The Effects of Preterm Birth on Visual Function in Childhood

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Abstract

Preterm birth and retinopathy of prematurity (ROP) are associated with reduced visual outcomes in childhood. However, the effects of other neonatal morbidities and perinatal care on visual outcomes in later childhood are relatively unknown. This thesis reports follow-up studies that investigated the long-term effects of preterm birth, neonatal nutrition, ROP and neonatal hyperglycaemia, and, in a follow-up of a randomised controlled trial, the effect of tight glycaemic control treatment of hyperglycaemia, on visual outcomes at 7-10 years of age.

Composite outcomes were used to assess visual function. Overall visual outcome was defined as good vision, no strabismus, and having depth perception without the need for spectacles. Binocular visual outcome assessed oculomotor function and depth perception, while functional visual outcome assessed how well the child could normally see.

Overall visual outcome did not differ between groups in all our follow-up studies. Hyperglycaemia was not associated with an increased incidence of ROP. However, in children who had neonatal hyperglycaemia, high blood glucose concentration was associated with a thicker crystalline lens and reduced visual acuity. Tight glycaemic control of neonatal hyperglycaemia using insulin increased the risk of hypoglycaemia and was associated with reduced binocular visual acuity. A change in nutritional management increased neonatal protein and decreased carbohydrate intake, which was associated with poorer binocular and functional visual outcomes. Children who had ROP as preterm babies had overall visual function similar to children not exposed to ROP and those born at term. However, they were at higher risk of adverse functional visual outcomes and ocular structural changes. Overall, preterm birth was also associated with poorer binocular and functional visual outcomes, and ocular structural changes.

A quarter of children born preterm had signs of functional visual impairment in mid childhood. Although preterm birth, neonatal hyperglycaemia, ROP and neonatal nutrition did not affect overall visual outcomes, these neonatal morbidities were associated with reduced binocular and functional visual development, and ocular structure, which could have ongoing effects on vision in later life. As these morbidities are potentially modifiable, further investigation into perinatal care and neonatal nutrition may improve long term visual outcomes in children born preterm.

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Abbreviations

95% CI	95% confidence intervals
ANOVA	Analysis of variance
ANZNN	Australian and New Zealand Neonatal Network
B4SC	Before school check
BGC	Blood glucose concentration
BPD	Bronchopulmonary dysplasia
BW	Birth weight
cm	Centimetres
CRIB-II score	Clinical Risk Index for Babies score
CRYO-ROP	Cryotherapy for Retinopathy of Prematurity
cyl	Cylinder
D	Dioptres
DC	Cylindrical power in dioptres
DS	Spherical power in dioptres
Δ	Prism dioptres
ETDRS	Early Treatment Diabetic Retinopathy Study
ETROP	Early Treatment for Retinopathy of Prematurity
EVA	Electronic visual acuity tester
EYE-SPY study	Examining Young Eyes for Signs of PrematuritY study
g	Grams
$g.kg^{-1}.day^{-1}$	Grams per kilogram per day
GA	Gestational age
HINT trial	Randomised control trial of tight glycaemic control in very low birth weight hyperglycaemic preterm babies
HUI	Health Utility Index
ICROP	International Classification of Retinopathy of Prematurity
IGF	Insulin-like growth factor
IGFBP	Insulin-like growth factor binding proteins
IQR	Interquartile range
IVH	Intraventricular haemorrhage
IVN	Intravenous nutrition/Parenteral nutrition
$kcal.kg^{-1}.day^{-1}$	Kilocalories per kilogram per day

kg	Kilograms
logMAR	Logarithm of the minimum angle of resolution
µm	Micrometre
µV	Microvolt
MABC-2	Movement Assessment Battery for Children 2nd Edition
$mmol.L^{-1}$	Millimoles per litre
MRI	Magnetic resonance imaging
ms	millisecond
n	Number of participants
NEC	Necrotising enterocolitis
NICU	Neonatal intensive care unit
NZ Dep	New Zealand Deprivation Index
O_2	Oxygen
OCT	Optical coherence tomography
OFC	Occipitofrontal head circumference
OR	Odds ratio
P-value	Probability value
P_aO_2	Arterial partial pressure of oxygen
pERG	Pattern electroretinogram
PIANO study	Protein, Insulin and Neonatal Outcomes Study
PPROM	Preterm premature rupture of membranes
pVEP	Pattern visually evoked potential
PVL	Periventricular leukomalacia
RDK	Random dot kinematograms
RDS	Respiratory distress syndrome
ROP	Retinopathy of prematurity
SD	Standard deviation
SGA	Small for gestational age
SEP	Spherical equivalent power
$Sp0_2$	Peripheral capillary oxygen saturation
TNO	Test for Stereoscopic Vision
$U.kg^{-1}$	Units per kilogram
VA	Visual acuity
VEGF	Vascular endothelial growth factor

VMI	Visual motor integration
WISC	Wechsler Intelligence Scale for Children
z-score	Standard score

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Nature of contribution by PhD candidate	Coordinating the recruitment of term born controls for the visual assessment part of the PIANO study; performed visual assessments and data collection, processing and analysis for the PIANO study (visual assessment) and writing of the thesis chapters.
by PhD candidate (%)	80

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Professor Frank Bloomfield	Conceptualised and designed the PIANO study
Dr Anna Tottman	Conceptualised and designed the PIANO study, coordinated and performed data collection, neonatal data collection, analysed metabolic and developmental data (Primary outcomes for Chapter 3-5)
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Certification by Co-Authors

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1 Introduction

1.1 Preterm Birth

Preterm birth is common: worldwide, approximately 15 million preterm babies are born before 37 weeks' gestational age annually and over 1 million babies die due to complications from preterm birth (Howson et al., 2012). The annual incidence of very preterm birth (at less than 32 weeks gestational age) in New Zealand is 2.5% (Auckland District Health Board., 2016). Since the 1950s, there has been a reduction in neonatal mortality in developed countries, with one perinatal centre showing survival of extremely low birth weight babies (<1000g) increasing from less than 10% in 1959 to over 60% in 2009, and for very low birth weight babies (<1500g) from 50% to over 90% during the same time period (Battin et al., 2012; Stoll et al., 2015). The improvement in survival rates of preterm babies is a result of advances in neonatology and obstetrics such as the introduction of incubators (Baker, 2000) and thermoregulation (Buetow & Klein, 1964; Silverman et al., 1958), mechanical ventilators, antenatal corticosteroids (Brownfoot et al., 2013; Liggins & Howie, 1972; Roberts & Dalziel, 2013), neonatal nutrition (Cornblath et al., 1966; Tizard, 1967; Wu et al., 1967), continuous positive airway pressure support (Gregory et al., 1971; Stevens et al., 2014), surfactants (Fujiwara et al., 1980; Soll, 1998; Soll & Özek, 1997), and probiotics (Alfaleh et al., 2014).

Babies who are born very preterm and survive are at risk of life-long disability (Saigal, 2014) including chronic lung disease (Islam et al., 2015; O'Reilly et al., 2013), cerebral palsy (Gladstone, 2010; Vincer et al., 2014; Wang et al., 2014), and neurodevelopmental disabilities including visual impairment (Philip & Dutton, 2014; Tan et al., 2015), cognitive deficits (Anderson & Doyle, 2008; Hallin et al., 2010; Horwood et al., 1998) and behavioural problems (Hack et al., 1995; Ritchie et al., 2015; Wy et al., 2015). Preterm birth may also be associated with risks of developing diabetes mellitus (Hovi et al., 2007; Kajantie et al., 2015) and cardiovascular disease (Hack et al., 2005; Mathai et al., 2015; Ueda et al., 2014) in later life, and may also affect the health of future offspring (Derraik et al., 2015; Mathai et al., 2013). The long-term effects of preterm birth may be secondary to the effects of perinatal insults to multiple organ systems e.g. growth restriction (Kallankari et al., 2015; Longo et al., 2012; Streimish et al., 2012), and chorioamnionitis (Bolton et al., 2015; Wang et al., 2014); premature exposure to extrauterine life and immature organ systems e.g. patent ductus arteriosus (Rolland et al., 2015; Shima et al., 2013), retinopathy of prematurity (ROP), intraventricular haemorrhage (IVH) (Calisici et al., 2014; Wy et al., 2015) and respiratory distress syndrome (RDS) (Hartnett & Penn, 2012; Tan et al., 2015); and side effects of treatments e.g. oxygen supplementation for RDS (The BOOST II United Kingdom Australia and New Zealand Collaborative Groups, 2013) and insulin treatment for neonatal

hyperglycaemia (Alsweiler et al., 2012; Kaempf et al., 2011). Clinicians now aim to improve not only the survival rate, but also the quality of life of the preterm children who survive (Crowther et al., 2013; Darlow et al., 2015; Partridge et al., 2015; The EXPRESS Group, 2010). Despite advances in neonatal care, resulting in improvement in survival rates and reduced severe adverse outcomes, children and adults born preterm are still more likely to have poorer outcomes in neurosensory function (Breeman et al., 2015; Husby et al., 2013; Tan et al., 2015), health (Bolton et al., 2015; Saigal et al., 2007; Sipola-Leppanen et al., 2015) and academic achievement (Johnson et al., 2011) than individuals born at full term (Hack, 2009; Saigal, 2014). Although being born very preterm is associated with higher incidence of functional limitations, the individuals and their parents are generally satisfied with their quality of life at different life stages (Saigal et al., 2006; Saigal et al., 1996; Saigal et al., 2000).

1.1.1 Risk factors and management

Preterm birth is one of the leading causes of early death in children, accounting for 15% of deaths under 5 years of age in 2013 worldwide (Liu et al., 2015). Preterm birth can occur spontaneously due to conditions such as preterm premature rupture of membranes (PPROM), intrauterine infection, and preterm labour (Brik et al., 2014; Esplin et al., 2015); or it may be iatrogenic, through induction or caesarean section, due to obstetric indications such as pre-eclampsia and maternal medical disorders (Joseph et al., 2014; Rana et al., 2013), or fetal indications such as fetal anomaly and intrauterine fetal growth restriction (Chang et al., 2013; The GRIT Study Group, 2003). Preterm birth is associated with many different risk factors or combination of risk factors including: multiple pregnancy (Schaaf et al., 2011), infection (Esplin et al., 2015; Gagliardi et al., 2013; Manuck et al., 2015), health and age of the mother (Carolan et al., 2013; Cnattingius et al., 2013; Donoghue et al., 2013; Subramanian et al., 2012), social economic status (Donoghue et al., 2013), and lifestyle during pregnancy (Baba et al., 2012; Donoghue et al., 2013); but in many cases, preterm birth is idiopathic (Kharrazi et al., 2012). These risk factors are not only associated with preterm birth; some of these risk factors e.g. PPROM and intrauterine fetal growth restriction are independently associated with adverse developmental outcomes (Armstrong-Wells et al., 2015; Gagliardi et al., 2013; Kallankari et al., 2015).

The management of preterm birth involves either treatments for the prevention or delaying of preterm birth, or using interventions that reduce mortality and adverse outcomes associated with preterm birth (Chang et al., 2013; Iams et al., 2008). Current management has focussed more on lessening the effect of adverse outcomes as there has been limited success with preventing preterm birth (Simmons et al., 2010). In many cases, delaying preterm birth does not improve neonatal mortality or outcomes, or preterm birth is not delayed successfully (Anotayanonth et al., 2014; Rafael

et al., 2014). Often treatments are used to delay preterm birth long enough to administer antenatal medications to the mother such as corticosteroids (Roberts & Dalziel, 2013) and magnesium sulphate (Han et al., 2010) to improve neonatal outcomes associated with preterm birth. Surfactants (Soll & Özek, 1997), mechanical ventilation (Stevens et al., 2014), corticosteroids (Shah et al., 2007) and nutrition (Barros et al., 2010) are also used to lower the risk of adverse neonatal outcomes of babies born preterm.

1.1.2 Neonatal complications

Preterm children have greater risk of developing neonatal complications when compared to children born at full term. These include RDS, metabolic disorders such as neonatal hypo- and hyperglycaemia, sepsis, brain injury from IVH and periventricular leukomalacia (PVL), sensory impairments such as hearing and visual deficits, and feeding difficulties (Simmons et al., 2010; Wang et al., 2011), Due to these complications, babies born preterm may be hospitalized for longer periods of time, they may need extra specialist care throughout their lives and many develop neurodevelopment disabilities such as cerebral palsy, cognitive delay and visual impairment (Allen et al., 2011). There are a wide range of outcomes for these preterm individuals and interventions are implemented according to the difficulty experienced. As many of these complications coexist, it is important that they are managed appropriately to improve quality of life for the individuals and their families.

1.2 Respiratory Distress Syndrome

Preterm babies are at high risk of lung damage secondary to both lung immaturity at the time of birth and postnatal ventilation. RDS is a common condition in preterm babies characterised clinically by presence of cyanosis, grunting respirations, retractions, tachypnoea and requiring increased oxygen requirement (Sweet et al., 2013). Radiographic findings of a classical ‘ground glass’ appearance of the lungs and air bronchogram confirm the diagnosis of RDS. However, due to earlier surfactant replacement therapy and ventilation, the radiological appearance of the lungs may not be as severe as classical signs (Sweet et al., 2013). Before the use of mechanical ventilation and widespread use of antenatal corticosteroids, it was one of the leading causes of neonatal death (Battin et al., 2012; Simmons et al., 2010). Particularly since the introduction of antenatal corticosteroid administration, the number of deaths from RDS or related conditions have decreased dramatically, with a reduction from 90% to less than 5% of neonatal deaths of babies with a birth weight ≤1500g at National Women’s Health Neonatal Intensive Care Unit (NICU), Auckland, New Zealand over a 50 year period

(Auckland District Health Board., 2016; Battin et al., 2012). Apart from the acute presentation of RDS, babies with RDS have an increased risk of bronchopulmonary dysplasia (BPD), which is a serious life-long adverse outcome of preterm birth, which can have great impact on quality of life (Islam et al., 2015). In 1967, BPD was first described as a chronic lung disease associated with mechanical ventilation for RDS (Northway et al., 1967). Since then, despite increasing survival rates for preterm birth, incidence of BPD has largely been unchanged (Van Marter et al., 2009). However, the characteristics of this disease have changed and less severe forms of BPD are now being observed (Jobe, 2011). In BPD, there is reduced number and enlargement of aveoli, which results in reduced surface area for gas exchange (Husain et al., 1998). According to Shennan *et al.* (1988), requiring oxygen supplementation at 36 weeks' corrected gestational age was a good predictor of abnormal lung function (Shennan et al., 1988), which is now the criteria used to define BPD. Risk factors for development of BPD include preterm birth (gestational age ≤30 weeks), presence of patent ductus arteriosus (PDA), mechanical ventilation on day 7, increased positive inspiratory pressure, and high fluid volume (Cunha et al., 2005; Jobe, 2011). RDS and BPD can cause long-term disability in individuals born preterm: in early childhood, there is higher risk of persistent wheezing and diagnosis of asthma; in later years, widespread involvement of peripheral airways can lead to chronic obstructive pulmonary disease and emphysema (Baraldi et al., 2009; Broström et al., 2010).

1.2.1 Management

Management of RDS includes surfactant replacement therapy, prophylactic antenatal corticosteroid administration, and use of mechanical ventilation and supplemental oxygen.

1.2.1.1 Surfactants

In 1959, Avery and Mead hypothesized that lung prematurity and associated lack of surfactant were the main cause of RDS (also known as hyaline membrane disease) as they could not find surfactant in the lungs of babies who had died of RDS (Avery & Mead, 1959). Surfactant is a phospholipid and protein mixture produced by lung pneumocytes to negate the surface tension between the air-alveolar interfaces and prevent the alveolar sacs from collapsing when exhaling. Production of surfactant begins around week 24, and it is not until after week 30 that there is sufficient surfactant production and alveolar surface area for gas exchange (Gross, 1990; Warburton et al., 2010). The efficacy of surfactant replacement therapy, either for prophylaxis or as treatment for reducing RDS, has been studied in many clinical trials. Different exogenous surfactants have been used, including surfactants derived from animal (mainly bovine and porcine) tissue and synthetic surfactants

(Clements & Avery, 1998). Both animal-derived and synthetic surfactants, whether as prophylaxis or treatment of RDS, have been reported to reduce the risks of pneumothorax, pulmonary emphysema, neonatal mortality and BPD, although animal-derived surfactant may be more effective at decreasing risk of pneuomothorax (Ardell et al., 2015; Seger & Soll, 2009; Soll, 1998; Soll & Özek, 1997). In some trials, risks of intraventricular haemorrrhage or late mortality were reduced but animal-derived surfactant use has been associated with increased risk of necrotizing enterocolitis and non-severe IVH. However, the benefits of animal-derived surfactant on decreasing risk of mortality outweigh the risk (Ardell et al., 2015; Singh et al., 2015; Soll, 1998).

1.2.1.2 Antenatal corticosteroids

In 1969, Liggins and Howie first conducted a randomised controlled trial of antenatal corticosteroid in mothers who were in threatened with preterm delivery or had planned delivery before 37 week's gestation (Liggins & Howie, 1972), which resulted in fewer deaths of children born spontaneously in the corticosteroid group compared to the control group and a lower incidences of RDS (Liggins & Howie, 1972). Many randomised trials of antenatal corticosteroids have since been conducted and it has been shown that a single dose of antenatal corticosteroid (betamethasone, dexamethasone or hydrocortisone) administered up to 7 days prior to preterm birth is effective at reducing respiratory stress syndrome and neonatal mortality (Roberts & Dalziel, 2013). The effect of multiple doses of corticosteroids for preterm babies born more than 7 days following antenatal corticosteroids administration, particularly longer-term outcomes are not clear. However multiple dose corticosteroids appears to reduce the occurrence of neonatal RDS by 17% and reduces the need for mechanical ventilation, oxygen supplementation and surfactant administration (Crowther et al., 2011). Possible mechanisms for accelerating lung tissue maturation by corticosteroids is through maturation of type II pneumocytes for surfactant production, lung tissue structural differentiation (Asabe et al., 2007; Kikkawa et al., 1971), thinning of pulmonary arteries (Roubliova et al., 2008), and increase antioxidants (Arima et al., 2008). Antenatal corticosteroids use has greatly improved neonatal survival through reduction of RDS and IVH (Battin et al., 2012; Roberts & Dalziel, 2013).

1.2.1.3 Oxygen supplementation

As well as surfactant replacement therapy and prophylactic antenatal corticosteroid administration, many preterm babies also require supplementary oxygen to sustain life (Askie & Henderson-Smart, 2009; Avery & Oppenheimer, 1960). Oxygen supplementation for preterm babies has been routinely used since the 1940s and has reduced the mortality rate of many vulnerable babies (American Academy of Pediatrics, 1976; Askie, 2013; Avery & Mead, 1959). However, the optimal dose of oxygen

needed by preterm babies is still under contention (Askie, 2013; Jeenakeri & Drayton, 2009; Schmidt et al., 2013; Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network Support, 2010; The BOOST II United Kingdom Australia and New Zealand Collaborative Groups, 2013). The dilemma faced by health practitioners caring for preterm babies is that hypoxia is associated with cerebral palsy and mortality, while hyperoxia damages brain and lung tissue in the form of BPD through oxidative and mechanical stress, and increases risk of developing severe ROP (American Academy of Pediatrics, 1976; Stevens et al., 2014; The BOOST II United Kingdom Australia and New Zealand Collaborative Groups, 2013).

Before the 1960s, the need for oxygen supplementation by a baby was guided by clinical observations of skin cyanosis, heart rate and the amount of effort used for breathing. Later, introduction of blood gas sampling and transcutaneous monitoring enabled more precise monitoring of oxygen concentration in the form of arterial partial pressure of oxygen (P_aO_2) (Walsh et al., 2009). Many guidelines for oxygen supplementation were based on $P_aO_2$measurements.(American Academy of Pediatrics and American College of Obstetricians and Gynecologists., 1983; Myers & American Association for Respiratory Care (AARC), 2002) but since the 1980s, continuous non-invasive monitoring of peripheral capillary oxygen saturation (SpO_2) with pulse oximetry has become the main method of monitoring oxygen needs in preterm babies (Finer & Leone, 2009; Jennis & Peabody, 1987). Oxygen concentration within the body can fluctuate rapidly due to metabolic activity, gas exchange, oxygen dissociation rate, blood flow and the fraction of inspired oxygen (Higgins et al., 2007). Since there is an asymptotic relationship between $SpO_2$and the high and low ranges of P_aO_2, changes in higher oxygen tensions are not reflected in the changes in saturation (Émond et al., 1993; Quine & Stenson, 2009). These factors have contributed to the difficulty of finding the optimal oxygen therapy needed by babies born preterm.

The optimal SpO_2 or PaO_2 required by preterm babies has been extensively investigated since the 1950s when it was discovered that uncontrolled oxygen supplementation for respiratory distress resulted in many cases of blindness from ROP (Patz et al., 1952). In the1970s and 1980s, a “second wave” of ROP was noted as more babies born extrememly preterm were surviving, and there was a renewed interest into the effects of oxygen therapy for preterm babies (Gilbert, 2008). Using transcutaneous oxygen tension monitoring, an association between more hours with P_aO_2 over 80mmHg and greater incidence and severity of ROP was found, particularly when oxygen partial pressures were raised during the second to fourth week of life (Flynn et al., 1992). In 1983, a recommended clinical guideline for neonatal P_aO_2 to be maintained at 50-90mmHg was established

(American Academy of Pediatrics and American College of Obstetricians and Gynecologists., 1983), which was later updated to 50-80mmHg in 1988 (American Academy of Pediatrics and American College of Obstetricians and Gynecologists, 1988). As pulse oximetry has gradually replaced frequent monitoring of P_aO_2, studies investigated the relationship between P_aO_2 and SpO_2, showing that the upper limit P_aO_2 of 80mmHg equated to SpO_2 of over 95%; suggesting that perhaps a lower P_aO_2 target would be more acceptable.

For better monitoring of oxygen supplementation, a range for optimal SpO_2 for healthy development was needed. Between September 1996 and September 2000, a randomised multicentre trial, Benefits of Oxygen Saturation Targeting (BOOST), was established to investigate whether oxygen supplementation targeting higher than standard range SpO_2 would improve growth and neurodevelopmental outcomes (Askie et al., 2003). Babies born at less than 30 weeks' gestational age who remained on supplemental oxygen at 32 weeks postmenstrual age were randomised to either a target SpO_2 range of 91-94% (standard-saturation group) or 95-98% (high-saturation group). There were no significant differences between weight, length or head circumference at 38 weeks' postmenstrual age or corrected age of 12 months between the two groups. The proportion of babies with major developmental abnormality (blindness, cerebral palsy or reduced score of 2SD below the mean on the revised Griffiths Mental Developmental Scales), and rate of ROP or neonatal mortality were not statistically significantly different between the groups. However, a larger proportion of babies in the high-saturation group were still dependent on oxygen supplementation after 36 weeks' postmenstrual age and at discharge. This led the authors to suggest that there was no evidence that higher SpO_2 had any benefit on growth and neurodevelopment (Askie et al., 2003).

Further randomised trials with international collaboration investigated the efficacy of supplemental oxygen targeting SpO_2 of 85-89% compared with 91-95% in babies born ≤28 weeks' gestational age, starting within 24 hours of birth (SUPPORT Study group of the Eunice Kennedy Shriver NICHD Neonatal Research Network, 2010; The BOOST II United Kingdom Australia and New Zealand Collaborative Groups, 2013). A meta-analysis of the five studies (3 BOOST II trials, SUPPORT trial and COT trial) revealed a higher risk of mortality and necrotizing entercolitis in the low saturation target group compared to the high saturation target group (Manja et al., 2015). However, there were lower incidences of severe ROP and BPD in the low saturation target group (SUPPORT Study group of the Eunice Kennedy Shriver NICHD Neonatal Research Network, 2010; The BOOST II United Kingdom Australia and New Zealand Collaborative Groups, 2013). Incidences of brain injury and patent ductus arteriosus were not significantly different between the groups (Saugstad & Aune, 2014). The studies

found no difference in the composite of death or severe neurosensory disability at 18-24 months between the groups (Darlow et al., 2014; Schmidt et al., 2013; Vaucher et al., 2012). The different studies came to different conclusions, with the BOOST II trials suggesting that there should be avoidance of oxygen saturation less than 90% (The BOOST II United Kingdom Australia and New Zealand Collaborative Groups, 2013); the SUPPORT trial recommended caution in targeting low concentrations of oxygen saturation (SUPPORT Study group of the Eunice Kennedy Shriver NICHD Neonatal Research Network, 2010) while the authors of the COT trial did not find evidence to avoid lower oxygen saturations in the upper 80% range (Schmidt et al., 2013). The optimal oxygen supplementation for babies born preterm remains contentious and further investigation into length of oxygen therapy, effects of intermittent hypoxia or hyperoxia at various postmenstrual ages, customising oxygen monitoring delivery, and the needs of babies at different gestational ages may contribute to understanding on the best treatment for this vulnerable group of babies (Saugstad & Aune, 2014).

1.3 Retinopathy of Prematurity

ROP is a common proliferative retinal vascular disease in babies born very preterm. Up to 68% of babies <1251g birth weight develop ROP and the incidence and severity of ROP increases with lower birth weight and gestational age, such that up to 80% of babies with a birth weight <1000g have ROP (Early Treatment for Retinopathy of Prematurity Cooperative Group, 2005; Palmer et al., 1991). The effects of ROP on vision vary from normal vision in mild ROP through to no perception of light following full retinal detachment in individuals with severe ROP. Although laser treatment of severe ROP has reduced the incidence of retinal detachment, in the United States, ROP is still the third leading causes of childhood blindness (14%), following cortical visual impairment (56%) and optic nerve hypoplasia (15%) (Kong et al., 2012; Repka et al., 2011). In New Zealand, the incidence of blindness resulting from ROP in babies <1000g birth weight was found to be 7% in a 1986 study investigating the national incidence of acute ROP in very low birth weight babies (Darlow, 1988). Since then, there have been advances in neonatal care, and changes in screening and treatment of severe ROP. Therefore, visual outcomes of ROP and its treatment need further evaluation to investigate the effectiveness of current ROP management and screening.

1.3.1 Embryology of the human eye

The embryonic development of the eye begins at around 22 days following gestation and involves neural and surface ectoderm, optic neural crest, and mesoderm tissue (O'Rahilly, 1975; Snell et al., 1998). The process begins at the lateral portion of the forebrain and the ectoderm forms a pouch, which dilates to form the optic vesicle and optic stalk at approximately day 24, which are the structural basis of the eye (O'Rahilly, 1975). Between day 28 and 31, the surface ectoderm of the optic vesicle thickens to form the lens placode (future crystalline lens, corneal epithelium) while the optic vesicle neural ectoderm grows back on itself to form a two-layered optic cup (future retina, optic nerve fibres and smooth muscle of the iris) (O'Rahilly, 1975). The inferior edge of the optic cup does not close fully and becomes continuous with a groove in the optic stalk, known as the optic/choroidal fissure, which provides the passageway for the blood vessels innervating the eye. In the sixth week, the mesenchyemal cells invade into the optic fissure, while bringing the hyaloid artery, which supplies the embryonic lens with nutrients) (O'Rahilly, 1975). By week seven, the optic fissure closes to form the optic canal (houses the future optic nerve and central retinal blood vessels) and the retina begins to differentiate into different layers (O'Rahilly, 1975). The retina is formed from two main layers: pigmented layer and the neural layer (Snell et al., 1998). The pigmented layer becomes the retinal pigmented epithelium and the neural layer forms the ganglion, amacrine, Müller, bipolar and photoreceptor cells. From week eight, the ganglion cells form the optic nerve fibres that contribute to the nerve fibre layer and connections from the retina to the brain (O'Rahilly, 1975). By week 20, the ganglion cell layer can be seen throughout the retina, while the other retinal neural layers become defined in the periphery between 25 to 30 weeks' gestational age, with retinal cell division ceasing around 30 week's gestational age (Provis et al., 1985). It has been hypothesised that the ganglion cells start to migrate away from the central retina into the perifoveal and perimacular areas from approximately 12 weeks' gestational age, and this process appears to accelerate over the last few weeks of gestation. This cellular migration continues until around 4 months of age, which coincides with foveal maturation (Provis et al., 1985; Snell et al., 1998). Foveal maturation is characterised by increasing density of photoreceptors in the central retina, while the ganglion cells and inner retinal cells are displaced from the central retina to enable light to directly fall on the photoreceptors to optimise resolution and optical quality (Provis et al., 2013).

In the early stages of embryonic ocular development, the nutrients to the eye are supplied by the hyaloid artery (Snell et al., 1998). From approximately 15-16 weeks' gestational age, the mesenchymal cells start to proliferate and invade into the nerve fibre layer on either side of the hyaloid artery; as these cells differentiate into endothelial cells, these later form capillaries (Ashton, 1970; Madan, 2003).

Meanwhile, the hyaloid artery gradually regresses from approximately 19 week's gestational age and by 29 week's gestational age, the hyaloid artery is typically completely regressed. However in some babies, a hyaloid remnant may be present in the eye following birth (Achiron et al., 2000). From approximately 25 weeks' gestational age, the central retinal artery and vein that supply the inner retina start to form from the capillaries, while some of the side-branching capillaries retract to produce areas of perivascular capillary-free zones (Madan, 2003; O'Rahilly, 1975). The growth of blood vessels progresses outwards from the optic disc to the peripheral retina in response to the differentiation process of retinal cells that is accompanied by an increase in metabolic activity (Ashton, 1969). As the same time, choroidal blood vessels (developed from mesenchymal cells between 9 weeks' and 5 months' gestational age) (O'Rahilly, 1975) beneath the peripheral retina no longer provide enough oxygen for the retinal cells and this relative lack of oxygen stimulates the release of vascular endothelial growth factor (VEGF) from neural cells of the retina, which aid in new blood vessel formation (Heidary et al., 2009; Madan, 2003). The blood vessels track along the nerve fibre layer to reach the nasal peripheral retina at approximately 36 weeks' gestation and by 38 weeks' gestation, the retina is fully vascularised apart from a small area known as the foveal avascular zone (Ashton, 1970; Ashton, 1969; Engerman, 1976; Provis & Hendrickson, 2008). There are no blood vessels at the fovea to ensure that light can fall directly on the photoreceptors (Provis et al., 2013).

1.3.2 Postnatal ocular growth

Normal ocular growth is not well understood as focus has been on studying the development of visual function and refractive error. Although it is unclear when the ocular tissues cease to grow or change, it has been proposed that most of the changes in axial length happens before 30 months after birth (Fledelius & Christensen, 1996). This may coincide with the changes in the orbit size (Edward & Kaufman, 2003). Ocular growth can be influenced by changes in visual function such as seen in light deprivation and myopia progression (Mutti et al., 2007), as well as by ethnicity (Ip et al., 2008). Based on studies on ocular refractive development, axial length becomes longer with age (Hashemi et al., 2015; Shih et al., 2011). The development of other ocular components including anterior chamber depth and corneal curvature are less clear (Chen et al., 2010; Fledelius & Stubbaard, 1986; Hashemi et al., 2015). Lens thickness appears to reduce in thickness after birth but increases with age in adults (Augusteyn, 2010; Hashemi et al., 2015), while corneal thickness appears to stay similar throughout life (Ehlers & Hansen, 1976). One study investigated ocular biometry using post-mortem eyes (from individuals aged 1 day to 104 years) and proposed that there was no further growth in the ocular globe after 1 year of age (Augusteyn et al., 2012). These highlight the need for further longitudinal studies to better understand postnatal ocular growth.

1.3.3 Pathogenesis of retinopathy of prematurity

The pathogenesis of ROP is hypothesized to be separated into two phases: Phase 1 Hyperoxia and Phase 2 Hypoxia (Hartnett & Penn, 2012). VEGF is an important molecule driving blood vessel growth by causing endothelial cells to proliferate and migrate (Le, 2017). In phase 1 of ROP pathogenesis, the preterm born baby does not have a fully vascularised retina and due to the hyperoxic environment compared to *in utero*, particularly in babies who have under-developed lungs and require oxygen supplementation, there is reduction of VEGF synthesis in the retina (Hartnett & Penn, 2012; Madan, 2003). In response, the peripheral retinal blood vessels cease to grow, and occasionally, the blood vessels may retract (Kwinta et al., 2008; Palmer et al., 1991). Children who developed ROP requiring treatment have been found to have lowered serum VEGF levels between 29 and 31 weeks' gestational age compared to preterm children who do not develop ROP (Kwinta et al., 2008). As the preterm baby grows and the retina becomes more metabolically active (around 31 weeks' gestational age), there is a greater demand for oxygen, which cannot be supplied by the retracted blood vessels or the choroidal blood vessels and phase 2 of ROP pathogenesis ensues (Kwinta et al., 2008; Palmer et al., 1991). This results in increase of hypoxia induced factor 1-α, which in turn upregulates VEGF expression in the avascular retina and causes subsequent uncontrolled proliferation of blood vessels (Flynn & Chan-Ling, 2006; Heidary et al., 2009). Similar to other retinal vasoproliferative diseases, these new blood vessels have weak capillary walls, which have an increased risk of haemorrhage (Madan, 2003). Fibrous attachments to the vitreous humour following a haemorrhage can result in retinal detachment and profound visual impairment (Weakley & Spencer, 1992).

1.3.4 Historical perspectives

ROP was first recognised in 1942 by T. L. Terry and he named the condition as retrolental fibrosis due to observation of connective tissue being connected to the retina and the crystalline lens (Terry, 1946). Terry subsequently observed that this condition had a higher incidence in babies born preterm. Oxygen supplementation was eventually recognised as one of the important risk factors for the development of ROP (Patz et al., 1952), and contention of optimal oxygen supplementation of babies born preterm remains at present as reducing oxygen use in preterm babies reduces the incidence of ROP, but at the same time increases the incidence of cerebral palsy and mortality (Aclimandos, 2011; STOP-ROP Multicenter Study Group, 2000; The BOOST II United Kingdom Australia and New Zealand Collaborative Groups, 2013). However, excessive oxygen therapy alone was not the only cause of ROP as even with reduction of oxygen supplementation; by the 1980's, the incidence of ROP had continued to rise with advances in neonatal care increasing survival of more preterm babies at lower gestational

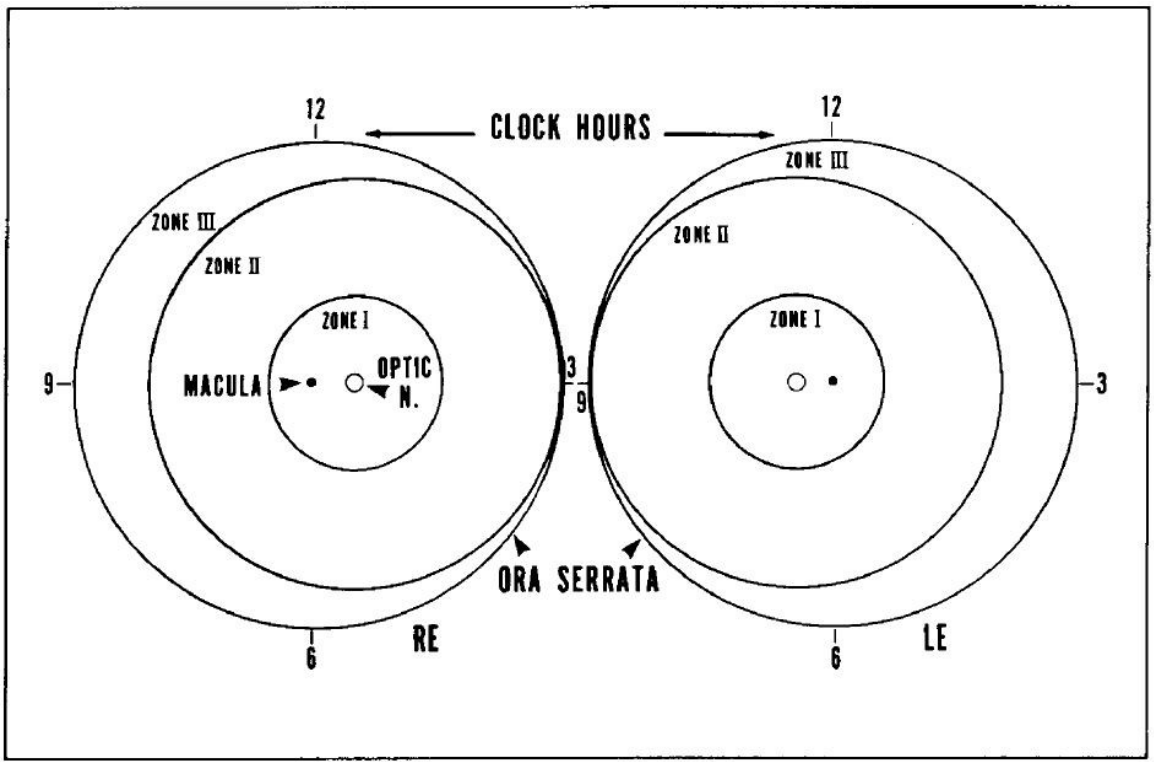
ages (Patz, 1984). In response, ROP classification was standardised, in order to introduce screening protocols and provide a basis for multicentre research into appropriate ROP treatment (An International Committee for the Classification of Retinopathy of Prematurity, 2005; The Committee for the Classification of Retinopathy of Prematurity, 1984). An international classification system of the different stages of active ROP was developed in 1984 and the resulting system was published as the "International Classification of Retinopathy of Prematurity" (ICROP) (The Committee for the Classification of Retinopathy of Prematurity, 1984). The ICROP described ROP according to location (3 zones), extent (clock positions), severity (5 stages) and different abnormal vascular signs (The Committee for the Classification of Retinopathy of Prematurity, 1984). This system has subsequently been revised twice; in 1987 to include details of retinal detachment classification (Patz, 1987), and in 2005 to clearly define aspects of aggressive ROP and pre-plus disease (An International Committee for the Classification of Retinopathy of Prematurity, 2005).

1.3.5 International Classification of Retinopathy of Prematurity

The acute stages of ROP are divided into zones, stages and extent (Figure 1-1). The retina is divided into three circles or zones, which are centred on the optic disc and these zones define the location of ROP. Zone I is delineated by an imaginary boundary where the radius of the circle is twice the distance from the optic disc to the macula. Zone II is the area from the optic disc to the nasal ora serrata and the same distance temporally from the optic disc, not including zone I. Zone III is the rest of the retina temporally that is not within Zone I or Zone II (The Committee for the Classification of Retinopathy of Prematurity, 1984).

The stages of ROP describe the severity and the changes of the retina. Stage 1 is a thin demarcation line separating the vascular and avascular part of the retina. Stage 2 is when the line becomes thicker and starts to occupy a volume with height and width. It is now known as a ridge and this thickened tissue extends from the retina towards the vitreous. When the ridge develops fibrovascular proliferations and growth of new blood vessels towards the vitreous, ROP is classified as stage 3. Depending on the area measured with clock hours and the zone that is affected, stage 3 can indicate moderate or severe ROP. Stage 4 and stage 5 are classification of retinal detachments; stage 4 is partial retinal detachment and stage 5 is full retinal detachment. Apart from the zones, stages and extent, signs that indicate severe ROP are presence of blood vessel tortuosity and dilatation (plus and pre-plus disease, which is determined by the extent of the affected area using clinical judgement), vitreous haze (breakdown of the blood-ocular barrier), iris blood vessel engorgement, haemorrhages and loss of pupil rigidity.

Figure 1-1 ROP zones and extent



From (The Committee for the Classification of Retinopathy of Prematurity, 1984)

Although it is difficult to classify the signs seen following regression of ROP, (treated by ablation or untreated and spontaneous resolution), the ICROP (1987 and 2005) describes the abnormalities and these can be divided into two areas and several types. In the peripheral retina, changes can be seen in the blood vessels (avascular retina, abnormal branching, interconnections and telangiectasia) and abnormal retinal structure (pigmentation, vitreoretinal interface changes, thinning and degeneration, peripheral folds, and retinal breaks and detachments). Posterior changes can also be seen in the vasculature (tortuosity, straightening of the temporal arcade blood vessels and change in the angle of the temporal arcades) and also in the retinal structure (macular folds and stretching, pigmentation, vitreoretinal interface changes and vitreous membranes, dragging of the retina over the optic disc, and tractional retinal detachments) (An International Committee for the Classification of Retinopathy of Prematurity, 2005; Patz, 1987).

1.3.6 Screening and diagnosis

ROP screening is aimed at identifying babies with severe ROP who require treatment to prevent vision loss. The American Academy of Pediatrics recommends that screening for ROP should be performed in “babies with birth weight <1500g or gestational age <30 weeks, and some babies with a birth weight

between 1500g and 2000g or gestational age of ≥30 weeks with an unstable clinical course" (such as those requiring cardiorespiratory support) as they are most at risk of developing ROP (Section on Ophthalmology American Academy of Pediatrics and American Academy of Ophthalmology and American Association for Pediatric Ophthalmology and Strabismus, 2013). Screening is initiated by 31 weeks' postmenstrual age or 4 weeks after birth, whichever is later. Before 30 weeks' postmenstrual age, babies have hazy corneas, which limit the effectiveness of viewing the retina and subsequent ablation therapy (O'Keefe & Kirwan, 2008; Reynolds et al., 2002). Depending on the severity of ROP detected, screening is performed between one to three weeks apart. ROP screening is usually continued until there is no risk of severe ROP progression or full retinal vascularization. ROP requiring treatment is defined as: Type I ROP (High risk prethreshold): zone 1 any stage ROP with plus disease; zone 1 stage 3 ROP with or without plus disease; and zone II stage 2 or 3 ROP with plus disease (Early Treatment for Retinopathy of Prematurity Cooperative Group, 2003). At National Women's Health, ROP screening differs slightly from the American Academy of Pediatrics guidelines, where children with birth weight <1250g, or <30 weeks' gestational age, or selected babies ≥1250g and ≥30 weeks with an unstable clinical course and are believed to be at high risk of developing ROP are screened. The incidence of severe ROP at babies born ≥1250g and ≥30 weeks is very low in New Zealand so they are not routinely screened (Dai et al., 2015).

Retinal examination using binocular indirect ophthalmoscopy, where a magnifying lens was used to view the retina through pharmacologically dilated pupils, was the original gold standard for ROP screening (Section on Ophthalmology American Academy of Pediatrics and American Academy of Ophthalmology and American Association for Pediatric Ophthalmology and Strabismus, 2013). However, many centres binocular indirect ophthalmoscopy for ROP screening has been replaced by wide-field digital retinal photography to obtain static images of the retina (Kemper, Wallace, et al., 2008). Digital retinal photography has been widely used in diabetic retinopathy screening as it allows for remote and consistent diagnosis of diabetic retinopathy, and the recordings can be stored (Hutchinson et al., 2000). However, in ROP screening, there was controversy whether digital retinal imaging should be used by itself or as an adjunct to indirect ophthalmoscopy (Section on Ophthalmology American Academy of Pediatrics and American Academy of Ophthalmology and American Association for Pediatric Ophthalmology and Strabismus, 2013; Trese, 2008). The limitations of using indirect ophthalmoscopy included: the lack of ophthalmologists with the expertise required to obtain views of the retina (Kemper, Freedman, et al., 2008), particularly in preterm babies where the eyes are small and possibly have obscuration from media opacities; large inter-observer variability and documentation by drawings could be subjective (Trese, 2008); and the discomfort and possible

adverse complications (such as retinal haemorrhages and transient bradycardia) resulting from the examination (Laws et al., 1996; Mavrofrides et al., 2006). These factors increased the trend towards using wide-field digital retinal imaging for routine ROP screening. The main limitations of wide-field digital retinal imaging are the skill and expertise needed to take the photographs (Section on Ophthalmology American Academy of Pediatrics and American Academy of Ophthalmology and American Association for Pediatric Ophthalmology and Strabismus, 2013); the possibility of poor quality retinal images (Dai et al., 2011); the lack of a stereoscopic view due to a flat image (Schwartz et al., 2000) and constraints in imaging the far peripheral retina (Dai et al., 2011). However, in cases where images were unclear and unable to be processed, repeat imaging or indirect ophthalmoscopy have been used.

ROP screening effectiveness and cost is influenced by a lack of paediatric ophthalmology expertise and the large workload. Some babies can be screened up to 45 weeks' postmenstrual before there is regression of ROP (Reynolds et al., 2002). In the United States, ROP screening examinations can be performed by only 11% of ophthalmologists, of which only 6% provide ROP treatment (Kemper, Freedman, et al., 2008). In New Zealand, there is a growing demand for more ophthalmologists to meet the services required in the population (Pick et al., 2008). As a result, there has been a trend towards telemedicine as this allows remote screening and more effective use of the ophthalmologists involved. The initial establishment cost of using wide-field digital retinal imaging can be high (Dai et al., 2011) but a study in the United States (2008), calculated in the long-term, that the costs per quality-adjusted life year gained was $USD 3193 using telemedicine compared standard ophthalmoscopy at $USD 5617 (Jackson et al., 2008). In 2013, there was a revised joint statement on ROP screening that recommended the use of telemedicine should "comply with the timing and other recommendations outlined in the guidelines" and "indirect ophthalmoscopy be performed at least once by a qualified ophthalmologist before treatment or termination of acute phase screening of ROP for infants at risk for ROP" (Section on Ophthalmology American Academy of Pediatrics and American Academy of Ophthalmology and American Association for Pediatric Ophthalmology and Strabismus, 2013). There is evidence of comparable accuracy and reliability of using telemedicine in detecting ROP that requires treatment compared to indirect ophthalmoscopy (Dai et al., 2011; Fijalkowski et al., 2013), but there remains a need to assess long-term visual outcomes as well as anatomical outcomes from using retinal photo-screening and a need for guidelines in ROP telemedicine screening to ensure screening is consistent for babies at risk of ROP.

1.3.7 Treatment

Peripheral retinal ablation treatment of threshold ROP (defined as five or more contiguous or eight cumulative clock hours of stage 3 ROP in zone 1 or 2 in the presence of 'plus' disease) was first studied in a large multicentre study of 291 babies by the Cryotherapy for Retinopathy of Prematurity Cooperation Group (Cryo-ROP study) (Cryotherapy for Retinopathy of Prematurity Cooperative Group, 1988; Palmer et al., 1991). The babies were randomised to either having no treatment or cryotherapy within 72 hours of reaching threshold ROP (Cryotherapy for Retinopathy of Prematurity Cooperative Group, 1988). At the 15 year follow-up study, unfavourable visual acuity outcomes (defined as best corrected visual acuity (VA) equal to or worse than 20/200 [6/60]) remained less frequent in the treated group compared to the untreated group (44.7% v 64.3%, $p \leq 0.001$) (Palmer et al., 2005). Many children with ROP less than threshold experience spontaneous resolution of their ROP without treatment. However, these children were at risk of retinal changes such as displacement of retinal vessels, atypical vascular changes in the peripheral retina, and changes to the vitreous and retina interface, which could precipitate retinal tears and retinal detachments later in life (Bonamy et al., 2013; Gallo et al., 1991; Repka, 2002). Of a group of 108 patients who previously had ROP, 58 patients had been referred to a retinal referral centre for evaluation of ROP, and none had symptoms that were thought to require frequent eye examination (Kaiser et al., 2001; Tasman et al., 2006). However, 15 of these patients (26%) went on to develop a retinal tear or retinal detachment. These patients were aged from 3 months to 53 years of age (mean age of 26 years of age) at their first eye examination (Kaiser et al., 2001). These data demonstrate the importance of children with a history of severe ROP to be followed-up regularly.

Following the Cryo-ROP study, there was a change in ablation method from cryotherapy to laser photocoagulation as laser photocoagulation therapy appeared to result in better outcomes with less adverse complications at the time of therapy (McLoone et al., 2007; Ng et al., 2002; Shalev et al., 2001). Subsequently, another large randomized control study (n=401) to investigate earlier treatment of ROP using laser photocoagulation was initiated (Early Treatment ROP (ETROP) study) (Hardy et al., 2004). The authors found that treatment of Type 1 prethreshold ROP (defined as any stage of ROP in zone 1 or zone 2 with plus disease; or stage 3 in zone 1 without plus disease) was associated with improved visual outcomes, while treatment for Type 2 prethreshold ROP (zone II stage 1 or 2 ROP without plus disease and zone II stage 3 ROP without plus disease) was not indicated as it was likely to regress (77.3%) like other milder forms of ROP (Early Treatment for Retinopathy of Prematurity Cooperative Group et al., 2010; Good, 2004). The use of avascular retinal ablation for Type 1 prethreshold ROP reduced the risk of retinal detachment and improved VA outcomes compared to eyes treated at

threshold (25.1% v 32.8%, p=0.02) (Early Treatment for Retinopathy of Prematurity Cooperative Group et al., 2010). Despite the good results of early ablative treatment, retinal detachments still occurred in 89 of 718 treated eyes (12%), with 2 eyes developing retinal detachments between the age of 9 months and 6 years of age (Repka et al., 2011). These data not only highlight the need for continued follow-up after a baby has been discharged from hospital, but also emphasises that more research is needed to prevent ROP and develop further improvements in treatment strategies.

Although ablation therapy for ROP reduces the risk of retinal detachment, it is at the expense of destroying the ablated peripheral retinal tissue, which can affect peripheral vision (Kremer et al., 1995). Therefore, other forms of treatment such as use of supplementation oxygen or intravitreal anti-VEGF treatment have been investigated.

In view of the two phase ROP pathogenesis process (1.3.3), it has been hypothesised that supplemental oxygen in the hypoxic stage may help with revascularisation of the retina in a more controlled way by halting ROP progression and aiding ROP resolution (Benner et al., 1993; Lloyd et al., 2003). The Supplemental Therapeutic Oxygen for Prethreshold ROP (STOP-ROP) study was a randomized trial comparing the effects of two oxygenation strategies on the progression of pre-threshold ROP to threshold ROP (STOP-ROP Multicenter Study Group, 2000). Babies who were diagnosed with pre-threshold ROP in at least one eye and who did not have a median pulse oximetry reading greater than 94% saturation while babies breathing room air were randomised to either targeting 89-94% or 96-99% oxygen saturation. The rate of progression from prethreshold to threshold ROP between the groups was not significantly different, conventional group 48.5% v supplemental group 40.9%, p=0.32 (1-tailed). There was no difference in growth, neuromotor development and mortality between the groups, but the supplemental group were more likely to remain on supplemental oxygen for longer, have more adverse pulmonary events and needing hospital care at three months corrected age (STOP-ROP Multicenter Study Group, 2000). As this is the only randomised controlled trial of the effects of supplemental oxygen as a treatment for ROP and long-term follow-up was not performed, more investigation would be required to determine whether supplemental oxygen in established ROP would be beneficial (Lloyd et al., 2003).

Anti-VEGF agents also target the second phase of ROP pathogenesis by reducing VEGF from that is upregulated due to the relative hypoxia to stop blood vessel growth. The largest multicenter randomized control trial for intravitreal bevacizumab therapy in the treatment of ROP to date, Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity (BEAT-ROP) study,

occurred between March 2008 and August 2010 (Mintz-Hittner et al., 2011). The trial included 150 babies who had birth weight ≤1500g and were born at ≤30 weeks' gestational age. Both eyes were randomly assigned to undergo either laser therapy or intravitreal bevacizumab (anti-VEGF agent) when they reached stage 3+ ROP in zone I or zone II. Babies with stage 4 or 5 ROP were excluded. Conventional laser therapy was given to the babies assigned to the laser group, while intravitreal bevacizumab was prepared as a solution of 0.625mg in 0.025ml solution and was initiated when the baby was assigned to the intravitreal bevacizumab group. By 54 weeks' postmenstrual age, 2 out of 62 eyes of babies with zone I disease and 4 out of 76 eyes of babies with zone II disease had recurrence of ROP after intravitreal bevacizumab treatment while 23 out of 66 eyes of babies with zone I disease and 9 out of 40 eyes of babies with zone II disease had recurrent ROP following laser therapy. The odds ratio for recurrence with intravitreal bevacizumab for the combined zones was 0.17 (95%CI 0.05, 0.53) (p=0.002). Through this trial, intravitreal bevacizumab treatment for stage 3+, zone I ROP disease was found to be more effective than conventional laser therapy. However, the trial was too small to assess safety and dosing was not investigated. There was a follow-up of these children at 2 and a half years of age; children who had laser photocoagulation had significantly higher magnitude and prevalence of myopia than children who had intravitreal bevacizumab monotherapy (Geloneck et al., 2014). There is a paucity of data on the long-term effects of anti-VEGF treatment in preterm babies with severe ROP (VanderVeen et al., 2017). A recent retrospective review has found higher risk of severe neurodevelopmental disabilities at 18 months of age after bevacizumab treatment for severe ROP compared to laser photocoagulation (Morin et al., 2016). Further research into long-term outcomes, safety and dosage is required before the widespread use of anti-VEGF in babies with severe ROP (Darlow, 2015; Sankar et al., 2012).

1.3.8 Visual outcomes

ROP and its treatments have many effects on visual outcomes. As well as a higher risk of developing retinal detachments in later life, ROP has been associated with poorer VA (Larsson et al., 2005; Palmer et al., 2005), increased incidence and magnitude of refractive error (Holmström et al., 1999), reduced contrast sensitivity (Larsson et al., 2006), and reduced visual field (McLoone et al., 2007; Quinn et al., 2011, 1996) when compared to children without ROP and children born full term.

1.3.8.1 Strabismus

Strabismus (misalignment of the eyes) is a common condition affecting children born preterm (Holmström et al., 2006). It affects up to 22% of children born preterm but its relationship with ROP is

unclear (Fielder et al., 2014; Holmström et al., 1999; Pennefather et al., 1999). Studies have reported a higher incidence of strabismus in children with ROP than those reported for children born at full term. However, the data on whether ROP is an independent risk factor for strabismus are divided (Al Oum et al., 2014; Holmström et al., 1999; Schalij-Delfos et al., 2000). Severe ROP has been associated with strabismus and reduced VA (Hellgren et al., 2016; VanderVeen et al., 2011). The ETROP trial showed a high prevalence of strabismus (42%) in children who had a history of high-risk prethreshold ROP (VanderVeen et al., 2011), which is similar to other studies in preterm children showing an increased risk of strabismus with cicatricial ROP and treated ROP (Hellgren et al., 2016; Pennefather et al., 1999). One potential confounding factor is that there is increased risk of brain injury or white matter changes in babies with severe ROP that can also contribute towards visual dysfunction and strabismus (Glass et al., 2017; Hellgren et al., 2007). In the ETROP trial, the majority of children with prethreshold ROP had esotropia and 80% of children who were visually impaired as a result of ROP or cerebral had strabismus (VanderVeen et al., 2011). Despite these uncertainties, as strabismus can reduce VA and binocular vision, it is essential that children with strabismus are followed closely. Current treatment for strabismus include treatment to correct the ocular misalignment, optical correction for refractive strabismus and treatment for amblyopia associated with strabismus (Korah et al., 2014; K. Taylor & Elliott, 2014).

1.3.8.2 Refractive error

ROP has been associated with increased incidence of refractive error, which has been hypothesised to be one of the mechanisms by which ROP is associated with reduced vision in childhood (Hsieh et al., 2012; O'Connor et al., 2007). Hsieh et al found an increase in incidence and magnitude of myopia with the severity of ROP (Hsieh et al., 2012). However, there are contradicting views on whether laser treatment or cryotherapy increases myopia incidence and magnitude (Algawi et al., 1994; Choi et al., 2000; Connolly et al., 2002; Quinn et al., 2001). Quinn *et al*. (2013) suggest that ablation therapy does not increase the incidence of myopia; rather, myopia is correlated with the severity of ROP (Quinn et al., 2013). In their recent 6 year follow-up of children, in the ETROP trial, more than 60% of children treated with laser for ROP had myopia (>-0.25D) and 33% had myopia above -5.00D (Quinn et al., 2013). The incidence of myopia in children who had laser treatment for threshold ROP was more than double of those for whom ROP did not reach threshold (untreated because their ROP spontaneously regressed). The analysis excluded children who had untreated ROP that progressed and resulted in conditions that made refracting difficult or had undergone procedures other than ablation therapy. This study concluded that there appeared to be a higher incidence of myopia in laser treated eyes than untreated regressed ROP, because vision was preserved in those with severe ROP (who would

have been blind without laser treatment), who were more prone to be myopic (Quinn et al., 2013). Myopia is common in children born preterm who did not develop ROP, with approximately 3-20% of children born preterm developing myopia (Hsieh et al., 2012). In a large population study in Australia (Sydney Myopia Study), which included both children born preterm and at full term, the overall incidence of myopia in children was 2.2% at 6 years of age (French et al., 2013; Ojaimi et al., 2005). However, children born preterm who had severe ROP (treated or untreated ROP) had an even higher incidence of myopia, with 30-80% of children with any ROP becoming myopic (Hsieh et al., 2012). The increased incidence of myopia in children who had ROP as a preterm baby may be due to altered growth of the anterior chamber depth and optical components (corneal curvature and crystalline lens thickness) rather than an increased axial length which is seen in children with infantile myopia and myopia which develops in adolescence (Cook et al., 2008; Lee et al., 2017). Some studies in children with ROP suggested that rod outer segments are damaged due to the insult of ROP on the retina and change in peripheral retinal profile, which may be related to the development of myopia (Barnaby et al., 2007; Hansen & Fulton, 2000).

1.3.8.3 Astigmatism

Children born preterm have commonly been reported to have a higher prevalence of astigmatism compared to the general population. Clinically significant astigmatism has been defined as cylindrical power ≥1.00DC (Holmström et al., 1998). In the Sydney Myopia Study, the prevalence of astigmatism was 4.8% in a population cohort of 1712 children at the age of 6 years (Huynh et al., 2006). In children born preterm, those with no ROP, mild ROP or spontaneously regressed severe ROP had a similar prevalence of astigmatism (10-20%) at 10 years of age (Larsson & Holmström, 2006). In the ETROP trial, 43% of eyes treated at high-risk prethreshold ROP developed astigmatism over 1.00D at 3 years of age and 50% at 6 years of age, which is similar to a population study in Sweden (Davitt et al., 2009, 2011; Larsson & Holmström, 2006). There is a tendency of increasing incidence and magnitude of astigmatism with severity of ROP but it does not seem to be correlated with retinal residua (Quinn et al., 1992; Yang et al., 2013), while the magnitude of astigmatism appears to correlate well with corneal curvature (Yang et al., 2013). There is inconclusive data as to whether ablation therapy for ROP has any effect on the prevalence of astigmatism but there is general agreement for the need of early and continuous follow-up of preterm children with or without ROP as a baby to screen for significant astigmatism, as uncorrected astigmatism can result in amblyopia (Davitt et al., 2011; Larsson & Holmström, 2006; Yang et al., 2013).

1.3.8.4 Contrast sensitivity

Contrast threshold is the measure of the minimum difference in luminance of an object and its background before it can be detected or resolved (Richman et al., 2013), of which contrast sensitivity is the inverse. While VA is a function of vision at high contrast, contrast sensitivity is important for activities of daily living as visual conditions encountered everyday show varying levels of contrast. Reduced contrast sensitivity can also be an indication of brain injury in the absence of any signs of ocular abnormalities (Pelli & Bex, 2013). Children born preterm have reduced contrast sensitivity at 10 years of age across all spatial frequencies when compared to children born full term (1.49 to 1.73 preterm v 1.30 to 1.68 term, $p<0.05$) (Larsson et al., 2006). Severe ROP also appears to reduce contrast sensitivity across all spatial frequencies compared to babies without ROP (Cryotherapy for Retinopathy of Prematurity Cooperative Group, 2001a) but this has not been a universal finding (Larsson et al., 2006). Although contrast sensitivity in children with severe ROP was not affected by cryotherapy or laser photocoagulation, reduced sensitivity to high spatial frequencies (seen as a reduction in VA) have been found in children who had cryotherapy for severe ROP compared to children without ROP (Cryotherapy for Retinopathy of Prematurity Cooperative Group, 2001; McLoone et al., 2006). The literature in this area is limited and would benefit from more research into contrast sensitivity at different spatial frequencies within the different ROP severity groups.

1.3.8.5 Peripheral Vision

Laser photocoagulation and cryotherapy reduce peripheral retinal tissue at the point where the avascular retina has been ablated following severe ROP (Early Treatment for Retinopathy of Prematurity Cooperative Group, 2005; Palmer et al., 1991). Visual fields in patients who have previously had laser photocoagulation or cryotherapy have a slight constriction of 3-37% in the peripheral visual field after treatment and visual field deficits correspond with treated areas (Cryotherapy for Retinopathy of Prematurity Cooperative Group, 2001b; Kremer et al., 1995; McLoone et al., 2007). This small reduction in visual field does not have functional significance in most patients and this loss of visual field does not appear to progress with age (Kremer et al., 1995; McLoone et al., 2007). When visual fields in children following cryotherapy for threshold ROP were compared with children who had spontaneously regressed threshold ROP, there was less constriction in the treated group. This indicates that although ablative treatment reduces visual field, it preserves more of the visual field than no ablative treatment in threshold ROP (Cryotherapy for Retinopathy of Prematurity Cooperative Group, 2001b; Quinn et al., 1996). Wide-field retinal imaging (Witmer & Kiss, 2013) allows correlation of structure of the peripheral retina and visual field function. Cortical damage from PVL and optic atrophy (either associated with PVL or from a loss of optic nerve axons due to ROP damage

to the inner retina) can cause defects in peripheral vision so more research in this area would give insight into the causation of visual field constriction and its effects (Jacobson & Dutton, 2000; Repka, 2002; Siatkowski et al., 2013). There has been growing evidence of cortical damage being associated with childhood blindness and visual impairment (Haddad et al., 2007; Hellgren et al., 2009; Repka, 2002; Rudanko et al., 2003; Slidsborg et al., 2012). Studying the optic nerve and retina may allow further investigation into whether visual impairment in ROP is due to damage of the retina, cortex or both.

1.3.8.6 Electrophysiology

Ocular electrophysiology is the measure of the electrical properties of biological cells and tissues in the eye and brain to evaluate visual function with different visual stimuli (Heckenlively & Arden, 2006). Clinically, ocular electrophysiology can be used to evaluate visual function objectively when the child is unable to give verbal responses (van Genderen et al., 2006). Flash electroretinogram (ERG) is most commonly used to assess ocular development through evaluating the photoreceptor and inner nuclear layers of the retina (Holder et al., 2010). Children born preterm who previously had ROP appear to have a delayed rod photoreceptor response, possibly due to rod outer segments dysfunction, particularly in the parafoveal area (Barnaby et al., 2007; Reisner et al., 1997). Barnaby *et al* studied the dark adapted threshold of children without ROP and those with mild ROP over 3-9 sessions before 18 months of age, and found that there was slower development of thresholds in the parafoveal area compared to the retinal periphery in children who had mild ROP, to reach levels found in adults (Barnaby et al., 2007). The average age that children with previous ROP reached adult threshold levels was 12.11 months compared to 6.25 months in term born children ($p<0.01$); and there was also a slower median catch up to threshold levels between the parafoveal area and peripheral retinal area in the children with ROP when compared to age-matched term born children (0.03 log unit.months^{-1} v 0.14 log unit.months^{-1}, $p<0.01$) (Barnaby et al., 2007). For those with a history of ROP, particularly those who developed high myopia (>-5.00D), elevated parafoveal threshold remained in older children and into adolescence (Hansen et al., 2015; Quinn et al., 1992). In rat models, the rod outer segment structure and molecular properties are disturbed in active stages of ROP through the lack of oxygen (Jiang et al., 2002). Rod cells possibly contribute to the progression of ROP through the increasing demand for aerobic energy, which results in hypoxia of the peripheral retina and subsequent abnormal blood vessel growth (Fulton, Akula, et al., 2009). There appears to be a correlation in reduced rod sensitivity and amplitude of response with increasing severity of ROP; it has been proposed that in severe ROP, the acute vascular abnormalities associated with injury to the post-receptor neural circuitry is irreparable (Harris et al., 2011). Cone function and macular function is

thought to be slightly reduced in children with mild ROP, but to a lesser extent than rod function (Ecsedy et al., 2011; Fulton et al., 2005). A recent study has found reduced rod and cone function in children aged 6.5 years who were born at less than 27 week's gestational age and did not find an association with ROP (Molnar et al., 2017). Further investigation would be required to clarify whether gestational age is associated with retinal dysfunction and whether these abnormalities contribute towards the adverse visual outcomes experienced by children born preterm.

1.3.8.7 Retinal and Optic Nerve Structure

Different layers of the retina have been assessed in children born preterm using optical coherence tomography. In normal development, differentiation and neuronal cell growth of the fovea is completed by 29 weeks of gestation (Maldonado et al., 2011). However, following preterm birth, there appears to be disruption in migration of the inner layers of the retina, which results in a thicker profile at the fovea, particularly in children who previously had ROP (Åkerblom et al., 2011; Baker & Tasman, 2010; Ecsedy et al., 2007; Fieß et al., 2017; Wang et al., 2012b; Yanni et al., 2012). It is uncertain whether foveal thickness affects VA as there have been varying results (Recchia & Recchia, 2007; Reynolds et al., 1993; Soong et al., 2008; Yanni et al., 2012). In a study by Free *et al.*, abnormal development of the fovea correlated with a decrease in gray matter volume at the occipital cortex (Free et al., 2003). It is unknown whether gray matter volume is also reduced following ROP. Apart from changes in the retina, some studies have suggested preterm children may also be at higher risk of optic nerve hypoplasia (Arnold, 2008) and changes to the optic nerve tissue volume and cupping area (Fledelius, 1978). Evaluating the macula and peripapillary nerve fibre layer using optical coherence tomography and electrophysiological diagnostic tests such as pattern electroretinogram (pattern ERG) and pattern visually evoked potentials (pattern VEP), which measure electrical activity in the retinal ganglion cells and cortical function (Holder et al., 2010), may give more insight into optic nerve function. There have been conflicting results from different studies regarding peripapillary nerve fibre layer thickness so more research is needed in this area (Tariq et al., 2011; Wang et al., 2012a). It is speculated that ablation therapy or severe ROP could possibly have a destructive effect on ganglion cells but the exact mechanism is unknown; also whether these retinal abnormalities affect visual function still require clarification (Åkerblom et al., 2012).

1.4 Cortical Visual Processing, Neuropsychological Development and Preterm Birth

Although ROP treatments have greatly reduced the incidence of blindness in preterm babies, preterm birth has been associated with a number of visual deficits that may be due to abnormal cortical development or brain injury (Lennartsson et al., 2014; Pavlova et al., 2006; Thompson et al., 2014). Children born preterm are at risk of mild visual impairment (reduced best-corrected visual acuity) (Haugen et al., 2012), strabismus (Marlow et al., 2005; VanderVeen et al., 2011), abnormal stereopsis (Geldof et al., 2014), and refractive error (Larsson et al., 2005; Quinn et al., 2013). These deficits are likely to be detected through childhood vision screening programmes, ophthalmological follow-up or optometric care (Cotter et al., 2015; Hopkins et al., 2013). However, other vision problems that have been linked to preterm birth are not routinely screened for due to time constraints and the need for challenging and/or non-standardised tests (Hopkins et al., 2013; Tschopp et al., 1998). These include reduced visual fields (Larsson et al., 2004; Lennartsson et al., 2014), impaired contrast sensitivity (Larsson et al., 2006), and cortical processing deficits revealed by tasks requiring global form and motion perception or visual-motor integration (Braddick et al., 2003; Butcher et al., 2012; Chaminade et al., 2013; Dall'oglio et al., 2010; Downie et al., 2003; Foulder-Hughes & Cooke, 2003; Jakobson et al., 2006; Jakobson & Taylor, 2009; MacKay et al., 2005; Santos et al., 2009; Williamson et al., 2014). Such deficits may contribute to the difficulties in learning, attention, behaviour and cognition that some children born preterm experience despite having normal or near-normal VA (Aarnoudse-Moens et al., 2011; De Kieviet et al., 2012; Foulder-Hughes & Cooke, 2003; Johnson et al., 2011; Marlow et al., 2007; Simms et al., 2015). Reduced performance in neuropsychological tests of vision have also been shown in children born preterm with brain injury (Fazzi et al., 2009; Luu et al., 2009; Taylor et al., 2004).Therefore, it is important to consider the development of visual perception and visuomotor integration in children with a history of preterm birth, and their associations with neurological development.

1.4.1 Preterm birth associated brain injury, microstructural changes and visual outcomes

Brain injury in preterm birth can have lasting effects on all aspects of development including cognition, mobility, social cognition and vision (Duerden et al., 2013). Intraventricular haemorrhage (IVH) and PVL are common causes of neonatal mortality and morbidity in extremely low birth weight babies (Guzzetta, Cioni, et al., 2001; Zhang et al., 2013). With the advances of neonatal care and earlier screening programmes, there has been a reduction in cerebral related mortality (Heuchan et al., 2002).

However, many studies of IVH, periventricular haemorrhages and PVL in children born preterm have shown a wide range of associated adverse visual outcomes such as strabismus (Cioni et al., 1997; Resch et al., 2015), refractive error (Harvey et al., 1997), reduced VA (Uggetti et al., 1996; Weinstein et al., 2012), visual field deficits (Jacobson et al., 2006; Lennartsson et al., 2014; Weinstein et al., 2012), oculomotor issues (Fazzi et al., 2012), and optic atrophy and optic nerve hypoplasia (Jacobson et al., 2003). Vision related brain structures affected by ischaemia and haemorrhage (Pike et al., 1994) include white matter tracts (optic radiation) (Thompson et al., 2014), lateral geniculate nucleus (Uggetti et al., 1996), corpus callosum (Skranes et al., 2007), central gray matter (Sripada et al., 2015) and the thalamus (Ricci et al., 2006). There is difficulty with understanding the effect of brain damage on visual outcomes due to a variable presentation following brain damage, age of which the damage happens and the age of which testing is performed, the variety of tests used, and the majority of research has been based on case studies and small cohort studies (O'Shea et al., 2009; Volpe, 2009).

Cerebral palsy is a common condition affecting children born preterm; the worldwide prevalence for cerebral palsy is 2.11 per 1000 live births and it is much more common in children who are born very preterm compared to children born after 36 weeks' gestational age (111.80 v 1.35 per 1000 live births) (Oskoui et al., 2013). Cerebral palsy is a term used to describe "*a group of disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain*" (Workshop on Definition and Classification of Cerebral Palsy, July 2004) (Rosenbaum et al., 2007). Cerebral palsy can be a result of brain insults throughout the fetal development until infancy and is often associated with hypoxia or infections, particularly PVL (Drougia et al., 2007; Wang et al., 2014). Current management is aimed at improving physical function and reducing functional disability (Novak et al., 2013). However, cerebral palsy is a life-long condition and can affect all aspects of daily living, particularly in severe cases (Krakovsky et al., 2007). As well as the distinctive motor and postural impairments, cerebral palsy has also been associated with other adverse outcomes including epilepsy (Johnson et al., 2002), visual impairment (Fazzi et al., 2012; Kozeis et al., 2015), intellectual disability (Gabis et al., 2015; Johnson et al., 2002), and behavioural deficits (Cummins et al., 2005). Refractive error and strabismus have common been found in children with cerebral palsy, and incidence of visual deficits appear to increase with more severe cerebral palsy (Dowdeswell et al., 1995; Ghasia et al., 2008; Saunders et al., 2010). Early treatment for strabismus in the children with milder forms of cerebral palsy may improve binocular vision (Collins, 2014). Cerebral visual impairment is also common in children with cerebral palsy, where there can be reduction in VA, visual field loss or deficits in visual perception in the absence of ocular pathology (Fazzi et al., 2012; Guzzetta, Mercuri, et al., 2001). These visual deficits

have been proposed to be associated with eye movement disorders and reduced motor development common seen in children with cerebral palsy (Guzzetta, Mercuri, et al., 2001; Lew et al., 2015).

Preterm birth and low birth weight have been associated with several changes in brain microstructure. In a study of 108 participants at 16 years old, brain structure via MRI and neuropsychological outcomes were compared between adolescents born with very low birth weight (<1500g) and term born controls (Taylor et al., 2011). Lower birth weight was significantly associated with overall reduced brain volumes as well as reduced volumes of pericallosal cerebral white matter, grey matter and caudate nucleus; lateral ventricles were larger and corpus callosum had a smaller total area. These changes in brain structure were associated with poorer performance in tests of IQ, perceptual-motor organization and executive function (Taylor et al., 2011). Changes within the corpus callosum and white matter tracts have also been demonstrated in other studies. Diffusion tensor imaging studies have shown lowered fractional anisotropy (directional diffusion within white matter) in the corpus callosum and white matter association tracts (Kelly et al., 2014; Skranes et al., 2008; Sripada et al., 2015). These microstructural changes were associated with lowered performance in visuomotor integration. However, all these studies included individuals with abnormal cranial ultrasounds near birth or cerebral palsy (Skranes et al., 2008; Sripada et al., 2015; Taylor et al., 2011). Therefore, it is unknown whether the visual motor integration deficits are due to preterm birth or the changes to brain structure associated with preterm birth.

1.4.2 Dorsal and ventral processing streams

Late last century, Mishkin and Underleider identified two cortical pathways for visual processing (Mishkin & Ungerleider, 1982; Mishkin et al., 1983). One pathway involving the inferior temporal cortex and supporting object recognition while the other involving the posterior parietal cortex and supporting object localisation (Mishkin & Ungerleider, 1982; Mishkin et al., 1983). The resulting dual pathway theory of visual processing was further developed by Goodale and Milner (Goodale & Milner, 1992). They described a ventral cortical stream receiving input from the parvocellular layers of the lateral geniculate nucleus and projecting through the ventral regions of the visual cortex to the temporal lobe and a dorsal stream with magnocellular input projecting through dorsal areas of the visual cortex and area V5 to the parietal lobe (Goodale & Milner, 1992). The ventral stream is concerned with form perception (what an object is), and the dorsal stream supports motion perception, object localisation and visuomotor control (how to interact with an object) (Goodale & Milner, 1992). Although these cortical streams differ in their functional specialisations, it is now clear that they are interconnected and rely on a number of common cortical areas (Braddick et al., 2000).

Motion integration is sequential and begins with the detection of motion signals within small, local regions of the visual field (Smith et al., 1998). Local motion signals can be generated by changes in luminance (first-order motion) or changes in components of the visual scene other than luminance such as contrast, depth or texture (second order motion) (MacKay et al., 2005; Smith et al., 1998). Detection of first order motion is hypothesised to involve processing at the level of the primary visual cortex (V1) whereas second order motion may involve both the primary and extrastriate visual cortices (Smith et al., 1998). Subsequent processing in extrastriate dorsal stream areas such as V3 accessory cortical area (V3A) (Tootell et al., 1997), and V5 (also called the middle temporal area (MT)) (Watson et al., 1993) enable integration of local signals into a coherent, global perception of motion (Braddick et al., 2000). Similarly, global form perception is hypothesized to involve local feature processing at the level of the primary visual cortex, followed by feature integration within ventral areas of the extrastriate visual cortex and the inferior temporal cortex (Wilson & Wilkinson, 2015).

Psychophysical coherence threshold testing is frequently used to assess global motion (Livingstone & Hubel, 1987; Newsome & Pare, 1988; Taylor et al., 2009). The measurement of global motion perception typically involves a stimulus known as a random dot kinematogram (RDK) (Newsome & Pare, 1988). The stimulus is constructed from a field of moving dots. A certain proportion of the dots move in the same direction (signal dots) and the remaining dots move in random directions (noise dots). The observer's task is to indicate the direction of the signal dots. By varying the proportion of signal to noise (coherence) within the stimulus, it is possible to measure a motion coherence threshold which provides an estimate of the signal to noise ratio required for a particular level of task performance. Lower motion coherence thresholds indicate a higher sensitivity to global motion (Newsome & Pare, 1988). The underlying concept is that areas such as V5 are required to integrate the local motion signals generated by each dot into a global percept of coherent motion. Importantly, parameters such as dot speed, size, density, and stimulus presentation time can significantly influence motion coherence thresholds (Narasimhan & Giaschi, 2012).

1.4.3 Dorsal and ventral processing in children born preterm

Motion integration impairments in children born preterm have been revealed through psychophysical testing when compared to children born at full term (Atkinson & Braddick, 2007; Downie et al., 2003; Jakobson et al., 2006; MacKay et al., 2005; Taylor et al., 2009). Yet, form perception is relatively spared in children born preterm (Geldof et al., 2014; MacKay et al., 2005; Taylor et al., 2009). Consequently, the dorsal stream has been hypothesized to be particularly vulnerable to the effects of preterm birth on brain development (Braddick et al., 2003; Taylor et al., 2009).

MacKay *et al*. tested a group of 19 children born very preterm (ranging from 25-32 week's gestational age) and 19 children born at full term for sensitivity to first and second order local motion, and first order global motion at 6 years of age (MacKay et al., 2005). The local motion task involved direction discrimination (up/down) of a horizontally oriented sinusoidal grating that was either luminance modulated (first order) or contrast modulated (second order). Discrimination of the global motion direction (up/down) was tested using an RDK with variable coherence constructed from 300 black dots presented on a white background. The preterm group exhibited lower sensitivity to motion on all the tasks compared to the control group (MacKay et al., 2005). In particular, of the 19 children born preterm, only one child performed at the same level as the term born controls for all three motion types (MacKay et al., 2005). In contrast, when children in the same study were asked to indicate the orientation of the stationary stripes of the local motion task stimulus (either luminance or contrast modulated) as a test of form perception, there was no difference in sensitivity between children born preterm and those born at full term (MacKay et al., 2005). Taylor *et al*. later tested global motion, global form and biological motion in a similar population of children; although they found that children born preterm had reduced performance in all tasks, there was relative sparing of global form perception compared to global motion (Taylor et al., 2009). Both these studies suggest a differential effect of preterm birth on form and motion perception, which supports the theory of dorsal stream vulnerability (MacKay et al., 2005; Taylor et al., 2009).

As well as impairments in global motion perception, a number of studies have reported that children born preterm have reduced perception of motion-defined form (Downie et al., 2003; Jakobson et al., 2006) and biological motion (Pavlova et al., 2006; Williamson et al., 2014), both of which involve motion integration. The effect of brain injury on dorsal stream functioning has also been investigated in children born preterm. Downie *et al*. investigated whether motion-defined form perception was affected by periventricular brain injury (PVBI), which was defined as germinal matrix/IVH or hypoxic/ischaemic injury (Downie et al., 2003). The preterm group was divided into two subgroups: 11 children with normal head ultrasound scans and 24 children with PVBI and both subgroups performed significantly worse in the motion-defined form task than children born at full term, while there was no difference in performance between the children born preterm with and without PVBI (Downie et al., 2003). Conversely, Jakobson *et al*. found that the children who were born preterm and had no PVBI or ROP (n=11) had motion-defined form perception comparable to term born controls while children with mild PVBI (n=10; severe PVBI was excluded), ROP (n=12; most with stage 1 or 2 ROP) or both mild PVBI and ROP (n=10) had impaired motion-defined form perception (Jakobson et al., 2006). The authors concluded that mild ROP and PVBI are likely to be important risk factors for the

anomalous development of motion-defined form perception in children born preterm (Jakobson et al., 2006).

PVL and ROP have been associated with alterations in the optic radiations; however, it is unclear whether these alterations play a role in the development of motion perception deficits noted in children born preterm (Fledelius, 1978; Thompson et al., 2014). Few studies have measured motion perception specifically in children who previously had ROP (Jakobson et al., 2006; MacKay et al., 2005; Taylor et al., 2009) and the majority of experiments have involved the central visual field which is less likely to be affected by appropriately treated ROP. Therefore, the relative contributions of preterm birth *per se*, PVBI and ROP to motion-defined form perception impairments remains unclear. Past studies have included small numbers of subjects, particularly those who had PVBI or ROP, and the age range of tested children has varied. Therefore, further research with stratified groups is warranted.

Estimates of the normal developmental trajectories for form and motion perception differ between studies. For example, Parrish et al. found that while motion perception was adult-like at approximately 7 years of age, the ventral pathway continued to mature into late childhood (Parrish et al., 2005). But, in other studies, global motion, global form and biological motion perception were found to become mature between 7-14 years of age (Hadad et al., 2011; Parrish et al., 2005; Taylor et al., 2009; Williamson et al., 2014). Maturation of motion-defined form for children born at full term has also been reported to extend into the adolescence period (Bertone et al., 2010). These differences are perhaps the result of using different tests and parameters to evaluate visual perception. The majority of studies in preterm populations include children with immature form and motion perception. Therefore, it is currently unknown whether the effects of preterm birth on global motion perception that have been reported reflect a delay in maturation or an absolute deficit.

At present, we can only speculate on the real-world implications of the dorsal stream deficits that have been associated with preterm birth. Motion coherence thresholds measured using RDKs are correlated with reading rate in school aged children (Englund & Palomares, 2012; Kassaliete et al., 2015); nevertheless, the evidence between impaired motion perception and poorer reading performance is controversial (Skottun, 2015). In addition to reading speed, motion perception has also been linked to social cognition, particularly impaired biological motion perception (Pavlova, 2012; Williamson & Jakobson, 2014; Williamson et al., 2014). The combined effect of global motion and biological motion deficits may be associated with the lower educational achievement (Johnson et al.,

2011; Saigal, 2014) and poorer social relations (Hille et al., 2008) that have been reported in long-term follow-up studies of preterm birth. More data are needed to affirm these associations.

Motion processing can be improved through intensive training; a process known as perceptual learning (Masland, 1969; Urner et al., 2013). It is possible that perceptual learning could be used to improve global and biological motion perception in children born preterm. However, it is unknown whether training using specific tasks to improve certain aspects of motion perception will also translate to improvement in tasks involving more complex cortical processing such as visuomotor integration or reading (Nishina et al., 2009; Sasaki et al., 2009). In summary, current open questions in the field include whether reduced motion perception in children born preterm with or without PVL affects their ability to perform daily activities, the associations between ROP and motion perception, and whether early motion perception screening with potential early training would be beneficial for these children.

1.4.4 Neuropsychological tests

Tests of neuropsychological function and visuomotor integration also involve measures of dorsal stream function (Mishkin & Ungerleider, 1982; Santos et al., 2009). Based on results from studies using neuropsychological tests, there is a general consensus that children born preterm perform poorly in tasks involving motor skills (Clark & Woodward, 2010; Foulder-Hughes & Cooke, 2003; Marlow et al., 2007), aspects of visual perception such as discriminating line orientations, naming shapes or matching block patterns (Butcher et al., 2012; Marlow et al., 2007), and visuomotor integration (Foulder-Hughes & Cooke, 2003; Goyen et al., 2011) when compared to children of the same age who were born at full term. These deficits continue into later childhood (Molloy et al., 2013; Santos et al., 2009) and are even seen in adulthood (Chaminade et al., 2013). Furthermore, the incidence has not changed with advances in neonatal care (Geldof et al., 2012). Chaminade et al suggested that adults who were born preterm are unable to effectively use higher-order processing to perform action recognition tasks and thereby, compensate by relying heavily on low-level visual information (Chaminade et al., 2013). Many studies have found deficits in motor skills in children born preterm, especially in those who have had PVL (Maitre et al., 2009) or cerebral palsy (Palisano et al., 1997). Reduced VA (O'Connor et al., 2009) and severe ROP (Goyen et al., 2006; O'Connor et al., 2009) have also been associated with poorer visuomotor skills, particularly fine motor skills. Despite the advances in neonatal care and treatments, the proportion of children born preterm with minor motor skill deficits has remained higher than children born at full term (Foulder-Hughes & Cooke, 2003; Husby et

al., 2013; Marlow et al., 1993). More research into the underlying factors associated with reduced visuomotor skills are required to tailor management for these frequent and ongoing deficits.

Böhm *et al*. and Marlow *et al*. reported that children born preterm were more likely to perform poorly compared to term born controls in the NEPSY visual perception and motor skills domain (Bohm et al., 2004; Marlow et al., 2007). After intelligence was adjusted for, in Marlow's study, the preterm group still had poorer performance in the visual perception domain than term born controls (Marlow et al., 2007). Similarly, using VMI testing, children born preterm were also found to obtain standard scores that were significantly lower than children born at full term and performance remained poor after adjusting for cognitive scores (Foulder-Hughes & Cooke, 2003; Goyen et al., 2011). Performance in motor skills, visual perception and visuomotor integration tasks appear to be correlated with gestational age and birth weight, where children born at lower gestational ages and lower birth weights have poorer performance (Foulder-Hughes & Cooke, 2003). Poor depth perception has been associated with reduced fine motor skills (Alramis et al., 2016). Therefore, abnormal stereopsis may be one of the contributors towards the lowered performance in motor skills and visuomotor integration in children born preterm particularly as many children have strabismus and reduced stereopsis (Jakobson et al., 2006; Pennefather et al., 1999; Stephenson et al., 2007).

In young adults born preterm, lowered visuomotor integration scores have been associated with cortical changes including thinning in the lateral areas of temporal and parietal lobes along with thickening of the frontal lobe; reduced cortical surface area primarily in the frontal, temporal and parietal lobes; and reduced fractional anisotropy and radial diffusivities in association tracts, which may indicate changes in white matter structure (Sripada et al., 2015). Ventricular dilatation, corpus callosum thinning and impaired white matter structure have also been associated with reduced visuomotor and visual perceptual performance in adolescents born with very low birth weight (Constable et al., 2008). These findings highlight the complexity of the processes governing visuomotor and perceptual performance; understanding these factors, their aetiology and interconnections will provide insight into prevention and management of neuropsychological deficits associated with preterm birth.

Few studies have investigated the possible association between ROP severity and visual-motor integration (Beligere et al., 2015; Goyen et al., 2006; Molloy et al., 2016; O'Connor et al., 2009). At 3 years of age, visual-motor integration ability was not found not to vary significantly as a function of ROP severity in a cohort 45 children with stage 1-3 ROP (Goyen et al., 2006). However, O'Connor *et al*.

found a statistically lower score on fine motor skills tasks in children with zone 1 ROP (n=27) compared to those with zone 2 ROP (n=23); zone 1 is closer to the macula, the centre of vision, and likely to indicate more severe ROP (O'Connor et al., 2009). Children with severe ROP are more likely to have reduced vision, strabismus/amblyopia or refractive error, which can all affect visuomotor integration; consequently, there is an uncertainty of whether ROP *per se* affects visuomotor development, particularly as there is a paucity of longitudinal data (Goyen et al., 2006). However, all children born preterm with or without ROP or brain injury are at higher risk of deficits in these domains compared to children born at full term and may benefit from early screening (Goyen et al., 2011, 2006).

1.4.5 Implications of deficits in visual perception and visuomotor integration

From preschool to adolescence, visual perception, motor skills and visuomotor integration have been associated with educational outcomes, learning, behaviour and attention (Johnson et al., 2011; Molloy et al., 2015; Saigal, 2014). Children born very preterm experience less favourable academic outcomes, particularly in mathematics. In a cohort study of 204 children born extremely preterm (≤25 weeks gestational age) who were assessed at 6 years of age, 180 did not have any significant neurologic abnormality and were taught at a mainstream school (Marlow et al., 2007). However, the prevalence of impairments in visuospatial, visuomotor co-ordination, attention-executive function and gross motor function were higher than in their classmates born at full term. After adjusting for cognitive function, the academic performance of the children born preterm remained poorer than their classmates. The authors suggest that cognitive (Kaufman Assessment Battery for Children) and visuomotor (NEPSY and Movement Assessment Battery for Children) scores explained approximately 54% of the variance in academic performance for the children born preterm (Marlow et al., 2007).

At the 11-year follow-up, the children born preterm had significantly lower reading and mathematics scores when compared to their term born classmates. After exclusion of children with serious cognitive impairment and adjusting for the Mental Processing Composite, the effect size for mathematics was still large (Johnson et al., 2011). This difficulty in mathematics has been reported in other studies of school-aged children who were born very preterm or extremely preterm (Aarnoudse-Moens et al., 2011; Simms et al., 2014). For children born at full term who have difficulties with mathematics (developmental dyscalculia), the underlying mechanism has often been attributed to imprecise mathematical reasoning and structural/functional abnormalities in the intraparietal sulci areas of both cortical hemispheres (Price et al., 2007). However, in children born preterm, the mechanism has been associated with visuospatial working memory, visual processing and executive function skills. This is because the differences in mathematics ability in children born preterm

compared to term born children appeared to be minimised when adjustments for working memory and visual perception were made (Simms et al., 2014). Although visual perception has been shown to be impaired in many children who are born preterm, including those who are deemed "healthy" (absence of congenital malformations or major neurological/sensory problems); there is a lack of routine screening protocols in place to detect visual perception problems in children born preterm (Dall'oglio et al., 2010; Geldof et al., 2014).

1.5 Neonatal Hyperglycaemia

Babies who are born preterm are at high risk of developing neonatal hyperglycaemia. It has been estimated that approximately 50% of extremely low birth weight babies develop hyperglycaemia (blood glucose concentrations (BGC) >150mg.dL^{-1} or 8.3mmol.L^{-1}) during their first week of life (Hays et al., 2006). There is uncertainty of the prevalence of neonatal hyperglycaemia in babies born preterm due to a number of factors including the lack of a standard definition of neonatal hyperglycaemia (Hey, 2005; Pildes, 1986), blood sampling method (Beardsall et al., 2013; Woo et al., 2014), and the populations of babies studied (Beardsall et al., 2010; Pertierra-Cortada et al., 2014). Neonatal hyperglycaemia is associated with increased mortality (Alsweiler et al., 2013; Stensvold et al., 2015) and adverse outcomes such as sepsis (Andersen et al., 2004; van der Lugt et al., 2010), IVH (Auerbach et al., 2013; Hays et al., 2006) and ROP (Au et al., 2015; Lee et al., 2016; Mohamed et al., 2013). However, it is unknown whether there is a causal association between hyperglycaemia and these factors, or if it is purely a marker of severe illness (Hey, 2005). A recent retrospective observational study showed no associations between neonatal hyperglycaemia and neonatal outcomes or outcomes at 2 years of age after adjusting for gestational age, birth weight and socioeconomic status, which suggests that it is likely that neonatal hyperglycaemia is not an independent predictor of outcomes (Tottman et al., 2017). Currently, the main treatment of neonatal hyperglycaemia consists of insulin infusion and/or reducing the glucose intake of the parenteral feed (Sinclair et al., 2011).

1.5.1 Pathogenesis

Neonatal hyperglycaemia has been proposed to arise from multifactorial origins including iatrogenic glucose infusion overload (Stensvold et al., 2015), anomalous regulation of endogenous glucose production (Chacko et al., 2011; Farrag et al., 1997), relative insulin insufficiency (Hawdon et al., 1995; Mitanchez-Mokhtari et al., 2004), and reduced insulin sensitivity (Blanco et al., 2015; Mitanchez-Mokhtari et al., 2004). Using steady state glucose infusion with tracer infusion, it has been estimated

that babies born preterm have a basal glucose production rate of 3-7mg.kg^{-1}.min^{-1} (Bier et al., 1977; Farrag et al., 1997; Tyrala et al., 1994). Tyrala *et al*. found that babies born with a birth weight less than 1100g were only able to produce 33% of their daily glucose requirements (Tyrala et al., 1994). As a result, preterm babies are administered intravenous glucose infusion at a rate of 4-7mg.kg^{-1}.min^{-1} to meet basal glucose requirement as they are often unable to have enteral feeds in the first few days of life (Driscoll et al., 1972; Farrag et al., 1997; Hawdon et al., 1993; Mitanchez, 2007). However, intravenous glucose infusion has been associated with increased risk of hyperglycaemia (Cowett et al., 1979; Stensvold et al., 2015). It has been proposed that in order to reduce risk of hyperglycaemia while balancing BGC to prevent hypoglycaemia and fulfilling energy requirements, basal glucose rates should be accounted for when giving intravenous glucose (Sunehag & Haymond, 2002).

Despite monitoring of BGC and maintenance of intravenous glucose infusions to match basal energy requirements, some babies continue to be at risk of hyperglycaemia (Farrag & Cowett, 2000; Mitanchez, 2007). Hawdon et al found higher insulin concentrations in babies born preterm than babies born at full term (median 3.0 v 1.5mU.L^{-1}, $p<0.01$) (Hawdon et al., 1993). The same group later discovered that 34-70% of the total concentration of insulin and pro-peptides in a group of babies born preterm (25-34 weeks) were proinsulin or partially processed proinsulin molecules (Hawdon et al., 1995). Proinsulin is approximately ten times as less sensitive to plasma glucose than insulin (Mitanchez-Mokhtari et al., 2004). This has led to the hypothesis that the islet β-cells from the immature pancreas secrete proinsulin rather than insulin and these proinsulin molecules are not entirely cleaved into insulin (Kairamkonda & Khashu, 2008; Mitanchez-Mokhtari et al., 2004), resulting in reduced sensitivity to insulin, and subsequent reduced glucose uptake into peripheral tissues and the liver, and may increase gluconeogenesis (Blanco et al., 2015; Mahaveer et al., 2012).

Concurrently, raised plasma glucose concentrations are not accompanied by an increase in insulin production (Goldman & Hirata, 1980). In adults, there is reduced glucose production when the rate of glucose delivered to the liver is equal to or more than the hepatic glucose output (Farrag et al., 1997). However, many studies have shown even when plasma glucose concentrations are high, there is incomplete auto-regulation of glucose production in babies born preterm (Chacko et al., 2011; Farrag et al., 1997; Sunehag et al., 1994). A combination of defective insulin production and relative insulin insufficiency reduces the uptake of glucose from the bloodstream into tissues and causes poor regulation of insulin and glucose production. In conjunction with high glucose intake from intravenous glucose infusion to meet daily energy requirements, the result is a higher risk of transient neonatal hyperglycaemia in many babies born preterm.

1.5.2 Associated risk factors

Neonatal hyperglycaemia has been associated with lower gestational age and birth weight (Beardsall et al., 2010; Louik et al., 1985), illness and sepsis (Andersen et al., 2004; Fitzgerald et al., 1992), postnatal corticosteroid use (Koivisto et al., 2007), intravenous glucose infusions (Sunehag & Haymond, 2002; van der Lugt et al., 2010), brain injury (Alexandrou et al., 2010; Auerbach et al., 2013; Efron et al., 2003; Wikström et al., 2011), and ROP (Ertl et al., 2006; Garg et al., 2003; Kaempf et al., 2011; Mohamed et al., 2013). However, most of the research in these areas has been observational studies; therefore, causative associations have not been determined (Decaro & Vain, 2011). Infection and stress have been shown to be accompanied by hyperglycaemia in babies born preterm, especially if the baby was stable previously (Hey, 2005). A possible mechanism for hyperglycaemia with infection and stress is the increase in cortisol levels and pro-inflammatory markers that reduce insulin release as well as promote gluconeogenesis (Beardsall et al., 2010; Lilien et al., 1979). A long exposure time (>7 days) of antenatal corticosteroid may increase the risk of babies born preterm developing hyperglycaemia. However, the mechanisms behind the increase in blood sugar is unknown and it may be due to stress or nutrition related processes (Koivisto et al., 2007).

Neonatal hyperglycaemia has been implicated to be associated with cerebral injury, particularly IVH and white matter damage (Alexandrou et al., 2010; Hays et al., 2006). The associations are not very clear as other neonatal morbidities such as hypoxia from respiratory disorders and complicated labour may also result in brain injury. It is very important to investigate this association as cerebral injury can have varying effects on different functional aspects of an individual including mobility, cognition, behaviour, vision and hearing; and increase risk of mortality at term-equivalent age (Alexandrou et al., 2010; du Plessis, 2008). It has been proposed that the association between hyperglycaemia during the first 24 hours of life and white matter reduction is not a causal effect. However, it has been suggested that increasing blood glucose could increase oxidative stress and this may injure the oligodendrocytes and neurons (Alexandrou et al., 2010). Neonatal hyperglycaemia has also been hypothesised to reduce cerebral activity and increase the blood acidosis (Granot et al., 2012; Wikström et al., 2011). Another proposed theory on the association between hyperglycaemia and cerebral damage is that high BGCs exacerbate ischaemia by increasing lactic acid in affected areas. This combined with the high levels of metabolism within the neonatal brain can result in extensive cerebral damage (Efron et al., 2003). Currently, there is not enough evidence to establish the association between brain injury and neonatal hyperglycaemia in babies born preterm.

Neonatal hyperglycaemia has been found to be associated with the development of ROP of different severities in various retrospective case-control and cohort studies. In 2003, Garg *et al*. were first to identify a relationship between neonatal hyperglycaemia and ROP (Garg et al., 2003). Several retrospective case-control and cohort studies have since reported a higher incidence of ROP in babies with higher glucose concentrations or longer duration of hyperglycaemia. Some studies have also reported that hyperglycaemia is associated with higher incidence of severe ROP requiring treatment (Ertl et al., 2006; Slidsborg et al., 2017). Each study used different definitions of hyperglycaemia, i.e. >8.5mmolL^{-1} on 2 occasions at least 2 hours apart (Ertl et al., 2006); >150mg.dL^{-1} whole blood concentration (Mohamed et al., 2013); >150mg.dL^{-1} plasma glucose concentration (Ahmadpour-Kacho et al., 2014; Garg et al., 2003). However, a recent systematic review and meta-analysis of 9 studies showed no association of hyperglycaemia or increasing mean glucose concentration with ROP after adjusting for birth weight and gestational age (Au et al., 2015). Although the authors found an association between longer duration of hyperglycaemia and ROP, but this was only based on 3 out of the 9 studies (Au et al., 2015). In a retrospective database review of 24,548 babies born with birth weight <1000g and gestational age ≤32 weeks, neonatal hyperglycaemia was not found to be associated with severe ROP (any ROP requiring cryotherapy, laser therapy, vitrectomy, or intravitreal injection) (Lee et al., 2016). However, there was a trend for insulin use to be associated with severe ROP. From current evidence, neonatal hyperglycaemia has not been shown to be a definite risk factor for ROP and further investigation is required to determine whether there is a casual relationship.

1.5.3 Screening and diagnosis

A standard definition of neonatal hyperglycaemia has not been determined as BGC is a continuous measurement and no specific glucose concentration threshold has been found to show adverse effects in all babies born preterm with neonatal hyperglycaemia (Hey, 2005). The generally agreed definition for neonatal hyperglycaemia based on historical studies and statistical analysis is whole BGC >7mmol.L^{-1}, which is approximately 11-18% less than plasma BGC (~8.3-8.5mmol.l^{-1}) (Farrag & Cowett, 2000; Hey, 2005; Kuwa et al., 2001). BGC is generally measured from blood samples collected using a heel prick test, venepuncture or from an arterial line in the NICU (Barker & Rutter, 1995; Brehmer, 2014). Although small blood samples via heel prick test can be quickly obtained, sampling can cause discomfort for the baby (Shah & Ohlsson, 2011). The accuracy of the tests to measure a "true measurement" of BGC can be affected by many variables including sample collection method and location (Kuwa et al., 2001), method of blood analysis (Carroll et al., 1970; Williams et al., 1970), and possible issues with blood glucose measurement devices (Rebel et al., 2012). Most current clinical

methods provide measurements at a single point of time, which reduces the ability for monitoring small short fluctuations in BGC.

To improve monitoring of changes in BGC, which is important in assessing treatment for neonatal hyperglycaemia, investigations into continuous glucose monitoring have been undertaken. Beardsall *et al*. performed a validation study on the use of a continuous glucose monitoring sensor (CGMS System Gold, Medtronic, Minneapolis, Minnesota, USA) in a cohort of 188 control babies participating in the Neonatal Insulin Replacement Therapy in Europe Trial (NIRTURE) (Beardsall et al., 2013). A disposable glucose oxidase-based platinum electrode sensor was inserted subcutaneously in the lateral thigh of the infant within 24 hours of birth. The sensor was used up to 7 days and the authors did not report any adverse effects at the site of insertion. The study concluded that the CGMS was good at screening for hyperglycaemia above 10mmol.L^{-1} (sensitivity 88%, specificity 98%, positive predictive value 90% and negative predictive value of 98%) but it was not as good for detecting hypoglycaemia below 2.6mmol.L^{-1} (sensitivity 17%, specificity 100%, positive predictive values 40% and negative predictive value 99%) (Beardsall et al., 2013). One of the limitation of the CGMS is the need of calibration with glucose concentrations measured from blood samples, which means blood samples would still be needed (Beardsall et al., 2013). More research would be needed to identify the benefits of using continuous glucose monitoring compared to intermittent glucose blood sampling and also the effects of using the continuous glucose monitoring devices for a longer period of time before these devices can be used in a clinical setting.

1.5.4 Treatment

The two main treatment options for neonatal hyperglycaemia are reducing glucose infusion rate and/or using an insulin infusion (Ogilvy-Stuart & Beardsall, 2010). Typically, the glucose infusion rate given to babies born preterm is much higher than the basal endogenous glucose production rate of 4-7mg.kg^{-1}.min^{-1} in order to provide the necessary basic energy requirements (Bottino et al., 2011). One study suggested that a stable preterm baby would require 6mg.kg^{-1}.min^{-1} of glucose infusion with an additional 2-3mg.kg^{-1}.min^{-1} dose to support protein production; and that a higher infusion rate would be needed for babies born preterm who were ill (Thureen, 1999). The minimum amount of glucose infusion needed to support the growth of the baby without increasing the BGC has not been identified (Kairamkonda & Khashu, 2008). The other form of treatment of neonatal hyperglycaemia is the use of an insulin infusion. Although insulin is used routinely to treat high BGC in adults with type 1 diabetes mellitus (Klein et al., 2008), the effects of insulin on growth in babies born preterm are poorly understood (Beardsall & Dunger, 2008; Bottino et al., 2011; Kairamkonda & Khashu, 2008). There is

evidence from randomised controlled studies of early insulin therapy to prevent neonatal hyperglycaemia (NIRTURE trial) (Beardsall, Vanhaesebrouck, et al., 2007) and tight glycaemic control of preterm hyperglycaemic babies using insulin (HINT trial) (Alsweiler et al., 2012) showing no improvement in mortality rate or reduction of adverse outcomes. The HINT trial showed a reduced linear growth and increase in fat mass with insulin treatment in babies born preterm with neonatal hyperglycaemia (Alsweiler et al., 2012). Although tight glycaemic control reduced BGC in babies with neonatal hyperglycaemia, babies also had higher risk of becoming hypoglycaemic, which has been associated with increased risk of occipital lobe damage and visual impairment (Tam et al., 2008). More studies on the long-term effects of insulin treatment are needed to clarify the effectiveness of this treatment (Bottino et al., 2011; Ogilvy-Stuart & Beardsall, 2010).

1.6 Neonatal Nutrition and Growth

Providing optimal nutrition for babies born preterm is important for the optimal growth and neurodevelopment of the baby. However, the optimal nutritional intake for babies born very preterm is unknown (Cormack et al., 2016; Uthaya & Modi, 2014). Babies born preterm often have reduced postnatal growth compared to babies who remain *in utero* and this has been associated with poorer neurodevelopment (Cooke, 2005; Yeung & Smyth, 2003). Current research in this area has focused on the nutritional intake that would enable the very preterm born baby to grow at a similar rate as an intrauterine fetus of the same gestational age and whether improvement in extrauterine growth would be associated with improved health and neurodevelopment (Cormack et al., 2016). However, this has been complicated by several issues including the difficulty of accurately measuring intrauterine nutrition and fetal growth compared to postnatal preterm growth (Elirenkranz et al., 1999; Hendricks, 1964; Kennaugh & Hay, 1987), differing methods of providing nutrition and measuring extrauterine growth (Uthaya & Modi, 2014; Young et al., 2016), and the ability to provide the baby with the recommended nutritional intake (Cormack et al., 2011). This is further complicated by uncertainty as to whether the growth of a preterm born baby at the rate of which they would have grown if they had remained *in utero* would actually enable the child to have a healthy development or not (Thureen & Heird, 2005). Nutrition near birth may also alter the risk of metabolic disease in later life (Ong et al., 2015; Tinnion et al., 2014).

1.6.1 Fetal growth

Before a baby is born, all the nutrients for the fetus are provided *in utero* by the mother through the placenta, and fetal growth is determined by many factors including genetics, maternal health, maternal nutrition, and fetal absorption of nutrients (Gluckman & Hanson, 2004). The majority of fetal energy is provided by metabolism of glucose (80% of energy requirement), lactate and amino acids that are transported from maternal blood to the fetus through the placenta (Herrera & Ortega-Senovilla, 2017; Murphy et al., 2006). Fetal growth is predominantly mediated by insulin-growth factors (IGF-1 and IGF-2) and leptin (Clemmons, 1997; Jones & Clemmons, 1995). Early in gestation, IGF-2 is the main regulator of growth and it is not affected by maternal nutrition (Gicquel & Le Bouc, 2006). After the first 2 months of gestation, fetal growth becomes more dependent on IGF-1, which is sensitive to maternal nutrition. IGF-1 continues to be important in growth following birth (Gluckman & Hanson, 2004). It has been found that the majority of fetal weight gain is between 20 weeks and full term (Hendricks, 1964). This weight gain is from hypertrophy of cells and increasing stores of fuel until full term (Monk & Moore, 2004). When a baby is born preterm, the baby has not been able to build up a reservoir of nutrients, and with the loss of nutrients from the mother, combined with the immaturity of the gastrointestinal system and liver, the baby is reliant on parenteral and/or enteral nutrition to sustain life (Sunehag & Haymond, 2002; Thureen & Heird, 2005). The preterm born baby is at an increased risk of malabsorption and malnutrition as the gastrointestinal system continues to mature after birth, and this is significant particularly as this is during the time of rapid growth (Dobbing & Sands, 1973; Neu, 2007). Therefore, it is essential to understand the best nutritional intakes for optimal growth in this sensitive time. Babies born preterm rarely grow at intrauterine rates, even with current nutritional recommendations; therefore, it is unknown whether aiming for intrauterine growth rate is realistic (Cormack et al., 2016). Babies born preterm are also at risk of health problems, which may also affect nutritional intake (Fitzgerald et al., 1992).

1.6.2 Parenteral nutrition for babies born preterm

Many postnatal nutritional recommendations are based on attempting to improve weight gain to match expected intrauterine weight according to gestational age of the preterm born baby and aim to provide necessary nutrients for metabolism and growth (Cormack et al., 2016). As babies born preterm are at risk of necrotising enterocolitis (NEC), respiratory disease and gastrointestinal immaturity (delay of hormone production and lowered intestinal motility), these babies are often started on parenteral nutrition via intravenous infusion of nutrients, although recently small enteral feeds are recommended from day one after birth (Dutta et al., 2015; Ziegler, 2011). Babies born

preterm have a high rate of insensible water loss, due to the large surface skin area and increased permeability of water through the epidermis, which can cause significant dehydration (Rutter & Hull, 1979). This loss of water affects the electrolyte balance of the baby and this needs to be accounted for when giving parenteral nutrition to provide adequate water, energy and caloric requirements while maintaining acid-base balance and electrolyte balance (Bhatia, 2006). Nutritional requirements for babies born preterm vary with gestational age and health status. It has been estimated that in stable babies who were born preterm and weighing <1500g require approximately 120kcal.kg^{-1}.day^{-1} for sustained growth (Denne, 2001), while fetal uptake of protein between 23 and 27 weeks' gestational age has been estimated to be between 3.6 to 4.8g.kg^{-1}.day^{-1} (Hay et al., 1999). Babies who are sick may need additional energy due to increased metabolic rates (Fitzgerald et al., 1992). Parenteral nutrition is given intravenously and consists of: carbohydrate, protein, fat, nitrogen, electrolytes, fluid, minerals, and trace elements (Brine & Ernst, 2004). Investigations of the proportions of these substrates required by babies born preterm have been conducted; however, in this review, we will focus on protein supplementation.

1.6.3 Protein supplementation

Protein supplementation for babies born preterm has been investigated since the 1940s (Heird & Anderson, 1977). Protein supplementation in enteral feeding increases weight gain. However, high daily protein intake (>4.5g.kg^{-1}) is associated with reduced poorer neurodevelopment and higher incidence of strabismus, as well as an increased risk of metabolic acidosis (Heird & Anderson, 1977). In the 1970s, babies who received only glucose infusion via parenteral nutrition were found to have a high rate of protein breakdown and increased weight loss (Heird & Anderson, 1977). Subsequently, protein supplementation was introduced into parenteral nutrition. However, the optimal nutritional intake and when to initiate supplementation for preterm born babies remains contentious (American Academy of Pediatrics Committee on Nutrition, 1977; Cormack et al., 2016; Trivedi & Sinn John, 2013). Current recommended protein supplementation in the first month after birth is between 3.5 to 4.5 g.kg^{-1}.day^{-1} (De Curtis & Rigo, 2012). However, often the baby is unable to reliably reach the recommended intakes as babies born preterm are administered low fluid volumes in the first week after birth, to reduce risk of patent ductus arteriosus and often are in need of additional infusions of medications, which reduce the volume of nutritional intake (Bhatia, 2006; Brine & Ernst, 2004). It is unknown whether current recommendations are optimal for growth and neurodevelopment.

Several studies have investigated different formulations of parenteral nutrition solutions on outcomes in children born with birth weight <1000g or <1500g (Christmann et al., 2016; Cormack et al., 2011;

Cormack & Bloomfield, 2013). The majority of studies have not found any difference in neonatal growth or early childhood development with increase of protein intake in the first week after birth (Cester et al., 2015; Christmann et al., 2016). In one study, babies in the higher protein intake group had a higher incidence of BPD but babies with BPD had similar fluid, lipid and protein intakes (Cormack & Bloomfield, 2013). At 2 years corrected age, there was no difference in the incidence of cerebral palsy or sensory impairment between the babies who had the lower or higher protein intake (Cester et al., 2015). There is paucity of data on the effects of neonatal nutrition on visual outcomes. One study found no difference in incidence of cerebral palsy or sensory impairment at 2 years correct age between preterm babies who had a lower or higher protein intake, while another study found a stronger response to global motion in 5 month-old babies who were born with very low birth weight and had an enhanced nutritional formulation compared to those who had a standard formulation (Blakstad et al., 2015). For longer term follow-up, one study found no associations between early postnatal nutrition and anthropometry measurements at 6 years of age (Peiler et al., 2013). Whereas, in the same cohort at 9.5 years of age, children who had higher early protein intake were found to have increased abdominal fat mass (Stutte et al., 2017). A Cochrane review of 4 randomised control trials comparing early (protein administered within the first 24 hours of birth) and late (protein administered after the first 24 hours of birth) protein supplementation for babies born preterm (gestational age <37 weeks) found no difference in mortality, early and late growth or neurodevelopment between these two modes of protein supplementation (Trivedi & Sinn John, 2013). From these data, protein supplementation may alter growth, but it is apparent that the optimal dose and timing of protein supplementation is unclear. As studies compared different values of nutritional intake, used various methods to calculate nutritional intake and measured growth and neurodevelopment with varying methods, it is difficult to ascertain the effect of protein supplementation on short term and long-term growth and neurodevelopment (Cormack et al., 2016). More consistency in reporting and randomised controlled trials with long-term follow up are required to shed light in this area.

1.6.4 Insulin-like growth factor 1, growth and neonatal complications

Insulin-like growth factors (IGFs) are peptide hormones that have similar structure to proinsulin; there are two main forms: IGF-1 is predominantly involved in postnatal growth and shares some of the functions of insulin while IGF-2 is involved in fetal growth and development, particularly in late gestation (Daughaday & Rotwein, 1989). The main function of IGF-1 is to mediate growth and differentiation through the IGF-1 receptor pathway and through modulation of growth hormone activity, but it also able to mediate glucose uptake via the insulin receptor at a lower affinity compared

to insulin (Jones & Clemmons, 1995; Ullrich et al., 1986). IGF-1 is mainly produced in the liver and is regulated by growth hormone and by insulin-like growth factor binding protein (IGFBP) via insulin (Clemmons, 1997; Schwander et al., 1983). Based on rat models that have shown poorer weight gain, lower serum IGF-1 concentration and severe neovascularisation in the retina when given inadequate postnatal nutrition, it has been hypothesised that postnatal nutrition in babies born preterm is important in regulating IGF-1 concentrations, which in turn affect growth and subsequent visual development (Hellström et al., 2016).

Although some studies have shown lowered IGF-1 concentration in babies with severe ROP, there are conflicting data (Hellstrom et al., 2001; Lineham et al., 1986; Löfqvist et al., 2006; Peirovifar et al., 2013). IGF-1 has been hypothesised to be an important molecule in ROP pathogenesis via regulating cell growth and VEGF gene expression (Hellström et al., 2003). In a murine model, lower serum IGF-1 concentration or blockage of the IGF-1 receptor was associated with lowered VEGF expression and VEGF activity, which inhibited retinal neovascularisation (Leske et al., 2006; Smith et al., 1999). Slower head growth postnatally in babies born preterm has been associated with increased risk of stage 3 ROP, while better neonatal weight gain has been shown to decrease risk of severe ROP(Löfqvist et al., 2006; Wu et al., 2012). However, the recent changes in neonatal nutrition have not appeared to improve postnatal growth (Cormack et al., 2011), and it has been shown that mean protein intake does not correlate with head circumference standard deviation score or development of ROP (Löfqvist, Andersson, et al., 2006; Löfqvist et al., 2006).

Apart from associations with ROP, lowered IGF-1 concentrations of preterm babies in the first 28 days after birth have been associated with increased risk of hyperglycaemia (Beardsall et al., 2014). Studies of diabetes in adults have also found lowered plasma IGF-1 concentrations (Shishko et al., 1994; Teppala & Shankar, 2010). Insulin and IGF-1 have similar properties and both can bind to both insulin and IGF-1 receptors, which has been shown to modulate serum IGF-1 concentrations (Jones & Clemmons, 1995; Ogilvy-Stuart et al., 1998). When there are low serum insulin concentrations, IGFBP-1 concentrations are elevated, which further inhibits release of IGF-1 (Jones & Clemmons, 1995). Insulin has a negative association with IGFBP-1. Therefore, with insulin treatment for neonatal hyperglycaemia, it is postulated that elevated levels of insulin will increase IGF-1 levels, which in turn promote retinal neovascularisation through upregulation of VEGF (Yoo et al., 2007). It has been hypothesised that with early elective insulin therapy or IGF infusion, the increase in IGF-1 and VEGF levels may promote normal retinal blood vessel growth in phase 1 ROP development and stop ROP progression (Beardsall et al., 2007; Ley et al., 2012; Löfqvist et al., 2009). From the current evidence,

any causative associations between lowered IGF-1 concentrations and neonatal hyperglycaemia are speculative. More research would be needed to ascertain the relationships between neonatal nutrition, postnatal growth and IGF-1 concentration, and between IGF-1, neonatal hyperglycaemia, and ROP before further investigation into the efficacy of insulin treatment or IGF-1 replacement in these conditions could be conducted (Beardsall et al., 2014; Ley et al., 2012).

1.7 Long-Term Vision Follow-up in New Zealand

In New Zealand, all babies born at <30 weeks' gestational age or birth weight <1250g, and selected babies outside these criteria with an unstable clinical course are recommended to be screened for ROP (Dai et al., 2015). For preterm babies who do not undergo ROP treatment, it is recommended they are reviewed as outpatients 6 months after discharge from acute ROP screening; while babies who had ROP treatment are reviewed 3 months after discharge from acute ROP screening and followed-up 12 monthly thereafter until the individual is able to be seen by community optometrists (Dai et al., 2015).

The Ministry of Health funds two national programmes to screen vision at different stages of childhood: B4 School Check and Year 7 vision check (Ministry of Health, 2008, 2014). Both programmes do not screen children who are already under ongoing care with an ophthalmologist or optometrist. The B4 School Check is a screening programme that assesses behaviour/development, growth, oral health, immunisation and hearing/vision screening in children who turn four after 1st June 2008 (Ministry of Health, 2008). Parents are also given information about health and referrals are made to appropriate services if deficits are noted in any of the above areas. Vision screening as part of the B4 School Check consists of distance VA testing using a letter chart, to screen for signs of amblyopia (lazy eye), refractive error or strabismus (squint) (Ministry of Health, 2008). Some of the children who miss the B4 school check vision module at 4 years of age may undergo vision screening at 5-6 years of age. The vision screenings are performed at the preschool/school that the child attends. The Year 7 vision check is similar to the B4 school check where distance VA is tested. Year 7 boys also have an Ishihara Colour Vision Test (Ministry of Health, 2014). It is known that preterm children with or without previous ROP are more likely to have poorer visual outcomes than children born at full term. However, it is unknown whether the B4 school check is able to adequately screen for the individuals in this population group who may need referral for further investigation and management of their vision.

1.8 Aims of this Thesis

Children born preterm are at risk of adverse visual outcomes, mainly due to ROP. However, since updates to ROP screening and earlier treatment of severe ROP, there has been paucity of data on the visual outcomes of children with ROP, particularly in New Zealand. Alarmingly, in 2010, global estimation of visual impairment from ROP were 20,000 babies becoming blind or severely visually impaired, and 12,300 developing mild or moderate visual impairment from ROP (Blencowe et al., 2013), which suggests that ROP remains a significant risk factor for visual impairment in preterm babies.

Preterm birth *per se* has been associated with adverse visual outcomes (O'Connor et al., 2007), independent of the effect of ROP. This may be due to the numerous complications of preterm birth and the treatment that preterm babies receive. One of the neonatal complications that affects many preterm babies is neonatal hyperglycaemia, which has been associated with ROP. Hyperglycaemia is often treated with insulin, which can cause hypoglycaemia. Hypoglycaemia has been associated with visual impairment. There are no long-term data on the effects of neonatal hyperglycaemia and its treatment with insulin on visual outcomes in later childhood.

Due to immaturity of organs at birth, preterm babies require parenteral nutrition to sustain life and are susceptible to effects of neonatal complications and treatments. Poor postnatal growth has been implicated as a cause of impaired neurodevelopment. However, there has been no consensus on the most effective nutrition for optimal growth and development. It is also unknown whether current nutrition regimes affect visual development.

The aim of the matched-control cohort described in chapter 3 was to determine whether neonatal hyperglycaemia affects visual outcomes and ocular growth at 7 years of age, and whether neonatal hyperglycaemia is associated with an increased risk of ROP.

The aim of the follow-up of a randomised controlled trial of tight glycaemic control with insulin for hyperglycaemia described in chapter 4 was to investigate whether tight glycaemic control using insulin compared with standard glycaemic control had any effects on visual outcomes and ocular growth at 7 years of age.

The aim of the neonatal nutrition cohort described in chapter 5 was to determine whether a reformulation of neonatal nutrition at the National Women's Health NICU affected visual outcomes and ocular growth at 7 years of age.

The aim of the EYE-SPY study described in chapter 6 was to investigate the effects of ROP on long-term visual development following updates to screening and earlier treatment of severe ROP. Functional visual outcomes, peripheral retinal findings and ocular biometry, and refractive error were compared between preterm children who had ROP, preterm children who did not develop ROP and children born at full term.

For the final aim of this thesis, data was pooled from both the PIANO and EYE-SPY studies (described in chapter 7) to explore how preterm birth affects visual outcomes in later childhood.

2 Methods

2.1 PIANO study

2.1.1 Study design

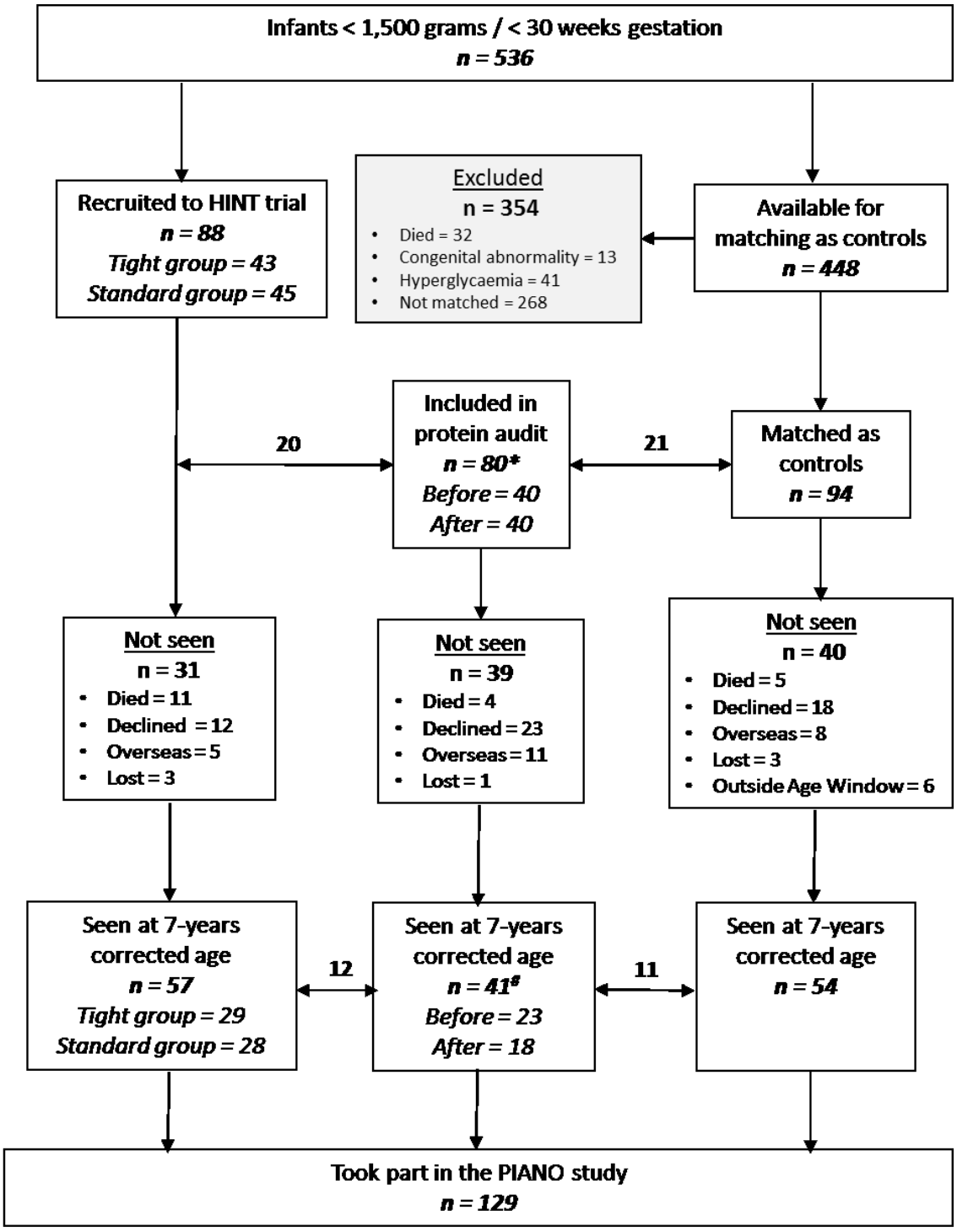
The Protein, Insulin and Neonatal Outcomes (PIANO) study was a follow-up cohort study of four overlapping groups of children. Between July 2005 and October 2008, 536 babies with birth weight <1,500g or gestational age <30 weeks were born at or admitted to the National Women's Health NICU, Auckland, New Zealand. Of these babies, 88 developed neonatal hyperglycaemia (defined as 2 consecutive BGC >8.5mmol.L^{-1} at least 4 hours apart) and were recruited into a randomised controlled trial (Hyperglycaemia and Insulin in Neonates Trial – HINT (Alsweiler et al., 2012). The HINT trial investigated the effects of managing neonatal hyperglycaemia with tight or standard (standard practice for insulin therapy of the NICU at the time of the trial) glycaemic control using insulin treatment on growth. During this period, there was also a change in intravenous nutritional practice, where the total protein intake during the first week of life was increased by reformulation of intravenous nutrition (IVN), while total intravenous fluid and sodium intake were reduced; an audit of these changes were performed from April 2006 to July 2007 (Cormack et al., 2011). For the PIANO study, children randomised to the HINT trial were matched with a preterm control who did not meet our criteria for hyperglycaemia taken from the Nation Women's Health NICU admission data. Children who were part of the IVN audit (April 2006 to July 2007) were also invited to participate in the PIANO study. Outside the main PIANO study cohort, to determine the effect of preterm birth on visual outcomes, a cohort of children who were born at ≥38 weeks' gestational age (term controls) were also recruited to participate in the PIANO visual assessment. Therefore, four sub-cohorts were defined from this study: HINT follow up cohort, neonatal hyperglycaemia follow up cohort, neonatal nutrition follow up cohort, and preterm birth follow up cohort.

2.1.2 Objectives

The overall objective of the PIANO study was to investigate the long-term metabolic, physical, neurodevelopmental and visual outcomes of neonatal hyperglycaemia, insulin treatment and neonatal protein intake. As part of the PIANO study, the research in this thesis will discuss whether neonatal hyperglycaemia (Chapter 3), tight glycaemic control of neonatal hyperglycaemia using insulin treatment (Chapter 4), neonatal nutritional intake (Chapter 5), and preterm birth (Chapter 7) affect visual outcomes in later childhood; and whether these factors are associated with ROP.

2.1.3 PIANO study strobe diagram

Figure 2-1 PIANO study strobe diagram



* Includes 20 infants from the HINT trial, 21 matched control infants and 39 additional infants only in the audit group.
\# Includes 12 infants from the HINT trial, 11 matched control infants and 18 additional infants only in the audit group.

2.1.4 Participants

2.1.4.1 HINT trial

Of the 536 babies with birth weight <1500g or gestational age <30 weeks who were admitted to National Women's Health NICU between July 2005 and October 2008, 154 babies developed hyperglycaemia (defined as 2 consecutive BGC >8.5mmol.L^{-1} at least 4 hours apart) and 88 of these hyperglycaemic babies were recruited in the HINT trial. Babies who were hyperglycaemic because of iatrogenic overdose of glucose, had major congenital malformation or were judged to be dying were excluded from participating in the HINT trial. BGCs were measured using a glucose oxidase method (ABL700, Radiometer Ltd, Copenhagen, Denmark) and urine was tested for glycosuria using urine test strips (Multistix reagent strips, Bayer Healthcare, Auckland, New Zealand). Insulin was administered by continuous intravenous infusion (Actrapid, Novo Nordisk, Bagsværd, Denmark). The babies were randomized into either the tight glycaemic control (Tight) group (n=43) or standard glycaemic control (Control) group (n=45) according to the NICU guidelines at the time. Babies in the tight group were administered an insulin infusion at 0.05U.kg^{-1}.h^{-1} upon randomisation and the infusion rate titrated to maintain BGC between 4 and 6mmol.L^{-1}. Babies randomised to the control group were only treated with insulin if they met all of the following criteria: BGC >10mmol.L^{-1} or persistent glycosuria >2^{+}; tolerating <100 kcal.kg^{-1}.day^{-1}; >72 hours of age, and not acutely stressed. If these babies were treated with insulin, BGC was maintained between 8 to 10mmol.L^{-1} by using an insulin infusion started at 0.05U.kg^{-1}.$hour^{-1}$ (Table 2-1). Growth measures of lower leg length using a neonatal knemometer (Force Technology, Copenhagen, Denmark), weight and occipitofrontal head circumference were measured. Other measures were myocardial assessment by echocardiography (HDI 5000, 7.5-11MHz probe, Philips Healthcare, Best, Netherlands), and plasma cortisol, insulin and IGF-1 concentrations. At 7 years corrected age, there were 77 survivors in this cohort (9 neonatal deaths and 2 post-neonatal deaths). Children from the HINT trial who participated in the PIANO study were included in the HINT follow-up cohort and the neonatal hyperglycaemia cohort arms of the PIANO study.

Table 2-1 BGC target ranges for HINT trial

	Tight glycaemic control	Standard glycaemic control
Before randomisation	2.6 to 8.5 mmol.L^{-1}	
After randomisation		
Insulin fusion given*	4 to 6 mmol.L^{-1}	8 to 10 mmol.L^{-1}
Not on insulin infusion	-	2.6 to 10 mmol.L^{-1}

For the standard glycaemic control group, insulin was only commenced if BGC >10 mmol.L^{-1}.

2.1.4.2 Matched controls of HINT babies

Each of the 77 surviving HINT participants was matched with a child who was born at <30 weeks' gestational age and / or <1500g birth weight and was admitted to National Women's Health NICU between July 2005 and October 2008 but had not met criteria for the diagnosis of hyperglycaemia for the HINT trial.

Matching was performed on a hierarchical basis according to the following variables:

1) Sex
2) Gestational age (± one week)
3) Birth weight z-score (± 0.5SD)
4) Date of birth (± three months)
5) NZ deprivation index at pregnancy booking (low, medium, high)
6) Multiple birth (single/multiple)
7) CRIB II score (Clinical Risk In Babies) (Parry, Tucker, & Tarnow-Mordi, 2003) (low, medium, high)

Babies who were known to have died prior to being discharged from National Women's Health NICU and those with major congenital abnormalities were excluded. During the control cohort matching process, paired matching of each case with the above hierarchical variables was not always possible due to the small number of babies available for matching. Matching for CRIB-II score was discontinued during recruitment as CRIB-II scores in the hyperglycaemic cases were significantly higher than in potential controls, resulting in matching not being feasible. Children who participated in the PIANO study were included in the neonatal hyperglycaemia cohort arm of the PIANO study.

2.1.4.3 IVN audit

Two cohorts of babies who weighed <1500g at birth, admitted within 24 hours of birth to the National Women's Health NICU and remained there for 30 days were part of a retrospective IVN audit (Cormack et al., 2011); these children were also followed up in the PIANO study. One cohort ('before' group) was born in the 8 months (April to December 2006) before the IVN solution changes, while the other

cohort ('after' group) was born during the 8 months following the change (January to July 2007). For the 'before' group (n=40), babies were given the P10 formulation (a standard IVN solution) from birth. For the 'after' group (n=40), babies with birth weight >1000g or beyond 48 hours after birth were given the P100 formulation (concentrated IVN solution); while babies with birth weight <1000g were given a starter solution for the first 2 days after birth before P100 was given. Details of the composition the different formulations, protocol for administration and nutritional intake are found in Table 2-2, Table 2-3, and Table 2-4) Due to the high osmolality of the starter solution, central venous access was required. For both P10 and P100, any difference between the daily IVN and lipid fluid intake and total prescribed daily fluid intake after taking account of additional infusions (e.g. arterial line fluids and medications) was made up with 10% dextrose solution. The total enteral and intravenous intakes for each day of the first 4 weeks after birth were collected and the mean daily protein and energy intakes were calculated for each week. Data of fluid intake, daily serum sodium and potassium concentrations, and base deficit for the first 30 days of life was collected. Growth data at birth, 4 weeks, 8 weeks and discharge were also collected. These babies were invited to participate in the neonatal nutrition cohort of the PIANO study. Of the 80 babies in the IVN audit, 21 babies also participated in HINT and 22 babies were a matched control for HINT. There were babies in the HINT trial or were matched controls who were not part of the protein audit but were included in the neonatal nutrition cohort of the PIANO study.

Table 2-2 Composition of intravenous nutrition before and after reformulation

		Before	After	
Nutrients	**Units per litre**	**Original IVN formulation 'P10'**	**IVN reformulation 'P100'**	**Starter solution (Days 1 to 2 for BW <1000g)**
Energy	kcal	422	497	781
Protein	g	20	38	67.9
Glucose	g	100	100	150
Sodium	mmol	30	55	3.5
Potassium	mmol	30	21.9	0
Calcium	mmol	14	17	16.4
Phosphate	mmol	14	19	0
Zinc	mg	2.7	4.4	5
Magnesium	mmol	1.2	2.8	0
Acetate	mmol	20.4	56.7	67.9
Chloride	mmol	30	28	0
Osmolarity	$mOsm.kg^{-1}$ H_20	817	1067	1424

Units: kcal kilogram calorie, g grams, mmol millimole, mg milligram, $mOsm.kg^{-1}$ H2O milliosmole per kilogram of water.

Table 2-3 Daily fluid volume of intravenous nutrition before and after reformulation

	Before reformulation	After reformulation	After reformulation BW <1000g
Starting volume	60-90 ml.kg^{-1}.day^{-1}	60 ml.kg^{-1}.day^{-1}	30 ml.kg^{-1}.day^{-1} for two days
Daily volume increase	30 ml.kg^{-1}.day^{-1}	15 ml.kg^{-1}.day^{-1} until 120 ml.kg^{-1}.day^{-1}, then 30 ml.kg^{-1}.day^{-1}	
Full IVN volume	180 ml.kg^{-1}.day^{-1} (165 ml.kg^{-1}.day^{-1} P10 + 15 ml.kg^{-1}.day^{-1} 20% lipid emulsion)	180 ml.kg^{-1}.day^{-1} (90 ml.kg^{-1}.day^{-1} P100 + 75 ml.kg^{-1}.day^{-1} 10% dextrose + 15 ml.kg^{-1}.day^{-1} 20% lipid emulsion)	

Note: The differences between IVN + lipid + medications + enteral daily fluid intake and total prescribed daily fluid intake were made up with 10% dextrose. Units: ml.kg^{-1}.day^{-1} millilitres per kilogram per day.

Table 2-4 Nutritional intake of the original ('P10') and reformulated ('P100') intravenous nutrition per day when administered as per unit protocol

		Before		After		
Nutrients	**Units**	**Nutritional intake from 'P10' + lipid + 10% Dextrose per kg.day^{-1}**		**Nutritional intake from 'P100' + lipid + 10% Dextrose per kg.day^{-1}**		**Nutritional intake from starter solution + 10% Dextrose per kg.day^{-1}**
		Day 1	**Day 7**	**Day 1**	**Day 7**	**Day 1**
Fluid	ml	60	180	60	180	60
Energy	kcal	33	100	41	103	46
Protein	g	2.0	3.3	1.6	3.5	2.0
Glucose	g	5.5	16.5	4.0	16.5	5.0
Sodium	mmol	1.7	4.8	3.7	5.0	1.1
Potassium	mmol	1.7	5.0	1.1	2.0	0.0
Calcium	mmol	0.8	2.3	0.7	1.5	0.5

Note: For both formulations, the lipid emulsion used was Intralipid 20% (Fresenius Kabi AB, Uppsala, Sweden), which contained 2.0 kcal.mL^{-1} energy. Units: kcal kilogram calorie, g grams, mmol millimole, ml millilitre.

2.1.4.4 Term born controls

The term born controls (born ≥38 weeks' gestational age) were recruited from the friends and siblings of the preterm born children participating in the PIANO study at the same age. However, there were difficulties with recruitment, and later, term controls were also sought from children who had participated in the "Preterm birth and the role of gut bacteria in metabolism" study, through advertising within the University of Auckland and Auckland District Health Board, Facebook, and by word of mouth. Our Facebook advertisement was targeted at females between 18-65+ years of age (potentially mothers or grandmothers of children) within a 25-mile radius from the centre of Auckland.

2.1.4.5 PIANO study follow-up study inclusion and exclusion criteria

Inclusion criteria for the main PIANO study cohort (preterm-born):

1) Born at <30 weeks' gestational age and / or <1500 g birth weight
2) Corrected age from seven years to seven years and five months
3) Parent/guardian gave written informed consent to participate

Inclusion criteria relevant to the separate sub-cohorts are listed below.

2.1.4.5.1 *HINT Follow-up Cohort*

Tight Group

Had neonatal hyperglycaemia (2 consecutive BGC >8.5mmol.L^{-1} at least 4 hours apart) and were randomised to the Tight Glycaemic Control Group in the HINT trial

Control Group

Had neonatal hyperglycaemia (2 consecutive BGC >8.5mmol.L^{-1} at least 4 hours apart) and were randomised to the Standard Glycaemic Control Group in the HINT trial

2.1.4.5.2 *Neonatal Hyperglycaemia Follow-up Cohort*

Hyperglycaemic Group

Had neonatal hyperglycaemia (2 consecutive BGC >8.5mmol.L-1 at least 4 hours apart) and participated in the HINT trial

Non-hyperglycaemic Group

Did not meet our criteria for neonatal hyperglycaemia (2 BGC readings >8.5mmol.L^{-1} at least 4 hours apart) and was matched to a child in the HINT trial according to the criteria in 2.1.4.2.

2.1.4.5.3 *Neonatal Nutrition Follow-up Cohort*

Children were eligible if they:

1) Had full nutritional data for postnatal days 1-7;
2) Born at National Women's Health or transferred in at <24 hours; and
3) Remained at National Women's Health at least until day 7 after birth

Before IVN Reformulation Group (Before)

Born on or before 31st December 2006

After IVN Reformulation Group (After)

Born on or after 1st January 2007

2.1.4.5.4 *Preterm Follow-up Cohort*

Preterm Group

Same criteria as the main PIANO study cohort

Term born controls (Growth, scarring and vision assessment only)

Born at ≥38 weeks' gestational age, seven years of age at the time of the PIANO vision assessment and parent/ guardian gave written informed consent to participate

Exclusion criteria for the PIANO study were:

1) Major congenital abnormalities
2) Severe congenital eye disease likely to affect visual function

2.1.4.6 Tracking

All eligible participants were traced through hospital records, general practitioners, family contacts and social media by a research nurse and study doctor. Care was taken to exclude children who died or suffered traumatic brain injury after the neonatal period. A letter was sent to the most recent known address inviting participation into the PIANO study upon the potential participant turning 7 years corrected age. If no response was received two weeks following the letter invitation, a telephone call was made to ensure the letter was received, with a subsequent home visit if no contact could be made by telephone. The window of eligibility for the PIANO study was within 6 months from 7 years corrected age. Term-born children were contacted via mail, telephone or email and asked to participate in the study.

2.1.5 Perinatal data collection

Maternal, antenatal and neonatal baseline characteristics were collected for all children eligible for the PIANO study by the study doctor from neonatal records and the Australian & New Zealand Neonatal Network (ANZNN), which has a prospectively managed database for high-risk babies who were born at NICU's in Australia and New Zealand. The incidence of neonatal complications and nutritional intake for the first month after birth were also collected.

- For children in the HINT follow-up and neonatal hyperglycaemia follow-up cohorts, available data of glycaemic status up to 36 weeks' postmenstrual age were collected. This included BGC, insulin dose, and IGF-1 concentration. Glucose variability was calculated from the standard deviation of the logarithm of the mean BGC.
- For children in the protein follow-up cohort, parenteral and enteral amounts of protein, carbohydrates, fat and energy were collected for the first 2 weeks after birth.
- Anthropometric measures such as birth weight, height and head circumference were expressed as z-scores using normative data from Fenton growth chart at birth and in infancy (Fenton et al., 2013), and British World Health Organisation growth standards (UK90 chart) at 7 years of age (Wright et al., 2002).

- Socioeconomic deprivation for our participants at birth was measured using the New Zealand Deprivation Index 2006 (NZDep2006) that used data from the 2006 census to reflect deprivation from home address at birth (Salmond et al., 2007), and NZDep 2013 based on data from the 2013 census and home address at the time of assessment was used for participants at 7 years of age (Atkinson et al., 2014). The NZDep index is an ordinal scale ranging from 1 to 10, with 1 representing the areas with least deprivation and 10, the areas with the most deprivation.
- Growth velocity from birth to 28 days, and from birth to day of assessment at 7 years of age were calculated using the exponential method (Patel et al., 2005):

  $$\text{Growth velocity} = [1000 \times \text{Ln}(W_2/W_1)]/(D_2-D_1)$$

  where W_1 is the weight of the first time point (I.e. date at birth), and W_2 is the weight at the second time point (28 days after birth or at 7 years of age); D_1 is the first time point (I.e. date at birth), and D_2 is the date at the second time point; Ln is the natural logarithm.
- Ethnicity was classified into groups with reference to a priority system (Level 1) used by the Ministry of Health in New Zealand (Ministry of Health, 2010) and New Zealand National Standards (Education Counts, 2012). For an individual who identified with more than one ethnic group, the priory ranking used was:
  1) Māori
  2) Pacific
  3) European
  4) Asian/Other

2.1.6 Ethics

Ethical approval was obtained from the Northern Y Regional Ethics Committee (NTY/12/05/035) of the New Zealand Ministry of Health. Following an amendment to include term born children as term controls for the growth, body scarring and visual assessment, ethical approval was obtained from the Northern B Ethics Committee. Written informed consent was obtained from the parents or legal guardians on behalf of each participant. As well as signing the consent form, there were separate consents (circling yes or no) for some of the tests including instillation of cycloplegic eye drops and for collection of confidential data such as medical records and B4 School Check data.

2.1.7 PIANO study assessment protocol

2.1.7.1 Venue for follow-up assessments

The majority of assessments were performed at the University of Auckland Grafton Campus: Clinical Research Unit within the Liggins Institute, Optometry Eye Clinic and the Centre of Advanced MRI (Faculty of Medical and Health Science). In some cases where the participant was unable to attend the assessment at the specified venue, the child's home, other clinical centres and schools were used by request from the family (MRI, metabolic assessments and part of the visual assessments were not performed).

2.1.7.2 Vision assessment

For all measurements of vision in separate eyes, the results were recorded as better and poorer eye according to the following hierarchical order: visual acuity, least refractive error, and then random assignment by random number generator. For children who wore spectacles, tests were performed with and without their spectacles.

2.1.7.2.1 *Measurement of visual acuity*

Presenting distance vision, otherwise named as visual acuity (VA) in this thesis, was measured monocularly and binocularly using a logarithm of minimum angle of resolution (LogMAR) crowded test (Keeler Ltd., United Kingdom) viewed at 3 metres from largest to smallest (measures VA from 0.800 to -0.300logMAR) (McGraw & Winn, 1993). Children who were not confident in letter naming were given a matching card to use. VA was recorded as the smallest page with two letters correct; each letter was scored on the line. In a previous study, children aged 2.5-16 years (mean 4.3±1.0 years in 50 children 5 years or younger; mean 8.9±2.3 years in 53 children over 5 years of age) had monocular VA ranging from 0.3 to -0.125 logMAR (mean -0.04) (Jones et al., 2003). In 116 visually normal children with mean age of 5.32±1.15 years, 95% of test-retest discrepancies did not exceed 1 logMAR line for VA measured using the Keeler chart (McGraw et al., 2000).

2.1.7.2.2 *Binocular vision assessment*

- Ocular alignment was examined using cover-uncover test and alternating cover test at both 6m and 40cm. Any ocular misalignment was measured using the prism cover test and recorded as distance (distance, near or constant), laterality (right, left or alternating), direction (horizontal, vertical, torsional), magnitude, and ability to regain fusion (recovery movement, with phoria). For children who were unable to complete the ocular alignment testing, Hirschberg's corneal reflex observation was used as a gross guide. In 2588 children aged between 3 to 5 years, the sensitivity

of the cover-uncover test for detecting strabismus was 60% and for detecting amblyopia was 27% at specificity of 94% (The Vision In Preschoolers Study Group, 2005).

- Binocular motor fusion was assessed by the 20Δ base-out prism test while the child was fixating on a small target at 40cm.
- Ocular motility was examined in all cardinal positions using the Broad H test. Nystagmus (involuntary eye movements) and palpebral aperture abnormalities (eyelid retraction or ptosis) were screened for during ocular motility in different areas of gaze.
- Near point of convergence and amplitude of accommodation was measured using a Royal Air Force (RAF) convergence rule (Neely, 1956). Amplitude of accommodation was measured with a push up test where a small target was brought closer to the participant's eye (one eye covered at a time) and the distance in dioptres that the target first became blurry was noted.
- Pupillary light reflex was examined using a swinging flashlight test to look for signs of afferent pupillary defects or anisocoria (different sized pupils). A small target was brought up close to the participant to check for pupillary near reflex.

2.1.7.2.3 *Stereoacuity*

- The Toegepast Natuurkundig Onderzoek (TNO) test for stereoscopic vision sixteenth edition (Laméris Ootech, Nieuwegein, The Netherlands) (Walraven, 1975) uses random dot stereograms printed in complimentary colours (red and green) to measure stereoacuity and does not contain any monocular cues. Four ungraded screening plates assess presence of suppression and stereopsis, while three diagnostic plates present pac-man shapes (or missing piece of cake) at disparities between 480 to 15 seconds of arc. The participant was asked to wear red-green glasses and to name or point the direction that the pac-man shapes were facing. The plate with the smallest disparity at which one shape was identified correctly when both the shapes at one step larger disparity were answered correctly was recorded. If suppression was present, it was also noted. For children aged between 4 and 78 years of age (mean 19.09±15.12 years), TNO had a sensitivity of 83.1% for detecting strabismus with 95% confidence.
- The Stereo Fly Test 2007 edition (Vision Assessment Corporation, Illinois, U.S.A.) is a standard clinical test of both gross and fine stereo vision using polaroid vectograms was also used to measure gross stereopsis and could test disparities between 800 to 40 seconds of arc.

2.1.7.2.4 *Global motion perception*

Global motion perception was assessed psychophysically using random dot kinematograms (RDK) projected on a 16-inch HP s7540 CRT monitor (Hewlett-Packard, Houston, Texas, U.S.A.). The RDK stimulus used to measure motion coherence thresholds was programmed and ran on MATLAB 2010a using Psychophysics Toolbox extensions. Our stimulus (Chakraborty et al., 2015) consisted of 100

white dots (132.8cd.m^{-2}) presented on a mean-luminance (53.1cd.m^{-2}) background in circular aperture enclosed in a black square. When the participant was seated 40cm from the screen, the size of the circular aperture was 5°. The dots were constrained to not cover over the central fixation point. The diameter of each dot was 0.235° and moved at a speed of 6°s^{-1}. To prevent the participant from tracking the dots, the dots were limited-lifetime and had a 5% chance of disappearing in each frame and reappearing in a random area within the stimulus. The RDK stimulus was shown on the screen for 2000msec, while the participant fixated on the black dot in the centre of the screen. The participant was asked to respond to whether "more of the dots were moving upwards or downwards. Motion coherence was measured using a two-down (two correct answers to lower coherence), one-up (one correct answer resulted in higher coherence) adaptive staircase procedure. Coherence was changed by 50% after the first presentation, and then by 12% for presentations thereafter. Ten reversals were measured and the last eight reversals were averaged to give a motion coherence threshold (Chakraborty et al., 2015). Throughout the assessment, the researcher gave encouragement to the participant to keep trying and reminding them to continue fixating on the fixation dot; no positive or negative feedback was provided by the computer for each trial.

2.1.7.2.5 *Ocular biometry*

Ocular biometry was measured using a LenStar LS 900 Non-contact Biometer (Haag-Streit Diagnostics, Japan), which uses optical low coherence reflectometry (Buckhurst et al., 2009) to capture measurements of corneal thickness, corneal curvature, anterior chamber depth, lens thickness, axial length, pupil diameter and white-to-white distance. Standard measurements were made; five scans were performed on each eye and the results were averaged to give a mean measurement for each of the different ocular biometrical parameters.

2.1.7.2.6 *Cycloplegic autorefraction*

With parental/guardian consent and child assent, one drop of Cyclopentolate 1% (Bausch & Lomb, New Zealand) was instilled into each eye of the participant. Cyclopentolate is a muscarinic antagonist, which prevents accommodation of the eyes and causes pupil dilation; maximum cycloplegic effect is after 40mins after instillation ("Data sheet - minims cyclopentolate hydrochloride," 2015). Pupil reactions were checked after at least 40 minutes as a measure of efficacy of the eyedrops. If pupils were dilated and non-reactive to light, autorefraction and keratometry were measured using a Nidek AR-20 Handheld Autorefractor (Nidek Inc., Japan); 5 to 10 measurements were made per eye and averaged. If an acceptable cycloplegic effect was not seen (pupils reacting to light or fluctuating auto-refraction was observed), auto-refraction was measured but not included in the analysis.

The refractive error was recorded as:

"Spherical power in dioptres (D)"/ "negative cylindrical power in dioptres (DC)" x "axis of astigmatism"

For simplification, refractive error was also reported as spherical equivalent power (SEP), which was calculated by: spherical power + (cylindrical power / 2)

In a study by Iuorno *et al*., out of 109 children aged between 37 to 107 months, 11 children were unable to complete autorefraction by either the Welch Allyn SureSight handheld autorefractor or nidek AR-20 handheld autorefractor. There were no statistically significant differences found in cycloplegic refractive error measurements between the nidek handheld autorefractor and retinoscopic refraction by an experienced paediatric ophthalmologist (Iuorno et al., 2004).

2.1.7.2.7 *Retinal photography*

Retinal abnormalities were screened using retinal photography by a Canon CR-1 Mark II (Canon, Tokyo, Japan). Images were assessed after data collection was completed. As all images were graded subjectively using clinical judgement by one observer (optometrist collecting the data), images were placed in alphabetical order by the initials of the participant, and right eye was assessed for the first participant, and then left eye was assessed for the second participant, and then the right eye was assessed for the third participant and so on, to reduce bias. The observer was blinded to the group allocation. Ten percent of the images were also reviewed by a separate observer (an optometrist who was familiarised with the grading system), and where there were differences, these were reassessed and discussed between both observers, and a consensus was reached.

- The quality of the images was assessed subjectively (clarity, artefacts and missing areas) out of ten, with ten being best quality, and if the images were of gradable quality, the retina was assessed and graded as:
    1) No abnormalities or signs of normal variants (not clinically significant)
    2) Clinically significant abnormalities (requiring follow-up more frequent than the biannual routine follow-up, requiring referral for further investigation or requiring treatment)
    3) Unable to grade

    Signs of non-clinically significant abnormalities included but were not limited to anomalous blood vessel anatomy such as isolated arterial vascular tortuosity, congenital retinal macrovessel, and cilioretinal artery; obliquely inserted optic nerves and isolated pigment or peripapillary atrophy (without signs of myopia or dragging of discs). Signs of clinically significant abnormalities include but were not limited to blood vessel abnormalities such as telangiectasia, haemorrhage, neovascularisation and blood vessel straightening or narrowing/dilation; macula abnormalities such as ectopia or deposits; retinal abnormalities such as tears, breaks, retinal detachment,

fibrous tissue, hyper- / hypo-pigmentation; optic nerve abnormalities such as tilted discs affecting vision, drusen, optic pit, oedema and pallor.

- Blood vessel tortuosity was subjectively graded as nil, mild, and severe.

  Examples of blood vessel tortuosity grading and the form for grading are found in appendix 9.1.1.

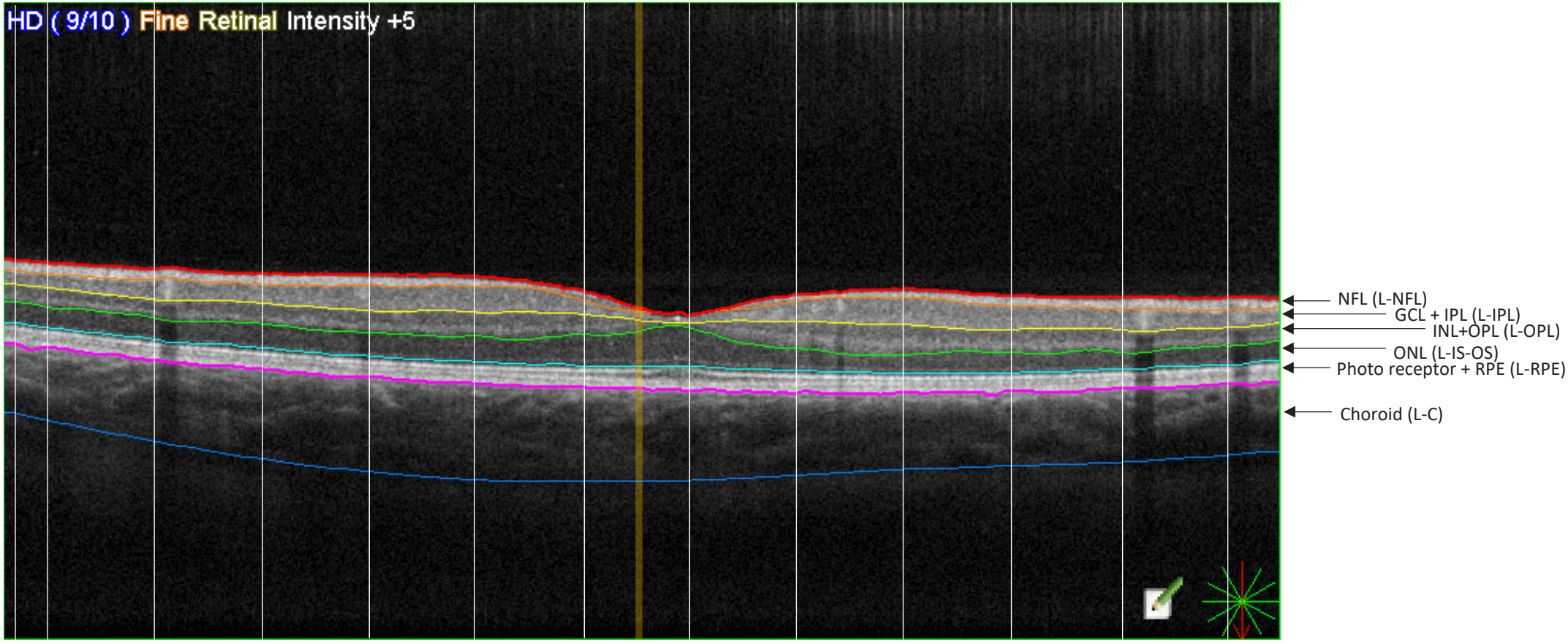
2.1.7.2.8 *Optical coherence tomography (OCT)*

OCT of the macula was performed using a Nidek RS-3000 Advance (Nidek Inc., Japan), which uses a 880nm light source and has a resolution of 4-20µm resolution with a maximum scan speed of 53,000 A-scans per second. The OCT software can perform analysis for automated segmentation, macular thickness maps, RNFL thickness maps and optic nerve analysis. Parameters used were 6-line radial macular scan, 15 frames and 1024 fine resolution. Where automated segmentation was misaligned due to poor image quality, segmented layers of the retina were adjusted to account for the misalignment. Although each scan was centred on the macula at the beginning, due to movement from participants, many children did not complete all 6 slices for each eye, and the system analyses could not be used. Therefore, each image slice of the retina was separately segmented into 12 sections (0.5mm in length each) centred on the centre of the macula (the centre of the macula was denoted as the thinnest part of the slice) (Figure 2-2). Each full section was included in the analysis, with thicknesses for each layer from the centre two sections averaged as "central retina" (central 1mm), the two sections on either side averaged as "mid peripheral retina" (central 3mm excluding the central 1mm), and all other sections pooled as "peripheral retina". Central retina/mid peripheral retina/peripheral retina for each slice were averaged for all 6 scans, or for the number of usable slices. Note: OCT measurements can be affected by ocular magnification due to difference in optical length of the machine and the axial length of the eye and other optical components. This is particularly important for assessing retinal lesions that are parallel to the retina. Although axial length of children is shorter than the OCT optical length, with the small ranges of axial length and the self adjustment of focus by the OCT machine, the full retinal thickness (perpendicular to the retina) is not expected to vary significantly between participants (Wang et al., 2007).

2.1.7.3 Magnetic resonance imaging (MRI): Brain (Not included in this thesis)

MRI scans were acquired by a MR technologist/radiographer and analysed by a doctoral candidate. A Siemens MAGNETOM Skyra 3T with a 70cm bore and 32 channel head-coil at the Centre for Advanced MRI, University of Auckland, New Zealand was used to acquire structural (T1 and T2 weighted), microstructural (diffusion) and functional (resting state and task) brain scans. Acquisition of all images was completed in approximately one hour. If any incidental findings occurred, a paediatric radiologist reviewed the images and the principal investigator discussed the results with the parents/guardians of the child.

Figure 2-2 Layer segmentation and sections of an OCT retinal slice



Abbreviations: NFL nerve fibre layer, GCL ganglion cell layer, IPL inner plexiform layer, INL inner nuclear layer, OPL outer plexiform layer, ONL outer nuclear layer, RPE retinal pigment epithelium. The yellow line denotes the centre of the scan but as you can see the thinnest part of the scan (the fovea/macula) is not centred on the image. The white lines denote the sections across the retina. Across the scan horizontally, it is a 6mm scan with 1024 points at which it was scanned.

2.1.7.4 Metabolic assessment (not included in this thesis)

2.1.7.4.1 *Intravenous glucose tolerance test (IVGTT):*

The fasted IVGTT according to Bergman's Minimal Model (Bergman et al., 1987) was performed by a trainee neonatologist and research nurse. After numbing the skin with topical anaesthetic, an intravenous cannula was inserted; scarring of veins or pain on insertion in some children prevented canalisation. Blood samples were acquired at baseline, following administration of a glucose bolus and following administration of 0.015U.kg^{-1} Actrapid bolus (Novo Nordisk, Auckland) for measurement of insulin and glucose concentration. This entire procedure was completed in approximately two hours. Insulin sensitivity and secretion, glucose effectiveness, and growth hormone response to insulin induced stress were analysed from the glucose and insulin concentrations from centrifuged plasma and entered into MinMod Millennium software (MinMod Inc., USA).

2.1.7.4.2 *Protein milkshake:*

Each child was randomised to either having a low or high protein milkshake, which was used to determine whether the children could tolerate the taste of a protein drink as a complementary diet.

2.1.7.4.3 *Body composition and bone mass:*

Total body composition and bone mass were measured using dual-energy X-ray absorptiometry (DXA), Lunar Prodigy DXA (GE Healthcare, United Kingdom).

2.1.7.5 Paediatric physical and medical assessment (not included in this thesis unless specified)

A doctor with paediatric experience conducted the physical and medical assessment, which comprised of growth measurements (height, head circumference, weight, abdominal circumference and body mass index), gross motor function score (neurological assessment), and general physical health and body scarring examination.

2.1.7.5.1 *Standing height (included in this thesis)*

Standing height was measured three times using a stadiometer. The participant was asked to stand with feet flat together and with their heels against a wooden block to ensure their back and body was parallel to the stadiometer (shoes and bulky or heavy clothing were taken off before measurements). The participant was instructed to stand with their legs straight, shoulders level, with arms loosely by their sides and to look straight ahead. The sliding horizontal headpiece was then adjusted to firmly touch the top of the head and the height measurement in centimetres to one decimal place was read off the scales.

2.1.7.5.2 *Weight (included in this thesis)*

Weight was measured using a digital scale (Tanita Baby & Mommy Scale BD-1582, Tanita Corporation of America, Inc). The digital scale was placed on a hard surface and allowed to be reset to zero. The participant was then asked to stand with both feet in the centre of the scale. Weight was recorded in kilograms to one decimal place.

2.1.7.5.3 *Occipitofrontal head circumference (included in this thesis)*

Occipitofrontal head circumference was measured with a paper tape measure (accurate to 1 mm) over the most prominent part at the back of the head and along the forehead above the eyebrows. This was measured three times and recorded in centimetres to one decimal place.

2.1.7.6 Developmental assessment (included in this thesis)

The developmental assessment was performed by research nurses (trained to perform these tests reliably) and comprised of assessment of physical movement, vision-motor co-ordination, cognitive ability, behaviour/social ability of the participant, as well as a short test of vocabulary of the parent.

2.1.7.6.1 *Movement Assessment Battery for Children – Second Edition (Movement ABC-2) (included as part of primary outcome)*

The Movement ABC-2 (Pearson Assessment, London) is a test of fine and gross motor function for ages between 3:0 and 16:11 years (Brown & Lalor, 2009). There are eight sections assessing manual dexterity, ball skills and dynamic balance; as well as participant's attitudes and behaviour regarding their motor function.

2.1.7.6.2 *Wechsler Intelligence Scale for Children IV – Australian version (WISC®-IV) (included as part of primary outcome)*

The WISC-IV (Harcourt Assessment Inc., Australia) is a test of intelligence quotient for ages between 6:0 and 16:11 years, and involves 15 subtests that determine the participant's ability in 4 main areas: verbal comprehension, perceptual reasoning, working memory and processing speed (Kaufman & Flanagan, 2009). A full-scale intelligence quotient is also determined.

2.1.7.6.3 *Test of Everyday Attention for Children (TEA-Ch)*

The TEA-Ch (Pearson Assessment, London) is a test of attention and determine the participants ability in selective, sustained and control/switching of attention, as well as performance in dual tasks of auditory and visual modalities.

2.1.7.6.4 *Beery-Buketenica Developmental Test of Visual-Motor Integration (VMI) (included in this thesis as primary outcome and as part of Chapter 6 ROP)*

The Beery VMI (Pearson Education, Inc.: PsychCorp, U.S.A.) is a test of visuomotor coordination for ages 2-100 years (Beery et al., 1997), involving visual motor integration, visual perception and motor coordination. The participant was instructed to copy the forms/shapes shown in the Beery visual motor integration booklet. When the participant had made three consecutive errors, the test could be stopped. The participant was then asked to do the two standardized optional supplemental tests of visual perception and motor coordination that used the same geometric shapes as the Beery VMI. In the visual perception task, the participant was asked to match the set of 30 shapes with other similar looking shapes of different sizes, orientation and details within a 3-minute time limit. In the motor coordination task, the participant was given 5 minutes to draw the geometric shapes within an outline of the shape. These three tests were timed and scored according to the VMI manual (Beery et al., 1997). We reported standard scores and percentiles.

2.1.7.6.5 *Behavior Rating Inventory of Executive Function (BRIEF®) Parent and Teacher*

The BRIEF Parent and Teacher (PAR 2000) are two questionnaires used to assess executive functioning in the home and within the school environment.

2.1.7.6.6 *Child Behaviour Checklist (CBCL) and Teacher's Report Form (TRF)*

The CBCL (Aseba®) is a parent completed questionnaire to assess behavioural/emotion problems and adaptive characteristics of children. There is also a version for teachers known as the TRF (Aseba®), which contains similar questions.

2.1.7.6.7 *Peabody Picture Vocabulary Test, Fourth Edition (PPVT™-4)*

The PPVT-4 (NCS Pearson, Inc.) was used in this study to measure American English vocabulary of parents of participants to assess the effects of parental literacy on child outcomes (Weiner & Craighead, 2009).

2.1.7.7 Questionnaires: Home, family and child health (Partially included in this thesis)

- A home and family questionnaire, and child health questionnaire were sent to the parents or guardians of each participant to be filled before the assessment date. These questionnaires consisted of questions regarding demographics of the family, living situation, medical history of the family, maternal history during pregnancy, and child health and quality of life.
- Health status was assessed using a multi-attribute approach through the Health Utilities Index (HUI) Mark II system (Feeny et al., 1995). This system grades the health status in 7 attributes

including sensation, mobility, emotion, cognition, self-care, pain and fertility. For each of these attributes, there is a grading between 1 and 5 depending on the attribute and it assesses function and disability in those areas. In our study, parents of participants were asked to grade the health status of their child; fertility was deemed not relevant by the investigators and was not used in this study. Although an overall score can be calculated using vectors, as fertility was not assessed, the vector analysis could not be performed. For sensation, 4 grades that were used included: 1) Able to see, hear, and speak normally; 2) Requires equipment to see or hear or speak; 3) Sees, hears, or speaks with limitations even with equipment; 4) Blind, deaf, or mute.

2.1.7.8 Questionnaires: Teacher and school (not included in this thesis)

On the assessment day, parents/guardians were asked for their permission to send two questionnaires to the child's teacher, BRIEF® teacher (PAR 2000) (Gioia et al., 2010), and TRF (Aseba®) (Achenbach, 2011) to complete. If consent was given, questionnaires were sent out on the day of the assessment.

2.1.7.9 B4 school check (B4SC) (included in this thesis)

The B4SC is a free health and development screening programme of 4-year-old children within New Zealand. This data is collected by the Ministry of Health. If health, behaviour, social, and developmental concerns are identified, children are referred to an appropriate service provider. For the vision testing session, the child's vision in each eye is tested using a Parr Letter-Matching Test or Sheridan Gardner Chart (Ministry of Health, 2008). At 4 years of age, children with 6/9 vision or better in both eyes are considered a pass and no further action is taken. If the child has 6/9 or worse in one eye and 6/6 in the other eye, a rescreening is arranged for 3 to 6 months' time. For children with vision 6/12 or worse in either or both eyes, the child is referred for an ophthalmic assessment. During the rescreen, if the child's vision is 6/6 or better in both eyes, the rescreen is considered a pass and no further action is taken. If there is no change in vision or their vision has become worse in either eye, the child is referred for an ophthalmic assessment. Children under ophthalmic care (ophthalmologist or optometrist) or with prescribed spectacles are usually not screened; referral is not initiated regardless of vision if screened, while vision results are passed onto the parent or caregiver (Ministry of Health, 2008). For the PIANO study, a grouped application to the Ministry of Health to make this information available to the PIANO study group was made for children's whose parents consented.

2.1.7.10 Summary of assessment schedule

7:30am – The family arrived at the Liggins Institute and consenting procedure was initiated (The child was fasted over the previous night and would have local anaesthetic cream applied to the anecubital fossae approximately ½ to 1 hour prior to arrival). Anthropometry measurements, and DXA scan would then be performed.

8:00am – The study doctor explained the procedure of the IVGTT to the family and with the child's assent, the test would be initiated. The child was occupied by watching a movie or playing games during this time.

10:00am – Following the completion of the blood test, the child was given the protein milkshake, before breakfast was served.

10:30am – The study research nurse performed a developmental assessment with the child.

12:30pm – The family would then be given a lunch break.

01:15pm – After lunch, the child would have an MRI scan. During the structural scans, a movie was played to keep the child attentive and still.

02:30pm – Following the MRI scan, the child underwent the vision assessment and paediatric/medical assessment.

The entire assessment would typically be completed by 4:30pm or 5:00pm. Some of the assessments were rearranged for twins and some assessments were spread out over two days due to availability of the MRI scanner.

2.1.8 Outcome Measures

2.1.8.1 Primary outcome

Neurodevelopmental impairment was defined as any of:

- Wechsler Intelligence Scale for Children 4th ed. (WISC-IV) full scale IQ (FSIQ) <85 (1SD below the mean)
- Movement Assessment Battery for Children-2 (MABC-2) total score ≤ 5thcentile
- Cerebral palsy
- Blindness (presenting VA of 6/60 or worse in the better eye); and / or
- Deafness requiring hearing aids

2.1.8.2 Secondary visual outcomes

2.1.8.2.1 *Visual function*

Full definitions list for the following outcomes can be found in 2.3.

- Favourable (Table 2-5) overall visual outcome was defined as:
  - Good distance VA (equal or better than 6/12 vision in the better eye)
  - No strabismus
  - Passing TNO stereoacuity (≤240 seconds of arc)

- Not requiring spectacles for refractive error in either eye (SEP) between -0.50DS and +2.00DS, and cylindrical power (CYL) ≥-1.00DC)

I.e. Adequate vision and stereoacuity for daily activities, in the absence of strabismus, without the need for optical correction

- Favourable binocular visual outcome was defined as:
  - No strabismus
  - No nystagmus
  - Normal ocular motility (no ocular muscle weakness or over-action)
  - Normal convergence (convergence to ≤10cm from eyes)
  - Presence of motor fusion (overcoming 20Δ base out prism in both eyes)
  - Passing TNO stereoacuity
- Favourable functional visual outcome was defined as:
  - Good distance VA
  - No strabismus
  - Passing TNO stereoacuity

I.e. Adequate vision and stereoacuity for daily activities, in the absence of strabismus (with or without visual aids).

Table 2-5 Criteria for favourable or unfavourable outcome in the composite visual outcomes

Composite Outcomes	Component Test completion	Criteria
Favourable visual outcome	Completed all tests	Pass all tests
Unfavourable visual outcome	Completed all tests	At least one bad outcome in any of the tests
	Did not complete all tests	At least one bad outcome in any of the completed tests
Missing	Did not complete all tests	Passed all completed tests*

**Missing because it would be uncertain whether the child would pass or fail the remaining tests that were not completed.*

- Other visual outcomes:
  - VA better than 6/7.5 in the better eye
  - Monocular and binocular VA (logMAR)
  - Difference in VA between eyes (logMAR)
  - Log stereoacuity
  - Global motion perception threshold

2.1.8.2.2 *Ocular structure*

- Retinal posterior pole (central) findings (2.1.7.2.7):
  - No abnormalities or signs of normal variants (not clinically significant)
  - Clinically significant abnormalities
  - Unable to grade
- Ocular biometry:
  - Anterior chamber depth (mm)
  - Axial length (mm)
  - Lens thickness (mm)
  - Corneal curvature – flat and steep meridian (mm)
  - Central retinal thickness (µm)
- Retinal thickness:
  - Central retinal thickness (µm)
  - Mid-peripheral retinal thickness (µm)
  - Peripheral retinal thickness (µm)

2.1.8.2.3 *Refractive error*

- Refractive error was defined as any of:
  - Myopia SEP ≤-0.50DS
  - Hyperopia SEP >+0.50DS
  - Significant hyperopia SEP ≥+2.00DS
  - Astigmatism CYL ≥1.00DC
  - Anisometropia SEP or CYL difference between the eyes ≥1.00D

2.2 EYE-SPY study

2.2.1 Study design

The EYE-SPY study was a single-centre cohort follow-up study of children who were screened for ROP at National Women's Health NICU during their neonatal period. This included children who were diagnosed with ROP (ROP group) and children who were not diagnosed with ROP (No ROP group). A cohort of term-born controls was also recruited (Term control group).

2.2.2 Objectives

To determine the associations between preterm birth, ROP and its treatment, and cortical damage in relation to visual outcomes in later childhood.

2.2.3 Participants

2.2.3.1 Participant description

The EYE-SPY study cohort consisted of eight to ten-year-old children born or treated at National Women's Health NICU (Auckland, New Zealand) between 1st January 2006 and 30th December 2008 inclusive. In 2006, there was a change from using indirect ophthalmoscopy to wide-field digital retinal imaging for ROP screening, as well as implementation of earlier treatment for severe ROP (Dai et al., 2015). Babies who were born with a gestational age <30 weeks and/or birth weight <1250g underwent photoscreening for ROP between 4-6 weeks after being born (Kuschel & Dai, 2007) and were graded according to the ICROP standards (Figure 1-1) (An International Committee for the Classification of Retinopathy of Prematurity, 2005). Those with prethreshold ROP (zone I ROP: any stage with plus disease; zone I ROP: stage 3—no plus disease; or zone II: stage 2 or 3 with plus disease) were treated using laser photocoagulation therapy, while babies who did not meet these criteria were followed up between 1 and 3 weeks depending on the severity of ROP (Kuschel & Dai, 2007). Follow up examination procedures were based on the joint guidelines published by the American Academy of Pediatrics in 2006 (American Academy of Pediatrics, 2006). All babies who were screened for ROP were scheduled for a 6 month follow up examination through the hospital's ophthalmology department.

2.2.3.2 Inclusion and exclusion criteria

Inclusion criteria were:

ROP group

- Screened for ROP at National Women's Health between the years 2006 and 2008
- Diagnosed with any stage of ROP, including those treated for ROP

No ROP group

- Screened for ROP at National Women's Health between the years 2006 and 2008
- Not diagnosed with ROP

Term control group

- Born at ≥38 weeks' gestational age

All participants were seen at 8 to 10 years of age inclusive (corrected age for children born preterm) and parental/guardian written informed consent were obtained.

Exclusion criteria were

- Severe congenital eye disease likely to affect visual function

2.2.3.3 Tracking

For the EYE-SPY study, all children who underwent ROP screening at National Women's Health NICU between 2006 and 2008 were identified through the prospectively maintained National Women's Health maternity database. All eligible participants were traced through hospital records, general practitioners, family contacts and social media. ROP status was initially determined through the ANZNN database and confirmed from ROP screening data in medical records. Care was taken to exclude children who died or suffered traumatic brain injury after the neonatal period. Upon turning eight years of corrected age, parents of preterm children eligible for the study were sent a letter to their most recent known address inviting participation into the EYE-SPY study. If no response was received two weeks following the letter invitation, a telephone call was made to ensure the letter was received.

Children born at full term (≥38 weeks' gestational age) were recruited from the friends and siblings of the cases and negative controls at the same age for the term control group. Term-born controls were also sought from the schools of participants in the EYE-SPY study. After parental consent was received, a letter with recruitment packs were sent to the school of the participant and the participant's classroom teacher was asked to distribute the recruitment packs to up to five children in their class who were of similar sex, ethnicity and age to the participant. The recruitment pack contained information about the study and also an "interest in participation" form with a self-addressed envelope; interested parents were then contacted via mail, email or telephone call for recruitment. Other term controls were recruited in a similar manner as the PIANO study. (2.1.4.6).

2.2.4 Perinatal data collection

Maternal, antenatal and neonatal baseline characteristics were collected for all children eligible for the EYE-SPY study from neonatal records and the ANZNN database similar to the PIANO study (2.1.5). The incidence of neonatal complications were also collected. Anthropometry, socioeconomic status, growth velocity and ethnicity were collected or calculated with the same procedure as the PIANO study (2.1.5).

2.2.5 Sample size

From estimations of ROP and ROP treatment at National Women's Health NICU between 2006 and 2007, we estimated 20% of children who had ROP would have scarring on the peripheral retina and hypothesized that children who did not have ROP would not have scarring. To reduce the incidence of scarring from 20% to 0.5% with 80% power, alpha 0.05, two tailed testing required 35 children in each group, x 3 groups = 105 babies. We added 5 extra children in each group to allow for children who would not tolerate or who would be uncooperative with the testing. The expected total sample size was 120 children. Recruitment of children for the ROP group was stopped after reaching 44 children; while recruitment for preterm children who previously did not have ROP continued.

2.2.6 Ethics

Ethical approval was obtained from the Northern A Health and Disability Ethics Committee (14/NTA/66) of the New Zealand Ministry of Health. Māori consultation was included in the ethical application process. Written informed consent was obtained from the parents or legal guardians on behalf of each participant; assent was given from the child. As well as signing the consent form, there were separate consents (circling yes or no) for instillation of cycloplegic eye drops and electrophysiology measurements.

2.2.7 EYE-SPY study assessment protocol

2.2.7.1 Venue for follow-up assessments

The majority of assessments were performed at the University of Auckland Grafton Campus Optometry Eye Clinic. Where the participant was unable to attend the assessment at the specified venue, if requested by the family, a local optometry practice was used (electrophysiology and visual field were not performed, while other tests such as optical coherence tomography and wide-field retinal imaging were dependent on the availability of equipment).

2.2.7.2 Vision assessment

Vision assessment was performed in a similar manner as the PIANO study (2.1.7).

2.2.7.2.1 *Measurement of visual acuity*

Distance VA was measured monocularly and binocularly using a Model 11-WIN Electronic Visual Acuity (EVA) tester (Jaeb Center for Health Research, U.S.A.) (Beck et al., 2003), which was viewed via a laptop screen placed at 3 metres from the participant. The letter sizes were configured according to the Early

Treatment Diabetic Retinopathy Study (ETDRS) with logMAR progression. The stimuli consisted of high-contrast black and white letters (98% contrast) with a luminance between 85 to 105cd.m^{-2}. An adaptive staircase showed a single letter with crowding bars with size between 1.6 to -0.5logMAR to evaluate a VA threshold.

2.2.7.2.2 *Binocular vision assessment*

The binocular vision assessment consisted of ocular alignment, ocular motility and 20Δ base-out prism assessment (2.1.7.2.2). Sensory fusion was tested using Worth's four dot test (Mayou, 1936), which consists of 2 green dots, 1 red dot and 1 white dot. The participant is asked to view the dots through red and green glasses. If 4 dots are perceived, sensory fusion is present; only 3 green dots or only 2 red dots signify suppression (the white dot will appear red or green depending on which eye is suppressed); alternating 2 or 3 dots signifies alternating vision; and 5 dots signify diplopia.

2.2.7.2.3 *Refractive error assessment*

The participants' refraction was measured using retinoscopy without cycloplegia, subjective refraction and cycloplegic auto-refraction. Refractive error was recorded according to the PIANO study protocol (2.1.7.2.6).

- For retinoscopy without cycloplegia, the participant was instructed to look at a fixation target on a mirror viewed at 6m. The fixation target was generated by a computerised letter chart, Medmont AT-20R Acuity Tester (Medmont International Pty Ltd, Vermont, Australia). This letter chart was also used for testing VA during the subjective refraction. The participant's eyes were blurred with plus lenses and retinoscopy was performed with loose lenses along the two major meridians.
- Using the retinoscopy results as a baseline, subjective refraction was performed monocularly by showing the participant different spherical lens combinations to find the least minus lens that produced least blur and best VA. The cylindrical component was determined using the Jackson Cross Cylinder (JCC) method. Following the subjective refraction, VA was measured using the Medmont AT-20R Acuity Tester and recorded in Snellen notation in logarithmic steps, and then converted to logMAR.
- Cycloplegic auto-refraction was performed as in 2.1.7.2.6.

2.2.7.2.4 *Colour vision*

Colour vision was assessed using the Ishihara Tests for Colour-Blindness, 24-plate 2009 edition (Kanehara Trading Inc., Tokyo, Japan) and Farnsworth D-15 Dichotomous Colour Blindness Test (Richmond Products, New Mexico, U.S.A). This test was performed at 75 cm from the participant. To be considered having normal colour vision, no more than 2 plates could be incorrectly identified out

of the 16 plates. If only nine or less plates were identified correctly, colour vision was regarded to be deficient. In those cases, the participant was asked to perform the Farnsworth D-15 test. Where the participant was asked to arrange 15 small coloured caps starting from the blue reference cap in a sequential hue progression to purple, and the results recorded. This test can be used to differentiate between protan (red deficiency), deutan (green deficiency) and tritan (blue deficiency). In the cases where the type of colour deficiency could not be differentiated, this was noted.

2.2.7.2.5 *Other visual tests*

Pupillary light reflex testing, stereoacuity, global motion perception, ocular biometry and retinal photography were performed as per 2.1.7.2 protocols.

2.2.7.2.6 *Visual field*

Peripheral visual fields of each eye were tested monocularly using the Medmont automated perimeter M600 (Medmont Pty Ltd., Camberwell, Victoria, Australia). The perimeter consists of a part hemispherical bowl with a radius of 300mm, which has a viewing distance of 320mm. The light stimuli are produced by pale green LEDs (wavelength of 565nm) with maximum luminance of 320 candela ($cd.m^{-2}$) and these are presented against a background luminance of 3.2$cd.m^{-2}$ in the bowl. The stimuli size is Goldman size III (0.43°) and the stimuli are arranged concentrically at various eccentricities ranging from 3° to 80°. In this study, a custom test was run using a three-zone strategy at 119 locations in the visual field with stimuli lying in rings located at 3°, 6°, 10°, 15°, 22°, 30°, 40°, 50°, 60°, 70° and 80°. For a three-zone strategy, the result for each point was classified as seen, relative defect or absolute defect. Reliability of the visual field result was defined as between 20-50% fixation loss (this higher than usual, which is 20%; this range was chosen as the blind spot could be seen when testing the nasal visual field), and false positive equal or less than 33% (Heijl & Patella, 2002).

2.2.7.2.7 *Electrophysiology*

The two electrophysiological diagnostic tests used within this study were pattern-reversal visual evoked potentials (pattern-reversal VEP)(Odom et al., 2010) and pattern electroretinogram (PERG) (Bach et al., 2013) using the RETI-port/scan21 system (Roland Consult, Germany). These were run according to the International Society for Clinical Electrophysiology of Vision (ISCEV) standard from 2009 (Odom et al., 2010) and 2012 (Bach et al., 2013). Pattern-reversal VEP is a measure of the functional integrity of the visual system from the primary visual cortex to the retina and PERG is a measure of the retinal ganglion cell function. For these protocols, no standard international reference ranges were available, therefore, our laboratory established normal values for our equipment and patient population in term children between 8-10 years of age.

2.2.7.2.7.1 Pattern-reversal VEP procedure

Electrodes were placed according to the 10-20 placement system (Jasper, 1958). The viewing distance was 100cm at eye level and the participant was asked to look at the fixation cross on a computer screen showing a black and white checkerboard patterned stimulus with 88.5% contrast subtending 1 degree of arc and 15 minutes of arc (0.25 degree of arc). During the protocol, there was alternating contrast reversal of black and white checks (black to white and white to black) at a reversal rate of 1.54 reversals per second through a bandpass of 1-50Hz, for one hundred sweeps. Two averages were performed for each task to verify the reproducibility of the measurements. The N75 and P100 peaks of the pattern-reversal VEP waveform were analysed. Latency of the peaks and amplitude between the peaks were measured. This test was performed monocularly.

2.2.7.2.7.2 PERG procedure

A silver fibre electrode (active) was placed on the lower conjunctival fornix without touching the cornea and the skin electrode placed near the nasal canthus. The reference gold cup electrodes were placed on the outer canthus of each eye and the ground electrode was place on the central forehead (Bach et al., 2013). The viewing distance was 100cm at eye level and the participant was asked to look at the fixation cross on a computer screen showing a black and white checkerboard patterned stimulus with 88.5% contrast subtending 0.8 degrees of arc. During the protocol, there was alternating contrast reversal of black and white checks (black to white and white to black) at a reversal rate of 4.29 reversals per second through a bandpass of 5-50Hz for one hundred sweeps. Two averages were performed for the task to verify the reproducibility of the measurements. The N35, P50, N95 peaks of the pERG waveform were analysed. Latency of the peaks and amplitude between the peaks were measured. This test was performed binocularly.

2.2.7.2.8 *Ultra-widefield digital retinal imaging (OPTOS)*

Peripheral retinal health was assessed by ultra-widefield digital retinal imaging using an Optos 200Tx (Optos plc, Scotland), which is an ultra-widefield scanning laser ophthalmoscope. The exposure time of the image is 0.3 seconds and resolution is approximately 14µm. Using an excitation wavelength of 532nm, autofluorescent images can also be acquired (Heussen et al., 2012).

- Similar to the retinal photography grading in the PIANO study (2.1.7.2.7), images were assessed after data collection was completed, and graded by one observer using clinical judgement. As the OPTOS images were more prone to artefacts due to dust on the mirror, images were placed in alphabetical order by the initials of the participant and both eyes were assessed at the same time. If smudges or dust spots were found in the same area on an image, then they were classified as artefacts. The observer was blinded to group allocation. Ten percent of the images were also reviewed by a separate observer (an optometrist who was familiarised with the grading system),

and where there were differences, these were reassessed and discussed between both observers to reach a consensus.

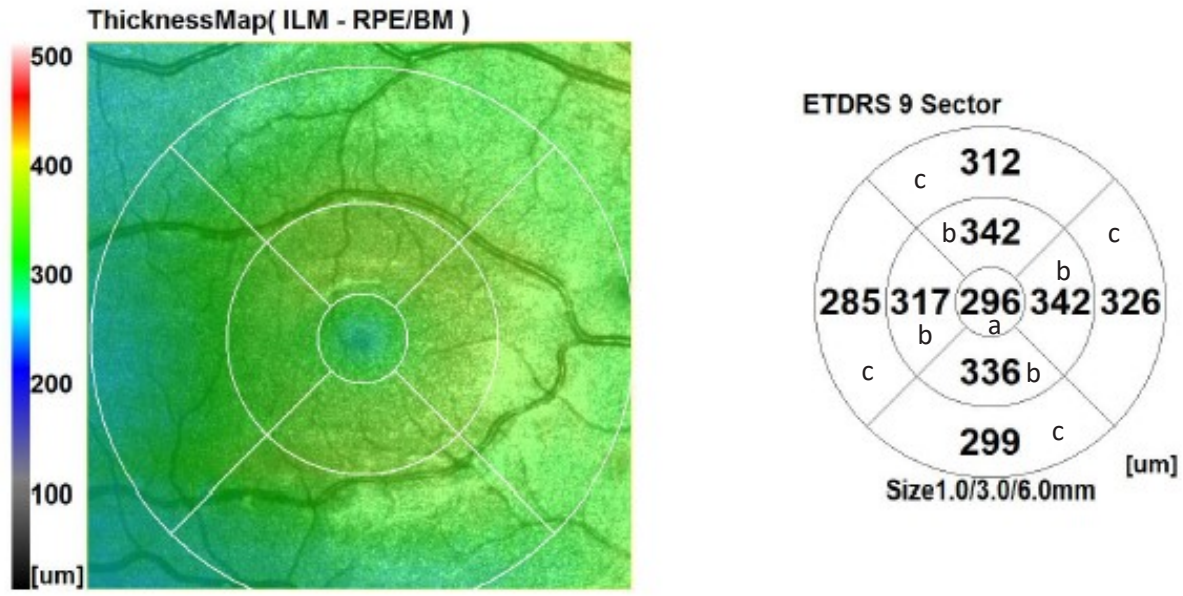
- The quality of the images was assessed subjectively (clarity, artefacts and missing areas) out of ten with ten being best quality, and if the images were of gradable quality, the retina were assessed and graded as:
  1) No peripheral retinal changes
  2) Non-clinically significant peripheral retinal changes
  3) Clinically significant retinal abnormalities (requiring follow-up more frequent than the biannual routine follow-up, requiring referral for further investigation or requiring treatment)
  4) Unable to grade

  Grading was based on typical peripheral retinal findings in children born preterm (An International Committee for the Classification of Retinopathy of Prematurity, 2005; Mintz-Hittner & Kretzer, 1994). Signs of non-clinically significant peripheral retinal changes included but not limited to anomalous blood vessels such as isolated arterial vascular tortuosity; isolated hypo/hyperpigmentation such as tessellation or congenital hypertrophy of the retinal pigmented epithelium, or incomplete vascularisation of the retina, or remnants of ROP ridge that is not associated with traction of the retina. Signs of clinically significant abnormalities include but not limited to blood vessel abnormalities such as telangiectasia, haemorrhage, neovascularisation and blood vessel narrowing/dilation; or retinal abnormalities such as tears, breaks, retinal detachment, fibrous tissue with traction.

2.2.7.2.9 *OCT*

OCT of the macula and optic nerve were performed using Nidek RS-3000 Advance (Nidek Inc., Japan). Parameters used were the 6x6mm macula map and 6x6mm disc map, both 64 frames at 1024 fine resolution. With the macula and disc map, the image was able to be centred (i.e. by moving the white ring in Figure 2-3 to have the macula in the centre of the white circle*) following acquiring images and analysed by the OCT software even with some movement of the participant. From the ETDRS sector output (Figure 2-3), retinal thickness was obtained (central (a), mid peripheral (average of b) and peripheral retina (average of c). If there was movement and unreliable results from the scan, affected rings were excluded from the analysis.

Figure 2-3 OCT macula map output



2.2.7.3 Visual/motor assessment

Visuo-motor integration was measured with the same procedure used in the PIANO study (2.1.7.6.4).

2.2.7.4 Growth assessment

Weight, height and head circumference were measured with the same procedure as in the PIANO study (2.1.7.4).

2.2.7.5 Questionnaires

- Health status was assessing using a multi-attribute approach through the Health Utilities Index (HUI) Mark III system (Feeny et al., 1995). This system grades the health status in 7 attributes including vision, hearing speech, ambulation, dexterity, emotion, cognition and pain. For each of these attributes, there is a grading between 1 and 6 depending on the attribute and it assesses function and disability in those areas. An overall score can be calculated using vectors. Using a reference table and formula u* = 1.371 (b1*b2*b3*b4*b5*b6*b7*b8) – 0.371, a utility score for an individual can be calculated, with Dead=0.00 to Perfect Health=1.00. “b(n)” corresponds to each of the attributes (Furlong et al., 1998).
- Self-reported visual ability was assessed using the Cardiff Visual Ability Questionnaire for Children (Khadka et al., 2010), which is a 25-item questionnaire asking how eye sight causes difficult in the areas of education, near vision, distance vision, getting around, social interaction, entertainment and sports. Not all the questions were applicable to children in New Zealand primary schools and as a result, many of the questionnaires were incomplete. Therefore, the results were not reported in this thesis.

2.2.7.6 B4 school check

Procedure performed the same as in the PIANO study (2.1.7.9).

2.2.8 Outcome Measures

2.2.8.1 Primary outcome

Presence of retinal scarring in either or both eyes (any development of fibrous tissue in the retina).

2.2.8.2 Secondary outcomes

2.2.8.2.1 *Visual function*

- Favourable overall visual outcome was defined as in 2.1.8.2.1, except a combination of subjective and cycloplegic refractive error results were used.
- Binocular and functional visual outcome; blindness, stereoacuity, and global motion perception threshold as defined in the PIANO study (2.1.8.2.1).
- Favourable aided visual outcome was defined as:
  - No amblyopia (best corrected VA equal or better than 0.2logMAR, and difference between eyes <0.2logMAR)
  - No strabismus
  - Passing TNO stereoacuity

  I.e. Adequate best corrected vision and stereoacuity for daily activities, in the absence of strabismus.
- Other visual function outcomes:
  - VA better than 6/7.5 in the better eye
  - Presenting binocular distance VA (logMAR)
  - Presence of sensory fusion (4 dots seen on Worth's dot test)
  - Log stereoacuity
  - Pass Ishihara colour vision (≤2 plates incorrect)
  - Amblyopia

2.2.8.2.2 *Ocular structure*

- Retinal posterior pole (central) findings:
  - No abnormalities or signs of normal variants (not clinically significant)
  - Clinically significant abnormalities
  - Unable to grade

- Peripheral retina:
  - Non-clinically significant peripheral retinal changes
  - Clinically significant retinal abnormalities
- Retinal vascular tortuosity in the better and poorer VA eye
  - Nil
  - Mild
  - Severe
- Ocular biometry:
  - Central corneal thickness (µm)
  - Anterior chamber depth (mm)
  - Axial length (mm)
  - Lens thickness (mm)
  - Corneal curvature – flat and steep meridian (mm)
- Retinal thickness:
  - Central retinal thickness (µm)
  - Parafoveal retinal thickness (µm)
  - Peripheral retinal thickness (µm)

2.2.8.2.3 *Refractive error*

- Refractive error was defined as per PIANO study (2.1.8.2.3):
  - Myopia
  - Hyperopia
  - Significant hyperopia
  - Astigmatism
  - Anisometropia

2.2.8.2.4 *Visual field*

- Reliability
  - Fixation loss between 20% and 50% inclusive; and
  - False positive less or equal to 33%

2.2.8.2.5 *Electrophysiology*

- Pattern electroretinogram
  - N35 latency (ms)
  - P50 latency (ms)
  - N95 latency (ms)

- N35-P50 amplitude (μV)
- P50-N95 amplitude (μV)

- Pattern visually evoked potentials (for both check size 15 minutes and 1 degree)
  - N75 latency (ms)
  - P100 latency (ms)
  - N75-P100 amplitude (μV)

2.2.8.2.6 *Beery visual motor integration*

- Beery visual motor integration
- Beery visual perception
- Beery motor coordination

Standard scores and percentiles were reported

2.2.8.2.7 *Overall visual status and need for follow-up*

- Vision follow-up required, defined as:
  - Visual function: amblyopia, or VA poorer or equal to 6/12 in the better eye; or
  - Refractive error: optical correction required in either eye; or
  - Ocular structure: strabismus, or retinal posterior pole or peripheral retina requiring follow-up
- Vision follow-up required, and has not had previous ocular assessment, defined as:
  - Vision follow-up required, and
  - Previous ocular assessment: visual assessment at hospital, ophthalmology or optometry clinics, or B4 School Vision check, has spectacles
- Vision follow-up required, which has not been identified previously
- Types of visual problems not previously identified

2.3 Definitions

2.3.1 Neonatal complications

- Bronchopulmonary dysplasia (chronic lung disease): babies born at <32 week's gestational age and receiving any respiratory support (supplemental oxygen, intermittent positive pressure ventilation or continuous positive airways pressure) for a chronic lung disorder at 36 week's postmenstrual age

- Early onset sepsis: presence of at least one episode of systemic sepsis (isolation of an organism from at least one blood or cerebrospinal fluid culture) with initial symptoms before 48 hours after birth
- High BGC: BGC >8.5mmol.L^{-1}
- Hypoglycaemia: BGC <2.6mmol.L^{-1} (severe <1.5mmol.L^{-1})
- Intraventricular haemorrhage: worst grade of haemorrhage seen on either side of the head during the first ten days of life (Papile et al., 1978)
    - None – examined and no haemorrhage
    - Grade 1 – subependymal germinal matrix haemorrhage
    - Grade 2 – IVH with no ventricular distension
    - Grade 3 – IVH with ventricle distended with blood
    - Grade 4 – intraparenchymal haemorrhage

  Severe IVH was classified as grade 3 or 4
- Late onset sepsis: presence of at least one episode of blood or cerebrospinal fluid infection with initial symptoms occurring from 48 hours after birth
- Necrotising enterocolitis: signs of pneumatosis intestinalis, portal vein gas, persistent dilated loop on serial X-rays, or abdominal wall cellulitis with palpable abdominal mass (Bell et al., 1978)
- Neonatal hyperglycaemia: 2 consecutive measurements of BGC >8.5mmol.L^{-1}, at least 4 hours apart
- Recurrent hyperglycaemia: at least one BGC >8.5mmol.L^{-1}
- Retinopathy of prematurity: worst stage of retinopathy seen in either eye prior to going home, defined according to ICROP (The Committee for the Classification of Retinopathy of Prematurity, 1984). Severe ROP was classified as stage 3 or 4

2.3.2 Other neonatal outcomes

- Apgar score: a clinical score used as an indicator of health of a baby based on five characteristics (heart rate, respiratory condition, muscle tone, reflexes and colour). Scored from 0 to 10 with best health being 10
- CRIB II score: system scored according to five-items (sex, birth weight, gestational age at birth, temperature at admission and base excess) to calculate adjusted risk of mortality for babies in neonatal intensive care. Scored from 0 to 27 (more risk with higher score) (Parry et al., 2003)
- Neonatal surgery: a baby admitted for intensive care and had surgery that involved opening a body cavity during admission

- Small for gestational age: birth weight <10th percentile for gestational age according to the Fenton chart for babies born preterm (Fenton et al., 2013)

2.3.3 Age

- Corrected age: the age of the child from the expected date of delivery
- Gestational age: completed days or weeks after the onset of the last normal menstrual period at birth
- Postmenstrual age: number of weeks after the onset of the last normal menstrual period to day of neonatal assessment

2.3.4 Visual outcomes

- Amblyopia: best corrected VA equal or better than 0.2logMAR, and difference between eyes <0.2logMAR (Note: Amblyopia is defined as a unilateral or bilateral reduction of best corrected VA that is associated with a developmental disorder of the central nervous system, and usually occurs in the setting of an otherwise normal eye (Wallace, Repka, et al., 2018). However, in children born preterm, there are potential visual threatening retinal changes from conditions such as ROP and preterm birth. Also, best corrected VA may improve with refractive adaption (Gao et al., 2018), which can only be assessed when the child returns for multiple visits. Therefore, in our study, we could not confirm amblyopia diagnosis, and our diagnosis of amblyopia was based on the best corrected VA after subjective refraction during the assessment and no observable anterior eye disease, media opacities or retinal pathology that are associated with vision loss. As thickened central retina is common in preterm birth but has not been reliably associated with visual loss (Bowl et al., 2016), this was not considered a retinal pathology associated with vision loss in our study.)
- Blindness: presenting VA of 6/60 or worse in the better eye
- Failing ocular motility: any restriction or overaction of any ocular muscles
- Good distance VA: VA of equal or better than Snellen 6/12 in the better eye
- Motor fusion present: overcoming 20Δ base out prism in both eyes
- Nystagmus: involuntary oscillation of the eyes (latent movement only present when one eye is covered)
- Passing convergence: convergence to equal or less than 10cm from the eyes
- Passing TNO stereoacuity: ≤240 seconds of arc

- Refractive error:
    - Anisometropia ≥1.50D between eyes
    - Astigmatism ≥-1.00DC
    - Hyperopia >+0.50DS
    - Myopia ≤-0.50DS
    - Significant hyperopia >+2.00DS
- Requiring spectacles: SEP ≤-0.50DS and >+2.00DS, and/or cylindrical power ≥-1.00DC)
- Strabismus: heterotropia at distance and/or near fixation, intermittent or constant

2.3.5 Developmental outcomes

- Cerebral palsy: based on fixed abnormal neurology with abjudication by a group of Paediatricians if diagnosis was unclear. Cerebral palsy was classified using the Gross Motor Function Classification System (Mild: ≤grade II, Moderate: grade III, Severe: ≥grade IV) (Papile et al., 1978)
- Cognitive impairment: Wechsler Intelligence Scale for Children Full Scale Intelligence Quotient <85 (1SD below the mean)
- Motor impairment: Movement Assessment Battery for Children-2 total score ≤5thcentile

2.4 Statistical analyses

Statistical calculations were performed using SPSS Statistics 22 (IBM) and graphs were plotted in Prism 7 for Windows (GraphPad Software, Inc).

Normally distributed data were reported as means ± standard deviations (SD) and analysed by student t-test. Non-parametric variables were report as medians (interquartile range IQR) and were analysed by Mann U Whitney test if the data could not be log-transformed. Categorical data was analysed using Chi-squared test or Fisher's exact tests for small cell counts. Qualitative data such as retinal imaging and questionnaires were coded and reported as numbers (proportions) and means±SD and analysed as categorical data.

Maternal and perinatal characteristics of eligible children for follow-up at 7 years of age (assessed and not assessed) in the PIANO study and for children assessed in the EYE-SPY study at 8 to 10 years of age were first summarised descriptively and compared using the tests above. Similarly, nutritional intake in the first week and first month after birth, and growth were summarised and reported as above.
Potential confounders for children who were assessed at 7 to 10 years of age, likely to be strongly associated with outcomes were compared between the groups for each sub-cohort. Outcomes that differed by more than 10% between the two groups or were statistically significantly different were considered covariates in analyses when comparing outcomes of the two groups. Adjustment for multiple comparisons were not made due to the complexity of the data.

The primary and secondary outcomes of children who were assessed at 7 to 10 years of age were compared between the two groups using unadjusted and adjusted generalised linear regression models and reported as odds ratios (OR) or mean differences between the groups. 95% confidence intervals (95%CI) and p-values were used to evaluate the differences. For groups of more than two, *post-hoc* analyses were used to differentiate differences between groups (reported for before adjustment of potential confounders). *Post-hoc* analyses used were: Tukey for parametric data with similar variance, Dunnett's T3 for parametric data with differential variance, and Bonferroni for categorical data. For additional analyses, various parameters such as VA and refractive error were further separated into groups of severity, while other parameters such as stereopsis were converted into logarithmic scale or inversed to encompass all data. No assessable stereoacuity was coded as 48,000 seconds of arc (Log 4.68), which is 10x the highest disparity tested.

Generalised linear regression models were used for the exploratory analyses visual outcomes that were statistically significantly different between comparison groups in each chapter. The association between neonatal factors or exposures that were different between groups and visual outcomes at 7 to 10 years were explored using a logit (Binomial distribution) or identity (Normal distribution) link as appropriate. Regression models were adjusted for potential confounders. For each exposure, results were presented as odds ratio or mean difference with associated 95% confidence intervals and p-values. All exposures with p-value <0.15 were then entered into a multiple regression analysis to further explore the association between exposures and visual outcomes; exposures that were measuring similar outcomes were excluded (e.g. exposures showing collinearity). Factorial analysis of variance was used for groups of more than two and for repeated measures.

A pairwise deletion method was used to account for missing data by discarding cases in tests where missing data were observed (Peugh & Enders, 2004); the number of missing data for each tests were represented in the tables and figures where appropriate. Imputations were not appropriate for this cohort as children were only seen at one time point, which meant that there were no data to accurately estimate missing data. For composite measures, to compare the effects of missing data on analyses, two methods were employed: 1) removing participants with missing data from the components of the composite before analysis, and 2) analysing presence of unfavourable outcomes, which may have included some participants with missing data. A statistically significant result was taken as a p-value <0.05.

2.5 PIANO and EYE-SPY study summary

Table 2-6 PIANO and EYE-SPY study summary

Study Summary		
Study Name	Protein, Insulin and Neonatal Outcomes (PIANO) Study	Examining Young Eyes for Signs of PrematuritY (EYE-SPY) Study
Research Question:	How does preterm birth, neonatal complications and treatments affect visual development at 7 years of age?	How does preterm birth and ROP affect visual function and ocular structure at 8-10 years of age?
Aims	To investigate whether neonatal hyperglycaemia, insulin treatment and neonatal nutrition affect visual outcomes at seven years of age	To investigate the associations between ROP, ROP treatment, preterm birth and cortical damage on visual development at eight to ten years of age
Study design	**HINT follow-up cohort** Follow-up of a randomised controlled trial **Neonatal hyperglycaemia follow-up cohort** Case-control matched cohort **Neonatal nutrition follow-up cohort** Cohort observational study	**ROP follow-up cohort** Cohort observational study
Participants		
Cohorts	**HINT follow-up cohort** Tight Group: Born preterm and developed neonatal hyperglycaemia* and, randomised to the Tight Group in the HINT trial Control Group: Born preterm and developed neonatal hyperglycaemia, and randomised to the Standard Group in the HINT trial **Neonatal hyperglycaemia follow-up cohort** Hyperglycaemic Group: Born preterm and developed neonatal hyperglycaemia, and participated in the HINT trial Non-hyperglycaemic Group: Born preterm and did not develop neonatal hyperglycaemia **Neonatal nutrition follow-up cohort** Before Group: Preterm and born on or before 31st December 2006 After Group: Preterm and born on or after 1st January 2007 **PIANO vision assessment only** Term Group: Born at full term, aged 7 years	**ROP follow-up cohort** ROP Group: Born preterm and screened for ROP between years 2006 and 2008, and diagnosed with ROP No ROP Group: Born preterm and screened for ROP between years 2006 and 2008, and was not diagnosed with ROP Term Group: Born at full term, aged 8-10 years

Inclusion criteria	Preterm: Born at <30 weeks' gestational age and/or <1500g birth weight	Preterm: Born at <30 weeks' gestational age and/or <1250g birth weight, and screened for ROP
	Term controls: Born at ≥38 weeks' gestational age	
	Aged seven years (preterm: corrected age)	Aged eight to ten years of age (preterm: corrected age)
	Parent/guardian written informed consent to participate	
Exclusion criteria	Children with a severe congenital eye disease not due to ROP, likely to affect visual function	
Ethical approval	Approval by Northern Y Regional Ethics Committee and Northern B Ethics Committee (NTY/12/05/035)	Approval by Northern A Health and Disability Ethics Committee (14/NTA/66)
Assessments		
Venue of assessments	Clinical Research Unit, Optometry Eye Clinic and Centre of Advanced MRI at the University of Auckland Grafton Campus	Clinical Research Unit and Optometry Eye Clinic at the University of Auckland Grafton Campus, local optometry practices
Vision assessments (in order of assessment)	Distance visual acuity (Keeler chart)	Distance visual acuity (EVA tester)
	Binocular vision: ocular alignment, 20Δ base out prism test, ocular motility, near point of convergence, amplitude of accommodation, nystagmus and ptosis	Binocular vision: ocular alignment, 20Δ base out prism test and ocular motility
	Pupillary light reflex	
		Retinoscopy and subjective refraction
	Stereoacuity (Stereo Fly and TNO)	
		Colour vision (Ishihara and D15)
	Global motion perception (RDK)	
	Ocular biometry (LenStar)	
		Visual field (Medmont - custom parameters, peripheral 135° three zone screening)
		Electrophysiology (Roland - pattern VEP and pattern ERG according to the ISCEV standards)
	Cycloplegic autorefraction (CYC 1.0% and Nidek AR-20 Handheld Autorefractor)	
	Retinal photography	
	Wide-field digital retinal imaging (Optos); For the PIANO study, Optos imaging only available for participants after October 2014, and results not presented.	
	Optical coherence tomography (Nidek RS3000 Advanced): For the PIANO study, a 6-line radial macular scan was used; for the EYE-SPY study, a macular map and optic nerve map was used.	
Other assessments (in order of assessment)	Intravenous glucose tolerance test	
	Protein milkshake	

	Paediatric medical assessment	
	Physical growth assessment: For the PIANO study, standing height, sitting height, head circumference, weight, abdominal circumference and body mass index were measured; for the EYE-SPY study, standing height, head circumference and weight were measured	
	Body scarring	
	Body composition and bone mass (DEXA)	
	Fine and gross motor function (Movement Assessment Battery for Children)	
	Visuomotor co-ordination (Beery Visual Motor Integration Score)	
	Cognitive assessment (Wechsler Intelligence Scale for Children, and Test of Everyday Attention for Children)	
	Behavioural assessment (BRIEF Parent and Child Behaviour Checklist)	
	Parental vocabulary test (Peabody Picture Vocabulary Test)	
	Structural and functional brain scans (MRI)	
	Questionnaires: For the PIANO study, Home and family, child health, teachers - BRIEF teacher and Teacher's Report form were collected; for the EYE-SPY study, Cardiff Visual Ability Questionnaire for Children, and Multi-Attribute Health Status: Health Utilities Index Mark 3 Questionnaire were collected.	
	B4 School Check	

**Neonatal hyperglycaemia was defined as 2 consecutive BGC >8.5mmol.L-1 at least 4 hours apart. Note: For the PIANO study, term children were assessed on visual function, body scarring and growth measurements only*

3 Effects of Neonatal Hyperglycaemia in Babies Born Preterm on Visual Outcomes at Seven Years of Age

3.1 Introduction

Transient neonatal hyperglycaemia is commonly experienced by babies born very preterm, with up to 60% of extremely low birth weight babies (birth weight <1000g) having whole BGC greater than (>150mg.dL^{-1}) 8.3mmol.L^{-1} (Hays et al., 2006). For 50% of the babies, high BGC persisted in the first week after birth. Preterm birth is associated with adverse visual outcomes including reduced VA, and an increased risk of strabismus and refractive error (O'Connor et al., 2007). Although neonatal hyperglycaemia and visual development have been studied extensively in babies born very preterm, these conditions have only been investigated separately. Therefore, it is unknown whether there is an association between neonatal hyperglycaemia and visual development in later childhood.

Neonatal hyperglycaemia is associated with increased mortality (Hays et al., 2006; Stensvold et al., 2015) and adverse outcomes such as sepsis (Andersen et al., 2004; van der Lugt et al., 2010), IVH (Auerbach et al., 2013; Hays et al., 2006) and ROP (Au et al., 2015; Lee et al., 2016; Mohamed et al., 2013). However, it is unknown whether there is a causal association between hyperglycaemia and these factors, or if it is purely a marker of severe illness (Hey, 2005).

High BGC in diabetes mellitus (type I and II) are associated with ocular changes and subsequent vision loss (Bourne et al., 2013; Yau et al., 2012). Common signs of diabetic retinopathy include retinal thickening, microvascular changes, haemorrhages, exudates due to loss of blood vessel pericytes in the earlier stages, and macula oedema, ischaemia and neovascularisation in more severe stages (Ciulla et al., 2003; Stitt et al., 2016). Other common ocular changes include development of cataracts and loss of corneal sensitivity. The mechanism by which hyperglycaemia results in diabetic retinopathy is unclear but it has been proposed that hyperglycaemia causes diabetic retinopathy by multiple processes including inflammation, oxidative stress, loss of blood-retinal barrier, VEGF production, protein kinase c – diacylglycerol pathway, neural damage, genetics and advanced glycation end products formation (Antonetti et al., 2006; Cai & Boulton, 2002; Stitt et al., 2016). Similar to ROP, due to ischaemia of the retina, there is upregulation of VEGF and new blood vessels are produced; these blood vessels are leaky. Subsequent fibrosis and attachment to the vitreous body can result in retinal detachment (Caldwell et al., 2003; Hartnett & Penn, 2012). The risk of diabetic retinopathy progression is increased with longer presence of hyperglycaemia (Klein et al., 1994; Sartore et al., 2013). However, it is unknown whether the transient hyperglycaemia experienced by babies born

preterm affects visual outcome in later childhood, either by increasing the incidence of ROP, or via direct effects on the eye.

Many babies born preterm have ROP, a proliferative retinal vascular disease that can affect vision in varying degrees; from normal vision in mild ROP through to no perception of light following full retinal detachment in individuals with severe ROP (Hartnett & Penn, 2012). The risk of developing any severity of ROP has been shown to be related to increasing duration of hyperglycaemia and the daily mean BGC in the first 30 days of life (Blanco et al., 2006; Chavez-Valdez et al., 2011; Garg et al., 2003; Mohamed et al., 2013; Slidsborg et al., 2017). However, these studies have used various definitions of neonatal hyperglycaemia. Recent reviews of babies born with birth weight <1000g and gestational age ≤32 weeks concluded that the current evidence does not show that hyperglycaemia is a definite risk factor for ROP, and hyperglycaemia and insulin intake are not associated with severe ROP (Au et al., 2015; Lee et al., 2016). As most studies on hyperglycaemia and ROP were small and retrospective in nature, further investigation with an agreed definition of hyperglycaemia, with and without insulin use, are needed to determine whether there is a casual relationship between hyperglycaemia and ROP.

The aim of this study was to to determine whether neonatal hyperglycaemia *per se* affects visual outcomes and ocular growth at 7 years of age, and whether neonatal hyperglycaemia is associated with an increased risk of ROP. We hypothesise that while neonatal hyperglycaemia *per se* does not affect ocular growth or visual outcomes; neonatal hyperglycaemia associated with an increased risk of ROP may affect visual outcomes. In this chapter, we report the vision results from the neonatal hyperglycaemia cohort follow-up arm of the PIANO study.

3.2 Methods

Five hundred and thirty six babies were born at <30 weeks' gestational age or <1500g birth weight at National Women's Health between July 2005 and October 2008, of whom 154 babies developed hyperglycaemia (2 consecutive measurements of BGC >8.5mmol.L^{-1}, at least 4 hours apart). Eighty eight of these babies participated in a randomised, controlled non-blinded trial of tight glycaemic control in very low birth weight hyperglycaemic preterm babies (HINT trial) (2.1.4.1). Children of the HINT trial were invited to take part in the PIANO study at 7 years of corrected age and included as the Hyperglycaemic group in the neonatal hyperglycaemia follow-up cohort. Each child from the HINT trial was matched with a child who was born at <30 weeks' gestational age or <1500g birth weight and was

admitted to the National Women's Health NICU between July 2005 and October 2008 but had not met criteria for the diagnosis of hyperglycaemia in the neonatal period (2.1.4.2). The matching variables in a hierarchical order were: sex, gestational age, birth weight, date of birth, NZ deprivation index at pregnancy booking, multiple birth and CRIB-II score. These matched children were invited to be part of the PIANO study and formed the Non-hyperglycaemic group in the neonatal hyperglycaemia follow-up cohort. During this process, paired matching of each case with all variables was not always possible due to the small numbers available for matching. Matching for CRIB-II score was discontinued during recruitment as CRIB-II scores in the hyperglycaemic cases were significantly higher than in potential controls, resulting in infeasible matching.

Full details of inclusion and exclusion criteria, recruitment details, and visual assessment can be found in 2.1.

The primary outcome was neurodevelopmental impairment at 7 years of age.

Secondary outcomes assessed were composite visual function including overall visual outcome, binocular visual outcome, and functional visual outcome. Other visual outcomes included VA, global motion perception, ocular structure and refractive error.

3.2.1 Statistical analyses

Statistical calculations were performed using SPSS Statistics 23 (IBM) and graphs were plotted in Prism 7 for Windows (GraphPad Software, Inc). Details for standard statistical analyses can be found in 2.4.

As the neonatal hyperglycaemia cohort of the PIANO study involved matching participants between the groups, each of the matching criteria could be a potential confounder. To account for differences between the two groups, the data were adjusted for the matching variables of sex, multiple birth, gestational age, birth weight z-score, CRIB-II score and NZ Deprivation Index at birth using logistic or linear regression.

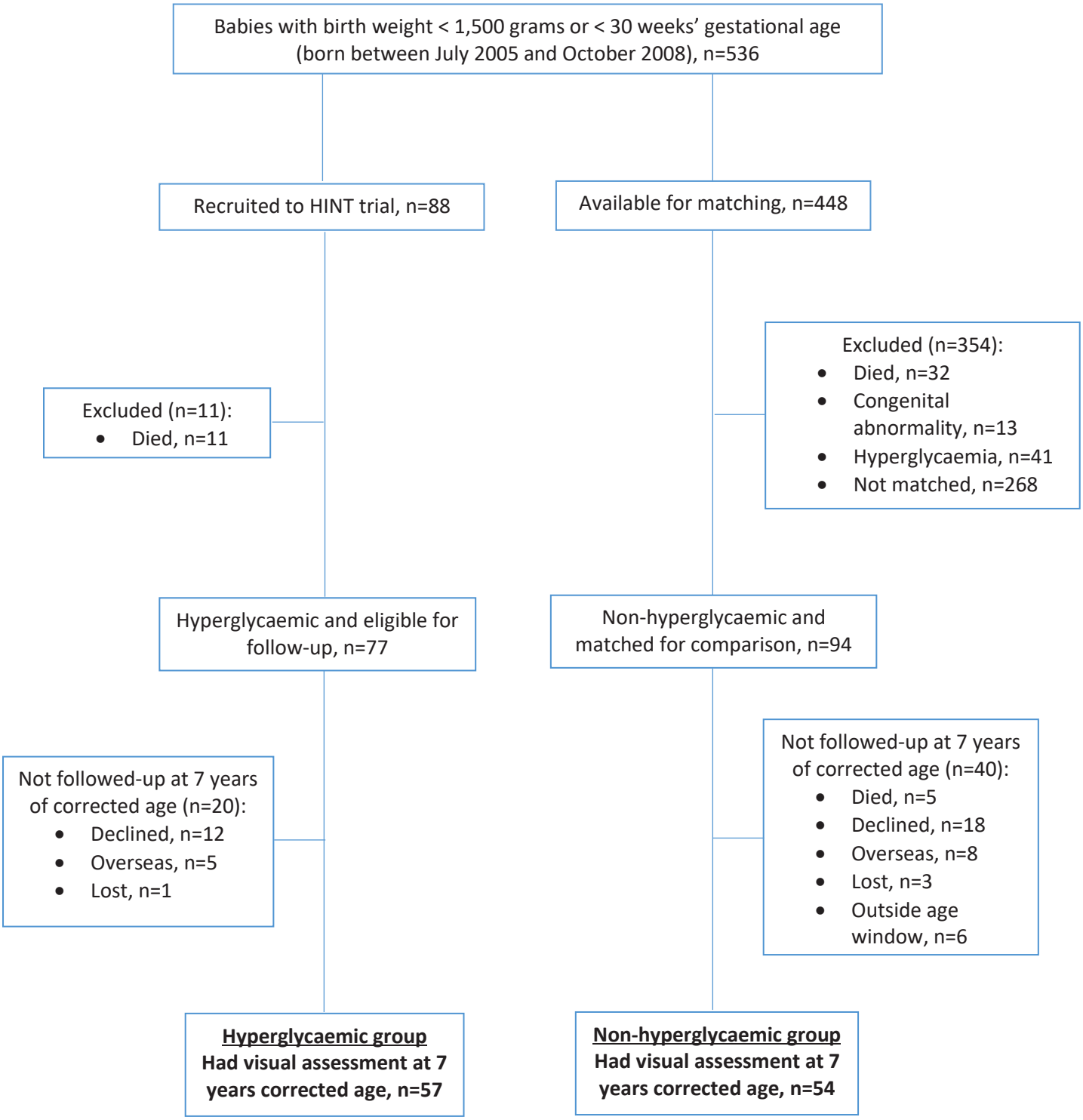
3.3 Results

Of the 88 babies who developed neonatal hyperglycaemia and were randomised to the HINT trial, 11 died before 7 years corrected age. Of the 77 surviving children, 57 (74%) were included as the Hyperglycaemic group and were followed-up at 7 years of age. From the other 448 eligible babies, 94 babies who did not develop hyperglycaemia met the matching criteria; and of these, 54 (57%) were followed-up as part of the Non-hyperglycaemic group. This resulted in 111 children being assessed at 7 years of corrected age (Figure 3-1).

Children who were assessed at 7 years of age had similar maternal characteristics including ethnicity, multiple pregnancy, maternal diabetes and socioeconomic status (Table 3-1) compared with those not assessed. More mothers of children who did not develop neonatal hyperglycaemia and were not assessed had a complete course of antenatal steroids compared to those Non-hyperglycaemic and assessed. There was no differences in maternal characteristics between assessed children in the Hyperglycaemic and Non-hyperglycaemic groups.

Neonatal baseline characteristics were similar between children assessed and not assessed at 7 years of age (Table 3-2), except children in the Hyperglycaemic group who were not assessed had higher birth weight, length and head circumference z-score than those assessed. At 28 days after birth, not assessed children of the Hyperglycaemic group continued to have higher mean weight z-scores. Glycaemic measures (Table 3-3) within the first 28 postnatal days were similar between those assessed and not assessed. No differences were found in the number of days until enteral feeds were established and nutritional intake in the first month after birth, neonatal complications or length of neonatal stay between those assessed and not assessed.

Figure 3-1 Strobe diagram of children participating in the vision assessment of the neonatal hyperglycaemia cohort follow-up arm of the PIANO study at seven years of age



Note: there were two categories of "died" for the Non-hyperglycaemic group: some of the children were known to have died as a prior to discharge from the NICU and were excluded before matching, while other children died after discharge from the NICU and were not known to have died until after matching.

Table 3-1 Maternal characteristics of children in the neonatal hyperglycaemia cohort follow-up arm of the PIANO study

	Hyperglycaemic group (n=77)			Non-hyperglycaemic group (n=89)			Hyperglycaemic v Non-hyperglycaemic (assessed) P-value
	Assessed (n=57)	Not assessed (n=20)	Assessed v not assessed P-value	Assessed (n=54)	Not assessed (n=35)	Assessed v not assessed P-value	
Maternal diabetes	2 (3.5%)	1 (5%)	0.77	4 (7%)	0 (0%)	0.10	0.43
Maternal insulin	0 (0%)	1 (5%)	0.26	3 (3%)	0 (0%)	0.16	0.11
Multiple pregnancy	20 (35%)	8 (40%)	0.69	13 (24%)	5 (14%)	0.26	0.22
Ethnicity							
Māori	20 (35%)	7 (35%)	0.11	11 (20%)	4 (11%)	0.09	0.77
Pacific Island	7 (12%)	7 (35%)		8 (15%)	6 (17%)		
European	19 (34%)	3 (15%)		6 (11%)	11 (32%)		
Asian/Other	11 (19%)	3 (15%)		6 (11%)	11 (32%)		
Deprivation index							
Most deprived (10)	11 (19%)	5 (25%)	0.69	11 (20%)	5 (14%)	0.19	0.29
Least deprived (1)	6 (11%)	0 (0%)		5 (9%)	0 (0%)		
Received antenatal steroids							
Any	48 (84%)	19 (95%)	0.22	51 (94%)	34 (97%)	0.55	0.08
Complete course	26 (46%)	10 (50%)	0.72	26 (48%)	26 (74%)	0.01	0.55

Data are n (%)

Table 3-2 Baseline characteristics of children in the neonatal hyperglycaemia cohort follow-up arm of the PIANO study

	Hyperglycaemic group			Non-hyperglycaemic group			Hyperglycaemic v Non-hyperglycaemic (assessed) P-value
	Assessed (n=57)	Not assessed (n=20)	Assessed v not assessed P-value	Assessed (n=54)	Not assessed (n=35)	Assessed v not assessed P-value	
Gestational age (weeks)	25.0 (25.0, 27.0)	25.0 (24.0, 26.0)	0.29	26.0 (26.0, 28.0)	27.0 (26.0, 29.0)	0.12	< 0.01
Birth measurements							
Weight (g)	790 (700, 855)	851 (700, 993)	0.22	988 (885, 1130)	950 (790, 1160)	0.68	< 0.01
Weight z-score	-0.13 ± 0.91	0.47 ± 0.90	0.01	0.32 ± 0.85	0.03 ± 0.97	0.13	< 0.01
Crown-heel length (cm)	33.3 (31.5, 34.4)	34.0 (31.0, 37.0)	0.19	35.5 (33.5, 37.5)	35.0 (34.5, 37.0)	1.00	< 0.01
Length z-score	-0.29 ± 1.15	0.36 ± 1.08	0.04	0.26 ± 0.92	0.06 ± 1.06	0.37	< 0.01
Head circumference (cm)	23.5 (22.5, 24.8)	24.0 (22.6, 26.0)	0.30	25.0 (23.7, 26.0)	24.7 (24.2, 25.8)	0.99	< 0.01
Head circumference z-score	-0.02 ± 1.14	0.67 ± 1.21	0.03	0.42 ± 0.95	0.12 ± 1.19	0.20	0.03
Small for gestational age	8 (14%)	1 (5%)	0.28	3 (6%)	4 (11%)	0.32	0.14
Neonatal complications							
NEC	1 (2%)	0 (0%)	1.00	4 (7%)	1 (3%)	0.83	0.15
IVH (grade III/IV)	4 (7%)	2 (10%)	0.67	2 (4%)	0 (0%)	0.25	0.45
PVL	0 (0%)	0 (0%)	-	0 (0%)	0 (0%)	-	-
ROP (grade I/II)	34 (61%)	14 (74%)	0.41	36 (72%)	16 (49%)	0.03	0.22
ROP (grade III/IV)	9 (16%)	3 (15%)	0.98	4 (7%)	1 (3%)	0.35	0.21
ROP treatment	8 (14%)	3 (15%)	0.92	2 (4%)	1 (3%)	0.85	0.06
Early onset sepsis	0 (0%)	1 (5%)	0.09	1 (2%)	2 (6%)	0.32	0.30
Late onset sepsis	12 (21%)	7 (35%)	0.21	7 (13%)	4 (11%)	0.83	0.26
BPD	24 (42%)	9 (45%)	0.82	12 (22%)	12 (34%)	0.21	0.03
Postnatal steroids	19 (35%)	7 (35%)	1.00	7 (13%)	7 (20%)	0.37	< 0.01
Discharged with home O_2	19 (33%)	5 (25%)	0.09	11 (20%)	7 (20%)	0.97	0.12
Major neonatal surgery	7 (12%)	2 (10%)	0.79	3 (6%)	1 (3%)	0.55	0.22

	Hyperglycaemic group			Non-hyperglycaemic group			Hyperglycaemic v Non-hyperglycaemic (assessed) P-value
	Assessed (n=57)	Assessed (n=54)	Not assessed (n=35)	Assessed (n=54)	Not assessed (n=35)	Assessed v not assessed P-value	
CRIB-II score	11 ± 2	12 ± 3	0.42	9 ± 3	9 ± 2	0.64	< 0.01
Apgar score							
1 minute	5 ± 2	6 ± 2	0.29	6 ± 2	6 ± 2	0.64	0.02
5 minutes	8 ± 2	8 ± 2	0.30	8 ± 2	8 ± 2	0.87	0.09
Nutrition							
Ever received parenteral nutrition	57 (100%)	20 (100%)	-	54 (100%)	35 (100%)	-	-
Age enteral feeds established (days)	13 ± 5	13 ± 4	0.61	10 ± 4	10 ± 4	0.90	0.02
Nutritional intake (mean)							
Protein ($g.kg^{-1}.day^{-1}$)							
Week 1	2.60 ± 0.45	2.61 ± 0.41	0.93	2.77 ± 0.45	2.65 ± 0.54	0.28	0.05
Month 1	3.31 ± 0.27	3.22 ± 0.30	0.21	3.42 ± 0.32	3.42 ± 0.34	0.96	0.01
Carbohydrate ($g.kg^{-1}.day^{-1}$)							
Week 1	10.73 ± 1.70	10.89 ± 1.32	0.73	10.55 ± 1.49	10.87 ± 1.92	0.39	0.56
Month 1	14.45 ± 1.45	14.42 ± 1.27	0.95	14.65 ± 1.50	14.77 ± 1.71	0.73	0.49
Fat ($g.kg^{-1}.day^{-1}$)							
Week 1	3.32 ± 0.71	3.14 ± 0.57	0.33	3.69 ± 0.77	3.44 ± 0.89	0.17	0.01
Month 1	5.75 ± 0.85	5.75 ± 0.64	0.99	6.06 ± 0.99	6.04 ± 0.91	0.93	< 0.01
Energy ($kcal.kg^{-1}.day^{-1}$)							
Week 1	79.44 ± 9.80	78.19 ± 7.54	0.63	83.12 ± 10.24	81.28 ± 14.02	0.48	0.06
Month 1	121.00 ± 14.19	120.30 ± 11.14	0.86	125.20 ± 15.43	125.60 ± 15.94	0.92	0.14

	Hyperglycaemic group			Non-hyperglycaemic group			Hyperglycaemic v Non-hyperglycaemic (assessed) P-value
	Assessed (n=57)	Assessed (n=54)	Not assessed (n=35)	Assessed (n=54)	Not assessed (n=35)	Assessed v not assessed P-value	
Anthropometry 28 days							
Weight (g)	1053 (960, 1235)	1080 (925, 1363)	0.73	1288 (1158, 1526)	1390 (1170, 1470)	0.77	< 0.01
Weight z-score	-0.95 ± 0.66	-0.63 ± 0.68	0.02	-0.60 ± 0.66	-0.70 ± 0.83	0.54	0.02
Crown-heel length (cm)	33.7 (34.4, 37.3)	36.3 (34.8, 37.9)	0.50	38.6 (36.5, 40.6)	39.0 (37.5, 40.5)	0.54	< 0.01
Length z-score	-1.13 ± 0.91	-0.81 ± 1.08	0.19	-0.49 ± 0.67	-0.58 ± 1.12	0.69	< 0.01
Head circumference (cm)	25.0 (24.1, 26.2)	24.5 (23.7, 26.7)	0.94	26.2 (25.5, 27.7)	27.0 (25.5, 28.0)	0.29	< 0.01
Head circumference z-score	-1.50 ± 0.85	-1.28 ± 1.04	0.36	-0.93 ± 0.79	-0.93 ± 0.89	1.00	< 0.01
Growth velocity 28 days ($g.kg^{-1}.day^{-1}$)	11.4 ± 2.8	11.2 ± 2.5	0.87	11.1 ± 4.1	8.7 ± 3.0	0.09	0.71
Length of neonatal stay (days)	98 ± 24	111 ± 39	0.09	86 ± 25	78 ± 24	0.16	0.01

Data are n (%), mean±standard deviation, median (interquartile range). Abbreviations: NEC necrotizing enterocolitis, IVH intraventricular haemorrhage, PVL periventricular haemorrhage, ROP retinopathy of prematurity, BPD bronchopulmonary dysplasia, O_2 oxygen supplementation, g grams, cm centimetres, $g.kg^{-1}.day^{-1}$ grams per kilogram per day, $kcal.kg^{-1}.day^{-1}$ kilocalories per kilogram per day.

Table 3-3 Neonatal blood glucose characteristics of the Hyperglycaemic and Non-hyperglycaemic groups

	Hyperglycaemic group			Non-hyperglycaemic group			Hyperglycaemic v Non-hyperglycaemic (assessed) P-value
	Assessed (n=57)	Not assessed (n=20)	Assessed v not assessed P-value	Assessed (n=54)	Not assessed (n=35)	Assessed v not assessed P-value	
Mean number of blood glucose readings	96 ± 54	93 ± 62	0.80	39 ± 36	33 ± 22	0.40	< 0.01
Insulin infusion prior to 36 weeks' postmenstrual age	44 (77%)	15 (75%)	0.84	0 (0%)	0 (0%)	0.76	< 0.01
Neonatal hyperglycaemia*	57 (100%)	20 (100%)	-	0 (0%)	0 (0%)	-	-
High BGC (> 8.5 mmol.L^{-1})^							
At least one episode	57 (100%)	20 (100%)	-	26 (48%)	14 (40%)	0.45	< 0.01
At least one episode ≥ 3 days	47 (83%)	17 (85%)	0.79	4 (7%)	3 (9%)	0.84	< 0.01
Days at least one episode	9.0 ± 7.2	8.7 ± 8.3	0.85	0.8 ± 1.2	1.1 ± 2.6	0.55	< 0.01
Hypoglycaemia							
Any (BGC < 2.6 mmol.L-1)	35 (61%)	9 (45%)	0.20	17 (32%)	9 (26%)	0.56	< 0.01
Severe (< 2.0 mmol.L^{-1})	13 (23%)	4 (20%)	0.80	5 (9%)	7 (20%)	0.15	< 0.05
Extreme (< 1.5 mmol.L^{-1})	6 (11%)	3 (15%)	0.59	4 (7%)	1 (3%)	0.36	0.57
BGC (mmol.L^{-1})							
Minimum	2.44 ± 0.86	2.55 ± 0.79	0.63	2.86 ± 0.87	2.80 ± 0.75	0.74	< 0.01
Mean	6.58 ± 0.92	6.56 ± 0.89	0.95	5.17 ± 0.55	5.27 ± 0.72	0.50	< 0.01
Maximum	14.38 ± 5.62	13.76 ± 4.55	0.66	8.52 ± 1.88	8.87 ± 3.43	0.54	< 0.01

*Data are n (%), mean±standard deviation. Abbreviation: BGC blood glucose concentration. Note: Many babies in the Non-hyperglycaemic group had ^transient high blood glucose concentrations (1 isolated episode of >8.5mmol.L-1 in one day with no other blood glucose readings >8.5mmol.L-1 within four hours) without meeting our criteria of *neonatal hyperglycaemia (2 or more episodes of >8.5mmol.L-1 within 4 hours)*

For the children who were assessed at 7 years of age, the Hyperglycaemic group were born with a lower gestational age than the Non-hyperglycaemic group, and they were smaller in stature, weight and head circumference, which remained to 28 days following birth (Table 3-2). They also had a lower CRIB-II score and Apgar scores. The Hyperglycaemic group had a higher incidence of BPD and were more likely to receive postnatal steroids. However, the incidence of other neonatal complications were similar to the Non-hyperglycaemic group. Babies in the Hyperglycaemic group tended to have more treatment for severe ROP. There were no differences between the groups on being discharged with home oxygen. All babies had received parenteral nutrition; babies in the Hyperglycaemic group took longer for enteral feeds to be established and also stayed in the NICU for longer than the babies in the Non-hyperglycaemic group. The Hyperglycaemic group had less protein and fat intake in the first month after birth.

Variability of BGC (lower minimums and higher maximums) between birth and 36 week's corrected gestational age were higher in the Hyperglycaemic group and they had more blood glucose readings than the Non-hyperglycaemic group (Table 3-3). Of the babies in the Non-hyperglycaemic group, 48% had transient high BGC (at least one episode of BGC >8.5mmol.L^{-1}) but did not reach our definition of hyperglycaemia (at least two consecutive measures of BGC >8.5mmol.L^{-1} at least 4 hours apart). Insulin was administered to 77% of children in the Hyperglycaemic group. The Hyperglycaemic group experienced more frequent and severe hypoglycaemia than the Non-hyperglycaemic group.

By the age of the assessment at a mean of 7.2 corrected years, there were no differences in weight, height and head circumference between children who previously had neonatal hyperglycaemia and those who did not develop hyperglycaemia (Table 3-4). Characteristics of the children were similar between the groups except there were more males in the Non-hyperglycaemic group.

The proportion of children with neurodevelopmental impairment in the Hyperglycaemic and Non-hyperglycaemic groups were similar after adjusting for matching criteria (Table 3-5). Individual components of the primary outcome were similar between the groups. There were no children with blindness.

Table 3-4 Characteristics of children at the time of assessment in the neonatal hyperglycaemia cohort follow-up arm of the PIANO study at seven years of age

	Hyperglycaemic group (n=57)	Non-hyperglycaemic group (n=54)	Hyperglycaemic v Non-hyperglycaemic P-value
Age at assessment (years)	7.2 ± 0.1	7.2 ± 0.1	0.66
Male	25 (44%)	34 (63%)	0.04
Deprivation index			
Most deprived (10)	11 (19%)	11 (20%)	0.29
Least deprived (1)	6 (11%)	5 (9%)	
Year at school	3 (1, 4)	3 (2, 3)	-
Anthropometry			
Weight (kg)	23.2 (19.9, 27.0)	24.0 (22.1, 27.1)	0.42
Weight z-score	0.11 ± 1.58	0.17 ± 1.26	0.83
Height (cm)	123.1 (118.2, 127.1)	123.5 (119.7, 129.0)	0.34
Height z-score	0.12 ± 1.14	0.28 ± 1.29	0.45
Head circumference (cm)	51.5 (50.1, 52.7)	51.6 (50.8, 53.3)	0.22
Head circumference z-score	-1.18 ± 1.29	-0.98 ± 1.57	0.47
Growth velocity ($g.kg^{-1}.day^{-1}$)	1.25 ± 0.11	1.26 ± 1.0	0.85

Data are n (%), mean±standard deviation, median (range). Abbreviations: kg kilogram, cm centimetres, $g.kg^{-1}.day^{-1}$ grams per kilogram per day

Table 3-5 Primary outcome of children assessed in the neonatal hyperglycaemia cohort follow-up arm of the PIANO study at seven years of age

	Hyperglycaemic group (n=57)	Non-hyperglycaemic group (n=54)	Unadjusted OR (95%CI)	P-value	*Adjusted OR (95%CI)	P-value
Neurodevelopmental impairment	32 (56%)	19 (35%)	2.36 (1.08, 5.14)	0.03	1.91 (0.71, 5.08)	0.20
WISC FSIQ <85	26 (46%)	14 (26%)	2.40 (1.07, 5.36)	0.03	2.01 (0.69, 5.83)	0.20
MABC-2 total score ≤5th centile	18 (32%)	14 (26%)	1.32 (0.59, 2.93)	0.50	0.86 (0.33, 2.21)	0.75
Cerebral palsy	6 (11%)	3 (6%)	2.00 (0.48, 8.38)	0.34	2.42 (0.48, 12.29)	0.29
Blind	0 (0%)	0 (0%)	-	-	-	-
Deaf	1 (2%)	1 (2%)	-	-	-	-

**Adjusted for sex (male/female), multiple birth (yes/no), gestational age, birth weight z-score, and NZ Deprivation Index at birth, and CRIB-II score. Abbreviations: WISC FSIQ Wechsler Intelligence Scale for Children Full Scale Intelligence Quotient, MABC-2 Movement Assessment Battery for Children Second Edition.*

There were no statistically significant differences in overall, binocular or functional visual outcomes between children who were in the Hyperglycaemic group compared to those in the Non-hyperglycaemic group (Table 3-6).

Children who had neonatal hyperglycaemia had poorer binocular distance VA and had higher incidence of strabismus than the children who did not have hyperglycaemia (Table 3-6). The higher incidence of strabismus in the Hyperglycaemic group was no longer statistically significant after adjustment for neonatal risk factors. There were no other differences in visual function between the groups.

The proportion of children having ocular abnormalities requiring further follow-up or referral was similar in both groups (Table 3-6). The majority of children had normal ocular findings or had signs of normal variations in ocular structure that did not require extra follow-up outside of routine eye check.

There were no differences in refractive error except astigmatism of the better eye was more common in the Non-hyperglycaemic group than the Hyperglycaemic group after adjustment for matching criteria (Table 3-6).

Ocular biometry components of anterior chamber depth and corneal curvature were similar between children of the Hyperglycaemic and Non-hyperglycaemic groups (Table 3-8). Central cornea was thicker and axial length was shorter in the Hyperglycaemic group, which was no longer statistically significant after adjusting for matching criteria. The crystalline lens of the better eye was thicker in the Hyperglycaemic group. There were no differences between the groups in central retinal (macula) thickness.

Table 3-6 Visual functional outcomes of children assessed in the neonatal hyperglycaemia cohort follow-up arm of the PIANO study at seven years of age

	Hyperglycaemic group (n=57)	Non-hyperglycaemic group (n=54)	Unadjusted OR or mean difference (95%CI)	P-value	*Adjusted OR or mean difference (95%CI)	P-value
Favourable overall visual outcome	27/49 (55%)	27/46 (59%)	0.62 (0.40, 1.85)	0.71	0.59 (0.20, 1.78)	0.35
Favourable binocular visual outcome	23/54 (43%)	22/54 (41%)	1.08 (0.48, 2.44)	0.85	1.56 (0.58, 4.17)	0.38
Favourable functional visual outcome	33/52 (64%)	41/54 (76%)	0.55 (0.24, 1.28)	0.16	0.93 (0.32, 2.72)	0.90
Distance VA in better eye						
Equal or better than 6/12	54/55 (98%)	54/54 (100%)	-		-	
Normal v mild to severe impairment	45/56 (80%)	48/52 (92%)	0.34 (0.10, 1.14)	0.08	0.89 (0.24, 3.32)	0.86
LogMAR	0.00 ± 0.13	-0.04 ± 0.12	0.05 (0.00, 0.09)	0.05	0.04 (-0.02, 0.09)	0.18
Presenting binocular distance VA (logMAR)	0.00 ± 0.16	-0.09 ± 0.11	0.08 (0.03, 0.14)	< 0.01	0.07 (0.01, 0.13)	0.03
Other visual outcomes						
Presence of strabismus	11/57 (19%)	2/54 (4%)	6.22 (1.31, 29.45)	0.02	2.50 (0.42, 14.71)	0.32
Pass stereoacuity (TNO)	36/51 (71%)	41/54 (76%)	0.76 (0.32, 1.82)	0.54	0.84 (0.28, 2.54)	0.76
Not requiring spectacles	37/46 (80%)	37/45 (82%)	0.89 (0.31, 2.56)	0.83	0.93 (0.23, 3.79)	0.91
Presence of nystagmus	2/56 (4%)	0/54 (0%)	-		-	
Normal ocular motility	48/55 (87%)	51/54 (94%)	0.40 (0.10, 1.64)	0.20	0.74 (0.14, 3.97)	0.73
Normal convergence	40/50 (80%)	44/52 (85%)	0.73 (0.25, 2.13)	0.56	0.89 (0.22, 3.57)	0.87
Presence of motor fusion	33/53 (62%)	36/53 (68%)	0.78 (0.34, 1.79)	0.56	0.76 (0.27, 2.09)	0.59
Mean global motion perception threshold	48.50 ± 21.43	46.26 ± 22.59	2.23 (-5.82, 10.28)	0.59	-3.24 (-14.06, 7.58)	0.55

**Adjusted for sex (male/female), multiple birth (yes/no), gestational age, birth weight z-score, NZ Deprivation Index at birth, and CRIB-II score. Data are n (%), mean±standard deviation, OR odds ratios. Abbreviations: VA visual acuity*

Table 3-7 Ocular structural and refractive outcomes of children assessed in the neonatal hyperglycaemia cohort follow-up arm of the PIANO study at seven years of age

	Hyperglycaemic group (n=57)	Non-hyperglycaemic group (n=54)	Unadjusted OR or mean difference (95%CI)	P-value	*Adjusted OR or mean difference (95%CI)	P-value
Ocular structure						
Retinal posterior pole (central) findings			1.00		1.00	
No abnormalities or non-clinically significant findings	45/57 (79%)	44/54 (82%)				
Clinically significant findings	5/57 (9%)	4/54 (7%)				
Unable to assess	7/57 (12%)	6/54 (11%)				
Refractive error						
SEP of the better VA eye			0.27		0.91	
Myopia	3/46 (6%)	3/45 (7%)				
Hyperopia	22/46 (48%)	29/45 (64%)				
Significant hyperopia (> +2.00 D)	4/26 (9%)	0 (0%)				
SEP of the poorer VA eye			0.13		0.29	
Myopia	3/46 (7%)	5/45 (11%)				
Hyperopia	25/46 (54%)	31/45 (69%)				
Significant hyperopia (> +2.00 D)	3/46 (7%)	1/45 (2%)				
Astigmatism						
Better eye	6/46 (9%)	8/45 (18%)	0.44 (0.12, 1.58)	0.20	0.14 (0.02, 0.90)	0.04
Poorer eye	7/46 (15%)	8/45 (18%)	0.83 (0.27, 2.52)	0.74	0.36 (0.08, 1.65)	0.19
Anisometropia	2/45 (4%)	0/45 (0%)	-		-	

**Adjusted for sex (male/female), multiple birth (yes/no), gestational age, birth weight z-score, NZ Deprivation Index at birth, and CRIB-II score. Data are n (%), OR odds ratios. Abbreviations: SEP spherical equivalent power, VA visual acuity, D dioptres*

Table 3-8 Ocular biometry for children assessed in the neonatal hyperglycaemia cohort follow-up arm of the PIANO study at seven years of age

	Hyperglycaemic group (n=57)	Non-hyperglycaemic group (n=54)	Unadjusted mean difference (95%CI)	P-value	*Adjusted mean difference (95%CI)	P-value
Central corneal thickness (µm)						
Better VA Eye	549 ± 35	535 ± 32	14 (0, 27)	0.05	8 (-9, 25)	0.34
Poorer VA Eye	549 ± 40	533 ± 31	16 (1, 30)	0.03	10 (-7, 27)	0.26
Anterior chamber depth (mm)						
Better VA Eye	3.34 ± 0.29	3.43 ± 0.25	-0.09 (-0.20, 0.02)	0.09	-0.05 (-0.08, 0.16)	0.49
Poorer VA Eye	3.36 ± 0.30	3.42 ± 0.26	-0.05 (-0.17, 0.06)	0.36	0.00 (-0.15, 0.14)	0.97
Axial length (mm)						
Better VA Eye	22.07 ± 0.91	22.57 ± 0.75	-0.50 (-0.85, -0.15)	<0.01	-0.37 (-0.79, 0.05)	0.08
Poorer VA Eye	22.12 ± 0.99	22.59 ± 0.73	-0.46 (-0.82, -0.10)	0.01	-0.35 (-0.78, 0.09)	0.12
Lens thickness (mm)						
Better VA Eye	3.83 ± 0.27	3.69 ± 0.22	0.14 (0.04, 0.24)	<0.01	0.14 (0.01, 0.26)	0.03
Poorer VA Eye	3.80 ± 0.27	3.70 ± 0.22	0.10 (0.00, 0.24)	0.06	0.10 (-0.03, 0.22)	0.13
Corneal curvature (mm)						
Flat Meridian Better VA Eye	7.67 ± 0.26	7.73 ± 0.27	-0.06 (-0.17, 0.05)	0.25	-0.03 (-0.15, 0.10)	0.70
Flat Meridian Poorer VA Eye	7.68 ± 0.26	7.73 ± 0.27	-0.05 (-0.16, 0.06)	0.09	-0.02 (-0.15, 0.11)	0.73
Steep Meridian Better VA Eye	7.50 ± 0.28	7.61 ± 0.26	-0.11 (-0.22, 0.00)	0.06	-0.05 (-0.18, 0.08)	0.45
Steep Meridian Poorer VA Eye	7.51 ± 0.28	7.56 ± 0.25	-0.05 (-0.16, 0.06)	0.35	-0.01 (-0.14, 0.12)	0.87
Central retinal thickness (µm)^						
Better VA Eye	273 ± 28	274 ± 23	-2 (-13, 10)	0.77	-1 (-15, 12)	0.78
Poorer VA Eye	273 ± 0.27	274 ± 0.23	-1 (-12, 10)	0.89	-2 (-14, 11)	0.80

**Adjusted for sex (male/female), multiple birth (yes/no), gestational age, birth weight z-score, NZ Deprivation Index at birth, and CRIB-II score. ^Missing data for central retinal thickness: Hyperglycaemic group - 21 for better and poorer VA eye; Non-hyperglycaemic group – 9 better eye, 8 poorer eye. Data are n (%), mean±standard deviation. Abbreviations: VA visual acuity.*

Similar proportions of children in the Hyperglycaemic and Non-hyperglycaemic groups were reported by their parents to have previously been reviewed by ophthalmology or optometry (Table 3-9). At 7 years of age, the proportion of those still under review had decreased. Compared to the Non-hyperglycaemic group, children in the Hyperglycaemic group tended to require vision follow-up and be prescribed spectacles. They also were more likely to have previous ocular surgery or treatment for ocular problems. The majority of children who brought their spectacles to the assessment for measurement met our criteria for requiring spectacles (Table 3-6, Table 3-9). Parent-reported sensory ability of the children (vision, hearing and speech) were similar between the two groups.

Table 3-9 Parent-reported ocular history and quality of life of children assessed in the neonatal hyperglycaemia cohort follow-up arm of the PIANO study at seven years of age

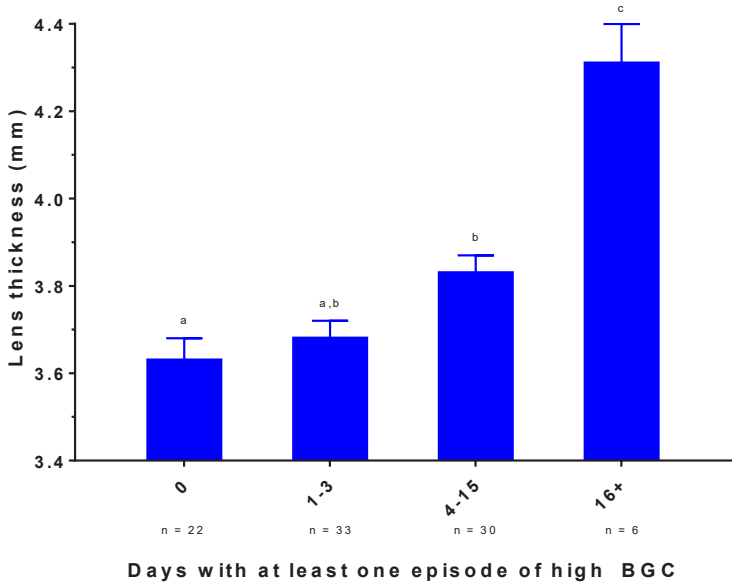
	Hyperglycaemic group (n=57)	Non-hyperglycaemic group (n=54)	P-value	Adjusted P-value*
Eye care provider				
Currently under care	10/55 (18%)	3/53 (6%)	0.07	0.25
Previously under care	31/55 (56%)	26/53 (49%)	0.45	0.35
Previous ocular surgery/treatment	13/57 (23%)	3/54 (6%)	0.01	0.26
Strabismus	1/13 (8%)	0/3 (0%)		
Laser for severe ROP	9/13 (70%)	1/3 (33%)		
Patching for amblyopia	3/13 (23%)	2/3 (67%)		
Other^	2/13 (15%)	0/3 (0%)		
Wears spectacles	14/57 (25%)	6/54 (11%)	0.07	0.46
HUI2 Sensation#	n=56	n=53	0.14	0.90
1	47 (84%)	49 (93%)		
2	9 (16%)	3 (6%)		
3	-	1 (2%)		
4	-	-		

**Adjusted for sex (male/female), multiple birth (yes/no), gestational age, birth weight z-score, NZ Deprivation Index at birth, and CRIB-II score. ^Other included one child who was prescribed prism spectacles for diplopia and one child had atropine drops. #The scale is 1 (able to see, hear, speak normally for age) to 4 (blind, deaf or mute), specifics of the categories can be found in 2.1.7.7.*

Visual outcomes that were different between the Hyperglycaemic and Non-hyperglycaemic groups were lens thickness and VA. Exploratory analyses of associations between exposures (such as neonatal complications or treatments) and visual outcomes were performed (Table 9-1 for lens thickness, Table 9-2 for VA).

For lens thickness, the exposures that had statistical significance <0.15, which were entered into a separate multiple regression model were BPD, postnatal steroid, insulin, recurrent hyperglycaemia (Figure 3-2), mean BGC and covariates (sex, gestational age and birth weight z-score); the model was significant in predicting lens thickness (adjusted R^2=0.23, F=4.35, p<0.001). Only mean BGC added statistical significance to the prediction (Table 3-10). With every increase of the mean BGC by 1mmol.L^{-1}, lens thickness was thicker by 0.08mm.

Figure 3-2 Lens thickness v days with high BGC for all the children within the neonatal hyperglycaemia follow-up arm of the PIANO study



Adjusted for sex, gestational age and birth weight z-score. Data is mean lens thickness, with standard error of the mean shown as error bars. ANCOVA: F=14.58, p<0.0001. Non-matching letters indicate a significant difference (p<0.05) between days with high BGC.

For binocular VA, the exposures that had statistical significance <0.15, which were entered into a separate multiple regression model were BPD, postnatal steroid, fat intake month 1, insulin, maximum BGC (Figure 3-3), lens thickness and covariates; the model was significant in predicting lens thickness (adjusted R^2=0.25, F=4.04, p<0.001). Only lens thickness added statistical significance to the prediction (Table 3-11). With every increase of lens thickness by 0.1mm, VA was reduced by 0.02logMAR (1 letter on a chart).

Table 3-10 Summary of multiple regression analysis for neonatal glycaemic status, neonatal complications and treatment, and covariates v lens thickness in the better eye at seven years of age

Exposures (reference)	B	SE_B	β	P–value
Intercept	2.68	0.52		< 0.0001
BPD (no)	0.06	0.06	0.11	0.33
Postnatal steroid (yes)	-0.11	0.07	-0.18	0.13
Insulin (yes)	-0.05	0.07	-0.10	0.45
Recurrent hyperglycaemia (no)	0.06	0.07	0.11	0.43
Mean BGC (mmol.L-1)	0.08	0.03	0.33	0.01
Sex (male)	-0.07	0.05	-0.13	0.17
Gestational age (weeks)	0.03	0.02	0.18	0.17
Birth weight z-score	0.01	0.03	0.04	0.70

Abbreviations: B = unstandardized regression coefficient; SE_B = standard error of the coefficient; β = standardized coefficient; BPD bronchopulmonary dysplasia

Table 3-11 Summary of multiple regression analysis for neonatal glycaemic status, neonatal complications and treatment, neonatal nutrition, and covariates v binocular visual acuity at 7 years of age

Exposures (reference)	B	SE_B	β	P-value
Intercept	-0.87	0.31		0.01
BPD (no)	0.01	0.03	-0.05	0.64
Postnatal steroid (yes)	-0.02	0.03	-0.06	0.63
Fat intake month 1 ($g.kg^{-1}.day^{-1}$)	0.01	0.02	0.05	0.64
Insulin (yes)	-0.06	0.03	-0.22	0.09
Maximum BGC ($mmol.L^{-1}$)	0.000	0.003	0.003	0.98
Lens thickness (mm)	0.22	0.06	0.44	< 0.001
Sex (male)	0.00	0.03	0.01	0.92
Gestational age weeks	0.00	0.01	0.00	0.98
Birth weight z-score	-0.00	0.02	-0.02	0.85

Abbreviations: B = unstandardized regression coefficient; SE_B = standard error of the coefficient; β = standardized coefficient; BPD bronchopulmonary dysplasia

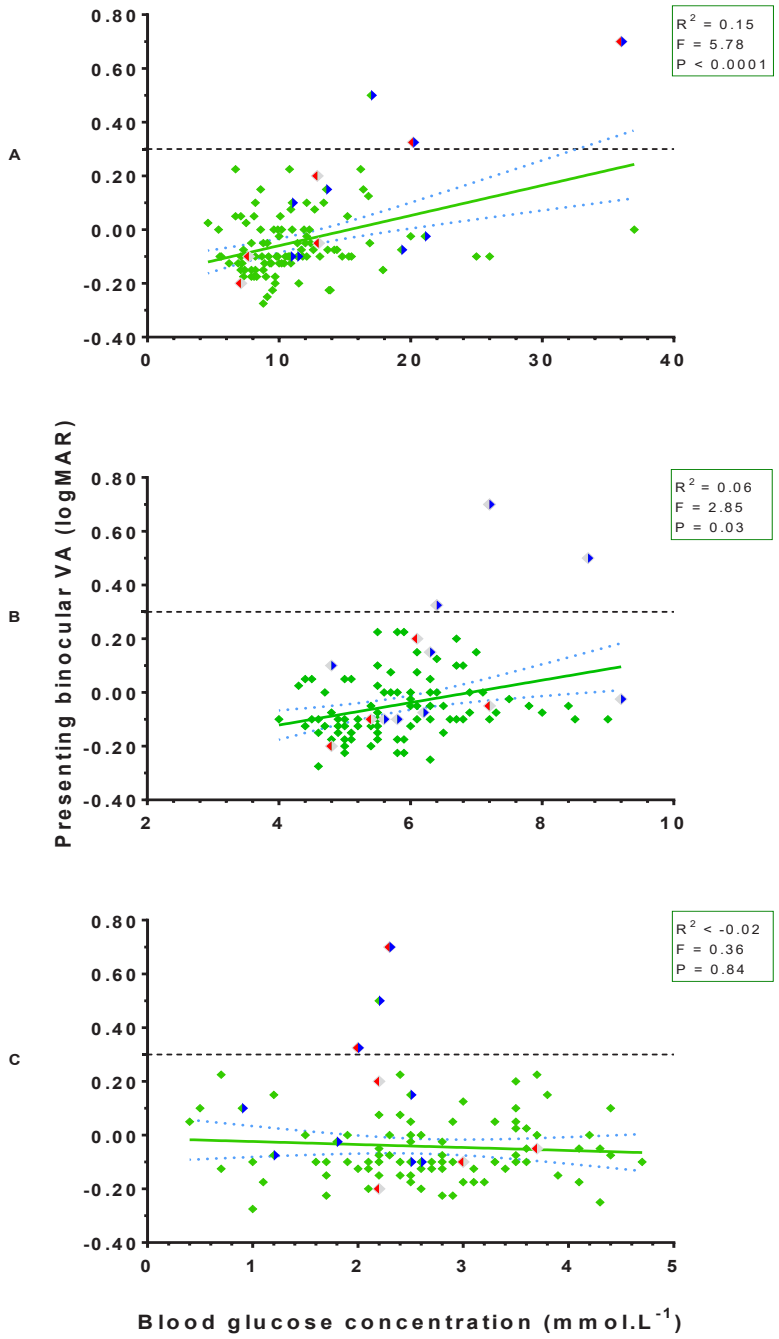
Associations between hyperglycaemia and ROP were assessed with linear regression of BGC. Maximum BGC was higher in the ROP treated compared to the ROP not treated/no ROP groups after adjusting for sex, gestational age and birth weight z-score (Figure 3-4). Minimum and mean BGC were similar between the no ROP, ROP untreated and ROP treated groups. Using logistic regression, minimum BGC was not associated with having ROP or requiring laser treatment for severe ROP (Table 9-3, Table 9-4). Increasing mean BGC and older gestational age were associated with reduced odds of

having ROP. Increasing maximum BGC was associated with increased odds of requiring ROP treatment while older gestational age was associated with reduced odds of requiring ROP treatment. Gestational age was more significant in predicting ROP or requiring ROP treatment (Table 9-4). Older gestational age was associated with reduced mean (adjusted R^2=0.05, χ^2=6.90, p=0.01) and maximum (adjusted R^2=0.05, F=6.40, p=0.01) BGC.

As hyperglycaemia was significantly associated with both lens thickness (Table 3-10) and ROP (Figure 3-4), an analysis was conducted to explore the interaction effect between hyperglycaemia and ROP on lens thickness. There were no statistically significant interactions between hyperglycaemia (Hyperglycaemic/Non-hyperglycaemic groups) and ROP (no ROP/ROP untreated/ROP treated) on lens thickness in the eye with better VA (F=0.39, p=0.54) or presenting binocular VA (F=0.01, p=0.93). No outliers were identified but not all the residuals were normally distributed, and heterogeneity of variances for both comparisons were present as none of the children who did not develop hyperglycaemia had ROP treatment. Main effect for hyperglycaemia and ROP were analysed, which indicated the main effect for ROP was statistically significant (F=3.35, p=0.04 for lens thickness; F=3.82, p=0.03 for present binocular VA). ROP treatment was associated with a thicker crystalline lens compared to not treated ROP (mean difference 0.26mm, 95%CI 0.01-0.50, p=0.04). ROP treatment was associated with poorer VA compared to no ROP and not treated ROP (no ROP: mean difference 0.20logMAR, 95%CI 0.02-0.38, p=0.03, ROP untreated: mean difference 0.19 logMAR, 95%CI 0.02-0.37, p=0.02).

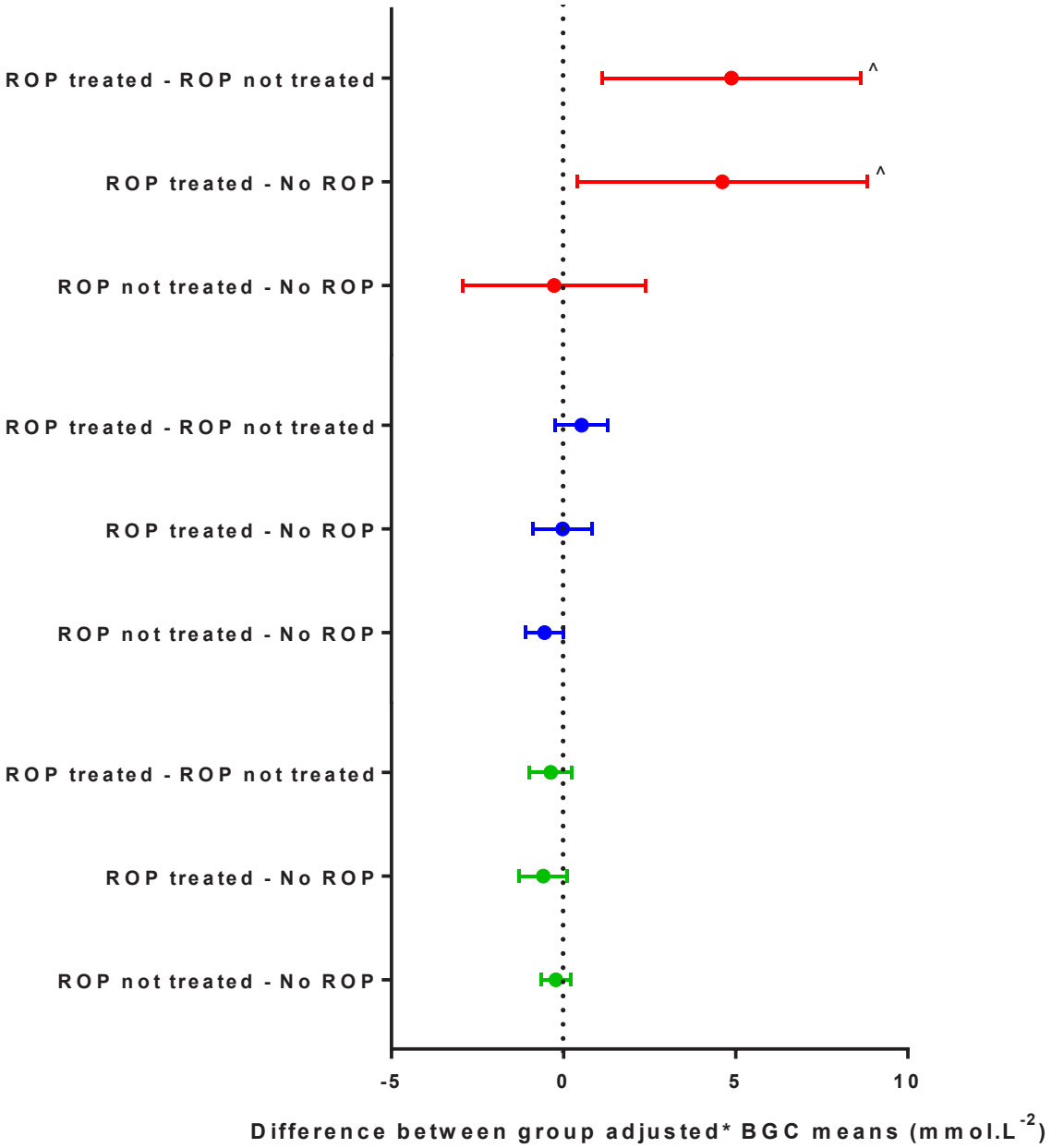
Fifty two children (47%) in the whole neonatal hyperglycaemia follow up cohort who were assessed at 7 years of age had experienced at least one episode of hypoglycaemia (<2.6mmol.L^{-1}) before 36 weeks' postmenstrual age. Those who developed hypoglycaemia tended to have poorer binocular VA than those who did not develop hypoglycaemia (mean difference 0.05logMAR, 95%CI -0.01-0.11, p=0.09). Presence of hypoglycaemia and severity of hypoglycaemia were not associated with overall visual outcome, binocular outcome or functional visual outcome. Global motion coherence threshold tended to be higher in those who developed hypoglycaemia than those who did not develop hypoglycaemia (51.64±22.82 v 43.77±20.64; t=-1.84, mean difference -7.86, 95%CI -16.32-0.59, p=0.07).

Figure 3-3 Scatterplots of BGCs from birth to 36 weeks' postmenstrual age v presenting binocular VA for all the children within the neonatal hyperglycaemia follow-up arm of the PIANO study



Presenting binocular visual acuity compared with (A) maximum BGC, (B) mean BGC and (C) minimum BGC (n=111), for all the children in the neonatal hyperglycaemia cohort (green), for children who had ROP treated with laser photocoagulation (blue) and for children who had grade 3-4 IVH (red). Green solid line is the best fit line with the blue dotted lines the 95% confidence interval of the best fit line. The black dashed line is the level of visual acuity of 6/12, the points below this line signify visual acuity adequate for most daily tasks. Adjusted R^2 values are given and P-values are adjusted for sex, gestational age, and birth weight z-score.

Figure 3-4 Mean difference in neonatal BGC according to ROP status



*Mean difference and 95% confidence intervals of minimum (green), mean (blue), and maximum (red) neonatal BGC between no ROP (n=23), ROP not treated (n=73) and ROP treated groups (n=10). *Adjusted for sex, gestational age and birth weight z-score. ^For maximum BGC mean difference between ROP treated and ROP not treated (p=0.01), ROP treated and No ROP (p=0.03) groups on post-hoc testing.*

3.4 Discussion

Neonatal hyperglycaemia affects many babies born very preterm (Beardsall et al., 2010) and has been associated with an increase incidence of ROP (Ahmadpour-Kacho et al., 2014; Ertl et al., 2006; Garg et al., 2003; Mohsen et al., 2014), which can cause poor visual function in later life (Blencowe et al., 2013). This is the first study to investigate the effects of neonatal hyperglycaemia in children born very preterm on visual outcomes in later childhood. In our cohort, neonatal hyperglycaemia was not associated with neurodevelopmental impairment or blindness at 7 years of age. We found that neonatal hyperglycaemia was not associated with overall visual function or refractive error development. However, our results suggest that neonatal hyperglycaemia may increase lens thickness, and reduce binocular VA. Our exploratory analysis showed that while neonatal hyperglycaemia, as defined in this study, was not associated with ROP, a higher BGC in the overall cohort was associated both with a diagnosis of ROP and a need for treatment. This is consistent with recent reviews that have shown that hyperglycaemia is not associated with ROP (Au et al., 2015) or severe ROP (Lee et al., 2016), while retrospective studies have shown that babies with ROP had higher mean BGC (Ertl et al., 2006; Garg et al., 2003; Mohsen et al., 2014). Although it remains unclear whether hyperglycaemia *per se* causes these changes in vision in our study, it highlights the importance of more understanding in this area, particularly the long-term effects of neonatal hyperglycaemia on development, and continued research into optimal treatment.

In our study, despite stringent matching criteria between the two groups, children in the Hyperglycaemic group were more likely to have been born earlier and smaller and had a higher CRIB-II score (i.e. more ill) than children who did not develop hyperglycaemia. Neonatal hyperglycaemia is strongly associated with lower gestational age and birth weight, and increased illness severity (Beardsall et al., 2010); which may have contributed in our inability to match children according to CRIB-II score during recruitment. To reduce confounding by these differences in matching, all matching criteria were adjusted for in our primary and secondary analyses. Although there was high incidence of neurodevelopmental impairment in the Hyperglycaemic group, after adjustment for matching criteria, the difference in neurodevelopment impairment between the groups was no longer statistically significant. In the literature, neonatal hyperglycaemia has been associated with increased mortality and morbidity (Alexandrou et al., 2010; Hays et al., 2006) but there has been a paucity of data on the effects of neonatal hyperglycaemia on neurodevelopment, particularly in later childhood. One retrospective study found poorer neurological outcome (abnormalities in tone, reflexes, movements and asymmetry) at 2 years corrected age associated with neonatal hyperglycaemia that had been treated with insulin (van der Lugt et al., 2010), while another study found that neonatal

hyperglycaemia was not associated with poorer neurodevelopment at 2 years corrected age (Bayley III) (Ramel et al., 2013). Concurrently, children born at lower gestational age and birth weight have been shown to be at higher risk of neurodevelopmental impairment (Arpino et al., 2010; Bhutta et al., 2002; Hutchinson et al., 2013). These suggest that neonatal hyperglycaemia *per se* is not independently associated with neurodevelopment.

There was no difference in overall, binocular and functional visual outcomes between the Hyperglycaemic and Non-hyperglycaemic groups. Most other visual outcomes were also similar between the groups except for lens thickness, binocular VA and astigmatism in the better eye. Both groups of children had mean VA comparable to other similar population studies of school children (gestational age not always reported) (Haugen et al., 2012; Robaei et al., 2005). When we compared the proportion of children with normal v mild-severe visual impairment in the Hyperglycaemic and Non-hyperglycaemic groups, there were no group differences; and the majority of children in both groups had better than 6/12 (0.3logMAR) VA in the better eye (6/12 vision would be adequate for most daily activities and is a transitional point towards having difficulties in daily activities) (International Council of Ophthalmology, 2002). These findings suggest that children born very preterm who developed neonatal hyperglycaemia have similar visual function to those who did not develop neonatal hyperglycaemia but may have some subclinical changes in visual function.

Children in our hyperglycaemia group had a thicker crystalline lens than in the Non-hyperglycaemic group. Similarly, children and adults with type 1 diabetes mellitus have thicker crystalline lenses than non-diabetic individuals (Løgstrup et al., 1997; Wiemer et al., 2008; Wiemer et al., 2008b). In diabetics, lens thickness has been shown to have a positive correlation with duration of diabetes. Individuals with diabetes are also likely to have a shallower anterior chamber depth, higher risk of hyperopia, and have retinal changes, which was not a trend found in our population (although, all cases of significant hyperopia in our study were in the Hyperglycaemic group) (Donaghue et al., 2005; Geloneck et al., 2015; Løgstrup et al., 1997). Through our exploratory analyses, we found that higher mean BGC in the first 28 postnatal days was associated with an increase in lens thickness, which may have also been due to ROP. Our results suggest that neonatal hyperglycaemia may have lasting effects on lens development, even though transient high BGC was experienced over a short period of time.

There were no differences in refractive error between the groups, even though lens thickness was thicker and axial length tended to be shorter in the Hyperglycaemic group. The incidence of astigmatism in the better VA eye was higher in the Non-hyperglycaemic group after adjustment for

matching criteria. The main ocular component that causes astigmatism is corneal curvature, but lens curvature and location can also cause astigmatism (Shankar & Bobier, 2004). We did not find corresponding changes in corneal curvature with astigmatism and were unable to evaluate lens biometrics apart from lens thickness. Therefore, we were unable to confirm whether the higher incidence of astigmatism was associated with hyperglycaemia. Although babies born preterm have been reported to be at risk of myopia and have larger variations in refractive error in childhood (Cryotherapy for Retinopathy of Prematurity Cooperative Group, 1994; Quinn et al., 1998; Scharf et al., 1978); the increase in lens thickness (increasing refractive power) and trend for reduced axial length (to match the increased refractive power) in our study, suggests that the VA reduction experienced by the Hyperglycaemic group was unlikely to be due to refractive error.

Hypoglycaemia particularly over prolonged periods, has previously been associated with an increased risk of visual impairment and occipital damage (Tam et al., 2008). In our cohort, there were no differences in overall, binocular or functional visual outcome between children with hypoglycaemia and those who did not have hypoglycaemia, which is similar to a recent study of late preterm children where neonatal hypoglycaemia was not associated with poorer visual outcome or global motion perception (McKinlay et al., 2017). There was trend for poorer binocular VA and higher global motion coherence thresholds in children who experienced at least one episode of neonatal hypoglycaemia. However, from our data, hyperglycaemia or insulin may have more effect on binocular VA than hypoglycaemia.

Several studies have suggested that there is a relationship between hyperglycaemia and ROP (Ertl et al., 2006; Garg et al., 2003; Mohamed et al., 2013). These studies first selected groups according to ROP status (e.g. No ROP v ROP, no to mild ROP v moderate to severe ROP) and then compared mean BGC within these groups. When we compared BGC between children with no ROP, ROP untreated and ROP treated, there was a higher maximum BGC between the ROP treated group compared to the no ROP and ROP untreated groups. One case-control study compared BGC in babies with stage 3 or stage 4 ROP (ROP group; n=16) with babies who did not develop ROP or had stage 1 ROP (control group; n=31) (Garg et al., 2003). The authors found that babies in the ROP group had significantly higher maximum, median and mean serum and whole BGC but they did not adjust for gestational age and birth weight, which was reported as adequately matched (Garg et al., 2003). As we did not find a difference in most of our glycaemic measure, we also used logistic regression to investigate this further. We found that lower mean BGC was associated with increased odds of having ROP, while having higher maximum BGC was associated with increased odds of ROP treatment. However,

gestational age was more significant in predicting ROP or ROP treatment than BGC, with increasing gestational age being associated with reduced odds of ROP or ROP treatment. This is similar to a finding from a database review of 24,548 babies who had a birth weight <1000g and gestational age ≤32weeks, where hyperglycaemia and insulin use were not associated with severe ROP after adjustment for various neonatal factors such as gestational age, male sex, Apgar score and ventilation (Lee et al., 2016). Similarly, in the meta-analysis of a systemic review, although duration of hyperglycaemia was associated with ROP (adjusted OR 1.08 (95%CI 1.01 – 1.15), p=0.03, four studies included), the association between mean glucose concentration and ROP was not significant (adjusted OR 1.08 (95%CI 0.97 – 1.20, p=0.15, three studies included) (Au et al., 2015). These data suggest that neonatal hyperglycaemia does not cause ROP but may reflect that babies with neonatal hyperglycaemia are born smaller and earlier, and therefore at greater risk of developing ROP.

A major strength of our study was that by having a multidisciplinary approach, we were able to evaluate metabolism, growth, neurodevelopment, brain structural development and motor development in a cohort of children born preterm as well as visual function. As the children within the Hyperglycaemic group were involved in the HINT randomised controlled trial, glycaemic status of these babies was followed closely, and neonatal history was available for these babies, which enabled an in depth understanding of the relationships between neonatal glycaemic status and outcomes in later childhood. However, one major limitation was that the study was observational in nature, which meant that causation could not be established between neonatal hyperglycaemia and visual outcomes. Also, due to the complexity of this study, many tests were performed on one day. Therefore, we were unable to perform some tests such as contrast sensitivity or best corrected VA, which would be useful in evaluating further how the mild deficits we found influenced daily functioning. The study involved a small group of children who were subjected to many interventions from birth due to preterm birth and many had neonatal complications. When the children were stratified into groups for analysis to account for the complexity of interventions, this resulted in small groups that lacked power to investigate the effect of the complications. We attempted to account for this source of variance by setting specific outcomes before analysis and identifying other analyses as exploratory in nature.

Another limitation we encountered was due to the selection of the cohort. The Hyperglycaemic group consisted of children in the HINT trial, which was comparing tight v standard control of neonatal hyperglycaemia (Alsweiler et al., 2012); and therefore, a large proportion of the children in the trial were administered insulin. Thus, we were unable to separate the effects of hyperglycaemia and insulin on visual outcomes. Another difficulty we encountered was a lack of consensus of a definition for

neonatal hyperglycaemia, which is apparent from the studies of ROP and neonatal hyperglycaemia. We had a stringent definition for hyperglycaemia, which was based on the original HINT trial where hyperglycaemia was defined as two consecutive measures of 8.5mmol.L^{-1} at least 4 hours apart, to ensure that babies had sufficiently prolonged hyperglycaemia to require insulin treatment (Alsweiler et al., 2012). That meant up to half of the children in the Non-hyperglycaemic group experienced at least one episode of high BGC and were considered Non-hyperglycaemic. To account for this possible confounder, we used multiple linear regression to assess whether there were any relationships between BGC and visual outcomes separately from the Hyperglycaemic and Non-hyperglycaemic groups as well as comparing between those groups.

In conclusion, we found that neonatal hyperglycaemia was not associated with neurodevelopmental impairment. Overall visual outcome was similar between children with previous neonatal hyperglycaemia and those who did not develop hyperglycaemia, with the majority of these children having a favourable visual outcome. However, we found a thicker crystalline lens profile in the children from our Hyperglycaemic cohort being similar to that found in children with type 1 diabetes mellitus, suggesting that even transient BGC may have long-term effects on ocular growth. However, the associations between ocular growth and VA are unclear and our observational study is unable to derive causation. Certainly, the reduction in VA in the Hyperglycaemic group is statistically significant and on the borderline of clinical significance. Therefore, randomised controlled trials of treating neonatal hyperglycaemia are needed, to confirm if treatment of neonatal hyperglycaemia can improve long-term visual outcomes. Long-term investigation is particularly essential as visual function for school work and learning will become more important as these children grow older.

4 Effect of Tight Glycaemic Control with Insulin in Preterm Babies with Neonatal Hyperglycaemia on Visual Outcomes at Seven Years of Age

4.1 Introduction

In the third trimester, glucose is the main source of energy for growth, particularly in the brain and vital organs of the fetus (Hay, 2006; Sunehag & Haymond, 2002). The brain to body weight ratio of babies born preterm or at full term are much larger than adults and the brain expends up to 90% of total body glucose (Bier et al., 1977; Sunehag & Haymond, 2002). The fetus *in utero* is supplied with glucose from the mother via the placenta (Mitanchez, 2007). When a baby is born very preterm, the baby is cut-off from its supply of glucose before there is sufficient accumulation of glycogen and fat stores to produce enough glucose required for maintaining life, and the immature gastrointestinal system is unable to digest food readily (Sunehag & Haymond, 2002). Therefore, most of these babies require supplemental glucose intake via parenteral infusions initially to meet their daily energy requirements (Mitanchez, 2007). However, combinations of iatrogenic glucose infusion overload (Stensvold et al., 2015), anomalous regulation of endogenous glucose production (Chacko et al., 2011), relative insulin insufficiency (Mitanchez-Mokhtari et al., 2004) and reduced insulin sensitivity (Mitanchez-Mokhtari et al., 2004) results in many babies born very preterm developing hyperglycaemia.

Neonatal hyperglycaemia is associated with increased mortality (Stensvold et al., 2015), and adverse outcomes such as sepsis (van der Lugt et al., 2010), IVH (Auerbach et al., 2013) and ROP (Mohamed et al., 2013). The basal endogenous glucose production rate of babies born preterm is approximately 4-7mg.kg^{-1}.minute^{-1} and typically, these babies are given a glucose infusion rate exceeding this rate in order to provide the necessary basic energy requirements (Bottino et al., 2011). However, the minimum amount of glucose infusion needed to support the growth of the baby without increasing BGC has not been identified and this may differ from baby to baby (Kairamkonda & Khashu, 2008). Current forms of management of neonatal hyperglycaemia comprise of insulin infusion and/or reducing glucose intake of the parenteral feed (Bottino et al., 2011; Ogilvy-Stuart & Beardsall, 2010). However, a standard definition of neonatal hyperglycaemia has not been elucidated and the best form of management for neonatal hyperglycaemia is unclear (Bottino et al., 2011; Hey, 2005). It is also unknown whether improving neonatal hyperglycaemia will reduce neonatal complications or adverse outcomes in later childhood.

Insulin is commonly used to treat type 1 diabetes mellitus and also for type 2 diabetes mellitus not responsive to other treatments, as it has been shown to be effective at reducing high BGC and associated microvascular complications (Fullerton et al., 2016; Swinnen et al., 2009). Continuous intravenous infusion of insulin in babies born preterm is also effective in controlling high BGC (Collins Jr. et al., 1991). However, insulin infusion increases the risk of hypoglycaemia (Beardsall et al., 2008), which is associated with increased mortality and risk of damage to the occipital lobe and white matter (Burns et al., 2008; Gataullina et al., 2012). In a mild oxygen-induced retinopathy rat model, insulin upregulated VEGF expression and induced extraretinal neovascularisation and intraretinal haemorrhage (Yoo et al., 2007). In some adults with diabetes, insulin may initially worsen retinopathy (Dahl-Jørgensen et al., 1985). The long-term effects of insulin on growth and neurodevelopment in children born preterm who had neonatal hyperglycaemia are poorly understood (Bottino et al., 2011).

Recent randomised control studies of early insulin therapy to prevent neonatal hyperglycaemia (Beardsall et al., 2008) and tight glycaemic control of hyperglycaemic babies who were born preterm (HINT trial) (Alsweiler et al., 2012) have demonstrated lower BGCs but also increased risk of hypoglycaemia. The HINT trial showed a slower lower leg growth rate with greater head circumference growth and greater weight gain in the tight group compared to babies in the control group at 36 week's postmenstrual age (Alsweiler et al., 2012). Neither study found any difference in mortality rate or reduction of adverse outcomes (Alsweiler et al., 2012; Beardsall et al., 2007).

The aim of this study was to investigate whether tight glycaemic control using insulin compared with standard glycaemic control had any effects on visual outcomes and ocular growth at 7 years of age. In this chapter, we report the vision results from the HINT follow-up arm of the PIANO study.

4.2 Methods

At National Women's Health, Auckland, New Zealand, between July 2005 and October 2008, 154 babies born at <30 weeks' gestational age or <1500g birth weight developed neonatal hyperglycaemia (2 consecutive measurements of BGC >8.5mmol.L^{-1}, at least 4 hours apart) and were invited to participate in the randomised, controlled non-blinded trial of tight glycaemic control in very low birth weight hyperglycaemic preterm babies (HINT trial) (2.1.4.1). Eighty eight eligible babies participated in the HINT trial, of whom 43 were randomised to the tight glycaemic control group ("Tight" group) and were immediately started on insulin at rate of 0.05U.kg^{-1}.h^{-1} and titrated to target BGCs of 4-6mmol.L^{-1}, while 45 babies were randomised to the standard practice glycaemic control group

("Control" group) and were only commenced on insulin (also starting rate of 0.05U.kg^{-1}.h^{-1}) if the baby met the neonatal unit's criteria for neonatal insulin therapy at the time. Children of the HINT trial were invited to take part in the HINT follow-up arm of the Protein, Insulin and Neonatal Outcomes (PIANO) follow-up study when they turned 7 years corrected age.

Full details of the HINT trial, inclusion and exclusion criteria, recruitment details, and the PIANO visual assessment can be found in 2.1.

The primary outcome was survival without neurodevelopmental impairment at 7 years of age.

Secondary outcomes assessed were composite visual function including overall visual outcome, binocular visual outcome, and functional visual outcome. Other visual outcomes included VA, global motion perception, ocular structure and refractive error.

4.2.1 Statistical analyses

Statistical calculations were performed using SPSS Statistics 23 (IBM) and graphs were plotted in Prism 7 for Windows (GraphPad Software, Inc). Details for standard statistical analyses can be found in 2.4.

As randomisation in the HINT trial was stratified by sex (male/female) and weight for gestational age (small for gestational age [birth weight <10th percentile]/appropriate for gestational age); these factors were adjusted for in the analyses including the exploratory analyses. Of the pre-specified potential confounders (gestational age, NZ Deprivation Index at birth, birth plurality, and protein intake in the first 14 postnatal days), birth plurality was found to differ by more than 10% between the Tight and Control groups, and therefore, included as a covariate variable for the analyses.

4.3 Results

Of the 88 babies enrolled in the HINT trial between July 2005 and October 2008, 11 died before 7 years of corrected age. Of the remaining 77 children, 20 children were not assessed at 7 years of age (Figure 4-1). A total of 57 children (65% of those who were randomised, 74% of those alive at 7 years of age) were assessed as part of the HINT follow-up cohort (Tight group n=29, Control group n=28) at 7.2 years corrected age.

Maternal characteristics (Table 4-1) of children in the Tight and Control groups were similar and there were no significant differences between children assessed and not assessed at 7 years of age.

Baseline characteristics (Table 4-2) of children assessed and not assessed at 7 years of age were similar, except children who were assessed were more likely to have a lower weight, height and head circumference z-score at birth. Children in the Tight group had similar baseline characteristics as the Control group apart from lower weight and head circumference at birth in the Tight group. These differences in anthropometry were no longer present by 28 days after birth for both assessed and not assessed, Tight and Control groups. All the children had similar parenteral nutritional intake and there were no differences in the incidence of neonatal complications (Table 4-2).

There were no statistically significant differences in glycaemic status between the children assessed and not assessed at 7 years of age and a similar proportion were given an insulin infusion for neonatal hyperglycaemia (Table 4-3). Of the children assessed at 7 years of corrected age, children in the Tight group had more glucose readings and were more likely to have been given an insulin infusion than the Control group (Table 4-3). Due to protocol violation, one baby in the Tight group did not receive insulin. Minimum and mean BGC were lower in the Tight group than the Control group; there were no difference in maximum BGC or BGC variability between the groups. Children in the Control group had a higher proportion of BGC more than 8.5 $mmol.L^{-1}$. Hypoglycaemia and severe hypoglycaemia were more common in the Tight group, and children in the Tight group received a higher total dose of insulin than the Control group. Half of the children in the Control group who had hypoglycaemia did not receive an insulin infusion. There were no differences between the Tight and Control groups in the proportion of BGC within the targeted BGC for each group (Table 4-3, Table 2-1). IGF-1 and IGF-2 concentrations were similar between the groups.

Figure 4-1 Strobe diagram of children participating in the vision assessment of the HINT trial follow-up arm of the PIANO study at seven years of age

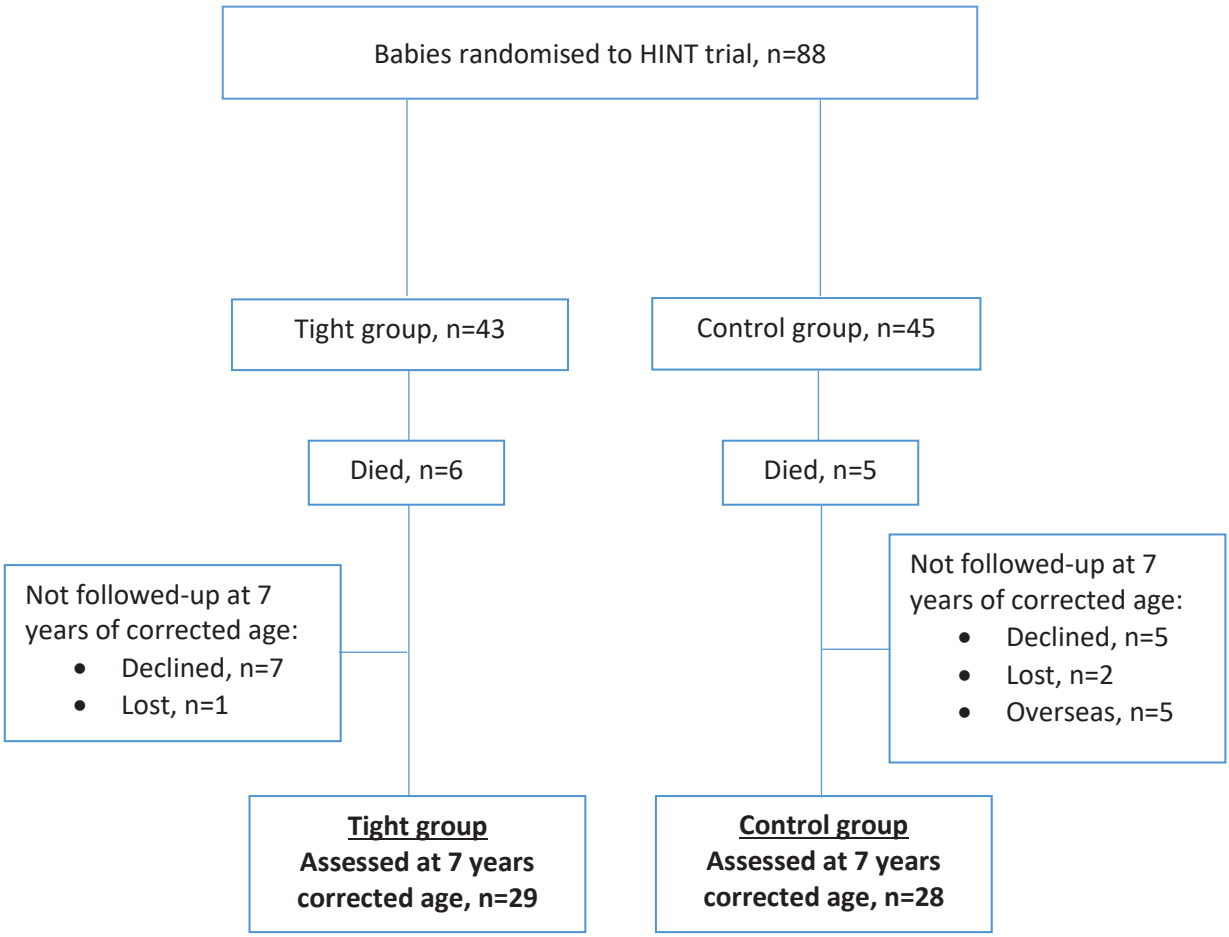


Table 4-1 Maternal characteristics of the babies in the HINT trial and children assessed in the HINT follow-up arm of the PIANO study

	Total randomised in HINT trial (n=88)	Randomised in HINT and eligible for PIANO study, not assessed (n=20)	Children assessed at 7 years corrected age in the HINT trial follow-up arm of the PIANO study (n=57)			Assessed v not assessed P-value
			Tight group (n=29)	Control group (n=28)	Tight v Control P-value	
Maternal diabetes	4 (5%)	1 (5%)	2 (7%)	0 (0%)	0.49	1.00
Maternal insulin	1 (1%)	1 (5%)	0 (0%)	0 (0%)	-	0.26
Multiple pregnancy	32 (36%)	8 (40%)	12 (41%)	8 (29%)	0.31	0.69
Ethnicity						
Māori	32 (36%)	7 (35%)	10 (34%)	10 (36%)	0.29	0.11
Pacific Island	14 (16%)	7 (35%)	4 (14%)	3 (11%)		
European	25 (29%)	3 (15%)	7 (24%)	12 (43%)		
Asian/Other	17 (19%)	3 (15%)	8 (28%)	3 (11%)		
Deprivation index						
Most deprived (10)	18 (20%)	5 (25%)	8 (28%)	3 (11%)	0.09	0.69
Least deprived (1)	6 (7%)	0 (0%)	4 (14%)	2 (7%)		
Received antenatal steroids						
Any	77 (88%)	19 (95%)	24 (83%)	24 (86%)	1.00	0.44
Complete course	40 (45%)	10 (50%)	14 (48%)	12 (43%)	0.43	0.72

Data are n (%)

Table 4-2 Baseline characteristics of the babies in the HINT trial and children assessed in the HINT follow-up arm of the PIANO study

	Total randomised in HINT trial (n=88)	Randomised in HINT and eligible for PIANO study, not assessed (n=20)	Children assessed at 7 years corrected age in the HINT trial follow-up arm of the PIANO study (n=57)			Assessed v not assessed P-value
			Tight group (n=29)	Control group (n=28)	Tight v Control P-value	
Gestational age (weeks)	25.0 (25.0, 27.0)	25.0 (24.0, 26.0)	25.0 (24.5, 27.0)	25.0 (25.0, 27.8)	0.67	0.29
Birth measurements						
Weight (g)	793 (691, 908)	851 (695, 966)	725 (665, 845)	825 (719, 925)	0.04	0.22
Weight z-score	-0.03 ± 0.92	0.47 ± 0.90	-0.17 ± 0.87	-0.10 ± 0.96	0.77	0.01
Crown-heel length (cm)	33.0 (31.5, 34.5)	34.0 (31.0, 37.0)	32.5 (31.0, 34.0)	34.0 (32.0, 34.5)	0.21	0.19
Length z-score	-0.16 ± 1.10	0.36 ± 1.10	-0.28 ± 1.23	-0.30 ±1 .09	0.97	0.04
Head circumference (cm)	23.5 (22.5, 25.0)	24.0 (22.6, 26.0)	23.3 (22.0, 24.0)	24.0 (23.0, 25.0)	0.01	0.30
Head circumference z-score	0.11 ± 1.16	0.67 ± 1.21	-0.27 ± 1.18	0.22 ± 1.07	0.12	0.03
Small for gestational age	10 (11%)	1 (5%)	4 (14%)	4 (14%)	1.00	0.43
CRIB-II score	12 ± 3	12 ± 3	11 ± 2	11 ± 3	0.93	0.42
Apgar score						
1 minute	5 ± 2	6 ± 2	5 ± 2	6 ± 2	0.12	0.29
5 minutes	8 ± 2	8 ± 2	7 ± 2	8 ± 2	0.20	0.30
Neonatal Complications						
NEC	3 (3%)	1 (3%)	1 (3%)	0 (0%)	1.00	1.00
IVH (grade III/IV)	8 (9%)	2 (10%)	3 (10%)	1 (4%)	0.61	0.65
PVL	2 (2%)	0 (0%)	0 (0%)	0 (0%)	-	0.39
ROP (grade III/IV)	13 (15%)	3 (15%)	6 (21%)	3 (11%)	0.47	1.00
ROP treatment	12 (14%)	3 (15%)	6 (21%)	2 (7%)	0.25	1.00

	Total randomised in HINT trial (n=88)	Randomised in HINT and eligible for PIANO study, not assessed (n=20)	Children assessed at 7 years corrected age in the HINT trial follow-up arm of the PIANO study (n=57)			Assessed v not assessed P-value
			Tight group (n=29)	Control group (n=28)	Tight v Control P-value	
Early onset sepsis	1 (1%)	1 (5%)	0 (0%)	0 (0%)	-	0.26
Late onset sepsis	24 (27%)	7 (35%)	7 (24%)	5 (18%)	0.56	0.24
BPD	35 (40%)	9 (45%)	13 (45%)	11 (39%)	0.67	0.82
Postnatal corticosteroids	29 (33%)	7 (35%)	8 (28%)	11 (39%)	0.34	1.00
Discharged with home O_2	24 (27%)	5 (25%)	12 (41%)	7 (25%)	0.19	0.49
Major neonatal surgery	12 (14%)	2 (10%)	5 (17%)	2 (7%)	0.42	1.00
Nutrition						
Ever received parenteral nutrition	88 (100%)	20 (100%)	29 (100%)	28 (100%)	-	-
Age enteral feeds established (days)	13 ± 4	13 ± 4	12 ± 5	13 ± 4	0.53	0.61
Nutritional intake (mean)						
Protein ($g.kg.day^{-1}$)						
Week 1	2.58 ± 0.47	2.61 ± 0.41	2.55 ± 0.46	2.65 ± 0.44	0.38	0.93
Month 1	3.28 ± 0.30	3.22 ± 0.30	3.28 ± 0.26	3.34 ± 0.27	0.40	0.21
Carbohydrate ($g.kg.day^{-1}$)						
Week 1	10.68 ± 1.61	10.89 ± 1.32	10.55 ± 1.37	10.93 ± 2.00	0.41	0.73
Month 1	14.36 ± 1.40	14.42 ± 1.27	14.23 ± 1.59	14.67 ± 1.28	0.26	0.95
Fat ($g.kg.day^{-1}$)						
Week 1	3.28 ± 0.70	3.14 ± 0.57	3.35 ± 0.76	3.29 ± 0.68	0.77	0.33
Month 1	5.74 ± 0.85	5.75 ± 0.65	5.59 ± 1.02	5.91 ± 0.63	0.16	0.99
Energy ($Kcal.kg.day^{-1}$)						
Week 1	78.78 ± 9.76	78.19 ± 7.54	78.90 ± 8.50	80.00 ± 11.12	0.68	0.63
Month 1	120.29 ± 13.85	120.29 ± 11.14	118.44 ± 16.40	123.47 ± 11.33	0.19	0.86

	Total randomised in HINT trial (n=88)	Randomised in HINT and eligible for PIANO study, not assessed (n=20)	Children assessed at 7 years corrected age in the HINT trial follow-up arm of the PIANO study (n=57)			Assessed v not assessed P-value
			Tight group (n=29)	Control group (n=28)	Tight v Control P-value	
Anthropometry 28 days						
Weight (g)	1050 (953, 1265)	1080 (910, 1374)	1040 (871, 1165)	1143 (964, 1286)	0.17	0.73
Weight z-score	-0.89 ± 0.67	-0.63 ± 0.68	-0.92 ± 0.64	-0.98 ± 0.59	0.72	0.06
Length (cm)	35.7 (34.4, 37.3)	36.3 (34.7, 38.1)	35.5 (34.1, 37.0)	36.0 (34.4, 37.6)	0.55	0.50
Length z-score	-1.13 ± 0.91	-0.81 ± 0.82	-1.12 ± 0.99	-1.14 ± 0.85	0.94	0.19
Head circumference (cm)	25.0 (24.1, 26.2)	24.5 (23.7, 26.7)	24.9 (23.4, 25.9)	25.0 (24.1, 26.8)	0.32	0.94
Head circumference z-score	-1.50 ± 0.85	-1.28 ± 1.04	-1.60 ± 0.89	-1.40 ± 0.81	0.42	036
Growth velocity 28 days ($g.kg.day^{-1}$)	10.95 ± 3.38	9.74 ± 3.00	11.42 ± 2.83	11.08 ± 4.06	0.71	0.09
Length of neonatal stay (days)	101 ± 29	111 ± 39	103 ± 26	93 ± 22	0.13	0.09

Data are n (%), mean±standard deviation, median (interquartile range). Abbreviations: NEC necrotizing enterocolitis, IVH intraventricular haemorrhage, PVL periventricular haemorrhage, ROP retinopathy of prematurity, BPD bronchopulmonary dysplasia, O2 oxygen supplementation, g grams, cm centimetres, $g.kg^{-1}.day^{-1}$ grams per kilogram per day, $kcal.kg^{-1}.day^{-1}$ kilocalories per kilogram per day.

Table 4-3 Glycaemic status of children in the HINT trial follow-up arm of the PIANO study

	Total randomised in HINT trial (n=88)	Randomised in HINT and eligible for PIANO study, not assessed (n=20)	Children assessed at 7 years corrected age in the HINT trial follow-up arm of the PIANO study (n=57)			Assessed v not assessed P-value
			Tight group (n=29)	Control group (n=28)	Tight v Control P-value	
Mean number of glucose readings	95 ± 58	93 ± 62	111 ± 52	81 ± 52	0.04	0.80
BGC (mmol.L^{-1})						
Minimum	2.49 ± 0.93	2.55 ± 0.79	2.17 ± 0.85	2.73 ±0.80	0.01	0.63
Mean	6.67 ± 0.97	6.56 ± 0.89	6.21 ± 0.55	6.95 ± 1.08	< 0.01	0.95
Maximum	14.40 ± 5.25	13.76 ± 4.55	14.97 ± 6.68	13.78 ± 4.30	0.43	0.66
Variability (SD of the mean)	-	-	2.38 ± 0.75	2.46 ± 0.94	0.74	-
High BGC						
At least one episode of high BGC (> 8.5 mmol.L^{-1})	88 (100%)	20 (100%)	29 (100%)	28 (100%)	-	-
At least one episode of high BGC on 3 or more days	73 (83%)	17 (85%)	23 (79%)	24 (86%)	0.73	1.00
Proportion of BGC > 8.5 mmol.L^{-1}	20 ± 12	17 ± 9	15 ± 7	23 ± 12	< 0.01	0.45
Hypoglycaemia						
Any (BGC < 2.6 mmol.L-1)	50 (57%)	9 (45%)	22 (76%)	13 (47%)	0.02	0.20
Severe (< 2.0 mmol.L^{-1})	21 (24%)	4 (20%)	10 (35%)	3 (11%)	0.03	1.00
Extreme (< 1.5 mmol.L^{-1})	12 (14%)	3 (15%)	5 (17%)	1 (4%)	0.19	0.69
Proportion of BGC < 2.6 mmol.L^{-1}	2 ± 2	1 ± 2	2 ± 2	1 ± 1	0.12	0.56
Insulin (U.kg^{-1})						
Received insulin infusion	70 (80%)	15 (75%)	28 (97%)	16 (57%)	< 0.01	1.00
Total dose of insulin received	12.09 ± 15.13	8.39 ± 10.38	19.56 ± 17.39	6.27 ± 12.02	< 0.01	0.25

	Total randomised in HINT trial (n=88)	Randomised in HINT and eligible for PIANO study, not assessed (n=20)	Children assessed at 7 years corrected age in the HINT trial follow-up arm of the PIANO study (n=57)			Assessed v not assessed P-value
			Tight group (n=29)	Control group (n=28)	Tight v Control P-value	
BGC within target (%)	68 ± 18	73 ± 17	66 ± 16	71 ± 19	0.33	0.27
2.6 – 8.5 mmol.L-1	78 ± 11	82 ± 9	83 ± 7	76 ± 12	< 0.01	0.41
4.0 – 6.0 mmol.L-1	38 ± 13	41 ± 12	43 ± 10	36 ± 12	0.03	0.52
IGF concentration ($ng.mL^{-1}$)						
IGF-1	5.63 ± 3.88	5.67 ± 2.64	6.11 ± 4.98	6.13 ± 3.55	0.99	0.71
IGF-2	6.62 ± 3.91	7.13 ± 5.76	7.00 ± 4.05	6.32 ± 2.10	0.47	0.68

Data are n (%), mean±standard deviation. Abbreviations: BGC blood glucose concentration, IGF insulin-like growth factor, $mmol.L^{-1}$ millimole per litre, $U.kg^{-1}$ units per kilogram, $ng.mL^{-1}$ nanogram per millilitre. Blood glucose concentration targets until 36 weeks' corrected age (Table 2-1).

At the time of the assessment at 7 years corrected years, characteristics of the children in the Tight and Control groups remained similar, except that children in the Tight group were shorter in stature (Table 4-4).

Table 4-4 Characteristics of children at the time of assessment in the HINT follow-up arm of the PIANO study at seven years of age

	Tight group (n=29)	Control group (n=28)	Tight v Control P-value
Corrected age at assessment (years)	7.2 ± 0.1	7.2 ± 0.2	0.69
Male	11 (38%)	14 (50%)	0.36
Deprivation index			
Most deprived (10)	5 (17%)	2 (7%)	0.37
Least deprived (1)	3 (10%)	3 (11%)	
Anthropometry			
Weight (kg)	23.0 (19.3, 25.2)	24.7 (20.3, 29.0)	0.17
Weight z-score	-0.12 ± 1.60	0.35 ± 1.54	0.27
Height (cm)	121.0 (116.2, 125.0)	125.0 (120.1, 128.4)	0.01
Height z-score	-0.22 ± 1.17	0.47 ± 1.01	0.02
Head circumference (cm)	51.4 (50.0, 52.1)	51.6 (50.3, 53.1)	0.44
Head circumference score	-1.28 ± 1.34	-1.07 ± 1.26	0.56
Growth velocity ($g.kg^{-1}.day^{-1}$)	1.26 ± 0.10	1.25 ± 0.11	0.85

Data are n (%), mean±standard deviation, median (interquartile range). Abbreviations: $g.kg^{-1}.day^{-1}$ grams per kilogram per day

The primary outcome was analysed for 68 children from the HINT trial, which included the 57 children assessed at 7 years of age and 11 children who had died before 7 years of age (Table 4-5). There were no differences between the Tight and Control groups for the primary outcome of survival without neurodevelopmental impairment. More than 50% of the surviving children had neurodevelopmental impairment. None of the children had impairment due to blindness.

Table 4-5 Primary outcome of the HINT follow-up arm of the PIANO study at seven years of age

	Tight group (n=35)	Control group (n=33)	Unadjusted OR (95%CI)	P-value	*Adjusted OR (95%CI)	P-value
Survival without neurodevelopmental impairment	14 (40%)	11 (33%)	1.33 (0.46, 3.66)	0.49	1.14 (0.14, 3.20)	0.58
Died	6 (17%)	5 (15%)	1.16 (0.29, 4.57)	0.69	1.38 (0.35, 5.42)	0.67
Assessed at 7 years of corrected age	n=29	n=28	-		-	
Neurodevelopmental Impairment	15/29 (52%)	17/28 (61%)	0.69 (0.24, 2.01)	0.50	0.75 (0.25, 2.21)	0.58
WISC FSIQ <85	12 (41%)	14 (50%)	0.71 (0.24, 2.04)	0.51	0.74 (0.25, 2.20)	0.59
MABC-2 total score ≤5th centile	9 (31%)	9 (32%)	0.95 (0.31, 2.88)	0.93	0.99 (0.29, 3.43)	0.99
Cerebral palsy	3 (10%)	3 (11%)	0.96 (0.17, 5.38)	0.96	1.02 (0.18, 5.74)	0.99
Blind	0 (0%)	0 (0%)	-	-	-	-
Deaf	0 (0%)	1 (4%)	-	-	-	-

**Adjusted for sex (male/female), weight for gestational age (SGA/AGA) and multiple birth (yes/no). Data are n (%), mean±standard deviation.*

Overall, binocular and functional visual outcomes were similar between the children in the Tight and Control groups (Table 4-6). There were no differences in visual function between the two groups except children in the Tight group presented with a poorer binocular distance VA (VA with both eyes together) after adjusting for sex, being small for gestational age and multiple birth. Refractive error (Table 4-7) and ocular biometry (Table 4-8) were similar between both groups.

There were no significant differences in the number of children with ocular abnormalities requiring further follow-up or referral between the two groups (Table 4-6). The majority of children had normal ocular findings or had signs of normal variations in ocular structure that did not require extra follow-up outside of routine eye check. The most common normal variant findings were tortuosity of the retinal blood vessels, peripapillary atrophy (would be followed-up in the presence of other signs of pathologic myopia) or pigment around the optic nerve, and presence of a cilioretinal artery. 3/4 (75%) of the children who were identified with ocular findings that required further follow-up had ROP-related or ROP treatment-related ocular changes (Table 4-9).

Table 4-6 Visual functional outcomes of children assessed in the HINT trial follow-up arm of the PIANO study at seven years of age

	Tight group (n=29)	Control group (n=28)	Unadjusted OR or mean difference (95%CI)	P-value	*Adjusted OR or mean difference (95%CI)	P-value
Favourable overall visual outcome	13/25 (50%)	14/23 (61%)	0.64 (0.21, 2.00)	0.45	0.68 (0.22, 2.12)	0.50
Favourable binocular visual outcome	11/28 (39%)	12/26 (46%)	0.75 (0.26, 2.23)	0.61	0.85 (0.28, 2.56)	0.77
Favourable functional visual outcome	15/26 (58%)	18/26 (69%)	0.61 (0.19, 1.89)	0.39	0.61 (0.19, 2.00)	0.41
Distance VA in Better Eye						
Equal or better than 6/12	27/27 (100%)	27/28 (96%)	-		-	
Normal v mild to severe impairment	22/27 (82%)	25/28 (89%)	0.53 (0.11, 2.47)	0.47	0.44 (0.11, 1.72)	0.24
LogMAR	0.01 ± 0.12	0.00 ± 0.14	0.01 (-0.06, 0.08)	0.71	0.02 (-0.05, 0.10)	0.53
Presenting binocular distance VA (logMAR)	0.04 ± 0.18	-0.04 ± 0.13	0.08 (0.00, 0.16)	0.07	0.09 (0.00, 0.18)	0.04
Other visual outcomes						
Presence of strabismus	7/29 (24%)	4/28 (14%)	1.91 (0.51, 7.20)	0.35	1.95 (0.45, 8.50)	0.38
Pass stereoacuity (TNO)	17/25 (68%)	19/26 (73%)	0.78 (0.24, 2.55)	0.68	0.71 (0.21, 2.39)	0.58
Not requiring spectacles	17/23 (74%)	20/23 (87%)	0.42 (0.09, 1.96)	0.46	0.38 (0.08, 1.89)	0.24
Presence of nystagmus	1/28 (4%)	1/28 (4%)	-		-	
Normal ocular motility	22/27 (81%)	26/28 (93%)	0.34 (0.06, 1.87)	0.21	0.36 (0.05, 2.70)	0.32
Normal convergence	20/26 (77%)	20/24 (83%)	0.67 (0.19, 2.36)	0.53	0.93 (0.23, 3.70)	0.91
Presence of motor fusion	14/25 (56%)	19/28 (68%)	0.60 (0.20, 1.84)	0.37	0.83 (0.25, 2.75)	0.75
Mean global motion perception threshold	48.50 ± 21.43	46.26 ± 22.59	2.23 (-5.82, 10.28)	0.59	-2.27 (-11.21, 6.67)	0.62

**Adjusted for sex (male/female), weight for gestational age (SGA/AGA) and multiple birth (yes/no). Data are n (%), mean±standard deviation.*

Table 4-7 Ocular structural and refractive outcomes of children assessed in the HINT trial follow-up arm of the PIANO study at seven years of age

	Tight group (n=29)	Control group (n=28)	Unadjusted OR or mean difference (95%CI)	P-value	*Adjusted OR or mean difference (95%CI)	P-value
Ocular structure						
Retinal posterior pole (central) findings			0.35		0.55	
No abnormalities or non-clinically significant findings	23/29 (79%)	23/28 (82%)				
Clinically significant findings	1/29 (3%)	3/28 (11%)				
Unable to assess	5/29 (17%)	2/28 (7%)				
Refractive error						
SEP of the better VA eye			0.20		0.62	
Myopia (< -0.50 D)	3/23 (13%)	0/23 (0%)				
Hyperopia (> +0.50 D)	10/23 (44%)	12/23 (52%)				
Significant hyperopia (> +2.00 D)	1/23 (4%)	3 (13%)				
SEP of the poorer VA eye			0.19		0.56	
Myopia (< -0.50 D)	3/23 (13%)	0/23 (0%)				
Hyperopia (> +0.50 D)	11/23 (48%)	14/23 (61%)				
Significant hyperopia (> +2.00 D)	1/23 (4%)	2/23 (9%)				
Astigmatism						
Better eye	3/23 (13%)	1/23 (4%)	0.30 (0.03, 3.15)	0.61	0.19 (0.02, 2.48)	0.21
Poorer eye	4/23 (17%)	3/23 (13%)	0.71 (0.14, 3.61)	1.00	0.62 (0.11, 3.40)	0.59
Anisometropia	2/23 (4%)	0/22 (0%)	-		-	

**Adjusted for sex (male/female), weight for gestational age (SGA/AGA) and multiple birth (yes/no). Data are n (%), mean±standard deviation. Abbreviations: SEP spherical equivalent power, VA visual acuity, D dioptres*

Table 4-8 Ocular biometry visual outcomes of children assessed in the HINT follow-up arm of the PIANO study at seven years of age

	Tight group (n=29)	Control group (n=28)	Unadjusted mean difference (95%CI)	P-value	*Adjusted mean difference (95%CI)	P-value
Central corneal thickness (µm)						
Better VA Eye	554 ± 32	543 ± 37	11 (-9, 31)	0.27	9 (-11, 29)	0.36
Poorer VA Eye	553 ± 40	545 ± 39	8 (-14, 31)	0.47	7 (-14, 28)	0.50
Anterior chamber depth (mm)						
Better VA Eye	3.34 ± 0.29	3.34 ± 0.29	0.00 (-0.17, 0.16)	0.93	0.03 (-0.14, 0.20)	0.72
Poorer VA Eye	3.38 ± 0.26	3.35 ± 0.35	0.03 (-0.14, 0.20)	0.74	0.01 (-0.17, 0.19)	0.89
Axial length (mm)						
Better VA Eye	22.01 ± 0.77	22.14 ± 1.05	-0.13 (-0.66, 0.40)	0.63	-0.09 (-0.63, 0.46)	0.75
Poorer VA Eye	22.17 ± 0.88	22.09 ± 1.10	0.08 (-0.49, 0.64)	0.79	0.13 (-0.46, 0.71)	0.67
Lens thickness (mm)						
Better VA Eye	3.80 ± 0.29	3.84 ± 0.25	-0.04 (-0.20, 0.11)	0.58	-0.02 (-0.18, 0.14)	0.79
Poorer VA Eye	3.79 ± 0.30	3.81± 0.25	-0.02 (-0.18, 0.13)	0.78	0.00 (-0.16, 0.16)	0.99
Corneal curvature (mm)						
Flat Meridian Better VA Eye	7.63 ± 0.20	7.71 ± 0.31	-0.08 (-0.23, 0.07)	0.27	-0.04 (-0.17, 0.10)	0.59
Flat Meridian Poorer VA Eye	7.66 ± 0.23	7.71 ± 0.29	-0.05 (-0.20, 0.10)	0.53	0.00 (-0.15, 0.14)	0.95
Steep Meridian Better VA Eye	7.45 ± 0.24	7.55 ± 0.32	-0.09 (-0.25, 0.07)	0.26	-0.06 (-0.21, 0.09)	0.40
Steep Meridian Poorer VA Eye	7.48 ± 0.25	7.55 ± 0.31	-0.07 (-0.23, 0.09)	0.38	-0.04 (-0.19, 0.11)	0.61
Central retinal thickness (µm)^						
Better VA Eye	278 ± 29	266 ± 25	12 (-6, 31)	0.19	13 (-8, 33)	0.22
Poorer VA Eye	278 ± 29	267 ± 24	11 (-7, 30)	0.23	12 (-8, 32)	0.24

**Adjusted for sex (male/female), weight for gestational age (SGA/AGA) and multiple birth (yes/no). Data are n (%), mean±standard deviation. ^Missing data for central retinal thickness: Tight group – 9 for better and poorer VA eye; Control group – 12 for better and poorer eye. Abbreviations: VA visual acuity*

Table 4-9 Ocular findings referred for further follow-up for children assessed in the HINT follow-up arm of the PIANO study

Participant Identifier	Tight/Control	Ocular findings
1	Control	Dot haemorrhages in peripheral retina
2	Control	Large ROP-related pigmented lesion in central macula
3	Tight	Macula ectopia with temporal retinal blood vessel straightening, peripheral retinal scarring from ROP photocoagulation treatment
4	Control	Macula ectopia with temporal retinal blood vessel straightening, myopic optic discs, peripheral retinal scarring

For exploratory analyses, simple linear regression models with adjustment for glycaemic control, sex, small for gestational age and multiple birth were performed on exposures that were different between the Tight and Control groups in relation to presenting binocular VA (Table 9-5). These variables included birth weight, birth head circumference, mean number of glucose readings, minimum and mean BGC, proportion of BGC >8.5mmol.L^{-1}, proportion of children with an episode of hypoglycaemia (hypoglycaemia or severe hypoglycaemia), total dose of insulin received, proportion of children within glycaemic targets of 2.6-8.5 and 4.0-6.0mmol.L^{-1}, and height at 7 years of age. Number of BGC readings was a confounding variable.

Exposures that predicted binocular VA ($p<0.15$) were mean number of BGC readings, received insulin infusion, total insulin dose, and proportion of BGC 4-6mmol.L^{-1}. Total insulin dose showed collinearity to mean number of BGC readings and received insulin infusion. A multiple linear regression model was used to test whether total insulin dose and proportion of BGC 4-6mmol.L^{-1} with adjustment for sex, small for gestational age and multiple birth, were predictive of binocular VA; the model was statistically significant. The R^2 for the overall model was 23% with an adjusted R^2 of 15%, which was a small to medium effect size, and was statistically significant ($F=2.95$, $p=0.02$). Total insulin dose was statistically significant in predicting binocular VA with every increase of 1U.kg^{-1} total insulin dose associated with reduction of binocular VA by 0.004logMAR (Table 4-10).

Table 4-10 Summary of multiple regression analysis for total insulin dose, proportion of BGC 4-6 mmol.L-1, hypoglycaemia and covariates v presenting binocular VA

Variable	B	SE_B	β	P-value
Intercept	0.002	0.08		0.98
Total insulin dose ($U.kg^{-1}$)	0.004	0.001	0.41	<0.01
Proportion BGC 4-6 $mmol.L^{-1}$	-0.002	0.002	-0.15	0.24
Sex	-0.001	0.041	-0.003	0.98
Small for gestational age	0.06	0.06	0.13	0.33
Multiple birth	0.03	0.04	0.10	0.47

Note: B = unstandardized regression coefficient; SE_B = standard error of the coefficient; β = standardized coefficient; $U.kg^{-1}$ Units per kilogram; $mmol.L^{-1}$ millimoles per litre.

There were no statistically significant interactions between insulin infusion and ROP on presenting binocular VA (F=0.08, p=0.78). No outliers were identified but not all the residuals were normally distributed, and heterogeneity of variances for both comparisons were present as none of the children who were not administered insulin infusion had ROP treatment. Main effect for insulin infusion and ROP were analysed, which indicated the main effect for ROP was statistically significant (F=4.84, p=0.01 for binocular VA). ROP treatment was associated with poorer VA by 0.21logMAR than no ROP and ROP untreated groups (95%CI: no ROP 0.04-0.36, p 0.01; ROP untreated 0.07-0.36, p<0.01).

4.4 Discussion

Neonatal hyperglycaemia is associated with mortality and neonatal complications in babies born very preterm (Hays et al., 2006; van der Lugt et al., 2010). However, the optimal treatment for neonatal hyperglycaemia is unclear and randomised control studies on early insulin therapy and tight glycaemic control have not shown an improvement in mortality or a reduction in adverse outcomes (Alsweiler et al., 2012; Beardsall et al., 2008). This is the first study to investigate the effects of tight glycaemic control of neonatal hyperglycaemia in babies born preterm on visual outcomes in later childhood. In our study, children who had tight glycaemic control of neonatal hyperglycaemia had similar incidence of surviving without neurodevelopmental impairment at 7 years corrected age as those who had the standard glycaemic control at the time of treatment. None of the children had neurodevelopmental impairment due to blindness. There were no differences in incidence of ROP between the groups. Tight glycaemic control did not affect overall visual development as measured by visual function, ocular structure and refractive error distribution, but a reduction in binocular distance VA was found in the Tight glycaemic control group. These data suggest that children who received tight glycaemic control are at an increased risk of neonatal hypoglycaemia and reduced VA long-term. Therefore,

treatment with tight glycaemic control with insulin aiming for BGC between 4-6mmol.l^{-1} is not indicated.

Although two thirds of the children in our cohort had a favourable visual outcome, binocular VA was reduced by almost one logMAR line in the Tight glycaemic group compared to the Control group. Unlike studies of diabetes mellitus (Bourne et al., 2013; Fullerton et al., 2016; Yau et al., 2012), the reduction of VA in our study was not associated with refractive error or retinal structural changes or ocular biometry as these outcomes were similar between the two treatment groups. Most of the significant retinal findings we found were related to ROP rather than the changes typically found in diabetic retinopathy. Through exploratory analysis, higher total dose of insulin received was associated with reduction in binocular VA. This VA reduction may be due to insulin having adverse effects on the visual pathway outside the eye.

There were no differences in incidence of ROP between the Tight and Control groups in our study. A retrospective database study found an increased 1.34 odds (95%CI 1.02-1.76) of severe ROP for BGC >150mg.dL-1 (8.3mmol.L^{-1}) in the presence of insulin use (Lee et al., 2016). In our study, there were no interactions between insulin and ROP on binocular VA but treated ROP (indicative of severe ROP) was associated with poorer VA than untreated ROP or no ROP groups. It is interesting to note that none of the children who did not have insulin infusion had treatment for ROP. This is similar to the results from our neonatal hyperglycaemia follow-up cohort arm (chapter 3), where none of the children who did not develop hyperglycaemia had ROP treatment. Only children with neonatal hyperglycaemia were administered insulin infusion, which would suggest that there may be an effect of insulin and/or neonatal hyperglycaemia on severe ROP development. Although this may be a pathway by which VA is reduced in the Tight glycaemic control group, it is known that children who have lower gestational age are more susceptible neonatal hyperglycaemia, and therefore, more likely to require insulin (Beardsall et al., 2010; Hays et al., 2006), and risk of ROP is also higher (Early Treatment for Retinopathy of Prematurity Cooperative Group, 2005).

One difficulty in maintaining intensive insulin therapy in adults is the higher risk of hypoglycaemia (Fullerton et al., 2016) and in our study, there was higher incidence of hypoglycaemia in the Tight group compared to the Control group. However, children born preterm also develop hypoglycaemia even without insulin treatment as half of the children who had hypoglycaemia in the Control group did not receive an insulin infusion. This is likely due to limited glycogen stores in babies born preterm (Mitanchez, 2007). Hypoglycaemia is a concern as, when prolonged, it is associated with brain damage

(particularly occipital lobe injury), neurodevelopmental impairment and death (Tam et al., 2008; Yalnizoglu et al., 2007). Although more children in the Tight group developed hypoglycaemia, there were no differences in survival without neurodevelopmental impairment nor in incidence of visual impairment between the Tight and Control groups. A recent study of children born moderate to late preterm at 4 and half years of age reported that neonatal hypoglycaemia was not associated with an increased risk of neurosensory impairment but was associated with visual motor impairment, and this was dose-dependent, with higher risk in children with severe, recurrent or clinical undetected hypoglycaemia (McKinlay et al., 2017). It is important to note that the babies in our study had their BGC monitored frequently, which would have meant that often hypoglycaemia would be promptly treated before prolonged exposure. In our exploratory analysis, we found that hypoglycaemia was also not associated with the reduced VA found in the Tight group. This suggests hypoglycaemia associated with tight glycaemic control of neonatal hyperglycaemia does not affect visual development at 7 years of age.

As well as higher risks of hypoglycaemia with tight glycaemic control, there is often difficulty in maintaining a stable BGC, particularly due to the need for regular monitoring of BGC and changes in metabolism or illness that can cause BGC fluctuations (Beardsall et al., 2010; Fitzgerald et al., 1992; Fullerton et al., 2016; Hirsch & Brownlee, 2005). In our study, only two thirds of the BGC of both groups were within the intended target range and the most common reason for withdrawal from the original HINT trial was due to the need of numerous heel pricks for monitoring BGC (Alsweiler et al., 2012). Children in the Tight group had a higher proportion of BGC within 4 to 6mmol.L^{-1}, which tended to be associated with better VA. However, total insulin dose was more predictive of VA, with a higher dose associated with reduced VA. It is unknown whether this isolated reduction in VA is clinically significant as all other visual functions and neurodevelopment were not affected, and VA can be affected by many factors including ocular and brain development, neurodevelopment and visual experience. Magnetic resonance imaging of the brain was also conducted in our study. Further processing of this data to identify whether there were any changes to the brain from hypoglycaemia that were related to visual function may be indicated.

A strength of the study was that we were following up children from a randomised controlled trial of tight glycaemic control. Maternal and baseline characteristics for the children were available and were well matched between the two groups, which reduced potential confounders. For the children who were assessed at 7 years of age, there were differences between the groups in birth weight and birth head circumference, but z-scores were similar between the groups. Three quarters of the available

children in the HINT trial were assessed at 7 years of age and these children had similar baseline characteristics as those who were not assessed. Therefore, our sample was representative of the children who were involved in the HINT trial. However, we were limited by a small sample size and the original study was not powered to investigate the large number of outcomes we had. Therefore, we cannot exclude the possibility that tight glycaemic control may worsen visual function in babies born preterm.

In conclusion, we found that tight glycaemic control did not affect survival with neurodevelopmental impairment or overall visual outcomes at 7 years of age. However, less than two thirds of the children had no neurodevelopmental impairment or favourable visual outcome. Tight glycaemic control was associated with reduced VA, with higher dose of insulin associated with poorer VA. Although the long-term implications of this VA reduction are unknown, treatment with tight glycaemic control with insulin is currently not indicated.

5 Effects of Neonatal Nutritional Intake in Preterm Babies on Visual Outcomes at Seven Years of Age

5.1 Introduction

Babies born preterm frequently have poor postnatal growth, which is associated with poor neurodevelopment (Cooke, 2005; Yeung & Smyth, 2003). Adequate nutrition following very preterm birth is important for the optimal growth and neurodevelopment of the baby. However, there is no consensus on the optimal nutritional intake for babies born very preterm (Cormack et al., 2016; Uthaya & Modi, 2014). Current research in this area has focused on the nutritional intake that would enable the very preterm born baby to grow at a similar rate as an intrauterine fetus of the same gestational age. However, whether faster extrauterine growth is associated with improved health and neurodevelopment has not been determined (Cormack et al., 2016).

Babies born preterm have not accumulated the necessary reservoir of nutrients before birth to be self-sufficient, and with the loss of nutrients from the mother after birth, combined with the immaturity of the gastrointestinal system and liver, the baby is reliant on parenteral and/or enteral nutrition to sustain life (Sunehag & Haymond, 2002; Thureen & Heird, 2005). Preterm babies are at an increased risk of malabsorption and malnutrition while the gastrointestinal system continues to mature after birth. This is particularly significant as these problems occur during a time of rapid growth (Neu, 2007). Babies born preterm are also at risk of health problems, which may affect nutritional intake (Fitzgerald et al., 1992). Therefore, it is essential to understand the nutritional intake for optimal growth and development in this sensitive time.

Parenteral nutrition is given intravenously and can consist of a combination of: carbohydrate, protein, fat, nitrogen, electrolytes, fluid, minerals, and trace elements (Brine & Ernst, 2004). In the 1970s, babies who received only glucose infusion via parenteral nutrition were found to have a high rate of protein breakdown and increased weight loss (Heird & Anderson, 1977). Subsequently, protein supplementation was introduced into parenteral nutrition. Although protein supplementation in enteral feeding was found to increase weight gain, high daily protein intake (>4.5g.kg^{-1}) was associated with poorer neurodevelopment, higher incidence of strabismus and increased risk of metabolic acidosis (Heird & Anderson, 1977). The optimal nutritional intake and when to initiate supplementation for babies born preterm remains contentious (American Academy of Pediatrics Committee on Nutrition, 1977; Cormack et al., 2016; Trivedi & Sinn John, 2013).

There have been no prospective studies investigating the effects of nutritional intake in early life on visual development in children born preterm. However, a few retrospective studies have investigated the effects of early postnatal nutrition and early growth on the development of ROP in preterm babies (Cester et al., 2015; Porcelli & Weaver, 2010). Slower postnatal head growth has been associated with increased risk of stage 3 ROP. However, mean protein intake did not correlate with head circumference standard deviation score or development of ROP (Löfqvist, Andersson, et al., 2006; Löfqvist, Engström, et al., 2006). IGF-1 has been found to be an important regulator in the early growth of babies born preterm and higher concentrations of IGF-1 have been associated with a lower risk of ROP (Hellström et al., 2003; Löfqvist, Engström, et al., 2006). However, the relationship between neonatal nutritional intake and IGF-1 concentrations is unclear (Challa et al., 2001; Engström et al., 2005; Hansen-Pupp et al., 2011). One study has found better global motion perception at 5 months of age in very low birth weight babies who had an enhanced nutritional diet (higher protein, energy, fat intake, essential fatty acids and vitamin A intake) (Blakstad et al., 2015). From the current research in this area, it is unknown whether early nutritional intake of babies born preterm affects visual development in later childhood.

During 2005 and 2006, there were updates to the recommended nutrient intakes for babies with birth weight <1500g (Tsang et al., 2005). This led to changes in the nutrition provided to low birth weight babies in neonatal units. For example, in January 2007, National Women's Health Neonatal Unit (Auckland, New Zealand) initiated a reformulation of full intravenous nutrition (IVN) for babies with birth weight <1500g to increase administration of protein from 3.3 to 3.5g.kg^{-1}.day^{-1} and to reduce intravenous fluid in the first week after birth. These changes were to ensure additional non-nutritional fluids such as medication and intravenous fluids did not change nutritional intake and at the same time, potentially reduce the risk of patent duct arteriosus, necrotizing enterocolitis and mortality (Cormack et al., 2011). An audit of this change in intravenous nutrition was performed in two cohorts of 40 babies born with birth weight <1500g (before and after the change). The after group received more protein, less carbohydrate and lower fluid volume than the before group (Cormack et al., 2011). There were no differences in growth, incidence of neonatal complications, or neurodevelopment at 18 months corrected age between the two groups. However, babies who had a higher mean enteral protein intake in the first 2 weeks were more likely to have higher cognitive and motor scores at 18 months corrected age (Cormack et al., 2011). Since then, recommended protein supplementation has been increased to between 3.5 to 4.5g.kg^{-1}.day^{-1} in the first month of birth (De Curtis & Rigo, 2012). However, it is unknown whether current recommendations are optimal for growth and neurodevelopment (Cormack et al., 2016).

The aim of this study was to determine whether a reformulation of neonatal nutrition at the National Women's Health NICU affected visual outcomes and ocular growth at 7 years of age. We hypothesised that neonatal nutrition would not directly affect ocular growth and subsequent visual outcomes. In this chapter, we report the vision results from the neonatal nutrition cohort follow-up arm of the PIANO study.

5.2 Methods

In January 2007, there was a reformulation of full IVN at National Women's Health Neonatal Unit (Auckland, New Zealand) to align with changes to recommended nutritional intake for babies with birth weight <1500g (Cormack et al., 2011). The original IVN formulation 'P10' (standard IVN solution containing amino acids, minerals and electrolytes, made up in 10% dextrose solution) was given from birth if a baby was born on or before 31st December 2006. After the reformulation (from 1st January 2007), babies weighing <1000g were given starter solution for the first two days, while babies weighing >1000g or babies beyond 48 hours after birth were given 'P100' (concentrated IVN solution) (see Methods: Table 2-2, Table 2-3). This formula change included increasing administration of protein while reducing intravenous fluid in the first week after birth and reducing potassium and sodium intake in the first two days after birth (Table 2-4).

Between July 2005 and October 2008, 536 babies with birth weight <1500g or <30 week's gestational age were admitted to the National Women's Health NICU. Children meeting the inclusion criteria (full nutritional data for postnatal days 1-7 available, born at National Women's Health or transferred in at <24 hours, and remained at National Womens' Health until day 7) were invited to participate in the PIANO study at 7 years of age and were included in neonatal nutrition cohort. Children born on or before 31st December 2006 were part of the 'Before' group (before the reformulation of intravenous nutrition), while children born on or after 1st January 2007 were part of the 'After' group (2.1.4.5.3).

Full details of inclusion and exclusion criteria, recruitment details, and visual assessment can be found in 2.1.

The primary outcome was neurodevelopmental impairment at 7 years of age.

Secondary outcomes assessed were composite visual function including overall visual outcome, binocular visual outcome, and functional visual outcome. Other visual outcomes included VA, global motion perception, ocular structure and refractive error.

5.2.1 Statistical analyses

Statistical calculations were performed using SPSS Statistics 22 (IBM) and graphs were plotted in Prism 7 for Windows (GraphPad Software, Inc). Details for standard statistical analyses can be found in 2.4.

Potential confounders likely to be strongly associated with outcomes included sex, gestational age, birth weight z-score, NZ Deprivation at birth, multiple birth and CRIB score. These were compared between the Before and After groups for children who were assessed at 7 years of age. Only sex and birth weight z-score differed by more than 10% between the two groups and were considered covariates in analyses when comparing outcomes of the two groups including the exploratory analyses.

5.3 Results

Of the 536 babies with birth weight <1500g or <30 weeks' gestational age admitted to the National Women's Health NICU between July 2005 and October 2008, 221 babies met the inclusion criteria. Of these, 88 babies who developed neonatal hyperglycaemia were randomised to the HINT trial, 94 babies were non-hyperglycaemic and were matched as controls of the HINT babies for the neonatal hyperglycaemia case-control cohort of the PIANO study, and 80 babies were from Cormack's protein audit (Cormack et al., 2011) as described in the introduction of this chapter (Figure 5-1). Nineteen of these babies did not survive to 7 years of age and one baby was born in another hospital before being transferred to National Women's Health after 24 hours.

Of the surviving 201 eligible children, 89 were in the Before group and 112 in the After group of the neonatal nutrition cohort of the PIANO study. 34 children in the Before group and 39 children in the After group were not assessed at 7 years of age (Figure 5-1). This resulted in 128 children being assessed at a mean 7.2 (SD0.1) years of corrected age, of whom 55 children were in the Before group and 73 children were in the After group. Thirty six children from Cormack's protein audit (Cormack et al., 2011) were followed-up in the PIANO study.

Figure 5-1 Strobe diagram of children participating in the vision assessment of the neonatal nutrition cohort follow-up arm of the PIANO study who had a visual assessment

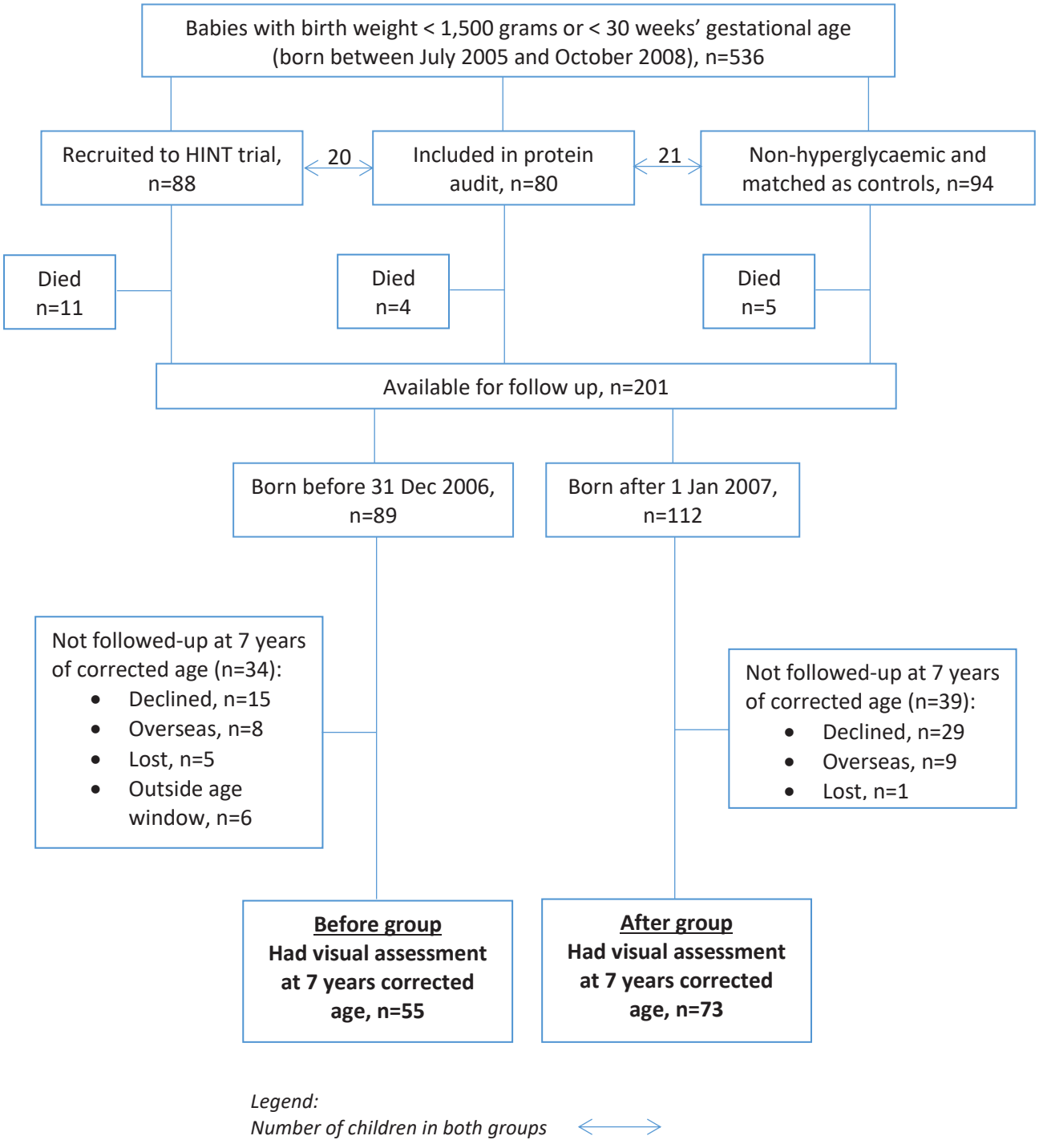


Table 5-1 Maternal characteristics of children in the neonatal nutrition cohort follow-up arm of the PIANO study

	Before group (n=89)			After group (n=112)			Before v After (assessed) P-value
	Assessed (n=55)	Not assessed (n=34)	Assessed v not assessed P-value	Assessed (n=73)	Not assessed (n=39)	Assessed v not assessed P-value	
Maternal diabetes	3 (6%)	0 (0%)	0.28	3 (4%)	4 (10%)	0.24	1.00
Maternal insulin	2 (4%)	0 (0%)	0.52	1 (1%)	3 (8%)	0.12	0.58
Multiple pregnancy	13 (24%)	8 (24%)	0.99	22 (30%)	9 (23%)	0.43	0.41
Ethnicity			0.13			< 0.01	0.28
Māori	13 (24%)	8 (24%)		19 (26%)	7 (18%)		
Pacific Island	4 (7%)	8 (24%)		12 (16%)	5 (13%)		
European	30 (55%)	12 (35%)		30 (41%)	8 (21%)		
Asian/Other	8 (15%)	6 (18%)		12 (16%)	19 (49%)		
Received antenatal steroids							
Any	52 (95%)	31 (94%)	1.00	64 (88%)	39 (100%)	0.03	0.19
Complete course	29 (53%)	19 (56%)	0.48	31 (42%)	28 (72%)	< 0.01	0.05

Data are n (%). Due to rounding, percentages may not add up to 100%.

Table 5-2 Neonatal baseline characteristics of children in the neonatal nutrition cohort follow-up arm of the PIANO study

	Before group (n=89)			After group (n=112)			Before v After (assessed) P-value
	Assessed (n=55)	Not assessed (n=34)	Assessed v not assessed P-value	Assessed (n=73)	Not assessed (n=39)	Assessed v not assessed P-value	
Gestational age (weeks)	26.0 (25.0, 29.0)	27.5 (26.0, 29.0)	0.27	26.0 (25.0, 27.0)	27.0 (26.0, 28.0)	0.11	0.52
Birth weight g	850 (715, 1040)	1093 (740, 1300)	0.14	900 (770, 1020)	930 (815, 1150)	0.13	0.80
z-score	-0.02 ± 0.93	0.17 ± 1.05	0.40	0.06 ± 0.95	0.06 ± 0.85	0.98	0.64
Small for gestational age	5 (9%)	4 (12%)	0.73	9 (12%)	3 (8%)	0.54	0.56
CRIB-II score	10 ± 3	9 ± 3	0.28	10 ± 3	9 ± 3	0.18	0.58
Apgar score							
1 minute	5 ± 3	6 ± 2	0.26	6 ± 2	5 ± 2	0.94	0.94
5 minutes	8 ± 2	8 ± 2	0.27	8 ± 2	8 ± 1	0.34	0.88
Neonatal complications							
NEC	2 (4%)	2 (6%)	0.64	3 (4%)	1 (3%)	1.00	1.00
IVH (grade III/IV)	1 (2%)	1 (3%)	1.00	6 (8%)	2 (5%)	0.71	0.24
PVL	0 (0%)	0 (0%)	-	0 (0%)	0 (0%)	-	-
ROP (grade III/IV)	5 (9%)	2 (6%)	0.70	10 (14%)	3 (8%)	0.54	0.50
ROP treatment	6 (11%)	2 (3%)	0.71	7 (10%)	3 (8%)	1.00	0.81
Early onset sepsis	0 (0%)	1 (3%)	0.38	1 (1%)	3 (8%)	0.12	0.38
Late onset sepsis	9 (16%)	6 (18%)	0.88	14 (19%)	8 (21%)	0.87	0.68
BPD	13 (24%)	10 (29%)	0.55	26 (36%)	12 (31%)	0.61	0.15
Postnatal steroids	10 (19%)	7 (21%)	0.84	17 (23%)	8 (21%)	0.74	0.55
Discharged with home O2	14 (25%)	5 (15%)	0.23	20 (27%)	8 (21%)	0.42	0.81
Major neonatal surgery	3 (5%)	2 (6%)	1.00	9 (12%)	2 (5%)	0.32	0.19
Length of neonatal stay (days)	84 ± 25	85 ± 41	0.87	93 ± 27	82 ± 30	0.06	0.06

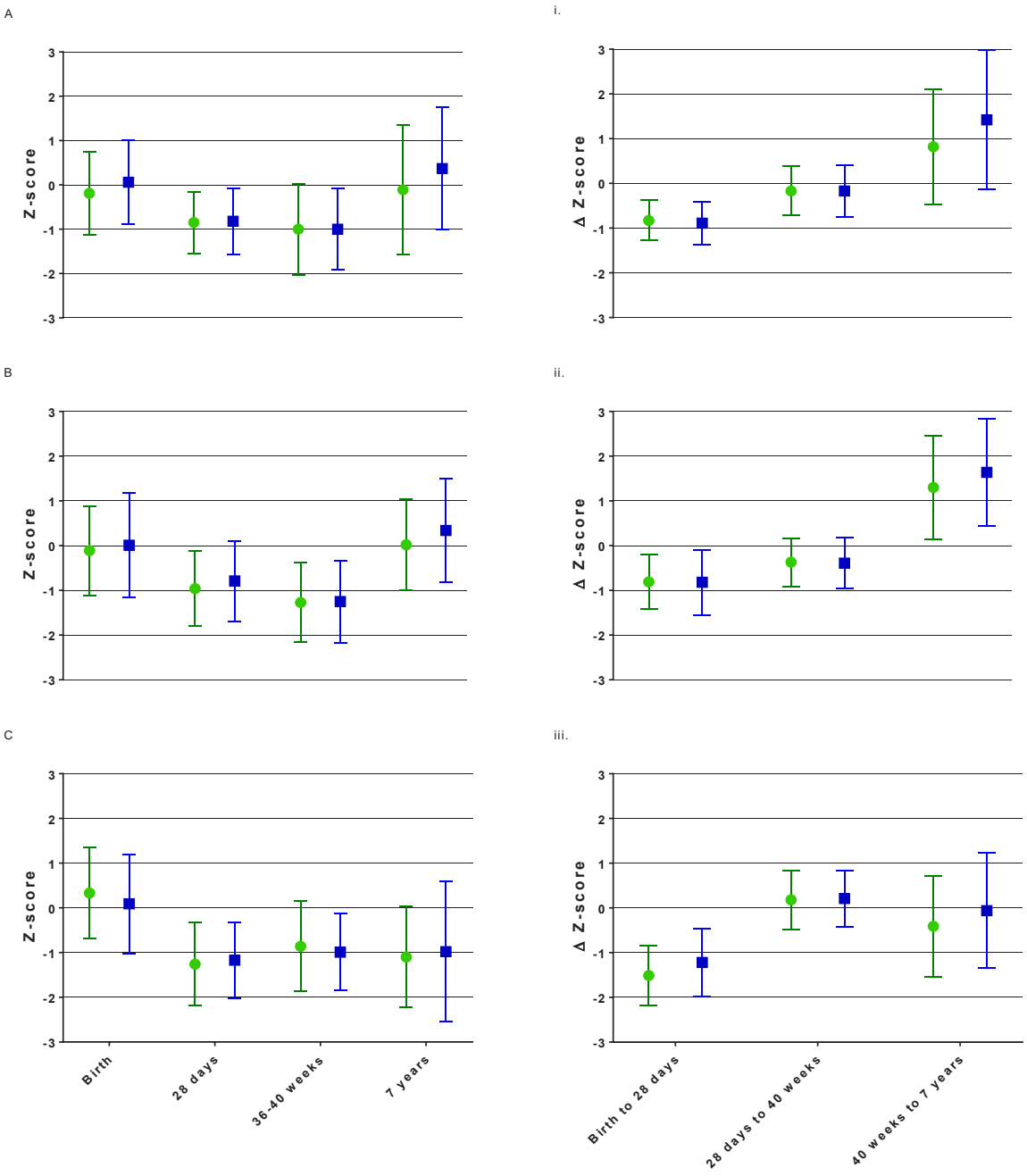
Data are n (%), mean±standard deviation, median (interquartile range). Abbreviations: NEC necrotizing enterocolitis, IVH intraventricular haemorrhage, PVL periventricular haemorrhage, ROP retinopathy of prematurity, BPD bronchopulmonary dysplasia, O2 oxygen supplementation

Table 5-3 Neonatal nutrition of children in the neonatal nutrition cohort follow-up arm of the PIANO study

	Before group (n=89)			After group (n=112)			Before v After (assessed) P-value
	Assessed (n=55)	Not assessed (n=34)	Assessed v not assessed P-value	Assessed (n=73)	Not assessed (n=39)	Assessed v not assessed P-value	
Received PN nutrition	55 (100%)	34 (100%)	-	73 (100%)	39 (100%)	-	-
Full enteral feeds established (days)	11 ± 4	11 ± 5	0.52	12 ± 4	11 ± 3	0.88	0.12
P:E ratio ($g.kcal^{-1}.kg^{-1}$)							
Day 0 to 7	2.77 ± 0.23	2.84 ± 0.22	0.18	3.68 ± 0.43	3.69 ± 0.40	0.90	0.001
Day 0 to 14	2.70 ± 0.12	2.75 ± 0.15	0.09	3.18 ± 0.35	3.19 ± 0.28	0.88	< 0.001
Proportion parenteral protein received							
Day 0 to 7	73 ± 18	72 ± 22	0.81	83 ± 15	84 ± 13	0.73	< 0.0001
Day 0 to 14	40 ± 21	44 ± 27	0.43	55 ± 22	53 ± 21	0.66	< 0.0001
Nutritional intake (mean)							
Protein ($g.kg.day^{-1}$)							
Week 1	2.34 ± 0.32	2.36 ± 0.40	0.74	2.92 ± 0.36	2.90 ± 0.42	0.78	< 0.0001
Month 1	3.32 ± 0.33	3.32 ± 0.34	0.97	3.41 ± 0.25	3.45 ± 0.31	0.53	0.06
Carbohydrate ($g.kg.day^{-1}$)							
Week 1	11.70 ± 1.42	11.70 ± 1.61	0.99	10.07 ± 1.38	10.10 ± 1.33	0.92	< 0.0001
Month 1	15.11 ± 1.47	15.29 ± 1.31	0.56	14.24 ± 1.30	14.27 ± 1.45	0.92	0.001
Fat ($g.kg.day^{-1}$)							
Week 1	3.60 ± 0.76	3.51 ± 1.04	0.68	3.48 ± 0.76	3.36 ± 0.64	0.39	0.39
Month 1	6.12 ± 0.83	6.12 ± 0.72	0.98	5.82 ± 0.91	5.95 ± 0.86	0.49	0.06
Energy ($kcal.kg.day^{-1}$)							
Week 1	84.39 ± 9.92	83.70 ± 15.47	0.82	80.08 ± 9.61	78.86 ± 8.98	0.51	0.01
Month 1	127.10 ± 13.90	127.90 ± 12.32	0.80	121.30 ± 14.08	122.90 ± 14.34	0.60	0.02

Data are n (%), mean±standard deviation. Abbreviations: P:E protein to energy ratio, $g.kg^{-1}.day^{-1}$ grams per kilogram per day, $kcal.kg^{-1}.day^{-1}$ kilocalories per kilogram per day

Figure 5-2 Growth measurements and change in growth of children in the neonatal nutrition cohort of the PIANO study from birth to seven years of age



Weight z-score (A), height z-score (B), and head circumference z-score (C) of the children in the Before (green) and After (blue) neonatal nutrition groups from birth to 7 years of age. Change in weight (i.), height (ii.), and head circumference z-score (iii.) from birth to 7 years of age. All comparisons between the Before and After groups showed p>0.05.

Children who were assessed at 7 years of age had similar maternal characteristics including maternal diabetes, multiple pregnancy and socioeconomic status (Table 5-1, Figure 5-3). In the After group, children of mothers of Asian or other ethnicity were less likely to be assessed at 7 years of age; mothers of assessed children were less likely to have received a complete course of antenatal steroids (Table 5-1). Of children who were assessed, more mothers in the Before group received a complete course of antenatal steroids than mothers in the After group. There were no statistical differences in neonatal baseline demographics and neonatal complications between children in the Before and After groups, assessed and not assessed at 7 years of age (Table 5-2).

Children in the After group had a significantly higher intake of protein in the first week after birth, lower intake of carbohydrate in the first week and month after birth, and tended to have lower fat intake in the first month after birth than children in the Before group (Table 5-3). In the first week and first month after birth, the After group had a lower energy intake than the Before group. The After group received more parental protein than the Before group and had more energy from protein.

There were no statistically significant differences in weight, height and head circumference z-score at birth, 28 days after birth and at 36-40 gestational weeks between the Before and After groups (Figure 5-2). At 36-40 gestational weeks, head circumference z-score in the After group was lower in the assessed children compared to the children not assessed at 7 years of age (-0.99 ± 0.86 v -0.44 ± 0.81, $p<0.01$). In the neonatal nutrition cohort between birth and 36-40 gestational weeks, there was a reduction in weight and height z-score before catch-up growth to 7 years of age. Head circumference measurements reduced over the first 28 days after birth and remained below the average head circumference of the general population of children of the same age at 7 years of age. Growth velocity from birth to 28 days after birth and from birth to day of assessment at 7 years of age was similar between the two groups (Table 5-4).

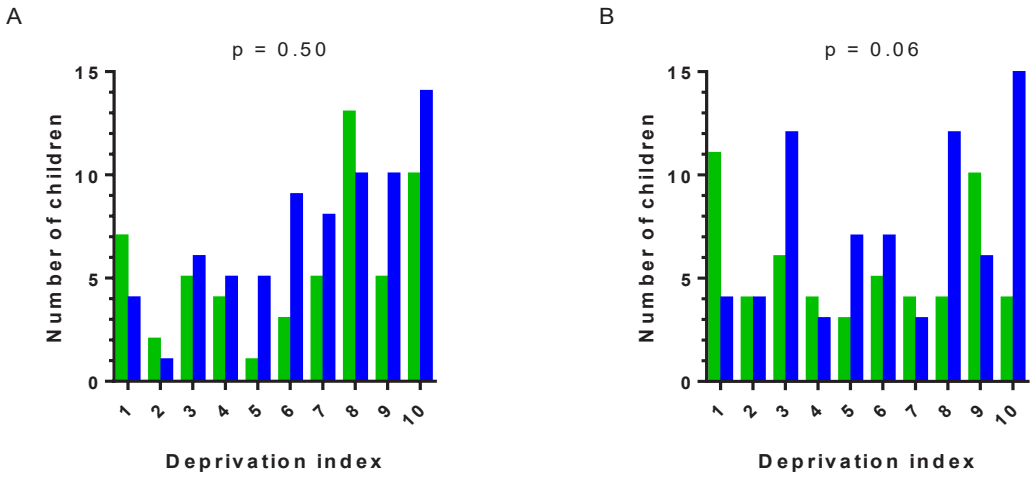
By 7 years of corrected age, weight, height and head circumference remained similar between children in the Before group and the After group (Figure 5-2). Age at assessment was similar between the groups, and there were a similar proportion of boys and girls participating in the study (Table 5-4). Children in the Before group tended to have higher socioeconomic status at 7 years of age (Figure 5-3).

Table 5-4 Characteristics of children at the time of assessment in the neonatal nutrition cohort follow-up arm of the PIANO study at seven years of age

	Before group (n=55)	After group (n=73)	P-value
Corrected age at assessment (years)	7.2 ± 0.1	7.2 ± 0.1	0.81
Male	26 (47%)	42 (58%)	0.25
Year level at school median (range)	3 (1, 3)	3 (2, 4)	0.71
Anthropometry			
Weight (kg)	23.2 (19.4, 25.4)	24.6 (22.1, 27.4)	0.18
Height (cm)	122.2 (118.1, 127.2)	124.4 (119.9, 129.0)	0.13
Head circumference (cm)	51.4 (50.5, 53.0)	51.6 (50.4, 53.0)	0.59

Data are n (%), mean±standard deviation, median (interquartile range). Abbreviations: kg kilogram, cm centimetres.

Figure 5-3 Socioeconomic status at birth and at time of assessment children assessed in the neonatal nutrition cohort follow-up arm of the PIANO study



Note: a lower number on the x-axis denotes less deprivation or higher socioeconomic status; socioeconomic status shown for (A) at birth, (B) at time of assessment; Before group (green), After group (blue).

Table 5-5 Primary outcome of children assessed in the neonatal nutrition cohort of the PIANO study at seven years of age

	Before Group (n=55)	After Group (n=73)	Unadjusted OR (95%CI)	P-value	*Adjusted OR (95%CI)	P-value
Neurodevelopmental impairment	**25 (45%)**	**30 (41%)**	**0.84 (0.39, 1.79)**	**0.65**	**0.78 (0.35, 1.70)**	**0.55**
WISC FSIQ <85	22 (40%)	20 (27%)	0.57 (0.25, 1.26)	0.16	0.52 (0.23, 1.17)	0.12
MABC-2 total score ≤5th centile	13 (24%)	22 (30%)	1.39 (0.60, 3.22)	0.44	1.36 (0.58, 3.19)	0.48
Cerebral palsy	1 (2%)	9 (12%)	7.59 (0.93, 62.09)	0.06	7.36 (0.88, 61.40)	0.07
Deaf	1 (2%)	1 (1%)	-		-	
Blind	0 (0%)	0 (0%)	-		-	

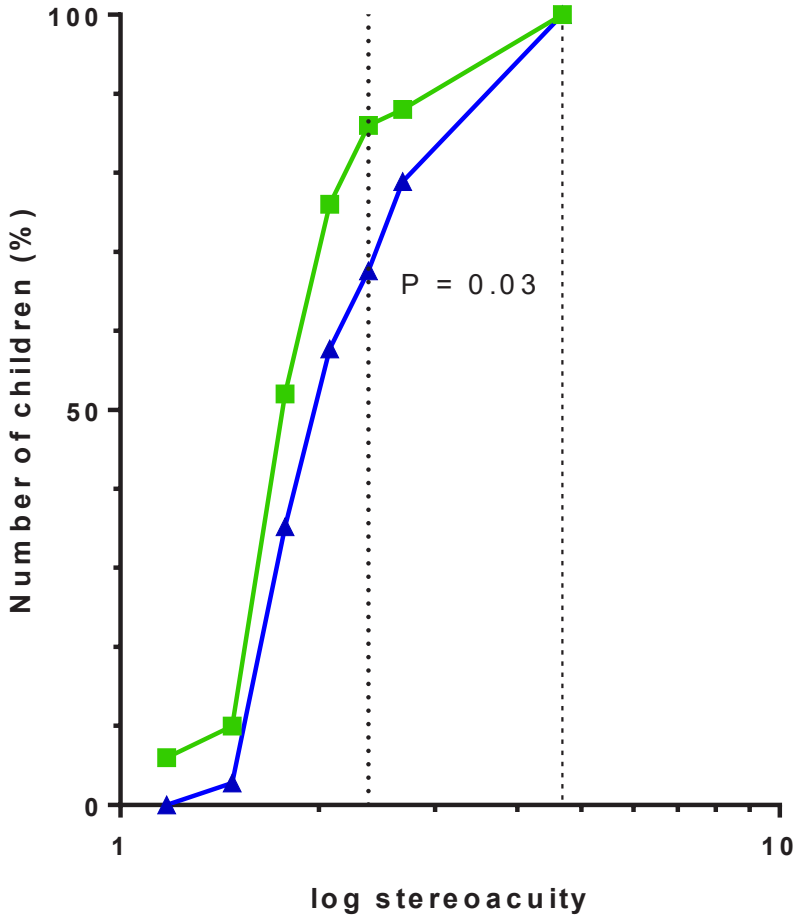
**Adjusted for sex (male/female) and birth weight z-score. Abbreviations: WISC FSIQ Wechsler Intelligence Scale for Children Full Scale Intelligence Quotient, MABC-2 Movement Assessment Battery for Children Second Edition.*

The incidence of neurodevelopmental impairment was similar between the two groups (Table 5-5). Children in the After group tended to have a higher incidence of cerebral palsy.

Overall visual outcome (good VA without strabismus, good depth perception, without the need for wearing spectacles) was similar between the Before and After groups (Table 5-6). Thirty three percent of children in the Before group (18/55) and twelve percent children in the After group (9/73) were unable to complete all the components of the composite visual outcome; the refractive error testing component was particularly affected. A functional visual outcome was analysed for all the children to exclude the refractive error component (good VA without strabismus, and good depth perception) and children in the After group were more likely to have an unfavourable functional visual outcome than children in the Before group (Table 5-6). Unfavourable binocular visual outcome was also more common in children in the After group than the Before group.

Children in the After group had poorer stereoacuity than children in the Before group (Table 5-6, Figure 5-4). There were no differences between the groups in other binocular tests including presence of nystagmus, ocular motility, convergence or motor fusion. Global motion perception was poorer in the Before group.

Figure 5-4 Cumulative stereoacuity distribution for children in the neonatal nutrition cohort follow-up arm of the PIANO study at seven years of age



Cumulative log stereoacuity distribution in the Before (green) and After (blue) groups. The dotted line at x = 2.38 denotes the passing mark of the test; the dashed line at x = 4.68 denotes no measurable stereoacuity. P-value adjusted for sex and birth weight z-score.

Table 5-6 Visual functional outcomes of children assessed in the neonatal nutrition cohort follow-up arm of the PIANO study at seven years of age

	Before group (n=55)	After group (n=73)	Unadjusted OR or mean difference (95%CI)	P-value	*Adjusted OR or mean difference (95%CI)	P-value
Favourable overall visual outcome	24/42 (57%)	39/69 (57%)	0.85 (0.36, 1.96)	0.95	0.99 (0.45, 2.17)	0.98
Favourable binocular visual outcome	27/52 (52%)	24/72 (33%)	0.46 (0.22, 0.96)	0.04	0.47 (0.22, 1.01)	0.05
Favourable functional visual outcome	41/50 (82%)	47/72 (65%)	0.41 (0.17, 0.98)	0.04	0.40 (0.16, 0.96)	0.04
Distance VA in better eye						
Equal or better than 6/12	54/55 (98%)	69/71 (97%)	-		-	
Better than 6/7.5	49/55 (90%)	57/71 (80%)	0.50 (0.18, 1.40)	0.18	0.53 (0.19, 1.49)	0.23
LogMar	-0.04 ± 0.12	0.00 ± 0.15	0.03 (-0.02, 0.08)	0.20	0.03 (-0.02, 0.07)	0.27
Distance VA in poorer eye (logMAR)	0.06 ± 0.19	0.09 ± 0.27	-0.03 (-0.11, 0.05)	0.47	0.06 (-0.06, 0.11)	0.66
Difference in VA between eyes (logMAR)	0.10 ± 0.15	0.10 ± 0.18	0.00 (-0.06, 0.06)	0.99	0.00 (-0.06, 0.06)	0.64
Presenting binocular distance VA (logMAR)	-0.05±0.12	-0.04±0.16	0.02 (-0.03, 0.06)	0.54	0.01 (-0.04, 0.06)	0.62
Other visual outcomes						
Presence of strabismus	6/55 (11%)	9/73 (12%)	1.15 (0.38, 3.45)	0.81	1.23 (0.39, 3.94)	0.72
Pass stereoacuity (TNO)	43/50 (86%)	48/71 (68%)	0.34 (0.13, 0.87)	0.02	0.34 (0.13, 0.84)	0.02
Not requiring spectacles	33/41 (80%)	55/66 (83%)	1.21 (0.46, 3.22)	0.70	1.23 (0.46, 3.28)	0.68
Presence of nystagmus	0/55 (0%)	2/72 (3%)	-		-	
Normal ocular motility	47/54 (87%)	68/72 (94%)	2.53 (0.70, 9.16)	0.16	2.62 (0.68, 10.18)	0.16
Normal convergence	44/50 (88%)	54/67 (81%)	0.57 (0.18, 1.82)	0.34	0.57 (0.18, 1.87)	0.36
Presence of motor fusion	34/50 (68%)	42/72 (58%)	0.66 (0.29, 1.51)	0.32	0.65 (0.28, 1.50)	0.31
Mean global motion perception threshold	54.16±23.50	45.06±22.34	-9.10 (-17.47, -0.73)	0.03	-8.95 (-17.52, -0.37)	0.04

**Adjusted for sex (male/female) and birth weight z-score. Data are n (%), mean±standard deviation. Abbreviations: VA visual acuity.*

Table 5-7 Ocular structural and refractive outcomes of children assessed in the neonatal nutrition cohort follow-up arm of the PIANO study at seven years of age

	Before group (n=55)	After group (n=73)	Unadjusted OR or mean difference (95%CI)	P-value	*Adjusted OR or mean difference (95%CI)	P-value
Ocular Structure						
Retinal posterior pole (central) findings			0.41		0.30	
No abnormalities or non-clinically significant findings	42/55 (76%)	62/73 (85%)				
Clinically significant findings	4/55 (4%)	5/73 (7%)				
Unable to assess	9/55 (16%)	6/73 (8%)				
Refractive error						
SEP of the better VA eye			0.83		0.69	
Myopia	2/41 (5%)	6/66 (9%)				
Hyperopia	23/41 (56%)	36/66 (55%)				
Significant Hyperopia (> +2.00 D)	2/41 (5%)	3/66 (5%)				
SEP of the poorer VA eye			0.78		0.64	
Myopia	3/41 (7%)	6/66 (9%)				
Hyperopia	27/41 (66%)	39/66 (59%)				
Significant Hyperopia (> +2.00 D)	2/41 (5%)	3/66 (5%)				
Astigmatism						
Better eye	4/41 (10%)	10/66 (15%)	1.65 (0.48, 5.66)	0.42	1.67 (0.48, 5.70)	0.42
Poorer eye	7/41 (17%)	11/66 (17%)	0.97 (0.34, 2.75)	0.96	0.98 (0.35, 2.77)	0.97
Anisometropia	0 (0%)	2 (1%)	-		-	

**Adjusted for sex (male/female) and birth weight z-score. Data are n (%), mean±standard deviation. Abbreviations: SEP spherical equivalent power, VA visual acuity, D dioptres.*

Table 5-8 Ocular biometry for children assessed in the neonatal nutrition cohort follow-up arm of the PIANO study at seven years of age

	Before group (n=47)	After group (n=58)	Unadjusted mean difference (95%CI)	P-value	*Adjusted mean difference (95%CI)	P-value
Central corneal thickness (µm)						
Better VA Eye	536 ± 34	545 ± 32	-9 (-22, 4)	0.16	-9 (-22, 4)	0.17
Poorer VA Eye	542 ± 42	542 ± 33	0 (-14, 14)	1.00	-1 (-13, 15)	0.92
Anterior chamber depth (mm)						
Better VA Eye	3.39 ± 0.30	3.40 ± 0.26	-0.01 (-0.12, 0.09)	0.81	0.00 (-0.11, 0.11)	0.98
Poorer VA Eye	3.38 ± 0.32	3.39 ± 0.26	-0.01 (-0.12, 0.10)	0.83	0.01 (-0.11, 0.12)	0.94
Axial length (mm)						
Better VA Eye	22.27 ± 0.97	22.37 ± 0.78	-0.10 (-0.44, 0.24)	0.56	0.03 (-0.28, 0.38)	0.76
Poorer VA Eye	22.29 ± 0.99	22.42 ± 0.82	-0.13 (-0.47, 0.21)	0.45	0.04 (-0.26, 0.41)	0.65
Lens thickness (mm)						
Better VA Eye	3.74 ± 0.23	3.75 ± 0.28	-0.01 (-0.11, 0.09)	0.82	-0.01 (-0.11, 0.10)	0.84
Poorer VA Eye	3.72 ± 0.24	3.77 ± 0.27	-0.05 (-0.15, 0.05)	0.83	-0.05 (-0.15, 0.05)	0.34
Corneal curvature (mm)						
Flat Meridian Better VA Eye	7.73 ± 0.29	7.68 ± 0.25	0.05 (-0.05, 0.15)	0.34	-0.13 (-0.17, 0.33)	0.18
Flat Meridian Poorer VA Eye	7.74 ± 0.29	7.69 ± 0.25	0.06 (-0.04, 0.16)	0.26	-0.14 (-0.18, 0.03)	0.14
Steep Meridian Better VA Eye	7.59 ± 0.30	7.52 ± 0.26	0.07 (-0.04, 0.17)	0.23	-0.15 (-0.19, 0.02)	0.10
Steep Meridian Poorer VA Eye	7.57 ± 0.29	7.51 ± 0.25	0.06 (-0.04, 0.16)	0.26	-0.14 (-0.18, 0.02)	0.13
Central retinal thickness (µm)^						
Better VA Eye	270 ± 22	276 ± 25	-5 (-15, 5)	0.29	1 (-6, 13)	0.43
Poorer VA Eye	270 ± 21	276 ± 24	-6 (-16, 3)	0.20	1 (-5, 14)	0.32

**Adjusted for sex (male/female) and birth weight z-score. ^Missing data for central retinal thickness: Before group - 19 for better eye and 18 poorer VA eye; After group – 12 better and poorer eye. Data are n (%), mean±standard deviation. Abbreviations: VA visual acuity.*

The proportion of children having ocular abnormalities requiring further follow-up or referral was similar in the Before and After groups (Table 5-7). The majority of children had normal retinal findings or had signs of normal variations in ocular structure that were not clinically significant. Clinically significant findings requiring extra follow-up included macula ectopia or macula scarring due to severe ROP (5 children), blood vessel straightening (2 children) and dot haemorrhages in the retina (2 children).

Refractive error distribution was similar between the Before and After groups, between both eyes, and there were no differences in incidence of astigmatism or anisometropia (Table 5-7). There were no differences in ocular biometry or retinal thickness between the two groups (Table 5-8).

Exploratory analyses of the association between exposures and visual outcomes different between the Before and After groups were performed (Table 9-6 for binocular visual outcome, Table 9-7 for functional visual outcome, Table 9-8 for stereoacuity (TNO), and Table 9-9 for global motion coherence). Confounders of Before and After groups for one or more of the visual outcomes were protein: energy ratio in week 1 after birth and days of neonatal stay.

For binocular visual outcome, the exposures that had statistical significance <0.15 and did not have collinearity with other exposures ("X" column of Table 9-6) were entered into a separate logistic regression model; these included proportion of parenteral protein in week 1 after birth, mean protein intake in week 1 after birth, cerebral palsy and gestational age, with covariates (sex, birth weight z-score). The model was not significant in predicting binocular visual outcome (Nagelkerke R^2=0.13, χ^2=12.07, p=0.06).

For functional visual outcome, the exposures that had statistical significance <0.15 and did not have collinearity with other exposures ("X" column of Table 9-7) were entered into a separate logistic regression model; these included proportion of parenteral protein in week 1 after birth, mean protein intake in week 1 after birth, cerebral palsy and gestational age, with covariates (sex, birth weight z-score). The model was significant in predicting binocular visual outcome (Nagelkerke R^2=0.30, χ^2=28.87, p=0.0001) and exposures that added significance to the model were cerebral palsy, gestational age, and birth weight z-score (Table 5-9). Lower gestational age and birth weight z-score, and presence of cerebral palsy were associated with increased odds of unfavourable functional visual outcome.

Table 5-9 Exposures in a logistic regression model predicting likelihood of unfavourable functional visual outcome based on proportion of parenteral protein week 1, mean protein intake week 1, likely to have cerebral palsy, gestational age, sex, and birth weight z-score

Variable	B	SE	Wald	df	P-value	Odds ratio	95%CI for odds ratio	
							Lower	Upper
Proportional parenteral protein week1 (%)	-0.01	0.02	0.76	1	0.38	0.99	0.96	1.02
Mean protein week1 ($g.kg.day^{-1}$)	0.94	0.61	2.35	1	0.13	2.55	0.77	8.41
Cerebral palsy	3.12	1.15	7.33	1	0.007	22.74	2.37	218.15
Gestational age (weeks)	-0.53	0.17	9.58	1	0.002	0.59	0.42	0.82
Sex (male)	-0.09	0.46	0.04	1	0.84	0.91	0.37	2.26
Birth weight z-score	-0.99	0.35	8.05	1	0.005	0.37	0.19	0.74
Constant	11.38	4.54	6.28	1	0.01	87242.82		

Abbreviations: B = unstandardized regression coefficient; SE_B = standard error of the coefficient; β = standardized coefficient; BPD bronchopulmonary dysplasia, $g.kg.day^{-1}$ grams per kilogram per day.

Table 5-10 Exposures in a logistic regression model predicting likelihood of failing stereoacuity (TNO) based on mean protein intake week 1, likely to have cerebral palsy, gestational age, sex, and birth weight z-score

Variable	B	SE	Wald	df	P-value	Odds ratio	95%CI for odds ratio	
							Lower	Upper
Mean protein week1 ($g.kg.day^{-1}$)	0.93	0.55	2.83	1	0.09	2.53	0.86	7.45
Cerebral palsy	2.18	0.90	5.82	1	0.02	8.83	1.50	51.86
Gestational age (weeks)	-0.44	0.17	7.05	1	0.008	0.64	0.46	0.89
Sex (male)	0.09	0.47	0.03	1	0.85	1.09	0.44	2.73
Birth weight z-score	-0.66	0.33	3.85	1	0.05	0.52	0.27	1.00
Constant	7.76	4.25	3.33	1	0.07	2349.34		

Abbreviations: B = unstandardized regression coefficient; SE_B = standard error of the coefficient; β = standardized coefficient; BPD bronchopulmonary dysplasia, $g.kg.day^{-1}$ grams per kilogram per day.

For stereoacuity, the exposures that had statistical significance <0.15 and did not have collinearity with other exposures ("X" column of Table 9-8) were entered into a separate logistic regression model; these included mean protein intake in week 1 after birth, cerebral palsy and gestational age, with covariates (sex, birth weight z-score). The model was significant in predicting stereoacuity (Nagelkerke R^2=0.23, χ^2=20.70, p=0.001) and the exposures that added significance to the model were cerebral palsy and gestational age (Table 5-10). Children with cerebral palsy had 8.83 times higher odds to fail TNO than children without cerebral palsy. Lower gestational age was associated with increased likelihood of having a poorer stereoacuity.

For global motion coherence threshold, none of the exposure were statistically significant <0.15 in predicting motion perception (Table 9-9).

When cases of cerebral palsy were excluded in a sensitivity analysis, the difference between the Before and After groups in passing stereoacuity (TNO) was no longer statistically significant (Table 5-11). Children in the Before group tended to have lower incidence of unfavourable binocular visual outcome but tended to have poorer performance in global motion perception. Functional visual outcome was similar between children in the Before and After groups.

As cerebral palsy is a condition that affects movement and posture, Movement ABC scores were analysed to assess whether there were any associations with the reduced binocular visual outcome and stereoacuity in the After group.

A binomial logistic regression was performed to ascertain the effects of failing the Movement ABC test, gestational age, sex and birth weight z-scores on the likelihood of unfavourable binocular visual outcome. The model was statistically significant, (Nagelkerke R^2=0.20, χ^2=17.70, p=0.001), and Movement ABC and birth weight z-score added significance (Table 5-12). Children who failed the Movement ABC test had 2.81 times odds of having an unfavourable binocular visual outcome. Increasing birth weight z-score was associated with increased odds of favourable binocular visual outcome.

Table 5-11 Composite visual outcomes, stereopsis and global motion perception in the neonatal nutrition cohort of the PIANO study when excluding cerebral palsy

	Before group (n=55)	After group (n=73)	Unadjusted OR or mean difference (95%CI)	P-value	*Adjusted OR or mean difference (95%CI)	P-value
Favourable overall visual outcome	24/41 (59%)	39/61 (64%)	0.80 (0.35, 1.79)	0.58	0.76 (0.33, 1.73)	0.63
Favourable binocular visual outcome	27/51 (53%)	23/63 (37%)	0.51 (0.24, 1.09)	0.08	0.52 (0.24, 1.11)	0.09
Favourable functional visual outcome	41/50 (82%)	46/64 (72%)	0.56 (0.23, 1.39)	0.21	0.54 (0.22, 1.40)	0.19
Pass stereoacuity (TNO)	43/50 (86%)	46/63 (73%)	0.44 (0.17, 1.167)	0.10	0.43 (0.16, 1.16)	0.10
Mean global motion perception threshold	53.26 ± 22.82	44.92 ± 22.22	-8.34 (-16.76, 0.08)	0.05	-8.07 (-16.61, 0.46)	0.06

**Adjusted for sex (male/female) and birth weight z-score. Data are n(%), mean±standard deviation.*

Table 5-12 Logistic regression model predicting likelihood of unfavourable binocular visual outcome based on failing Movement ABC, gestational age, sex, and birth weight z-score

Variable	B	SE	Wald	df	P-value	Odds ratio	95%CI for odds ratio	
							Lower	Upper
Movement ABC (fail)	1.03	0.48	4.58	1	0.03	2.81	1.09	7.23
Gestational age (weeks)	-0.06	0.14	0.18	1	0.97	1.02	0.46	0.89
Sex (male)	0.02	0.46	0.002	1	0.67	0.94	0.72	1.23
Birth weight z-score	-0.003	0.001	5.03	1	0.03	0.997	0.99	1.00
Constant	3.01	3.20	0.94	1	0.33	22.18		

Abbreviations: B = unstandardized regression coefficient; SE_B = standard error of the coefficient; β = standardized coefficient

Movement ABC test was not associated with stereoacuity (Nagelkerke R^2=0.05, χ^2=4.14, p=0.25) after adjustment for sex and birth weight z-score.

Exposures associated with cerebral palsy were investigated as children in the After group tended to have higher incidence of cerebral palsy. The exposures that had statistical significance <0.15 and did not have collinearity with other exposures ("X" column of Table 9-10) were entered into a separate multiple regression model; these included protein in week1 and fat in month1, with covariates (sex, birth weight z-score). The model was significant in predicting cerebral palsy (Nagelkerke R^2=0.20, χ^2=11.37, p=0.02) and protein intake in the first week after birth added significance to the model (Table 5-13). Increase in protein intake in the first week after birth was associated with increasing likelihood of having cerebral palsy.

Table 5-13 Exposures in a logistic regression model predicting likelihood of cerebral palsy based on mean protein intake week 1, mean fat intake month 1, sex, and birth weight z-score

Variable	B	SE	Wald	df	P-value	Odds ratio	95%CI for odds ratio	
							Lower	Upper
Mean protein week1 ($g.kg.day^{-1}$)	2.46	0.96	6.56	1	0.01	11.73	1.78	77.23
Mean fat month1 ($g.kg.day^{-1}$)	-0.58	0.34	2.86	1	0.09	0.56	0.29	1.10
Sex (male)	0.01	0.72	0.00	1	0.99	1.01	0.25	4.17
Birth weight z-score	0.27	0.41	0.45	1	0.50	1.31	0.59	2.92
Constant	-6.14	3.21	3.66	1	0.06	0.002		

Abbreviations: B = unstandardized regression coefficient; SE_B = standard error of the coefficient; β = standardized coefficient; BPD bronchopulmonary dysplasia, $g.kg.day^{-1}$ grams per kilogram per day.

5.4 Discussion

Nutrition in babies born preterm has been shown to be crucial to survival, growth and neurodevelopment, and recent developments have seen updates to recommended neonatal nutritional intake (Bhatia et al., 2013; Tsang et al., 2005). We investigated the effects of a reformulation of intravenous nutrition on visual outcomes in later childhood in children born very preterm. Following the reformulation, babies had higher protein intake in the first week after birth, lower carbohydrate intake in the first week and first month after birth but a decrease in energy intake in the first week and first month after birth. We found that the incidence of neurodevelopmental impairment was similar between the groups Before and After the reformulation. However, children in the After group tended to have a higher risk of cerebral palsy. Children who were administered the reformulated intravenous nutrition were also more likely to have an unfavourable functional and binocular visual outcome, and poorer depth perception but better global motion perception. These changes to visual function and a possible increase in cerebral palsy are of a concern, especially as current guidelines recommend an even higher protein intake than that given in the reformulated intravenous nutrition (Cester et al., 2015).

The current literature on neonatal nutrition in babies born preterm has focussed on neurodevelopment and growth, particularly in early childhood. However, there is a paucity of data relating to neonatal nutrition and visual outcomes in later childhood. Studies evaluating visual development in two year old children did not show differences in visual impairment following increases to neonatal protein intake but one study found better motion perception in children who had higher neonatal protein intake (Blakstad et al., 2015; Cester et al., 2015; Cormack et al., 2011). As a result, we hypothesised that neonatal nutrition would not have any direct effect on ocular structure and visual outcomes, particularly as children born preterm are exposed to many neonatal complications such as ROP, IVH and PVL, which can affect visual development (Jacobson et al., 1998). These neonatal complications are unlikely to be influenced by nutritional intake. In our study, overall visual outcomes were not different between the groups Before and After the reformulation of nutrition. There were also no differences in ocular structure or the incidence of refractive error between the two groups. In babies born preterm and at full term, some data suggest that supplementing formula or breast milk with long-chain polyunsaturated fatty acid supplementation such as docosahexaenoic acid may improve maturation of the visual cortex and visual development (Birch et al., 2002; Hoffman et al., 2003; Singhal et al., 2007). However, a recent Cochrane review of fatty acid supplementation in formula milk for babies born preterm did not find evidence of benefit or harm to VA (measured by Teller or Lea acuity cards or visual evoked potential) or

neurodevelopment at 12 months of age (Moon et al., 2016). As studies have used various regimes for supplementation (dosage and duration), and measurements of VA varied between groups, meta-analysis could not be performed (Moon et al., 2016). We found poorer binocular and functional visual outcome in the After group. This was likely to be driven by higher incidence of poor stereoacuity in the After group in both the binocular and functional visual outcome as other components of the composite outcomes were not significantly different between the groups.

Perception of stereoacuity is a result of a complex amalgamation of various processes. The development of stereoacuity depends on equal VA in both eyes, oculomotor control and sensory fusion of the two eyes, and cortical development of binocularity (Birch, 1985; Braddick & Atkinson, 1983; Nishida et al., 2001). Therefore, any problems along the visual pathway can affect the quality of stereoacuity. In our cohort, the reduction in stereoacuity in the After group was not associated with VA, refractive error or ocular structural differences. Therefore, the difference in stereoacuity was likely to be as a result of head and eye alignment dysfunction or altered cortical processing. Exploratory regression analyses revealed that cerebral palsy, gestational age and birth weight z-score were predictive of stereoacuity. Children with cerebral palsy have been reported to have a high frequency of strabismus (20-90%), absent binocular vision (no sensory or motor fusion) and strabismic amblyopia (Ghasia et al., 2008). The higher incidence of poor stereopsis in cerebral palsy may be associated with ocular muscle dysfunction similar to that of disorders in overall movement and posture in cerebral palsy (Ghasia et al., 2008). In agreement with this previous work, half the children with cerebral palsy in our study had strabismus.

While children in the After group of our study had poorer stereoacuity, they also had better global motion perception than children in the Before group. Processing of global motion involves early localised motion processing in the primary visual cortex and visual area 2 (Smith et al., 1998), before subsequent integration of localised motion into a global motion perception in extrastriate dorsal stream areas such as V3A (occipital lobe near the parieto-occipital sulcus) (Tootell et al., 1997) and V5 (posterior parietal cortex) (Watson et al., 1993). Global motion perception in early childhood has been proposed to reflect brain and neurodevelopment, and it is relatively independent from other visual functions such as VA and contrast sensitivity (Chakraborty et al., 2015). Impairments in global motion perception have been found in children born preterm when compared to children born at full term, while form perception performance has been similar between children born preterm and children born at full term (MacKay et al., 2005; Taylor et al., 2009). This has led to the hypothesis of the dorsal stream vulnerability in babies born preterm, which has also been seen in various developmental

disorders (Atkinson & Braddick, 2007; Braddick et al., 2003). In our study, the motion coherence thresholds were higher (poorer performance) than those reported by other studies with similar populations of preterm children and children with hemiplegic cerebral palsy (Gunn et al., 2002; MacKay et al., 2005), which had their own comparison groups of children born at full term. In chapter 7, we will compare global motion perception between children born preterm and children born at full term. Although there was a 9% coherence difference in motion perception performance between the Before and After groups, none of the exposures that were different between the groups were statistically significant in predicting motion perception. Therefore, it is unknown how global motion perception is influenced by nutritional intake.

Both stereoacuity and motion perception involve dorsal stream processing. However, in our study, the reformulation of intravenous nutrition affected these functions in a disparate way, where there was better stereoacuity in the Before group while the After group were more sensitive to motion perception. One possible explanation for this effect could be that there was an impairment in fine oculomotor control required for stereoscopic depth perception, while cortical processing within the dorsal stream was enhanced in the After group compared to the Before group. This hypothesis is partially supported by the higher rates of cerebral palsy and possible oculomotor control deficits in the After group. Although there were no statistically significant differences between the groups in the oculomotor tests such as convergence, ocular motility and motor fusion; children who failed in the Movement ABC test were more likely to have reduced binocular vision but not stereoacuity, which suggests that these children may have subtle oculomotor control deficits. After excluding children with cerebral palsy, there was no longer a difference in functional visual outcome and stereoacuity between the groups, while binocular visual outcome continued to be significantly poorer in the After group, suggesting that even children without cerebral palsy may experience oculomotor control deficits. In terms of dorsal stream function, one study investigated visual perception in babies born at a very low birth weight and found that babies with higher protein and fat intake had stronger visual event-related potential responses to global motion perception (Blakstad et al., 2015). This suggests that the After group may have experienced superior dorsal stream development in comparison to the Before group, resulting in lower motion coherence thresholds. This explanation is speculative and the number of children with cerebral palsy was small. However, the results raise the intriguing possibility that stereopsis and global motion perception can be influenced differentially by neonatal treatments.

The majority of children in our cohort had a favourable functional visual outcome and had similar ocular findings to other contemporary population studies of preterm birth. An estimate in severe

impairment or blindness from ROP globally in 2010 was 1% in high income countries (Blencowe et al., 2013). In 1986, a study of ROP in New Zealand found the incidence of blindness resulting from ROP in babies with birth weight <1499g to be 2% (Darlow, 1988) and since then, there has been the introduction of telemedicine screening for ROP (Dai et al., 2011), laser photocoagulation of severe ROP at a prethreshold stage (Early Treatment for Retinopathy of Prematurity Cooperative Group, 2003), and more stringent protocol for oxygen supplementation (Darlow et al., 2014). None of the children in our study were legally blind, which could have reflected better neonatal management of ROP or a result of a selection/participation bias (a large part of the PIANO study assessment required being able to see to complete) and the small sample size. However, selection bias was unlikely as there were no differences in the incidence of severe ROP or treatment for ROP, severe IVH or PVL between children assessed and not assessed at 7 years of age. The incidence of strabismus and refractive error in our cohort were similar to other studies of preterm birth (Cooke et al., 2004; Haugen et al., 2012). Compared to children born at term, children in our study had similar VA but a higher incidence of strabismus and myopia. However, since there was no difference in ocular biometry and refractive error between the Before and After groups, it is possible the higher incidence of strabismus and myopia may be associated with preterm birth rather than neonatal nutrition. This will be discussed in more depth in chapter 7. Therefore, these data would suggest that neonatal nutrition does not affect ocular structural growth and refractive error development but may influence binocular visual function and cortical processing.

A limitation we encountered was that the two groups in our study were non-contemporaneous as we assessed a change in neonatal nutritional intake, where the old protocol was discontinued with the introduction of the new protocol. As well as the reformulation of neonatal nutrition, there were other changes to neonatal care around the same time period such as earlier treatment of ROP at a prethreshold level, use of telemedicine in ROP screening and comparison between two oxygen supplementation regimes (targeting oxygen saturation of 85 to 89% v 91 to 95%) (The BOOST II United Kingdom Australia and New Zealand Collaborative Groups, 2013), which could also affect visual development. However, with all these modifications, visual outcomes were expected to improve, and these were unlikely to affect our study as incidence of ROP and blindness were similar between the two groups. To reduce effects of confounding due to the different time period of birth, we tested the children when they became 7 years of corrected age (within a 6-month window) and used the same tests throughout the study. Upon analysing neonatal data from the two groups, maternal characteristics, the baby's baseline demographics and neonatal complications were similar between the groups. It would be impossible to match both groups exactly, but it would have been beneficial to

have tested the children at an earlier age as well as at 7 years of age (we have information from a before school vision screening but this did not include binocular vision (discussed more in chapter 7)) to have a better understanding of visual development and the determinants of factors that can affect vision in these children.

One difficulty with investigating neonatal nutritional intake is the struggle to reach recommended intakes, which can be due to the amount of fluid given (such as medication and arterial line fluids), bioavailability of the nutrients, metabolism (particularly when the baby is ill), and loss of nutrients in feeding tubes (Cormack et al., 2011; Cormack et al., 2016; Ramel et al., 2014). This may have affected the nutritional intake in our study as the ideal protein administration change was from 3.3 to 3.5g.kg^{-1}.day^{-1} but the babies in the Before group only received an average 2.34g.kg^{-1}.day^{-1} of protein and the After group received 2.92g.kg^{-1}.day^{-1} in the first week after birth. However, one strength of our study was that we were able to collect details of the separate components of the nutritional intake of the babies in the first month after birth, which enabled us to investigate each component for association with visual outcomes. One area that could be further investigated is whether visual outcomes are affected by nutritional intake via parenteral or enteral feeding, as studies have suggested a possible differential effect on outcomes such as NEC and growth, and the babies in the After group had higher parenteral nutrition (Hay, 2008). However, there is collinearity between protein intake, energy from protein and parenteral nutrition, which can confound the effect of the nutrients on visual outcomes. There also needs to be more consistency in calculating and reporting of parenteral and enteral nutritional intakes before comparison with other studies can be made (Cormack et al., 2016).

In conclusion, we have shown that a change in neonatal nutritional intake in babies born preterm did not alter the incidence of neurodevelopmental impairment at 7 years of age but may increase the risk of cerebral palsy. The change in neonatal nutritional intake did not affect overall visual outcome and was unlikely to affect ocular structure and refractive error development in children born preterm. However, we found that after the reformulation, there were reduced binocular and functional visual outcomes, which were associated with cerebral palsy, gestational age and birth weight. The current recommendations for neonatal protein intake is higher than the intake investigated in this study (Agostoni et al., 2010). As our study highlights a possible association between increased protein intake and increased risk of cerebral palsy and poorer long-term visual outcomes, further randomised controlled trials or larger cohort studies are needed to investigate these associations before there is widespread implementation of higher neonatal protein intake. Currently, there is a multicentre, two-arm, double blind, randomised controlled trial in babies born extremely preterm (n=430) assessing

whether providing an extra 1 to 2g.kg^{-1}.d^{-1} protein in the first 5 days after birth will improve neurodevelopmental outcomes and growth at 2 years of age (Bloomfield et al., 2015). Long-term follow-up of this cohort, including visual outcomes, will provide more insight into the effects of neonatal protein intake on development.

6 Effects of Retinopathy of Prematurity in Babies Born Preterm on Visual Outcomes at Seven Years of Age

6.1 Introduction

ROP is a common proliferative retinal vascular disease in babies born very preterm. Approximately two thirds of babies with birth weight <1251g develop ROP. The incidence and severity of ROP increases with lower birth weight and gestational age, such that babies with a birth weight <1000g have an incidence of ROP greater than 80% (Early Treatment for Retinopathy of Prematurity Cooperative Group, 2005; Palmer et al., 1991). In New Zealand, the incidence of blindness resulting from ROP in babies <1000g birth weight was found to be 7% in a 1986 study investigating the national incidence of acute ROP in very low birth weight babies (Darlow, 1988). Since the 1940s, ROP has been identified as a major cause of visual impairment in children born very preterm (Terry, 1946), and oxygen supplementation has been recognised as an important risk factor for ROP development (Hartnett & Penn, 2012). Despite advances in neonatal care in controlling oxygen supplementation, stringent screening (classification of ROP and telemedicine) and treatment for ROP (ablation therapy and anti-vascular growth factor injections), ROP remains a leading cause of childhood visual impairment worldwide (Blencowe et al., 2013).

ROP is characterised by abnormal growth of peripheral retinal blood vessels in response to altered retinal oxygen concentrations when a baby is born very preterm (Hartnett & Penn, 2012). The peripheral retina is only fully vascularised near full term; therefore, when a baby is born preterm, areas of the peripheral retina remain avascular (Ashton, 1969). After birth, the baby is exposed to a relatively hyperoxic environment compared to *in utero* and this downregulates VEGF production, halting the growth of the blood vessels in the peripheral retina (Hartnett & Penn, 2012). This can be exacerbated by oxygen supplementation given to babies with immature lungs. As the retina becomes more metabolically active (after approximately 31 weeks' GA), the existing blood vessels cannot adequately meet the oxygen demands, which upregulates VEGF production in the retina, resulting in uncontrolled proliferation of blood vessels (Hartnett & Penn, 2012). These new blood vessels extend from the retina into the vitreous as extraretinal fibrovascular proliferations, which, in turn, can lead to retinal detachment and subsequent vision loss. This process of ROP has been categorised using a system of zones (locations on the retina), stages (severity) and extent (angular extent of retinal area affected in clock hours) according to the International Classification of Retinopathy of Prematurity (An International Committee for the Classification of Retinopathy of Prematurity, 2005).

In order to reduce the risk of retinal detachment, babies with birth weight <1250g or gestational age <30 weeks are screened for ROP at around 31 weeks' postmenstrual age or 4 weeks after birth (Section on Ophthalmology American Academy of Pediatrics and American Academy of Ophthalmology and American Association for Pediatric Ophthalmology and Strabismus, 2013). Screening stops when the retina is fully vascularised or when ROP has regressed. Since 2005, at National Women's Health, ROP screening has been performed using a wide-field digital retinal camera and static photos of different quadrants of the retina are taken to look for signs of ROP and to determine high risk prethreshold ROP, or Type 1 ROP (Stage 3 in Zone1 without plus disease, or any stage in Zone 1 or 2 with plus disease) (Dai et al., 2011). If high risk prethreshold ROP is noted, then laser ablation of the avascular retina is initiated (Early Treatment for Retinopathy of Prematurity Cooperative Group, 2003). This reduces retinal oxygen demand and the retinal blood vessels cease to grow. Two large randomised controlled trials, the Multicentre trial of Cryotherapy for ROP in 1986 and Early Treatment ROP trial in 2002, have shown that ablation treatment of severe ROP reduces the incidence of retinal detachment and improves VA (Good, 2004; Palmer et al., 2005). However, ablation therapy destroys the ablated retinal tissue so other forms of treatment such as intravitreal bevacizumab (anti-VEGF treatment) have been investigated (Law et al., 2010). Early evidence showed that anti-VEGF treatment reduced risk of retinal detachment in preterm babies with type 1 ROP when used in conjunction with laser treatment, and in monotherapy, reduced the risk of refractive errors. However, safety and dosage of bevacizumab in children and effects of bevacizumab on long-term visual development remain unclear. Both these treatments are aimed at severe ROP, but in most cases ROP spontaneously regresses without treatment (Austeng et al., 2010).

Apart from risk of retinal detachment, severe ROP has been associated with other adverse visual outcomes such as myopia, reduced VA, strabismus, changes in ocular structural development (increase in foveal thickness and dysfunctional growth of the anterior eye), rod photoreceptor dysfunction, and reduced visual field (Cooke et al., 2004). As well as ROP, cortical damage can also affect visual function and children born preterm are at increased of cortical damage from IVH and PVL (Kong et al., 2012). Many of these adverse visual outcomes have been investigated in cases of severe ROP but it is unclear whether visual outcomes are affected in preterm children with mild ROP or without ROP.

The aim of this study was to investigate the effects of ROP on long-term visual development following updates to screening and earlier treatment of severe ROP. Functional visual outcomes, peripheral retinal findings and ocular biometry, and refractive error were compared between preterm children

who had ROP, preterm children who did not develop ROP and children born at full term. We hypothesised that children with previous ROP, including mild ROP, would have poorer visual outcomes than preterm children who were not diagnosed with ROP, and only children who had laser treatment for ROP would have retinal scarring. In this chapter, we report the results from the EYE-SPY study.

6.2 Methods

The Examining Young Eyes for Signs of PrematurityY (EYE-SPY) study was an observational follow-up study of visual outcomes of preterm born children at the ages eight to ten years (2.2.3). Inclusion criteria were those with birth weight <1250g or gestational age <30 weeks, born at, or admitted to, National Women's Health between 1st January 2006 and 30th December 2008, and had undergone screening for ROP. Children who were born preterm did not have ROP were part of the 'No ROP' group while children with ROP at any stage were part of the 'ROP' group. A cohort of children who were born at full term (born ≥38 weeks' gestational age) were also recruited as part of the 'Term control' group.

The cohort size was based on the incidence of ROP and laser treated ROP at National Women's Health between 2006 and 2007. We estimated 20% of children who had ROP would have scarring on the peripheral retina from laser treated ROP. To reduce the incidence of scarring from 2% to 0.5% with 80% power and alpha 0.05; two tailed testing required 35 children in each group. ROP status was based on data collected by ANZNN and then confirmed with reports from neonatal records.

Full details of inclusion and exclusion criteria, recruitment details, and visual assessment can be found in 2.2.

The primary outcome was scarring of the peripheral retina in either or both eyes.

Secondary outcomes assessed were composite visual function including overall visual outcome, binocular visual outcome, aided visual outcome, and functional visual outcome. Other visual outcomes included VA, global motion perception, refractive error, ocular biometry, retinal structure, visual field and electrophysiology. Other outcomes included visual motor integration, health-related quality of life and anthropometry.

6.2.1 Statistical analyses

Statistical calculations were performed using SPSS Statistics 22 (IBM) and graphs were plotted in Prism 7 for Windows (GraphPad Software, Inc). Details for standard statistical analyses can be found in 2.4.

Age at assessment was considered a potential confounder likely to be strongly associated with outcomes and was a covariate in analyses when comparing the three groups.

6.3 Results

Between 1st January 2006 and 31th December 2008, 237 babies with birth weight <1250g or gestational age <30 weeks were born or admitted to National Women's Health and received ROP screening. From the neonatal records, 49 babies (21%) did not develop ROP and 188 (79%) babies developed ROP. A total of 64 children were assessed between 8 to 10 years corrected age, of whom, 17 children (35% of those who did not develop ROP) were in the No ROP group, and 47 children (25% of those who developed ROP) were in the ROP group (Figure 6-1). A cohort of 37 children born at full term were recruited as the Term control group.

Mothers of children in the Term group were more likely to be older during pregnancy and less likely to undergo caesarean section (Table 6-1). None of the children in the Term group were born of multiple birth. Socioeconomic status distribution differed between the groups at birth (Figure 6-2), while mean NZ Dep score was not statistically significantly different.

Children in the ROP and No ROP groups had similar baseline characteristics and neonatal complications (Table 6-2, Table 6-3) except for ethnicity, respiratory support and length of neonatal stay. In terms of neonatal treatment, children in the ROP group received more respiratory support and had a longer neonatal stay than the children in the No ROP group. Children in our preterm groups had similar baseline characteristics to the eligible preterm children who were not assessed except for gestational age and ethnicity. There were similar number of children born of Māori and Pacific descent between all three groups who were assessed, but there were fewer children of European descent in the No ROP group compared to the Term group. Children in the term group were born at a median gestational age of 40 weeks and were born with numerically higher weight, crown-heel length and head circumference than children born preterm; z-scores of the anthropometric measurements were not statistically significantly different between the three groups. The proportion born small or large

for gestational age was similar between all three groups. Children in the term group had higher Apgar scores and had a shorter neonatal stay than children born preterm.

At the time of the EYE-SPY study assessment, the Term group was significantly older than the ROP group (median (IQR), ROP: 8.8 (8.5, 9.0) years; No ROP: 8.9 (8.7, 9.4) years; Term: 9.2 (8.8, 10.1) years, p<0.001). Distribution of socioeconomic status was similar between all three groups (Figure 6-2). Children in the ROP group weighed less than children in the No ROP group and the Term group; and were shorter and had a smaller head circumference than children in the Term group.

Figure 6-1 Strobe diagram of children in the preterm cohort of the EYE-SPY study who had a visual assessment at eight to ten years of age inclusive

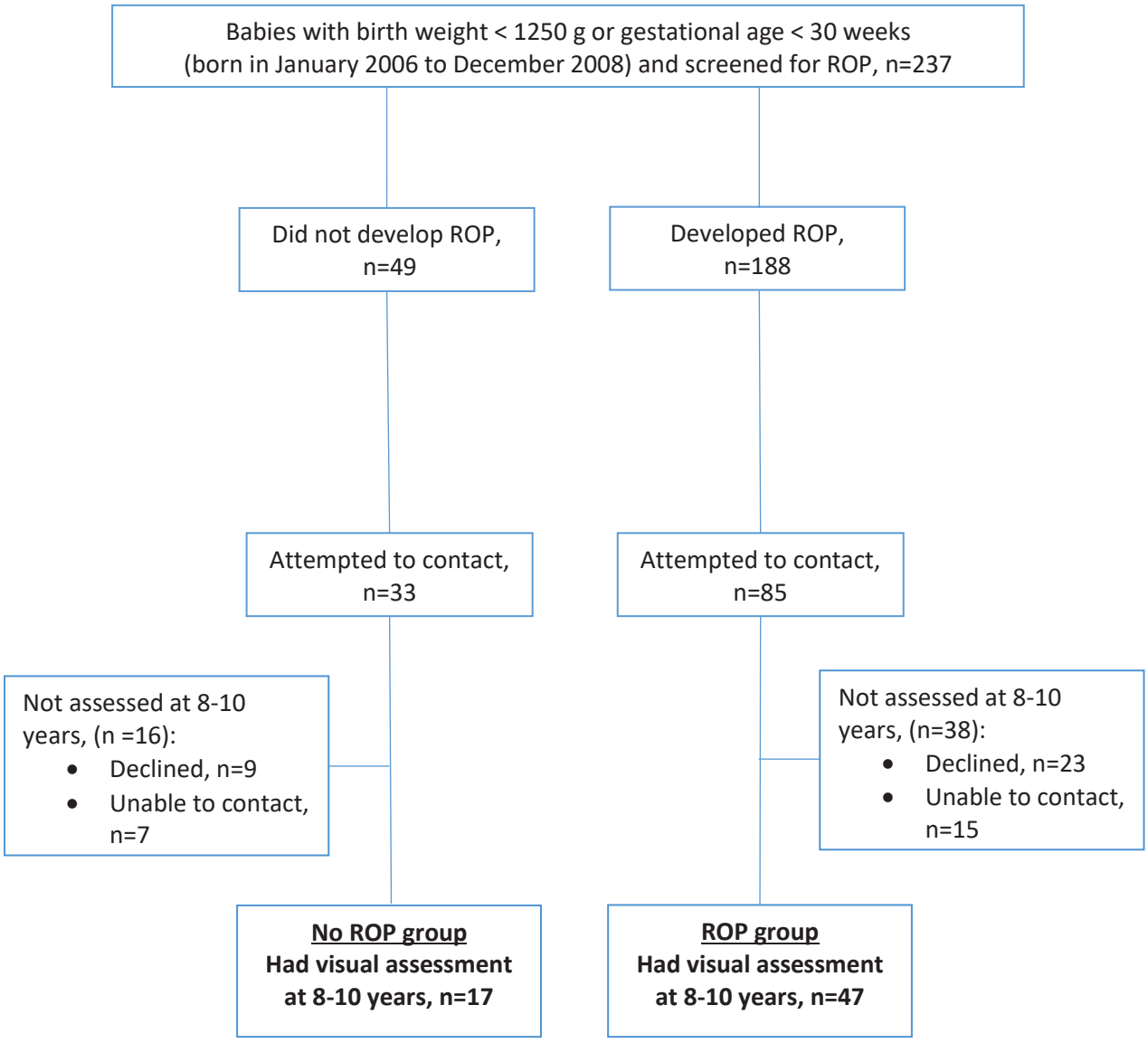
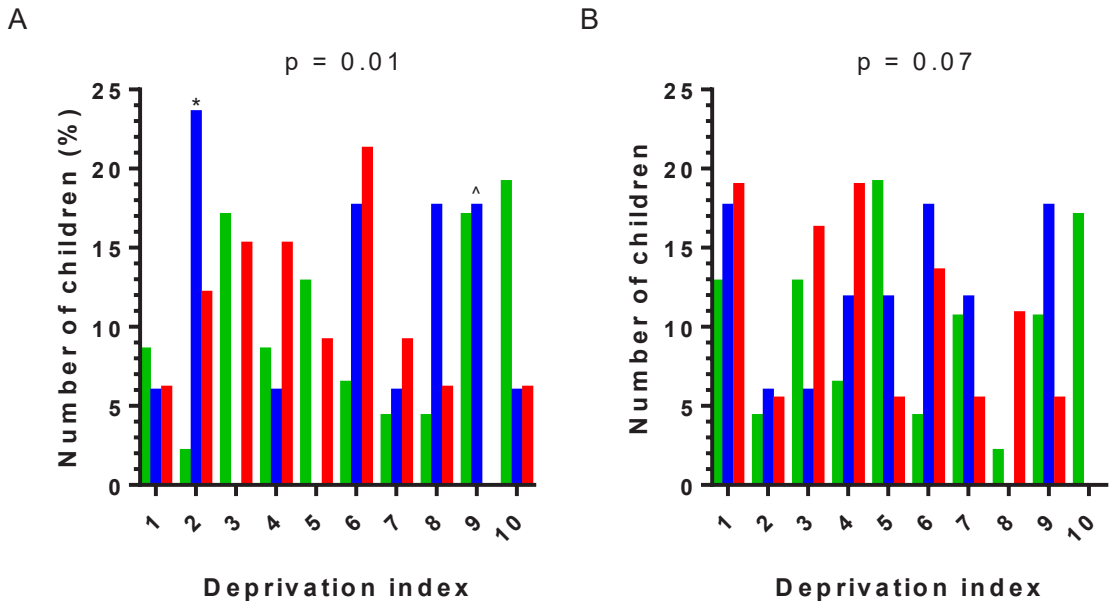


Table 6-1 Maternal characteristics of children in the EYE-SPY study

	ROP group (n=47)	No ROP group (n=17)	Term control group (n=37)	ROP v No ROP v Term P-value
Maternal age (years)	29.4 ± 6.5[a]	28.6 ± 5.3[a]	33.8 ± 4.1[b*]	< 0.01
Maternal diabetes	0 (0%)	1 (6%)	1/30 (3%)	0.25
Multiple pregnancy	15 (33%)[a]	6 (35%)[a]	0 (0%)[b#]	< 0.0001
Caesarean Section	28 (60%)[a]	14 (82%)[a]	8/28 (29%)[b^]	0.001
Antenatal steroids given				
Any	44 (94%)	16 (94%)	-	-
Complete course	21 (45%)	8 (47%)	-	-

**Data was available for 29 mothers, #data was available for 33 families, ^ data available for 28 mothers. Data are n (%), mean±standard deviation. Non-matching superscript letters indicate a significant difference (p<0.05) amongst groups on post hoc analysis. Due to rounding, percentages may not add up to 100%.*

Figure 6-2 Socioeconomic status of children assessed in the EYE-SPY study, at birth and at time of assessment



*Note: a lower number on the x-axis denotes less deprivation or higher socioeconomic status; ROP group (green), No ROP group (blue), term control group (red). Socioeconomic status at birth (A), and at time of assessment (B): *No ROP group had higher incidence than ROP group; term group were similar to No ROP and ROP groups. ^Term group had lower incidence than ROP and No ROP groups.*

Table 6-2 Baseline characteristics of children in the EYE-SPY study

	All eligible preterm children (n=237)	All eligible preterm children (not assessed) (n=173)	Children assessed in the EYE-SPY study				Preterm assessed v not assessed P-value
			ROP group (n=47)	No ROP group (n=17)	Term control group (n=28/37)	ROP v No ROP v Term P-value	
Gestational age (weeks)	26.0 (25.0, 28.0)	26.0 (25.0, 28.0)	27.0 (26.0, 28.0)[a]	27.0 (26.0, 29.0)[a]	40.0 (39.0, 41.0)[b]	< 0.001	0.02
Birth weight g	920 (758, 1055)	733 (905, 1058)	900 (780, 1008)[a]	1030 (889, 1160)[a]	3620 (3155, 3955)[b^]	< 0.001	0.33
z-score	-0.04 ± 0.90	-0.14 ± 0.88	-0.08 ± 0.96	-0.26 ± 0.99	-0.09 ± 1.01[^]	0.79	0.39
Weight for gestational age						0.98	0.66
Small	20 (8%)	14 (8%)	4 (9%)	2 (12%)	3 (9%)		
Large	13 (5%)	11 (6%)	2 (4%)	0 (0%)	1(3%)		
Sex (male)	137 (58%)	102 (59%)	22 (47%)	13 (77%)	22 (61%)	0.09	0.55
Ethnicity						< 0.01	0.01
NZ European	83 (35%)	53 (31%)	26 (55%)[a,b]	4 (24%)[b]	24 (68%)[a]		
Māori	80 (34%)	61 (35%)	12 (26%)[a]	7 (41%)[a]	5 (14%)[a]		
Pacific Island	32 (14%)	21 (12%)	8 (17%)[a]	3 (18%)[a]	2 (5%)[a]		
Asian/Other	35 (15%)	38 (22%)	1 (2%)[a]	3 (18%)[a]	5 (14%)[a]		
ROP status*						-	0.56
No ROP	49 (21%)	32 (19%)	-	17/64 (27%)	-		
Stage 1 ROP	92 (39%)	69 (67%)	23/64 (36%)	-	-		
Stage 2 ROP	70 (30%)	51 (30%)	19/64 (30%)	-	-		
Stage 3 ROP	23 (10%)	19 (11%)	4/64 (6%)	-	-		
Stage 4 ROP or worse	3 (1%)	2 (1%)	1/64 (2%)	-	-		
Treated ROP	25 (11%)	22 (13%)	3 (5%)	-	-	-	0.07

	All eligible preterm children (n=237)	All eligible preterm children (not assessed) (n=173)	Children assessed in the EYE-SPY study				Preterm assessed v not assessed P-value
			ROP group (n=47)	No ROP group (n=17)	Term control group (n=28/37)	ROP v No ROP v Term P-value	
Birth Crown-heel length cm	-	-	34.2 (33.0, 36.5)[a]	37.0 (34.5, 38.0)[a]	52.0 (50.0, 54.0)[b]	< 0.001	-
z-score	-	-	-0.52 ± 2.64	-0.01 ± 0.89	0.32 ± 1.37	0.24	-
Birth OFC cm	-	-	24.8 (23.5, 26.1)[a]	25.9 (24.6, 27.8)[a]	35.0 (34.5, 36.0)[b]	< 0.001	-
z-score	-	-	0.16 ± 1.28	0.29 ± 0.71	0.05 ± 0.98	0.78	-
Apgar score							
1 minute	5 ± 2	5 ± 2	6 ± 2[a]	6 ± 3[a]	9 ± 1[b]	< 0.0001	0.64
5 minutes	8 ± 2	8 ± 2	8 ± 2[a]	8 ± 2[a]	10 ± 1[b]	< 0.0001	0.95
Length of neonatal stay (days)	-	-	88 ± 22[a]	69 ± 22[b]	5 ± 7[c]	< 0.0001	-

**For preterm children who were assessed, the denominator is all assessed preterm children; ROP status based on ANZNN data and validated by clinical notes for assessed children. ^For children the term group where neonatal data was not available, the birth weight reported by the parent was used for analysis. Data are n (%), mean±standard deviation, median (interquartile range). Non-matching superscript letters indicate a significant difference (p<0.05) amongst groups on post hoc analysis. Abbreviations: g grams, cm centimetres, ROP retinopathy of prematurity, OFC occipitofrontal circumference.*

Table 6-3 Neonatal complications and neonatal treatment in preterm babies from the EYE-SPY study

	ROP group (n=47)	No ROP group (n=17)	P-value
Glycaemic status			
Hyperglycaemia (> 8.5 mmol.L^{-1} x2)	20/46 (44%)	5/17 (29%)	0.31
Hypoglycaemia (< 2.6 mmol.L^{-1})	19/46 (41%)	6/17 (35%)	0.67
Insulin	11/45 (24%)	2/17 (12%)	0.49
Necrotising enterocolitis	2/45 (4%)	1/16 (6%)	1.00
Periventricular leukomalacia	0/44 (0%)	0/15 (0%)	-
Intraventricular haemorrhage (IVH)	7/45 (16%)	4/17 (24%)	0.48
IVH (grade I/II)	4/45 (9%)	3/17 (18%)	0.36
IVH (grade III/IV)	3/45 (7%)	1/17 (6%)	
Infection			
Early-onset infection	0/46 (0%)	0/17 (0%)	-
Late-onset infection	8/46 (17%)	1/17 (6%)	0.42
Bronchopulmonary dysplasia	5/47 (11%)	0/17 (0%)	0.31
Respiratory support			
IPPV (hours)	68.0 (10.0, 207.0)	19.0 (0.00, 47.5)	0.09
CPAP (hours)	1105.0 (652.5, 1278.0)	619.0 (171.0, 911.0)	0.01
%O_2 at 28 days	21 (21, 30)	21 (21, 23)	0.17
%O_2 at 36 weeks	21 (21, 25)	21 (21, 21)	0.21
Home oxygen	6/47 (13%)	0/17 (0%)	0.18
Major neonatal surgery	2/46 (4%)	2/17 (12%)	0.29

Data are n (%), median (interquartile range). Abbreviations: IPPV intermittent positive pressure ventilation, CPAP continuous positive airway pressure, O_2 oxygen, mmol.L-1 millimole per litre

There were no statistically significant differences in the primary outcome of retinal scarring between the No ROP, ROP and Term groups (Table 6-4). Two children in the ROP group with retinal scarring had laser treatment for severe ROP, and one child with severe ROP was blind following bilateral retinal detachment.

There were no differences between the groups in overall visual outcome (Table 6-4). Binocular visual outcome was poorer in the no ROP compared to the ROP and Term groups. Aided visual outcome (best corrected VA without strabismus or amblyopia, and good depth perception) was poorer in the ROP group compared to the Term group, while functional visual outcome, which excluded the refractive error component (good VA without strabismus, and good depth perception) tended to be poorer in the ROP group compared to the Term. Binocular, aided, and functional visual outcome were no longer statistically significantly different following adjustment for age.

Table 6-4 Primary outcome, composite visual outcomes, and anthropometry of children in the EYE-SPY study at eight to ten years of age

		ROP group (n=47)	No ROP group (n=17)	Term control group (n=37)	P-value	*Adjusted P-value
Primary outcome: retinal scarring		**2/45 (4%)**	**0/15 (0%)**	**0/34 (0%)**	**0.65**	-
Blindness		1/46 (2%)	0/17 (0%)	0/37 (0%)	-	-
Composite Visual Outcomes						
Favourable overall visual outcome		21/44 (48%)	8/14 (57%)	20/32 (63%)	0.43	0.29
Favourable binocular visual outcome		22/45 (49%)[a,b]	5/17 (29%)[b]	24/36 (67%)[a]	0.03	0.09
Favourable aided visual outcome		32/46 (70%)[a]	13/17 (77%)[a,b]	33/36 (92%)[b]	0.04	0.14
Favourable functional visual outcome		33/46 (72%)[a]	14/17 (83%)[a,b]	33/36 (92%)[b]	0.07	0.09
Anthropometry						
Weight	kg	28.6 (24.7, 32.3)[a]	31.8 (29.6, 42.4)[b]	31.1 (27.4, 37.0)[b]	< 0.01	-
	z-score	0.05 ± 1.17[a]	1.07 ± 1.35[b]	0.40 ± 0.83[a,b]	0.02	0.01
Height	cm	131.4 (129.1, 134.5)[a]	134.7 (130.4, 143.2)[a,b]	138.0 (135.1, 143.7)[b]	< 0.001	-
	z-score	0.03 ± 0.82[a]	0.55 ± 1.23[a,b]	0.53 ± 0.78[b]	0.01	0.04
OFC	cm	52.4 (51.1, 53.9)[a]	52.9 (52.2, 55.0)[a,b]	53.9 (52.2, 54.9)[b]	0.01	-
	z-score	-0.85 ± 1.17[a]	-0.23 ± 1.64[a,b]	-0.18 ± 0.98[b]	0.03	0.04

**Adjusted for age at assessment. ^Corrected age for preterm groups. Data are n (%), mean±standard deviation, median (interquartile range). Non-matching superscript letters indicate a significant difference (p<0.05) amongst groups on post hoc analysis. Abbreviations: kg kilogram, cm centimetres.*

Table 6-5 Functional visual outcomes for children in the EYE-SPY study at eight to ten years of age

	ROP group (n=47)	No ROP group (n=17)	Term control group (n=37)	P-value	*Adjusted P-value
Distance VA in Better Eye					
Equal or better than 6/12 (aided)	44/46 (96%)	17/17 (100%)	36/36 (100%)	0.67	1.00
Equal or better than 6/12	46/47 (98%)	16/17 (94%)	35/36 (97%)	0.58	0.71
Better than 6/7.5	44/47 (94%)	16/17 (6%)	34/36 (94%)	1.00	0.99
LogMar	-0.02 ± 0.32	-0.04 ± 0.17	-0.11 ± 0.10	0.22	0.36
Distance VA in Poorer Eye (logMAR)	0.04 ± 0.33	0.06 ± 0.24	-0.05 ± 0.14	0.23	0.24
Presenting Binocular Distance VA (logMAR)	-0.10 ± 0.10	-0.10 ± 0.15	-0.15 ± 0.09	0.09	0.10
Binocular vision					
Presence of strabismus	8/46 (17%)[a]	1/17 (6%)[a,b]	0/36 (0%)[b]	0.02	0.57
Presence of phoria	23/46 (50%)	12/17 (71%)	22/36 (61%)	0.30	0.46
Normal ocular motility	35/46 (76%)	13/17 (77%)	34/36 (94%)	0.05	0.18
Normal convergence	35/39 (90%)	14/17 (82%)	35/36 (97%)	0.18	0.25
Presence of motor fusion	32/45 (71%)	9/17 (53%)	26/36 (72%)	0.36	0.30
Presence of sensory fusion	34/45 (76%)	13/17 (77%)	33/36 (92%)	0.12	0.34
Pass stereoacuity (TNO)	37/45 (82%)	14/17 (82%)	34/36 (94%)	0.25	0.26
Other visual outcomes					
Pass colour vision (Ishihara)	42/44 (96%)	17/17 (100%)	35/36 (97%)	1.00	1.00
Not requiring spectacles (autorefraction)	27/41 (66%)	9/14 (64%)	21/31 (68%)	1.00	0.73
Not requiring spectacles (subjective)	37/46 (80%)	14/17 (82%)	30/36 (83%)	0.94	0.82
Amblyopia	3/45 (7%)	3/17 (18%)	1/36 (3%)	0.15	0.19
Mean global motion perception threshold	34.77 ± 16.39[a]	32.45 ± 11.96[a,b]	26.57 ± 12.62[b]	0.05	0.10

**Adjusted for age at assessment. Data are n (%), mean±standard deviation. Non-matching superscript letters indicate a significant difference (p<0.05) amongst groups on post hoc analysis. Abbreviations: VA visual acuity, logMAR logarithm of the minimum angle of resolution.*

Table 6-6 Retinal outcomes for children in the EYE-SPY study at eight to ten years of age

	ROP group (n=47)	No ROP group (n=17)	Term control group (n=37)	P-value	*Adjusted P-value
Retinal posterior pole (central) findings				1.00	-
No abnormalities or non-clinically significant findings	44/47 (94%)	17/17 (100%)	34/37 (92%)		
Clinically significant findings	1/47 (2%)	0/17 (0%)	1/37 (3%)		
Unable to assess	2/47 (4%)	0/17 (0%)	2/37 (5%)		
Retinal photo quality^	8.6 ± 1.4	8.4 ± 1.1	8.9 ± 0.9	0.40	
Peripheral retinal findings					
Non-clinically significant peripheral retinal findings	17/45 (38%)[a]	2/15 (13%)[a,b]	4/34 (12%)[b]	0.02	0.01
Clinically significant findings	1/45 (2%)	0/15 (0%)	1/34 (3%)	1.00	-
OPTOS image quality	8.1 ± 1.1	7.9 ± 1.4	8.0 ± 1.0	0.76	
Retinal vascular tortuosity					
Better VA eye				< 0.0001	-
Nil	26/44 (59%)[a]	2/17 (12%)[b]	35/35 (100%)[c]		
Mild	15/44 (34%)[a]	12/17 (71%)[b]	0/35 (0%)[c]		
Severe	3/44 (7%)[a,b]	3/17 (18%)[b]	0/35 (0%)[a]		
Poorer VA eye				< 0.0001	-
Nil	21/44 (48%)[a]	5/17 (29%)[a]	32/35 (91%)[b]		
Mild	19/44 (43%)[a]	9/17 (53%)[a]	3/35 (9%)[b]		
Severe	4/44 (9%)[a,b]	3/17 (18%)[b]	0/35 (0%)[a]		

**Adjusted for age at assessment. ^Subjective measure of quality by observer, 1 poor quality, 10 good quality. Data are n (%), mean±standard deviation. Non-matching superscript letters indicate a significant difference (p<0.05) amongst groups on post hoc analysis. Abbreviations: VA visual acuity*

All functional visual outcomes were similar between the No ROP, ROP and Term groups (Table 6-5). There were no differences in monocular or binocular presenting VA, binocular vision and other visual outcomes between all three groups. Pair-sampled test showed that the poorer VA eye had statistically significantly poorer VA than the better VA eye (Better v poorer eye: mean difference -0.07logMAR (95%CI -0.09, -0.05), p<0.0001). There was a higher incidence of strabismus and higher global motion threshold (lower sensitivity) in the ROP group compared to the Term group, which was no longer statistically significant after adjusting for age.

There were no differences in central retinal findings between the three groups (Table 6-6). The majority of children had no abnormalities or non-clinically significant findings. Children in the ROP group were more likely to have peripheral retinal changes than the Term group. Clinically significant peripheral retinal changes were few. Peripheral retinal changes that were found in our study are listed in Table 6-7. The No ROP group had a higher incidence of retinal vascular tortuosity than the Term group. Inter-observer quality scores were higher for both central retinal and peripheral retinal images for observer 1 compared to observer 2 (central; mean±SD, observer 1: 8.8±0.9, observer 2: 7.7±1.5, p=0.01; peripheral, observer 1: 8.7±0.9, observer 2: 7.8±1.1, p=0.01).

Table 6-7 Peripheral retinal changes of children in the EYE-SPY study at eight to ten years of age

	ROP group (n=45)	No ROP group (n=15)	Term control group (n=34)	P-value	
Ridge remnant					
Better VA eye	3 (7%)	1 (7%)	0 (0%)	0.28	0.86
Poorer VA eye	4 (9%)	1 (7%)	0 (0%)	0.19	0.84
Incomplete vascularisation					
Better VA eye	8 (18%)	2 (13%)	0 (0%)	0.02	0.63
Poorer VA eye	8 (18%)	1 (7%)	0 (0%)	0.02	0.47
Pigmentary changes*					
Better VA eye	2 (4%)	0 (0%)	3 (9%)	0.57	0.88
Poorer VA eye	1 (2%)	0 (0%)	1 (3%)	1.00	0.83
Retinal scarring					
Better VA eye	2 (5%)	0 (0%)	0 (0%)	-	-
Poorer VA eye	2 (5%)	0 (0%)	0 (0%)	-	-
Other*					
Better VA eye	2 (5%)	0 (0%)	0 (0%)	-	-
Poorer VA eye	1 (2%)	0 (0%)	0 (0%)	-	-

**Pigmentary changes included congenital hypertrophy of the retinal pigmented epithelium, bear tracks and pigment spots. ^One participant had white fibrous tissue with an appearance of a vitreoretinal tuft, and one participant had mottling of pigment in both eyes in the mid-peripheral retina.*

Refractive error distribution was similar between the all three groups, and there were no differences in incidence of astigmatism or anisometropia (Table 6-8). There were no differences in the ocular biometry components of anterior chamber depth and lens thickness between the three groups (Table 6-9). Central corneal thickness of the poorer VA eye was thinner in the ROP group compared to the term control group. Axial length was shorter, and the cornea was steeper in the ROP group compared to both the No ROP and Term groups.

Central retinal thickness was thicker in the preterm groups compared to the term control group (Table 6-10). There were no differences in parafoveal retinal thickness or peripheral retinal thickness between the three groups.

Visual field testing was attempted on the majority of children; only a third of the children of the ROP group had reliable results. Visual field results were not reported.

There were no differences between the three groups in latency and amplitude of the components of the pattern electroretinogram (Table 6-11) and pattern visual evoked potential (Table 6-12). For the pattern visual evoked potential, at check size 15 minutes, the poorer VA eye had longer latency in the N75 component and lower N75-P100 amplitude than the better VA eye (Table 6-12). The difference in N75-P100 amplitude remained statistically significant after adjustment for age.

Children in the ROP group had lower standard score in the Beery visual motor integration test than the Term group (Table 6-13). Children in the No ROP group performed poorer in the supplementary visual perception and motor components of the Beery test than the Term group.

There were differences between the three groups in past ocular surgery/therapy but *post hoc* analyses could not distinguish between the groups (Table 6-14). Numerically, children in the ROP group had more treatment for strabismus and ROP. More children in the Term group were reported to have family ocular history than the No ROP group, the most common being refractive error. More children born preterm were assessed for vision problems as an outpatient and 14% of these children were prescribed spectacles. The majority of all the children received a B4 school vision screening at 4 years of age and approximately two thirds of children passed the screening. A similar proportion of children in all three groups wore spectacles. There were similar ratings of vision health-related quality of life among the groups; the ROP group had a poorer overall utility score than the No ROP group.

Table 6-8 Refractive error outcomes for children in the EYE-SPY study at eight to ten years of age

	ROP group (n=47)	No ROP group (n=17)	Term control group (n=37)	P-value	*Adjusted P-value
Refractive error					
SEP of the better VA eye					
Myopia	2/46 (4%)	1/17 (6%)	2/36 (6%)	0.67	0.57
Hyperopia	9/46 (20%)	1/17 (6%)	4/36 (11%)		
Significant Hyperopia (> +2.00 D)	3/46 (7%)	0/17 (0%)	0/36 (0%)		
SEP (D)	+0.27 ± 1.36	+0.08 ± 0.21	+0.16 ± 0.60	0.74	-
SEP of the poorer VA eye					
Myopia	3/46 (7%)	2/17 (12%)	4/36 (11%)	0.67	0.69
Hyperopia	13/46 (28%)	2/17 (12%)	8/36 (23%)		
Significant Hyperopia (> +2.00 D)	4/46 (9%)	0/20 (0%)	1/36 (3%)		
SEP (D)	+0.45 ± 1.49	+0.11 ± 0.41	+0.24 ± 0.73	0.47	-
Astigmatism					
Better eye	1/46 (2%)	0/17 (0%)	1/36 (3%)	1.00	-
Poorer eye	5/46 (11%)	2/17 (12%)	2/36 (6%)	0.65	-
Anisometropia	0/44 (0%)	1/17 (6%)	0/35 (0%)	0.18	-

**Adjusted for age at time of assessment. Data are n (%), mean±standard deviation. ^No significant differences between groups using Bonferroni post hoc analysis. Non-matching superscript letters indicate a significant difference (p<0.05) amongst groups on post hoc analysis. Abbreviations: D dioptres, SEP spherical equivalent power.*

Table 6-9 Ocular biometry of children in the EYE-SPY study at eight to ten years of age

	ROP group (n=39)	No ROP group (n=13)	Term control group (n=36)	P-value	*Adjusted P-value
Central Corneal Thickness (µm)					
Better VA Eye	535 ± 35	548 ± 38	552 ± 33	0.08	0.10
Poorer VA Eye	533 ± 33[a]	551 ± 36[a,b]	553 ± 32[b]	0.02	0.02
Anterior Chamber Depth (mm)					
Better VA Eye	3.48 ± 0.28	3.60 ± 0.28	3.62 ± 0.29	0.08	0.17
Poorer VA Eye	3.46 ± 0.30	3.63 ± 0.27	3.62 ± 0.29	0.04^	0.09
Axial Length (mm)					
Better VA Eye	22.54 ± 0.83[a]	23.16 ± 0.64[b]	23.09 ± 0.78[b]	< 0.01	< 0.01
Poorer VA Eye	22.50 ± 0.83[a]	23.16 ± 0.70[b]	23.06 ± 0.80[b]	< 0.01	0.01
Lens Thickness (mm)					
Better VA Eye	3.58 ± 0.23	3.59 ± 0.22	3.56 ± 0.22	0.90	0.95
Poorer VA Eye	3.59 ± 0.26	3.58 ± 0.22	3.56 ± 0.22	0.83	0.91
Corneal Curvature (mm)					
Flat Meridian Better VA Eye	7.67 ± 0.30[a]	7.90 ± 0.26[b]	7.89 ± 0.23[b]	0.001	< 0.001
Flat Meridian Poorer VA Eye	7.66 ± 0.31[a]	7.92 ± 0.31[b]	7.90 ± 0.23[b]	0.001	< 0.001
Steep Meridian Better VA Eye	7.53 ± 0.31[a]	7.75 ± 0.26[b]	7.75 ± 0.23[b]	0.001	0.001
Steep Meridian Poorer VA Eye	7.53 ± 0.32[a]	7.73 ± 0.28[a,b]	7.74 ± 0.23[b]	0.001	< 0.01

**Adjusted for age at time of assessment. ^No significant differences between groups using Bonferroni post hoc analysis. Data are mean±standard deviation. Non-matching superscript letters indicate a significant difference (p<0.05) amongst groups on post hoc analysis. Abbreviations: VA visual acuity, µm micrometre, mm millimetre.*

Table 6-10 Retinal thickness of children in the EYE-SPY study at eight to ten years of age

	ROP group (n=36)	No ROP group (n=11)	Term control group (n=25)	P-value	*Adjusted P-value
Central Retinal Thickness (µm)*					
Better VA Eye	290 ± 28[a]	291 ± 13[a]	262 ± 14[b]	< 0.0001	< 0.0001
Poorer VA Eye	291 ± 29[a]	288 ± 14[a]	262 ± 11[b]	< 0.0001	< 0.0001
Parafoveal Retinal Thickness (µm)*					
Better VA Eye	342 ± 18	346 ± 13	342 ± 14	0.77	0.77
Poorer VA Eye	342 ± 19	344 ± 11	342 ± 13	0.86	0.81
Peripheral Retinal Thickness (µm)^					
Better VA Eye	311 ± 16	311 ± 17	309 ± 13	0.82	0.85
Poorer VA Eye	307 ± 18	312 ± 16	310 ± 12	0.58	0.68

**Adjusted for age at time of assessment. Data are mean±standard deviation. Non-matching superscript letters indicate a significant difference (p<0.05) amongst groups on post hoc analysis *From ROP group, 10 children missing for better eye, 12 missing for poorer eye; from No ROP group, 7 missing for better eye, 5 missing for poorer eye; from Term control group, 12 missing for better eye, 13 for poorer eye. ^From ROP group, 16 missing for better eye, 14 missing for poorer eye; from No ROP group, 5 missing for better eye, 9 missing for poorer eye; from Term control group, 16 missing for better eye, 14 missing for poorer eye. Abbreviations: VA visual acuity, µm micrometre.*

Table 6-11 Latency and amplitude of pattern electroretinogram components of children in the EYE-SPY study at eight to ten years of age

	ROP group (n=37)	No ROP group (n=9)	Term control group (n=28)	P-value (Between eyes)	*Adjusted P-value (Between eyes)	P-value (Between groups)	*Adjusted P-value (Between groups)
N35 latency (ms)							
Better VA Eye	27.3 ± 3.6	28.2 ± 3.5	26.7 ± 3.1	0.92	0.76	0.68	0.80
Poorer VA Eye	27.4 ± 4.0	27.7 ± 3.7	27.3 ± 2.9				
P50 latency (ms)							
Better VA Eye	50.4 ± 2.9	50.1 ± 4.1	50.0 ± 1.9	0.65	0.16	0.35	0.30
Poorer VA Eye	51.1 ± 2.4	50.1 ± 2.8	50.0 ± 2.0				
N95 latency (ms)							
Better VA Eye	89.5 ± 6.9	91.0 ± 11.0	90.0 ± 7.3	0.92	0.65	0.71	0.46
Poorer VA Eye	89.4 ± 6.3	91.4 ± 6.5	90.0 ± 6.3				
N35-P50 amplitude (µV)							
Better VA Eye	3.3 ± 1.1	3.1 ± 0.9	3.1 ± 0.9	0.34	0.72	0.94	0.38
Poorer VA Eye	3.0 ± 0.8	3.0 ± 0.9	3.1 ± 1.0				
P50-N95 amplitude (µV)							
Better VA Eye	4.9 ± 1.7	4.9 ± 1.2	4.4 ± 1.3	0.48	0.32	0.70	0.55
Poorer VA Eye	4.3 ± 1.2	4.9 ± 1.2	4.6 ± 1.5				

**Adjusted for age at time of assessment. Data are mean±standard deviation. Non-matching superscript letters indicate a significant difference (p<0.05) amongst groups on post hoc analysis. Abbreviations: VA visual acuity, ms milliseconds, µV microvolts.*

Table 6-12 Latency and amplitude of pattern visual evoked potential components of children in the EYE-SPY study at eight to ten years of age

	ROP group (n=41)	No ROP group (n=10)	Term control group (n=36)	P-value (Between eyes)	*Adjusted P-value (Between eyes)	P-value (Between groups)	*Adjusted P-value (Between groups)
Check size: 15 minutes							
N75 latency (ms)							
Better VA Eye	78.1 ± 6.8	78.4 ± 6.5	79.2 ± 5.2	0.04	0.09	0.31	0.43
Poorer VA Eye	78.2 ± 7.2	83.4 ± 4.9	79.6 ± 6.0				
P100 latency (ms)							
Better VA Eye	112.6 ± 9.5	111.8 ± 7.6	109.5 ± 7.0	0.18	0.31	0.46	0.70
Poorer VA Eye	113.1 ± 9.3	112.4 ± 6.9	111.8 ± 7.4				
N75-P100 amplitude (µV)							
Better VA Eye	17.3 ± 8.5	19.5 ± 6.6	20.9 ± 8.2	0.05	0.02	0.14	0.33
Poorer VA Eye	17.4 ± 8.6	15.2 ± 7.8	20.1 ± 8.2				
Check size: 1 degree							
N75 latency (ms)							
Better VA Eye	70.3 ± 6.6	70.1 ± 5.1	71.1 ± 6.6	0.99	0.45	0.81	0.95
Poorer VA Eye	69.7 ± 6.8	71.6 ± 7.4	70.2 ± 6.0				
P100 latency (ms)							
Better VA Eye	105.9 ± 6.8	108.2 ± 9.8	107.0 ± 6.1	0.60	0.61	0.67	0.80
Poorer VA Eye	107.0 ± 6.5	108.1 ± 8.5	107.4 ± 6.1				
N75-P100 amplitude (µV)							
Better VA Eye	17.8 ± 9.0	17.1 ± 6.8	22.1 ± 8.6	0.81	0.92	0.11	0.20
Poorer VA Eye	19.9 ± 9.1	16.0 ± 6.6	21.8 ± 9.3				

**Adjusted for age at time of assessment. Data are mean±standard deviation. Non-matching superscript letters indicate a significant difference (p<0.05) amongst groups on post hoc analysis. Abbreviations: VA visual acuity, ms milliseconds, µV microvolts.*

Table 6-13 Beery visual motor integration score for children in the EYE-SPY study at eight to ten years of age

	ROP group (n=45)	No ROP group (n=17)	Term control group (n=36)	P-value	*Adjusted P-value
Beery visual motor integration					
Standard score	90 ± 10[a]	90 ± 15[a,b]	97 ± 14[b]	0.03	0.01
Percentile	27 ± 20[a]	31 ± 28[a,b]	44 ± 27[b]	0.01	0.01
< 10th percentile	7 (16%)	3 (18%)	5 (14%)	0.93	0.96
Beery visual perception					
Standard score	103 ± 11[a,b]	97 ± 11[a]	108 ± 9[b]	< 0.01	0.01
Percentile	57 ± 23[a,b]	45 ± 26[a]	68 ± 20[b]	< 0.01	0.01
< 10th percentile	2 (4%)	0 (0%)	0 (0%)	0.66	1.00
Beery motor coordination					
Standard score	93 ± 13[a,b]	88 ± 14[a]	96 ± 13[b]	0.14	0.04
Percentile	36 ± 26[a]	27 ± 26[a]	42 ± 25[a]	0.14	0.04
< 10th percentile	10 (22%)	5 (29%)	4 (11%)	0.23	0.22

**Adjusted for age at time of assessment. Data are mean±standard deviation. Non-matching superscript letters indicate a significant difference (p<0.05) amongst groups on post hoc analysis.*

Table 6-14 Ocular history for children in the EYE-SPY study at eight to ten years of age

	ROP group (n=44)	No ROP group (n=20)	Term control group (n=37)	P-value	Adjusted P-value
Past ocular surgery/therapy	11 (23%)[a]	0 (0%)[a]	2 (5%)[a]	0.01*	0.16
Strabismus	6 (55%)	0 (0%)	0 (0%)		
Laser for ROP	3 (27%)	-	-		
Patching	4 (36%)	0 (0%)	1 (50%)		
Vision training	1 (9%)	0 (0%)	1 (50%)		
Family ocular history	24 (52%)[a,b]	5 (29%)[b]	25/36 (70%)[a]	0.03	0.02
Strabismus	2 (8%)	0 (0%)	4 (16%)		
Amblyopia	5 (21)	0 (0%)	2 (8%)		
Refractive error	13 (54%)	5 (100%)	17 (68%)		
Colour deficiency	2 (8%)	0 (0%)	6 (24%)		
Spectacles worn	8 (17%)	2 (12%)	2/36 (6%)	0.35	0.23
Hospital eye follow-up					
Previously followed-up in outpatient clinic	32 (68%)a	7 (47%)a	4 (12%)b	< 0.0001	< 0.0001
Age of most recent exam (years)	2.1 (0.8, 6.3)	1.9 (0.5, 6.9)	-	-	-
Spectacles prescribed	4 (13%)	1 (14%)	0 (0%)	1.00	0.97
Treatment initiated*	7 (22%)	1 (14%)	1 (25%)	1.00	0.98
B4 school check visual outcomes				0.84	-
Pass	32 (68%)	11 (65%)	25 (68%)		
Rescreen	3 (6%)	2 (12%)	2 (5%)		
Referred	3 (6%)	2 (12%)	4 (11%)		
Under care	3 (7%)	0 (0%)	0 (0%)		
Not done	6 (13%)	2 (12%)	6 (16%)		
Health Utilities Index – 3^ Vision[#]				0.96	-
1	41 (89%)	16 (94%)	34 (94%)		
2	3 (7%)	1 (6%)	1 (3%)		
3	1 (2%)	-	1 (3%)		
4	1 (2%)	-	-		
Overall utility score[§]	0.93 ± 0.12[a]	0.98 ± 0.03[b]	0.98 ± 0.09[a,b]	0.04	

**On post hoc testing, no differences were found between the groups. ^In the preterm group, there is 1 missing. [#]The scale is 1 (good vision) to 6 (unable to see), specifics of the categories can be found in 2.2.7.5. [§]Dead = 0.00 and Perfect Health = 1.00. Data are median (interquartile range), n (%), mean±standard deviation. Non-matching superscript letters indicate a significant difference (p<0.05) amongst groups on post hoc analysis. Due to rounding, percentages may not add up to 100.*

Up to 40% of all the assessed children had visual findings that required further follow-up (Table 6-15). Children in the preterm groups were more likely to have had a previous eye assessment at a hospital, ophthalmology or optometry clinic, or B4 school screening than the Term group. There were no differences between the three groups in proportion of children requiring a vision follow-up, vision follow-up required when no previous ocular assessment had been done, or vision findings that were not identified previously. The type of visual problems identified were similar between the groups.

Table 6-15 Overall visual status and need for vision follow-up of children assessed in the EYE-SPY study at eight to ten years of age

	ROP group (n=47)	No ROP group (n=17)	Term control group (n=37)	P-value	Adjusted P-value
Vision follow-up required	18 (41%)	5 (25%)	8 (22%)	0.14	0.26
Refractive error	9/18 (50%)	3/5 (60%)	6/8 (75%)		
VA	4/18 (22%)	3/5 (60%)	1/8 (13%)		
Ocular structure	10/18 (56%)	1/5 (20%)	1/8 (13%)		
No previous ocular assessment^	13 (30%)[a]	10 (50%)[a]	32 (87%)[b]	< 0.0001	< 0.0001
Vision follow-up required and no previous ocular assessment^	2/47 (4%)	4/17 (27%)	5/37 (14%)	0.54	0.12
Vision follow-up required, which has not been identified previously	4/47 (9%)	4/17 (24%)	6/37 (16%)	0.78	0.29
Types of visual problems not previously identified	n=4	n=4	n=6	0.32	-
Refractive error	2 (50%)	3 (75%)	5 (83%)		
VA	0 (0%)	1 (25%)	0 (0%)		
Ocular structure	2 (50%)	0 (0%)	1 (17%)		

**Adjusted for age and NZ Deprivation Index at time of assessment. ^Previous ocular assessment include assessment at hospital, ophthalmology or optometry clinics (or has spectacles), or B4 School Vision check. Data are n (%). Non-matching superscript letters indicate a significant difference (p<0.05) amongst groups on post hoc analysis.*

For exploratory analyses, visual outcomes were compared between children with complete vascularisation of the retina and those who did not have complete vascularisation (Table 6-16, Table 6-17). Peripheral retinal vascularisation was not associated with visual function, refractive error or electrophysiology. Children with incomplete vascularisation had steeper corneal curvature and thicker retinas (Table 6-16).

Table 6-16 Visual function in children with complete retinal vascularisation in the better eye compared to children with incomplete retinal vascularisation in the better eye

	Complete vascularisation (n=84)	Incomplete vascularisation (n=10)	P-value
Favourable overall visual outcome	42/77 (55%)	5/9 (56%)	1.00
Favourable binocular visual outcome	43/83 (52%)	6/10 (60%)	0.74
Favourable aided visual outcome	65/83 (78%)	9/10 (90%)	0.68
Favourable functional visual outcome	67/83 (81%)	9/10 (90%)	0.68
Presenting Binocular Distance VA (logMAR)	-0.11 ± 0.12	-0.13 ± 0.05	0.59
Other Visual Outcomes			
Presence of strabismus	9/84 (11%)	0/12 (0%)	0.59
Normal ocular motility	67/84 (80%)	10/10 (100%)	0.20
Normal convergence	71/77 (92%)	9/10 (90%)	0.59
Presence of motor fusion	56/83 (68%)	7/10 (70%)	1.00
Presence of sensory fusion	65/83 (78%)	10/10 (100%)	0.20
Pass stereoacuity (TNO)	72/83 (87%)	9/10 (90%)	1.00
Pass colour vision (Ishihara)	79/82 (96%)	10/10 (100%)	1.00
Amblyopia	6/83 (7%)	1/10 (10%)	0.56
Mean global motion perception threshold	30.72 ± 14.21	38.06 ± 20.61	0.15
Beery visual motor integration (standard score)	93 ± 13	91 ± 10	0.67

Data are n (%), mean±standard deviation.

As there was a lower N75-P100 amplitude in the poorer VA eye, further analysis was conducted. Simple linear regression modelling showed that increasing N75-P100 amplitude was associated with better VA (adjusted R^2=0.04, F=4.55, p=0.04, unstandardized coefficient =-0.004 (95%CI -0.01, 0.00).

Simple linear regression modelling was also used to assess whether the components of ocular biometry were related to VA. None of the ocular biometry components in the poorer VA eye were predictive of VA in the same eye (Table 6-18).

Table 6-17 Other visual functions and ocular structural differences in the better VA eye of children with complete retinal vascularisation compared to children with incomplete retinal vascularisation

	Complete vascularisation (n=84)	Incomplete vascularisation (n=10)	P-value		Complete vascularisation (n=84)	Incomplete vascularisation (n=10)	P-value
Refractive error				**Pattern electroretinogram**	n=63	n=9	
Spherical equivalent power				N35 latency (ms)	27.6 ± 4.4	26.5 ± 2.9	0.49
Myopia	4/84 (5%)	1/10 (10%)	0.70	P50 latency (ms)	50.5 ± 3.1	49.5 ± 2.3	0.33
Hyperopia	13/84 (16%)	1/10 (10%)		N95 latency (ms)	89.7 ± 9.1	85.5 ± 6.4	0.18
Significant Hyperopia (> +2.00 D)	3/84 (4%)	0/10 (0%)		N35-P50 amplitude (µV)	3.2 ± 1.0	3.5 ± 0.9	0.40
Astigmatism	1/84 (1%)	1/10 (10%)	0.20	P50-N95 amplitude (µV)	4.6 ± 1.6	4.9 ± 0.9	0.66
Ocular biometry	n=76	n=10		**Pattern visual evoked potential**	n=73	n=12	
Central corneal thickness (µm)	545 ± 35	532 ± 34	0.29	15 minutes			
Anterior chamber depth (mm)	3.55 ± 0.29	3.55 ± 0.27	0.97	N75 latency (ms)	78.5 ± 6.0	79.8 ± 4.4	0.50
Axial length (mm)	22.83 ± 0.84	22.86 ± 0.58	0.93	P100 latency (ms)	111.2 ± 8.1	110.6 ± 10.6	0.82
Lens thickness (mm)	3.58 ± 0.22	3.54 ± 0.23	0.63	N75-P100 amplitude (µV)	19.4 ± 8.7	15.7 ± 4.8	0.19
Corneal curvature (mm)				1 degree			
Flat meridian	7.80 ± 0.28	7.64 ± 0.27	0.09	N75 latency (ms)	70.8 ± 6.4	67.9 ± 5.0	0.18
Steep meridian	7.67 ± 0.29	7.48 ± 0.25	0.05	P100 latency (ms)	106.6 ± 6.6	105.8 ± 8.8	0.73
Retinal thickness	n=62	n=10		N75-P100 amplitude (µV)	20.1 ± 9.2	15.6 ± 5.3	0.14
Central	275.7 ± 23.0	309.3 ± 20.2	< 0.0001				
Parafoveal	341.1 ± 14.8	353.1 ± 19.2	0.03				
Periphery (n=53 v 7)	308.6 ± 13.8	322.7 ± 17.8	0.02				

Data are n (%), mean±standard deviation. Non-matching superscript letters indicate a significant difference (p<0.05) amongst groups on post hoc analysis. Abbreviations: µm micrometres, mm millimetres, ms milliseconds, µV microvolts.

Table 6-18 Simple linear regression of ocular biometry and visual acuity in the poorer visual acuity eye

	Adjusted R^2	F	P-value
Central corneal thickness (μm)	-0.01	0.13	0.73
Anterior chamber depth (mm)	-0.01	0.03	0.86
Lens thickness (mm)	-0.01	0.61	0.44
Axial length (mm)	-0.01	0.23	0.64
Corneal curvature (mm)			
Flat meridian	-0.01	0.59	0.45
Steep meridian	-0.01	0.41	0.53

Abbreviations: μm micrometres, mm millimetre.

The relationship between anthropometry and ocular growth was assessed using simple linear regression modelling. Increasing height z-score (adjusted R^2=0.10, F=10.38, p<0.01, unstandardised coefficient=0.30 (95%CI 0.11, 0.48)) and head circumference z-score (adjusted R^2=0.07, F=6.86, p=0.01, unstandardized coefficient=0.18 (95%CI 0.04, 0.32)) at time of assessment were associated with longer axial length, which remained statistically significant after adjusting for age at assessment (height p<0.01; head circumference p<0.001).

6.4 Discussion

ROP has been associated with adverse visual outcomes, particularly retinal detachment and childhood visual impairment in severe cases (Blencowe et al., 2013). A comprehensive assessment of visual outcomes in late childhood of children born preterm who were at risk of ROP has not been conducted in New Zealand since a series of follow-up studies on a cohort born in the 1986 (Darlow, 1988; Darlow, Clemett, et al., 1997; Darlow et al., 2003; Darlow, Horwood, et al., 1997). There have been changes in neonatal care at National Womens' Health NICU (Auckland, New Zealand), with updates to recommendations for screening and managing ROP in 2006 (American Academy of Pediatrics, 2006); around the same time, ROP screening was changed from using indirect binocular ophthalmoscopy to digital retinal screening in 2006 (Dai et al., 2011) while there was also a reformulation of neonatal nutrition in 2007. The NICU was also part of an international trial of oxygen supplementation between 2006 and 2010 (The BOOST II United Kingdom Australia and New Zealand Collaborative Groups, 2013). Our study investigated the effects of ROP on visual outcomes in later childhood in children born very preterm between 2006 and 2008 who were screened for ROP and managed according to updated recommendations. We have shown that there were no differences in the incidence of retinal scarring between children in the No ROP, ROP and Term control groups, and only children who had laser treatment for severe ROP had retinal scarring. Children who had ROP had similar visual outcomes as

children who were born preterm and did not develop ROP and were similar to children born at full term in the majority of visual outcomes. The main differences in outcome found between groups were ocular structural changes. The ROP group had shorter axial length and steeper corneal curvature, and higher incidence of non-clinically significant peripheral retinal changes than the Term group but these was not associated with visual function. Therefore, it is unknown the implications of these changes. Overall, there were no differences between the groups in the proportion of children who had adverse visual outcomes that required follow-up for adverse visual outcomes, which had not been previously identified. This suggests that the majority of children born preterm with ROP who have had appropriate screening and treatment have similar visual outcomes to children born preterm without ROP and children born at full term at 8-10 years of age.

The proportions of preterm babies who developed ROP in our study was similar to multicentre trials in the 1980s to 2000s that showed approximately two thirds of babies with birth weight <1251g developing ROP, and approximately a third of those with ROP developing pre-threshold ROP (Early Treatment for Retinopathy of Prematurity Cooperative Group, 2005; Palmer et al., 1991). However, the incidence of ROP in our study was significantly higher than that found in babies born in 1986 with birth weight 500 to 1499 g in New Zealand (Darlow, 1988). This may have been in part due to our study not screening babies with birth weight >1250g who have reduced risk of developing ROP, and the use of objective photographic documentation of ROP (Dai et al., 2015). Although a recent review of children with moderate to severe visual impairment has shown that significant visual impairment has reduced in New Zealand, ROP remains prevalent in preterm babies (Tan et al., 2015). We investigated the effects of ROP on visual outcomes and 5% of the children with previous ROP had retinal scarring from laser treatment, which is lower than expected in the general ROP population (Blencowe et al., 2013; Early Treatment for Retinopathy of Prematurity Cooperative Group, 2005). This may have been due to the higher median gestational age of children in our study as ROP is more prevalent in babies born earlier and younger (Blencowe et al., 2013; Darlow et al., 2005), and suggests that the children in our cohort may have had less severe ROP. The Term control group from our study were originally recruited from friends and siblings of the preterm children. However, due to the low response, we resorted to recruit participants born at full term through advertising (University of Auckland, New Zealand and social media) and word of mouth. As a result, our Term group consisted of mainly self-responders to advertising, unlike other studies where term participants were recruited through hospitals, schools, via postcode or age-matching (Larsson et al., 2012; O'Connor et al., 2002; Soong et al., 2008). Our Term group were older and differed in socioeconomic status (deprivation status at the time of the assessment) as well as ethnicity; we adjusted for age at the time of assessment (corrected

age for children born preterm) as a potential confounder. Seventy percent of the Term group were reported to have a family ocular history, which may have indicated that some of the children participated in our study due to parental concern of ocular problems. There have not been any population studies on visual outcomes and ocular biometry in New Zealand. However, presence of myopia in our Term group were slightly higher than those reported in an Australian study between 6 and 17 years of age (2.2-4.1%) (French et al., 2013) and spherical equivalent was less hyperopic (Ip et al., 2008), while ocular biometry was between those reported for Australian 6 to 12 year old children (Ip et al., 2008; Ojaimi et al., 2005). These factors combined with the difficulty of recruiting preterm children who were not diagnosed with ROP could limit the applicability of our results in the general ROP population. However, we were able to collect neonatal data for the majority of children and found that the main differences in the groups were due to preterm birth (i.e. gestational age, Apgar score, length of neonatal stay etc.). We were also able to assess a wide variety of visual function for these children at 8-10 years of age, which will provide a baseline for further investigation in the effects of preterm birth and ROP on visual outcomes.

While there was no difference in overall visual outcome between the three groups of children in our study, the ROP group tended to have poorer functional visual outcome and No ROP group tended to have poorer binocular visual outcome compared to children born at full term. Studies of children born preterm have shown a slight reduction in convergence and reduced depth perception when compared to children born at full term, which we did not find in our study (Geldof et al., 2014; Larsson et al., 2012). This may be due to missing slight reductions in convergence by using a pass/fail criteria compared to mean distance of convergence used in other studies, and also we were unable to measure convergence in 17% of the children in the ROP (due to strabismus, or poor concentration). We used a different depth perception test compared to other studies and chose a more liberal pass/fail screening criteria according to the test manual (Toegepast Natuurkundig Onderzoek, 2012) as we were mainly evaluating whether a child had gross depth perception, which would not pick up subtle changes in stereoacuity. Although there was no statistically significant difference between the preterm and term groups in the presence of strabismus, only children who were born preterm had strabismus (particularly in the ROP group) and numerically, the incidence of strabismus was similar to other populations of children born preterm and higher than term populations (Fielder et al., 2014; Hellgren et al., 2016; Holmström et al., 1999). As strabismus was more common in the preterm groups, both with and without ROP, and contributes to both binocular and functional visual outcomes, it is likely that it plays a significant role in visual outcomes of children born preterm.

In our study, there were no differences in refractive error between the groups, which differs from other studies where ROP has been associated with a higher incidence and magnitude of refractive error, particularly myopia (Hellgren et al., 2016; Quinn et al., 1998). This may be due to the myopia in the term group being higher than expected in the general population (French et al., 2013) and lower number of children with severe ROP, which is associated with myopia (Quinn et al., 2013). However, the mean SEP was less hyperopic compared to other Western countries (Fledelius et al., 2015; Hellgren et al., 2016; Ip et al., 2008), which may have been due to the measurement of our participants with subjective refraction compared to other studies that have generally used cycloplegic refraction (Choong et al., 2006). Although cycloplegic refraction is more repeatable than subjective refraction, not all the children were willing to have cycloplegic eye drops and for some children, even after waiting for 40 minutes, the cycloplegia was not complete (Bullimore et al., 1998; Manny et al., 1993). Therefore, to encompass more of the children, subjective refraction was used predominantly, and where subjective refraction could not be performed, auto-refraction results were used if available.

Although there were no differences in refractive error across our study, our results from ocular biometry measurements showed shorter axial length and steeper corneal curvature in the ROP group compared to the No ROP and Term group. This is similar to a study that reported that eyes affected by severe ROP were more likely to be smaller and have steeper corneas (Cook et al., 2008). However, some studies have found no difference in axial length in children with severe ROP who had laser treatment compared to term children and severe ROP not requiring treatment (McLoone et al., 2006; Yang et al., 2010). Steeper corneal curvature is typically associated with increased myopia but as there was no difference in refractive error between our groups, it is likely the corneal curvature power was neutralised by the shorter axial length. The central cornea was thinner in the eye with poorer VA but was not associated with VA. The significance of the difference in central corneal thickness is unknown as most studies have investigated the significance of central cornea thickness on intraocular pressure rather than other visual outcomes (Doughty & Zaman, 2000; Uva et al., 2011). One study has found that central corneal thickness and diameter in babies born preterm decreases towards term age but the babies were not followed up later (Chen et al., 2010). Anterior chamber depth was not different between the groups in our study, which differs from other studies where anterior chamber depth was shorter in children with ROP, particularly severe ROP (Cook et al., 2008; McLoone et al., 2006). However, this may be due to the lower incidence of myopia in our study. In chapter 7, we can see that children with ROP or IVH have a wider distribution and higher magnitude of refractive error than children born preterm without these conditions and children born at full term.

Central retinal thickness was thicker in the preterm groups compared to the term control group. This is consistent with other literature on preterm birth (Ecsedy et al., 2007; Park & Oh, 2012). However, we did not find a difference between the ROP and No ROP groups, which differs from the literature where more severe ROP is associated with thicker central retinal thickness (Ecsedy et al., 2007; Hammer et al., 2008; Wu et al., 2012). This may be in part due to the small numbers of children who were able to complete the optical coherence tomography test and the relatively small proportion of children in our ROP group who had severe ROP (stage 3 or worse ROP, n=5). The small numbers available were particularly evident where there was missing data for almost half of the children for peripheral retinal thickness due to movement during the testing procedure. The optical coherence tomography test we used did not have eye tracking function during the scan. Therefore, any movement during the test would result in misalignment of the slices, which usually happened towards the end of a scan during acquisition of peripheral slices. Our study was not powered to investigate differences between the different stages of ROP. Although there were differences in central retinal thickness between preterm and term children, VA was not different across the groups, which suggests that preterm-related retinal thickness changes are not associated with VA and is consistent with reports from other studies (Bowl et al., 2016; Villegas et al., 2014; Wu et al., 2012).

In our study, less than 5% of children required further follow-up outside of routine or referral for retinal or optic nerve abnormalities, and there were no differences between the three groups. However, children in both the ROP and no ROP groups had more changes to the peripheral retina and tortuosity of blood vessels than the term group. Changes to the peripheral retina in children with previous ROP have been noted since the 1980s and have been thought to be of no significance to visual outcomes. However, children who previously are born preterm have an increased risk of retinal detachment in later life (Bonamy et al., 2013; Kaiser et al., 2001; Tasman et al., 2006). We did not find any severe changes such as macular folds or signs of cicatricial retinopathy, which were prominent during the use of cryotherapy before laser ablation therapy became the mainstay treatment (Good, 2006; Ng et al., 2002). In the preterm groups, the common changes in the peripheral retina we found were areas of non-vascularised retina and white fibrous tissue within the retina which may be remnants of ROP, while in the term group, we found benign pigmentary changes. In our exploratory analysis, we found that the incomplete vascularisation in the peripheral retina did not affect visual outcomes or ocular structure apart from being associated with increased retinal thickness. The significance of the association between incomplete vascularisation and retinal thickness is unknown but increased central retinal thickness is associated with preterm birth. It can be speculated that the incomplete vascularisation is a marker of immaturity of the retina. Studies of myopia assessing

peripheral refraction have hypothesised that the peripheral retina is important in refractive error development and ocular growth (Charman & Radhakrishnan, 2010; Mutti et al., 2007; Smith et al., 2009); as ROP affects the peripheral retina, it may be a driving factor of changes in ocular structural development, particularly as we have found changes in axial length and corneal curvature between our groups. One thing to note is that our study was very small and the number of children with incomplete vascularisation was also small. Unexpectedly, we found incomplete vascularisation in both the ROP and no ROP groups. This could mean that there are retinal blood vessel changes outside of ROP, especially since there was more tortuosity of blood vessels in the No ROP group than the ROP group. It also cannot be excluded that it is possible some of the children in the No ROP may have had undetected mild ROP that spontaneously regressed without treatment as one child in the No ROP group that had fibrous tissue within the retina resembling remnants of a ROP ridge.

Several studies of electroretinogram and dark adaptation have shown defective rod activity in children born preterm, with or without ROP (Fulton et al., 2009; Reisner et al., 1997). In our study, we used pattern electroretinogram and pattern visual evoked potential components to assess whether preterm birth and ROP affected central retinal and post-retinal electrophysiological activity. There were no differences in latency or amplitude for any of the components of the pattern electroretinogram and pattern visual evoked potential between the three groups. Other studies have found conflicting results in pattern visual evoked potential (Feng et al., 2011; O'Reilly et al., 2010), which could have been due to different a different test setup, small sample size and different inclusion criteria. When we compared the two eyes, for the small check size in pattern visual evoked potential (requiring better VA), there was lower amplitude (smaller signal) of the N75-P100 component in the poorer VA eye compared to the better VA eye, which corresponded with the VA measures (Sokol, 1980). Due to the small number of children, we were not able to determine whether the difference between eyes were different across the groups. As retinal findings and electroretinogram results were similar between the groups and between the eyes, this difference in VA and amplitude in the electrophysiology would suggest that there may be changes in the visual pathway outside the retina between the eyes. Further investigation is required to understand the effects of ROP on electrophysiological activity of the visual pathway.

Global motion coherence assesses the ability to integrate local motion cues into a global precept of motion and is a test of dorsal stream function (Braddick et al., 2003). The dorsal stream has been hypothesised to be vulnerable to the effects of prematurity. We did not find a difference in global motion perception between the three groups in our study, although children in the ROP group tended

to have poorer motion perception than term controls. However, children in the ROP group had poorer visuomotor integration standard scores than children in the term group, which is an area that involves dorsal stream function. Children in the No ROP group had poorer visual perception and motor co-ordination scores compared to the Term group. Other studies in children born at a younger gestational age have shown more impairment of visuomotor integration in children with severe ROP compared to those with less severe ROP or no ROP and also an association between reduced VA and visuomotor integration (Goyen et al., 2006; Molloy et al., 2016). However, of the children with ROP in our study, the majority had ROP that did not require treatment. Reduced visuomotor integration performance has been suggested to contribute towards cognitive impairment and may affect handwriting and learning in children born preterm (Marlow et al., 2007; Pinheiro et al., 2014). Although binocular visual outcome was not statistically significantly different between the groups, a recent study has suggested that abnormal binocular vision reduces fine manipulation skills, which may contribute to reduced visuomotor skills (Alramis et al., 2016). Our results suggest that ROP may subtly affect dorsal stream function, which may be related to preterm birth as the ROP group had similar results to the No ROP group.

At eight to ten years of age, children who previously had ROP had statistically significantly lower weight, height and z-score than children born at full term. Other studies of children born preterm have shown similar findings (Cooke & Foulder-Hughes, 2003; Kitchen et al., 1992) and in adolescents, while weight differences between preterm and term groups became less apparent, preterm individuals continued to be shorter (Roberts et al., 2013). Postnatal nutrition has been proposed to be an important factor in growth of babies born preterm (Pfister & Ramel, 2014). Impaired growth, particularly before 24 months of age has been associated with poorer neurodevelopment and motor development (Cooke & Foulder-Hughes, 2003; Ranke et al., 2015). Poor postnatal growth has been associated with increased risk of ROP and it has been hypothesised to be due to lowered IGF-1 in the neonatal period (Hård et al., 2013; Löfqvist et al., 2006). Axial length was associated with both height and head circumference growth, which is consistent with other studies showing correspondence between physical growth and ocular growth (Mutti et al., 2007; Wang et al., 2011). However, it is unknown whether improvements in physical growth to similar to children at full term would affect ocular growth and subsequent visual functional outcomes.

A few limitations to our study were identified. Firstly, our study was a non-blinded observational study from a single centre NICU. The main assessor of the study was part of the recruitment team and since the recruitment of the preterm children were according to having ROP or not having ROP as the main

criteria, it was not possible to have the assessor blinded to ROP status of the child. To reduce bias, the assessor followed the protocol of the study for all children and where possible, for data that was analysed subjectively after the assessment, data files were either randomly ordered or put into alphabetical order before processing, then separated into the three groups (ROP, no ROP, term) after all the data had been processed. Data such as coding of retinal images and electrophysiology were confirmed by a second observer. No attempt to analyse the data was made until all data had been collected. The study involved a small group of children and we were unable to recruitment as many children without ROP as planned. This was due to small number of children available in a short time frame, and also that we only found out some of the children who were classified as not having developed ROP from the ANZNN database were later confirmed to have ROP through neonatal clinical records. As a result, the power of the study was limited particularly as a large number of variables were measured and some of the children were unable to complete all the tests. However, by measuring different aspects of vision, we were able to have a more holistic view of how ROP and preterm birth affect visual outcomes in later childhood.

Visual acuity is one of the most common outcomes in vision research, but it is only one aspect of vision and does not always correlate with ocular structural changes. Various outcomes such as contrast sensitivity, structural outcomes, data binning and test batteries have been used to report visual outcomes. However, each study uses different definitions for visual outcomes, which limits comparison between studies (Good & Hardy, 2001; Hellgren et al., 2016). Also, quality of vision is a continuum as different aspects of vision can contribute to the overall vision. Therefore, there is no "composite" visual outcome that encompasses visual function fully. We chose a retinal scarring as our primary outcome as we wanted to investigate whether children born preterm with or without ROP would have more significant peripheral retinal changes that affected vision than children born at full term. However, due to the small number of children with retinal scarring and limited to children with ROP, a functional visual outcome such as blindness or VA equal or better than 6/12 would have been a better choice. In our study, we used various composite outcomes to describe visual function more broadly, but we may have been strict with our criteria for favourable outcome as only half of the children in our study had a favourable overall visual outcome. Therefore, we introduced a functional visual outcome (good presenting VA and stereoacuity without strabismus) to assess how well the children were "seeing" at the time of assessment (what they "normally" see). At the same time, we need to consider that we do not fully understand the implications of the "unfavourable" visual outcomes in the real world. As more studies use composite outcomes, there needs to be more

standardisation on reporting of visual outcomes and better evaluation of the effects of vision on daily activities to better understand the implication of changes in vision.

In conclusion, children in the ROP group had better visual outcomes than previously reported in the literature and the majority of children who require vision follow-up have been identified through vision screening programmes and eye care services in New Zealand. However, children who previously had ROP tended to have reductions in binocular and functional visual outcome. ROP was also associated with reduced visual motor integration and ocular structural changes. Therefore, ROP remains a condition associated with adverse visual outcomes, particularly as up to 30% of children with previous ROP had reduced functional vision that could not be improved with spectacles. Preterm children who do not develop ROP have similar visual function to children born at full term but remain at risk of visual impairment and changes to ocular structure. Further long-term investigation into the reduced visual function and ocular changes in preterm birth and ROP are needed to understand their implications on daily activities. It is particularly important to follow-up the peripheral retinal changes especially since ROP and preterm birth have previously been associated with changes to vision and increased risk of retinal detachment in later life. Current vision screening and management of children born preterm in New Zealand appear to detect most children requiring vision follow-up.

7 Effects of Preterm Birth on Visual Outcomes in Later Childhood

7.1 Introduction

Babies born preterm are at risk of neonatal complications and side effects of treatments which can increase the risk of visual impairment in later life, such as: oxygen supplementation for RDS (Askie & Henderson-Smart, 2009); metabolic disorders such as neonatal hypoglycaemia or hyperglycaemia (chapter 3); brain injury from IVH and PVL (Bolisetty et al., 2014; McDonnell & O'Connor, 2015), and ROP (Blencowe et al., 2013; Fielder et al., 2014). ROP is a proliferative retinal vascular disease that affects up to 68% of babies born with a birth weight of less than 1251 grams (Early Treatment for Retinopathy of Prematurity Cooperative Group, 2005). Severe ROP is recognised as a major cause of childhood visual impairment in children born preterm. In 2010, it was estimated that more than 30,000 preterm babies had visual impairment due to ROP globally (Blencowe et al., 2012). However, even without neonatal complications such as ROP or brain injury, preterm birth *per se* has also been implicated with adverse visual outcomes (Cook et al., 2008; O'Connor & Fielder, 2008).

Common visual functions affected in preterm birth include VA, contrast sensitivity, ocular alignment and eye movements, stereoacuity, visual field, visual perception, and light adaptation (Fulton et al., 2009; O'Connor et al., 2007). Ocular changes such as a shallower anterior chamber, thicker crystalline lens and steeper corneal thickness have been noted; these changes have been associated with high refractive errors, particularly myopia (Cook et al., 2008; Fielder et al., 2014). Children born preterm also have changes in foveal morphology, where there appears to be a disruption in migration of inner retinal layer cells, resulting in a thicker fovea with a shallower foveal pit (Maldonado et al., 2011). The implication of the foveal changes on visual function remains uncertain. Preterm birth has also been associated with an increased risk of strabismus (Hellgren et al., 2016). However, a recent population study found that although children born preterm continue to have a higher frequency of visual deficits, the associations between visual impairment and gestational age are not apparent when there is an adjustment for ROP treatment (a surrogate for severe ROP). This suggests that ROP may have more effect on visual impairment than gestational age (Hellgren et al., 2016).

The aim of this chapter was to explore how preterm birth affects visual outcomes in later childhood. Long-term vision results will be presented for children who participated in the PIANO or EYE-SPY follow-up studies.

7.2 Methods

Children born very preterm who previously had been cared for in the National Women's Health NICU between July 2005 and December 2008 were invited to participate in the Protein, Insulin and Neonatal Outcomes (PIANO) study and Examining Young Eyes for Signs of PrematuritY (EYE-SPY) study at seven to ten years corrected age. A cohort of children who were born at full term of the same age range were invited to participate as term controls in these studies.

Full details of inclusion and exclusion criteria, recruitment details and vision tests can be found in 2.1, and 2.2. For children who participated in both the PIANO and EYE-SPY studies, only data from the assessment with the most complete dataset were used in this chapter.

Visual outcomes assessed were composite visual function including overall visual outcome, binocular visual outcome, and functional visual outcome. Other visual outcomes included VA, global motion perception, ocular structure and refractive error. Other outcomes included anthropometry and B4 school vision check.

VA was measured using different tests in the PIANO and EYE-SPY tests. These tests were only comparable for binocular VA (Appendix 9.5). Therefore, logMAR VA for the better and poorer eye were not reported in this chapter.

7.2.1 Statistical analyses

Statistical calculations were performed using SPSS Statistics 22 (IBM) and graphs were plotted in Prism 7 for Windows (GraphPad Software, Inc). Details for standard statistical analyses can be found in 2.4.

7.3 Results

One hundred and twenty nine children born preterm and 23 term controls participated in the PIANO study and 64 children born preterm and 37 term controls participated in the EYE-SPY study; 35 children born preterm and 3 children born at full term participated in both studies. This resulted in 158 children in the Preterm group and 57 children in the Term group being assessed between seven and ten years of age (Figure 7-1).

Figure 7-1 Strobe diagram of children from the PIANO and EYE-SPY studies analysed in this chapter

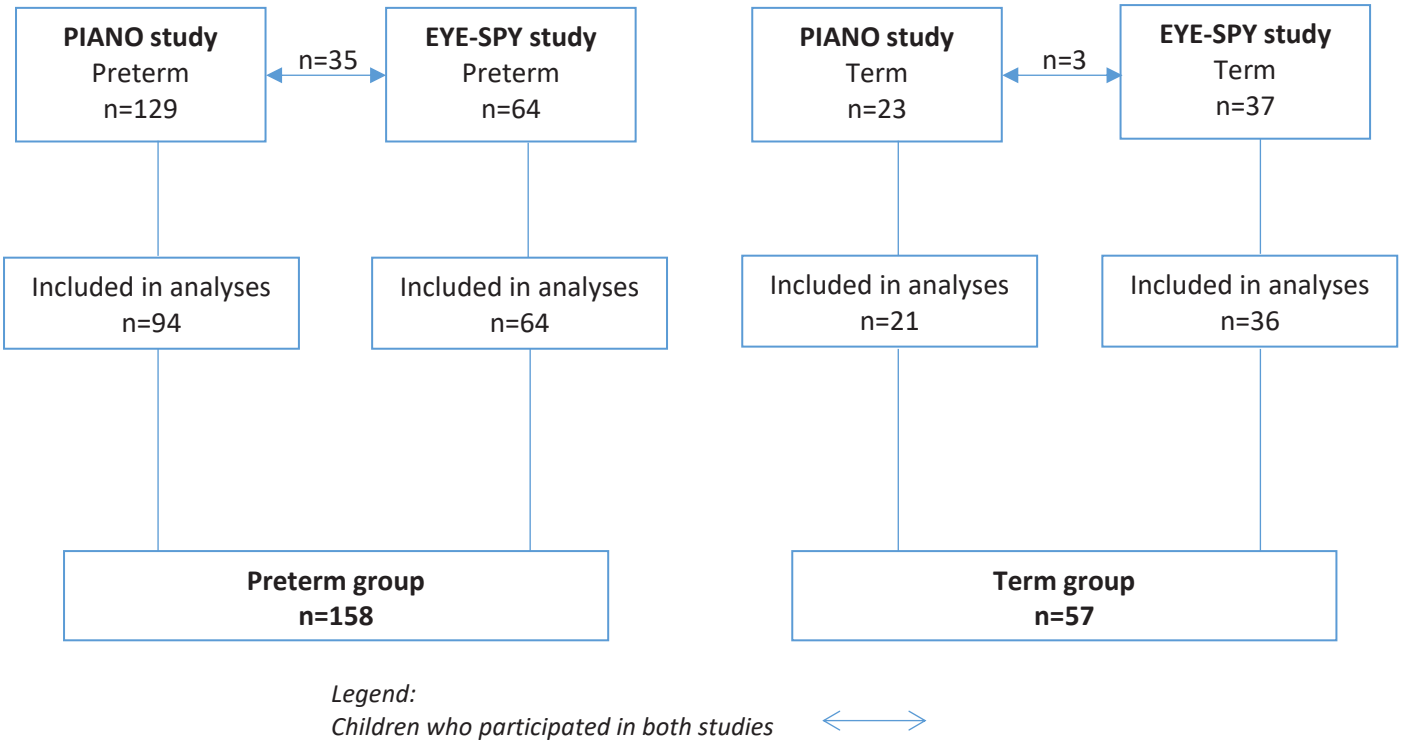


Table 7-1 Baseline neonatal characteristics for children assessed in the PIANO and EYE-SPY studies at seven to ten years of age inclusive

	Preterm group (n=158)	Term group (n=57)	P-value
Gestational age (weeks)	26 (25, 28)	40 (39, 41)	< 0.001
Birth measurements			
Weight (g)	902.5 (755.0, 1041.3)	3650.0 (3350.0, 3928.8)	< 0.001
Weight z-score	-0.04 ± 0.93	0.03 ± 0.91	0.62
Crown-heel length (cm)	34.5 (32.5, 37.0)	52.0 (50.5, 54.0)	< 0.001
Length z-score	-0.20 ± 1.69	0.46 ± 1.23	0.02
Head circumference (cm)	24.6 (23.3, 26.3)	35.5 (35.0, 36.5)	< 0.001
Head circumference z-score	0.17 ± 1.08	0.33 ± 0.93	0.38
Small for gestational age	16/158 (10%)	3/53 (6%)	0.62
Large for gestational age	6/158 (4%)	2/53 (4%)	
Apgar score			
1 minute	6 ± 2	8 ± 1	< 0.0001
5 minutes	8 ± 2	10 ± 1	< 0.0001
Length of neonatal stay (days)^	85 (67, 104)	3 (2, 4)	< 0.001
NZ deprivation index at birth			
Most deprived (10)	29/157 (19%)	3/51 (6%)	< 0.01
Least deprived (1)	12/157 (8%)	4/51 (8%)	

Data are n (%), mean±standard deviation, median (interquartile range), apart from for ^median (min, max). ^Preterm group missing 1, Term group missing 19. Abbreviations: g grams, cm centimetres

Baseline neonatal characteristics (Table 7-1) of the children differed between the Preterm and Term groups except for birth weight z-score, head circumference z-score at birth and number of children born small for gestational age. The Preterm group were born earlier and shorter with lower Apgar scores at 1 minute and 5 minutes and were discharged home later than the Term group. Babies born preterm were also more likely to be born to families living in higher deprivation areas. Children in the Preterm group were at risk of neonatal complications, with the most common being ROP, followed by glycaemic imbalance, BPD, IVH and late-onset infection (Table 7-2).

Table 7-2 Descriptive statistics of the neonatal complications and neonatal treatment of the Preterm group in the PIANO and EYE-SPY studies

Neonatal complications and treatment	
Glycaemic status	
Hyperglycaemia (BGC > 8.5 mmol.L^{-1})*	97/157 (62%)
Hypoglycaemia (BGC < 2.6 mmol.L^{-1})*	67/157 (43%)
Insulin Treatment	51/156 (33%)
Necrotising enterocolitis	7/155 (5%)
Periventricular leukomalacia	0/148 (0%)
Intraventricular haemorrhage (IVH)	29/153 (19%)
IVH (grade I/II)	21 (14%)
IVH (grade III/IV)	8 (5%)
Retinopathy of prematurity (ROP)	109/151 (72%)
ROP (stage 1/2)	92 (61%)
ROP (stage 3/4)	17 (11%)
Treated ROP	13/158 (8%)
Infection	
Early-onset infection	1/157 (0.6%)
Late-onset infection	26/157 (17%)
Bronchopulmonary dysplasia	35/158 (22%)
Respiratory support	
IPPV (hours)	49.0 (4.5, 280.5)
CPAP (hours)	1001.0 (457.5, 1287.0)
Home oxygen	30/158 (19%)
Major neonatal surgery	14/157 (9%)

At least one episode of blood glucose concentration in the specified range. Data are n (%), median (interquartile range). Abbreviations: BGC blood glucose concentration IPPV intermittent positive pressure ventilation, CPAP continuous positive airway pressure, mmol.L-1 millimole per litre

At the time of the PIANO and EYE-SPY study assessments, the children in the Term group were older than the Preterm group. Children in the Preterm group remained shorter than children in the Term group and also had smaller head circumference. More children in the Preterm group were living in the

most deprived areas. There were differences in the ethnicity distribution between groups, with a higher proportion of children of Māori and Pacific Island descent in the Preterm group, while a higher proportion of children in the Term group were of European ethnicities (Table 7-3). Children born preterm were more likely to have received past ocular surgery or therapy, with treatment for ROP being most common in this group (Table 7-4). The Preterm group tended to have been prescribed spectacles more. A similar number of children from both groups had a before school vision screening (Table 7-4). Of those who passed the before school vision screening, the majority had favourable functional visual outcome at 7-10 years of age. The before school vision screening was less likely to identify children with unfavourable overall and binocular visual outcome. The preterm group had more unfavourable binocular visual outcome.

Table 7-3 Characteristics of children at the time of PIANO and EYE-SPY studies assessment at seven to ten years of age inclusive

	Preterm group (n=158)	**Term group (n=57)**	**P-value**
Age at assessment (years)*	7.9 ± 0.9	8.7 ± 1.2	< 0.0001
Male	86 (54%)	34 (60%)	0.54
Ethnicity			
NZ Māori	43/154 (28%)[a]	7/57 (12%)[b]	<0.01
Pacific Island	25/154 (16%)[a]	2/57 (4%)[b]	
NZ European	69/154 (45%)[a]	39/57 (68%)[b]	
Asian/Other	17/153 (11%)[a]	9/57 (16%)[a]	
Anthropometry			
Weight (kg)	25.5 (22.3, 30.8)	29.3 (26.2, 34.3)	< 0.001
Weight z-score	0.19 ± 1.41	0.43 ± 0.77	0.12
Height (cm)	127.8 (121.9, 132.7)	134.0 (128.0, 141.3)	< 0.001
Height z-score	0.18 ± 1.10	0.51 ± 0.75	0.01
Head circumference (cm)	52.0 (51.0, 53.3)	53.7 (52.0, 54.8)	< 0.001
Head circumference z-score	-0.89 ± 1.40	-0.20 ± 0.94	0.0001
Growth velocity ($g.kg^{-1}.day^{-1}$)	1.15 ± 0.14	0.67 ± 0.06	< 0.0001
NZ deprivation index at time of assessment			
Most deprived (10)	21/158 (13%)	1/56 (2%)	0.01
Least deprived (1)	19/158 (12%)	11/56 (20%)	

**Corrected age for Preterm group. Non-matching superscript letters indicate a significant difference (p<0.05) amongst groups on post hoc analysis. Data are median (interquartile range), n (%), mean±standard deviation. Abbreviations: kg kilogram, cm centimetres, $g.kg^{-1}.day^{-1}$ grams per kilogram per day. Due to rounding, percentages may not add up to 100%.*

Table 7-4 Parent-reported ocular history and B4 school check visual outcomes of children assessed in the PIANO and EYE-SPY studies at seven to ten years of age inclusive

	Preterm group (n=158)	Term group (n=57)	P-value	*Adjusted P-value
Spectacles worn	24 (15%)	3 (5%)	0.05	0.24
Past ocular surgery/therapy	*26 (17%)*	*3 (5%)*	*0.03*	*0.14*
Strabismus	6 (4%)	0 (0%)		
Laser for ROP	14 (9%)	-		
Patching	8 (5%)	1 (2%)		
Vision training	4 (3%)	2 (4%)		
B4 school check visual outcomes^	*117 (74%)*	*48 (84%)*	*0.12*	*0.82*
Pass	101 (64%)	42 (74%)	0.19	-
Rescreen	7 (4%)	2 (4%)		
Referred	9 (6%)	4 (7%)		
Under care	13 (8%)	0 (0%)		
Declined	4 (3%)	0 (0%)		
Not done	24 (15%)	9 (16%)		
Of those passing B4 school check				
Favourable overall visual outcome	60/87 (69%)	24/36 (67%)	0.80	0.84
Favourable binocular visual outcome	52/98 (53%)	29/42 (69%)	0.09	0.04
Favourable functional visual outcome	85/99 (86%)	38/42 (91%)	0.59	0.55

**Adjusted for age at assessment, ethnicity and NZ deprivation index at assessment. ^Children in the Pass, Rescreen, and Referred categories were considered as had B4 school check; other categories considered B4 school check not done. Data are n (%). Due to rounding, percentages may not add up to 100.*

There were no statistically significant differences in overall visual outcomes between children in the Preterm group compared to those in the Term group (Table 7-5). Children in the Preterm group were more likely to have poorer binocular and functional visual outcome, which remained after adjusting for age at the time of assessment, ethnicity and deprivation. One child in the Preterm group was blind from severe ROP, while there were no cases of blindness in the Term group. There was poorer distance binocular VA (with two eyes together), and higher incidence of strabismus found in the Preterm group, which were no longer statistically significant after adjustment for potential confounders. Other visual functions were not different between the Preterm and Term groups except for poorer stereoacuity in the Preterm group.

The proportion of children having ocular abnormalities requiring further follow-up or referral was similar in both the Preterm and Term groups (Table 7-6). There was a trend of more hyperopia in the poorer VA eye of children in the Preterm group. No statistically significant differences in refractive error were found between the two groups (Table 7-6, Figure 7-2).

Table 7-5 Visual functional outcomes of children assessed in the PIANO and EYE-SPY studies at seven to ten years of age inclusive

	Preterm group (n=158)	Term group (n=57)	OR or mean difference (95%CI)	P-value	*Adjusted OR or mean difference (95%CI)	P-value
Favourable overall visual outcome^	76/141 (54%)	33/49 (67%)	0.57 (0.29, 1.12)	0.10	0.62 (0.28, 1.39)	0.25
Favourable binocular visual outcome	66/153 (43%)	41/56 (73%)	0.28 (0.14, 0.54)	0.0001	0.32 (0.15, 0.69)	< 0.01
Favourable functional visual outcome	110/153 (72%)	52/56 (93%)	0.20 (0.07, 0.58)	0.001	0.25 (0.08, 0.78)	0.02
Distance VA in Better Eye						
Blindness (6/60 or worse)	1/157 (0.6%)	0/57 (0%)	-		-	
Equal or better than 6/12	152/156 (97%)	55/56 (98%)	0.69 (0.08, 6.25)	0.74	0.41 (0.03, 5.08)	0.49
Better than 6/7.5	136/156 (87%)	54/56 (96%)	0.25 (0.06, 1.11)	0.07	0.51 (0.10, 2.57)	0.42
Presenting binocular distance VA (logMAR)	-0.05 ± 0.22	-0.13 ± 0.08	0.09 (0.04, 0.13)	0.01	0.05 (-0.02, 0.12)	0.13
Binocular visual outcomes						
Presence of strabismus	20/157 (13%)	1/56 (2%)	8.00 (1.05, 62.50)	0.02	5.36 (0.63, 45.34)	0.12
Pass stereoacuity (TNO)	116/152 (76%)	54/56 (97%)	0.12 (0.03, 0.51)	0.001	0.17 (0.04, 0.77)	0.02
Log stereoacuity	2.32 ± 0.85 (~209 secs of arc)	1.88 ± 0.46 (~76 secs of arc)	0.44 (0.26, 0.63)	< 0.001	0.41 (0.14, 0.67)	< 0.01
Normal ocular motility	132/155 (85%)	52/56 (93%)	0.44 (0.15, 1.33)	0.15	0.35 (0.10, 1.19)	0.09
Normal convergence	122/141 (87%)	54/56 (97%)	0.24 (0.05, 1.05)	0.06	0.33 (0.07, 1.669)	0.18
Presence of motor fusion	100/152 (67%)	44/56 (79%)	0.52 (0.26, 1.08)	0.08	0.53 (0.23, 1.21)	0.13
Mean global motion perception threshold	42.48 ± 20.52	34.58 ± 22.63	7.90 (1.25, 14.54)	0.02	3.97 (-3.28, 11.22)	0.28

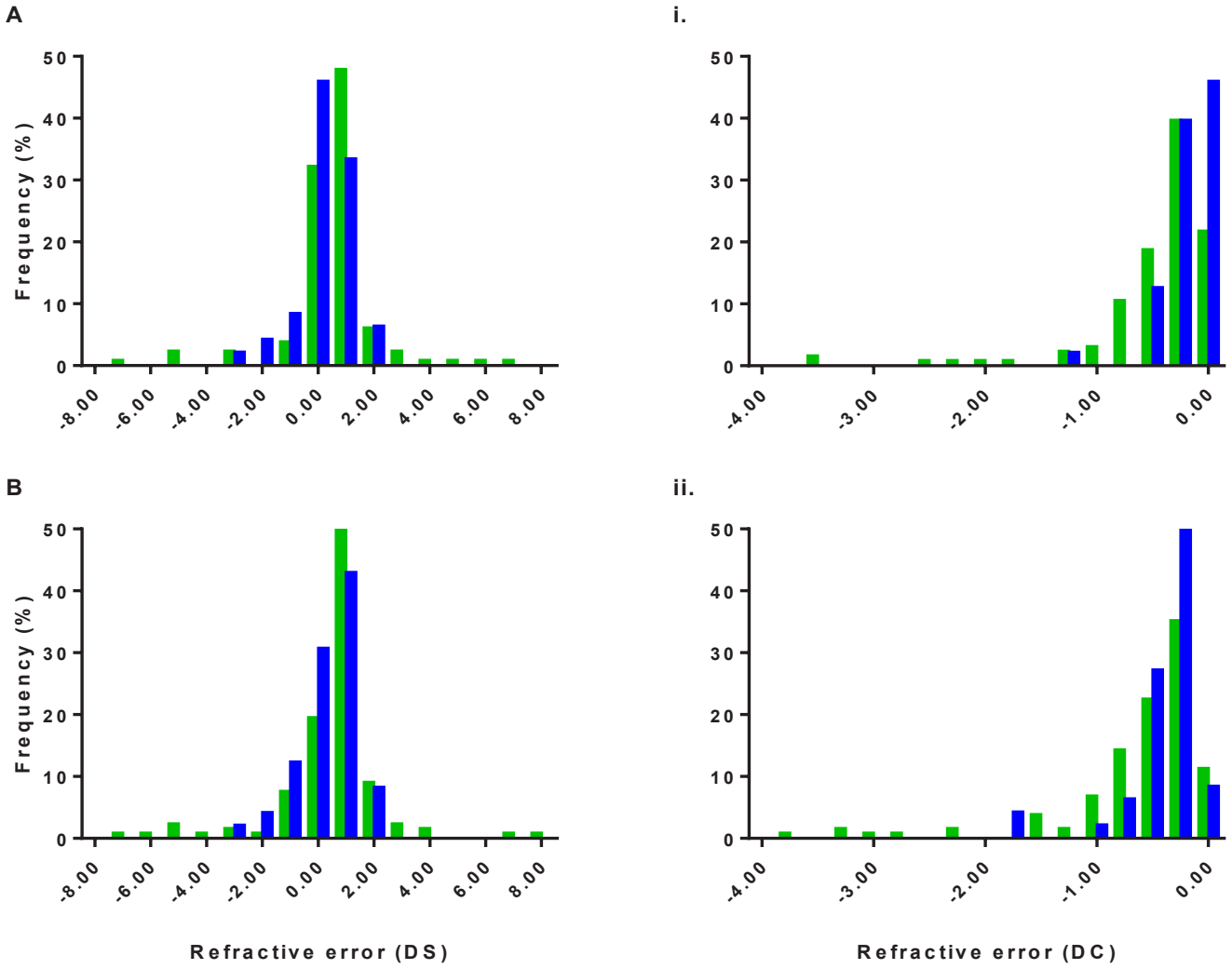
**Adjusted for age at assessment, ethnicity and NZ deprivation index at assessment. ^Missing due to some of the children not having cycloplegic eye drops, which was a necessary requirement for the measurement of refractive error by auto-refraction; refractive error was a component of the overall visual outcome composite. Data are n (%), mean±standard deviation.*

Table 7-6 Ocular structural and refractive outcomes of children assessed in the PIANO and EYE-SPY studies at seven to ten years of age inclusive

	Preterm group (n=158)	Term group (n=57)	OR or mean difference (95%CI)	P-value	*Adjusted OR or mean difference (95%CI)	P-value
Ocular structure						
Retinal posterior pole (central) findings			0.67		-	
No abnormalities or non-clinically significant findings	135/158 (85%)	52/57 (91%)				
Clinically significant findings	9/158 (6%)	1/57 (2%)				
Unable to assess	14/158 (9%)	4/57 (7%)				
Refractive error^						
SEP of the better VA eye			0.21		0.33	
Myopia (≤ - 0.50)	12/134 (9%)	7/48 (15%)				
Hyperopia (> +0.50)	72/134 (54%)	19/48 (40%)				
Significant hyperopia (> +2.00 D)	7/134 (5%)	1/48 (2%)				
SEP of the poorer VA eye			0.12		0.05	
Myopia (≤ - 0.50)	19/134 (14%)	9/49 (18%)				
Hyperopia (> +0.50)	85/134 (63%)	23/49 (47%)				
Significant hyperopia (> +2.00 D)	10/134 (8%)	2/49 (4%)				
Astigmatism						
Better eye	12/134 (9%)	1/48 (2%)	4.62 (0.59, 36.55)	0.11	1.92 (0.19, 19.61)	0.58
Poorer eye	20/134 (15%)	3/48 (6%)	2.63 (0.75, 9.29)	0.12	1.82 (0.44, 7.58)	0.41
Anisometropia	4/133 (3%)	0/49 (0%)	-		-	
Not requiring spectacles	99/134 (74%)	34/48 (71%)	1.16 (0.56, 2.44)	0.68	1.12 (0.44, 2.80)	0.82

**Adjusted for age at assessment, ethnicity and NZ deprivation index at assessment. Data are n (%), mean±standard deviation. Due to rounding, percentages may not add up to 100%. Abbreviations: logMAR logarithm of the minimum angle of resolution, SEP spherical equivalent power, VA visual acuity, D dioptres.*

Figure 7-2 Refractive error distribution of children assessed in the PIANO and EYE-SPY studies at seven to ten years inclusive



Spherical equivalent power (DS) of the better VA eye (A), poorer VA eye (B); cylindrical power (DC) of the better VA eye (i.), poorer VA eye (ii.) of the children in the Preterm group (green) and Term group (blue). All comparisons between the Preterm and Term groups showed p>0.05.

Table 7-7 Ocular biometry and retinal thickness of children assessed in the PIANO and EYE-SPY studies at seven to ten years of age inclusive

	Preterm group (n=158)	Term group (n=57)	Mean difference (95%CI)	P-value	*Adjusted mean difference (95%CI)	P-value
Central corneal thickness (µm)						
Better VA Eye[a]	542 ± 34	550 ± 30	-9 (-19, 2)	0.10	-11 (-23, 3)	0.06
Poorer VA Eye[b]	542 ± 34	551 ± 29	-9 (-19, 1)	0.09	-11 (-23, 0)	0.05
Anterior chamber depth (mm)						
Better VA Eye[c]	3.45 ± 0.29	3.59 ± 0.29	-0.15 (-0.24, -0.06)	0.001	-0.11 (-0.21, -0.01)	0.03
Poorer VA Eye[d]	3.44 ± 0.30	3.60 ± 0.29	-0.16 (-0.25, -0.07)	0.001	-0.12 (-0.22, -0.01)	0.03
Axial length (mm)						
Better VA Eye[a]	22.45 ± 0.88	23.04 ± 0.71	-0.60 (-0.85, -0.33)	< 0.0001	-0.40 (-0.69, -0.11)	0.01
Poorer VA Eye[b]	22.45 ± 0.91	23.02 ± 0.74	-0.57 (-0.84, -0.30)	< 0.0001	-0.41 (-0.71, -0.11)	0.01
Lens thickness (mm)						
Better VA Eye[e]	3.70 ± 0.26	3.60 ± 0.25	0.10 (0.02, 0.18)	0.02	0.03 (-0.06, 0.12)	0.51
Poorer VA Eye[e]	3.70 ± 0.27	3.59 ± 0.23	0.11 (0.03, 0.19)	< 0.01	0.04 (-0.05, 0.12)	0.41
Corneal curvature (mm)						
Flat Meridian Better VA Eye[a]	7.70 ± 0.27	7.91 ± 0.24	-0.21 (-0.30, -0.13)	< 0.0001	-0.21 (-0.30, -0.11)	< 0.0001
Flat Meridian Poorer VA Eye[d]	7.70 ± 0.28	7.92 ± 0.25	-0.21 (-0.30, -0.13)	< 0.0001	-0.22 (-0.31, -0.12)	< 0.0001
Steep Meridian Better VA Eye[a]	7.55 ± 0.28	7.77 ± 0.24	-0.22 (-0.31, -0.14)	< 0.0001	-0.20 (-0.30, -0.10)	0.0001
Steep Meridian Poorer VA Eye[d]	7.54 ± 0.28	7.76 ± 0.24	-0.22 (-0.30, -0.13)	< 0.0001	-0.20 (-0.30, -0.11)	0.0001
Central retinal thickness (µm)						
Better VA Eye[f]	282 ± 25	257 ± 17	24 (17, 31)	< 0.0001	31 (22, 39)	< 0.0001
Poorer VA Eye[f]	281 ± 25	257 ± 17	25 (18, 32)	< 0.0001	32 (23, 40)	< 0.0001

**Adjusted for age at assessment, ethnicity and NZ deprivation index at assessment. Data are n (%), mean±standard deviation. From the Preterm group, number of missing: [a]27, [b]25, [c]26, [d]24, [e]28. [f]There were 45 missing from the Preterm group and 15 missing from the Term group.*

Of the ocular biometry components, the crystalline lens was thicker in the eyes of children born preterm, but the difference was no longer statistically significant different following adjustment for potential confounders (Table 7-7). Children in the Preterm group had shorter anterior chamber depth and axial length and had steeper corneal curvature along both flat and steep meridians. The Preterm group tended to have thinner central corneal thickness. The central retina of children in the Preterm group was also thicker than children in the Term group.

Excluding children who previously had any stages of ROP or IVH, there were 33 children who were born preterm with median gestational age of 28 weeks (IQR 25, 28) and birth weight of 935 g (IQR 777, 1098). There were no statistically significant differences in overall visual outcomes between children in the Preterm group (excluding ROP and IVH) compared to those in the Term group (Table 7-8). Children in the Preterm group were more likely to have poorer binocular and functional visual outcome. After adjusting for age at the time of assessment, ethnicity and NZ Dep score, functional visual outcome was no longer significantly different between the groups, but binocular vision tended to be poorer in the Preterm group. After excluding cases of ROP or IVH, none of the children had blindness. All other visual functions were not different between the Preterm and Term groups after adjustment for potential confounders.

The proportion of children having ocular abnormalities requiring further follow-up or referral was similar in both the Preterm and Term groups when ROP and IVH were excluded (Table 7-9). A larger proportion of children in the Term group had myopia in the better VA eye, while children born Preterm without ROP or IVH had higher incidence of astigmatism in the poorer VA eye (Table 7-9).

Of the ocular biometry components, there were no differences between the Preterm and Term groups in central corneal thickness, anterior chamber depth and lens thickness (Table 7-10) when preterm children who previously had ROP or IVH were excluded. Axial length was shorter in the Preterm group, but the difference was no longer statistically significant following adjustment for potential confounders, particularly ethnicity. Steeper corneal curvature along both flat and steep meridians and thicker central retinal thickness in the Preterm group remained after excluding children with previous ROP or IVH.

Table 7-8 Visual functional outcomes of children assessed in the PIANO and EYE-SPY studies, excluding preterm children with ROP and/or IVH

	Preterm group (n=33)	Term group (n=57)	OR or mean difference (95%CI)	P-value	*Adjusted OR or mean difference (95%CI)	P-value
Favourable overall visual outcome	15/28 (54%)	33/49 (67%)	0.56 (0.22, 1.45)	0.33	0.83 (0.25, 2.75)	0.76
Favourable binocular visual outcome	13/32 (41%)	41/56 (73%)	0.25 (0.10, 0.63)	< 0.01	0.32 (0.11, 1.98)	0.05
Favourable functional visual outcome	25/32 (78%)	52/56 (93%)	3.64 (0.97, 13.60)	0.09	0.50 (0.11, 2.26)	0.37
Distance VA in Better Eye						
Blindness (6/60 or worse)	0/33 (0%)	0/57 (0%)	-		-	
Equal or better than 6/12	33/33 (100%)	55/56 (98%)	-	1.00	-	1.00
Better than 6/7.5	31/33 (94%)	54/56 (96%)	0.57 (0.08, 4.28)	0.63	0.40 (0.04, 3.95)	0.38
Presenting binocular distance VA (logMAR)	-0.10 ± 0.08	-0.13 ± 0.08	0.04 (0.00, 0.07)	0.06	0.03 (-0.01, 0.07)	0.17
Other visual outcomes						
Presence of strabismus	5/33 (15%)	1/56 (2%)	9.80 (1.09, 90.91)	0.03	2.85 (0.22, 37.18)	0.43
Pass stereoacuity (TNO)	27/32 (84%)	54/56 (97%)	0.20 (0.04, 1.10)	0.10	0.49 (0.06, 3.73)	0.49
Log stereoacuity	2.18 ± 0.80 (~151 secs of arc)	1.88 ± 0.46 (~76 secs of arc)	0.30 (-0.01, 0.61)	0.06	0.19 (-0.10, 0.49)	0.20
Not requiring spectacles	21/33 (75%)	34/48 (71%)	1.24 (0.43, 3.56)	0.70	1.26 (0.32, 5.00)	0.48
Normal ocular motility	28/33 (85%)	52/56 (93%)	0.43 (0.11, 1.73)	0.28	0.71 (0.15, 3.46)	0.67
Normal convergence	26/30 (87%)	54/56 (97%)	0.24 (0.04, 1.40)	0.18	0.21 (0.02, 2.11)	0.19
Presence of motor fusion	20/32 (63%)	44/56 (79%)	0.46 (0.17, 1.19)	0.08	0.46 (0.14, 1.49)	0.19
Mean global motion perception threshold	42.16 ± 20.53	34.58 ± 22.63	7.58 (-2.16, 17.32)	0.13	2.58 (-8.34, 13.50)	0.64

**Adjusted for age at assessment, ethnicity and NZ deprivation index at assessment. Data are n (%), mean±standard deviation. Abbreviations: logMAR logarithm of the minimum angle of resolution, TNO is the name of the stereoacuity test.*

Table 7-9 Ocular structural and refractive outcomes of children assessed in the PIANO and EYE-SPY studies, excluding preterm children with ROP and/or IVH

	Preterm group (n=33)	Term group (n=57)	OR or mean difference (95%CI)	P-value	*Adjusted OR or mean difference (95%CI)	P-value
Ocular structure						
Retinal posterior pole (central) findings			1.00		-	
No abnormalities or non-clinically significant findings	30/33 (91%)	52/57 (91%)				
Clinically significant findings	1/33 (3%)	1/57 (2%)				
Unable to assess	2/33 (6%)	4/57 (7%)				
Refractive error						
SEP of the better VA eye			0.05		-	
Myopia	0/28 (0%)	8/48 (17%)				
Hyperopia	15/28 (54%)	20/48 (40%)				
Significant hyperopia (> +2.00 D)	1/28 (4%)	1/48 (2%)				
Range (D)	-0.38 to 3.07	-2.69 to 2.07				
SEP power of the poorer VA eye			0.19		-	
Myopia	3/29 (10%)	9/49 (18%)				
Hyperopia	20/29 (69%)	23/49 (47%)				
Significant hyperopia (> +2.00 D)	1/29 (3%)	2/49 (4%)				
Range (D)	-1.38 to 2.32	-2.75 to 2.44				
Astigmatism						
Better eye	2/28 (7%)	1/48 (2%)	3.62 (0.31, 41.80)	0.55	3.62 (0.16, 82.04)	0.42
Highest cyl better eye (DS)	-1.37	1.37				
Poorer eye	6/29 (21%)	3/48 (6%)	3.91 (0.90, 17.09)	0.07	9.65 (1.31, 71.12)	0.03
Highest cyl poorer eye (DS)	-3.75	-1.87				
Anisometropia	1/28 (4%)	0/49 (0%)	-		-	

**Adjusted for age at assessment, ethnicity and NZ deprivation index at assessment. Data are n (%), mean±standard deviation. Due to rounding, percentages may not add up to 100%. Abbreviations: VA visual acuity, D dioptres, cyl cylindrical power. Note: Unable to calculate adjusted p-values for retinal findings and spherical equivalent power (SEP) due to small number of children.*

Table 7-10 Ocular biometry of children assessed in the PIANO and EYE-SPY studies, excluding preterm children with ROP and/or IVH

	Preterm group (n=33)	Term group (n=57)	Mean difference (95%CI)	P-value	*Adjusted mean difference (95%CI)	P-value
Central corneal thickness (µm)[#]						
Better VA Eye	543 ± 37	550 ± 30	-8 (-23, 8)	0.32	-6 (-23, 11)	0.47
Poorer VA Eye	545 ± 42	551 ± 29	-6 (-21, 10)	0.45	-3 (-21, 14)	0.71
Anterior chamber depth (mm)[#]						
Better VA Eye	3.51 ± 0.30	3.59 ± 0.29	-0.09 (-0.22, 0.05)	0.21	-0.10 (-0.25, 0.05)	0.20
Poorer VA Eye	3.52 ± 0.28	3.60 ± 0.29	-0.08 (-0.21, 0.05)	0.22	-0.08 (-0.23, 0.07)	0.27
Axial length (mm)[#]						
Better VA Eye	22.55 ± 0.81	23.04 ± 0.71	-0.49 (-0.84, -0.15)	< 0.01	-0.30 (-0.67, 0.08)	0.13
Poorer VA Eye	22.57 ± 0.84	23.02 ± 0.74	-0.45 (-0.81, -0.10)	0.01	-0.27 (-0.66, 0.12)	0.18
Lens thickness (mm)[#]						
Better VA Eye	3.64 ± 0.20	3.60 ± 0.25	0.04 (-0.07, 0.15)	0.47	0.03 (-0.10, 0.15)	0.65
Poorer VA Eye	3.65 ± 0.20	3.59 ± 0.23	0.05 (-0.05, 0.15)	0.31	0.02 (-0.10, 0.14)	0.72
Corneal curvature (mm)						
Flat Meridian Better VA Eye	7.71 ± 0.28	7.91 ± 0.24	-0.20 (-0.32, -0.08)	< 0.01	-0.15 (-0.29, -0.01)	0.03
Flat Meridian Poorer VA Eye	7.74 ± 0.31	7.92 ± 0.25	-0.18 (-0.31, -0.06)	< 0.01	-0.14 (-0.28, 0.00)	0.05
Steep Meridian Better VA Eye	7.58 ± 0.29	7.77 ± 0.24	-0.19 (-0.32, -0.06)	0.01	-0.13 (-0.27, 0.01)	0.06
Steep Meridian Poorer VA Eye	7.58 ± 0.29	7.76 ± 0.24	-0.18 (-0.30, -0.06)	< 0.01	-0.14 (-0.27, -0.01)	0.04
Central retinal thickness (µm)^						
Better VA Eye	282 ± 18	257 ± 17	24 (14, 34)	< 0.0001	28 (18, 39)	< 0.0001
Poorer VA Eye	280 ± 19	257 ± 17	23 (14, 33)	< 0.0001	30 (20, 40)	< 0.0001

**Adjusted for age at assessment, ethnicity and NZ deprivation index at assessment. Data are n (%), mean±standard deviation. [#]From the Preterm group, there were 6 missing for better eye and 5 missing for poorer eye. ^From the Preterm group, there were 16 missing for the better eye and 13 for the poorer eye; from the Term group, there were 15 missing for both better and poorer eye.*

7.4 Discussion

Children born preterm had similar overall visual outcome as children born at full term but had poorer binocular vision and had changes to ocular structure. The two groups of children in our study differed in several respects of baseline characteristics and demographics such as age at assessment, ethnicity and socioeconomic status. The risk of adverse visual outcomes in children born preterm was reduced after adjusting for age, ethnicity and NZ Dep score. As well as differences in visual outcomes, children born preterm were also shorter and had smaller head circumference than the term children by 7 to 10 years of age. Children born preterm who did not have ROP or IVH (which can increase the risk of visual impairment) had similar visual outcomes to children born at full term but poorer binocular visual outcomes, and changes in corneal curvature and central retinal thickness remained. Only 21% of the children in our preterm cohort did not have ROP or IVH, which limited the power of this analysis. This suggests that the majority of long-term visual deficits in children born preterm are secondary to potentially modifiable complications of preterm birth. Further research to reduce the incidence of ROP and IVH, and improve the treatment of these conditions, could improve long-term visual outcomes in children born preterm.

In our cohort, there was no difference in the overall visual outcome between children born preterm and those born at full term. However, more than 30% of the children in both groups had an unfavourable visual outcome. This differs from a study in Sweden of six year old children who were born before 27 weeks' gestational age that found 38% of the preterm group and 6% of the control group had a poor composite score (based on VA worse than 20/60, strabismus and refractive error) (Hellgren et al., 2016). Our criteria for unfavourable visual outcome were stricter than the Swedish study with a lower threshold of good VA and a lower cut-off for refractive error, which may in part explain the higher incidence of unfavourable outcome in our study. We measured refractive error using auto-refraction after cycloplegia. However, many of the children were unable to complete the refractive error component of our visual outcome due to non-consent for cycloplegic eye drops (the main reasons were declining by parent or child or shortage of time due to the test duration), which limited the applicability of this composite outcome.

For the other composite outcomes measured, preterm children were more likely to have unfavourable binocular and functional visual outcomes compared to the term group. Similarly, 25% of ten year old children born at a birth weight of 1500g or less were found to have visual dysfunction (VA equal or poorer than 0.1logMAR in the better eye, strabismus and reduced contrast sensitivity in at least 3/5

measured frequencies) in a Swedish population study (Holmström et al., 1998). Stereoacuity was present in both the binocular and functional visual outcome and was reduced in the Preterm group, which suggests that children born preterm are at increased risk of binocular vision and functional visual problems predominantly from reduced stereoacuity.

Binocular vision involves oculomotor and sensory information, and in our study, we measured binocular vision with a composite measure that included both of these components (ocular alignment, ocular motility, convergence, motor fusion and stereoacuity) (O'Connor & Birch, 2010). The higher proportion of unfavourable binocular vision outcome in the Preterm group is consistent with other studies, where strabismus, reduced convergence and stereopsis impairment were more common in children born preterm (Geldof et al., 2014; Larsson et al., 2012; Lindqvist et al., 2008). In our study, there were no statistically significant differences between the groups in oculomotor functions needed for motor fusion, including absence of strabismus, and good ocular motility and convergence after adjustment for potential confounders. Although the difference in incidence of strabismus was not statistically significant between the groups, numerically, similar proportions of strabismus in the Preterm group have been found in other studies of children born preterm (Hellgren et al., 2016). The proportion of children with reduced stereoacuity was also similar to that found in previous studies (Hellgren et al., 2007). Binocular vision, particularly stereopsis (fine binocular depth perception, which can only be present if there is both motor and sensory fusion) and increased area of visual field from combining images from both eyes is important for many daily activities such as reading and moving around in the environment. Therefore, these visual changes may contribute towards the poor academic performance seen in children born preterm (Molloy et al., 2016). Our results highlight the importance of screening for binocular vision in children born preterm.

The global motion perception threshold was similar between the Preterm and Term groups after adjustment for the difference in age between the groups, which is different from two other studies that have found reduced motion perception in children born preterm (MacKay et al., 2005; Taylor et al., 2009). In these two studies, sex, age, intelligence, parental education and family income were screened for and were similar between Preterm and Term groups. The children who had major sensory impairment, were born small for gestational age or had undergone shunting for posthaemorrhagic hydrocephalus were excluded, which in our study were not exclusion criteria. However, in our exploratory analysis of children born preterm and who did not have ROP or IVH, motion perception remained similar between children born preterm and those born at full term. In both studies age at testing was controlled for as motion perception has been found to improve with age (MacKay et al.,

2005; Taylor et al., 2009). MacKay *et al*. did not find a correlation between birth weight and global motion perception in a preterm group, although they did not use corrected age to account for the gestational age difference (MacKay et al., 2005). The thresholds from our study were higher (poorer motion perception) than those of MacKay *et al*. and Taylor *et al*. even though the children in our study were of a slightly higher age. This could have been due to the difference in stimulus of the coherence pattern; our stimulus consisted of slower moving dots in a lower density, which has been found to result in higher thresholds (Narasimhan & Giaschi, 2012).

Although ROP is associated with changes in the retina (Fielder et al., 2014), we did not find any differences in the retinal and optic nerve structure between the Preterm and Term groups. In the Preterm group, the majority of clinically significant retinal abnormalities were due to ROP such as macular ectopia and temporal blood vessel straightening. As only the posterior pole of the retina was examined (central retina) and ROP is predominantly a peripheral retinal condition, this may have contributed to the low incidence of retinal findings. Three eyes (1%) from our study would meet the unfavourable structural outcome criteria of the multicentre studies of ROP (retinal detachment or fold or lesion involving fovea, or view of macula blocked by cataract or fibrous membrane), which is consistent with results from the natural history cohort of the Cryo-ROP study at five and a half years of age (Palmer et al., 1991). All three eyes had laser treatment for severe ROP. When children that were born preterm and had ROP or IVH were excluded, differences in retinal structural abnormalities were no longer present. Therefore, unfavourable retinal structural changes in preterm birth appear to be associated with ROP, particularly severe ROP that requires treatment. Intravitreal anti-VEGF treatment is showing promise in reducing refractive error but further investigation into long-term visual outcomes and safety of use in babies born preterm are required (Darlow, 2015; Geloneck et al., 2014; VanderVeen et al., 2017).

The proportions of children with myopia, hyperopia and astigmatism were not statistically significantly different between the Preterm and Term groups of our cohort. We did not find high proportions of significant myopia (<-5.00D) that are often reported in studies of children born preterm (Hsieh et al., 2012; Quinn et al., 1998). However, the Preterm group had wider ranges of refractive error, and most cases of significant myopia or hyperopia were from the Preterm group, which is similar to other recent population studies in Europe (Fledelius et al., 2015; Hellgren et al., 2016). The proportion of myopia in our Term group was higher than reported in other contemporary studies. Our Term group may not have been representative of the general population as participants were mainly self-responders to advertising on social media or through the University of Auckland, and some parents may have

responded to advertising due to concerns for their child's vision. In addition, ethnicity has been associated with differential risk of refractive error, with children of Asian ethnicities with higher prevalence of myopia compared to European ethnicities (French et al., 2013; Ojaimi et al., 2005). However, this is different from our study as there were more children of European descent in our Term group. Some of the children were still able to accommodate significantly during the auto-refraction measurement even after cycloplegic drops were instilled, making the result unreliable and this may have contributed to the higher incidence of myopia. However, these possibilities do not explain the differences in ocular biometry found between the groups. During childhood and adolescence, the axial length of the eye becomes longer, anterior chamber depth increases, lens thickness becomes thinner and corneal curvature becomes less steep (Fledelius & Stubbaard, 1986; Hashemi et al., 2015; Shih et al., 2011). In emmetropia, the ocular biometry components have co-ordinated growth (Shih et al., 2011). Children from our Preterm group generally had smaller eyes (shorter anterior chamber depth and axial length) accompanied by steeper corneal curvature, which is consistent with data from a younger cohort of preterm children (Cook et al., 2008). Therefore, our data indicate that preterm birth affects ocular growth.

Preterm birth is associated with many neonatal complications and the majority of children (80%) in our preterm cohort experienced ROP or IVH, which can affect visual outcomes. In our exploratory analyses, we excluded children who previously have ROP and/or IVH and compared the Preterm and Term groups to assess the effects of preterm birth *per se* on visual outcomes. Preterm children who did not have ROP or IVH were born at an older gestational age and were heavier at birth. The majority of the visual outcomes were no longer different between the groups, including all the composite visual outcomes. Although not statistically significant, binocular visual outcome and VA in the better eye tended to be worse in the Preterm group. A population study in Sweden of children born in 1988-1990 found slightly reduced VA at 10 years of age with preterm birth *per se*, while a more recent Danish study in 4 year old children who were born preterm found no differences in VA, refractive error and astigmatism when comparing preterm children who did not have ROP and term controls (Fledelius et al., 2015; Larsson et al., 2005). In our study, the Preterm group tended to have a higher proportion of astigmatism in the eye with the poorer VA. The differences in ocular biometry we found in the entire Preterm group compared to the Term group mostly disappeared after excluding children who previously had ROP or IVH; only corneal curvature remained steeper in the Preterm group, which may be associated with the higher incidence of astigmatism in the Preterm group. Central retinal thickness was thicker in the whole Preterm group and remained statistically significant after excluding ROP and IVH cases, which is consistent with other studies. However, many children at the beginning of our

study did not complete the test as we did not have a spectral domain optical coherence tomography until part way through the recruitment process. The implications of these ocular changes on visual outcome is unclear as no studies have investigated the effects of thicker retinal thickness associated with preterm birth in later life. Although the differences in visual outcome were no longer statistically significant between the Preterm and Term groups in the exploratory analyses, the absolute proportions with unfavourable visual outcomes remained similar. This suggests that preterm birth *per se* may subtly affect visual outcomes as well as having association with ocular structural changes.

In New Zealand, preterm babies who had ROP are reviewed through ophthalmology services at least up to 6 months after discharge from the NICU. For the general population, there is a children's vision screening as part of the B4 School Check (B4SC) programme, at 4 years of age, which tests VA (Ministry of Health, 2008). Although this programme does not screen children already in the care of an ophthalmologist or optometrist, the majority of children in our study were assessed and a similar proportion of preterm children and term controls were referred for further testing of vision. Our results were similar to a retrospective review of children referred from the B4SC to an outpatient clinic where 4% of 3273 were referred from the vision screening (Anstice et al., 2012) and a recent report from Growing Up in New Zealand showed that 70% of children had completed the B4SC before 4.5 years of age (Morton et al., 2017). The B4SC was found to have 47% positive predictive value in the retrospective review (Anstice et al., 2012), while in our study, of those who passed the B4SC vision screening, two thirds had a favourable overall visual outcome, and the majority had favourable functional visual outcome. However, half of the preterm children who passed the B4SC had an unfavourable binocular visual outcome at 8-10 years of age. As children born preterm have higher risk of poorer binocular visual outcome, particularly strabismus and reduced stereoacuity, vision screening for these children may benefit from having a test for binocular vision such as a stereoacuity test (Cotter et al., 2015). The Growing Up in New Zealand study found that at 4.5 years of age, 28% of vision problems were identified at the B4SC while 26% were identified earlier by parents (Morton et al., 2017), confirming that parents are important in helping identify potential visual problems in their children. Raising awareness of the potential visual problems associated with preterm birth and communication with parents may help to reduce the impact of adverse visual outcomes in children born preterm (Dai et al., 2015; A. L. Hård & Hellström, 2006).

There were several limitations for this chapter. Results from two observational studies were combined together in this chapter to explore the effects of preterm birth on visual outcomes in a larger cohort. However, the visual assessment for these two studies varied in some of the tests. For example, VA

was measured with different letter charts and nystagmus was not measured in the EYE-SPY study. In the PIANO study, children born preterm were subjected to a much longer assessment that involved tests of cognition, neurodevelopment, and metabolic outcome, while the term born children only did the visual assessment. Therefore, for the Preterm group, fatigue could have affected their performance in the visual assessment, which was often the final assessment in the day, and the differences we found between the groups could have reflected this. However, this is unlikely as visual outcomes from our study appear to be similar to those reported in the literature (Hellgren et al., 2016). Another limitation was that the proportion of children born preterm and children born at term were different between the groups, which may have contributed to the age difference between the groups. We were unable to precisely match children born preterm with term controls, even though we first attempted to recruit term born friends or family members of preterm participants. However, due to the difficulty with finding participants in this manner, we relied on recruitment through advertising on social media and our institute. This resulted in differences in ethnicity and age between the groups, also, the possibility of parents responding to the advertising due to concerns for their child's vision. To reduce confounding by these differences, we used composite measures and adjusted for age, ethnicity and deprivation scores.

Another limitation we encountered was the difficulty with comparing our results with data from other studies. The definition for visual outcomes vary across studies, particularly for refractive error and VA. An example is some studies have defined myopia as >-3.00D, while other studies have used -1.00D as a cut-off and still others have used -0.50D (Hashemi et al., 2015; Hellgren et al., 2016; Ojaimi et al., 2005). Also, children were assessed at an age when visual function and ocular structure were still developing. Therefore, with a cross-sectional study, it was unknown whether the differences between the groups were absolute or whether these would change over time. It may have been useful to measure visual function with best corrected spectacles to assess whether the differences in visual function we found could be correctable. However, due to the time constraints, we were unable to do this. There is also a need for population norms to compare visual outcomes. We have compared data from Europe and Australia, but their distribution of ethnicity is quite different from New Zealand. All these variables highlight the importance of standardisation of visual function reporting and longer-term follow-up to fully understand the impact of preterm birth on visual outcome.

In conclusion, we did not find any difference in overall visual outcome between children born preterm and children born at full term in later childhood. However, children born preterm are at risk of an unfavourable binocular and functional visual outcome, particularly reduced stereoacuity, which is

consistent with findings reported in the literature. Children born preterm also have changes to ocular structure, which include shorter axial length, steeper corneal curvature and thicker central retinal thickness. The implications of these changes in ocular structure are unknown. Although preterm children without ROP or IVH have similar visual functional outcomes as children born at term, ocular structural changes are still present. With up to 30% of children born preterm with unfavourable functional visual outcome, this highlights the importance of understanding whether these adverse visual outcomes continue into adolescence and whether they affect daily activities.

8 Conclusions

Since the 1940s, ROP has been known to be associated with adverse visual outcomes, such as retinal detachment and blindness (Terry, 1946). Although there have been improvements in the management of ROP including classification of ROP (The Committee for the Classification of Retinopathy of Prematurity, 1984), ablation therapy for severe ROP (Cryotherapy for Retinopathy of Prematurity Cooperative Group, 1988), structured screening programmes (American Academy of Pediatrics, 2006) and more understanding of the mechanisms of ROP (Darlow, 2015; Hartnett & Penn, 2012), which have improved visual outcomes greatly compared to when ROP was first discovered, ROP remains one of the leading causes of childhood visual impairment (Blencowe et al., 2013; Chong & Dai, 2014). One difficulty with studying visual outcomes in children with ROP is that past studies have shown that preterm birth *per se* has also been associated with increased risk of adverse visual outcomes, which include reduced VA, increased incidence of strabismus and refractive error, and cerebral visual impairment (O'Connor et al., 2002). Preterm birth is also associated with other neonatal complications such as neonatal hyperglycaemia (Beardsall et al., 2010) and IVH (Bolisetty et al., 2014), with babies born younger or smaller with increased risk of these complications. Neonatal hyperglycaemia has been associated with ROP and may increase risk of visual impairment, and tight glycaemic control of hyperglycaemia with insulin can cause hypoglycaemia, which is associated with adverse visual outcomes from occipital lobe injury. Babies born preterm also have poor postnatal growth, which has been linked to neonatal nutrition (Cooke, 2005; Yeung & Smyth, 2003). The contribution of these risk factors, apart from ROP, on visual outcomes had not been studied previously.

In New Zealand, ROP has only previously been studied in a cohort of children born in 1986 (Darlow, Clemett, et al., 1997) and through retrospective review of medical records (Tan et al., 2015). In 2006, there were updates to the criteria for treatment of severe ROP at the National Women's Health NICU (Auckland, New Zealand) following the recommendations of a large randomized trial of early treatment of ROP in 2004 that showed ablation treatment of Type 1 ROP improving ocular structural and functional visual outcomes (Good, 2004). At the same time, there were changes from using indirect ophthalmoscopy for ROP screening to using wide-field digital retinal imaging (Dai et al., 2015). As well as adopting a new protocol for ROP management, there were also updates to neonatal intravenous nutrition guidelines (Tsang et al., 2005) and a randomized controlled trial of tight glycaemic control with insulin for neonatal hyperglycaemia (Alsweiler et al., 2012). This provided a unique opportunity to investigate the long-term effects of preterm birth, neonatal nutrition, ROP and neonatal hyperglycaemia on visual outcomes at 7-10 years of age. Visual outcomes were also assessed

in a follow-up of the randomised controlled trial of tight glycaemic control treatment of neonatal hyperglycaemia.

Overall visual outcome (the number of children having good vision, including not requiring spectacles) were similar between groups in each cohort reported in this thesis. However, preterm birth increased the risk of unfavourable binocular visual function and preterm children tended to have poorer functional visual outcome. Binocular vision is dependent on the combination of oculomotor function and sensory information. In children born preterm, there were higher incidences of strabismus (misalignment of the eyes) and reduced stereoacuity, which have been reported in previous studies (Lindqvist et al., 2008; O'Connor et al., 2004). Children with neonatal hyperglycaemia according to our criteria (at least two consecutive measures of BGC >8.5mmol.L^{-1} at least 4 hours apart) had more strabismus than children without hyperglycaemia but this was no longer significant after adjusting for matching criteria. A similar trend was seen between children with ROP compared to preterm children without ROP and children born at full term, and also between preterm and term born children. This suggests that ROP, hyperglycaemia and preterm birth are not independently associated with strabismus.

Neonatal nutrition did not affect the risk of strabismus but higher protein intake in the first week after birth was associated with increased risk of cerebral palsy, which was associated with reduced stereoacuity. In our study, although there was higher incidence of cerebral palsy in the group receiving the new formulation of nutrition, the incidence of cerebral palsy was similar to those reported in the literature for children born preterm (Allen et al., 2011). The higher incidence of poor stereopsis associated with cerebral palsy may be due to ocular muscle dysfunction similar to the overall movement and posture dysfunction characterised by cerebral palsy. But even without cerebral palsy, children who had the reformulated intravenous nutrition (higher protein intake with reduced carbohydrate and fluid intake) appeared to have poorer motor skills and poorer binocular vision without the reduction in stereoacuity, which suggests that the change in nutrition may be associated with the subtle oculomotor deficits. There were several concurrent changes to the intravenous nutrition, making it difficult to confirm which nutrient change was most likely associated with the differences in visual outcome between the groups. Further investigation is needed to determine whether increased protein intake via intravenous nutrition is detrimental to binocular vision. This is important as current recommendations for protein intake in preterm babies is higher than those we investigated.

In the EYE-SPY follow-up study, the incidence of ROP was similar to that reported by large randomized trials of ROP treatment (Early Treatment for Retinopathy of Prematurity Cooperative Group, 2005; Palmer et al., 1991) but more than previously reported in New Zealand (Darlow, 1988);. the incidence of blindness was 2% in children with ROP, which was similar to previously reported (Darlow, Horwood, et al., 1997). ROP was found to be associated with poorer functional visual outcome (defined as VA equal or better than 6/12 in the better eye, no strabismus and stereoacuity equal or better than 240 seconds of arc) and changes to retinal structure and ocular biometry. Many studies of ROP have shown an increased incidence of myopia in children with ROP, which increased with ROP severity and ablation treatment for ROP (Fielder et al., 2014; O'Connor & Fielder, 2008). However, our study did not show any difference in refractive error in children with ROP compared to children born at full term even though there were changes in ocular biometry, with thinner and steeper corneas, and shorter axial length in children with ROP. This was perhaps due to the poor representation of our term group. Compared to studies in Australia, the incidence of myopia was higher in our term cohort (French et al., 2013). This reflects that some of the term children in our study may have participated due to parental concerns of ocular problems. The lower incidence of myopia in our ROP cohort could also be due to the high proportion of children who had relatively mild ROP, with only 3 children having severe ROP that needed treatment. Children born preterm had a similar incidence of refractive error as children born at full term, although it appears that they are more susceptible to a wider range of refractive error and astigmatism. Although we did not find an effect of ROP on refractive error; to confirm this, more understanding of refractive error development in children in New Zealand is needed, as currently there are no population studies of refractive errors in childhood in this population.

Despite there being few cases of severe ROP that needed treatment in our study and most cases of ROP spontaneously regressed without treatment, 10% of the children had incomplete vascularization of the peripheral retina. Historical studies of ROP have focused on cicatricial retinal changes as these have been associated with visual impairment (Cryotherapy for Retinopathy of Prematurity Cooperative Group, 2002; Palmer et al., 2005). Mild ROP has been associated with some peripheral retinal changes but the effects of these changes on visual outcome are unclear; although in the majority of cases, mild ROP is associated with no visual impairment or minor visual deficits (An International Committee for the Classification of Retinopathy of Prematurity, 2005; Mintz-Hittner & Kretzer, 1994; O'Connor et al., 2004). Our data supported this as incomplete retinal vascularization did not affect visual outcomes. However, there was steeper corneal curvature and thicker retinas in the children with incomplete vascularisation; the implications of these ocular changes are unknown.

It would be important to follow-up these changes to assess whether these increase the risk of retinal detachment or adverse visual outcomes in babies born preterm in later life.

Increased central retinal thickness has been consistently seen in babies born preterm and does not appear to affect visual function (Park & Oh, 2012). It has previously been proposed that there is disruption to the parafoveal migration of the inner layers of the retina following preterm birth, which results in a shallower optic pit and thicker foveal profile (Maldonado et al., 2011; Provis et al., 2013; Yanni et al., 2012). In the children who had incomplete retinal vascularization, there was thicker central retinal thickness. Since the retina has been thought to be a principle driving factor of myopia development (Charman & Radhakrishnan, 2010), this leads to the speculation that retinal development in preterm birth may be important in understanding the ocular growth dysfunction, which can affect incidence of refractive error and anisometropic strabismus. Children born preterm with and without ROP typically have changes in the peripheral retina, and these children are at risk of developing refractive error; these peripheral retinal changes may have also affected the growth of the eye. Longitudinal studies of retinal and ocular development in preterm babies would be required to test this hypothesis.

Ocular biometry changes seen in children born preterm were steeper corneal curvature and tendency of thinner corneal thickness. Shorter axial length was associated with ROP and this has been reported in previous studies (Cook et al., 2008). Children with ROP also had steeper corneal curvature than children without ROP or children born at full term. However, in most of those studies, the smaller eye and steeper cornea were associated with increased incidence of myopia, and was associated with more severe ROP, which we did not find (Fledelius & Fledelius, 2012). One thing to note is that myopia is usually associated with longer axial length, which differs from reports of children with ROP, where myopia tends to be associated with shorter axial length and steeper corneal curvature (O'Connor et al., 2002; Xie et al., 2009). Due to the small number of children with severe ROP in our study, we were unable to analyse ocular biometry according to ROP severity. As ocular biometry did not appear to correlate with VA, it is unknown the significance of these changes in children born preterm. Preterm children were often shorter and had a smaller head circumference than children born at term, especially if the child had ROP. Axial length was associated with both height and head circumference, which is consistent with other studies showing correspondence between physical growth and ocular growth (Wang et al., 2011). It is unknown whether improvements in physical growth in children born preterm would affect ocular growth and subsequent visual functional outcomes. Many studies have investigated the changes in ocular growth between birth and term age in babies born preterm, with

and without ROP (Cook et al., 2008; Uva et al., 2011). However, there has been paucity of data comparing these ocular biometry variances in childhood or adolescence past when ocular growth has stabilised with a term group, and in the understanding of how these changes affect visual function rather than only refractive error development. This highlights the importance of understanding the long-term consequences of abnormal ocular growth on vision into adolescence and adulthood.

Neonatal hyperglycaemia and tight glycaemic control with insulin did not affect overall functional visual outcome. High BGC was associated with reduced VA and lens thickness, while VA was also reduced with increasing insulin dosage. Similar to a recent systematic review, we found that neonatal hyperglycaemia was not associated with ROP (Au et al., 2015). Although there were no differences in incidence of treated ROP between our hyperglycaemic and non-hyperglycaemic groups, when we analysed BGC across the entire cohort, higher BGC was associated with increased risk of severe ROP that required treatment. The difference could be due to a large number of children in our Non-hyperglycaemic group having high BGC, even though they did not meet our criteria for neonatal hyperglycaemia that needed treatment. This was the first study to show a correlation between high BGC and increasing crystalline lens thickness in babies born preterm. Increased lens thickness has been reported in individuals with diabetes mellitus (both type I and type II) but in most cases, high BGCs have been prolonged, which is different from the transient nature of neonatal hyperglycaemia (N. G M Wiemer et al., 2008). The increased lens thickness in diabetes may be from influx of glucose and water into the lens and could be a precursor to cataract formation (Bron et al., 1993; Nanouk G. M. Wiemer et al., 2008). It may be beneficial to investigate whether lens thickness changes are seen in children born to mothers with gestational diabetes as those children may have been subject to increased BGC around the same gestational age at which children born preterm have neonatal hyperglycaemia. Lens thickness also changes in childhood and becomes thinner with age (Hashemi et al., 2015). It is unclear when ocular components cease to grow as factors such as genetics, environment and visual needs can affect myopia development (Pärssinen et al., 2014). Therefore, it is important to investigate further whether the lens thickness changes we found continue throughout later childhood and adolescence, whether there is increased risk of cataracts in these children, and to investigate the functional implications of these differences since lens thickness was associated with VA in this cohort.

Children who had tight glycaemic control with insulin for neonatal hyperglycaemia had a higher incidence of hypoglycaemia, although half the children in the standard control group who developed hypoglycaemia did not have an insulin infusion. Hypoglycaemia in our cohort did not affect survival

without neurodevelopment and did not affect the incidence of overall visual impairment. Children who had experienced at least one episode of hypoglycaemia tended to have poorer binocular VA and higher global motion coherence threshold (lowered sensitivity to global motion). However, hyperglycaemia and insulin were found to be more significantly associated with binocular VA than hypoglycaemia. In the literature, visual impairment from hypoglycaemia was often associated with damage to the occipital lobe of the brain (Tam et al., 2008). Children in the PIANO study have undergone magnetic resonance imaging of the brain; further processing of this data may help to identify whether there were any effects of hypoglycaemia on brain structure responsible for visual function.

Global motion coherence performance, which has been proposed to represent the integrity of the dorsal stream in brain development (Braddick et al., 2016), was similar between children born preterm compared to children born at full term. This was incongruous with the literature, where preterm birth was associated with poorer global motion perception (MacKay et al., 2005; Taylor et al., 2009). However, children with ROP tended to have poorer motion perception and had a poorer visuomotor integration standard score than children born at full term, while preterm children without ROP had poorer visual perception and motor co-ordination scores compared to term controls. Visual motor integration also involves dorsal stream function and has been suggested to contribute towards cognitive development, handwriting, and learning. Although our results suggest that ROP may subtly affect dorsal stream function, but preterm birth may also be implicated as the results from the ROP group was similar to that found in the No ROP group.

An unexpected finding from our study was a differential effect of nutrition on stereacuity and global motion perception. Children who were born after reformulation of neonatal nutrition had poorer stereoacuity but better global motion perception. None of the neonatal risk factors or known exposures or neonatal nutritional intake experienced by the babies that were different between the Before and After group were statistically significant in predicting motion perception, which meant this difference in motion perception could be due to an unknown exposure or due to a direct effect of a nutritional component. Further investigation would be required to validate whether there is a relationship between nutritional intake and global motion perception, and whether global motion perception can be modulated by changes in neonatal nutrition.

A major strength of our studies was that we had a multidisciplinary approach to evaluate different areas of development in a cohort of children born preterm as well as visual function. Part of the PIANO

study was a follow-up of a randomised controlled trial (HINT trial), which meant groups were well matched in many maternal and baseline characteristics. For many of the children, neonatal history was available, which enabled an in depth understanding of the relationships between neonatal risk factors, exposures and outcomes in later childhood. In the preterm groups, differences were often due to the underlying factors that predisposed a child to develop a neonatal complication (i.e. babies who developed hyperglycaemia were often born younger, smaller and were sicker). We reduced errors from incongruous groups by identifying neonatal risk factors and exposures that were potential confounders and adjusting for these in analyses.

One of the main limitations was that most of the studies reported in this thesis were observational studies, except a follow-up of a randomised controlled trial, which meant that causation could not be established between exposures and visual outcomes. Also, due to the complexity of this study, many interventions were identified, and a wide range of tests were performed, so when children were stratified by the different interventions, the resulting groups were small and lacked power to investigate the effects of the interventions on visual outcomes. This may have further been affected by loss to follow-up. Depending on the reason not being follow-up, bias could be introduced; for example if one group had more deaths than the other, an important exposure might be missed; or if it is hard for a participant to attend the follow-up, disability might be missed (Doyle et al., 2018). In our study, we compared the maternal and baseline characteristics of the children who were assessed and not assessed and found similar characteristics between groups. Therefore, it is likely that our samples were representative of the children in the original study. Multiple comparisons were another issue we encountered due to the complexity of the study, which can increase the likelihood of a false positive statistically significant difference between groups. A common way of dealing with multiple comparisons is by adjusting the statistical significant power threshold such as the Bonferroni correction, where the power threshold (usually 0.05) is divided by the number of comparisons or family-wise comparisons (Dunnett, 2012). However, in our study, it was difficult to calculate the number of variables to correct for and if too many variables are corrected for, the Bonferroni correction can miss true differences between groups. Another method for considering multiple comparisons is to estimate a false discovery rate but this method relies on assumptions of likelihood of having false positives for each test (Narum, 2006). We attempted to account for these sources of variance by setting specific outcomes before analysis and identifying other analyses as exploratory in nature.

To study the effects of preterm birth on visual outcomes, we recruited a cohort of children born at full term as a comparison group. Term controls were originally recruited from friends and siblings of the preterm children in an attempt to account for socioeconomic status and ethnicity. However, we had a lukewarm response and thus we expanded our recruitment by using advertising and word of mouth. This resulted in many self-responders to advertising and it was likely some children participated due to parents having a concern for vision, which was highlighted by the high incidence of family history reported by parents of the term controls. Compared to the preterm groups, children in the term groups were older and had different socioeconomic status and ethnicity. There was a difference in age as some of the term control group were invited from siblings, friends and classmates of the children born preterm who had participated. Although there could have been up to 6 months difference between children born preterm and children born at full term, it was unlikely for this age difference at 7 years of age to result in significant differences in vision measured from the majority of the visual tests used in this study (Wallace et al., 2018). When we compared visual outcomes from our term group with a population study from Australia, we found higher incidence of myopia but similar ocular biometry, which indicated that it was possible that our term control groups may not have been representative of children in the general population (French et al., 2013; Ojaimi et al., 2005). Currently, there is a study on childhood development in New Zealand, which may be a good opportunity to collect population based visual outcomes for comparison to future studies in preterm birth (Morton et al., 2017), while the data collected from our studies will be useful as a baseline for future studies of visual outcomes in children born preterm.

Several composite outcomes were used in our studies, which were used to describe visual function more broadly than using VA only. However, difficulties with using a composite outcome included choosing tests to be part of the composite and the criteria for passing or failing a test when it is in a composite outcome, and comparability with other studies. Only half of the children had a favourable overall visual outcome, which could indicate that the criteria for a favourable outcome we chose was too strict. Although VA is still the most common endpoint of vision studies, various outcomes such as contrast sensitivity, structural outcomes, data binning and test batteries have been used to report visual outcomes. However, each study uses different definitions for visual outcomes, which limits comparison between studies (Good & Hardy, 2001; Hellgren et al., 2016). Refractive error definition is particularly problematic as the range of myopia and hyperopia is on a continuous scale. For example, studies have used a cut-off point for myopia ranging from -0.25D to -3.00D, and for hyperopia +0.50D to +2.00D, which can make a big difference to the incidence reported (Hellgren et al., 2016; Quinn et al., 2013; Yang et al., 2013). Quality of vision is a continuum as different aspects of vision can

contribute to the overall vision, so there is no “composite” visual outcome that encompasses visual function fully. However, there is a need for standardisation on reporting of visual outcomes in a holistic way and better evaluation of the effects of vision on daily activities to better understand the implication of changes in vision.

To encompass the data from both eyes, we separated the data from the right and left eye into better and poorer eye based on VA, refractive error and random assignment in a hierarchial manner. VA did not always correspond to ocular structural changes, which resulted in some children having a “poorer” outcome for some of the refractive or ocular structural outcomes in the eye of “better” VA. In general, the classification of better or worse eye was largely “correct” as we found that the difference in VA between the eyes was in the same direction as that of the results from the N75-P100 amplitude for the 15 minutes check size on the pattern visual evoked potential test in the ROP chapter. Being able to compare visual function and ocular structure in each eye separately was useful particularly in cases of ROP and strabismus which can affect the right or left eye differentially.

In summary, firstly, our studies suggest that preterm birth, ROP, neonatal hyperglycaemia and tight glycaemic control with insulin, and neonatal nutrition were not associated with overall visual outcome at 7-10 years of age. Secondly, preterm birth is associated with adverse binocular and functional visual outcomes. Preterm birth is also associated with changes of ocular structure including steeper corneal curvature and a thicker central retinal thickness, though the implications of these changes are unclear. Thirdly, although preterm babies are at high risk of developing ROP, children with previous ROP have better visual outcomes than previously reported in the literature. However, ROP continues to increase risk of deficits in binocular and functional vision, and is associated with shorter axial length, steeper corneal curvature, thicker central retinal thickness and non-clinically significant changes to the peripheral retina. Fourthly, neonatal hyperglycaemia is unlikely to be independently associated with ROP, rather, neonatal hyperglycaemia and ROP are more common in preterm children born with younger gestational age and lower birth weight. There were changes in lens thickness and VA associated with hyperglycaemia, which require further investigation to understand the long-term consequences of these changes. Fifthly, neonatal nutrition did not affect ocular structural development in children born preterm, but binocular vision and stereoacuity appeared to be changed by neonatal nutrition, which suggests that appropriate alterations in neonatal nutrition and treatment may be able to improve visual outcomes in children born preterm. Lastly, despite improvement in perinatal care, updates in ROP screening and treatment, and vision screening programmes for children, up to 25% of preterm children have visual dysfunction in later childhood. Neonatal hyperglycaemia

appeared to contribute toward poorer binocular visual outcome, but treatment with tight glycaemic control did not seem to improve outcomes and instead, reduced VA; while nutritional changes reduced hyperglycaemia but was associated with unfavourable binocular vision. As there were differences in the care that the children received since their neonatal period, there were exposures that we could not control for. The moderate sensitivity of the tests that we used may have missed some of the clinically important effects, particularly as the children may have not always been able to complete all the tests. However, these issues highlight the importance of long term follow-up in ex-preterm children to determine the longer-term implications of our findings. Further investigation into the optimal perinatal care of babies born preterm is warranted as neonatal complications are potentially modifiable, and reduced morbidities may improve visual outcomes in later childhood.

Future Directions:

Based on the studies in this thesis, there are several areas where further research is needed: 1) standardisation of vision reporting; 2) understanding the association between clinical visual function and daily activities; 3) normative population data; 4) neonatal nutrition; and 5) long term follow-up of children born preterm.

1) There are no internationally recognised or widely used test batteries for studying vision in children. Visual acuity is the main reported outcome and used to infer the performance of other visual functions (International Council of Ophthalmology, 2002). However, there are numerous tests for visual acuity and it only assesses a small part of vision. Some studies have attempted to assess other visual functions such as contrast sensitivity and electrophysiology as these may be better indicators of functional ability in daily activities (Leat et al., 2009). The tests for these visual functions can be time consuming and there is a lack of standardisation of reporting. This is also seen for other common visual functions such as refractive error or oculomotor function, which creates a difficulty in comparing across studies (Committee for the Classification of Eye Movement Abnormalities and Strabismus (CEMAS) Workshop, 2001; Holden et al., 2016). Standardisation of visual outcomes including visual acuity, oculomotor function, binocular function, refractive error and ocular health for different age groups would broaden understanding in visual function as well as aid in pooling of data in various studies where it may be difficult to obtain large enough sample sizes in one study alone.
2) Apart from increased risk of adverse visual outcomes, children born preterm also have higher risk of reduced quality of life, and poorer academic attainment when compared to children born at full term (Saigal, 2014). These may be affected by other adverse outcomes such as

neurodevelopmental impairment, motor deficits and poor health (Saigal et al., 2007). Understanding the association between clinically measured visual function with functional vision for daily activities may aid in assessing whether the adverse visual outcomes that we found in our study contributes to the risk of other adverse outcomes in children born preterm.

3) In New Zealand, there is paucity of childhood visual outcomes in the general population as most studies have investigated vision in groups at risk of visual deficits such as ROP or cerebral visual impairment (Chong et al., 2014; Darlow et al., 1997). Our study showed that it is difficult to find a representative term control group due to various reasons such as self-selection by parents and ability for the children to complete all the visual tests. Most of the "normative" data for children's vision in New Zealand have been based on data collected from the B4 school check vision screening programme but there is a high false positive rate of referrals from this vision screening programme and the referral process is determined by visual acuity data (Anstice et al., 2012). The "Growing Up in New Zealand" long-term study of childhood development provides an opportunity to collect population based visual outcomes for future studies in children (Morton et al., 2017).
4) Nutrition in babies has been hypothesised to be associated with growth and neurodevelopment. We have shown a difference in stereoacuity performance between preterm children who were born before and after a change in intravenous nutrition, which suggests that neonatal nutrition may affect visual outcomes in later childhood. Although these children have been exposed to numerous risk factors and different levels of eye care since birth (which may all affect later visual outcomes), it is important to further investigate whether modifying neonatal nutrition may affect these visual outcomes. Currently, a randomised controlled trial is investigating the effects of neonatal protein intake (higher intake than given to the children in our study) in babies born preterm on growth and neurodevelopment (Bloomfield et al., 2015); visual outcomes gathered from this study may give us more insight on the effects of protein on visual function.
5) Finally, we found that preterm birth, neonatal complications (neonatal hyperglycaemia and ROP), and neonatal interventions (tight glycaemic control with insulin for neonatal hyperglycaemia and neonatal nutrition) were associated with some adverse visual outcomes in later childhood. However, it is unknown whether these visual deficits are absolute changes or whether they may improve with age as visual development can continue into adolescence. Therefore, it is important to continue to follow-up these children to understand the impact of these visual deficits on daily living.

9 Appendix

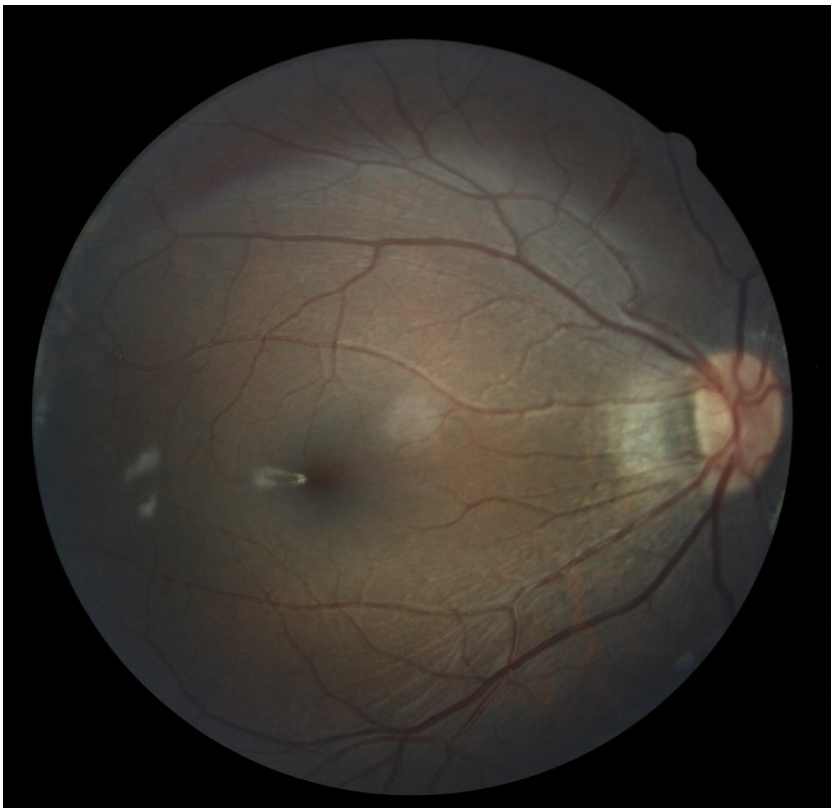
9.1 Retinal Grading

9.1.1 Posterior pole (central) findings

9.1.1.1 Macular ectopia

Macular ectopia was defined as the macula lying outside of an area 2-3 disc-diameters from the temporal margin of the disc and outside of the horizontal confines of the optic disc.

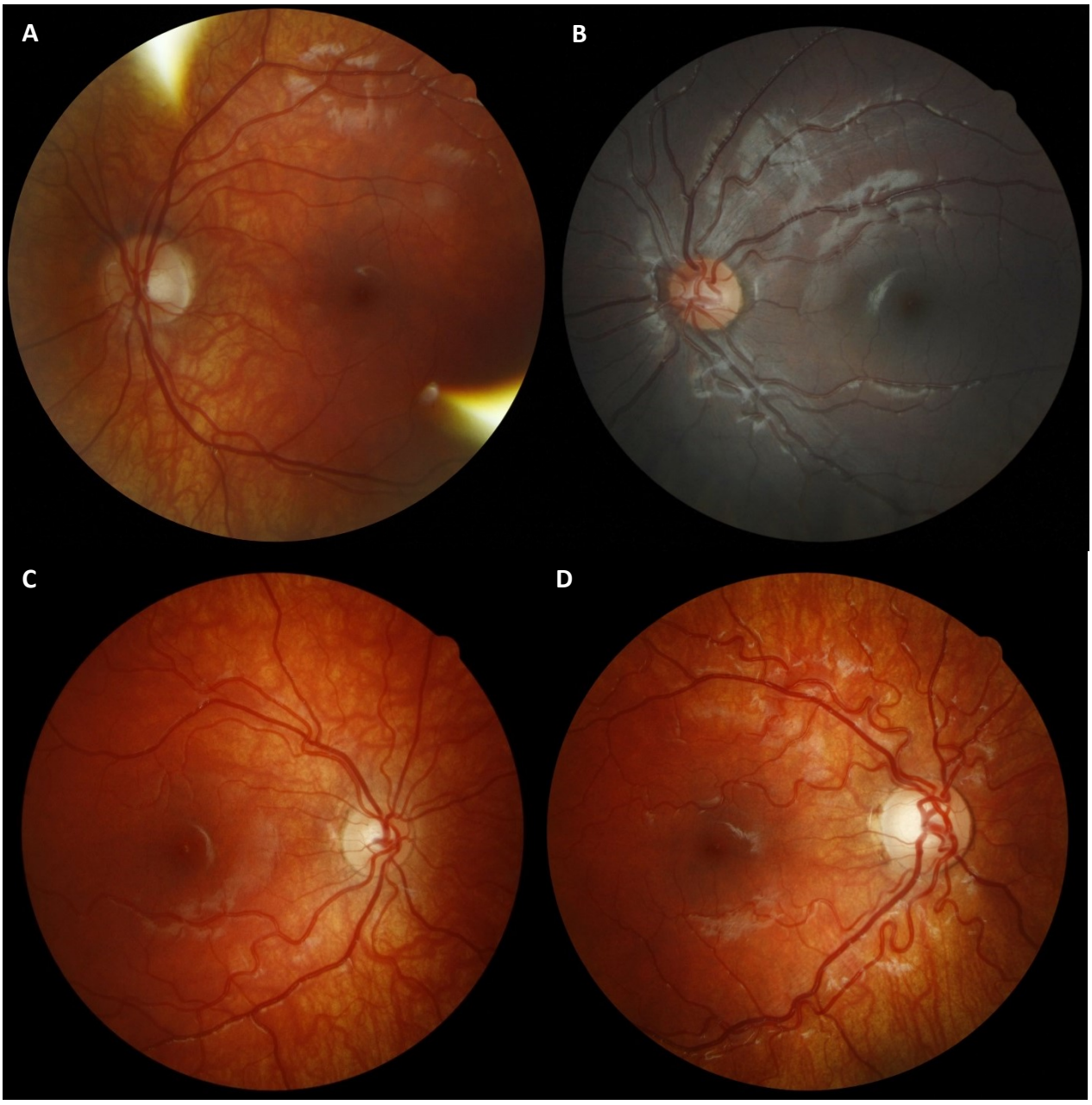
Figure 9-1 Example of macular ectopia and blood vessel straightening



9.1.1.2 Blood vessel tortuosity

Blood vessel tortuosity was subjectively graded based on the following photos:

Figure 9-2 Examples of retinal blood vessel tortuosity grading

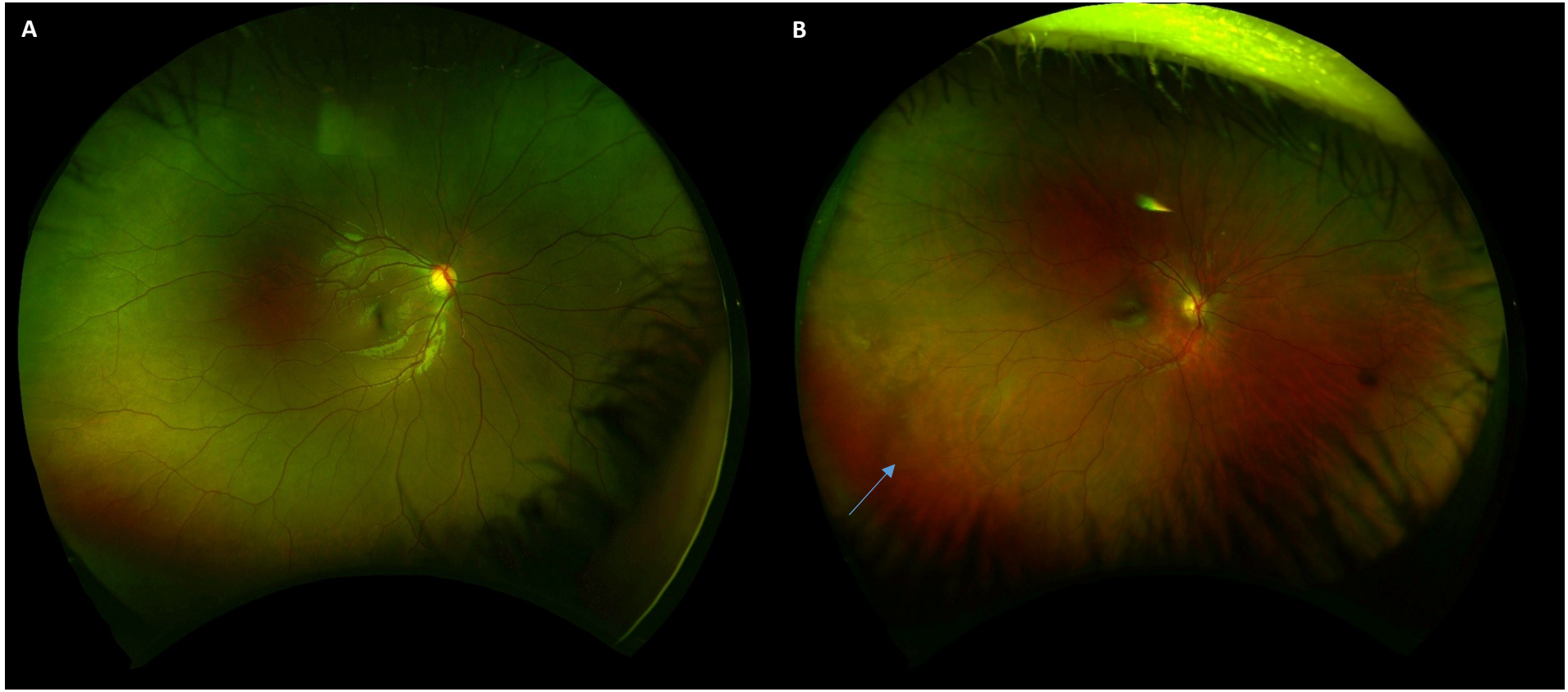


A) non-tortuous, B) mild tortuosity of a child of Asian descent, C) mild tortuosity of a children of NZ European descent, D) severe tortuosity

9.1.2 Peripheral retinal grading

9.1.2.1 Vascularisation

Figure 9-3 Examples of retinal vasculature in OPTOS images



A) *fully vascularised peripheral retina, B) non-vascularised area of the retina shown by the arrow*

9.2 Neonatal Hyperglycaemia: Tables of Exploratory Analyses

Table 9-1 Multiple regression of association between exposure (X) and lens thickness in the better eye, adjusted and not adjusted, for the neonatal hyperglycaemia cohort arm of the PIANO study

Exposure X	Unstandardised coefficient (95%CI) for each variable (P-value)						Model adj R^2 (P-value)
	X	X*	GA	BW z-score	Sex (female)	Group (hyper)	
Birth OFC z-score	-0.01 (-0.04, 0.02) (0.34)	0.01 (-0.07, 0.08) (0.88)	0.003 (-0.03, 0.04) (0.86)	0.00 (-0.10, 0.10) (0.99)	-0.08 (-0.18, 0.04) (0.18)	0.14 (-0.02, 0.26) (0.03)	0.02 (0.24)
Apgar 1 min	-0.02 (-0.04, 0.01) (0.11)	-0.02 (-0.04, 0.01) (0.17)	0.01 (-0.03, 0.05) (0.50)	0.03 (-0.04, 0.10) (0.45)	-0.09 (-0.20, 0.02) (0.09)	0.17 (0.05, 0.29) (0.01)	0.08 (0.04)
BPD	0.11 (-0.002, 0.22) (0.05)	0.09 (-0.03, 0.21) (0.14)	0.01 (-0.03, 0.05) (0.67)	0.03 (-0.04, 0.10) (0.44)	-0.08 (-0.19, 0.02) (0.12)	0.15 (0.04, 0.27) (0.01)	0.07 (0.04)
Postnatal steroids	0.20 (0.08, 0.31) (0.001)	0.18 (0.04, 0.31) (0.01)	0.02 (-0.02, 0.06) (0.31)	0.02 (-0.05, 0.09) (0.50)	-0.07 (-0.17, 0.04) (0.23)	0.14 (0.03, 0.26) (0.02)	0.13 (<0.01)
Age to enteral feed	-0.004 (-0.02, 0.01) (0.53)	-0.01 (-0.02, 0.00) (0.14)	-0.01 (-0.04, 0.03) (0.74)	0.02 (-0.05, 0.09) (0.58)	-0.06 (-0.16, 0.04) (0.26)	0.18 (0.07, 0.30) (0.01)	0.09 (0.03)
Protein week1	0.02 (-0.10, 0.14) (0.76)	0.04 (-0.08, 0.16) (0.50)	-0.002 (-0.04, 0.03) (0.92)	0.02 (-0.05, 0.09) (0.60)	-0.08 (-0.19, 0.03) (0.16)	0.17 (0.05, 0.29) (0.01)	0.05 (0.09)
Protein month1	-0.05 (-0.23, 4.52) (0.54)	0.01 (-0.16, 0.19) (0.88)	-0.01 (-0.05, 0.03) (0.56)	0.01 (-0.06, 0.08) (0.74)	-0.07 (-0.17, 0.04) (0.22)	0.17 (0.05, 0.28) (0.01)	0.07 (< 0.05)
Fat week1	0.01 (-0.07, 0.08) (0.84)	0.04 (-0.04, 0.11) (0.32)	-0.004 (-0.04, 0.03) (0.82)	0.01 (-0.06, 0.08) (0.74)	-0.08 (-0.19, 0.02) (0.13)	0.17 (0.05, 0.29) (0.01)	0.06 (0.07)
Fat month1	-0.03 (-0.09, 0.04) (0.40)	0.01 (-0.06, 0.07) (0.85)	-0.01 (-0.05, 0.03) (0.55)	0.01 (-0.06, 0.08) (0.75)	-0.07 (-0.17, 0.04) (0.21)	0.17 (0.05, 0.28) (0.01)	0.07 (< 0.05)

28 day weight z-score	-0.01 (-0.09, 0.07) (0.82)	0.01 (-0.15, 0.17) (0.88)	-0.01 (-.05, 0.03) (0.58)	0.01 (-0.11, 0.12) (0.93)	-0.07 (-0.17, 0.04) (0.20)	0.17 (0.05, 0.28) (0.01)	0.07 (< 0.05)
28 day height z-score	-0.04 (-0.11, 0.03) (0.21)	-0.02 (-0.13, 0.09) (0.70)	-0.02 (-0.06, 0.03) (0.43)	0.01 (-0.10, 0.12) (0.81)	-0.10 (-0.22, 0.02) (0.10)	0.16 (0.03, 0.30) (0.02)	0.09 (0.04)
28 day OFC z-score	-0.03 (-0.10, 0.05) (0.47)	0.01 (-0.09, 0.11) (0.86)	-0.02 (-0.07, 0.03) (0.42)	-0.004 (-0.11, 0.10) (0.94)	-0.10 (-0.22, 0.01) (0.09)	0.17 (0.04, 0.29) (0.01)	0.09 (< 0.05)
Length of neonatal stay	0.002 (0.000, 0.004) (0.07)	0.002 (-0.001, 0.01) (0.12)	0.02 (-0.03, 0.07) (0.35)	0.04 (-0.04, 0.11) (0.31)	-0.09 (-0.20, 0.01) (0.08)	0.16 (0.04, 0.28) (0.01)	0.08 (0.04)
Number of BGC readings	0.002 (0.001, 0.003) (< 0.0001)	0.002 (0.001, 0.004)^ (0.0001)	0.04 (0.001, 0.08) (< 0.05)	0.03 (-0.03, 0.10) (0.30)	-0.07 (-0.17, 0.03) (0.14)	0.05 (0.07, 0.17) (0.38)	0.20 (< 0.001)
Insulin infusion	0.18 (0.07, 0.28) (0.001)	0.16 (-0.01, 0.33)^ (0.07)	0.002 (-0.03, 0.04) (0.89)	0.01 (-0.06, 0.08) (0.72)	-0.08 (-0.18, 0.03) (0.16)	0.04 (-0.13, 0.21) (0.65)	0.08 (0.03)
Proportion BGC > 8.5	0.01 (0.01, 0.01) (0.0001)	0.01 (0.005, 0.02)^ (0.001)	-0.004 (-0.04, 0.03) (0.81)	-0.02 (-0.08, 0.05) (0.66)	-0.07 (-0.17, 0.03) (0.18)	-0.04 (-0.20, 0.12) (0.64)	0.17 (0.001)
Number of days > 8.5	0.02 (0.01, 0.03) (< 0.0001)	0.02 (0.02, 0.03)^ (< 0.0001)	0.03 (-0.01, 0.06) (0.14)	-0.01 (-0.07, 0.05) (0.77)	-0.07 (-0.16, 0.03) (0.16)	-0.03 (-0.16, 0.10) (0.64)	0.28 (< 0.0001)
Recurrent hyperglycaemia	0.19 (0.09, 0.29) (< 0.001)	0.18 (0.01, 0.35)^ (0.03)	0.01 (-0.03, 0.05) (0.59)	0.02 (-0.05, 0.09) (0.61)	-0.05 (-0.16, 0.06) (0.37)	0.03 (-0.14, 0.20) (0.74)	0.10 (0.02)
Hypoglycaemia	0.07 (-0.04, 0.18) (0.19)	0.03 (-0.09, 0.14) (0.63)	0.00 (-0.04, 0.04) (1.00)	0.02 (-0.05, 0.09) (0.60)	-0.08 (-0.19, 0.03) (0.14)	0.15 (0.03, 0.27) (0.01)	0.05 (0.09)
Severe hypoglycaemia	0.06 (-0.09, 0.20) (0.45)	0.03 (-0.12, 0.18) (0.67)	-0.002 (-0.04, 0.03) (0.92)	0.02 (-0.05, 0.09) (0.59)	-0.08 (-0.19, 0.02) (0.13)	0.16 (0.04, 0.28) (0.01)	0.05 (0.09)
BGC min	-0.03 (-0.09, 0.03) (0.34)	-0.01 (-0.09, 0.06) (0.74)	0.00 (-0.04, 0.04) (1.00)	0.02 (-0.06, 0.10) (0.59)	-0.08 (-0.19, 0.03) (0.13)	0.16 (0.04, 0.28) (0.01)	0.05 (0.10)
BGC mean	0.10 (0.05, 0.15) (< 0.0001)	0.11 (0.05, 0.18)^ (< 0.01)	-0.01 (-0.05, 0.02) (0.54)	-0.03 (-0.10, 0.04) (0.39)	-0.07 (-0.17, 0.03) (0.16)	-0.03 (-0.19, 0.13) (0.72)	0.16 (< 0.01)

BGC max	0.02 (0.01, 0.03) (< 0.01)	0.02 (0.001, 0.03)^ (0.03)	-0.004 (-0.04, 0.03) (0.82)	0.002 (-0.07, 0.07) (0.96)	-0.10 (-0.20, 0.01) (0.07)	0.07 (-0.07, 0.21) (0.33)	0.10 (0.02)

**Adjusted for sex, birth weight z-score, sex (male/female) and Hyperglycaemic/Non-hyperglycaemic group. ^Confounder of Hyperglycaemic/Non-hyperglycaemic group.*
Note: for every one step increase in X, there is "unstandardized coefficient" millimetre change in lens thickness (-ve unstandardized coefficient is thinner lens thickness).

Table 9-2 Multiple regression of association between exposure (X) and presenting distance binocular visual acuity, adjusted and not adjusted, for the neonatal hyperglycaemia cohort arm of the PIANO study

Exposure X	Unstandardised coefficient (95%CI) for each variable (P-value)						Model adj R^2 (P-value)
	X	X*	GA	BW z-score	Sex (female)	Group (hyper)	
Birth OFC z-score	-0.01 (-0.03, 0.02) (0.73)	-0.01 (-0.06, 0.03) (0.54)	0.01 (-0.01, 0.03) (0.53)	0.03 (-0.02, 0.09) (0.25)	-0.03 (-0.09, 0.02) (0.24)	0.10 (0.04, 0.17) (< 0.01)	0.06 (0.06)
Apgar 1 min	-0.004 (-0.02, 0.01) (0.56)	-0.001 (-0.02, 0.01) (0.85)	0.003 (-0.02, 0.02) (0.79)	0.02 (-0.02, 0.06) (0.32)	-0.03 (-0.09, 0.02) (0.24)	0.10 (0.04, 0.16) (< 0.01)	0.06 (<0.05)
BPD	0.06 (0.004, 0.12) (0.04)	0.05 (-0.01, 0.12) (0.08)	0.01 (-0.01, 0.03) (0.38)	0.03 (-0.01, 0.06) (0.16)	-0.03 (-0.08, 0.02) (0.27)	0.10 (0.04 0.16) (< 0.01)	0.09 (0.01)
Postnatal steroids	0.08 (0.01, 0.14) (0.02)	0.06 (-0.01, 0.13) (0.11)	0.01 (-0.01, 0.03) (0.39)	0.03 (-0.01, 0.06) (0.18)	-0.02 (-0.08, 0.04) (0.48)	0.09 (0.03, 0.16) (< 0.01)	0.09 (0.02)
Age to enteral feed	0.001 (-0.01, 0.01) (0.77)	-0.001 (-0.007, 0.004) (0.66)	0.01 (-0.01, 0.03) (0.33)	0.02 (-0.01, 0.05) (0.16)	-0.04 (-0.08, 0.01) (0.14)	0.11 (0.06, 0.17) (0.0001)	0.11 (0.01)
Protein week1	0.01 (-0.05, 0.07) (0.75)	0.03 (-0.03, 0.09) (0.35)	0.003 (-0.02, 0.02) (0.75)	0.02 (-0.02, 0.06) (0.29)	-0.03 (-0.08, 0.03) (0.33)	0.11 (0.04, 0.17) (0.001)	0.07 (0.03)
Protein month1	-0.05 (-0.14, 0.05) (0.34)	-0.02 (-0.12, 0.08) (0.72)	0.003 (-0.02, 0.02) (0.78)	0.02 (-0.02, 0.05) (0.35)	-0.03 (-0.08, 0.03) (0.35)	0.10 (0.04, 0.16) (< 0.01)	0.06 (< 0.05)
Fat week1	-0.05 (-0.09, -0.01) (0.01)	-0.04 (-0.08, -0.002) (0.04)	0.004 (-0.01, 0.02) (0.67)	0.02 (-0.02, 0.06) (0.25)	-0.03 (-0.08, 0.03) (0.35)	0.09 (0.03, 0.15) (0.01)	0.10 (0.01)
Fat month1	-0.04 (-0.07, -0.01) (0.01)	-0.04 (-0.07, -0.01) (0.02)	0.01 (-0.01, 0.03) (0.40)	0.02 (-0.01, 0.06) (0.24)	-0.02 (-0.07, 0.04) (0.54)	0.10 (0.03, 0.16) (< 0.01)	0.11 (0.01)
28 day weight z-score	-0.01 (-0.05, 0.04) (0.80)	-0.01 (-0.09, 0.07) (0.76)	0.002 (-0.02, 0.02) (0.86)	0.03 (-0.04, 0.09) (0.44)	-0.03 (-0.08, 0.03) (0.34)	0.10 (0.04, 0.16) (< 0.01)	0.06 (0.04)

28 day height z-score	-0.01 (-0.04, 0.03) (0.72)	0.03 (-0.03, 0.09) (0.29)	-0.01 (-0.03, 0.02) (0.67)	-0.02 (-0.07, 0.04) (0.61)	-0.03 (-0.09, 0.03) (0.31)	0.12 (0.05, 0.19) (0.001)	0.10 (0.02)
28 day OFC z-score	-0.01 (-0.05, 0.02) (0.44)	0.00 (-0.05, 0.05) (1.00)	-0.01 (-0.03, 0.02) (0.69)	0.01 (-0.05, 0.06) (0.80)	-0.03 (-0.09, 0.03) (0.36)	0.11 (0.04, 0.17) (< 0.01)	0.09 (0.03)
Length of neonatal stay	0.001 (0.000, 0.003) (0.01)	0.002 (0.001, 0.004) (0.001)	0.03 (0.004, 0.05) (0.02)	0.04 (0.004, 0.08) (0.03)	-0.04 (-0.09, 0.01) (0.14)	0.11 (0.05, 0.16) (0.01)	0.15 (< 0.001)
Number of BGC readings	0.001 (0.001, 0.002) (< 0.001)	0.001 (0.001, 0.002)^ (< 0.001)	0.02 (0.002, 0.04) (0.03)	0.03 (-0.01, 0.06) (0.13)	-0.02 (-0.08, 0.03) (0.37)	0.05 (-0.01, 0.11) (0.13)	0.17 (< 0.001)
Insulin infusion	0.10 (0.05, 0.15) (< 0.001)	0.08 (-0.01, 0.16)^ (0.08)	0.01 (-0.01, 0.02) (0.62)	0.01 (-0.02, 0.05) (0.42)	-0.03 (-0.08, 0.03) (0.34)	0.04 (-0.05, 0.13) (0.34)	0.09 (0.01)
Proportion BGC > 8.5	0.004 (0.001, 0.006) (< 0.01)	0.002 (-0.002, 0.01) (0.37)	0.003 (-0.02, 0.02) (0.78)	0.01 (-0.02, 0.05) (0.45)	-0.03 (-0.08, 0.03) (0.11)	0.07 (-0.02, 0.16) (0.11)	0.07 (0.03)
Number of days > 8.5	0.01 (0.01, 0.01) (0.0001)	0.01 (0.004, 0.02)^ (0.001)	0.01 (-0.01, 0.03) (0.19)	0.01 (-0.03, 0.04) (0.63)	-0.02 (-0.08, 0.03) (0.37)	0.02 (-0.05, 0.10) (0.45)	0.15 (0.001)
Recurrent hyperglycaemia	0.08 (0.03, 0.14) (< 0.01)	0.04 (-0.05, 0.13) (0.36)	0.01 (-0.01, 0.03) (0.59)	0.02 (-0.02, 0.05) (0.31)	-0.02 (-0.08, 0.03) (0.40)	0.07 (-0.02, 0.16) (0.11)	0.07 (0.03)
Hypoglycaemia	0.05 (-0.01, 0.10) (0.08)	0.04 (-0.02, 0.09) (0.22)	0.01 (-0.01, 0.03) (0.56)	0.02 (-0.01, 0.06) (0.19)	-0.03 (-0.08, 0.02) (0.28)	0.10 (0.03, 0.16) (< 0.01)	0.07 (0.02)
Severe hypoglycaemia	-0.004 (-0.08, 0.07) (0.91)	-0.01 (-0.09, 0.06) (0.72)	0.002 (-0.02, 0.02) (0.80)	0.02 (-0.02, 0.05) (0.40)	-0.03 (-0.08, 0.03) (0.29)	0.10 (0.04, 0.16) (0.001)	0.06 (0.04)
BGC min	-0.01 (-0.04, 0.02) (0.47)	-0.01 (-0.04, 0.03) (0.67)	0.004 (-0.02, 0.02) (0.68)	0.02 (-0.02, 0.06) (0.28)	-0.03 (-0.09, 0.02) (0.27)	0.10 (0.04, 0.16) (< 0.01)	0.06 (0.04)
BGC mean	0.04 (0.02, 0.07) (0.001)	0.02 (-0.02, 0.06) (0.23)	0.001 (-0.02, 0.02) (0.88)	0.01 (-0.03, 0.05) (0.64)	-0.03 (-0.08, 0.03) (0.30)	0.06 (-0.02, 0.15) (0.15)	0.07 (0.02)
BGC max	0.01 (0.01, 0.02) (0.0001)	0.01 (0.004, 0.02)^ (0.001)	0.003 (-0.01, 0.02) (0.71)	0.01 (-0.03, 0.04) (0.62)	-0.04 (-0.10, 0.01) (0.10)	0.04 (-0.03, 0.11) (0.28)	0.15 (< 0.001)

Lens thickness	0.25 (0.16, 0.34) (< 0.0001)	0.22 (0.13, 0.31)^ (< 0.0001)	0.00 (-0.02, 0.02) (1.00)	0.00 (-0.03, 0.03) (0.98)	-0.01 (-0.05, 0.04) (0.79)	0.05 (0.00, 0.11) (> 0.05)	0.27 (< 0.0001)

**Adjusted for sex, birth weight z-score, sex (male/female) and Hyperglycaemic/Non-hyperglycaemic group. ^Confounder of Hyperglycaemic/Non-hyperglycaemic group.*
Note: for every one step increase in X, there is "unstandardized coefficient" logMAR change in visual acuity (-ve unstandardized coefficient is improvement in visual acuity).

Table 9-3 Logistic regression of association between exposure (X) and ROP (no ROP v ROP), adjusted and not adjusted, for the neonatal hyperglycaemia cohort arm of the PIANO study

Exposure X	Odds ratio (95%CI) for each variable (P-value)					Model R^2 (P-value)
	X	X*	GA	BW z-score	Sex (female)	
Minimum BGC	0.66 (0.38, 1.16) (0.15)	0.67 (0.35, 1.27) (0.22)	0.72 (0.49, 1.04) (0.08)	1.33 (0.69, 2.58) (0.40)	0.65 (0.24, 1.76) (0.40)	0.15 (0.03)
Mean BGC	0.76 (0.49, 1.20) (0.24)	0.58 (0.34, 0.96) (0.04)	0.59 (0.41, 0.86) (0.01)	1.05 (0.59, 1.88) (0.86)	0.58 (0.21, 1.61) (0.30)	0.19 (0.01)
Maximum BGC	1.06 (0.94, 1.19) (0.36)	1.01 (0.90, 1.13) (0.86)	0.66 (0.46, 0.95) (0.02)	1.09 (0.62, 1.91) (0.77)	0.64 (0.23, 1.75) (0.39)	0.13 (> 0.05)

**Adjusted for sex, birth weight z-score, sex (male/female) and Hyperglycaemic/Non-hyperglycaemic group. Note: for every one step increase in X, there is "odds" of ROP.*

Table 9-4 Logistic regression of association between exposure (X) and ROP (ROP untreated v ROP treatment), adjusted and not adjusted, for the neonatal hyperglycaemia cohort arm of the PIANO study

Exposure X	Odds ratio (95%CI) for each variable (P-value)					Model R^2 (P-value)
	X	X*	GA	BW z-score	Sex (female)	
Minimum BGC	0.39 (0.16, 0.95) (0.04)	0.40 (0.12, 1.30) (0.13)	0.44 (0.21, 0.93) (0.03)	0.95 (0.29, 3.04) (0.93)	1.02 (0.23, 4.56) (0.98)	0.26 (0.02)
Mean BGC	1.90 (1.06, 3.41) (0.03)	1.60 (0.78, 3.25) (0.19)	0.42 (0.20, 0.88) (0.02)	0.50 (0.15, 1.61) (0.24)	0.99 (0.22, 4.35) (0.99)	0.25 (0.02)
Maximum BGC	1.15 (1.03, 1.29) (0.01)	1.20 (1.03, 1.40) (0.02)	0.35 (0.16, 0.79) (0.01)	0.45 (0.14, 1.52) (0.20)	1.99 (0.36, 11.14) (0.43)	0.34 (< 0.01)

**Adjusted for sex, birth weight z-score, sex (male/female) and Hyperglycaemic/Non-hyperglycaemic group. Note: for every one step increase in X, there is "odds" of requiring ROP treatment.*

9.3 Tight Glycaemic Control: Tables of Exploratory Analyses

Table 9-5 Multiple regression of association between exposure (X) and binocular visual acuity, adjusted and not adjusted, for the HINT follow-up cohort arm of the PIANO study

Exposure X	Unstandardised coefficient (95%CI) for each variable (P-value)						Model adj R^2 (P-value)
	X	X*	Sex (female)	Weight for GA (SGA)	Multiple Birth (Yes)	Group (Tight)	
Number of BGC readings	0.001 (0.000, 0.002) (0.01)	0.001 (0.000, 0.002)^ (0.02)	-0.02 (-0.10, 0.07) (0.68)	0.06 (-0.06, 0.18) (0.31)	-0.07 (-0.16, 0.02) (0.11)	0.06 (-0.03, 0.14) (0.17)	0.13 (0.04)
Minimum BGC	-0.01 (-006, 0.04) (0.58)	0.01 (-0.05, 0.06) (0.83)	-0.02 (-0.11, 0.07) (0.62)	0.02 (-0.11, 0.15) (0.73)	-0.07 (-0.16, 0.02) (0.13)	0.09 (0.002, 0.19) (0.05)	0.02 (0.32)
Mean BGC	0.03 (-0.02, 0.08) (0.18)	0.07 (0.02, 0.11) (0.01)	-0.03 (-0.11, 0.06) (0.53)	0.06 (-0.06, 0.18) (0.29)	-0.07 (-0.15, 0.02) (0.14)	0.14 (0.05, 0.23) (<0.01)	0.14 (0.03)
Proportion BGC >8.5	0.003 (-0.001, 0.007) (0.19)	0.005 (0.001, 0.01) (0.02)	-0.02 (-0.11, 0.06) (0.58)	0.05 (-0.07, 0.17) (0.43)	-0.06 (-0.15, 0.03) (0.18)	0.13 (0.04, 0.22) (0.01)	0.12 (0.05)
Hypoglycaemia	0.06 (-0.02, 0.15) (0.24)	0.04 (-0.05, 0.14) (0.36)	-0.02 (-0.11, 0.07) (0.67)	0.004 (-0.12, 0.13) (0.95)	-0.07 (-0.16, 0.02) (0.13)	0.08 (-0.01, 0.17) (0.09)	0.03 (0.25)
Severe hypoglycaemia	-0.04 (-0.14, 0.07) (0.48)	-0.07 (-0.18, 0.04) (0.20)	-0.01 (-0.10, 0.08) (0.80)	0.04 (-0.08, 0.17) (0.51)	-0.06 (-0.15, 0.03) (0.19)	0.11 (0.02, 0.19) (0.02)	0.05 (0.19)
Insulin infusion	0.09 (-0.01, 0.19) (0.06)	0.09 (-0.03, 0.20) (0.14)	-0.02 (-0.10, 0.07) (0.73)	0.03 (-0.09, 0.15) (0.62)	-0.08 (-0.17, 0.01) (0.08)	0.06 (-0.04, 0.15) (0.23)	0.06 (0.15)
Total dose insulin	0.004 (0.002, 0.006) (0.001)	0.004 (0.001, 0.006)^ (0.01)	-0.01 (-0.10, 0.07) (0.75)	0.05 (-0.07, 0.17) (0.39)	-0.05 (-0.14, 0.04) (0.39)	0.04 (-0.05, 0.13) (0.42)	0.14 (0.03)
Proportion BGC 2.6-8.5	-0.003 (-0.07, 0.001) (0.19)	-0.005 (-0.01, 0.00) (0.04)	-0.02 (-0.11, 0.06) (0.57)	0.03 (-0.09, 0.15) (0.59)	-0.06 (-0.15, 0.03) (0.17)	0.12 (0.04, 0.21) (0.01)	0.10 (0.06)

Proportion BGC 4-6	-0.003 (-0.007, 0.00) (0.09)	-0.004 (-0.08, 0.001) (0.02)	-0.01 (-0.10, 0.07) (0.77)	0.02 (-0.10, 0.14) (0.72)	-0.06 (-0.15, 0.03) (0.16)	0.12 (0.03, 0.20) (0.01)	0.12 (0.04)
7y height z-score	0.01 (-0.03, 0.05) (0.72)	0.02 (-0.02, 0.06) (0.30)	-0.01 (-0.10, 0.08) (0.75)	0.03 (-0.09, 0.16) (0.59)	-0.07 (-0.16, 0.02) (0.14)	0.10 (0.01, 0.19) (0.02)	0.04 (0.23)

**Adjusted for sex (male/female), weight for gestational age (SGA/AGA), multiple birth (yes/no) and Tight/Control group. ^Confounder of Tight/Control group. Note: for every one step increase in X, there is "unstandardized coefficient" logMAR change in visual acuity (-ve unstandardized coefficient is better visual acuity).*

9.4 Neonatal Nutrition: Tables of Exploratory Analyses

Table 9-6 Multiple regression of association between exposure (X) and unfavourable binocular visual outcome, adjusted and not adjusted, for the neonatal nutrition cohort arm of the PIANO study

Exposure X	Odds ratio (95%CI) for each variable (P-value)					Model Nagelkerke R^2 (P-value)
	X	X*	BW z-score	Sex (male)	Group (after)	
Completed maternal course steroids	1.45 (0.41, 5.09) (0.57)	1.30 (0.36, 4.74) (0.69)	0.97 (0.64, 1.45) (0.86)	1.27 (0.61, 2.63) (0.53)	2.09 (1.00, 4.38) (0.05)	0.05 (0.30)
P:E ratio 7d	2.78 (1.42, 5.47) (< 0.01)	3.49 (1.18, 10.30) (0.03)^	0.97 (0.64, 1.46) (0.88)	1.24 (0.59, 2.63) (0.57)	0.71 (0.22, 2.34) (0.58)	0.11 (0.04)
P:E ratio 14d	3.22 (1.05, 9.84) (0.04)	2.34 (0.54, 10.10) (0.25)	0.97 (0.65, 1.45) (0.87)	1.29 (0.62, 2.71) (0.50)	1.37 (0.51, 3.68) (0.53)	0.06 (0.23)
Proportion parenteral protein 7d	1.02 (1.00, 1.04) (0.05)	1.02 (0.99, 1.04) (0.15)	0.96 (0.64, 1.43) (0.83)	1.25 (0.60, 2.62) (0.55)	1.82 (0.84, 3.92) (0.13)	0.07 (0.14)
Proportion parenteral protein 14d	1.02 (1.00, 1.03) (0.08)	1.01 (0.99, 1.03) (0.21)	0.97 (0.65, 1.46) (0.90)	1.28 (0.61, 2.68) (0.51)	1.75 (0.81, 3.81) (0.16)	0.06 (0.21)
Protein week1	2.41 (1.06, 5.51) (0.04)	1.76 (0.60, 5.16) (0.30)	0.97 (0.64, 1.44) (0.86)	1.25 (0.60, 2.60) (0.55)	1.53 (0.58, 4.00) (0.39)	0.06 (0.22)
Protein month1	1.20 (0.35, 4.09) (0.77)	0.98 (0.28, 3.49) (0.98)	1.00 (0.67, 1.49) (0.98)	1.24 (0.60, 2.60) (0.56)	2.00 (0.94, 4.24) (0.07)	0.04 (0.42)
Carbohydrate week1	0.92 (0.74, 1.16) (0.48)	1.04 (0.80, 1.36) (0.75)	0.98 (0.66, 1.48) (0.92)	1.25 (0.60, 2.60) (0.55)	2.28 (0.97, 5.33) (0.06)	0.05 (0.31)
Carbohydrate month1	0.94 (0.73, 1.21) (0.63)	1.00 (0.77, 1.32) (0.98)	1.00 (0.66, 1.50) (0.99)	1.24 (0.60, 2.60) (0.56)	2.00 (0.92, 4.33) (0.08)	0.04 (0.42)

Fat week1	0.71 (0.44, 1.15) (0.17)	0.74 (0.45, 1.20) (0.22)	1.00 (0.67, 1.50) (1.00)	1.23 (0.59, 2.57) (0.58)	2.08 (0.99, 4.35) (0.05)	0.07 (0.18)
Fat month1	0.86 (0.57, 1.31) (0.49)	0.74 (0.45, 1.20) (0.22)	1.00 (0.67, 1.50) (1.00)	1.23 (0.59, 2.57) (0.58)	1.95 (0.93, 4.13) (0.05)	0.07 (0.18)
Energy week1	0.98 (0.95, 1.02) (0.29)	0.99 (0.95, 1.03) (0.51)	0.98 (0.65, 1.46) (0.92)	1.26 (0.61, 2.62) (0.54)	2.03 (0.96, 4.28) (0.07)	0.06 (0.27)
Energy month1	0.99 (0.97, 1.02) (0.54)	1.00 (0.97, 1.02) (0.82)	0.99 (0.67, 1.49) (0.98)	1.24 (0.59, 2.59) (0.57)	1.96 (0.93, 4.16) (0.08)	0.04 (0.41)
Days of neonatal stay	1.02 (1.00, 1.03) (0.05)	1.01 (1.00, 1.03) (0.08)	0.96 (0.64, 1.44) (0.86)	1.33 (0.63, 2.79) (0.46)	1.90 (0.90, 4.03) (0.09)	0.08 (0.10)
NZDep 7 years	1.05 (0.93, 1.18) (0.44)	1.03 (0.91, 1.16) (0.67)	0.97 (0.65, 1.45) (0.89)	1.26 (0.61, 2.63) (0.53)	2.07 (0.98, 4.36) (0.06)	0.05 (0.30)
Cerebral palsy	7.03 (0.86, 57.35) (0.07)	5.72 (0.68, 47.77) (0.11)	0.94 (0.63, 1.42) (0.78)	1.24 (0.59, 2.60) (0.57)	1.88 (0.89, 3.99) (0.10)	0.09 (0.08)
Gestational age	0.86 (0.71, 1.04) (0.13)	0.84 (0.67, 1.04) (0.11)	0.83 (0.53, 1.30) (0.83)	1.27 (0.61, 2.66) (0.53)	2.04 (0.97, 4.31) (0.06)	0.06 (0.12)

**Adjusted for sex, birth weight z-score and Before/After group. ^Confounder of Before/After group. Note: for every one step increase in X, there is "odds" of unfavourable binocular visual function.*

Table 9-7 Multiple regression of association between exposure (X) and unfavourable functional visual outcome, adjusted and not adjusted, for the neonatal nutrition cohort arm of the PIANO study

Exposure X	Odds ratio (95%CI) for each variable (P-value)					Model Nagelkerke R^2 (P-value)
	X	X*	BW z-score	Sex (male)	Group (after)	
Completed maternal course steroids	1.54 (0.42, 5.65) (0.51)	1.52 (0.39, 5.91) (0.55)	0.72 (0.46, 1.12) (0.15)	0.86 (0.38, 1.97) (0.72)	2.47 (1.02, 6.02) (0.05)	0.08 (0.15)
P:E ratio 7d	1.84 (0.89, 3.77) (0.10)	1.08 (0.35, 3.28) (0.90)	0.73 (0.47, 1.13) (0.16)	0.86 (0.38, 1.97) (0.73)	2.37 (0.62, 9.02) (0.21)	0.07 (0.17)
P:E ratio 14d	2.56 (0.82, 8.06) (0.11)	1.28 (0.28, 5.94) (0.76)	0.72 (0.46, 1.12) (0.15)	0.85 (0.37, 1.94) (0.69)	2.38 (0.76, 7.47) (0.14)	0.08 (0.14)
Proportion parenteral protein 7d	1.01 (0.98, 1.03) (0.51)	1.00 (0.98, 1.03) (0.92)	0.73 (0.47, 1.13) (0.16)	0.86 (0.38, 1.97) (0.73)	2.50 (0.99, 6.28) (0.05)	0.07 (0.17)
Proportion parenteral protein 14d	1.01 (0.99, 1.03) (0.27)	1.01 (0.99, 1.03) (0.59)	0.72 (0.46, 1.12) (0.15)	0.85 (0.37, 1.94) (0.69)	2.48 (0.99, 6.25) (0.05)	0.08 (0.13)
Protein week1	2.39 (0.96, 5.97) (0.06)	1.65 (0.50, 5.44) (0.41)	0.72 (0.46, 1.12) (0.15)	0.87 (0.38, 1.99) (0.75)	1.87 (0.60, 5.85) (0.28)	0.08 (0.13)
Protein month1	1.24 (0.31, 4.99) (0.76)	0.87 (0.20, 3.68) (0.85)	0.74 (0.47, 1.16) (0.19)	0.80 (0.35, 1.86) (0.61)	2.62 (1.05, 6.56) (0.28)	0.07 (0.19)
Carbohydrate week1	0.88 (0.68, 1.13) (0.31)	0.96 (0.71, 1.30) (0.79)	0.72 (0.46, 1.13) (0.15)	0.86 (0.38, 1.97) (0.73)	2.39 (0.90, 6.38) (0.08)	0.07 (0.17)
Carbohydrate month1	0.94 (0.71, 1.26) (0.70)	0.98 (0.72, 1.35) (0.92)	0.74 (0.47, 1.16) (0.19)	0.81 (0.35, 1.86) (0.62)	2.54 (1.02, 6.35) (0.05)	0.07 (0.19)
Fat week1	1.21 (0.72, 2.04) (0.47)	1.35 (0.78, 2.32) (0.28)	0.70 (0.44, 1.10) (0.12)	0.89 (0.39, 2.04) (0.78)	2.64 (1.08, 6.45) (0.04)	0.09 (0.11)

Fat month1	1.01 (0.63, 1.61) (0.98)	1.06 (0.64, 1.76) (0.82)	0.74 (0.48, 1.16) (0.19)	0.82 (0.35, 1.91) (0.65)	2.60 (1.06, 6.38) (0.04)	0.07 (0.19)
Energy week1	1.01 (0.97, 1.05) (0.73)	1.02 (0.98, 1.06) (0.41)	0.72 (0.46, 1.12) (0.14)	0.88 (0.39, 2.02) (0.77)	2.71 (1.10, 6.70) (0.03)	0.08 (0.13)
Energy month1	1.00 (0.97, 1.03) (0.94)	1.00 (0.97, 1.03) (0.91)	0.74 (0.48, 1.16) (0.19)	0.81 (0.35, 1.88) (0.63)	2.59 (1.05, 6.37) (0.04)	0.07 (0.19)
Days of neonatal stay	1.04 (1.02, 1.06) (0.0001)	1.04 (1.02, 1.06) (0.0001)^	0.65 (0.39, 1.08) (0.10)	0.99 (0.41, 2.42) (0.99)	2.17 (0.84, 5.61) (0.11)	0.07 (0.0001)
NZDep 7 years	1.08 (0.95, 1.24) (0.22)	1.06 (0.93, 1.22) (0.39)	0.73 (0.47, 1.14) (0.17)	0.86 (0.38, 1.97) (0.72)	2.37 (0.96, 5.82) (0.06)	0.08 (0.13)
Cerebral palsy	22.56 (2.66, 191.58) (< 0.01)	18.94 (2.14, 167.29) (0.91)	0.70 (0.44, 1.12) (0.14)	0.83 (0.35, 1.97) (0.67)	1.86 (0.74, 4.69) (0.19)	0.19 (0.001)
Gestational age	0.80 (0.64, 1.00) (0.05)	0.65 (0.48, 0.88) (0.01)	0.45 (0.25, 0.82) (0.01)	0.91 (0.39, 2.15) (0.84)	2.68 (1.05, 6.84) (0.04)	0.18 (< 0.01)

**Adjusted for sex, birth weight z-score and before/after group. ^Confounder of before/after group. Note: for every one step increase in X, there is "odds" of unfavourable functional visual function.*

Table 9-8 Multiple regression of association between exposure (X) and failing TNO stereoacuity, adjusted and not adjusted, for the neonatal nutrition cohort arm of the PIANO study

Exposure X	Odds ratio (95%CI) for each variable (P-value)					Model Nagelkerke R^2 (P-value)
	X	X*	BW z-score	Sex (male)	Group (after)	
Completed maternal course steroids	1.85 (0.50, 6.81) (0.36)	1.70 (0.44, 6.57) (0.44)	0.84 (0.52, 1.34) (0.45)	1.01 (0.43, 2.40) (0.98)	2.90 (0.12, 7.53) (0.03)	0.08 (0.15)
P:E ratio 7d	2.08 (0.97, 4.45) (0.06)	1.11 (0.35, 3.49) (0.86)	0.85 (0.53, 1.35) (0.48)	1.01 (0.43, 2.39) (0.98)	2.73 (0.68, 11.01) (0.16)	0.07 (0.19)
P:E ratio 14d	2.69 (0.82, 8.76) (0.10)	1.09 (0.23, 5.18) (0.91)	0.84 (0.53, 1.34) (0.46)	0.99 (0.42, 2.37) (0.99)	3.01 (0.91, 9.93) (0.07)	0.08 (0.16)
Proportion parenteral protein 7d	1.01 (0.98, 1.04) (0.49)	1.25 (0.57, 2.76) (0.58)	0.84 (0.53, 1.35) (0.47)	1.01 (0.43, 2.39) (0.98)	2.51 (0.82, 7.72) (0.11)	0.08 (0.17)
Proportion parenteral protein 14d	1.01 (0.99, 1.03) (0.27)	1.14 (0.59, 2.21) (0.64)	0.84 (0.53, 1.34) (0.47)	1.00 (0.42, 2.37) (1.00)	2.87 (1.01, 0.82) (0.03)	0.08 (0.15)
Protein week1	2.92 (1.11, 7.72) (0.03)	1.83 (0.53, 6.31) (0.34)	0.83 (0.52, 1.34) (0.45)	1.02 (0.43, 2.42) (0.96)	2.07 (0.62, 6.93) (0.24)	0.08 (0.13)
Protein month1	1.07 (0.26, 4.50) (0.92)	0.73 (0.16, 3.32) (0.69)	0.87 (0.54, 1.40) (0.56)	0.94 (0.39, 2.25) (0.89)	3.13 (1.17, 8.39) (0.02)	0.07 (0.20)
Carbohydrate week1	0.87 (0.67, 1.14) (0.32)	1.00 (0.74, 1.37) (0.99)	0.85 (0.53, 1.35) (0.49)	1.01 (0.43, 2.39) (0.98)	2.99 (1.04, 8.61) (0.04)	0.07 (0.19)
Carbohydrate month1	0.88 (0.65, 1.19) (0.42)	0.95 (0.68, 1.32) (0.74)	0.86 (0.53, 1.39) (0.54)	0.95 (0.40, 2.27) (0.91)	2.89 (1.08, 7.72) (0.03)	0.07 (0.21)
Fat week1	1.26 (0.73, 2.17) (0.40)	1.37 (0.77, 2.42) (0.28)	0.82 (0.51, 1.32) (0.42)	1.06 (0.44, 2.51) (0.91)	3.09 (1.18, 8.08) (0.02)	0.09 (0.12)

Fat month1	0.94 (0.58, 1.53) (0.81)	1.02 (0.61, 1.70) (0.95)	0.87 (0.54, 1.40) (0.57)	0.95 (0.40, 2.30) (0.92)	3.01 (1.15, 7.89) (0.03)	0.07 (0.21)
Energy week1	1.01 (0.97, 1.06) (0.62)	1.02 (0.98, 1.07) (0.33)	0.84 (0.52, 1.34) (0.46)	1.05 (0.44, 2.49) (0.92)	3.25 (1.23, 8.60) (0.02)	0.08 (0.13)
Energy month1	0.99 (0.96, 1.02) (0.67)	1.00 (0.97, 1.03) (0.92)	0.87 (0.54, 1.40) (0.56)	0.95 (0.39, 2.27) (0.90)	2.98 (1.14, 0.88) (0.03)	0.07 (0.21)
Days of neonatal stay	1.03 (1.01, 1.05) (0.001)	1.03 (1.01, 1.05) (0.001)	0.74 (0.44, 1.26) (0.27)	1.12 (0.45, 2.78) (0.81)	2.70 (0.99, 7.36) (0.05)	0.22 (0.001)
NZDep 7 years	1.10 (0.96, 1.26) (0.20)	1.07 (0.93, 1.24) (0.34)	0.85 (0.53, 1.35) (0.49)	1.00 (0.42, 2.38) (1.00)	2.79 (1.07, 7.31) (0.04)	0.08 (0.14)
Cerebral palsy	11.13 (2.11, 58.66) (0.01)	8.15 (1.49, 44.51) (0.02)	0.84 (0.52, 1.37) (0.48)	0.99 (0.41, 2.42) (0.98)	2.31 (0.86, 6.17) (0.10)	0.15 (0.01)
Gestational age	0.79 (0.62, 1.00) (0.05)	0.68 (0.50, 0.92) (0.01)	0.56 (0.31, 1.03) (0.06)	1.07 (0.44, 2.61) (0.88)	3.14 (1.16, 8.46) (0.02)	0.15 (0.01)
Global motion coherence	1.02 (1.00, 1.04) (0.07)	1.02 (1.00, 1.04) (0.03)	0.80 (0.49, 1.30) (0.36)	1.00 (0.41, 2.47) (1.00)	3.25 (1.19, 8.87) (0.02)	0.12 (0.04)

**Adjusted for sex, birth weight z-score and before/after group. Note: for every one step increase in X, there is "odds" of failing TNO stereoacuity.*

Table 9-9 Multiple regression of association between exposure (X) and global motion coherence, adjusted and not adjusted, for the neonatal nutrition cohort arm of the PIANO study

Exposure X	Unstandardised coefficient (95%CI) for each variable (P-value)					Model Adjust R^2 (P-value)
	X	X*	BW z-score	Sex (female)	Group (after)	
Completed maternal course steroids	-7.87 (-23.03, 7.29) (0.31)	-6.92 (-22.08, -8.25) (0.37)	0.69 (-3.74, 5.12) (0.76)	2.10 (-6.25, 10.45) (0.62)	-8.60 (-17.08, -0.21) (0.05)	0.01 (0.23)
P:E ratio 7d	-3.04 (-10.58, 4.50) (0.43)	8.53 (-3.35, 20.41) (0.16)	0.66 (-3.74, 5.05) (0.77)	2.15 (-6.16, 10.45) (0.61)	-16.40 (-29.71, -3.07) (0.02)	0.02 (0.14)
P:E ratio 14d	-3.85 (-16.54, 8.85) (0.55)	10.50 (-6.32, 27.32) (0.22)	0.83 (-3.57, 5.23) (0.71)	1.03 (-7.33, 9.38) (0.81)	-14.34 (-25.61, -3.08) (0.01)	0.03 (0.14)
Proportion parenteral protein 7d	0.00 (-0.24, 0.24) (0.99)	0.08 (-0.17, 0.33) (0.53)	0.50 (-3.92, 4.93) (0.82)	2.06 (-6.31, 10.42) (0.63)	-9.72 (-18.48, -0.96) (0.03)	0.01 (0.26)
Proportion parenteral protein 14d	0.04 (-0.15, 0.23) (0.69)	0.11 (-0.09, 0.31) (0.27)	0.90 (-3.50, 5.31) (0.69)	1.08 (-7.28, 9.44) (0.80)	-11.07 (-19.84, -2.31) (0.01)	0.02 (0.16)
Protein week1	-4.86 (-14.18, 4.46) (0.30)	2.56 (-9.48, 14.59) (0.67)	0.51 (-3.92, 4.94) (0.82)	2.02 (-6.36, 10.39) (0.64)	-10.42 (-21.33, 0.49) (0.06)	0.01 (0.29)
Protein month1	0.96 (-13.33, 15.25) (0.89)	3.88 (-10.53, 18.29) (0.60)	0.84 (-3.62, 5.30) (0.71)	0.88 (-3.62, 5.30) (0.84)	-9.98 (-18.61, -1.34) (0.02)	0.01 (0.24)
Carbohydrate week1	1.66 (-0.93, 4.24) (0.21)	0.40 (-2.61, 3.42) (0.79)	0.60 (-3.87, 5.07) (0.79)	2.05 (-6.33, 10.43) (0.63)	-8.28 (-18.07, 1.51) (0.10)	0.01 (0.30)
Carbohydrate month1	1.52 (-1.51, 4.55) (0.32)	0.67 (-2.53, 3.87) (0.68)	0.98 (-3.55, 5.51) (0.67)	1.04 (-7.42, 9.49) (0.81)	-9.00 (-17.89, -0.11) (0.05)	0.01 (0.26)
Fat week1	-2.17 (-7.72, 3.39) (0.44)	-2.75 (-8.34, 2.83) (0.33)	0.85 (-3.61, 5.31) (0.71)	2.26 (-6.13, 10.58) (0.60)	-9.17 (-17.59, -0.76) (0.03)	0.02 (0.22)

Fat month1	2.81 (-2.13, 7.76) (0.26)	2.02 (-2.99, 7.03) (0.43)	0.80 (-3.65, 5.26) (0.72)	0.57 (-7.96, 9.09) (0.90)	-9.10 (-17.65, -0.56) (0.03)	0.02 (0.22)
Energy week1	-0.01 (-0.44, 0.42) (0.96)	-0.12 (-0.55, 0.32) (0.59)	0.58 (-3.85, 5.01) (0.80)	2.08 (-6.29, 10.45) (0.62)	-9.43 (-18.04, -0.82) (0.03)	0.01 (0.28)
Energy month1	0.16 (-0.14, 0.47) (0.29)	0.11 (-0.21, 0.42) (0.51)	0.91 (-3.56, 5.38) (0.69)	0.78 (-7.70, 9.26) (0.86)	-9.04 (-17.66, -0.43) (0.04)	0.01 (0.23)
Days of neonatal stay	0.10 (-0.06, 0.26) (0.21)	0.14 (-0.03, 0.30) (0.10)	0.39 (-3.99, 4.77) (0.86)	1.58 (-6.72, 9.88) (0.71)	-10.26 (-18.75, -1.78) (0.02)	0.03 (0.11)
NZDep 7 years	-0.12 (-1.48, 1.24) (0.86)	0.09 (-1.28, 1.46) (0.90)	0.51 (-3.93, 4.94) (0.82)	2.01 (-6.37, 10.39) (0.64)	-9.03 (-17.57, -0.49) (0.64)	0.01 (0.30)
Cerebral palsy	4.32 (-12.54, 21.17) (0.61)	7.59 (-9.35, 24.54) (0.38)	0.45 (-3.97, 4.86) (0.84)	2.18 (-6.18, 10.53) (0.61)	-9.56 (-18.07, -1.04) (0.03)	0.01 (0.23)
Gestational age	86.85 (29.08, 144.63) (< 0.01)	-1.91 (-4.34, 0.52) (0.12)	-1.30 (-6.25, 3.66) (0.61)	1.95 (-6.35, 10.24) (0.64)	-9.52 (-17.90, -1.13) (0.03)	0.03 (0.12)

**Adjusted for sex, birth weight z-score and before/after group. Note: for every one step increase in X, there is "unstandardized coefficient" % change in global motion perception (-ve unstandardized coefficient is better global motion perception)*

Table 9-10 Multiple regression of association between exposure (X) and presence of cerebral palsy, adjusted and not adjusted, for the neonatal nutrition cohort arm of the PIANO study

Exposure X	Odds ratio (95%CI) for each variable (P-value)					Model Nagelkerke R^2 (P-value)
	X	X*	BW z-score	Sex (male)	Group (after)	
Completed maternal course steroids	2.70 (0.50, 14.48) (0.25)	2.05 (0.36, 11.5) (0.42)	1.35 (0.64, 2.84) (0.44)	1.22 (0.32, 4.73) (0.77)	7.04 (0.86, 58.05) (0.07)	0.13 (0.13)
P:E ratio 7d	5.27 (1.39, 19.91) (0.01)	3.48 (0.54, 22.50) (0.19)^	1.37 (0.64, 2.91) (0.42)	1.19 (0.30, 4.63) (0.81)	2.25 (0.14, 36.99) (0.57)	0.15 (0.08)
P:E ratio 14d	8.51 (1.83, 39.63) (0.01)	4.67 (0.75, 28.97) (0.10)^	1.32 (0.61, 2.85) (0.47)	1.31 (0.33, 5.23) (0.71)	3.35 (0.32, 35.59) (0.32)	0.17 (0.05)
Proportion parenteral protein 7d	1.03 (0.98, 1.09) (0.24)	1.02 (0.97, 1.07) (0.51)	1.38 (0.65, 2.94) (0.40)	1.21 (0.31, 4.66) (0.79)	6.36 (0.75, 53.92) (0.09)	0.13 (0.14)
Proportion parenteral protein 14d	1.02 (1.00, 1.05) (0.11)	1.02 (0.99, 1.05) (0.32)	1.37 (0.64, 2.93) (0.42)	1.24 (0.32, 4.81) (0.76)	6.19 (0.73, 52.53) (0.10)	0.14 (0.11)
Protein week1	8.98 (1.57, 51.24) (0.01)	5.30 (0.60, 46.88) (0.13)	1.40 (0.65, 3.03) (0.39)	1.22 (0.31, 4.75) (0.78)	2.79 (0.24, 32.52) (0.41)	0.16 (0.06)
Protein month1	1.54 (0.14, 16.62) (0.72)	1.05 (0.08, 14.18) (0.97)	1.34 (0.64, 2.82) (0.44)	1.24 (0.32, 4.79) (0.76)	7.64 (0.92, 63.41) (0.06)	0.12 (0.15)
Carbohydrate week1	0.90 (0.60, 1.35) (0.61)	1.25 (0.75, 2.07) (0.39)	1.46 (0.68, 3.14) (0.34)	1.24 (0.32, 4.80) (0.76)	10.86 (1.09, 108.32) (0.04)	0.13 (0.13)

Carbohydrate month1	0.84 (0.54, 1.30) (0.43)	1.00 (0.60, 1.68) (0.99)	1.34 (0.63, 2.85) (0.45)	1.24 (0.32, 4.79) (0.76)	7.70 (0.90, 66.25) (0.06)	0.12 (0.15)
Fat week1	0.95 (0.40, 2.25) (0.90)	0.98 (0.40, 2.40) (0.97)	1.37 (0.65, 2.90) (0.41)	1.21 (0.31, 4.67) (0.78)	7.35 (0.90, 60.25) (0.06)	0.12 (0.17)
Fat month1	0.62 (0.35, 1.11) (0.11)	0.68 (0.36, 1.28) (0.23)	1.32 (0.61, 2.84) (0.48)	1.19 (0.30, 4.68) (0.80)	6.88 (0.83, 56.92) (0.07)	0.15 (0.09)
Energy week1	1.00 (0.94, 1.07) (0.92)	1.02 (0.95, 1.10) (0.55)	1.37 (0.65, 2.91) (0.41)	1.25 (0.32, 4.86) (0.75)	8.13 (0.97, 68.56) (0.05)	0.12 (0.15)
Energy month1	0.98 (0.94, 1.01) (0.20)	0.98 (0.94, 1.03) (0.43)	1.31 (0.61, 2.79) (0.49)	1.23 (0.32, 4.77) (0.77)	6.97 (0.84, 57.84) (0.07)	0.13 (0.12)
Days of neonatal stay	1.02 (0.99, 1.04) (0.14)	1.02 (0.99, 1.04) (0.24)	1.40 (0.63, 3.08) (0.41)	1.30 (0.33, 5.09) (0.70)	6.41 (0.77, 53.28) (0.09)	0.14 (0.10)
NZDep 7 years	1.11 (0.89, 1.38) (0.36)	1.08 (0.86, 1.36) (0.51)	1.40 (0.66, 2.94) (0.38)	1.17 (0.30, 4.55) (0.82)	7.07 (0.86, 58.41) (0.07)	0.12 (0.14)
Gestational age	0.82 (0.57, 1.19) (0.30)	0.86 (0.54, 1.36) (0.51)	1.19 (0.49, 2.87) (0.70)	1.24 (0.32, 4.79) (0.76)	7.23 (0.88, 59.30) (0.07)	0.12 (0.14)

**Adjusted for sex, birth weight z-score and before/after group. Note: for every one step increase in X, there is "odds" of cerebral palsy.*

9.5 Preterm Birth: Comparison of Visual Acuity Test Chart

Visual acuity was measured using the Keeler LogMAR crowded test chart in the PIANO study and the electronic visual acuity tester (EVA) in the EYE-SPY study. We performed a simple comparison between the two tests on a group of adults (n=14) who did not have any congenital eye problems. Presenting VA was measured, with a random order of eye and test performed.

Paired sample testing showed that for monocular testing, VA was lower (better) in the EVA test compared to the Keeler test (Right eye EVA v Keeler: mean difference -0.05logMAR (95%CI -0.09, -0.01), p=0.01; Left eye EVA v Keeler: mean difference -0.04logMAR (95%CI -0.08, 0.00), p=0.04).

Paired sample testing showed that for binocular testing, VA was not statistically significantly different between the two tests (Both eyes EVA v Keeler: mean difference -0.01logMAR (95%CI -0.05, 0.02), p=0.47). Therefore, in chapter 7, we have only reported a binocular logMAR VA (combined from PIANO and EYE-SPY studies) and not for each eye separately.

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