristics of astigmatic refractive error in European populations determined using a Big-Data approach.” The International Myopia Conference. Aston University, Birmingham, UK, September 2017. (Refer to appendix 5 for poster presented)

“The Potential value of Big Data for Epidemiological Studies of Refractive Error.” The Association for Research in Vision and Ophthalmology Annual Meeting. Baltimore, USA, May 2017. (Refer to appendix 5 for poster presented)

Structured PhD Programme Modules Completed

It is a requirement by TU Dublin to undertake a number of post-graduate modules (discipline-specific skills 20 ECTS, and employability skills 20 ECTS).

Modules completed as part of the Structured PhD programme:

Discipline-specific postgraduate modules:

TU Dublin Glaucoma Detection and Decision-making in Optometric Practice – 10 ECTS credits

TU Dublin Authoring Principles – 10 ECTS credits

Employability Skills Training:

University of Limerick Reporting Results in Physical Science – 6 ECTS credits

Datacamp Suite of R Modules – 6 ECTS credits

TU Dublin Postgraduate Diploma in Third Level Education – 60 ECTS credits (awarded 10 ECTS credits awarded toward structured PhD programme)

Additional Postgraduate Modules Completed:

University of Cardiff Postgraduate Diploma in Therapeutic Prescribing for Optometrists – 60 ECTS credits