UTS UNIVERSITY OF TECHNOLOGY SYDNEY

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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Signature: Production Note: Signature removed prior to publication. Date: 22/02/2020

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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.

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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