Aniseikonia:
A Potential Barrier To Neural Plasticity

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A thesis submitted in fulfilment of the requirements for the degree of Doctor of Philosophy in Optometry and Vision Science, the University of Auckland, 2022.

Abstract

Aims: Aniseikonia represents a potential barrier to neuroplasticity, which may limit visual outcomes in children with anisometropic amblyopia. Full refractive correction is the initial treatment for amblyopia, which corrects image focus, but image size differences are often neglected. We aimed to identify the potential impact of aniseikonia by investigating current treatment outcomes in New Zealand children, measuring aniseikonia subjectively in amblyopia, and through incorporating aniseikonia correction at the time of initial treatment for anisometropic amblyopia in children.

Methods: A retrospective chart review of children that failed preschool vision screening investigated causes of visual impairment and treatment outcomes of children seen in hospital eye services (HES).

A cross-sectional study used clinical and psychophysical methods to quantify aniseikonia in isometropia, anisometropia and amblyopia.

A prospective double-masked randomised clinical trial (Measuring aniseikonia & investigating neuroplasticity and image factors in amblyopia (MAGNIFY) study) compared the effectiveness of aniseikonia-correcting lenses to standard spectacle lenses for the treatment of anisometropic amblyopia. A novel, compact spectacle wear monitor was designed and tested to be used by children enrolled in the MAGNIFY study.

Results: Children referred to HES following a failed B4 School vision screening test mostly commonly had reduced visual acuity due to refractive error, and anisometropia was the most common cause of amblyopia. Treatment disengagement was found to be higher-than-expected in Māori and Pacifica children highlighting potential health service-related inequalities.

Subjective aniseikonia can successfully be measured in anisometropic amblyopia with greater amounts found compared to those with anisometropia alone. The ongoing MAGNIFY study found, at the mid-term analysis, that distance visual acuity of all amblyopic eyes improved by 4 lines and stereoacuity improved by 2 octaves after 15 weeks of spectacle wear. Optical treatment was well tolerated, and adherence was high.

However, broken or damaged spectacles can disrupt treatment and be a burden for families. The SpecsOn monitor was found to measure spectacle wear accurately and reliably.

Conclusion: Aniseikonia frequently occurs in anisometropia and clinical assessment of subjective aniseikonia in anisometropic amblyopia is possible. Optical treatment is a safe and acceptable treatment for anisometropia and amblyopia.

Acknowledgements

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Glossary of Abbreviations

AI3	Aniseikonia Inspector Version 3
ANOVA	Analysis of Covariance
ANZCTR	Australia New Zealand Clinical Trial Registry
Arc Sec	Seconds of Arc
B4 School	Before school vision screening
BCVA	Best corrected visual acuity
BPEDS	Baltimore Pediatric Eye Disease Study
BSV	Binocular Single Vision
CAT test	The Contrast-balanced Aniseikonia Test
D	Dioptre
DC	Dioptre Cylinder
DHB	District Health Board
DS	Dioptre Sphere
e-ETDRS test	Electronic Early Treatment of Diabetic Retinopathy Study visual acuity testing protocol
ER-QOL	Eye-Related Quality Of Life
EVA	Electronic Visual Acuity
HES	Hospital Eye Service
IQR	Inter Quartile Range
ITT	Intention-To-Treat
LE	Left Eye
Log10	Logarithm base 10.
LogMAR	Logarithm of the minimum angle of resolution
MAGNIFY study	Measuring aniseikonia & investigating neuroplasticity and image factors in amblyopia study
MEPEDS	Multi Ethnic Pediatric Eye Disease Study
MMRM	Mixed model for repeated measure
NAT	New Aniseikonia Test
NHI	National Health Index number
OCT	Optical Coherence Topographer
PEDIG	Paediatric Eye Disease Investigator Group
RCT	Randomised Clinical Trial

RE	Right Eye
RT	Robertson Technique
SD	Standard Deviation
SER	Spherical Equivalent Refraction
STARS	The Strabismus, Amblyopia and Refractive Error in Singaporean Children
VA	Visual Acuity
WCTO	Well Child Tamariki Ora

Publisher Approvals

This thesis contains four manuscripts that have been published as original peer-reviewed journals. These journals have been reformatted with publisher approvals to be included in Chapters 2, 4, 5 & 6. This page details the full reference of the published versions of the manuscripts and details permission for reproduction of these articles.

Chapter 2: Aniseikonia and anisometropia: implications for suppression and amblyopia

Article reference: South, J., Gao, T., Collins, A., Turuwhenua, J., Robertson, K. and Black, J. (2019), Aniseikonia and anisometropia: implications for suppression and amblyopia. *Clin Exp Optom,* 102: 556-565. https://doi.org/10.1111/cxo.12881

Publisher: John Wiley and Sons

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Chapter 4: Clinical Aniseikonia in Anisometropia and Amblyopia

Article reference: South, J., Gao, T., Collins, A., Lee, A., Turuwhenua, J. and Black, J., 2020. Clinical Aniseikonia in Anisometropia and Amblyopia. *British and Irish Orthoptic Journal*, 16(1), pp.44–54. DOI: http://doi.org/10.22599/bioj.154

Publisher: White Rose University Press

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Chapter 5: Development of a Spectacle Wear Monitor System: SpecsOn Monitor

Article reference: South, J., Roberts, P., Gao, T., Black, J., & Collins, A. (2021). Development of a Spectacle Wear Monitor System: SpecsOn Monitor. *Transl Vis Sci Technol*, *10*(12), 11. https://doi.org/10.1167/tvst.10.12.11

Publisher: The Association for Research in Vision and Ophthalmology

Chapter 6: Measuring aniseikonia and investigating neuroplasticity and image factors in amblyopia (MAGNIFY): study protocol for a randomised clinical trial

Article reference: South, J., Gao, T., Turuwhenua, J., Roberts, P., Lee, A., Collins, A., & Black, J. (2022). Measuring aniseikonia and investigating neuroplasticity and image factors in amblyopia (MAGNIFY): study protocol for a randomised clinical trial. *Trials 23***,** 358. https://doi.org/10.1186/s13063-022-06159-2

Publisher: BioMed Central Ltd, Springer Nature

Chapter 1

Introduction

Binocular vision allows us to see a single image through the combination of disparate retinal images from both eyes. This provides binocular summation and stereoscopic depth to guide our movements and performance. In the clinical management of binocular vision, it is important that through the combination of the right and left eyes a single clear image is seen. Normal development of binocular functions requires the images from both eyes to be of equal size, shape, clarity and brightness to be combined into a single percept. Any disruption to the visual experience during the first few years of life (Hubel & Wiesel, 1970; Hubel et al., 1977), known as the sensitive period (Daw, 1998), can result in a cortical visual developmental disorder known as amblyopia. Amblyopia commonly results from misalignment of the eyes (strabismus) or a difference in focusing power between the two eyes (anisometropia) or a combination of both these factors. Anisometropia is found in two thirds of amblyopia cases (PEDIG, 2002) and is a significant risk factor in developing amblyopia. Anatomically, anisometropia results from a difference in axial lengths of the two eyes (Rabin et al., 1983; Sorsby, 1962b) which can also cause a difference in the image size perceived by each eye, aniseikonia (Lancaster, 1938). In the correction of anisometropia, spectacle lenses are often used to equalise the focus between the eyes, giving clear images to each eye, however the image size difference is not routinely addressed in clinical practice even though these combined lenses are widely available.

Optical treatment is the initial phase of amblyopia therapy (Royal College of Ophthalmologists, March 2012; Wallace et al., 2018) and often optical correction alone can resolve amblyopia (Chen et al., 2007; Cotter et al., 2006; Moseley et al., 2002; Stewart et al, 2004). However, the simple act of prescribing spectacles to restore clear vision inadvertently introduces a further difference in image sizes seen by the two eyes due to the spectacle lens optics (Chapter 2, section 2.3-2.5) (Remole, 1989a). Inherent aniseikonia is compounded and the treatment of anisometropia is now contributing to a

fusional barrier which may precipitate suppression of dissimilar images and lead to the development of amblyopia (South et al., 2019).

This thesis examines optical aniseikonia caused by interocular differences (anisometropia) and the possible relationship with amblyopia development. The primary hypothesis this thesis examines is correcting for aniseikonia at the same time as correcting for defocus, at initial diagnosis, will improve the visual outcomes following the optical treatment phase of anisometropic amblyopia

1.1 Thesis structure

Four main projects are described in this thesis through separate chapters. In Chapter 3 a retrospective review study was undertaken to identify common refractive errors in pre-school aged children in Auckland, New Zealand and how this compares to others around the world. Overseas population studies on preschool children have found an association between increasing ametropia and anisometropia and consequently amblyopia. However, little information is available on the New Zealand population. Currently aniseikonia is largely ignored in the management of anisometropia and to date measurement of aniseikonia has not been attempted in anisometropic amblyopia due to the assumption that suppression of one eye will prevent the image size differences being identifiable and therefore difficult to compare. Chapter 4 contains a published manuscript detailing how aniseikonia is measurable in anisometropia with or without amblyopia and that greater amounts of aniseikonia are found with increasing anisometropia (South et al., 2020).

The main hypothesis, providing aniseikonia correction lenses will improve image clarity and reduce the retinal size differences producing better visual acuity and stereoacuity improvements after 15 weeks of optical treatment for children with anisometropia, is examined through the MAGNIFY study. Whilst developing the proposal for the MAGNIFY research project (Chapters 6 and 7) the need for an accurate system for spectacle wear adherence was essential to assess whether the two types of lenses (aniseikonia correction lenses and standard lenses) would result in different visual outcomes from the optical treatment phase. This system needed to be suitable for a young (pre-school) paediatric population and be adaptable to a wide range of spectacle

frames. Chapter 5 presents a published manuscript of the design, development and testing of a custom-built removable spectacle adherence monitor for children (South et al., 2021).

The MAGNIFY study was originally designed as a feasibility study due to paucity in the literature surrounding gold standard testing for aniseikonia in children and the fact that the measurement of aniseikonia had previously not been attempted in children with anisometropic amblyopia. However, whilst undergoing application for ethical approval it became apparent that the study was in fact an intervention study in line with a clinical trial. The design of the study was changed to a prospective double masked randomised clinical trial and Chapter 6 contains a published manuscript describing the rationale and methodology of this study (South et al., 2022).

Following ethical approval and successful registration of the MAGNIFY study as a clinical trial, recruitment commenced in January 2020. Soon after recruitment commenced the COVID-19 pandemic arrived onto New Zealand shores and recruitment was suspended during COVID-19 pandemic alert levels 3 and 4. Further and ongoing disruptions related to multiple lockdowns and changes in alert levels meant that recruitment and data collection were significantly impacted right through to the submission of this thesis. As a result, the mid-term provisional results for the MAGNIFY study are presented in Chapter 7.

Overall discussion and thesis conclusions are provided in Chapter 8. Due to the nature of the thesis with publications there is a minor amount of repetition of literature in some of the published manuscripts in Chapters 2, 4, 5 and 6.

1.2 Published manuscripts included in this thesis:

Chapter 2- Aniseikonia and anisometropia: implications for suppression and amblyopia. South, J., Gao, T., Collins, A., Turuwhenua, J., Robertson, K., & Black, J. (2019). *Clinical & Experimental Optometry*. https://onlinelibrary.wiley.com/doi/pdf/10.1111/cxo.12881

Chapter 4- Clinical Aniseikonia in Anisometropia and Amblyopia. South, J., Gao, T., Collins, A., Lee, A., Turuwhenua, J., & Black, J. (2020). *British and Irish Orthoptic Journal*, *16*(1), 44-54. https://doi.org/10.22599/bioj.154

Chapter 5- Development of a Spectacle Wear Monitor System: SpecsOn Monitor. South, J., Roberts, P., Gao, T., Black, J., & Collins, A. (2021). *Translational Vision Science & Technology*, *10*(12), 11. https://doi.org/10.1167/tvst.10.12.11

Chapter 6- Measuring aniseikonia and investigating neuroplasticity and image factors in amblyopia (MAGNIFY): study protocol for a randomised clinical trial. South, J., Gao, T., Calderwood, M., Turuwhenua, J., Roberts, P., Lee, A., Collins, A., & Black, J. (2022). *Trials 23***,** 358. https://doi.org/10.1186/s13063-022-06159-2

Chapter 2

Literature Review

Partial content of this chapter contains a manuscript submitted to the journal 'Clinical and Experimental Optometry' and was published as *"Aniseikonia and Anisometropia: implications for suppression and amblyopia"*. Authors: Jayshree South, Tina Gao, Andrew Collins, Jason Turuwhenua, Kenneth Robertson, Joanna Black. 2019, volume 102, issue 6, pages 556-565. Thesis author Jayshree South conducted a review of the literature and prepared the manuscript.

2.1 Introduction

Aniseikonia is a condition where there is a perceived difference in image size or shape between the eyes. Perceived image sizes are determined by a combination of factors, including the angular sizes of images falling on each retina, the distribution of the retinal receptive fields and the cortical mapping of the visual fields in the brain. Aniseikonia can result when there are substantial differences between the two eyes or in the visual pathways for any of these factors. Aniseikonia can disrupt binocular vision, but currently, is not routinely screened for in most optometric settings.

A number of authors in the 1880s recognised that correction of anisometropic refractive errors may change retinal image size (Ames, 1935; Donders, 1864). Ames (1935) and other researchers at Dartmouth Eye Institute led the early research into aniseikonia. However, It wasn't until 1932 that the term "aniseikonia" was first coined by Walter B. Lancaster (Lancaster, 1938). The term, derived from the Greek, translates to "unequal images". Although much research was conducted from the mid-1930s through to the 1980s, aniseikonia has largely been ignored in clinical practice until very recently. There has been a renaissance of research surrounding aniseikonia following advancements in multifocal lens designs in cataract surgery (Langenbucher, 2008; Rutstein et al., 2006), retinal surgeries such as epiretinal membrane peels (Benegas et

al., 1999; Kim et al., 2013; Okamoto et al., 2012, 2014) and refractive surgeries (Enoch, 1997), which have resulted in an increase in the number of reported cases of aniseikonia (Hodgetts, 2012; Okamoto, 2017; Rutstein et al., 2015).

This review aims to summarise the currently known causes and effects of aniseikonia, outline a range of clinical measurement techniques, and describe how aniseikonia can be treated. Our particular focus will be the optical types of aniseikonia associated with anisometropia. These are the most commonly encountered types in primary eye-care settings, though the literature in this area is scarce. We will also discuss the potential benefits of aniseikonia correction in patients with anisometropic amblyopia.

2.2 What is Aniseikonia?

Aniseikonia can be classified as physiological, neurological, retinally-induced or optical. It is clinically quantified via the percentage difference in perceived image size between the right and left eyes. Conventionally, the image size percentage difference is described as more than or less than compared to the less ametropic eye.

2.2.1 Physiological aniseikonia

In normal binocular vision, sensory fusion is the process by which the visual cortex combines images from the two eyes into a single percept (Renne et al., 1953). Usually, the images from the two eyes are not identical, because each eye views objects from a slightly different perspective, producing differences in perceived image size and shape depending on object position and distance. These disparities in ocular images, termed physiological aniseikonia, are processed by the visual cortex to produce stereopsis (Lancaster, 1942).

2.2.2 Neurological aniseikonia

Neurological or cortical aniseikonia arises from cortical neural processing, which functions to reduce image size disparities arising from other causes, such as optical aniseikonia in myopic and hypermetropic eyes (Bradley et al., 1983). This is potentially an active, adaptive process, allowing people to tolerate small amounts of aniseikonia without detrimental effects on binocular vision.

2.2.3 Retinally-induced aniseikonia

A change in the retinal receptor distribution from retinal asymmetry or pathology will cause the same physical size retinal image to be captured by a different number of photoreceptors, resulting in a change in perceived image size and shape. This can occur in conditions such as epiretinal membranes, macular oedema, or axial myopia. Epiretinal membranes that cause macular contraction compress photoreceptors closer together, so that a retinal image with the same angular size now stimulates more photoreceptors, resulting in macropsia (image appears larger than normal) in the affected eye(s) (Benegas et al., 1999; Okamoto et al., 2014). Conversely, if the photoreceptors are stretched across a larger retinal area such as in high axial myopia, central serous chorioretinopathy (Hisada, 1992) or macular oedema, the same retinal image stimulates fewer photoreceptors, resulting in micropsia (image appears smaller than normal). Aniseikonia can arise from both overall differences in image sizes between eyes and localised distortions in image shape, producing severe symptoms. Retinally-induced aniseikonia can be difficult to treat because the magnitude of aniseikonia can vary across the visual field (de Wit, 2007; de Wit & Muraki, 2006; Rutstein, 2012). Even after appropriate surgery or treatment for the underlying conditions, photoreceptor spacing may not fully recover, leaving the patient with distorted vision (Okamoto et al., 2014).

2.2.4 Optical aniseikonia

Optical types of aniseikonia are caused by inter-ocular differences in the internal and external refractive components of the eye. Internal components include the cornea, lens and axial length, where inter-ocular differences may cause inherent aniseikonia. Aniseikonia may also be induced by procedures that alter internal refractive components, such as corneal laser surgery or cataract surgery. External factors refer to spectacles or contact lenses used to correct ametropia. In anisometropia, both the internal refractive components and the externally worn lenses differ substantially between eyes, and this can lead to optical aniseikonia.

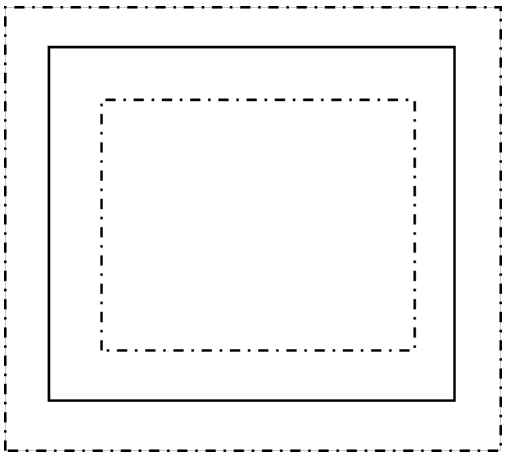
In normally-sighted adults, artificial anisometropia is sometimes deliberately induced surgically or optically to alleviate presbyopia, known as Monovision correction. Monovision correction can disrupt binocular vision, causing reduced stereopsis (Back

1989; Erickson 1992; Fawcett et al., 2001; Kirschen et al., 1999; Mcgill & Erickson 1988) and absence of foveal fusion (Heath, 1986; Kirschen et al., 1999) in adults with previously normal binocular vision. Whether these binocular disturbances may also occur with other types of optically-induced aniseikonia is unknown.

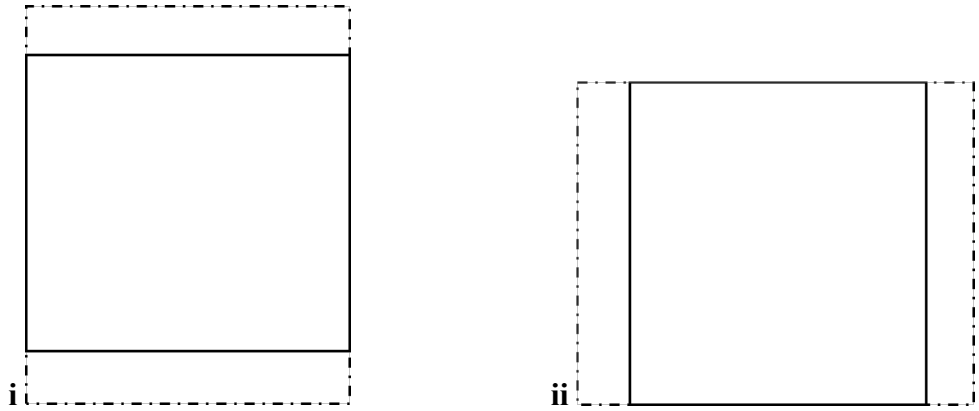
The remainder of this review will explore the non-surgical and non-disease-related aspects of optical aniseikonia.

2.3 Aniseikonia in Anisometropia

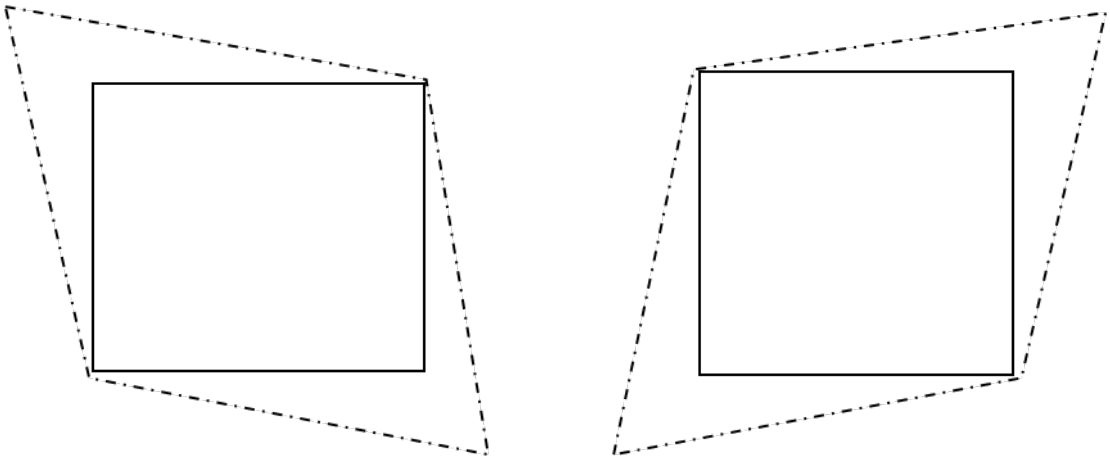
Anisometropia is a difference in refractive error between the eyes, which may arise naturally or be optically/surgically induced. In the context of naturally-occurring anisometropia, a difference of 1 dioptre (D) or greater in spherical equivalent refraction is usually considered a significant threshold, because it is sufficient to potentially cause amblyopia in young children (Donahue, 2005; Ingram & Walker 1979; Latvala et al., 1996). Aniseikonia in anisometropia can be of two types: overall aniseikonia, affecting the entire visual field equally in all meridians, or meridional aniseikonia, affecting the perceived image size in only one meridian compared to the corresponding meridian in the other eye. The meridians affected may be vertical, horizontal or oblique (Figure 1).



A. Overall aniseikonia. Aniseikonia is increased equally in all meridians



B. Meridional aniseikonia. The ocular image in one eye is increased or decreased in the i vertical; or the ii horizontal meridian



C. Meridional aniseikonia. The ocular image is increased or decreased in the oblique meridian.

Figure 1. Types of aniseikonia in anisometropia (A, B & C).

In the context of anisometropia, aniseikonia can result from anatomical axial length differences, differences in photoreceptor spacing between eyes or cortical adaptations, and can also be optically induced by spectacle or contact lens corrections for anisometropia. The patient's perceived aniseikonia is a product of all of these factors.

2.3.1 Refractive and axial anisometropia

Anisometropia is often classified as either refractive or axial in origin. The type of anisometropia affects the theoretical sizes of the retinal images, which is the physical size of the image projected onto the retina, prior to any retinal or cortical visual processing. In refractive anisometropia, the optical powers of the ocular refractive components (for example, corneal curvatures or the positions/powers of the lenses) are different between eyes, but axial lengths are similar. Whereas in axial anisometropia, the overall refractive powers are similar in the two eyes, but axial lengths differ (Rabin et al., 1983). It is commonly assumed that if the spherical anisometropia is 2 Dioptres or greater, then the anisometropia is likely to be axial, whereas in lesser amounts of spherical anisometropia or for cylindrical differences, the anisometropia is likely to be refractive (Sorsby, 1962b). However, most patients with anisometropia have both axial and refractive differences between eyes, and it is rare to have purely axial or refractive anisometropia (Kramer et al., 1999).

2.3.2 Inherent anatomical differences and aniseikonia

In uncorrected axial anisometropia, the retinal image sizes are inherently different. For example, if the refractive error was +1.00 Dioptres in the right eye and +4.00 Dioptres in the left eye, then the uncorrected retinal image in the more hyperopic eye would be smaller than the less ametropic eye (Figure 2). Aniseikonia is present without refractive correction in figure 2 and prescribing spectacles can alter the amount of aniseikonia.

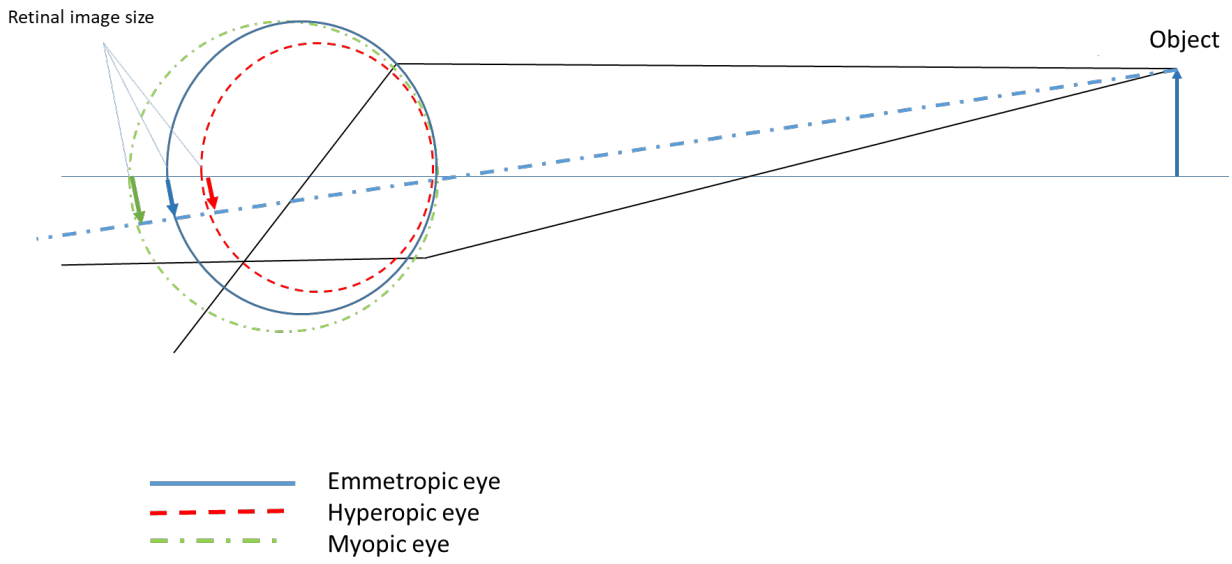


Figure 2. A larger retinal image size in axial myopia and a smaller retinal image size in axial hyperopia. The incongruous retinal images produced by axial anisometropia can result in inherent anatomical aniseikonia.

Inter-ocular differences in axial lengths, in conjunction with potential differences in photoreceptor density, can contribute to perceived image size differences (Bradley et al., 1983; Winn et al., 1988). This is referred to as inherent anatomical aniseikonia.

2.3.3 Optically induced aniseikonia

A regular ophthalmic lens placed in front of the eye can change both the image focus and the retinal image size. The amount of magnification produced is defined by spectacle magnification, which is calculated monocularly. If the lens-induced magnification changes are different for the two eyes, then this can cause optically-induced aniseikonia. Relative spectacle magnification is used to measure this optically-induced image size difference and is defined as the ratio of the spectacle magnification for one eye divided by the spectacle magnification of the other eye.

$$Spectacle\ Magnification = \frac{image\ size\ when\ wearing\ corrective\ lens}{image\ size\ when\ uncorrected}$$

2.3.4 Static versus dynamic aniseikonia

All of the types of aniseikonia discussed so far are static. However, optically-induced aniseikonia actually contains two components: static and dynamic.

Static aniseikonia refers to the differences in perceived image size when the eyes are stationary and viewing through the optical centres of the corrective lenses. This is measured using spectacle magnification. Dynamic aniseikonia refers to the prismatic effects induced by spectacle lenses when the eyes look away from the optical centres (Figure 3). This can produce anisophoria, where the ocular deviation changes with the direction of gaze (Millodot, 2009).

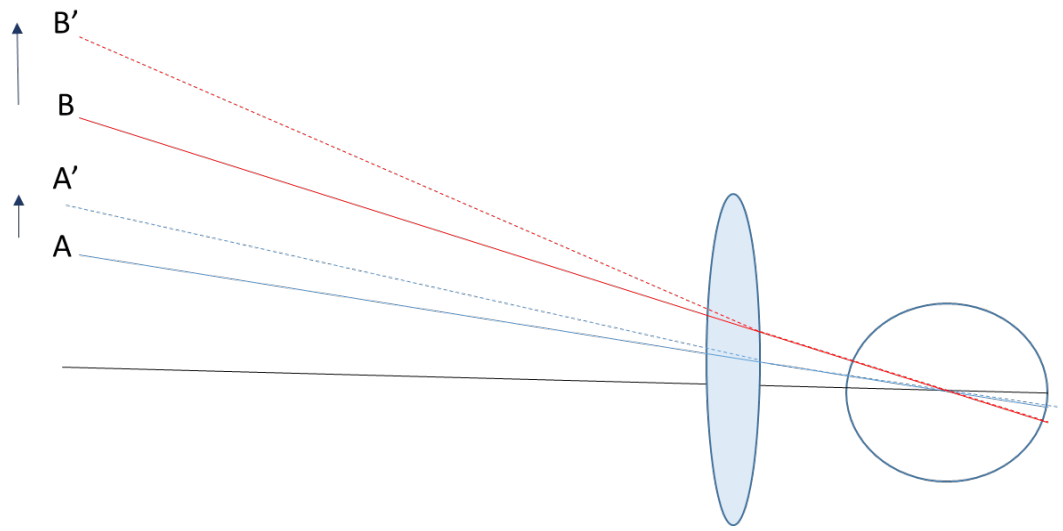


Figure 3. Diagram illustrating the increasing prismatic effect as the eye looks away from the optical centre of a concave lens. Rays A and B are displaced by the prismatic effect of the lens, appearing to come from A’ and B’.

The amount of induced prism when looking away from the optical centre for a single spectacle lens can be calculated using Prentice’s rule (Equation 1).

Prentice’s Rule ***P=dF***

where P=the prismatic power in prism dioptres, d=distance from the optical centre in centimetres and F=the Dioptric power of the lens

Equation 1.

When wearing an anisometropic correction, the amount of induced prism differs between eyes for all off-centre gazes, and the prism difference changes depending on the part of the spectacle lenses that the eyes look through, resulting in anisophoria.

Because anisometropic correction in spectacles induces both static and dynamic aniseikonia, patients must not only adapt to changes in perceived image sizes during sensory fusion, but also must adjust their pattern of oculomotor movement to compensate for spectacle-induced prismatic effects. The oculomotor system is able to produce disconjugate saccades and vergence adaptation for small amounts of spectacle-induced aniseikonia.(Bruno et al., 1995; van der Steen & Bruno, 1995). However, the

continually changing direction and magnitude of induced prismatic effects can make adaptation difficult, which can lead to dynamic aniseikonia being more symptomatic than static aniseikonia (Remole, 1989a). Induced vertical prism that differs between eyes with up or down gaze are usually the most difficult to overcome because of low vertical vergence reserves.

2.3.5 Knapp's Law

Knapp's Law is a rule-of-thumb to guide the prescribing of refractive correction to minimise optically-induced aniseikonia in patients with anisometropia. It states that in axial anisometropia, a spectacle lens placed at the anterior focal point of the eye will create the same retinal image size as a standard emmetropic eye. Therefore, to minimise optically induced aniseikonia, spectacle lens correction would be preferred in axial anisometropia, while contact lenses would be preferred in refractive anisometropia. However, the practical applicability of Knapp's Law has been disputed, and contact lenses have been found to be effective in both refractive and axial cases (Winn et al., 1988).

Knapp's Law may not be universally applicable in clinical cases because anisometropia is rarely purely axial or purely refractive (Awaya et al, 1982), and Knapp's law does not take into account the combined effects of axial length and ocular refractive components on retinal image sizes.

Importantly, Knapp's law also does not account for any retinally-induced aniseikonia that may result from differing photoreceptor densities between the two eyes. In longer, more myopic eyes, the same number of photoreceptors are spread over a larger surface area, while photoreceptors are relatively compacted in shorter or hyperopic eyes (Bradley et al., 1983; Kitaguchi et al., 2007). In addition, perceived image sizes are also influenced by the sizes and co-localisations of cortical receptive fields, which may either amplify or reduce perceived differences in image size. It is possible that cortical representations of size are flexible to some degree, allowing neuronal adaptations to minimise perceived aniseikonia. These retinal and cortical factors are difficult to quantify in normal clinical settings, thus the only way to accurately measure the overall amount of aniseikonia is to do so subjectively

2.4 When does Aniseikonia occur?

2.4.1 Emmetropisation

Emmetropisation is a process by which reduction in neonatal refractive error has been described in animal (McBrien & Norton, 1992; Wallman et al., 1981) and human studies (Mohindra & Held, 1981). The process coordinates the growth of the eye's optical and axial components moving the initial ametropia towards emmetropia.

Evidence suggests that the majority of ocular growth and refractive development is regulated by active visual feedback related to optical defocus as well as the passive proportional growth of the eye. However, it has been argued that emmetropisation is a passive postnatal continuation of a genetically guided embryological process.

2.4.2 Theories of emmetropisation

2.4.2.1 *Active emmetropisation*

The eye appears to be able to detect and respond to its own refractive error, as the change in refractive error and the axial growth during the emmetropisation process depends on the initial amount of ametropia (Mutti et al., 2005; Saunders et al., 1995). Numerous animal studies (McBrien & Norton, 1992; Wallman et al., 1981; Irving et al., 1992; Schaeffel et al., 1988; Smith Iii & Hung, 1999) have shown that the visual environment exerts a powerful influence on the refractive status by controlling the axial length of the eye during postnatal development in an active visual feedback process.

Evidence that visual feedback regulates ocular growth in animals comes from observations of restoring normal visual conditions in young animals that have had experimentally induced refractive error (Smith III et al., 1994; Troilo & Wallman, 1991; Wallman & Adams, 1987). An example of this is through the study by Troilo & Wallman (1991) who induced refractive error in chicks and monitored the changes once normal visual conditions were restored. They found that the chick eyes quickly returned to emmetropia by modulated growth of the posterior chamber which was largely guided by retinal defocus. Once normal conditions were restored the rate of recovery was related to several factors: the age at which deprivation was induced, the duration of

deprivation, the degree of refractive error induced and the age at which normal visual environment was restored.

In relation to humans, Saunders, Woodhouse, & Westall (1995) examined the rate of emmetropisation in human infants aged 0 to 17 months in a longitudinal study. They reported similar results to the animal studies where the rate of visual recovery from highly hyperopic or astigmatic errors was related to the initial level of ametropia and occurred most rapidly when the initial refractive error was the highest showing a strong drive to achieve emmetropia. Mutti et al. (2009) lends further support to active visual feedback but suggests the rate of axial growth is controlled by the accommodation effort exerted rather than through defocus. The level of hyperopic refractive error and the stimulus to accommodation poses a dose-dependent signal for emmetropisation rather than hyperopic defocus or lack of accommodation.

2.4.2.2 *Passive Emmetropisation*

Passive emmetropisation is understood to be a nonvisual execution of a genetic plan, that often continues postnatally as opposed to the visually guided control as discussed in 2.4.2.1. The shape-related mechanism controls changes between the corneal curvature, the axial length and the refractive error. An increase in the axial length results in a proportionate decrease of the dioptric power (cornea and lens become flatter) reducing the refractive error to achieve and maintain emmetropia (Troilo, 1992; Wallman et al., 1981).

The refractive state of the eye is strongly correlated with the axial length rather than the corneal curvature or the refractive power of the lens (Sorsby, 1962b). Larsen (1971) identified three growth phases of the axial length using ultrasound biometry on 896 infants and children in Norway: 1. a rapid postnatal growth from birth to 1.5 years; 2. a slower infantile phase from 2-5 years and 3. a slower phase still from 5-13 years reaching adult values. The negative correlation between the axial length and the refractive error can be observed in the first three years of life and is part of the critical development phase. The relationship between the refraction and axial length goes some way to explain the passive shape-related mechanism of passive emmetropisation.

2.4.3 Emmetropisation and anisometropia

Anisometropia is defined as a difference in refractive error between the two eyes of 1 dioptre spherical equivalent or more. Anatomically, anisometropia occurs due to a difference in eye size predominately due to a difference the in overall axial length of the eye (Huynh et al., 2006). Anisometropia is often classified as axial with positive correlations between axial length and interocular difference found in animal and human studies (Bradley et al., 1983; Deng et al., 2014; Siegwart & Norton, 2010; Smith et al., 2010; Sorsby, 1962b; Tong et al., 2006; Zhong et al., 2004) or refractive differences.

The natural history of uncorrected anisometropia, the changes that occur over time and the factors involved in the development of significant anisometropia, are not well established. While genetic factors are suggested to influence the development of refractive errors (in particular myopia and myopic anisometropia) (Dirani et al., 2006; Dirani et al., 2008; Sorsby & Leary, 1969) it is generally accepted that environmental factors also play a significant role. Transitory anisometropia during childhood has been reported to be part of the emmetropisation process (Abrahamsson & Sjöstrand, 1996) with even significant amounts of anisometropia (up to 5D) resolving with growth (Abrahamsson et al., 1990; Almeder et al., 1990; Yamashita et al., 1999) and consequentially being non-amblyogenic. At present, there is no certain way of knowing if anisometropia found at a certain timepoint is transitory or persistent. Abrahamsson et al. (1990) found 19 out of 33 children initially found to have anisometropia at age 1 year were no longer anisometropic at age 4 and 14 who were not anisometropic at 1 year went on to develop anisometropia. Children with lower amounts of anisometropia are more likely to be transitory (Almeder et al., 1990) and moderate levels of anisometropia (≥3.00D) are more likely to be persistent and therefore amblyogenic. Persistent moderate levels of anisometropia are also more likely to have associated aniseikonia and therefore likely to be a contributory factor in the development of suppression and amblyopia.

Despite the lack of concordance on the mechanism of emmetropisation, there is an agreement that significant levels of ametropia reduced rapidly before 12 months of age after which the refraction stabilises. Any residual significant level of ametropia beyond

12 months may signify a failure of the normal emmetropisation process with the potential to affect normal visual development.

2.4.4 Normal human refractive development

At birth, full term human new-borns demonstrate a wide range of refractive errors which are variable and appear to be normally distributed with a mean of around +2.00 dioptres (2 SD) (Banks, 1980). This changes to a less variable and more leptokurtic distribution in adulthood with a mean refraction of +0.75D (1 SD) (Sorsby et al, 1960). Emmetropisation occurs rapidly in the first three months (Mutti et al., 2005; Qiao-Grider et al., 2010) and by approximately age 3 years the distribution narrows and peaks around +0.75 dioptres of hyperopia (Ingram & Barr, 1979; Mutti et al., 2005). It is thought that this hyperopic defocus at birth modulates the growth of the eye to reduce the refractive error (Smith et al., 2010; Wildsoet, 1997) towards emmetropia, however the exact mechanism remains unknown.

2.4.5 Refractive Error in Children

Refractive error within the first six months is variable and widespread (Mohindra & Held, 1981) with the degree of variance reducing with age (Mutti et al., 2005). Studies of refraction observe most normally developing infants to be hyperopic with an average cycloplegic refractive error of +2.00D (Gwiazda et al., 1993; Mayer et al., 2001) with decreasing amounts of hyperopia with age. Hyperopia decreases most rapidly during the first 12 months of life (Ehrlich et al., 1997; Saunders, Woodhouse & Westall, 1995; Wood, Hodi & Morgan, 1995), followed by a period of slower change until 2 years old. Recent population based cross sectional studies however have found that although overall hyperopia is the most common refractive error found, the degree of hyperopia is dependent on geographic location and ethnicity, with Western populations having a higher prevalence of hyperopia (Giordano et al., 2009) and Asian populations having a higher prevalence of myopia and astigmatism (Dirani et al., 2010; Rose et al., 2009). The American BPEDS study found that although hyperopia was the most common refractive error (8.9% in the White and 4.4% in the African American population) the trend of hyperopic infants shifting towards emmetropia was not observed, but a small decline in hyperopia was observed between the ages of 6 and 23 months (Giordano et al., 2009). The MEPEDS study (Borchert et al., 2011) found hyperopia decreases from

6 months to 24 months of age after which the prevalence increases again and remains stable at the higher level which contrasts with the theory of declining hyperopia through to adolescence. On the Asian continent, the Singaporean STARS study found a higher prevalence of myopia in their population with 5.2% having myopia of at least -1.00D in children aged 6-72 months and 8.6% having astigmatism of at least 1.50D (Dirani et al., 2010). In the southern hemisphere an Australian study, with most of its cohort being of European-Caucasian and Asian ethnicity, found hyperopia (28.9%) and astigmatism (51.3%) were the more prevalent refractive errors with increasing prevalence for myopia in older children (Pai et al., 2011). The population of Aotearoa, New Zealand (hereafter referred to as New Zealand) is made up of a rich diversity of ethnicities that are very different to the rest of the world. Currently, no New Zealand based population prevalence studies exist, however, small regional prospective cross sectional and retrospective studies have reported astigmatism to be the primary cause of visual impairment in school aged children (Findlay et al., 2020; Langeslag-Smith et al., 2015; Muller et al., 2019).

Most studies (Ingram et al, 1979; Varghese et al., 2009; Zonis, 1974) have shown that anisometropia is common in infants at low levels (Abrahamsson, Fabian, & Sjöstrand, 1990) and is often transient with no real consequence (this is discussed further in section 2.4.3) however higher levels of anisometropia (>3.00D) are more likely to remain causing an amblyogenic risk. Similarly, astigmatism has also been shown to be dynamic with decreasing astigmatism between the ages of 12 months and 4 years old with the most pronounced change occurring in the first year of life (Abrahamsson et al., 1988). Gwiazda et al. (1993) found that hyperopic children with against-the-rule-astigmatism lost their astigmatism but maintained the hyperopia at 6 months but those with with-the-rule astigmatism lost both astigmatism and hyperopia.

Overall, it appears that refractive error is variable in the first years of life after which it stabilises around the age of 24 months. Higher levels of ametropia demonstrate a greater decline (Atkinson et al., 2000; Saunders, Woodhouse & Westall, 1995). Persisting levels of high refractive error after the age of 24 months may lead to a greater risk of amblyopia. Although a number of overseas prevalence studies have reported on the prevalence of refractive error this appears to vary depending on the global region (Hashemi et al., 2017).

2.4.6 Refractive error and amblyogenic risk factors

Since our ability to prevent the development of amblyopia is limited, it is important to detect risk factors early during visual development when they are still amenable to treatment. The visual system is at increased risk of developing amblyopia from visual deprivation, strabismus, and significant refractive error. Visual deprivation amblyopia is caused by an obstruction of the visual axis, commonly caused by cataracts or other media opacities e.g., vitreous haemorrhage, corneal opacification and ptosis. Deprivation amblyopia appears to be rare based on the primary causative factors such as infantile cataracts with an incidence of 0.03% of live births (Rahi & Dezateaux, 2001). Form deprivation prevents all visual input with no possibility of binocular co-operation resulting in much more severe amblyopia than strabismic or refractive types.

Misalignment of the visual axes is often caused by a failure of motor fusion or a defect with the extraocular muscles leading to strabismus. Amblyopia is common in unilateral strabismus where the fovea of only one eye maintains consistent fixation and the visual direction of the other eye is uncommon. This causes diplopia and confusion limiting spatial localisation and stereopsis thus stimulating sensory adaptations through active cortical inhibition (suppression) or development of anomalous retinal correspondence (Arnoldi, 2011; Herzau, 1996). Suppression is a consequence of strabismus to cope with the dissimilar input from the deviated eye. Sensory adaptations allow for a single percept to be visualised at the expense of normal binocular perception and stereopsis. Chronic suppression from the deviating eye leads to strabismic amblyopia (Sengpiel & Blakemore, 1996; Sireteanu, 1982) and is one of the most common causes of childhood amblyopia with approximately two thirds of amblyopia being related to strabismus alone or in combination with a refractive error (PEDIG, 2002; Stewart et al, 2004).

Amblyopia due to refractive error (population prevalence of 2-3%) can be further divided into anisometropic amblyopia (a significant difference in refractive error between eyes) and ametropic amblyopia (high spherical or cylindrical refractive error). Bilateral ametropic amblyopia arises from large amounts of uncorrected refractive error, predominantly hyperopia and/or astigmatism in both eyes. The mechanism for ametropic amblyopia is presumed to be pattern vision deprivation caused by failure of both eyes to achieve a clear and focused retinal image leading to equally decreased

visual acuities. Uncorrected bilateral hyperopia without astigmatism tends to avoid the development of amblyopia due to the accommodative ability of the natural lens to achieve clear retinal images. However, there are children with hyperopia that do develop ametropic amblyopia, and this could possibly be due to reduced accommodative amplitudes often found in children with bilateral refractive errors (Schoenleber & Crouch, 1987; Werner & Scott, 1985). Meridional amblyopia is a term within ametropic amblyopia that refers to orientation dependant blur induced by uncorrected astigmatism where visual deprivation is specific to visual stimuli of certain orientation (Freeman et al., 1972; Mitchell et al., 1973). Oblique astigmatism is supposedly amblyogenic and more difficult to manage (Abrahamsson & Sjöstrand, 2003; Harvey, 2009; Harvey et al., 2007; Wallace et al., 2006).

Anisometropia causes image defocus on the retina in one eye resulting in reduced contrast sensitivity to high frequency inputs. Active inhibition of the fovea results to eliminate sensory interference caused by a focused and blurred image at the same fixation point. Persistent unilateral blur for a sufficiently long time (estimated to be approximately three years (Daw, 1998)) can result in amblyopia. Current knowledge does not allow us to know exactly which refractive errors will cause amblyopia given that anisometropia seen in infancy and early childhood is often transitory. However, in children aged 3-14 years an interocular difference of >1.00DS of hyperopia, >2.00DS of myopia and >1.50DC of astigmatism is associated with increased risk of developing amblyopia (Weakley, 2001). Despite Helveston (1966) finding no relationship between a higher risk of amblyopia with higher levels of anisometropia in an adult population the more recent cross sectional and population based studies have found the severity of amblyopia increases with increasing refractive error and interocular difference (Leon et al., 2008; Tarczy-Hornoch et al., 2011; Weakley, 2001) and is more common with anisohyperopia than anisomyopia (Afsari et al., 2013; Borchert et al., 2010). If the anisometropia is optically corrected, the resulting aniseikonia, which is discussed in more detail in section 2.3, maybe another amblyogenic factor.

2.4.7 Microtropia and anisometropia

The term microtropia, coined by Lang (Lang, 1969) describes a small angle strabismus (<5 degrees) with a high degree of binocular cooperation achieved through abnormal

retinal correspondence with normal fusion and reduced or absent stereopsis. Microtropia has been further defined as “microtropia without identity” where a small movement is observed on the cover/uncover test and a “microtropia with identity” where no movement is observed on the cover/uncover test but eccentric fixation is identified with assessment of fixation using visuoscopy or fixation ophthalmoscopy (Ansons & Davis, 2001).

Microtropia is often associated with anisometropic amblyopia (Hardman-Lea et al., 1991; Helveston & von Noorden, 1967; Houston et al., 1998; Lang, 1983; von Noorden, 1996), with foveal suppression and uniocular eccentric fixation often of the more ametropic eye. Hyperopic anisometropia with a flick esotropia is commonly associated with microtropia with the common belief that an esotropic microtropia develops secondary to central foveal suppression (Setayesh et al., 1978; von Noorden, 1996) due to anisometropia. Others have hypothesised that microtropia is due to innate inability or loss of prior bifoveal fusion (Parks, 1969; Wilson et al., 1993). This theory however does not provide a rationale as to why the microtropia develops following foveal suppression and why the deviation is esotropic in direction. Birch et al (2013) have suggested that the esotropic movement seen is due to fixation instability rather than a strabismus. In a prospective cross-sectional study of anisometropic children aged 5-13 years old, eye tracking was used to investigate the accuracy of eye fixation for 30 seconds. In children with anisometropia a brief saccadic oscillation was observed, and waveform analysis found it to be consistent with that seen in fusional maldevelopment nystagmus with a slow nasal drift and a rapid refixation movement outwards. This fixation instability was strongly associated with reduced stereoacuity, and they suggest that the disruption of bifoveal fusion due to anisometropia directly affects binocular experience during visual development resulting in fixation instability seen during cover testing.

Most studies of anisometropic amblyopia tend to combine microtropia along with strabismus and it is difficult from these studies to know if failure of anisometropic amblyopia treatment is due to undetected microtropia (Chen et al., 2007; Levi et al., 2011; Stewart et al , 2004), especially in cases of microtropia with identity.

2.4.8 Prevalence of anisometropia and therefore aniseikonia

Given that the inherent anatomical differences underlying anisometropia can cause a difference in retinal image sizes, and refractive correction for anisometropia can produce additional changes to retinal image size, we can postulate that the prevalence of aniseikonia would follow the prevalence of anisometropia.

Over a life span, the prevalence of anisometropia follows a U-shaped pattern. Anisometropia of ≥1 Dioptre in spherical equivalent has a high prevalence in the first few weeks of life (Fulton et al., 1980; Varghese et al., 2009; Zonis, 1974) and decreases in early childhood with emmetropisation (Atkinson et al., 1996). Current estimates suggest that 2-5% of the school-aged population have anisometropia (Afsari et al., 2013; Borchert et al., 2010; Deng & Gwiazda, 2012; Donahue, 2005). In adolescence, anisometropia increases along with the onset of myopia (Lin, 1995; Parssinen, 1990), with prevalence stabilising at about 10% between the ages of 20-40 years (Qin et al., 2005). Then, prevalence progressively increases with the onset of presbyopia to 30-40% (Weale, 2002). This post-presbyopic increase in anisometropia may be due to myopic shifts accompanying the development of asymmetric nuclear cataracts or the age-related accommodative failure due to peripheral lenticular changes. However, these changes have also been postulated to occur due to cortical changes within the neural substrate affecting the interaction of information between the two eyes with advancing age (Brown et al., 1993).

Anisometropia is commonly associated with high ametropia - anisomyopia and anisoastigmatism (Qin et al., 2005) in particular (Sorsby et al,.1962a; Tanlamai & Goss 1979). Significant cylindrical refractive error is also strongly associated with anisometropia (Deng & Gwiazda, 2012 & Qin et al., 2005). Population-based studies on preschool children have found that myopia of ≤1.00 Dioptre, hyperopia of >2.00 Dioptres and astigmatism of ≥1.50 Dioptres were associated with higher risks of developing anisometropia (Afsari et al., 2013; Friedman et al., 2009; Borchert et al., 2010 & Dirani et al., 2010) and consequentially developing amblyopia.

Large scale population based cross sectional and longitudinal studies (Table 1) have found higher prevalence of anisometropia in 6-11 month olds, supporting the theory of emmetropisation occurring relatively independently in each eye despite both eyes being

under identical conditions (Abrahamsson, Fabian, & Sjöstrand, 1990). The BPEDS study (Giordano et al., 2009) found 7.2% of African Americans and Whites were found to have anisometropia (≥1DSER) at 6-11 months old. This reduced to 3.2% and 4.5% respectively at age 12-23 months and remained stable thereafter through the preschool years. Borchert, et al. (2010) reported similar numbers in the MEPEDS with 7.8% of Hispanics and 4.7% of African Americans aged 6-11 months with anisometropia ≥1D. The anisometropia decreased in the Hispanic population to 5% in the 12-23 month age group but did not reduce in the African American population, but like the BPEDS study, anisometropia did not change significantly after 12 months old. Afsari et al. (2013) reported on the Australian population and found a lower prevalence of anisometropia (≥ 1D SER) at 4.7% in their 6-11 month age group which reduced to 3% at age 12-23 months. The STARS (Dirani et al., 2010) study found very low prevalence for anisometropia in their population but the criterion for anisometropia was ≥2D SER in this study. It is also worth noting that these studies used different methods for measuring refractive error, some used cycloplegia with autorefraction whereas others used cycloplegic retinoscopy (see Table 1). At 6-11 months old they reported a prevalence of 0% with no significant change at and beyond 12 months of age. These cross sectional population based studies are in agreement that the prevalence of anisometropia reduces from birth and appears to stabilise around 12 months old (Afsari et al., 2013; Borchert, et al., 2010; Giordano et al., 2009; Ingram & Barr, 1979). In older school children the prevalence has been indicated to be between 2.5% and 5% (De Vries, 1985; Phelps & Muir, 1977). Longitudinal studies (Abrahamsson et al., 1990; Almeder et al., 1990; Ingram & Barr, 1979) however, have shown that although the overall prevalence of anisometropia was stable there was considerable variation within individuals.

Although low levels of anisometropia ≤1.5D SER appear to be transitory with little consequence on visual development, greater levels ≥2D SER appear to be more significant in relation to visual development. Abrahamsson found 30% of children identified to have anisometropia of ≤2.5D SER at 1 year of age remained anisometropic at 4 years of age and this increased to 90% when anisometropia at 1 year was found to be ≥3.0D SER. Many studies have reported a greater prevalence and severity of

anisometropia in cases with high ametropia (in particular myopia) (De Vries, 1985; Huynh et al., 2006; Sorsby & Leary, 1969; Tanlamai, 1979; Tong et al., 2006). Significant cylindrical refractive error is also strongly associated with developing anisometropia (Deng & Gwiazda, 2012; Qin et al., 2005). It appears that the regulatory mechanisms involved with active emmetropisation become ineffective with large amounts of anisometropia and result in a disruption to visual development, which may precipitate the development of amblyopia if the anisometropia persists.

Overseas population based studies on preschool aged children have found that myopia of ≤1.00 dioptre, hyperopia of >2.00 dioptres and astigmatism of ≥1.50 dioptres were associated with higher risks of developing anisometropia (Afsari et al., 2013; Borchert et al., 2010; Dirani et al., 2010; Friedman et al, 2009) and consequentially developing amblyopia. However, there is little data on the New Zealand population and although small cohort group studies are available, they are not fully representative of our population as a whole. New Zealand has a unique population that cannot be matched to any other around the world and yet most of our policies and guidelines for treatment of eye related disorders in pre-schoolers are guided by overseas population studies (Royal College of Ophthalmologists, March 2012; Wallace et al., 2018).

Table 1. Prevalence studies of anisometropia and main findings

Authors/ Study groups	Population	Age	Number	Technique	Definition of anisometropia (Dioptre difference between eyes)	Prevalence of anisometropia	Prevalence of amblyopia	Study design	Main findings
The BPEDS Baltimore Paediatric Eye Disease Study (Giordano et al 2009)	African American, White	6-72 months	2298	70% Cycloplegic autorefraction 18.9% Streak Retinoscopy	≥1D SER ≥2D ≥3D	4.3 % AA 5% W 1%AA 1.5% W 0.2% AA 0.7% W	-	Population based, Cross sectional	SE Refractive error did not change significantly after 12 months ● 7.2% & 7.1% of 6 -11-month-olds had anisometropia >1D ● Decreased to 3.1% & 4% 12-23 months and remained stable through to preschool years
Multi-Ethnic Paediatric Eye Disease Study MEPEDS (Borchet et al 2010)	Hispanic and African American	6-72 months	6024	Cycloplegic Autorefraction	≥1D SER ≥1D Cyl ≥3D SER or Cyl	4.3% H 4.2% AA 5.6% H 4.5% AA ≤0.4% both groups	-	Population based, cross sectional study	Anisometropia does not diminish beyond 1 year of age ● 7.8% of Hispanics and 4.7% of African Americans aged 6-11 months with anisometropia ≥1D
Strabismus, Amblyopia and Refractive error in Singapore Study STARS (Dirani et al 2010)	Singaporean Chinese	6-72 months	3009	Cycloplegic autorefraction	≥2D	0.6%	-	Population based, cross sectional study	● 0% at 6-11 months old no significant change beyond 12 months ● High prevalence of myopia 11% & WTR astigmatism 8.6%

Authors/ Study groups	Population	Age	Number	Technique	Definition of anisometropia (Dioptre difference between eyes)	Prevalence of anisometropia	Prevalence of amblyopia	Study design	Main findings
Sydney Paediatric Eye Disease Study SPEDS (Afsari et al 2013)	• European - Caucasian, • East-Asian, • South-Asian • Middle Eastern	6-72 months	2090	Cycloplegic autorefraction retinoscopy	≥1D	SER 2.7% Cyl 3.0%	12.4%	Population based, cross sectional study	• Higher prevalence of aniso in 6-11 months • No age-related increase in SE or Cylindrical aniso prevalence after 12 months • Positive correlation between anisometropia and ametropia
					≥2D to compare to STARS	SER 0.6% Cyl 0.3%	33.2%		
Deng 2012	Caucasian	6 months to 15 years	1827	Non-cycloplegic retinoscopy	≥1D SE	1.69 % 6mnth 1.27 % 5yr 5.77 %12-15yr	-	Longitudinal (3years)	• U-shape in prevalence of anisometropia across the 3 age groups • Anisometropia increased from 5-15 years with eye growth towards myopia • Positive correlation between anisometropia and ametropia

Authors/ Study groups	Population	Age	Number	Technique	Definition of anisometropia (Dioptre difference between eyes)	Prevalence of anisometropia	Prevalence of amblyopia	Study design	Main findings
Yamashita 1999	Japanese	6-11 years	350	Cycloplegic auto refraction	3.1% ≥1D 0.9% ≥2D	4.3%	-	Longitudinal	• Inter-eye spherical difference remained statistically unchanged. • Significant anisometropia is rare amongst school aged children • 15% had individual variability
De Vries 1985	Dutch-Rotterdam	unclear	1356	Cycloplegic streak retinoscopy	≥2D SER or Cyl	4.7%	53%	Longitudinal Mean Follow up 4 years (Range 2-8years)	• Anisometropia is a stable condition with small changes • Positive association between increasing amounts of anisometropia and amblyopia • 53% of amblyopia found in pure anisometropes
Abrahamsson 1990	Swedish	1-4 years	310	Cycloplegic streak retinoscopy	1 year ≥1D SER ≥2D SER 4 years ≥1D SER ≥2D SER	 11% 2% 9% 2%	28.6%	Longitudinal study (3 years)	• Persistent anisometropia at risk of developing amblyopia • Inter-individual variability

Authors/ Study groups	Population	Age	Number	Technique	Definition of anisometropia (Dioptre difference between eyes)	Prevalence of anisometropia	Prevalence of amblyopia	Study design	Main findings
Laatikainen 1980	Finnish	7-15	411	Cycloplegic streak retinoscopy	≥1D SER	3.6%	0.5%	Population based cross sectional study	General refractive error moves towards myopia

AA= African American W= White, H=Hispanic, SER= Spherical Equivalent Refraction, Cyl= Cylindrical

2.5 Why does aniseikonia matter?

2.5.1 Clinically significant aniseikonia

In visually-normal individuals, acutely-induced static aniseikonia generally becomes symptomatic at 3-5% magnification difference between eyes (Awaya et al, 1982; Enoch, 1997; Katsumi et al., 1986; Oguchi & Mashima, 1989) (Table 2). Some individuals sensitive to aniseikonia may report symptoms with less aniseikonia, but it is possible that these symptoms are caused by spectacle-induced anisophoria (Remole 1989 & Remole 1984) rather than static aniseikonia.

Table 2. Summary table on the amount of aniseikonia and the possible effects.

Amount of aniseikonia	Binocular summation (electrophysiology)	Binocular summation (contrast sensitivity)	Stereopsis	Symptoms
0-0.75%	Binocular amplitude larger than the monocular amplitude (summation)	Normal contrast sensitivity	Good stereopsis	Clinically asymptomatic
1-2%	Binocular amplitude larger than the monocular amplitude (summation)	Normal contrast sensitivity	Good stereopsis	Clinically asymptomatic
3%	Binocular amplitude larger than the monocular amplitude (summation)	Contrast sensitivity reducing	Decreased stereopsis	Asthenopia, headache in patients with reduced fusional capabilities
5%	Binocular amplitude reduced to same as monocular amplitude (no summation)	Significantly reduced Contrast sensitivity	Significantly reduced stereopsis	Asthenopia, headache, difficulty reading & diplopia
over 5%	Binocular amplitude below the monocular amplitude (inhibition)	No measurable contrast sensitivity	No stereopsis	Retinal rivalry or active inhibition (suppression) of one eye

All studies were carried out on normal adults with no or low refractive error with aniseikonia induced using size lenses. (Jimenez et al., 2004; Katsumi et al., 1986; Oguchi & Mashima, 1989).

2.5.2 Symptoms of aniseikonia

It is uncommon for a patient with aniseikonia to complain of unequal image size or distorted images. Only 6% of patients reported this as a symptom in a survey questionnaire of 500 patients suspected of aniseikonia following refractive correction (Bannon, 1944). Instead, patients with symptomatic aniseikonia often present with symptoms common to other binocular vision disorders, such as asthenopia (67%), headache (67%), difficulty reading (27%), and diplopia (11%) in vertical gaze. Often, patients continue to have symptoms even after receiving lenses to correct refractive error, prismatic correction for ocular deviations.

2.5.3 Binocular function and aniseikonia

Static aniseikonia has a non-linear effect on binocular vision (Table 2). Below about 3% perceived image size difference, image fusion and stereopsis are generally not affected, however some patients may experience asthenopic symptoms. Image size differences of 3-5% will begin to impair binocular visual functions (Katsumi et al., 1986), resulting in reduced binocular summation and stereopsis in objectively measured visually evoked potentials (Jimenez et al., 2004; Oguchi & Mashima, 1989). Above about 5% image size difference, the patient may experience diplopia in parts of the visual scene, and suppression may be needed to prevent diplopia. This binocular inhibition is presumably due to the active suppression of inputs from one eye, which prevents stereopsis and causes binocular performance to become worse than monocular viewing (Oguchi & Mashima, 1989).

2.6 Critical periods of visual development

The visual system is a complex interconnected matrix of multiple sub-components, each having its own period of plasticity and susceptibility to disruption. The development of the visual system relies on complex afferent and efferent feedback connections between these different visual function components. Full maturation of each component likely relies on the full development and maturation of the preceding interconnected component and critical periods last longer at higher levels of the visual system. During visual development three important overlapping phases have been identified as follows: The 'critical period' which defines the normal developmental maturation process during which disruption can lead to irreversible anatomical and physiological changes in the visual system (Daw, 1998; Hubel & Wiesel, 1970). The 'sensitive period' follows requiring a period of constant normal input to either eye to consolidate neural processes in order to achieve higher cortical functions like binocular single vision (Birch et al., 1993; Vaegan & Taylor, 1979). Finally comes the 'treatment period' which refers to a window of time where removal of the amblyogenic factors and re-establishment of visual function is permitted. The earlier the amblyopia treatment is started the better the visual outcome will be.

2.6.1 Critical and sensitive periods

In the mammalian visual system the information from the two eyes is combined in the primary visual cortex. In humans the inputs from the right and left eye terminate in separate layers of the lateral geniculate nucleus which then project onto the ocular dominance columns in the primary visual cortex (V1). Hubel and Wiesel led the way in describing changes in the ocular dominance cells through their work on monocular deprivation in the primary visual cortex of cats (Wiesel & Hubel, 1963) and adult macaque monkeys (Hubel et al., 1977). Their work established the term "critical period" when describing an innate period of susceptibility during normal visual development where changes in the external visual environment can alter pre-existing neuronal connections. Ocular dominance columns are described as regions of neurons in the visual cortex that responds to the stimulation from either the left or right eye, and can be defined both anatomically and physiologically (Hubel & Wiesel, 1969). In a normally developed visual system, the area of dominance columns for each eye is the same, and

each cortical cell responds to visual input predominantly according to its column. In the absence of normal sensory inputs the input from the stronger normal eye competes with the poor vision in the deprived eye. This results in the stronger synaptic connections being retained and the non-functional, unused connections being "pruned' and decay as a result. This experience dependant response of synaptic overproduction and subsequent reduction is essential for the individual to respond to environmental conditions allowing for fine tuning and modification as needed. These experience dependant changes can be referred to as ocular dominance plasticity also known as the 'critical period'. In humans the critical period is thought to start somewhere between birth and 6 months of age, peaking at 1-2 years of age with a decline between 2 and 8 years of age (Daw, 1998). This corresponds to the time of greatest growth of the head and the eyes when the distance between the two eyes becomes larger and the cortical neurons fine tune their connections allowing and maintaining fine stereoscopic vision during this divergence of the visual axes.

Monocular deprivation studies have shown shrinkage of the ocular dominance columns within the primary visual cortex dedicated to the form deprived eye soon after birth. This results in amblyopia far greater than that found in amblyopia related to strabismus or anisometropia. Partial visual deprivation induced through strabismus or anisometropia has been reported to have minimal effects on the ocular dominance columns (Daw et al., 1992; Horton & Stryker, 1993; LeVay et al., 1980), with minimal or no shrinkage of the ocular dominance columns. Recent studies on strabismus induced changes have shown that the visual system in humans is most susceptible to the effects of strabismus around the time stereopsis first emerges and not immediately after birth as proposed by the monocular deprivation studies (Mori et al., 2002). Strabismus observation studies suggest the sensitive period for stereopsis peaks around the age of 3.5 months (Birch & Petrig, 1996) with an endpoint that previously was considered to be around the age of 8 years, but recent evidence shows it could extend into adulthood (Fawcett et al., 2005).

The peak of the critical period or ocular dominance plasticity (aged 1-2 years) signals the start of the next developmental stage, the sensitive period which refers to a phase where persistent abnormal input can alter the visual function. Continuous prolonged periods of normal vision are required to consolidate the neural pathways.

Neuroplasticity gradually reduces as visual maturation is reached and the neural system grows resistant to abnormal sensory input. Disruption of visual experience during the sensitive period can result in a loss of visual function that persists even after optical or ocular correction has occurred. The sensitive periods for strabismic amblyopia and anisometropic amblyopia appear to be similar, beginning at around 6 weeks of age (Birch et al., 1993) and ending around 8 years of age (Vaegan & Taylor, 1979) with a peak of neuroplasticity between 9-18 months of age and this matches that of the critical period. However, anisometropia is common in the first year of life with approximately 30% of infants having anisometropia of >1.00 dioptre at birth (Abrahamsson & Sjöstrand, 1996; Varghese et al., 2009) which resolves with no adverse effect on visual development. It is only greater amounts of persistent (≥3D after 12 months of age) anisometropia that risk becoming amblyogenic. Although clinical belief holds amblyopia treatment to be more successful in the early stages of visual development when neuroplasticity is greatest, recent evidence suggests that binocular visual function is suppressed or inactive, particularly in anisometropic amblyopia under normal viewing conditions rather than permanently lost. Clinical trials and case studies have demonstrated visual acuity improvements in patients up to 17 years old although prolonged treatment is required for the same amount of visual improvement (Mintz-Hittner & Fernandez, 2000; Scheiman et al., 2008; Singh et al., 2008).

2.6.2 Optical Treatment of Amblyopia

Full correction of any refractive error is the first step in the standard treatment of amblyopia, a process termed “refractive adaptation” or “optical treatment” (Cotter et al., 2012; Cotter et al., 2006; Mosley et al., 2002; Stewart et al., 2004). Optical treatment has been particularly important in the treatment of anisometropic amblyopia. In anisometropia without strabismus the refractive correction will provide clear focused images to the retina, improving the quality of visual input and re-establishing binocular function. Even where strabismus is present, refractive correction can help to reduce the angle of deviation especially in the case of intermittent strabismus (Cotter et al., 2012).

Simply correcting refractive error does not immediately resolve amblyopic deficits and restore normal levels of acuity. Full time daily wear of the refractive correction is required for visual acuity and stereopsis to gradually improve over several weeks or months which has been termed “optical treatment” or “refractive adaptation” (Cotter et

al., 2006; Stewart et al 2004). The delayed improvement in visual acuity is presumed to be due to cortical adaptations occurring to an increased range of spatial frequency and balanced binocular viewing. Therefore, wearing optical correction is now considered an important independent phase of clinical amblyopia treatment (Cotter et al., 2012; Repka & Holmes, 2012). In anisometropic amblyopia, a period of 16-22 weeks of optical treatment only has been shown to improve visual acuity in the amblyopic eye by 2 lines (≥0.200 logMAR) in 25-45% of children 3-7 years of age with no prior treatment. Interocular difference also reduced to ≤0.100 logMAR with optical treatment resulting in successful treatment as defined by interocular VA of 1 logMAR line or less is considered a normal level of acuity (Cotter et al., 2012; Cotter et al., 2006; Moseley et al., 2002; Stewart et al, 2004). One third of children see a resolution of amblyopia with optical treatment alone removing the need for adjunct occlusion therapy and reducing treatment burden on the child and their families. With accumulated evidence from multiple large-scale clinical trials, the current preferred practice guidelines for amblyopia treatment now recommend optical treatment for a minimum of 8 weeks or until vision stabilises as the first line of amblyopia treatment in refractive and strabismic amblyopia (Royal College of Ophthalmologists, March 2012; Wallace et al., 2018) and many studies now incorporate an optical treatment phase of 4-18 weeks prior to commencing further amblyopia therapy (Birch et al., 2015; Gao et al., 2018; Li et al., 2014; Scheiman et al., 2005; Stewart et al., 2004).

2.6.3 Amblyopia, suppression and aniseikonia

At least two-thirds of patients with amblyopia have anisometropia (Barrett et al., 2013; Friedman et al, 2009; Robaei et al., 2006), thus we may expect aniseikonia to be common in patients with amblyopia. However, patients with anisometropic amblyopia rarely report aniseikonia symptoms, and image size issues are rarely considered in the clinical management of anisometropic amblyopia. Anisometropic amblyopia is associated with reduced binocularity, and the severity of binocular deficits, such as reduced fusion, poor or absent stereopsis, and reduced binocular summation, are correlated with the degree of anisometropia (Donahue, 2005; Levi et al., 2011). Suppression of the amblyopic eye, a binocular adaptation which imbalances the relative weighting of inputs from each eye during cortical binocular combination, is common in all types of amblyopia (Hess et al., 2014; Levi et al., 2007). It is possible that

aniseikonia is present in anisometropic amblyopia but not experienced by the patient due to the image from the amblyopic eye being too poor in quality or too strongly suppressed for the binocular image size difference to be recognised under normal viewing conditions. Alternatively, cortical adaptations may reduce any perceived image size differences between eyes. Because of the difficulty caused by suppression, it is not clear what physical image size difference is required for patients with amblyopia to experience aniseikonia.

Clinically anisometropic amblyopia is diagnosed when reduced visual acuity is found in association with anisometropia in the absence of other pathology and is often identified during preschool vision assessments. The name anisometropic amblyopia implies a strong causative effect, however, the exact mechanism of anisometropic amblyopia is poorly understood. The majority of literature suggests that anisometropia leads to amblyopia (Cobb et al., 2002; Fielder & Moseley, 1996; Weakley, 1999; Abrahamsson & Sjöstrand, 1996; Smith et al., 1985). Anisometropic amblyopia is thought to result from monocular deprivation caused by chronic unilateral blur of the more ametropic eye (Cobb et al., 2002; Fielder & Moseley, 1996; Weakley, 1999; Abrahamsson & Sjöstrand, 1996; Smith et al., 1985). von Noorden further suggested active foveal inhibition of the more defocused eye occurs to eliminate sensory interference caused by two differently focused images which causes a loss of binocular co-operation and function. It is this loss of binocular function that influences the development of amblyopia rather than optical blur itself. Tomaç et al (2002) lent support to this theory through finding the depth of amblyopia was related more to deteriorated binocular function than to the magnitude of anisometropia. However, there is also evidence to support amblyopia being the primary cause, with resulting anisometropia due to interference during emmetropisation (Kiorpes & Wallman, 1995). Kiorpes and Wallman made the observation that amblyopia preceded anisometropia in monkeys with surgically induced strabismus and amblyopia (Troilo & Judge, 1993). Another study observed the development of anisometropia following short-term monocular deprivation in marmosets, supporting the notion that cortical deficit can influence ocular growth (Smith et al., 1999). Either way, the onset of anisometropia and amblyopia are likely to occur at different times and the larger the magnitude of anisometropia the greater the chance of developing amblyopia. This relationship is possibly due to defocus and aniseikonia, as the presence of significant aniseikonia itself requires some suppression

to prevent diplopia and confusion. Thus, it is possible that aniseikonia is present in patients with amblyopia but not experienced by the patient due to the image from the amblyopic eye being too poor in quality or being too strongly suppressed for the binocular image size difference to be recognised under normal viewing conditions.

Full correction of any anisometropia (optical treatment) is the first step in the standard treatment of amblyopia (Cotter et al., 2012; Cotter et al., 2006; Stewart et al., 2004). However, spectacle and contact lens corrections for anisometropia can induce aniseikonia, which will be combined with any existing inherent anatomical or neurological aniseikonia. The current clinical refractive correction guidelines for anisometropic amblyopia aim to image focus for the two eyes, recommending full correction of the anisometropic difference in refractive error (Brooks, 2018; Cotter et al., 2006), but failing to address differences in image size.

If the optically induced aniseikonia from refractive correction worsens existing aniseikonia, then it is possible that this will lead to an increased need for suppression, in addition to that from anisometropic blur. This will in turn further limit binocular visual functions. Clinical trials investigating standard amblyopia therapies of optical treatment, occlusion, and/or atropine penalisation have shown reasonable efficacy, but about half of the treated children are left with residual visual acuity deficits (Repka et al., 2005; Stewart et al., 2005), and about three-quarters of children treated for anisometropic amblyopia are left with sub-normal stereoacuity (Stewart et al., 2013; Wallace, 2018). Significant aniseikonia is known to limit binocular functions like stereoacuity in adults with normal visual history (Katsumi et al., 1986; Oguchi & Mashima, 1989), therefore it is possible that aniseikonia also limits stereoacuity in children with anisometropic amblyopia. Correcting aniseikonia as part of the anisometropic correction may reduce the stimulus for developing suppression, leading to improved binocular visual outcomes from optical treatment of anisometropic amblyopia. There is currently no clinical trial-quality evidence to support or refute this hypothesis. Available evidence is limited to individual case reports (Shaw & Bobier 2012). Further research with well-controlled, large-scale cohort studies and randomised clinical trials is needed.

2.6.4 Adherence to Amblyopia treatment

A common challenge when prescribing amblyopia treatment is non-adherence to prescribed time which is common to other aspects of prescribed medical interventions and imposes a considerable financial burden upon health care systems (Osterberg & Blaschke, 2005; Vermeire et al., 2001). Clinically, adherence is only assessed indirectly and subjectively via patient or parental/caregiver reporting which generally overestimates adherence (Drews-Botsch et al., 2016; Fielder et al., 1995).

Previous amblyopia studies using objective occlusion dose monitoring show that compliance with occlusion/patching treatment for amblyopia is a limiting factor for good visual outcomes. On average, children only receive 44% to 57% of the prescribed patching time (Awan et al., 2005; Loudon et al., 2006; Pradeep et al., 2014; Stewart et al., 2004; Tjiam et al., 2012; Wallace et al., 2013), and individual patching compliance varies from 0% to 100% of the hours prescribed. A prospective study in a small cohort of children, which used a modified occlusion dose monitor to measure spectacle compliance, showed that spectacle compliance also suffered a similar range of interindividual variability (Maconachie et al., 2016) as adherence to occlusion. Importantly, good compliance with spectacle wear during the first six weeks of refractive adaptation has been found to be associated with a better overall visual outcome for amblyopia treatment, particularly for anisometropic amblyopia (Maconachie et al., 2016). In addition, compliance with spectacle wear has also been shown to be associated with improved literacy levels (Bruce et al., 2018; Harvey et al., 2016) and better letter identification ability in children. Recent trials on binocular treatments of amblyopia using videogames also saw adherence to treatment as a problematic factor in determining treatment success. The BRAVO clinical trial (Gao et al., 2018) compared an active contrast balanced videogame to a placebo game in children 7 years and older and adults with amblyopia and found adherence to be significantly less than prescribed and highly variable (Gao et al., 2021). Overall compliance appears to decline with longer treatment duration and emotional impact (Holmes et al., 2003; Hrisos et al., 2004; Loudon et al., 2009) and poor parental understanding (Newsham, 2002) of the treatment seem to be important factors affecting adherence.

2.7 Testing for Aniseikonia

Most aniseikonia tests use anaglyphic or polarised filters to control which targets are seen by each eye (with the integration of a binocular fusion-lock target) and involve direct size comparisons of dichoptic targets. These techniques work well on patients with functional binocular vision and minimal suppression of either eye. However, patients with co-existing amblyopia and more severe suppression may struggle to appreciate targets shown to the amblyopic eye, making direct comparison of image sizes difficult. Recent research shows that adjusting the image contrast and/or luminance presented dichoptically to each eye can overcome this suppression, allowing both targets to become simultaneously visible (Ding & Levi, 2014; Hess et al., 2014; Maehara et al., 2011; Hess, 2014), however, this has not been implemented into clinical or research-based aniseikonia tests.

2.7.1 Size Lenses

Size lenses, also clinically referred to as ‘iseikonic’ or ‘aniseikonic’ lenses, are a particular type of afocal lens which produce prescribed magnification (defined as a percentage) but do not change the vergence of incident parallel rays (Figure 4). This means that all size lenses have vertex powers of zero (plano).

Size lenses can be used in clinical practice to empirically correct subjectively perceived aniseikonia, for example in a trial frame, to confirm that correcting a certain amount of aniseikonia will provide symptomatic relief. This magnification factor can then be combined with the required dioptric power for correcting refractive error into spectacle lenses. Comprehensive explanations of the optical principles, along with worked examples, can be found in textbooks such as Clinical Management of Binocular Vision (Scheiman & Wick 2008) and Clinical Optics (Fannin & Grosvenor 1996). Size lenses are also often used in research to induce aniseikonia in participants with normal binocular vision, in order to investigate the accuracy of testing paradigms (De Wit 2003).

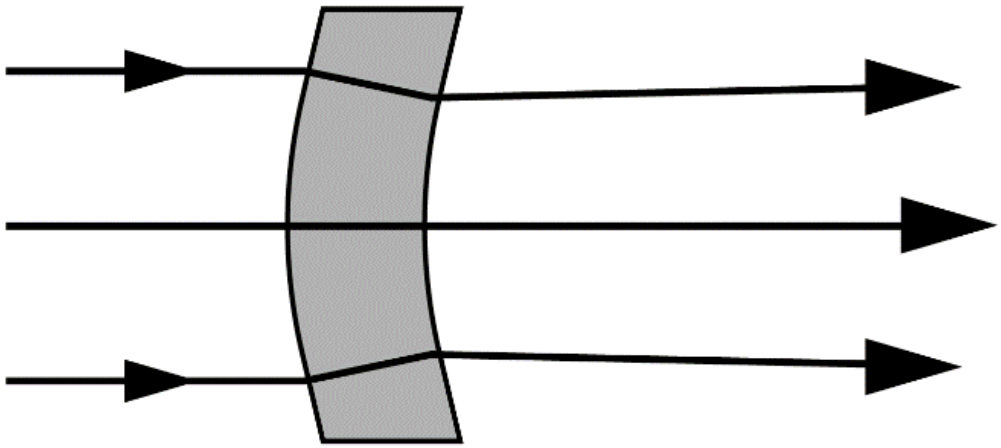


Figure 4. An Afocal Size Lens. Both incident rays and emergent rays are parallel, with vergence only occurring within the lens. The principle points and focal points are at infinity, therefore the lens does not have power.

2.7.2 The Robertson Technique:

This is a method for the screening and measurement of spectacle lens induced optical aniseikonia, using the neutralisation of vertical anisophoria. A modified Maddox rod technique is used at a distance of one metre. The horizontal line and penlight will be seen as overlapping if the patient is looking through the optical centres of the lenses. The light is then gradually moved upwards and downwards while the patient follows with their eyes, keeping their head position stable. If dynamic aniseikonia is present, then the light and the line should move apart, and the larger image will be seen at the more peripheral position on both up and down gaze (Figure 5). Prisms are used to measure the amount of vertical anisophoria for each gaze position (Table 3), which can be used to calculate the amount of dynamic aniseikonia. From this value the static aniseikonia can then be inferred (Remole 1989a; Remole 1989b; Remole & Robertson 1996).

Figure 5. Robertson technique. The eye seeing the pen torch has the larger image, therefore the light is seen above the line in up-gaze and below the line in downgaze.

Table 3. Amount of dynamic aniseikonia in lens-induced anisophoria measured by the Robertson Technique at one metre.

The Maddox rod over the left eye, the results show that the image was on average 5.8per cent larger than that of the right eye.

Light position (cm)	Measured vertical prism	Line position (cm)	Induced dynamic aniseikonia
40	2.5 BD	42.5	6.3%
30	1.5 BD	31.5	5.0%
20	1 BD	21	5.0%
10	0.5 BD	10.5	5.0%
0	0	0	0
-10	0.5 BU	-10.5	5.0%
-20	1.5 BU	-21.5	7.5%
-30	1.5 BU	-31.5	5.0%
-40	3 BU	-43	7.5%

Due to the dissociated viewing conditions and use of a light target, the Robertson technique can often be successfully used in patients with shallow suppression. It is relatively easy to perform and requires only a simple positional judgement by the patient. However, dynamic aniseikonia measurements can be complicated by co-existing vertical deviations and large horizontal deviations. This can be accounted for by measuring the underlying ocular deviations without refractive correction in the required directions of gaze, and then subtracting these measurements from the measured anisophoria during the calculations for spectacle induced aniseikonia.

2.7.3 Direct Comparison Techniques

2.7.3.1 *Eikonometer*

Traditionally, aniseikonia has been measured using a direct comparison eikonometer. This uses polarising filters to dissociate the two eyes, and patients must judge the

relative positions of four lines while the relative magnification of the lines are changed. If aniseikonia is present, one set of lines will appear misaligned. This method relies on binocular simultaneous perception, so it cannot be administered if there is central suppression. Another problem is that it is often difficult to judge the displacements accurately and the displaced images may be measuring a heterophoria or an apparent disparity caused by a misalignment of optical centres of the correcting lenses instead of aniseikonia (García-Pérez, 2015).

2.7.3.2 *Maddox Rod Test (Brecher test)*

The Brecher test uses a Maddox rod oriented to produce vertical streaks and two small light sources held about 20cms apart (Brecher, 1951). The aim is to compare whether the separation of the two lights is the same as the separation between the streaks. Size lenses are used to equalise the separation between the lights and between the streaks, allowing a measure of the perceived aniseikonia. The advantage of this test is that any heterophoria can be corrected using loose prims first, so that it will not confuse the measurement of aniseikonia, and the test can be performed in patients with shallow suppression, with the aid of neutral density filters over the dominant eye to reduce luminance if necessary. However, the test cannot be performed if strong suppression is present.

2.7.3.3 *Double Maddox rod test (Miles Test)*

This modification of the Brecher test uses two penlights and two Maddox rods (Miles 1947). If aniseikonia is present, there will be some stereoscopic disparity because one of the lines will be horizontally displaced compared to the other. The aim is to determine which red line appears closer to the patient. Size lenses are then used over the corresponding eye until both red lines appear to be in the same plane. This test requires an astute patient with good stereoacuity and therefore cannot be performed in patients with strong suppression.

2.7.3.4 *The New Aniseikonia Test (Awaya)*

This test involves a booklet viewed through red-green anaglyphic glasses (Awaya S, 1982). The booklet contains 24 pairs of red-green semi-circle targets presented in one per cent magnification increments from 0 to 24%. The aim is to find a pair of semi-circles that appear equal in size. The test is simple and easy to administer but has been found to significantly underestimate the amount of aniseikonia due to design issues,

including colour-size illusions and interactions between static and dynamic aniseikonia as the patient moves their eyes to look through the booklet. (Amos, 1987; García-Pérez, 2015; McCormack et al., 1992).

2.7.3.5 *The Aniseikonia Inspector Version 3*

This computer-based test requires patients to directly compare two rectangles viewed through red-green anaglyphic glasses, thus simultaneous perception with minimal suppression is required (de Wit, 2003). The forced-choice method and the short testing time (approx. 4 minutes) make this a simple and quick test to be performed in all age groups, including children aged as young as 5 years (Kehler et al 2014).

The Aniseikonia Inspector version 3 has been found to underestimate induced aniseikonia (McCormack et al., 1992). Binocular fusion of the two dichoptically presented rectangles, along with colour-size illusions, may contribute to the tendency for underestimation (García-Pérez, 2015).

2.7.4 Techniques based on stereopsis or spatial distortion

2.7.4.1 *Space Eikonometer*

The space eikonometer contains three-dimensional targets inside an enclosed box (Ames, 1945; Ogle, 1946). A red cross is seen in the centre with two vertical green lines in front and two bright white lines behind the cross (Figure 6). The presence of aniseikonia will make the red cross target appear tilted. The amount of aniseikonia is then measured by using size lenses to correct the tilt until the target appears parallel with the frontoparallel lane. This measurement of aniseikonia is dependent on the effect of image size differences on stereopsis and the perception of spatial relationships between objects, and thus requires patients to have good binocular vision, normal retinal correspondence, and the ability to make astute spatial judgements. This test only measures up to 5% of aniseikonia, as above this value binocular vision tends to break down.

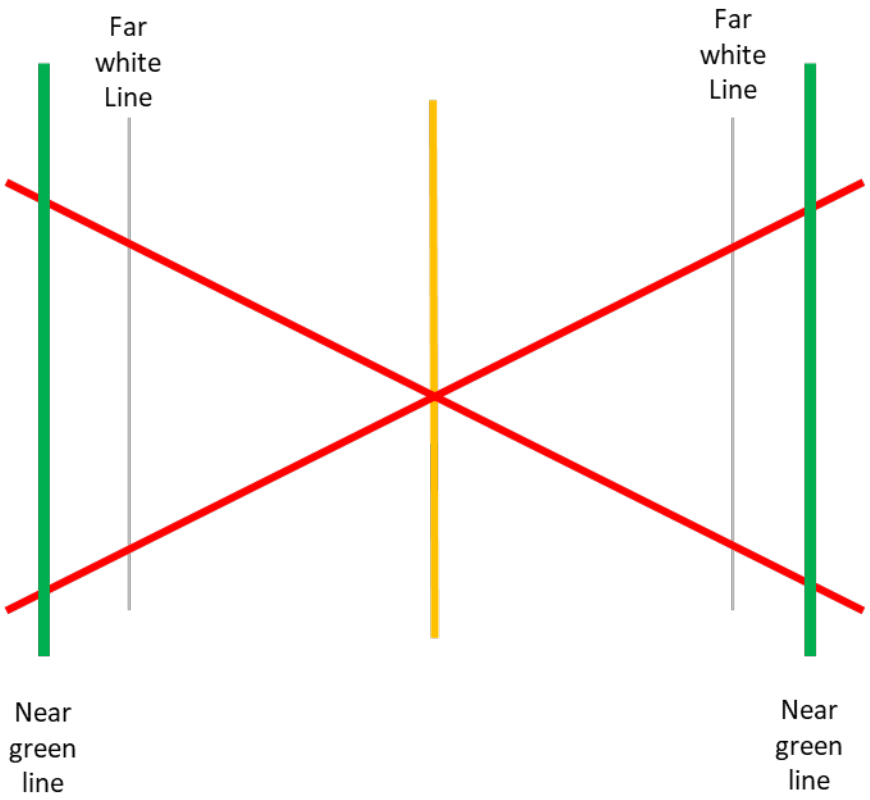


Figure 6. Space Eikonometer target. Patient's task is to report on the relative positions of the lines as the magnification is changed until all the lines appear equidistant.

2.7.5 Calculation through biometry/use of refractive error

Clinically, empirical calculations or approximations of aniseikonia based on the anisometropic difference in refractive error are often used. The common approximation is 1% of aniseikonia per Dioptre of spherical anisometropic difference. For example, a patient with a prescription of +3.00 D right eye and +6.50 D left eye would be assumed to have 3.5% of aniseikonia when corrected with spectacles.

Recent advances in technology have resulted in a number of affordable ocular biometry tools for use in clinical practice. These machines can measure ocular refractive parameters such as axial length, corneal and lens curvatures, and the positions of ocular components, allowing calculations of axial and refractive differences in power. So far, ocular biometry technology have been used mostly in patients undergoing refractive and/or cataract surgery, and in myopia control. This technology has not been widely

applied in the assessment of aniseikonia. However, with the development of appropriate ocular refractive models and investigations of aniseikonia in real patients, biometry may become a valuable tool in the assessment of aniseikonia, particularly in patients who cannot complete traditional aniseikonia tests.

2.8 Treatment of Aniseikonia

Aniseikonia can be treated with various refractive correction options, which aims to reduce retinal and/or perceived image size differences between eyes. To determine the most appropriate management for each patient, it is imperative to measure the subjective magnitude of aniseikonia and to consider the underlying cause(s) of aniseikonia, any refractive errors, and whether prismatic correction is also needed for oculomotor conditions. A number of practical factors also need to be considered including the patient's age, current refractive correction, ability to wear contact lenses and the potential cosmesis of a spectacle correction.

If aniseikonia is not evident without correction and is caused solely by the spectacle correction, then equal magnification lenses can be prescribed. This can be done by adjusting the spectacle magnification induced by each lens (Equation 2) so that both lenses induce a similar amount of magnification, resulting in a relative spectacle magnification ratio close to 1, or zero induced aniseikonia (see Table 4 for worked example). However, in cases where some inherent anatomical, retinally-induced, or neurological aniseikonia exists, it is important to correct the subjectively measured aniseikonia. That is, the correction should neutralise the combined effects of all internal and optically-induced types of aniseikonia, so that the patient may perceive equal sized images and achieve optimal binocular vision. Spectacle magnification can be manipulated by adjusting lens base curves, centre thicknesses and/or refractive indices. The magnification induced by the lens Power Factor, which is determined by back vertex power and vertex distance (Linksz & Bannon 1965; Ryan 1975), usually cannot be easily altered if the refractive error is to be fully corrected.

$$SM = M_p \times M_s = \left(\frac{1}{1 - dF_v{}'}\right)\left(\frac{1}{1 - \frac{t}{n}F_1}\right)$$

M_p = Power Factor, M_s = Shape Factor, d= Back vertex distance in metres, F_v' = Back vertex power in dioptres t = centre thickness in metres, n = refractive index, F_1 = Front surface power in dioptres

Equation 2. Spectacle magnification equation.

Table 4. An example of changing lens parameters to reduce spectacle induced aniseikonia.

Correction	Eye	Rx	n	d (mm)	t (mm)	F_1 (D)	Induced lens Magnification	Optically induced Aniseikonia
Standard Spectacle Lenses	RE	+2.00	1.498	15	2.2	6.50	+4.09%	3.65%
	LE	+4.00	1.498	15	3.2	6.50	+7.88%	
Iseikonic Spectacle Lenses	RE	+2.00	1.6	15	6	8.50	+6.49%	0.69%
	LE	+4.00	1.6	15	2.5	5.00	+7.22%	

To reduce the optically-induced aniseikonia for this anisometropic spectacle correction, the base curve (F_1) and centre thickness (t) for the less plus right lens have been increased to increase its magnification effect, and the base curve and centre thickness of the more plus left lens have been decreased to reduce induced magnification. The net result is less optically-induced aniseikonia from spectacles. A higher refractive index (n) was selected to allow both lenses to be made thinner, improving cosmesis. D= vertex distance (incl. cornea to pupil distance)

While it is possible to mathematically design a pair of iseikonic anisometropic lenses to reduce or eliminate perceived image size differences, it can be challenging to manufacture such a pair of spectacles. One lens (usually the less plus lens) will often need to be very thick to counteract the magnification induced by lens power, which can make the spectacles cosmetically unappealing and also alter the fitted vertex distance, changing the effective power of the lens. High amounts of aniseikonia may not be fully correctable, due to physical limitations in lens grinding and glazing. Readers interested in the mathematical details of adjusting lens parameters are advised to consult textbooks such as Clinical Optics (1996), System for Ophthalmic Dispensing (2007), Clinical Management of Binocular Vision (2008) and publications by McNeil & Bobier (2017), Linkz & Bannon (1965) and Remole (1989). Alternatively, a number of software packages are available to make iseikonic lens calculations, and some optical companies provide specialised services for iseikonic lenses, providing order forms for clinicians to

collect the required information, which the company uses to perform the necessary calculations while keeping within the practical limits of wearable and cosmetically-acceptable spectacles (McNeill & Bobier 2017).

In the clinic, reduced-power balance lenses are often used for patients who are deemed at risk of aniseikonic symptoms, though in most cases the patient's actual perceived aniseikonia is not assessed. Prescribing a balance lens involves deliberately under-correcting or not correcting the anisometropia, which equalises the physical appearance and weight of spectacle lenses, improving cosmesis and reducing optically-induced anisophoria. However, this deprives the patient of potential binocular vision, and in the case of patients with anisometropic amblyopia, not correcting the full amount of anisometropia will hinder amblyopia therapy.

Contact lenses have been shown to be effective in relieving aniseikonia symptoms in most cases and are currently the method of choice to correct large amounts of anisometropia (Remole, 1984; Rose & Levinson, 1972; Winn et al., 1988). Contact lenses sit much closer to the entrance pupil of the eye, reducing the optically induced magnification effect caused by lens power. Contact lenses also remain centred on the cornea with eye movements, and thus do not induce dynamic aniseikonia (anisophoria). However, they are not always suitable for all patients: for example, young children or elderly patients.

2.9 Summary

Many common ocular conditions can result in differences in retinal image size, which can lead to perceived aniseikonia. Substantial differences in image sizes may cause visual discomfort and can hinder binocular vision in adults with normal visual history.

Aniseikonia is likely to be present in many patients with anisometropia, as both anisometropia itself and the optical correction for anisometropia can cause aniseikonia. However, patients with anisometropic amblyopia may not be able to perceive binocular differences in image size due to central suppression, leading to difficulties in obtaining accurate measurements of aniseikonia. Thus, the true prevalence of aniseikonia in this population is currently unknown, and requires further study.

Even after anisometropia has been corrected by conventional spectacles, aniseikonia may remain as a barrier to binocularity, stimulating suppression and limiting binocular visual improvement in patients with anisometropic amblyopia. It is possible that correcting aniseikonia along with anisometropia during the initial optical treatment period for anisometropic amblyopia will reduce the need to develop suppression and improve overall treatment outcomes. To test this hypothesis, we need to address the following questions:

1. Are common refractive errors overseas also common in the New Zealand preschool population (where amblyopia treatment is often commenced), and what are the outcomes of these treatments? (Chapter 3)

2. Is subjective aniseikonia measurable in anisometropia with or without amblyopia? Can we predict this amount through optical modelling? (Chapter 4)

3. Treatment adherence can affect visual outcomes. How are we going to account for adherence in assessing treatment outcomes for aniseikonia correction lenses versus standard anisometropic lenses? (Chapter 5)

4. **Main Research Question:** Does correcting for image size difference at first diagnosis of anisometropia improve visual function in children undergoing optical treatment for anisometropic amblyopia? Chapters 6 & 7)

Chapter 3

Retrospective Review of Preschool Vision screening and Amblyopia treatment in Auckland and Waitematā District Health Boards.

3.1 Background and rationale

Pre-school children are affected by a wide range of eye and vision disorders, the most common being significant refractive error and amblyopia. Amblyopia affects 1-5% (Attebo et al., 1998; Holmes & Clarke, 2006; Robaei et al., 2006) of the population worldwide with previous New Zealand estimates at 3.5% (Wilson & Welch, 2013). Pre-school vision screening programmes aim to identify amblyopia and its risk factors such as significant refractive error, strabismus and pathology. If left untreated, amblyopia has the potential to affect a child's (Holmes et al., 2011) learning and educational development (Chua & Mitchell, 2004), with difficulties continuing into teenage and adult years (Packwood, 1999; Webber et al., 2008; Burke et al., 1997; Coats et al., 2000; Olitsky et al., 1999). Quality of life is further impacted by the emotional impact and increased risk of visual impairment due to loss of vision in the non-amblyopic eye which carries a projected lifetime risk of visual loss of at least 1.2% (Rahi et al., 2002). Treatment of amblyogenic risk factors, such as correcting refractive error or surgery to remove an opacity or correct ptosis, is the first step of amblyopia treatment. This is followed by a period of occlusion/penalisation therapy (Clarke et al., 2003; Holmes et al., 2011; Jonas et al., 2017; Taylor et al., 2012). Amblyopia treatment is most effective if commenced before the age of 7-8 years, prior to the end of the sensitive period of visual development (Daw, 1998; Holmes et al., 2011).

In New Zealand, the B4 School vision screening assessment, part of the national Well Child Tamariki Ora health programme, is aimed at identifying amblyopia prior to children starting school. Distance visual acuity is assessed using the New Zealand designed Parr Letter Matching test, which consists of a single letter surrounded by crowding bars and is performed at a 4m testing distance (Parr, 1981). Although the Parr

test has a non-standardised progression of letter sizes and uses letters that do not have equal legibility, it is found to have a similar sensitivity to the more standardised Lea symbols test and the spot vision screener (Findlay et al., 2021). The vision test is administered by vision hearing technicians in a community setting with referral protocols in place to guide referral pathways for pass, fail and rescreen outcomes.

National referral guidelines (Health, 2008) recommend children who fail vision screening with vision of 6/9 (0.200 LogMAR) or worse in the better-seeing eye are referred to hospital eye services (HES), community optometrists or private ophthalmologists and this pathway can vary between DHBs. For instance, in South Auckland (Counties Manukau District Health Board), children who fail vision screening regardless of their visual acuity are referred to the HES, whereas in Waitematā and Central Auckland District Health Boards, only the more moderate cases (0.300logMAR or worse in the worse seeing eye) are referred to the HES. Milder vision deficits are referred to community optometrists, which in New Zealand are not part of the publicly funded health system and private payment is usually required. There is no follow up to ensure children have completed these referrals and no evaluation of outcomes.

Previous overseas studies have found refractive error and anisometropia to be the most common cause of amblyopia in this population (Lennerstrand & Rydberg, 1996; Williams et al., 2001). Recent New Zealand studies have shown a similar prevalence of refractive error, with bilateral astigmatism being the most common type of refractive error (Findlay et al., 2020; Langeslag-Smith et al., 2015) and anisometropia being the most common type of amblyopia (Anstice et al., 2012). It is generally accepted that early treatment following detection results in more improvement in visual acuity, depending on adherence to treatment. In New Zealand the B4 School vision screening programme is considered to function well with good population coverage (Findlay et al., 2020; Langeslag-Smith et al., 2015; Muller et al., 2019) but the results of amblyopia treatments following this population screening have not been reported.

3.2 Aims

3.2.1 Primary outcome

1. To identify the number of children who have a moderate level of amblyopia (corrected visual acuity worse than 0.300 logMAR in one eye) identified through

the B4 School screening programme between 1 January 2017 and 31 January 2018, inclusive.

2. To assess the improvement in distance visual acuity with glasses and occlusion therapy through the Greenlane, Auckland District Health Board (ADHB) and Waitakere, Waitematā District Health Board (WDHB) public hospitals.

3.2.2 Secondary outcomes

Outcomes examined:

- Treatments prescribed and duration of treatments
- Treatment acceptability in the ADHB and WDHB areas
- Estimated adherence to amblyopia therapy based on clinical reports

This will provide information on the effectiveness of the B4 School screening for detection of moderate levels of amblyopia and the outcomes from treatments provided by the public hospital. Information on the differences between the two DHBs could assist future planning for Health NZ.

3.3 Methodology

3.3.1 Study Design

This is a retrospective chart review of children referred to the Greenlane and Waitematā eye department following a failed B4 School vision screening test between 1 January 2017 and 31 January 2018, inclusive. Records of children who received follow up treatments at the hospital eye clinics were reviewed until their most recent visit to examine the course and outcomes of treatments provided.

3.3.2 Ethical Approval

Ethical approval for the study was granted by the University of Auckland Health Research Ethics Committee and fulfilled the tenets of the Declaration of Helsinki. Institutional approval was granted by the Auckland District Health Board Research Review Committee.

3.3.3 Study Criteria

Based on the clinical record the following criteria were met for inclusion in this study:

- Referred with a failed B4 school vision screen
- Reside in the ADHB and WDHB catchment area
- Children aged 4 to 5 years old
- Reduced visual acuity (≥0.300 logMAR) due to refractive error such as myopia, hyperopia and astigmatism.
- Reduced vision due to strabismus

Exclusion Criteria included:

- Reduced vision which arises from ocular pathology: including congenital cataract (aphakia/pseudophakia), keratoconus or if they have any co-existing ocular pathology
- Previous intraocular surgery
- Any known neurological conditions that could potentially affect vision

3.3.4 Participants

The eye services data analyst identified potentially suitable clinical records. These were new patients, aged four to five years when they first attended the joint orthoptic-optometry clinics at Auckland District Health Board (ADHB) and Waitematā District Health Board (WDHB) eye clinics between the dates of 1 January 2017 and 31 December 2018. Potential records were identified using unique identifying National Health Index (NHI) numbers. Confirmation of referral from the vision hearing technicians for a failed vision screening were made via electronic clinical records. Once deemed eligible, clinical records were reviewed, including the initial visit and any follow-up visits until their most recent visit to examine the course and outcomes of treatments provided.

3.3.5 Referral Grading

Children referred following a failed vision screening are triaged by the hospital eye service according to referral visual acuity using the criteria set out in Table 5.

Table 5. Hospital Triage Criteria for Failed B4-School Vision Screening Referrals

Age	Vision Screening Result	Triage Outcome
<5yrs	uncorrected VA 0.400 or worse in one or both eyes	within 6 weeks
<5yrs	uncorrected VA of 0.300 or worse in both eyes	within 16 weeks
>5yrs	uncorrected VA 0.300 or worse in both eyes	see community optometrist
≤7yrs	uncorrected VA with a difference of 3 lines or more	within 6 weeks
Any age	unable to complete community screening	within 16 weeks

3.3.6 Clinical Examination

The methods described below are standard protocols for the joint orthoptic and optometry clinics at the hospital eye departments. Orthoptists complete patient history, visual acuity and binocular function assessments at each hospital visit and a cycloplegic refraction and ocular health assessment is provided by a paediatric optometrist for a complete eye examination on an annual basis or as required.

3.3.6.1 *Visual acuity*

Uncorrected distance visual acuity was tested with the Keeler Crowded logMAR visual acuity chart (Keeler Ltd) with a matching card for RE and LE. If children were unable to identify or match letters, the Linear Crowded Kay Picture test (Kay Pictures Ltd) was used with a matching card. Both of these tests were performed at three metres. Visual acuity was converted to the resolution (logMAR) format at the data collection phase.

3.3.6.2 *Cover test, ocular motility and stereovision*

Unaided cover/uncover and alternating cover testing was performed at both 0.33m and 6m distances. Ocular motility was tested in free space with a penlight and binocular convergence was tested in free space using a suitable accommodative target. Binocular functions were tested with a 20 Δ base out test for peripheral fusion and stereoacuity was assessed using the Frisby stereoacuity test. The 4 Δ test was used to assess bifoveal fixation where microtropia was suspected.

3.3.6.3 *Refraction*

Spectacles were prescribed based on cycloplegic retinoscopy using 1% cyclopentolate (additional 1% tropicamide was used in children with dense iris pigmentation). A minimum of 40 minutes was allowed for full dilation and retinoscopy was only performed once the pupils were no longer reactive. Spectacle prescriptions were given using the eye clinic prescribing guidelines (Leat, 2011) as follows: Hypermetropia: not under-corrected by more than +1.50D spherical equivalent and the reduction in plus sphere must be identical between the two eyes. Anisometropia: full correction of the anisometropic difference. Astigmatism: full cylinder power prescribed. Myopia: full correction prescribed.

3.3.6.4 *Definition of Amblyopia*

Unilateral amblyopia was defined as a 2-line difference in the best corrected VA, with ≥0.300 logMAR in the worse eye, in the presence of one or more of the following amblyogenic factors: (i) strabismus, (ii) anisometropia consistent with worse eye; ≥1.50D SE anisohyperopia, ≥2.50D SE ansiomyopia or ≥1.50D ansioastigmatism, (iii) evidence of visual axis obstruction present for more than a week in early childhood (e.g. cataract, significant corneal opacity, ptosis or eye lid haemangioma). Bilateral amblyopia was defined as bilateral reduced best corrected visual acuity of ≥0.300 logMAR with bilateral significant ametropia (hyperopia ≥3.50D SE, myopia ≥2.50 SE and astigmatism of ≥1.50D).

3.4 Data Collection

Author JS collected all the data via electronic records. Physical paper records were reviewed for missing data as required. Basic demographic data including ethnicity and home address to verify catchment area were recorded, and unaided visual acuities at referral as tested by the vision hearing technicians, were recorded and converted to logMAR equivalent for comparison. At the initial hospital visit, hospital unaided visual acuities, refractive error, ocular alignment and diagnoses were collected. For those children that required further treatment, type of treatment, number of treatment visits, adherence to treatment and overall duration of treatment data were collected. These were then analysed in three groups:

- moderate to severe levels of reduced visual acuity (≥0.300 logMAR in one or both eyes)
- mild reduced acuity (0.200 to 0.280 logMAR in one or both eyes)
- normal visual acuity for age (better than 0.200 LogMAR in both eyes)

Treatment acceptability overall was categorised by the number of children that started treatment and completed treatment through to discharge, started treatment but did not complete treatment or did not attend following the initial visit.

3.5 Data analysis

All data was de-identified to ensure patient anonymity. Data analysis was conducted using IBM SPSS Statistics (version 25). Demographic data, entering vision screening results, and clinical results from the hospital visits were described as percentages, mean and standard deviations. Changes in visual acuity from baseline to discharge were compared using the paired t-test. Treatment duration was described as median and interquartile ranges. Visual acuity was recorded in logMAR, and a two-way repeated measures ANOVA investigated the interaction between the visual acuity tested by Parr vision and the hospital-based Crowded Keeler and the Linear Crowded Kay Picture tests. Diagnoses made after the first assessment were collated and compared against current international standard definitions of significant refractive error and amblyopia. The Fisher Exact test was used to compare treatment outcomes and acceptability between ethnic groups.

3.6 Results

3.6.1 The B4 school Vision Screening

The B4 School check has good coverage in the study areas with 99.6% of children completing vision screening. 6.1% (n=1588) children failed the vision screening and referred for further assessment. Only 22.7% (n=361) of these were seen in the public hospital. It is not known whether the remainder of the children were seen by community optometrists or private ophthalmologists or did not seek further assessment.

A breakdown of the children referred to the HES following failed vision screening is shown in Figure 7.

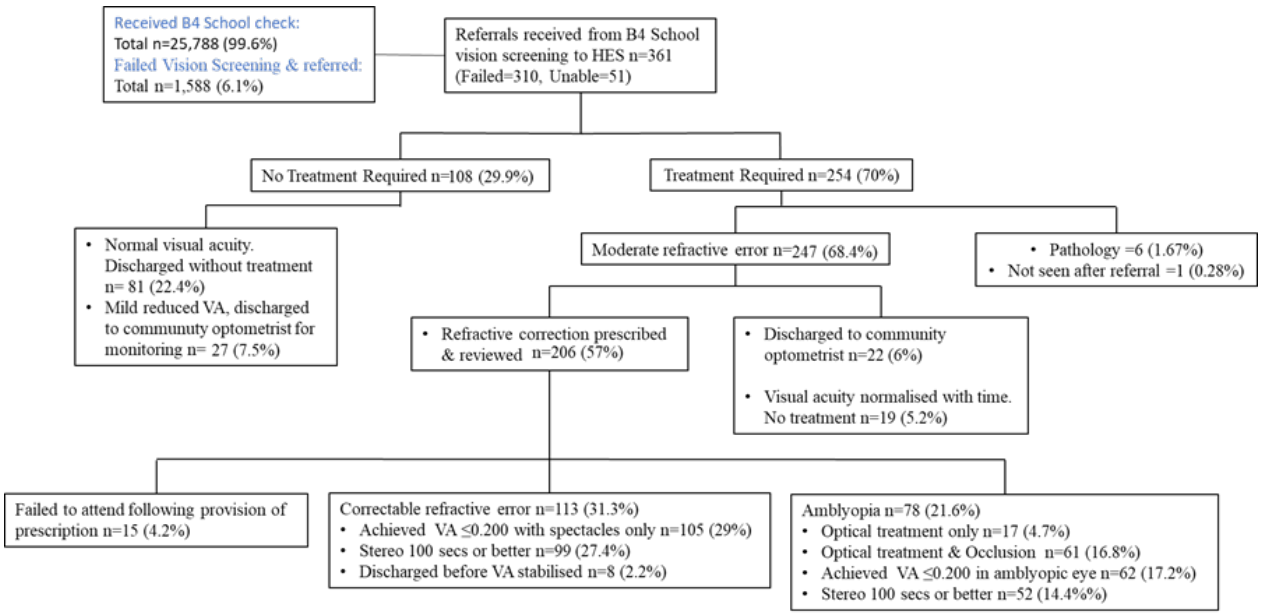


Figure 7. Flow chart of all children referred to the HES following failed B4 school vision screening.

3.6.2 Study cohort

680 patients were identified as new patients seen in the joint orthoptic-optometry clinics at Greenlane and Waitakere hospitals from January 1 2017, to December 31 2018. 361 of these were identified as eligible children who had failed (n=310) or were unable (n=51) to complete the vision screening test during the B4 School screening check. Six (1.67%) children were excluded from analysis due to newly diagnosed pathology and one child did not attend any appointments at the hospital. Charts for the 354 patients that met the study inclusion criteria were reviewed via electronic clinical records.

All 50 children unable to complete community vision screening were seen within the 16 weeks' timeframe (median 106, IQR range 66-132.8 days). Five out of eight children with uncorrected vision of 0.300 logMAR or worse in both eyes at referral were seen within the recommended time frame of 16 weeks with a median wait time of 115.50 days (IQR range 86.5-171.5 days). Most of the children (n=280) referred to the HES had uncorrected vision of 0.400 logMAR or worse in one or both eyes. The median wait time was 82 days (IQR range 50-124 days) with only 49 children being seen within the

recommended six weeks from receiving the referral. A few children (n=16) were referred with unaided visions of 0.300 logMAR or better in their worse seeing eye due to parental concern about an eye condition. The median wait for these children was 90 days (IQR range 59.8-114.0) and the mean (SD) referral visual acuity was 0.262 (SD 0.081) logMAR in the worse seeing eye.

3.6.3 Demographics

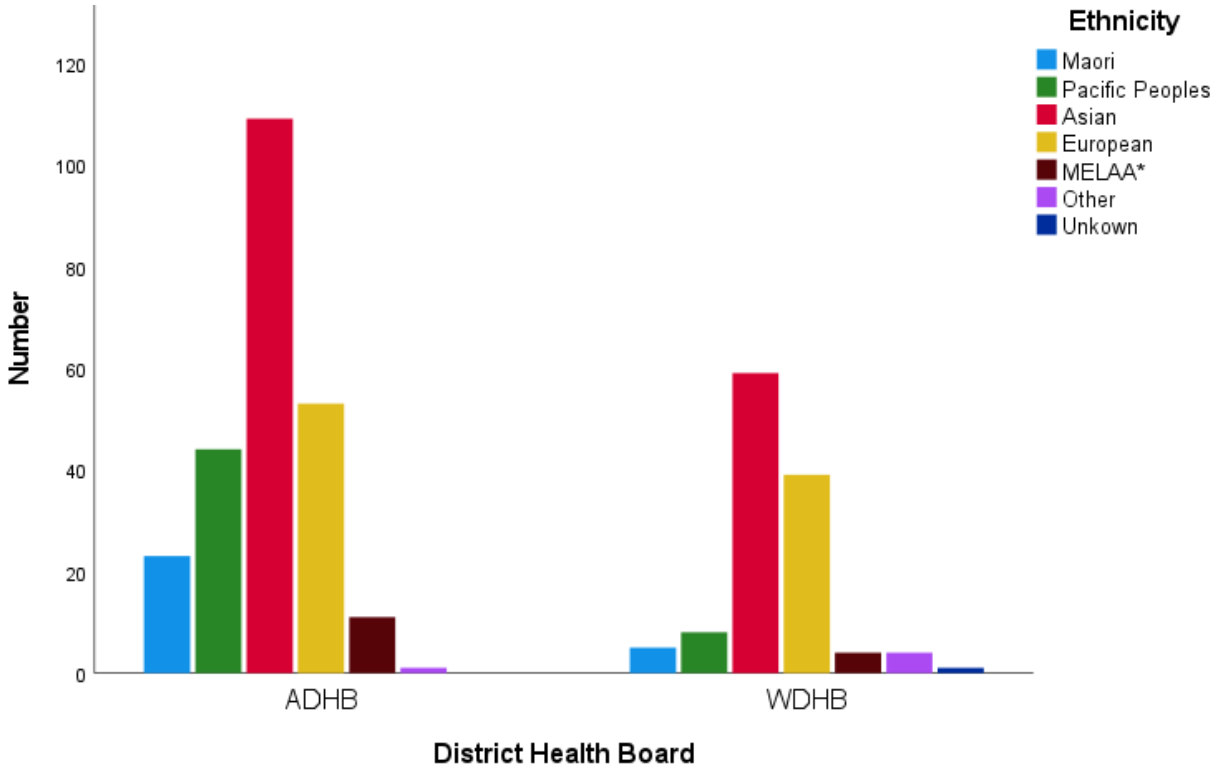
Demographics are given in Table 6. The average age at referral was 4.4 years old (range 4 to 8.5 years, 53.7% male).

Table 6. Demographic Characteristics

			N (%)	
Male n (%)	194 (53.7)			
Female n (%)	167(46.3)			
Age at referral (mean years (SD))	4.4 (0.57)			
Ethnicity and DHB of the study sample n (%)		**ADHB**	**WDHB**	**Total**
Māori		23 (6.3)	5 (1.4)	28 (7.8)
Pacific (Tongan, Samoan, Cook Island Māori, Fiji)		44 (12.2)	8 (2.2)	52 (14.4)
Other (NZ European, Chinese, Indian etc.)		174 (48.2)	107 (29.6)	281 (77.8)
Referral Pathway n (%)				
VHT		312 (86.4)		
Community optometry		26 (7.2)		
GP		16 (4.4)		
Orthoptist		5 (1.4)		
Other		2 (0.6)		

DHB = District Health Board, ADHB=Auckland District Health Board, WDHB=Waitakere District Health Board, VHT = Vision Hearing Technicians, GP=General Practitioner, SD=Standard Deviation, NZ = New Zealand.

Both DHB catchments included in this study have a lower proportion of Māori and a higher proportion of Pacific people compared to the national population. Further ethnicity breakdown (Figure 8) shows a large proportion (46.5%) of this study sample is Asian which includes, Chinese, Indian, and Southeast Asian, followed by European (25.5%).



**Middle Eastern/Latin American/African*

Figure 8. Prioritised Ethnicity Classification in ADHB and WDHB (Ministry of Health, 2017)

3.6.4 Visual acuity

Initial hospital-assessed unaided visual acuity was compared to the referral visual acuity to assess the reliability of the screening and hospital-based tests. The Crowded Keeler logMAR visual acuity test (McGraw & Winn, 1993) is commonly used in hospital eye services throughout New Zealand. Where letter matching is not possible the linear Crowded Kay Picture is used.

3.6.4.1 *Crowded Keeler*

228 children were tested with both Parr visual acuity test and Crowded Keeler logMAR visual acuity test. A two-way ANOVA revealed that there was a statistically significant interaction between the visual acuity tested by Parr vision (mean 0.423 logMAR) test and visual acuity tested by Crowded Keeler logMAR (mean 0.368 logMAR) acuity test ($f(1, 228) = 21.192$, $p = <0.001$).

3.6.4.2 *Linear Crowded Kay Picture test*

68 children completed both Parr visual acuity and the Linear Crowded Kay Picture tests. A two-way ANOVA revealed that there was a statistically significant interaction between the visual acuity tested by Parr vision test (mean 0.429 logMAR, range 0.00 to 0.700 logMAR) and visual acuity tested by Linear Crowded Kay Picture (mean 0.289 logMAR, range -0.200 to 1.050 logMAR) test (f (1, 68) =43.054, p= <0.001).

The differences between the Parr test and the Crowded Keeler test (0.055 logMAR) were not clinically important, at only half a line difference. However, the linear Crowded Kay Picture test appeared to overestimate visual acuity by approximately one and a half lines on average (0.142 logMAR), which is clinically important (Figure 9).

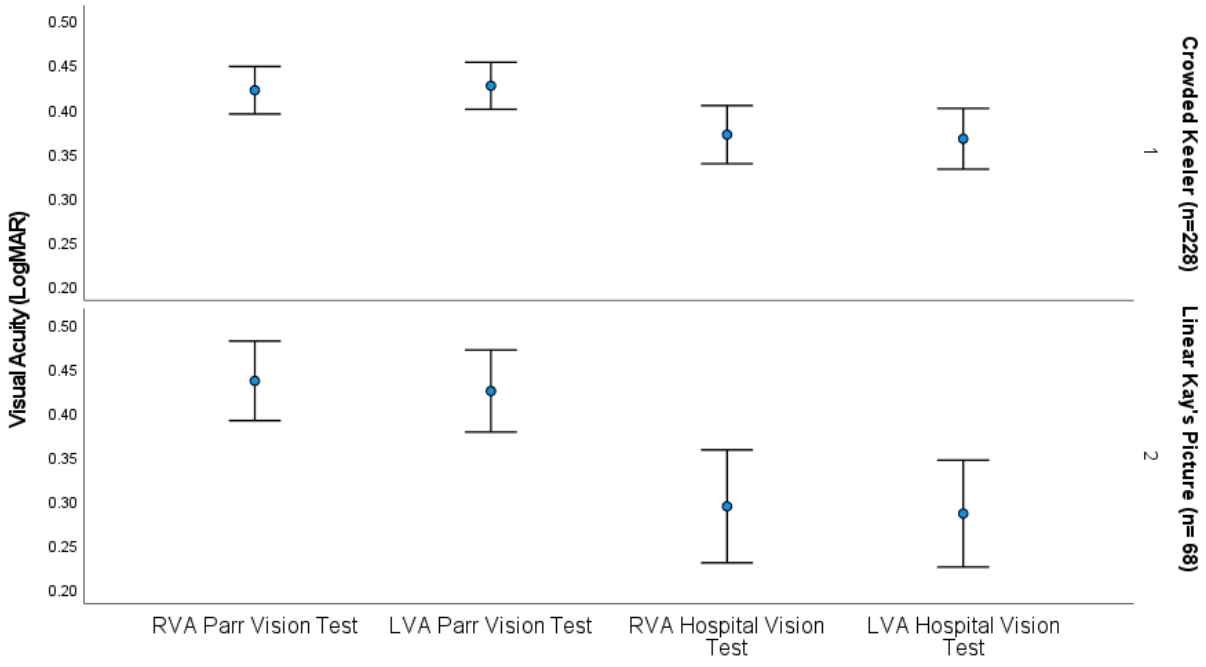


Figure 9. Unaided visual acuity of both eyes as tested on the screening Parr test and the hospital-based Keeler crowded and Kay picture linear crowded test.

3.6.5 Prevalence of refractive errors

Following cycloplegic refraction 354 children were categorised into the following groups.

3.6.5.1 *Normal uncorrected visual acuity Group*

Visual acuity of 0.200 logMAR or better was found in 59 (16.3%) children (66% male) of which 26 (7.2%) were previously unable to complete vision screening in the community setting. The mean referral visual acuity found at screening for this group was right eye 0.351 (SD 0.21) logMAR, left eye 0.370 (SD 0.24) logMAR. No significant eye conditions were found in 51 children, of which 44 were discharged at first visit and 7 were subsequently discharged without treatment after an average of 2.2 visits (SD 0.45).

3.6.5.2 *Mildly reduced corrected Visual acuity group (0.200 logMAR to 0.280 logMAR)*

Mildly reduced visual acuity was identified in 49 (13.6%) children. The mean (SD) visual acuity in the worse vision eye at the initial hospital visit was 0.231 (0.31) logMAR and 0.179 (0.59) logMAR in the fellow eye. No refractive error was found in 22 (44.9%) children and the presumed reason for reduced acuity was due to reduced co-operation with the acuity testing than truly reduced acuity. Bilateral refractive error was identified in 24 children, of which 17 (70.8%) had bilateral astigmatism, and 3 had anisometropic refractive error. Refractive correction was prescribed to all 27 children and only one child with ansiohyperopia had a microtropia that required occlusion treatment. All the other children were discharged after a mean (SD) of 3.04 (1.99) hospital visits for continued routine follow up with the community optometrists.

3.6.5.3 *Moderately reduced corrected visual acuity group (≥0.300 LogMAR)*

Visual acuity of 0.300 logMAR or worse in one or both eyes was identified in 247 (68.4%) children. The average wait for the first appointment was 88.4 (50.5) days, twice the recommended time frame. Following the first appointment 22 (8.9%) were discharged; 8 (36.4%) were found to have no significant refractive error and no other reason for reduced visual acuity. 10 were found to have mild myopia and discharged for monitoring by community optometrists. Two had bilateral astigmatism, one had bilateral hyperopia and the one that had mild hyperopic anisometropia was already being treated by a community optometrist.

Of the remaining 225 (62.3%) children that required review, 19 did not have significant refractive error but visual acuity was reduced. Visual acuity normalised

over time without treatment in 14 children and 5 failed to attend any further appointments after the initial visit. A breakdown of the refractive errors found in the remaining 206 children is given in Table 7 and the amblyogenic risk factor including ocular pathology is given in Table 8.

Table 7. Prevalence of refractive errors of 206 children treated and followed in the HES

	Māori n (%)	**Pacific Peoples n (%)**	**Other n (%)**	**Total n (%)**
No significant error	0 (0)	0 (0)	1 (0.5)	1 (0.5) *
Anisometropia				
Hyperopia ≥+2.00 SE	4 (1.9)	2 (1.0)	35 (17.0)	41 (19.9)
Myopia ≤-0.50 SE	0 (0)	0 (0)	4 (1.9)	4 (1.9)
Astigmatism ≥0.75	0 (0)	4 (1.9)	17 (8.3)	21 (10.2)
Hyperopic astigmatism	1 (0.5)	0 (0)	12 (5.8)	13 (6.3)
Myopic astigmatism	1 0.5	0 (0)	5 (2.4)	6 (2.9)
Total Anisometropia	**6 (2.9)**	**6 (2.9)**	**73 (35.4)**	**85 (41.3)**
Bilateral				
Hyperopia ≥+2.00 SE	0 (0)	1 (0.5)	5 (2.4)	6 (2.9)
Myopia ≤-0.50 SE	2 (1.0)	1 (0.5)	16 (7.8)	19 (9.2)
Astigmatism ≥0.75	4 (1.9)	10 (4.9)	39 (18.9)	53 (25.7)
Hyperopic astigmatism	1 (0.5)	0 (0)	9 (4.4)	10 (4.9)
Myopic astigmatism	1 (0.5)	5 (2.4)	26 (12.6)	32 (15.5)
Total Bilateral	**8 (3.9)**	**17 (8.3)**	**95 (46.1)**	**120 (58.3)**
Overall Total	**14 (6.8)**	**23 (11.2)**	**169 (82.0)**	**206 (100)**

**One child had primary microtropia without refractive error*

Table 8. Amblyogenic Risk factor

	Māori	Pacifica	Other	Total
Anisometropia				
Myopia (SE) ≥2.50	0 (0)	0 (0)	2 (0.9)	2 (0.9)
Hyperopia (SE) ≥1.50	4 (1.9)	2 (0.9)	38 (17.9)	44 (20.8)
Astigmatism ≥1.50	1 (0.5)	1 (0.5)	21 (9.9)	23 (10.8)
Bilateral				
Myopia (SE) ≥2.50	0 (0)	0 (0)	4 (1.9)	4 (1.9)
Hyperopia (SE) ≥3.50	0 (0)	1 (0.5)	5 (2.4)	6 (2.8)
Astigmatism ≥1.50	8 (3.8)	19 (9.0)	69 (32.5)	96 (45.3)
Strabismus *	3 (1.4)	0 (0)	32 (15.1)	35 (16.5)
Ocular Pathology	2 (0.9)	3 (1.4)	1 (0.5)	6 (1.4)
Total	**18 (8.5)**	**26 (12.3)**	**172 (81.1)**	**216 (101.9)**

**Percentage is over a 100 as a number of children had Strabismus associated with significant refractive error*

3.6.6 Treatment

3.6.6.1 *Refractive Correction*

206 children were prescribed spectacles at the first visit with a planned review after 8 to 17 weeks, however 15 (7.3%) children failed to attend any further appointments. The reason for nonattendance is unknown. Regular monitoring of 191 (92.7%) children was conducted every 8- to 17-weekly intervals depending on the clinician's judgement. There were 113 children that required spectacle treatment only and 93% (n=105) achieved visual acuity of ≤0.200 logMAR with a mean (SD) interocular difference of 0.022 (0.048) logMAR between the two eyes. The review period was a median of 17 weeks (IQR 13-21) with an attendance rate of 90.5% (n=95) until discharge. Eight children were discharged to community optometrists for follow up before visual acuity stabilised when wearing their refractive correction. Refractive error was non amblyogenic with seven out of eight children having myopic astigmatism and one child having bilateral astigmatism. Distribution of refractive error in the group that did not require amblyopia treatment is given in Table 9.

Table 9. Distribution of refractive error in children that did not require amblyopia treatment

Anisometropia	**n**	**%**
Hyperopia ≥+2.00 SE	3	2.7
Myopia ≤-0.50 SE	1	0.9
Astigmatism ≥0.75	13	11.5
Hyperopic astigmatism	5	4.4
Myopic astigmatism	3	2.7
Total Anisometropia	**25**	**22**
Bilateral		
Hyperopia ≥+2.00 SE	1	0.9
Myopia ≤-0.50 SE	18	15.9
Astigmatism ≥0.75	40	35.4
Hyperopic astigmatism	4	3.5
Myopic astigmatism	25	22.1
Total Bilateral	**88**	**78**
Total	**113**	**100**

The mean visual acuity at baseline in the worse seeing eye was 0.497 logMAR (SD 0.186, range 0.300 to 1.200 logMAR) and 0.331 logMAR (SD 0.172, range 0.000 to 1.200 logMAR) in the fellow eye. The mean interocular difference at baseline was 0.166 logMAR (SD 0.170). The mean visual acuity at discharge was 0.094 logMAR (SD 0.063) in the worse seeing eye and 0.072 logMAR (SD 0.076) in the fellow eye. A paired t-test comparing visual acuity in the worse-seeing eye from baseline to discharge found a significant improvement of 0.394 (SD 0.213) logMAR lines, t(111)=19.568, p=0.000. Interocular difference also improved by a mean (SD) of 0.022 (0.048) logMAR between the two eyes t(111)= 9.050, p=0.000). Visual acuity in the fellow eye improved significantly by 2 and a half lines (mean 0.250, SD 0.175) t(111)=15.073, p=0.000) (see Figure 10).

Median stereoacuity was found to be 85 secs of arc (IQR 85-150) at discharge. The majority of these children (89.5%, n=94) had no ocular deviation, 5.7% had exophorias, 2.9% had intermittent distance exotropias, 1% had fully accommodative esotropia and 1% had an esophoria at discharge.

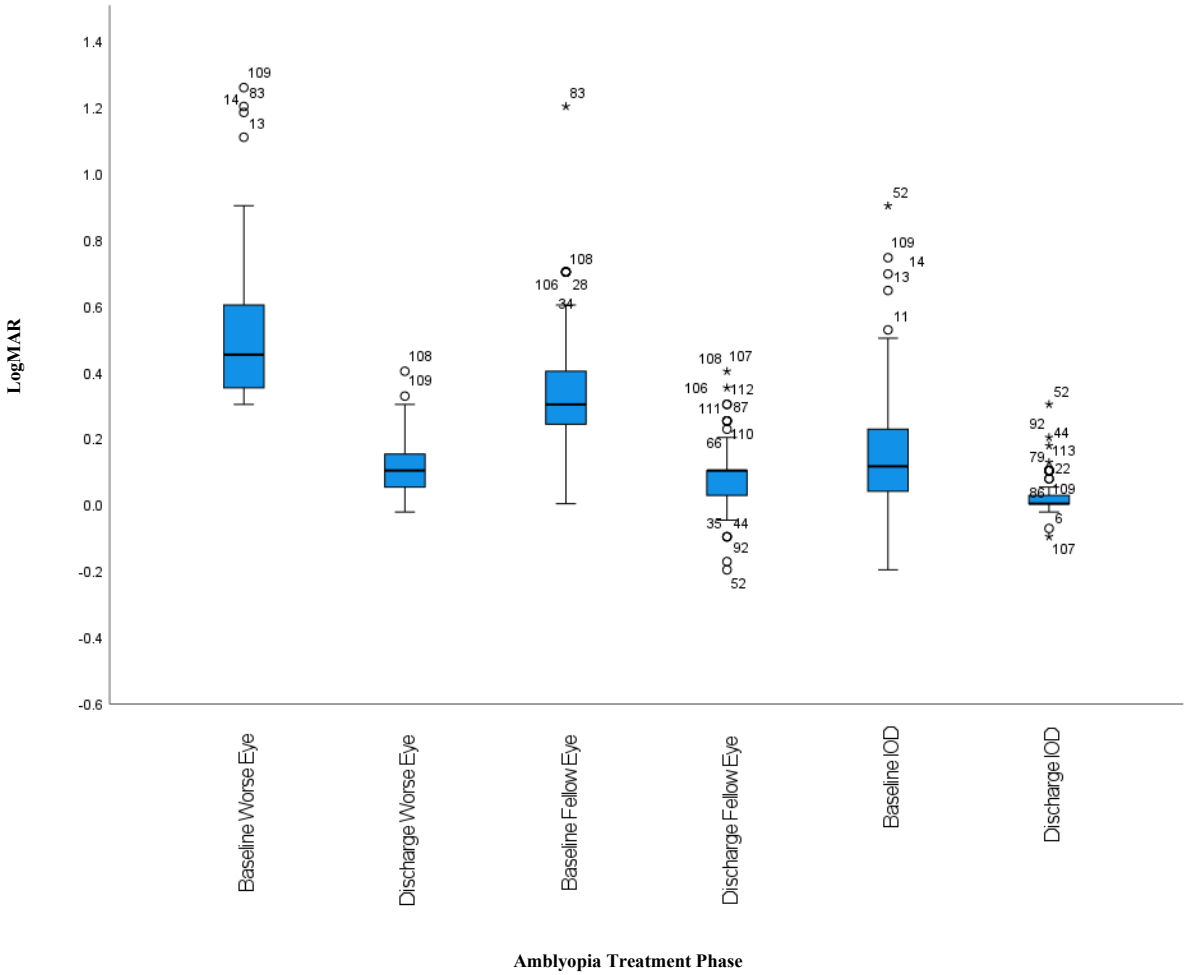


Figure 10. Box and whisker plot with outliers showing the visual acuity of each eye following refractive correction from baseline to discharge from hospital care.

3.6.7 Amblyopia

Refractive correction was worn by 78 (21.6%) children who were then diagnosed with amblyopia. 44.9% had purely anisometropic amblyopia (mostly due to anisohyperopia (19), aniso astigmatism (5), and ansio hyperopic astigmatism (5)), 23.1% were in the presence of anisometropia and microtropia (mainly due to anisohyperopia (15)) and 19.2% had combined refractive and strabismic amblyopia and 12.8% had bilateral amblyopia. There was one child with a microtropia unrelated to refractive error. The type of amblyopia and the associated refractive error is given in Table 10.

Table 10. Type of Amblyopia and Associated Refractive Error

Amblyopia Type	N (%)	Associated mean refractive error (D) (SD)
Anisometropia	35 (44.9)	+2.92 (1.34) IOD
Anisometropia and Microtropia	17 (21.8)	+4.24 (1.97) IOD
Combined Refractive and Strabismic	15 (19.2)	RE +3.46 (2.94) LE +3.39 (3.35)
Bilateral astigmatism	8 (10.2)	RE -3.94 (1.23) LE -3.66 (1.29)
Bilateral hyperopia	2 (2.6)	RE +6.07 (2.74) LE+6.26 (3.01)
Strabismic	1 (1.3)	0

IOD- Inter Ocular Difference

3.6.7.1 *Refractive adaptation*

Visual acuity in the amblyopic eye improved by a mean of 0.246 (SD 0.242) logMAR from baseline with a median optical treatment period of 19.6 weeks (IQR 13-26) after which visual acuity stabilised and 17 (22%) children required no further treatment.

3.6.7.2 *Occlusion treatment*

Following optical treatment, 61 children were prescribed adjunct occlusion therapy. One child with primary microtropia without refractive error is included in this group. Mean visual acuity at baseline in the amblyopic eye was 0.763 logMAR (SD 0.29, range 0.300 to 1.300) and 0.137 logMAR (SD 0.16, range -0.200 to 0.600) in the fellow eye with a mean (SD) interocular difference of 0.621 (SD 0.35).

Paired t-test comparing the improvement of visual acuity in the amblyopic eye found a significant improvement of mean 0.521 (SD 0.292) ($t(77)= 15.72$, $p=0.000$) from baseline to the end of occlusion treatment. Interocular difference also significantly improved by a mean of 0.368 (SD 0.322) ($t(77)=10.107$, $p=0.000$). The fellow eye visual acuity improved by a mean of 0.153 (SD 0.176) ($t(77)$ 7.695 $p= 0.000$) (See Figure 10). Only 9.8% (n=6) of children achieved stereoacuity of better than 100 secs of arc. No stereoacuity was demonstrable in 36.1% (n=22) of children at the end of occlusion treatment and 50.8% (n=31) had less than 100 secs of arc (median 150, IQR 0-300). Types of strabismus identified in this group are shown in Table 11. As expected, 18 children with microtropia who required occlusion treatment had associated anisometropia of mean SE of 5.03D (SD 1.2) and one child had anisomyopia of -8.75D SE

Table 11. Types of Strabismus in children requiring further occlusion amblyopia treatment

Type of Deviation	No. (%)
Microtropia	18 (29.5)
Partially accommodative Esotropia	6 (9.8)
Infantile Esotropia	1 (1.6)
Fully accommodative Esotropia	1 (1.6)
Large angle Esophoria	1 (1.6)
Constant Exotropia	1 (1.6)

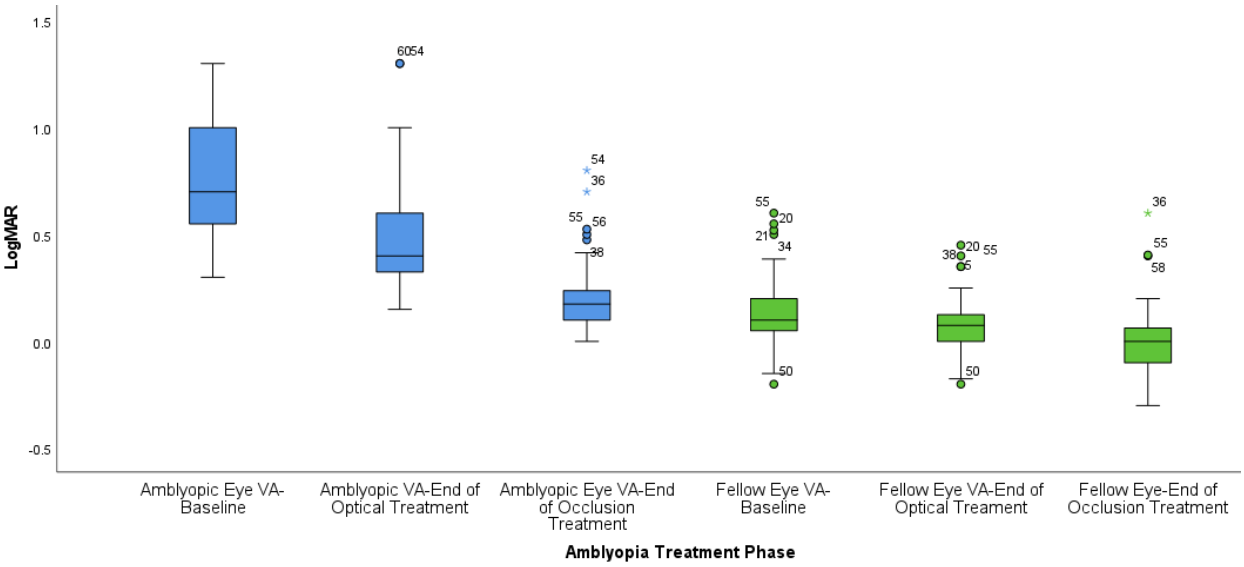


Figure 11. Box and whisker plot with outliers showing the visual acuity of either eye through the amblyopia treatment phases

Both atropine and patching were offered as first-line treatment. In this audit 11 (17.7%) children were commenced on atropine occlusion with the remainder opting for conventional occlusion. Prescription of patching ranged from 1 hour to 6 hours but most frequently was prescribed for 2 hours daily (59.7%). Adherence with spectacles was still high at 87.1% wearing full time, however, adherence with occlusion was not as good with only 69.4% adhering to occlusion time as prescribed. As expected, adherence with atropine occlusion (81.8%) was better than with conventional occlusion (69.4%). The duration of occlusion treatment was on average 471.46 days (SD 9.0). A third of children (n=19) did not complete treatment due to nonattendance at various stages of

treatment, however,r 57.9% of these children had visual acuity better than 0.300 logMAR in their amblyopic eye at their last recorded hospital visit.

3.6.7.3 *Stereoacuity*

Of the 206 children treated in the HES, 41.8% achieved stereoacuity of 100 secs of arc or better at the end of treatment. Children that received spectacles only treatment were more likely to achieve stereoacuity of 100 secs of arc or better (94%) compared to those that required additional occlusion therapy (66.7%).

3.6.7.4 *Overall Treatment*

Overall, out of the 25,788 children that received vision screening in the ADHB and WDHB regions, 6.1% (1,588) failed and were referred for further assessment. Only 22.7% (361) were referred to the HES. Of 361 children that were referred to the HES, 81 (22.4%) children were found to have normal visual acuity and discharged without treatment. After completing refractive and occlusion therapy 81% of children achieved visual acuity of 0.200 logMAR or better in the worse-seeing eye. A paired samples t-test found a significant improvement of visual acuity by an average of four logMAR lines (mean 0.440, SD 0.260) n=189 p=<0.001 from baseline to the end of optical and/or occlusion treatment and an average of 0.205 logMAR (0.190) n=189, p=<0.001 in the fellow eye, with a mean improvement of 0.235 logMAR (0.266 SD) in interocular difference achieved at the end of treatment. Spectacle treatment was well tolerated but concurrence with occlusion treatment was poor.

3.6.8 Treatment acceptability

3.6.8.1 *Treatment adherence*

Spectacles seemed to be well tolerated with adherence to fulltime spectacle wear, measured subjectively by verbal parental reporting, being high at 83.8%. There were only three children that delayed getting spectacles following the issue of a prescription as the parents believed that spectacles would make the child's eyes worse. Whanau (families) that attended a second hospital visit were provided with further education and all three had purchased and were wearing spectacles fulltime by the third visit. It is possible that the education provided at the first hospital visit was not clear enough for some whanau that did not attend following the first appointment.

3.6.8.2 *Ethnicity-related differences in health outcomes*

Treatment acceptability overall was determined by the number of children that started treatment and completed treatment through to discharge (n=278, 78.6%), started treatment but did not complete treatment (n=71, 20.1%) or did not attend following the initial visit (n=26, 7.3%) (Figure 12). We infer that those who completed treatment found the treatment acceptable. The Fisher Exact test examined the relationship between the likelihood of treatment completion and ethnicity and found that a higher-than-expected proportion of Pacifica children did not attend any further appointments after the initial visit (p=<0.001). Within ethnicities, group analysis also showed a higher-than-expected number of Pacifica (25.8%) and Māori (22.2%) children did not complete treatment once it was commenced when compared to non-Māori and non-Pacifica children (14.1%).

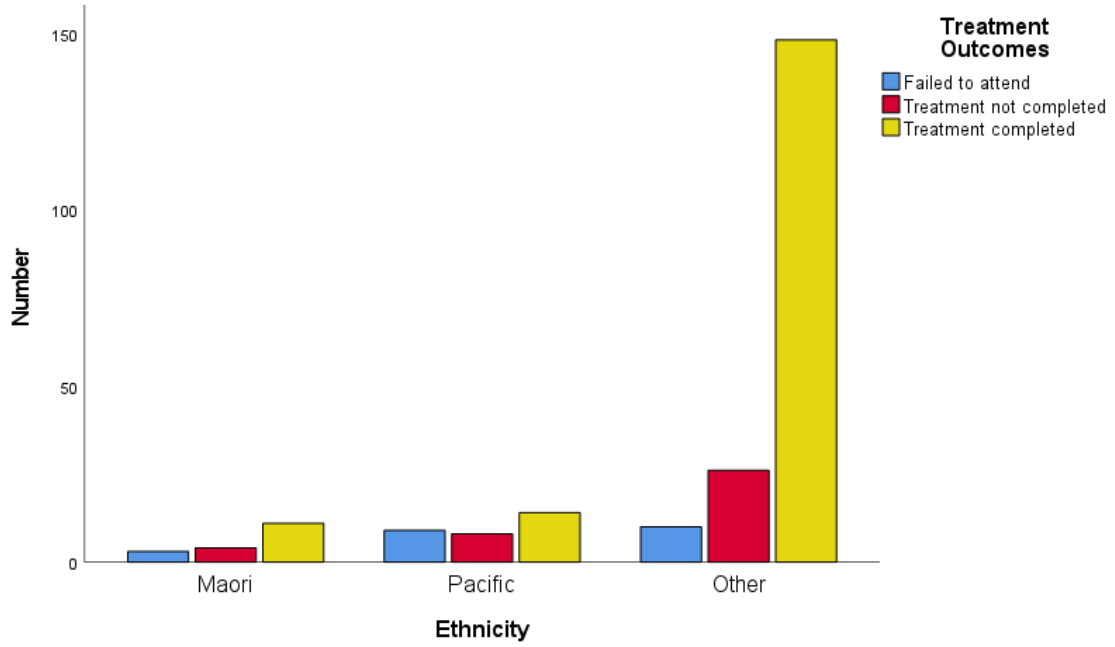


Figure 7. Ethnicity related treatment outcomes

3.7 Discussion

This study aimed to identify the prevalence of refractive error and amblyopia in the preschool population of New Zealand. Population based vision screening is important in identifying treatable conditions that can reduce visual acuity in children, potentially affecting learning and educational development. This study lends further support to the

fact that clinically optical treatment is effective and well accepted in the treatment of refractive amblyopia commonly found during preschool vision screening. It was found that children referred to hospital eye services following a failed B4 School vision screening test gained significant improvement in their visual acuity following treatment. At the end of spectacle and occlusion treatments (where needed), 81.6% achieved a visual acuity of 0.200 logMAR or better in the worse-seeing eye and 76.4% achieved an interocular difference of 0.100 logMAR or less. However, this study also highlights that some groups are more likely to access and complete treatment than others. This simple effective treatment is not equally accessible to all children in New Zealand. We recommend universal support for subsidised access to spectacles and amblyopia treatment such as patches for all children during the sensitive period of visual development where active amblyopia treatment is most effective.

3.7.1 Referral Criteria

The current vision screening protocol in New Zealand uses the Parr vision test with crowding bars which is not supported by international evidence for satisfactory sensitivity and specificity, with other visual acuity tests performing better (Findlay et al., 2020). The Parr Vision test has several disadvantages including non-standardised progression through letter sizes and letters being of unequal legibility. Although single letters are surrounded by crowding bars in this test, amblyopic children achieve better visual acuity results with this test compared to a linear test due to reduced crowding effects and contour interactions often found with line or whole chart visual acuity tests (Fern et al., 1986; Leat et al., 1999; Manny et al., 1987).

Current referral guidelines suggest a re-screen of children with visual acuity of 0.200 (6/9) in one eye and 0.00 (6/6) in the other eye when tested with the Parr vision test. If visual acuity remains reduced, then referral is recommended. This referral criterion was discussed in a recent review of the B4 school vision screening programme as part of the National Well Child Tamariki Ora (WCTO) programme conducted in 2019 (Health, 2020). This study observes that children referred with visual acuity of 0.200 (6/9) often have mild refractive error that can be managed by the prescription of spectacles. This finding was used to inform decisions around clinical referral criteria as part of the WCTO review process with recommendations to update the referral criteria to any child scoring 0.200 (6/9) in one or both eyes to be referred to the community optometrists for

assessment and child scoring 0.300 (6/12) or worse in either or both eyes on the screening Parr vision test should be referred to the HES for further assessment.

3.7.2 Screening and Hospital Based Visual Acuity Tests

It is important to know if the screening Parr test produces comparable results to the visual acuity tests used in the hospital system to ensure treatment is not delayed for children with significantly reduced visual acuities. The Crowded Keeler logMAR visual acuity test (McGraw & Winn, 1993) is commonly used in hospital eye services throughout New Zealand, Australia and the United Kingdom. The letter matching ability makes it a popular choice for use in preschool age children (Rydberg et al., 1999) and offers a high degree of testability (Cyert et al., 2003) and test-retest variability (Holmes et al., 2001). Although this study showed a statistically significant difference between the two tests, a 0.051 to 0.056 logMAR is a difference of half a line which in the context of amblyopia detection is not clinically significant. This systematic difference means that amblyopia is still appropriately detected and diagnosed with the current Parr test used in screening.

Due to the letter recognition ability of some children and unfamiliarity with letters of the English alphabet, a picture test is often preferred to ensure equity for all children. Although the Crowded Kay picture test has been shown to overestimate visual acuity, for monitoring of amblyopia treatment it is important to use tests that are comparable allowing consistent results when moving from one measure to another as the cognitive ability of the children develops. In this study the Crowded Kay Picture appeared to overestimate visual acuity by one and a half lines (0.150) when compared to the Parr vision test. This is a known limitation of this test (Anstice & Thompson, 2014; Elliott & Firth, 2009; O'Boyle et al., 2017) and an average adjustment of +0.10 logMAR is recommended when visual acuity test scores are required to be changed to the more robust letter testing. Caution must also be applied clinically when discharging children based on visual acuity measured using the Crowded Kay Picture test alone without refraction as the Kay optotypes are less sensitive to astigmatism induced blur which can result in children with astigmatism being missed.

Most children referred from the B4 school vision screening were found to have refractive error that was correctable with the provision of spectacles. This suggests that

children with visual acuity ≤0.300 logMAR could be referred to community optometrists to help manage service loads in hospital eye departments. However, previously published audits across New Zealand have found between 20-48% (Findlay et al., 2020; Langeslag-Smith et al., 2015; Muller et al., 2019) of children that failed screening do not present to an eye care professional for further assessment. One of the reasons for this is that the onus of organising an appointment for further assessment is on the parents or caregivers, which can be seen as not important due to the lack of knowledge of potential harms if vision problems are left untreated. In New Zealand, optometry is not public health funded and requires private funding which can be a potential barrier for some whānau (families). A contribution towards the cost of spectacles is available for children through the Enable subsidy but is only available with a valid community services card available to low-income families. This falls short of other high-income countries such as the UK, some Australian states and Canada that universally fund eye care for all children under the age of 16 years (Alberta, 2022; Australia, 2021; Manitoba, 2021; NHS, 2020; Ontario, 2021; Quebec, 2020). Some optometry practices do offer free eye tests for children but often there is a lack of suitable equipment and experience in dealing with young pre-school children which results in referral to the hospital system for management.

3.7.3 Refractive error

From the total cohort 58% needed refractive correction, of which 31% only needed spectacles to improve visual acuity. Bilateral myopia and bilateral astigmatism were the most common refractive errors found in the group that needed spectacles only which is in line with other studies (Pai et al., 2012; Pascual et al., 2014). However, unlike other studies conducted in the Western regions of the world, we did not find a high rate of high hyperopia in our cohort, and this may be due to the difference in the ethnicity of the sample in this study. This study had a high proportion of Asian children who have a higher prevalence of myopia and astigmatism (Dirani et al., 2010; Saw et al., 2006) and Māori and Pacific Peoples that have a higher prevalence of astigmatism (Findlay et al., 2020; Langeslag-Smith et al., 2015). Even though 29% of children who failed vision screening were found to have amblyogenic bilateral refractive error, only 2% of children went on to develop bilateral amblyopia which is higher than the estimated prevalence of 0.5% (Haase & Mühlig, 1979) in a Western population. Stereoacuity of

100 seconds of arc or better was achieved by 94% of children that required spectacles treatment only.

Anisometropia was identified in 23.5% of children referred to the HES from a failed vision screen and aniso hyperopia, aniso astigmatism and aniso hyperopic astigmatism all were more likely to be related to unilateral amblyopia in our study. This finding is supported by an Australian population-based prevalence of amblyopia study that found the prevalence of amblyopia in the presence of anisometropia to be 56.7% compared to children without anisometropia (0.8%) (Robaei et al., 2006)

Children with anisometropia are more likely to experience aniseikonia due to the inherent anatomical differences between the two eyes causing a difference in retinal image clarity and image size. Spectacles correct for image defocus but do not address image size and the act of wearing spectacles for anisometropia can also sometimes worsen the aniseikonia (Remole, 1989a). Theoretically, significant aniseikonia may also impact stereoacuity in children, thus potentially limiting visual recovery in anisometropic amblyopia. In this study the average visual acuity at the end of occlusion therapy was 0.204 LogMar with an interocular difference of 0.183 logMAR and median stereoacuity was 85 secs of arc (IQR 85-150). It is possible that aniseikonia is potentially responsible for the plateauing of vision found during standard treatment protocols (Birch, 2013; Gunton, 2013) and the associated reduced stereoacuity (Wallace et al., 2011) which often results. The study also found 4% of children did not achieve visual acuity of ≤0.200 LogMAR or better and interestingly 10 out of 16 children had anisometropia of 4 dioptres or greater of interocular difference. It is possible that aniseikonia could be a limiting factor in these children.

3.7.4 Amblyopia and Visual Acuity

Amblyopia is often defined as visual acuity of 0.200 logMAR or worse and an interocular difference of 0.200 logMAR in the presence of amblyogenic factors which requires treatment (Holmes & Clarke, 2006). There is some argument however that mild amblyopia does not socially impact a person's quality of life even if the better-seeing eye is lost through injury or disease, and that only moderate levels of amblyopia of 0.300 logMAR or worse, which precludes driving in most countries, require treatment. Ideally children identified with milder vision impairment would be managed by

community optometrists or joint community orthoptic-optometry clinics, however as previously discussed the current system does not equitably deliver these services.

This study found 16.9% of all children referred to the hospital eye services had moderate levels of amblyopia. Low rates of strabismic amblyopia and higher rates of refractive amblyopia in this study were due to the study design and sample bias, as the B4 School vision screening at age 4 years specifically targets children with refractive amblyopia who often show no other overt signs of visual impairment. In New Zealand, strabismus and significant ocular pathology is usually detected during Well Child assessments that occur at younger ages, prior to the B4 School check.

In this study, 44.9% of children were found to have amblyopia due to anisometropia alone or in combination with a microtropia which is less than population studies that found about two thirds of children with amblyopia have anisometropia alone or in combination with strabismus (Barrett et al., 2013; Friedman et al, 2009; PEDIG, 2002; Robaei et al., 2006). Optical treatment alone was effective in resolving amblyopia in 32% (n=17) of children with anisometropic amblyopia. Children that required further occlusion treatment were more likely to have anisometropia alone (57.4%) or in combination with a microtropia (29.5%) with 59% having anisometropic hyperopic refractive error. 42.6% of children achieved equal visual acuity (IOD ≤0.100) following occlusion treatment. Stereoacuity of 100 seconds of arc or better was achieved by 66.7% (52) of children that required amblyopia treatment. Treatment duration was a mean of 471.46 days (SD 9.0) with more frequent hospital visits (average of 6.56 visits, SD 2.81) which is similar to the findings of a South Auckland study (Langeslag-Smith et al., 2015).

3.7.5 Treatment acceptability

Children that engaged with the HES and completed treatment had clinically significant improvement in their visual acuity. Good adherence (83.3%) was reported with spectacle correction however adherence with occlusion was lower with only 69.4% adhering to the prescribed time. Poor adherence to amblyopia treatment is known to limit visual outcomes (Bruce et al., 2018; Drews-Botsch et al., 2016; Fielder et al., 1995; Gao et al., 2021; Loudon et al., 2006; Maconachie et al., 2016; Wallace et al., 2013), especially where treatment is prolonged. Poor parental understanding of the

ocular condition and treatment are factors that have been highlighted as important factors affecting concurrence with treatment. Targeted educational material used in randomised clinical trials (Loudon et al., 2006; Tjiam et al., 2012) has demonstrated an effective improvement in adherence highlighting the need for continued education and investment of the child and parent in amblyopia treatment.

Ethnicity was not related to treatment adherence in our study, with no significant difference found between ethnicities. However, we did find that a higher-than-expected proportion of Pacifica children did not attend any further appointments after the initial visit ($p=<0.001$) and a higher-than-expected number of Pacifica (25.8%) and Māori (22.2%) children did not complete treatment once it was commenced when compared to non-Māori and non-Pacifica children (14.1%). In New Zealand, Pacific and Māori children are overrepresented in lower socioeconomic groups and the cost related to amblyopia treatment (cost of spectacles and patches, parental or caregivers' loss of earnings due to attending outpatient appointments and cost of car parking at the hospital) could be a reason for non-attendance. Additionally, cultural factors such as racial discrimination and mistrust of the health system could be reasons for underutilisation of the health services by the Māori and Pacific population (Harris et al., 2012; Paine et al., 2018). A spectacle subsidy is available to contribute towards the cost of spectacles, but this is means-tested and only available with a valid community services card. It is a complex and arduous system that is not well known by the general public and often families on the lower end of the income scale do not qualify for a community services card, further exacerbating the health-related inequalities.

What is also concerning is the large number of children that failed vision screening but not seen in the HES. It is not known whether these children presented to other eyecare professionals for further assessment as there is no active system to monitor children after referral. This was evident through a recent prospective study in 6 to 7-year-olds that found almost a third of children at school had significant refractive error that was previously undetected (Findlay et al., 2020). This suggests that children who are not seen in the HES at age 4-5 years are not seeking health care elsewhere or those that have been prescribed treatment are non-adherent and likely to be lost to follow up. Difficulty in accessing spectacles from community optometrists could also be a reason for children not returning to the HES. Previous New Zealand and overseas studies have shown families with low

socioeconomic status (Bruce et al., 2018; Findlay et al., 2020; Solebo et al., 2015), are more likely to have children with an eye disorder (mainly amblyopia) than those in higher status groups. However, they are significantly less likely to consult an eye care specialist (odds ratio 0·65, 95% CI 0·43–0·98) (Solebo et al., 2015). If this is the case, then more needs to be done to ensure equitable access to eye health care with systems that actively monitor treatment access and outcomes. Information from this study contributed to the WCTO review suggesting moving the B4 school vision screening to a national screening unit to allow for better reporting of the vision screening outcome and reporting for each child. A centralised integrated database aligned with NHI numbers is needed to record vision screening results. This information should be made available to all health professionals across the lifespan of the individual and allow for data collation nationally and locally to facilitate governance and quality improvement of the vision screening programme.

One of the main limitations of this study is the small sample size which reduces the power to detect statistically important differences when comparing between ethnic groups. However, even though the number of Māori and Pacific people's populations were small, they were representative of the population that make up the two DHBs. This study was a retrospective chart review and therefore the prevalence of refractive error and amblyopia found in our cohort cannot be extrapolated to be taken as a total population prevalence. Further population-based studies would be required to determine the true prevalence and factors associated with amblyopia across New Zealand.

3.8 Conclusions

Children identified with reduced unaided visual acuity through the B4 School screening programme that went on to have timely treatment gained significant improvement in visual acuities providing strength for the effectiveness of the vision screening program. The majority of children in this study had refractive errors that required prescription of spectacles. There is possibly a role for community optometrists or joint community based orthoptic-optometry clinics to see these low to mild amblyopia risk children. This would reduce the burden on hospital eye departments and allow the specialist paediatric services to deal with significant amblyopia and conditions that require more specialist care and treatment. Public funding would be required to ensure there are no barriers to treatment access at community optometrists for all children in New Zealand.

Anisometropia was the most common cause of amblyopia in children that attend the HES following failed vision screening. The majority achieved visual acuity of 0.200 logMAR or better and just under half achieved stereoacuity of 100secs of arc or better. However, anisometropia of 4 dioptres of interocular difference or more was associated with those that failed to achieve good visual acuity or stereoacuity and it is possible that aniseikonia is a limiting factor in these children.

Chapter 4

Clinical Aniseikonia in Anisometropia & Amblyopia

The study presented in Chapter 3 identified anisometropia as a common cause of amblyopia in the preschool population with persistent visual acuity and stereoacuity deficits following amblyopia treatment. Therefore, in part, this chapter presents a study to investigate subjective aniseikonia in people with anisometropia and anisometropic amblyopia. This chapter also presents an optical model to estimate perceived aniseikonia using biometry and refractive data.

This chapter contains a manuscript submitted to 'The British and Irish Orthoptic Journal' and was published as *"Clinical Aniseikonia in Anisometropia and Amblyopia"*. Authors: Jayshree South, Tina Gao, Andrew Collins, Arier Lee, Jason Turuwhenua, Joanna Black. Accepted for publication 02 November 2020, volume 16, issue 1, pages 44-54. Thesis author Jayshree South led the study design, protocol development, collected study data, contributed to analyses and prepared the manuscript.

In the absence of a gold standard aniseikonia test and in situations where subjective aniseikonia measurement is not possible, biometry and refractive data may be useful in predicting the theoretical magnitude of aniseikonia. In conjunction with Auckland Bioengineering Institute an optical modelling system was designed and built and this is described in detail in section 4.7. Adult data from the anisometropic amblyopia group and the isometropic control group collected in the Clinical Aniseikonia in Anisometropia and Amblyopia study was used to test the model.

4.1 Introduction

Aniseikonia is a binocular vision disorder where images perceived by the two eyes differ in size and/or shape. In the context of anisometropia, aniseikonia can result from inherent anatomical differences (axial length and/or refractive components within the

eye), differences in photoreceptor spacing between eyes, and cortical adaptations. Aniseikonia can also be optically induced by spectacles or contact lenses used in the correction of anisometropia. The patient's perceived aniseikonia, as measured clinically or using psychophysical methods, is a product of all these factors.

Anisometropia occurs when there is a significant difference in refractive error between the two eyes (defined as a difference of greater than 1.00DS in spherical equivalent) and increases the risk of amblyopia in young children (Caputo et al., 2007; Donahue, 2005; Ingram, 1979; Weakley, 2001). The resulting unequal focus results in persistent blur on one retina which leads to suppression. Anisometropia is refractive and/or axial in origin and the type affects the theoretical sizes of the retinal images leading to perceived aniseikonia. The difference in image sizes hinders fusion and may further stimulate suppression. Chronic suppression due to blur and possibly unequal image size leads to the development of amblyopia.

Clinically, the first step in standard amblyopia treatment involves correction of refractive error (Cotter et al., 2006; Moseley et al., 2002; Royal College of Ophthalmologists, March 2012; Stewart et al, 2004; Wallace et al., 2018). Approximately 30% of children achieve equal visual acuity with refractive correction alone (Chen et al., 2007; Cotter et al., 2012; Cotter et al., 2006; Stewart et al, 2004). The remaining 70% of children require additional occlusion or penalisation treatments. However, even though the current standard treatments can be effective, approximately half of treated children are left with residual deficits in visual acuity, and most do not achieve age-normal stereoacuity, despite good adherence to amblyopia treatment (Scheiman et al., 2005; Scheiman et al., 2008; Wallace et al., 2011). Given that about two-thirds of children with amblyopia have anisometropia, and children with anisometropia are likely to experience both anatomical and spectacle-induced aniseikonia, it is possible that aniseikonia may be a barrier to binocularity, stimulating suppression and limiting binocular visual improvement. Correcting aniseikonia along with anisometropia may improve visual outcomes, but this has not been directly investigated in children previously and is not considered in current clinical guidelines for amblyopia treatment.

Accurate measurement of aniseikonia is often not attempted in anisometropic amblyopes, as subjective aniseikonia tests are often thought to be too difficult to

administer in these patient groups, due to age, poor vision, or absent binocular vision (Davis, 1959). Most aniseikonia measurement tools rely on direct comparison of images seen by each eye, requiring simultaneous binocular perception or stereopsis. It is assumed that direct comparison tasks are not possible in amblyopes due to the image from the amblyopic eye being too poor in quality or too strongly suppressed for the binocular image size difference to be recognised. As a result, few studies (Lubkin et al., 1999; Romano & Kohn, 1972) have attempted to measure aniseikonia in non-fusing participants. Instead, clinicians often rely on estimations or empirical calculations of aniseikonia using the anisometropic difference in refractive error. The common clinical rule-of-thumb is 1% of aniseikonia per dioptre of spherical anisometropic difference (Berens & Bannon, 1963; Ogle, 1950). This rule is based solely on theoretical optics (Davis, 1959; Ryan, 1975) which overestimates aniseikonia and can be misleading. These estimations do not account for retinal differences (Benegas et al., 1999; Okamoto et al., 2014), cortical adaptations, (Bradley et al., 1983) or any compounded aniseikonia induced by the spectacle corrections. Therefore, calculations from refractive error alone do not provide an accurate solution for the management of aniseikonia.

Children with anisometropia are rarely symptomatic of aniseikonia, which may be due to cortical adaptations such as suppression. However, strong suppression is more associated with strabismus or stimulus deprivation amblyopia whereas patients with anisometropic amblyopia and no strabismus often demonstrate lower levels of suppression, allowing for limited binocular functions such as fusion, gross stereopsis, and some reduced binocular summation (Donahue, 2005; Levi et al., 2011; Weakley, 2001).

Recent investigations into binocular treatment methods for unilateral amblyopia have demonstrated that binocular mechanisms are intact, but are suppressed in order to cope with dissimilar images in the two eyes. The interocular suppression associated with amblyopia can be overcome by adjusting the image contrast or luminance dichoptically presented to each eye, until the targets from either eye become simultaneously visible and equally salient (Harauzov et al., 2010; He et al., 2006; Hess et al., 2010; Mansouri et al., 2014; Maya-Vetencourt et al., 2012). Given that binocular mechanisms appear intact in anisometropic amblyopia, subjective aniseikonia should be measurable as long as suppression can be overcome during testing.

Internationally, there does not appear to be a "gold standard" test used for the measurement of aniseikonia. The Aniseikonia Inspector version 3 (AI3) (Optical Diagnostics, Culemborg, The Netherlands) (Kehler et al., 2014) and the New Aniseikonia Test (NAT) (Good-Lite Company, Tokyo, Japan) (McCormack et al., 1992) are two of the more routinely used clinical tests but there is a lack of evidence around test comparisons and reliability between tests. In this study, we investigated the use of four different subjective aniseikonia tests on three groups of participants: those with anisometropic amblyopia, anisometropia and no amblyopia, and isometropic controls. Our aim was to assess whether subjective aniseikonia can be successfully measured in anisometropic amblyopia, and to examine the correlations between the four aniseikonia tests and refractive error.

4.2 Methodology

This study was approved by the University of Auckland Human Participants Ethics Committee and adhered to the principles of the Declaration of Helsinki. Written informed consent was obtained for adult participants (16 years and over) and parents/guardians of child participants, and verbal assent was obtained for child participants.

4.2.1 Participants

19 participants (age range 15-52 years) with healthy eyes and no previous history of eye surgery were recruited into three study groups: 1) Anisometropic amblyopia, 2) Anisometropic control and 3) Isometropic control. Recruitment of participants was through the University of Auckland optometry clinic and local optometrist and orthoptic referrals.

4.2.2 Group Criteria:

- **Anisometropic Amblyopia group:** best corrected visual acuity (BCVA) of ≥0.20 logMAR in the amblyopic eye and ≤ 0.10 logMAR in the fellow eye, with an interocular difference of ≥ 0.2 log units (2 lines). Anisometropia was ≥1.00 DS difference in spherical equivalent refraction (SER). Participants with manifest or intermittent strabismus were excluded, however primary microtropia was accepted.

- **Anisometropic Control group** (anisometropia without amblyopia): had BCVA of ≥ 0.10 logMAR in each eye and less than two lines difference between the eyes. They may have previously undergone amblyopia treatment and achieved best-corrected visual acuity of 0.10 logMAR or better in the amblyopic eye. Anisometropia was ≥1.00 dioptre in SER. All participants in this group had no manifest strabismus and normal binocular vision, as determined by normal horizontal and vertical fusional vergence amplitudes and stereoacuity of 100 secs of arc or better on the Randot Preschool Stereoacuity Test (Stereo Optical.co.inc).

- **Isometric Control group** (no anisometropia or amblyopia): BCVA ≤ 0.10 logMAR in each eye, no history of amblyopia or other binocular vision disorders, no manifest strabismus, and stereoacuity of 100 secs of arc or better on the Randot Preschool Stereoacuity Test

- Participants in all groups had less than -6.00 DS of myopia and less than +8.00 DS of hyperopia (SER). Astigmatism difference between eyes in any meridian was 3.00 DC or less.

4.2.3 Study procedure

All participants completed a full clinical assessment, including detailed ocular history, distance best corrected visual acuities measured using the highly standardised E-ETDRS protocol on the Electronic Visual Acuity (EVA) Tester (Beck et al., 2003), cover test, ocular motility, convergence, Bagolini striated glasses at 1/3 metre and 6 metres, and the Randot preschool stereoacuity test (Stereo Optical Co. Inc, Chicago, IL,USA) at 40cm. Objective visuoscopy and the four-dioptre reflex test were used to assess fixation. Ocular biometry was measured using the LenStar LS 900, retinoscopy (non-cycloplegic) and subjective refraction were completed. All tests were conducted by the same examiner (an experienced orthoptist) to ensure consistency, with retinoscopy and subjective refractions verified by an optometrist. If participants were not currently wearing the correct prescription, then all tests were performed with the full subjective refraction in trial frames. Otherwise, the participant's habitual glasses or contact lenses were used during testing. For amblyopic participants, the non-amblyopic fellow eye was deemed to be dominant. For non-amblyopic participants, eye dominance was determined using Hole-in the-hand-test (Walls, 1951).

Subjective aniseikonia was measured using the following four methods:

- **The Aniseikonia Inspector Version 3 (AI3)** is a computer-based clinical test requiring the direct comparison of two rectangles viewed through red-green anaglyphic glasses. The glasses were worn with the red filter over the right eye for all participants. Testing was conducted at a viewing distance of 45cm. The standard "Screen" procedure was used to measure aniseikonia for targets of 4- and 8-degree field angles. Each measurement consisted of 12 presentations of varying amounts of object size difference, where the participant identified which of the two targets appeared larger using the keyboard. The Aniseikonia Inspector performs a small fixation disparity test before aniseikonia measurement is taken. Two targets are presented and moved relative to each other on the screen correcting small amounts of horizontal and vertical fixation disparities. The participants were then instructed to notify the examiner if the two images moved out of alignment during the test. The test was performed in a dimmed room and the participant was instructed to keep their head as still as possible throughout testing. The participant was observed to ensure they maintained head position and encouraged to fix centrally throughout testing.

- **The New Aniseikonia Test booklet (NAT)** (Good-Lite Company, Tokyo, Japan) contains 24 pairs of semi-circle targets presented in 1% magnification increments from zero to 24%. These are viewed through red-green anaglyphic glasses with the red filter over the right eye. The participant viewed the booklet at 40cm and was asked to find the pair of semi-circles that appeared most equal in size. Each set of semi-circles had a number which indicated the percentage of aniseikonia.

- **The Contrast-balanced Aniseikonia Test (CAT)** is a novel psychophysical procedure which allowed participants to make manual adjustments before testing to a) align dichoptic images to compensate for any phorias, and b) equalise perceived contrast of dichoptic images to compensate for any suppression. The grayscale semi-circle targets were viewed through 3D glasses at a distance of 45cm and a 30-trial psi-marginal adaptive staircase was employed (Kontsevich & Tyler, 1999; Prins, 2013) to determine the threshold of equal perceived image size between the two eyes. The size of objects shown to each eye at this threshold of subjective equality is used to calculate the amount of perceived aniseikonia.

- **The Robertson Technique (RT)** is a modified penlight and Maddox rod technique that measures spectacle-induced aniseikonia via neutralisation of the induced vertical anisophoria. This test differs from the other three as it is a measure of dynamic aniseikonia, not static aniseikonia. A Maddox rod lens is placed over the dominant eye and the participant views a pen torch at one metre with both eyes. The horizontal line image seen by the dominant eye would appear to overlap the pen torch seen by the non-dominant eye if the participant viewed through the optical centres of the lenses. The participant is instructed to hold their head still in this position and the light is moved up or down while the participant follows using eye movements only. If dynamic aniseikonia is present the light and the line will move apart, with the larger image seen at the more peripheral position. Prisms are then used to measure the amount of vertical anisophoria for specific positions of gaze above and below the optical centre direction. These prism measurements are then used to calculate the amount of dynamic aniseikonia (South et al., 2019). From this anisophoria, the static aniseikonia can be inferred (Remole, 1989a; Remole 1989b; Remole, 1996).

All participants wore their full refractive correction where required with the appropriate near addition (if required). Participants requiring trial frame correction were given a minimum of 15 minutes to adapt to the lenses prior to attempting the aniseikonia tests. The order of aniseikonia tests for each participant was determined using a computer-generated random order sequence.

4.3 Statistical analyses

Results from successfully completed subjective aniseikonia tests were converted to the same units for comparison.

The aniseikonia value was calculated as below:

$$\frac{Perceived\ size\ in\ nondominant\ or\ amblyopic\ eye - \ Perceived\ size\ in\ dominant\ or\ fellow\ eye}{Perceived\ size\ in\ dominant\ or\ fellow\ eye} \times 100\%$$

The amount of anisometropia for each participant was calculated as "signed anisometropia" based on their refractive error, using the formula

$\boldsymbol{SE_{NdE} - SE_{DE}}$ (SE_{NdE} = *Spherical Equivalent Non-Dominant Eye,* SE_{DE} = *Spherical Equivalent Dominant Eye).*

We preserved the signed information in this calculation instead of using the clinical convention of the absolute amount of anisometropia, as anisometropic spectacle correction is a contributor to the total amount of aniseikonia, and thus whether the non-dominant eye was wearing a more plus or more minus lens than the dominant eye is important for analyses. Direct values of dynamic aniseikonia calculated from the Robertson Technique were used for comparison to the other static aniseikonia tests.

The association between the four different aniseikonia tests was evaluated using Bland-Altman analysis in GraphPad Prism 8.2.1. No literature was available to define acceptable limits of agreement for aniseikonia tests. Pearson's correlation coefficient analysis was conducted using SPSS version 25 (IBM). The association between the amount of aniseikonia and the amount of signed anisometropia was evaluated using Pearson's correlation coefficient. A p-value of <0.05 was used as the threshold for statistical significance for all tests. No adjustments were made for multiple comparisons.

4.4 Results:

Participants included (M=4, F=15, age range=15-52 years) in the study are summarised in Table 12. Five participants habitually wore glasses and three habitually wore contact lenses, and all had prescriptions less than six months old. Nine participants did not routinely wear correction, requiring trial lenses during testing. Interestingly, the Anisometropic Amblyopia group were the least likely to wear habitual correction with only two out of seven wearing up to date refractive correction. In the Anisometropic Amblyopia group the average (SD) amount of signed anisometropia was 4.07D (1.54) with an average (SD) of 3.12% (2.96) of aniseikonia and average (SD) acuity of 0.40 (0.20) logMAR in the amblyopic eye. Six out seven of these participants had previously undergone occlusion therapy. In the Anisometropic Control group the average (SD) amount of signed anisometropia was 0.40D (2.84) with an average (SD) of -0.06% (0.66) of aniseikonia and -0.03 (0.12) logMAR acuity in the non-dominant eye. Only one participant had previously had occlusion therapy. The Isometropic Control group

had an average (SD) of 0.30D (0.32) of signed anisometropia, an average (SD) of 0.17% (0.72) of aniseikonia and an average (SD) acuity of -0.05 (0.10) logMAR units.

Eighteen out of nineteen participants were able to complete all four subjective aniseikonia tests. Only one participant from the Anisometropic Amblyopia group (AA04) was unable to perform two of the tests (RT and AI3) due to a decompensated phoria and loss of fusion during the tests.

Table 12. Participant characteristics and aniseikonia test results

Anisometropic Amblyopia Group														
Study Group	**Participant Age (Y)**	**LogMAR Acuity**		**Cover Test**	**Bagolini Striated Glasses**	**Stereopsis (secs/arc)**	**Signed Anisometropia (D)***	**SE Refractive Error**		**Method of refractive correction**	**RT (%)**	**AI3 (%)**	**NAT (%)**	**CAT (%)**
		RVA	**LVA**											
AA03	52	0.50	0.00	2 xp	BSV	400	4.88	5.88	1	Contact lenses with glasses for reading add	-0.60	-1.48	1.01	0.42
AA04	18	-0.10	0.30	Micro	Central Suppression	Nil	5.38	-0.5	4.88	Trial frames	-	-	10.00	3.52
AA05	15	-0.10	0.70	Micro	L Suppression	Nil	5.75	-0.25	5.5	Trial frames	1.79	3.50	3.00	0.05
AA10	23	0.20	-0.10	6 xp	BSV	600	4.75	2.5	-2.25	Trial frames	6.82	10.50	6.38	7.05
AA16	22	-0.10	0.60	Micro	Central Suppression	200	3.75	0.5	4.25	Trial frames	1.82	6.00	2.00	1.76
AA17	20	-0.20	0.30	Ortho	BSV	800	2.00	0.5	2.5	Trial frames	4.33	-1.50	0.00	2.39
AA19	22	-0.10	0.20	Ortho	BSV (with int supp @times)	100	2.00	0	2	Habitual Glasses	-0.50	1.50	2.00	2.06
										Mean	**2.28**	**3.09**	**3.49**	**2.33**
										Std Dev	**2.87**	**4.65**	**3.50**	**2.41**
Anisometropic Control Group														
Study Group	**Participant Age (Y)**	**LogMAR Acuity**		**Cover Test**	**Bagolini Striated Glasses**	**Stereopsis (secs/arc)**	**Signed Anisometropia (D)***	**SE Refractive Error**		**Method of refractive correction**	**RT (%)**	**AI3 (%)**	**NAT (%)**	**CAT (%)**
		RVA	**LVA**											
AC02	28	-0.10	0.10	Ortho	BSV	100	3.00	2.13	5.13	Trial frames	4.53	1.52	0.00	-1.13

AC11	22	-0.20	-0.20	4 xp	BSV	40	3.25	-3.25	-0.75	Contact lenses	0.32	1.52	-3.00	-0.39
AC13	28	-0.10	-0.10	4 xp	BSV	40	-1.50	-0.38	-1.88	Habitual Glasses	1.75	0.00	-1.00	-3.29
AC14	28	0.00	0.10	1 xp	BSV	40	-3.25	-3.38	-6.63	Trial frames	-0.23	-1.50	0.00	0.84
AC18	46	-0.10	0.00	12 xp	BSV	40	-1.63	-0.38	-2	Trial frames	0.63	-1.70	1.00	-0.65
AC23	21	-0.10	-0.10	Ortho	BSV	40	2.50	-2.5	0	Habitual Glasses	1.99	-1.50	-1.00	-0.09
										Mean	**1.58**	**0.31**	**-0.74**	**-0.93**
										Std Dev	**1.75**	**1.62**	**1.41**	**1.35**

Isometropic Control Group

Study Group	**Participant Age (Y)**	**LogMAR Acuity**		**Cover Test**	**Bagolini Striated Glasses**	**Stereopsis (secs/arc)**	**Signed Anisometropia (D)***	**SE Refractive Error**		**Method of refractive correction**	**RT (%)**	**AI3 (%)**	**NAT (%)**	**CAT (%)**
		RVA	**LVA**											
IC01	31	-0.10	-0.10	1 xp	BSV	40	0.63	-5.38	-4.75	Habitual Glasses	-0.51	-1.50	-1.00	-0.79
IC07	38	0.10	-0.10	Ortho	BSV	40	0.25	0	-0.25	No ref correction	0.01	0.50	0.00	-0.32
IC08	23	0.10	-0.10	Ortho	BSV	40	0.13	-0.25	-0.38	Trial frames	0.12	2.56	1.01	0.14
IC15	28	-0.10	-0.10	Ortho	BSV	40	0.00	-0.5	-0.5	Trial frames	0.00	-0.50	0.00	0.09
IC20	19	-0.20	-0.20	1 xp	BSV	40	0.00	-2.38	-2.38	Habitual Glasses	0.00	0.50	1.00	-0.92
IC22	21	0.00	0.00	Ortho	BSV	60	0.75	-0.75	-1.5	Contact Lenses	0.00	-0.50	1.01	3.28
										Mean	**-0.06**	**0.18**	**0.34**	**0.25**
										Std Dev	**0.22**	**1.39**	**0.82**	**1.55**

**Anisometropia was calculated to match the signed percentage of aniseikonia using the following formula:* $\boldsymbol{SE_{NdE} - SE_{DE}}$ *(SE_{NdE} = Spherical Equivalent Non-dominant Eye, SE_{DE} = Spherical Equivalent Dominant Eye) AA=Anisometropia Amblyopia, AC=Anisometropic Control, IC= Isometropic Control, SE=Spherical Equivalent, D=Dioptre, Y=Years, BSV= Binocular Single Vision, xp=Exophoria, Micro=Microtropia, Ortho=Orthotropia*

The Anisometropic Amblyopia Group (Figure 13a) generally demonstrated the greatest amount of aniseikonia (range -1.50% to +10.50%) followed by the Anisometropia Control group (Figure 13b) (range -3.30 to +4.50%) and the Isometropic Control group (Figure 13c) (range -1.50 to +3.28%). This is further described for each of the aniseikonia tests in Table 13.

Table 13. Range of aniseikonia per test for the 3 study groups

	AI3	**NAT**	**CAT**	**RT**
Anisometropia amblyopia	-1.50% to +10.50%	+0.02% to +10.00%	+0.05% to +7.00%	-0.60% to 6.82%
Anisometropic Control	-1.70% to +1.99%	-3.00% to +1.00 %	-3.29% to +0.84%	-0.23% to 4.53%
Isometropic Control	-1.50% to +2.56%	-1.00% to +1.00%	-0.92% to 3.28%	-0.51 to 0.1%

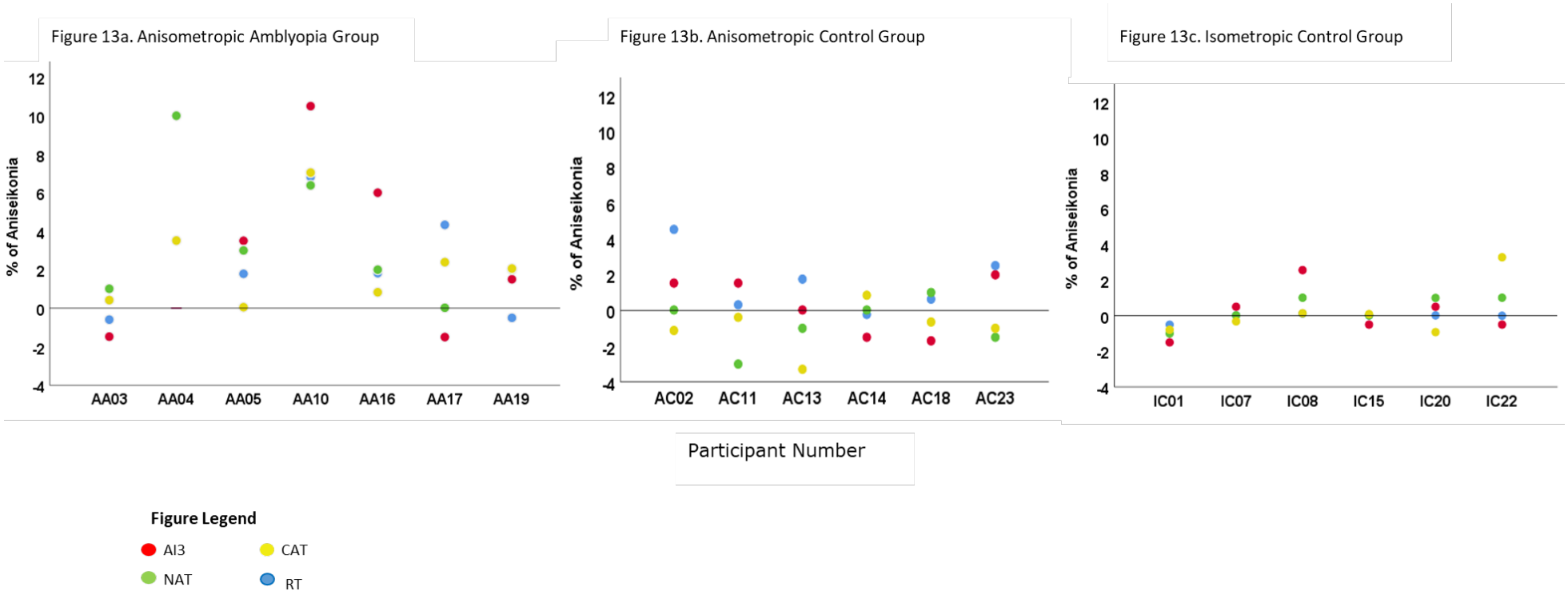


Figure 8. **(a-c). Inter-test Reliability in 3 Study Groups**. Showing greatest amount of aniseikonia in the Anisometropic Amblyopia Group.

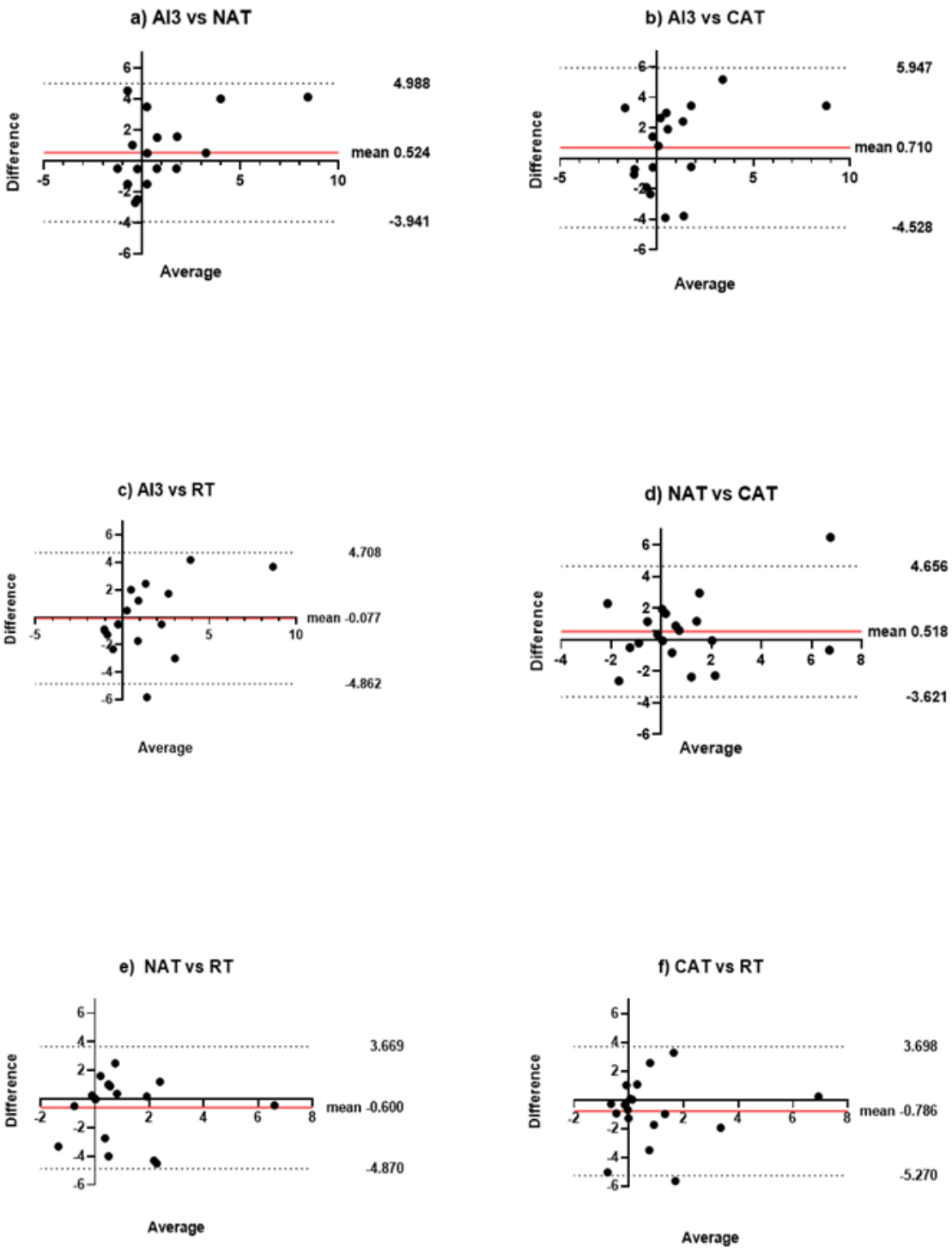


Figure 9. **(a-f). Bland-Altman plots for repeated measurements of the four aniseikonia tests.** The central solid red line shows the mean difference, and the upper and lower broken lines show the 95% limits of agreement.

Table 14. Results of Bland-Altman analysis for repeated measurements and Pearson's correlation values of the four aniseikonia tests

Bland Altman results for repeated measures of the four aniseikonia tests			Pearson's Correlation Coefficient values	
Test	**Mean Difference (%)**	**95% limits of agreement (%)**	**R -values**	**P-value**
AI3 vs NAT	0.52	-3.94 to 5.00	0.679	0.002
AI3 vs CAT	0.71	-4.53 to 5.95	0.536	0.022
AI3 vs RT	-0.08	-4.86 to 4.71	0.618	0.006
NAT vs CAT	0.52	-3.62 to 4.66	0.689	0.001
NAT vs RT	-0.60	-4.87 to 3.67	0.432	0.073
CAT vs RT	-0.79	-5.27 to 3.70	0.434	0.072

Bland Altman analysis (Figure 14 and Table 14) demonstrated a low level of bias between methods. However, the 95% limits of agreement showed variability which was greater in the anisometropic amblyopia group.

A significant trend of increasing subjective aniseikonia with increasing amounts of signed anisometropia was observed across all four tests (Figure 15). Three out of the four tests showed significant correlation with the signed anisometropia (AI3 $r=0.63$ $p=0.005$, NAT $r=0.54$ $p=0.017$ and RT $r= 0.50$ $p= 0.035$). However, the fitted trendlines are all flatter than the "1% per Dioptre" rule of thumb.

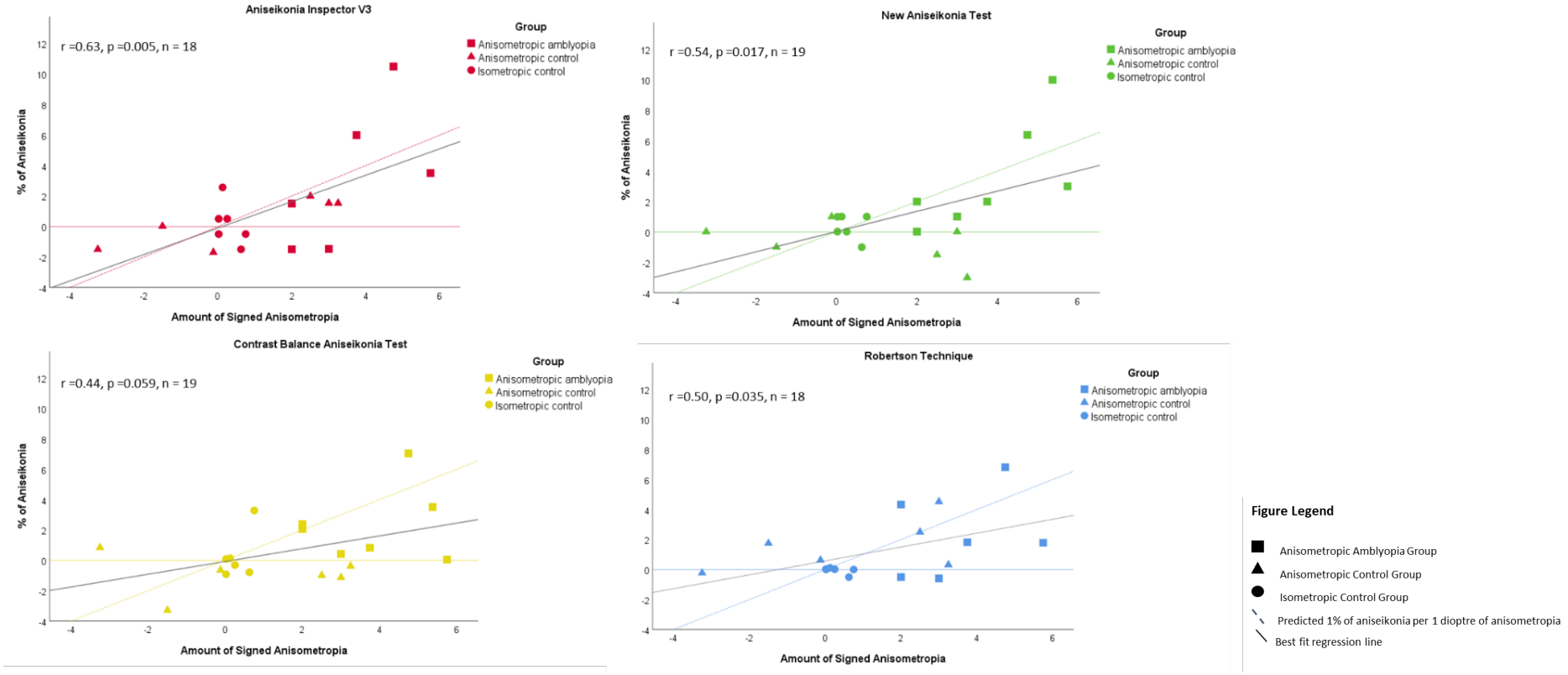


Figure 10. Amount of aniseikonia versus signed anisometropia

4.5 Discussion:

Our results show that subjective aniseikonia can be successfully measured in anisometropic amblyopia using both clinical and psychophysical dichoptic methods in our adult cohort. As expected, subjective aniseikonia was correlated with anisometropia, and was highest on average in the anisometropic amblyopia group and lowest in the isometropic control group. Our results also demonstrate that the increase in subjective aniseikonia with increase in signed anisometropia does not support the 1% per Dioptre clinical rule of thumb, suggesting that clinical approximations are likely to be inaccurate in anisometropic patients. Actual measurements of subjective aniseikonia should be attempted in patients with anisometropia to provide more precise information for clinical decisions. The three static aniseikonia tests showed good correlation with low levels of bias, however there were clinically significant levels of variability demonstrated between the tests. This variability was greater in those with anisometropic amblyopia as expected due to difficulty in size judgements associated with worse visual acuity in the amblyopic eye. No test has superseded the Eikonometer which was the previous gold standard, however this test is no longer in production and no longer commercially available (Rutstein et al., 2006). The variability found between the tests suggests future studies should aim to provide a gold standard test and to establish clinically acceptable limits of agreement and test-retest variability between aniseikonia tests.

All participants except one were able to perform all four aniseikonia tests. This is the first study demonstrating that aniseikonia tests can be reliably performed in adults with anisometropic amblyopia. Previous studies have excluded participants who did not demonstrate simultaneous perception or stereopsis (Antona et al., 2007; Awaya, 1982; Kehler et al., 2014; Lubkin et al., 1999) as aniseikonia was assumed to be difficult to measure in amblyopia due to suppression. While Lubkin et al. (1999) investigated the relationships between aniseikonia, anisometropia, strabismus and amblyopia, their participants had very low levels of suppression as they were required to have stereopsis of 100 secs of arc or better to perform Space Eikonometry. Our study successfully measured subjective aniseikonia even in the anisometropic amblyopia group, which included participants with residual amblyopia, reduced or nil stereoacuity, and demonstrable suppression on Bagolini lenses.

Chronic suppression in anisometropic amblyopia develops due to the diminished image clarity and contrast in one eye during the early critical period of visual development (Levi et al., 2011). Recent binocular theories of amblyopic visual deficits suggest that binocular visual function is suppressed or inactive under normal viewing conditions, and not permanently lost. Our results support this theory, as our participants with anisometropic amblyopia were able to complete direct comparison tests, which require binocular simultaneous perception. It is possible that they were able to overcome suppression simply through red/green anaglyphic dissociation or by viewing contrast-balanced dichoptic stimuli. Suppression in anisometropic amblyopia is also spatial frequency dependent, with more unbalanced suppression at higher spatial frequencies (Kwon et al., 2015; Movshon et al., 1987). The tests we used all had relatively large, solid shapes and minimal high-spatial frequency textures, which should stimulate less suppression than finely detailed gratings or small targets. The dichoptic shapes also did not overlap in visual space, preventing binocular rivalry, and were framed by binocular stimuli to encourage peripheral fusion. All these factors allow for the measurement of aniseikonia even in the presence of amblyopic suppression.

The Robertson Technique uses simple equipment that is already found in most orthoptic clinics to measure dynamic aniseikonia (Remole, 1989a; Remole, 1989b) and a static percentage difference can be derived from this measurement (Remole, 1989b). Remole (1989a) suggested correcting two-thirds of measured dynamic aniseikonia should provide overall symptomatic relief. However, looking at our results, correcting two-thirds of the dynamic amount would result in under or overcorrection of the aniseikonia for some participants. Contact lenses have been shown to be effective in reducing symptoms of both static and dynamic aniseikonia (Rose & Levinson, 1972; Winn et al., 1988). Contact lenses sit closer to the entrance pupil than spectacles reducing the optically induced magnification effect caused by lens power. Contact lenses also remain centred on the cornea during eye movements and therefore dynamic aniseikonia is not induced. However, they are not always suitable for all patients such as elderly patients or young children. The range of refractive correction used in this study including contact lenses, habitual glasses and trial frames could account for the variability in the range of aniseikonia measured in the three study groups (see Table 12). The majority of participants in the anisometropic amblyopia group had trial frame corrections as they were wearing balance lens prescriptions or were not routinely using any refractive

correction. Clinically, deliberate under correction using reduced-power balance lenses are often prescribed to adult patients with large amounts of anisometropia to reduce the risk of aniseikonia symptoms. In most cases the actual amount of aniseikonia perceived by the patient is not assessed. Deliberate under correction of anisometropia or not correcting anisometropia without assessing aniseikonia deprives patients of binocular vision.

One participant with anisometropic amblyopia was unable to complete the AI3 and RT due to decompensation of a horizontal and vertical phoria during testing and intermittent central suppression. The AI3 allowed correction of small horizontal and vertical fixation disparities up to four secs of arc but our participant's vertical disparity was beyond this limit. Vertical prisms in trial frames were used in an attempt to aid fusion during both the AI3 and RT tests, but poor motor fusion resulted in intermittent diplopia, triggering suppression and making it difficult to perceive and maintain alignment of the targets. Interestingly, the participant was able to appreciate some image size differences between eyes during moments without suppression and was able to perform the NAT. It is likely this participant was not maintaining central fixation and therefore not truly performing a size discrimination task (Garcia-Perez & Peli, 2015). Alternating suppression may have allowed for the image sizes to be perceived uniocularly and a comparison made. The opposing half circle targets and colour contrast of the NAT may have further helped identify which eye was seeing which image while uniocular comparisons were made. The CAT test is a novel technique based on the dichoptic method to assess aniseikonia in the presence of suppression and was piloted in this study. It allowed a larger adjustment of vertical and horizontal alignment to compensate adequately for this participant's phoria, and contrast adjustment to overcome suppression, allowing a measurement of subjective static aniseikonia to be obtained. This participant's example illustrates the difficulty in performing dichoptic tests on patients with abnormal motor and sensory binocularity. An optimal aniseikonia test needs to be able to overcome issues such as loss of fusion and suppression.

The two more well-known clinical aniseikonia tests, NAT and the AI3, showed good correlation between tests ($r=0.679$ $p=0.002$), and a low level of bias. The newly developed CAT also showed significant correlation with both these tests (NAT $r=0.689$ $p=0.001$, AI3 $r=0.536$ $p=0.022$) and the Robertson technique shows good correlation

with the AI3 (Table 12. Mean -0.08 r=0.618 p=0.006) which provides a good clinical test alternative using equipment that is already found in most orthoptic clinics compared to expensive software purchases. These tests all measure static aniseikonia using direct comparison of perceived image size under dichoptic conditions, and therefore similar results are expected. Overall, the AI3 and the NAT static aniseikonia tests appear to be useful in anisometropic amblyopia, and limitations to direct comparison methods may be addressed by further refinement of digital or paper-based methods (such as the CAT test).

This study shows a significant trend of increasing subjective aniseikonia with increasing amounts of anisometropia but does not support the 1% per Dioptre clinical rule which was also reported by Lubkin et al. (1999). This suggests other factors such as cortical and retinal adaptations may be contributing to the final perceived amount of aniseikonia, and empirical calculations alone do not provide an accurate solution for the management of aniseikonia. We acknowledge the small sample size in this study does not allow for an accurate calculation of average percentage of aniseikonia per dioptre of anisometropia and a larger sample size would be required for a true estimation. Recruitment of participants within the three groups with the specific criteria was challenging, however the sample size in this study is similar to other recent studies in this area (Atchison et al., 2020; Primiano Junior et al., 2019). A larger population level study is an area that requires further research, which would increase statistical power and reduce the margins of error. Lubkin and Linksz (1977) studied the interrelationships among aniseikonia, anisometropia, strabismus and amblyopia and noted a 4.4-fold increased risk of aniseikonia in anisometropia but did not look at the degree of aniseikonia in relation to the amount of anisometropia. As far as we know, the quantitative relationship between aniseikonia and anisometropia in those with anisometropic amblyopia has not been studied. However, despite being small in scale, our study suggests that aniseikonia is likely to be common in those with anisometropic amblyopia. Much larger cohorts would be needed to examine the true prevalence. It is promising that simple clinical tests can be used to measure subjective aniseikonia in this patient population.

4.6 Conclusion

Aniseikonia is likely to be present in patients with anisometropia, due to the inherent anatomical causes of anisometropia and spectacle corrections used for treatment. We have shown that aniseikonia occurs in patients with anisometropic amblyopia and that subjectively perceived aniseikonia can be reliably measured despite amblyopia and suppression. The greater amounts of aniseikonia found in the anisometropic amblyopia group is in line with the hypothesis that aniseikonia may contribute to suppression and may limit binocular visual recovery in anisometropic amblyopia. It is possible that correcting aniseikonia simultaneously with anisometropia at first diagnosis will reduce the need to develop suppression and improve the overall visual outcomes from amblyopia treatments. To investigate this hypothesis, a randomised clinical trial that directly compares visual outcomes from aniseikonia correction versus standard spectacle correction for anisometropic amblyopia, titled Measuring aniseikonia: investigating neuroplasticity and image factors in amblyopia (MAGNIFY) study (ACTRN12620000061932), is currently underway. Further investigations into whether providing aniseikonia correction in older children/adults with anisometropic amblyopia could improve spectacle compliance and visual function would also contribute to the understanding of the role of aniseikonia in anisometropic amblyopia.

4.7 Optical Modelling

In the absence of a gold standard aniseikonia test and in situations where subjective aniseikonia measurement is not possible, biometry and refractive data may be useful in predicting the theoretical magnitude of aniseikonia.

Anisometropia at an anatomical level is caused by a difference in eye size, predominantly due to vitreous chamber asymmetry leading to a significant difference in overall axial length of the eye (Huynh et al., 2006). Differences in power may also exist between the refractive structures of the eye, including corneal curvature, biconvex intra-ocular lens curvatures and lens positioning. Aniseikonia can also result from the refractive correction used in the correction of anisometropia. Differences in retinal photoreceptor spacing and cortical adaptations can also induce aniseikonia. In the absence of an optimal aniseikonia test, especially for children, and the laborious methods involved in calculating aniseikonia using geometrical optics, empirical estimations have been favoured (Davis, 1959; Ryan, 1975).

With recent advancement in technology, we now have precise ocular biometry measurement tools allowing for measures of ocular parameters such as axial length, lens thickness, corneal and lens curvatures, and the position of the ocular components. To date, use of this technology has been limited to patients undergoing cataract and refractive surgery and in myopia control (Cruickshank & Logan, 2018). This technology has not been widely applied in the assessment of aniseikonia where biometric data of eye size differences could help accurately predict the theoretical magnitude of aniseikonia, optimise spectacle lens design, and allow for an accurate prediction of aniseikonia in instances where subjective aniseikonia is not possible such as in young children where anisometropia is typically diagnosed.

Using the biometry data collected from the clinical participants in the Clinical Aniseikonia in Anisometropia and Amblyopia study (Chapter 4), we tested to see if magnification error between the eyes could be predicted using optical modelling methods. Magnification differences between eyes were determined by creating a consistent model eye that produced a focused retinal image in the corrected and uncorrected states for the anisometropic amblyopia group and the isometropic control group. The anisometropic control group were not included as this proof of concept study was assessing the ability to predict aniseikonia in a group known to have subjectively demonstrable aniseikonia compared to the control group.

4.8 Individualized eye models.

The relaxed Le Grand eye model (LeGrand & El Hage, 2013) was used as the basis for individualised eye models. Individualised eye model distances were constructed from the following biometry measures: 1) lens thickness, 2) axial length, 3) central corneal thickness, and 4) anterior chamber depth. The anterior cornea was modelled by a toric surface with powers specified by sphere/cylinder and axis. Biometry data were collected using the LenStar LS 900, and subjective refractions at 6 metres were used to calculate ocular power.

The lens prescription (determined by subjective refraction) for each participant was modelled by a thin sphero-cylindrical lens added at a vertex distance of 12 mm for glasses and trial frames and 0 mm for contact lens wear and no refractive correction (as in Table 15). However, the personalised eye model was not fully correcting in the distance resulting in a small power error (estimated -1.13D - +2.68D see adjustment

column of Table 15). A possible source of this error may be the assumptions made due to limitations in measurement of the refractive components within the eye (see Table 16 for details used in the eye model). The posterior corneal curvature is difficult to measure in situ without expensive specialist imaging equipment. Refractive and cataract surgeries, where corneal curvatures are routinely measured to control the refractive outcome of surgery, use a keratometric index (Olsen, 1986) to estimate the total corneal refractive power from the anterior corneal curvature measurement. This is based on the premise that the anterior and posterior corneal curvatures have a constant and linear relationship (Fam & Lim, 2007). Another potential source of error maybe due to the personalised eye model assuming a single refractive index of 1.42 whereas studies recently have described the lens having a gradient refractive index distribution which changes with age (Birkenfeld et al., 2014). Due to the difficultly in measuring the lens in situ, an assumed value of 1.42 was used. Standard values for the anterior and posterior crystalline lens curvatures were assumed in the optical model.

Table 15. Summary of participant information

Isometric Control Group						
Participant ID	Eye	Dominant	Type of refractive correction	Rx (D)	Vertex Distance (mm)	Adjustment (D)
IC01	OD	Y	Glasses	-5.25/-0.25 x 105	12	0.21
	OS		Glasses	-4.75	12	0.05
IC07	OD	Y	No correction	0	0	1.54
	OS		No correction	-0.25	0	1.77
IC08	OS	Y	Trial frames	-0.25/-0.25 x 74	12	1.95
	OD		Trial frames	0/-0.50 x 95	12	1.85
IC15	OD	Y	Trial Frames	-0.50	12	-0.15
	OS		Trial Frames	-0.50	12	0.11
IC20	OD	Y	Glasses	-2.00/-0.75 x 90	12	2.68
	OS		Glasses	-1.75/-0.75 x 95	12	2.06
IC22	OS	Y	Contact Lenses	-1.75	0	0.45
	OD		Contact Lenses	-1.00	0	0.30
Anisometropic Amblyopia Group						
Participant ID	Eye	Dominant	Type of refractive correction	Rx (D)	Vertex Distance (mm)	Adjustment (D)
AA03	OD	Y	Contact Lenses	+6.00/-0.25 x 105	0	3.19
	OS		Contact Lenses	+0.25	0	-1.93
AA05	OD	Y	Trial frames	-0.25	12	2.98
	OS		Trial frames	+6.50/-2.00 x 180	12	4.52
AA10	OD	Y	Trial Frames	+2.50	12	-0.82
	OS		Trial Frames	-2.25	12	-0.02
AA17	OD	Y	Trial frames	+0.50	12	3.06
	OS		Trial frames	+2.75	12	3.48
AA19	OD	Y	Glasses	-0.25	12	2.54
	OS		Glasses	+2.00	12	2.94

To compensate for these assumptions, an adjustment lens was added at the corneal plane. This was interpreted as an additional optical focal plane correction (F_A) added at the cornea (Hernandez et al., 2015; Rozema et al., 2011) and as such was maintained regardless of correction (Figure 16). The small amount of adjustment was similar for all individuals showing that the error was likely due to the assumptions of natural variation

in the power of the crystalline lens, and posterior cornea (Hernandez et al., 2015). The additional adjustment was purely spherical, and the correction was performed for the dominant and non-dominant eyes separately. The magnitude of the correction was determined using optimisation provided by the fsolve function provided by MATLAB (Natick, VA). This function minimized the image displacement from the retina, by varying the power of the lens F_A iteratively according to standard optimisation procedures. For each iteration, ray-tracing estimated the location of the circle of least confusion from the retina. This distance was then minimized to yield the final adjustment (Hernandez et al., 2015). The ray-tracer was a custom astigmatic paraxial ray-tracer written in MATLAB by manuscript co-author Dr Turuwhenua.

Table 16. Represents eye model details for the right eye of a single participant (IC01) and Figure 16 presents the corresponding optical model.

ID	Type	Description	Index	Radius (mm)	Power (D)	Thickness (mm)	Stop
1	Index	Air	1.0000				
2	sphcyl	Spectacle prescription			-5.25/-0.25 x 105		
3	Index	air	1.0000			1200	
4	sphcyl	Optical focal plane correction lens			0.21		
5	Index	Air	1.0000				
6	sphsurf	Anterior cornea		(7.97, 7.89)	47.79/-0.48 x 066		
7	Index	Cornea	1.3771			0.55	
8	sphere	Posterior cornea		6.50	-6.11		
9	Index	Aqueous	1.3374			3.36	
10	sphere	Anterior lens		10.20	8.10		Y
11	Index	Lens	1.4200			3.58	
12	sphere	Posterior lens		-6.00	14.00		
13	Index	vitreous	1.3360			19.01	
14	Img	image					

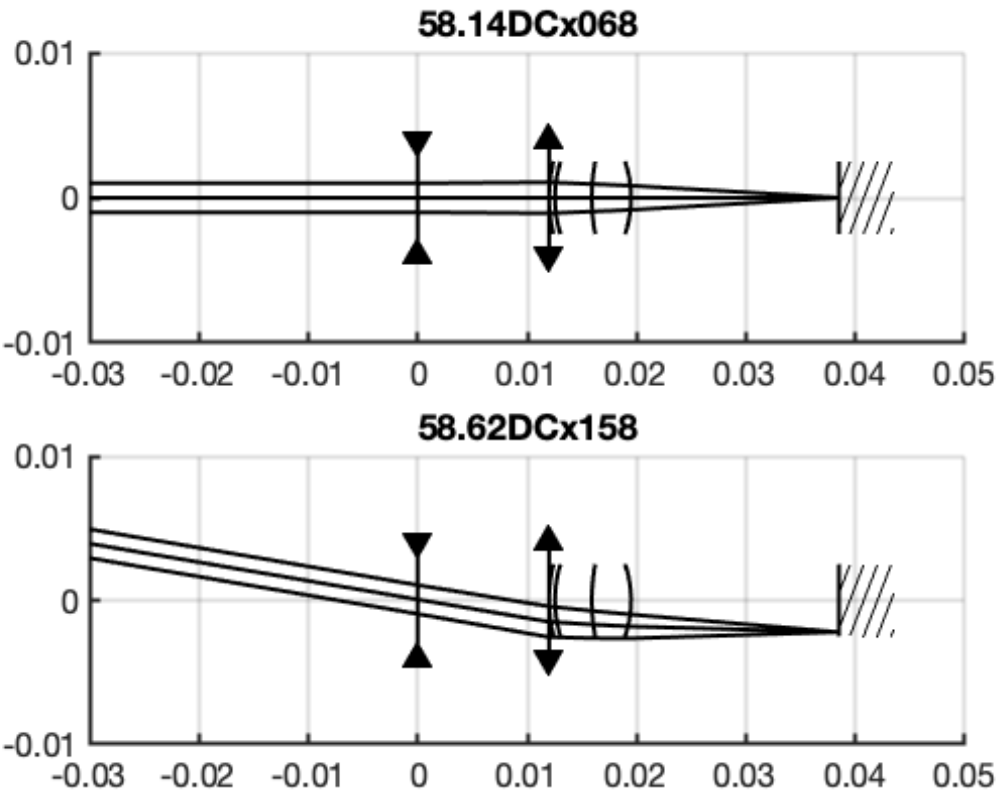


Figure 11. Eye Model for IC01 (OD). Eye model information for the two principal axes (68 degrees and 158 degrees). Inwardly pointed arrows indicate the location of the (negative) spectacle correction (-5.25/-0.25 x 105). Outwardly pointed arrows indicate the location of the adjustment lens (F_A = 0.21D).

4.8.1 Calculation of magnification using basic images (with and without refractive correction).

Eyes were corrected for refractive error for all participants in both groups in Table 15. For each distance corrected eye, the basic or blur free image of an off-axis object point (nominal vertical height was 1m) was determined. This was determined by the ray that passed from the object, through the centre of the aperture stop (as indicated as the anterior lens surface of the model) of the system to the retina. The transverse magnifications were calculated for each participant from the ratio of the object height to image height, $M = h_i/h_o$, for the dominant (M_{dom}) and non-dominant (M_{non}) eyes and also, whether wearing correction or not wearing correction. This provided the percent error in magnification between eyes.

$$M_{\%error} = \left| \frac{M_{non} - M_{dom}}{M_{dom}} \right| \times 100\%$$

The transverse magnifications were calculated for a range of distances over the distance of 0.4 to 3 m to assess whether there was any variation to the estimated magnification as a function of distance. However, results below are only provided for 0.4 m, which is comparable with the distance at which subjective aniseikonia tests are performed.

Tables 17 and 18 present a summary of magnification error (as percent error) between the two eyes for a distance of 0.4m in normal and anisometropic participants. The magnification is presented in two forms: 1) the ratio of total length of the image, and 2) the height of the image along the y-axis only.

Table 17. Summary of Magnifications (distance of 0.4m) Isometropic Control Group

		Mag. Dominant		Mag. Non-Dominant		Y Mag. % Error	
Participant ID	Dominant Eye	Corrected	Uncorrected	Corrected	Uncorrected	Corrected	Uncorrected
IC01	OD	0.0427	0.0460	0.0427	0.0457	-0.0173	0.6866
IC07	OD	0.0417	0.0417	0.0416	0.0416	0.3333	0.2652
IC08	OS	0.0400	0.0401	0.0402	0.0402	-0.4400	-0.0561
IC15	OS	0.0423	0.0426	0.0421	0.0424	0.6021	0.5999
IC20	OD	0.0399	0.0410	0.0400	0.0410	-0.2766	0.0711
IC22_CL*	OS	0.0438	0.0440	0.0430	0.0432	1.6924	1.9319
IC22_no CL*	OS	0.0436	0.0430	0.0428	0.0430	1.7169	1.9492

Table 17 Summary of magnifications for the participants. Minimal magnification difference between the eyes.

Table 18. Summary of Magnifications (distance of 0.4m) Anisometropic Amblyopia Group

		Mag. Dominant		Mag. Non-Dominant		Y Mag. % Error	
Participant ID	Dominant Eye	Corrected	Uncorrected	Corrected	Uncorrected	Corrected	Uncorrected
AA03_CL*	OS	0.0409	0.0407	0.0419	0.0376	-2.5596	7.6834
AA03_UA*	OS	0.0405	0.0405	0.0381	0.0381	5.9356	5.9356
AA05	OD	0.0401	0.0402	0.0375	0.0353	6.3183	12.3075
AA10	OS	0.0438	0.0453	0.0430	0.0414	1.8320	8.5928
AA17	OD	0.0419	0.0416	0.0412	0.0396	1.7159	4.9403
AA19	OD	0.0392	0.0392	0.0378	0.0376	3.5541	4.1799

Table 18 Summary of magnifications for the participants with anisometropia and amblyopia. Shows clinically significant magnification difference between the eyes.

**CL=contact lens, UA= Unaided*

For the Isometropic control group the magnification difference was found to be negligible and clinically significant magnification difference was found in the anisometropic amblyopia group as expected (Table 19). There was no statistically significant difference between the four subjective aniseikonia tests and optical

modelling $\chi^2(0.908)$ p= 0.923 in isometropic control group or the anisometropic amblyopia group $\chi 2(0.408)$ p=0.975 group.

Table 19. Comparing subjectively measured aniseikonia to the magnification percentage predicted by personalised optical modelling

Isometropic Control Group												
Study Group	**Participant Age (Y)**	**LogMAR Acuity**		**Signed Anisometropia (D)***	**SE Refractive Error**		**Method of Refractive correction**	**RT (%)**	**AI3 (%)**	**NAT (%)**	**CAT (%)**	**Optical Modelling with Refractive Correction (%)**
		RVA	LVA									
IC01	31	-0.10	-0.10	0.63	-5.38	-4.75	Habitual Glasses	-0.51	-1.50	-1.00	-0.79	-0.02
IC07	38	0.10	-0.10	0.25	0.00	-0.25	No ref correction	0.01	0.50	0.00	-0.32	0.33
IC08	23	0.10	-0.10	0.13	-0.25	-0.38	No ref correction	0.12	2.56	1.01	0.14	-0.44
IC15	28	-0.10	-0.10	0.00	-0.50	-0.50	Trial frames	0.00	-0.50	0.00	0.09	0.60
IC20	19	-0.20	-0.20	0.00	-2.38	-2.38	Habitual Glasses	0.00	0.50	1.00	-0.92	-0.28
IC22	21	0.00	0.00	0.75	-0.75	-1.50	Contact Lenses	0.00	-0.50	1.01	3.28	1.69
							Mean	**-0.06**	**0.18**	**0.34**	**0.25**	**0.32**
							Std Dev	**0.22**	**1.39**	**0.82**	**1.55**	**0.78**
Anisometropic Amblyopia Group												
Study Group	**Participant Age (Y)**	**LogMAR Acuity**		**Signed Anisometropia (D)***	**SE Refractive Error**		**Method of Refractive correction**	**RT (%)**	**AI3 (%)**	**NAT (%)**	**CAT (%)**	**Optical Modelling with Refractive Correction (%)**
		RVA	LVA									
AA03	52	0.50	0.00	4.88	5.88	1.00	Contact lenses with glasses for reading add	-0.60	-1.48	1.01	0.42	-2.56
AA05	15	-0.10	0.70	5.75	-0.25	5.50	Trial frames	1.79	3.50	3.00	0.05	6.32
AA10	23	0.20	-0.10	4.75	2.50	-2.25	Trial frames	6.82	10.50	6.38	7.05	1.83
AA17	20	-0.20	0.30	2.00	0.50	2.50	Trial frames	4.33	-1.50	0.00	2.39	1.72
AA19	22	-0.10	0.20	2.00	0.00	2.00	Habitual Glasses	-0.50	1.50	2.00	2.06	3.55
							Mean	**2.28**	**3.09**	**3.49**	**2.33**	**2.17**
							Std Dev	**2.87**	**4.65**	**3.50**	**2.41**	**3.23**

Table 19. Summary of measured subjective aniseikonia for each participant in the two groups and the magnification difference between eyes as estimated by the personalised optical model

4.9 Discussion

The personalised optical model described using biometry and refractive data is consistent with subjective amounts of magnification in normal and anisometropic amblyopia participants showing little or no magnification error between the eyes in the isometropic control group and clinically significant magnification error between the two eyes was observed in the anisometropic amblyopia group. The optical model found magnification error decreased from the uncorrected to corrected refractive state. This is consistent with expectations of Knapp's rule, which predicts reduced aniseikonia with spectacle lens correction.

The optical model shows theoretical differences in relative image size between the eyes are present in anisometropic eyes by an average of 2.17% (3.23) which is consistent with the magnification differences measured on subjective aniseikonia tests. Subjective aniseikonia was highest on average in the anisometropic amblyopia 3.12% (2.96) group and lowest in the isometropic control group 0.17% (0.72) and optical modelling estimated an average of 0.32% (0.78) in the isometropic group. On average optical modelling appears to estimate slightly less aniseikonia than that measured subjectively in both groups. This may be due to retinal and cortical adaptations however one would expect the optically modelled amount to be greater than the subjectively measured amount as you would assume the cortical adaptations would attempt to reduce magnification differences to promote binocular cooperation. Nevertheless, this lends support to the theory that optical modelling is a feasible and accurate method of predicting magnification differences between eyes in anisometropic patients.

Predicting refractive outcomes using optical modelling is not a new concept and has been used in myopia control studies to predict myopia from biometric data (Cruickshank & Logan, 2018), however it has only recently been applied to predicting aniseikonia. A recent study by Langenbucher et al. (2021) presented a mathematical concept and calculation scheme to derive lateral magnification in patients undergoing cataract surgery. The optical model required standard biometry data, refractive data, phakometry and anterior segment OCT measurements to predict the final image size difference. Although they present a robust calculation scheme, accurate measurements of all these elements would be difficult to obtain in pre-school children, where aniseikonia assessment and correction may have the most beneficial impact. The optical

model described here utilises biometric and refractive data only to predict relative magnification, with assumptions made around the crystalline lens surface powers in the absence of phakometric data. This makes it a more convenient application for use in children where multiple accurate measurements may be difficult. Our model also has the capability to account for astigmatism (not used in this study), which has not been addressed by other models previously. Further validation of the method is required with larger samples of normative data with subsequent known amounts of aniseikonia induced using size lenses and comparing this to the predicted magnification difference from the optical model. The method also needs to be applied to a younger cohort to see if age related lens changes would require an adjustment to be made to the assumed refractive index of the lens.

Optical modelling can provide a more accurate patient specific prediction of percentage magnification rather than an estimate based on empirical calculations. However optical modelling is still inferior to subjective measurements, which accounts for retinal and cortical adaptations. Given that subject measurements are difficult in young children, this would be a more accurate estimation method to determine optimum shape and power factors to be accounted for in the design of an aniseikonia correction lens, thus reducing aniseikonia and promoting binocularity.

4.10 Overall Conclusion

Aniseikonia is a product of anisometropia, and our findings provide further support as to how interlinked the optics, physiology, and aetiology of anisometropic eyes are in the amount of subjective aniseikonia experienced by an individual. The optical model shows it is possible to predict the magnification differences between eyes in the anisometropic amblyopia group and the isometropic control group. The predicted magnification difference was consistent at a group level with the magnification differences measured using subjective aniseikonia tests. Our findings confirm the importance of understanding the cause of aniseikonia in anisometropia to determine the most appropriate management for each patient. It is important to measure the subjective magnitude of aniseikonia and to consider the underlying cause(s) of aniseikonia to ensure that management and interventions are the most appropriate for each individual patient.

Chapter 5

Development of a Spectacle Wear Monitor System: SpecsOn Monitor

Spectacle adherence is correlated with visual improvements during optical treatment of amblyopia. Chapter 4 has provided new evidence that aniseikonia is a product of anisometropia but when it comes to testing the main research question an objective method of monitoring spectacle wear adherence is required to determine whether the visual acuity and binocular function outcomes are related to spectacle adherence.

This chapter contains a manuscript submitted to the journal 'Translational Vision Science & Technology' and was published as *"Development of a Spectacle Wear Monitor System: SpecsOn Monitor"*. Authors: Jayshree South, Paul Roberts, Tina Gao, Joanna Black and Andrew Collins, 2021, volume 10, issue 12, pages 11. Thesis author Jayshree South contributed to concept and design of the SpecsOn monitor, led study design, collected data, contributed to data analysis and prepared the manuscript.

5.1 Introduction

A common challenge when prescribing spectacles for children in conditions such as amblyopia (decreased acuity in the absence of pathology) is poor spectacle adherence (compliance) to prescribed wear time. Approximately 69% to 80% of children with amblyopia have refractive error in at least one eye (PEDIG, 2002; Polling et al., 2012; Robaei et al., 2006; Sapkota et al., 2013). Adherence to full-time spectacle wear is essential for optimal outcomes from the optical treatment phase and can affect the commencement of additional and adjunct treatment (Cotter et al., 2012; Cotter et al., 2006; Moseley et al., 2002; Stewart et al, 2004).

In current clinical settings, adherence to spectacle wear is only assessed indirectly and subjectively via parental reporting (Drews-Botsch et al., 2016; Fielder et al., 1995) which is generally expected to overestimate adherence. Medical non-adherence, also found in other aspects of prescribed medical interventions, imposes a considerable

financial burden upon health care systems (Osterberg & Blaschke, 2005; Vermeire et al., 2001). Current amblyopia research shows a wide variability in adherence to occlusion therapy (Awan et al., 2005; Loudon et al., 2006; Stewart et al., 2017; Wallace et al., 2013). Adherence to spectacle wear also displays a similar range of inter-individual variability with a potential dose-response relationship with visual improvements directly correlated to hours of spectacle wear (Maconachie et al., 2016). If first-line optical treatment is made more effective, then this strategy would decrease the number of children needing patching and atropine treatments, shortening treatment time, decreasing treatment burden, and be a substantial cost saving to health systems.

A review of the literature reveals few existing objective spectacle adherence monitors. Monitors described were often modified from their original purpose such as thermal sensors designed for monitoring transportation temperatures of foods or laboratory materials (Lentsch et al., 2018), detecting wear of orthodontic appliances, (Januschowski et al., 2013) and monitoring the wear of eye patches (occlusion dose monitors) (Fielder et al., 1995; Maconachie et al., 2016; Simonsz et al., 1999). Early iterations of research-purposed sensors were large bulky devices that were not aesthetically pleasing (Fielder et al., 1995; Simonsz et al., 1999), and were shown to negatively impact adherence in children (Horwood, 1998). Battery life and data storage were also limited, and data evaluation described as “laborious” (Fronius et al., 2006). Newer sensors like the SmartButton data logger (Lentsch et al., 2018) and the TheraMon orthodontic microsensor (Januschowski et al., 2013) are two systems that have been re-purposed to monitor adherence with spectacle wear as these devices are smaller and lighter than previous devices. These sensors take continuous temperature measurements, where a significant change in temperature is used to determine whether the spectacles are on or off. These devices have, however, only been tested on an adult population (Januschowski et al., 2013; Lentsch et al., 2018). The positioning of the sensors at the end of the spectacle arm behind the ear makes the monitors more discreet. However, in a pre-school population where amblyopia treatment is often initiated, they are a potential swallowing or choking hazard given that children are prone to chew on the end of the spectacle arm where the sensor is placed. Temperature sensors are known to have a higher rate of false positive readings if held in the hand, in a pocket, or placed in a warm environment (Fronius et al., 2006) such as a car parked outside (Lentsch et al., 2018). Sensors like the SmartButton and TheraMon which measure a single

temperature are also more susceptible to error-inducing manipulations and false readings.

Liquid crystal, “shutter glasses”, offer an alternate approach to amblyopia treatment. A new electronic frame designed to be used with the shutter glasses contains a combination of temperature and capacitive sensors and can detect wear time and occlusion time and measure the state of wear position (Januschowski et al., 2021). However, to date this remains a proof-of-concept design. With recent technological advancements in myopia research, a number of wearable devices have been developed to provide real time objective measures of light intensity, physical activities and distance to reading material through use of light, gyroscopic, acceleration and infrared sensors (Pajic et al., 2020; Wen et al., 2019). These sophisticated multifunctional devices are designed to fit a variety of frames but again are not designed to specifically measure spectacle adherence. The devices require regular recharging, posing a burden on parents to remember to recharge the device which risks lost data. In addition, the devices are not designed from a safety perspective for a younger population. These devices are also expensive.

The aim of this study was to custom design and pilot test a removable device (integrating sensors, microprocessor, data storage and energy source) that accurately and objectively monitors spectacle wear in an adult cohort to provide validation before use in a preschool population. Although spectacle wear behaviour is not different between adults and children, the pilot study recruited adult participants to prove the design concept and to ensure data recorded could reliably be compared with diary entries. The SpecsOn device can also be applied to a wide range of other clinical and research applications in the treatment of childhood vision conditions that require spectacle treatment such as myopia, hyperopia and accommodative esotropia.

5.2 Methods

5.2.1 System Design

We required an accurate monitoring system that was compact, would attach securely to most frames, and was safe, following medical device safety guidelines for children (Medsafe NZ and European standards (International Organization for Standardization (2011); International Organization for Standardization (2012); British Standards

Institution (2006); International Standardization Organization (2016); Standards New Zealand (2019)) guidelines). Data collected needed to be stored on-device for at least six weeks, the typical clinical follow-up period for amblyopia therapies, so an adequate power supply was also required.

During the design phase we considered several types of sensors such as mechanical, proximity, magnetometer, accelerometers, and other biosensors such as pulse oxygen monitors. However, these were either susceptible to false positive readings, require intensive computation to determine motion, or were difficult to implement physically. For greater accuracy we initially created a prototype using a touch-sensitive capacitive sensor (similar to smartphone screens) embedded in the nose pad of the spectacle frame. The nose pad position was chosen because it would likely generate the least number of false positives compared with placing elsewhere on the frame. The electronic components were to be discreetly housed internally in a three-dimensional printed side arm of the spectacle frame (see Figure 17). However, after initial testing of the capacitive sensor prototype, several factors made us rethink this approach. The capacitive sensor in the nose pad design required the frame to be a part of the circuitry connecting the sensor to the processer. This factor meant the device could only be used with metal frames or if conductive material was incorporated into plastic frames. This did not fulfil our requirement for the device to be easily adaptable to a wide variety of frames, because the design required side arms to be three-dimensionally printed individually.

17A. Electronics board for a capacitive sensor 17B. Side arm housing for the electronics board

Figure 12. Computer Aided Designs for a capacitive sensor system

The final version, the SpecsOn monitor, is externally mounted under the arm of the spectacles (Figure 18) using a detector incorporating two temperature sensors with 0.02°C resolution and 0.5°C accuracy (MLX90615, Melexis NV, Leper, Belgium). One sensor, directed at the wearer's temple, measures skin temperature using an infrared detector, the other measuring the device's temperature as an estimate of the ambient temperature.

Temperature measurements are taken at 1-minute intervals for phase one testing and 5-minute intervals for phase two testing and written to non-volatile memory with 12 weeks of storage capacity. The device is battery powered with a capacity for 15 weeks recording. Analysis of the two temperature measures can determine if the spectacles are being worn. These components are safely enclosed in a water-resistant skin-safe silicone casing which allows the monitor to fit most spectacle frames. Data is downloaded from memory via a physical connector and a USB interface unit and interpreted via custom analysis software.

Figure 13. SpecsOn monitor attached to the side arm of the spectacle frame.

5.2.2 Participants

This study was approved by the University of Auckland Human Participants Ethics Committee (Reference number 023301) and adhered to the principles of the Declaration of Helsinki. Adult participants for both phases were recruited from the students and staff at the University of Auckland School of Optometry and Vision Science. All participants in both phases were self-reported to be free of eye disease and written informed consent was obtained from all participants.

5.2.2.1 *Phase One: Laboratory based*

Adult participants who wore contact lenses or were non/part-time spectacle wears were asked to sit and watch a short movie or continue with their normal computer-based tasks for 60 minutes (in the laboratory or an office setting) while wearing a pair of study frames with the SpecsOn monitor attached. In this phase the temperature measurements were taken at 1-minute intervals. A researcher remained in the room and asked the participant to put on or remove the study spectacles according to a pre-determined schedule and this process was manually recorded by the researcher.

5.2.2.2 *Phase Two: Real World*

Adult participants who habitually wore spectacles full-time or part-time were recruited. The SpecsOn device was attached to the side arm of their spectacles (see Figure 18), and they were asked to wear their spectacles as usual under normal conditions. For one participant this practice happened to include when they travelled to Fiji. The SpecsOn device was adjusted to measure temperature at 5-minute intervals to optimise data storage. Participants were provided with a diary and asked to record when they wore and removed their spectacles over a 7-day period. Participants were also asked to record a general description of activities and environmental conditions each day and where spectacles were stored when not worn, in order to compare the effects of different activities such as exercise, weather conditions such as wind or rain, and any relevant environmental factors like ambient temperature.

5.3 Data Analysis

Data were downloaded from the device's memory via a USB interface and saved to a computer using custom software created with LabVIEW 2013 (National Instruments, Austin, TX, USA). Wear times were identified from the temperature differential between the skin and the device sensors and compared with the manual log kept by participants. To confirm whether the SpecsOn monitor had accurately captured the spectacle-wear in phase one, a custom program (MATLAB R2018b, MathWorks Inc, Natick, MA) was used to calculate wear time and compare against the researcher's manual records of when the spectacles were put on or removed. Spectacles were considered on if the skin temperature was 4°C greater than the device temperature. Data from the temperature sensors were distributed normally.

For the analysis of phase two data, the calculation method was changed to a threshold technique to improve correlation between actual and calculated wear times and to account for changes in ambient temperature during day-to-day activities. The threshold, Equation 1, was determined after plotting the temperature differential against ambient temperature for all participants. An example of this data is shown in Figure 19. Data above the threshold represented intervals when spectacles were identified as being worn, those below represented when the spectacles were off. Microsoft Excel was used to perform this analysis and compare data from manual logs to verify correct wear times for each participant.

Equation 1.

$$\Delta t > \left((-0.21 \times Ambient\ Temperature) + 7\right) = \text{Spectacles On}$$

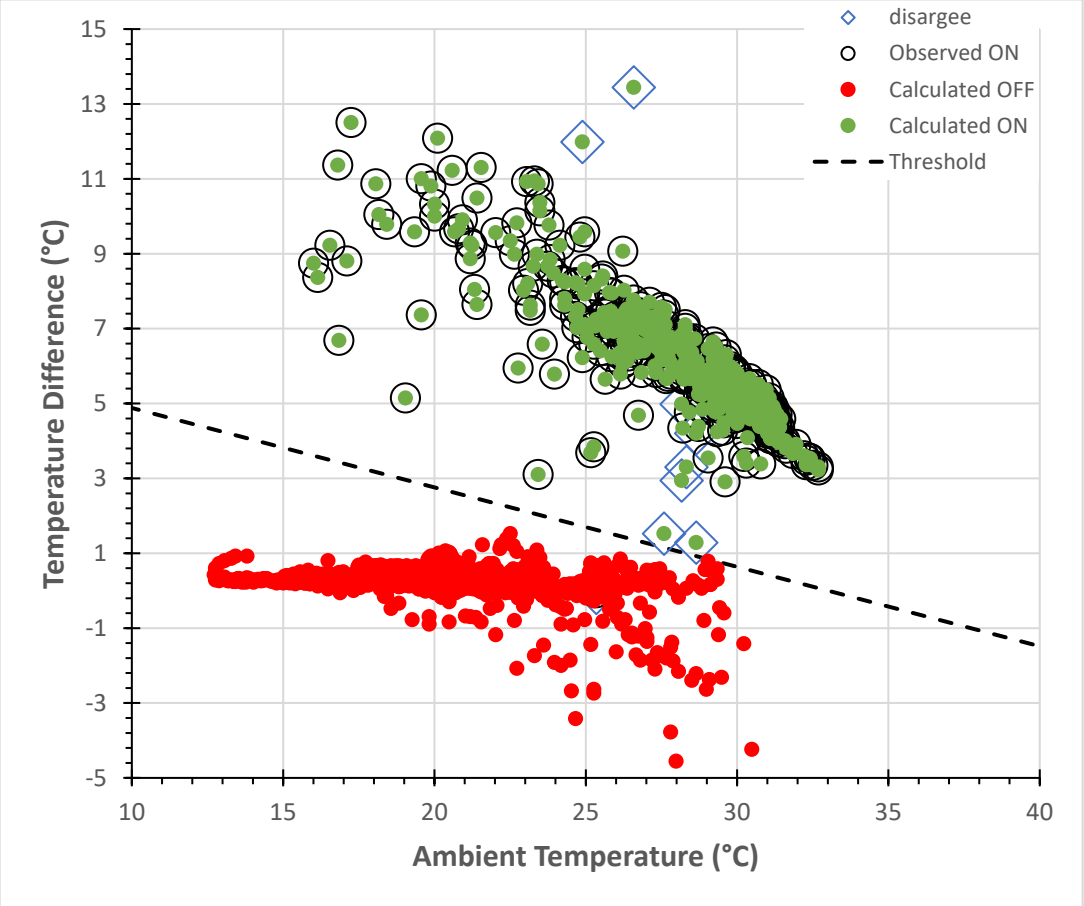


Figure 14. Sample of the threshold analysis plot from participant JS1 in phase 2. Shows good agreement, between the manual logs (observed ON) and the calculated wear time (calculated ON).

5.4 Results

All participants in phase one (n=10) and in phase two (n=5) completed data collection. The results from both phases show good agreement between the threshold temperature differential method and the manual logged wear times.

5.4.1 Phase One results

The mean wear time temperature from the skin sensor was 33.6 ±0.75 °C and from the device sensor was 26.3 ±1.05 °C for phase one testing. The mean temperature differential between the two sensors during wear was 7.2 ±1.59 °C across all 10 participants. Wear time was calculated based on a temperature differential of greater than 4°C difference between the skin and the device temperature (Figure 20). Good agreement between the manual logs and the calculated wear time shows the SpecsOn device was accurately measuring spectacle wear time.

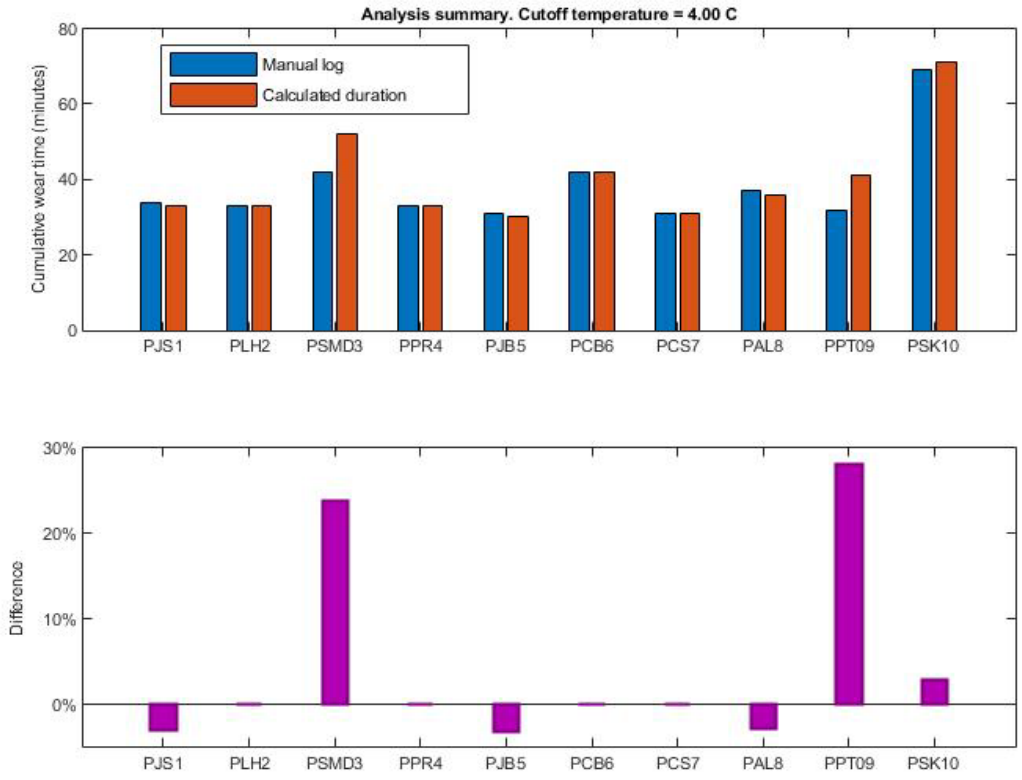


Figure 15. Good agreement using a 4°C differential between skin and device temperature and the manually recorded log to calculate wear time.

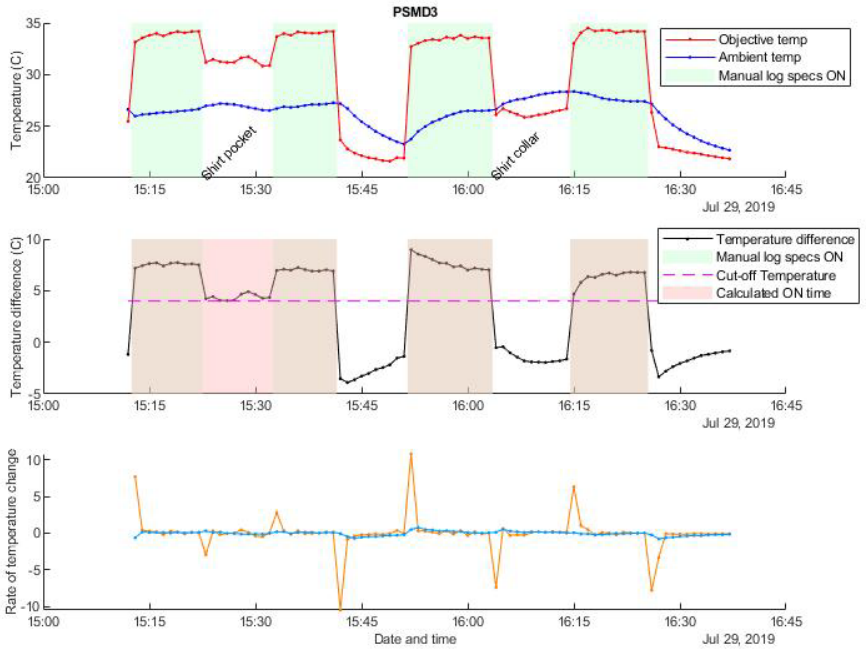


Figure 21A. Participant PSMD03

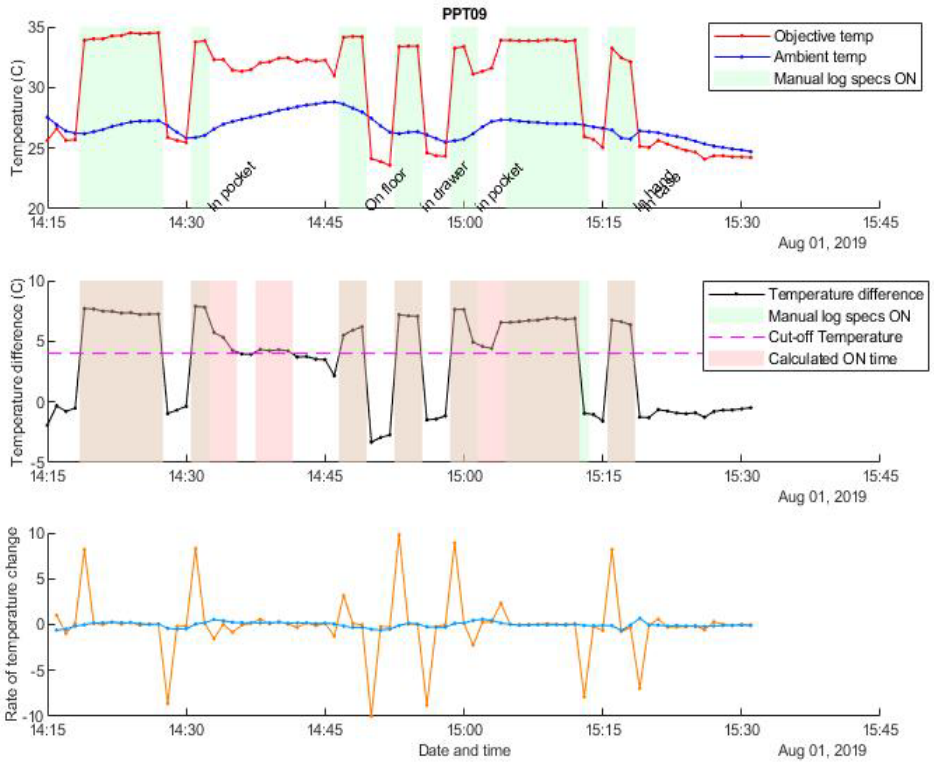


Figure 21B. Participant PPT09

Figure 16. False positive error for participants' **A** PSMD3 and **B** PPT09 calculated wear time from spectacles being placed in shirt pockets

Two participants (PSMD3 and PPT09) had a higher percentage difference between the calculated wear time and the manually recorded logs (Figure 20). These participants were asked to place the spectacles in shirt pockets during phase one testing to see if this common behaviour would generate a false positive error. The temperature differential decreased slightly when the spectacles were placed in the pockets, and it was more difficult to determine a calculated wear time based on the 4°C differential (Figure 20). However, on closer examination of the data it was clear to see where the temperature of the skin sensor fell slightly as the spectacles were removed and placed into the pocket. The time the spectacles were kept in the pocket also recorded a lower skin temperature that was distinguishable from when they were being worn on the face (Figure 21).

5.4.2 Phase Two Results

During phase two the devices were subject to a wider range of environmental conditions and routine spectacle wear behaviours to determine further potential sources of errors. Extreme activities such as placing the spectacles close to a fireplace for 30 minutes where the skin temp ranged from 25.9°C to 45.0°C and the device temp ranged from 24.6°C to 26.6°C, or putting the spectacles in the fridge for 20 minutes where the skin temp range was 6.1°C to 10.3°C and the device temp range was 8.9°C to 20.6°C did not cause a false positive error. Other common spectacle wear behaviours such as placing spectacles in a shirt, jacket, or trouser pocket, being hung off a shirt collar and spectacles folded and held in the hand (with a hand near the sensor) did not cause false positive errors. Placing spectacles on the forehead or on top of the head did result in "Calculated ON" errors which are shown as the "Disagree" points in Figure 19. However, looking closely at the raw data (Table 20) a significant decrease in the temperature differential from 7.8°C to 2.9°C is evident and this lower differential was maintained whilst the spectacles were placed on top of the head (2.9°C, 3.3°C and 4.2°C) before rapidly decreasing once the spectacles were removed. Even, in warmer climates (Fiji,18°C - 37°C as opposed to New Zealand,12°C - 35°C) the device was able to accurately detect spectacle wear (see Appendix 1) but wear time was difficult to calculate based on the 4°C temperature differential cut off. Therefore, a threshold analysis, as described elsewhere in this article, was used to improve accuracy in warmer ambient temperatures. Overall, there was 99% agreement between the calculated wear time based on the threshold temperature differential and the detailed manual logs for all five participants (Table 21).

Table 20. Sample Log showing a decrease in the differential temperature when the spectacles were moved to be placed on top of the head

Skin Temperature	Device Temperature	Temperature Differential	Diary On/Off	Observed On/Off	Calculated On/Off
31.85	22.51	9.34	On	On	On
34.35	26.59	7.76	On	On	On
31.11	28.17	2.94	Off on head	Off	On
31.63	28.33	3.3	Off on head	Off	On
32.85	28.65	4.2	Off on head	Off	On
23.43	27.99	-4.56	Took off	Off	Off
22.63	24.49	-1.86	Off	Off	Off
22.53	22.95	-0.42	Off	Off	Off

Table 21. Success rate for detecting overall spectacle wear using the SpecsOn monitor

Participants	Calc ON (h)	Calc OFF (h)	Calc total h (Calc ON + Calc OFF)	Logged Total (h)	Disagree (h)	Agreement between Calculated and Logged (%)
PR	51.5	357.7	409.2	409.2	2.0	99.51
JSNZ	39.3	393.3	432.6	439.2	2.2	99.50
AC	54.7	97.6	152.3	167.0	1.0	99.34
TG	80.3	107.8	188.0	187.9	0.3	99.82
JB	87.2	122.6	209.8	209.2	1.1	99.48
JSFJ*	2.8	217.8	220.6	221.8	1.3	99.40

** Data from Fiji for participant JSFJ*

5.5 Discussion

Strong agreement between reported wear time and calculated wear time determined by a temperature differential threshold shows the SpecsOn monitor is 99% accurate in monitoring spectacle wear in an adult cohort during a variety of routine activities and ambient temperatures. The device was comfortable, secure, and unobtrusive to wear and easily fitted to a variety of frame styles. Data were easily downloaded via a USB interface unit and interpreted into clinically useful data such as total wear time.

The final version of the SpecsOn monitor included two temperature sensors, one located internally within the silicone packaging to estimate the ambient temperature and an

externally facing infra-red temperature sensor to measure skin temperature of the wearer's temple. This version was revised from our original concept based on capacitive sensing, which was initially considered to be advantageous over temperature sensing because capacitive sensors would only detect wear when in direct contact with skin. However, the high noise susceptibility of the small capacitive sensors, complexities integrating suitable sensor pads and the cost in producing an effective system (including 3-dimensional printed side arms to house components for a variety of frames) made us rethink our approach.

Skin contact temperature sensors have previously been used in studies to measure spectacle wear with varying success (Januschowski et al., 2013; Lentsch et al., 2018; Maconachie et al., 2016). The SmartButton temperature datalogger is one such device which was found to have an 80% success rate in detecting overall spectacle wear in adults (Lentsch et al., 2018). However, without a matching participant log it was difficult to confirm wear time patterns. Sensor loss owing to double sided adhesive failure and skin irritation from the silicone mounting against the skin were the main reasons for failure to collect data in that study. The Glasses Dose Monitor is another system that had been adapted from the coin sized Occlusion Dose Monitor first described by Simonsz et al. (1999). It is composed of two thermistors that measure the temperature difference between the front and the back of the sensor. A very small difference threshold of 0.3°C was used to indicate when the spectacles were being worn. Only 83% of the monitors in that study were successful in collecting data and again the main cause of failure was detachment and loss of the monitor. This presents a potential health and safety hazard because small detachable parts pose an ingestion or inhalation hazard (Standards New Zealand, 2019) to the pre-school population for whom amblyopia treatment is commenced routinely. With 99% detection, the SpecsOn monitor is a considerably more accurate system for detecting overall spectacle wear. The skin safe silicone casing of the SpecsOn monitor securely adheres the monitor to the arm of the spectacle frames making it significantly safer for use with the intended paediatric population.

Single temperature sensors used in previous studies have resulted in high false positive rates when the ambient temperature has exceeded 33°C (Januschowski et al., 2013) or 37°C (Lentsch et al., 2018). The advantage of the infrared sensor used in this study is that it only measures the temperature of the object that it is directed at (skin); a second

sensor is included which accounts for the effects of ambient temperature changes. Even in a warmer ambient environment (Fiji), the SpecsOn monitor was able to detect wear using the temperature differential between the skin and the device temperature sensors and appropriate threshold analysis (see Appendix 1). The SpecsOn monitor was tested in ambient temperatures from 12°C to 37°C. It is possible for false negative results to arise if the ambient temperature becomes hot enough to reach skin temperature, but this has not occurred in the temperate climate where this study was conducted.

The context sensitive smart spectacles (Januschowski et al., 2021) device is an electronic spectacle frame incorporating a combination of temperature and capacitive sensors. These sensors detect the position of liquid crystal shutter-glasses, used as an alternative to amblyopia treatment. They also detect when spectacles are removed and incorporate recognition of activities such as walking, sitting, and jumping, and so on. A small pilot study of this sophisticated design found a 91.4% agreement in detecting the correct position of spectacles when worn and a 100% agreement in detecting when the spectacles were taken off. The main aim of these spectacles is to monitor adherence to an alternative method of occlusion therapy in amblyopia. It could be adapted to monitoring adherence during the refractive adaption phase however the production of these electronic frames is still in the concept phase and likely to be expensive and difficult to accommodate different spectacle frames. Two very recent wearable objective measuring devices have become available. The Clouclip (Cao et al., 2020; Wen et al.) objectively measures near-work distance and duration in the investigation and prevention of myopia progression. It provides vibration alerts if the near-work activity is too close or if the duration of near work exceeds acceptable time limits. It incorporates a triaxial accelerometer that differentiates between wear and not wear states. However, the device cannot measure duration of wear alone and the accelerometer goes into sleep mode after 40 seconds if no change is detected. Therefore, it would be difficult to know if spectacles were being worn if a child were to be lying down and watching television or sitting still while engrossed in an activity. The Clouclip is a rechargeable device and is not too dissimilar in size to the SpecsOn monitor. However, the total battery life and time required to fully charge the device is not stated in the reporting literature (Cao et al., 2020; Wen et al.). Having a rechargeable battery places a burden on parents to remember to recharge the device. An exposed recharge port also means the device is not water resistant, which would not be ideal for a preschool population. The Vivior (Pajic et al.,

2020) is another recently developed device for measuring visual behaviour in adult patients undergoing cataract and refractive lens exchange surgery to improve treatment outcomes. This device however is designed to be used short term and only has a recording capacity of 16 hours which would not be ideal for amblyopia treatment monitoring. The device requires regular recharging and is also heavier at 14 grams, than the Clouclip and the SpecsOn devices which could affect comfort and the positioning of a child's frame. The advantage of the SpecsOn device is that it is powered by primary batteries for a duration of 15 weeks. Even though routine follow-up visits during amblyopia therapy typically occur at 6-week intervals, visits may be delayed or missed, risking lost data. A 15-week battery life allows the monitoring device to capture data for the full duration of the optical treatment phase, at least 12 weeks. Having the SpecsOn device will not necessarily change the review interval because the review time is based on the expected progression of visual acuity during optical treatment. The SpecsOn monitor is specifically designed for monitoring spectacle adherence. It is relatively compact in comparison with existing available options, more adaptable to a variety of frames and easier to produce. We are currently using the SpecsOn monitor in a clinical trial for preschool aged children. (MAGNIFY study ACTRN12620000061932). We hypothesise that temperature monitoring will accurately measure spectacle adherence in pre-school aged children.

The current design uses a USB interface to download the data but there is potential to use a Bluetooth (wireless) connection and a mobile device app in the future. The clinically relevant data from the SpecsOn monitor are easily retrieved and analysed. The data can be explored to review wear patterns such as overall adherence rate during waking hours, average weekly and daily wear times, through to the portion of each hour during a day that the spectacles are worn. This analysis allows accurate wear patterns to be determined and answer such questions as whether the participants only wore their spectacles at school.

One of the limitations of this study is that the SpecsOn monitor is larger than conceptualised and although it is small and discreet on an adult size frame, it may be more obvious on a child size frame. The final dimensions of the device were mainly due to limitations in decreasing the size of the hardware and components whilst maintaining sufficient battery capacity. We chose to use primary batteries instead of rechargeable,

because we felt expecting participants and parents to be responsible for recharging would be an extra burden, and risk missing recording data owing to flat batteries. A further size consideration was ensuring, in the unlikely event the participant removed the device from the spectacle frame, that the device's overall size complied with choke hazard standards for toys (Standards New Zealand, 2019). The SpecsOn monitor casing is made of medical grade silicone and is designed to sit far enough forward on the side arm, close to the hinge, to prevent it from touching the side of the face and causing irritation. The positioning and the size of the monitor may make it cosmetically unappealing to some. To overcome this factor, we plan to colour the silicone casing and allow participants to choose a colour to match the frame, making it more discreet. There is also an option to emboss patterns on to the silicone casing to make it more child friendly.

5.6 Conclusion

Spectacle adherence is correlated with visual improvements during optical treatment of amblyopia. The SpecsOn monitor offers a convenient, accurate and reliable system that does not require recharging to monitor spectacle adherence in children for the full duration of the optical treatment phase. This provides researchers with the tools to investigate factors influencing optical treatment such as adherence, wear patterns and the duration the refractive correction has been worn which could influence treatment outcomes and provide information in relation to timings of adjunct therapies. There is also a wide range of other clinical applications possible for this system in the treatment of childhood vision conditions that require spectacle treatment, such as accommodative esotropia, hyperopia, or myopia.

Chapter 6

Methodology of the MAGNIFY Study: Protocol

Chapters 2 and 4 have presented evidence that aniseikonia represents a potential barrier to neuroplasticity which may limit visual outcomes in children with anisometropic amblyopia. Full correction of refractive error is the first step in standard amblyopia treatment, which corrects for image focus but neglects image size differences. Could correcting aniseikonia at first diagnosis of anisometropia improve visual outcomes?

This Chapter includes a manuscript titled *"Measuring aniseikonia & investigating neuroplasticity and image factors in amblyopia (MAGNIFY): Study protocol for a randomised clinical trial"* Trials **23,** 358 (2022). https://doi.org/10.1186/s13063-022-06159-2 authored by Jayshree South, Tina Gao, Melinda Calderwood, Jason Turuwhenua, Paul Roberts, Arier Lee, Andrew Collins & Joanna Black. The introduction and objectives have been edited from the published manuscript to optimise the flow of this thesis. The manuscript outlines the methodology of the MAGNIFY study. Thesis author Jayshree South led the study design, protocol development, collected study data and prepared the manuscript.

6.1 Aim

The MAGNIFY study is a prospective double masked randomised clinical trial which aims to investigate the effectiveness of aniseikonia-correcting lenses compared to standard spectacle lenses for treatment of anisometropic amblyopia in children.

The trial protocol was accepted for publication in the Trials Journal in 2022 and this chapter contains the methodology of relating to the results presented in Chapter 7. This Clinical trial was registered with the Australia New Zealand clinical trial registry (ANZCTR) on 24 January 2020 under registration number ACTRN12620000061932. Protocol version 1 was developed on 13 November 2019. Recruitment started January 2020 and is due to be completed by October 2022.

6.2 Objectives and Hypothesis

6.2.1 Research hypothesis

Aniseikonia correction lenses will improve image clarity and reduce the retinal size differences producing better visual acuity and stereoacuity improvements after 15 weeks of optical treatment for children with anisometropia.

6.2.2 Study Objectives:

6.2.2.1 *Primary Objective*

To assess the change in visual acuity of the amblyopic eye from baseline after 15 weeks of wearing spectacle lenses that equalise retinal image size (iseikonic corrections) as well as retinal image clarity in children at first diagnosis of anisometropic amblyopia. We hypothesise that correction of aniseikonia will help binocularity, producing greater visual acuity and stereoacuity improvements after 15 weeks of optical treatment.

6.2.2.2 *Secondary Objectives*

Change from baseline in stereoacuity after 15 weeks of spectacle wear. Improvement in stereoacuity is a key secondary objective as correcting aniseikonia may reduce the binocular mismatch of image size, allowing improved binocular combination and stereopsis

Objective adherence with optical correction will also be assessed. Iseikonic corrections may improve spectacle comfort in those with anisometropia, which may then lead to better spectacle adherence and in turn, better visual outcomes.

6.3 Methods

6.3.1 Study design

The MAGNIFY study is a randomised clinical trial, designed as a superiority study with investigator and participant masking to treatment allocation, investigating the visual acuity and stereoacuity outcomes of incorporating aniseikonic correction (lenses that equalise image size and image clarity) into spectacles for children with anisometropic amblyopia compared to standard lenses which correct for image clarity only. This protocol was developed according to SPIRIT guidelines (Chan et al., 2013)

6.3.2 Setting

Data will be collected at the Optometry Clinic at the School of Optometry and Vision Science, the University of Auckland, Grafton Campus, Auckland, New Zealand.

6.3.3 Participants and Recruitment

Potential participants will be identified through referrals from paediatric ophthalmologists and experienced paediatric optometry clinics which follow the same prescribing guidelines for children. Initial diagnosis of anisometropia will be made following a comprehensive eye examination including binocular function testing and a cycloplegic refraction. Potentially suitable participants/parents/guardians will be given a copy of the participant information sheet by their eye care provider. With consent from the patient/parents/guardians, the eye care provider will send the contact information to a member of the study team who will contact the participant and invite them to a registration visit to assess eligibility. Parents/guardians of potential participants are also able to contact the study team directly and a copy of the participant information sheet will be sent either electronically or by mail, and consent will be sought to contact their eye provider for release of the relevant clinical information. The registration visit will be used for the consenting procedure and for assessing eligibility.

Recruitment began on 27 February 2020 and is scheduled to end 11 October 2022.

6.3.4 Eligibility

The following inclusion criteria exist for this trial:

- Children aged 4 to <8 Years old
- Anisometropia that has not yet been treated by spectacles or occlusion
- Uncorrected visual acuity in the worst eye of 6/12 (0.30 logMAR) or worse, with an interocular difference of 2 lines or more. Sound eye must be 6/7.5 (0.10 logMAR) or better, with an interocular difference of 2 lines or more.
- Anisometropia ≥1.50 DS difference in spherical equivalent (SER) between eyes as determined by cycloplegic refraction
- Astigmatism ≤3.00DC

- No manifest strabismus at near or distance on cover test
- Healthy eyes
- Willing and able to wear spectacles full-time

Exclusion Criteria are

- Myopia exceeding -6.00 DS in spherical equivalent
- Ocular pathology such as a congenital cataract (aphakia/pseudophakia), retinopathy of prematurity, keratoconus
- Previous eye surgery of any kind.
- Any known neurological conditions that could potentially affect vision
- Contact lens wear

6.3.5 Optical Treatment

Optical correction is prescribed based on a cycloplegic refraction that is not more than six months old. The correction will be prescribed using criteria designed by the Paediatric Eye Disease Investigator Group (Chen & Cotter, 2016) and must be as follows: ***Hypermetropia-*** not under-corrected by more than +1.50D spherical equivalent and the reduction in the plus sphere must be identical between the two eyes. ***Anisometropia-*** full correction of the anisometropic difference. ***Astigmatism-*** full cylinder power prescribed. ***Myopia-*** full correction of myopia. If the participant does not have a copy of a recent (<6 months old) cycloplegic refraction from their eye care provider, they will be asked to undergo a comprehensive eye examination including a cycloplegic refraction at the University of Auckland Optometry clinic. This will be used to confirm eligibility prior to being enrolled into the study.

6.3.6 Variable Definitions

6.3.6.1 *Visual Acuity*

Amblyopia impairs a broad range of visual functions in the affected eye including visual acuity (Holmes & Clarke, 2006), contrast sensitivity (Hess & Howell, 1977) and motion perception (Simmers et al., 2003; Thompson et al., 2012). As visual acuity is the gold

standard measure of visual function in clinical settings, a widely-accepted clinical definition of amblyopia is a difference in best corrected visual acuity between the two eyes of 0.20 log units in the presence of an amblyogenic factor and the absence of any ocular or optic nerve pathology (Holmes & Clarke, 2006). The amblyogenic factor of interest in this study is anisometropia of ≥1.50 DS difference in spherical equivalent. Distance visual acuity (VA) measures are collected separately for RE and LE. Distance visual acuity will be measured using the highly standardised HOTV protocol using the EVA system adopted by the Amblyopia Treatment Study group and recorded as logMAR units (Moke et al., 2001).

6.3.6.2 *Stereopsis*

Amblyopia is commonly associated with impaired stereoscopic depth perception under ordinary (binocular) viewing conditions (McKee et al., 2003). Stereopsis will be measured using the clinically well-established Randot Preschool test (Stereo Optical Co. Inc, Chicago, IL, USA) (Birch et al., 2008). Stereopsis will be analysed as a categorical outcome: "Improved" or "Not improved" at each follow-up compared to the baseline visit. The participant's stereopsis threshold is considered to have improved compared to baseline if there is a reduction in $\log_{10}$ (Threshold) value of 0.60 (2-octaves) or more (Adams et al., 2009), or if the participant's result changes from Nil Stereo to a measurable threshold. Stereopsis is considered to have worsened compared to baseline if there is an increase in $\log_{10}$ (Threshold) of 0.60 or more, or if the participant's result changes from a measurable threshold to Nil Stereo.

6.3.6.3 *Subjective aniseikonia*

Aniseikonia is likely to be present in those with anisometropic amblyopia (South et al., 2020; South et al., 2019). The difference in image sizes could potentially hinder binocular vision. Currently, estimations (Berens & Bannon, 1963; Ogle, 1950) or empirical calculations (Davis, 1959; Ryan, 1975) are used due to presumed difficulties in measuring subjective aniseikonia, especially in children. Estimations and empirical calculations however, do not take into account the retinal and cortical adaptations that may occur and therefore accurate measurement of subjective aniseikonia is important to determine the amount of image size difference individually experienced. Subjective aniseikonia is difficult to measure in adults and children, and currently there is no gold standard test available, and no tests are specifically designed for use in children. A

previous study successfully used the Aniseikonia Inspector Version 3 (Kehler et al., 2014) in school-aged children (5 to 13 years old). This current study uses two validated and commercially available tests: the Aniseikonia Inspector Version 3 (Optical Diagnostics, Culemborg, The Netherlands) and the New Aniseikonia (Awaya) Tests (Good-Lite Company, Tokyo, Japan) (Antona et al., 2007). These tests will be used to examine testability in children aged 4-<8 years old in the presence of anisometropic amblyopia.

6.3.6.4 *Spectacle Adherence*

Spectacle adherence is correlated with visual improvements during optical treatment of amblyopia. A wide range of inter-individual variability, with a potential dose-response relationship between visual improvements and hours of spectacle wear, have been previously shown (Maconachie et al., 2016). Currently, adherence with spectacle wear is only assessed indirectly and subjectively via parental reporting (Drews-Botsch et al., 2016; Fielder et al., 1995), which is generally expected to overestimate adherence. This study will include an optional custom-built objective monitoring device (SpecsOn monitor) (South et al., 2021) to monitor spectacle adherence alongside a daily spectacle wear diary for the first five weeks. Optional additional consent for the SpecsOn monitor will be provided on the consent form at the enrolment visit. The SpecsOn monitor is a small device externally mounted on the spectacle arm and incorporates two temperature sensors. One sensor, directed at the wearer's temple, measures skin temperature using an infrared detector, the other sensor measures the device's temperature as an estimate of the ambient temperature. Temperature measurements are taken at 5-minute intervals and written to non-volatile memory. Comparisons of the two temperature measurements can be used to determine if spectacles are being worn. The SpecsOn device will be removed after a minimum of five weeks and the glasses wear diary will be continued for the full 15-week duration. As not all participants will opt to wear the SpecsOn monitor, the glasses wear diary will be the main source for adherence monitoring data. Spectacle wear compliance will be based on the total time the participants wore their glasses as recorded in the participants daily wear diary. Diary recording will be encouraged at every study visit.

A participant is considered compliant if they have worn their glasses for ≥75% of their awake time. Awake time is estimated by parents and recorded at the registration visit.

6.3.7 Registration & Enrolment Visit

The registration visit will be used to screen, assess eligibility and enrol participants that meet the eligibility criteria. Demographic data, ocular and medical health history, and biometry using the LenStar LS 900 will be taken. Biometry data will be used to determine the basis of anisometropia. Optical Coherence Topography Scans of the macular (3D macula: 7x7mm) and retinal nerve fibre layer (3D Optic Disc 6x6mm scan) will be taken using the DRI Triton Optical Coherence Topographer to confirm eye health. Cover testing is performed at near and distance to screen for strabismus, but visual acuity, fusional vergence/peripheral fusion, ocular motility, and stereopsis will only be assessed if this information is not available from the referrer. Eligible participants will then be randomly allocated to either the control or the treatment group.

6.3.8 Randomisation

Participants will be randomised to the control standard lenses group or treatment aniseikonia-correcting lenses group after they are confirmed to be eligible for the trial and have consented to take part. Allocation to each group will at a 1:1 ratio using a computer-generated randomisation schedule (Dallal, 2020) by an unmasked study member. The schedule was generated using randomised permuted blocks with fixed block sizes. The block sizes will not be disclosed to ensure concealment. Unmasked study staff will perform spectacle dispensing to ensure correct fitting and make all spectacle adjustments required at data collection visits.

6.3.9 Appointment Schedule

6.3.9.1 *Baseline Visit*

The Baseline visit is when participants collect their new spectacles. This visit contains the first aided visual acuity and binocular function assessment. A minimum of 15 minutes of adaptation time to the new spectacles will be given before vision testing is commenced. To allow adaptation time, testing is to be carried out in the following order:

1. Dispensing and spectacles fitting by unmasked examiner
2. Parent and child to complete PedEyeQ questionnaire
3. Spectacle adherence diary given and explained

4. Distance Visual acuity test using the EVA tester
5. Cover test with refractive correction in place at 33cm and 6m
6. Cover test without refractive correction at 33cm and 6m
7. Ocular motility
8. Horizontal fusional vergence range test using prism fusion range at 33cm and 6m.

   If horizontal fusional vergence range testing is not possible then peripheral fusion will be assessed using the 20Δ base out test in front of either eye. If a 20Δ prism is not overcome then a 10Δ base out prism will be used.
9. Vertical fusional vergence range test using the prism fusion range at 6m
10. Stereopsis using the Randot Preschool stereotest
11. Aniseikonia Inspector V3
12. The New Aniseikonia Test (Awaya)

The PedEyeQ questionnaire will be used to assess functional vision and eye-related quality of life (ER-QOL) in children and their parents (Leske et al., 2019). Following the baseline visit, participants will be asked to wear their spectacles full-time until they have completed 15 weeks of spectacle wear.

6.3.9.2 *5-weeks, 10-weeks, and 15-weeks Follow-up Visits*

Participants will be required to attend three 20-minute follow-up visits, at 5, 10, and 15 weeks from baseline. At each follow-up visit, a research orthoptist masked to the child's treatment allocation will assess visual acuity, stereopsis, ocular alignment, near point of convergence, horizontal fusional vergence range or 20Δ base out test for peripheral fusion, bifoveal fixation using the 4Δ base out reflex test, and visuoscopy. Subjective aniseikonia will be reassessed at the 15-week follow-up visit only. Adherence with spectacle wear will be monitored by completing a daily spectacle wear diary which will be checked and encouraged at each follow-up visit. Objective monitoring with the SpecsOn spectacle-mounted adherence monitor will be removed after a minimum of 5 weeks. However, if participants are willing, this may be extended to 10 weeks.

6.4 Intervention

Participants are allocated to one of two groups, either the Control Group (standard spectacles) with lenses that correct only refractive error, or the Treatment Group (iseikonic spectacles) where lenses incorporate aniseikonia correction as well as refractive correction. Participants will be provided with spectacles at no cost to them for full-time wear for 15 weeks and will be able to keep these spectacles after study participation. Aniseikonia correction will be provided using SHAW lenses (Canada) (https://shawlens.com) through the local Australasia distributor, CR Surfacing labs. Standard amblyopia Shaw lens ordering procedures will be followed. The Shaw lens design software uses ray tracing algorithms to optimise the base curve to reduce aniseikonia.

The software uses either a static magnification value obtained from size lenses measurements or limits of vertical and horizontal fusion measured by vergence reserves to optimise the lens design for each individual. The software also uses the face form angle, bridge vertex and axial length in order to establish the expected location of the centre of rotation relative to the spectacle lens position. Based upon the resulting model, the software identifies the optimal base curvature, centre thickness, index of refraction and progressive lens geometry to correct the aniseikonia and reduce the induced anisophoria associated with anisometropia and face form angle (https://shawlens.com). For the MAGNIFY study the limits of vertical and horizontal fusion will be used to design the SHAW lens where possible. However, as the majority of children will be between the ages of 4 and 5 years, a quantitative measurement of vergence reserves may not possible. In this instance the refractive error and face form measurements will be sent to SHAW lens to design lenses which provide 0% magnification difference in the horizontal meridian. This provides equal images sizes at a retinal level allowing for binocular fusion.

Iseikonic lenses are sometimes used in optometry practices in New Zealand and overseas for optical correction in children and adults with anisometropia to help reduce visual discomfort and aid in adaptation. The optional objective spectacle monitoring device (South et al., 2021) will be fitted to the spectacle frames and parents of all participants will be asked to complete a daily spectacle wear diary to monitor adherence.

6.4.1 Intervention modifications and adherence

Asthenopia can result from adaptation to new lenses and may initially cause some discomfort, but this should improve within the first few weeks and persistence with the spectacles will be encouraged. Adherence to spectacles will objectively be monitored for the first five weeks but participants will fill out a daily spectacle wear diary for the full 15-weeks where they will be required to record times when spectacles were removed, the duration without spectacles and the activities that required them to remove the spectacles. Diary entries will be checked and encouraged at all follow-up visits. No other concomitant therapy for amblyopia or alternative refractive correction is allowed for the full 15-week period.

6.5 Masking

The clinical examiner, participants and their parents will remain masked to treatment allocation throughout the whole study. Personnel involved in recruitment, data collection (assessing the outcomes) and those involved with data entry, data cleaning, and analysing the results will also be masked until the code is broken after data lock. Masked clinical examiners may be able to identify treatment allocation if they look closely at the spectacles. Therefore, masked clinical examiners will not handle the spectacles at all. Any adjustments required to the frames or assessment of repairs will be performed by unmasked study staff, who do not conduct any clinical examinations. Participants and parents/caregivers attending visits will also be instructed that the masked clinical examiner will not be able to answer any questions about their lenses. Participants will be informed about their group allocation by letter/report once all data has been collected and analysed.

6.6 Study Schedule

The study schedule is summarised in Figure 22.

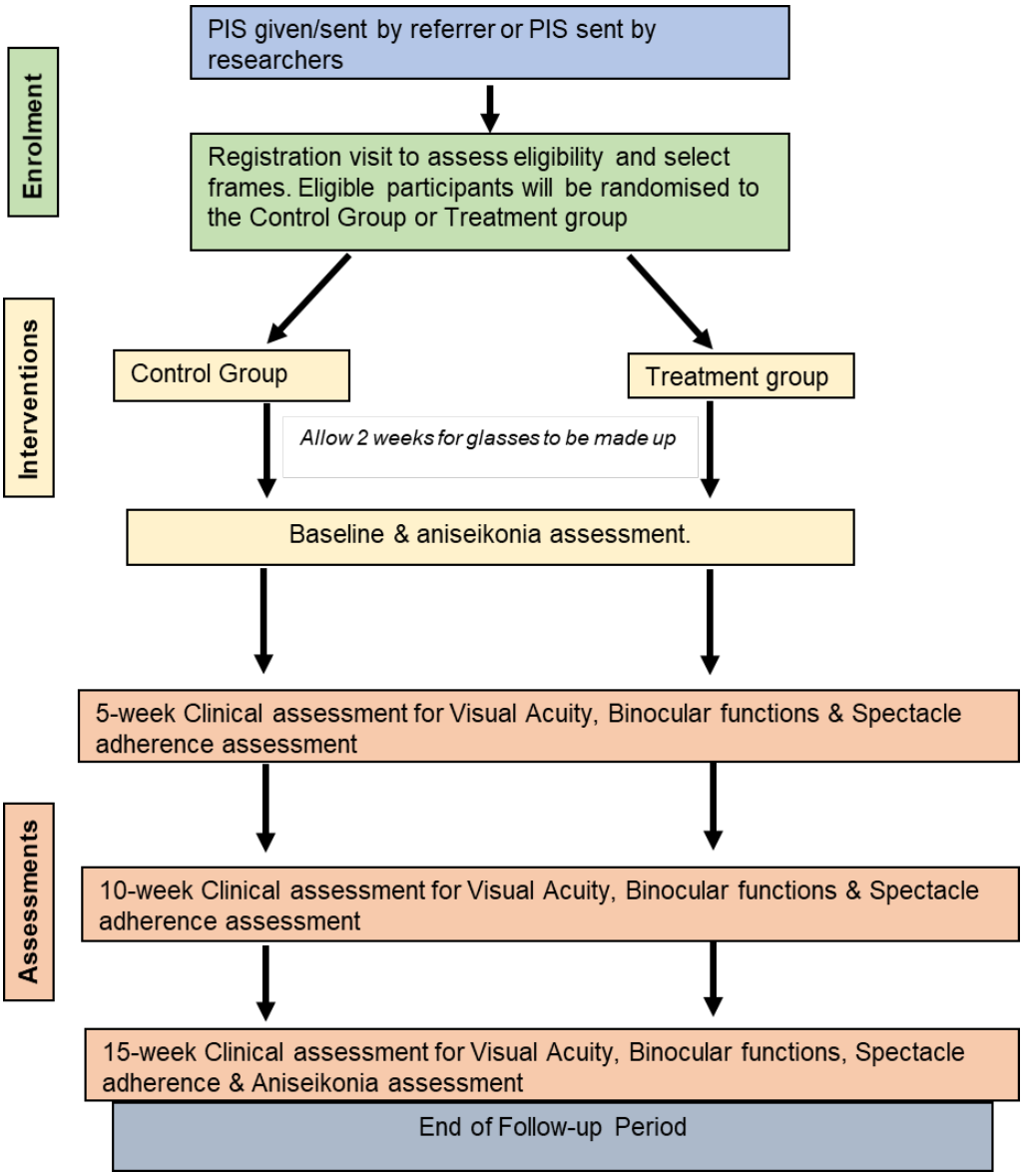


Figure 17. Schematic summary of the MAGNIFY schedule of enrolment, interventions, and assessments.

6.7 Data collection

6.7.1 Outcome

Outcome measures will be assessed at 5-, 10-, and 15-weeks post-baseline by a masked clinical examiner. All study members will be trained on study requirements. Masked clinical examiners will use standard clinical measurements to complete paper-based data collection forms designed by study investigators. Baseline and outcome measures are summarised in Table 22. A trial management team will be checking the integrity of

data collected on the paper forms as they are entered onto the database to ensure data quality and completeness.

6.7.1.1 *Primary Outcome*

The primary outcome measure will be change in amblyopic eye VA from baseline to the 15-week outcome visit, measured using the highly standardised HOTV protocol on the Electronic Visual Acuity (EVA) testing system (Moke et al., 2001).

6.7.1.2 *Secondary Outcomes*

- Change from baseline in distance visual acuity of the amblyopic eye at the 5- and 10-weeks post baseline assessment
- Change from baseline in distance visual acuity of the fellow eye at 5-, 10-, and 15-weeks
- Change from baseline in interocular acuity difference at 5-, 10-, and 15-weeks
- Change from baseline in stereopsis at 5-, 10-, and 15-week follow-up visits, measured using the highly standardised Randot Preschool stereotest (Birch et al., 2008)
- Spectacle wear adherence at 5-, 10- and 15-week visits, measured using the daily spectacle-wear diary
- PedEyeQ quality of life metric questionnaire to assess functional vision and eye-related quality of life (ER-QOL) in children and their parents (Leske et al., 2019)

Table 22. Schedule of tests and follow up visits

Measures	Registration	Baseline Assessment	5 weeks	10 weeks	15 weeks
Demographics	✓				
Visual acuity	✓*	✓	✓	✓	✓
Ocular alignment	✓	✓	✓	✓	✓
Motor fusion	✓*	✓	✓	✓	✓
4Δ test	✓		✓	✓	✓
Visuoscopy			✓	✓	✓
Stereopsis	✓**	✓	✓	✓	✓
Subjective Aniseikonia Tests		✓			✓
Biometry	✓				
OCT	✓				
PedEyeQ		✓			✓
Serious adverse events			✓	✓	✓
Spectacle Adherence			✓	✓	✓
Allocation	✓				

**Unaided visual acuity is measured at the registration visit if not available from the referrer. The Keeler LogMAR chart will be used in the study for those who require measurement at the registration visit.*

***Tests done by study clinicians only if relevant information is not available from the referrer.*

6.7.2 Participant Retention

Once a child is randomised, study staff will make every possible effort to follow the child for the entire study period. Reminders of upcoming study visits will be sent via the preferred method of communication indicated at the enrolment visit and contributions will be made towards travel costs for each visit.

6.7.3 Conclusion of the Study

At the end of the 15-week study period all participants will be referred back to the eye care provider that referred them with a full report of their status. If vision in the amblyopic eye has not sufficiently improved after 15 weeks of fulltime spectacle wear, further amblyopia treatment (such as patching therapy) will be provided by referral to the appropriate eye care provider. Any adverse events to the participant and/or spectacles will be monitored and recorded as appropriate.

6.7.4 Sample size

A sample size of 50 patients (25 per arm) will provide 95% power at p=0.05 to detect a minimal clinically important difference of 0.20 log units improvement in visual acuity as tested on the EVA test (Felius et al., 2003; Holmes et al., 2001) at 15 weeks, assuming a standard deviation of 0.17 (To et al., 2011). This sample size allows for an overall loss-to-follow-up of 15% (Scheiman et al., 2008) (Calculated using GraphPad Sat Mate 2.0).

6.8 Data management

All participants will be assigned a unique identification code to protect confidentiality immediately following data collection. All clinical data will be collected, recorded, stored and analysed under this unique research code. All paper-based clinical documents will be safely stored in a locked secure cabinet at the School of Optometry and Vision Science for six years before being securely destroyed. De-identified electronic data will be stored indefinitely on password-protected computers to allow comparison to future data sets. Consent Forms and referral letters, which contain identifying information, will be held in a secure location, separate from the research data for a period of six years.

6.9 Data analysis

Statistical analyses will be performed using SAS version 9.4. All statistical tests will be two-tailed and at a 5% significance level throughout the analyses, and all treatment evaluations will be performed on the principle of 'intention to treat' unless otherwise specified. The ITT population will consist of all randomised participants according to their randomised group, regardless of the treatment actually received and subsequent withdrawal or deviation from the protocol. People who subsequently withdraw from the study will contribute their data already collected in the ITT analysis. A per protocol analysis will also be performed on the primary outcome to assess the robustness of the results. Randomised participants who have no major protocol violations will be included in this subset for analysis. Relevant protocol violations may include errors in treatment assignment, the use of excluded medication, poor compliance, loss to follow-up and missing data. For this trial, possible conditions of major protocol violation include:

1. Poor spectacle wear compliance (<75% of waking hours)

2. Loss to follow-up and missing outcome

3. Follow-up visits fall out of time window: out of ± 7 days for 5-, 10- and 15-week follow-up visits

The study investigators will conduct a blinded review of all participants with protocol violations before final data analysis and make a decision on the list to be excluded from the per protocol set. Participants that withdraw will contribute data to the point of withdrawal unless data withdrawal is specifically requested. No adjustments for multiple comparisons are planned for any of the outcomes. No imputation will be performed for missing data.

All results will be presented overall and by treatment groups. Summaries of continuous variables which are normally distributed will be presented as means and standard deviations or medians and inter-quartiles for skewed data, while categorical variables will be presented as frequencies and percentages.

For logMAR visual acuity, smaller or more negative values equal better vision. For this study, change from baseline (0 week) to follow-up in distance visual acuity of the amblyopic eye will be calculated as (Baseline – Follow-up). Positive change from baseline values indicate there is improvement, and negative values indicates worsening of the condition.

When the method of mixed model for repeated measure (MMRM) is used, the model will include treatment, time, treatment by time interaction, baseline value as fixed effects, and subject as random effect, unless otherwise stated. The within-subject errors will be modelled using an appropriate covariance matrix. Candidate structures include but are not restricted to unstructured, autoregressive, Toeplitz, compound symmetry and spatial. The Kenward-Roger method will be used to estimate the denominator degrees of freedom for fixed effects.

Results will be published in journals and through conference presentations to the relevant professional groups. Participants can choose to receive a summary of the overall trial results by letter/report once all data has been collected and analysed. This is an option on the consent form.

6.10 Data Monitoring

An independent monitor will check the existence and correct date for all signed Consent Forms. The monitor will also sample over 10% of all randomised participants to check accuracy of data on the database against source data. This trial is considered to be low risk and, therefore, establishing a Data Safety Monitoring Committee for the trial is not necessary.

Interim analysis is performed when 50% of the patients have been randomised and completed the 15-week follow up. The interim analysis is performed by an independent statistician, masked to treatment allocation.

6.10.1 Harm

We do not expect any adverse effects to arise from the lenses in this study, as both types of lenses are currently used in New Zealand and overseas in the treatment of anisometropic amblyopia in children. Normal spectacle lenses have been shown to resolve amblyopia in 30% of children and no adverse effects have been reported (Cotter et al., 2006; Gao et al., 2018; Stewart et al, 2004). Aniseikonia lenses have been found to reduce asthenopic symptoms (headaches/eyestrain/blurry vision) that are normally associated with adapting to a new prescription in adults (McNeill & Bobier, 2017), and there have not been any reports of adverse effects from clinical use in children.

Adverse events unrelated to the study treatment may occur, e.g., circumstances that prevent the child wearing their glasses such as illness or broken glasses. These events will be documented and monitored closely throughout the clinical trial.

All adverse events and spectacle related incidents occurring during the trial and that are observed by study personnel or reported by the participant will be recorded, whether or not attributed to trial treatment. Adverse events will be collected systematically at each follow-up visit and open-ended questioning will encourage participants to report on unexpected adverse events. Those that are considered related to the trial treatment as judged by a qualified investigator will be followed either until resolution, or the event is considered stable. It will be left to the judgement of the qualified study investigators to decide whether or not an adverse event is of sufficient severity to require discontinuing the participant from the study. A participant may also voluntarily withdraw from participating in the study due to what he or she perceives as an intolerable adverse

effect. If either of these occurs, the participant will undergo follow-up visits for trial assessment and be given appropriate care under medical supervision until symptoms cease, or the condition becomes stable.

An independent monitor will review the source documents (paper data collection forms) and determine whether the data reported in the database system are complete and accurate. Quality assurance of the lenses and spectacles will be undertaken by the unmasked team members that are responsible for ordering lenses and quality checking them for correction prescription and lens allocation.

6.11 Ethical considerations

Ethical approval has been granted by the University of Auckland Human Participants Ethics Committee (023628). Assent will be sought prior to study enrolment from all children. Written informed consent will be signed by the parent/guardian of the child before any data collection procedures. All participants (or parents/guardians of participants) may withdraw at any time from the study.

6.11.1 Consent and Assent

Participant's caregivers and children themselves will be given participant information sheet prior to the enrolment visit. Both children and care givers will be encouraged to ask questions and have an informed discussion on what is involved with study participation. The research orthoptist will then obtain written consent from the caregivers and assent will be sought from children prior to collection of any data. There are no current plans for using data collected in this study in future studies.

6.11.2 Confidentiality

All participants will be assigned a unique identification code at enrolment to protect confidentiality. All clinical study data will be collected, recorded, stored and analysed under this unique research code. A document linking the code with the participant's name will be stored independently of the clinical data and will be available only to the researchers. This linking document will be destroyed after six years.

All clinical documents will be safely stored confidentially in a locked secure cabinet at the University of Auckland for six years before being securely destroyed. De-identified

electronic data will be stored indefinitely on password-protected computers to allow comparison to future data sets. Consent Forms will be held by the Department in a secure location, separate from the research data for a period of six years.

6.11.3 Protocol amendments

Any modifications to the protocol which may impact on the conduct of the study, potential benefit of the patient or may affect patient safety, including changes of study objectives, study design, patient population, sample sizes, study procedures, or significant administrative aspects will require a formal amendment to the protocol. Such amendment will be agreed upon by MAGNIFY study group and approved by the University of Auckland Human Participants Ethics Committee prior to implementation.

6.12 Discussion

This is the first double-masked, randomised clinical trial investigating aniseikonia-correction in optical treatment of anisometropic amblyopia. Significant aniseikonia is known to limit binocular functions such as stereoacuity in adults with normal visual history (Katsumi et al., 1986; Lovasik & Szymkiw, 1985; Oguchi & Mashima, 1989), therefore it is possible that aniseikonia also limits stereoacuity in children with anisometropic amblyopia. Correcting aniseikonia as part of the anisometropic correction may reduce the stimulus for developing suppression, leading to improved binocular visual outcomes from optical treatment of anisometropic amblyopia. There is currently no clinical trial-quality evidence to support or refute this hypothesis. Available evidence is limited to individual case reports where rigorous protocols have not been utilised (Shaw & Bobier, 2012).

Adherence to full time spectacle wear is essential for optimal visual outcomes. However clinically, spectacle adherence is only assessed indirectly via subjective parental reporting which is generally expected to overestimate adherence (Drews-Botsch et al., 2016; Fielder et al., 1995). Current amblyopia research shows a wide variability in adherence to amblyopia treatments like occlusion (Awan et al., 2005; Loudon et al., 2006; Stewart et al., 2017; Wallace et al., 2013), and parental over reporting of treatment adherence (Gao et al., 2021; Holmes et al., 2016; Manh et al., 2018). Adherence with spectacle wear also displays a similarly wide range of interindividual variability (Maconachie et al., 2016) and likely to suffer similar parental over estimation

of adherence. In this study the SpecsOn monitor (South et al., 2021) will be used alongside the daily spectacle wear diary to examine the effectiveness of the monitor in a clinical-like setting where children are reviewed routinely for amblyopia treatment. Not all participants will opt to have the device put onto their spectacles and therefore we will not have complete data from all the enrolled participants in the study. However, data on objective assessment of adherence will contribute to the design and methodology of future studies of optical treatment.

Aniseikonia is likely to be present alongside anisometropia, as retinal image size difference caused by anisometropia itself and the spectacle lens induced magnifications from the optical correction of anisometropia both cause aniseikonia (Kramer et al., 1999; Rabin et al., 1983; Sorsby, 1962b). Retinal image size differences in anisometropia may be a contributing factor in stimulating suppression and the development of amblyopia (Katsumi et al., 1986; Lovasik & Szymkiw, 1985; Oguchi & Mashima, 1989). Correcting image size difference alongside defocus in the treatment of significant anisometropia may further reduce the need to develop suppression and optimise visual recovery. However subjective assessment of aniseikonia in preschool children with anisometropic amblyopia has not been reported on. It is presumed to be difficult due to potential suppression and the lack of binocularity required to complete direct comparison tests using the currently available tests. At present there is no gold standard test for assessing subjective aniseikonia, with no tests designed for or validated in children. This study will use two commercially available tests to assess the reliability of measuring aniseikonia in preschool children with anisometropic amblyopia providing guidance for the design and methodology of future studies.

Providing aniseikonia corrections at first diagnosis of significant anisometropia may help us understand the importance of subjective aniseikonia measurements and its role in the treatment of anisometropic amblyopia.

Chapter 7

Provisional Results of the Measuring aniseikonia and investigating neuroplasticity and image factors in amblyopia (MAGNIFY) study: A Randomised clinical trial

Recruitment for the MAGNIFY study commenced in January 2020 following a change in design from a feasibility study to a clinical trial. Soon after recruitment commenced, the COVID-19 pandemic arrived onto New Zealand shores and recruitment was suspended during COVID-19 pandemic alert levels 3 and 4. Further disruptions related to multiple lockdowns have meant that recruitment and data collection were significantly impacted. As a result, the MAGNIFY study is still currently underway as of the writing of this thesis. To preserve the integrity of the clinical trial unmasking of the interim data is not possible. This chapter will present provisional analyses from the first 20 participants recruited into the MAGNIFY study.

As described in Chapter 6, the Aniseikonia Inspector Version 3 and the New Aniseikonia Test (Awaya) were two methods to be used in the MAGNIFY study for assessing subjective aniseikonia. However, these tests proved to be unreliable in children aged 4 -5 years old in this study and have not been included in the analysis. Although biometry and refractive data were collected, the absence of subjective aniseikonia data means that it is not possible to compare the optical modelling results to the subjective aniseikonia experienced by children with anisometropia.

7.1 Baseline Characteristics

Between January 2020 and August 2021, 31 children were screened and assessed for eligibility. Of these 11 were excluded, with six declining to participate and five being non-contactable or had already received glasses. Twenty children were randomised but one child received glasses under COVID-19 level 4 lockdown and did not complete a baseline assessment and therefore excluded. The remaining 19 children were included

in this analysis and the study progression stages are shown in Figure 23 and baseline characteristics are shown in Table 23.

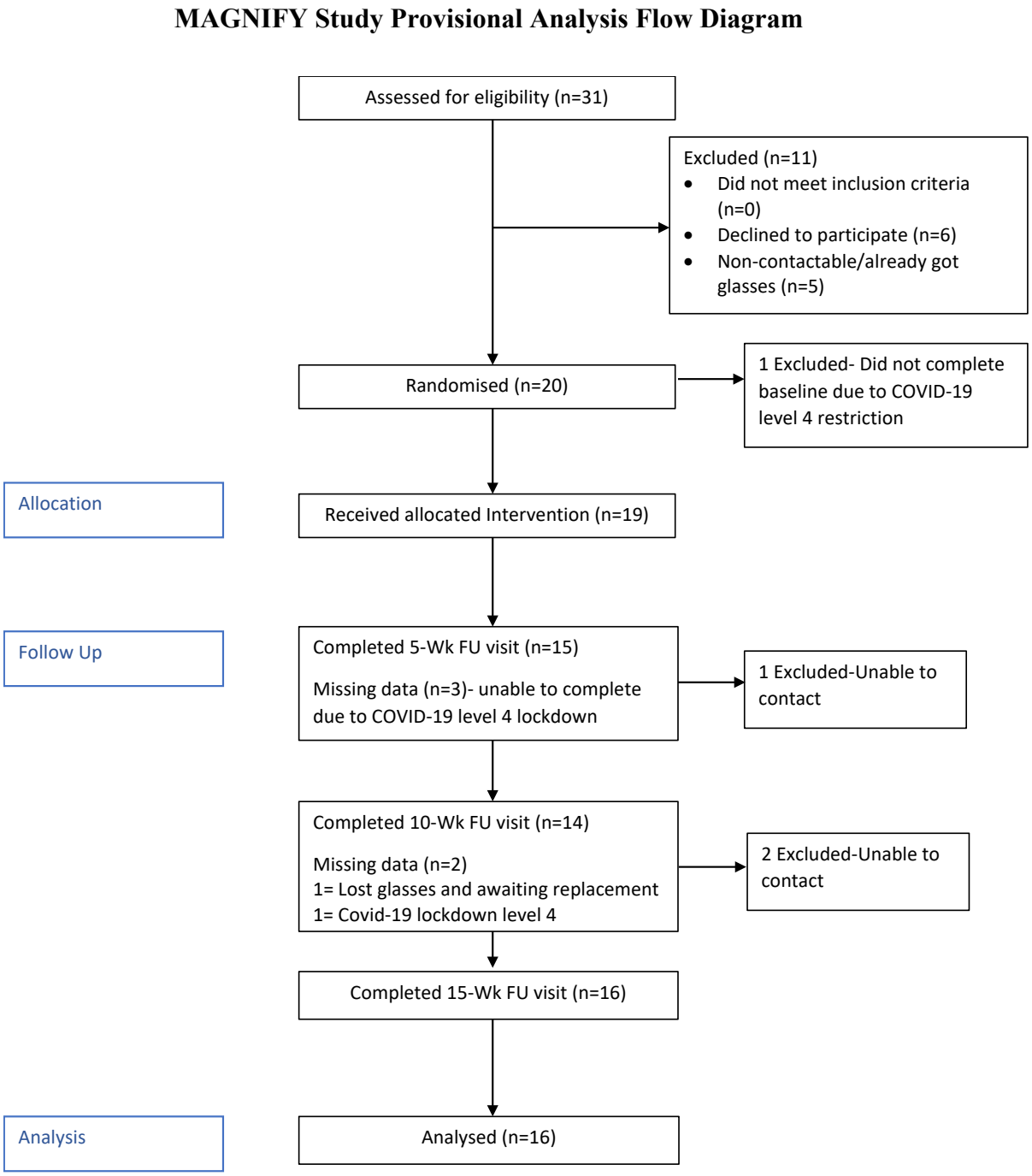


Figure 18. MAGNIFY Study Provisional Analysis Flow Diagram

Table 23. Baseline Characteristics of participants at Randomisation

	No. (%)
Characteristic	**Total**
Female	10 (52.63%)
Age at randomization, y	
Mean (SD) (range 4.15-5.95)	4.84 (0.48)
Ethnicity*	
Māori	4 (21.05)
Pacific People	2 (10.53)
Asian	6 (31.58)
MELAA	1 (5.26)
European	6 (31.58)
Spherical Equivalent of cycloplegic refraction, mean (SD)	
Amblyopic eye (D)	4.68 (1.19)
Fellow eye (D)	1.15 (1.07)
Baseline Distance VA (HOTV test at 3m), Mean (SD), LogMAR	
Amblyopic eye VA	0.579 (0.17)
Range	0.200 to 0.900
Fellow eye VA	0.037 (0.15)
Range	-0.100 to 0.400
Baseline Stereoacuity (Randot Preschool Test)	
Binocular function score, log (seconds of arc), mean (SD)	2.65 (0.27)
Nil Stereoacuity	6
Near maximum angle of strabismus†	
Orthotropic	12
Phoria 1-15Δ	6
Intermittent tropia/strabismus 1-15 Δ	1
Distance maximum angle of strabismus†	
Orthotropic	17
Phoria 1-15Δ	2
Intermittent tropia/strabismus 1-15 Δ	0

**Percentages in this subsection may add up to more than 100% because some participants identified with more than one ethnicity*

†Measured using the prism alternate cover test through optimal refractive correction

7.2 Primary Outcome: Amblyopia Eye Distance Visual Acuity

The 15-week primary outcome visit was completed by 16 out of 19 (84%) children. The mean (SD) refractive error (SE) was +4.68D in the amblyopic eye and +1.15D (1.07) in the fellow eye. A significant improvement (t (15) =10.136; p=<0.001) in distance visual acuity (LogMAR) of the amblyopic eye from baseline (mean 0.41; SD 0.16 logMAR) to the 15-week outcome visit (mean 0.17; SD 0.19 logMAR) was observed in all 16 participants. 66.7% of children improved by 3 lines (0.320 LogMAR) or more after the first five weeks of glasses wear. Resolution of amblyopia was seen in one participant (6.25%). VA improvement slowed to 0.05 logMAR from week 5 to week 10 and 0.04 logMAR from week 10 to week 15 (see Figure 24). Amblyopia had resolved (defined as one line or less difference between visual acuity of fellow and amblyopic eye) in 50% of participants at the 15-week outcome visit.

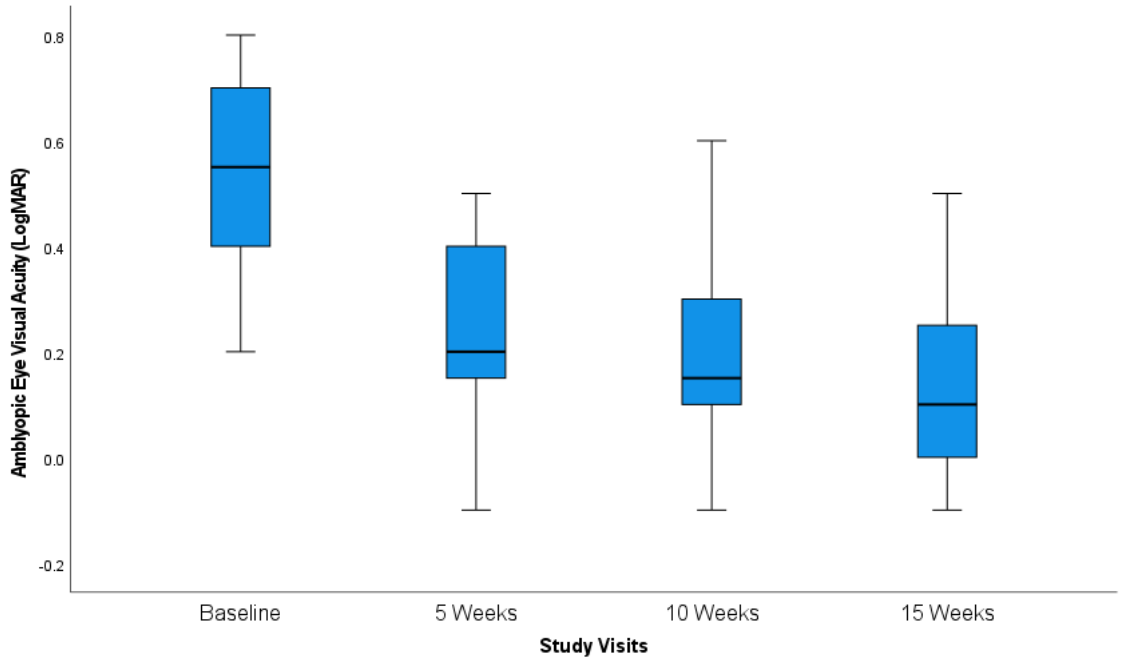


Figure 19. Box and whisker plot showing the change in visual acuity of the amblyopic eye at each study visit

7.3 Secondary Outcomes

7.3.1 Interocular difference in visual acuity

The change in interocular difference from baseline (mean 0.54; SD 0.19 logMAR) to the 15-week outcome visit (mean 0.23; SD 0.20logMAR) was significant (t (15) =8.172;

p=<0.001) showing a similar plateauing trend as the change in the amblyopic eye distance visual acuity after five weeks of glasses wear (see Figure 25).

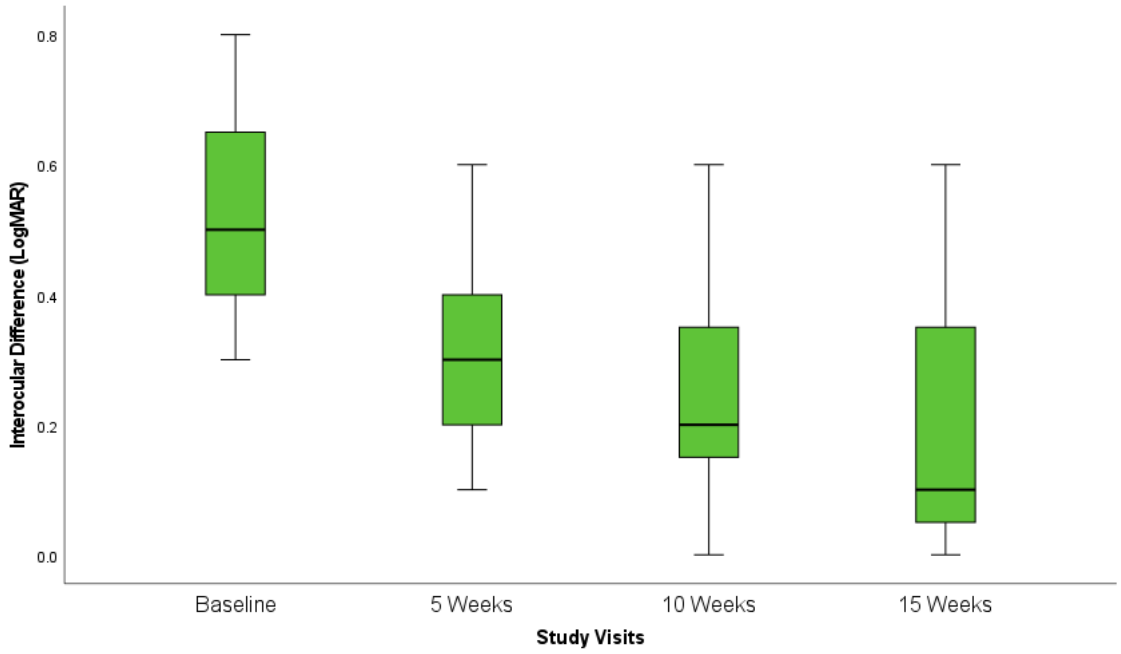


Figure 20. Box and whisker plot showing the change in interocular difference at each study visit

7.3.2 Fellow Eye Distance Visual Acuity

Distance visual acuity of the fellow eye improved by a mean of 0.10 (SD 0.13) logMAR from the baseline (0.04 logMAR) to the 15 week (-0.06) outcome visit in 16 out of 19 (84%) participants.

7.3.3 Stereoacuity

Stereoacuity at 15-weeks post baseline had improved by more than two octaves (0.75 (SD 0.60) $\log_{10}$ (arcsec)) in 87.5% (n=14) of participants, of which five had no demonstrable stereoacuity at baseline. Wilcoxon signed-rank test showed a statistically significant change (Z= -3.295 p=0.015) in stereoacuity from baseline to the 15-week outcome visit as seen in Figure 26. Results of the Spearman's correlation indicated a significant association between improvements in stereoacuity and improvements of visual acuity of the amblyopic eye from baseline to the 15-week outcome visit

r(16)=0.53, p=0.035 (Figure 27). Stereoacuity of 100 secs of arc or better was achieved by 10 participants.

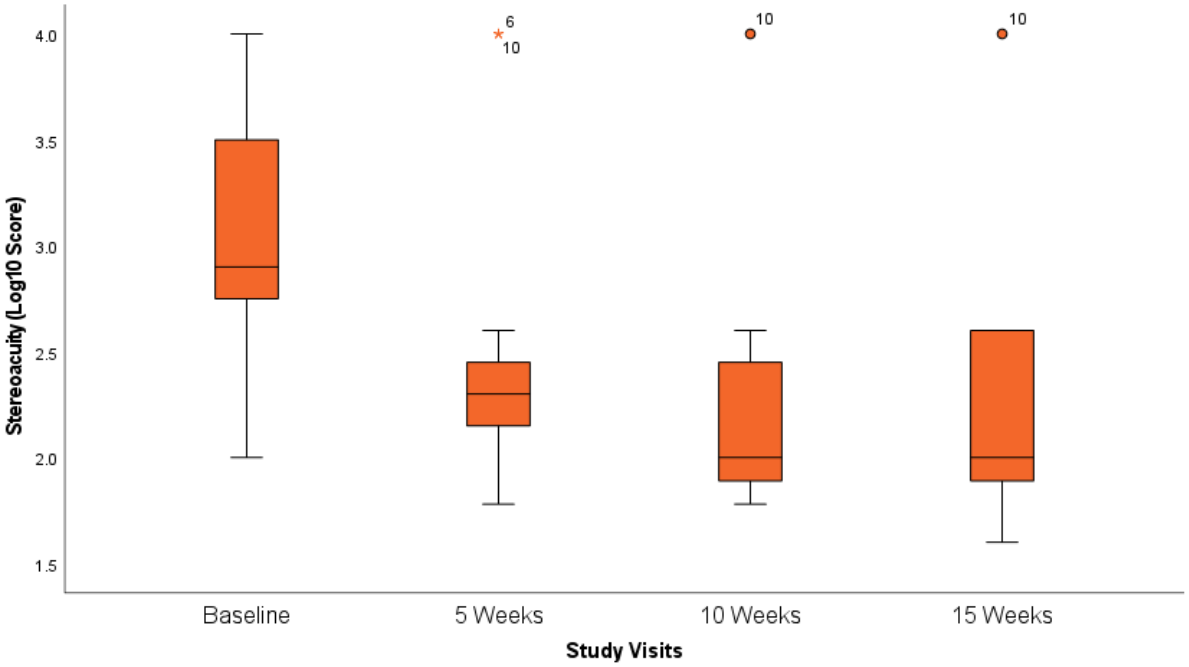


Figure 21. Box and whisker plot showing the improvement in stereoacuity from baseline to 15-week outcome visit.

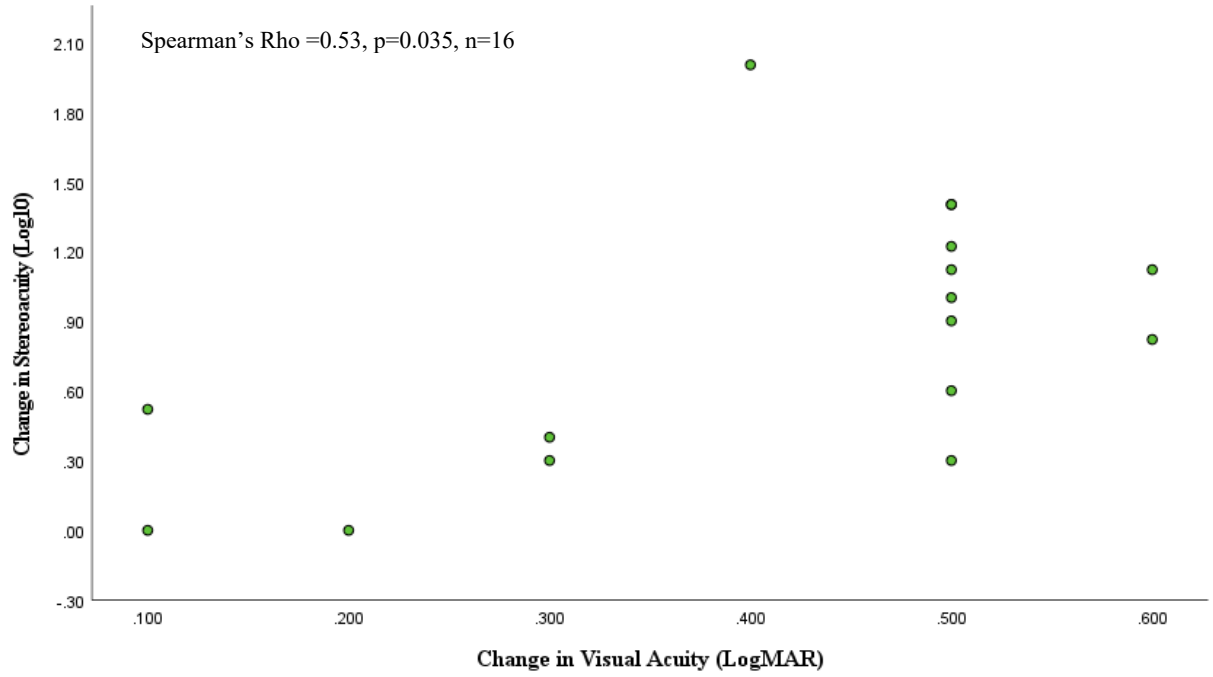


Figure 22. Improvements in amblyopic eye visual acuity and stereoacuity from baseline to 15-week outcome visit.

7.3.4 Assessment of Foveal fixation

The 4Δ base out prism test and visuoscopy were performed for assessment of foveal fixation at the 5-week follow up visit. The 4Δ test was reliably performed on 15 out of 18 children and tested at each follow up visit. Visuoscopy was reliably performed in 10 out of 18 children but COVID-19 safety procedures prevented four children from undergoing visuoscopy assessment at any follow up visit due to the proximity required for assessment. The testability of the two foveal fixation tests and the results of the tests are given in Table 24.

Table 24. Testability of the two Foveal Fixation Tests and the Outcomes

Registration no.	4Δ Test	Fixation Confirmed	Visuoscopy	Fixation Confirmed
001CT	Bifoveal	Y	Central & steady	Y
002VL	Bifoveal	Y	Central & steady	Y
004NS	Bifoveal	Y	Poor fix	N
005PG	Bifoveal	Y	Central & steady	Y
006EP	Inconclusive	N	Central & steady	Y
007JP	R central suppression	Y	R Parafoveal	Y
008EL	Inconclusive	N	Inconclusive	N
009SC	Bifoveal	Y	Inconclusive	N
010TP	Bifoveal	Y	Central & steady	Y
011KT	L central suppression	Y	Left parafoveal	Y
012LH	Bifoveal	Y	Central & steady	Y
013IL	Bifoveal	Y	Central & steady	Y
014JR	Bifoveal	Y	Central & steady	Y
015JC	L central suppression	Y	Inconclusive	N
016HI	Bifoveal	Y	COVID-19 restrictions	N
017SK	Bifoveal	Y	COVID-19 restrictions	N
018BR	Inconclusive	N	COVID-19 restrictions	N
020AP	Bifoveal	Y	COVID-19 restrictions	N

7.3.5 Spectacle Wear Adherence

Adherence to spectacle wear was defined as the mean number of hours per day the glasses were worn, divided by the estimated number of hours awake per day, multiplied by 100%. The spectacle wear diary was completed and returned by 12 participants. Diaries for six participants were not returned and two participants were lost to follow-up. Participants were considered adherent if spectacles were worn ≥75% of their awake time. Figure 28 shows that adherence as reported by the daily spectacle wear diary was high with a median of 96% (SD 14) adherence for the full duration of the study. It is possible that the children who did not return the diaries were non-adherent, although adherence was verbally reported to be "worn all day" by five out of six children during follow-up visits. Only one child was reported to have poor adherence, only wearing their spectacles three out of seven days. The adherence percentage was greater than 100 in some children, as the average wear time logged in the diary was more than the stated parental estimate of the number of hours awake per day.

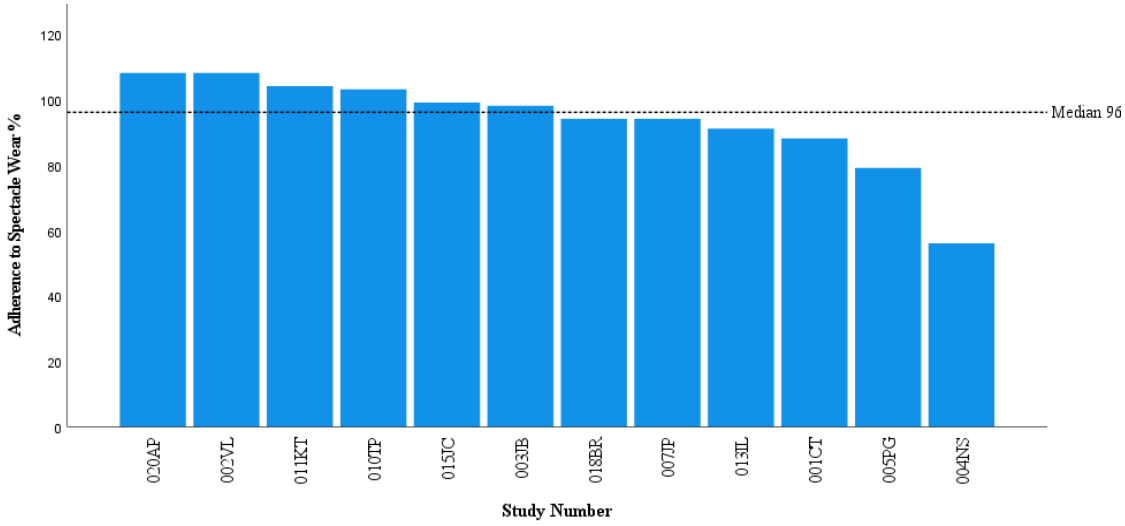


Figure 23. Adherence to Spectacle Wear as reported by Daily Spectacle Wear Diary

7.3.5.1 *Objective adherence monitoring*

The SpecsOn monitor was attached to 19 out of 20 frames. COVID-19 level 4 lockdown prevented one participant from having the SpecsOn monitor attached to their spectacle frame. Two devices were not returned due to participants being lost to follow-up. For the 11 participants who returned a diary and had the SpecsOn monitor, there was no significant difference between the subjectively reported (median 93%, mean 94.6%, SD

9.1) and objectively measured (median 84%, mean 85.9%, SD 10.3) (t=(10), 1.758, p=0.55) spectacle adherence. However, children who were non-adherent were also less likely to return a daily wear diary as shown in Figure 29. Overall four out of six children who did not return a diary were shown to be non-adherent with the SpecsOn monitor.

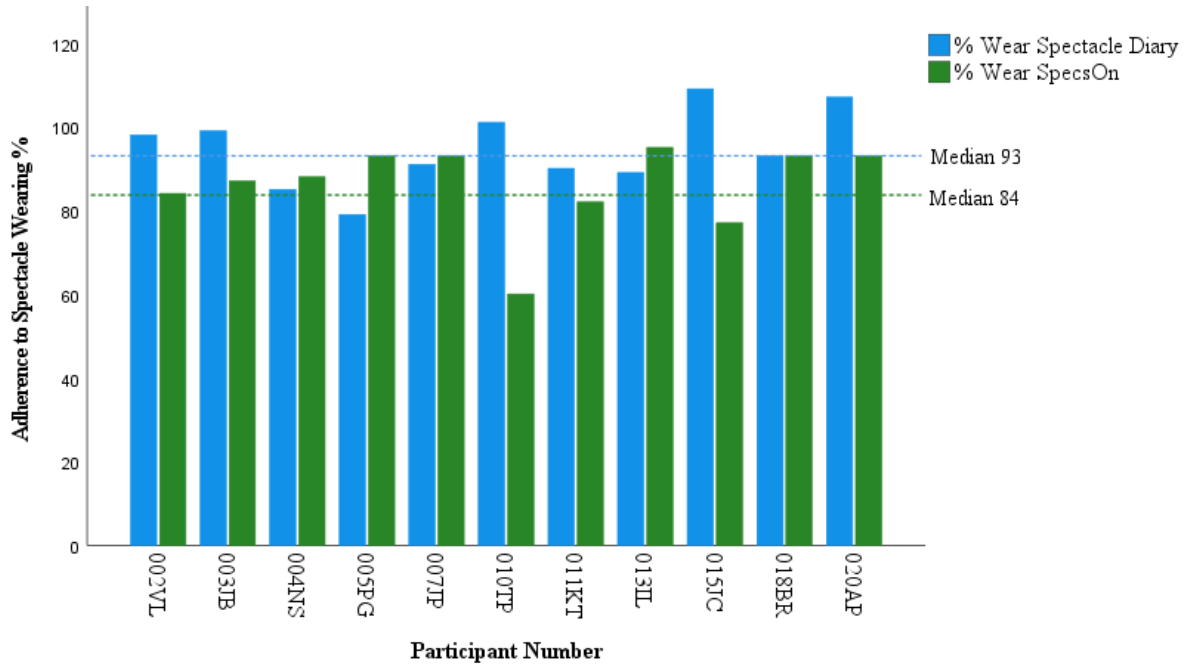


Figure 24. Adherence to Spectacle Wear Diary compared to SpecsOn monitor

Pearson's correlation did not observe an association between adherence as assessed by diary or SpecsOn monitor and visual acuity gain (Diary r(8)=0.27, p=0.519, SpecsOn monitor r(14)-0.28, p=0.341).

7.3.6 Subjective Aniseikonia Tests

The two subjective aniseikonia tests used in this study were found to be unreliable. The Aniseikonia Inspector version 3 was completed by 18 out of 19 participants but only 6 out of 19 (32%) children were deemed to have good concentration during testing. Approximately two thirds (63%) of children had poor concentration or were guessing during testing and one child refused to complete the test. To obtain an accurate assessment of a person's subjective aniseikonia the patient must maintain central fixation whilst judging size difference. Even though the participants were instructed to fix centrally, most were found to be looking around the screen and/or around the room.

Concentration seemed to wain quickly and children would remove the glasses or look away from the screen or were visibly seen to lose concentration. Constant reminders were given to keep looking at the screen but this often led to random guess responses.

The New Aniseikonia Test was completed by all participants and aniseikonia was found to be between 0-2% magnification difference in 94% of the children. Again this test was found to be unreliable as the children did not tend to look through all the options as instructed and tended to pick either the 0% (32%) or 1% (42.1%) magnification difference as they were the first two options. To perform the test accurately central fixation must be maintained however it was difficult for young children to maintain steady central fixation.

7.3.7 Functional Vision and Eye-Related Quality of Life

The 0–4-year-old version of the PedEyeQ questionnaire (Hatt et al., 2019) assessed functional vision and eye related quality of life (ER-QOL) in children and their parents through parent and proxy components within the questionnaire. Using a 3-point frequency scale the proxy component assessed three domains (Functional, Bothered, and Social) and the parent component assessed four domains (see Table 25) and each domain was given a calculated Rasch score (0=worst, 100=best). In this study parental concern regarding the child's eye condition scored the lowest, meaning greater concern felt by parents, at the baseline visit but this concern had improved by the 15-week follow up visit. Functional vision and quality of life remained high across all other domains from both proxy and parent perspectives.

Table 25. PedEyeQ Domains and scores for Proxy and their Parents at the Baseline and 15-Week Study Visits

Proxy PedEyeQ		**Functional**	**Bothered**	**Social**
Study visit administered	**n**	**Median (Range) PedEyeQ scores**		
Baseline	17	85 (25-100)	100 (20-100)	94 (34-100)
15 Week Follow up	8	92 (75-100)	90 (90-100)	97 (56-100)

Parent PedEyeQ		**Impact on Parent/family**	**Worry re: Child's Eye Condition**	**Worry re: Child's self-perception and Interactions**	**Worry re: Child's Visual Function**
Study visit administered	**n**	**Median (Range) PedEyeQ scores**			
Baseline	17	98 (60-100)	60 (5-100)	86 (21-100)	84 (25-100)
15 Week Follow up	8	100 (90-100)	82 (55-100)	93 (64-100)	84 (69-100)

7.4 Adverse Events

Asthenopic symptoms such as headaches/eyestrain/blurry vision have been reported when adapting to a new prescription by adults but are not often experienced by children. In the MAGNIFY study no adverse events related to the study treatment were observed by study personnel or reported by the participants. Spectacle wear, however, was disrupted in 43.8% (n=7) of participants due to broken or damaged spectacles throughout the study period with three children breaking their spectacles more than once. Table 26 shows the frequency of damage to spectacles at the 3 study visits.

Table 26. Spectacles damaged or broken

Study visit	**% (n)**
0-5 Weeks	29.4 (5)
5-10 Weeks	31.3 (5)
10-15 Weeks	12.5 (2)

7.5 Discussion

This study found an improvement of 4 lines (0.410 LogMAR) in distance visual acuity of the amblyopic eye after 15 weeks of spectacle wear and a reduction in interocular difference of 3 lines (0.330 logMAR). This is consistent with numerous previous studies Moseley et al. (2002), Stewart et al. (2004) and Cotter et al. (2006) showing visual acuity improvement in anisometropic amblyopia with refractive correction wear alone (Chen et al., 2007; Cotter et al., 2006; Stewart et al, 2004). This led to the change in preferred practice guidelines for the treatment of amblyopia (Ophthalmology, September 2017; Royal College of Ophthalmologists, March 2012) where optical treatment (refractive adaptation) is accepted as the first line of treatment amblyopia and this study lends further support to this first treatment phase. Although a minimum of 12-14 weeks of initial optical treatment is recommended, there is evidence that suggests maximum visual acuity can be achieved much earlier (Chen et al., 2007; Cotter et al., 2006; Moseley et al., 2002a; Stewart et al, 2004). In our study, 50% of participants showed an improvement in visual acuity at the 5-week visit, with resolution of amblyopia seen in 6.25%. This is similar to the findings of Cotter et al. (2006) who found 21% of participants had improved by 3 lines or more at the first 5-week review and resolution of amblyopia occurred in 7%. Limited improvement was seen after 15 weeks in this group. A prospective study by Moseley et al. (2002) assessed patients weekly until either resolution in the amblyopic eyes or stabilisation of visual acuity, and also observed significant gains from 3 to 22 weeks with an average of 18 weeks before acuity gain plateaued. This finding was parallel to Chen et al. (2007) who found considerable improvement in their anisometropic amblyopia cohort in 4 to 12 weeks before plateauing.

The pathophysiology of anisometropic amblyopia as discussed in Chapter 2 suggests that lack of high spatial frequency input due to unilateral blur reduces cortico-neural sensitivity. Theoretically, correcting the refractive error and eliminating retinal blur should result in a gain in visual acuity as neural sensitivity increases with the resumption of binocularly concordant high spatial frequency input. In line with this, improvements in stereoacuity have been observed during the optical treatment phase although substantiating literature is sparse, possibly due to optical and occlusion treatment not being distinguished as separate treatment phases until recently. The MOTAS study did separate these phases and found that stereoacuity improvements

were more likely to be gained in the optical treatment phase than the occlusion phase and that better stereoacuity was associated with better baseline visual acuity which was also observed by Wallace et al. (2011).

In the MAGNIFY study, improvement in stereoacuity was observed as visual acuity improved with optical treatment alone. The improvement seen in stereoacuity with refractive correction results from spectacle correction restoring binocular high spatial frequency content being received by both eyes promoting binocular interaction (Moseley et al., 2002). Holopigian et al. (1986) also suggested that anisometropic amblyopes retain low spatial frequency interaction and both eyes can be used in instances of similar contrast sensitivity input received by both eyes. Further support for treatment aimed at the binocular visual system rather than monocular treatment such as patching comes from improvement of visual acuity in anisometropic amblyopia following dichoptic contrast balancing treatment or videogames (Birch, 2013; Black et al., 2012; Hess et al., 2010; Knox et al., 2012; Li et al., 2013; Li et al., 2014; Spiegel et al., 2013; To et al., 2011). Contrast balancing reduces the contrast of the stimulus to the dominant eye allows the higher contrast image in the amblyopic eye to be processed equally, potentially allowing binocular combination.

Despite visual acuity returning to near normal following anisometropic amblyopia treatment, some studies have reported deficits in stereoacuity levels. Wallace et al. (2011) found improvement of the amblyopic eye within one line difference of the fellow eye but stereoacuity was worse than that of an age-matched normal control group. It is suggested that partial foveal suppression or some other central limitation (Wallace et al., 2011), could be responsible for the stereoacuity deficit. Both the MAGNIFY study and the retrospective review for preschool vision screening and amblyopia treatment study presented in Chapter 3 observed deficits in stereoacuity following amblyopia therapy with only 9.8% achieving stereoacuity levels better than 100 secs of arc in the review study and 62.5% in the MAGNIFY study. Reduced binocularity is associated with increasing degrees of anisometropia (Chen et al., 2007; Levi et al., 2011; Rutstein & Corliss, 1999; Weakley, 2001) and the clinical aniseikonia in anisometropia and amblyopia study presented in Chapter 4 observed increasing amounts of subjective aniseikonia with increasing amounts of anisometropia. The greater amounts of aniseikonia in the anisometropic amblyopia group suggests that a greater degree of

aniseikonia along with increased blur is a contributing factor in the stimulation of suppression limiting binocularity and stereoacuity. However, this cannot be supported or refuted by the preliminary results of the MAGNIFY study and must await final unmasking of the treatment groups, which may show some differences in improvement of visual acuity and stereoacuity between the treatment groups receiving the aniseikonia correction lenses and the standard lenses.

Although all of our participants were identified as having anisometropic amblyopia at baseline, three children subsequently were identified as having a microtropia without identity following adaptation to their refractive correction. It is possible that the five children with visual acuities of ≥0.200 logMAR had undetected microtropia with identity (Hardman Lea et al., 1991), commonly found in association with anisometropia (Hardman Lea et al., 1991). Although both the 4Δ base out test and visuoscopy were performed, often the results were inconclusive due to poor fixation on account of the significantly reduced amblyopic acuity or were unable to be performed due to COVID-19 restrictions. Without objective assessment of the fixation point on the retina, a microtropia with identity can be missed as the 4-dioptre base out test alone is not a reliable indicator for the presence of central suppression (Frantz et al., 1992). Studies investigating anisometropic amblyopia often do not consider microtropia as its own entity and tend to group together microtropia without identity with strabismus (Chen et al., 2007; Donahue, 2005; Levi et al., 2011; PEDIG, 2002; Rutstein & Corliss, 1999; Steele et al., 2006). The mechanisms of a microtropia and strabismus are different in that abnormal retinal correspondence and eccentric fixation with normal peripheral motor fusion are characteristic of microtropia with identity, whereas normal retinal correspondence with the absence of motor fusion is more common in strabismus (Helveston & von Noorden, 1967; Lang, 1983; von Noorden, 1996). Stewart et al. (2004) observed the presence of eccentric fixation in children with poorer visual acuity outcomes. Therefore, a failure of anisometropic amblyopia treatment could in fact could be due to undetected microtropia, which anatomically limits the potential of visual acuity gain and in turn also limits stereoacuity.

The Aniseikonia Inspector and the New Aniseikonia Tests have been shown to be reliable measures of aniseikonia in adults. However we found these tests too difficult for the preschool children in the MAGNIFY study. Kehler et al. (2014) successfully

used the Aniseikonia Inspector version 3 in visually normal school aged children aged 5 to 13 years. However the preschool children in this study had a mean age of 4.8 years and had anisometropic amblyopia which may make size judgement more difficult resulting in disengagement from the test. There have been no other subjective aniseikonia tests that have been reported in the literature to be used in a preschool population. With the absence of a paediatric aniseikonia test it is difficult to accurately measure image size difference in this age group and ocular modelling may be an more accurate method of assessing aniseikonia in preschool children.

Poor adherence is often reported as a major contributing factor to failure of occlusion therapy. Studies investigating adherence in amblyopia treatment often focus on monitoring adherence to occlusion rather than spectacle wear. Factors affecting adherence include emotional impact (Holmes et al., 2003; Hrisos et al., 2004; Loudon et al., 2009), poor parental understanding (Newsham, 2002) and negative social perception related to spectacle wear (Castanon Holguin et al., 2006; Keay et al., 2010; Odedra et al., 2008). The MAGNIFY study observed high rates of adherence to spectacle wear but this could be due to selection bias. Often families that partake in research are motivated to follow treatment and thus are more likely to adhere to prescribed times. It is also possible that in the MAGNIFY study, participants were motivated to wear spectacles due to the knowledge of being actively monitored with the SpecsOn monitor. Conversely, children that did not return a diary showed a pattern of non-adherence. However, based on parental reports, adherence to spectacle wear remained high even following removal of the SpecsOn monitor. Currently, clinical adherence to spectacle wear is monitored indirectly through parental verbal reporting or by completing daily wear diaries (Drews-Botsch et al., 2016; Fielder et al., 1995), however these have been found to overestimate adherence, which is also found in other types of prescribed medical interventions (Gao et al., 2021; Osterberg & Blaschke, 2005; Vermeire et al., 2001). Our study did not find a significant difference between adherence reported through daily wear diaries and objectively monitored by the SpecsOn monitor in the first five weeks of spectacle wear. Again, this could possibly be due to highly motivated participants and parents, but we also did not objectively monitor adherence for the full duration of the study. Children who are new to spectacle wear often take time to adapt to them and develop the habit of daily wear. Once spectacle adaptation has occurred, the assumption is that they are likely to be consistent with wearing behaviour. However, it

is possible that treatment fatigue was not captured in this study as only the first five weeks were objectively monitored.

Overall, spectacles were well tolerated in the children enrolled in this study and adherence was high. During optical treatment in the MAGNIFY study no other adverse events related to the treatment were reported, indicating that optical treatment is a very safe method for amblyopia treatment. One of the main findings in this study was that almost half of the children broke or damaged their spectacles during the study period. Clinicians are often met with disruption to amblyopia treatment due to broken or damaged spectacles but this is not reported in the literature. It is important to consider the number of children that require replacements for their spectacle correction as this can negatively affect adherence, especially if there is a long period between breakage and replacement. The cost involved in replacing spectacles in countries where eye care is not fully publicly funded can be a barrier to treatment affecting equality in eyecare. In New Zealand the Enable subsidy entitlements allow one pair of spectacles to be claimed per year. If the spectacles are broken within 12 months or if whanau are not entitled to the Enable subsidy then the cost of replacement falls personally on families who may struggle to fund the replacement. This may cause some whanau to disengage from treatment and/or attending appointments in the HES. In the MAGNIFY study we were able to replace lost, damaged or broken spectacles and therefore were able to monitor the frequency of loss and damage and identify this as an important factor in the treatment outcomes of amblyopia.

7.6 Conclusion

Optical treatment is effective in restoring retinal image clarity and promoting binocularity, leading to a resolution of amblyopia in approximately 30% of children with anisometropic amblyopia. Spectacles are generally well tolerated by children. Adherence to spectacle wear as reported subjectively through a parental diary was found to be as reliable as the objective monitoring method. However, children that did not return a diary were less likely to adhere to prescribed wear time and therefore objective monitoring in these children would be informative of daily and overall wear patterns. Quality of health as measured by the PedEyeQ questionnaire was not severely impacted by spectacle wear, indicating that spectacles are well accepted in this preschool age group. Reporting on the rate of replacement spectacles required during

amblyopia treatment may assist in future planning and funding allocation of eye services in the public health system, reducing financial barriers and health related inequality.

Chapter 8

Overall discussion and conclusions

This thesis examined the role of aniseikonia in anisometropia and anisometropic amblyopia. Chapter 2 provided a comprehensive review of the available literature and provided consolidation between theoretical knowledge, clinical observations provided by reported case studies and methods of testing aniseikonia. The chapter concluded that aniseikonia is likely to be present in those with anisometropia as both anisometropia itself and the optical treatment for correcting anisometropia can cause aniseikonia. The difference in image size caused by anisometropia may subsequently lead to image suppression and amblyopia. This led to the hypothesis that correcting anisometropia and aniseikonia simultaneously, particularly at the initial diagnosis of anisometropia, would reduce image size difference between eyes, thus reducing the need to develop suppression and improve visual acuity outcomes for anisometropic amblyopia. This presented us with four research questions that needed to be addressed prior to examining the main hypothesis. This final chapter will discuss the results in relation to these questions, strengths and weaknesses of the research projects and the implications for future research and clinical management of amblyopia.

8.1 Research Questions

8.1.1 Question 1: Are common refractive errors overseas also common in the New Zealand preschool population (where amblyopia treatment is often commenced), and what are the outcomes of these treatments?

The clinical profile of children in amblyopia studies (Birch & Holmes, 2010; PRDIG Group 2002; Shaw et al., 1988; Woodruff et al., 1994) suggests that mechanisms responsible for amblyopia vary with age. Strabismus is strongly associated with amblyopia in the first year of life with anisometropia either alone or in combination with strabismus becoming more prominent by the third year and responsible for nearly two thirds of amblyopia by the fifth year of life. This indicates that anisometropia most likely develops later during visual development, possibly after the age of three years,

which is in line with the longitudinal finding of Abrahamsson et al. (1990) and Abrahamsson & Sjöstrand, (1996). National vision screening programmes have been established worldwide to identify amblyopia with a screening age of 3 to 4 years old prior to starting school. In New Zealand, the B4-school vision screening is part of a national health screening programme conducted at age 4-5 years old to identify amblyopia that may affect a child's educational journey. If left untreated, amblyopia has the potential to affect a child's (Holmes et al., 2011) learning and educational development (Chua & Mitchell, 2004), with difficulties continuing into teenage and adult years (Packwood, Rychwalski & Keech 1999; Webber et al., 2008; Burke et al., 1997; Coats et al., 2000; Olitsky et al., 1999)

Bilateral refractive error (58.3%) and anisometropia (41.3%) were the most common cause of reduced visual acuity found in preschool children that failed vision screening in the central and west Auckland regions as described in Chapter 3. Bilateral astigmatism and myopia were the most common causes of bilateral refractive error and these results are in line with overseas population studies (Dirani et al., 2010; Saw et al., 2006; Pai et al., 2012; Pascual et al., 2014), which also have a higher proportion of Asian children as seen in our cohort. The Australian SPEDS study (Pai et al., 2012) found astigmatism and hyperopia were the most common cause of refractive error. However, but we did not find a high rate of hyperopia in our cohort this may be due to a higher sample of Asian ethnicity in our study. The higher rate of astigmatism found in the study described in Chapter 3 also supports other studies within New Zealand. In South Auckland, Langeslag-Smith et al (2015) found 66% of their preschool cohort had astigmatism as cause of reduced visual acuity in their failed preschool vision screening population and Findlay et al (2020) found 31.6% of 6 to 7 year olds had astigmatism as a cause of reduced visual acuity during school screening.

Myopia (less than or equal to -0.50D) was found in 11% of children in our study which was the same as that found by Dirani et al (2010) in the STARS study but more than that reported by MEPED study (6.6% of African -American and 3.7% of Hispanic children) and the BPEDS study (5.5% in African-American and 0.7% in Caucasian)

Anisometropia was identified as 41.3% of children referred to the HES and 23.5% had anisometropia related to amblyopia. This finding supports the finding of the STARS study which found a 60% prevalence of anisometropia but again the rate of

anisometropia in our study was higher than that found in the SPEDS (5.3%) and MEPEDS (3.8%) population studies.

Large overseas population studies have identified that refractive error is a common cause of amblyopia in this 3-6 year-old age group with anisometropia being the most common mechanism. In New Zealand population level data is lacking, but the retrospective review of preschool vision screening and amblyopia treatment in an Auckland and Waitematā District Health Boards study (Chapter 3) supports these overseas findings and those of previous New Zealand based studies (Findlay et al., 2020; Langeslag-Smith et al., 2015).

Chapter 3 identified correctable refractive error as the most common cause of reduced screening visual acuity. From the total cohort 58% of children required refractive correction, of which 38% only required glasses to improve visual acuity to normal levels. Moderate amblyopia (≥0.300 LogMAR) was identified in 17% of children referred to the HES of which 15% had anisometropia either alone or in combination with strabismus. As previous large clinical studies have established (Chen et al., 2007; Cotter et al., 2012; Cotter et al., 2006; Moseley et al., 2002; Stewart et al, 2004), optical treatment was effective in resolving 32% of anisometropic amblyopia in our cohort and those that required occlusion were more likely to have an associated micro strabismus. This is the first New Zealand based study that has identified common causes of amblyopia from preschool vision screening fails in two out of the three Auckland region health boards. This study is in line with previous work showing that children with anisometropia greater than 1.00D are more likely to develop amblyopia (Donahue, 2005; Ingram et al., 2009; Weakley et al., 2001) and this is most commonly identified at preschool vision screening assessments. As discussed in Chapter 2, we expect aniseikonia to be associated with anisometropia due to the inherent anatomical differences between the two eyes which result in both different refractive errors and different sized retinal images. The difference in retinal image size can be impacted further by spectacle magnification created by corrective spectacle lenses used in the treatment of anisometropia. Current prescribing guidelines do not account for aniseikonia; thus, it is possible that image size difference between the two eyes in anisometropia is a contributory factor in the development of amblyopia and/or in limiting visual improvements during treatment.

8.1.2 Question 2: Is subjective aniseikonia measurable in anisometropia with or without amblyopia? Can we predict this amount through optical modelling?

Aniseikonia is present in anisometropia and can successfully be subjectively measured in anisometropia and anisometropic amblyopia using clinical and psychophysical dichoptic methods as demonstrated for the first time in Chapter 4. Previous reporting of aniseikonia has been limited to case studies in adults with persistent asthenopia following treatment for significant long standing anisometropia (McNeill & Bobier, 2017; Shaw & Bobier, 2012) and often measurement of aniseikonia is not attempted. Subjective aniseikonia tests are thought to be too difficult to administer due to poor vision and suppression. However, the study described in Chapter 4 found that measurement of aniseikonia was subjectively possible even in participants with suppression and that subjective aniseikonia was correlated with anisometropia. Higher amounts of aniseikonia were found in adults with anisometropic amblyopia than either anisometropic adults without amblyopia or isometropic controls. The fact that dichoptic measurement of subjective aniseikonia is possible lends support to the theory that binocular visual function is suppressed or inactive under normal viewing conditions and not permanently lost in amblyopia (Hess et al., 2010; Hess et al., 2012; Knox et al., 2012).

Currently there is no accurate method for assessing aniseikonia in children. Instead clinical estimations are made using the 1% per dioptre clinical rule of thumb (Berens & Bannon, 1963; Ogle, 1950) or empirical calculations (Davis, 1959; Ryan, 1975). Children with anisometropic amblyopia often have lower levels of suppression and binocular functions such as fusion, binocular summation and gross stereopsis are often retained. This suggests that binocular targeted testing would allow for a more accurate assessment of subjective aniseikonia in children. The Aniseikonia Inspector version 3 has been shown to successfully measure subject aniseikonia in school age children (5-13 years old) in one study (Kehler et al., 2014), however this was lens-induced aniseikonia in otherwise visually normal children. Ideally a paediatric aniseikonia test would be engaging and allow for adjustment of image contrast or luminance presented dichoptically to each eye to permit suppression to be overcome to allow simultaneous perception, akin to the CAT test described in Chapter 4.2.3.

In this thesis we examined whether magnification error between the eyes can be predicted using optical modelling methods. This could be a more accurate method of estimating aniseikonia in the absence of a clinical paediatric aniseikonia test. In collaboration with the Auckland Bioengineering Institute, we developed an individualised optical model that produced a focused retinal image in the corrected and uncorrected states. The application of this model (Chapter 4.7), using biometry and refractive data collected in the Clinical Aniseikonia in Anisometropia study (Chapter 4.1) shows that it is possible to predict magnification differences between eyes in patients with anisometropia. As discussed in section 4.9, although previous research has already presented an optical model to predict aniseikonia, it requires multiple measurements that would be difficult in a preschool age group. The model that we have described in this thesis requires refractive and biometry data only, which are more likely to be obtained from preschool children. Biometry equipment is now readily found in most paediatric eye assessment centres due to their being commonly used in myopia control.

Our findings confirm that aniseikonia is a product of anisometropia and that optical modelling is a feasible method of predicting aniseikonia in adults. As part of the MAGNIFY study described in Chapter 6, biometry and refractive data have been collected in children, however due to the Aniseikonia Inspector version 3 and the Awaya aniseikonia test being unreliable in children it is difficult to determine the subjective aniseikonia experienced by children and thus difficult to compare optical modelling results with subjective measurements as described in Chapter 4.

8.1.3 Question 3: Treatment adherence can affect visual outcomes. How does one account for adherence when assessing treatment outcomes for aniseikonia correction lenses versus standard anisometropic lenses?

Treatment success for amblyopia therapy is limited by adherence to treatment prescribed (Awan et al., 2005; Loudon et al., 2006; Pradeep et al., 2014; Stewart et al., 2004; Tjiam et al., 2012; Wallace et al., 2013). The Measuring aniseikonia: investigating neuroplasticity and image factors in amblyopia (MAGNIFY) study (Chapter 6) was a prospective double masked clinical trial that investigated the effectiveness of aniseikonia correcting lenses to standard spectacle lenses for the treatment of anisometropic amblyopia in children. This research study examined the main set out in section 2.9. Whilst developing the proposal for this research project it

became clear that an accurate system for spectacle wear adherence was essential to assess whether the two types of lenses would result in different visual outcomes from the optical treatment phase.

In collaboration with the Auckland Bioengineering Institute, we designed and produced a compact device that fits securely to a wide range of spectacle frames and was found to have a 99% detection rate of overall wear time in our pilot study in adults. The SpecsOn monitor is being trialled for a minimum of five weeks in the MAGNIFY study (section 6.3.6.4) alongside a daily spectacle wear diary to monitor adherence in the target population for which the device was designed. We decided to make wear of the SpecsOn monitor optional when completing consent for all participants in the MAGNIFY study as the device was larger than conceptualised. Due to the financial limitations of this project, it was not possible to reduce the size of the device whilst ensuring adequate battery power and data storage capacity for a 15-week period. The device was also designed to meet child health and safety standards as discussed in Chapter 5, as very small devices may pose a choking hazard. This thesis presented the first prototype of the SpecsOn monitor and future iterations of the device can be refined and made smaller by using custom components and circuitry.

In the current MAGNIFY study, participants (aged 4 to 5 years) completed to date, none of the children who wore the SpecsOn reported the device to be obtrusive or uncomfortable, and all children wore the device for the full five weeks allowing accurate monitoring of adherence of overall wear time. The results of the MAGNIFY study (Chapter 7) did not find a significant difference between adherence monitored objectively and reported subjectively through a daily wear diary in participants who had both available. It is important to note that children who are less compliant with adherence were also less likely to keep or return a daily wear diary which biases the results. The advantage of having an objective monitor removes the need for subjective reporting and provides clinically relevant data that can easily be viewed and explored to review wear patterns such as daily wear times or overall wear time. These factors could influence optical treatment outcomes between the two lenses in the MAGNIFY study but could also provide information in relation to timings for adjunct therapy in routine clinical care.

8.1.4 Question 4: Main Research Question: Does correcting for image size difference at first diagnosis of anisometropia improve visual function in children undergoing optical treatment for anisometropic amblyopia?

Despite the COVID-19 pandemic the MAGNIFY clinical trial has successfully recruited half of the required participants and is still underway. The MAGNIFY study commenced recruitment in January 2020 (registered double-masked clinical trial). The study involved a comparison of treatments for preschool children with anisometropia, requiring a number of in-person clinic visits (over 15 weeks) to complete testing. However, soon after recruitment commenced, the COVID-19 pandemic hit, and recruitment was suspended due to government restrictions preventing in-person clinical and research appointments. The vast majority of participants for this study were recruited through the B4 School vision screening programme. Children who fail the visual screening were referred to public ophthalmology clinics (ADHB, CMDHB), optometrists (both public and private), and private ophthalmologists for further assessment. Children who fit the tight inclusion criteria set out in Chapter 6 were then referred to the MAGNIFY study by eye-care providers. During a total of 11 months of lockdowns over the last two years, the B4 school screening teams were not able to continue with screening and optometry practices and routine private and public ophthalmology clinics were not operating at usual capacity, which majorly limited our recruitment. It took time for the various screening and hospital systems to catch up once each lockdown period was eased and referrals had increased, as parents/caregivers were often cautious about attending in-person appointments and enrolment uptake was slow. Further disruption to the study was caused by missed appointments during time sensitive data collection windows. The more recent arrival of the Omicron variant in January 2022 has further delayed the resumption of vision screening in schools. Since the change to the COVID pandemic protection framework (traffic light system), Auckland has mostly been at the red alert level. This is the strictest alert level in the protection framework, and only allows for the more urgent or severe cases (such as asymmetric/absent red reflexes, white pupil and infective or inflammatory disease) to be seen in the DHB clinics, with routine assessments (such as for anisometropic amblyopia, the target population in the MAGNIFY study) being a low priority. The main referral pathway for children who fail vision screening in the Auckland region is through the public ophthalmology and optometry clinics, and the backlog of patients with a higher priority is causing further delay in referral to the MAGNIFY study.

Despite the unprecedented and unpredictable disruptions for the past two years, the MAGNIFY clinical trial enrolled half of the required sample size (20), all of whom finished strict data collection visits. Due to ongoing recruitment and requirements to maintain the integrity of the double-masked clinical trial, only the overall preliminary results were reported in Chapter 7 as it was not possible to unmask the treatment groups at the time of thesis submission. In the 20 children who completed data collection, distance visual acuity in the amblyopic eye improved by an average of 4 lines after 15 weeks of spectacle wear. However, we expect children in both treatment groups to improve, as they go from an uncorrected refractive state to receiving more binocularly balanced and focused retinal images. The results from the MAGNIFY study support the premise that optical treatment is effective in restoring retinal image clarity and prompting binocularity, leading to a resolution of amblyopia in about a third of children with anisometropic amblyopia (Chen et al., 2007; Cotter et al., 2012; Cotter et al., 2006; Moseley et al., 2002; Stewart et al, 2004).

In adults, symptoms of aniseikonia often present as asthenopia or difficulty with reading and binocular comfort following refractive correction of anisometropia (Bannon, 1944) but this was not evident in the MAGNIFY study cohort. Spectacle correction was generally well accepted and adherence to full time wear (≥75% of the awake time) was high, with 96% of children in this preliminary analysis reporting full time spectacle wear. However, once the treatment groups are unmasked, we may find that both groups show similar improvements and similar levels of adherence (supporting the null hypothesis), or that there will be some differences in improvements of visual acuity or adherence or both.

8.2 Summary

Anisometropia is a common condition identified during preschool vision screening programmes that are valuable in identifying preventable visual impairment. Refractive amblyopia accounted for most of the visual impairment identified in this preschool vison screening cohort and optical treatment is an effective method of treatment in most children with anisometropic amblyopia. Aniseikonia is likely to have a similar prevalence as anisometropia and therefore likely to be a factor in the development of anisometropic amblyopia and with adherence to spectacle wear. The conclusion of the MAGNIFY study will provide evidence to reject or accept the null hypothesis.

8.3 Strengths and Limitations

This thesis presented several novel studies investigating aniseikonia in anisometropia and amblyopia. Aniseikonia is often studied in adults and children with optically induced aniseikonia using size lenses. The Clinical Aniseikonia in Anisometropia Amblyopia study (Chapter 4) specifically investigated aniseikonia in adults with anisometropic amblyopia. We identified that aniseikonia can subjectively be measured in people with anisometropic amblyopia. This is the first study to our knowledge to present a quantitative relationship between aniseikonia and anisometropia in those with anisometropic amblyopia. The greater amounts of aniseikonia found in the anisometropic amblyopia group is in line with the hypothesis that aniseikonia may contribute to suppression and may limit binocular visual recovery in anisometropic amblyopia. This led to the main experimental hypothesis that correcting aniseikonia simultaneously with anisometropia at first diagnosis will reduce the need to develop suppression and improve the overall visual outcomes from amblyopia treatments. This hypothesis can only be accepted or rejected following conclusion of the MAGNIFY study. During the investigation of measuring aniseikonia in those with anisometropic amblyopia, a contrast-balanced aniseikonia test was used which is described in section 4.2.3. This novel psychophysical procedure allowed participants to make manual adjustments to compensate for any phorias and equalise perceived contrast of dichoptic images to compensate for any suppression. This test is still in the experimental stages and further validation in adults and then children is required before it can be considered for clinical use.

One of the overarching themes that is apparent through the investigation of anisometropia in this thesis is that optical treatment is an effective modality for the treatment of refractive amblyopia and, in particular, anisometropic amblyopia. The retrospective review study is the first study, to our knowledge, to review the outcomes of children seen in the HES following a failed B4 school vision screening result in the ADHB and WDHB catchment areas. The study highlighted that clinically, optical treatment is generally well accepted by all children regardless of background. However, it demonstrates that some groups were more likely to access and complete treatment than others. Māori and Pacifica children were more likely to disengage from the HES than non-Māori and non-Pacifica children. These inequities may have been due to the costs and treatment burden related with amblyopia treatment (cost of spectacles and

patches) including parental/caregiver's loss of earning from attending hospital appointment and transportation costs. Cultural factors such as racial discrimination and mistrust of the health system maybe further reason for these inequalities (Harris et al., 2012) but this was not specifically explored in this thesis. As discussed in Chapter 3, the Enable spectacle subsidy is available to contribute towards the cost of a pair of spectacles for whanau that hold a community services card. Accessing the funding via an accredited Enable optometrist/ophthalmologist (optometrists and ophthalmologists have to apply for accreditation) is not easy as this information is not readily available and requires parents/caregivers to have internet access to locate these specific details. Service location and business hours of accredited providers may make it more difficult to access especially if the commute times are long and/or the location is not serviced by public transport or does not offer free car parking.

Chapter 7 (section 7.4 Adverse Events) highlighted that children often break/damage or lose their spectacles and this can happen multiple times throughout the course of treatment. Costs of replacement or repair are not available through the Enable subsidy within 12 months of a claim. Reporting on the rate of spectacle replacement is not often included in the investigation of amblyopia treatment even though broken, lost or damaged spectacles that are not replaced affects treatment outcomes. The MAGNIFY study is the first study to our knowledge that has reported broken, lost or damaged spectacles as adverse events that may affect treatment outcomes. The cost of replacement may prevent some families from continuing with treatment. In New Zealand the cost of repair or replacement is not covered by the Enable subsidy for those that are able to claim it, and this cost burden falls on whānau which could further contribute to financial barriers and the health-related inequality seen across New Zealand. From the findings of this thesis, it is recommended that universal support is required for subsidised access to spectacles and other amblyopia treatment (such as eye patches) for all children, especially those in the sensitive period for visual development (< 8 years old) where amblyopia therapies are most effective. The provision of this service may lead to better treatment outcomes reducing the need for further occlusion treatment undertaken by the HES in New Zealand and in turn reducing the burden on the health system. The findings in Chapter 3 of this thesis provide further contribution to New Zealand based literature on refractive error and amblyopia which can be used to guide government policies. The findings from Chapter 3 directly contributed to the

Ministry of Health WCTO vision screening review. The WCTO is a national New Zealand programme supporting the health, development and wellbeing of children from birth to 5 years old. In 2019 the Ministry of health commenced a review of the programme to ensure it was delivering optimal outcomes for all children and their families. Several suggestions made by the vision screening review team resulted from the outcome of this study (see sections 3.7.1 and 3.7.5). Information on the differences between DHBs in this thesis and those of other New Zealand based studies, can assist future planning for Health NZ.

Adherence to treatment is a problem in all aspects of medical care and in amblyopia treatment it has been directly shown to affect the outcome of amblyopia therapy. There are several monitors currently available that have been adapted from their original purpose to monitor spectacle wear. Several of the devices available are not adaptable to existing frames and are expensive. Those that are adaptable are less reliable and pose a health safety risk in pre-school children. To our knowledge the manuscript included in Chapter 5 is the first to describe an inexpensive compact device that is specifically designed to be adaptable to a wide range of spectacle frames and specifically developed to be used by pre-school children during the optical treatment phase. The ease of data retrieval and analysis is also a strength of this device as the clinically relevant data can provide overall wear time as well as being able to be analysed for more specific questions such as spectacle adherence during weekends. The SpecsOn device can also be employed by a wide range of other clinical and research applications in the treatment of childhood vision conditions that require monitoring of spectacle wear including hyperopia, myopia and accommodative esotropia. Future iterations of the device may include a reinforcement feature, for example, an app alert that is sent to parents or caregivers if the spectacles have been removed for a prolonged period or a visible indicator incorporated into the device to show daily wear time has been achieved.

The MAGNIFY study is the first double-masked randomized clinical trial to investigate aniseikonia correction lenses at first diagnosis of anisometropia that improve image clarity and reduce retinal size difference to produce better visual acuity and stereoacuity improvements after 15 weeks of optical treatment in children with anisometropia. The study followed best practice for amblyopia treatment including 15 weeks of optical treatment, standardised clinical measurements and double-masking of treatment

allocation. To preserve the integrity of this landmark trial, the treatment allocation cannot be unmasked while the clinical trial continues to recruit and collect data. This presents a major limitation of this thesis, as without the results of this clinical trial, the main hypothesis connecting aniseikonia and anisometropic amblyopia remains unanswered. Completion of the MAGNIFY study was significantly hindered by the COVID-19 pandemic over the last two years. However, I am expecting to resume recruitment in May 2022, after the peak of the Omicron surge currently coursing through New Zealand. Once recruitment is fully under way, we estimate that the remaining 20 participants will be recruited within 6 to 9 months.

8.4 Future Research

This research highlights many areas for further potential investigation. The MAGNIFY study will resume in May 2022 and on completion of the study, if significant differences between the treatment groups are found, the result will provide significant evidence towards the importance of aniseikonia in those with anisometropia. The Shaw lenses used in the MAGNIFY study are widely available to practitioners around the world, however the proprietary design limits fully understanding the makeup of the lenses. If aniseikonia-correction lenses are effective, then this presents a potential for additional lens designs to be developed. Currently the existence and importance of aniseikonia is assumed through inference from optical theory and adult case studies. The rejection of the null hypothesis will transform the clinical treatment of children with anisometropia by providing correction of retinal image size as well as image focus at diagnosis of anisometropia. This will be invaluable in improving outcomes from optical treatment, reducing the demand for additional occlusion treatment, and contribute towards understanding the causes of visual deficits in anisometropic amblyopia.

A new vision screening protocol developed from the findings of the retrospective review study in Chapter 3 should be evaluated to ensure all children are able to access amblyopia treatment starting with optical treatment. This should include all the children that do not present for further assessment and the reasons for this in order to fully understand the barriers related to access to eye care. The retrospective chart review study described in Chapter 3 provided information of common refractive errors and rates of amblyopia identified during B4 School vision screening assessment. However, population-based studies investigating visual impairment would be required to

determine the true prevalence and factors associated with amblyopia and its risk factors across New Zealand. A cross-sectional population study should include all children aged 36 to 84 months selected through postcode random cluster sampling, stratified by socioeconomic status, to ensure true representation of the population.

Subjective aniseikonia can be successfully measured in anisometropic amblyopia using psychophysical dichoptic and clinical methods as discussed in Chapter 4. The published manuscript provided data on the New Aniseikonia Test and the Aniseikonia Inspector Version 3 which are two of the routinely used clinical tests. Chapter 4 showed good correlation between the tests with low levels of bias in the absence of a gold-standard test for subjective aniseikonia. This is the first study that we know of that has attempted to use these tests on people with naturally occurring anisometropia rather than lens-induced aniseikonia in visually normal adults. This provides us with a reliable method for assessing subjective aniseikonia in future research investigating factors which contribute to perceived aniseikonia.

The investigation of aniseikonia in children is significantly limited by a lack of a suitable paediatric aniseikonia test. Previously the belief of aniseikonia testing being too difficult to assess in the presence of suppression and significantly reduced visual acuity has limited development in this area. The dichoptic method used by the CAT test in Chapter 4 is a promising method requiring further development and validation in adults prior to being tested in children and can be helpful for future research in psychophysical and clinical studies. Once a validated paediatric test is available, the investigation of aniseikonia alongside optical modelling will provide us with a better understanding of the role of aniseikonia in anisometropia. Currently in the absence of paediatric tests, predicting aniseikonia through optical modelling is potentially a useful method of estimating perceived aniseikonia. Further research using biometry data from children with and without anisometropia and anisometropic amblyopia to predict aniseikonia using the optical model described in Chapter 4 is required to provide further evidence in this age group.

8.5 Overall Conclusion

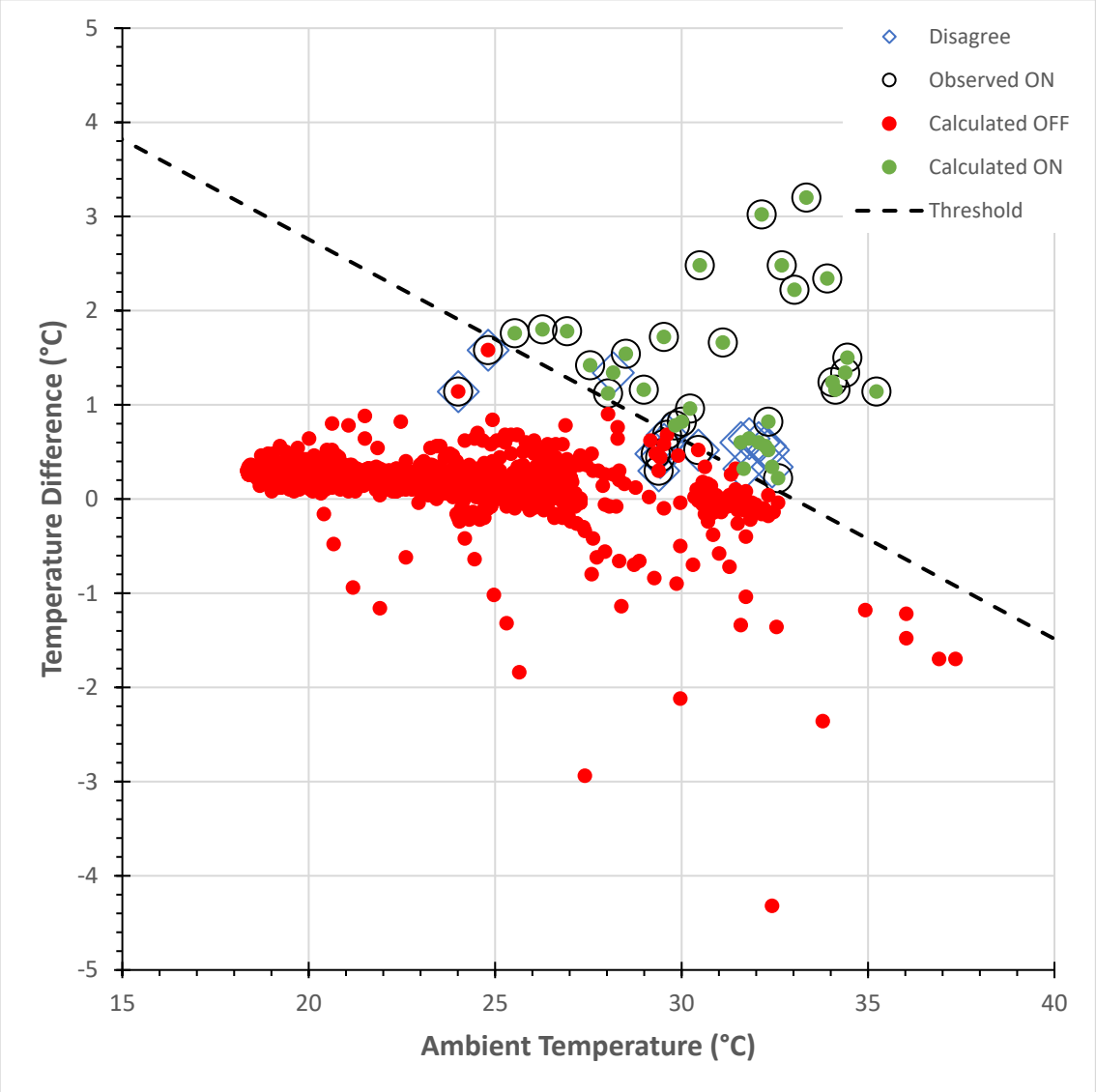
Aniseikonia is closely associated with anisometropia, and our findings through this thesis are further testimony as to how interlinked the optics, physiology, and aetiology of anisometropic eyes are in the amount of subjective aniseikonia experienced by an individual.

This thesis provides further scientific support for the optical treatment phase for amblyopia, and in particular anisometropic amblyopia. We established that anisometropia was commonly associated with moderate levels of reduced visual acuity identified through preschool screening and seen in the HES in two out of three Auckland regional health boards. Optical treatment is a safe and acceptable treatment for anisometropia, however access to this simple and effective treatment is not equitable in New Zealand and a universally subsidised approach to eyecare for all children is required to address health inequities across New Zealand. Treatment success is directly associated with adherence with prescribed treatment, which in amblyopia is often subjectively monitored. A novel objective SpecsOn monitor designed specifically for monitoring optical treatment in preschool children was prototyped and tested as part of this thesis, which has potential to provide in-depth knowledge around wear patterns that may influence visual outcomes. This thesis provided new evidence that aniseikonia is a product of anisometropia. Clinically applicable methods have been presented for estimating and accurately measuring perceived aniseikonia in anisometropic amblyopia. The new optical model presented in this thesis provides a tool to estimate aniseikonia in younger patients who cannot give reliable subjective responses, allowing researchers to investigate factors influencing optical treatment, which could further improve outcomes. Visual deficits often remain following amblyopia treatment for anisometropia, and aniseikonia maybe a contributory factor. The MAGNIFY study is ongoing, however on conclusion of the study, the results will contribute additional evidence to that already presented in this thesis on the importance of aniseikonia in anisometropia and anisometropic amblyopia.

Appendix 1. Supplementary SpecsOn analysis plot of wear time in warmer ambient temperature.

This appendix contains a sample of the analysis plot of wear time in a warmer ambient temperature from Chapter 5. The plot below shows that spectacle wear time was detectable even in warmer climates (Fiji,18°C - 37°C as opposed to New Zealand,12°C - 35°C).

Sample plot shows good agreement in detecting spectacle wear based on threshold analysis.



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