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Development of vision and strabismus in childhood: prevalence and risk factors

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under the supervision of Professor Kathryn Rose and Dr Amanda French

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Certificate of original authorship

I, Felicia Christabelle Adinanto declare that this thesis, is submitted in fulfilment of the requirements for the award of Doctor of Philosophy, in the Graduate School of Health at the University of Technology Sydney. This thesis is wholly my own work unless otherwise referenced or acknowledged. In addition, I certify that all information sources and literature used are indicated in the thesis. This document has not been submitted for qualifications at any other academic institution.

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It takes a village to raise a child,

I am blessed to be the child in a village of extraordinary women.

The first woman I must thank, is my darling mother who took a leap across the ocean in search of a better life. Thank you Mum and Dad for raising me with strong discipline and selfless love. You have given me so much in life and I wouldn't be here without the hard work you've put into providing the best in life for Rick, Janica and myself.

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Thesis Abstract

The reported prevalence of strabismus is highly variable, as is the sampling and methodologies used to ascertain strabismus. There are a number of risk factors that have been linked to strabismus including; familial predisposition, refractive error, various genetic syndromes, developmental conditions and ethnicity. More recently, birth-related factors have been consistently identified, such as prematurity, low birth weight, maternal and infant health. A systematic analysis of past reports of strabismus prevalence may clarify trends in the occurrence of strabismus. Determination of strabismus in population-based representative samples using gold standard techniques may provide a more accurate indication of current prevalence and associated risk factors.

The aims of this thesis were to investigate the:

i. Current prevalence of strabismus in Australian children compared to historical and international estimates
ii. impact of age, ethnicity and refractive error on the prevalence of childhood strabismus and type of strabismus
iii. impact of birth factors on the development of strabismus and other ocular conditions, particularly admission to Neonatal Intensive Care Units (NICU).
iv. normal development of vision and ocular motility in infants admitted to NICU
v. need for vision screening in infants admitted to NICU and, recommend the most appropriate tests and time/age to provide vision screening for these infants.

To address the aims of the thesis, research methodology included; 1) a systematic review and meta-analysis of the literature on the prevalence of childhood strabismus, examining changes over time, 2) an analysis of pre-existing data sets to determine the influence of age, ethnicity, refractive error and birth factors and 3) the Neonatal Vision

Study (NVS), a prospective longitudinal cohort study of infants admitted to NICU to investigate the normal development of vision and ocular motility in infants admitted to NICU. It is anticipated in future that this cohort of children will be followed until at least school-age. The pre-existing population-representative data sets of children used were the; Sydney Paediatric Eye Disease Study (SPEDS), the Sydney Myopia Study (SMS) and Sydney Adolescent Vascular and Eye Study (SAVES) collectively known as the Sydney Childhood Eye Studies (SCES). These studies included a total of 7266 children ranging from 6 months to 17 years of age.

The systematic literature review and meta-analysis suggested that there has been a significant decline in the prevalence of childhood strabismus globally between the 1940's to 1980's and more recent stabilisation in the last two decades to a prevalence of 2.6%. This decline in the prevalence of strabismus over time may be the result of changes in environmental risk factor exposures. While there were no differences in the overall prevalence of strabismus between ethnic groups, there was a difference in the prevalence of the type of strabismus present between ethnicities but, the reasons for these differences are not clear. These findings provide a greater understanding of current rates of strabismus within various populations globally, set the direction for subsequent analyses of pre-existing population-based data and the independent project of this PhD thesis, the NVS.

From the preexisting data, it was found the prevalence of strabismus was stable earlier in childhood and later increased with age, predominately due to an increase in the prevalence of intermittent exotropia in the adolescents in the SAVES study. The main contributing factor to the development of strabismus in this study was significant refractive error, both myopia and hyperopia, as well as anisometropia. Examining the two longitudinal cohorts of children from SMS and SAVES, it was evident that 25% of 6 year old children with myopia at baseline develop intermittent exotropia by the time they were 12 years old. This investigation also revealed that while there is incident

strabismus occurring, the rate of successful strabismus treatment is high, therefore prevalence rates tend not vary due to cases of recovery from strabismus being offset by new cases of strabismus.

A number of studies investigating childhood ocular conditions, including strabismus, amblyopia and refractive error and associated risk factors have identified a number of modifiable antenatal risk factors including; maternal health, low birth weight, premature birth and admission to neonatal intensive care units (NICU). Current screening regimes specifically target premature and low birth weight infants who are deemed at significant risk for retinopathy of prematurity (ROP). However, there is an overall lack of routine screening and ongoing follow-up for infants who have been admitted to NICU and who are potentially at risk of adverse ocular outcomes, independently of ROP. This concern is heightened by the rising prevalence of infants being admitted to NICU over the past decade, especially in Australia. The investigation reported here included the 6 month to 6 year old children from SPEDS and SMS to establish if there was an overall higher prevalence of eye conditions in children admitted to NICU than those who were not. It was found that there was a greater prevalence of anisometropia, myopia and strabismus in children who had been admitted to NICU. This greater risk for eye conditions with admission to NICU was independent of other known risk factors; such as prematurity and low birth weight, suggesting that there is need for ocular screening and surveillance of all children admitted to NICU, beyond those deemed at risk of ROP.

The majority of infants recruited in the NVS were born prematurely and of low birth weight. Development of visual acuity (VA) at three months was most highly correlated to corrected age, however by 12 months, the chronological age of the infant was more indicative of mean VA. A large proportion of three month old infants were also strabismic on cover test and unable to demonstrate binocular vision however, this is considered to be a result of an immature ocular motor system rather than pathological

strabismus requiring treatment. By six months postnatal age, the majority of infants were much more testable and outcomes for ocular alignment and ocular motility testing were comparable to those at 12 months of age. However, more strabismus was evident at 12 months that at six months of age.

Testability for binocular and monocular Teller Acuity Cards was considerably higher than the optokinetic nystagmus (OKN) drum. In these premature infants the inability to visually respond to the rotation of the OKN drum appears to be due to the lack of sufficient ocular motility required to achieve the normal OKN responses. It is therefore more meaningful to use other tests that measure ocular motor and sensory function such as examining ocular alignment, the presence of binocular vision, ocular movements and convergence. This study additionally indicates the appropriate age to vision screen infants admitted to NICU may be at six months, as testability is high and it is early enough to provide intervention for detected conditions.

Overall, the investigations in this thesis have provided further insight into the prevalence of strabismus within representative populations and an at-risk population; infants admitted to NICU. In addition, this thesis has shown the impact of a variety of risk factors for strabismus and has found that refractive errors and birth-related factors are the most pertinent to the development of strabismus in children. Further, this thesis has examined the impact of admission to NICU on the prevalence of ocular conditions, independent of ROP, prematurity and low birth weight. Finally, the visual development of infants who have been admitted to NICU has been determined, with age norms for premature and low birth weight infants for various measures of ocular function, beyond visual acuity, with recommendations for the most appropriate age and protocol for screening these at-risk infants.

Preface: Statement of contribution to the thesis

This PhD presents findings from the Sydney Childhood Eye Studies and the Neonatal Vision Study. The Sydney Childhood Eye Studies, also known as; Sydney Paediatric Eye Disease Study, Sydney Myopia Study and Sydney Adolescent and Vascular Eye Study was a series of three large population-based samples of children aged 6 months to 17 years conducted during 2003-2011. I was not involved in the design or data collection of the Sydney Childhood Eye Studies. However, I used the knowledge acquired from conducting my systematic literature review and meta-analysis on the prevalence of strabismus (Chapter 2) to form the research questions in chapter 4 and 5. I also determined the most appropriate analyses for answering the research questions, conducted and interpreted the statistical analyses and described these in chapters 3-5.

The Neonatal Vision Study was designed as it was recognised in chapter 5 that the neonatal intensive care unit is a location where many at-risk infants can be identified to determine if screening is required for these children. I designed the protocol for the Neonatal Vision Study and was responsible for contacting the appropriate Heads of Departments (Neonatal Care and Ophthalmology) at the Royal Prince Alfred Hospital to negotiate a feasible study which would provide vision screening for these at-risk infants who might not otherwise be seen, create a referral pathway for any infants found to have an ocular condition, while ensuring research integrity and collect appropriate data. It was important that I was familiar with the Sydney Paediatric Eye Disease Study as the two methodologies needed to be compatible so that visual outcomes between infants admitted to NICU as part of the Neonatal Vision Study and a sample of age-matched norms from Sydney Paediatric Eye Disease Study could be compared. After acquiring ethics approval 2017, I conducted all the recruitment, orthoptic assessments at three, six and 12 months, data entry and statistical analyses to conceptualise the research questions to be answered in chapters 6 and 7.

Publications and Presentations

Parts of this thesis have been presented in the following forms.

A journal publication from this thesis (Chapter 2) is currently under peer review by Acta Ophthalmologica: Adinanto FA, French AN, Rose KA. Trends in the prevalence of strabismus over time: A systematic review and meta-analysis.

National and international presentations:

Adinanto FA, French AN, Rose KA. The Prevalence of Strabismus. 2015; Orthoptic Association of Australia; 72nd Annual Scientific Conference, Wellington, New Zealand

Adinanto FA, French AN, Rose KA. The Prevalence of Strabismus: A systematic literature review. 2016; The Association for Research in Vision and Ophthalmology (ARVO) Conference, Seattle, Washington USA.

Adinanto FA, French AN, Rose KA. Risk factors for Esotropia and Exotropia. 2016; The International Orthoptic Association Congress, Rotterdam, Netherlands

Adinanto FA, French AN, Rose KA. Risk factors for Esotropia and Exotropia. 2016; Orthoptic Association of Australia; 73rd Annual Scientific Conference, Melbourne, Australia

Adinanto FA, French AN, Rose KA. The prevalence of esotropia and exotropia by age. 2017; Asia ARVO, The Association for Research in Vision and Ophthalmology Conference, Brisbane, Australia

Adinanto F, French AN, Rose KA. Variations in the Prevalence of Strabismus by Age. 2017; Orthoptic Association of Australia; 74rd Annual Scientific Conference, Perth, Australia

Adinanto F, French AN, Rose KA. Prevalence of Eye Conditions in Children Admitted to Neonatal Intensive Care Units in a Population-Based Sample. 2018; ARVO, The Association for Research in Vision and Ophthalmology Conference, Honolulu, Hawaii

Adinanto F, French AN, Rose KA. Prevalence of Eye Conditions in Children Admitted to Neonatal Intensive Care Units. 2018; Orthoptic Association of Australia; 75th Annual Scientific Conference, Adelaide, Australia

Adinanto F, French AN, Rose KA. Access to Eye Care Services by Schoolchildren in a Longitudinal Cohort. 2019; ARVO, The Association for Research in Vision and Ophthalmology Conference, Vancouver, Canada

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Glossary of Abbreviations

Abbreviation	Full term
ABS	Australian Bureau of Statistics
ANOVA	Analysis of Variance
BSV	Binocular single vision
CI	Confidence interval
cpd	Cycles per degree
CRYO-ROP	Cryotherapy for Retinopathy of Prematurity Study
D	Dioptres
DC	Dioptres cylinder
DS	Dioptres sphere
e-ROP	Evaluation of Acute-Phase Retinopathy of Prematurity Study
ETDRS	Early Treatment of Diabetic Retinopathy Study
ETROP	Early Treatment for Retinopathy of Prematurity Study
EVA	Electronic Visual Acuity
g	Grams
IBM	International Business Machines Coporation
IOL	Intaocular Lens
IVF	In Vitro Fertilisation
LogMAR	Logarithm of the minimum angle of resolution
MeSH	Medical subject headings
MOOSE	Meta-analysis of observational studies in epidemiology
NICU	Neonatal Intensive Care Units
NVS	Neonatal Vision Study
OCT	Optical coherence tomography
OECD	Organisation for Economic Co-operation and Development
OKN	Optokinetic nystagmus

OMS	Ocular movements
OR	Odds ratio
PD	Prism dioptre
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
RAF	Royal Air Force
RAPD	Relative afferent pupillary defect
ROP	Retinopathy of prematurity
RPAH	Royal Prince Alfred Hospital
SAVES	Sydney Adolescent Vascular and Eye Study
SCES	Sydney Childhood Eye Studies
SCN	Special Care Nursery
SER	Spherical equivalent refraction
SES	Socioeconomic status
SMS	Sydney Myopia Study
SPEDS	Sydney Paediatric Eye Disease Study
SPSS	Statistical package for the social sciences
STARS	Strabismus, Amblyopia, and Refractive Error in Singapore
TAC	Teller Acuity Cards
UK	United Kingdom
USA	United States of America
UTS	University of Technology Sydney
VA	Visual Acuity
VEP	Visually evoked potentials

CHAPTER 1: Introduction

1.1 Strabismus

1.1.1 Overview of strabismus

Strabismus is an overarching term for both manifest and latent deviations of the eyes. When classifying strabismus, it can be described by the direction, frequency, size, onset and cause. Manifest strabismus is the misalignment of the visual axes of the two eyes resulting in the disruption of normal binocular single vision. Manifest strabismus is also known as heterotropia and commonly referred to as a squint. A manifest strabismus may be constant (present at all times) or intermittently present, with functional binocular single vision being used when the strabismus is not manifest. A manifest strabismus can be concomitant, resulting from an issue with sensory fusion or incomitant, related to issues with extraocular muscle function. Concomitant strabismus can be influenced by accommodation, lack of binocular vision and loss of vision in one eye. Incomitant strabismus are less common in childhood. These strabismus can be paralytic, myogenic or restrictive in nature, causing variation in the size of the deviation with position of gaze. A latent strabismus is only present when sensory fusion is suspended and is referred to as a heterophoria. Heterophoria is a normal manifestation of the eyes moving into their physiological position of rest when there is suspension of fusion, unlike constant and intermittent strabismus which are considered pathological.

The direction of the strabismus is important in classifying the type and diagnosing the cause, with an outward (exo) deviation referred to as an exotropia/exophoria and an inward (eso) deviation, an esotropia/esophoria. Vertical strabismus is far less common in childhood and is often associated with an ocular motility condition such as, Brown’s syndrome, congenital fourth cranial nerve palsy or present in combination with a horizontal deviation.

Accommodative esotropia is associated with hyperopic refractive error, which causes the exertion of additional accommodation to clear vision and consequently because of the linked accommodative convergence, an over-convergence, resulting in an esotropia. Of the different types of esotropia, accommodative esotropia is generally considered the most common (53% of esotropias).[1] A study of incidence and types of esotropia based on 385 retrospectively identified cases of esotropia in paediatric patients found that fully accommodative esotropia (that can be completely resolved by the use of glasses to correct the hyperopia) was most common (36%), with a further 10% of cases with partially accommodative esotropia.[2] The second most common type of esotropia in this study was acquired non-accommodative esotropia (17%) and infantile esotropia was present in 8%. Congenital esotropia generally refers to esotropia that has its onset before the age of six months. Most congenital esotropia are constant and large angle deviations, often preventing the development of binocular vision as they are present during the critical period of neural development.[3] There are strong indications that early surgical intervention in infantile esotropia has, by aligning the eyes, the potential to allow for the development of some binocular vision to develop and as such, early detection is important.[4] Birch et al. 2002 investigated the risk factors for an accommodative esotropia arising after surgical alignment for infantile esotropia.[5] They found that children with delayed surgery or who had compromised stereopsis and with any level of hyperopia, had a significant risk of later developing accommodative esotropia.

Few population studies have reported the prevalence of the different types of exotropia individually. However, it is generally agreed that intermittent exotropia is more common than constant exotropia.[6-10] Govindan et al. (2005) reported the incidence of different types of exotropia in a retrospective study of paediatric patients with a diagnosis of exotropia (n=205) in Olmsted County, Minnesota over a 10 year period.[8] The prevalence was approximately 1% in children under 11 years of age and reduced in

older children with an estimated incidence of 64.1/ 100,000 per year. The most common forms of exotropia were intermittent exotropia (52%), intermittent exotropia associated with convergence insufficiency (20%), those associated with neurological and developmental conditions such as; cerebral palsy and developmental delay (15%), and sensory exotropia (8%).

Suppression of the deviated eye is a sensory adaptation that is exhibited in children to remove the double images that result from misaligned eyes, otherwise known as diplopia. While suppression prevents unwanted diplopia in early childhood it can result in amblyopia. Amblyopia is defined as reduced vision in the absence of pathology or uncorrected refractive error. In children with strabismus it develops as a consequence of suppression whereas in children with ptosis, cataract, significant bilateral refractive error or anisometropia, visual development is arrested due to the lack of a visual stimulus that has clear form. Strabismus has been shown to increase the risk of a child developing amblyopia by 28 to 65 times as compared to a child without strabismus.[11,12] Without the appropriate interventions, conditions such as refractive error and strabismus can result in amblyopia, which is preventable but if left untreated, results in permanent vision loss in the eye that cannot be treated in adulthood.

1.1.2 Genetic risk factors for strabismus

There are a number of genetic causes and risk factors for strabismus, with higher rates of strabismus noted in association with a number of genetic syndromes and other systemic and ocular conditions. Genetic risk factors range from craniofacial abnormalities that anatomically cause misalignment of the eyes, to neuro-developmental conditions that impair sensory development and subsequently result in concomitant strabismus (strabismus that is not caused by motor dysfunction that does not vary in different positions of gaze).[13-15] Dysinnervation of extraocular muscles can result from genetic syndromes such as Duane's retraction syndrome, where there is

congenital absence or partial absence of the sixth cranial nerve and the third cranial nerve aberrantly supplies innervation to the lateral rectus muscle[16] or Congenital Fibrosis of the Extraocular Muscles (CFEOM) where there is impaired innervation of extraocular muscles resulting in eventual fibrosis of these muscles.[17] Genetic mutations can also cause mitochondrial defects and result in conditions such as, Kearns-Sayre syndrome which includes retinal pigment degeneration external ophthalmoplegia which is a chronic and progressive weakness or impairment of the extraocular muscles.[18]

Congenital anomalies have been reported to be associated with an increased risk of strabismus. For example, cerebral palsy has prevalence of strabismus rates of 17.5%.[15] Children with hydrocephalus have a prevalence rate of strabismus of 32.7-68.9% and those who have had shunt revisions are at even greater risk of strabismus.[14,19] Up to 97% of children who have Down syndrome have been reported to have, ocular conditions, with 32.5% having strabismus, 62.3% hyperopia and 59.7% astigmatism.[20] In particular, Down syndrome is associated with an increased risk of esotropia with a reported prevalence of between 18% to 22%, as well as associated hyperopia and accommodative esotropia.[21,22]

While the contribution of genetics is clear for rare syndromic strabismus and some forms of incomitant strabismus, it is less clear how genetics are related to more common concomitant strabismus. There have been a number of studies examining the contribution of family history of strabismus to the risk of strabismus in offspring. A systematic review of seven studies investigating odds of strabismus in cases where there was a family history, concluded that there is a consistent link between a family history of strabismus and strabismus in offspring.[23] A population-based study in the United Kingdom (UK), found that children who have a first degree relative with strabismus or amblyopia are 2.4 times more likely to develop strabismus themselves.[24] Heritability based on siblings with strabismus varies significantly in the reported

literature, with estimates from 2 to 41 times greater risk of strabismus.[11,25] One clinical study of children attending paediatric eye care for strabismus, reported that 56% of those with esotropia and 17% of those with exotropia have at least one first degree relative with strabismus.[26]

While there are strong associations between esotropia and a family history of strabismus, the potential contribution of moderate to high hyperopia that can be familial[27] should also be considered. Follow-up of children known to have a family history of strabismus, demonstrated that 17% developed strabismus and all of those who developed esotropia had been hyperopic from infancy and had remained hyperopic.[28]

Genetic studies of twins have found concordance for strabismus to be higher in monozygotic twins compared to dizygotic twins, suggesting some inheritance is likely.[29-31] However, these studies do not always account for other confounding variables, as twins, especially monozygotic twins, are often born premature and of low birth weight, which are independently known risk factors for strabismus.[25,32] While genetic studies provide important information on the risk of developing strabismus,[27] there is a high prevalence of concomitant strabismus in these studies, which is known to also have significant non-genetic risk factors.

1.1.3 Environmental risk factors for strabismus

There have been a number of epidemiological studies that have investigated environmental risk factors for strabismus. Some modifiable risk factors for strabismus explored in the literature include maternal health during pregnancy, gestational factors and infant antenatal care.[24,25,33,34] In 2006, a report on the younger cohort (aged 6 years) from the population-representative Sydney Myopia Study (SMS) investigated a wide range of potential risk factors for strabismus.[34] Children with strabismus and particularly esotropia, were more likely to be of European Caucasian ethnicity.

However, this association was no longer significant after adjustment for hyperopia, indicating that a higher prevalence of hyperopia in children of European Caucasian ethnicity may have been a contributing factor. In addition, children who were premature at birth (<37 weeks), low birth weight (<2500g) and admitted to a neonatal intensive care unit (NICU) after birth were more likely to be strabismic and the risk was increased for both esotropia and exotropia when these factors were present. Interestingly, children who were both premature and not breastfed were at a particularly high risk of strabismus. However, this may have reflected the inability to breastfeed extremely premature infants rather than a direct association with breastfeeding and has not been found in subsequent study.[11] Chew (1994) had previously also reported an association between strabismus, European Caucasian ethnicity, lower birth weight, greater maternal age and maternal smoking.[25]

A number of additional studies have confirmed the relationship between low birth weight, prematurity <37 weeks gestation and strabismus, with the estimated risk in the range of two to four-fold.[25,32-34] This risk of developing strabismus has been shown to increase further in children who are born extremely premature, <32 weeks gestation, and of very low birth weight <1500g.[35] Maternal smoking, although not significantly associated with strabismus in the report by Robaei et al. (2006),[34] has been reported to be associated with strabismus in a number of other studies.[24,25,31,33,36] While defining potentially modifiable risk factors plays a major role in the prevention of strabismus, the mechanisms for how these gestational factors impact the development of binocular vision and ocular alignment is not well understood. As these birth factors, along with admission to NICU are highly correlated, it is difficult to determine the relative influence of each on the development of strabismus.

A series of linked large, population-based studies of infants and pre-school children using similar methodology have been conducted in recent years. These include; the Strabismus, Amblyopia and Refractive Error in Singaporean Preschoolers Study

(STARS) and the Multi-ethnic Pediatric Eye Disease Study (MEPEDS) and Baltimore Pediatric Eye Disease Study (BPEDS) in the United States (US). These studies have all sampled children aged six months to six years. In STARS, admission to NICU was associated with strabismus, but birth weight, prematurity and maternal smoking were not.[11] Chia et al. (2013) also reported that those of higher socioeconomic status (SES), measured by higher household income and with higher levels of parental education were less likely to have strabismus. The Avon Longitudinal Study of Parents and Children (ALSPAC), similarly found that low SES was associated with increased rates of strabismus.[24] SMS, however, found there was no relationship of strabismus with SES.[34] Cotter et al. (2011) also reported from the MEPEDS and BPEDS samples that there was no association of esotropia and exotropia with factors that would indicate SES, such as care giver's education, household income and/or acquisition of health insurance.[33]

In examining associations with refractive error, Cotter et al. found bilateral astigmatism of ≥ 1.5 D, anisometropia ≥ 1.0 D difference or 0.5 to 1.0D of astigmatic anisometropia or myopia of at least 1.0D were associated with exotropia while, hyperopia more than 5.0D and anisometropia are associated with esotropia. In other studies of pre-school children aged three to six years in China and in the UK have found hyperopia greater than 2.0D is a significant risk factor for the development of esotropia, as are low levels of anisometropia <0.5D.[37,38]

1.1.4 Treatment of strabismus

Treatment of strabismus has been well established with the first form of treatment provided usually being the prescription of glasses to correct any associated refractive errors. The second form of treatment which may be provided is patching for associated amblyopia which may have developed as a consequence of strabismus. The Pediatric Eye Disease Investigator Group (PEDIG) investigated different treatment regimens for the management of amblyopia and recommend a period of refractive adaptation for

16-18 weeks before commencing patching.[39] Without equal vision in both eyes, subsequent treatments using orthoptic exercises or strabismus surgery to realign the eyes may not be as effective.

The treatment of infantile esotropia is predominately aimed at achieving a cosmetically acceptable alignment of the eyes using strabismus surgery. However, there is some evidence for early surgical intervention to provide the opportunity for binocularity.[40] The treatment of accommodative esotropia is dependent on the prescription of glasses to fully correct hyperopia, which is the cause of the esotropia. It has been found that children who have an onset of accommodative esotropia later in childhood have better binocular outcomes compared to those who develop the condition within the first year of life.[41] In addition, children who have a higher accommodative convergence to accommodation ratio are at greater risk of decompensation of their esotropia than those with a normal accommodative convergence to accommodation ratio.[42]

Whether intervention is a valuable approach to treating intermittent exotropia is a topic of debate, with a 2013 Cochrane systematic review finding only one randomised control trial (RCT) eligible for inclusion that suggested unilateral surgery is more effective than bilateral surgery.[43] But, whether surgery is necessary in most cases is not known, with some children remaining well-controlled and infrequently dissociating to a manifest exotropia while others deteriorate, sometimes with decompensation of the intermittent exotropia to constant exotropia.[44,45] A 2015 RCT by PEDIG examined the outcomes of patching treatment versus observation only and found that deterioration over the six month study period was uncommon and did not differ between the patching and observation groups.[46] This suggests that ongoing disruption of fusion hastened decompensation to a manifest exotropia.

1.2 Thesis overview

The investigations in this thesis aim to provide further insight into the prevalence of childhood strabismus within representative populations and an at-risk population of infants admitted to NICU. Although associated risk factors for strabismus have been identified, there is limited longitudinal data to establish causality and describe the natural history of strabismus with age. Further, this thesis examines the visual and ocular development of infants who have been admitted to NICU in order to determine if there is a need for routine screening of these infants in Australia. The body of work completed is presented in the format of a thesis by compilation. The following section provides a brief overview of each chapter and an outline of the thesis structure to facilitate reading.

Chapter 2 of this thesis is a systematic literature review and meta-analysis of the prevalence of childhood strabismus over the past 2 decades. The chapter is presented in the form of a journal article which has been submitted for publication and is currently under review. This chapter aims to identify any trends which may have occurred in the prevalence of strabismus over time with current rates varying between 2 and 4%.[34,47,48] It also explores the current prevalence of strabismus and whether there are any trends by age and ethnicity. In order to determine an accurate estimation of prevalence rates globally, the meta-analysis only includes papers that used a gold standard method of cover test for determining the prevalence of strabismus in population or school-based samples of children. The paper also explores the difference between the prevalence of esotropia and exotropia as they have an apparent different aetiology.

Chapter 3 presents the protocol for attaining the pre-existing data used in the analysis for this thesis. These studies collectively known as the Sydney Childhood Eye Studies (SCES) were conducted between 2003 and 2011. The data was attained from two studies, the population- based sample of children aged six months to six years known

as the Sydney Paediatric Eye Disease Study (SPEDS) and the SMS that consisted of two cohorts aged six and 12 years at baseline and who were then followed-up five to six years later in the Sydney Adolescent Vascular and Eye Study (SAVES) then aged 12 and 17 years. The studies used where possible parallel methods and were designed using age-appropriate and gold standard testing techniques to assess visual acuity, ocular alignment, ocular pathologies and determine refractive error using cycloplegia. The methodological similarity between these studies made it possible to pool the data used in chapters 4 and 5.

Chapter 4 presents the prevalence of strabismus by age within the pre-existing SCES data of children aged 6 months to 17 years. As the large sample includes children over a wide age range, trends in the development of esotropia and exotropia can be explored more fully. It is anticipated that esotropia would be more prominent in younger age groups, due to the presence of congenital esotropia and accommodative esotropia, while exotropia is often considered developmental, often occurring later in childhood. In addition to age, the presence of two sufficiently sized samples of different ethnicity due to the diversity of Sydney's population, allowed for any differences in esotropia and exotropia to be investigated by ethnicity. The longitudinal data of the SMS children followed-up in SAVES also allowed for the impact of strabismus treatment and the development of refraction on the incidence of strabismus to be explored.

With the collection of birth history through parental questionnaires, the impact of birth factors, and in particular, admission to NICUs on the development of ocular conditions was investigated in chapter 5. This chapter uses the six month to six year old participants of the pre-existing SCES data to determine if infants admitted to NICU are at greater risk of ocular conditions, as previously published data had identified admission to NICU as a risk factor for strabismus and amblyopia in the six year old children.[34,49]

Chapter 6 presents the background literature on the development of vision, binocular vision and refractive errors. The neonatal care unit, prematurity, birth weight trends, the impact of prematurity and low birth weight on retinopathy and other ocular conditions are also reviewed. The chapter includes the design and protocol for the Neonatal Vision Study, a prospective study of a cohort of infants admitted to the Royal Prince Alfred Hospital (RPAH) NICU.

Chapter 7 presents the findings from the 66 infants admitted to the RPAH NICU who were recruited between 2017 and 2020. The vision assessments at three, six and 12 months of age are presented to demonstrate the development of vision and ocular alignment in these infants who are predominately born prematurely and of low birth weight. As three month old infants showed variability in the tests they were able to perform and their responses to the Teller Acuity Cards, OKN drum, prism fusion test, convergence and ocular movements were compared to determine if there were any trends in the development of vision and ocular motility. These tests were repeated at subsequent visits and additionally cycloplegic refraction was carried out at age 12 months.

The final chapter summarises the findings of this thesis and discusses the potential impact of the findings in each chapter. This chapter also includes suggestions for potential ongoing research to further our understanding of strabismus, and in particular the development of ocular conditions in early infancy, with a particular focus on infants born prematurely, of low birth weight or who require admission to NICU who are at greater risk of ocular conditions and require early intervention. This final chapter provides recommendation and justification for providing screening and surveillance of vision and ocular alignment in these at-risk infants.

CHAPTER 2: Trends in the prevalence of childhood strabismus over time: A systematic review and meta-analysis

2.1 Abstract

Purpose: To determine the current prevalence of childhood strabismus and whether it has altered over time.

Methods: Papers were sourced from PubMed, Medline and Wiley Online using MeSH terms; epidemiology, prevalence, strabismus, esotropia and exotropia, in addition, hand searching was conducted for earlier papers. All identified titles and abstracts were assessed by two reviewers against an inclusion criteria of population or school-based sample and a cover test by a qualified examiner, as the gold standard method for detecting strabismus. Data was extracted from 52 papers, synthesized following MOOSE and PRISMA guidelines and statistical analyses were performed using IBM SPSS.

Results: There was an overall decline in the prevalence of childhood strabismus over time ($r=-0.3$, $p=0.002$) from a mean prevalence of 4.5% pre-1960, to a more stable prevalence of 2.6% by 2010-2018. In parallel, the prevalence of esotropia has declined ($r=-0.7$, $p<.0001$), however, prevalence of exotropia has increased ($r=0.4$, $p=0.015$). In particular, there has been a decline in overall strabismus ($r=-0.53$, $p= 0.006$) and esotropia prevalence ($r=-0.66$, $p= 0.001$) in European Caucasian populations. There was no difference in the overall prevalence of strabismus between ethnicities ($p=0.14$) however, the type of strabismus varied, with more esotropia in European Caucasian children compared to a high prevalence of exotropia in Asian children, while those of Middle Eastern origin had more esotropia earlier in childhood and exotropia later in adolescence.

Conclusion: There has been a decline in the prevalence of strabismus globally, stabilizing in the past 2 decades. No difference in overall prevalence of strabismus was found between ethnic groups. However, there was a difference in the type of strabismus.

2.2 Introduction

Strabismus is a common childhood condition where the eyes are misaligned, which can cause amblyopia, loss of vision in the misaligned eye, which if untreated can be permanent.[47,50,51] This has been shown to result in a greater than normal risk of visual impairment later in life.[52] Strabismus can also result in the loss of binocularity, including stereopsis. This may be of some functional relevance as there is some evidence that the performance of daily tasks, such as pouring water, diminishes proportionally with reductions in stereopsis.[53] An additional consequence of strabismus is the potential for negative perception of individuals with strabismus by caregivers, peers and even by themselves, due to the cosmetic appearance of their ocular alignment.[54-58] Studies of the psychosocial impact of strabismus demonstrate negative perceptions of individuals with strabismus when rated on qualities such as intelligence, health, trustworthiness and happiness compared to those with straight eyes.[59] These negative perceptions even develop in children as young as 6 years old.[60] This highlights the concerns of those with strabismus, that they may be perceived poorly by others due to their appearance.[61] Studies measuring quality of life in individuals with strabismus before and after surgery found psychosocial benefits socially, emotionally, and functionally in children, adolescents and adults when eyes were aligned to a cosmetically acceptable position.[54,59,62]

Early intervention for strabismus is imperative for optimal treatment outcomes[62,63] and therefore, timely screening should be emphasised to facilitate early detection and treatment. This is most apparent in the surgical correction for infantile esotropia for the development of binocular single vision (BSV) as it would otherwise not develop. The best outcomes for BSV occur when strabismus surgery to correct for infantile esotropia is performed before age 2, with up to 78% having BSV restored, compared to 64% when between 2 to 4 years.[4] The management of strabismus can be complex, requiring a combination of optical correction, orthoptic treatment and strabismus

surgery. Childhood strabismus is the primary risk factor for between 15-29% of children with amblyopia[48,64-66] and it requires intensive treatment to improve visual acuity.[67]

There are well-known hereditary and genetic risk factors for strabismus, including craniofacial abnormalities and neuro-developmental conditions, as well as the well-known link with a family history of strabismus.[13,68] Studies investigating childhood strabismus and associated risk factors have also identified a number of potentially modifiable risk factors for the development of strabismus including; maternal smoking, low birth weight and premature birth.[13,25,34,69,70] While hereditary and genetic risk factors do not vary over decades, relatively recent improvements in maternal and neonatal health [71] such as a reduction in the rates of maternal smoking during pregnancy through public health approaches in some locations, may have had an effect.[72-75] In addition, specific factors have also been identified for esotropia and exotropia independently.[25,34] It could be expected that the reduction in the exposure of infants in utero and at birth to various modifiable risk factors, could influence the prevalence of overall strabismus, esotropia and exotropia. Recent reports in population-based studies of young children have found that the prevalence of strabismus to be approximately 2-4%.[34,47,48] However, whether this represents a reduction in prevalence over time has not been systematically investigated. The aim of this meta-analysis is to determine the current and historical prevalence of strabismus and whether the prevalence of strabismus has changed throughout the 20th to 21st century.

2.3 Methods

2.3.1 Literature Search Strategy

A comprehensive search of electronic databases was conducted using PubMed, Medline (OVID) and Wiley Online Library. The search strategy used for PubMed utilised the following terms: ("epidemiology"[Subheading] OR "epidemiology"[All Fields] OR "prevalence"[All Fields] OR "prevalence"[MeSH Terms]) AND "strabismus"[MeSH Terms]. The search strategy for Medline was (exotropia.mp. or exp Exotropia/) AND (esotropia.mp. or exp Esotropia/) AND (exp Prevalence/) AND (Children.mp. or exp Child/) AND (exp Strabismus/). Finally, a Wiley Online Library was performed using search terms Prevalence AND Children AND population AND Strabismus in FullText AND Prevalence AND Children AND population AND Esotropia in FullText AND Prevalence AND Children AND population AND Exotropia in FullText. Only papers available in English language were considered. In addition to the search of electronic databases, hand searching of relevant journals, journal articles and textbooks further identified relevant references published between 1900 and 1945. A hand search of references lists of papers published between 2005 and 2018 was also conducted to ensure no recent papers had been missed by the search of databases.

2.3.2 Inclusion Criteria

Papers were selected, critically analysed and synthesized following the Meta-analyses Of Observational Studies in Epidemiology (MOOSE) and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Figure 2.1). The inclusion criteria consisted of papers with full access that reported the prevalence of strabismus in population or school-based samples of children, examined using cover test performed by a qualified examiner such as an ophthalmologist, orthoptist or optometrist, as the gold standard test to detect strabismus.[76] Where there may be older participants included in the study sample, discretion was used by the reviewer as to whether it was appropriate to include or exclude the paper based on the sample

being made up of predominantly children less than 18 years old. Studies of younger children were defined where the oldest children < 8 years old while studies of older children included children aged ≥ 8 years or where the youngest child was aged 5 and the age ranged into adolescence. Clinical samples were excluded on the basis that they are not population-based with the sample having a possibility of bias towards a higher prevalence of strabismus cases. This is clearly demonstrated in one study where the prevalence of strabismus within the clinical sample was 13% compared to 1.7% in the general population.[77]

2.3.3 Statistical Analyses

Data was extracted from the papers for inclusion in the meta-analysis, which was conducted using IBM SPSS Statistics version 22. The mean prevalence of strabismus for each decade was calculated to determine the trends in the prevalence of strabismus from 1941 – 2018. Papers were categorised according to the following time periods of publication; Pre-1960, 1960-1969, 1970-1979, 1980-1989, 1990-1999, 2000-2009 and 2010-current. One-way ANOVA were used to determine if there was a significant change in the prevalence of strabismus, esotropia and exotropia between the decades. In addition, correlation coefficients were used to determine the relationship between year and overall strabismus prevalence, and esotropia and exotropia separately. Sample sizes ranged widely from 122 to nearly 100,000 children. Comparison between ethnicities was only able to be performed for the ethnic groups most commonly reported on, that is; European Caucasian, Asian and Middle Eastern ethnicity. Ethnic groups were classified according to the predominant ethnicity present within the sample or if ethnicity was not specified, the predominant ethnicity within the location. Those identified as having a European Caucasian population in the meta-analysis included study samples who were identified as a population of European Caucasian, white or non-Hispanic white children. Papers identified as Asian included those of predominantly children of Asian, East Asian, and South East Asian ethnicity

but, excludes studies of predominately South Asian children. Where the prevalence was reported by ethnic group in the one study, these were included as separate entries in the comparisons of strabismus prevalence between ethnicities. The difference in prevalence of strabismus between ethnicities, locations and population versus school-based samples was compared using ANOVA and Independent T-test.

In addition, a meta-analysis was performed as described by Neyeloff et al.[78] to determine the weighted average prevalence of strabismus across papers and homogeneity of papers published between 2000 and 2018. Data was extracted from the these studies and the number of cases of strabismus were divided by the total number of participants and used to calculate standard errors, variance, weighted effect size and create a forest plot.

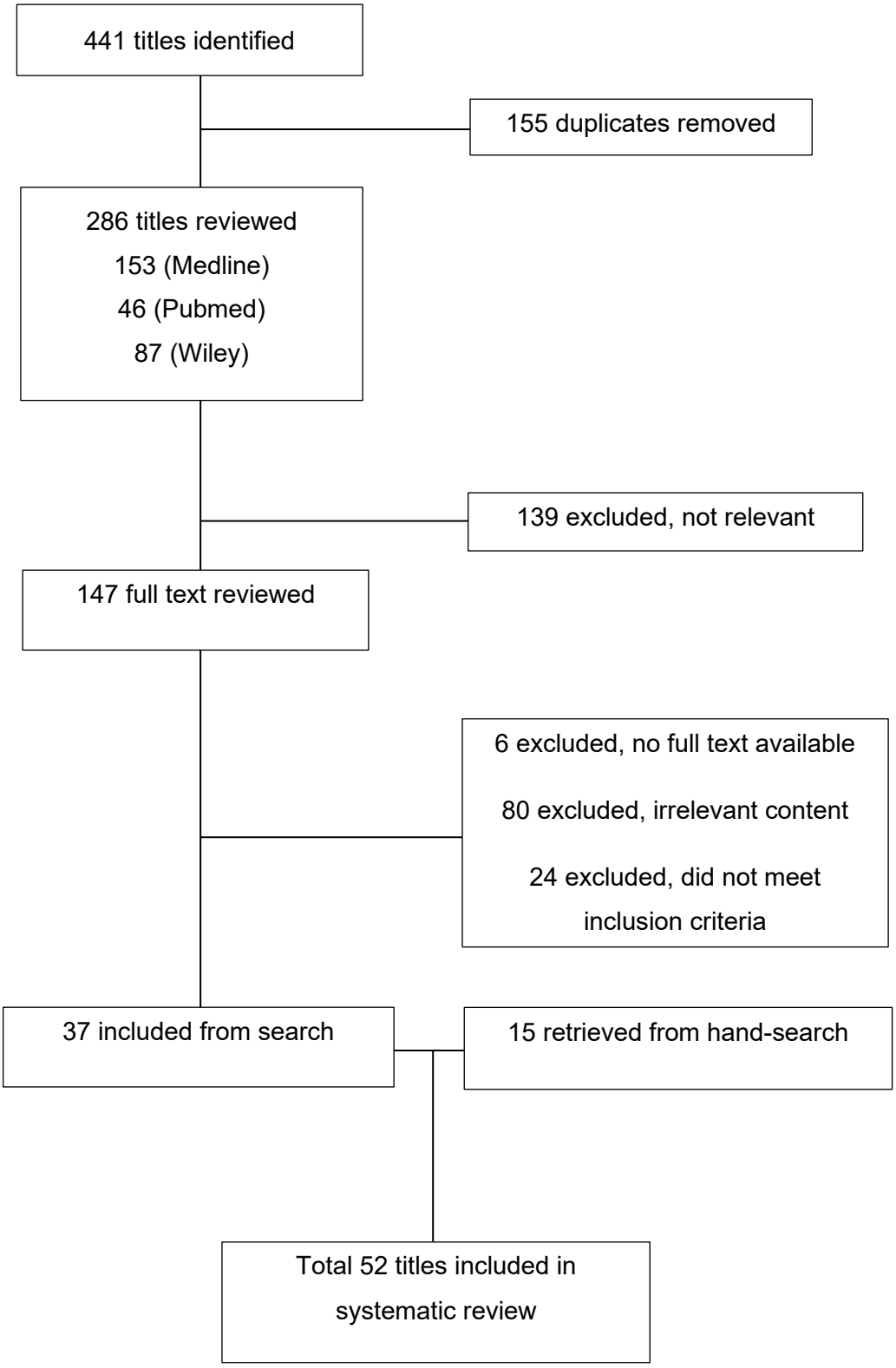


Figure 2.1 PRISMA 2009 flow diagram of literature search and study selection

2.4 Results

2.4.1 Characteristics of studies included

A total of 441 titles were identified. Of these, 155 duplicates were removed before a title search was then conducted to identify 147 papers that were to be reviewed in full by two investigators to determine if they met the inclusion criteria. A total of 110 papers were excluded due to; no access to the full paper (n=6), prevalence was reported but the paper did not meet the inclusion criteria (n=24) or the paper did not report prevalence of strabismus (n=80). Overall, 37 studies identified through the database search met the inclusion criteria. An additional 16 titles were identified from hand-searching of reference lists of relevant titles. It is to be noted that the majority of papers reflect the prevalence in high income, developed economies (n=34) or middle income and developing economies (n=18).

There were 57 reported separate strabismus prevalence rates extracted from 52 papers published between the years 1941 and 2018. These were used in this meta-analysis to determine if there have been any changes to prevalence of overall strabismus over time (Table 2.1). These include 47 reports of the prevalence of esotropia and exotropia separately. The majority of the studies included predominantly European Caucasian children (n=26) or Asian children (n=11). There were 39 prevalence rates extracted which included a younger sample of children and 18 prevalence rates extracted from samples of older children. The prevalence of strabismus did not differ between younger and older aged children (2.75% vs 2.93%, respectively, p=0.6). There were no significant differences in the number of papers which used younger or older samples in each decade (p=0.95). There were a total of 24 population based studies and 28 school or preschool-based studies. There was no significant difference in prevalence of strabismus between studies which used population-based samples and those that were school/preschool-based (3.01% vs 2.64%, respectively, p=0.2).

2.4.2 Prevalence of strabismus over time

Figure 2.2 shows the prevalence of strabismus has significantly declined by almost half in several decades (p=0.02), corresponding to a declining trend in the prevalence of strabismus over time (r= -0.4, p=0.002). Prior to 1960, the mean prevalence of strabismus was 4.51% (95% CI 3.65-5.37, n= 3) and this was reduced to a mean prevalence of 3.11% (95% CI 1.26-4.97, n=3) in 1960-1969, and further reduced to 2.15% (95% CI 0.35-3.95, n=5) in 1970-1979. The prevalence of strabismus stablised by the 1990's at 2.50% in 1990-1999 (95% CI 1.40-3.60, n=7), 2.73% in 2000-2009 (95% CI 2.27-3.18, n= 14) and 2.6% in 2010-2019 (95% CI 2.03-3.16, n=24). Similarly, the prevalence of esotropia has shown a declining trend over time (r= -0.66, p<.0001), while the prevalence of exotropia has increased (r= 0.35, p=0.015) between 1960 and 2018.

When taking age into consideration, within samples of younger children, there was a declining trend in the overall prevalence of strabismus (r= -0.39, p=0.014) and esotropia (r= -0.57, p=0.001), but no significant change in the rate of exotropia (r= 0.29, p=0.14). In older children, the overall prevalence of strabismus has not changed over time (r-0.14, p=0.59), however there was a significant reduction in the prevalence of esotropia (r-0.76, p<.0001) and increase in the prevalence of exotropia (r=0.53, p=0.03).

The papers published prior to 1980 were predominately of European Caucasian children. When determining the prevalence of strabismus over time in children of European Caucasian decent only, the trends remain significant for strabismus overall (n=26, r= -0.53, p= 0.006) and esotropia (n=21, r= -0.66, p= 0.001). However, exotropia was reasonably stable in this population (n=21, r= 0.30, p=0.18), indicating the decline in the prevalence of strabismus in European Caucasian children is a result of reduction in the prevalence of esotropia.

Table 2.1. Descriptive results of the 53 studies included in the meta-analysis

Study	Author	Year	Location	Sample	Ethnicity*	Age	n	Prevalence of Strabismus	Prevalence of Esotropia	Prevalence of Exotropia
1	Knudtzon [79]	1941	Denmark	School	European Caucasian	Grade 1-9	2000	5.2		
2	McNeil [80]	1955	UK	Population	European Caucasian	5-15 years	12568	3.41	3.27	0.13
3	Frandsen [81]	1958	Denmark	Population	European Caucasian	0-18 years	16046	5.6		
4	Frandsen [82]	1960	Denmark	School	European Caucasian	0-6 years	3570		3.81	0.53
						7-20 years	10537		3.36	1.06
5	Miller [83]	1960	UK	Population	European Caucasian	5 years	851	4.7		
6	Nordlow [6]	1964	Sweden	Population	European Caucasian	9 years	6004	3.86	3.38	0.43
7	Adelstein [84]	1967	UK	Population	European Caucasian	6 years	12512	4.3		
8	Graham [85]	1974	UK	Population	European Caucasian	5-6 years	4784	4.37	3.6	0.77
9	Brown [86]	1977	Australia	Population	European Caucasian	5 years	5430	3.5		
10	Kohler [77]	1978	Sweden	Population	European Caucasian	7 years	2178	1.8	1.74	0.14
11	Friedman [7]	1979	Israel	Population	Middle Eastern	2 years	38000	1.3	0.95	0.3
12	Laatikainen [87]	1979	Finland	School	European Caucasian	7-15 years	411	4.6	2.92	1.7
13	Cohen [88]	1981	USA	School	African American	4 years	651	1.4		
14	Macfarlane [89]	1987	Australia	School	European Caucasian	Grade 1	877	2.85	1.6	1.03
15	Lennerstrand [90]	1989	Sweden	Population	European Caucasian	5 - 10 years	1047	2.2	0.86	0.57
16	Chew [25]	1994	USA	Population	Other	7 years	39227	4.3	3.03	1.25
17	Fitzgerald [91]	1994	Australia	School	European Caucasian	3 years	3020	2.5	1.06	1.46
18	See [92]	1996	China	School	East Asian	5-12 years	862	1.62		
19	Stidwell [93]	1997	UK	Population	European Caucasian	6+ years	58951	3.4	2.65	0.79

20	Lithander [94]	1998	Oman	School	Middle Eastern	6-12 years	6292	0.87	0.41	0.24
21	Preslan [95]	1998	USA	School	Other	4-8 years	680	3.1	2.79	0.29
22	Kvarnstrom [96]	2001	Sweden	Population	European Caucasian	4-10 years	3126	2.68	1.5	0.58
23	Nepal [97]	2003	Nepal	School	Other	5-16 years	1100	1.6	0.09	1.55
24	Ohlsson [98]	2003	Mexico	School	Hispanic	12-13 years	1035	2.3	0.77	0.58
25	Tananuvat [99]	2004	Thailand	School	South East Asian	6-7 years	3467	1.79	0.52	1.27
26	Donnelly [100]	2005	Ireland	Population	European Caucasian	5-8 years	1582	3.98	3.35	0.63
27	Grönlund [101]	2006	Sweden	Population	European Caucasian	4-15 years	143	3.5	2.8	0.7
28	Robaei [102]	2006	Australia	School	European Caucasian	12 years	2352	2.7	0.89	1.15
29	Robaei [34]	2006	Australia	School	European Caucasian	6 years	1739	2.8	1.55	1.15
30	Williams [24]	2008	UK	Population	European Caucasian	7 years	7825	2.3	1.64	0.47
31	Drover [103]	2008	Canada	School	European Caucasian	4 years	946	4.3		
32	MEPEDS Group [65]	2008	USA	School	African American	6-72 months	3005	2.5	1.1	1.36
					Hispanic	6-72 months	3003	2.4	0.87	1.47
33	Friedman [48]	2009	USA	Population	African American	6-71 months	1268	2.05	1.03	1.03
					European Caucasian	6-71 months	1030	3.3	1.46	1.75
34	Garvey [104]	2010	Canada	School	Other	3-5 years	909	1.3	0.33	0.88
35	Yekta [105]	2010	Iran	School	Middle Eastern	7-17 years	2683	2.02	0.56	1.16
36	Faghihi [106]	2011	Iran	School	Middle Eastern	6-21 years	2150	3	0.88	2.09
37	Fan [107]	2011	Hong Kong	School	East Asian	3-5 years	623	2.33 (2006-7)	0.48	1.77
						3-5 years	829	1.70 (1996-7)	0.24	1.45
38	Chia [11]	2013	Singapore	School	South East Asian	6-72 months	2992	0.8	0.1	0.67
39	McKean-Cowdin [47]	2013	USA	School	Asian	2.5 years	1522	3.5	1.38	2.1
					European Caucasian	2.5 years	1514	3.2	2.31	0.73

40	Fu [108]	2014	China	School	East Asian	14 years	2260	5	0.09	4.51
41	Lanca [109]	2014	Portugal	School	Hispanic	6-11 years	672	4	2.08	1.79
42	Ying [110]	2014	USA	School	African American	3-5 years	2072	2.5		
					American Indian	3-5 years	343	2.9		
					Asian	3-5 years	145	0.95		
					European Caucasian	3-5 years	481	4.59		
					Hispanic	3-5 years	796	2.47		
43	Hashemi [111]	2015	Iran	School	Middle Eastern	7 years	3675	1.68	1.09	0.68
44	Larsson [112]	2015	Sweden	Population	European Caucasian	10 years	217	3.2	0.92	2.3
45	Zhu [37]	2015	China	Population	East Asian	3 years	5831	5.8	0.77	4.63
46	Bruce [38]	2016	UK	Population	Other	4-5 years	17018	2.4	1.05	1.26
47	Yekta [113]	2016	Iran	Population	Middle Eastern	4-6 years	3765	1.21	0.22	0.17
48	Hashemi [114]	2017	Iran	Population	Middle Eastern	0-5 years	122	1.09		
49	Pan [115]	2017	China	School	East Asian	6-14 years	9263	3.53	0.3	2.85
50	Torp-Pedersen [116]	2017	Denmark	Population	European Caucasian	0-6 years	96842	1.35	1.07	0.19
51	Yekta [66]	2017	Iran	School	Middle Eastern	6-15 years	1375	1.9	0.65	1.24
52	Schaal [117]	2018	Brazil	Population	Other	1-12 years	1852	1.6	1.13	0.32

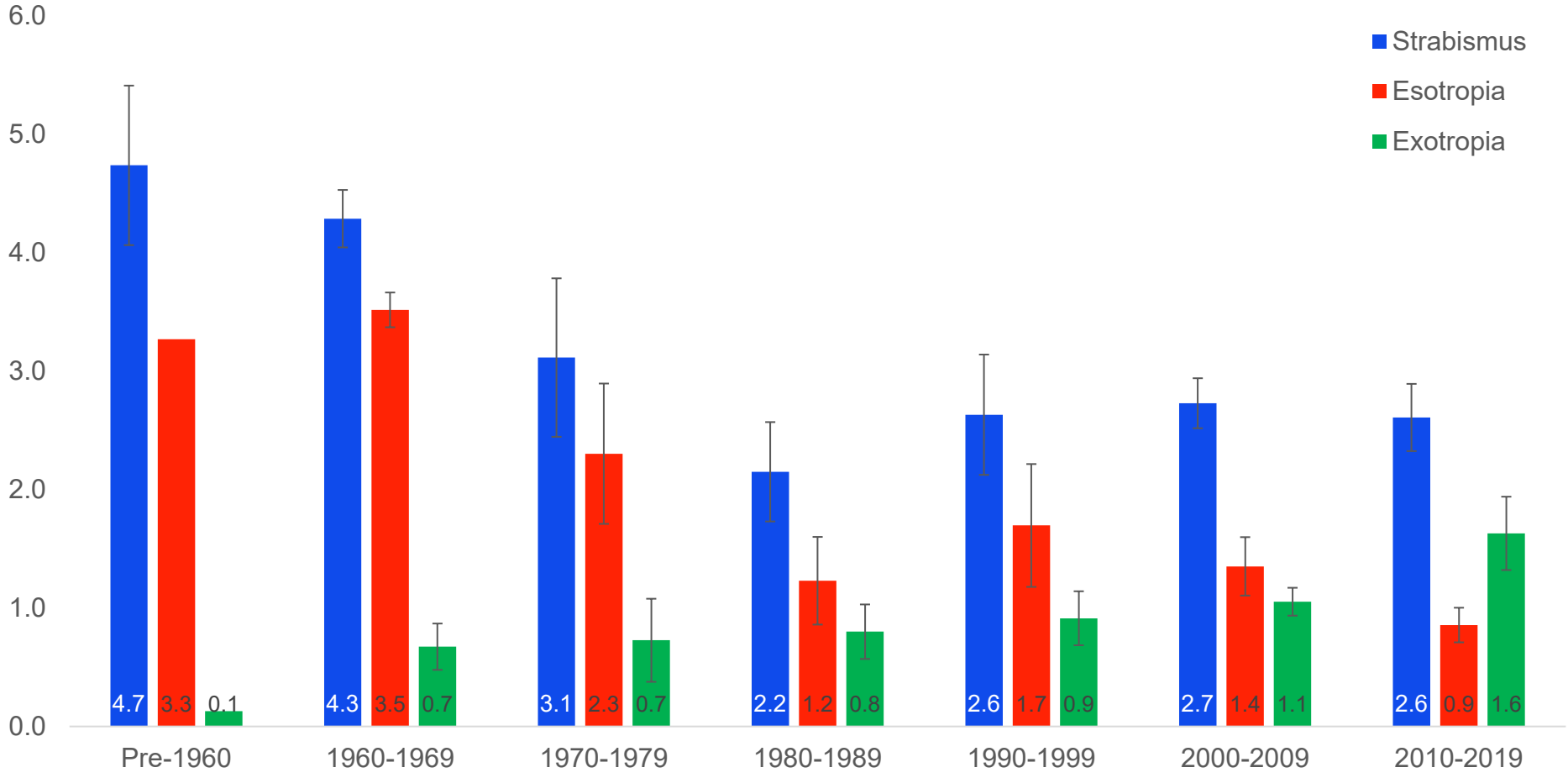


Figure 2.2 The prevalence of strabismus, esotropia and exotropia over time

2.4.3 Current Prevalence of Strabismus

The two most recent decades demonstrated a stable prevalence of strabismus and were used to determine the current prevalence estimates. Of the 31 papers published between 2000 and 2018, the mean prevalence of strabismus was 2.95% (range, 0.80% - 5.80%). The meta-analysis of the 38 prevalence rates extracted found the random-effects prevalence of strabismus was 2.68% (95% CI 2.34-3.33) and heterogeneity was low (I^2= 3.32%). Figure 2.3 demonstrates the forest plot of the random effects model on the current prevalence of strabismus. There were 28 studies that included type of strabismus. From these studies the current mean prevalence of esotropia was 1.06% (range, 0.09-3.35) and exotropia 1.39% (range, 0.17-4.63).

When considering the prevalence of strabismus by ethnicity, there was no overall difference in the prevalence of strabismus (p=0.14). However, there was a significant difference in the prevalence of esotropia (p=0.006) and exotropia (p=0.04). When comparing the most frequently reported ethnic groups, the overall prevalence of strabismus was not significantly different between children of European Caucasian ethnicity (n=12, 3.15%), Asian ethnicity (n=7, 3.05%) and Middle Eastern Ethnicity (n=6, 1.82%, p=0.10). However, esotropia was more common amongst European Caucasian children (1.75%) compared to children of Asian ethnicity (0.52%, p= 0.003) and Middle Eastern ethnicity (0.68%, p= 0.02). Conversely, exotropia was more common in Asian children (2.54%) compared to European Caucasian children (0.97%, p=0.01). There were no difference in the prevalence of exotropia in European Caucasian and Middle Eastern children (p=0.78). Between children of Asian and Middle Eastern ethnicity, there were no differences was found in the prevalence of esotropia or exotropia (p=0.52 and p=0.08, respectively). The prevalence of esotropia and exotropia was similar in children of African-American (n = 2 papers, 1.07% and 1.20%, respectively) and Hispanic descent (n = 3 papers, 1.24% and 1.28%, respectively). When examining the prevalence of strabismus between children of the

same ethnicity residing in different locations, no significant difference in prevalence of strabismus was found for either European Caucasian or Asian children (p=0.08 and p=0.21, respectively). When considering the type of strabismus in European Caucasian or Asian children residing in different locations, there were also no significant differences in esotropia (p=0.44 and p=0.36 respectively) and exotropia (p=0.80 and p=0.26, respectively). This would indicate ethnicity may be a better indicator of type of strabismus than location.

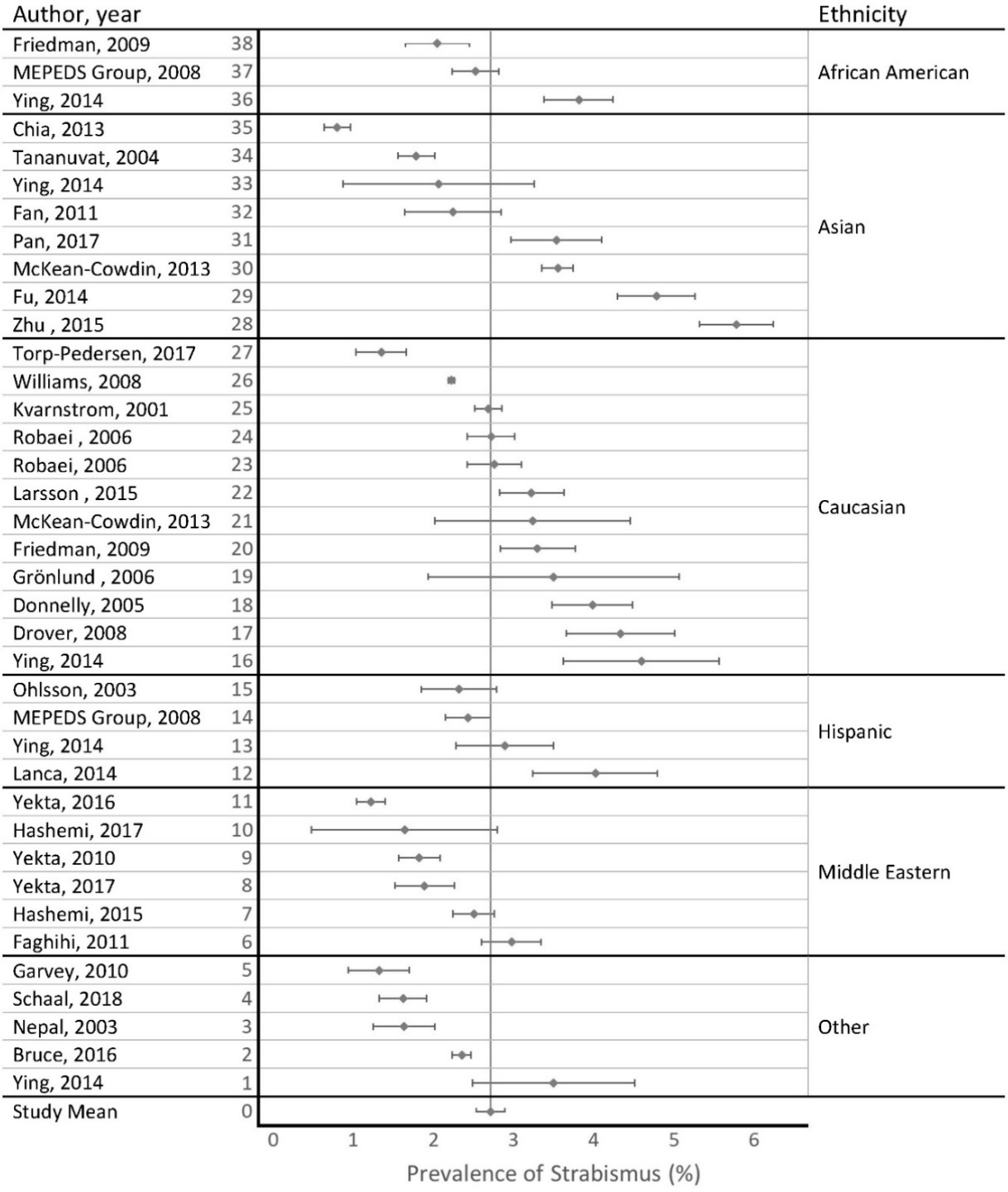


Figure 2.3 Random effects model of the prevalence of strabismus, 2000-2018

2.5 Discussion

This meta-analysis has found there has been a significant decline in the prevalence of childhood strabismus from an estimated prevalence of 4.5% prior to the 1970's to a more stable prevalence of 2.6% found in more recently published population and school-based studies. The declining trend in overall prevalence has occurred in parallel with an even more dramatic reduction in the prevalence of esotropia, from 3.5% to 0.8% within the same timeframe. This is in contrast with the apparent increase in the prevalence of exotropia, which has risen from 0.5% to 1.6% over the past few decades. Despite a wide range in the prevalence of strabismus reported in different populations and variation in the type of strabismus in children of different ethnicities, no significant differences were found in the overall prevalence rates based on ethnicity or country of residence. This indicates that there is a similar prevalence of overall strabismus affecting children globally.

A steady decline in the prevalence of overall strabismus was observed from pre-1960 to 1979, as determined from the 13 publications during this period. However, it is important to acknowledge that all but one of these were from countries with a predominately European Caucasian population. For this reason, the trends in prevalence in European Caucasian populations were re-analysed separately in this meta-analysis. This analysis again revealed a significant decline in the prevalence of overall strabismus and esotropia, but there was no significant change in the prevalence of exotropia, which remained relatively stable throughout 1940-2018. Considering trends within individual countries with available prevalence data over several decades, the earliest study identified in this meta-analysis reported the prevalence of strabismus in Denmark was 5.20%[79] in school aged children, later reducing to 4.34%[81] in 1960 and currently reported at 1.35%.[116] In the UK, early studies found the prevalence to be 3.4%[80] to 4.7%,[83] whereas more recent studies have reported prevalence of 2.1%[38] to 2.3%.[24] A similar trend in overall prevalence is

noted in Australia, with the prevalence declining from 3.5%[86] in the 1970s to between 2.5% and 2.8% from the 1990's to current times.[34,91] Thus, a closer examination of countries for which data is available over time, demonstrates that this declining trend in the prevalence of strabismus is consistent across a number of individual developed countries of predominantly European Caucasian origin.

A similar analysis of the prevalence of esotropia over time, within individual countries with a predominantly European Caucasian population, showed a parallel decline to that observed for overall strabismus. The prevalence of esotropia in Denmark, 1960, was 3.81%[82] and this declined to 1.07% in 2017 in children aged 0-6 years old.[116] Similarly, in the UK the prevalence of esotropia was 3.27%[80] in 5-15 year old children in 1955, declining to 2.65%[93] in 1997 and further reducing to 1.64% by 2008 in 7 year old children.[24] Studies conducted in Sweden also demonstrate a decline in the prevalence of esotropia from 3.38% in 1964[6] to 1.5% in 2001.[96] While the prevalence of esotropia has consistently declined across populations, there has been a much more stable prevalence of exotropia in children living in developed countries of predominately European Caucasian decent. The prevalence of exotropia in children living in Denmark between 1960 and 2017 was 0.53%-0.19%.[82,116] Children aged 5-7 years old living in the UK had a prevalence of exotropia of 0.13%[80] in 1955 and 0.47% in 2008.[24] The prevalence of exotropia in Sweden has also been stable at 0.43% in 1964[6] and 0.70% in 2006.[101] The trends within European Caucasian populations suggest the decline in the prevalence of overall strabismus can be predominately attributed to a decline in esotropia, as the prevalence of exotropia was relatively stable throughout the past few decades.

There is a known link between the prevalence of strabismus and antenatal risk factors, which raises the question whether a decline in prevalence could be related to changes in risk factor exposure. A comparison of children who were born prematurely and full-term, reported a much higher prevalence of strabismus in children who were

premature compared to those full term, with a higher proportion of esotropia in premature children compared to full-term children who have a relatively higher proportion of exotropia, highlighting the impact of antenatal factors on the prevalence of strabismus and in particular, esotropia.[118] Esotropia has been previously linked to a number of birth related risk factors including; maternal smoking, prematurity, low birth weight, and hyperopic refractive error[11,24,33] while exotropia has been more closely related to congenital abnormalities.[32] Maternal smoking during pregnancy has been reducing over time,[72-75] which may be related to public health campaigns and increased awareness of the risks associated with smoking. Therefore, the observed decline in prevalence of strabismus and particularly, in esotropia could be related to improvements in maternal health during pregnancy. A direct comparison of population-based studies in locations with varied rates of birth-related risk factors may be best placed to determine which factors have the greatest impact on the prevalence and type of strabismus that occurs. Similarly, an analysis of trends in the prevalence of hyperopic refractive error may further reveal an association with the decline in esotropia. While some may speculate that the rise in the prevalence of myopia may be shifting the refractive profile of populations,[119] it is to be noted that this has predominantly occurred in East Asian populations, while the decline in esotropia has been in European Caucasian populations without a dramatic increase in the prevalence of myopia.[120]

Although an increase in the prevalence of exotropia over time is observed when all sources are considered, this was not present when European Caucasian populations were considered alone and appears to be an artefact of the addition of papers from Asian and Middle Eastern populations, published after 1990 and who appear to have a higher proportion of exotropia when compared to European Caucasian populations. Prior to 1990, studies of Asian populations' could not be identified while, there was only one paper from a Middle Eastern population and one American African population

study. Therefore, this meta-analysis is unable to determine if there have been changes in the prevalence of strabismus, esotropia and exotropia in these ethnicities.

While this paper may not be the first to note the difference in type of strabismus present between ethnicities, it is the first study to cumulate this finding and determine a consistent trend over time and across multiple locations. The current meta-analysis has demonstrated the prevalence of strabismus is generally similar between ethnic groups but, the proportion of esotropia and exotropia varies. Esotropia was more prevalent in populations of European Caucasian origin, while exotropia was more common in populations of Asian ethnicities. Within studies of Middle Eastern children, reports of the prevalence of strabismus in younger children aged 7 or less found proportionally more esotropia[113,121] while in older children aged 6 years to adolescence, there was more exotropia.[66,105,106] Studies of Asian children consistently report a greater prevalence of exotropia regardless of age.[11,37,47,108,115] Globally, the prevalence of strabismus overall does not vary significantly between ethnicities or location. However, as international migration increases and the proportion of different ethnicities residing in one location may vary, there may be a change in the prevalence of esotropia and exotropia in that location. The impact of this is emphasised in the meta-analysis of European Caucasian children only, as the prevalence of exotropia revealed no significant change over time while exotropia prevalence increases when other ethnicities are included in the analysis.

2.6 Conclusion

This systematic literature review and meta-analysis has found the current prevalence of strabismus is 2.6%. The strengths of this meta-analysis of childhood strabismus lies in the use of only population or school-based studies with a clear definition of a standard for assessment of strabismus. However, limitations occur when studies report the prevalence of strabismus overall, rather than esotropia and exotropia separately and ambiguity in some of the older papers where there is limited description of methods used. This prevalence appears to have declined since the 1980's and the declining trend in the prevalence of strabismus is due to the decline in the prevalence of esotropia amongst European Caucasian populations. Although there is no difference in the overall prevalence of strabismus in children of various ethnicities, there is a clear difference in the type of strabismus present with, a greater prevalence of esotropia in European Caucasian children in comparison to the greater prevalence of exotropia in Asian children.

CHAPTER 3: Methods for pre-existing data sets from the Sydney Childhood Eye Studies

3.1 Overview of the Sydney Childhood Eye Studies

The Sydney Childhood Eye Studies comprised two population-based studies of children of different ages. In 2003 to 2005, the Sydney Myopia Study (SMS) recruited a random cluster sample of children from 55 primary and secondary schools in the Sydney metropolitan area from two age cohorts; Grade 1 children aged 6 and Year 7 aged 12 years. The methods of this study have been published elsewhere,[122] but relevant details of this study will be described in this chapter. The SMS children were then followed up 5-6 years later in the Sydney Adolescent Vascular and Eye Study (SAVES) using the same methodology with the younger cohort now aged 12 and the older cohort 17 years. The second study, the Sydney Paediatric Eye Disease Study (SPEDS) examined children aged between 6 months to 6 years of age from 2007 – 2009. The method of enumerating this sample of infants and pre-school children was first published by Leone et al, 2012.[123] Children across all studies underwent an age appropriate, comprehensive ocular examination including; visual acuity, and cycloplegic autorefraction using cyclopentolate (Table 3.1). Questionnaires were used to obtain demographic and health information including the presence of risk factors, such as; premature birth, low birth weight and maternal smoking. Copies of the questionnaires are included in Appendix 1.

3.2 The Sydney Myopia Study and Sydney Adolescent Vascular and Eye Study

3.2.1 Sydney Myopia Study demographics

SMS examined a total of 4090 children in two cohorts aged 6 and 12 years old. The Sydney metropolitan area was stratified by socioeconomic status (SES) using the ABS 2001 census data. From the census data, 34 primary schools and 21 secondary schools across Sydney were randomly selected. These include 5 primary schools and 2 high schools in the top SES with a random but proportionate mix of public, religious and private schools. Each school was approached by the study team to establish willingness to participate and with the principal of the school's agreement, information sessions were held with teachers, parents and pupils. Information packages including information sheets, consent forms and questionnaires were sent to all eligible children and their families. Questionnaires completed by parents of participating children, included questions regarding sociodemographic information such as ethnicity, parental education and employment; the child's birth and medical history and typical daily activities on weekdays and weekends (See Appendix 1a).

3.2.2 Sydney Myopia Study protocol

The study team included ophthalmologists, medical practitioners, orthoptists and optometrists. Examination included visual acuity, orthoptic assessment, dilated fundus exam and cycloplegic refraction. Visual acuity was measured for each eye separately using a retro-illuminated LogMAR chart (Vectorvision^{TM} CSV-1000; Vectorvision,Inc., Arcanum, OH) at 2.44m aligned with the now accepted worldwide standard scientific protocol for vision testing, the Early Treatment of Diabetic Retinopathy Study (ETDRS).[124] Orthoptic assessments included a cover test, prism bar cover test, ocular movements, convergence near point and stereoacuity conducted by an orthoptist to establish ocular alignment, size of deviation where present and presence of binocular vision. The cover test included cover/uncover to detect a manifest strabismus and

alternate cover to detect heterophoria at both near and distance fixation, with and without glasses, if worn. If any ocular misalignment was noted on cover test, then prism bar cover tests were performed using a Luneau prism bars in 2-5 prism dioptre (PD) increments. Ocular movements were assessed as was convergence near point using the RAF ruler. The presence of binocular single vision was screened using the Lang II stereo card (Lang-stereotest, Forch, Switzerland), the TNO test for measurement of stereoscopic vision (Lam´eris Ootech BV Nieuwegian, The Netherlands) and 4 dioptre prism test to detect microtropia.

After the instillation of Amethocaine Hydrochloride 1%, eye drops, cycloplegia was achieved using Cyclopentolate 1% and Tropicamide 1% in two cycles, 5 minutes apart. Cycloplegia was confirmed by checking pupil reaction to light and an accommodative target once the pupil dilated to ≥6mm in diameter. The Canon autorefractor (model RK-F1; Canon, Tokyo, Japan) was used to measure refraction. If the pupil was not sufficiently dilated for fundus examination, 2.5% phenylephrine was also administered. Ocular biometry was measured after dilation using the IOLMaster™ (Carl Zeiss, Meditec AG Jena, Germany) while the Haag-Streit slit-lamp (Koeniz, Switzerland) was used to examine the anterior segment of the eye. Optical Coherence Tomography (OCT): Stratus OCT3™ (Model 3000; Zeiss,Meditec Inc., CA, USA) was used for posterior segment examination along with fundus photography using a Canon 60◦ Mydriatic Fundus Camera (model CF-60UVi, Canon Inc., Tokyo, Japan).

3.2.3 Sydney Adolescent Vascular and Eye Study Protocol

SAVES was a 5-6 year follow-up of children who participated in SMS conducted between 2009 and 2011. A total of 2804 children participated in SAVES, of which 2090 were followed-up from SMS (see table 3.2). Of the original 34 primary schools assessed in SMS, children were still enrolled in 13 of these primary schools and were re-examined at those schools. Follow-up for the children from the other 21 primary schools were conducted at their secondary school or by individual invitation to attend

an eye clinic. Of the 21 secondary schools examined in SMS, 20 still had the same children enrolled at the school and were re-visited to conduct the ocular examinations. The children of the secondary school that was not re-visited were individually invited to attend an eye clinic. The detailed questionnaires were again administered to parents for updated information such as socioeconomic status (parental employment and home ownership), the child's health and ocular health and symptoms since SMS and recent data on daily activities.

3.3 The Sydney Paediatric Eye Disease Study

3.3.1 The Sydney Paediatric Eye Disease Study demographics

To obtain the SPEDS sample, metropolitan Sydney was stratified into three geographical regions; inner city, suburban and outer suburban based on Australian Bureau of Statistics (ABS) 2006 census data and random cluster sampling of suburbs stratified by socio-economic status was conducted within these regions. Suburbs with moderate proportions of preschool-aged children were randomly selected from each stratified region. A total of four suburbs; one outer suburban, one inner city and two suburban suburbs were included in the study. The inclusion of these suburbs was considered to be sufficient for a representative sample of reasonable size providing prevalence estimates for preschool-aged children residing in Sydney.

The 2006 ABS census map was used to identify all households within the selected suburbs and information sheets about the study were delivered to each. Flyers were also placed at local health care centres, preschools and day care centres. Recruitment staff then door-knocked to identify households that included children within the age range 6 months to 6 years for inclusion in the study and invited them to participate in the study.

Households with eligible children were provided a package that included information and consent sheets and two questionnaires and an arranged appointment time at a study clinic located at either Quaker's Hill or Campsie. The two questionnaires to be completed by parents included a total of 176 questions to obtain information on ethnicity, parental education and employment, the child's birth and medical history, as well as ocular information for the child and their family members (see Appendix 1b). Where available, infant health records supplied by the state government, also known in New South Wales as "the Blue Book", provided further information on birth data and admission to neonatal intensive care during infancy. A copy of the birth information

page in the Blue Book was photocopied to obtain accurate birth parameters as entered by the hospital staff at the time of birth (see Appendix 2).

3.3.2 The Sydney Paediatric Eye Disease Study protocol

SPEDS enumerated 3333 children aged 6 months to 6 years and examined a total of 2462 children (74% participation rate). Ocular examinations were conducted by medical officers and orthoptists. These included age-appropriate assessment of visual acuity, orthoptic assessment, cycloplegic refraction and dilated fundus exam. Visual acuity was measured for each eye separately using; Teller Acuity Cards II (Stereo Optical Co. Inc., Chicago, IL) for children aged <24 months, the Electronic Visual Acuity (EVA) system at 3m (Jaeb Centre for Health Research, Tampa, Florida) for children ≥24 months and additionally, retro-illuminated LogMAR chart with EDTRS or HOTV optotypes at 2.44m (Vector Vision CSV-1000, Vector Vision, Inc., Dayton, OH) for children aged ≥30 months if they were able.

Ocular alignment was examined using a cover test (cover/uncover) to detect strabismus or alternate cover to detect heterophoria for both near and distance fixation and with and without glasses, if worn. The size of ocular misalignment was measured using prisms and where a prism cover test could not be performed, an objective Krimsky test was used to estimate strabismus size. Ocular motility and measurement of convergence near point were also performed. Binocular single vision was assessed using a 15 dioptre prism to elicit a fusional response and 4 dioptre prism to detect a microtropia, in addition to the Lang II stereo card (Lang stereotest, Forch, Switzerland) where possible either by pointing or preferential looking in infants <30 months of age. Measurement of stereoacuity was made using the Randot preschool stereoacuity test (Stereo Optical Co. Inc., Chicago, IL) for children aged ≥30 months and Stereo Smile test II (Stereo Optical Co. Inc., Chicago, IL) for children aged <30 months.

Cycloplegia was achieved using; Amethocaine 0.5% followed by two cycles, 5 minutes apart of Cyclopentolate 0.5% for children younger than 12 months or Cyclopentolate 1% for children 12 months and Tropicamide 1%. Cycloplegic refraction was obtained using either Retinomax K-Plus 2 (Nikon Corporation, Tokyo, Japan) or streak retinoscopy, and the Canon RK-F1 table-mounted autorefractor (Canon, Tokyo, Japan) when able. For children who failed to dilate sufficiently for fundus examinations, an additional drop of Phenylephrine 2.5% was administered. The anterior eye was examined using a Haag-Streit slit-lamp (Koeniz, Switzerland). After cycloplegia a fundus exam was made by indirect ophthalmoscope. Retinal photographs were taken by a non-telecentric fundus camera (Canon CF-60UVi fundus camera, CF-DA camera adapter, EOS-lOD digital camera; Canon Inc., USA) and ocular biometry using an IOLMaster (IOLMaster, Carl Zeiss Meditec, Jena, Germany) in children ≥30 months.

3.4 Common protocols between studies

The same examination protocols were used in the SMS and SAVES studies while parallel assessments were carried out in the SPEDS, but adapted to be age-appropriate for the differing age range in that study, see table 3.1. The protocols for establishing refractive error and the presence of strabismus were consistent across SMS, SAVES and in the children aged greater than 12 months from SPEDS. Measures of visual acuity were consistent in children aged greater than 30 months, namely using ETDRS standard protocol, across all three studies in some cases using the HOTV optotypes and matching card. Stereoacuity was screened using Lang II in all studies, however the method of detailed measurement varied related to age. The protocol for detecting strabismus was also the same in all children and measurements were obtained by prism bar cover test or Krimsky in younger children who were unable to fixate for a sufficient period of time.

Table 3.1 Procedure for the three studies

	Sydney Myopia Study (2003-2005) and Follow-up Sydney Adolescence Vascular and Eye Study (2009-2011)	**Sydney Paediatric Eye Disease Study (2007-2009)**
Questionnaires	Information provided by parents and participants aged ≥12years	Information provided by parents
Vision test	LogMAR chart with EDTRS	• Teller Acuity Cards II, <24 months • EVA system, ≥24 months • HOTV LogMAR, ≥30 months if able
Ocular alignment	Cover test and ocular movements by an orthoptist	
Measurement of deviations	Prism bar cover test	• Prism bar cover test • Krimsky, if unable to fixate
Binocular Single Vision	• Lang II • TNO	• Lang II, all children • 15 dioptre prism, <30 months • Stereo Smile test II, <30 months • Randot preschool stereoacuity test, ≥30 months
Other Binocular Functions	Fusional response to the 4 dioptre prism Convergence near point by RAF Rule or estimation in infants <30 months	
Dilating drops	• Amethocaine 1% • Cyclopentolate 1% • Tropicamide 1% • Phenylephrine 2.5%, as required	• Amethocaine 0.5% • Cyclopentolate 0.5%, <12 months • Cyclopentolate 1%, ≥12months • Tropicamide 1% • Phenylephrine 2.5%, as required
Ocular Pathology	• Slit lamp • OCT • IOL Master • Fundus photo • Fundus exam by indirect ophthalmoscope	
Cycloplegic Refraction	Autorefraction using a Canon RK-F1 table-mounted autorefraction	• Streak retinoscopy • Retinomax K-Plus 2 • Canon RK-F1 table-mounted autorefraction

3.5 Ethics approval

Ethics approval for all three studies was obtained from the Human Research Ethics Committee of the University of Sydney, and the studies adhered to the tenets of the Declaration of Helsinki. In addition, SMS and SAVES obtained ethics approval from the New South Wales Department of Education and Training, and the Catholic Education Office. Informed written consent was obtained from at least one parent or participants who were over the legal age of consent (18 years) prior to examination. Consent was also obtained from each child verbally able to do so prior to commencing the examination on the day.

3.6 Definitions

Ocular conditions were classified based on the findings of the assessment conducted as part of the studies. Any children reported to have received treatment for a condition, but who did not present with abnormal ocular findings at the time of examination were not included as having an ocular condition for the purposes of prevalence calculations.

3.6.1 Strabismus

Strabismus was identified when an eye turn was present at near or distance fixation at the time of examination as determined by cover un-cover test. Children with strabismus were tested with and without any refractive correction if worn, and with and without an accommodative target to determine the presence of an accommodative component to the strabismus. An esotropia was identified when the child had a manifest inward eye turn and exotropia was identified when the child had a manifest outward eye turn. A strabismus was classified as a constant strabismus when it was manifestly present at both near and distance fixation on cover test. Microtropia was defined as a small angle strabismus of less than or equal to 10 prism dioptres with demonstrable but reduced binocular vision using abnormal retinal correspondence. An intermittent strabismus was determined when the child demonstrated both a manifest

strabismus and a latent deviation under different cover test conditions, with the presence of binocular single vision to demonstrate functional use of the two eyes together when the strabismus was not manifest.

3.6.2 Refractive error

Refractive error was defined according to the spherical equivalent refraction (SER) where this was significant in one or both eyes. Myopia was classified as ≤-0.50 dioptres (D), moderate myopia ≤-1.5D. Hyperopia was determined by SER ≥+2.00D and high hyperopia ≥+3.5D. Anisometropia was determined by a difference of ≥1D between the spherical equivalent refraction of each eye.

3.6.3 Amblyopia

Amblyopia was identified if there was a ≥2 line difference between the visual acuity of the two eyes in the absence of pathology and in the presence of a risk factor, such as strabismus or refractive error, the most significant risk being anisometropic refractive errors.

3.6.4 Ocular pathology

Ocular pathology was noted as present if there were any identified abnormalities detected by slit lamp (anterior ocular pathology) and fundus examination either by OCT, indirect ophthalmoscopy or fundus photo (posterior ocular pathology).

3.6.5 Antenatal factors

Children reported to have spent any time in a neonatal intensive care unit (NICU) from either the parental questionnaire or Blue Book data were considered as having been admitted to NICU.

Children born earlier than 37 weeks were defined as being of premature gestational age. Infants born at 28 to 32 weeks gestation are very preterm, less than 28 weeks gestation extremely preterm and those born after 42 weeks gestation are late term.

Children born less than 2500g were identified as low birth weight and those born more than 4200g were of high birth weight. Infants born

Chronological age refers to the infant's age from birth whereas, corrected age takes into account how early the infant was born. Very low birth weight is considered those born less than 1500g and extremely low birth weight is less than 1000g.

3.6.6 Ethnic groups

Ethnicity was ascertained by the self-identified ethnic origin of both parents, using ethnic categories consistent with the Australian Standard Classification of Cultural and Ethnic Groups.[125] Children were classified into the most commonly reported ethnicities; European Caucasian, East Asian, South Asian, Middle Eastern or Other.

3.7 Statistical analysis

The databases were stored using Microsoft Access database software. Questionnaire and examination variables were coded for SPEDS, SMS and SAVES individually before the data sets were combined to provide a larger data set for analysis. All statistical analyses were performed using IBM SPSS Statistics for Windows (Version 25.0. Armonk, NY). Data were stratified by age, ethnicity and admission to NICU as appropriate for the aim of each chapter and the frequency of eye conditions including; strabismus, amblyopia, refractive error and ocular pathology were calculated. Differences in prevalence and incidence between groups were assessed using Chi-Square Test of Independence. Univariate logistic regression analyses were performed to calculate odds ratios (OR) and 95% confidence intervals (95% CI) of ocular conditions according to potential risk factors. Multivariate logistic regression analyses were then performed to determine relative contribution of identified risk factors on the prevalence and incidence of ocular conditions and the interaction between predictors. Additional detailed description of the statistical analyses performed for each chapter is contained within the relevant chapter.

3.8 Comparison of demographic information between studies

There were a total of 7266 children with ocular examinations across the three studies; 2425 in SPEDS, 4090 in SMS and 2804 in SAVES. Table 3.2 presents the demographic details of children included in each of the three studies. There were no statistically significant gender differences between any of the age groups included in the study (p=0.10). The lower prevalence of females to males in the younger age groups reflect the birth ratio 49% female births in Australia.[126] The higher rate of females at age 17 may reflect the higher retention rate of females in Year 12 (the final year of high school) compared to males.[127] There was an overall trend for increasing myopia and decreasing hyperopia between studies (p<.0001). Of particular significance, there was more myopia the 12 year old cohorts of SAVES than SMS (p=0.043), whereas hyperopia was not significantly different between the two groups (p=0.50)

Overall, there is a difference in the proportion of children of various ethnic groups, with a lower prevalence of European Caucasian children in the 6 month to 6 year old children in SPEDS compared to SMS and SAVES (p<.0001). When only the two most prevalent ethnicities were compared, there was no difference in the proportion of children of European Caucasian and East Asian ethnicity between the two SMS cohorts, 6 years and 12 year old. However, a significant difference was observed between the two SAVES cohorts, 12 years and 17 years old (p=0.007), with more European Caucasian children in the 12 year old cohort compared to the 17 year old cohort. A higher proportion of children of European Caucasian ethnicity and a lower proportion of children of East Asian ethnic background was present in the 6 year old age group who were followed-up in the SAVES 12 year age group, resulting in the observed differences. Between SMS 12 and SAVES 12 year old children, there was also a significant difference in ethnicity (p<0.0001). There was a higher prevalence of

East Asian children in SAVES 12 year compared to SMS 12 year age group who had a higher proportion of European Caucasian children.

Of the children in SMS, 79.84% of the younger cohort and 71.06% of the older cohort were followed up at SAVES. There was a significant difference in the ethnicity of children who were followed up compared to those who were not. In the younger cohort, those who were followed up at 12 years old were more likely to be European Caucasian than East Asian ($p=0.029$). In the older cohort, those who were followed-up at 17 years were more likely to be East Asian than European Caucasian ($p<.0001$). Between those who were followed up and those who were not, there was no statistically significant difference in the prevalence of strabismus in either the younger cohort ($p=0.25$) or the older cohort ($p=0.35$). There were also no differences in the prevalence of esotropia, exotropia, type of strabismus and reports of strabismus treatment.

Table 3.2 Demographic information of all children included in the three studies

Study	Sydney Paediatric Eye Disease Study	Sydney Myopia Study		Sydney Adolescence Vascular and Eye Study *(follow-up & new participants)*		Sydney Adolescence Vascular and Eye Study *(new participants only)*	
Total n	2425	1741	2353	1121	1686	226	488
Age Group	6 months – 72 months	6 years	SMS12 years	SAVES12 years	17 years	New SAVES12 years	New 17 years
Mean Age (range)	41.4 months (5 months – 107 months)	6.7 years (5.5-9.1 years)	12.7 years (11.1-14.4 years)	12.5 years (10.7-15.2 years)	17.3 years (15.8-23.9 years)	11.7 years (10.7-13.1 years)	17.5 years (15.9-23.9 years)
Female % (n)	47.1% (1158)	49.4% (860)	49.4% (1163)	48.3% (542)	51.3% (865)	49.1% (111)	55.3% (270)
Ethnicity %							
European Caucasian	45.8	63.7	59.9	66.1	56.3	41.2	48.7
East Asian	21.0	17.2	15.0	17.3	20.3	35.3	26.1
South Asian	13.3	2.2	5.5	1.0	6.7	1.5	10.4
Middle Eastern	9.0	4.8	7.1	4.3	6.9	2.9	7.2
Other	11.0	12.1	12.5	11.3	9.8	19.1	8.8
Refractive Error %							
Hyperopia	5.5	3.7	2.7	3.1	1.8	3.0	2.5
Myopia	4.0	1.7	13.0	15.5	24.2	30.6	28.1
Anisometropia %	2.8	1.6	4.3	4.4	4.7	7.8	6.2

3.9 Summary of methods

The Sydney Childhood Eye Studies were conducted between 2003 and 2011. SPEDS included a population based sample of children aged 6months – 6 years. SMS was a population based, cluster sample of school children in two cohorts; 6 and 12 years old. Children who participated in SMS were then followed-up in SAVES 5-6 years later at age 12 and 17 years old. The ocular assessment for all participants in the Sydney Childhood Eye Studies are comparable, with age-appropriate testing methods for the detection of ocular conditions such as refractive error and strabismus. Chapter 4 and chapter 5 of this thesis utilises this large pre-existing data set. Chapter 4 includes all children to determine the prevalence of strabismus in each age group and the impact of risk factors such as refractive error, anisometropia and ethnicity on the prevalence of strabismus including esotropia and exotropia individually. Chapter 5 utilises the SPEDS sample and the 6 year old sample of SMS children to determine the impact of admission to NICU on the development of ocular conditions in childhood.

CHAPTER 4: Impact of Age, Ethnicity and Refractive Error on the Development of Strabismus

4.1 Introduction

The prevalence of childhood strabismus is reported to be between 0.8-5.8% in studies of school or population-representative samples.[37,64,110,116] These prevalence rates include both esotropia and exotropia, which are separately reported to have a prevalence between 0.1-3.2%[11,47] and 0.2- 4.6%,[37,116] respectively (also see Chapter 2, Table 2.1). There are also variations in the reports of population-based prevalence of strabismus according to the age of children studied, with a lower prevalence of strabismus seen in younger children compared to older children.[104,108,109,115] The prevalence of strabismus in younger children, from birth to 6 years of age, is reported to be between 0.8-1.4%[11,104,114,116] whereas in school-aged children, 6-14 years, the prevalence of strabismus is reported to be between 3.5 – 5%.[108,109,115] This variation in prevalence may be due to the differing age of onset of different types of strabismus. Infantile esotropia is typically diagnosed early in infancy when the child presents with a large esotropia that does not resolve in the first few months of life.[3] In contrast, intermittent exotropia is typically diagnosed later in childhood, with a mean age of onset between 4.9-6.3 years.[128,129]

The prevalence of esotropia and exotropia is also found to vary between children of different ethnicities, with children of European Caucasian origin having a higher proportion of esotropia than children of East Asian ethnicity who have a correspondingly higher proportion of exotropia.[37,47,108,116] It is therefore possible that variations in the reported prevalence of strabismus between studies may depend on the age, refractive error and ethnicity of those children included in the sample.

While the prevalence of strabismus, including esotropia and exotropia, and the association of refractive errors with strabismus have been previously reported in populations of differing ethnicities, these are often reported within a narrow age range. The suite of Sydney Childhood Eye Studies (SCES) provides a unique opportunity to examine the impact of age and refractive errors on the type of strabismus across a

wide age range. Understanding of the respective impact of these factors at differing ages can enable a greater understanding of their combined risk for the development of strabismus. The potential benefit of identifying the typical age of onset and associated risk factors for different types of strabismus, is that it could facilitate age-appropriate screening and direct management strategies.

This chapter aims to determine whether there is a difference in the prevalence of strabismus overall, as well as esotropia and exotropia individually, in the series of population-based samples of children aged between 6 months to 17 years from the SCES, comprising the Sydney Paediatric Eye Disease Study (SPEDS) and the Sydney Myopia Study (SMS) and its follow-up study the Sydney Adolescent and Vascular Eye Disease Study (SAVES). The current analysis provides a possibly unique exceptional opportunity to examine the prevalence of strabismus within an ethnically diverse population of children and adolescents in the same geographical location, to investigate whether differences in the prevalence of strabismus with age are primarily age-related or arise from other risk factors. The follow-up of children in the SAVES longitudinal study also provides the possibility to study incident strabismus over a period of 5-6 years in childhood (aged 6-12 years) and adolescence (12 to 17 years).

4.2 Statistical Analysis

4.2.1 Cross sectional analysis of three studies

To determine the prevalence of strabismus by age, participants of the three studies were divided into 7 age groups. SMS (6 and 12 year old) and SAVES (12 and 17 year old) age cohorts were used as individual age groups according to mean age, while SPEDS was divided into three age groups 0.5-2 years, >2-4 years and >4-6 years. The prevalence of strabismus, esotropia and exotropia were calculated in these stratified age groups. Esotropia and exotropia was then further divided into constant (including microtropia) and intermittent types to determine the prevalence of each type of strabismus. Differences in prevalence rates between age and ethnic groups were assessed using a Chi-Square Test of Independence. Children older than 72 months who participated in SPEDS (n=252) were excluded from this analysis. These children were predominately examined at the request of a parent concerned about the child's ocular status or they were siblings of a younger participant who was found to have an ocular abnormality which produced a biased sample in this particular group of children. The prevalence of strabismus in this biased age-sample was 4.4%. As the SAVES children were a follow-up study of the baseline SMS cohorts, there is a combination of children followed-up from SMS and new children recruited and included in the cross-sectional analysis of the prevalence rates for strabismus in the SAVES 12 years and 17 years age groups.

4.2.2 Logistic Regression Models of Risk Factors for Strabismus

The univariate and multivariate regression analyses of risk factors for strabismus included all children who participated in SPEDS aged ≤72 months and all those in SMS or those who participated in SAVES only. For children who participated in both SMS and SAVES, only the first assessment (baseline) was included in these analyses. For this analysis, age was categorised as; 0-2 years, >2 - ≤4 years, >4 - ≤6 years, >6 - ≤10 years, >10 - ≤15 years and >15 - ≤17 years. Ethnicities included in the model were

European Caucasian, East Asian and Other, as the two defined ethnicities represented individually more than 10% of the population and therefore could be analysed separately. Refractive errors included hyperopia ≥+3D, myopia ≤-0.5D and these were compared to emmetropia to mild hyperopia, namely >-0.50 to <+3D. Anisometropia was also included when there was a ≥1D difference in spherical equivalent refractive error between the child's eyes.

4.2.3 Longitudinal data analysis

For the longitudinal analysis to determine the incidence of strabismus and examine the impact of treatment and refractive errors, only children who participated in both SMS and SAVES were included. Chi-Square tests were used to determine if there were any differences in the proportion of children with strabismus between baseline and follow-up, and the incidence of strabismus between the two timeframes. Incidence rates for strabismus were determined from the number of children without strabismus at baseline who presented with a strabismus at the follow up examination and are calculated as incident cases per 1000 children per year. Children who were found not to have a strabismus at baseline were then analysed to assess the impact of refractive errors on the development of strabismus and different categories of strabismus.

4.3 Results

4.3.1 Cross-sectional prevalence of strabismus

Table 4.1 describes the prevalence of strabismus across the three studies in age categories. Overall, there was a significant difference in the prevalence of strabismus between the 7 age groups (p=0.03). The highest prevalence of strabismus was found in the two cohorts of adolescent children participating in SAVES at 12 and 17 years old (4.1% and 4.3%, respectively). Between all other age groups from SPEDS and SMS aged 6 months to 12 years old, there was no significant difference in the prevalence of strabismus (mean prevalence 2.8%, p=0.99). When comparing the closest age groups between studies; the overall prevalence of strabismus was similar between the SPEDS >4 to ≤6 years age group and the SMS 6 year old age group (p=0.24). However, there was a significantly higher prevalence of strabismus in the SAVES 12 year olds compared to the SMS children 5 years earlier at the same age of 12 years (p=0.02).

Table 4.1 Prevalence of any strabismus, esotropia, exotropia in the three studies by age groups

Age Group (n)		Any Strabismus	Esotropia	Exotropia
SPEDS	0.5 - ≤2 years (667)	2.8%	1.3%	1.5%
	>2 - ≤4 years (764)	2.9%	1.0%	1.8%
	>4 - ≤6 years (687)	2.9%	1.0%	1.9%
SMS	6 years (1740)	2.7%	1.4%	1.2%
	12 years (2353)	2.7%	1.2%	1.4%
SAVES	12 years (1120)	4.1%	1.3%	2.7%
	17 years (1685)	4.3%	0.7%	3.6%

4.3.2 Cross-sectional prevalence of esotropia and exotropia by age groups

Overall there was a significant difference in the prevalence of esotropia compared to exotropia across all age groups (p<.0001), see table 4.1. In the 6-24 month old age group from SPEDS there was a relatively similar prevalence of esotropia and exotropia, as there was in the SMS 6 year old and 12 year old samples of children and the prevalence of esotropia did not change significantly from the youngest children to the adolescents at age 17 years (p=0.31). The prevalence of exotropia, however, increased with age (p<.0001), particularly in those examined as part of SAVES. This rise in the prevalence of exotropia accounted for the overall higher prevalence of exotropia in the children as a whole, with exotropia occurring three times more frequently than esotropia in those aged 17 years.

Comparison of the samples from different studies at the same ages, revealed there was a slightly higher proportion of exotropia to esotropia in the >4 - ≤6 years old children in SPEDS compared to the similarly aged SMS 6 year olds who had a more even distribution of exotropia to esotropia, but this difference was not statistically significant (p=0.29). However, there was a significant difference in the proportion of exotropia between the 12 year old children in SMS and the similarly aged later SAVES cohort (p=0.03), with a much higher prevalence of exotropia in the SAVES 12 years cohort. This accounted for the observed difference in overall strabismus between the cohorts (see Table 4.1).

4.3.3 Cross-sectional prevalence of types of esotropia and exotropia by age groups

For infants aged >0.5 - ≤2 years, constant esotropia was the most prevalent form of strabismus and its prevalence was lower in the older children, though this reduction was not significant (p=0.61). In this youngest age group prevalence of constant

exotropia was also relatively high. Again there was a similar drop in the prevalence of constant exotropia with age. However, it is to be noted that at age 17 the prevalence of constant exotropia rose again to a level that was equivalent to that of the youngest age group.

By far the most common form of strabismus was intermittent exotropia, which consistently increased in frequency with age from 0.7% in the youngest age group to 2.8% at 17 years (p<.0001, Table 4.2). However, the prevalence of intermittent esotropia remained relatively stable across all ages (0.3% to 0.8%, p=0.22).

Between studies and matched age samples, there were no significant differences in the prevalence of type of esotropia or exotropia in the >4 - ≤6 years old children in SPEDS and 6 year olds in SMS (p=0.37). However, there was a significantly higher prevalence of intermittent exotropia in the SAVES 12 years cohort when compared to the 12 year old children in SMS (p=0.02).

Table 4.2 Prevalence of each type of esotropia and exotropia in the three studies by age groups

Age Group		Constant Esotropia	Intermittent Esotropia	Constant Exotropia	Intermittent Exotropia
SPEDS	>0.5 - ≤2 years	1.0%	0.3%	0.8%	0.7%
	>2 - ≤4 years	0.8%	0.3%	0.1%	1.7%
	>4 - ≤6 years	0.7%	0.3%	0.1%	1.8%
SMS	6 years	0.6%	0.8%	0.1%	1.1%
	12 years	0.5%	0.7%	0.2%	1.2%
SAVES	12 years	0.8%	0.5%	0.5%	2.2%
	17 years	0.4%	0.3%	0.8%	2.8%

4.3.4 Cross-sectional prevalence of strabismus by ethnicity and age group

Overall, there was no significant difference in the total prevalence of strabismus between children of different ethnicities (p=0.23). When comparing the two largest ethnic groups, children of European Caucasian (56.8%) and East Asian (18.1%) ethnicity, again there was no difference in overall prevalence of strabismus (p=0.45). However, there was a significant difference in the type of strabismus with more exotropia present in children of East Asian origin compared to those of European Caucasian ethnicity (p<.0001). In children of European Caucasian origin, there was no significant trend in the prevalence of total strabismus with age (p=0.90) see table 4.3. However, in the East Asian children, there was a trend towards an increasing prevalence of strabismus overall, from 1.4% in the youngest age group to 5.6% in the oldest cohort that was predominately due to a higher prevalence of intermittent exotropia in the older age groups, but this was not statistically significant (p=0.07). While intermittent exotropia was the most common type of strabismus present in all ethnic groups (p=0.002), in the European Caucasian children this was observed only in the older children in the SAVES cohort.

Table 4.3 Prevalence of each type of esotropia and exotropia by ethnicity

		n	Constant Esotropia	Intermittent Esotropia	Constant Exotropia	Intermittent Exotropia	Total Strabismus
European Caucasian							
SPEDS	**0.5 - ≤2 years**	304	1.3%	0.0%	1.0%	1.6%	3.9%
	>2 - ≤4 years	354	1.1%	0.0%	0.0%	1.7%	2.8%
	>4 - ≤6 years	313	1.3%	0.3%	0.3%	1.6%	3.5%
SMS	**6 years**	1101	0.8%	1.0%	0.1%	0.9%	2.8%
	12 years	1405	0.6%	0.9%	0.3%	0.9%	2.7%
SAVES	**12 years**	629	0.6%	0.6%	0.2%	1.0%	2.4%
	17 years	743	0.4%	0.7%	0.7%	1.1%	2.9%
East Asian							
SPEDS	**0.5 - ≤2 years**	135	0.7%	0.0%	0.7%	0.0%	1.4%
	>2 - ≤4 years	150	0.0%	0.7%	0.0%	1.3%	2.0%
	>4 - ≤6 years	149	0.0%	0.0%	0.0%	2.0%	2.0%
SMS	**6 years**	298	0.0%	0.3%	0.0%	1.7%	2.0%
	12 years	352	0.6%	0.3%	0.0%	2.6%	3.5%
SAVES	**12 years**	165	1.2%	0.0%	1.2%	3.6%	6.0%
	17 years	267	0.0%	0.0%	1.9%	3.7%	5.6%

4.3.5 Ethnicity, age, gender and refractive error and the risk of developing strabismus

Demographic information such as the mean age, gender and ethnicity of the children included in the univariate and multivariate logistic regression models are provided in table 4.4. The prevalence of strabismus, refractive error and anisometropia of these children are also included for reference.

Univariate odds ratios and 95% CI for risk of prevalent strabismus, esotropia and exotropia according to ethnicity, age, gender and refractive errors including anisometropia are detailed in table 4.5. In the univariate analysis, adolescents aged >15 -17 years had significantly greater odds of having strabismus (OR, 2.08; 95% CI 1.15-3.76), in particular exotropia (OR, 3.55; 95% CI 1.69-7.46) than younger children. Female children had a greater risk of developing strabismus overall (OR, 1.39; 95% CI 1.05-1.82). As might be expected from the previous description of the distribution of types of strabismus by ethnic origin in this chapter, children of East Asian ethnicity had significantly lower risk of esotropia (OR, 0.45; 95% CI 0.21-0.94), compared to European Caucasian children. Anisometropia and hyperopia were highly significant risk factors for strabismus, and for esotropia and exotropia individually. Myopic refractive errors conferred an increased risk of strabismus and exotropia, but not esotropia.

The multivariate model included age, gender, ethnicity, refractive error and anisometropia (Table 4.6). In this model, age, gender and ethnicity were no longer a significant risk factors. Children who were clinically significantly hyperopic remained more than nine times more likely to have strabismus (OR, 9.41; 95% CI 6.10 – 14.51) and even more likely to have developed esotropia (OR, 17.65; 95% CI 9.95-31.31) and 3.11 times more likely to have exotropia (95% CI 1.49-6.50). Children who were myopic had three times the risk of having any strabismus (OR, 3.05; 95% CI 1.83-

5.09) and had an odds ratio of 3.92 for exotropia (95% CI 2.13 - 7.22). Anisometropia also remained a significant risk factor for strabismus, and both esotropia and exotropia in the multivariate analysis, independent of myopia and hyperopia, age and ethnicity.

Table 4.4 Mean age, gender, ethnicity and prevalence of strabismus, refractive error and anisometropia of children included in the logistic regression models

Age Group (n)	Mean Age	Female	European Caucasian	East Asian	Strabismus	Hyperopia ≥+3.0D	Myopia ≤-0.5D	Anisometropia Diff ≥1D
0.5 - ≤2 years (704)	1.17 years	44.9%	45.3%	20.6%	2.8%	6.0%	4.3%	3.6%
>2 - ≤4 years (779)	3.03 years	45.8%	46.6%	19.6%	2.9%	5.0%	4.2%	2.5%
>4 - ≤6 years (786)	5.15 years	49.2%	45.8%	23.3%	2.9%	4.3%	2.5%	2.5%
>6 - ≤10 years (1644)	6.75 years	48.8%	64.6%	16.1%	2.7%	3.8%	1.6%	1.5%
>10 - ≤15 years (2579)	12.62 years	49.4%	59.4%	15.6%	3.0%	2.7%	14.5%	4.6%
>15 - ≤17 years (488)	17.48 years	55.3%	47.2%	26.4%	5.7%	2.3%	28.7%	6.3%

Table 4.5 Univariate analysis of age, gender, ethnicity, refractive error and anisometropia for strabismus

		Strabismus OR	95% CI	Esotropia OR	95% CI	Exotropia OR	95% CI
Age	**0.5 - ≤2 years**	1.00					
	>2 - ≤4 years	1.01	0.54-1.89	0.77	0.30-2.02	1.23	0.54-2.78
	>4 - ≤6 years	1.03	0.56-1.91	0.76	0.29-1.97	1.20	0.53-2.71
	>6 - ≤10 years	0.94	0.54-1.62	1.04	0.48-2.26	0.77	0.36-1.66
	>10 - ≤15 years	1.06	0.64-1.77	1.01	0.48-2.10	1.09	0.54-2.18
	>15 - ≤17 years	**2.08**	**1.15-3.76**	0.45	0.12-1.68	**3.55**	**1.69-7.46**
Gender	**Male**	1.00					
	Female	**1.39**	**1.05-1.82**	1.29	0.84-1.97	1.36	0.95-1.95
Ethnicity	**Caucasian**	1.00					
	East Asian	0.93	0.62-1.38	**0.45**	**0.21-0.94**	1.56	0.95-2.56
	Other	0.87	0.61-1.24	0.65	0.38-1.12	1.19	0.74-1.92
Refractive Error	**>-0.5 - <+3D**	1.00					
	Hyperopia ≥+3D	**14.52**	**10.09-20.89**	**27.01**	**16.87-43.25**	**4.74**	**2.53-8.91**
	Myopia ≤-0.5D	**4.36**	**3.04-6.27**	2.03	0.94-4.36	**5.81**	**3.83-8.82**
Anisometropia	**No Anisometropia**	1.00					
	Anisometropia	**9.35**	**6.45-13.55**	**10.76**	**6.43-17.99**	**6.91**	**4.18-11.44**

Table 4.6 Multivariate analysis of age, gender, ethnicity, refractive error and anisometropia for strabismus

		Strabismus OR	95% CI	Esotropia OR	95% CI	Exotropia OR	95% CI
Age	**0.5 - ≤2 years**	1.00					
	>2 - ≤4 years	1.20	0.60-2.42	0.68	0.24-1.91	1.88	0.71-5.01
	>4 - ≤6 years	1.23	0.62-2.46	0.68	0.24-1.90	1.82	0.68-4.84
	>6 - ≤10 years	1.16	0.62-2.16	1.03	0.45-2.35	1.22	0.48-3.12
	>10 - ≤15 years	1.04	0.57-1.90	0.92	0.41-2.05	1.17	0.48-2.86
	>15 - ≤17 years	0.93	0.28-3.01	0.59	0.07-5.10	1.22	0.28-5.25
Gender	**Male**	1.00					
	Female	1.23	0.89-1.69	1.11	0.69-1.78	1.23	0.81-1.89
Ethnicity	**Caucasian**	1.00					
	East Asian	0.79	0.50-1.26	0.56	0.25-1.24	1.05	0.59-1.85
	Other	0.93	0.63-1.38	0.91	0.50-1.65	1.04	0.62-1.75
Refractive Error	**>-0.5 - <+3D**	1.00					
	Hyperopia ≥+3D	**9.41**	**6.10-14.51**	**17.65**	**9.95-31.31**	**3.11**	**1.49-6.50**
	Myopia ≤-0.5D	**3.05**	**1.83-5.09**	1.57	0.57-4.34	**3.92**	**2.13-7.22**
Anisometropia	**No Anisometropia**	1.00					
	Anisometropia	**3.41**	**2.10-5.52**	**2.95**	**1.51-5.78**	**3.24**	**1.67-6.31**

4.3.6 Strabismus treatment in SPEDS and SMS

The questionnaire contained questions pertaining to previous treatment for strabismus, including glasses, patching for amblyopia, eye exercises and surgery. The proportion of children who reported receiving treatment for strabismus was greatest in 6 year old children (2.2%) from SMS, with other age groups reporting treatment in the range of 0.1-0.9% (p<.0001, Table 4.7). In the younger children aged 6 months to 48 months, all those reporting strabismus treatment were found to have strabismus at the time of the assessment by the study team. From 49 months to 12 years across both SPEDS and SMS, there was a substantial number of children (between 25.0 to 41.2%) whose parents reported that their child had received strabismus treatment and who were found not to have a manifest strabismus at the time of assessment.

When considering only children with esotropia, the 6 year old age group had the highest rate of receiving treatment (57.9%) while none of the parents of nine younger children with esotropia aged 6 months to ≤2 years, reported that their child had received treatment. Of those with exotropia, there were no significant differences in treatment rates between the age groups (p=0.16), although none of the parents of the >25 - ≤48 month old children with exotropia reported that their child had undergone any treatment for strabismus.

Table 4.7 Reported strabismus treatment and strabismus status at baseline

Age Group		Reported strabismus treatment	Did not have strabismus at assessment	Had strabismus at assessment
SPEDS	>0.5 - ≤2 years	0.1%	-	100.0%
	>2 - ≤4 years	0.3%	-	100.0%
	>4 - ≤6 years	0.6%	25.0%	75.0%
SMS	6 years	2.2%	41.2%	58.8%
	SMS 12 years	0.9%	27.8%	72.2%

4.3.7 Longitudinal follow-up of strabismus

Between SMS baseline data and SAVES follow-up there were 2093 children who formed the two longitudinal cohorts. There was a significant increase in the prevalence of strabismus in the younger SMS cohort between their baseline assessment at an average age of 6 years when followed-up a mean of 6.0 ±0.77 years later in SAVES then aged 12 years, (2.3% to 3.4%, p<.0001; n=886). In this cohort there was a significant change in the distribution of esotropia and exotropia, with increased prevalence of exotropia (p<.0001) at the older age. Intermittent exotropia was the most common type of strabismus at both baseline and follow-up, with a significant increase in the proportion of intermittent exotropia (0.9% to 1.9%, p<.0001) at follow up.

The older SMS cohort at baseline aged 12 years were followed up a mean of 4.5 ±0.68 years later at the mean age of 17 years. For this cohort, the prevalence of strabismus was found to be similar at the baseline assessment aged 12 and at follow up at 17 years (3.0% and 3.8% respectively, p=0.15; n=1132). Unlike the younger cohort, in the older cohort there was not a significant change in the overall prevalence of esotropia to exotropia (p=0.24). However, there was a change in the distribution in the types of esotropia and exotropia present (p=0.02). Intermittent exotropia was the most common form of strabismus present, both baseline and follow-up, increasing from 1.5% at baseline to 2.3% at follow-up while intermittent esotropia reduced slightly from 0.9% at baseline to 0.3% at follow-up.

Further investigation of the longitudinal change in strabismus, revealed there were a number of cases of strabismus that had resolved between baseline and follow-up. In the younger cohort, 52.6% of those who had a strabismus at 6 years were no longer found to have a strabismus at follow-up. Of those who had a strabismus in the older cohort at age 12, 91.2% no longer had a manifest strabismus at follow-up. The majority of these resolved cases were of intermittent esotropia and intermittent exotropia. Of those with intermittent esotropia at baseline, 66.7% of the younger cohort

and 90% of the older cohort no longer had a manifest strabismus at follow-up. Of those with intermittent exotropia at baseline, 62.5% of the younger cohort and 94.4% of the older cohort no longer had a manifest strabismus at follow-up. It is unclear whether this is a result of treatment or natural recovery.

Of the 15 children in the younger cohort whom it was reported had received strabismus treatment at baseline and who had strabismus, seven still had strabismus at follow-up and three of these were still undergoing treatment, while the remaining four did not report that they were still receiving treatment. For the eleven children in the older cohort who had strabismus at baseline and who reported having treatment, only one still had strabismus and was receiving ongoing treatment.

4.3.8 Incident strabismus and the impact of refraction

The reduction in cases of strabismus did not markedly change the prevalence of strabismus between baseline and follow-up, because it was off-set by the detection of new cases. The incidence rate of strabismus was 7.97/1000 children per year in the younger cohort and 16.26/1000 children per year in the older cohort. The largest number of new cases were of intermittent exotropia, making up 75% of new cases of strabismus in the younger cohort (n=15) and 60.5% of new cases of strabismus in the older cohort (n=26). The incidence of intermittent exotropia was 5.98/1000 children in the younger cohort and 9.83/1000 children in the older cohort.

Of the children who did not have strabismus at baseline, the percentage of incident strabismus at follow-up is reported by baseline refraction in table 4.8. In the younger cohort, 4.3% of hyperopic children and 25.0% of myopic children developed strabismus, compared to only 1.9% of emmetropic children ($p<.0001$). All incident strabismus in those children in the younger cohort who had baseline myopia and hyperopia was of intermittent exotropia type. In the older cohort incident strabismus was not significantly associated with refractive error ($p=0.91$), with no hyperopic

children developing strabismus, and only 3.6% of emmetropic and 4.2% of myopic children developing strabismus.

Table 4.8 Percentage of incident strabismus in children who were followed-up between SMS and SAVES by baseline refractive error

		No strabismus	Esotropia		Exotropia		p-value
			Constant	Intermittent	Constant	Intermittent	
12 years	>-0.5 - <+3D	98.1%	0.1%	0.2%	0.2%	1.3%	P<.0001
	Hyperopia ≥+3D	95.7%	0	0	0	4.3%	
	Myopia ≤-0.5D	75.0%	0	0	0	25.0%	
17 years	>-0.5 - <+3D	96.4%	0.5%	0.4%	0.6%	2.1%	P=0.91
	Hyperopia ≥+3D	100%	0	0	0	0	
	Myopia ≤-0.5D	95.8%	0	0	1.2%	3.0%	

4.4 Discussion

This chapter has examined the prevalence of strabismus through childhood and adolescence, how it changes with age and analysed factors that may influence both the change of the type of prevalent strabismus, as well as the occurrence of new strabismus and recovery from strabismus. This is important for public health interventions such as implementing vision screening and determining the cost-effectiveness of these programs. While constant esotropia and exotropia are the most prevalent forms of strabismus in infancy, below the age of two years, this reverses at older ages with exotropia becoming more prevalent than esotropia, largely due to an increase in intermittent exotropia. Although the constant strabismus of infancy is likely to be more influenced by birth-related factors, which will be discussed in greater detail in the next chapter, the increase in intermittent exotropia seems to be more related to the development of myopic refractive errors in younger children.

The prevalence of strabismus determined from the combined SCES (3.3%) is compatible to rates reported in other population-based and/or school-based childhood studies conducted in recent decades (see Chapter 2, Table 2.1). For the younger children aged six or less, the prevalence of strabismus in SPEDS and SMS six year olds is remarkably similar to that reported by MacFarlane and colleagues[89] (1987) in Grade 1 Australian school children (2.85%) and Fitzgerald[91] in Australian three year olds in 1994 (2.5%) although overall lower than that found in 1977 in over 5,000 five year old Australian school children (3.5%).[86] It is also within the range of the prevalence of strabismus found in the SPEDS large sister studies, the Multi-Ethnic Pediatric Eye Disease Study, known as MEPEDS[65] (2.5% in African American and 2.4% in Hispanic children) and the Baltimore Pediatric Eye Study (BPEDS) which also examined children in a similar age range (2.1% in African American and 3.3% in White children), the latter being comparable to the European Caucasian children in SPEDS who overall had a prevalence of strabismus of 3.1%. The third sister study, the

Strabismus, Amblyopia and Refractive Error in Singaporean Children (STARS) study had a notably lower prevalence of strabismus in children in the same age range (0.8%) that in part was determined by the very low prevalence of esotropia (0.1%) in this population of young East Asian children.[47,64] While the prevalence of strabismus was lower in the East Asian children (2.4%) than the European Caucasian children (3.2%) in SPEDS, it was not as low as found in STARS.

Comparable studies for the older children in the SCES are not as readily available with no Australian study of strabismus prevalence in older children and limited comparisons to be made at the same ages in the literature, particularly the older adolescents. The prevalence of strabismus in the 12 year children in SAVES parallel those reported in previous studies of between 4 to 5%.[108,109,115]

When examining the prevalence of strabismus by age in the SCES it is clear that between 6 months to 12 years of age the overall prevalence of strabismus was stable but thereafter increased with age. Interestingly, in the study by Pan and colleagues[115] of over 9,000 children in China, a similar rise in the prevalence of strabismus was noted when their population sample was stratified by age with a prevalence of 2.47% in the children aged 6 – 8 years to a prevalence of strabismus of 4.96% in the oldest group aged 12 – 14 years. However, this has not been uniformly observed, as a study examining 6 to 21 year olds in Iran did not observe a rise in the prevalence of strabismus with increasing age.[106]

The apparent anomaly of a higher prevalence of strabismus in the SAVES 12 year old cohort (4.1%) than the previous SMS 12 year old cohort at baseline (2.7%) seems to be largely due to an increase in the prevalence of exotropia, in particular intermittent exotropia. In looking at the characteristics that differed between the two samples of 12 year olds (see Chapter 3, Table 3.2) the follow-up SAVES cohort of 12 year olds had a significantly higher proportion of children of East Asian origin ($p<.0001$) but ethnicity

was not associated with exotropia on univariate or multivariate analysis in this study. However, the SAVES 12 year olds did have a higher prevalence of myopia (p=0.043) and this factor was significantly associated with exotropia after adjustment for age, gender, ethnicity and anisometropia. Additionally, a quarter of the SAVES 12 year old who were myopic at baseline aged 6 had developed intermittent exotropia at follow-up examination while, myopia at baseline aged 12 (SMS) was not significant for the incidence of intermittent exotropia at age 17.

The potential impact of increasing age on prevalent strabismus is best demonstrated with the longitudinal cohort data from the SMS and SAVES studies. Interestingly, both the younger 6 year old and older 12 year old cohort in SMS began with a similar prevalence of strabismus at 2.7% at the time of the baseline examination. In SAVES, the 5-6 year follow-up of these cohorts at 12 and 17 years, the prevalence had increased but between cohorts remained similar at 4.1% and 4.3%, respectively. This demonstrates an increase in strabismus occurred over a similar period of time in both cohorts, irrespective of their age. However, on multivariate analysis with age adjusted for ethnicity, gender, refractive error and anisometropia, the impact of age on strabismus disappears.

The longitudinal data does however, reveal incident strabismus occurs throughout childhood, with the greatest incident rate occurring in the children from age 12 to 17 years at over 16 new cases per 1,000 adolescents, while there were a large number of pre-existing cases of strabismus that resolved over the follow-up period. The combination of incident strabismus and effective treatment occurring in other children at that age, resulted in a relatively stable prevalence of strabismus overall.

The risk of developing strabismus increased with refractive error, regardless of whether the child had hyperopia, myopia or anisometropia. In the multivariate analysis, a child with hyperopia of more than three dioptres had a greater than nine times risk of

strabismus and even more so, esotropia with odds greater than 17, compared to a child whose refraction is in the normal range between emmetropia to mild hyperopia. This finding is consistent with existing literature which has previously highlighted the significance of hyperopia on the development of strabismus, particularly esotropia.[37,38] This study confirms the significant impact of hyperopia as a risk for esotropia which was most prevalent in the younger ages and additionally, the significance of moderate to high hyperopia in adolescence for the development of intermittent exotropia.

The relationship between refractive error and type of strabismus is also evident when comparing the younger 6-72 month old children in SPEDS with its sister studies. In SPEDS there was an overall prevalence of strabismus of 3% with a balanced prevalence of esotropia to exotropia and similar proportions of hyperopia to myopia. The MEPEDS 6-72 month old children of White origin, had a similar overall prevalence of strabismus to SPEDS but a 3:1 ratio of esotropia to exotropia[47] and a correspondingly higher prevalence hyperopia.[130] In contrast STARS 6-72 month old Chinese children had a much lower prevalence of strabismus, a 1:7 ratio of esotropia to exotropia[64] and significantly higher prevalence myopia, 11% with less hyperopia at 1.2%.[131] These studies help to emphasise the impact of refraction on strabismus, between studies of children of similar ages.

The relationship between myopia and exotropia has previously been reported in the literature.[33,37] However, most studies that have examined the relationship between age, refraction and strabismus are limited to smaller age ranges. This may possibly limit the significance of myopia as a risk factor for strabismus. As myopia is predominantly a refractive error that develops with age and posterior ocular growth, it is more prevalent in adolescence in Australia.[120] The impact of myopia on the development of intermittent exotropia is most evident in the 12 and 17 year olds in SAVES. Using the longitudinal data, this study found a quarter of the 6 year old children in SMS who did not have strabismus but had myopia at baseline developed

intermittent exotropia by age 12 as compared to 3% of the 12 year old myopic children in SMS developing intermittent exotropia by age 17 years. This finding suggests that earlier onset of myopia is causal for intermittent exotropia and remains a significant, albeit weaker, risk factor in later adolescence. It also appears that the impact of age on the prevalence of strabismus may be more so an indicator of the refractive status of the cohort rather than a true effect of age.

It is well understood how significant anisometropia may interrupt and weaken fusion of images from the two eyes because of inherent differences in the images, compromising the capacity for binocular vision.[132] Similarly, the role of hyperopia and its demands on accommodation for clear vision in the development accommodative esotropia are clear. This is particularly the case in fully accommodative esotropia that can be completely corrected by wearing the appropriate strength of convex (plus) lenses.

The mechanism by which significant hyperopia and the onset of myopia may cause intermittent exotropia is less clear. Some of the explanation may lie in the relationship between accommodation and convergence, more specifically, the accommodative convergence to accommodation (AC/A) ratio and refractive error. It is possible that some children with a significant degree of hyperopia find the constant exertion of a high degree of accommodation difficult and tiring.[133] Therefore, if the child does not accommodate continuously to maintain clear vision, they will subsequently exert less accommodative convergence. This may cause their eyes to dissociate from an exophoria to exotropia. However, the relationship between hyperopia and intermittent exotropia is an area of some controversy with some reporting that the correction of hyperopic refractive errors increases exotropia[134] while others state that it reduces the frequency and size of intermittent exotropia.[135,136] Without a full analysis of all factors in children with hyperopia and intermittent exotropia, including cycloplegic refraction, measurement of AC/A ratio and assessment of binocularity including fusional ranges, it

is difficult determine the precise mechanism linking hyperopia and intermittent exotropia.

Conversely, those who are myopic have less need to accommodate and there is evidence, from a follow-up study of children aged 6 to 14 years, of more accommodative lag in children after the onset of myopia compared to those who remain emmetropic.[137] This could potentially contribute to increased exotropia in these children, as with less accommodation there may be less accommodative convergence exerted to maintain ocular alignment, while there is retention of binocular vision, hence the intermittent nature of the exotropia. However, there is some evidence that children with myopia have a higher AC/A ratio, likely compensating for the decreased need to accommodate[138] and as such, may not impact ocular alignment. This requires further investigation to determine whether there is a difference in AC/A ratio for children with myopia who develop intermittent exotropia compared to those who do not.

The increase in the prevalence of myopia over the past few decades[119] raises concern for a potential increase in the prevalence of strabismus, in particular, intermittent exotropia. The prevalence of myopia in East and South East Asia has been reported to be as high as 80-90%[139] and the prevalence of intermittent exotropia also appears to be increasing.[140] This adds greater urgency for interventions to prevent the onset and slow progression of myopia as there are additional implications for ocular alignment.

The data from the SCES indicates that the active treatment of strabismus appears to be highly successful. By 17 years of age, over 85% of those with baseline strabismus did not have strabismus at follow-up. Interestingly, the positive effects of strabismus treatment were not evident in the children aged 4 years or less in the SPEDS study, so it is possible active treatment was still required to ensure good visual acuity in both eyes and to stabilise binocular function where possible at an age when neural plasticity is still evident. It was also evident that intermittent strabismus, whether esotropia or

exotropia, were more amenable to treatment than constant strabismus. This is unclear whether a specific form of treatment is more effective than another or whether the underlying deviation persists, but control of the deviation improves over time.

Although there are limitations to using cross-sectional data of different samples to examine trends with age, this study has demonstrated variation in the prevalence of strabismus and types of strabismus across age groups by utilising three large population-based studies of children with similar protocols across a wide age range and in a population with a variety of ethnicities, including a significant population of European Caucasian origin and another of East Asian origin. The SMS and SAVES studies have also provided novel longitudinal data of incident strabismus in two cohorts of children from 6-17 years of age, showing that there is incident strabismus, particularly intermittent exotropia, occurring throughout childhood. It has also demonstrated a causal relationship between the early onset of myopia and the development of intermittent exotropia. This study has highlighted the significance of the relationship between refraction and strabismus and the age at which refraction is most influential in the development of strabismus. While showing that the prevalence of overall strabismus appeared relatively steady in childhood and rising only in adolescence, the prevalence was in fact determined by the occurrence of incident cases and the resolution of cases initially seen at baseline.

4.5 Conclusion

In conclusion, this study has been able to demonstrate that while the prevalence of strabismus may not vary with age until later in adolescence, there are significant changes in those who are diagnosed with strabismus due to the success of treatment for strabismus and the increasing incidence rates in late childhood/adolescence. This appears to be in part, related to the development of refractive errors, mainly myopia development. There are significant implications for this finding as the prevalence of myopia has been rising over past decades. This chapter additionally demonstrates there is a difference in the aetiology of esotropia and exotropia. While reporting overall prevalence of strabismus is significant for the cost-benefit analysis of implementing vision screening, the differences in the prevalence, risk factors and onset of esotropia and exotropia should be taken into consideration. In particular, intermittent exotropia is highly variable between cohorts and age groups and appears to be strongly influenced by the changes in refraction status with age. Perhaps fortunately, intermittent strabismus may be the form of strabismus most able to be resolved by treatment.

CHAPTER 5: Prevalence of Eye Conditions in Children Admitted to Neonatal Intensive Care Units in a Population-Based Sample

5.1 Introduction

The Australian and New Zealand Neonatal Network reported in 2016 that 2.8% of all infants born in Australia and New Zealand were admitted to a neonatal intensive care unit (NICU).[141] This percentage had significantly increased from 1.8% in 1995[142] and 2.4% in 2005.[143] In contrast to the rise in NICU admissions, the proportion of infants born prematurely and of low birth weight who are admitted to NICU has decreased. Of the infants who were admitted to NICU in 2016, 35% were born before 32 weeks gestation and 29% weighed less than 1500g, compared to 50% who were premature and 44% with low birth weight in 1995.[141,142] In addition, 96% of infants admitted to NICU were able to go home in 2016, indicating substantially improved survival rates from 88% in 1995.[141-144] Overall, this suggests that there has been a significant change in the demographics of infants being admitted to NICU, coupled with a greater rate of survival.

Low birth weight and prematurity have previously been linked to an increased risk of strabismus, amblyopia and refractive error.[34,38,145-147] In addition, NICU admission has independently been identified as a risk factor for the development of strabismus[34] and amblyopia,[12] although the cause of this association is unclear. As the management of some ocular conditions, in particular amblyopia, is time-critical to the period of neural plasticity in childhood, early detection and intervention is essential to preventing long-term vision loss. Despite this, current vision screening regimes in NICU exclusively target the detection of retinopathy of prematurity (ROP),[148,149] which has been reported to occur in 40-61% of premature and low birth weight infants in the initial weeks following birth.[150,151]

Children identified as having ROP through NICU-based screening programs are referred for further ocular management, while infants not exhibiting signs of ROP, may not be offered this ongoing eye care. Thus, ophthalmic screening and ongoing follow-up eye care is generally not made available to all infants admitted to NICU, despite the

increased risk of ocular conditions. Previous reports have also linked low birth weight, maternal smoking during pregnancy and low socioeconomic status (SES) to strabismus.[33,34] As such, infants who may be at risk of ocular conditions and who are currently not screened within existing neonatal programs may include those who are from more disadvantaged backgrounds and therefore less likely to access tertiary eye care services in the absence of screening.[152] Based on current evidence, there is a need for more targeted screening to be available for infants admitted to NICU who are not necessarily at risk of ROP, but still have an increased risk of adverse ocular outcomes.

Despite the known risk of ocular conditions in babies admitted to NICU, the rate of ocular conditions within a representative sample of children with a history of admission to NICU has not yet been examined to determine the potential need for an extension of existing screening programs. Such data would indicate the population rate of ocular conditions within this vulnerable group compared to their peers who had not be admitted to NICU. The series of Sydney Childhood Eye Studies examined vision, refractive error, strabismus and ocular conditions in a population-based and representative age sample of Australian pre-school and school-aged children. One of these, the Sydney Myopia Study (SMS) has previously reported risk factors associated with strabismus and amblyopia for Grade 1 children aged 6 years.[12,34] The current investigation reports the prevalence of all eye conditions present in children admitted to NICU in children aged between 6 months and 6 years from the Sydney Paediatric Eye Disease Study (SPEDS) and the 6 year old cohort from the SMS. In addition, this study will further investigate the relationship between admission to NICU independent of previously identified risk factors for eye conditions, such as low birth weight and prematurity.

5.2 Statistical Analysis

All children in SPEDS and the 6 year old sample from SMS were included in the analysis of eye conditions present in children admitted to NICU. Questionnaire and examination variables were coded for SPEDS and SMS individually before the data sets were combined to provide a larger number of NICU admissions and improve statistical power for analysis. Children were grouped according to those who had been admitted to NICU and those who had not. Birth factors such as premature birth, birth weight were also included for analysis. Chi-Square tests for independence and Pearson's correlations were used to compare the prevalence of any eye condition, refractive error, amblyopia, strabismus and ocular pathology between children who had a history of admission to NICU and those who did not. The impact of birth factors including, gestational period, birth weight and multiple birth on the prevalence of ocular conditions was also investigated. Univariate logistic regression analyses were performed to calculate odds ratios (OR) and 95% confidence intervals (CIs) to investigate significant risk factors for each ocular conditions. Multivariate logistic regression analyses were also performed to determine the interaction between NICU admission and other birth factors on prevalent ocular conditions.

5.3 Results

A total of 3221 children from SPEDS and SMS had questionnaire and ocular examination data available for analysis. Of these, 198 children had been admitted to an NICU in infancy of whom 46.7% were born premature and 39.2% were of low birth weight. The proportion of children with prematurity and low birth weight was significantly higher in those admitted to NICU (p<.0001) than those who had not been admitted (Table 5.1). A statistically significant correlation was found between birth weight and gestation period (r=0.52, p<.0001), birth weight and admission to NICU (r=0.36, p<.0001), and gestation period and admission to NICU (r=0.38, p<.0001). There was no significant difference in gender (p=0.7) or age (p=0.7) between those admitted and not admitted to NICU.

Table 5.1 Demographics for children who had been admitted to Neonatal Intensive Care Units (NICU) compared to those who had not been admitted

	Not admitted to NICU % (n)	Admitted to NICU % (n)	P-Value
Gender (Female)	48.7% (1471)	46.0% (91)	0.74
Low Birth Weight	3.7% (104)	39.2% (73)	<.0001
High birth weight	5.9% (166)	3.2% (6)	
Premature	4.9% (145)	46.7% (91)	<.0001
Late term (<42wk)	6.4% (189)	4.1% (8)	

5.3.1 Prevalence of ocular conditions in children admitted to NICU

Table 5.2 compares the prevalence of conditions at the time of examination between children who had been admitted to NICU and those who had not. Overall, the prevalence of any eye condition including refractive error, strabismus and ocular pathology was significantly higher in children admitted to NICU (22.7%), than those not admitted to NICU (17.0%, p=0.04).

Table 5.2 Prevalence of Conditions (%) by admission to Neonatal Intensive Care Units (NICU)

	Not admitted to NICU %	Admitted to NICU %	p-value
Any eye condition	**17.0**	**22.7**	**0.04**
Amblyopia	1.6	2.9	0.27
Strabismus	**2.7**	**6.1**	**0.006**
Esotropia	1.0	2.0	0.17
Exotropia	**1.7**	**4.0**	**0.02**
Anisometropia	**2.4**	**5.7**	**0.005**
Refractive error	19.2	21.6	0.12
Hyperopia (>+2.00DS)	16.0	14.9	0.27
Myopia (<-0.50DS)	**3.2**	**6.7**	**0.02**
Anterior pathology	4.6	4.0	0.72
Posterior pathology	**3.0**	**6.1**	**0.01**

While the overall prevalence of refractive error in the children who had been admitted to NICU was similar to that of the population of children not admitted to NICU, there was a significantly higher prevalence of myopia (6.7% vs 3.2%, p=0.02). Anisometropia was also significantly higher in children admitted to NICU (5.7% vs 2.4%, respectively, p=0.005) but this was not related to the direction of their spherical refraction (hyperopia ≥+2D 36.4%, myopia ≤-1.50DS, 36.4%). Of the children with clinically significant hyperopia (≥+2D), 40% had anisometropia. While mild myopia between 0.05D and -1.5D appeared to confer no risk of anisometropia, those with myopia of ≤-1.50DS had the greatest prevalence of anisometropia (66.7%). A proportion of children admitted to NICU had significant astigmatism (13.8%) however, astigmatic difference between the two eyes did not make a significant contribution to the prevalence of anisometropia in these children.

There was a significantly higher prevalence of strabismus in children admitted to NICU (6.1%), compared to those not admitted (2.7%, p=0.006). There was additionally a difference in the type of strabismus present, with a greater prevalence of exotropia in children who had been admitted to NICU (4.0% vs 1.2%, p=0.02). The prevalence of amblyopia was nearly twice as high in children who had been admitted to NICU, although this difference did not reach statistical significance (2.9%, 1.6% respectively, p= 0.3). However, the rate of amblyogenic risk factors according to recommended preschool vision screening guidelines[153] was significantly higher in the children admitted to NICU than those not admitted (8.0%, 13.0% respectively, p= 0.016).

The prevalence of anterior ocular pathologies did not differ between children admitted to NICU and those who were not (p=0.7) However, signs of posterior ocular pathologies such as; asymmetrical optic discs, congenital hypertrophy of the retinal pigment epithelium and pupillary membrane were more common in children admitted to NICU (6.1%), compared to those not admitted (3.0%, p=0.02). There was only one child who had been admitted to NICU and had a reported history of resolved

retinopathy of prematurity. There were no other detected ocular conditions in this child when tested at age 6 years old.

5.3.2 Birth-related factors and risk of ocular conditions

Univariate odds ratios and 95% CI for various conditions according to birth-related risk factors (premature gestational period, low birth weight and NICU admission) are detailed in table 5.3 and multivariate odds for NICU admission are contained in table 5.4. Children admitted to NICU overall had a greater risk of developing strabismus (OR, 2.34; 95% CI 1.25-4.36) than those born with low birth weight (OR, 1.95; 95% CI 1.05-3.62) while gestational age/prematurity was not significant. When adjusted for birth weight (OR, 2.15; 95% CI 1.05-4.37) or gestational age (OR, 2.67; 95% CI 1.32-5.37), admission to NICU remained a significant risk factor for strabismus. A model including admission to NICU, birth weight and gestational age only marginally increased the odds for strabismus (OR 2.46; 95% CI 1.18 – 5.16). Low birth weight remained a risk factor for strabismus when adjusted for prematurity (OR, 2.33; 95% CI 1.04-5.24), but not when adjusted for admission to NICU.

In the univariate model children admitted to NICU were at greater risk of exotropia (OR, 2.45; 95% CI 1.14-5.23) while esotropia was not significant. Admission to NICU remained a significant risk factor for developing exotropia in the multivariate model adjusting for both gestational age and birth weight (OR, 3.87; 95% CI 1.66-8.99). However, children born prematurely were at increased risk of developing esotropia (OR, 2.403; 95% CI 1.05-5.48) but, this did not remain significant when adjusted for the other birth factors.

Children who had been admitted to NICU had two times the odds of developing myopia (OR, 1.94; 95% CI 1.05-3.60), compared to children who had not been admitted. This association remained significant when adjusted for prematurity (OR, 2.02; 95% CI 1.01-4.03), but not when adjusted for low birth weight (OR, 1.33; 95% CI

0.63-2.82) or for birthweight and prematurity combined (OR, 1.57; 95% CI 0.72-3.41). Admission to NICU also significantly increased the odds of developing anisometropia (OR, 2.47; 95% CI 1.29-4.75), as did low birth weight (OR, 2.17; 95% CI 1.2-4.28). NICU admission remained significantly associated with increased odds of anisometropia after adjustment for prematurity (OR, 2.88; 95% CI 1.39-6.00) and prematurity and low birth weight together (OR, 2.56; 95% CI 1.16-5.69). Low birth weight remained significant when adjusted for prematurity (OR, 2.39; 95% CI 1.04-5.49), but not prematurity and admission to NICU (OR, 2.09; 95% CI 0.80-5.45).

Admission to NICU was not associated with an increased risk of developing amblyopia (OR, 1.57; 95% CI 0.36-6.81). However, high birth weight was identified as a significant risk factor for amblyopia with an OR of 3.00 (95% CI 1.13-7.93). This association remained significant when adjusted for admission to NICU, birth weight or gestational age independently (OR, 3.33; 95% CI 1.24-8.92 and OR, 3.05; CI 1.12-8.29, respectively), and the three factors together (OR, 3.27; 95% CI 1.19-8.98).

Consistent with the similar prevalence of anterior ocular pathology between children who had been admitted to NICU and those who had not, there was no significant risk of developing anterior ocular pathologies associated with admission to NICU, gestational age or birth weight. Admission to NICU was associated with an increased risk of developing posterior ocular pathologies (OR, 2.096; 95% CI 1.13-3.90). This remained significant when adjusted for gestation and birthweight independently (OR, 2.43; 95% CI 1.22-4.85 and OR, 2.70; CI 1.35-5.42, respectively), and in a multivariate analysis with all three factors (OR, 2.75; 95% CI 1.33-5.67).

Table 5.3 The impact of risk factors on ocular conditions, univariate odds ratios (OR) and 95% confidence intervals (CI)

Ocular Condition	Admitted to NICU		Prematurity		Late Term		Low birth weight		High birth weight	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Amblyopia	1.80	0.63 - 5.17	1.29	0.45 - 3.69	1.05	0.32 - 3.46	1.50	0.45 – 5.00	**3.00**	**1.13 - 7.93**
Strabismus	**2.34**	**1.25 - 4.36**	1.18	0.61 - 2.29	0.62	0.23 - 1.70	**1.95**	**1.05 - 3.62**	1.43	0.68 – 3.00
Esotropia	2.05	0.72 - 5.88	**2.40**	**1.05 - 5.48**	0.90	0.22 - 3.78	2.24	0.94 - 5.36	0.41	0.06 - 2.99
Exotropia	**2.45**	**1.14 - 5.23**	0.54	0.17 - 1.72	0.48	0.12 - 1.96	1.68	0.71 - 3.97	2.22	0.99 - 4.95
Anisometropia	**2.47**	**1.29 - 4.75**	1.34	0.66 - 2.71	0.39	0.10 - 1.60	**2.17**	**1.10 - 4.28**	1.61	0.73 - 3.56
Refractive error	1.14	0.80 - 1.63	1.21	0.80 - 1.82	1.02	0.62 - 1.69	1.33	0.85 - 2.07	1.52	0.98 - 2.36
Hyperopia	0.94	0.63 - 1.42	1.22	0.89 - 1.66	0.84	0.56 - 1.26	1.03	0.71 - 1.49	0.99	0.67 - 1.45
Myopia	**1.94**	**1.05 - 3.60**	1.02	0.53 - 1.98	1.10	0.53 - 2.29	1.69	0.91 - 3.13	1.52	0.78 - 2.95
Anterior pathology	0.87	0.42 - 1.81	1.06	0.59 - 1.89	0.97	0.49 - 1.94	1.09	0.56 - 2.10	1.34	0.71 - 2.53
Posterior pathology	**2.10**	**1.13 - 3.90**	1.05	0.52 - 2.10	1.11	0.51 - 2.41	1.08	0.50 - 2.37	1.57	0.78 - 3.17

Table 5.4 The impact of admission to NICU on risk of ocular conditions, multivariate odds ratios (OR) and 95% confidence intervals (CI).

Ocular Condition	OR	95% CI
Amblyopia	1.92	0.56 – 6.65
Strabismus	**2.46**	**1.18 – 5.16**
Esotropia	1.12	0.31 – 4.02
Exotropia	**3.87**	**1.66 – 8.99**
Anisometropia	**2.56**	**1.16 – 5.69**
Refractive error	0.94	0.61 – 1.43
Hyperopia	0.81	0.50 – 1.30
Myopia	1.57	0.72 – 3.41
Anterior pathology	0.54	0.20 – 1.44
Posterior pathology	**2.75**	**1.33 – 5.67**

Note: Multivariate model adjusted for birth weight and length of gestation

5.4 Discussion

The chapter investigates the prevalence of ocular conditions in a large population-based sample of children who had been admitted to NICU in infancy, compared to those who had not. Overall the prevalence of ocular conditions in children with NICU admission was higher than those who had not been admitted to NICU. The higher prevalence of eye conditions overall in children who had been admitted to NICU in this sample can be attributed to a greater prevalence of myopic and anisometropic refractive errors, strabismus, and posterior ocular pathologies. The increased odds of developing anisometropia, strabismus and posterior ocular pathologies in children admitted to NICU was independent of the known birth-related risk-factors of prematurity and low birth weight. This study provides estimates of the prevalence of conditions within this at-risk group of children and suggests that in addition to those already screened for ROP, more routine screening and recommendations to parents for follow-up of children admitted to NICU is warranted.

The prevalence of refractive error between children admitted or not admitted to NICU was similar in this study. However, there was a higher prevalence of myopia in children admitted to NICU, and no difference in hyperopia prevalence. The greater risk of myopia associated with prematurity and low birth weight has been well established.[154,155] Myopia of prematurity has been identified as a consequence of the halted growth of the eye after premature birth, resulting in a steeper corneal curvature and thicker lens with greater refracting power.[156] Overall the odds for developing myopia in this study was greatest in children admitted to NICU. With the high covariance between prematurity, low birth weight and admission to NICU, this may result in admission to NICU being the measure of the greatest risk for early myopia. Such early onset myopia with continued ocular growth through childhood and adolescence, indicates a significant risk of future high myopia in these children.[157] This may place these children at a substantial risk of developing high myopia-related, sight-

threatening ocular pathologies such as myopic maculopathy.[158] However, if their myopia is more lenticular in origin than axial length, they may have a different risk of developing maculopathy to those myopic children who are predominantly axial in origin. This would need to be investigated in a long-term cohort of young myopes. As uncorrected refractive error is thought to adversely affect school performance[159] early screening to detect myopia in these children is warranted and may also provide an opportunity to implement strategies[160,161] to limit the development of high myopia.

Children admitted to NICU were 2.5 times more likely to have anisometropia than children who had not been admitted to NICU. There is limited literature reporting the natural history and associated risk factors for anisometropia, with studies that report on anisometropia focusing primarily on its role as a risk factor for amblyopia and strabismus.[162,163] Within the children admitted to NICU with significant myopia (≤ -1.5D), more than half had anisometropia. The increased prevalence of anisometropia was also present in children who had clinically significant hyperopia. The increased risk of anisometropia with greater refractive error observed in this study is consistent with previous observations.[164,165] There is scope for more research into the development and progression of anisometropia, while identification of possibly modifiable risk factors in children admitted to NICU could facilitate early intervention to reduce anisometropia and associated amblyopia risk.

Previous research relating strabismus to birth-related factors has focused predominately on the relationship with prematurity,[166-168] and low birth weight.[169,170] However, studies that have included NICU admission as an independent risk factor have consistently reported an association between strabismus and NICU admission, independent of both prematurity and low birth weight.[11,34] The current study additionally delineates between risk factors and type of strabismus that develop. A greater risk for esotropia was found in children born prematurely, independent of birth weight. There was a greater risk for exotropia with admission to NICU, than the risk of having any

strabismus at all, independent of prematurity and birth weight. This was unexpected given the known associations between both esotropia and exotropia individually with a number of birth-related factors.[11,33,34,38] There is a need for more detailed analysis of the causes for admission to NICU, treatments provided and other co-morbidities that may contribute to the development of strabismus in children admitted to NICU.

Identifying NICU admission as an independent risk factor for strabismus and anisometropia, suggests there may be additional as yet unidentified factors to which children admitted into NICU are exposed. Infants born with congenital anomalies are over-represented in NICU, making up 12% of infants admitted to NICU in 2016.[141] Children who have congenital anomalies are known to be at greater risk for the development of both refractive errors and strabismus.[15,171-173] However, as our study included 6 year old school children in SMS, children with severe congenital anomalies may be under-represented in this sample, which decreases the likelihood that the higher prevalence of strabismus and anisometropia in this sample admitted to NICU is due to an association with severe medical conditions. It is clear that while the specific relationship between NICU admission and higher prevalence of eye conditions requires further exploration, there is also a need for early ocular screening for these children who have a high prevalence of amblyogenic risk factors and sight limiting refractive errors.

5.5 Conclusions

Our study has shown there is a significant risk associated with NICU admission for the development of anisometropia, and strabismus, particularly exotropia in early childhood. These associations are independent of known risk factors such as prematurity and low birth weight. It is known that anisometropia, and strabismus are significant risk factors for amblyopia and early detection of conditions such as amblyopia and strabismus can improve effectiveness of treatment. Myopia and high myopia were also more prevalent in children admitted to NICU, putting these children at potential risk of myopic ocular pathologies later in life. This study highlights the need to further explore factors associated with NICU admission that may play a role in the development of these eye conditions. In the absence of a clearly defined factor for the higher prevalence of ocular conditions in children admitted to NICU, parents should be informed of the increased risk and the need for vision screening for their children. In addition, greater priority should be placed on creating a standardised vision screening protocol for all children who have been admitted to NICU in infancy.

CHAPTER 6: Background Literature and Methods for the Neonatal Vision Study

6.1 Visual development in infants

6.1.1 Development of vision

In the first months after birth, the eye and visual system undergo a number of anatomical changes to further the development of vision. One of the key components of the visual system that determines the limits of visual acuity is the configuration of retinal elements, particularly the fovea. The density of cone photoreceptors in the fovea is what sets the spatial frequency limits for vision and the visual acuity thresholds that can be reached.[174] At birth, the neonatal fovea differs from an adult fovea; it is larger at 1100μm in diameter and does not have a defined foveal pit. The lack of foveal pit is due to incomplete migration of retinal ganglion cell and inner nuclear layers outwards and away from the fovea, obstructing light from reaching the photoreceptor layer directly.[175,176] In addition, the cones themselves are not fully developed, are thicker in diameter with a shorter outer segment than seen in adult retina, limiting how densely cones can be positioned in the fovea.[176]

By 15 months of age, the foveal pit has been formed with the competition of migration of the inner retinal layers.[177] In addition, the diameter of the fovea has reduced and the density of cones in this area has substantially increased.[177] However, there are continued changes in the development of cones with their diameter not reaching adult size until 45 months of age with ongoing changes to outer segment length and cone density in the fovea continuing even after this age.[177]

A further anatomical change that occurs is progressive myelination of the optic nerve and pathways, allowing for rapid nerve conduction of visual information for processing in the visual cortex. Magoon and Robb (1981) studied the development of myelin in infants and children.[178] The intracranial optic nerve had some myelin present at 32 weeks of gestation and these myelin sheaths had become thicker and covered the

majority of nerve fibres by full term. The optic nerve portion of the pathway, closest to the globe was the last to become myelinated, with most fibres myelinated by seven months of age. Over the first two years of life, there was a significant thickening of myelin sheaths and more modest increases in thickness thereafter.

Given the anatomical restrictions on visual acuity in infants, newborns typically have poor visual acuity. However, rapid gains are made in the first few months of life (see review by Teller, 1997[179]). In 1962, Frantz et al. described the visual maturation pattern in infants in the first 6 months of life performing forced-choice preferential looking using gratings and found that under one month of age the minimum separable angle of the gratings that could be detected was 40 minutes of arc, compared to 5 minutes of arc at six months of age.[180] Mayer and Dobson in 1982, again using gratings and forced-choice preferential looking, investigated 50 infants and children of different ages to determine their visual acuity norms for age.[181] They similarly found that there were increases in visual acuity from only 6 minutes of arc at five months to adult levels by five years of age.

In 1995, Mayer et al. established normative visual acuity for 460 children between the ages of one month to four years of age using Teller Acuity Cards (TAC), as shown in figure 6.1.[182] All children were full term and otherwise healthy and without significant refractive error. Mean monocular visual acuity increased from 0.94 cycles per degree (cpd) at one month of age to 24.81 cpd at 48 months of age. In a larger and population-based study of 646 healthy and full-term infants from birth to 36 months of age, Salomao and Ventura (1995) reported a similar increase in visual acuity with age.[183] At 2 weeks, mean acuity was 0.66 cpd and had increased to over 17 cpd at 30 months onwards.

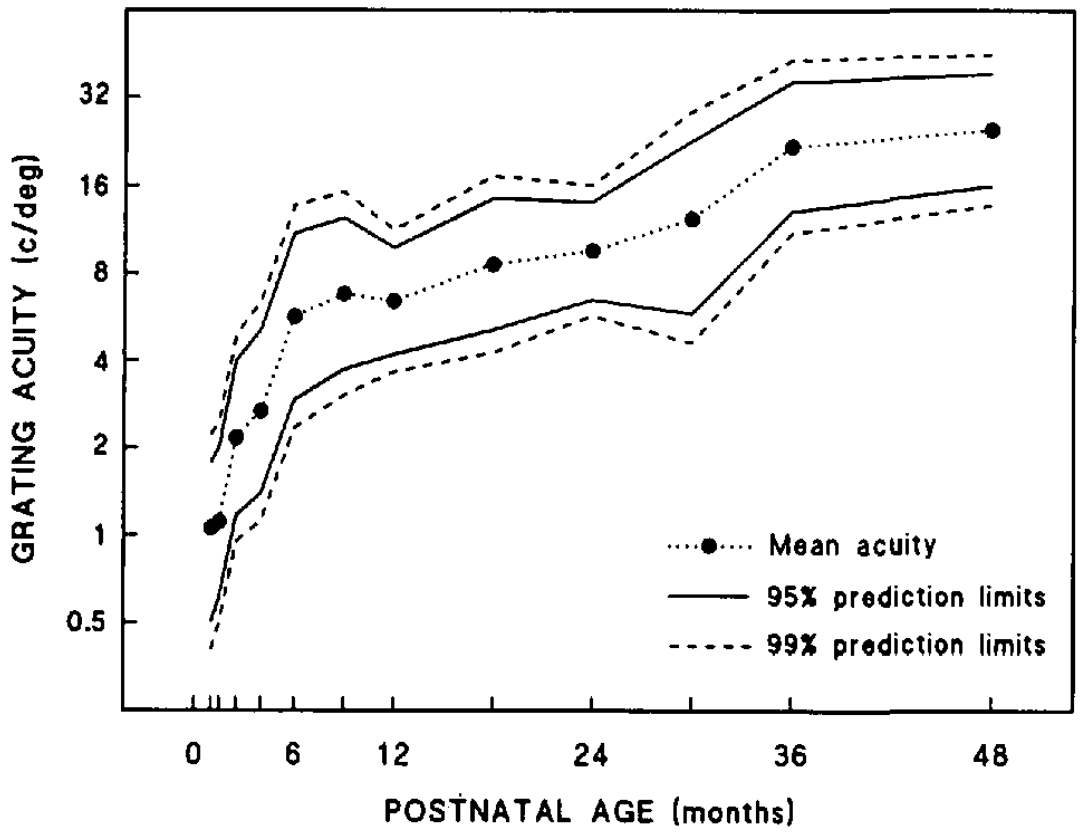


Figure 6.1 Normative mean visual acuity from Teller Acuity Cards with age. Reproduced from Mayer et al. (1995)[182]

Leone et al. (2014) examined normative visual acuity by age for 2463 children from six months to six years from the population-based Sydney Paediatric Eye Disease Study (SPEDS).[184] Younger children were examined using TAC, while older children (≥24 months) were tested using the Amblyopia Treatment Study (ATS) protocol with the Electronic Visual Acuity (EVA) tester and additionally LogMAR HOTV or ETDRS if able. This study showed improvement in visual acuity with increasing age across all visual acuity tests used, with adult-like levels of visual acuity (6/6 Snellen equivalent) reached at five years of age using the ATS EVA but not yet being reached in the oldest age sampled using the LogMAR HOTV or ETDRS (Figure 6.2) mostly likely due to the greater cognitive demand of these more complex linear visual acuity tests. The most rapid rate of visual acuity improvement was seen in the children aged less than 24

months, corresponding with anatomical development occurring within the eye, along with cortical development, particularly myelination of optic axons.

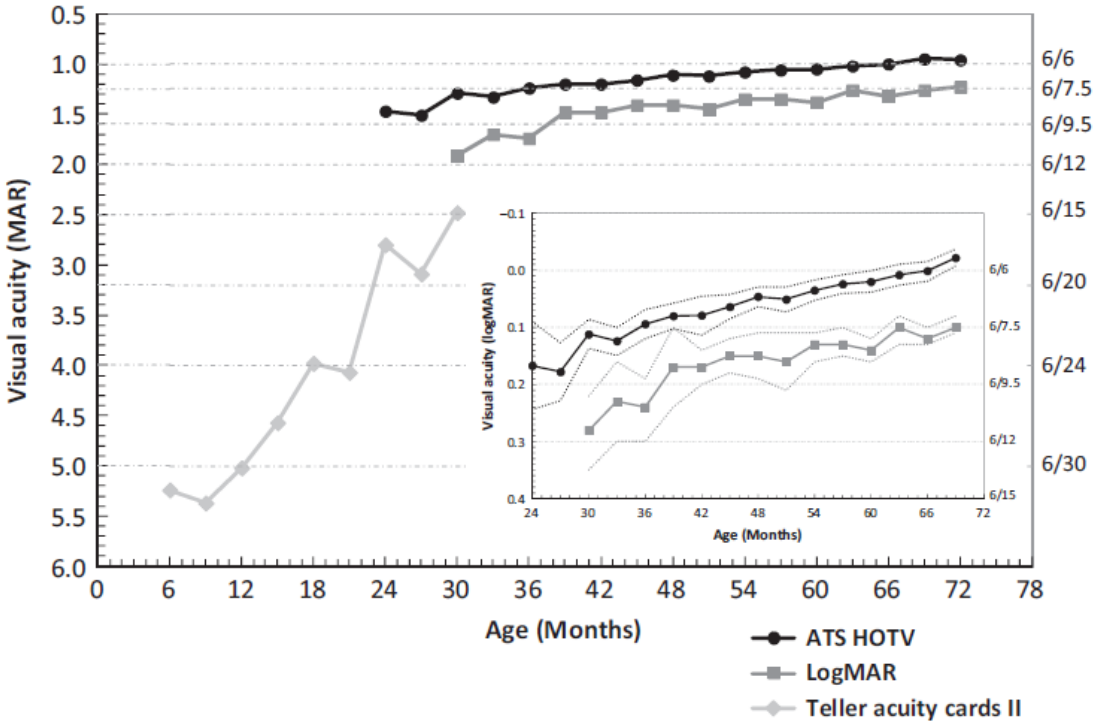


Figure 6.2 Normative mean visual acuity with age using Teller Acuity Cards II, the Amblyopia Treatment Study (ATS) HOTV Electronic Visual Acuity (EVA) Tester and LogMAR (HOTV and ETDRS). Reproduced from Leone et al. 2014.[184]

The optokinetic nystagmus (OKN) drum is widely used for visual acuity assessment as it utilises the infant's ability to track an object at an early age, with the ability to resolve the stripes on the drum providing an indication of gross visual acuity. When comparing a stationary to a moving test object, full term infants have demonstrated a preference for moving targets as early as one month old.[185] However, the use of OKN for visual acuity testing is limited by difficulties in retaining the attention of infants and it has been noted in early literature that the absence of an OKN response in younger infants may be due to an absent or immature ocular motor system rather than visual acuity of the eye.[186] OKN responses have also been demonstrated in the absence of a visual

cortex, highlighting its relationship to the ocular motor system rather than sensory system.[187] OKN responses are known to be asymmetrical with more consistent and earlier developed temporal to nasal responses than nasal to temporal responses.[188] This asymmetry has been proposed to be due to immature input to the nucleus of the optic tract to dorsal terminal nucleus, the link between sensory information from the retina to the motor outputs of OKN in the brainstem.[189]

6.1.2 Development of refractive errors

Emmetropia is a refractive state where the axial length of the eye is matched to its optical power, thereby optimally focusing light on the retina to produce clear vision.[177,190-192] Conversely, if the optical power of the anterior segment and the axial length of the eye is unbalanced, a refractive error will result. A short axial length causes hyperopia, with light entering the eye virtually coming to a focus behind the retina and a longer axial length results in myopia, with light coming to a focus in front of the retina. At birth, the spread of refraction has a normal distribution with the majority of infants having a refractive error in the hyperopic range and a small proportion who are myopic.[191,193-195] The high prevalence of hyperopia in neonates is related to their short axial length, and relatively established anterior segment in comparison to an adult eye as the posterior of the eye develops later than the anterior segment embryologically.

In the first year of life, the optical system of the eye undergoes significant anatomical and physiological development. Anatomically, there is axial elongation of the eye, reductions in cornea and lens power, followed by stabilisation of the anterior segment and development of the fovea. These changes contribute to both rapid increases in vision and progression towards emmetropia. Emmetropisation is an active process that reduces both myopic and hyperopic neonatal refractive errors, causing the distribution of refraction to become peaked around the mean (kurtotic) and a gradual shift in this

mean towards mild levels of hyperopia.[191,192,195-197] Through emmetropisation, the mean refraction in infancy decreases substantially from an average of +2.20 dioptres (D) at birth, to +1.60D by 12 months of age.[195] Emmetropisation, as a term, implies the endpoint of this process is emmetropia. However, most children remain in the refractive range of mild hyperopia throughout childhood,[197] and it has been suggested that mild hyperopia is actually the intended endpoint of the process.[198]

There have been a handful of longitudinal studies of newborn emmetropisation over the first year of life that have shown axial elongation to be a key component of this process.[192,196] The length of an infant eye is reported to be between 15mm and 17mm at birth, elongating at approximately 0.12mm/week in the first year of life.[190,192,193] Pennie et al. (2001) found that the rate of axial elongation was greatest in the first six months and then slowed significantly.[192] Anterior chamber depth has been found to increase in parallel with axial elongation from 1.91mm as a newborn to 2.81mm at 12 months.[192] The rate of axial elongation is related to the amount of refractive error at birth, with infants born with higher hyperopia demonstrating a greater rate of axial elongation compared to those with less hyperopia, indicating that emmetropisation is a visually-driven process.[191,196] This is supported by evidence from animal studies that suggest normal emmetropisation is influenced by exposure to visual stimulus in the form of myopic and hyperopic defocus.[199]

Studies have further documented changes in the power of the cornea and the crystalline lens throughout early emmetropisation.[193,196] In 1985, Gordon et al. cross-sectionally investigated the ocular biometric measures of a sample 79 patients ranging in age from newborns to adults.[193] The average corneal curvature of infants was significantly steeper and there was a flattening of corneal curvature between newborns and those who were six months of age, after which, there was no significant difference with further increases in age. Mutti et al. (2005) conducted a larger, longitudinal study of 222 infants at three and six months of age and showed that there is a significant

reduction in corneal power between these ages, in addition to a significant reduction in crystalline lens power and thickness.[196] Interestingly, the rate of corneal and lens power reduction was correlated with the amount of axial elongation that occurred, largely off-setting the impact of axial elongation on refraction. However, lens and corneal power changes were largely outpaced by axial elongation, causing the overall reduction of hyperopia.

After the first year of life, axial length elongation slows substantially but, continues at a reduced rate throughout childhood and adolescence. Axial elongation at this age, appears to be more aligned with passive growth and continues to slow with increasing age. With this, the mean refraction further shifts towards emmetropia throughout childhood. At age six years, the population-based Sydney Myopia Study (SMS) reported the mean refraction to be +1.26D[200] and at 12 years, this was lower at +0.48D.[201] Despite the gradual reduction in mean refraction, the majority of children remain mildly hyperopic throughout childhood and into young adulthood.[120] With continued axial elongation, children with less a hyperopic refraction at a younger age are at risk of excessively axial elongating and thereby becoming myopic, with those with a refraction of ≤+1.00 D at age 6 years at substantial risk.[202] Lens thinning, which continues to occur until approximately the age of 10 years and slows thereafter, does counteract some of the axial elongation occurring, effectively staving off the development of myopia.[203,204] However, children nearing the onset of myopia have accelerated lens thinning that appears to be largely depleted once they become myopic.[205]

For most children with significant hyperopic refractive errors, continued eye growth throughout childhood will result in a reduction of their hyperopia, however, some children with significant hyperopia will not reach emmetropia and will remain hyperopic.[206] Jones et al (2005) showed that emmetropic and hyperopic children shift their refraction in a myopic direction at a similar rate, however, a hyperopic child is

likely to remain hyperopic if the amount of eye growth is not sufficient to compensate for the initial high hyperopia.[204]

6.1.3 Development of binocular vision

Binocular vision is the ability to perceive images by each eye and cortically fuse these to appreciate a single image with depth. In 1901, Worth described three grades of binocular vision; simultaneous perception, fusion and stereopsis.[207] Grade one, simultaneous perception requires similar images to be perceived or seen at the same time by each eye and to be cortically superimposed as a single image. Grade two, fusion is the ability to perceive these images as one combined image (sensory fusion) and to maintain the single image over a range of eye movements (motor fusion). The image perceived by each eye must be of similar shape, clarity, brightness and size to facilitate fusion. If the two eyes do not perceive a similar image, for instance, if one image was severely degraded, then fusion may not occur. Stereopsis is the highest grade of binocular vision and, involves the interpretation of horizontal disparity between images as depth.

There are a number of anatomical and physiological requirements for normal binocular vision in humans. Firstly, the two eyes must have equal or near equal vision and both fovea must be visually aligned with each other in order that the visual scenes in each eye are similar. These images from each eye must be received in the same hemisphere of the occipital cortex, achieved by crossing of optic nerve fibres from the nasal retina at the optic chiasm to travel in the optic tract with the corresponding temporal fibres from the other eye allowing alignment between the retinal points in each eye. Finally, binocular cortical cells that specifically respond to input from both eyes, need to be present in the primary visual cortex (V1) to combine images from each eye into a single image with depth.

It has long been known that early visual experiences are important for normal development of binocular vision. Throughout the 1960s and 1970s, a series of animal studies by Hubel and Wiesel defined key parameters around the development of cortical cells in the primary visual cortex in response to visual experiences. They found that within the visual cortex of both cats and macaque monkeys, while there are some cortical cells that respond to stimuli from each eye individually, there are a proportion of binocularly-driven cortical cells which respond to information that is simultaneously received by both eyes.[208-211] Further, when visual information was deprived from one or both eyes by suturing the eyes shut at birth or early in life, the proportion of binocular cortical cells was substantially reduced.[210-212] Similarly, animals reared with both convergent and divergent strabismus have been found to have fewer binocular cortical cells.[213,214] Thus, interruption of visual input to one or both eyes early in life can prevent the development of normal binocular vision, as can ocular misalignment or strabismus, by preventing similar visual input being received simultaneously by both eyes.

The period of life where the availability of normal visual stimuli is essential for normal cortical development and when disruption of this stimuli, even for short periods of time, can cause severe and permanent loss of visual function is termed the ‘critical period’. In Hubel and Wiesel’s experiments, the critical period was suggested to be the first 3 months of life.[213] In humans, the critical period for development is generally considered to be the first year of life, with studies of early strabismus surgery in infants showing that there is certainly the potential for the development of some binocular vision and stereopsis in children with good surgical outcomes during this period.[215,216] The first three months of life have been suggested to be particularly pertinent for normal binocular development.[217] The ‘critical period’ is followed by a longer period of neuroplasticity in which there is potential for both the development and treatment of neuro-sensory adaptations to the visual experience such as, amblyopia and

suppression. This period of plasticity is typically considered to continue until 8-10 years of age, with some suggesting it continues to as late as 12 years.[218,219]

In children, the development of normal binocular vision can be influenced by a number of disease processes. For instance, conditions which cause reduced visual stimulation to one eye such as, a congenital cataract or ptosis can prevent the development of binocularly-driven cortical cells. Anisometropia, where there is a difference in refractive error in each eye can cause the image to one eye to be blurred or misalignment of the eyes (strabismus) that is constantly present from birth is also a likely cause of binocular vision failing to develop. While, strabismus can impact the development of normal binocular vision, the development of binocular vision early in life also facilitates the maintenance of straight ocular alignment and coordinated ocular motility. Vision loss can also prevent the development of binocular vision or suspend the use of normal binocular vision and cause sensory strabismus.[220]

Binocular vision testing is clinically used to demonstrate the two eyes are cortically linked. A number of largely experimental studies of binocular vision development in infants have been conducted and have shown that the majority of infants at three months old demonstrate some binocularity.[221-223] Using visually evoked responses (VEP) Braddick et al. (1980), tested infants between four to 36 weeks for binocularity.[221] Infants were presented with red-green patterns while wearing red-green goggles for VEP testing and those at three months of age consistently demonstrated the presence of cortical cells activated by binocular stimuli. An additional longitudinal study by the same authors, found that the median age at which binocularity was evident was 11.4 weeks of age.[222] A further study, also using VEPs and examining both stereoscopic and non-stereoscopic binocular stimulus, demonstrated that the development of binocular cortical cells by 10-19 weeks of age, precedes perception of stereopsis.[223]

Birch et al (1982) investigated the development in infants ability to appreciate crossed (in front of the point of fixation) and uncrossed (behind the point of fixation) disparity as stereoacuity, in both cross-sectional and longitudinal studies using preferential looking.[224] They found that before four months of age, 76% of infants did not appreciate any stereoacuity. However, by six months of age, 78% of infants had not only developed stereoacuity but, were capable of resolving the smallest disparity tested as stereoacuity. This study also found a difference in the timing of the development of stereoacuity based on crossed and uncrossed disparity. Crossed disparity was appreciated earlier in development by a greater proportion of infants compared to uncrossed disparity. The longitudinal data revealed that once the development of stereoacuity had begun, it progressed to high levels within a short timeframe of five weeks. This study was in agreement with the timing of development of stereoacuity reported in previous work[221-223] but, utilised a method more similar to standard clinical tests of stereoacuity.

Consistent with this timing, an experimental study of infants' ability to catch a ball of three different sizes under binocular and monocular conditions, demonstrated that catching a ball was significantly improved under binocular viewing compared to monocular from three months of age. Between three to six months, catching a larger ball resulted in more successful catches than smaller balls, however by seven to eight months, the size of the ball was less significant and binocularity significantly improved ball catching regardless of ball size.[225]

A key component of binocular vision is the ability to maintain a single image through stabilised fixation and coordinated eye movements and thus, the development of the ocular motor system is another element that is necessary for normal binocular vision development. Infants are known to often have ocular misalignment, sometimes transient and changing in direction early in life.[226,227] This appears to stabilise within the first months after birth.[226] It has been suggested that neonatal misalignments are

associated with the development of the vergence system, as attempted convergence tended to occur in parallel with more frequently observed misalignment and ceased as vergence movements become more accurate.[226]

In full-term, healthy infants aged between two to 21 weeks, it was found that within the first month, infants were able to achieve ocular alignment independent of binocular fusion development that developed later at 12.8 weeks.[228] While convergence started to develop at four to six weeks, most infants were able to converge fully by 13.7 weeks. The rapid appearance of both sensory fusion and motor convergence near to three months after birth, suggests that these functions may share a common developmental trigger, potentially the ability to appreciate disparity cues.[228] By 22 weeks of age, infants demonstrate a preference for targets with depth rather than a flat image.[228]

6.2 About Neonatal Intensive Care Units (NICU)

The majority of infants who are born in a hospital stay in level I newborn nurseries before being discharged to go home. For some infants, more medical attention is required and they may be admitted to level II neonatal intensive care units (NICU), also known as special care nurseries (SCN). SCNs are for infants born prematurely but at more than 32 weeks gestation, who weigh between 1500g to 2500g and who may have short-term mild illnesses. Infants who require extensive medical care including; those who are born <32 weeks gestation, have a birth weight <1500g, have congenital malformations and those who require surgical intervention, will be admitted to a level III NICU. Medical interventions for such young infants can be for ventilation assistance using intermittent positive pressure ventilation and continuous positive airway pressure (CPAP) or may involve major surgery such as gastrointestinal and cardiac procedures. The risk of an infant being admitted to NICU is greatest in infants who have been delivered by cesarean after the onset of labor, followed by those delivered by cesarean before labor onset and those with instrumental intervention, as compared to unassisted vaginal delivery, at a gestational age between 38 and 40 weeks.[229]

The Australian Institute of Health and Welfare annually releases a report of infant births and maternal health, “Australia’s mothers and babies”. The first of these reports was released in 1991[230] and the most recent in 2017.[231] Data extracted from the series of reports over the most recent decade (2007-2017) is presented in figure 6.3.[231,232] This demonstrates a clear trend towards increased infant admission to SCU and NICU from 14.5% in 2007 to 18% in 2017. There has also been a slight increase in the prevalence of prematurity and low birth weight, however the proportion of very low birth weight babies born <1500g has not appeared to increase, nor has the rate of multiple births.

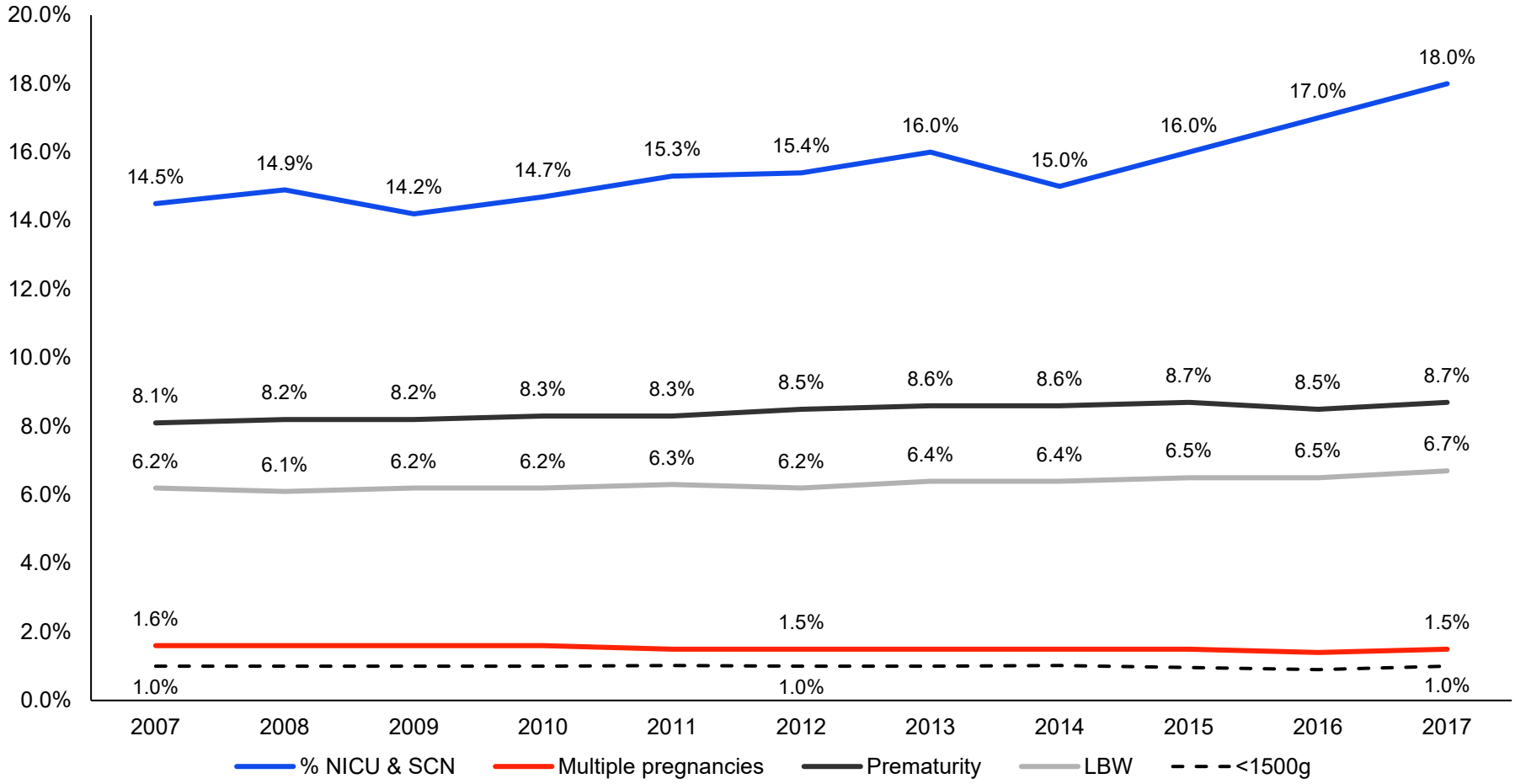


Figure 6.3 Australian Institute of Health and Welfare (AIHW) perinatal statistics

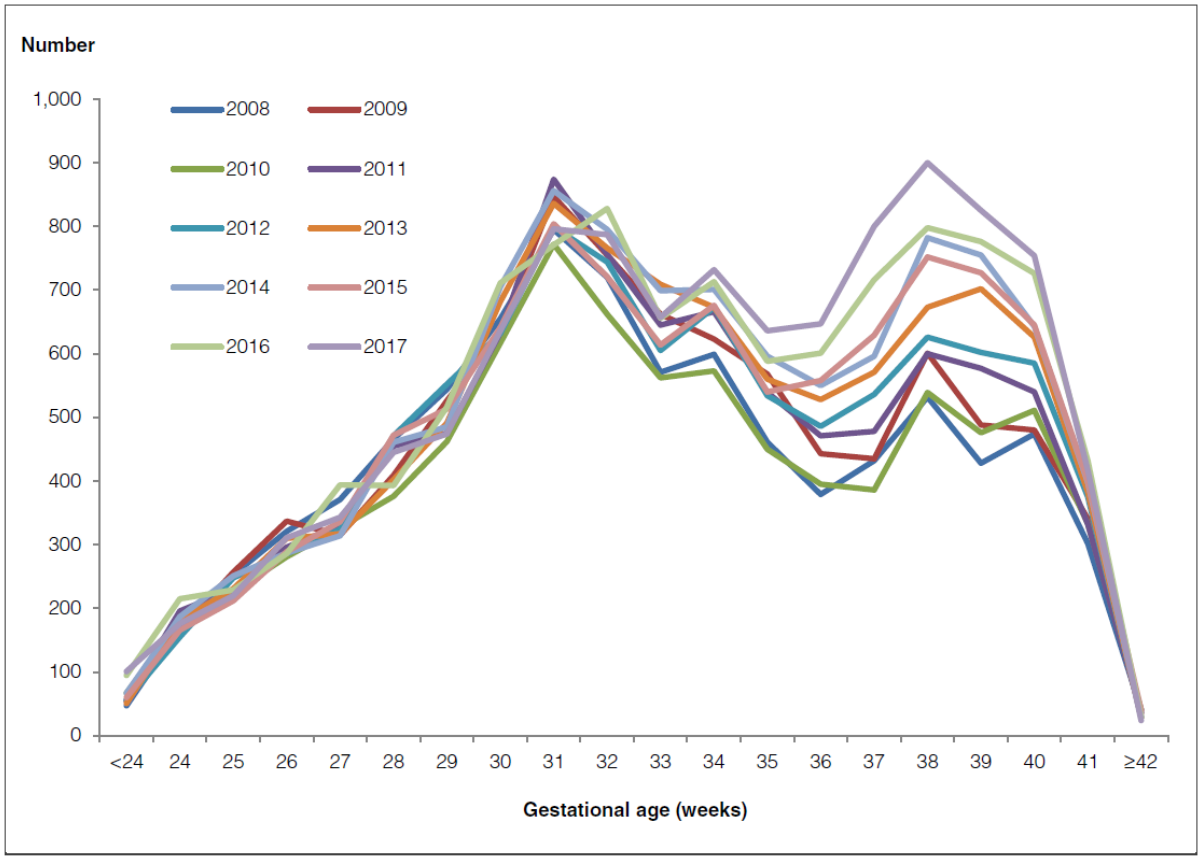
In Australia between 1994 to 2003, there has been a reported increase in spontaneous preterm labour of relatively healthy women, with no comorbidities.[233] A recent study on the rates of NICU admission in the USA has additionally found that the rate of NICU admission increased by 23% between 2007-2012, with increasing admissions of infants with higher birth weights and longer gestation periods.[234] This change in the demographic profile of infants admitted to NICU, raises concerns that infants who should otherwise be healthy, may be admitted to NICU and utilising highly specialised care, especially since there is high variability in admission rates between hospitals.[235,236]

A study of NICUs in the UK highlighted the variability between access to intensive neonatal care across the UK and the impact of the increasing demand for this level of care, with infants more frequently having to be transferred between NICUs when hospitals lack the number of beds required.[237] Studies have now moved towards interventions to reduce the burden of higher rates of admission to NICU including, education for parents to enable them to care for their infants and use of specialised teams to provide support for mothers to take over the care of their infants once they no longer require active medical intervention.[238,239]

The Australian and New Zealand Neonatal Network (ANZNN) release annual reports regarding high-risk infants (<32 weeks gestation or <1500g at birth or who received assisted ventilation, major surgery or therapeutic hypothermia) admitted across all 29 level III and level II NICUs in Australia and New Zealand. Of the infants born in Australia and New Zealand in the most recent 2017 report, 10,681 infants were considered high-risk babies admitted to NICU, representing 2.9% of all live births.[240] This was slightly higher than the 2.8% of all live births in 2016.[141] Of these high risk infants admitted to NICU, 32.8% were born prematurely at <32 weeks gestation and 27.8% were very low birth weight <1500g.[240] There were 17.2% multiple births in the 2017 cohort, 50.5% were born <32 weeks gestation and 95.9% <37 weeks gestation.

Other high-risk infants admitted to NICU had a variety of antenatal and postnatal complications.

Figure 6.4, from the 2017 ANZNN report shows the 10 year trends for gestation age. There is an apparent increase in the proportion of high-risk infants admitted to NICU with greater gestational age, while, those of lower gestational age have been consistently included in this cohort of infants. However, as noted in the AIHW data, the proportion of infants born preterm has been increasing, which may be contributing to the increased rates of NICU admission.[231]



Note: Data on the ANZNN registrants from two level III NICUs were not available in 2010.

Figure 6.4 Trends in gestational age at birth of level III registrants, Australian and New Zealand Neonatal Network (ANZNN) 2008–2017. From the Report of the ANZNN, 2017.

Infants admitted to NICU have high rates of survival in Australia, with those born at a later gestational age and of higher birth weight, having greatest odds of survival.[240] The survival rate of infants who have been admitted to level III NICU has been increasing steadily in Australia, with 89% surviving in 1995, increasing to 93% in 2005 and 96% in 2017.[240]

6.2.1 Prematurity and low birth weight

It has been estimated that the prevalence of premature births before 37 weeks gestation ranges from as high as 13% in South East Asia and Sub-Saharan Africa to 8.6% in developed countries.[241] Infants born weighing 2500 grams or less are considered to be low birth weight and this occurs in approximately 7.9% of births.[242] The Organisation for Economic Co-operation and Development (OECD) has estimated that the global rate of low birth weight rate is 6.5% but, with variation between 9.4% in countries like Japan and Greece and lower than 5% in Nordic and Baltic countries.[243] In Australia, 8.7% of infants were born before 37 weeks gestation and 6.7% were born of low birth weight in 2017.[231]

Most preterm births occur after 31 weeks and are associated with a number of risk factors including; poor maternal health, lower socioeconomic status (SES), maternal smoking, intra-uterine infection, multiple gestation, pre-eclampsia and congenital malformation.[244,245] Between 1989 to 2001, ruptured membrane and spontaneous preterm birth as a cause for preterm birth declined, while medically-indicated preterm birth based on preserving the health of the infant or mother has significantly increased.[246] The increased rate of medically-indicated preterm births has been linked with an increase in the number of children conceived by in vitro fertilisation (IVF).[247] While prematurity and low birth weight are related, intrauterine growth retardation also contributes to a significant proportion of those born of low birth weight, independent of

prematurity.[248] Risk factors for low birth weight include low sociodemographic factors, poor maternal health and lower access to health care.[249,250]

Healthy late preterm infants go on to achieve as well as full-term equivalents in cognitive and social milestones.[251] However, children born 30-34 weeks gestation and of lower birth weight exhibit neuropsychological delays despite being otherwise healthy at age 3-4 years of age, demonstrating the potential for the persistence of long-term neurological effects of premature birth.[252] There is also strong evidence for long-term cognitive impact from being born at an extremely low birth weight, with 9% of these children having cognitive impairment and the majority of these children failing to reach the expected cognitive standards for their age at 5 years.[253] For those born at a very low birth weight, there are also implications for educational achievement with less low birth weight young adults completing high school or attaining tertiary education.[254]

There is variability in the survival rates of infants born premature from 74.8% to 93.2% in Europe,[255] 84.2% in Australia and New Zealand,[141] 71.6% in the USA[256] and 87% in Japan.[257] While there have been reductions in the mortality rate of infants born at a very low birth weight, with 96% of those born between 1251g to 1500g surviving, there are further advances to be made to improve developmental outcomes for these infants.[258,259] Perinatal factors such as birth weight, gestational age, gender and treatment required during admission to NICU have a collective role in the survival rate of an infant.[258,260,261] While there are improved survival rates for infants who are born premature and of very low birth weight in high-income countries, there is increasing evidence that such early preterm birth should be prevented to avoid major disabilities.[262] In contrast to the improved survival rates for very early preterm infants in high income countries, infants who are moderate and late preterm infants often fail to survive in low-income countries due to a lack of basic medical care.[241]

6.3 Ocular conditions in premature and low birth weight infants

6.3.1 Retinopathy of Prematurity (ROP)

Retinopathy of Prematurity (ROP) is a common ocular consequence of prematurity and low birth weight, where neurovascular growth within the eye does not completely develop or is immature at birth. This can lead to visual impairment and in severe cases, retinal detachment and more severe loss of vision.[148] The International Classification of Retinopathy of Prematurity, last revised in 2005, defines five stages of disease to describe vascular abnormalities at the junction of the vascular and avascular retina.[263] Stage 1 and 2 refer to generally mild retinal vascular abnormalities, while stage 3 includes severe neovascularisation and likely visual impairment and stage 4 and 5 include partial and complete retinal detachment, respectively, with the likelihood of more severe visual impairment or blindness. ROP is considered one of the most serious sight-threatening ocular consequences of being born prematurely and of low birth weight and thus, this condition has been given substantial attention in the scholarly literature and also in service provision within NICU and SCN.

Infants considered at risk of ROP are generally those who are born ≤ 32 weeks preterm and who weigh ≤1500g at birth, although ROP can occur in premature and low birth weight infants above this range. Both prematurity and low birth weight have a dose-response relationship with ROP, where lower birth weight and gestational age infants are at considerably greater risk of developing ROP.[264] The proportion of premature and low birth weight infants who develop ROP to some degree has been reported to be as high as above 60%, although significant variation in reported rates exists.[150,151,265] Of the infants with stage 3-5 ROP, many will require surgical intervention to preserve visual acuity and prevent other adverse outcomes, whereas, in infants with stage 1 or 2 ROP the condition often regresses without

intervention.[148,149,266] There are global differences in the incidence of ROP, with higher overall rates and greater rates of disease requiring treatment in low and middle income countries.[267] In addition, the range of birth weights and gestational age over which cases of ROP occur, varies more widely in lower and middle income countries.

A number of studies have been conducted over a broad period of time to examine incidence rates for ROP, risk factors associated and changes over time. A retrospective study in the United States (US) based on the National Inpatient Sample, a 20% representative sample of all hospital discharges, examined births between 1997 and 2005 for the incidence of ROP and associated factors.[268] Infants were excluded if they were less than 28 days old to reduce the impact of infant mortality on the rates calculated. Of 34 million live births, it was reported that 58,722 infants were diagnosed with ROP, representing an overall incidence of 0.17%. The incidence of ROP increased in a stepwise fashion with lower birth weight while infants of low birth weight with longer stays in hospital were at a further elevated risk.

The incidence rate reported in this study was considerably lower than other reports, owing to the inclusion of infants of all birth weights rather than only those of low birth weight and at significant risk of ROP. For instance, Quinn et al (2016) examined the rates of ROP in pooled data from three clinical studies, the Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) study, the Early Treatment for Retinopathy of Prematurity (ETROP) trials and the Telemedicine Approaches for Evaluation of Acute-Phase Retinopathy of Prematurity (e-ROP) study, also in the US.[265] These studies enrolled over 12,000 infants with a birth weight <1251g over the period 1986 to 2013. In each of the three studies, the incidence of ROP was similar, at close to two-thirds of the population studied and remained relatively stable over time.

In most Australian and New Zealand NICUs, ophthalmic screening of the retina has been established to ensure routine care is provided for babies at risk of ROP,

however, screening criteria is variable between hospitals. Between 2012 and 2016, 31.2% to 28.8% of infants met the eligibility criteria for ROP screening, being of less than 31 weeks gestational age and 1250g at birth, with 83% receiving an eye assessment in level III NICU.[141,269] The majority of those infants who are screened for ROP are found to have no ROP, less than a third are diagnosed with stage 1 or 2 ROP[141] and close to 10% are diagnosed with stage 3-5 ROP.[264] Although screening criteria for ROP is not standardised between hospitals providing neonatal care, the majority of infants who are at risk are identified and receive appropriate treatment. However, of infants who were premature and low birth weight at risk of ROP, who were cared for in level II facilities (SCN) in 2017, only 51.1% received screening for ROP.[240]

6.3.2 Risk of other ocular conditions

It has been reported that infants who are admitted to NICU, those of low birth weight or premature birth and those with ROP are all at a higher risk of developing strabismus and high refractive errors.[156,270,271] Up to 46% of infants who are born premature and of low birth weight will have strabismus, amblyopia and/or refractive error.[35] These children are also at greater risk of reduced vision and reduced contrast sensitivity.[272] Examining premature infants only, 22% have been reported to have strabismus.[151] Infants with ROP have a further increased risk of adverse ocular outcomes compared to those born prematurely and with low birth weight but without ROP.[151,273,274] The risk of developing strabismus is highest in infants with ROP and a number of studies have also reported increased risk of myopia.[155,166,273,275] In addition, infants with ROP and who receive treatment have been shown to have an even greater risk of myopia and strabismus.[154]

There is an increased prevalence of hyperopia, myopia and astigmatism in premature children compared to full term children.[154,155,191] In addition, children of low birth weight have also found to be more anisometropic than age matched peers, while those with

cranial abnormalities tended to have more hyperopia and astigmatism.[191] A study of ocular biometry in children born prematurely found myopia to be associated with a shallow anterior chamber depth, thicker lens and corneal astigmatism while hyperopia was predominately the result of a short axial length.[156] In particular, children with ROP have been reported to have a short axial length, but with a thick and more convex lens resulting in more myopic refraction despite the axial length of the eye, as well as, more corneal astigmatism.[156]

6.4 Visual development in premature and low birth weight infants

Studies of the visual acuity development of preterm infants have primarily used two techniques; clinical testing using preferential looking and electrophysiological testing of visually evoked potentials (VEP). Testing visual acuity using preferential looking is well established, and the Teller Acuity Cards (TAC) have been shown to provide reliable visual acuity results in infants.[276] While the use of preferential looking is standard clinical practice, it has been shown that infant responses to preferential looking produce lower visual acuity results than visually evoked potentials (VEP).[277] VEP testing is useful for demonstrating that visual input is being received by the cortex, even if it is not recognised as a visual image, such as in children with cortical vision loss.[278] Similarly, there is evidence from experimental studies of monkeys that in the absence of a visual cortex, VEP can still be generated.[279] However, VEPs are not widely performed as a test of visual acuity as it is invasive and not a feasible to perform on all infants. It is therefore important to establish visual acuity norms using clinical tests in infant populations who are at risk of delayed visual acuity attainment such as those who are born premature and of low birth weight.

There have been only a handful of investigations into the visual acuity development of infants of premature birth in comparison to infants of full term birth (see reviews by Madan, 2005[280] and Birch and O'Connor, 2002[5]). The majority of studies have had limited success in conclusively determining whether preterm birth results in accelerated visual development due to additional extrauterine time exposure to visual stimulus or, whether visual development is pre-programmed to occur at a specific gestational times.

There is some evidence that preterm infants are visually-behind their age-matched peers early in life. Using preferential looking, Van Hof-Van Duin and Mohn (1986)

established that 36 premature infants had lower visual acuity when the chronological age of the infant was compared to 91 age-matched norms.[281] However, when corrected age was utilised, premature infants were able to demonstrate visual acuity development in line with age corrected-matched norms. Dobson et al (1980) similarly showed that preterm infants examined at eight and 12 weeks of chronological age had significantly poorer visual acuity in comparison to age-matched full term infants.[282] There was no longer a significant difference in an infant's visual acuity when their age corrected for their due date was compared to age-matched infants at four, eight and 12 weeks. In 2008, Ricci et al using gratings for preferential looking, showed that at two days old at least 95% of full term infants were able see 0.86 cycles per degree (cpd) or higher[283] whereas 97% of premature infants were only able to achieve 0.64 cpd at 35 weeks, again suggesting visual acuity attainment is likely to be equivalent to corrected age, not chronological age and that visual experience does not accelerate visual acuity as measured by forced preferential looking.[284] However, quite interestingly, Van Hof-Van Duin and Mohn's study found that by six to eight months, the preterm infants had caught up to the visual acuity norms for chronological age of full-term infants, suggesting some slight acceleration in visual development in the lead up to their expected date of term.[281] This has been supported by more recent findings.[285,286]

Studies of VEPs in preterm infants have also had variable findings. Norcia et al. (1987) suggested that visual acuity development was accelerated in preterm infants compared to full term infants.[287] In contrast, a study by Roy et al. (1994) investigated the pattern VEP response of 24 preterm and 24 full term infants, both aged at approximately a mean of three months corrected and chronological age, respectively, found both groups had a faster progression of improvement in responses over the first three months of postnatal age.[288] This followed by slower improvements, however, the responses for the preterm infants consistently lagged behind those of the full term infants. When compared to corrected age, the preterm infants appeared to develop at

a rate that was equal to or slightly faster than the full term infants, suggesting again that visual acuity development was related to gestational age rather than postnatal age. In a similar study, Atkinson et al. (2002) concluded that premature infants did not have a significantly accelerated or decelerated development of cortical VEPs when tested at the same age after term.[289] The authors pointed out that because VEPs are cortically generated they are more related to cortical development, but cannot take into consideration the development of the eye and retinal structures, optical system or myelination of the pathways that are essential for visual acuity.

There have been very few studies of the development of other visual functions such as ocular motility and binocular vision in preterm infants. Ricci et al. (2008) investigated ocular motility, tracking and attention at distance fixation in preterm infants.[284] They found that by 40 weeks of postmenstrual age, infants were able to perform most tests of these tests of visual function. For ocular motility function and vertical and arc tracking, the preterm infants were more mature than previously described for full term infants, while attention at distance and stripe discrimination (visual acuity test method) was more developed in the full term infants and aligned with the corrected age in preterm infants. Thus, the authors suggested that while preterm infant vision matures with cortical development according to corrected age, ocular motility is developed with visual experience and occurs at an accelerated rate for preterm infants.

Only one study has investigated other visual functions in premature infants and directly compared to full term infants.[290] Weinacht et al. (1999) measured ocular alignment, convergence, motor fusion and optokinetic nystagmus (OKN) in addition to grating acuity in 79 full term infants and 18 low-risk preterm infants (mean gestational age 33 weeks). Ocular alignment was seen at a postmenstrual age of 46 weeks for both full term and preterm infants, however this corresponded to a postnatal age of five weeks of age for full term infants and 12 weeks for preterm infants. Convergence was also delayed in the preterm infants, occurring fully at seven weeks postnatal for full term

infants and 13 weeks for those who were preterm. Again this was not different when postmenstrual age was considered. A similar pattern was noted for fusion elicited with four dioptre prism held base out, for vertical pursuit eye movements and OKN. As such, these findings indicate that various visual and ocular motor functions occur at the same time for preterm and full term infants and that there is no advancement of these functions in preterm infants resulting from an extended period of visual experience, in contrast to the findings of Ricci et al.[284]

6.5 Purpose of the Neonatal Vision Study

Chapter 4 of this thesis has clearly shown the strong relationship between refractive error, anisometropia and the development of strabismus. In addition, chapter 5 has identified admission to neonatal intensive care units (NICU) as a risk factor for all three ocular conditions, regardless of gestational age or birth weight. Identifying NICU as a risk factor allows for a unique opportunity to assess these high risk children early in life for these ocular conditions, as they typically also receive follow-up care for general health within NICU programs.

Vision screening and the opportunity for ongoing ocular care for infants admitted to NICU is currently not standardised or widely available for all infants. Current ocular screening regimes in Australian and New Zealand NICU exclusively target the detection of ROP in at-risk infants. At the Royal Prince Alfred Hospital (RPAH), infants born ≤25 weeks and/or <1250g are identified as at-risk for ROP. These infants are selectively screened at two weeks old for ROP and provided treatment if necessary. Those infants who have been screened, but who do not require intervention for ROP are followed-up with an ocular assessment within six months after discharge and subsequent follow-up is determined by the ophthalmologist.

The developmental follow-up scheme established at RPAH includes an overall health check as well as a vision test at eight months for infants who are preterm, low birth weight or deemed at risk of cardiac or developmental abnormalities. However, these assessments are performed by neonatal care nurses who observe for obvious ocular anomalies and assess the infant's ability to fix and follow an object binocularly, with no formal vision testing performed. Any infants with suspected visual abnormalities at this check who do not already receive eye care are referred to the RPAH eye clinic for follow-up and detailed ocular examination. While this follow-up scheme may detect more obvious ocular conditions that are present at that age including; severe visual

impairment, infantile esotropia and congenital ptosis, more subtle conditions such as refractive error, anisometropia, amblyopia and small angle or intermittent strabismus are likely to be under-detected.

Unfortunately, infants who do not meet either of the above criteria are not eligible for early ocular health screening and will be discharged with no long-term follow-up of their visual status. Likewise, infants with mild ROP which regresses may subsequently be discharged. This is despite the increased risk of amblyogenic and strabismic risk factors; anisometropia and myopic and hyperopic refractive errors as well as, strabismus itself in children admitted to NICU, independent of prematurity, low birth weight and ROP, as discussed in chapters 4 and 5. As these infants admitted to NICU are at a greater risk of these visual conditions and more generally visual impairment, there is a case to be made for more broad vision screening of this at-risk population. This is especially true given the time-critical nature of treatment for infantile strabismus and amblyopia. As such, early detection and provision of appropriate eye care is essential to preventing long term vision loss and subsequent visual disability in these infants.

There is a clear need for a wider and standardised screening regimes to be available for infants admitted to NICU who are not just at risk for ROP but still have an increased risk of these other adverse ocular outcomes. The detailed study of infants admitted to NICU; the Neonatal Vision Study (NVS) was designed to further explore and define the need for and appropriate timing of vision screening in infants who have been admitted to NICU.

6.6 Aims of the Neonatal Vision Study

The aims of the NVS were to:

1. Establish the prevalence of any eye conditions in infants admitted to NICU at ages three, six and 12 months
2. To determine normative age and developmental milestones for vision and ocular alignment in infants who had been admitted to NICU
3. Compare infants admitted to NICU to a population-based sample of age-matched controls (SPEDS study) to determine if there is a difference between expected development for chronological age in those admitted to NICU, specifically those who are of low birth weight and premature
4. Determine possible screening tests that may be used for the detection of ocular anomalies early in life and provide recommendations for standardised targeted screening regimes that may be implemented within NICU and in follow-up care.

6.7 Neonatal Vision Study methods

6.7.1 Sampling and recruitment

Royal Prince Alfred Hospital (RPAH) at Camperdown in Sydney, was selected as the recruitment site for the study, being a major Sydney metropolitan hospital, with a large neonatal care unit of 34 NICU beds. RPAH also has an eye clinic with available space and appropriate testing equipment on site. The inclusion criteria was any infant admitted to NICU who were; less than three months old at time of recruitment, resided within Sydney, NSW and who had parental consent to participate. For this study, all infants with and without suspected ROP were invited to participate in the ocular/visual assessment. Parents of infants in NICU were notified of the study through flyers in the NICU wards and information sheets inserted in information packs given to parents prior to their infants being discharged from the hospital. In addition, researchers attended “Baby Gyms”, a support program for parents of recently discharged infants to provide further information about the study and recruit parents interested in participating. All parents who expressed interest in the study were subsequently emailed by researchers to make an appointment at the RPAH eye clinic for assessments when the infant reached three, then six and 12 months of chronological age.

6.7.2 Ethics approval for the Neonatal Vision Study

Ethics approval for the NVS was obtained from the Sydney Local Health District, RPAH Human Research Ethics Committee and ratified by the Human Research Ethics Committee of the University of Technology Sydney (UTS). The study adhered to the tenets of the Declaration of Helsinki and all personnel involved in the study complied with the Child Protection (Prohibited Employment) Act of NSW, 1998. Informed written consent was obtained from at least one parent prior to examination. Parents and

guardians of participating infants were provided the opportunity read the information sheet outlining the intent of the study and to ask questions prior to signing the consent form.

6.7.3 Neonatal Vision Study procedure

A total of 66 infants were recruited from the RPAH level II and III NICU between December, 2017 and February, 2020. The ocular assessments were conducted by an orthoptist (the study author) in the RPAH Eye clinic including; visual acuity testing, corneal reflections and cover test for ocular alignment, ocular motility assessment, and a check for any ocular pathology by ophthalmoscope. The final follow-up examination at 12 months also included cycloplegic refraction and a dilated fundus exam by a paediatric ophthalmologist. The three and six month assessments were conducted in orthoptic-led NVS clinics while the 12 month examinations were conducted in the fortnightly baby clinic with the consultant paediatric ophthalmologist. Infants were placed in an upright position in their parents lap or seated in the pram in an upright position for the duration of the ocular assessment. By 12 months, a small number of infants chose to sit in the seat alone with parents beside them for safety. Occlusion for monocular testing was preformed using adhesive eye patches (Ortopad Soft, Junior, 64 x 52mm). Any infants who refused occlusion by adhesive patching were occluded using the palm of the parent's hand with careful attention by the orthoptist to ensure appropriate occlusion.

Visual acuity was tested binocularly and monocularly using Teller Acuity Cards II (Stereo Optical Co. Inc., Chicago, IL) at 55cm. A staircase and threshold procedure[291] was used for TAC testing starting at the largest grating, 0.23 cpd. Cards were presented binocularly first with progressively reduced gratings until the infant would no longer preferentially fixate on the gratings, at which point, the card before would be checked an additional two times to confirm threshold visual acuity. The last four cards

achieved would then be presented monocularly to establish threshold visual acuity for the right and left eye. Each eye was tested in random order. For repeat assessments, at six and 12 months, the staircase procedure would begin at the card above the threshold grating the infant could achieve at the last visit.

An eight inch Optokinetic Nystagmus Drum (Richmond products Inc., Albuquerque, NM) was attempted on all infants binocularly and monocularly. The OKN drum (20 cm x 15 cm), was held at 40-50cm from the infant with a rotation speed of 15-20 rotations/minute. Binocular OKN was performed to both the left and right. Monocular OKN for each eye was performed with the drum rotated both nasal to temporal and temporal to nasal. The order of occlusion and direction of drum rotation both binocularly and monocularly was randomised to prevent any bias in these measures.

Ocular alignment was determined by examination of corneal reflections for symmetry and if the infant could maintain fixation on a finger puppet, a cover test (cover/uncover) to detect strabismus or alternate cover to detect heterophoria was performed. If a strabismus was detected, an objective Krimsky prism test was used to measure strabismus size, or a prism bar cover test (PBCT) was performed if possible. Ocular movements in the 9 positions of gaze were tested using a small, illuminated toy (3x3cm). The light inside the toy retained infant attention and allowed for corneal reflections to be observed during ocular movements. Convergence near point (CNP) was performed by obtaining the infants attention with a finger puppet held 60cm away and brought in towards the nose. The point at which the infants eye/s deviated was estimated from the nose and recorded as the CNP in cm. Presence of binocular vision was detected using the 15 prism dioptre (PD) base out test, where a 15 PD loose prism was held base out over the infant's eye as they fixed on the small illuminated toy at a distance of approximately 30cm. A fusional response was present if a conjugate movement of both eyes towards the apex of the prism, followed by a disjugate movement the other eye was observed. The prism was held over the eye for 3

seconds to determine if the infant could maintain fusion before the prism was removed and a divergence eye movement was observed to restore the eyes into their original position. Each eye was tested in random order and if the infant could not fuse 15 PD, then 10 PD would be attempted.

An undilated ophthalmoscope assessment was also conducted by the orthoptist at every assessment to detect any signs of ocular pathology and assess pupils. Room illumination was reduced and the eyes were observed through the ophthalmoscope for opacities in the optical media, equal pupil size, equal brightness of red reflexes, and direct and consensual reaction to light. Cycloplegia at 12 months was achieved using 1 drop each of; Tetracaine 0.5%, Cyclopentolate 1% and Phenylephrine 2.5%. Pupils were assessed for dilation and reactivity to ensure adequate cycloplegia and a repeat cycle of drops were administered if required. Cycloplegic refraction was by streak retinoscopy and detailed dilated fundus exam was performed using an indirect ophthalmoscope.

Any infant who required ongoing care for an ocular condition detected on examination was referred for followed-up in the paediatric ophthalmology clinic at RPAH or referred to their local paediatric ophthalmologist. The need for referral was indicated if the infant failed to demonstrate vision on TAC testing at age six months or had a significant difference of more than 1 TAC card between their two eyes, had significant refractive error, any strabismus or other ocular pathology detected on examination.

In addition to the eye examination, the parents or guardians of the infant were asked to complete a questionnaire (Appendix 3). The purpose of the questionnaire was to obtain information on demographics, family history of eye conditions, maternal health during pregnancy and the infant’s general health.

6.8 Statistical analyses

All statistical analyses were performed using IBM SPSS Statistics for Windows (Version 25.0. Armonk, NY). Frequencies were used to determine the proportion of the sample with certain demographics including; ethnicity, level of education and employment status of parents, as well as the general health of mothers during pregnancy. Frequencies were also used to determine the prevalence of strabismus, refractive error. Infant birth factors such as premature birth, birth weight and time spent in NICU were also determined. Paired T-Tests were conducted to elucidate differences in visual acuity scores and convergence near point over the 3 assessments, while Chi-square test of independence was used to evaluate trends in OKN responses, ocular alignment, binocular vision and ocular motility development. Univariate and multivariate linear regression models were also used to determine the impact of chronological age, corrected age, gestation and birth weight.

To compare between the NVS infants who were predominately born premature and of low birth weight and age- matched infants from SPEDS, a one-way ANOVA was used to determine differences between mean TAC scores while Chi-square test of independence were used to determine the difference between the prevalence of ocular conditions at six and 12 months of age.

CHAPTER 7: Neonatal Vision Study Results

7.1 Demographics

7.1.1 Antenatal factors

There were a total of 66 infants assessed from the Royal Prince Alfred Hospital, Camperdown, Sydney, between February 2018 and February, 2020. All 66 infants received an initial assessment at approximately 3 months post-natal (mean age, 3.72 months), 51 received a second assessment 3 months later (mean age, 6.84 months) and to date 29 have received a third visit at 12 months of age (mean age, 13.10 months). These included 35 (53.0%) female infants. There were 21 (31.8%) who were born as twins and 14 infants (21.2%) who were conceived by IVF. The majority of infants were born prematurely (92.2%) and of low birth weight (82.8%) with a mean gestation age of 32.97 weeks (range 25-39 weeks) and mean birth weight of 1852.14g (range 107-3380g). All infants who were of multiple birth were born premature and of low birth weight. Ten infants had been admitted just to the SCU while 56 had been admitted to both SCU and NICU, with a mean time of 20 days in the NICU.

7.1.2 Parent demographics

From the parental questionnaire, 51.6% of mothers and 91.2% of the mother's partners stated they were employed full time. The majority of mothers had completed a university bachelor degree (50.0%) or higher degree (37.1%). Of the mother's partners, 22.8% had completed a technical certificate or diploma, 45.6% a university bachelor degree and 21.1% a higher tertiary degree. The predominant ethnicity was European Caucasian with 56.1% of infants having both parents of this ethnic background. Of the remaining 29 infants, four were of South East Asian ethnicity, two were South Asian, one East Asian, 13 were of a mixed background, four had one parent's ethnicity unknown and five had no ethnicity reported.

It was reported that 71% of mothers had been diagnosed with and/or required medical intervention during pregnancy for conditions including; high blood pressure, gestational diabetes, asthma, pre-eclampsia, anaemia, preterm pre-labour rupture of membranes, antepartum haemorrhage, intrauterine growth restriction and foetal distress.

7.1.3 Infant health and family history of eye conditions

Of the 66 infants, 14.8% had been diagnosed with one or more medical conditions including; low muscle tone, cardiovascular conditions, respiratory issues, and dermatosis. A family history of any eye condition was present in 58.5% including; 52.3% with a family member wearing glasses, 10.8% with strabismus, 3.1% with low vision and 7.7% had other eye conditions such as a colour vision defect or myopic retinopathy.

7.2 Vision assessments at three, six and 12 months

7.2.1 Teller Acuity Scores

Figure 7.1 demonstrates infants mean binocular and monocular TAC scores at three, six and 12 months of age. At the first visit, the mean binocular TAC score for the 65 infants who were able to perform the test was 1.46cpd ±1.06. There was a significant improvement at six months to a mean of 4.97cpd ±2.16 (n=51, p<.0001) and further improvement at the final assessment, with a mean of 14.46cpd ±7.32 (n=29, p<.0001). Of these 29 infants, four were tested at 15 months of age or more. If removed from the to create a group of 12 month old infants, the average binocular TAC score was 13.44 cpd, ranging widely from 3.2 to 26cpd.

There were no statistically significant differences between the TAC scores of the right and left eye at the first visit (p=0.32), second visit (p=0.18) and third visit (p=0.16). Therefore, only the right eye TAC scores are reported for monocular TAC score in this thesis. A similar pattern of improvement was observed for monocular TAC scores from 1.39cpd ±1.08 at three months (n=61), improving to 4.65cpd ±2.09 at six months (n=51, p<.0001) and again improving to 12.47cpd ±7.58 at the final assessment (n=29, p<.0001). However, when the older infants (≥15 months of age) are removed the average monocular TAC score became 11.12cpd. Of the infants at the 12 month assessment, two had a one card difference in visual acuity scores between the two eyes. As these children had cycloplegic refraction at 12 months, it was established that one of these children had a high hyperopic refractive error >+5.5D and the other was found to have an intermittent exotropia.

There was a moderate correlation between TAC scores at three months and six months, with infants who achieved higher TAC scores at three months, also achieving a higher TAC score at six months (n=47; r=0.476, p<.0001). However, between six and 12 months (n=25; r= 0.20, p= 0.33) and, three and 12 months (n=27; r= -0.214,

p=0.29), TAC scores were not correlated, possibly due to all infants reaching a much higher TAC score by 12 months assessment regardless of their initial visual acuity.

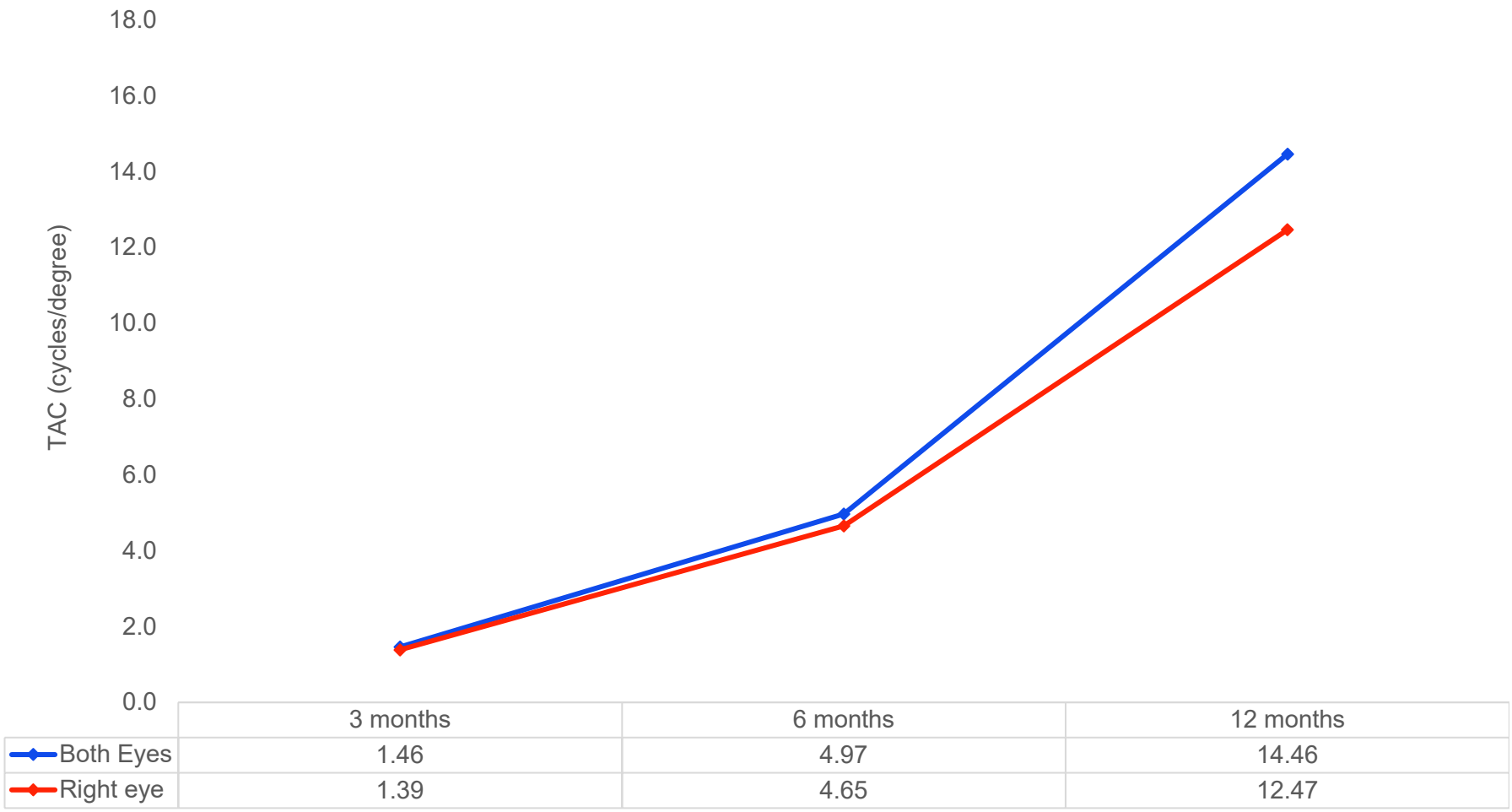
At the three month assessment, four infants were unable to achieve a binocular or monocular TAC score as they exhibited no preference for fixation of any of the target grids. These infants' ages ranged between 2.37 and 4.12 months chronologically but taking gestation into account, their corrected age was 1.29 to 4.71 weeks and were amongst the youngest infants by corrected age. However, other infants within the same age range were able to achieve both binocular and monocular TAC. Those infants who could not achieve a TAC score appeared not to be visually able to perform the task, rather than being uncooperative, so the negative result on TAC testing was felt to be reflective of poor visual acuity. A further four infants were unable to be tested monocularly due to strong objection to occlusion over either eye. One infant also failed to complete TAC as they fell asleep during the assessment. Testability at three months old for binocular TAC was 98.5% and for monocular TAC, 92.4%.

7.2.2 Optokinetic Nystagmus Drum

At three months of age, 56 out of 66 infants (84.9%) were able to perform binocular OKN and testability only improved slightly to 86.3% of the 51 infants tested at six months and 89.7% of the 29 infants tested 12 months. Monocular OKN was less testable, with only 78.8% of three month olds, 84.31% of six month olds and 79.31% of 12 month old infants being able to perform the task.

In those who were able to perform monocular OKN, responses to rotating the drum in a temporal to nasal direction appeared to be more developed before the responses to rotation in the nasal to temporal direction, with 44.2% of three month old infants demonstrating a response to the temporal to nasal direction compared to only 36.5% in the nasal to temporal direction (Figure 7.2). At six months, all infants were able to respond to OKN drum rotation in the temporal to nasal direction, with only 88% able to

demonstrate an OKN response to rotation in a nasal to temporal direction. By 12 months, all infants were able to respond normally and symmetrically to monocular OKN rotation in both directions.



	3 months	6 months	12 months
Both Eyes	1.46	4.97	14.46
Right eye	1.39	4.65	12.47

Figure 7.1 Mean binocular and monocular Teller Acuity Card scores at three, six and 12 months

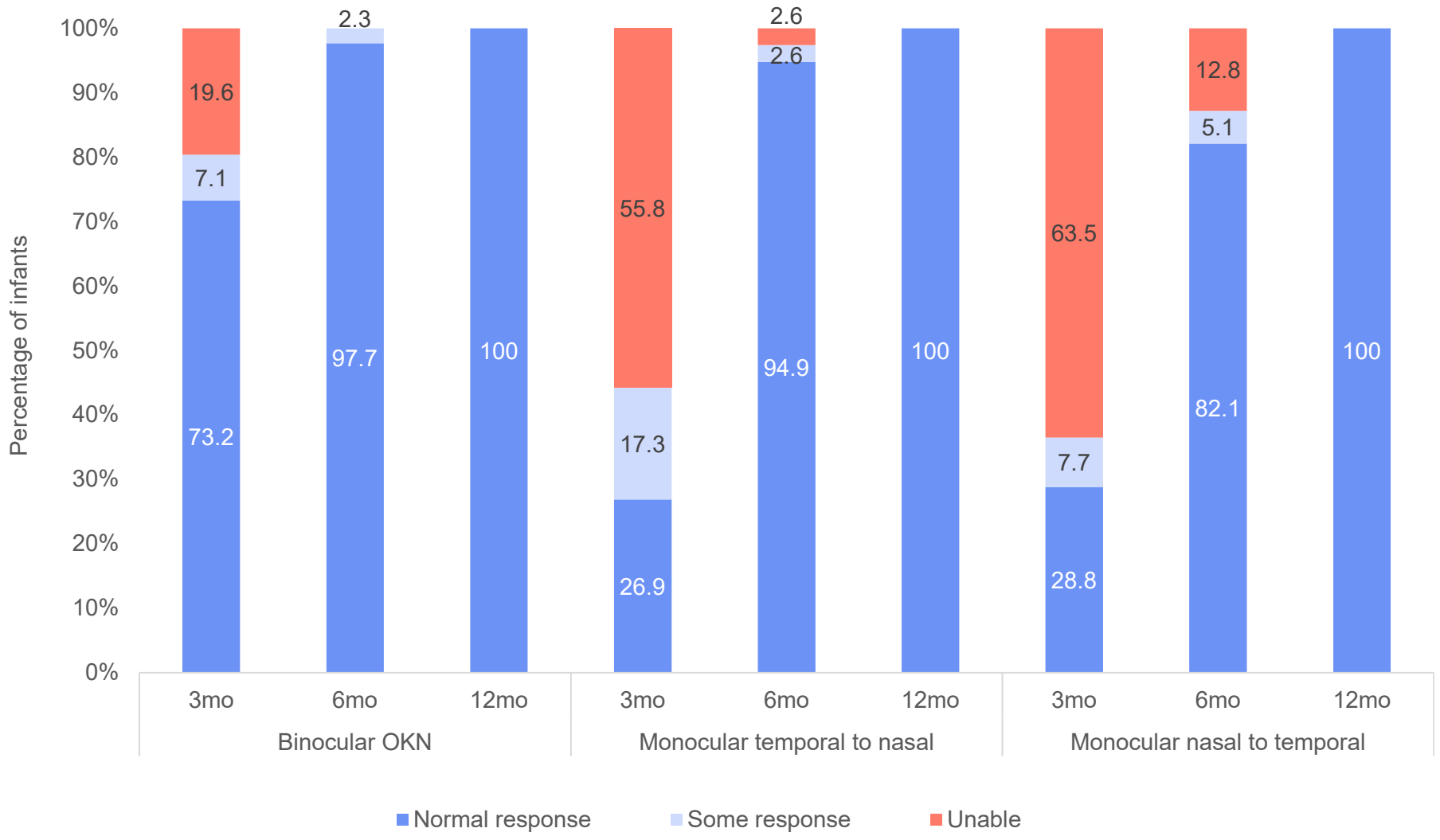


Figure 7.2 Binocular and monocular OKN responses of those who could perform OKN at age three, six and 12 months

7.2.3 Ocular Alignment

At the three month assessment, 53.8% of the 66 infants were able to demonstrate straight ocular alignment, while 46.2% of babies were still developing ocular alignment with the majority of these babies presenting with a constant exotropia (60%), followed by intermittent exotropia (26.6%) and intermittent esotropia (13.4%). By the second assessment at six months of age, the majority of infants had achieved straight ocular alignment and only two out of 51 infants (3.9%) presented with an intermittent exotropia. One of these infants remained an intermittent exotropia at 12 months and the other had not attended follow-up at 12 months.

At the final visit, five of the 29 infants assessed had strabismus (17.3%), two had an intermittent esotropia and three had an intermittent exotropia. The two infants who had an intermittent esotropia at 12 months had an initial delay in achieving ocular alignment, demonstrating an exotropia at three months of age, before demonstrating orthophoric alignment at the second visit aged six months and then developing an intermittent esotropia by 12 months. Of the infants who had an intermittent exotropia at 12 months, one was a constant exotropia at three months and developed an intermittent exotropia at six months, the second case had no manifest strabismus at three and six months before developing an intermittent exotropia by 12 months. The third case demonstrated an intermittent exotropia at three months and 12 months only. None of the infants who had a strabismus at 12 months had significant refractive errors for age, with their refractions ranging from +1.5D to +2.5D.

7.2.4 Binocular Vision

The development of binocular vision followed a similar trend to that of ocular alignment. At the first visit, just over a third of infants (39.7%) were able to overcome a 15 dioptre prism and maintain fusion for three seconds, 22.2% were only able to achieve fusion briefly or could only fuse a smaller prism of 10 dioptres while 38.1% were unable to demonstrate any fusional movement. By the second visit, the majority

of infants (96.1%) were able to fuse a 15 dioptre prism and therefore demonstrating binocular vision while 3.9% were unable to maintain fusion for 3 seconds or could only fuse the smaller 10 dioptre prism. All infants tested at 12 months were able to demonstrate binocular vision, overcoming a 15 dioptre prism and maintain fusion for three seconds.

7.2.5 Ocular Motility

At three months of age there were only 26.2% of infants who had full range of ocular movements in the horizontal and vertical direction. There were 36.9% who were only able follow the target to left and right, while 36.9% were able to demonstrate some vertical eye movements however, these vertical movements were not fully into up or down gaze. Between the visit at three months and six months of age, there was significant improvements in ocular movements ($p<.0001$), with 54.9% of infants achieving full horizontal and vertical eye movements and 45.1% still developing vertical gazes. By 12 months, all infants assessed were able to demonstrate full ocular movements in all directions.

Disjugate eye movements were also assessed by performing convergence near point (CNP). At three months of age, 31.3% of infants could demonstrate convergence. Of these infants who were able to converge, the mean CNP was 7.27cm±6.85. At the six month assessment, 98.5% of infants were able to converge and the mean CNP was 3.52cm±4.36 which was a significant improvement from the earlier assessment ($p=0.005$). At 12 months, all infants could converge and the mean CNP was 4.21cm ±5.89SD which was not significantly different to that of the mean CNP at six months of age ($p=0.85$).

7.2.6 Ocular Pathology

Initial eye problems detected in NICU or by the general practitioner before assessment for this study was present in 13.6% of infants. Two infants had blocked tear ducts at

three months that had resolved by the six month assessment with gentle massage and warm compress. There were 2 cases of hemangioma over the eyelid that were present from birth, no other associated complications were detected on assessment for this study. Of the five infants with ROP on initial visit, all four cases of mild or stage 1 ROP had regressed without intervention while one infant diagnosed with stable stage 3 ROP received peripheral laser before three months of age. Apart from the infants who had a diagnosis of ROP, no other parents reported knowing if their infant had been seen by an ophthalmologist or not during the infants time in NICU and were not aware of any scheduled eye appointments intended for their infant, including the two infants who had an obvious hemangioma.

There were few infants with newly detected ocular pathology at any age in this study, as those who had ROP had been screened and detected in NICU. The presence of hemangioma was also detected in NICU as these were obvious signs of pathology. However, there were three infants who were diagnosed at 12 months by the orthoptist with mild congenital ptosis with no more than 3mm difference between the palpebral fissures and confirmed by the paediatric ophthalmologist.

7.2.7 Summary of assessment outcomes

Between three to 12 months of age, there were significant improvements visual acuity, ocular alignment and ocular motility. While most infants were able to perform TAC and OKN, the TAC was more testable and appeared to produce reliable results whereas OKN was difficult to perform reliably, particularly at three months of age. Visual acuity improved steadily between three to six months of age and six to 12 months of age. While three month old TAC scores were able to provide an indication for the expected TAC scores at six months, neither three month nor six month assessments were correlated to 12 month old TAC scores. This suggests that between six and 12 months, there is significant improvement in TAC scores so that by 12 months of age,

most infants reach a similar TAC score, regardless of their scores at three and six months.

OKN response, ocular alignment, binocular vision, convergence and ocular motility on the other hand, appear to improve significantly between the three and six months assessments, with almost all infants demonstrating good ocular alignment and functional use of the two eyes for fusion and ocular motility by six months of age that did not significantly improve further by 12 months. At three months, the development of ocular alignment and binocular vision appear to occur as infants achieved ocular alignment and then using ocular alignment to develop binocularity. By six months, all infants were able to demonstrate fusion, even if they were only able to demonstrate fusion briefly or only on a smaller 10 dioptre prism. This coincides with the majority of infants achieving ocular alignment at this age. Intermittent strabismus at three and six months was found mostly infants still developing of ocular alignment. However, by 12 months of age, intermittent strabismus does not appear to be due to ongoing development of ocular alignment. This suggests these infants require ongoing follow-up and intervention, as all but one infant in this study who had intermittent strabismus at 12 months had previously demonstrated orthophoric ocular alignment at three and/or six months of age that subsequently became impaired.

7.3 Impact of prematurity and low birth weight on vision

At three months, both chronological and corrected age was significantly correlated to monocular TAC scores (r=0.65, p<.0001 and r=0.80, p<.0001, respectively). This correlation with TAC score was also present at six months but had reduced slightly for chronological (r= 0.54, p<.0001) and corrected age (r=0.58, p<.0001). At 12 months of age only chronological age was correlated to monocular TAC score (r= 0.50, p<0.006) while, corrected age was no longer a significant factor (r=0.32, p=0.09). Binocular TAC scores were also correlated to chronological age at three months (r=0.67, p<.0001) and six months (r=0.60, p<.0001), as was corrected age at three months (r=0.81, p<.0001) and six months (r=0.65, p<.0001). At 12 months, neither chronological nor corrected age were correlated with binocular TAC score. Gestation and birth weight were not significantly correlated with binocular or monocular TAC scores at any age.

Univariate linear regression models were performed for the impact of chronological age, corrected age, gestation and birth weight on TAC scores. Gestation and birth weight were not significant predictors of binocular or monocular TAC score. However, chronological age and corrected age were both significant predictors of TAC score at three and six months (Table 7.1). At 12 months, chronological age was a significant predictor of monocular TAC score (β=0.744, 95% CI 0.228-1.259, p=0.006) while, none of the variables were significant predictors of binocular TAC score.

A multivariate model containing chronological age and corrected age at both three and six months revealed that corrected age was significantly more predictive of binocular TAC score than chronological age, which became insignificant in the model. The addition of chronological age in the model containing corrected age did not substantially increase the r^2, with this only increasing to 0.67 from 0.66. Although corrected age was also a significant predictor of monocular TAC score at three months, neither chronological nor corrected age were significant for monocular TAC score at six months of age.

Table 7.1 Univariate and multivariate linear regression models for the impact of age and birth factors on TAC scores at three, six and 12 month assessments

3 month assessment	**Binocular TAC scores**								
	Univariate					**Multivariate**			
		r^2	**β**	**95% CI**	**p-value**	**r^2**	**β**	**95% CI**	**p-value**
	Chronological age	0.454	0.164	0.118-0.209	<.0001	0.668	0.028	-0.028-0.085	0.310
	Corrected age	0.663	0.205	0.168-0.243	<.0001		0.029	0.124-0.241	<.0001
	Gestation	0.028	0.061	-0.031-0.153	0.189				
	Birth weight	0.004	0	-	0.606				
	Monocular TAC scores								
	Univariate					**Multivariate**			
		r^2	**β**	**95% CI**	**p-value**	**r^2**	**β**	**95% CI**	**p-value**
	Chronological age	0.422	0.169	0.117-0.221	<.0001	0.656	0.035	-0.025-0.096	0.242
	Corrected age	0.647	0.214	0.172-0.256	<.0001		0.188	0.127-0.249	<.0001
	Gestation	0.036	0.068	-0.025-0.162	0.149				
	Birth weight	0.005	0	-	0.586				
6 month assessment	**Binocular TAC scores**								
	Univariate					**Multivariate**			
		r^2	**β**	**95% CI**	**p-value**	**r^2**	**β**	**95% CI**	**p-value**
	Chronological age	0.359	0.200	0.123-0.276	<.0001	0.650	0.048	-0.111-0.207	0.549
	Corrected age	0.417	0.234	0.153-0.315	<.0001		0.188	0.016-0.361	0.033
	Gestation	0	-0.008	-0.214-0.198	0.938				
	Birth weight	0.018	0	-	0.358				
	Monocular TAC scores								
	Univariate					**Multivariate**			
		r^2	**β**	**95% CI**	**p-value**	**r^2**	**β**	**95% CI**	**p-value**
	Chronological age	0.295	0.176	0.098-0.254	<.0001	0.337	0.052	-0.114-0.217	0.531
	Corrected age	0.331	0.202	0.118-0.287	<.0001		0.153	-0.027-0.332	0.093
	Gestation	0.001	-0.018	-0.218-0.183	0.860				
	Birth weight	0.003	0	-	0.693				

7.4 Relationship between visual functions at three months

7.4.1 Visual Acuity and Optokinetic Nystagmus Drum

While both TAC and OKN testing give an indication of vision, there was no significant difference in mean TAC scores between infants who were able to perform binocular and monocular OKN (Table 7.2). All 14 infants who could not perform binocular OKN were able to demonstrate vision on TAC. Almost all infants who were unable to achieve monocular OKN nasal to temporal (92%) and those unable to perform monocular OKN temporal to nasal (89.5%), were able demonstrate vision on TAC, despite failing the OKN. All infants who were able to perform monocular OKN temporal to nasal could perform TAC.

Of the four infants who could not perform TAC, three were able to perform binocular OKN but not monocular OKN. One infant did not achieve results on either TAC or OKN and was only three weeks of corrected age at the time of assessment despite being four months old chronologically.

Table 7.2 Mean TAC score by OKN drum response

Binocular TAC Scores			
OKN direction	**Normal OKN Response**	**Absent OKN Response**	**p value**
Binocular OKN	1.43 ± 1.05	1.11 ± 0.62	0.29
Monocular Nasal to Temporal	1.58 ± 0.95	1.30 ± 1.02	0.36
Monocular Temporal to Nasal	1.74 ± 0.97	1.25 ± 0.98	0.12
Monocular TAC Scores			
OKN direction	**Normal OKN Response**	**Absent OKN Response**	**p value**
Binocular OKN	1.35 ± 1.04	0.93 ± 0.58	0.17
Monocular Nasal to Temporal	1.48 ± 1.00	1.22 ± 1.01	0.41
Monocular Temporal to Nasal	1.59 ± 0.94	1.20 ± 1.02	0.23

7.4.2 Optokinetic Nystagmus Drum and Convergence

There was a significant relationship between convergence and binocular OKN responses (p=0.014). Binocular OKN appears to develop along with convergence as 41.5% of the 41 infants able to perform binocular OKN were also able to perform convergence, while only one infant out of 15 who could not perform binocular OKN could demonstrate convergence. A similar relationship is observed when using monocular OKN with only 5 of the 14 infants who could perform monocular OKN temporal to nasal direction able to perform CNP while the majority who could not perform monocular OKN in the temporal to nasal direction were also unable to perform convergence (73.7%, p=0.021). This coincidence of visual responses was not seen with monocular OKN rotated in the opposite (nasal to temporal) direction and convergence (p=0.11). There was no significant relationship between OKN response and fusion by 15 dioptre prism test, ocular alignment or ocular movements found in this study.

7.4.3 Prism fusion test and ocular motility

There was a clear relationship between demonstrating binocularity on the prism fusion test and development of ocular movements and convergence with 24 of the 25 infants unable to demonstrate fusion also being unable to demonstrate convergence (p<.0001). Of the 24 infants who could demonstrate fusion, 65.2% could also demonstrate convergence, compared to only 1 infant who could demonstrate convergence but not fusion, suggesting fusion develops before convergence.

A similar relationship was demonstrated between the prism fusion test and ocular movements (p=0.005). Out of 25 infants who could demonstrate convergence, 21 were able to demonstrate horizontal and vertical eye movements and three could perform horizontal eye movements only. Of the 17 infants who had full ocular movements, 14 were able to demonstrate fusion. Most infants demonstrated horizontal eye movements on ocular movement testing at three months. Fusion and vertical ocular

movements appear to develop variably with some infants able to demonstrate fusion before vertical eye movements (n=7) and others demonstrating vertical eye movements before fusion (n=9).

7.4.4 Ocular movements and convergence

The development of ocular movements precede convergence with 22 infants demonstrating horizontal and vertical eye movements before convergence whereas only three infants were able to demonstrate convergence before demonstrating vertical eye movements (p=0.021). Nine infants were able to demonstrate full ocular movements horizontally and vertically before developing any signs of convergence.

7.4.5 Summary of visual functions at three months of age

At three months of age, there was the greatest variation in infant responses to testing and this provided the opportunity to differentiate between what may be poor testability due to infant attention, lack of response due to under-developed visual functions and what may be abnormal for this unique population of at-risk children.

While, the OKN Drum can be used to demonstrate the presence of vision, early studies have expressed the limitations of the OKN as it is dependent on the development of the infant's ocular motor pathways to achieve the appropriate responses. This study therefore compared OKN responses to visual acuity and orthoptic measures of ocular alignment and motility. It was found that TAC is more testable than OKN drum in infants. Almost all infants who could not perform monocular OKN were able to perform TAC testing. The development of monocular OKN symmetry has been suggested to coincide with the development of binocularity.[188] In this study, there appears to be an order of which motility develops with the most infants achieving horizontal eye movement before three months while convergent eye movements was only evident in less than a third of these infants (Figure 7.3).

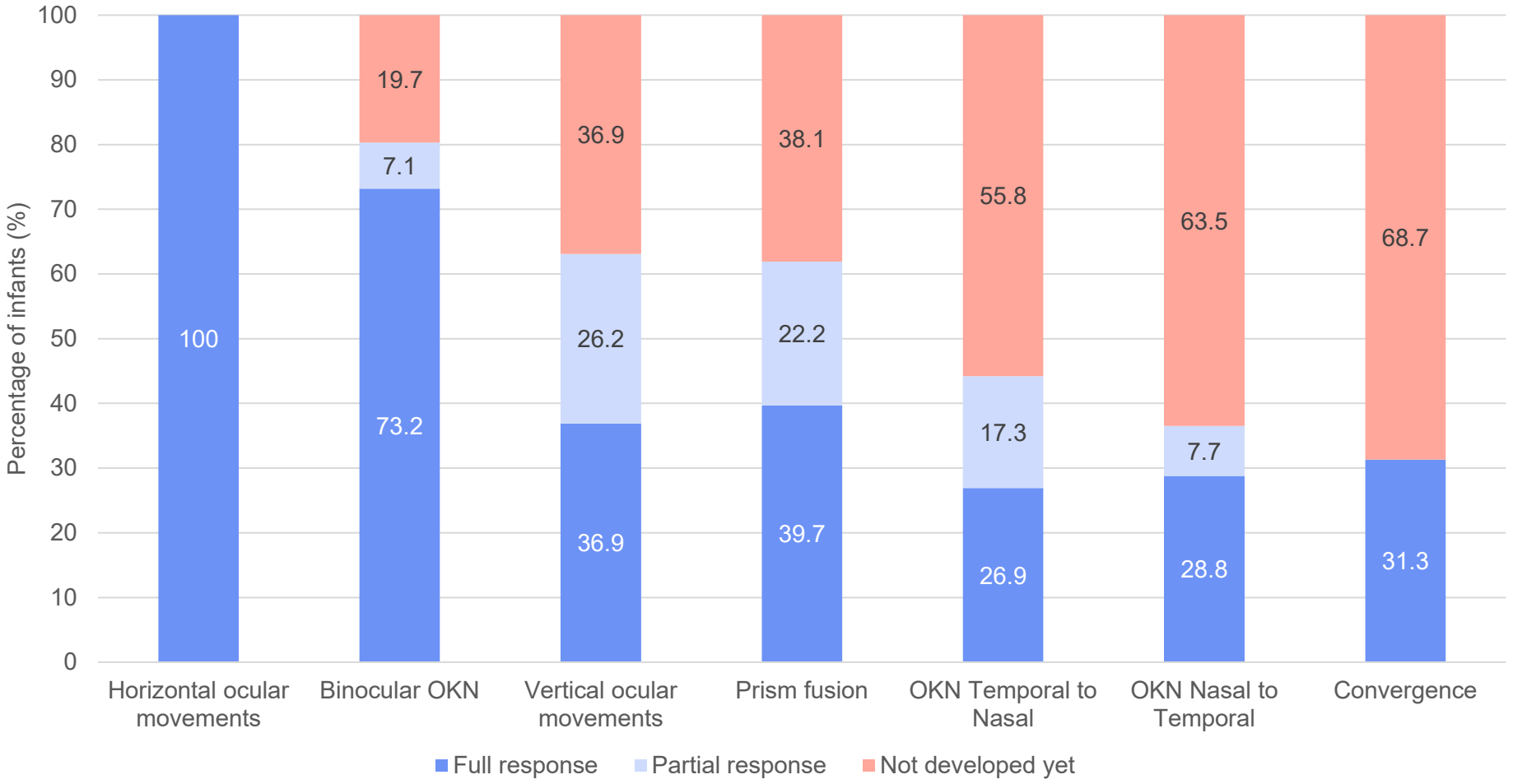


Figure 7.3 Percentage of infants who achieved each aspect of ocular motility at three months

7.5 Comparison of Neonatal Vision Study and Sydney Paediatric Eye Disease Study infants at six months and 12 months

All infants aged 5-8 months who were born >36 weeks, >1500g and had not been admitted to NICU from SPEDS were selected as an age-matched comparison sample for the six month old Neonatal Vision Study (NVS) infants. Similarly, infants aged 11-15months in SPEDS were selected by the same criteria for gestation and birth weight and non-admittance to NICU as an age-matched comparison for the 12 month old NVS infants. There were no statistically significant differences in age between the six month old SPEDS sample (mean age at assessment 7.06 months) and six month old NVS sample (mean age at assessment 6.85 months, p=0.22). However, taking prematurity into account, there was a statistically significant difference between the mean age of the six month old SPEDS sample and the mean corrected age of the NVS sample (5.40 months, p<.0001). Similarly, there were no age differences between the mean age of the SPEDS 12 month old (12.99 months) and NVS 12 month olds mean chronological age (13.01 months, p=0.71) but there was a difference between the SPEDS mean age and NVS mean corrected age (11.35 months, p<.0001).

No differences in the proportion of males to females were found between SPEDS and NVS samples at six months and 12 months of age (both, p=0.94). There was however, a difference in the ethnic distribution, as there was significantly more infants of European Caucasian background in the NVS study at six months (p=0.04) and 12 month olds (p=0.004) compared to the SPEDS comparative samples. The six month old NVS sample had a lower mean gestational age (32.55 weeks) and mean birth weight (1792.02g) compared to SPEDS (39.59 weeks and 3462.43g, both p<.0001). This was also the same at 12 months of age with a lower mean gestational age (32.41 weeks) and birth weight(1785.41g) in the NVS sample compared to SPEDS (39.35 weeks and 3503.94g, both p<.0001).

7.5.1 SPEDS and NVS comparison at six months

Between the SPEDS and NVS samples at six months of age, there was a statistically significant difference in mean binocular TAC scores with, a higher mean TAC score of 6.11cpd±2.18 in the SPEDS infants compared to 4.97cpd±2.16 in the NVS sample (p=0.002). Although there was a slight difference between monocular scores, achieved by the six month old SPEDS infants (5.43cpd±2.49) and the NVS infants (4.65cpd±2.10) this did not reach statistical significance (p=0.052).

The mean convergence near point of infants in NVS was reduced compared to SPEDS at six months of age (4.76cm vs 1.37cm, p<.0001). At six months of age, 96.1% of NVS infants and 99.2% of SPEDS infants were able to demonstrate binocular vision (p=0.21). There was no difference in the prevalence of strabismus in the NVS samples at six months (3.9%) compared to the aged-matched six month old infants in SPEDS (5.1%, p=1.00). There were two cases of constant esotropia, two intermittent exotropia, one intermittent esotropia and one constant exotropia in the SPEDS sample, compared to two cases of intermittent exotropia in the NVS sample.

7.5.2 SPEDS and NVS comparison at 12 months

By 12 month old of age, the NVS infants had significantly better TAC scores overall compared to the SPEDS infants. Binocular TAC scores in the NVS infants (14.46cpd±7.32) was significantly higher than the infants in SPEDS (6.61cpd±2.58, p<.0001). A similar difference was seen in monocular scores, with NVS infants achieving 12.58cpd±7.58 compared to SPEDS infants, 5.34cpd±2.18 (p<.0001).

The prevalence of strabismus was significantly higher in the NVS sample (17.2%) compared to the SPEDS 12 month old sample (2.8%, p=0.008). There was one esotropia and one exotropia in the SPEDS sample, compared to two intermittent esotropia and two intermittent exotropia in the NVS sample. By 12 months, 100% of infants in NVS were able to demonstrate binocular vision compared to 98.5% of

SPEDS infants. However, in SPEDS, the small number of children who were unable to demonstrate binocular vision upon assessment were the children with constant strabismus. CNP 12 months of age, (1.64cm vs 6.5cm, p<.0001)

The mean right eye spherical equivalent refraction of the NVS infants at 12 months of age, as determined by cycloplegic streak retinoscopy was hyperopic at +2.10D ±1.15 (range -0.50 - +6.00D). There was no significant difference between the refraction measures between right and left eyes (p=0.85). This was significantly more hyperopic than the SPEDS 12 month old infants (+1.04D±0.92, p<.0001).

Of the 28 NVS infants who had cycloplegic refractions, five had hyperopia (17.9%) of greater than +3.00D and one child had a myopic refraction at -0.5D. Two children had astigmatism of greater or equal to 1D and one child had anisometropia of 1D difference between the two eyes. There a significant difference in the prevalence of refractive errors between the infants participating in NVS and SPEDS (p=0.008). The prevalence of hyperopia was higher in the NVS study compared to SPEDS (2.2%) whereas the prevalence of myopia was higher in the SPEDS study compared to NVS (5.5% vs 3.6%, respectively).

7.5.3 Summary of the comparison between the Neonatal Vision Study and Sydney Paediatric Eye Disease Study

Infants in the NVS study were age matched to SPEDS infants of the same age, however, this was by chronological age. The corrected age of the NVS infants was significantly younger, and lighter birth weight lighter in the NVS compared to SPEDS. The visual acuity of infants participating in the NVS study and SPEDS study was similar at six months however, TAC scores were significantly better in the NVS sample than the age-matched SPEDS sample at 12 months. This difference between the two samples may be a product of testing technique, however, both studies utilised a

staircase method of obtaining TAC visual acuity at 55cm and it is unlikely that examiner error would produce such a significant difference in TAC score**.**

The development of vision appears to improve significantly by 12 months so that the NVS infants who are considered premature and of low birth weight are comparable to the SPEDS age-matched sample, however, the development of ocular alignment appears to differ. The SPEDS infants at six months had more constant strabismus, while in the NVS sample intermittent esotropia was more common, possibly due to developmental immaturity. However, by 12 months, the prevalence of strabismus differed significantly with five out of the 29 children in the NVS sample affected by intermittent strabismus, compared to four out of the 141 age-matched SPEDS sample.

With ongoing data collection for the NVS study, the relationship between strabismus, hyperopia and other ocular outcomes can be further explored. It is currently difficult to determine associations and relationships in this small sample. However, despite the relatively small sample of NVS infants at six months and 12 months included in this study, it is already becoming evident that these at-risk infants, have a higher prevalence of strabismus and significant hyperopia ≥+3D.

7.6 Discussion

Most infants were testable for visual acuity using TAC, with all but one child testable binocularly at three months of age and a slightly lower rate of testability when attempting monocular testing at three months. The older infants at the six and 12 month assessments were all able to be tested both binocularly and monocularly. This would suggest that TAC is highly appropriate for examining visual acuity in this cohort of predominantly premature and/or low birth weight infants even at a young age.

Previous studies examining the norms for TAC visual acuity in babies and very young infants have noted a progressive improvement in TAC scores with age[182,183] with the youngest at 2 weeks of age and tested binocularly having an average score of 0.66cpd.[183] At an equivalent age of three months, Salomao and colleagues in their study of healthy infants found an average binocular mean acuity of 3.89cpd, better than that found in the NVS infants (1.46cpd). The mean acuity when tested monocularly was lower than that established binocularly, which is a well-known phenomenon in this form of visual acuity testing in infants[292] and is also evident in the NVS infants, with an average monocular TAC acuity of 1.38cpd, which is also lower than that found by Mayer and Ventura at 2.5 months of age (2.16cpd) and by Salomao and colleagues for infants three months of age (3.09cpd). This suggests that the visual acuity of the NVS infants at three months was reduced when compared to other samples of health infants at a similar age both binocularly and monocularly.

At the six month assessment the TAC acuity had improved in the premature/low birth weight NVS infants, with mean binocular and monocular TAC acuity now 4.97cpd and 4.65cpd, respectively. This again was lower than the mean binocular TAC acuity found in the SPEDS comparative infants and by Salomao (6.11 and 7.44cpd respectively) and the mean monocular acuity in SPEDS infants (5.43cpd) and others studies of 5.65 to 7.18cpd.[182,183] This pattern of improvement is consistent with the findings of van Hof-van Duin and Mohn who documented lower mean TAC scores for infants born

premature compared to full term infants at six months, but all infants, regardless of how premature at birth, were able to reach full term acuity norms by 8 months.[281] At the 12 months assessment the mean TAC acuity scores for the NVS infants had improved significantly and was binocularly now 14.46cpd, higher than that seen the 12 month olds in SPEDS (6.61cpd). When the four older NVS infants were removed from the analysis, the mean TAC acuity of 13.44cpd was still higher than that recorded by Salomao and colleagues in healthy 12 month old infants of 11.08cpd.

There is some suggestion in literature that the visual acuity of premature infants might be more matched to their corrected for gestation age than chronological age, which certainly seem to be evident at the three and six month visual acuity assessments for the NVS infants, though in this study by the 12 month assessment, the NVS infants acuity was associated only with their chronological age. As was previously suggested by van Hof-van Duin and Mohn, this implies that the visual acuity of premature infants is accelerating at a faster pace than that of full-term infants over the first 12 months since birth. The mechanism behind such an accelerated development and as indicated in this study, an over achievement of visual acuity at 12 months of age compared to age-matched-norms, is not clear and requires more careful examination in a larger cohort of premature/low birth weight infants.

The measure of the presence of vision using the rotating OKN drum, proved to be less reliable than the TAC which also yielded more information about the level of acuity visual in these infants. This is despite OKN having been earlier documented as an means of measuring visual acuity in young infants.[293] One of the earliest papers was by Gorman, Cogan and Gellis in 1957 who used a length of white material with uniform stripes to demonstrate infants as young as 1 day can generate OKN responses.[294] Frantz (1962), also demonstrated the relative comparability between TAC and OKN use as a measure of visual acuity.[180] However the authors made note that while positive responses prove the presence of vision, negative responses does not

necessarily mean the infant is blind. Use of the OKN as a form of assessing infant visual acuity is limited by the infants ability to retain attention and most importantly, the infant's development of ocular motility to facilitate the involuntary eye movements seen on OKN testing.[186] The use of an OKN in the setting of vision screening in NICU is not so much for visual acuity assessment, rather it can be used as a pass/fail test for the presence of vision or as a test for neurological conditions.

This study provides further evidence for the closer association between OKN and the development of ocular motility, in particular, convergence. Comparisons between tests shows the ability to demonstrate smooth pursuits and make a fast saccade to re-fixate, which are required to perform OKN develops after the development of horizontal tracking. While horizontal ocular movements were present in all infants at three months, binocular OKN was not present in all infants until the six month assessment. It was also evident in this study that the development of vertical ocular movements and fusion as demonstrated by a prism fusion test occurred almost at the same time as the development of binocular OKN.

Binocular OKN developed sooner than the monocular OKN response and it developed in a temporal to nasal direction before opposite nasal to temporal direction. The development of symmetrical monocular OKN responses was only present in 81% of six month old infants and by 12 months, all infants appeared to have mostly symmetrical responses. This early asymmetry in OKN responses was a similar finding to that of Naegele (1982) who demonstrated monocular OKN asymmetry using electro-oculography in infants up to 19 weeks old.[188] However, asymmetry in monocular OKN responses have been shown to occur in infants up to 24 months when utilising targets at the infant's threshold acuity.[189]

Convergence has been documented to develop early in healthy full-term infants, with approximately 50% of week old infants demonstrating the first signs of convergence,

defined as any bilateral adduction.[228] However, the infants in NVS had a delayed onset of convergent eye movements, with less than a third of infants able to demonstrate any convergence at a similar age of three months old. This is consistent with what has been demonstrated by Weinacht in 1999,[290] who demonstrated full convergence in full term infants at 7 weeks, while premature infants in the study were only able to demonstrate full convergence at 13 weeks. However, in both Thorn and Weinacht's studies, full convergence was defined as convergence within 12cm from the face, while current clinical cut-off recommendations for the normal convergence near point is 5cm.[295] In comparison, infants in the NVS who were able to converge at three months achieved a mean of 7.3cm, improving by six months of age to almost all infants being able to converge their eyes, with a mean CNP of 3cm. So while there is an initial delay in the development of convergence, most infants were able to converge by six months and reached full convergence at this age.

Ricci 2008,[284] examined visual functions of 109 infants who were born premature and of low birth weight, between 35 and 40 weeks post-menstrual age, which would mean that they were between one months and 15 weeks old chronologically. It was found that eye movements were present in all babies by 40 weeks and were able to track a target horizontally at 35 weeks post-menstrual-age. While the NVS found few infants demonstrating vertical eye movements at three months of age, the Ricci study found 95% of infants were able to track vertically by at a similar or younger. However, it is unclear if these were full vertical tracking eye movements or just any vertical eye movement. It should also be noted that the targets used in these Ricci study were large paddles, while the NVS used small lit-up toys as targets which may have been more difficult to keep viewing.

Thorn and colleagues demonstrated that there was an order to which ocular motility developed in infants. The first sign of convergence appear by 12 weeks in 60% of healthy full term infants, followed by fusion preference at 12.8 weeks and then full

convergence at 13.7weeks.[228] At three months of age, 62% of the NVS infants could demonstrate some form of fusion using the prism dioptre test, while only 31% could converge. The NVS used prism fusion to demonstrate the presence of fusion, and the onset of fusion before convergence here is a different phenomenon to that described by Thorn et. al. where infants are demonstrating a preference for fusion over retinal rivalry. This difference in timing of aspects of fusion in relation to convergence suggests that the impetus to overcome diplopia elicited by the prism dioptre test may precede convergence, while the appearance of preference for passive fusion over retinal rivalry may occur later.

Ocular alignment appeared to develop gradually from three through to six months of age in the NVS. Only half of the infants were able to demonstrate straight ocular alignment at three months whereas by six months, the majority of infants had straight eyes. Following-up the infants from three to 12 months in this group of at-risk infants made it clear that by 12 months more strabismus was evident than earlier. All but two of the five children who had presented with strabismus at 12 months had previously recorded straight ocular alignment at their three and/or six month assessment. The majority of infants who had a constant strabismus at three months were able to demonstrate straight ocular alignment and binocularity by six months. This would imply the majority of infants who are born premature and do not have ocular alignment at three months are in fact still developing ocular alignment. Horwood (2003)[226] demonstrated this elegantly by recruiting pregnant orthoptists to record observations of their infants ocular misalignment in infancy. It was found that ocular misalignment occurred at a time when vergence was developing and indicates an immature vergence system rather than ocular misalignment. Comparing the infants of NVS to their age-matched peers from SPEDS, differences in the prevalence of strabismus at six months are difficult to interpret, as the infants in the NVS study appear to be at an

age where they have just learnt how to maintain ocular alignment and achieve convergence.

However, it is evident that the prevalence of strabismus appears to be significantly higher in the NVS by the 12 month assessment, with 17.2% of infants having a strabismus compared to the 2.8% in the SPEDS sample (see Chapter 4). Bremer et. al. (1998),[275] found a similar prevalence of strabismus in premature infants, with 11.8% of infants who were at 12 months corrected age being found to have strabismus. Considering the majority of the NVS infants had developed straight ocular alignment and binocularity at six months, it will be of great interest to determine if this trend towards a high prevalence of strabismus continues in the remaining 22 infants who are yet to have their 12 month follow-up. It would be hoped by continuing the follow-up of these infants with potential to examine more detailed risk factors in a larger cohort may lead to some refinement of risk factors.

The increased risk of strabismus in premature and low birth weight infants has been well documented, with prevalence rate of strabismus as high as 14%[296] to 22%[35] in 5 year old children who had been born premature. The risk of strabismus is significantly higher in children who had received treatment for ROP as an infant, with 28.2% esotropia and 12.8% exotropia, equating to an overall strabismus prevalence of 41% by the time these children were 5-7 years old.[154] While there is a clear risk for strabismus in infants who have been admitted to a NICU, this study demonstrates there is a need for some caution to be taken when screening infants at three months of age for strabismus, as their ocular alignment is still developing and our study indicates that strabismus might not be detected until 12 months of age. As it is well known that strabismus is a risk factor for amblyopia, while no amblyopia was detected in these children as yet, ongoing surveillance is required to ensure timely treatment is provided if amblyopia develops.

Cycloplegic refractions of the infants in the NVS at 12 months revealed that the prevalence of significant hyperopia was high in this sample of infants (17.9%), compared to the prevalence of 2.2% in the SPEDS sample. The prevalence of refractive error in the NVS infants was similar to that of a study of 73 premature infants born at 30 to 36 weeks gestation by Spierer and colleagues, who found a prevalence of 28.77% for hyperopia and 2.74% for myopia in infants six months old, although their definition of myopia was less than -2 dioptres and therefore would provide an underestimation of the prevalence of myopia compared to this study.[286] Hebbandi and colleagues (2008),[296] also found infants born less than 1000g and 28 weeks gestation have greater prevalence of hyperopia ≥+2.0 (8%) and myopia of less than -0.5 dioptres (12%), with greater risk of these ocular conditions in those infants who had ROP. They concluded by recommending that all premature infants receive follow-up ocular care. The one child who had myopia at 12 months in this study had a history of regressed mild ROP, fitting with the well-known greater risk of myopia with ROP. With ongoing follow-up of the infants with regressed ROP, it is expected that more of these infants may become myopic later in life. It should also be noted that the SPEDS age-matched sample of normative infants excluding a birth history of no premature birth, low birth weight or admission to NICU had a low prevalence of hyperopia (2.2%) compared to that reported for the overall SPEDS sample of close to 6% at a mean age of 1.17 years (Chapter 4, Table 4.4), further emphasising the role of adverse birth factors on the development of refractive errors.

7.7 Conclusion

In this study of infants who had been admitted to NICU they were predominantly admitted for premature birth and/or low birth weight. There was a high prevalence of strabismus, refractive errors and ocular pathologies in this sample. While most instances of ocular pathology, particularly those who had ROP were detected before they attended the three month assessment as part of the study, the strabismus and refractive errors found would not have been detected in these infants had they not participated in the NVS study, with the majority of parents reporting no formal eye care being provided for their infants.

As most infants at three months are still developing vision and eye movements, eye care professionals such as orthoptists or ophthalmologists are best suited for determining whether an infant's responses to testing are due to an immature visual system or a sign of an ocular problem. The use of TAC to determine visual acuity in three month old infants is most appropriate, with higher testability using TAC and quantification of level of visual acuity than using an OKN drum. In addition, tests such as prism fusion test, convergence and ocular movements were convenient, easily and rapidly performed and important for the assessment of the ocular and visual development these at-risk infants. By six months, all these tests were achievable. Abnormal results at six months of age should indicate the need for further investigation and follow-up to determine if the infant is still developing visual functions or there is potentially an ocular issue. Results of the testing at 12 months, show that this age may give a more definitive indication of the need for further surveillance and/or intervention.

CHAPTER 8: Thesis discussion

The current prevalence of strabismus is estimated to be 2.6%, as determined by the meta-analysis in chapter 2. This has declined significantly from 4.5% prior to 1960 and is reflective of a reduction in esotropia prevalence. While the prevalence of exotropia appeared to increase with time, this was confounded by the inclusion of recent studies of populations of more varied ethnicity. Utilising only those studies of populations of European Caucasian ethnicity, it is evident that the prevalence of exotropia has remained stable over time. The meta-analysis identified that while the prevalence of strabismus overall may not vary between ethnicities, there appears to be a difference in the type of strabismus present with a greater proportion of esotropia in European Caucasian children and exotropia in Asian children.

The question of why there would be a difference in type of strabismus found between ethnic groups led to the investigation of risk factors including age, ethnicity and refraction in chapter 4, using the series of existing data sets; the Sydney Childhood Eye Studies (SCES). This collective sample of 7266 children aged between 6 months and 17 years, with population-representative variation of ethnic backgrounds, provided an ideal opportunity to differentiate the influence of various factors including; age, ethnicity and refractive error on the prevalence of strabismus and its subtypes.

It was evident from chapter 4 of this thesis that refractive errors are significant risk factors for the development of strabismus and particularly, significant hyperopia, myopia and anisometropia, play a role in the development of intermittent exotropia. This increased risk of developing strabismus with refractive error was independent of age or ethnicity. Given the relationship between refraction and strabismus, it is possible that the observed decline in the prevalence of strabismus and variations in the proportion of esotropia compared to exotropia between ethnic groups revealed in

chapter 2, may be related to a difference in the refractive error of the children in the sample.

It has been well documented that the prevalence of myopia, particularly in East Asian countries has been rising and myopia is occurring at an earlier age of onset.[119] This has known implications in terms of increased visual impairment and the development of myopic ocular pathologies, but based on the findings of this thesis, may also increase the occurrence of intermittent strabismus. The longitudinal data contained in chapter 4 additionally supports this, as a quarter of six year olds with myopia had developed an incident intermittent exotropia by 12 years of age. While refractive error management for these children will be ongoing, this thesis indicates that if children with early myopia who are also at risk of strabismus can be identified and treated early, there is a good opportunity to at least, improve or resolve strabismus and prevent further vision loss such as amblyopia.

The availability of longitudinal data to examine the incidence of strabismus and the success of treatment is a particular strength of the analysis in chapter 4 of this thesis. Based on those children who were followed-up between SMS and SAVES, intervention for strabismus is highly successful with over 90% of children treated for strabismus at 12 years no longer requiring treatment and achieving good ocular alignment by 17 years old. However, detail of treatment options used is not known. Thus, despite incident strabismus occurring, particularly in late childhood/ adolescence, the prevalence of strabismus remained relatively stable with age-related variation only noted at an older age. The most variable form of strabismus between cohorts and age groups was intermittent exotropia which, also appears to be most influenced by the changes in refraction with age and may be most able to be resolved by treatment. While there are limitations to the use of SMS 6 to 12 years and SAVES 12 to 17 years, as these are longitudinal assessments of two different cohorts, the

continuity with age and comparison of the two 12 year old assessments allows for a longitudinal interpretation of these results.

As there are clear birth-related risk factors also influencing the strabismus development, as well as refractive errors and pathology, chapter 5 examined the influence of Neonatal Intensive Care Unit (NICU) admission on the prevalence of ocular conditions. Findings of chapter 5 include consideration of the most common birth factors to prompt placement of a child in NICU; premature birth and low birth weight. It was clear in this analysis that regardless of why a child may be admitted to NICU, they are at greater risk of adverse ocular outcomes than those who have not been admitted. In particular, there is a higher prevalence of overall strabismus, exotropia, myopia and anisometropia. This study further reinforces the strong association between refractive error and the development of strabismus. In particular, the higher prevalence of myopia in these children at a young age (6 months to 6 years) would suggest that they are at greater risk of intermittent exotropia. Therefore, identifying these children and providing regular monitoring may be beneficial for both the management of their myopia and prompt treatment of any incident intermittent exotropia.

It is clear from this thesis that children admitted to NICU are at risk of ocular conditions and should be carefully screened and monitored for these to ensure early intervention and preservation of vision. This suggests that it would be strongly recommended that parents are informed of the increased risk and the need for screening of their children. A further recommendation arising from this thesis, is that current screening protocols in NICU that exclusively target children at risk of retinopathy of prematurity (ROP) are not sufficient to capture all children at risk of ocular conditions and that consideration should be given to extending screening to all children.

The Neonatal Vision Study (NVS) described in chapter 6 and 7 was a prospective cohort of 66 infants admitted to NICU who had been followed-up over the course of a year. While this was a relatively small sample compared to population-representative studies such as SCES, the study is of reasonable size compared to others that have specifically investigated the premature and low birth weight infants. There is limited previous literature on the visual development of preterm infants compared to age-matched normative data, particularly population-representative norms such as those available from SPEDS. This thesis supports the previous literature on visual development in preterm infants with the NVS infants demonstrating an initial delay in the development of visual acuity, followed by a significant improvement between six and 12 months of chronological age. This suggests that preterm infants are initially more comparable to full-term infants based on their gestational age but, catch-up to be comparable by chronological age over the first year of life. These findings provide an indication of the projected visual development of infants who are preterm that may be used as a benchmark for expected outcomes of vision screening at this young age.

This study is one of the few studies to investigate the development of ocular alignment, binocular vision and ocular motility in infants who are preterm and have been admitted to NICU. The majority of these infants were able to perform horizontal ocular movements from their first assessment at three months chronological age, however, vertical eye movements developed later. A similar proportion of infants who were able to demonstrate vertical ocular movement could also demonstrate fusion, indicating that these functions develop at a similar time but, one does not appear to be reliant on the development of the other. While this study agrees with previous literature that monocular optokinetic nystagmus (OKN) in a temporal to nasal direction develops before nasal to temporal OKN, this study is the first to compare monocular OKN to other visual functions. Considering monocular OKN temporal to nasal requires a similar eye movement to that of convergence, it is not surprising that most infants who

were able to demonstrate convergence at three months were also able to perform monocular OKN temporal to nasal. It is evident that at three months of age, premature infants are still developing ocular alignment and establishing binocularity. However, by six months of age, most preterm infants are able to respond well to an orthoptic assessment and therefore are able to be screened for visual development at this age.

Although the OKN is often used to indicate visual acuity in instances where infants cannot be tested by other means, Teller Acuity Cards (TAC) were able to be performed by most infants at all ages, and was considerably more testable than OKN. This is likely due to the fact that there were components of ocular motility required to perform binocular and monocular OKN that had not yet developed by this age in premature and low birth weight infants. It is apparent from these findings that OKN is of limited use as a test of vision and results are more dependent on normal ocular motility than visual acuity. Conversely, negative results on TAC were an accurate reflection of the infant's vision, indicating this is a more appropriate visual acuity test choice for all infants.

At 12 months of age, there was a significantly higher prevalence of strabismus and hyperopia in the NVS population of at-risk infants compared to the SPEDS age-matched norms. While visual acuity and orthoptic assessment at six months of age are useful for ensuring infants are visually developing as they should, the majority of those in this study who were found to have a strabismus, did not develop that strabismus until 12 months of chronological age. An orthoptic assessment including cover test, prism fusion, ocular movements and convergence would be appropriate for screening of infants admitted to NICU at 12 months to detect those with strabismus for early treatment. In addition, given the high rate of refractive errors and particularly hyperopic refractive errors, that are not readily detected by other means, cycloplegic refraction should be performed for infants who have been admitted to NICU.

In this study, it is unclear whether the majority of infants with significant hyperopia will have persistent hyperopia into childhood and adolescence and whether the rate of hyperopia is due to the fact that these infants were premature. Hyperopic infants should be monitored to ensure that accommodative forms of esotropia do not occur at an older age, given that the typical age of onset is 2-3 years for this condition. While the NVS has only detected one child with myopia, chapter 5 indicated that infants admitted to NICU were also at increased risk of myopic refractive errors. As myopia present early in life is likely to progress to high and pathological myopia, the progression of any myopic refractive errors that are present early should be closely monitored, given the high risk visual impairment. In addition to this one infant with myopia, there were two infants with astigmatism and one with anisometropia and cumulatively these give a rate of 14% for these refractive errors in the NVS. Including those with hyperopia, the total prevalence of significant refractive errors in the NVS was 32.1%. With further development of refraction with age, there is potential for a further increase in the prevalence of refractive errors. Compared to both the SPEDS study and the prevalence of refractive error in other population-representative studies of school-aged children, this rate of refractive error is exceptionally high.

A limitation of the current NVS study is the relatively small sample of infants who reached follow-up at 12 months although, this is one of the larger vision studies of infants admitted to NICU. It is intended that with ongoing recruitment for the NVS, we will be able to obtain a sufficiently large cohort to conduct further investigations into other potential risk factors linked to NICU admission that may causally explain the higher rates of ocular conditions including strabismus and refractive error in these children. For instance, the presence of systemic conditions, treatments received in NICU, length of stay in NICU and amount of prematurity and low birth weight can be further investigated. As infants are followed-up in the NVS, it would also be useful to extend the follow-up to school age to determine whether the infants with significant

refractive error retained this refractive error, and if there are other factors, such as environmental influences that contribute to any persistent refractive error. This would also provide an opportunity to investigate whether the children who develop strabismus later are those who had early refractive error or if there are additional contributing factors to later development of strabismus.

This thesis has contributed to an understanding of the current prevalence of strabismus and the decline in prevalence in recent decades. In addition, these studies have shown the impact of variations with age, ethnicity and refractive error on prevalence of strabismus and types of strabismus. These studies of strabismus and its management have shown the success of treatment, while incident strabismus occurs throughout childhood, maintaining an overall stable prevalence of strabismus. Further, this thesis has shown that there is significant risk of ocular conditions in infants admitted to NICU, irrespective of level of birth weight and gestational age. It has also defined the expected visual, binocular and ocular motor development of these at-risk infants over the first year of life. It is clear from our findings that all infants admitted to NICU are at significant risk of ocular complications and current screening protocols that exclusively target ROP are insufficient to detect these conditions and ensure early intervention. Thus, there is a need for wider, standardised vision screening of all infants admitted to NICU and based on our findings, this would be most appropriately conducted by an orthoptist at 12 months of age to detect strabismus and significant refractive error.

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Appendices

Appendix 1a:

Relevant excerpts from the SMS parental Questionnaire

ABOUT YOUR CHILD

Personal information

1. Your child's name: _____ _____
   (First name) *(Family name)*

2. Your child's address: _____

3. Suburb _____ Postcode ☐☐☐☐

4. How long has your child lived in the above suburb? ☐☐ / ☐☐
   (years) *(months)*

5. Since your child was born, where else has he/she lived?

	Location	Length of time at location	Age of child
1			
2			
3			
4			
5			
6			

6. Gender (please tick): ☐ Female ☐ Male

7. Date of birth: ☐☐ ☐☐ ☐☐☐☐
   (day) *(month)* *(year)*

8. In which country was your child born: _____

9. Your child's school is: _____

10. Your child's grade is: _____

Parental contact: _____

Telephone day: _____

Telephone night: _____

Mobile: _____

Email: _____

Could you please provide us with the name and address of three people we could contact to obtain a forwarding address for you if you were to move?

☐ No (go to question 15)

☐ Yes (please fill in details below)

11. **Contact 1**

Name _____Telephone _____

Address _____

Relationship _____

12. **Contact 2**

Name _____Telephone _____

Address_____

Relationship _____

13. **Contact 3**

Name _____Telephone _____

Address_____

Relationship _____

General Practitioner (GP)

Please state the details of your child's usual G.P.

14. Who is your child's GP? _____

15. What is the address of his/her surgery? _____

_____

When did your child last visit his/her GP? _____weeks/months ago *(please circle)*

16. On average, how many times per year does your child visit the GP? _____ per year

17. Please tick the box if you do not want a report outlining the results of the examination to also be sent to your nominated GP.

☐ I don't want a report to be sent to my child's GP.

Vision and Hearing Questions

This section has questions relating to your child's hearing and vision. The questions are important because certain hearing and eye conditions can affect your child's schooling. Basic hearing tests can be performed by a doctor or nurse. A detailed hearing test is performed by an audiologist (hearing practitioner) and a report is given to you.

18. Has your child ever had his/her hearing tested?
    - ☐ No (go to question 27)
    - ☐ Unsure (go to question 27)
    - ☐ Yes

19. If yes, what age? _____ Who performed the test? _____

21. Did you receive a report?
    - ☐ No
    - ☐ Unsure
    - ☐ Yes

22. Were there any abnormalities found with your child's hearing?
    - ☐ No
    - ☐ Unsure
    - ☐ Yes

23. Did your child visit a local doctor or a hearing specialist for further testing?
    - ☐ No
    - ☐ Unsure
    - ☐ Yes

24. Were you told what was wrong with your child's hearing?
    - ☐ No (go to question 27)
    - ☐ Unsure (go to question 27)
    - ☐ Yes

    If yes, the problem was? _____

25. How many months/years ago was the problem reported? ☐☐ / ☐☐
    (years) *(months)*

26. Which ear was involved?
    - ☐ Right ear
    - ☐ Left ear
    - ☐ Both ears
    - ☐ Unsure

In the past, your child may have had an eye test. This could have been part of a screening program at school, performed by a nurse or orthoptist, or a detailed eye examination by a medical eye specialist (ophthalmologist) or optometrist.

27. Has your child ever had his/her vision tested?
    - ☐ No (go to question 37)
    - ☐ Unsure (go to question 37)
    - ☐ Yes

28. If yes, what age? _____ Who performed the test? _____

29. Did you receive a report?

☐ No ☐ Unsure

☐ Yes

30. Were there any reported abnormalities with your child's eyes?

☐ No ☐ Unsure

☐ Yes

31. Did your child visit a local doctor or eye practitioner for further testing of the problem?

☐ No ☐ Unsure

☐ Yes

32. Were you told what was wrong with your child's eyes?

☐ No (go to question 35) ☐ Unsure (go to question 35)

☐ Yes

If yes, the problem was? _____

33. How many months/years ago was the problem reported? ☐☐ / ☐☐

(*years)* *(months)*

34. Which eye was involved?

☐ Right eye ☐ Left eye

☐ Both eyes ☐ Unsure

35. Does your child have any other sight problems?

☐ No (go to question 37) ☐ Unsure (go to question 37)

☐ Yes

36. What other sight problems does your child have?

☐ Totally blind in both eyes ☐ Partially blind in both eyes

☐ Totally blind in 1 eye only ☐ Partially blind in 1 eye only

☐ Glaucoma ☐ Trachoma

☐ Cataract ☐ Don't know

☐ Other (please describe) _____

37. Is your child colour blind?

☐ No ☐ Unsure

☐ Yes

The following section asks you about any visits your child may have had to an eye practitioner. An eye practitioner includes:
- ***Ophthalmologist (eye specialist)***
- ***Optometrist***
- ***Orthoptist (eye therapist)***

38. How long has it been since your child last consulted an eye specialist or optometrist?

☐ Never (go to question 42) ☐ 2 to less than 5 years
☐ Less than 1 year ☐ 5 years or more
☐ 1 to less than 2 years ☐ Don't Know (go to question 42)

39. Does your child attend regular eye examinations?

☐ No ☐ Unsure
☐ Yes

40. If yes, please fill in the details of the eye practitioner below. If you are unsure about the type of practitioner he/she is, tick the box marked "other" and state the name and suburb.

☐ **Ophthalmologist (Medical Eye Specialist)** ____/____/____ *(date last seen)*

Name: _____ Suburb: _____

☐ **Optometrist** ____/____/____ *(date last seen)*

Name: _____ Suburb: _____

☐ **Orthoptist** ____/____/____ *(date last seen)*

Name: _____ Suburb: _____

☐ **Other** ____/____/____ *(date last seen)*

Name: _____ Suburb: _____

41. Please tick how often the eye practitioner is seen (refer to the eye practitioner that the child sees most often)

☐ More than once in 6 months ☐ Once a year
☐ Every 6 months ☐ Less frequently than once a year

42. Does your child **currently** wear glasses or contact lenses to correct, or partially correct, his/her eyesight?

☐ No (go to question 45)
☐ Glasses
☐ Contact lenses

43. How often are the glasses or contact lenses used?

- ☐ All the time
- ☐ Only when eyes feel tired
- ☐ Sometimes
- ☐ Hardly ever

44. What sight problems do your child's glasses or contact lenses correct or partially correct? *(You may tick more than one box)*

- ☐ Astigmatism
- ☐ Short-sightedness / Myopia
- ☐ Long-sightedness / Hyperopia
- ☐ Don't know
- ☐ Other (please describe) _____

45. Has your child worn glasses or other optical correction such as contact lenses **in the past**?

☐ No (go to question 49) ☐ Unsure (go to question 49)

☐ Yes

If yes, please state the date and age when prescribed _____

Date stopped: ☐☐ / ☐☐☐☐
(month) *(year)*

Reason stopped _____

_____

46. How often did your child use their glasses / contact lenses?

- ☐ Most of the time
- ☐ Sometimes
- ☐ Only when eyes felt tired
- ☐ Hardly ever

We would like to know what glasses were previously prescribed. There are two ways we can find out this information. Firstly, by looking at your child's old glasses during his/her examination at school, OR, by viewing the prescription that the eye specialist / optometrist wrote out.

47. Do you have your child's old glasses?

☐ No (go to question 48) ☐ Unsure (go to question 48)

☐ Yes (could the child please bring the glasses with them to the examination)

48. Do you have a copy of your child's last prescription?

☐ No ☐ Unsure

☐ Yes

If yes, please attach the prescription or a copy of it to this page in the space provided below. Alternatively, you may write it down with the date it was prescribed:

_____

_____

_____

☐ Please tick if you want the original prescription to be returned to you

(Attach prescription here)

49. Has your child ever had any one or more of the following treatments for myopia (short-sightedness)?

- ☐ Bifocals
- ☐ Progressive lenses
- ☐ Atropine eye drops
- ☐ None of the above
- ☐ Don't know

50. Has your child ever worn an eye patch?

- ☐ No
- ☐ Unsure
- ☐ Yes

If yes, for how long? _____

51. Have you ever been told by a doctor or optometrist that your child has a strabismus (turned or lazy eye)?

- ☐ No (go to question 53)
- ☐ Unsure (go to question 53)
- ☐ Yes

52. Has your child received treatment for this condition?

- ☐ No
- ☐ Unsure
- ☐ Yes (please describe) _____

53. Has your child ever sustained any serious injury to the eyes or area around the eyes?

- ☐ No (go to question 55)
- ☐ Unsure (go to question 55)
- ☐ Yes

If yes, explain the injury (please describe) _____

_____

_____

54. Do you feel your child's vision was affected by the injury?

- ☐ No
- ☐ Unsure
- ☐ Yes

55. Has your child ever had eye surgery?

- ☐ No
- ☐ Yes (If yes, what was it for? Please tick)
  - ☐ *Strabismus (turned eye or lazy eye)*
  - ☐ *Other (please describe)* _____

56. Is your child currently using any eye drops/ointments?

☐ No ☐ Unsure

☐ Yes

If yes, please write down the name of all eye drops/ointments **currently** used.

	Name of eye drop/ointment	Times per day	Date started (month/year)	Reason for using
1.				
2.				
3.				

57. Has your child ever used eye drops/ointment in the past?

☐ No ☐ Unsure

☐ Yes

If yes, please write down the name of all eye drops/ointments **previously** used.

	Name of eye drop/ointment	Times per day	Duration of usage	Age at time of usage	Reason for taking
1.					
2.					
3.					

Your child may have never been diagnosed with an eye condition, however we would like to know about any concerns you or others might have with his/her eyes or vision.

58. Has your child ever complained of any eye or vision problems in the past?

☐ No (go to question 60) ☐ Unsure (go to question 60)

☐ Yes

59. Please tick below all symptoms experienced by your child:

☐ Blurred vision when looking in the distance ☐ Double vision

☐ Sore eyes (how often?) _____

☐ Other (please describe) _____

60. Does your child experience a headache when reading or doing close work?

☐ No (go to question 63) ☐ Unsure (go to question 63)

☐ Yes

61. If yes, how often?_____ and at what time of the day? (e.g. 2:30 pm) _____

62. How long do the headache symptoms last? (e.g. 30 min) ☐ / ☐☐
(hours) *(minutes)*

63. Has anyone ever thought there might be a problem with your child's eyesight?

☐ No (go to question 65) ☐ Unsure (go to question 65)

☐ Yes

64. What was thought to be wrong with his/her eyes?

☐ Squint (eyes not looking in same direction) ☐ Don't know

☐ Colour blind

☐ Something else (please describe) _____

65. Do you think your child might need to wear glasses?

☐ No ☐ Unsure

☐ Yes (please give the reason) _____

66. Have you noticed your child to have a turned or lazy eye?

☐ No (go to question 70) ☐ Unsure (go to question 70)

☐ Yes

67. What age was your child when you first noticed this? ☐☐ years ☐☐ months

68. Which eye was affected?

☐ Right eye ☐ Left eye

69. Has a doctor checked this?

☐ No

☐ Yes

If yes, how many year(s)/month(s) were there between the first time you noticed this and the time your child was seen by the doctor? ☐☐ years ☐☐ months

General Medical Details

This section will ask you questions relating to your child's general medical health. We are interested in both past and current medical conditions, and medicines that your child may have taken. A chronic illness or disability is a condition that has been detected in the past and is currently still ongoing, requiring treatment.

70. Has your child ever been diagnosed with a chronic illness or disability?

☐ No (go to question 75) ☐ Unsure (go to question 75)

☐ Yes

71. What was the nature of the illness or disability? (Please name or describe) _____

_____

72. Does your child still have this condition?

☐ No ☐ Unsure

☐ Yes

73. Does your child receive treatment for this condition?

☐ No (go to question 75) ☐ Unsure (go to question 75)

☐ Yes

74. Please tick the treatment(s) given:

☐ Medicine prescribed ☐ Surgery ☐ Given injections

☐ Physiotherapy ☐ Speech therapy ☐ Dental treatment

☐ Naturopathy ☐ Chiropractic treatment

☐ Homeopathic treatment ☐ Counselling / guidance

☐ Other (please describe)_____

Questions 75 to 81 refer to a condition that has been detected for the first time in the last 2 weeks. For example, the flu.

75. Has your child visited a doctor in the last 2 weeks?

☐ No (go to question 82) ☐ Unsure (go to question 82)

☐ Yes

If yes, what was the reason that you took your child to the doctor? (Please describe)_____

_____

76. Was any treatment given?

☐ No (go to question 82) ☐ Unsure (go to question 82)

☐ Yes

77. Please tick the treatment(s) given:

☐ Medicine prescribed ☐ Surgery performed or recommended

☐ Referred to another practitioner (specify)_____

☐ Other (specify)_____

78. Has your child had a second reason to visit a doctor during the last 2 weeks?

☐ No (go to question 82) ☐ Unsure (go to question 82)

☐ Yes

79. What was the illness or injury that caused your child's second visit to the doctor? _____

_____

80. Was any treatment given?

☐ No (go to question 82) ☐ Unsure (go to question 82)

☐ Yes

81. Please tick the treatment(s) given:

☐ Medicine prescribed ☐ Surgery performed or recommended

☐ Referred to another practitioner/ doctor

☐ Other (please describe)_____

Questions 82 – 89 refer to an illness that was severe enough to require your child's admission into hospital or day surgery. For example, appendicitis.

82. Has your child had a major illness in the past that has required admission to hospital or day surgery?

☐ No (go to question 90) ☐ Unsure (go to question 90)

☐ Yes

83. Please describe the reason for your child's admission? _____

_____

84. At what age did this occur? _____

85. Did your child have surgery?

☐ No (go to question 87) ☐ Unsure (go to question 87)

☐ Yes

86. Please name or describe the **surgical procedure** _____

87. What was the name of the hospital and in which suburb was it located?_____

_____

88. Has your child had more than one admission to hospital or day surgery?

☐ No (go to question 90) ☐ Unsure (go to question 90)

☐ Yes

89. Please list the name of the hospital, the suburb in which it was located, the reason for the admission and the date of the admission.

- Hospital: _____

Suburb: _____ Date: _____ / _____ / _____ *(day/month/year)*

Reason: _____

- Hospital: _____

Suburb: _____ Date: _____ / _____ / _____ *(day/month/year)*

Reason: _____

We wish to ask about any medications that your child is <u>currently</u> using, these include both prescribed and non-prescribed medications. Please note that vitamins, inhaled medicines, skin lotions, eye-drops, laxatives, homeopathic and herbal remedies should also be included.

90. Has your child taken any medication(s) in the last 2 weeks?

☐ No (go to question 91) ☐ Unsure (go to question 91)

☐ Yes *(If yes, please list all the medications in the table below)*

	Medication name	Method of intake (ie. oral, injected)	Number of times per day	Date started	Reason for taking
1					
2					
3					
4					
5					

91. In the **<u>past</u>** has there been any prescribed or non-prescribed medication(s) that your child has taken every day or nearly every day for a period of at least 3 months?

☐ No (go to question 94) ☐ Unsure (go to question 94)

☐ Yes

If yes please list:

1) ***Prescribed medication in Table A;***
2) ***Non-prescribed medication in Table B.***

92. **TABLE A: Please list all medications which were prescribed by a local doctor.**

	Medication name	Method of intake (ie oral, injected)	How many times a day	Duration in weeks	Reason for taking	Age at time
1						
2						
3						
4						
5						

93. **TABLE B: Please list all medications which were purchased over the counter (that is, a doctors prescription wasn't needed to purchase these medications)**

	Medication name	Method of intake (ie oral, injected)	How many times a day	Duration in weeks	Reason for taking	Age at time
1						
2						
3						
4						
5						

We would like to ask you about common medical conditions. Certain conditions have proven to be associated with myopia.

94. Has your child ever been told by a doctor or nurse that he/she has asthma?

☐ No (go to question 96) ☐ Unsure (go to question 96)

☐ Yes

95. Does your child still get asthma?

☐ No ☐ Unsure

☐ Yes

96. Do you (the mother) smoke?

☐ No

☐ Yes

97. Do other people living in your home smoke inside the house?

☐ No

☐ Yes

If you answered ***Yes*** to ***Questions 96 or 97***, please complete the table below.

Cigarettes/day	Mother	Father	Other
1-10/ day			
11-20/ day			
21-40/day			
41+/day			

98. Was there any delay in your child's early development?

☐ No ☐ Unsure

☐ Yes (Please tick below)

Delayed development in:

☐ Sitting

☐ Walking

☐ Talking

☐ Other (please describe) _____

99. Has your child experienced any difficulties with learning at school or pre-school?

☐ No ☐ Unsure

☐ Yes

If yes, please describe_____

100. Have you ever been told that your child has Attention Deficit Disorder (ADD) or Attention Deficit Hyperactivity Disorder (ADHD)?

☐ No (go to question 103) ☐ Unsure (go to question 103)

☐ Yes

101. What age was your child when you were first told that he/she had Attention Deficit Disorder (ADD) or Attention Deficit Hyperactivity Disorder (ADHD)

☐☐ Years ☐☐ Months ☐ Don't Know

102. Is your child receiving treatment for this disorder?

☐ No ☐ Unsure

☐ Yes

103. Has your child ever been diagnosed with any of the following? (Please tick)

☐ Epilepsy ☐ Meningitis

☐ Marfan Syndrome ☐ Down Syndrome

☐ Stickler Syndrome ☐ Diabetes

☐ Toxoplasmosis

☐ Other (please describe) _____

Birth History

Gestation and neo-natal.
The following questions are about your child's birth and early years.
If you still have your health record book (the blue/yellow book) it may help to look at it. These books record birth details.

Birth Details: Extract from Personal Child Health Record- TRANSCRIBE FROM:

NSW	**Blue Book**	**Page 39**
WA	**Yellow Book**	**Page 45**
SA	**Blue Book**	**Page 38**
Tas	**Blue Book**	**Page 57**
Qld	**Blue Book**	**Page 20**
Vic	**Yellow Book**	**"Birth, Vit K, Hep B, Newborn Examination" section**

104. Do you have your child's State Child Health Record (the blue/yellow book) available?

- ☐ No
- ☐ Yes

105. Delivery Type

- ☐ Normal
- ☐ Breech
- ☐ Caesarean
- ☐ Vacuum extraction
- ☐ Forceps
- ☐ Other
- ☐ Don't know

106. What was your child's birth weight? _____ Grams or _____ Pounds _____ Ounces

107. Birth length _____ cms

108. Birth head circumference _____ cms

109. What was your child's gestation period? ☐☐ weeks (go to question 111)

- ☐ Unsure (go to question 110)

If your child's gestation period in weeks is unknown, please try to answer the following question.

110. Was your child born

- ☐ Late (42 weeks or more)
- ☐ On time (37-41 weeks gestation)
- ☐ Early (33-36 weeks gestation)
- ☐ Very early (32 weeks or less)

111. Was your child admitted to a Neonatal Intensive Care Unit (NICU) after birth?

☐ No ☐ Don't know

☐ Yes

112. Was your child admitted to a Special Care Nursery (SCN) after birth?

☐ No (go to question 114) ☐ Don't know (go to question 114)

☐ Yes

(If your child was admitted to a NICU or SCN please answer the following question)

113. If known, please write down date of discharge. ☐☐ / ☐☐ / ☐☐
(day) (month) (year)

114. Was this a multiple pregnancy? (eg. twins or triplets)

☐ No, single birth ☐ Don't know

☐ Yes, twins

☐ Yes, triplets

☐ Yes, more than triplets

115. Was your child born:

☐ In a hospital or birthing centre? (Please name the hospital or birthing centre he/she was born in and the suburb)

Name of hospital _____

Suburb _____ State _____

☐ At home

☐ Other (please describe) _____

116. Did you use your child's health record book to answer the above questions?

☐ No

☐ Yes

117. Has your child ever been breastfed?

☐ No (go to question 119) ☐ Don't know (go to question 119)

☐ Yes

118. What is the total time your child was breastfed?

☐ Longer than 3 months

☐ Longer than 1 week but less than 3 months

☐ Less than one week

☐ Unsure

The mother's health during pregnancy can influence her child's development. We would like to know about specific conditions the mother may have experienced during the pregnancy.

119. Were there any problems with the pregnancy?

☐ No ☐ Unsure

☐ Yes (If yes, please describe)_____

_____

120. During the pregnancy, did the mother:

	Yes	No	Don't know
Have high blood pressure needing treatment? (admission to hospital or medication)	☐	☐	☐
Have diabetes needing insulin injections?	☐	☐	☐
Have diabetes but didn't have insulin injections?	☐	☐	☐
Have a high fever anytime during the pregnancy?	☐	☐	☐
Have Rubella (German measles)?	☐	☐	☐
Have Mumps?	☐	☐	☐
Have other health problems? (Please describe) _____	☐	☐	☐

_____

121. During the pregnancy, did the mother ever smoke cigarettes, cigars, pipes or other tobacco products?

☐ No (go to question 124) ☐ Don't Know (go to question 124)

☐ Yes

122. How often did the mother smoke cigarettes, cigars, pipes or other tobacco products, while she was pregnant with the child?

☐ Daily ☐ Not at all

☐ At least weekly, not daily ☐ Don't know

☐ Less often than weekly

123. During the pregnancy, did the mother:

☐ Reduce the amount of tobacco she smoked

☐ Try and give up smoking but were unsuccessful

☐ Successfully give up smoking

☐ None of the above

☐ Don't know

124. During the pregnancy, did the mother share a home with people who smoked indoors?

☐ No ☐ Unsure

☐ Yes

If yes please specify approximately how many cigarettes were smoked indoors in a day during the pregnancy_____

125. During the pregnancy, did the mother take any prescribed medications?

☐ No ☐ Unsure

☐ Yes (please write down the names of the medications and for how long they were taken in the table below)

Please list all medications which were prescribed by a local doctor

	Medication name	Method of intake (ie oral, injected)	How many times a day	Duration in weeks	Reason for taking
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					

126. During the pregnancy, did the mother take any over-the-counter medications?

☐ No ☐ Unsure

☐ Yes (please write down the names of the medications and for how long they were taken in the table below)

Please list all medications which were purchased over the counter (ie a doctors prescription wasn't needed to purchase these medications)

	Medication name	Method of intake (ie oral, injected)	How many times a day	Duration in weeks	Reason for taking
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					
15					

ABOUT YOUR FAMILY

This section will ask about your child's biological (natural) parents and family members to identify genetic associations. Children with parents who are myopic are more likely to develop myopia. In addition, people with particular ethnic backgrounds seem to develop myopia more than others. We realise that some parent(s) may not be the biological parent(s) and in some cases not have the knowledge to complete some sections. If this is the case, please tick unsure. Where possible it is preferable that the biological parent completes this section.

Biological Parents

161. Please tick the box that applies to your child:

- ☐ Both parents are the biological parents
- ☐ Current father is the biological father and current mother is not the biological mother
- ☐ Current mother is the biological mother and current father is not the biological father
- ☐ Current father is the biological father and no mother present (single father)
- ☐ Current mother is the biological mother and no father present (single mother)
- ☐ Both parents are **not the** biological parents
- ☐ Other (please describe) _____

162. Country of birth of both biological parents?

Mother _____ ☐ Tick if unsure

Father _____ ☐ Tick if unsure

163. What is the ethnic origin of the child's biological parents? (Provide more than one ethnic group if applicable; e.g. If the father's mother is Caucasian and father's father is East Asian, then you would tick both boxes in the father's column.)

	Mother	Father
Caucasian (European)	☐	☐
East Asian	☐	☐
Indian/ Pakistani/ Sri Lankan	☐	☐
African	☐	☐
Melanesian/ Polynesian	☐	☐
Middle Eastern	☐	☐
Indigenous Australian	☐	☐
South American	☐	☐
Unsure	☐	☐

Other (please describe)_____

Appendix 1b:

Sydney Paediatric Eye Disease Study Parental Questionnaire

THE SYDNEY CHILDHOOD EYE SURVEY QUESTIONNAIRE

Dear Parent,

We are very grateful for your participation with your child in this project. It will provide you with not only a comprehensive report regarding your child's eye health but will also ensure researchers obtain important information about general eye health for children in the Sydney area.

The purpose of this study

The National Health and Medical Research Council has funded the University of Sydney to undertake a survey of eye health in children aged up to 6 years within Sydney. The survey is called the Sydney Paediatric Eye Disease Study (Sydney Childhood Eye Survey).

We will look at the frequency of eye problems affecting children's eyes such as strabismus (turned eye), amblyopia (lazy eye or poor vision in one eye), and a need for glasses. You and your child are invited to participate in this large project that will involve children from a number of suburbs in Sydney the first being Quakers Hill and Acacia Gardens.

This questionnaire will give us important information relating to you, your child and your family. Please take as much time as necessary to complete it. All of the answers you provide will be regarded as strictly confidential.

Please bring this questionnaire with you on the day of your scheduled appointment or send back to us in the stamped self address envelope provided.

Common questions and answers

What happens in the eye examination?
Each child will have their vision tested, as well as tests to see how well the two eyes work together. Colour vision will also be tested. We will measure your child's refraction to see if they need glasses and we will have a look at the back of your child's eye. To do these tests all children will need eye drops. All the tests and eye drops we use are the same as your child would have if they had their eyes examined by an eye doctor or optometrist. You will be told the results of the eye examination, and if we find any problems you will be referred to an eye practitioner.

Will this eye examination cost me anything?
No! These eye examinations are provided without any cost to you or to Medicare. The cost is covered by the funds we receive from the National Health and Medical Research Council.

Guidelines

- Where possible we would like one parent or guardian to take responsibility for completing the questionnaire in consultation with other family members/caregivers.
- Please attempt to answer every question. In some circumstances you will be directed to skip questions because they do not apply to you.
- If you have difficulty with a question, please give the best response you can and make a comment in the margin.
- We understand that some children will not be living with both, or even one of their biological parents, and we ask you to please note this in completing the relevant parts of the questionnaire.
- The majority of questions in this questionnaire are standard questions derived from the Australian Bureau of Statistics (ABS) National Census, the NSW Child Health Survey and other international eye studies.
- Please feel free to ask our staff for assistance. They can be contacted on the telephone numbers below.

Please note: While it would greatly assist the examiners if the questionnaire was completed prior to your child's examination, it will be possible to collect it from you later.

Statement of confidentiality

Information that would permit the identification of any person completing this questionnaire will be regarded as strictly confidential. All information provided will be used only for the Sydney Childhood Eye Survey and will not be disclosed or released for any other purpose without your consent.

You may correct any personal information provided at any time by contacting:

Administration
Centre for Vision Research
Westmead Hospital
Telephone: 9845 9077
Fax: 9845 8345

Dr Kathryn Rose
Project coordinator
School of Applied Vision Sciences
Faculty of Health Sciences
University of Sydney
Telephone: 9351 9464
Fax: 9351 9359
Email: k.rose@fhs.usyd.edu.au

Professor Paul Mitchell
Project principal investigator
Centre for Vision Research
Department of Ophthalmology
University of Sydney
Westmead Hospital
Telephone: 9845 9077
Fax: 9845 8345
Email: paul_mitchell@wmi.usyd.edu.au

SECTION 1

General information about you and your children (section 2 will ask more detailed information about each child).

General Family and Contact Information					
The following section is to be answered for you and your entire family					
1a.	What is your full name? (name of person completing questionnaire)	_____			
1b.	What is your relationship to the child/children being tested?	☐ Biological mother ☐ Step-mother ☐ Adoptive mother ☐ Legal guardian ☐ Foster mother ☐ Grandmother ☐ Aunt ☐ Other female relative ☐ Other female non-relative (specify): _____ _____ ☐ Don't know		☐ Biological father ☐ Step-father ☐ Adoptive father ☐ Legal guardian ☐ Foster father ☐ Grandfather ☐ Uncle ☐ Other male relative ☐ Other male non-relative(specify): _____ _____ ☐ Don't know	
1c.	Is this the same for all children begin tested?	☐ Yes ☐ No (specify): _____ _____			
2a.	What is your partner's full name?	_____			
2b.	What is their relationship to the child/children being tested?	☐ Biological mother ☐ Step-mother ☐ Adoptive mother ☐ Legal guardian ☐ Foster mother ☐ Grandmother ☐ Aunt ☐ Other female relative ☐ Other female non-relative (specify): _____ _____ ☐ Don't know		☐ Biological father ☐ Step-father ☐ Adoptive father ☐ Legal guardian ☐ Foster father ☐ Grandfather ☐ Uncle ☐ Other male relative ☐ Other male non-relative(specify): _____ _____ ☐ Don't know	
2c.	Is this the same for all children begin tested?	☐ Yes ☐ No (specify): _____ _____			

3a.	What is your full address?	Address: _____ _____ Suburb: _____ Postcode: _____
3b.	Are there any other addresses where you/your child live for some of their time? (eg. Father/Mother/Grandparent)	Address: _____ _____ Suburb: _____ Postcode: _____
4.	How long have you lived at this address?	☐☐ years ☐☐ months
5.	If you move from your current address can you please provide us with the details of people we can contact to obtain a forwarding address?	
	Contact 1 Name: _____ Telephone: _____ Address: _____ _____ Relationship: _____ **Contact 2** Name: _____ Telephone: _____ Address: _____ _____ Relationship: _____	**Contact 3** Name: _____ Telephone: _____ Address: _____ _____ Relationship: _____ **Contact 4** Name: _____ Telephone: _____ Address: _____ _____ Relationship: _____
6.	Please provide us with your children's full names. Please place the details of your oldest child first. Please tick those children who are eligible to participate in this study.	
☐	**Child 1**: First name: _____ Family name: _____ Gender: _____ Date of birth: _____ Country of birth: _____	☐ **Child 2**: First name: _____ Family name: _____ Gender: _____ Date of birth: _____ Country of birth: _____
☐	**Child 3**: First name: _____ Family name: _____ Gender: _____ Date of birth: _____ Country of birth: _____	☐ **Child 4**: First name: _____ Family name: _____ Gender: _____ Date of birth: _____ Country of birth: _____

☐	**Child 5**: First name: _____ Family name: _____ Gender: _____ Date of birth: _____ Country of birth: _____	☐	**Child 6**: First name: _____ Family name: _____ Gender: _____ Date of birth: _____ Country of birth: _____
7.	Do you live in the same household with the child/children?	☐ ☐	Yes No

	For all of the following questions please tick the relevant box. Child 1 refers to your 1st ELIGBLE CHILD, Child 2 refers to your 2nd ELIGBLE CHILD, Child 3 refers to your 3rd ELIGBLE CHILD.		
8.	About how long has it been since your child/ children had a routine physical examination? (ie. not for a particular illness, but a general check-up)		**Child 1/ Child's name:** _____
		☐	Less than 1 year ago
		☐	More than 1 year but less than 2 years ago
		☐	More than 2 years but less than 5 years ago
		☐	Never
		☐	Don't know
			Child 2 / Child's name: _____
		☐	Less than 1 year ago
		☐	More than 1 year but less than 2 years ago
		☐	More than 2 years but less than 5 years ago
		☐	Never
		☐	Don't know
			Child 3 / Child's name: _____
		☐	Less than 1 year ago
		☐	More than 1 year but less than 2 years ago
		☐	More than 2 years but less than 5 years ago
		☐	Never
		☐	Don't know
9.	Where do you go for your child/children's routine care?	☐	Doctor's office
		☐	Baby Health Clinic
		☐	Medical Centre
		☐	Some other place (please specify): _____
		☐	Don't know

10.	Has your child stayed in hospital overnight or longer since he/she was born? (Please do not include the hospitalisation when he/she was born.)		**Child 1:** _____ ☐ Yes, ☐☐ times ☐ No (go to question 12) ☐ Don't know **Child 2**: _____ ☐ Yes, ☐☐ times ☐ No (go to question 12) ☐ Don't know **Child 3**: _____ ☐ Yes, ☐☐ times ☐ No (go to question 12) ☐ Don't know
11.	What was the reason(s) your child stayed in the hospital overnight or longer?		**Child 1**: _____ ☐ Asthma ☐ Respiratory disease/pneumonia ☐ Diarrhoea and/or dehydration ☐ Vomiting and/or dehydration ☐ Seizure ☐ Other - please specify: _____ ☐ Don't know **Child 2**: _____ ☐ Asthma ☐ Respiratory disease/pneumonia ☐ Diarrhoea and/or dehydration ☐ Vomiting and/or dehydration ☐ Seizure ☐ Other - please specify: _____ ☐ Don't know **Child 3**: _____ ☐ Asthma ☐ Respiratory disease/pneumonia ☐ Diarrhoea and/or dehydration ☐ Vomiting and/or dehydration ☐ Seizure ☐ Other - please specify: _____ ☐ Don't know

12.	Has your child had any surgery since birth?	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	**Child 1**: _____ Yes No (go to question 14) Don't know **Child 2**: _____ Yes No (go to question 14) Don't know **Child 3**: _____ Yes No (go to question 14) Don't know
13.	What surgery did he/she have?	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	**Child 1**: _____ Tonsils & adenoids Hernia Ear tubes Other surgery: _____ Don't know **Child 2**: _____ Tonsils & adenoids Hernia Ear tubes Other surgery: _____ Don't know **Child 3**: _____ Tonsils & adenoids Hernia Ear tubes Other surgery: _____ Don't know
14.	In the past 12 months, has your child been seen in the emergency room? If so, how many times?	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	**Child 1:** _____ Yes, ☐☐ times No (go to question 16) Don't know **Child 2**: _____ Yes, ☐☐ times No (go to question 16) Don't know **Child 3**: _____ Yes, ☐☐ times No (go to question 16) Don't know
15.	What were the reasons your child was seen in the emergency room?		Reason(s): _____ _____ _____

Parent Information			
16.	Parent's occupation(s):	Mother's occupation: _____ Current occupation: _____ Father's occupation: _____ Current occupation: _____	
17.	How would you describe the mother's employment status?	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	Employed full time (includes self employment) Employed part time (includes self employment) Unemployed Home duties Student and working Student and not working Retired Unable to work due to health problems Pensioner Other (please describe): _____ Don't know
18.	How would you describe the father's employment status?	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	Employed full time (includes self employment) Employed part time (includes self employment) Unemployed Home duties Student and working Student and not working Retired Unable to work due to health problems Pensioner Other (please describe): _____ Don't know
19.	What is the highest level of education completed by the mother?	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	Never attended school Some primary school completed Some high school completed Completed school certificate (Year 10 / 4th form) Completed HSC (Year 12 / 6th form) TAFE certificate or diploma, including trade certificate University, CAE or other tertiary institute degree Higher degree including a Masters or PHD Other (please describe): _____ Don't know

20.	What is the highest level of education completed by the father?	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	Never attended school Some primary school completed Some high school completed Completed school certificate (Year 10 / 4th form) Completed HSC (Year 12 / 6th form) TAFE certificate or diploma, including trade certificate University, CAE or other tertiary institute degree Higher degree including a Masters or PHD Other (please describe): _____ Don't know
21.	What sort of place does your family live in?	☐ ☐ ☐ ☐ ☐ ☐ ☐	Own house Own flat/unit Rented house Rented flat/unit With relatives Other (please describe): _____ Don't know

Parent History (to be answered by biological parents)			
BIOLOGICAL MOTHER SECTION			
22.	In what country were you born?	☐ ☐	Australia Other (specify) : _____
23.	What is your ethnic origin? (provide more than one ethnic group if applicable, eg. if your mother is Caucasian and your father is East Asian, then tick both boxes).	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	Caucasian (European) East Asian Indian/ Pakistani/ Sri Lankan African Melanesian/ Polynesian Middle Eastern Indigenous Australian South American Other (specify): _____ Don't know
24.	In general, would you say your health is…?	☐ ☐ ☐ ☐ ☐	Excellent Good Fair Poor Very Poor
Has a doctor advised you that you have any of the following conditions:			
25.	High Blood Pressure?	☐ ☐ ☐	Yes No (go to question 26) Don't know
	a) When was it first diagnosed?		☐☐ years ago
	b) For how many years has it been treated with medication?		☐☐ years

26.	Diabetes?	☐ ☐ ☐	Yes No (go to question 27) Don't know
	a) When was it first diagnosed?		☐☐ years ago
	b) In what year did you begin and finish each type of treatment? (if currently on treatment put 7777 as year finished)		
	Diet alone: started _____ finished _____		☐ Yes ☐ No ☐ Don't know
	Tablets: started _____ finished _____		☐ Yes ☐ No ☐ Don't know
	Insulin: started _____ finished _____		☐ Yes ☐ No ☐ Don't know
	No treatment		☐ Yes ☐ No ☐ Don't know
27.	High Cholesterol?	☐ ☐ ☐	Yes No (go to question 28) Don't know
	a) When was it first diagnosed?		☐☐ years ago
	b) Are you taking tablets?	☐ ☐ ☐ ☐ ☐ ☐	Gemfibrozil (lopid, ausgem) Fluvastatin (lescol, vastin) Simvastatin (lipex, zocor) Other (please specify): _____ No Don't know
28.	Asthma?	☐ ☐ ☐	Yes No (go to question 29) Don't Know
	a) When was it first diagnosed?		☐☐ years ago
29.	Angina?	☐ ☐ ☐	Yes No (go to question 30) Don't know
	a) When was it first diagnosed?		☐☐ years ago
	b) Was the diagnosis confirmed with an ECG?		☐ Yes ☐ No ☐ Don't know
	c) Name and address of Dr. who made diagnosis?		Name: _____ Address: _____ _____ Suburb: _____ Post Code: _____
	d) How often do you take anginine tablets or sprays?	OR	☐☐ times per day ☐☐ times per month
30.	Heart attack?	☐ ☐ ☐	Yes No (go to question 31) Don't know
	a) When was it first diagnosed?		☐☐ years ago

	b) Was the diagnosis confirmed with an ECG?		☐ Yes ☐ No ☐ Don't know
	c) Was it confirmed with a blood test?		☐ Yes ☐ No ☐ Don't know
	d) Name and address of Dr. who made diagnosis?		Name: _____ Address: _____ _____ Suburb: _____ Post Code: _____
	e) Were you admitted to hospital?		☐ Yes ☐ No ☐ Don't know
	f) For how long?		☐☐ days
	g) How was your heart attack treated	☐ ☐ ☐ ☐ ☐	Bypass Angioplasty Pacemaker Valve Replacement Other (specify) _____
	h) How many years ago?		☐☐ years ago
31.	Stroke?	☐ ☐ ☐	Yes No (go to question 32) Don't Know
	a) When was it first diagnosed?		☐☐ years ago
	b) Was the diagnosis confirmed with a CT scan?		☐ Yes ☐ No ☐ Don't know
	c) Name and address of Dr. who made diagnosis?		Name: _____ Address: _____ _____ Suburb: _____ Post Code: _____
	d) Were you admitted to hospital?		☐ Yes ☐ No ☐ Don't know Hospital _____ for ☐☐ days
	e) How did the stroke affect you?		☐Mild ☐Moderate
	f) Part of body affected	☐ ☐ ☐ ☐ ☐	Arm ☐ right ☐ left Leg ☐ right ☐ left Speech Other (specify) _____ Don't know
	g) How well have you recovered from the stroke?		_____ % recovery (100% is full recovery)
	h) How long did it take?		☐☐ months

	i) Which treatment did you receive?	☐ ☐ ☐ ☐	Aspirin, clopidogrel, persantin Anticoagulation (heparin, clexane and warfarin) None Don't know
32.	Have you had any multiple pregnancies? (eg. twins or triplets)	☐ ☐ ☐ ☐ ☐	No, single births only Yes, twins Yes, triplets Yes, more than triplets Don't know
33.	How old were you when your first child was born?	☐	☐☐ years old Don't know
34.	How old was your child's biological father when your first child was born?	☐	☐☐ years old Don't know
35.	Have you ever smoked cigarettes, cigars or a pipe regularly?	☐ ☐ ☐	Yes No (go to question 40) Don't know
36.	If yes, which of the following have you ever regularly smoked:		
	a) Cigarettes (ready made)	Age ☐☐ to age ☐☐	
	b) Cigarettes (roll your own)	Age ☐☐ to age ☐☐	
	c) Tobacco	Age ☐☐ to age ☐☐	
	d) Pipe	Age ☐☐ to age ☐☐	
	e) Cigars	Age ☐☐ to age ☐☐	
37.	Have you given up smoking?	☐ ☐ ☐	Yes No (go to question 39) Don't Know
38.	How much did you usually smoke a week before you stopped?		☐☐ Packs of manufactured cigarettes (20 per pack) ☐☐ Packets of hand-rolled cigarettes ☐☐ Cigars ☐☐ Packets of pipe tobacco Go to question 40.
39.	How much do you smoke per week currently?		☐☐ Packs of manufactured cigarettes (20 per pack) ☐☐ Packets of hand-rolled cigarettes ☐☐ Cigars ☐☐ Packets of pipe tobacco

40.	How often do you have an alcoholic drink?	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	Never (go to question 44) Less than once per week Once per week 1-2 days per week 3-4 days per week 5-6 days per week Every day Don't know
41.	What do you mostly drink?	☐ ☐ ☐ ☐ ☐ ☐ ☐	Light beer Beer Wine Spirits Fortified wine Other Don't know
42.	On days when you have a drink, how many drinks do you usually have?	☐ ☐ ☐ ☐ ☐ ☐	1-2 3-4 5-8 9-12 13 or more Don't know
43.	Has there ever been a time in your life when you regularly drank four or more alcoholic drinks a day?	☐ ☐ ☐	Yes No Don't know

BIOLOGICAL FATHER			
44.	In what country were you born?	☐ ☐	Australia Other (specify) : _____
45.	What is your ethnic origin? (provide more than one ethnic group if applicable, eg. if your mother is Caucasian and your father is East Asian, then tick both boxes).	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	Caucasian (European) East Asian Indian/ Pakistani/ Sri Lankan African Melanesian/ Polynesian Middle Eastern Indigenous Australian South American Other (specify): _____ Don't know
46.	In general, would you say your health is…?	☐ ☐ ☐ ☐ ☐	Excellent Good Fair Poor Very Poor
Has a doctor advised you that you have any of the following conditions:			
47.	High Blood Pressure?	☐ ☐ ☐	Yes No (go to question 48) Don't know
	a) When was it first diagnosed?		☐☐ years ago

	b) For how many years has it been treated with medication?		☐☐ years
48.	Diabetes?	☐ ☐ ☐	Yes No (go to question 49) Don't know
	a) When was it first diagnosed?		☐☐ years ago
	b) In what year did you begin and finish each type of treatment? (if currently on treatment put 7777 as year finished)		
	Diet alone: started _____ finished _____		☐ Yes ☐ No ☐ Don't know
	Tablets: started _____ finished _____		☐ Yes ☐ No ☐ Don't know
	Insulin: started _____ finished _____		☐ Yes ☐ No ☐ Don't know
	No treatment		☐ Yes ☐ No ☐ Don't know
49.	High Cholesterol?	☐ ☐ ☐	Yes No (go to question 50) Don't know
	a) When was it first diagnosed?		☐☐ years ago
	b) Are you taking tablets?	☐ ☐ ☐ ☐ ☐ ☐	Gemfibrozil (lopid, ausgem) Fluvastatin (lescol, vastin) Simvastatin (lipex, zocor) Other (please specify): _____ No Don't know
50.	Asthma?	☐ ☐ ☐	Yes No (go to question 51) Don't know
	a) When was it first diagnosed?		☐☐ years ago
51.	Angina?	☐ ☐ ☐	Yes No (go to question 52) Don't know
	a) When was it first diagnosed?		☐☐ years ago
	b) Was the diagnosis confirmed with an ECG?		☐ Yes ☐ No ☐ Don't know
	c) Name and address of Dr. who made diagnosis?		Name: _____ Address: _____ _____ Suburb: _____ Post Code: _____
	d) How often do you take anginine tablets or sprays?	OR	☐☐ times per day ☐☐ times per month
52.	Heart attack?	☐ ☐ ☐	Yes No (go to question 53) Don't know

	a) When was it first diagnosed?		☐☐ years ago
	b) Was the diagnosis confirmed with an ECG?		☐ Yes ☐ No ☐ Don't know
	c) Was it confirmed with a blood test?		☐ Yes ☐ No ☐ Don't know
	d) Name and address of Dr. who made diagnosis?		Name: _____ Address: _____ _____ Suburb: _____ Post Code: _____
	e) Were you admitted to hospital?		☐ Yes ☐ No ☐ Don't know
	f) For how long?		☐☐ days
	g) How was your heart attack treated	☐ ☐ ☐ ☐ ☐	Bypass Angioplasty Pacemaker Valve Replacement Other (specify) _____
	h) How many years ago?		☐☐ years ago
53.	Stroke?	☐ ☐ ☐	Yes No (go to question 54) Don't Know
	a) When was it first diagnosed?		☐☐ years ago
	b) Was the diagnosis confirmed with a CT scan?		☐ Yes ☐ No ☐ Don't know
	c) Name and address of Dr. who made diagnosis?		Name: _____ Address: _____ _____ Suburb: _____ Post Code: _____
	d) Were you admitted to hospital?		☐ Yes ☐ No ☐ Don't know Hospital _____ for ☐☐ days
	e) How did the stroke affect you?		☐Mild ☐Moderate
	f) Part of body affected	☐ ☐ ☐ ☐ ☐	Arm ☐ right ☐ left Leg ☐ right ☐ left Speech Other (specify) _____ Don't know
	g) How well have you recovered from the stroke?		_____ % recovery (100% is full recovery)
	h) How long did it take?		☐☐ months

	i) Which treatment did you receive?	☐ ☐ ☐ ☐	Aspirin, clopidogrel, persantin Anticoagulation (heparin, clexane and warfarin) None Don't know
54.	Have you ever smoked cigarettes, cigars or a pipe regularly?	☐ ☐ ☐	Yes No (go to question 59) Don't know
55.	If yes, which of the following have you ever regularly smoked:		
	a) Cigarettes (ready made)	Age ☐☐ to age ☐☐	
	b) Cigarettes (roll your own)	Age ☐☐ to age ☐☐	
	c) Tobacco	Age ☐☐ to age ☐☐	
	d) Pipe	Age ☐☐ to age ☐☐	
	e) Cigars	Age ☐☐ to age ☐☐	
56.	Have you given up smoking?	☐ ☐ ☐	Yes No (go to question 58) Don't Know
57.	How much did you usually smoke a week before you stopped?		☐☐ Packs of manufactured cigarettes (20 per pack) ☐☐ Packets of hand-rolled cigarettes ☐☐ Cigars ☐☐ Packets of pipe tobacco Go to question 59.
58.	How much do you smoke per week currently?		☐☐ Packs of manufactured cigarettes (20 per pack) ☐☐ Packets of hand-rolled cigarettes ☐☐ Cigars ☐☐ Packets of pipe tobacco
59.	How often do you have an alcoholic drink?	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	Never (go to question 63) Less than once per week Once per week 1-2 days per week 3-4 days per week 5-6 days per week Every day Don't know
60.	What do you mostly drink?	☐ ☐ ☐ ☐ ☐ ☐ ☐	Light beer Beer Wine Spirits Fortified wine Other Don't know

61.	On days when you have a drink, how many drinks do you usually have?	☐ ☐ ☐ ☐ ☐ ☐	1-2 3-4 5-8 9-12 13 or more Don't know
62.	Has there ever been a time in your life when you regularly drank four or more alcoholic drinks a day?	☐ ☐ ☐	Yes No Don't know

63. We would like to know whether other family members including the parents have eye conditions requiring correction with glasses, or contact lenses. Please fill out the table with reference to your child's biological family members. As a guide: indicate in the second column whether any family member has ever worn glasses or contact lenses. If your answer is no, then go to the next relative in the row below. If your answer is yes, please fill out the rest of the information in the row.

Family member	**Does he/she wear glasses or contact lenses?**	**At what age did he/she start wearing glasses?**	**What does he/she wear glasses or contact lens primarily for?**	**Do they have astigmatism?**
Father	☐ Yes: Glasses or contact lenses (please circle) ☐ No (go to next person) ☐ Don't know		☐ Seeing clearly in distance (e.g., television, movies) ☐ Reading, working at a computer, or other close work ☐ Equally important for distance and close work.	☐ Yes ☐ No ☐ Don't know
Mother	☐ Yes: Glasses or contact lenses (please circle) ☐ No (go to next person) ☐ Don't know		☐ Seeing clearly in distance (e.g., television, movies) ☐ Reading, working at a computer, or other close work ☐ Equally important for distance and close work.	☐ Yes ☐ No ☐ Don't know
Father's father	☐ Yes: Glasses or contact lenses (please circle) ☐ No (go to next person) ☐ Don't know		☐ Seeing clearly in distance (e.g., television, movies) ☐ Reading, working at a computer, or other close work ☐ Equally important for distance and close work.	☐ Yes ☐ No ☐ Don't know
Father's mother	☐ Yes: Glasses or contact lenses (please circle) ☐ No (go to next person) ☐ Don't know		☐ Seeing clearly in distance (e.g., television, movies) ☐ Reading, working at a computer, or other close work ☐ Equally important for distance and close work.	☐ Yes ☐ No ☐ Don't know

Mother's father	☐ Yes: Glasses or contact lenses (please circle) ☐ No (go to next person) ☐ Don't know		☐ Seeing clearly in distance (e.g., television, movies) ☐ Reading, working at a computer, or other close work ☐ Equally important for distance and close work.	☐ Yes ☐ No ☐ Don't know
Mother's mother	☐ Yes: Glasses or contact lenses (please circle) ☐ No (go to next person) ☐ Don't know		☐ Seeing clearly in distance (e.g., television, movies) ☐ Reading, working at a computer, or other close work ☐ Equally important for distance and close work.	☐ Yes ☐ No ☐ Don't know
Child's Sibling – Brother (d.o.b. _____)	☐ Yes: Glasses or contact lenses (please circle) ☐ No (go to next person) ☐ Don't know		☐ Seeing clearly in distance (e.g., television, movies) ☐ Reading, working at a computer, or other close work ☐ Equally important for distance and close work.	☐ Yes ☐ No ☐ Don't know
Child's Sibling – Sister (d.o.b. _____)	☐ Yes: Glasses or contact lenses (please circle) ☐ No (go to next person) ☐ Don't know		☐ Seeing clearly in distance (e.g., television, movies) ☐ Reading, working at a computer, or other close work ☐ Equally important for distance and close work.	☐ Yes ☐ No ☐ Don't know
Child's Sibling – Brother (d.o.b. _____)	☐ Yes: Glasses or contact lenses (please circle) ☐ No (go to next person) ☐ Don't know		☐ Seeing clearly in distance (e.g., television, movies) ☐ Reading, working at a computer, or other close work ☐ Equally important for distance and close work.	☐ Yes ☐ No ☐ Don't know
Child's Sibling – Sister (d.o.b. _____)	☐ Yes: Glasses or contact lenses (please circle) ☐ No (go to next person) ☐ Don't know		☐ Seeing clearly in distance (e.g., television, movies) ☐ Reading, working at a computer, or other close work ☐ Equally important for distance and close work.	☐ Yes ☐ No ☐ Don't know

SECTION 2

This is repeated for each child being examined.

CHILD No: 1 2 3 (please circle)/ CHILD'S NAME: _____			
General Information			
Questions 1- 3 may not need to be answered if BLUE BOOK has been provided.			
1.	Was your child born…?	☐ ☐ ☐ ☐	Late (42 weeks or more) On time (37-41 weeks gestation) Early (33-36 weeks gestation) Very early (32 weeks or less)
2.	Was your child born…?	☐ ☐ ☐	In a hospital or birthing centre? Name of Hospital: _____ Suburb: _____ State: _____ At home Other (please describe) _____ _____
3.	How much did your child weigh at birth?	☐☐☐☐ grams ☐ Don't know	
4.	Was your child admitted to a Neonatal Intensive Care Unit (NICU) after birth?	☐ ☐ ☐	Yes No Don't know
5.	Was your child admitted to a Special Care Nursery (SCN) after birth?	☐ ☐ ☐	Yes No Don't know
6.	During which week/month of pregnancy did you first visit a doctor?	☐☐ weeks OR ☐ months ☐ Don't know	
7.	During pregnancy did a doctor ever tell you that you had any of the following?		
	a) Toxaemia or pre-eclampsia	☐ ☐ ☐	Yes, which month? _____ No Don't know
	b) Anaemia or low blood count	☐ ☐ ☐	Yes, which month? _____ No Don't know
	c) High blood pressure that developed during pregnancy, but went away after the pregnancy was over	☐ ☐ ☐	Yes, which month? _____ No Don't know
	d) Gestational diabetes	☐ ☐ ☐	Yes, which month? _____ No Don't know

	e) Any other problem during the pregnancy (specify)_____	☐ ☐ ☐	Yes, which month? _____ Which child/children? _____ No Don't know
8.	At any time during the pregnancy with your child did you smoke?	☐ ☐ ☐	Yes No (go to question 11) Don't know
9.	During which months of the pregnancy with your child did you smoke? (Tick all months that apply.)	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	Month 1 Month 2 Month 3 Month 4 Month 5 Month 6 Month 7 Month 8 Month 9 All Don't know
10.	On average, how many cigarettes per day did you smoke?	☐☐ ☐	☐☐ cigarettes per day Don't know
11.	At any time during the pregnancy with your child did you drink alcohol?	☐ ☐ ☐	Yes No (go to question 15) Don't know
12.	During which months of the pregnancy with your child did you drink alcohol?	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	Month 1 Month 2 Month 3 Month 4 Month 5 Month 6 Month 7 Month 8 Month 9 All Don't know
13.	During the months you drank, how many days a week did you drink <u>or</u> if you only drank occasionally how many times in the month?	☐☐ ☐☐ OR ☐	☐☐ days per week ☐☐ days per month Don't know
14.	On average, how many drinks per day did you have?	☐☐ ☐	☐☐ drinks per day Don't know

History of Health Conditions

15.	Has a doctor ever diagnosed your child with a serious illness (such as any of the below)?						
	a) Asthma	☐	Yes	☐	No	☐	Don't know
	b) Chronic allergies or sinus trouble	☐	Yes	☐	No	☐	Don't know
	c) Mental retardation	☐	Yes	☐	No	☐	Don't know
	d) Cerebral palsy	☐	Yes	☐	No	☐	Don't know
	e) Down syndrome	☐	Yes	☐	No	☐	Don't know
	f) Very high fever that caused convulsions or seizures	☐	Yes	☐	No	☐	Don't know
	g) Other convulsions or seizures	☐	Yes	☐	No	☐	Don't know
	h) Coordination problem, motor delay, muscle weakness or paralysis	☐	Yes	☐	No	☐	Don't know
	i) Any heart condition	☐	Yes	☐	No	☐	Don't know
	j) Foetal alcohol syndrome	☐	Yes	☐	No	☐	Don't know
	k) Speech or hearing problems	☐	Yes	☐	No	☐	Don't know
	l) Attention or learning problems	☐	Yes	☐	No	☐	Don't know
	m) Developmental delay	☐	Yes	☐	No	☐	Don't know
	n) Diabetes	☐	Yes	☐	No	☐	Don't know
	o) Tumour or cancer	☐	Yes	☐	No	☐	Don't know
	p) Meningitis or encephalitis	☐	Yes	☐	No	☐	Don't know
	q) Headaches or migraine	☐	Yes	☐	No	☐	Don't know
	r) Other problems (specify) _____						

History of Ocular Conditions

16.	During the past 12 months have you noticed your child frequently squinting/ screwing up their face to concentrate?	☐ ☐ ☐	Yes No Don't know
17.	During the past 12 months has your child had difficulty drawing or colouring, besides not staying in the lines?	☐ ☐ ☐ ☐	Yes No Too Young Don't know
18.	Does your child close one eye or screw up his/her eyes when he/she is in bright sun light?	☐ ☐ ☐	Yes No Don't know
19.	Does your child close or cover one eye when (he/she) is concentrating on a task?	☐ ☐ ☐	Yes No Don't know
20.	Have you ever noticed one or both eyelids drooping?	☐ ☐ ☐	Yes No Don't know

21.	Have you noticed any thing else your child may do related to his/her eyesight?	☐ ☐ ☐	Yes (specify) _____ _____ No Don't know
22.	When was your child's last complete eye examination, one that included dilating of pupils where the doctor used bright lights to look in the back of his/her eyes?	☐ ☐ ☐ ☐ ☐	Never Within the past 12 months 1-3 years ago More than 3 years ago Don't know
23.	Amblyopia is poor vision in an eye that cannot be corrected with glasses or contact lenses and the eye looks normal. Has a doctor ever told you that your child had amblyopia or a lazy eye?	☐ ☐ ☐	Yes No (go to question 27) Don't know
24.	Was that in his/her right eye, left eye, or both eyes?	☐ ☐ ☐ ☐	Right eye Left eye Both eyes Don't know
25.	Has your child ever been treated for amblyopia?	☐ ☐ ☐	Yes No (go to question 27) Don't know
26.	What treatment(s) did your child receive?		

	a) Glasses or contact lenses	☐	Yes	☐	No	☐	Don't know
	b) Patching	☐	Yes	☐	No	☐	Don't know
	c) Eye drops	☐	Yes	☐	No	☐	Don't know
	d) Vision therapy	☐	Yes	☐	No	☐	Don't know
	e) Orthoptic treatment	☐	Yes	☐	No	☐	Don't know
	f) Other (specify) _____						

27.	Did you or did any of your child's relatives have amblyopia?	☐ ☐ ☐	Yes No (go to question 29) Don't know
28.	Which relatives? We are only interested in blood relatives.		

	a) Child's biological mother	☐	Yes	☐	No	☐	Don't know
	b) Child's biological father	☐	Yes	☐	No	☐	Don't know
	c) Child's biological sister	☐	Yes	☐	No	☐	Don't know
	d) Child's biological brother	☐	Yes	☐	No	☐	Don't know

29.	Strabismus (squint) is a condition in which the eyes are not properly lined-up. This happens when one eye looks straight ahead and the other eye crosses in or wanders out. Has a doctor ever told you that your child had strabismus?	☐ ☐ ☐	Yes No (go to question 33) Don't know
30.	Was that in his/her right eye, left eye, or both eyes?	☐ ☐ ☐ ☐	Right eye Left eye Both eyes Don't know

31.	Has your child ever been treated for strabismus (squint)?	☐	Yes No (go to question 33) Don't know				
32.	What treatment or treatments did your child receive?						
	a) Glasses or contact lenses	☐	Yes	☐	No	☐	Don't know
	b) Eye muscle surgery	☐	Yes	☐	No	☐	Don't know
	c) Patching	☐	Yes	☐	No	☐	Don't know
	d) Eye drops	☐	Yes	☐	No	☐	Don't know
	e) Orthoptic treatment	☐	Yes	☐	No	☐	Don't know
	f) Vision therapy	☐	Yes	☐	No	☐	Don't know
	g) Botulinum injections	☐	Yes	☐	No	☐	Don't know
	h) Other (specify) _____						
33.	Did you or did any of your child's relatives have strabismus (squint)?						
	a) Child's biological mother	☐	Yes	☐	No	☐	Don't know
	b) Child's biological father	☐	Yes	☐	No	☐	Don't know
	c) Child's biological sister	☐	Yes	☐	No	☐	Don't know
	d) Child's biological brother	☐	Yes	☐	No	☐	Don't know
34.	Has a doctor ever told you that your child has myopia or nearsightedness or needs to wear glasses to see far away?	☐	Yes No (go to question 37) Don't know				
35.	Was that in his/her right eye, left eye, or both eyes?	☐	Right eye Left eye Both eyes Don't know				
36.	Has your child ever been treated for his/her myopia or nearsightedness?	☐	Yes No Don't know				
37.	Does your child wear glasses?	☐	Yes No (go to question 40) Don't know				
38.	How old was your child when he/she began wearing glasses?	☐☐	years ☐☐ months Don't know				
39.	Does he/she need glasses primarily for:	☐	Viewing things clearly in the distance (e.g., television or the blackboard) Reading or other close work Equally important for distance and close work Don't know				

Eye Care			
40.	Has your child ever seen an eye practitioner(s)?	☐ ☐ ☐	Yes (please provide details below) No (go to question 43) Don't know
	a) Ophthalmologist	Name: _____ Suburb: _____ Date Last Seen: _____	
	b) Optometrist	Name: _____ Suburb: _____ Date Last Seen: _____	
	c) Orthoptist (Eye Therapist)	Name: _____ Suburb: _____ Date Last Seen: _____	
	d) Other/Don't know	Name: _____ Suburb: _____ Date Last Seen: _____	
41.	Which eye practitioner does your child see most often?	☐ ☐ ☐ ☐	a) Ophthalmologist b) Optometrist c) Orthoptist (Eye Therapist) d) Other/Don't know
42.	How often is that eye practitioner seen? (Refer to the eye practitioner that the child sees most often.)	☐ ☐ ☐ ☐	More than once in 6 months Once a year Every 6 months Less than once a year
43.	Has a doctor ever told you that your child has: (if yes, specify date diagnosed and treatment received)		
	a) Cataracts	☐ Yes ☐ No ☐ Don't know Date diagnosed: _____ Treatment received: _____	
	b) Glaucoma	☐ Yes ☐ No ☐ Don't know Date diagnosed: _____ Treatment received: _____	

	c) Retinopathy of prematurity	☐ Yes	☐ No	☐ Don't know
		Date diagnosed: _____ Treatment received: _____ _____		
	d) Eye tumour or retinoblastoma	☐ Yes	☐ No	☐ Don't know
		Date diagnosed: _____ Treatment received: _____ _____		
	e) Optic nerve hypoplasia	☐ Yes	☐ No	☐ Don't know
		Date diagnosed: _____ Treatment received: _____ _____		
	f) Nasolacrimal/tear duct blocked	☐ Yes	☐ No	☐ Don't know
		Date diagnosed: _____ Treatment received: _____ _____		
	g) Cortical visual impairment	☐ Yes	☐ No	☐ Don't know
		Date diagnosed: _____ Treatment received: _____ _____		
44.	What other eye or vision problems has he/she had?	(specify) _____ _____ _____		
45.	What treatment did your child receive?	(specify) _____ _____ _____		
46.	When did your child receive this treatment?	(specify) _____ _____ _____		

Outdoors			
47.	Does your child wear a hat that shades their face when going outside?	☐ ☐ ☐ ☐ ☐	All the time Most of the time Some of the time Never Don't know
48.	Does your child wear sunglasses when outside?	☐ ☐ ☐ ☐ ☐	All the time Most of the time Some of the time Never Don't know
49.	Do you ever take your child outside in a stroller or pram?	☐ ☐ ☐	Yes No (go to question 55) Don't know
50.	Does the pram/stroller have a top sun/weather canopy or hood?	☐ ☐ ☐	Yes No Don't know
51.	Do you use the weather canopy (ie. fully extend it) when going outside?	☐ ☐ ☐ ☐ ☐	All the time Most of the time Some of the time Never Don't know
52.	Does the pram/stroller have a totally covering sun/insect shade (often black mesh)?	☐ ☐ ☐	Yes No Don't know
53.	Do you use the sun/insect shade (ie. pull it over the front of the stroller/pram) when going outside?	☐ ☐ ☐ ☐ ☐	All the time Most of the time Some of the time Never Don't know
54.	Do you use an additional cover/shade such as a wrap/cloth to cover the front of the stroller/pram?	☐ ☐ ☐ ☐ ☐	All the time Most of the time Some of the time Never Don't know
55.	Do you have sunshades on the rear windows of your car?	☐ ☐ ☐	Yes No Don't know
56.	Do you have a car seat or car-capsule with a sun shade?	☐ ☐ ☐	Yes No Don't know
57.	Has your child ever had a case of sunburn?	☐ ☐ ☐ ☐ ☐	Once Twice Three times or more Never Don't know

58.	On average, how many **hours per day** does your child sleep?	☐	At night ☐☐ hours In the morning ☐☐ hours In the afternoon ☐☐ hours Don't know
59.	On average, how many **hours per day** would you say your child spends outdoors?	☐	During the week ☐☐ hours At the weekend ☐☐ hours Don't know

Activities questions – indoors

We would like to find out what kind of activities your child does. Some of these activities may not be appropriate for the age of your child, if so, tick the box marked "my child is too young".

60.	On average, how many **hours per day** does your child:		
	a) Read, or is read to?	☐ ☐ ☐ ☐ ☐ ☐	1 hour or more ½ hour or more, but less than 1 hour Less than ½ hour Never My child is too young Don't know
	b) Draw or paint?	☐ ☐ ☐ ☐ ☐ ☐	1 hour or more ½ hour or more, but less than 1 hour Less than ½ hour Never My child is too young Don't know
	c) Play with computers?	☐ ☐ ☐ ☐ ☐ ☐	1 hour or more ½ hour or more, but less than 1 hour Less than ½ hour Never My child is too young Don't know
	d) Play with hand-held computers or mobile phone games?	☐ ☐ ☐ ☐ ☐ ☐	1 hour or more ½ hour or more, but less than 1 hour Less than ½ hour Never My child is too young Don't know
	e) Play with toys?	☐ ☐ ☐ ☐ ☐ ☐ ☐	2 hours or more 1 hour or more ½ hour or more, but less than 1 hour Less than ½ hour Never My child is too young Don't know

	f) Watch television, DVDs, videos, including playing games (playstation/Wii/XBox etc)?	☐ 2 hours or more ☐ 1 hour or more ☐ ½ hour or more, but less than 1 hour ☐ Less than ½ hour ☐ Never ☐ My child is too young ☐ Don't know
There may be some other **indoor** activities that your child does. These could include attending kindergym, gymberoo or dancing, indoor swimming, playing a musical instrument or going to academic classes.		
61.	Are there any indoor activities like these that your child does on a **regular** basis? 'Regular' means once a week or more.	☐ Yes ☐ No (go to question 63) ☐ Don't know
62.	Name the activity, and indicate the **hours per week** that the child spends in that activity.	Activity: _____ for ☐☐ hours per week Activity: _____ for ☐☐ hours per week Activity: _____ for ☐☐ hours per week Activity: _____ for ☐☐ hours per week
63.	Some **indoor** activities that your child does are on an **irregular or infrequent** basis. Are there any other indoor activities that your child does on an **irregular** basis? 'Irregular' means less often than once a week.	☐ Yes ☐ No (go to question 65) ☐ Don't know
64.	Name the activity, and indicate the **hours per week** that the child spends in that activity.	Activity: _____ for ☐☐ hours per week Activity: _____ for ☐☐ hours per week Activity: _____ for ☐☐ hours per week Activity: _____ for ☐☐ hours per week

Child's Development			
65.	Do you have any concerns about your child's learning and development?	☐ ☐ ☐ ☐	Yes A little No (go to question 67) Don't know
66.	What are your concerns?	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	Seems behind Can't do what other kids the same age can Immature Learns slowly Late in learning to do things Does not learn Other (specify) _____ _____ Don't know
67.	Do you have any concerns about how your child talks and makes speech sounds?	☐ ☐ ☐ ☐	Yes A little No (go to question 69) Don't know
68.	What are your concerns?	☐ ☐ ☐ ☐ ☐ ☐ ☐	Not talking like he/she should Uses short sentences Can't always say what he/she means Doesn't always make sense Can't talk clearly Nobody understands what he/she is saying except family members Other (specify) _____ _____ Don't know
69.	Do you have any concerns about how your child understands what you say?	☐ ☐ ☐ ☐	Yes A little No (go to question 71) Don't know
70.	What are your concerns?	☐ ☐ ☐ ☐	Doesn't understand what you say Doesn't listen well Other (specify):_____ _____ Don't know
71.	Some children may have difficulty hearing and/or distinguishing sounds and voices, even with hearing aids. Do you think that your child has/or has had difficulty with this?	☐ ☐ ☐	Yes No Don't know
72.	Do you have any concerns about how your child uses his or her hands and fingers to do things?	☐ ☐ ☐ ☐	Yes A little No (go to question 73) Don't know

73.	What are your concerns?	☐ ☐ ☐ ☐ ☐ ☐ ☐	Can't stay in lines when colours Can't write his/her name Can't draw shapes Can't hold a pencil right Can't get food to mouth/messy eater Other (specify) _____ _____ Don't know
74.	Do you have any concerns about how your child uses his or her arms and legs?	☐ ☐ ☐ ☐	Yes A little No (go to question 76) Don't know
75.	What are you concerns?	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	Clumsy Walks funny Can't ride a bike yet Falls a lot Limps Poor balance Other (specify): _____ _____ Don't know
76.	Some children may have trouble learning to walk, move or work with small objects. Do you think that your child has/or has had difficulty with this?	☐ ☐ ☐	Yes No Don't know
77.	Do you have any concerns about how your child behaves?	☐ ☐ ☐ ☐	Yes A little No (go to question 79) Don't know
78.	What are your concerns?	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	Stubborn Over-active Short attention span Spoiled Aggravating Throws temper tantrums Only does what he/she wants Other (specify): _____ _____ Don't know
79.	Do you have any concerns about how your child gets along with others?	☐ ☐ ☐ ☐	Yes A little No (go to question 81) Don't know

80.	What are your concerns?	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	Wants to be left alone Mood swings, clingy Whiny Bothered by changes Disinterested in usual things Easily lead Acts mean Easily frustrated Bossy Shy Class clown Angry Hates me Other (specify): _____ _____ Don't know
81.	Do you have any concerns about how your child is learning to do things for (himself/herself)?	☐ ☐ ☐ ☐	Yes A little No (go to question 83) Don't know
82.	What are your concerns?	☐ ☐ ☐ ☐ ☐ ☐ ☐	Won't do things for him/herself Won't tell me when he/she is wet Not toilet trained yet Still wants a bottle Can't get dressed by him/herself Other (specify): _____ _____ Don't know
83.	Does your child attend preschool?	☐ ☐	Yes No (go to question 86)
84.	Do you have any concerns about how your child is learning preschool or school skills?	☐ ☐ ☐ ☐	Yes A little No (go to question 86) Don't know
85.	What are your concerns?	☐ ☐ ☐ ☐ ☐ ☐ ☐	Can't write his/her name Doesn't know colours or numbers Difficulty learning shapes Just not learning to read Can't remember letter sounds Other (specify): _____ _____ Don't know
86.	Do you have any other concerns about your child?	☐ ☐ ☐ ☐	Yes A little No (go to question 88) Don't know

87.	What are your concerns?	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	Ear infections Asthma Small for age Sick a lot I don't think he/she hears well He/she gets up too close to the TV and I worry about his/her sight Other (specify): _____ _____ Don't know

Nutrition

88.	Has your child ever been breastfed?	☐ ☐ ☐	Yes No (go to question 95) Don't know				
89.	Was your child breastfed when he/she first came home from hospital?	☐ ☐ ☐ ☐	Yes No Not born in hospital Don't know				
90.	Has your child ever been given infant formula regularly (at least once a day)?	☐ ☐ ☐	Yes No (go to question 92) Don't know				
91.	At what age was your child first given infant formula regularly?	☐☐ OR ☐☐ ☐	weeks months Less than 1 week Don't know				
92.	Since this time yesterday, has your child received any of the following?						
	a) Vitamins, mineral supplements, medicine	☐	Yes	☐	No	☐	Don't know
	b) Plain water	☐	Yes	☐	No	☐	Don't know
	c) Sweetened or flavoured water	☐	Yes	☐	No	☐	Don't know
	d) Fruit juice	☐	Yes	☐	No	☐	Don't know
	e) Tea or infusion	☐	Yes	☐	No	☐	Don't know
	f) Infant formula	☐	Yes	☐	No	☐	Don't know
	g) Tinned, powdered or fresh milk	☐	Yes	☐	No	☐	Don't know
	h) Solid or semi-solid food	☐	Yes	☐	No	☐	Don't know
	i) Other (specify) _____						
93.	Is your child currently being breastfed?	☐ ☐ ☐	Yes No Don't know				

94.	Including times of weaning, what is the total time that your child was breastfed?	OR ☐ ☐	☐☐ weeks ☐☐ months Less than one week Don't know
95.	Has your child ever been given solid food?	☐ ☐ ☐	Yes No (end of survey) Don't know
96.	At what age was your child first given solid food regularly?	OR ☐ ☐ ☐	☐☐ weeks ☐☐ months Never given solid food/not yet started Started but not regular Don't know
97.	How many serves of vegetables does your child usually eat each day? (one serve=1/2 cup cooked vegetables or 1 cup of salad vegetables)	OR ☐ ☐	☐ serves per day ☐ serves per week Doesn't eat vegetables Don't know
98.	How many serves of fruit does your child usually eat each day? (One serve=1 medium piece or 2 small pieces of fruit or 1 cup of diced pieces)	OR ☐ ☐	☐ serves per day ☐ serves per week Doesn't eat fruit Don't know
99.	How often does your child eat red meat, such as beef or lamb? Include all steaks, chops, roasts, mince, stir fries and casseroles. Do not include pork or chicken.	OR OR ☐ ☐	☐ times per day ☐ times per week ☐ times per month Rarely/never Don't know
100.	How often does your child eat meat products such as sausages, frankfurters, devon, ham, hamburgers or chicken nuggets?	OR OR ☐ ☐	☐ times per day ☐ times per week ☐ times per month Rarely/never Don't know
101.	How often does your child eat hot chips, French fries, wedges or fried potatoes?	OR OR ☐ ☐	☐ times per day ☐ times per week ☐ times per month Rarely/never Don't know
102.	How often does your child eat potato crisps or other salty snacks (such as Twisties or corn chips)?	OR OR ☐ ☐	☐ times per day ☐ times per week ☐ times per month Rarely/never Don't know

103.	How often does your child have meals or snacks such as burgers, pizza, chicken, or chips from places like McDonalds, Hungry Jacks, Pizza Hut, KFC, Red Rooster or local takeaway food places?	OR OR ☐ ☐	☐ times per day ☐ times per week ☐ times per month Rarely/never Don't know
104.	How often does your child have snack foods such as sweet or savoury biscuits, cakes, donuts or muesli bars?	OR OR ☐ ☐	☐ times per day ☐ times per week ☐ times per month Rarely/never Don't know
105.	How often does your child eat confectionary, such as lollies and chocolate?	OR OR ☐ ☐	☐ times per day ☐ times per week ☐ times per month Rarely/never Don't know
106.	How often does your child usually have something for breakfast?	☐ OR OR ☐ ☐	Everyday ☐ times per week ☐ times per month Rarely/never Don't know
107.	How often does your child eat dinner in front of the television?	☐ OR OR ☐ ☐	Everyday ☐ times per week ☐ times per month Rarely/never Don't know
108.	How many cups of milk does your child usually drink in a day? (1 cup=250ml, a household tea cup) (Includes cow's milk, soy milk, milk on cereal, flavoured milks)	OR OR ☐ ☐	☐ cups per day ☐ cups per week ☐ cup per month Doesn't drink milk (go to question 110) Don't know
109.	What type of milk does your child usually consume?	☐ ☐ ☐ ☐ ☐ ☐ ☐	Whole milk (regular, full-cream) Low/reduced fat milk Skim milk Evaporated or sweetened condensed Soy milk, regular (specify) _____ Soy milk, reduced fat (specify) _____ Other (specify) _____

110.	How many cups of soft drink, cordials, or sports drink, such as lemonade or Gatorade does your child usually drink? (1 cup=250ml. One can of soft drink = 1 ½ cups. One 500ml bottle of Gatorade = 2 cups)	OR OR ☐ ☐	☐ cups per day ☐ cups per week ☐ cup per month Doesn't drink soft drink Don't know
111.	How many cups of diet soft drink or diet cordial such as diet coke or diet sprite or coke zero does your child usually drink? (1 cup=250ml. One can of soft drink = 1 ½ cups. One 500ml bottle of Gatorade = 2 cups)	OR OR ☐ ☐	☐ cups per day ☐ cups per week ☐ cup per month Doesn't drink diet soft drink Don't know
112.	How many cups of fruit juice does your child usually drink? (1 cup=250ml, a household tea cup or 1 large popper)	OR OR ☐ ☐	☐ cups per day ☐ cups per week ☐ cup per month Doesn't drink fruit juice Don't know
113.	How many cups of water does your child usually drink in a day? (1 cup=250ml, a household tea cup, 1 average bottle of water = 2 ½ cups)	OR OR ☐ ☐	☐ cups per day ☐ cups per week ☐ cup per month Doesn't drink water Don't know

Appendix 2: NSW Health, My Personal Health Record (Blue book) birth details page

SMR010005

Birth details

To be completed by health professional.

Affix patient label here

Name of child

Name of birth facility

Date of birth / / Time of birth Sex m / f

Maternal information

Mother's name

Pregnancy complications

Blood group Anti D given y / n

Labour Spontaneous / Induced – reason / None – reason

Labour complications

Type of birth ☐ Normal ☐ Breech ☐ Forceps ☐ Caesarean ☐ Vac ext
Other

Neonatal information

Estimated gestation Apgar 1 minute 5 minutes

Abnormalities noted at birth

Problems requiring treatment

Birth weight (kg) Birth length (cm) Birth head circ (cm)

☐ Newborn Hearing Screen (SWIS-H) completed (refer to SWIS-H in this section)

☐ Newborn Bloodspot Screen Test Date / /
Other (specify) Date / /

☐ Vitamin K given ☐ Injection ☐ Oral 1st dose / / 2nd dose / /
3rd dose / /

☐ Hep B immunisation given Date given / /

Discharge information

Post partum complications

Feeding at discharge breast / bottle

Difficulties with feeding

Date of discharge / / Discharge weight (kg) Head circ (cm)

Signature

Designation

Original (White) PHR **Duplicate** (Yellow) ECHC **Triplicate** (Green) Hospital

6.1

Appendix 3:
Neonatal Vision Study Parental Questionnaire

Infant's ID No. _____

UTS
UNIVERSITY OF TECHNOLOGY SYDNEY

The Neonatal Vision Study:

Visual Outcomes for Infants Admitted to Neonatal Intensive Care Units

Parent / Guardian Questionnaire

Questionnaire Guidelines

- Where possible we would like one parent or guardian to take responsibility for completing the questionnaire in consultation with other family members/caregivers.
- Please attempt to answer every question. In some circumstances you will be directed to skip questions because they do not apply to you.
- If you have difficulty with a question, please give the best response you can and make a comment in the margin.
- We understand that some children will not be living with both, or even one of their biological parents, and we ask you to please note this in completing the relevant parts of the questionnaire.
- The majority of questions in this questionnaire are standard questions derived from the Australian Bureau of Statistics (ABS) National Census, the NSW Child Health Survey and other international eye studies.
- Please feel free to ask our staff for assistance. They can be contacted on the telephone numbers below.

Statement of confidentiality

Information that would permit the identification of any person completing this questionnaire will be regarded as strictly confidential. All information provided will be used only for the Neonatal Vision Study and will not be disclosed or released for any other purpose without your consent.

You may correct any personal information provided at any time by contacting:

Felicia Adinanto
Discipline of Orthoptics,
Graduate School of Health,
University of Technology Sydney
Telephone: 9514 4123
Email: felicia.adinanto@uts.edu.au

Neonatal Vision Study: Parent / Guardian Questionnaire

Part 1: General Family and Contact Information

The following section will ask questions regarding your family members and contact details.

General Family Information		
1	What is your full name? (name of person completing questionnaire)	_____ _____
2	What is your relationship to the child/children being tested?	_____
Please provide us with the full name and date of birth of the child participating in the study. If there are multiple children of the same birth who are participating in the study, please also include their details in the spaces provided.		

3a	Child 1 Name: _____ _____ Date of birth: ____ /____ /_____ Gender: M / F	3b	Child 2 Name: _____ _____ Date of birth: ____ /____ /_____ Gender: M / F
3c	Child 3 Name: _____ _____ Date of birth: ____ /____ /_____ Gender: M / F	3d	Child 4 Name: _____ _____ Date of birth: ____ /____ /_____ Gender: M / F

Contact information			
4	What is your full address?	Address:_____ _____ Suburb: _____ Postcode: _____ Is this where the child predominately lives? Yes / No Do you own this home? Yes / No Do you own other properties? Yes, _____ number of properties / No	
5	How long have you lived at this address?	☐☐ Years	☐☐ Months
6	What are your contact details?	Phone: _____ Mobile: _____ Email: _____	
If you move from your current address can you please provide us with the details of two people we can contact to obtain a forwarding address?			
7a	Contact 1 Name: _____ Telephone: _____ Address: _____ _____ _____ Relationship: _____	7b	Contact 2 Name: _____ Telephone: _____ Address: _____ _____ _____ Relationship: _____

Part 2: Parent Information

The following section will ask questions regarding parent employment and health.

Parent education and employment			
8	Parent's occupation(s):	Mother's current occupation: _____ If currently not working, what was the mother's previous occupation: _____ Father's current occupation: _____ If currently not working, what was the father's previous occupation: _____	
9	How would you describe the mother's employment status?	☐	Employed full time (includes self-employment)
		☐	Employed part time (includes self-employment)
		☐	Unemployed
		☐	Home duties
		☐	Student and working
		☐	Student and not working
		☐	Retired
		☐	Unable to work due to health problems
		☐	Pensioner
		☐	Other (please describe): _____
		☐	Don't know
10	How would you describe the father's employment status?	☐	Employed full time (includes self-employment)
		☐	Employed part time (includes self-employment)
		☐	Unemployed
		☐	Home duties
		☐	Student and working
		☐	Student and not working
		☐	Retired
		☐	Unable to work due to health problems
		☐	Pensioner
		☐	Other (please describe): _____

		☐	Don't know
11	What is the highest level of education completed by the mother?	☐	Never attended school
		☐	Some primary school completed
		☐	Some high school completed
		☐	Completed school certificate (Year 10 / 4th form)
		☐	Completed HSC (Year 12 / 6th form)
		☐	TAFE certificate or diploma, including trade certificate
		☐	University, CAE or other tertiary institute degree
		☐	Higher degree including a Masters or PHD
		☐	Other (please describe): _____
		☐	Don't know
12	What is the highest level of education completed by the father?	☐	Never attended school
		☐	Some primary school completed
		☐	Some high school completed
		☐	Completed school certificate (Year 10 / 4th form)
		☐	Completed HSC (Year 12 / 6th form)
		☐	TAFE certificate or diploma, including trade certificate
		☐	University, CAE or other tertiary institute degree
		☐	Higher degree including a Masters or PHD
		☐	Other (please describe): _____
		☐	Don't know
13	What sort of place does your family live in?	☐	Own house
		☐	Own flat/unit
		☐	Rented house
		☐	Rented flat/unit
		☐	With relatives
		☐	Other (please describe): _____
		☐	Don't know

Biological Mother's Health			
14	What country were you born in?		_____
15	What is your ethnic origin? (provide more than one ethnic group if applicable, e.g. if your mother is Caucasian and your father is East Asian, then tick both boxes)	☐	European Caucasian
		☐	East Asian
		☐	Southeast Asian
		☐	Indian/Pakistani/Sri Lankan
		☐	African
		☐	Melanesian / Polynesian
		☐	Middle Eastern
		☐	Indigenous Australian
		☐	South American
		☐	Other (specify): _____
16	Have you been diagnosed or treated for any of the following conditions by a doctor? (You may tick as many are relevant)	☐	High Blood Pressure
		☐	Diabetes
		☐	High Cholesterol
		☐	Asthma
		☐	Angina
		☐	Heart Attack
		☐	Stroke
		☐	Other: _____
		☐	Don't know
17	Do you have any other biological children other than the ones included in this study?	☐	Yes, How many children? _____
		☐	No
18	Have you had any multiple pregnancies? (e.g. twins, triplets etc.)	☐	Yes, How many sets of twins or triplets? _____
		☐	No
19	Have you ever received IVF treatment?	☐	Yes
		☐	No
20	Was the child (children) participating in the study	☐	Yes

	conceived by IVF?	☐	No
21	Have you ever smoked cigarettes, cigars or a pipe regularly?	☐	Yes
		☐	No (Go to question 26)
22	Have you ever given up smoking?	☐	Yes
		☐	No
23	How much did you usually smoke a week before you stopped?	☐☐ Packets of Cigarettes	☐☐ Packets of Hand-rolled cigarettes
		☐☐ Cigars	☐☐ Packets of Pipe tobacco
24	How much do you smoke per week currently?	☐☐ Packets of Cigarettes	☐☐ Packets of Hand-rolled cigarettes
		☐☐ Cigars	☐☐ Packets of Pipe tobacco
25	For how long did you give up smoking?	Approximate dates: __ __/ __ __ / __ __ to __ __/ __ __ / __ __	
26	How often do you have an alcoholic drink?	☐	Never
		☐	Once a year
		☐	Once a month
		☐	1-2 days per week
		☐	3-4 days per week
		☐	5-7 days per week
		☐	Don't Know
27	If you drink alcoholic beverages regularly, was there a time when you gave up drinking?	Approximate dates: __ __/ __ __ / __ __ to __ __/ __ __ / __ __	
28	On days when you have a drink, how many drinks do you usually have?	☐	1-2
		☐	3-4
		☐	5-8
		☐	9-12
		☐	13 or more
		☐	Don't know

Biological Father's Health			
29	What country were you born in?		_____
30	What is your ethnic origin? (provide more than one ethnic group if applicable, e.g. if your mother is Caucasian and your father is East Asian, then tick both boxes)	☐	European Caucasian
		☐	East Asian
		☐	Southeast Asian
		☐	Indian/Pakistani/Sri Lankan
		☐	African
		☐	Melanesian / Polynesian
		☐	Middle Eastern
		☐	Indigenous Australian
		☐	South American
		☐	Other (specify): _____
31	Have you been diagnosed or treated for any of the following conditions by a doctor? (You may tick as many are relevant)	☐	High Blood Pressure
		☐	Diabetes
		☐	High Cholesterol
		☐	Asthma
		☐	Angina
		☐	Heart Attack
		☐	Stroke
		☐	Other: _____
		☐	Don't know
32	Have you ever smoked cigarettes, cigars or a pipe regularly?	☐	Yes
		☐	No (Go to question 19)
33	Have you ever given up smoking?	☐	Yes
		☐	No
34	If you have ever given up smoking, for how long did you give up smoking?	Approximate dates: __ __ / __ __ / __ __ to __ __ / __ __ / __ __	

35	How much did you usually smoke a week before you stopped?	☐☐ Packets of Cigarettes	☐☐ Packets of Hand-rolled cigarettes
		☐☐ Cigars	☐☐ Packets of Pipe tobacco
36	How much do you smoke per week currently?	☐☐ Packets of Cigarettes	☐☐ Packets of Hand-rolled cigarettes
		☐☐ Cigars	☐☐ Packets of Pipe tobacco
37	How often do you have an alcoholic drink?	☐ Never	
		☐ Once a year	
		☐ Once a month	
		☐ 1-2 days per week	
		☐ 3-4 days per week	
		☐ 5-7 days per week	
		☐ Don't Know	
38	If you drink alcoholic beverages regularly, was there a time when you gave up drinking?	Approximate dates: __ __/ __ __ / __ __ to __ __/ __ __ / __ __	
39	On days when you have a drink, how many drinks do you usually have?	☐ 1-2	
		☐ 3-4	
		☐ 5-8	
		☐ 9-12	
		☐ 13 or more	
		☐ Don't know	

Part 3: Family History of Eye Problems

The following section will ask questions regarding the immediate family of the child / children participating in this study.

Family Member		Do they wear glasses or contact lenses?		Age that they started wearing glasses?	What do they wear glasses or contact lens for?		If they have any other eye conditions you are aware of please write these in the space provided for each person.
40a	Mother	☐	Yes		☐	Seeing clearly in the distance. (eg. watching TV)	☐ Visual Impairment/ Blindness ☐ Lazy eye/ Amblyopia ☐ Eye turn/ Strabismus (squint) Other:
		☐	No		☐	Reading, using a computer or other close work	
		☐	Not sure		☐	Equally important for distance and close work	
40b	Father	☐	Yes		☐	Seeing clearly in the distance. (eg. watching TV)	☐ Visual Impairment/ Blindness ☐ Lazy eye/ Amblyopia ☐ Eye turn/ Strabismus (squint) Other:
		☐	No		☐	Reading, using a computer or other close work	
		☐	Not sure		☐	Equally important for distance and close work	
40c	Mother's mother (Maternal Grandmother)	☐	Yes		☐	Seeing clearly in the distance. (eg. watching TV)	☐ Visual Impairment/ Blindness ☐ Lazy eye/ Amblyopia ☐ Eye turn/ Strabismus (squint) Other:
		☐	No		☐	Reading, using a computer or other close work	
		☐	Not sure		☐	Equally important for distance and close work	
40d	Mother's Father (Maternal Grandfather)	☐	Yes		☐	Seeing clearly in the distance. (eg. watching TV)	☐ Visual Impairment/ Blindness ☐ Lazy eye/ Amblyopia ☐ Eye turn/ Strabismus (squint) Other:
		☐	No		☐	Reading, using a computer or other close work	
		☐	Not sure		☐	Equally important for distance and close work	
40e	Father's mother (Paternal Grandmother)	☐	Yes		☐	Seeing clearly in the distance. (eg. watching TV)	☐ Visual Impairment/ Blindness ☐ Lazy eye/ Amblyopia ☐ Eye turn/ Strabismus (squint) Other:
		☐	No		☐	Reading, using a computer or other close work	
		☐	Not sure		☐	Equally important for distance and close work	
40f	Father's Father (Paternal Grandfather)	☐	Yes		☐	Seeing clearly in the distance. (eg. watching TV)	☐ Visual Impairment/ Blindness ☐ Lazy eye/ Amblyopia ☐ Eye turn/ Strabismus (squint) Other:
		☐	No		☐	Reading, using a computer or other close work	
		☐	Not sure		☐	Equally important for distance and close work	

Neonatal Vision Study: Parent / Guardian Questionnaire

Family Member		Do they wear glasses or contact lenses?		Age that they started wearing glasses?	What do they wear glasses or contact lens for?		If they have any other eye conditions you are aware of please write these in the space provided for each person.
41a	Sibling 1: Gender M / F DOB _ _/ _ _ / _ _	☐	Yes		☐	Seeing clearly in the distance. (eg. watching TV)	☐ Visual Impairment/ Blindness ☐ Lazy eye/ Amblyopia ☐ Eye turn/ Strabismus (squint) Other:
		☐	No		☐	Reading, using a computer or other close work	
		☐	Not sure		☐	Equally important for distance and close work	
41b	Sibling 2: Gender M / F DOB _ _/ _ _ / _ _	☐	Yes		☐	Seeing clearly in the distance. (eg. watching TV)	☐ Visual Impairment/ Blindness ☐ Lazy eye/ Amblyopia ☐ Eye turn/ Strabismus (squint) Other:
		☐	No		☐	Reading, using a computer or other close work	
		☐	Not sure		☐	Equally important for distance and close work	
41c	Sibling 3: Gender M / F DOB _ _/ _ _ / _ _	☐	Yes		☐	Seeing clearly in the distance. (eg. watching TV)	☐ Visual Impairment/ Blindness ☐ Lazy eye/ Amblyopia ☐ Eye turn/ Strabismus (squint) Other:
		☐	No		☐	Reading, using a computer or other close work	
		☐	Not sure		☐	Equally important for distance and close work	
41d	Sibling 4: Gender M / F DOB _ _/ _ _ / _ _	☐	Yes		☐	Seeing clearly in the distance. (eg. watching TV)	☐ Visual Impairment/ Blindness ☐ Lazy eye/ Amblyopia ☐ Eye turn/ Strabismus (squint) Other:
		☐	No		☐	Reading, using a computer or other close work	
		☐	Not sure		☐	Equally important for distance and close work	
41e	Sibling 5: Gender M / F DOB _ _/ _ _ / _ _	☐	Yes		☐	Seeing clearly in the distance. (eg. watching TV)	☐ Visual Impairment/ Blindness ☐ Lazy eye/ Amblyopia ☐ Eye turn/ Strabismus (squint) Other:
		☐	No		☐	Reading, using a computer or other close work	
		☐	Not sure		☐	Equally important for distance and close work	
41f	Sibling 6: Gender M / F DOB _ _/ _ _ / _ _	☐	Yes		☐	Seeing clearly in the distance. (eg. watching TV)	☐ Visual Impairment/ Blindness ☐ Lazy eye/ Amblyopia ☐ Eye turn/ Strabismus (squint) Other:
		☐	No		☐	Reading, using a computer or other close work	
		☐	Not sure		☐	Equally important for distance and close work	

Part 4: Child Information

The following section will ask health questions about the child participating in the study. Please fill one of these parts for each of the children participating in the study if there are more than one.

Child number: 1 / 2 / 3 / 4 **Child's Name:**_____

42	At how many weeks of gestation was your child born?	☐☐ Weeks ☐ Unsure	
43	Where was your child born?	☐	In a hospital or birthing centre? Name of Hospital/birthing centre: _____ Suburb: _____ State: _____
		☐	At home
		☐	Other (Please describe): _____ _____
44	How much did your child weigh at birth?	☐☐☐☐ grams	
45	Was this child born at a multiple birth? (e.g. Is your child a twin, triplet, etc.?)	☐	Yes How many children were born? _____
		☐	No
46	During your pregnancy were you or your child diagnosed or treated for any of the following health conditions by a doctor? (You may tick as many are relevant)	☐	High blood pressure
		☐	Gestational diabetes
		☐	High Cholesterol
		☐	Asthma
		☐	Angina
		☐	Toxaemia or pre-eclampsia
		☐	Anaemia or low blood count
		☐	Heart Attack
		☐	Stroke
		☐	Preterm pre-labour rupture of membranes (PROM)
		☐	Antepartum haemorrhage (APH)
		☐	Intrauterine growth restriction (IUGR)
		☐	Foetal distress
		☐	Congenital Anomalies

47	During your pregnancy were you or your child diagnosed or treated for any other health conditions by a doctor?	☐	Please Specify: _____ _____ _____ _____
		☐	Not Sure
48	If your child was admitted to a Special Care Nursery (SCN), how long was your child in SCN?	☐☐☐☐	days
		☐	Not Sure
49	If your child was admitted to a Neonatal Intensive Care Unit (NICU), how long was your child in NICU?	☐☐☐☐	days
		☐	Not Sure
50	Since the birth of your child, has a doctor ever diagnosed your child with any of the following conditions?	☐	Asthma
		☐	Chronic allergies or sinus issues
		☐	Down Syndrome
		☐	Cerebral Palsy
		☐	Coordination problem, motor delay, muscle weakness or paralysis (Please Specify) _____
		☐	Any heart conditions (Please Specify) _____
		☐	Hearing problems
		☐	Foetal alcohol syndrome
		☐	Diabetes
		☐	Meningitis or encephalitis
		☐	Convulsions or Seizures
		☐	Other conditions: _____ _____
		☐	Not Sure