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Childhood outcomes in children at risk of neonatal hypoglycaemia

Nataliia Burakevych

Abstract

Aim

The aims of this thesis are to (1) describe growth and neurodevelopmental outcomes of children born at risk of neonatal hypoglycaemia, a common condition that may be associated with adverse neurodevelopmental outcome; (2) investigate methods used for data collection in paediatric longitudinal studies; and (3) determine the relationships between glycaemic response to neonatal hypoglycaemia, its treatment, and later neurodevelopmental outcome.

Methods

Prospective study of children born at risk of neonatal hypoglycaemia at Waikato hospital (2006-2010), the CHYLD study. Intermittent blood and continuous interstitial glucose concentrations were recorded in the neonatal period. Hypoglycaemia (blood glucose concentration <2.6 mmol/l) was treated with breast milk, formula, dextrose gel, and intravenous dextrose.

At 2 and 4.5 years’ corrected age children were assessed for neurodevelopmental and general health status. Caregivers completed questionnaires about the medical history and social-emotional health of their children. Children’s hospital records were accessed and preschool screening data was obtained from the Before School Check programme.

Findings

Children in our study lived in more deprived areas compared to the national average, and approximately a third had neurosensory impairment at both 2 and 4.5 years. Neurodevelopmental outcomes were not related to neonatal risk factors.

We identified problems with several of the methods commonly used for follow-up assessments. Caregivers could not accurately recall previous hospital admissions at the 4.5 year assessment when compared to hospital records. Referral criteria for developmental and emotional health problems were not applied consistently in the Before School Check, and children who had problems often missed out on screening. In addition, assessment of motor function at 2 years was not predictive of motor difficulties at 4.5 years.
We found that treatment of neonatal hypoglycaemia was associated with different glycaemic responses in the six hour period after hypoglycaemia, and the rate of change in glucose concentrations was related to later neurodevelopmental outcome.

Conclusions

Our findings in an at-risk cohort of children with high impairment rates will help researchers and clinicians to plan future studies, draw attention to some limitations of the New Zealand preschool screening programme, and guide future research on treatment of neonatal hypoglycaemia to improve later outcomes.
Для Саші,

dякую за постійну підтримку.
Acknowledgements

I feel very lucky to have spent three and a half years with wonderful and bright people. I am indebted to the countless numbers of individuals whose contributions made this work possible. I cannot imagine receiving any better support than I received at the Liggins Institute. I would also like to thank The University of Auckland and Gravida for awarding me a Doctoral scholarship.

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I am grateful to my partner, Denis, for his unending love, patience and sense of humour which helped me maintain my sanity in difficult times, kept me in touch with the big wide world outside of my academic life and made my PhD journey so much more enjoyable.

My brother – thank you for always being there for me. You have been a pillar of support and strength for me all my life and I love you dearly.
Last, but not least, I would like to thank my parents for supporting me in this journey. It is a great gift to have you in my life, even though it has been from a distance at present. This accomplishment is yours as much as it is mine.
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<th>Full Form</th>
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<tr>
<td>AGA</td>
<td>Appropriate for Gestational Age</td>
</tr>
<tr>
<td>AIMS</td>
<td>Alberta Infant Motor Scale</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analysis of variance</td>
</tr>
<tr>
<td>ASQ</td>
<td>Ages and Stages Questionnaire</td>
</tr>
<tr>
<td>B4SC</td>
<td>Before School Check</td>
</tr>
<tr>
<td>Bayley-II</td>
<td>Bayley Scales of Infant Development, second edition</td>
</tr>
<tr>
<td>Bayley-III</td>
<td>Bayley Scales of Infant and Toddler Development, third edition</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
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<tr>
<td>CBCL</td>
<td>Child Behaviour Checklist</td>
</tr>
<tr>
<td>CDC</td>
<td>Centre for Disease Control and Prevention</td>
</tr>
<tr>
<td>CGM</td>
<td>Continuous Glucose Monitoring</td>
</tr>
<tr>
<td>CHYLD</td>
<td>Children with HYpoglycaemia and their Later Development</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Intervals</td>
</tr>
<tr>
<td>CO-OP</td>
<td>Cognitive Orientation to daily Occupational Performance</td>
</tr>
<tr>
<td>CT</td>
<td>Computed Tomography</td>
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<tr>
<td>DCD</td>
<td>Developmental Coordination Disorder</td>
</tr>
<tr>
<td>DEXA</td>
<td>Dual Energy X-ray Absorptiometry</td>
</tr>
<tr>
<td>ED</td>
<td>Emergency Department</td>
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<tr>
<td>EEG</td>
<td>Electroencephalogram</td>
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<tr>
<td>ENT</td>
<td>Ear, nose and throat</td>
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<tr>
<td>FSIQ</td>
<td>Full Scale Intelligence Quotient</td>
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<tr>
<td>GDR</td>
<td>Glucose delivery rate</td>
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<tr>
<td>GIT</td>
<td>Gastrointestinal</td>
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<tr>
<td>GLUT</td>
<td>Glucose transporter</td>
</tr>
<tr>
<td>GP</td>
<td>General Practitioner</td>
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<tr>
<td>HbA1c</td>
<td>Glycosylated haemoglobin</td>
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<tr>
<td>IDM</td>
<td>Infant of a diabetic mother</td>
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<tr>
<td>IG</td>
<td>Interstitial Glucose</td>
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IGFs     Insulin-like Growth Factors
IOTF     International Obesity Task Force
IQ       Intelligence Quotient
IUGR     Intrauterine Growth Restriction
IV       Intravenous
LGA      Large for gestational age
MABC-2   Movement Assessment Battery for Children, second edition
MD       Mean Difference
MRI      Magnetic Resonance Imaging
mRNA     messenger Ribonucleic acid
NHI      National Health Index
NTT      Neuromotor Task Training
NZ       New Zealand
NZDEP    New Zealand Deprivation Index
OR       Odds Ratio
PDI      Psychomotor Development Index
PEDS     Parental Evaluation of Developmental Status
SD       Standard Deviation
SDQ      Strengths and Difficulties Questionnaire
SDQ-P    Parent completed the Strengths and Difficulties Questionnaire
SDQ-T    Teacher completed the Strengths and Difficulties Questionnaire
SGA      Small for gestational age
UK       United Kingdom
US       United States
VLBW     Very Low Birth Weight
WHO      World Health Organisation
WPPSI-III Wechsler Preschool and Primary Scale of Intelligence, third edition
mg       milligram
mg/dl    milligram per deciliter
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<tr>
<td>min</td>
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<tr>
<td>mmol/l</td>
<td>millimole per litre</td>
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<tr>
<td>μmol/l</td>
<td>micromole per litre</td>
</tr>
<tr>
<td>kg</td>
<td>kilogram</td>
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<tr>
<td>kg/m²</td>
<td>kilogram per square meter</td>
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Chapter 1. Literature review.
1.1 Fetal metabolism

1.1.1 Changes in maternal metabolism during pregnancy
Maternal metabolism changes to accommodate the needs of the fetus during pregnancy (Tan & Tan, 2013). The first half of gestation is characterised by increased appetite and higher concentration of insulin and increased insulin sensitivity, all of which lead to fat accumulation (Buch, Hornnes, & Kuhl, 1986). The second half of gestation can be described as the catabolic phase. Plasma oestrogen concentrations increase and insulin sensitivity decreases which leads to utilisation of maternal fat stores (Herrera & Ortega-Senovilla, 2010; Herrera & Ortega-Senovilla, 2014). This additional energy is transferred to the fetus which grows rapidly during the second half of gestation.

1.1.2 Fetal energy requirements
Basic metabolic processes, development and growth require energy. The main fetal energy substrates are glucose, amino acids and lactate delivered to the fetus via the placenta from the maternal blood supply. While all those nutrients are transported to the fetus, the amount that is actually transformed into energy and tissue building blocks will vary depending on factors such as the rate of nutrient transfer across the placenta and uteroplacental consumption of nutrients. Further, fetal growth and energy requirements will also differ with gestational age (Aldoretta & Hay Jr., 1994).

Carbohydrates are the main source of energy for the fetus and account for about 80% of energy consumption. The fetus utilises glucose at a rate of 5-7 mg/kg/min which is around two times higher than the glucose utilisation rate of an adult (Hay Jr., 2006). Fetal glucose utilisation depends primarily on two factors: glucose and insulin concentrations. These factors act in cooperation and influence cellular uptake and utilisation of different nutrients. In sheep research it was shown that an increase in fetal glucose concentration resulted in increased glucose oxidation rate and fetal metabolism. The same was observed for insulin but the effect was not as great as for glucose (Hay Jr., DiGiacomo, Meznarich et al., 1989).

When conditions of pregnancy change (fasting, maternal hypo- or hyperglycaemia) adaptations of the fetus to these changes in the intrauterine environment take place. However, those adaptations in turn cause changes in fetal growth, metabolism and susceptibility to chronic diseases in later life (Smith & Ryckman, 2015). Therefore, fetal metabolic regulation in adequate and abnormal environments will be discussed further.
1.1.3 Nutrient transport across the placenta

Fetal metabolism is dependent on maternal supply of nutrients across the placenta and maternal metabolism changes to accommodate the additional needs for fuels during pregnancy. The placenta plays a crucial part in transport of nutrients to the fetus. Transport of nutrients and gases across the placenta involves simple and facilitated diffusion and active transport (Brett, Ferraro, Yockell-Lelievre et al., 2014). In rats, glucose was the main nutrient (measured as quantities of nutrient per fetal body weight) crossing the placenta, while amino acids contributed a smaller proportion and free fatty acids and glycerol were crossing the placenta in very small quantities (Herrera & Amusquivar, 2000).

- Glucose is transported by facilitated diffusion via the family of GLUT transporters (Barrosa, Yudilevich, Jarvis et al., 1995).
- Amino acids are transported actively via numerous transport mechanisms to ensure high concentrations of amino acids (higher than on the maternal side) reach the fetus (Jansson, 2001).
- Uptake of unesterified fatty acids occurs via binding and transport proteins while free fatty acids can diffuse via the membrane (Dutta-Roy, 2000).

1.1.4 Glucose transporters

Glucose crosses the placenta via carrier facilitated transport which is dependent on maternal glucose concentration, the difference in maternal-fetal glucose concentrations, and consumption of glucose by the placenta. Glucose transport (and also transport of other monosaccharides) is mediated by the GLUT transporter family (Hay Jr., 1991). Fourteen GLUT transporters that belong to three classes have been identified in human tissues, but the role of many of them remains unknown (Mueckler & Thorens, 2013). GLUT transporters that are present in the placenta have specific localisations, functions and different expression which can change throughout gestation.

GLUT-1 is expressed in most human tissues and has been widely studied. Expression of GLUT-1 in the placenta is high throughout the whole pregnancy and this is the main transporter of glucose (Illsley, 2000). GLUT-1 is found in both microvillus and basal membrane (Barrosa, Yudilevich, Jarvis et al., 1995; Jansson, Wennergren, & Illsley, 1993). However, expression is higher in the microvillus of the syncytiotrophoblast than in the basal membrane (Tadokoro, Yoshimoto, Sakata et al., 1996). Glucose transport is regulated via insulin-like growth factors
that increase GLUT-1 expression and therefore increase glucose uptake at the basal membrane (Baumann, Schneider, Malek et al., 2014).

GLUT-2 transporter has not been found in any of the placental tissues (Jansson, Cowley, & Illsley, 1995). mRNA of GLUT-3 is found in cells of the villi, while the protein is expressed in the endothelium of vessels and not in syncytiotrophoblast (Hauguel-de Mouzon, Challier, Kacemi et al., 1997; Jansson, Cowley, Illsley, 1995). Expression of this transporter decreases with gestational age (Ericsson, Hamark, Powell et al., 2005). GLUT-4 is considered an insulin-sensitive transporter as its response to insulin is rapid and it is localised with insulin receptors in intravillous stromal cells (Xing, Challier, Lepercq et al., 1998). GLUT-4 expression is lower at term than during the first trimester (Ericsson, Hamark, Powell et al., 2005). Glucose uptake increased by 182% in insulin-stimulated 6-8 weeks’ gestation placental tissues when compared to control while there was no significant difference between tissues at term. At the same time, basal glucose uptake of term placenta was higher than of first trimester samples (Ericsson, Hamark, Powell et al., 2005). This reduction in transporter expression and insulin sensitivity suggests that transport can be regulated by fetal insulin and in diabetic pregnancy this effect even in early periods may be responsible for fetal growth later in gestation. Early pregnancy is therefore a sensitive period when fetal growth and development can be altered.

GLUT-5 and GLUT-9 can transport fructose. GLUT-9 and its isoforms were found in human placenta at term (Bibee, Illsley, & Moley, 2011). However, it is not clear if fructose transport occurs in the placenta. GLUT-12 was identified in syncytiotrophoblast in early gestation but by term it was mainly located in arterial villous and stromal cells (Gude, Stevenson, Rogers et al., 2003).

1.1.5 Changed environment: adaptations of the placenta

The placenta synthesises and converts metabolites and hormones that affect fetal growth (Fowden & Forhead, 2004). In addition, the connection between the placenta and the fetus is reciprocal. This means that the fetus does not just accept nutrients from the maternal blood flow, but it has the ability to control to some extent its own metabolism and has effects on placental metabolism.

The morphological and physiological state of the placenta is associated with the efficiency of the nutrient transport and in turn fetal characteristics. For example, fetal weight has been shown to correlate positively with placental weight in sheep and humans (Mellor, 1983; Wallace, Horgan, & Bhattacharya, 2012). Placental size and structure alters over time to accommodate
increasing energy needs throughout pregnancy. In sheep, the peak of placental size occurs at mid-gestation and then decreases slightly over the rest of gestation. At the same time, the second half of gestation is characterised by a greater than 10-fold increase in placental surface area and fetal weight (Battaglia & Meschia, 1988). Human placental weight increases throughout the whole of gestation in average and large-for-gestational-age (LGA) fetuses whereas placental weight of small-for-gestational-age (SGA) fetuses did not increase from 36 weeks (Molteni, Stys, & Battaglia, 1978). The placenta is characterised by size but also transfer capacity. More efficient placentae transfer more nutrients (on a weight basis) than those that are less efficient (Fowden, Sferruzzi-Perri, Coan et al., 2009).

Adaptations of the placenta to a changed environment depend on the nature and duration of these altered conditions. Placental adaptation can be measured as placental efficiency calculated as grams of fetus per grams of placenta (Wilson & Ford, 2001). In vivo and in vitro studies investigated how interference with feto-placental growth alters nutrient transport across the placenta. Altered fetal growth as a result of dysregulation of energy balance presents as intrauterine growth restriction (IUGR) or overgrowth (macrosomia).

1.1.5.1 IUGR

IUGR can be caused by maternal undernutrition when nutrients are limited in the maternal circulation (Prada & Tsang, 1998). IUGR also occurs when maternal diet is adequate and nutrients are available in maternal circulation, but placental dysfunction results in limited nutrients and oxygen delivery to the fetus (Gerretsen, Huisjes, & Elema, 1981). In this case compensatory mechanisms take place but are insufficient to provide adequate nutrient intake.

In carunclectomised sheep the placentae transfers 40-50% more glucose than the placentae of a control group on a weight specific basis, but this still results in fetal growth restriction (Owens, Falconer, & Robinson, 1987; Owens, Falconer, & Robinson, 1989). The study by Jansson et al. showed that there were no differences between placental GLUT-1 expression in growth restricted (2 SD below mean) and normal fetuses (Jansson, Wennergren & Illsley, 1993). GLUT-3 protein expression on maternal side was increased in growth restricted placentae compared to normal while GLUT-1 and GLUT-4 expression did not differ (Janzen, Lei, Cho et al., 2013). This increased expression of GLUT-3 on the maternal side may suggest high uptake and consumption of glucose by the placenta and this glucose would not reach growth restricted fetuses. In addition, the concentration of amino acids in cord blood and expression of amino acid transporters expression was decreased in IUGR pregnancies (Cetin, Marconi, Corbetta et al., 1992; Sibley, 2009).
1.5.2 Overgrowth

Diabetes and obesity are factors that lead to fetal overgrowth characterised by high birth weight and fat mass (Šegregur, Bukovic, Milinovic et al., 2009). Placentae of diabetic mothers are enlarged, have vascular lesions and necrosis more often than normal placentae (Daskalakis, Marinopoulous, Krienesi et al., 2008) and low fetal-to-placental weight ratio (Lao, Lee, & Wong, 1997; Taricco, Radaelli, Nobile de Santis et al., 2003). Umbilical vein oxygen content and oxygen saturation are also low in diabetic pregnancies (Taricco, Radaelli, Rossi et al., 2009).

It was suggested that maternal hyperglycaemia causes fetal hyperglycaemia which in turn up-regulates expression of glucose transporters on the basal membrane and increases glucose uptake (Acosta, Ramirez, Lager et al., 2015; Gaither, Quraishi, & Illsley, 1999; Illsley, 2000; Jansson, Wennergren, & Powell, 1999). Moreover, increased activity of amino acid transport systems was found in diabetic women compared to controls (Jansson, Ylvén, Wennergren et al., 2002).

1.6 Fetal hormone secretion

The pancreas is comprised of two cell lineages: exocrine and endocrine. Islets of Langerhans form the endocrine part of the pancreas and secrete different hormones: glucagon (secreted by α-cells), insulin (secreted by β-cells), somatostatin, ghrelin and pancreatic polypeptide (Jennings, Berry, Strutt et al., 2015). Insulin and glucagon were found in human fetal pancreatic tissues by 8 weeks’ post-conception and clusters of insulin-producing cells were over ten times more prevalent than glucagon-producing cells (Piper, Brickwood, Turnpenny et al., 2004).

α-cells secrete glucagon which acts as an activator of liver glycogenolysis and gluconeogenesis (Quesada, Tudurı, Ripoll et al., 2008). α-cells do not respond to changes in glucose concentration rapidly, but are responsive to amino acid and catecholamine concentrations (Fowden & Hill, 2001).

β-cells secrete insulin and by mid gestation insulin secretion is well established. Insulin content in the pancreas increases with gestational age (Hellerstrom & Swenne, 1991). Insulin affects cells by stimulating preferential uptake of glucose for oxidative metabolism and thus spares amino acids for tissue growth (Fowden, 1992). Ablation of β-cells results in hyperglycaemia, low glucose utilisation rates and fetal growth restriction (Fowden, 1995). Both glucose and insulin regulate concentrations of insulin-like growth factors (IGFs). Concentrations of IGFs in utero are positively correlated with insulin concentrations (Fowden, 1989). IGFs are
important in feto-placental growth because they promote cell proliferation and differentiation (Jones & Clemmons, 1995).

β-cells act as nutrient sensors that secrete insulin in response to nutrient concentrations (mainly glucose and amino acids) in blood. In unstressed fetuses insulin concentration rises within 5-10 minutes after glucose infusion. When the infusion is continuous, fetal insulin concentration increases and then reaches a plateau (Fowden & Hill, 2001).

Different patterns of maternal glycaemic status and at different periods of gestation (duration and severity of hyper- or hypoglycaemia) lead to different responses of fetal β-cells and their capacity to synthesise insulin and respond to nutrient loads. For example, glucose and arginine were shown to increase fetal insulin secretion after chronic low-basal hyperglycaemia by late gestation in sheep while severe hyperglycaemia and chronic hypoglycaemia had the opposite effect (Carver, Anderson, Aldoretta et al., 1996).

Reduced nutrient supply might lead to impaired fetal β cell function and as a result abnormal insulin production (Nicolini, Hubinont, Santolaya et al., 1990), and reduced insulin positive content in the pancreas as well as pancreatic weight (Limesand, Jensen, Hutton et al., 2005).

Chronic late gestation fetal hypoglycaemia results in decreased insulin secretion by β-cells (Rozance, Limesand, Zerbe et al., 2007). The effect of hypoglycaemia was also tested on fetal sheep that were divided into two experimental groups: hypoglycaemic because of maternal insulin infusion for 2 weeks followed by a 5 day euglycaemic recovery period, and a no recovery group (Limesand & Hay Jr., 2003). Plasma insulin concentrations were reduced in hypoglycaemic subjects and returned to normal in the recovery group during the euglycaemic period. Glucose stimulated insulin secretion was the same as in the control group. However, glucose and arginine responsiveness of insulin-secreting cells was low. This study shows that insulin secretion recovers after hypoglycaemia but the delay in recovery and reduced responsiveness to nutrients may help explain the increase in the likelihood of developing type-2 diabetes in adult life after poor fetal growth.

1.2 Metabolic changes at birth

At birth the constant supply of energy fuels from the maternal pool is stopped. The brain and other organs are in need of an energy source until feeding is established. Metabolic changes
that occur at this stage must ensure adequate supply of glucose as a key fuel, and include glycogenolysis and gluconeogenesis (Hume, Burchell, Williams et al., 2005).

1.2.1 Glycogen and fat stores: fetal to neonatal life
Glycogen synthesis depends on enzymes that are indirectly regulated by insulin and glucocorticoids that become active during the second trimester (Mena, Llanos, & Uauy, 2001). Fetal glycogen synthesis starts during the second trimester and continues until 36 weeks, after which the synthesis rate increases rapidly until full term. Glucose is also converted to fat in the fetus during the third trimester. Fatty acids and cholesterol are also transported to the fetus from the mother via the placenta, and there is also evidence of cholesterol synthesis by the fetus in the third trimester (Herrera & Ortega-Senovilla, 2014). Therefore, by the end of gestation fat and glycogen have accumulated in fetal tissues.

The term human neonate has about 16% of body weight as fat content (Platt & Deshpande, 2005). Preterm neonates have lower fat content – less than 2% of their body weight. This is reflected in the finding that free fatty acid concentrations are lower in preterm neonates compared to term neonates during the first week of life (Hawdon, Ward Platt, & Aynsley-Green, 1992).

After birth, before feeding is established the glucose pool is mainly derived from glycogenolysis. Preterm neonates are considered to be at a high risk of developing neonatal hypoglycaemia due to their low glycogen deposits. Further, SGA babies born preterm are presumed to have very low glycogen deposits (Lubachenco & Bard, 1971). This was not supported by the findings of the study of preterm (≤32 weeks’ gestation) small for gestational age (SGA, only asymmetrically grown) and appropriate for gestational age (AGA - birth weight in the range from 10th to 90th centile) babies. The difference in glucose concentrations before and after glucagon administration which is an indicator of liver glycogen stores of the neonate was similar in both groups (van Kempen, Ackermans, Endert et al., 2005).

1.2.2 Insulin secretion and function in the neonate
After birth the pancreas has to change its hormone secretion pattern. First, stress related to birth causes a rise in glucagon and decline in insulin concentrations (Ktorza, Rihoreau, Nurjhan et al., 1985). As a result, key glycogenolytic and gluconeogenic enzymes are activated. This helps ensure a constant supply of glucose to vital organs until feeding is established.
Second, intermittent feeding established after birth leads to rapid changes in glucose concentrations. Therefore, insulin secretion by the pancreas has to adapt to such feeding-dependent fluctuations (Beardsall, Acerini, & Dunger, 2010). Moreover, insulin secretion is regulated by neural and endocrine mechanisms like incretins. Incretins are factors derived from intestinal mucosa in response to ingestion of nutrients, and have the ability to indirectly decrease glucose concentrations (Baggio & Drucker, 2007). For example, the supply of milk during feeding and release of incretins can cause insulin secretory responses and as a result lowers glucose concentration.

In babies born at a mean gestational age of 40 weeks, and not complicated by diabetes and multiple pregnancy, insulin and glucose concentrations were positively correlated on the seventh day after birth (Shields, Knight, Shakespeare et al., 2006). Further, concentrations of both insulin and glucose decreased with the increase in interval between feeding and blood measurement. Another study compared insulin and glucose concentrations between 0-6 days old preterm and term babies and older children (1 month – 10 years old). The positive relationship between blood glucose and plasma insulin concentrations were found for all three groups (Hawdon & Ward Platt, 1993). In older children blood glucose concentrations were higher compared to preterm and term neonates while plasma insulin concentrations were lower. In addition, insulin was not detected in children if the concentration of glucose was below 4.5 mmol/l whereas in term and preterm babies insulin was detected if blood glucose concentrations were below 2 mmol/l.

1.2.3 Neonatal gluconeogenesis

Gluconeogenesis is the metabolic process whereby glucose is synthesised from non-glucose precursors and recycled glucose carbon. It is dependent on cytosolic and mitochondrial enzymes. Therefore, for the neonate it is important to have a mature gluconeogenic system to synthesise glucose. After birth glucose supply from the mother ceases and glucose production is established. This is related to changes in glucagon concentration, catecholamine secretion and stimulation of sympathetic nervous system (Kalhan & Parimi, 2000). These hormones also stimulate lipolysis. Glucocorticoids have similar effect on adipose stores and in addition promote protein breakdown. As a result, the concentration of substrates available for gluconeogenesis increases (Mitanchez, 2007).

The ability of the neonate to synthesise glucose from gluconeogenic substrates has been demonstrated soon after birth. Around 60% of endogenous glycerol was converted to glucose
which was around 11% of hepatic glucose output in unfed term neonates in the first 8 hours after birth (Sunehag, Gustafsson, & Ewald, 1996). Recycled carbon is also a gluconeogenic substrate, with the parts of lactate and pyruvate that are not oxidised during glycolysis returning to liver where they undergo indirect conversion to glucose. Using tracer methodology it has been estimated that the contribution of recycled carbon to total glucose production is 13 to 35% in healthy neonates (Kalhan, Bier, Savin et al., 1980; Tserng & Kalhan, 1983). In addition, mean alanine contribution to glucose production in term unfed neonates measured 4 to 8 hours after birth was 9.3% of hepatic glucose production in AGA and 12.9% in SGA babies, although this difference between AGA and SGA babies was not statistically significant (Frazer, Karl, & Hillman, 1981).

In a cross-sectional study of term and preterm healthy neonates measuring blood glucose and alternative fuel concentrations during the first week after birth (Hawdon, Ward Platt & Aynsley-Green, 1992), there was negative correlation between blood concentrations of glucose and ketone bodies in term neonates on days 2 and 3. Preterm neonates had low ketone body concentrations and the correlation observed in term neonates was not present in this cohort. Glucose production and gluconeogenesis (calculated per unit of body weight) in preterm very low birth weight (VLBW) neonates was shown to be negatively correlated with body weight (Keshen, Miller, Jahoor et al., 1997). Therefore, there is evidence that neonates can use glucose converted from other substrates, but little is known about which babies have mature gluconeogenic systems to provide efficient energy for metabolism.

1.2.4 Alternative energy substrate for the brain

Alternative fuel utilisation by the brain after neonatal hypoglycaemia may be a mechanism of neuroprotection. Lactate has been recognised as a fuel source that can act as an alternative to glucose for the brain (Taher, Leen, Wevers et al., 2016). Studies of experimental animals and human adults have provided evidence that lactate is used by brain in vivo as energy substrate and can prevent neuronal injury during hypoglycaemia (Bouzier, Thiaudiere, Biran et al., 2000; Hassel & Bråthe, 2000; Maran, Crepaldi, Trupiani et al., 2000).

The ability of brain cells to use ketone bodies as a fuel source was shown in a study where children aged 6 weeks to 7 years were examined for cerebral arterio-venous differences in acetoacetate and hydroxybutyrate concentrations (Persson, Settergren, & Dahlquist, 1972). This study demonstrated a correlation between arterial concentrations of ketone bodies and
their cerebral arterial-venous differences, suggesting relationship between arterial supply and brain uptake. However, actual cerebral uptake of ketone bodies was not measured.

In a study of neonates, concentrations of alternative substrates were low and did not change during hypoglycaemic episodes in the first days after birth (Harris, Weston, Williams et al., 2011). Further, lactate concentration in plasma of neonates who were hypoglycaemic was higher in the first 48 hours after birth than β-hydroxybutyrate concentrations (Harris, Weston, & Harding, 2015). These studies show that brain cells may be capable of utilising not only glucose as a source of energy. Despite that, little is known about actual uptake of alternative substrates by the neonatal brain and its role in hypoglycaemic conditions.

1.2.5 Cerebral response to hypoglycaemia
Cerebral blood flow and plasma adrenalin and noradrenalin concentrations have been shown to differ between hypoglycaemic and normoglycaemic preterm neonates (mean gestational age 30.4 weeks, mean birth weight 1.41kg) while blood gas concentrations and arterial blood pressure were similar (Pryds, Christensen, & Friis-Hansen, 1990). Cerebral blood flow was significantly higher in neonates experiencing hypoglycaemia defined as blood glucose concentration less than 1.6 mmol/l (30 mg/dl) at 2 hours after birth. After hypoglycaemia was treated with intravenous glucose, cerebral blood flow decreased by 11.3% but was still 37.5 % higher than in the control group. Adrenalin concentrations were inversely correlated with blood glucose concentrations. Glucose infusion led to a decrease in adrenalin concentrations to reach control group values. Noradrenalin concentrations were stable throughout the whole study and did not change after glucose treatment. The results of this study suggest that increased cerebral blood flow helps compensates for substrate reduction during hypoglycaemia and adrenalin may be a major regulator of cerebral hyperperfusion. However, although some animal studies have found similar changes in cerebral blood flow (Anwar & Vannucci, 1988), others have reported contrary findings (Gardiner, 1980; Richardson, Hohimer, Bissonnette et al., 1985). Regardless of these discrepancies, from these findings it is impossible to conclude if there was increase in glucose uptake and utilisation by cerebral cells as blood flow changed.

1.2.6 Concentration of fuels after birth
Time and method used for measurement, as well as perinatal history, complications, weight gain during pregnancy, mode of delivery, sex of a baby, and insurance status of a mother are all associated with blood glucose concentrations in the neonate (Cole & Peevy, 1994; DePuy,
Coassolo, Som et al., 2009; Hedderson, Weiss, Sacks et al., 2006). Therefore, controversy exists around a normal range of fuels for a healthy neonate after birth.

In a study of healthy term breastfed neonates (Hoseth, Joergensen, Ebbesen et al., 2000) median glucose concentration was 3.1 mmol/l with a wide range from 1.4 to 5.3 mmol/l. Median glucose concentration was 3.0 mmol/l (range 1.4–5.2 mmol/l) during the first day and 3.4 mmol/l (1.9–5.3 mmol/l) on subsequent days. There were no statistically significant differences in glucose concentrations between boys and girls, those born via vaginal delivery or Caesarean section, or babies of smoking or non-smoking mothers.

In a study of neonates admitted to the neonatal unit within 24 hours of birth, mean blood glucose concentration was 4.8mmol/l in those who did not receive glucose boluses (Juthani, Kumar, & Williams, 2013). Neonates who received treatment had a mean glucose concentration of 3.2 mmol/l. In this study there was no standardised threshold when boluses where administered, and glucose concentrations at which treatment was provided ranged from 0.8 to 2.7 mmol/l.

Concentrations of glucose and other cerebral fuels were measured during 48 hours after birth in term neonates with no complications born in Nepal (De L Costello, Pal, Manandhar et al., 2000). Geometric mean (standard deviation) concentration of glucose was 2.47 (1.62) mmol/l during the first 12 hours and 2.79 (1.39) mmol/l from 12 to 48 hours. At the same time, geometric mean of β-hydroxybutyrate concentrations increased about 4 times (41µmol/l at 0-12 hours to 165µmol/l during 12-48 hours) while glycerol, pyruvate and lactate concentrations did not change substantially between 0-12 hours and 12-48 hours after birth. However, those values are not representative of a general population as the study was done in developing country and many mothers were anaemic, undernourished and did not attend antenatal clinics. Furthermore, neonates were nursed in different temperatures depending on the season of delivery.

1.3 Definition of neonatal hypoglycaemia

1.3.1 What is neonatal hypoglycaemia

Hypoglycaemia is a common metabolic condition in the neonate that is associated with adverse neurodevelopmental outcomes (Anderson, Milner, & Strich, 1967; Duvanel, Fawer, Cotting et al., 1999; Fong & Harvey, 2014). Some consider it to occur as part of the adaptation from intra-
uterine to extra-uterine life which does not require treatment unless symptoms are present, while others argue that inability of a neonate to adapt to the changes in the environment can be predicted, prevented and treated (Rozance, 2014; Tin, 2014).

Before the establishment of proper techniques to measure hormone and substrate concentrations in body fluids, detection of neonatal hypoglycaemia relied only on symptoms like tremor, seizures, hypotonia, and hypothermia (Rozance & Hay, 2006). The same symptoms may be indicative of other neurological conditions, thus making it difficult to distinguish between these conditions and make appropriate treatment decisions. However, development of new techniques for detection of glucose in blood or plasma allows medical practitioners to be more confident in their decision making and treatment plans. Researchers try to establish thresholds for safe glucose concentrations that would not cause any neurodevelopmental deficits, as well as concentrations that lead to poor neurodevelopmental outcomes that require close monitoring and treatment. Thresholds for glucose concentrations can be considered in relation to clinical signs or laboratory findings (concentrations of glucose in blood or plasma).

1.3.2 Thresholds used for defining hypoglycaemia
Thresholds are needed to establish which neonates are safe and will not develop adverse neurodevelopmental outcomes in later life and those who need monitoring and intervention if required to prevent any possible brain damage. Ranges of ‘safe’ glucose concentrations for babies born at risk and not at risk may vary. Such factors as metabolism, altered physiology and availability of alternative fuels should be taken into account as they are the reason for individual variability in neonatal glucose utilisation. The ability of neonates to use gluconeogenesis for fuel production differs depending on individual metabolism and conditions in-utero. For example, in the first few days after birth growth restricted neonates had higher lactate and lower ketone bodies concentrations, while there was no significant difference in glucose concentrations between SGA and AGA neonates (Hawdon & Ward Platt, 1993). Further, β-hydroxybutyrate concentrations were lower in infants of diabetic mothers compared to small neonates (Harris, Weston & Harding, 2015). In addition, 6 neonates in this study had low concentrations of both lactate and β-hydroxybutyrate and there was no pattern related to neonatal risk factor or feeding detected.

Hypoglycaemia in neonates did not have a clear cut-off until the late 20th century. The threshold for defining safe glucose concentrations differed significantly among health professionals not
only in various countries but even in the same hospital, ranging between 1 and about 4 mmol/l (Koh, Eyre, & Aynsley-Green, 1988). Definitions differed for full term and premature neonates. Small for gestational age or premature neonates were believed to have higher tolerance to low glucose supply and as a result their safe glucose concentration was considered to be lower than that for full term neonates. Moreover, there was no consensus in the literature on the operational threshold and clinical management based on glycaemic status. Results from questionnaires sent to neonatologists in United Kingdom and Australia in 1992 (Koh & Vong, 1996) revealed that there was still a wide variation among clinicians as to the definition of hypoglycaemia, but not as wide as in 1986. In contrast to 1986 data, the glucose concentration defining hypoglycaemia was considered similar for full term and preterm neonates. Furthermore, the median value for the lower glucose threshold increased in comparison to 1986 and the majority of neonatologists preferred to maintain glucose concentration at 2 mmol/l or above. There was also more consistency in the definition found in textbooks.

A more recent survey (Harris, Weston, Battin et al., 2009) showed that management of neonatal hypoglycaemia has become more standardised in Australia and New Zealand and there is an overall agreement on identification and management of this condition. The threshold used in most nurseries within the Australian and New Zealand Neonatal Network was 2.6 mmol/l and there were treatment protocols in use. Despite this, there was considerable variation observed when making decisions on provided clinical scenarios, with greater discrepancy in making treatment decisions about neonates with no clinical signs. Thus there is a widely accepted threshold for a lower limit of acceptable glucose concentrations but uncertainty remains about how to manage neonates with risk factors. Many recent publications define different glucose concentrations as being safe and causing no neurological impairment (Inder, 2008; Kwon & Tsai, 2007; Termote, Verswijvel, Gelin et al., 2008). Further, a workshop on neonatal hypoglycaemia called by the Eunice Kennedy Shiver National Institute of Child Health and Human Development (Hay, Raju, Higgins et al., 2009) concluded that single glucose concentration cannot be considered predictive of a negative neurological outcome in later life. Other aspects that should be considered include severity, duration, and frequency of hypoglycaemic episodes and available alternative metabolic fuels.

The changes that occurred in clinical practice and treatment protocols were based on studies aimed at measuring glucose concentration in normal and pathological conditions throughout pregnancy and the neonatal period.
Neurological symptoms were found to be linked to low glucose concentrations in preterm neonates born to mothers with pre-eclampsia (Cornblath, Odell, & Levin, 1959). Neurological symptoms observed at 40 to 57 hours of life were reversed immediately after glucose administration. Treatment had to be provided for some time in order to stabilise glucose concentration in blood and cerebrospinal fluid. Later neurological damage occurred in two out of eight neonates and one died in the third week of life.

A study aiming to define safe glucose threshold used measurements from full term neonates with no complications and with normal growth (Srinivasan, Pildes, Cattamanchi et al., 1986) showed that plasma glucose concentration was low at 1 and 2 hours of age but stabilized by 3 hours when glucose concentration remained over 40 mg/dl (2.2 mmol/l) and no symptoms of hypoglycaemia were observed. Symptomatic hypoglycaemia occurred in three neonates with glucose concentrations less than 25 mg/dl (1.4 mmol/l) during 3 hours after birth. These neonates were treated with intravenous glucose infusions until reaching a normal concentration defined as 35 mg/dl (1.9 mmol/l).

The threshold of 2.6 mmol/l arose from two studies published in 1988. In one study (Koh, Aynsley-Green, Tarbit et al., 1988) 17 children of the age range from 1 day to 12 years were examined to detect any relationship between blood glucose concentration and neural function. Brainstem auditory or somatosensory evoked potentials were registered after each blood sample collection (either venous or capillary). Abnormal evoked potentials were registered during hypoglycaemic episodes in 10 children of whom 5 were asymptomatic including 4 neonates. Glucose concentration did not differ significantly between those who developed symptoms and those who did not. Abnormal evoked potentials were not detected in those subjects who had blood glucose concentration ≥2.6 mmol/l.

In the second study (Lucas, Morley, & Cole, 1988) 661 pre-term infants were studied, of whom 443 experienced glucose concentration <2.6 mmol/l. At 18 months of age significant decline was observed in motor and mental development in babies who experienced repeated episodes of hypoglycaemia taking 2.5 mmol/l as a cut-off value for definition of hypoglycaemia. It was also reported that birth weight of less than 1000g increased the incidence of hypoglycaemia, with 39% of these neonates experiencing episodes of hypoglycaemia (glucose concentration <2.6 mmol/l) on three days or more. An independent factor associated with decreased developmental scores was the number of days on which hypoglycaemic episodes defined as 0-1.5 and 1.6-2.5 mmol/l occurred, while there was no correlation when glucose concentration
was in the range 2.6-4 mmol/l. In preterm infants without cerebral palsy, the number of days with hypoglycaemic episodes (glucose concentration < 2.6 mmol/l), showed a negative correlation with developmental scores.

Due to a large number of confounding factors and many aspects that might influence glucose concentration and its delivery to major glucose-dependent organs, there are number of difficulties associated with defining glucose threshold. This is one of the reasons why the debate about what to consider hypoglycaemia remains open.

1.4 Detection of hypoglycaemia

1.4.1 Clinical methods and imaging

Hypoglycaemia is detected using clinical signs and laboratory measurements of glucose concentrations. Clinical signs alone cannot be diagnostic of hypoglycaemia as similar symptoms may occur in other neonatal conditions. However, when present, the diagnosis of hypoglycaemia and adequate treatment is always considered. Clinical signs associated with hypoglycaemia are common but most cases are asymptomatic.

One of the first observations of clinical signs of neonatal hypoglycaemia was described in pregnancies associated with toxaemia (Cornblath, Odell & Levin, 1959). In all cases condition at birth was defined as fair or good. However, at 40-72 hours after birth, neonates experienced clinical signs that were reduced or completely lost after intravenous glucose infusions. Most common signs were convulsions, apnoea, tremor, cyanosis and limpness. Some signs that are common and relatively easily reversed are consciousness changes like lethargy, stupor and irritability (Rozance & Hay, 2010). In addition, neurological signs like hypotonia, circulatory collapse and tonic-clonic seizures with no laboratory indicators of neonatal sepsis can be suggestive of neonatal hypoglycaemia, but are not sufficient to confirm hypoglycaemia and possible brain damage.

One way of identifying the effect of hypoglycaemia on nervous tissues is histological findings after lethal outcomes. Case reports dating back to 1967 showed changes in anatomical structure of nerve cells in neonates who experienced hypoglycaemic episodes. The first is a case report of 6 neonates who died in the neonatal period either from hypoglycaemic damage or from other complications after experiencing hypoglycaemia (Anderson, Milner & Strich, 1967). In 5 cases calculated brain weight to liver weight ratio was higher than normal (defined as less than 3
after 28 weeks gestation) suggesting hypoglycaemia was caused by decreased liver glycogen stores. Histological samples of nervous tissues from treated and untreated neonates differed in terms of brain damage. Nuclear membranes in small nerve cells of untreated neonates were indistinct or absent while nuclei were pyknotic or fragmented. Large nerve cells had shrunken and stippled nuclei with chromatolysis present. In some cases there was not only severe degeneration of nerve cells but glial cells were affected in different parts of nervous system.

Another pathologic case study of brain changes after neonatal hypoglycaemia showed microcephaly with atrophic gyri and deep sulci (Banker, 1967). Dilated ventricles, loss of white matter, diffuse loss of nerve cells with increased microglia and astrocytes numbers, and smaller cortical spinal tract were features found in hypoglycaemic brain injury.

Another way of identifying the effect of hypoglycaemia on nervous tissue is neuroimaging. Magnetic Resonance Imaging (MRI) is a common method used to detect brain damage in neonates, including both structural and biochemical assessment using different MR techniques, and may be helpful in differentiating between different causes of the brain injury like hypoglycaemia, hypoxia-ischemia or sinus venous thrombosis (Boardman, Wusthoff, & Cowan, 2013).

A parieto-occipital pattern of injury was described in many case reports of babies who experienced symptomatic neonatal hypoglycaemia. Two cases of hypoglycaemic brain injury after uncomplicated pregnancy and delivery were described with similar clinical features (Traill, Squier, & Anslow, 1998). In 1-2 days after birth neonates had repeated seizures even after treatment. No metabolic condition was detected in one case but in the second case hypoglycaemia was caused by a glycogen storage disease. MRI scanning on the 6th day of life in both cases showed cortical and white matter low density which was most severe in the parieto-occipital region. Furthermore, a retrospective analysis of clinical records, computerised tomography (CT) and MRI scans of five babies who suffered brain injury caused by hypoglycaemia showed diffuse patterns of brain damage with parieto-occipital regions being most affected, confirming previous findings (Barkovich, Al Ali, Rowley et al., 1998). In one neonate the damage was severe and included damage to frontal lobes and globus pallidus. It was argued that such damage occurs after severe prolonged hypoglycaemia, but the information on duration and severity of hypoglycaemia was not sufficient to confirm this theory.

A more recent study that used three types of brain imaging: conventional, diffusion weighted and MR spectroscopy, in two term hypoglycaemic babies who had seizures also demonstrated
abnormalities in the parieto-occipital lobes (Kim, Goo, Lim et al., 2006). These abnormalities presented as lesions with restricted water diffusion, increased lactic-acid peak and decreased N-acetylaspartate peak during first-second week of life, while increased water diffusion and atrophy in affected zones were found 10 months later. Similarly, MRI-detected bilateral occipital lobe injury was described in a symptomatic baby who experienced seizures due to hypoglycaemia on the first day after birth (Vijay & Agarwal, 2010) parieto-occipital oedema and infarctions were described in another baby who presented with circulatory collapse and seizures (Termote, Verswijvel, Gelin et al., 2008).

A retrospective study also described an occipital pattern of brain injury detected using diffusion weighted MRI in the six-day period after the hypoglycaemia episode in 8 of 16 (50%) babies born at ≥37 weeks’ gestation, but not in the preterm babies (Tam, Widjaja, Blaser et al., 2008). In addition, diffusion weighted MRI when performed later than 6 days after the onset of hypoglycaemia could not detect any changes in the occipital lobe.

Contrary to the studies that reported typical occipital patterns of hypoglycaemic brain injury, another MRI study that included 35 term babies who experienced symptomatic neonatal hypoglycaemia found variable patterns of brain damage (Burns, Rutherford, Boardman et al., 2008). Close to two thirds of these babies did not have predominantly occipital injury, with parasagittal lesions, infarctions and thalamic injury being common. Further, severity and duration of hypoglycaemia were not associated with any specific pattern of injury (Burns, Rutherford, Boardman et al., 2008).

Therefore, susceptibility of parieto-occipital white matter to hypoglycaemic damage has been reported over decades (Filan, Inder, Cameron et al., 2006), but these studies included small number of babies and only those who experienced symptomatic hypoglycaemia. The pattern of brain injury in babies who had asymptomatic and undetected hypoglycaemia remains unclear.

1.4.2 Laboratory testing
Precise glucose measurements are essential for detection and management of hypoglycaemia. However, there are a number of problems with methodology used for measurements. First, the sample itself may be collected, stored or analysed using different techniques and reagents. In addition, the accuracy of measurement depends on the device that is used for the analysis. Requirements for methods of measuring glucose concentration are: easy to use by medical
personnel, minimally painful, causing no complications, available to measure frequent samples, accurate and produce measurements rapidly.

In current practice, glucose is measured using enzyme reaction-based glucose meters, point-of-care devices, which provide intermittent results, and continuous glucose monitors. Each method has strengths and limitations.

The gold standard for detecting glucose concentrations is considered to be enzyme-linked measurement like glucose oxidase, dehydrogenase or hexokinase. This method is not affected by haematocrit and less affected by other metabolites (Beardsall, 2010). However, the accuracy of measurements depends on the way the blood is handled. Time between collection and analysis depends on the facilities the hospital has, whether there are large numbers of samples or small, number of analysers, and location of the laboratory. A long interval does not allow for immediate hypoglycaemia management if required. Delay between blood collection and analysis can also allow glycolysis to occur in red cells even if preservative is added. For example, immediately analysed capillary and venous blood samples had higher glucose concentrations than those analysed 2 hours after collection (Elimam, Horal, Bergström et al., 1997).

Point-of-care devices are used as bedside measurement tools, as it takes only a few seconds to receive results. Fast measurements and small volumes of sample needed for analysis (Khan, Vasquez, Gray et al., 2006) are of particular importance for neonates who are at a higher risk of developing hypoglycaemia and in whom glucose concentrations may change rapidly. However, results from such meters are influenced by other factors like high haematocrit levels (Tang, Lee, Louie et al., 2000). When venous blood glucose concentrations ranging from 2.06 to 30.24 mmol/l were compared at different haematocrit levels (19.1%; 38.5%; 58.3%), differences were larger for lower and higher haematocrit values with smaller differences for normal haematocrit levels. Moreover, there was variability between different meters in their response to glucose concentrations at different haematocrit levels. These findings suggest that in addition to bias linked to the haematocrit effect on glucose concentrations, there would also be uncertainty about the accuracy of glucose measurements linked to the type of meter used. Some meters control for haematocrit when calculating glucose concentrations. However, evidence on their effectiveness in neonatal units is controversial (Beardsall, 2010). For example, a study of 71 neonates that evaluated use of point-of-care devices in neonatal hypoglycaemia found all of the five devices tested to be inaccurate (Ho, Yeung, & Young,
The best two out of five glucometers had 51% and 46.5% of measurements that differed from measurements using glucose oxidase method by less than 10%. Further, differences of 20% and more between glucose oxidase laboratory and point of care measurements occurred in 57% of samples in the hypoglycaemic (<2.77 mmol/l) range (Khan, Vasquez, Gray et al., 2006). Another study of 500 neonates admitted to intensive care unit found good correlation (correlation coefficient 0.7; P=0.000) between glucose concentrations measured by point-of-care devices and glucose oxidase method (Sreenivasa, Kumar, & Sreenivasa, 2015).

Therefore, concern about accuracy of point-of-care devices in the low glucose concentration range is justified as this is the measure on which treatment decisions are made (Freckmann, Pleus, Link et al., 2015). Point-of-care meters were designed for home use of diabetic patients to detect hyperglycaemic episodes and then make appropriate modifications to maintain glucose level at an acceptable range (Beardsall, 2010; Woo, Tolosa, El-Metwally et al., 2014). Therefore, their use in intensive care unit where other accompanying factors can influence meter readings may be not as valuable as in home settings for diabetic patients.

Continuous glucose monitoring has been used for self-monitoring of glucose concentrations in diabetic patients to prevent long-term complications (Schaepelynck-Bélicar, Vague, Simonin et al., 2003). Continuous glucose monitors comprise a sensor that is inserted under skin to measure glucose concentrations in interstitial fluid. The sensor consists of glucose oxidase platinum electrode that measures the current produced during oxidative reaction. Subsequently the current is transmitted onto the monitor where data are analysed every 10 seconds and then averaged every 5 minutes (De Block, Vertommen, Manuel-y-Keenoy et al., 2008). The use of continuous glucose monitors in measuring glucose concentrations in neonates is relatively recent. The advantage of this method is the ability to monitor glucose concentrations either retrospectively or in real-time.

There are several limitations of continuous glucose monitoring. One is its accuracy at low glucose concentrations. It is disputable whether episodes of very low glucose concentrations can be detected by the device built to detect high glucose concentrations in diabetic patients. Although in previously described studies agreement between intermittent blood and continuous glucose measures was relatively good, in the study including patients with well controlled diabetes (McGowan, Thomas, & Moran, 2002) 74% of paired concentrations of glucose were lower when measured by continuous monitors. The lowest correlation between the two methods occurred in subjects with the narrowest range of glucose concentration during 24 hour
observation. These results were obtained from an older children population (mean 18±3 years) and may suggest a possibility of overestimation of neonatal hypoglycaemia and unnecessary treatment measures in clinical practice. These data should be interpreted with caution as there are physiological differences in glucose metabolism between the neonatal period and adolescence. Another issue is the number of days for which glucose monitors can be tolerated and produce accurate results. The electrode is a foreign body thus can be covered by cells over time leading to loss of correlation between electrode signal and interstitial glucose concentration. That is why the sensor may need to be calibrated regularly and some consider it to be accurate for only up to 7 days (De Block, Vertommen, Manuel-y-Keenoy et al., 2008).

In very low birth weight infants (mean gestational age 27.5 ± 2.0 weeks and birth weight less than 1500g) there was good correlation (r =0.96, p <0.001) between data obtained from continuous interstitial and intermittent capillary glucose measurements with mean glucose concentration difference -0.25 mg/dl (0.014 mmol/l) (Platas, Thió Lluch, Pociello Almiñana et al., 2009). However, the correlation decreased when analysing lower glucose concentrations separately with correlation coefficient 0.395 for 40-69 mg/dl (2.2-3.8 mmol/l) glucose concentration range. When tested on larger neonates (≥32 weeks gestation, with risk factors for developing hypoglycaemia), there was good agreement between heel prick samples analysed using glucose oxidase methods and continuous glucose measurements (Harris, Battin, Weston et al., 2010) with 0.03 mmol/l mean difference for paired blood samples (95% CI: -1.02 to 1.08 mmol/l) for at least 7 days of monitoring. This agreement remained when analysing differences for low glucose concentrations (<3 mmol/l) when mean was 0.18 mmol/l (95% CI: -1.25 to 0.85 mmol/l). However, more neonates were identified as hypoglycaemic using continuous glucose monitors (44% vs. 33%). Neonates and their parents showed high tolerance to the continuous glucose monitor in both studies and it was an easy method to use by hospital staff. Some neonates appeared to experience brief pain at the time of sensor insertion but not afterwards. It may mean that this method is less painful than intermittent heel prick sampling for babies who need longer periods of monitoring.

Another factor to consider is the time it takes for the sensor to become stable after insertion that can last up to two hours (De Block, Vertommen, Manuel-y-Keenoy et al., 2008). This is the time after birth when concentrations of glucose tend to vary greatly, thus some episodes of hypoglycaemia may be misinterpreted. Furthermore, because of the time it takes glucose to diffuse from blood into the interstitial space, changes in interstitial glucose measurements may lag behind changes in blood concentrations by approximately 20 minutes (Reach & Choleau,
2008). As continuous glucose monitors record interstitial glucose concentrations, they may not work well in some neonates with oedema (Beardsall, Ogilvy-Stuart, Ahluwalia et al., 2005). Although, continuous glucose monitors have limitations, these are the only devices that provide data on glucose concentrations over a long period of time and therefore information about severity and frequency of hypoglycaemic episodes.

Measuring glucose concentrations in the neonatal intensive care unit is crucial for detecting hypoglycaemia and providing proper treatment. Therefore, devices designed for blood glucose analysis should be accurate and practical. For this reason, factors affecting the accuracy of measurements like blood handling and choice of the glucose meter should be taken into account and errors minimised. Although the glucose oxidase method has its limitations, it is a gold standard of measuring glucose concentrations. Continuous glucose monitoring is very useful for research and is the method that in the future may be more widely used for neonatal monitoring.

1.5 Management of neonatal hypoglycaemia

1.5.1 Treatment issues
Management of hypoglycaemia differs in different countries and in different hospitals. These discrepancies exist because of a big knowledge gap in this area. There are no methods that would allow clinicians to measure concentrations of glucose and alternative fuels that actually reach the brain. All the decisions are based on clinical presentation and laboratory measurements of peripheral blood. That is why some argue that a flexible approach is the best option for hypoglycaemia management (Rozance & Hay, 2010). Such an approach must be based not only on blood glucose concentrations but also on clinical assessment. However, while taking such approach it is arguable whether all hypoglycaemic episodes may be detected and treated. Hypoglycaemia often is undetected in generally well neonates, and outcomes in later life are unknown. At the same time controversial evidence in the literature can make clinicians unsure as to what treatment plan is appropriate for a neonate. For this reason guidelines for screening and intervention measures have been developed.

1.5.2 Guidelines for management of neonatal hypoglycaemia
Management of hypoglycaemia includes screening, prevention and treatment. Some actions can be undertaken during pregnancy like control of maternal glucose concentrations, control
of weight gain and if possible, avoiding administration of large doses of glucose during labour because it may cause hyperinsulinaemic hypoglycaemia (Williams, 1997). Maternal β-blocker use has also been found to be associated with significant hypoglycaemia in the neonate (Crooks, Deshpande, Hall et al., 1998).

Screening of neonates is mainly based on operational thresholds recommended for at risk babies (Cornblath, Hawdon, Williams et al., 2000). According to them, healthy term neonates after normal pregnancy do not require monitoring if no clinical signs are present. At risk neonates with altered metabolic adaptation require glucose monitoring, which should be established soon after birth and before feeding. If blood glucose concentration falls below 2mmol/l and does not improve after feeding, treatment should be considered.

Breastfeeding is considered the best preventive measure. All mothers should be encouraged to breastfeed as soon as possible assuming there are no maternal or neonatal conditions that make breast feeding impossible (Holmes, 2013). Early breastfeeding has been shown to stabilise glucose concentrations in neonates of diabetic mothers (Chertok, Raz, Shoham et al., 2009). If needed formula milk may be used and its quantities must be monitored and not exceed the required volumes. There has been evidence suggesting that metabolic adaptation can be altered by excessive formula feed supply while adequate breastfeeding leads to sufficient ketone body production, especially at low glucose concentrations after first day of life in SGA neonates (de Rooy & Hawdon, 2002). Exclusively breastfed neonates had higher ketone body concentrations than formula fed or formula supplemented group over the first week (SGA and LGA included in the study) while glucose concentration range was similar in those groups.

Many recommendations exist in published literature about glucose concentrations that should be maintained after birth to prevent neurological impairment (Filan, Inder, Cameron et al., 2006; Kwon & Tsai, 2007; Stanley, 2006). Many hospitals have their own protocols for hypoglycaemia management. These are mainly based on existing knowledge and provide clinicians with a management plan which includes screening and treatment.

Adherence to clinical guidelines on management and screening of neonatal hypoglycaemia study was audited in Australia (Sundercombe, Raynes-Greenow, Carberry et al., 2013). According to the protocol of Royal Prince Albert Hospital, Sydney, an acceptable glucose concentration is >2 mmol/l on day one and >2.5 mmol/l after 24 hours for at risk asymptomatic neonates, >34 weeks gestation. The Neonatal Intensive Care Unit (NICU) management protocol provides different thresholds for management depending on the risk factors. For
neonates born to diabetic mothers the operational threshold is the same as above. In preterm (<35 weeks gestation) or term neonates with any other condition glucose concentration >2.5 mmol/l is to be maintained at all times. The audit study aim was to define the adherence to the protocol from which seven criteria were selected. Median adherence was 73%. Feeding in the first hour after birth was the biggest issue. Out of 106 neonates only 39% received their first feed in the first hour after birth.

Canadian Paediatric Society guidelines on management of hypoglycaemia in the neonatal period recommend immediate treatment of symptomatic neonates with blood glucose concentration <2.6 mmol/l followed by investigation of reasons for this condition. Recommended treatment is intravenous dextrose. Management is advised for at risk neonates with a single glucose measurement (after feeding) <1.8 mmol/l or for neonates with repeated glucose concentrations <2.6 mmol/l. If they do not respond to increased calorie intake and the glucose concentration remains low, intravenous dextrose is the next management option. An audit study of Canadian guidelines was performed using literature and clinical review (Croke, Sullivan, Ryan-Drover et al., 2009). Clinical review found that when following these guidelines 5% of neonates defined as at risk were not screened for neonatal hypoglycaemia. At the same time 3% of healthy term neonates were identified as a group that needed treatment in the form of supplemental oral or intravenous therapy. Another discrepancy found was screening time, which is recommended at 2 hours but occurred closer to 3 hours after birth.

Dextrose gel was reported to be safe and easy to administer, and it reduced admission to neonatal intensive care unit for hypoglycaemia (Bennett, Headtke, & Rowe-Telow, 2015; Harris, Weston, Signal et al., 2013; Harris, Alsweiler, Ansell et al., 2016). Dextrose gel is recommended for treatment in Auckland clinical guidelines, which recommend monitoring of at risk neonates (<10 and >95 centile on customized charts, born to diabetic mothers, presenting with possible clinical symptoms and who have other medical conditions or complications) for at least 12 hours or at least 12 hours after the last detected episode (<2.6 mmol/l) (Newborn services clinical guideline, 2004). Feeding is the primary treatment option. However, if glucose concentrations remain in a 1.2-2.5 mmol/l range after 2 hours, 0.5 ml/kg oral 40% dextrose gel massaged into buccal mucosa should be administered followed by feeding. The procedure can be repeated if blood glucose concentration remains in the same range 30 minutes after first administration.
1.5.3 Choice of treatment

Generally accepted treatment plans for neonatal hypoglycaemia include appropriate feeding practices and external glucose supply, either oral or parenteral.

Breastfeeding is recommended for healthy neonates who can tolerate feeds during the first hour of life. Feeds should be frequent (10-12 times/day during the first few days) and on demand. If there is not enough breast milk to satisfy needs of a neonate, formula milk can be added to feeding regimen. However, doses should be controlled. In those neonates for whom enteral feeding is contraindicated, not well tolerated or glucose concentration remains under the operational threshold, glucose should be supplied from another source (Hawdon, 2008).

Glucose can be provided externally to satisfy demand of a neonate. There are two ways of glucose provision: oral and intravenous administration of diluted glucose solution and gel. It is unknown which treatment method is better in terms of cost-effectiveness, time it takes to stabilise glucose concentrations and minimal side effects.

The treatment regimen was evaluated in 23 hypoglycaemic neonates (Lilien, Pildes, Srinivasan et al., 1980). Symptomatic and asymptomatic neonates were treated with 200 mg/kg glucose mini-bolus (2 ml/kg of 10% dextrose) during one minute, after which 8 mg/kg/minute continuous glucose infusion rate was established. Data from this study were compared to results of an earlier study performed by the same group on neonates receiving only continuous glucose infusion at 8 mg/kg/min (Lilien, Grajwer, & Pildes, 1977). Mini-bolus treatment followed by immediate glucose infusion stabilised glucose concentrations faster and reduced number of hyperglycaemic episodes compared with solely glucose infusion therapy. However, response to treatment varied in different groups of neonates (AGA, SGA, LGA, infants of diabetic mothers [IDM]). Nevertheless, treatment guidelines are largely based on these studies.

Recommended glucose infusion rates may differ for at risk groups. For example, for neonates born at <32 weeks gestation glucose infusion rate should be at least 6 mg/kg/min, which is the approximate equivalent to hepatic glucose output. Infusion rate for severely growth restricted neonates is recommended at 6-8 mg/kg/min and in some cases can be more than 10 mg/kg/min (Deshpande & Platt, 2005).

Lipid supplementation is sometimes considered as a form of treatment. Medium chain triglycerides increase glucose concentrations via gluconeogenesis in SGA and preterm neonates (Sann, Mathieu, Lasne et al., 1981). However, more studies need to be done to prove its effectiveness in neonatal hypoglycaemia management.
Sometimes glucagon is considered for treatment of neonatal hypoglycaemia. Neonates born to diabetic mothers who received intravenous glucagon immediately after birth did not have hypoglycaemic episodes (Wu, Modanlou, & Karelitz, 1975). In a retrospective observational study of neonates who received glucagon infusions 0.5-1 mg/day, the number of hypoglycaemic episodes was significantly reduced and no severe episodes occurred after glucagon administration (Miralles, Lodha, Perlman et al., 2002). Nevertheless, glucagon can cause hyperglycaemia and as a result increased insulin secretion, which is why it should be used very carefully. In addition such treatment is expensive.

Treatment of hyperinsulinaemic neonatal hypoglycaemia continues into later life. Congenital hyperinsulinism is a broad term that includes a group of disorders that are different in their clinical, morphological and genetic characteristics (De León & Stanley, 2007). Depending on reoccurrence and severity of hypoglycaemic episodes, different approaches in treatment may be undertaken. Intravenous (IV) dextrose of high concentrations should be started and frequent blood glucose measurements taken. If a neonate does not respond to treatment, diazoxide and chlorthiazide are often prescribed. If hypoglycaemia remains resistant to such treatment, glucagon and octreotide are used (De León & Stanley, 2007; Kapoor, James, & Hussain, 2009). However, there are many cases when the hypoglycaemia cannot be managed by medications only and then surgical treatment is performed.

Management of hypoglycaemia is a widely discussed topic. Many issues remain unsolved as to screening and treatment measures. Although clinical guidelines are used by many hospitals, in practice they are not always followed. In a survey of neonatal hypoglycaemia management, there was good agreement as to which neonates should be screened (Harris, Weston, Battin et al., 2009). However, treatment plans varied and the variation was greater for asymptomatic neonates. 65% of nurseries reported different operational thresholds when treatment should be provided for the first 4 hours after birth, and 55% after 4 hours. Therefore, more information is needed for clinicians about screening, prevention and treatment of neonatal hypoglycaemia.

1.6 Neurodevelopmental outcomes

1.6.1 Risk factors for hypoglycaemia

Hypoglycaemia in the neonatal period is a common condition. A prospective study that compared treated hypoglycaemic neonates with matched controls assessed children every year (Pildes, Cornblath, Warren et al., 1974). Growth measures differed significantly between the two groups with hypoglycaemic neonates being lighter at 1 and 2 years, and shorter at 1 year.
only. Head circumference measures were significantly lower in the hypoglycaemic cohort at 2, 4 and 6 year examinations. Neurological impairment was higher in hypoglycaemic group with differences reaching significance at 2, 3 and 6 years. On the other hand, electroencephalogram (EEG) did not detect any differences between cases and controls.

Another study compared student achievement test scores of 10 year old children who had transient hypoglycaemia with those who had glucose concentrations in normal range during first 3 hours after birth (Kaiser, Bai, Gibson et al., 2015). Hypoglycaemia was defined by three cut-offs: <1.94 mmol/l (35 mg/dl), <2.22 mmol/l (40 mg/dl) and <2.5 mmol/l (<45 mg/dl). Neonatal hypoglycaemia was associated with decreased student achievement test scores (literacy and mathematics) when using each of the cut-offs.

Some neonates are monitored more closely than others if they belong to certain risk groups. Pre-term, growth restricted, small- and large-for gestational age and infants of diabetic mothers have been shown to have higher incidence of neonatal hypoglycaemia (Harris, Weston, & Harding, 2012; Holtrop, 1993; Maayan-Metzger, Lubin, & Kuint, 2009; Rozance, 2014).

1.6.2 Term and pre-term neonates
Neurological impairment was observed later in life in two cases who suffered hypoglycaemic brain injury after normal pregnancy and term delivery with no complications (Traill, Squier & Anslow, 1998). MRI scans performed at 10 months in first case and 7 years in the second showed cortical and white matter atrophy. In the first case neurological impairment was present in the form of spastic quadriplegia and epilepsy and visual impairment. In the second case developmental delay was detected at 3 years.

In a follow-up study of term neonates (>36 weeks gestational age) who experienced low glucose concentration episodes (<2.6 mmol/l) within the first 24 hours, neurodevelopment was assessed at 12 months (Tam, Haeusslein, Bonifacio et al., 2012). MRI scans performed between 2-5 days after birth showed that cortico-spinal tract was most affected by hypoglycaemia. This hypoglycaemia-cortico-spinal tract injury association remained significant when adjusted for hypoxia-ischaemia markers (OR 3.72; 95% CI: 1.02-13.57 with p= .047). At 12 months MRI-detected injury was associated with increased odds of receiving higher (worse) neuromotor score.

Follow-up of preterm neonates born before 32 weeks’ gestation did not show any differences in neurological and motor function at 2 and 15 years between those who had and did not have neonatal hypoglycaemic episodes (Tin, Brunskill, Kelly et al., 2012). This finding did not
change when children who had blood glucose concentration <2 mmol/l on at least 3 days during the whole 10 days assessment period were compared to matched controls.

1.6.3 IUGR/SGA/LGA/IDM

Low birth weight was found to be a significant factor for hypoglycaemic brain injury and symptomatic epilepsy in later life (Udani, Munot, Ursekar et al., 2009). Brain imaging (MRI or computed tomography [CT] scans from the medical records, if needed a new scan was performed) was used as the main method to detect neonatal hypoglycaemic brain injury while clinical history and laboratory blood glucose measurements were complimentary (only if sufficient data available) for diagnosis of neonatal brain injury. Children were included in the study if onset of symptomatic epilepsy occurred during the first 3 years after birth. From 23 children with typical hypoglycaemic brain injury pattern, 14 had hypoglycaemic episodes documented in their clinical records in the neonatal period, thus 9 neonates with no clinical data were excluded from the analysis. Neurological impairment in later life observed in this cohort of neonates included microcephaly, apraxia, autism and cortical visual impairment. The most prevalent type of seizures was infantile spasms, followed by partial and generalised seizures. Refractory seizures occurred in more than half of subjects.

LGA neonates are also a risk group for developing hypoglycaemia. The incidence of hypoglycaemia was shown to be 16% in large for gestational age term neonates born to non-diabetic mothers (Schaefer-Graf, Rossi, Bührer et al., 2002). Neurological impairment in these neonates was not supported by findings from the follow up of term LGA neonates (maternal diabetes was excluded) who were screened for hypoglycaemia during the first day after birth (Brand, Molenaar, Kaaijk et al., 2005). Neurodevelopmental scores at 4 years did not differ significantly between hypo- and normoglycaemic groups, nor between neonates who were treated with intravenous glucose and who were not.

Neonates born to diabetic mothers are considered to be at a high risk of developing hypoglycaemia in early life. Stenninger et al. showed changes in neurological function (after EEG, physical and psychological assessments) in neonates after diabetic pregnancy (Stenninger, Flink, Eriksson et al., 1998). The study included neonates born to mothers with insulin dependent and gestational diabetes that was treated with insulin. Neonates were divided in two groups: those who had glucose concentrations <1.5 mmol/l and those who did not, and stratified by gender and type of maternal diabetes. Follow up at 8 years found no differences between subjects and controls for growth measurements and neurological examination score.
Literature review

(muscle strength, movement, balance, coordination, tendon reflexes). However, children who had experienced neonatal hypoglycaemia showed worse results in minimal brain dysfunction screening, both in general score and in subtests. Moreover, developmental scores were significantly lower in the hypoglycaemic group. In regard to intellectual performance and neurological status, 30% of neonates from the study group born to diabetic mothers were defined as abnormal, based on developmental retardation and/or major central nervous system abnormality (Haworth, McRae, & Dilling, 1976). However, there were no significant differences in neurodevelopment between hypo- and normoglycaemic neonates from this group. In addition, no correlation was identified between severity and duration of hypoglycaemia and any negative outcomes. Another follow-up of neonates born to diabetic mothers (both gestational and insulin-dependent) showed normal intelligence quotient (IQ), physical and neurological status in all children at 5 years (Persson & Gentz, 1984).

1.6.4 More than one risk factor
Low birth weight neonates are also considered to be at a high risk of hypoglycaemic damage. In a study population of 661 preterm low birth weight (<1850 g) neonates assessed in relation to their neurodevelopment at 18 months corrected age, neurodevelopmental impairment presenting as either cerebral palsy or reduced developmental scores increased significantly with number of days on which hypoglycaemia occurred. Relative risk was 3.5 times higher in neonates who experienced hypoglycaemia on five days or more (p < 0.02) (Lucas, Morley & Cole, 1988).

Growth parameters and neurodevelopment of preterm (≤34 weeks) SGA (weight below 10th percentile) neonates was assessed in a follow-up study (Duvanel, Fawer, Cotting et al., 1999). Neonates with hypoglycaemic episodes (<2.6 mmol/l) were compared to non-hypoglycaemic neonates. Growth data included weight, length, head circumference and calculated body mass index (BMI) at birth and later follow up at 6, 12 and 18 months and 3.5 and 5 years of corrected age. In neonates who had 6 and more low blood glucose concentrations, head circumference values were lower at 12 and 18 months and 5 years. BMI calculated from birth measurements was lower in neonates with 6 and more recurrent hypoglycaemic episodes than in the control group (7.6 versus 8.3 kg/m²). Severity of hypoglycaemia was related to later growth, with moderate glucose concentrations (>1.6 to <2.6 mmol/l) associated with reduced head circumference at 18 months’ corrected age.
Hypoglycaemia in neonates with congenital hyperinsulinism is different in terms of reasons, mechanisms underlying condition and its treatment. Usually hypoglycaemic episodes are severe and difficult to manage. Long term outcomes in children after hyperinsulinaemic hypoglycaemia were assessed by comparing different treatment groups (diazoxide or surgery) (Cresto, Abdenur, Bergada et al., 1998). Follow-up included assessment of intellectual and school performance, and growth values. Neurological and intellectual abnormalities were detected in 11 out of 26 children (age not listed).

1.6.5 Controversial findings from studies of neonatal hypoglycaemia and later development

Studies investigating the effect of neonatal hypoglycaemia on later neurodevelopment have several limitations. It is difficult to compare them because of differences in study design and methodology. Most studies had small sample size thus results of those should be evaluated cautiously. Hypoglycaemic thresholds varied greatly between studies. Age at follow-up was described in a study protocol. However, not all of the data were clearly stated. In some cases, age was omitted or follow-up age did not have strict assessment windows. These and many other factors make most of the results difficult to interpret and compare.

1.7 Development and emotional health in young children

Development and emotional health problems include a wide range of issues that can be transient or long-term in a single or multiple domains. Some of the problems can be described as a certain diagnosis like autism spectrum disorder or oppositional defiant disorder; others do not meet criteria for a diagnosis but still cause difficulties in everyday life. Neurodevelopment is described as a pre-programmed process and this means that many serious conditions are established in early life and persist into adulthood. Nevertheless, neurodevelopment can be altered by the change in environmental factors. Therefore, it is important to assess children in early life and identify those in need of intervention and monitoring.

1.7.1 Prevalence of developmental and emotional health problems

Developmental and emotional problems are recognised chronic conditions that cause functional impairment (Halfon, Houtrow, Larson et al., 2012; Slomski, 2012). Prevalence of mental illness is reported from World Health Organisation (WHO) to be around 20% in children and adolescents (Belfer, 2008); this rate is similar in young children (Egger & Angold, 2006; Lavigne, LeBailly, Hopkins et al., 2009). In a healthy cohort of very young children,
which excluded those with a birth weight <2200 g, low Apgar scores, or who were adopted, 12-16% of 2 year olds and 6% of 1 year olds had subclinical and clinical emotional health problems (Briggs-Gowan, Carter, Skuban et al., 2001). In addition, children who experience problems in one domain may be at a higher risk of co-occurring problems in another domain. For example, clinically significant depressive symptoms are more common in preschool children who also have motor and speech difficulties (Fuhrmann, Equit, Schmidt et al., 2014). Similarly, delay in cognitive development may lead to social withdrawal, resulting in high rate of emotional problems. Prevalence of developmental delays in children under 3 years is reported to be 13% (Rosenberg, Zhang, & Robinson, 2008), and a similar rate of 13% of any type of developmental disability was found for a 3-17 year old cohort using health interview survey data (Boyle, Boulet, Schieve et al., 2011).

Developmental and emotional health problems also lead to increased cost of treatment throughout adult life. Expenditure on psychotherapy, hospital visits and admissions is higher in children with difficulties compared to those without (Kohlboeck, Romanos, Teuner et al., 2014). Moreover, childhood social-emotional problems are negatively associated with later income because of educational and work problems, and also problems inside a family (Smith & Smith, 2010).

1.7.2 Risk factors associated with developmental and emotional health problems
A variety of different risk factors are related to developmental delay in children (Table 1.7.2). Low household income and low maternal educational level (Boyle, Boulet, Schieve et al., 2011; Eapen, Zoubeidi, Yunis et al., 2006; Simon, Pastor, Avila et al., 2013), low birth weight (Verkerk, Jeukens-Visser, van Wassenaer-Leemhuis et al., 2014), prematurity, multiple gestation and intrauterine growth restriction (Thomaidis, Zantopoulos, Fouzas et al., 2014) are all associated with a higher rate of problems. Children from high socio-economic groups have higher scores on cognitive tests compared to those from lower socio-economic groups, and this difference is evident from under 2 years of age and increases as children grow (Feinstein, 2003). Emotional health problems are likewise associated with neonatal and socio-demographic characteristics (Table 1.7.2).
Table 1.7.2 Factors associated with increased risk of developmental and emotional health problems in children.

<table>
<thead>
<tr>
<th>Study</th>
<th>Domain</th>
<th>Measure</th>
<th>Age</th>
<th>Maternal or neonatal</th>
<th>Socio-economic</th>
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<td>Singh, Kenney, Ghandour et al., 2013</td>
<td>+</td>
<td>National Survey of Children’s Health</td>
<td>2-17 years</td>
<td>Prematurity: &lt;37 weeks’ gestation Birth weight: &lt;2500 g</td>
<td>Single-parent households, stepfamilies, low income</td>
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<td>de Jong, Verhoeven, Low et al., 2015</td>
<td>+</td>
<td>Bayley Scales of Infant and Toddler Development, Child Behaviour Checklist</td>
<td>2 years</td>
<td>Prematurity: 32-36 completed weeks’ gestation</td>
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<td>Jo, Schieve, Sharma et al., 2015</td>
<td>+</td>
<td>Diagnosis of autism or developmental delay, and receipt of special services as recalled by mother; The Strengths and Difficulties Questionnaire</td>
<td>6 years</td>
<td>Mother’s pre-pregnancy BMI ≥35</td>
<td>Maternal depression, stress of both parents (Parenting Stress Index questionnaire score)</td>
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<td>Huhtala, Korja, Lehtonen et al., 2014</td>
<td>+</td>
<td>Five to Fifteen questionnaire</td>
<td>4 years</td>
<td>Prematurity: &lt;37 weeks’ gestation; birth weight: ≤1500g; Admission to neonatal intensive care unit.</td>
<td>Maternal depression, stress of both parents (Parenting Stress Index questionnaire score)</td>
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<tr>
<td>Poehlmann, Hane, Burnson et al., 2012</td>
<td>+</td>
<td>Laboratory assessment of temperament; Parent Child Early Relational Assessment; Child Behaviour Checklist; Abbreviated Battery Scale</td>
<td>9 months, 36 months</td>
<td>Prematurity: &lt;37 weeks’ gestation; birth weight: &lt;2500g</td>
<td>Maternal frustration, anger, critical parenting</td>
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<td>Mansson &amp; Stjernqvist, 2014</td>
<td>+</td>
<td>Bayley Scales of Infant and Toddler Development, third edition</td>
<td>2.5 years</td>
<td>Prematurity: &lt;27 weeks’ gestation</td>
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<td>Kerstjens, Bocca-Tjeertes, De Winter et al., 2012</td>
<td>+</td>
<td>Ages and Stages Questionnaire</td>
<td>3.5-4 years</td>
<td>Neonatal hypoglycaemia (≥1 episode of plasma glucose concentration &lt;1.7mmol/l in the first 72 hours) in late pre-term babies (32-36 weeks’ gestation)</td>
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<td>+</td>
<td>Survey</td>
<td>Under 5 years</td>
<td>Cognitive problems in parents</td>
<td>Low socio-economic status based on income, parental education and occupation</td>
</tr>
<tr>
<td>Potijk, De Winter, Bos et al., 2014</td>
<td>+</td>
<td>Child Behaviour Checklist</td>
<td>4 years</td>
<td>Prematurity: 32 – 36 weeks’ gestation</td>
<td>Low income, low parental educational level</td>
</tr>
<tr>
<td>Davis, Sawyer, Lo et al., 2010</td>
<td>+</td>
<td>The Strengths and Difficulties Questionnaire</td>
<td>4-5 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lewis, Hope, &amp; Pearce, 2015</td>
<td>+</td>
<td>The Strengths and Difficulties Questionnaire</td>
<td>7 years</td>
<td></td>
<td>Low maternal educational level</td>
</tr>
<tr>
<td>Hoffman, Bann, Higgens et al., 2015</td>
<td>+</td>
<td>Brief Infant Toddler Social Emotional Assessment</td>
<td>1.5-1.8 years</td>
<td>Prematurity: &gt;27 weeks’ gestation; young mother’s age (&lt; 20 years)</td>
<td>Relocated &gt;3 times in &lt;2 years</td>
</tr>
</tbody>
</table>

BMI, body mass index
1.7.3 Screening for developmental and emotional health problems

Most screening tools designed to identify children with developmental and emotional health problems have been validated in many countries. Developmental and emotional health problems are often viewed as separate domains and different screening tools are used to identify those problems. Developmental problems are usually viewed as difficulties in gross and fine motor performance, language, cognitive delays and self-help, whereas emotional health usually includes regulation of behaviour, emotions, mood changes, attention and relationship with peers.

1.7.3.1 Identification of developmental problems in children

Assessment of cognitive function can be performed using tests directly administered by an examiner or indirectly based on information provided by parents or other informants who know a child well. Every test is designed to measure one or multiple domains of a certain age group (Lichtenberger, 2005). The timing of screening and the use of tests varies in different countries. Common practice is to screen children during routine health check visits, address any parental concerns and assess developmental milestones. However, evidence suggests that the ability of physicians to identify developmental delays in a busy primary care setting is often limited (Brown, Copeland, Sucharew et al., 2012). Therefore, many screening instruments are available that can identify developmental problems with reasonable sensitivity and specificity (Hamilton, 2006).

Administered screening tools are lengthy assessments that require time and staff expertise. Parent completed questionnaires are quick to complete, not as expensive as examiner-administered assessment, can be filled in at home and emailed or posted back to the healthcare centre. In addition, this way parents are able to actively engage in the child’s health and discuss results and their expectations of a child’s development with a healthcare professional (Mackrides & Ryherd, 2011).

Examiner administered tools measure cognitive ability of a child and provide comprehensive information on function of multiple domains. Bayley Scales of Infant Development, 3rd edition (Bayley-III) and Wechsler Preschool and Primary Scale of Intelligence, 3rd edition (WPPSI-III) are the most widely used assessment tools. Bayley-III is an assessment tool for children from 1 month till 3.5 years that assesses cognitive, language and motor scales (behaviour is assessed using parent completed questionnaire). WPPSI measures cognitive development of children from 2 years 6 months to 7 years 3 months as Full Scale IQ, Verbal IQ and Performance IQ (Lichtenberger, 2005).
Parental Evaluation of Developmental Status (PEDS) and Ages and Stages Questionnaire (ASQ) are the most widely used parent-completed screening questionnaires. ASQ is designed for 1 month-5.5 year old children and includes 21 questions related to fine and gross motor skills, language, adaptive behaviour and social performance. It also has questions about any general parental concerns. Completion and scoring of ASQ takes less than 20 minutes (Hamilton, 2006). PEDS has 10 questions about different domains for new-borns to 8 year old children. It quick to administer (less than 5 minutes) and score, and can be completed during regular health check visits and in busy settings (Schonwald, Huntington, Chan et al., 2009).

**1.7.3.2 Identification of emotional health problems**

Numerous screening tools are available for behavioural and emotional problems. Primary care is usually the first screening gate for young children. However, challenges for emotional health screening are similar to those for developmental screening, and in a busy primary care setting children are often not identified as having a difficulty. The use of standardised measures has been implemented in some practices, but it is challenging as this requires extra time for completing, scoring and discussing results with parents (Hill, Coie, Lochman et al., 2004). Another problem is the interpretation of behaviour and emotional problems in young children. Some difficult behaviours are typical for a preschool age group, and identification of abnormal can be challenging.

Mothers are most commonly asked to complete behaviour rating questionnaires as the person who knows the child best. However, child behaviour may change in different settings and a multi-informant approach is advised to obtain a comprehensive measure of child’s emotional status. Fathers and teachers can also be asked to complete a questionnaire in order to understand the behaviour of a child in different settings and circumstances (Kerr, Lunkenheimer, & Olson, 2007). The most widely used screening tools for emotional health problems are the Child Behaviour Checklist (CBCL) and the Strengths and Difficulties Questionnaire (SDQ). CBCL is a 100 item questionnaire (Achenbach, revised 2002) to screen children from 1.5 till 5 years. It provides scores and profiles, both of which can be used depending on the purpose of screening or assessment. SDQ is a shorter questionnaire than CBCL (Goodman, 2001), covers age band from 3 till 16 years, and consists of 25 questions divided into 5 scales.

**1.7.3.3 Barriers to effective screening**

Many countries have started promotion of early identification of concerns in children. The USA Head Start programme is one of the most known and described in literature (Feil, Small,
Forness et al., 2005; Mendez, 2010). Healthy Kids Check is a preschool screening implemented in Australia (Alexander, Brijnath, & Mazza, 2014), and New Zealand (NZ) has implemented the B4 School Check (B4SC) for early identification of any health concerns including developmental and emotional problems (B4 School Check | Ministry of Health NZ).

Similar barriers to screening are identifiable for screening programmes implemented in different countries (Morelli, Pati, Butler et al., 2014). First, professional training and staff availability can be a barrier. Many practitioners lack confidence and skills in the assessment of appropriate-for-age development and behaviour, and assessment of a change in that behaviour after intervention. The use of screening tools is also often limited due to different opinions on the most suitable tool for children in different age groups (Dobrez, Lo Sasso, Holl et al., 2001; Rydz, Shevell, Majnemer et al., 2005).

Second, resources are often limited and allocated to different services that provide care for different problems. Therefore, there is often also lack of monitoring of a child’s progress if a child is referred from one service to the other. In addition clinicians’ attitudes towards screening is negative in places where access to healthcare services is limited and thus children identified as having a difficulty cannot be referred (Alexander et al., 2014). Time constraint can also be a barrier, with limited time of both healthcare specialists and parents (Rydz et al., 2005).

1.7.4 Early intervention for developmental problems

Cognitive delay and language difficulties are associated with poor school performance and general health. Cognitive delays not only affect the child’s performance, emotional health and social interaction with peers, but also health of parents. Mothers of children with developmental problems often report depressive symptoms (Cheng, Palta, Poehlmann-Tynan et al., 2015) and poor general physical status (Eisenhower, Baker, & Blacher, 2009). Mothers of babies born with risk factors and admitted to neonatal intensive care after birth often show signs of anxiety that are associated with low cognitive and high externalising problems scores of their children at 2 years’ corrected age (Zelkowitz, Na, Wang et al., 2011). Therefore, early intervention should ideally target not only the child’s development, but also modify family environment, attitudes and knowledge of parents.

Findings are mixed regarding the effect of early intervention on cognitive development. For example, there was no difference in cognitive performance at 5 years in babies born preterm who received a developmental educational programme, intervention or standard care up to 2
years of age (Johnson, Ring, Anderson et al., 2005). In contrast, in a study of full term infants from low income families, preschool intervention (received up to 5 years) was effective in improving cognitive function up to 7 years following intervention (Campbell & Ramey, 1994). Children who receive intervention later in life (5-8 years) performed better than an untreated group, but not as well as a group treated at preschool age. In an Infant Health and Development Programme that included low birth weight premature children, those who were provided with an intervention at 2-3 years had higher WPPSI scores at 8 years than children who did not receive an intervention (Hill, Brooks-Gunn, & Waldfogel, 2003). This improvement was larger for children who attended more than 400 days of full day care and for children with birth weight >2000g compared to <2000g. Similarly, 2 year compared to 1 year attendance at a Head Start Programme resulted in better later academic achievements (Leow, Wen, & Korfmacher, 2015). Preschool boys from low socio-economic backgrounds performed better in cognitive, motor and visual-motor tasks, also improved participation in daily activities after an 8 months intervention compared to a control group (Golos, Sarid, Weill et al., 2011).

1.7.5 Early intervention for emotional health problems
Different studies show various results on the effect of intervention on behavioural and emotional health outcomes (Boyle, Sanders, Lutzker et al., 2010; Koldewijn, van Wassenaer, Wolf et al., 2010). Nevertheless, early intervention is the approach that is common in clinical practice and community health. Further, parents of children with social-emotional problems were reported to have a positive attitude to receiving a referral and help from health care specialists (Brown, Copeland, Sucharew et al., 2012). However, not all children who need an intervention actually receive it.

The focus of interventions is modification of a child’s environment, including changing parental views and practices, optimising parent-child interactions (Wiggins, Sofronoff, & Sanders, 2009), and also providing anger and anxiety coping mechanisms. Another form of intervention is school-based, focussed on improving social skills within a class and school environment.

Primary Care Triple P programme (Sanders, 2008) is an example of an early intervention aimed at improving skills of parents via individual sessions during which parents are trained to deal with a difficult child’s behaviours. Results of a randomised controlled trial in the Netherlands comparing the effect of Triple P with usual care provided to children with moderate social-emotional problems showed no significant differences between types of care (Spijkers, Jansen,
& Reijneveld, 2013). Only conduct problems improved significantly in children who received Triple P compared to those who were under usual care. In contrast, other studies have found a positive effect of Triple P on children’s emotional health and this effect was retained at a 4 month follow-up (Boyle, Sanders, Lutzker et al., 2010).

Another intervention programme aimed at improving parenting skills for preschool children is the US Family Check Up (Dishion, Shaw, Connell et al., 2008). This intervention is targeting families from deprived areas that are screened for family risk factors when a child is 2-3 years old. Long-term improvement in the child’s emotional health is aimed to be achieved via improved parenting skills using short (20-60 minutes) face-to-face or telephone contacts. Another brief intervention consisting of 3 group sessions improved behaviour of 3-4 year old children, and effects were still present at a 1 year follow-up (Bradley, Jadaa, Brody et al., 2003). The Incredible Years Parenting Programme is also reported to be effective in reducing child behaviour problems and effects remain for at least a year after the intervention (Jones, Daley, Hutchings et al., 2008).

1.8 Motor difficulties in children

1.8.1 Defining motor difficulties

The definition of motor difficulties in the literature varies widely and has many synonyms including clumsiness, motor learning difficulties or developmental coordination disorder (DCD) (Peters, Barnett, & Henderson, 2001). According to American Psychiatric Association manual of mental disorders, DCD is comprised of four criteria (American Psychiatric Association, 2013). First, performance in daily tasks that require motor proficiency is below the expected for age norms and intelligence. Second, difficulties in motor performance have significant impact on academic achievement or daily activities. Third, motor difficulties are not due to medical condition like muscular dystrophy or cerebral palsy, or Pervasive Developmental Disorder. And last, in the presence of intellectual disability, motor difficulties exceed those expected for the level of disability.

Difficulties with fine motor skills, gross motor skills or both domains may present as less accurate or slower movements (Visser, 2003). Motor difficulties are often present in children with autism, anxiety and attention deficit hyperactivity disorder. The underlying mechanism of developing DCD is not well understood (Wilson, 2005). DCD is sometimes explained by
atypical brain development or brain dysfunction that involves different parts of brain (Zwicker, Missiuna, Harris, & Boyd, 2012). Difficulties in motor performance at preschool age have been variably explained by DCD or by an environment where the child did not have an opportunity to learn the relevant skills (McPhillips & Jordan-Black, 2007). Children with motor difficulties often withdraw from many social and physical activities (Bouffard, Watkinson, Thompson et al., 1996). Furthermore, children with motor difficulties have higher BMI and lower cardiorespiratory endurance compared to children with no motor difficulties (Hands & Larkin, 2006). Therefore, children with motor difficulties are at a risk of poor general health and well-being (Pearsall-Jones, Piek, Rigoli et al., 2011; Schott, Alof, Hultsch et al., 2007).

Children understand that they have motor difficulties when they grow older and their perception of their own abilities makes them avoid leisure and organised sports activities. Therefore, children do not train and improve their skills, so that the gap in motor skills proficiency between motor impaired and non-impaired children increases (Cairney, Rigoli, & Piek, 2013).

Around of 8-20% of children were reported to have developmental coordination disorder in general populations (Tsiotra, Flouris, Koutedakis et al., 2006) and this figure is 20-40% for children born at risk such as extremely preterm or low birth weight children (Goyen & Lui, 2009; Synnes, Anderson, Grunau et al., 2015).

Follow-up of 5-7 year old children with low and high motor competence defined as low/very low or high/very high on the stay in step motor screening test (50-metre run, hop for distance, balance on one foot and volleyball bounce and catch tasks) showed that differences in motor skills remained stable between the two groups over five years while body composition also did not differ significantly (Hands, 2008). Similar results were found for children who were assessed at the age of 5 years and then followed up at 17 years (Cantell, Smyth, & Ahonen, 2003). Children with DCD performed worse on eight motor tasks and had lower self-perception of their performance compared to control group at 17 years.

1.8.2 Risk factors for motor difficulty

Many perinatal, neonatal and socio-demographic characteristics have been described as predictors or factors associated with poor motor development. Gestational age is the main factor associated with later motor difficulties (Cooke & Foulder-Hughes, 2003). Steroid administration and male sex are also factors that are associated with an increased risk of motor problems in extremely low birth weight or very preterm babies (Davis, Ford, Anderson et al.,
Literature review

2007). In another study male sex and lower birth weight were significant predictors of poor motor performance in a cohort of very low birth weight children when they were assessed at 4-5 years (Zwicker, Yoon, MacKay et al., 2013).

Infants of diabetic mothers are also at risk of poor neurodevelopment, including difficulties with motor performance. School age children born to type I or II diabetic mothers (mean age 8.09 years) had lower total, fine and gross motor scores measured using the Bruininks-Ozeretzky test compared to the control group (mean age 8.25 years) matched on age, socio-economic characteristics, family size and birth order (Ratzon, Dulitzky, & Ornoy, 2000). Motor performance was negatively associated with increased level of maternal glycosylated haemoglobin (HbA1c) and acetonuria during pregnancy. Similar results were found for children born to mothers with pre-gestational and gestational diabetes (Ornoy, 2005). Children born to mothers with gestational diabetes had lower total, fine and gross Bruininks-Ozeretzky motor scores than control children in a younger age group (5-8 years). However, this difference was not present for children from an older age group (9-12 years).

1.8.3 Development of motor function

Maturation of different cerebral areas and therefore different functions does not happen in a similar way; motor and sensory areas mature first, so that the density of synapses in sensory and motor cortical areas corresponds to adult density by preschool age (Casey, Tottenham, Liston et al., 2005). However, development of motor function is not a simple process as it involves integration of different cortical and also subcortical areas, which does not usually happen until adolescence. Therefore, a delay in one area leads to a delay in another linked area. Furthermore, motor abilities differ by sex, and differences in brain development between boys and girls may explain the variation in motor skills. In healthy neonates born preterm and scanned at 12 months of age, brain volume was larger in boys while white matter tract volumes were larger in girls (Liu, Metens, Absil et al., 2011). Therefore, many motor assessment tests take into account both sex and inter-individual differences to capture age-appropriate skills, and yield a motor score that can be compared to scores of other children from the same age group.
1.8.4 Identification of motor problems

1.8.4.1 Standardised motor assessments

Assessment of motor function is included in most neurodevelopmental assessments, and often involves complex assessment of multiple integrated functions. The most widely used tests include the following:

Bayley Scales of Infant and (toddler) development, 2nd edition (Bayley-II) have long been used to determine neurodevelopment of young children. The Psychomotor Development Index (PDI) included fine and gross motor components of the assessment (Bayley, 1993). Bayley-III (3rd edition) was introduced in 2006 and can be used to assess a child’s development from 1 to 42 months. The motor scale consists of fine and gross motor subtests which when summed yield a composite motor score (Bayley, 2006). Differences between scores of Bayley-II and Bayley-III have been reported (Vohr, Stephens, Higgins et al., 2012) with Bayley-III scores being higher than Bayley-II scores when administered to the same cohort of children, and the biggest difference was found for motor scores (Reuner, Fields, Wittke et al., 2013).

Peabody Developmental Motor Scales measure motor development up to the age of 5 years. They cannot be used for school aged children which is a limiting factor for follow-up assessments that last beyond 5 years (Darrah, Magill-Evans, Volden et al., 2007). The total motor quotient and also gross motor and fine motor quotients are obtained as a result of six subtests; four subtests measuring gross motor skills (reflexes, stationary gross motor skills, object manipulation and locomotion) and two subtests measuring fine motor skills (grasping and visual-motor integration) (Folio, 2000).

The Prechtl general movement examination is a neurological assessment involving observation of general whole body movements in infants without application of any stimulus or any observer interaction with a child (Prechtl, 1990). The duration of each movement can be from a few seconds to about a minute and they are well-coordinated. Videos are recorded for 10 minutes when a baby is quiet and alert in the supine position (Bruggink, Einspieler, Butcher et al., 2008). From the video three general movements are chosen to make a judgement about the neurological status of the child. Recordings of movements when a child is crying cannot be used. Recordings also allow comparing the change in general movements over time. Children can be assessed up to 5 months after birth and fidgety movements observed between 6 and 20 weeks after birth were shown to be predictive of cerebral palsy (Einspieler & Prechtl, 2005).
Furthermore, mild neurological impairment can be identified using general movements observation (Bruggink, Einspieler, Butcher et al., 2008).

The Alberta Infant Motor Scale (AIMS) is an observational assessment that measures gross motor function from birth to 18 months. Motor function is assessed in four positions: supine, prone, sitting and standing. Examiner interaction with the child is minimal, and involves mainly observation and helping to change to a required position for observation (Coster, Piper & Darrah, 1995).

The Hempel neurologic examination was developed to assess motor function in toddlers by assessing the quality of a movement (Hempel, 1993). Similarly to Prechtl neurological examination, the Hempel technique mainly involves observation of a child’s movements. The child is offered toys in the same standardised order and a list of movements and their quality is observed and judged by the examiner. Examples of such movements are ability to move shoulders in the same plane and keep pelvis in place at the same time, ability to change speed when crawling, and ability to avoid objects placed on the floor while walking.

The Movement Assessment Battery for Children, second edition (MABC-2), is a widely used tool to measure motor difficulties in 3-16 year olds (Henderson, Sugden & Barnett, 2007). MABC-2 has an examiner-administered component and a checklist (Brown & Lalor, 2009). MABC-2 assessment consists of 8 tasks that are divided into Manual Dexterity, Aiming and Catching, and Balance. The age of the child determines the difficulty of the task. A traffic light system helps interpret scores with red indicating significant motor difficulty (≤ 5th centile), yellow at risk of motor difficulty (≤ 15th centile) and green no motor difficulty. This is one of the most widely used motor tests.

**1.8.4.2 Prediction of motor outcomes by neuroimaging**

Magnetic Resonance Imaging can be used as a predictor of later motor impairment. It is often used in babies born very preterm to identify periventricular leucomalacia or intraventricular haemorrhage. White matter abnormality is detected by MRI signal change and is associated with adverse neurodevelopmental outcomes (Dyet, Kennea, Counsell et al., 2006). White matter lesions and not intraventricular haemorrhage detected by ultrasound scans were associated with adverse neurodevelopmental outcomes (including cerebral palsy and low motor scores) at 24 months’ corrected age in babies born <28 weeks’ gestation (O'Shea, Allred, Kuban et al., 2012). Further, white matter abnormality and cerebellar lesions detected by MRI near term were associated with significant neurodevelopmental impairment at 18-22 months.
(Hintz, Barnes, Bulas et al., 2015). An Australian study of infants born <30 weeks’ gestation compared MRI and General Movements assessments for their ability to predict motor outcomes in one-year-old infants (Spittle, Boyd, Inder et al., 2009). Both assessment of General Movements and MRI were predictive of motor function at one year as assessed by Alberta Infant Motor Scale and Neuro-Sensory Motor Development Assessment. Similarly, abnormalities of white matter on MRI at term equivalent age predicted cerebral palsy at 30 months’ corrected age with a sensitivity of 100% and specificity of 98% in babies born <27 weeks’ gestation (Skiöld, Eriksson, Eliasson et al., 2013). In the same study general movements assessed at 3 months’ corrected age, both alone and in combination with MRI findings, predicted cerebral palsy with a sensitivity of 50% and specificity of 92%. Brain imaging is often used in research to predict neurodevelopmental outcomes of children born at risk, but more investigation and development of quantitative measures is needed for it to be used widely (De Vries, van Haastert, Benders et al., 2011).

There is limited evidence of models that include risk factors and also findings of brain imaging and examiner-administered assessments results in prediction of later neurodevelopmental outcomes. For example, Janssen et al. have shown that a model that included PDI motor score <90 and behaviour rating score <26th percentile on the Bayley-II at two years, birth at <30 weeks’ gestation, being male and intraventricular haemorrhage could predict at risk motor difficulties (<15th centile on MABC) in 5-year-olds with 94% sensitivity and 50% specificity (Janssen, der Sanden, Akkermans et al., 2009).

The reason for investigation of factors and models that could predict later neurodevelopmental outcomes is that identification of children at risk of later impairment and provision of early intervention may improve outcomes.

1.8.5 Interventions to improve motor skills

Early interventions are often recommended for children with motor difficulties. Interventions can be administered by health care specialists and involvement of parents and teachers is also encouraged. Even if children cannot improve their motor skills, they may learn adaptive strategies and choose their occupation to result in a positive outcome in adult life. In one study, neurobehavioural intervention (up to 9 sessions) administered to very low birth weight children till 6 months’ corrected age resulted in higher aiming and catching scores at 5.5 year follow up (Van Hus, Jeukens-Visser, Koldewijn et al., 2013). However, a randomized controlled trial of auditory tactile visual vestibular intervention that started in hospital and lasted till 2 months’
corrected age in extremely premature babies or with central nervous system injury did not result in any motor differences between intervention and control groups at 1 year examination (Nelson, White-Traut, Vasan et al., 2001).

Some researchers suggest that children with motor difficulties may lack skills needed to solve the motor problems of a task. Therefore, motor intervention that involves just practice may not improve motor outcomes to a great extent. Alternative task-oriented interventions like neuromotor task training (NTT) and Cognitive Orientation to daily Occupational Performance (CO-OP) have been investigated (Niemeijer, Smits-Engelsman, & Schoemaker, 2007; Polatajko, Mandich, Missiuna et al., 2001). These types of intervention encourage children to identify and analyse their motor problems, reasons for the failed motor task and make a plan to improve performance in the next session.

NTT aims to identify and target specific motor skills that are difficult for a child. Such difficulties are analysed from the perspective of the task itself and an environmental condition that makes the task complicated. The intervention is usually administered by a trained therapist who gradually increases the complexity of the tasks. Children are provided with feedback to ensure better performance in the next session (Niemeijer, Smits-Engelsman, & Schoemaker, 2007). The CO-OP is an intervention where child plays the main role and includes self-instruction where a child identifies a goal, plans how to achieve it and identifies steps that were successful and not successful (Polatajko, Mandich, Missiuna et al., 2001).

Motor imagery training that includes visual imagery exercises has been shown to improve motor performance compared to a group who had a traditional physical training intervention and one that did not have any intervention (Wilson, Thomas, & Maruff, 2002). Imagery training included tracking the object in their imagination and guessing the time of its arrival at a certain location, copying relaxation arm postures to decrease muscle tension, and observation of video recordings of different motor skills followed by mental exercises when children were asked to imagine themselves performing the tasks they saw on the video.

In addition to intervention sessions, children are advised to practise at home to achieve a better outcome. Interactive games are often thought to be an approach to encourage children to participate and enjoy physical activities at home. Quite often parents are also encouraged to take part to engage their children (Ashkenazi, Weiss, Orian et al., 2013). The effectiveness of such activities needs further investigation, but this might be a promising strategy to improve motor skills and physical activity in children.
Dietary supplementation of omega-3 and omega-6 fatty acids was tested for improving developmental coordination disorder in 5-12 year old children (Richardson & Montgomery, 2005). No effect on motor skills was observed. Further, methylphenidate improved motor outcomes in 5-12 year old children with co-occurring developmental coordination disorder and attention deficit hyperactivity disorder, but these results cannot be applied to general population (Bart, Daniel, Dan et al., 2013).

Although motor difficulties are common in children, especially those born at risk, little is known about differences in brain structure between children with and without motor difficulties. Further, it is not known what age, type of training, and amount of learning is required to lead to permanent improvement in motor performance. Moreover, there is limited neurobiological data that could explain the mechanisms underlying the motor performance improvements.
Chapter 2. Introduction to the studies.
2.1 Aim of the thesis
The aim of this thesis was to describe neurodevelopmental and health outcomes of children born at risk of neonatal hypoglycaemia up to 4.5 years, which is a preschool age in New Zealand. The main objectives were to: (1) describe growth patterns and neurodevelopmental outcomes of children born with different risk factors; (2) investigate methods of data collection to assess physical, developmental and emotional health; (3) establish associations between neonatal glycaemic profiles and neurodevelopmental outcomes at 2 and 4.5 years.

We report a cohort of children born at risk of neonatal hypoglycaemia at Waikato Women’s Hospital. Neonates were recruited to neonatal studies and then invited for follow-up assessments, the CHYLD (Children with HYpoglycaemia and their Later Development) study (Chapter 3). This is a cohort at high risk of neurosensory impairment (Chapter 4). High impairment rates found at 2 years (McKinlay, Alsweiler, Ansell et al., 2015) and 4.5 years, coupled with difficulties in contacting and assessing children in some parts of New Zealand, make it important to understand how best to assess these children, obtain information about their health status, their developmental, emotional and behavioural problems, and how to identify those most at risk or have an impaired metabolic adaptation which leads to a high impairment rate.

In this thesis we describe the characteristics of CHYLD cohort (Chapter 4) and their health and development during the preschool period. We describe the growth and motor development of the CHYLD cohort, the associations between these and different risk factors (Chapter 5).

To determine the usefulness of different methods of collecting developmental data to predict later outcomes, we assessed agreement between caregivers’ reports of hospital admissions collected at the 4.5 year assessment and the data extracted from hospital records for about a half of our cohort while the data collection was still ongoing (Chapter 6). To investigate differences between detection rates of developmental and emotional health problems when using different tools, or when using the same tools, but in different settings, we compared data from assessments done during the preschool screening programme, the B4SC, using parent-completed questionnaires to that of the complex CHYLD clinical assessment (Chapter 7). This study included 274 children who were assessed up to August 2014, which was 57% of the 477 children finally assessed at 4.5 years.

Similarly, since motor performance of children was assessed at 2 and 4.5 years using different tools, we wanted to determine if motor problems identified using the widely used Bayley Scales
of Infant and Toddler Development, and neurological examination administered in early life can predict motor difficulty at the preschool age (Chapter 8).

Children in the CHYLD study cohort were born at risk of neonatal hypoglycaemia, and investigating associations between hypoglycaemia and later neurodevelopmental outcome in children born at risk was the main aim of the CHYLD study. Results of the 2 year follow-up study showed that hypoglycaemia ($\leq 2.6$ mmol/l) was not associated with adverse neurodevelopmental outcome (McKinlay, Alsweiler, Ansell et al., 2015). However, glucose concentrations in the higher but still normal range and unstable glucose concentrations, especially in neonates who experienced hypoglycaemia and were treated with dextrose, were associated with the adverse outcome. These findings raised concerns that treatment of hypoglycaemia might be contributing to the instability and impairment. Therefore, to investigate factors that contribute to glycaemic instability and relationship to adverse outcomes, we analysed continuous glucose data in neonates who had hypoglycaemia and had continuous glucose monitoring for 48 hours after birth (Chapter 9).

Last, we discuss findings of our studies, research and clinical implications and research gaps that need to be addressed in the future (Chapter 10).
3.1 Introduction

This chapter describes the neonatal cohorts that formed the CHYLD study, and the methods used for neonatal data collection and conduct of the 2 and 4.5 year follow-up assessments.

3.2 Neonatal studies

The CHYLD study comprises children born at risk of neonatal hypoglycaemia who were recruited in the neonatal period to the BABIES and Sugar Babies studies (Harris, Battin, Williams et al., 2009; Harris, Battin, Weston et al., 2010; Harris, Weston, Signal et al., 2013). The BABIES study investigated the associations between blood and interstitial glucose concentrations, alternative cerebral energy sources and brain function in neonates born at risk of neonatal hypoglycaemia and admitted to NICU. The Sugar Babies study investigated the effectiveness of treatment of hypoglycaemia with 40% dextrose gel in the first 48 hours after birth in neonates born at risk of neonatal hypoglycaemia. These studies were conducted by researchers from the Liggins Institute, University of Auckland and neonatal services at Waikato hospital. The Waikato hospital provides tertiary hospital, health and disability services to the entire Waikato region and central North Island of New Zealand.

Neonates recruited to both studies were born at risk of neonatal hypoglycaemia and were < 48 hours old. Risk factors for neonatal hypoglycaemia were: being born to a diabetic mother, small (birth weight <10th percentile or <2500g), large (birth weight >90th percentile or >4500g), moderate or late preterm (≥32 weeks in BABIES and 35-36 weeks in Sugar Babies), or with other conditions associated with hypoglycaemia (for example, respiratory distress or feeding difficulties). Neonates were excluded if they had congenital malformations, terminal conditions, received previous treatment for neonatal hypoglycaemia or had skin problems that could interfere with continuous glucose monitoring.

Hypoglycaemia was defined as a blood glucose concentration <2.6 mmol/l. Blood glucose concentration was measured in samples obtained by heel prick sampling and analysed using the glucose oxidase method. Blood samples were taken at 1 hour after birth, then every 2-4 hours before feeds in the first 24 hours, then every 6-8 hours in the second 24 hours, or as clinically indicated, until 3 consecutive measurements ≥2.6 mmol/l were obtained, and there was no longer clinical concern. Neonates who received 40% dextrose gel for treatment of hypoglycaemia followed by feeding had their blood glucose measured 30 minutes after treatment. If blood glucose was <2.6 mmol/l, additional gel and feeding were provided and
blood glucose measured again 30 minutes after the treatment. Neonates who did not respond to treatment received intravenous dextrose.

Neonates in both studies whose parents gave consent had interstitial glucose concentrations measured by continuous glucose monitoring (CGMS system gold, Medtronic, MiniMed, Northridge, CA, USA). The glucose sensor was inserted subcutaneously in the lateral thigh and remained in place for at least 48 hours and up to 7 days. Data from the interstitial glucose monitors were downloaded at the end of the monitoring period, and therefore were not available to the clinical or research staff and did not have any effect on management of the neonate.

Mothers of neonates in both studies were encouraged to breastfeed and have skin-to-skin contact as soon as possible after birth. Formula fed babies were given up to 60 ml/kg on the first day and up to 90 ml/kg on the second day.

Neonates in the BABIES Study were all admitted to neonatal intensive care unit, had EEG monitoring and blood taken for measurement of alternative cerebral fuels.

Neonates in the Sugar Babies Study who developed hypoglycaemia were randomised to receive 0.5 ml/kg of either 40% dextrose gel (200 mg/kg) or placebo gel (2% carboxymethyl cellulose) massaged into the buccal mucosa followed by feeding. Blood glucose concentration was measured 30 minutes after gel administration. The treatment was repeated if the glucose concentration remained low, with a maximum of 6 doses administered over 48 hours.

Data collected during these studies included intermittent blood glucose concentrations, continuous interstitial glucose concentrations, perinatal history, complications during and after birth, body size at birth, feeding practices, medications and treatment received, and neonatal hearing screening outcome.

3.3 Ethical approval

In most cases mothers likely to give birth to at risk babies were approached before birth and asked for consent for the recruitment of their baby after birth, although in some cases mothers were approached after the birth. Mothers provided written informed consent for the neonatal studies. The study was approved by the Northern Y Regional Ethics Committee (Approval number for BABIES is NTY/06/05/036 and for Sugar Babies NTY/08/03/025). The Sugar Babies clinical trial was registered with Australian New Zealand Clinical Trials Registry, number ACTRN12608000623392.
The 2 year follow-up study was approved by the Northern Y Health and Disability Ethics Committee (June 2010, reference number NTY/10/03/021) and an amendment was approved for the 4.5 year follow-up (June 2011).

Every family who agreed to be part of the CHYLD Study received an information pack prior to the assessment. On the day of the assessment the procedure was further explained by the researcher and informed consent form was obtained from the caregiver. An interpreter was offered if English was not the first language. Caregivers could stop the assessment at any time and withdraw the child from the study at any time and did not need to provide a reason for that decision.

Strict confidentiality was maintained by using study ID numbers for every child on all assessment forms. Contact information obtained from the caregiver questionnaire was used only by the CHYLD Study team members who arranged the assessment. It was separated from the other sections of the questionnaire and stored separately from the other study data, and was not available to research team members who took part in data analysis.

### 3.4 Recruitment and structure of follow-up studies

#### 3.4.1 Tracking families

All families were contacted by a study coordinator when the child was nearing the assessment age window. In order to avoid contacting any family whose child died, before making a contact with a family the study coordinator checked the National Health Index (NHI) database, using the unique identifier assigned to every child after birth. The database includes address, date of birth, sex, ethnicity, and date of death.

Families who were difficult to reach were located and contacted via their relatives, general practitioners (GPs) or midwives. Sometimes when the family could not be located researchers visited the last known address and tried to find a new address by contacting neighbours.

Assessment appointments were made for each child whose parents agreed to participate. Time and location depended mainly on family preferences. Assessment sites included our research house in Hamilton, hospital, or Plunket rooms, or if the family wished, a home visit was organised.
3.4.2 Assessment order
Assessments were planned to ensure that parts that most require the child’s concentration and attention were done first. Therefore, the assessment usually started with psychological followed by vision assessment. Neurological status, growth and general health were usually examined at the end. In some cases, if a parent or a researcher thought that a child was tired and could not continue with the tasks or perform to the best of their abilities, the assessment was split into two sections done on two different days. All assessors were blinded to the neonatal glycaemic history of the child.

3.4.3 Feedback for caregivers
After the assessment caregivers received feedback from assessors about their child’s performance and health on the day of the assessment. Caregivers were able to ask questions. Summary letters describing the assessment findings were sent to parents and GPs if a caregiver provided consent for this. If assessors identified any health or developmental problems, an appropriate referral to health providers was sent if a family agreed.

3.5 CHYLD two year follow-up
Parents of children who took part in BABIES and Sugar Babies studies were invited to participate in the 2 year follow-up study.

3.5.1 Eligibility
Children were assessed at 24 months’ corrected age ± 4 weeks. The follow-up started when some of the children were already older than the assessment window. Exclusion criteria were gestational age <35 weeks and known postnatal brain injury. These children’s details were recorded but not included in the analysis. Methods used for 2 year assessments have been reported elsewhere (Harris, Alsweiler, Ansell et al., 2016; McKinlay, Alsweiler, Ansell et al., 2015; Yu, Jacobs, Anstice et al., 2013).

3.5.2 Assessment at 2 years
The assessment consisted of developmental, vision and paediatric examinations (Table 3.5.2). Each part of the assessment was administered by a trained examiner. In addition, parents completed questionnaires on the general health of the child, household characteristics and environmental factors, pre-pregnancy, pregnancy and post-pregnancy exposures to tobacco, alcohol and drugs (prescribed and not prescribed). Questionnaires were posted to parents’
homes to be completed prior to the assessment. In some cases parents completed questionnaires on the day of assessment or afterwards and posted questionnaires back to the study coordinator.

### Table 3.5.2 Two year assessment tests

<table>
<thead>
<tr>
<th>Developmental assessment</th>
<th>Diagnostic measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive function: play, attention, memory, and receptive and expressive language</td>
<td>Bayley-Scales of Infants and Toddler Development, third edition (Bayley, 2006)</td>
</tr>
<tr>
<td>Motor and visual perception: fine and gross motor skills</td>
<td>Bayley-Scales of Infants and Toddler Development, third edition</td>
</tr>
<tr>
<td>Social-emotional domain and behaviour</td>
<td>Bayley-Scales of Infants and Toddler Development, third edition; parent questionnaire</td>
</tr>
<tr>
<td>Executive function: simple and complex response exhibition, attention shift</td>
<td>BRIEF-P (Gerstadt, Hong, &amp; Diamond, 1994; Sherman &amp; Brooks, 2010; Zelazo, 2006), multi-search/multi-location (Zelazo, Reznick, &amp; Spinazzola, 1998), snack delay, fruit stroop (Kochanska, Murray, &amp; Harlan, 2000), and reverse categorisation (Carlson, 2005)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vision assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>External and internal ocular health</td>
</tr>
<tr>
<td>Visual acuity</td>
</tr>
<tr>
<td>Ocular alignment</td>
</tr>
<tr>
<td>Non-cycloplegic refraction</td>
</tr>
<tr>
<td>Stereopsis</td>
</tr>
<tr>
<td>Motor fusion and motility/tracking</td>
</tr>
<tr>
<td>Function of the dorsal visual cortical stream (V5/MT)</td>
</tr>
<tr>
<td>Function of the primary visual cortex (V1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Physical examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tone, reflexes, gait, coordination</td>
</tr>
<tr>
<td>Weight, height, head circumference, mid-upper arm circumference, abdominal circumference</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parent questionnaires</th>
</tr>
</thead>
<tbody>
<tr>
<td>Illnesses, hospitalisations, interventions received, immunisations</td>
</tr>
<tr>
<td>Socio-economic status, ethnicity, mother’s and father’s education, siblings, alcohol, tobacco and drug use</td>
</tr>
</tbody>
</table>

3.5.3 Neurodevelopmental impairment

Co-primary outcomes at 2 years were prospectively defined as neurosensory impairment and processing difficulty. A child was classified as having neurosensory impairment if they had any of: Bayley-III cognitive or language composite scores <85 (more than 1 SD below the test mean), Bayley-III motor composite score <85 (more than 1 SD below the test mean), cerebral palsy, blindness or hearing problems requiring hearing aids. A child was classified as having a processing difficulty if motion coherence threshold (Yu, Jacobs, Anstice et al., 2013) or executive function scores were worse than 1.5 SD from the mean of the entire 2 year CHYLD cohort.

3.6 Follow-up at 4.5 years

Most of the data presented in this thesis were collected during the CHYLD 4.5 y follow-up assessment. The methodology used for data collection and analysis at 4.5 years are detailed below.
3.6.1 Eligibility
The window for assessment was 54 ± 2 months’ corrected age.

3.6.2 Assessment at 4.5 years
Assessment at 4.5 years consisted of developmental, vision and physical and motor skills examinations (Table 3.6.2).

Table 3.6.2 CHYLD 4.5 year follow-up: development and vision assessments

<table>
<thead>
<tr>
<th>Developmental assessment</th>
<th>Diagnostic measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive function: verbal performance, processing speed, language, Intelligence Quotient</td>
<td>WPPSI-III (Tylenda, Beckett, &amp; Barrett, 2007)</td>
</tr>
<tr>
<td>Motor and visual perception</td>
<td>Beery-Buktenica Developmental Test of VMI, 6th edition</td>
</tr>
<tr>
<td>Auditory discrimination and memory</td>
<td>Phelps Kindergarten Readiness Scale (Items 6-8) (Augustyniak, Cook- Cottone, &amp; Calabrese, 2004)</td>
</tr>
<tr>
<td>Social-emotional domain and behaviour</td>
<td>Strength and difficulties questionnaire (Achenbach, revised 2002; Goodman, 2001; Rutter, 2003)</td>
</tr>
<tr>
<td></td>
<td>Child Behaviour Checklist (Achenbach, 2002)</td>
</tr>
<tr>
<td></td>
<td>Social Communication Questionnaire (Rutter, 2003)</td>
</tr>
<tr>
<td>Executive function: simple and complex response exhibition, attention shift</td>
<td>BRIEF-P (Gerstadt et al., 1994; Sherman &amp; Brooks, 2010; Zelazo, 2006)</td>
</tr>
<tr>
<td></td>
<td>Gift wrap delay, Bear/Dragon, Dimensional Change Card Sort (Zelazo, 2006) Day/Night (Stroop) (Gerstadt, Hong, &amp; Diamond, 1994)</td>
</tr>
</tbody>
</table>

Vision assessment

| External and internal ocular health | External observation, Buckner’s/red reflexes, pupil examination, direct ophthalmoscopy |
| Visual acuity | Letter or picture matching (Rydberg, Ericson, Lennerstrand, Jacobson, & Lindstedt, 1999; Sheridan & Gardiner, 1970) |
| Ocular alignment | Cover tests, Hirschberg reflexes |
| Non-cycloplegic refraction | Autorefraction |
| Stereopsis | Randot Children’s test |
| Motor fusion and motility/tracking | 20diopter prism test, following light |
| Function of the dorsal visual cortical stream (V5/MT) | Global motion perception using random dot kinematograms with varied contrast (Chakraborty, Anstice, Jacobs et al., 2015) |
| Function of the primary visual cortex (V1) | |

BRIEF-P, Behaviour Rating Inventory of Executive Function, parent report.

3.6.3 Physical examination and medical history
Physical examination was undertaken by the candidate, including assessment of ears, growth and neurology, according to previously published methods (Crowther, Doyle, Haslam et al., 2007). Neurological examination included assessment of a child’s tone and tendon reflexes, presence of ankle clonus, Babinski response, and walking limitations. Absence or presence of cerebral palsy and its type was recorded by the assessor. The severity of cerebral palsy was defined according to Gross Motor Function Classification System for four to six year olds (Palisano, Rosenbaum, Bartlett et al., 2008).

A medical history was obtained from caregivers. Specific information was collected about postnatal problems involving the central nervous system, use of specialist and supportive interventions, malformations, and history of seizures. Immunisations were checked from records in the Well Baby Book (New Zealand Ministry of Health, Well Child Book) or parental report.
3.6.3.1 Motor skills assessment

Motor skills were examined using the Movement Assessment Battery for Children, second addition, age band 1 (Henderson, Sugden & Barnett, 2007). Assessment included manual dexterity tasks, aiming and catching, and balance. This examination took 20 to 40 minutes to complete.

Scores were interpreted using the traffic light system; significant impairment (red), below 5th percentile; at risk of movement impairment (orange), between 5th to 15th percentile; and normal movement for age (green), above 15th percentile (Henderson, Sugden & Barnett, 2007).

3.6.3.2 Anthropometric measurements

Weight was measured using electronic scales to the nearest 0.1 kg when the child was wearing light clothing. Height was measured using a stadiometer to the nearest 0.1 cm when the child was barefoot. Waist and head circumference were measured to the nearest 0.1 cm using a non-stretch tape measure, and the mean of three measurements was recorded.

Weight, height and head circumference measures were plotted on the New Zealand – WHO growth charts to assess percentile rank for each measure. Children who fell below the 10th or were above the 90th percentile were recorded on the summary report as being outside the average range for growth.

Sex- and age-specific Z-scores for anthropometric measurements were calculated electronically using WHO reference values (WHO | WHO anthro (version 3.2.2, January 2011) and macros). Corrected age was used for all analyses (A health professional’s guide for using the new WHO growth charts, 2010).

3.6.3.3 Selection of growth charts for the data analysis

A review of growth charts was undertaken to choose the most appropriate growth standards to analyse growth data obtained at 2 and 4.5 year assessments. Ideally, only one type of growth chart would be used as a reference for the whole CHYLD study, thus making data comparable from the neonatal period through to 4.5 years and possibly even longer. Further, charts had to allow for the analysis of data from both preterm and term babies, and for all measurements of interest. Ideally, charts would be appropriate for the multi-cultural population involved in this study and provide results that could be directly compared with other research done in the same field.
A review of the literature showed that a wide variety of measurement instruments are used in cohort studies with varying protocols and assessment techniques (Boluyt, van Kempen, & Offringa, 2006). With the development of new Centre for Disease Control and Prevention (CDC) and Euro-Growth reference charts in 2000 (Kuczmarski, Ogden, Grummer-Strawn et al., 2000; Van't Hof & Haschke, 2000b) and WHO Child Growth Standards in 2006 (Ziegler & Nelson, 2007) there was a possibility of making data uniform and accurate for most parts of the world. While USA, Canada and some regions of Australia used CDC charts in their clinical practice, over 100 countries have adopted WHO standards (WHO Multicentre Growth Reference Study Group & de Onis, 2006).

New Zealand has adopted the UK-WHO charts (Growth charts | Ministry of Health NZ) which are a combination of the WHO Child Growth Standard for the period two weeks to five years, and UK birthweight reference for pre-term and term infants born from 32 to 42 weeks’ gestation (Cole, Freeman, & Preece, 1998). NZ-WHO references have no centile lines for the first two weeks after birth to emphasise the fact that centile line was not as important as weight gain when compared to weight at birth because some babies lose weight after birth but then recover over the 2 week period (Growth charts | Ministry of Health NZ). Further, downwards height centile shift is observed on charts at two year mark. This occurred because of the difference of 0.73 cm between length and height measurements when the same cohort of children was measured, and 2 years is the age when length measurements are replaced with height.

Growth charts described above were assessed for suitability for use in this study. An important factor to consider in selecting a growth chart for the CHYLD study was the multi-ethnic composition of the cohort so the growth charts had to be globally representative. In this case, WHO charts were well-designed as data were collected in six different countries around the globe (WHO Multicentre Growth Reference Study Group & de Onis, 2006). Further, the WHO charts are considered a standard because they show the optimal growth of a child because of strict inclusion criteria like breastfeeding and growing in favourable conditions. In contrast to WHO, CDC charts (Kuczmarski, Ogden, Grummer-Strawn et al., 2000) were based on cross-sectional data collected from five US surveys and some data provided by clinics. Because of a small sample size there may be errors at extreme centiles. Euro-growth charts (Van’t Hof & Haschke, 2000a) were developed from the data from 22 sites in 11 European countries. Neither CDC nor Euro-growth charts controlled for feeding practices nor selected children without environmental constraints on growth which means they are reference growth charts but not a
standard of optimal growth. Moreover, CDC printed charts only provide centiles, whereas WHO charts have measurements described as centile and Z score values.

CDC and WHO charts include sex-specific weight for age, length/height for age, weight for length/height, BMI for age and head circumference for age. Waist circumference charts have not been published by either CDC or WHO. The limitation of CDC and Euro-Growth charts was the age of children they could be used for. Euro-Growth charts stop at 3 years of age, so could be used for neonatal versus 2 year-old comparisons but not 2 versus 4.5 year olds. CDC charts were available for use throughout childhood, except for head circumference for age which stops at 3 years.

When assessing growth of the same child using different charts, CDC and Euro charts had lower weight for age percentiles than WHO in the first six months, and higher from 6 months to 5 years of age. Length centiles were more similar amongst charts (Ziegler & Nelson, 2007). These differences may have been due to different population samples, inclusion criteria and withdrawal of participants.

We compared CDC, Euro-Growth and UK 1990 charts with WHO charts by calculating Z scores at 1, 2 and 4 years using weight-for-age, lengths/height-for age values equivalent to a Z score of 0, 1, 2, -1, -2 on the WHO chart for boys and girls. The largest discrepancy was found for weight-for-age measurement with many differences reaching more than 0.5 SD (Table 3.6.3.3.1). The differences for length/height-for-age were not as large, but still would have an important effect on data analysis.

### Table 3.6.3.3.1 Comparison of different growth charts at 1, 2 and 4 years.

<table>
<thead>
<tr>
<th>Measure</th>
<th>WHO (referent)</th>
<th>CDC 1 year</th>
<th>CDC 2 years</th>
<th>CDC 4 years</th>
<th>UK 1990 1 year</th>
<th>UK 1990 2 years</th>
<th>UK 1990 4 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight-for-age (boys)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
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<td>-0.45</td>
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<td>-1.6</td>
<td>-1.47</td>
<td>-1.49</td>
</tr>
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<td>-2.51</td>
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<td>-2.41</td>
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</tr>
<tr>
<td>+1</td>
<td>0.54</td>
<td>0.77</td>
<td>0.93</td>
<td>0.49</td>
<td>0.55</td>
<td>0.67</td>
<td>1.04</td>
</tr>
<tr>
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<td>1.65</td>
<td>1.75</td>
<td>2.2</td>
<td>1.56</td>
<td>1.64</td>
<td>1.87</td>
<td>1.63</td>
</tr>
<tr>
<td>Weight-for-age (girls)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>0.04</td>
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<td>0.49</td>
<td>0.65</td>
<td>0.66</td>
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<tr>
<td>+2</td>
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<td>2.35</td>
<td>1.61</td>
<td>1.57</td>
<td>1.63</td>
<td>1.87</td>
</tr>
<tr>
<td>Length or height-for-age (boys)</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<td>-0.74</td>
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<td>-1.01</td>
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<td>+2</td>
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<td>2.22</td>
<td>1.76</td>
<td>1.86</td>
<td>2.13</td>
<td>1.99</td>
</tr>
<tr>
<td>Length or height-for-age (girls)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>-1.02</td>
</tr>
<tr>
<td>-2</td>
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<td>-2.52</td>
<td>-2.3</td>
<td>-2.09</td>
</tr>
<tr>
<td>+1</td>
<td>0.82</td>
<td>1.36</td>
<td>1.5</td>
<td>0.72</td>
<td>0.65</td>
<td>0.93</td>
<td>1.1</td>
</tr>
<tr>
<td>+2</td>
<td>1.73</td>
<td>2.38</td>
<td>2.57</td>
<td>1.73</td>
<td>1.68</td>
<td>1.93</td>
<td>2.15</td>
</tr>
</tbody>
</table>

Data are Z scores calculated using each growth chart in turn from measurements taken from the WHO charts. WHO, World Health Organisation; CDC, Centre for Disease Control and prevention; UK, United Kingdom.
Although we wanted to find charts that would be suitable for use in both term and preterm neonates to compare birth and neonatal growth, WHO growth charts did not have reference values for preterm neonates. Instead they used 1990 UK reference data that were not representative of multi-ethnic population or the population that the CHYLD study investigated.

For birth weight measurements we therefore compared BEEBY charts, based on a New South Wales cohort (Beaby, Bhutap, & Taylor, 1996), with WHO charts. The 42 weeks’ gestation birth weight on the Australian charts was compared to two weeks after birth on the WHO charts as this was the age when term baby would have recovered the initial weight loss that occurred after birth (Table 3.6.3.3.2). The difference in growth pattern between those two charts was not as great as between the WHO and other reference charts at 1, 2 and 4 years. New South Wales reference values were based on growth measurements of 422,139 singleton neonates collected during five years with extreme outliers excluded from the analysis. Similar results were obtained from other birth growth charts that included more than one million neonates in Canada (Arbuckle, Wilkins, & Sherman, 1993).

Table 3.6.3.3.2 Comparison of WHO and BEEBY charts.

<table>
<thead>
<tr>
<th>Measurement</th>
<th>BEEBY value at 42 weeks gestation (referent)</th>
<th>WHO at 2 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight boys</td>
<td>0</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>-1</td>
<td>-0.92</td>
</tr>
<tr>
<td></td>
<td>-2</td>
<td>-1.95</td>
</tr>
<tr>
<td></td>
<td>+1</td>
<td>0.88</td>
</tr>
<tr>
<td></td>
<td>+2</td>
<td>1.65</td>
</tr>
<tr>
<td>Weight girls</td>
<td>0</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td>-1</td>
<td>-0.84</td>
</tr>
<tr>
<td></td>
<td>-2</td>
<td>-1.89</td>
</tr>
<tr>
<td></td>
<td>+1</td>
<td>0.93</td>
</tr>
<tr>
<td></td>
<td>+2</td>
<td>1.71</td>
</tr>
<tr>
<td>Length boys</td>
<td>0</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>-1</td>
<td>-1.23</td>
</tr>
<tr>
<td></td>
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<td>-2.27</td>
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<tr>
<td></td>
<td>+1</td>
<td>1.39</td>
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<tr>
<td></td>
<td>+2</td>
<td>2.96</td>
</tr>
<tr>
<td>Length girls</td>
<td>0</td>
<td>0.15</td>
</tr>
<tr>
<td></td>
<td>-1</td>
<td>-0.79</td>
</tr>
<tr>
<td></td>
<td>-2</td>
<td>-1.85</td>
</tr>
<tr>
<td></td>
<td>+1</td>
<td>1.31</td>
</tr>
<tr>
<td></td>
<td>+2</td>
<td>2.46</td>
</tr>
</tbody>
</table>

Data are Z scores calculated using WHO growth charts for measurements taken from the BEEBY chart.

For the CHYLD Study we decided to use BEEBY charts for preterm and term birth measurements as Z scores could be calculated for babies born at different gestational ages. For 2 and 4.5 year measurements, we planned to use WHO charts.
3.6.4 General health and family environment
General health and environmental factors were assessed using the Home and Family Questionnaire, which had three main sections. The first section included household characteristics including ethnicity, languages spoken, number of children living in the household, means of transportation, household income and if the child attended any type of pre-school facility. The second section was about the health history of the child: hospitalisations, medications, ear infections, feeding practices and referrals or any care the child received from specialists. The third section asked about health-related environmental exposures that happened during pregnancy and after birth (alcohol consumption, smoking, prescription drugs, marijuana or other drugs use).

3.6.5 Hospital records
Medical history was extracted from hospital files for each child whose caregiver provided consent to access hospital records. Inpatient admissions, Emergency Department and outpatient visits, their duration, referrals made and reason for a visit were recorded from discharge home after birth until the date of the CHYLD 4.5 year old assessment. Electronic files in the hospital database were checked for any possible visits to hospitals other than Waikato hospital, which was where the babies were initially recruited.

3.6.6 Neurosensory impairment
Neurosensory impairment was defined on the basis of developmental and vision tests at 4.5 years, neurological findings, and MABC-2 outcomes. A child was classified as having neurosensory disability if they had one or more of the following: WPPSI Full Scale IQ <85 (more than 1 SD below test mean), MABC-2 total score ≤15th centile, cerebral palsy, blindness, hearing impairment requiring hearing aids, Beery VMI score <85 (more than 1SD below test mean), motion coherence threshold or executive function scores worse than 1.5 SD from the mean of the entire 4.5 year CHYLD cohort.

3.6.7 The Before School Check
The Before School Check (B4SC) is a Ministry of Health national programme intended to detect general health and environmental factors that might have an influence on a child of pre-school age (B4 School Check | Ministry of Health NZ). All children in New Zealand are encouraged to have a B4SC at 4 years. If a child misses out on the assessment at 4 years they have an option of having another assessment up to 5 years when they start school. Data are stored in the B4 School Check National Information System. Data collected at the B4SC were
made available by the Ministry of Health for the use in the CHYLD Study for those children whose parents provided consent.

3.6.7.1 The B4 School Check assessment
The B4SC provides advice and support for parents, assesses the environment where the child lives, assesses the child’s development and health, and facilitates intervention for children who have problems. General health and family environment are assessed by the Child Health questionnaire. This contains questions about the child’s address, ethnicity, the preschool the child is enrolled in, other children in the family, immunisation history, hospital attendance record, present medical conditions, medication use, dental health etc. Children undergo hearing and vision screening, oral health screening, and height and weight measurements. Parents complete developmental and emotional health screening questionnaires. In addition, teachers are also sent a behavioural and emotional health screening questionnaire.

3.6.7.2 Hearing screening
Hearing assessment is done using audiometry, based on American guidelines (ASHA, 1997). Audiometry is not performed if a child is already under the care of ear nose and throat (ENT) or audiology services, uses hearing aid or has grommets. If required, audiometry assessment is followed by tympanometry. Audiometry outcomes are ‘pass’ if all hearing levels are obtained in both ears, and ‘refer’ if they do not pass audiometry in both ears. Tympanometry results determine whether the child is referred to a GP/ear nurse or to an audiology department.

3.6.7.3 Growth monitoring
Weight is measured using electronic floor scales. A portable stadiometer is used for measuring height. According to the protocol, two readings for both weight and height are taken. The average of the two measurements is recorded when the variation in weight is not greater than 0.5 kg and in height not more than 0.5 cm. If the variation is greater than allowed by the protocol, a third measurement is taken and the average calculated for the two closest readings.

Weight and height are plotted on the WHO growth charts for four year old children. However, if a child has the B4SC later, after the start of a school, results are plotted on the 5-19 year old reference charts. Children who have weight or height measurements below 3rd percentile, weight over 97th centile or BMI ≥21 should be referred according to the B4SC growth referral guideline.
3.6.7.4 Strength and Difficulties questionnaires

Strength and difficulties questionnaires (SDQ) are used for the assessment of children’s emotional and behavioural problems (Goodman, 2001). Questionnaires are completed by a caregiver, and also by a teacher where permission is given. The request for the SDQ teacher-version to be completed is initiated either by the B4SC provider or a parent.

SDQ has five subscales, of which four are summed to reach a total difficulties score. Results are interpreted according to the guidelines (Scoring the SDQ, www.sdqinfo.com). No intervention or referral is needed when the parent-completed total difficulties score is 0-13 and the teacher completed score 0-11. If the total difficulties score is 14-16 for the parent-completed or 12-15 for the teacher-completed questionnaire, parenting programmes may be recommended. If the scores are ‘of concern’, 17-40 for parent-completed and 16-40 for teacher-completed SDQ, then referral is made to a paediatrician, children mental health services or group special education.

3.6.7.5 Parental Evaluation of Developmental Status

Parental Evaluation of Developmental Status (PEDS) questionnaire is completed by parents at the B4SC assessment. PEDS is short (10 questions) and easy to administer (Glascoe, 2003). Parents list concern they have about child’s development by answering ‘no’, ‘yes’ or ‘a little’ to 10 questions about the child’s learning, development, behaviour, language, gross and fine motor function, social skills and self-help. All concerns are divided into significant and not significant. Two or more significant concerns results in a referral to a specialist services and one significant concern leads to a referral for a secondary assessment. Parents are offered advice and a follow-up assessment is organised for children whose parents have non-significant concerns.

3.7 Data analysis

Data were analysed using JMP software Version 11.2.0 (SAS Institute Inc., Cary, NC, 2013) or SAS version 9.4 (SAS Institute Inc. Cary NC). Characteristics of children included in the analyses were compared to those who were not included using one-way ANOVA, chi-square tests or Wilcoxon rank-sum test.

Missing data were not imputed as we cannot assume that data were missing at random since children who are lost to follow-up are more likely to have neurodevelopmental or other health problems compared to those who attend follow up assessments (Hille, Den Ouden, Stuifbergen et al., 2005). When the assessment test was administered but not completed because of
developmental or diagnosed neurological impairment, a score of 3 SD below the mean was assigned for that test.

Primary risk factors were assigned to neonates with multiple risk factors for neonatal hypoglycaemia in the following hierarchical order: infants of a diabetic mother, preterm, small, large and other. Specific statistical analyses are described in each chapter.
Chapter 4. The CHYLD study cohort description.
This chapter describes characteristics of the CHYLD Study cohort at baseline, and 2 and 4.5 year follow-up assessments. Neonatal and socio-demographic characteristics, as well as measures of growth and development are described.

### 4.1 Recruitment

Six hundred and fourteen neonates were recruited to the neonatal studies, BABIES and Sugar Babies (2 were recruited to both studies), most of whom lived in the Waikato region at the time of enrolment (Figure 4.1.1, A).

At 2 years, 528 children were eligible for follow-up (86% of the neonatal cohort), of whom 405 (77% of those eligible) were recruited and 404 were assessed (one child died after recruitment). Of 86 children not eligible for follow-up, two died, 65 were older than 2 years when follow-up started and 19 were born <35 weeks’ gestation. Of 123 children not recruited to 2 year follow-up, 79 families declined (64% of not recruited, 13% of neonatal cohort), contact was lost with 11 children (9% of not recruited, 2% of neonatal cohort) and 33 children were overseas (27% of not recruited, 5% of neonatal cohort). Of those recruited to the 2 year follow-up study, 18% had moved from the Waikato region to the lower North Island or South Island (Figure 4.1.1, B).

At 4.5 years, 604 children were eligible for follow-up (98% of the neonatal cohort), of whom 477 (79% of those eligible) were recruited and assessed. Of the ten children who were not eligible for follow-up, three children died and seven withdrew from the study prior to 4.5 year recruitment. Of 127 children not recruited at 4.5 years (21% of eligible, 21% of neonatal cohort), 92 families declined follow-up (72% of not recruited, 15% of neonatal cohort), eight children were lost to follow-up (6% of not recruited, 1% of neonatal cohort) and 27 children were living overseas (21% of not recruited, 4% of neonatal cohort). By 4.5 years more families (24%) had moved out of the Waikato region to live in Auckland, Eastern and central regions of the North Island and also the South Island. Fourteen children were assessed in Australia at 4.5 years (Figure 4.1.1, C).
Figure 4.1.1 Residence of participants recruited to neonatal and CHYLD follow-up studies

Figure 4.1.1 Residence of participants (number of children in each area). (A) Residence at birth (N=614), data missing for 88 babies; (B) Residence at 2 year follow-up (N=404), data not available for 30 children assessed at 2 year follow-up; (C) Residence at 4.5 year follow-up (N=477). 14 children were assessed in Australia.

4.2 Baseline characteristics of participants and non-participants

There were no significant differences between children who were and were not eligible for 2 year follow-up in sex, ethnicity and New Zealand deprivation index (Table 4.2.1). Children eligible for 2 year follow-up were more likely to be IDM or large compared to those not eligible. Further, eligible children had higher mean gestational age and birth weight compared to those not eligible, and were less likely to have experienced neonatal hypoglycaemia. Of children eligible for 2 year follow-up, those who were assessed were similar to those not assessed except that those assessed were less likely to be Asian.

There were no significant differences between children who were eligible and not eligible for 4.5 year follow-up. Of children eligible for 4.5 year follow-up, those who were assessed were more likely to be Maori and to live in less deprived areas than those not assessed (Table 4.2.2).
## Table 4.2.1 Baseline characteristics of children in neonatal and 2 year follow-up studies

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Neonatal cohort N=614</th>
<th>Eligible for 2 year follow-up N=527</th>
<th>Eligible children assessed at 2 years N=404</th>
<th>P</th>
<th>No N=123</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary risk factor:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDM</td>
<td>232 (38)</td>
<td>205 (39)</td>
<td>27 (31)</td>
<td>161 (40)</td>
<td>44 (36)</td>
<td>0.002</td>
</tr>
<tr>
<td>Preterm</td>
<td>216 (35)</td>
<td>171 (32)</td>
<td>45 (52)</td>
<td>129 (32)</td>
<td>42 (34)</td>
<td>0.002</td>
</tr>
<tr>
<td>Small</td>
<td>87 (14)</td>
<td>78 (15)</td>
<td>9 (10)</td>
<td>60 (15)</td>
<td>18 (15)</td>
<td>0.67</td>
</tr>
<tr>
<td>Large</td>
<td>56 (9)</td>
<td>54 (10)</td>
<td>2 (2)</td>
<td>42 (10)</td>
<td>12 (10)</td>
<td>0.67</td>
</tr>
<tr>
<td>Other</td>
<td>23 (4)</td>
<td>19 (4)</td>
<td>4 (5)</td>
<td>12 (3)</td>
<td>7 (6)</td>
<td>0.67</td>
</tr>
<tr>
<td><strong>Boys</strong></td>
<td>327 (53)</td>
<td>281 (53)</td>
<td>46 (53)</td>
<td>212 (52)</td>
<td>69 (56)</td>
<td>0.48</td>
</tr>
<tr>
<td><strong>Ethnicity:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New Zealand</td>
<td>325 (54)</td>
<td>280 (53)</td>
<td>45 (62)</td>
<td>215 (53)</td>
<td>65 (53)</td>
<td>0.002</td>
</tr>
<tr>
<td>European</td>
<td>215 (36)</td>
<td>195 (37)</td>
<td>20 (27)</td>
<td>149 (37)</td>
<td>46 (37)</td>
<td>0.002</td>
</tr>
<tr>
<td>Maori</td>
<td>23 (4)</td>
<td>21 (4)</td>
<td>2 (3)</td>
<td>21 (5)</td>
<td>0 (0)</td>
<td>0.002</td>
</tr>
<tr>
<td>Pacific Islanders</td>
<td>37 (6)</td>
<td>31 (6)</td>
<td>6 (8)</td>
<td>19 (5)</td>
<td>12 (10)</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Gestational age, weeks</strong></td>
<td>38 (36; 39)</td>
<td>38 (36; 39)</td>
<td>34 (33; 37)</td>
<td>&lt;0.0001</td>
<td>38 (36; 39)</td>
<td>38 (36; 39)</td>
</tr>
<tr>
<td>New Zealand Deprivation Index</td>
<td>7 (4; 9)</td>
<td>7 (5; 9)</td>
<td>7 (4; 9)</td>
<td>0.50</td>
<td>7 (4; 9)</td>
<td>7 (5; 9)</td>
</tr>
<tr>
<td>Birthweight, grams</td>
<td>3022 (880)</td>
<td>3110 (854)</td>
<td>2486 (852)</td>
<td>&lt;0.0001</td>
<td>3134 (844)</td>
<td>3029 (886)</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>339 (55)</td>
<td>273 (52)</td>
<td>66 (76)</td>
<td>&lt;0.0001</td>
<td>213 (53)</td>
<td>60 (49)</td>
</tr>
</tbody>
</table>

Data are number (percent), mean (standard deviation) or median (interquartile range). IDM, infant of a diabetic mother; Characteristics of children recruited and not recruited were compared using chi-squared tests or one-way ANOVA. 1 child died after recruitment. Data missing: ethnicity, 14; New Zealand Deprivation Index, 1. Hypoglycaemia defined as ≥1 blood glucose measurements <2.6 mmol/l.

## Table 4.2.2 Baseline characteristics of children in neonatal and 4.5 year follow-up studies

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Neonatal cohort N=614</th>
<th>Eligible for 4.5 year follow-up N=604</th>
<th>Eligible children assessed at 4.5 years N=477</th>
<th>P</th>
<th>No N=127</th>
<th>P</th>
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<tr>
<td><strong>Primary risk factor:</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDM</td>
<td>232 (38)</td>
<td>226 (37)</td>
<td>6 (60)</td>
<td>180 (38)</td>
<td>46 (36)</td>
<td>0.002</td>
</tr>
<tr>
<td>Preterm</td>
<td>216 (35)</td>
<td>214 (35)</td>
<td>2 (20)</td>
<td>168 (35)</td>
<td>46 (36)</td>
<td>0.002</td>
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<tr>
<td>Small</td>
<td>87 (14)</td>
<td>86 (14)</td>
<td>1 (10)</td>
<td>72 (15)</td>
<td>14 (11)</td>
<td>0.002</td>
</tr>
<tr>
<td>Large</td>
<td>56 (9)</td>
<td>55 (9)</td>
<td>1 (10)</td>
<td>39 (8)</td>
<td>16 (13)</td>
<td>0.002</td>
</tr>
<tr>
<td>Other</td>
<td>23 (4)</td>
<td>23 (4)</td>
<td>0 (0)</td>
<td>18 (4)</td>
<td>5 (4)</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Boys</strong></td>
<td>327 (53)</td>
<td>323 (53)</td>
<td>4 (40)</td>
<td>249 (52)</td>
<td>74 (58)</td>
<td>0.22</td>
</tr>
<tr>
<td><strong>Ethnicity:</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New Zealand</td>
<td>325 (54)</td>
<td>317 (54)</td>
<td>8 (80)</td>
<td>253 (53)</td>
<td>64 (55)</td>
<td>0.002</td>
</tr>
<tr>
<td>European</td>
<td>215 (36)</td>
<td>214 (36)</td>
<td>1 (10)</td>
<td>180 (38)</td>
<td>34 (29)</td>
<td>0.002</td>
</tr>
<tr>
<td>Maori</td>
<td>23 (4)</td>
<td>22 (4)</td>
<td>1 (10)</td>
<td>18 (4)</td>
<td>4 (3)</td>
<td>0.002</td>
</tr>
<tr>
<td>Pacific Islanders</td>
<td>37 (6)</td>
<td>37 (6)</td>
<td>0 (0)</td>
<td>22 (5)</td>
<td>15 (13)</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Gestational age, weeks</strong></td>
<td>38 (36; 39)</td>
<td>38 (36; 39)</td>
<td>38 (37; 40)</td>
<td>0.28</td>
<td>38 (36; 39)</td>
<td>38 (36; 39)</td>
</tr>
<tr>
<td>New Zealand Deprivation Index</td>
<td>7 (4; 9)</td>
<td>7 (4; 9)</td>
<td>7 (4; 10)</td>
<td>0.67</td>
<td>7 (4; 9)</td>
<td>8 (6; 9)</td>
</tr>
<tr>
<td>Birthweight, grams</td>
<td>3022 (880)</td>
<td>3015 (876)</td>
<td>3436 (1069)</td>
<td>0.13</td>
<td>2997 (861)</td>
<td>3081 (932)</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>339 (55)</td>
<td>335 (55)</td>
<td>4 (40)</td>
<td>276 (58)</td>
<td>59 (46)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Data are number (percent), mean (standard deviation) or median (interquartile range). IDM, infant of a diabetic mother; Characteristics of children recruited and not recruited were compared using chi-squared tests or one-way ANOVA. Data missing: ethnicity, 14; New Zealand Deprivation Index, 1. Hypoglycaemia defined as ≥1 blood glucose measurements <2.6 mmol/l.
4.3 Characteristics of the 2 year CHYLD cohort

At 2 years 404 children were assessed at a mean (SD) corrected age of 24 (1.8) months. Of these, 213 (53%) became hypoglycaemic (Table 4.2). Mean (SD) BMI was 17.2 (1.5) kg/m\(^2\) [Z score 1.0 (1.0)]. A total of 61 (15%) children were overweight and 8 (2%) were obese (De Onis, 2010) (Table 4.3). One quarter of the cohort were delayed in cognitive function, and almost a quarter in language (Table 4.3).

### Table 4.3 Characteristics of the 2 year CHYLD cohort

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N=404</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight, kg</td>
<td>13.0 (1.8)</td>
</tr>
<tr>
<td>Weight Z score</td>
<td>0.7 (1.1)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>86.5 (5.8)</td>
</tr>
<tr>
<td>Height Z score</td>
<td>-0.1 (1.1)</td>
</tr>
<tr>
<td>BMI kg/m(^2)</td>
<td>17.2 (1.5)</td>
</tr>
<tr>
<td>BMI Z score</td>
<td>1.0 (1.0)</td>
</tr>
<tr>
<td>MUAC, cm</td>
<td>16.4 (1.3)</td>
</tr>
<tr>
<td>MUAC Z score</td>
<td>1.0 (1.0)</td>
</tr>
<tr>
<td>Head circumference, cm</td>
<td>49.0 (1.8)</td>
</tr>
<tr>
<td>Head circumference Z score</td>
<td>0.9 (1.2)</td>
</tr>
<tr>
<td>Underweight(^a)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Overweight</td>
<td>61 (16)</td>
</tr>
<tr>
<td>Obese</td>
<td>8 (2)</td>
</tr>
</tbody>
</table>

Bayley-III scores:

- Cognitive composite score
  - < 1SD: 93 (10)  
  - 1SD above mean: 101 (25)
- Language composite score
  - < 1SD: 95 (14)  
  - 1SD above mean: 88 (22)
- Motor composite score
  - < 1SD: 99 (10)  
  - 1SD above mean: 35 (9)
- Social-emotional composite score
  - < 1SD: 103 (15)  
  - 1SD above mean: 66 (17)
- Executive function composite score
  - < 1SD: 10.4 (4.1)  
  - 1SD above mean: 57.6 (11.6)

Data are number (percent) or mean (standard deviation); BMI, body mass index; MUAC, mid upper arm circumference; \(^a\)Based on BMI measurements (De Onis, 2010): underweight, 2 SD below mean; overweight, 2 SD above the mean; and obese, 5SD above the mean. Data missing: weight, 10; height, 11; BMI, 12; MUAC, 15; head circumference, 11; Bayley-III: cognitive, 2; language and motor 3; social-emotional, 22; Executive function, 59; BRIEF-P, 6.

4.4 Characteristics of the 4.5 year CHYLD cohort

At 4.5 years 477 children were assessed at a mean (SD) corrected age of 54 (1.8) months. Of these 477 children, 276 (58%) became hypoglycaemic (Table 3.2). Mean (SD) BMI at 4.5 years for the entire cohort was 16.2 (1.7) kg/m\(^2\) [Z score 0.6 (1.1)]. Using recommended WHO BMI cut-offs (De Onis, 2010) 3 (1%) children were underweight, 44 (10%) children were overweight and 12 (3%) were obese (Table 4.4). Almost a fifth of the cohort were at least one SD below the test mean for cognitive function and also for language, almost a quarter for processing speed, and a quarter of the cohort were at risk of motor difficulty (≤15\(^{th}\) centile on MABC-2, Table 4.4).
Table 4.4 Characteristics of the 4.5 year CHYLD cohort

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N=477</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight, kg</td>
<td>18.5 (2.9)</td>
</tr>
<tr>
<td>Weight Z score</td>
<td>0.4 (1.0)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>106.6 (4.7)</td>
</tr>
<tr>
<td>Height Z score</td>
<td>0.1 (1.0)</td>
</tr>
<tr>
<td>BMI kg/m²</td>
<td>16.2 (1.7)</td>
</tr>
<tr>
<td>BMI Z score</td>
<td>0.6 (1.1)</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>43.8 (5.2)</td>
</tr>
<tr>
<td>Head circumference, cm</td>
<td>51.1 (1.7)</td>
</tr>
<tr>
<td>Head circumference Z score</td>
<td>0.7 (1.1)</td>
</tr>
<tr>
<td>Underweight†</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Overweight</td>
<td>44 (10)</td>
</tr>
<tr>
<td>Obese</td>
<td>12 (3)</td>
</tr>
</tbody>
</table>

WPPSI-III scores:
- Full Scale IQ: 98.0 (14.8)
- Verbal composite score: 98.3 (16.6)
- Performance composite score: 99.0 (13.8)
- Processing speed composite score: 96.2 (13.1)
- Executive function composite score: 13.6 (5.7)
- BRIEF-P global executive composite score: 52.1 (11.7)

MABC-2:
- Total, centile: 38.7 (29.5)
- ≤15th centile: 115 (25)
- ≤50th centile: 72 (16)
- Manual Dexterity, centile: 36.9 (28.7)
- Aiming and Catching, centile: 55.1 (28.4)
- Balance, centile: 35.4 (27.3)

Data are number (percent) or mean (standard deviation). BMI, body mass index; MUAC, mid upper arm circumference; SD, standard deviation.

†Based on BMI measurements (De Onis, 2010): underweight <2 SD below the mean; overweight, 2 SD above the mean; and obese, 3 SD above the mean.

Data missing: weight, 14; height, 11; BMI, 14; waist circumference, 19; head circumference, 13; WPPSI-III: full scale IQ and verbal, 7; performance, 6; processing speed, 29; Executive function, 17; BRIEF-P, 14; MABC-2, 23.

4.5 Discussion

4.5.1 Neonatal and socio-demographic characteristics of the CHYLD study cohort

The CHYLD study cohort comprised children born at risk of neonatal hypoglycaemia: born to diabetic mothers, preterm, small or large, or other conditions. Therefore, it is a group of neonates who are not representative of the general population of neonates born without known risk factors. Prevalence of births to diabetic mothers (both pre-existing and GDM) was 6.1% in 2008 in Australia (Abouzeid, Versace, Janus et al., 2014) and 3% in one of the New Zealand hospitals (Reddy, 2011), and prevalence of GDM reported in population based studies ranged from 2 to 17% worldwide depending on country and ethnicity (Hunt & Schuller, 2007). Of all births in New Zealand in 2014, 6.2% were born at 32-36 weeks’ gestation, 5.9% born small and 2.4% were large (Ministry of Health, Report on Maternity). Moreover, recruited neonates
were all born in a single centre, Waikato hospital, all of which means that the ethnic and socio-economic characteristics of the study population may not be representative of the whole New Zealand population.

Children eligible for 2 year assessment had higher birth weight and gestational age than those not eligible. This was due to the late start of the 2 year follow-up when many children recruited to the BABIES study, which recruited more preterm babies, were already older than the assessment window allowed. Further, because of logistic and funding limitations, a decision was made to exclude children born <35 weeks’ gestation from 2 year follow-up. At 2 years’ corrected age 77% of eligible children were assessed. More than a third of children assessed were Maori and only 5% were of Pacific origin. According to 2013 New Zealand census data for all births, 19% were of Maori origin and 10% of Pacific (Statistics New Zealand, Ethnicity, Census data). This difference reflects heterogeneous ethnic distribution across New Zealand. The CHYLD study cohort is representative of a Waikato population who have a higher proportion of Maori and lower proportion of Pacific Islanders, and also higher deprivation rates, than the national average (Ministry of Health, Population of Waikato).

Neonatal and socio-demographic characteristics were similar in children eligible and not eligible for 4.5 year follow-up. However, eligible children who were assessed at 4.5 years lived in less deprived areas than children who were not assessed. This could be explained by difficulties in tracking and assessing families who live in deprived areas (Orton, McGinley, Fox et al., 2015) especially when children are older and more families relocate to other areas.

4.5.2 Challenges of follow-up assessments

Difficulties arise when tracking children and organising follow up assessments. Most of the CHYLD Study cohort remained in the Waikato area at the time of 2 and 4.5 year follow-up assessments. However, at 2 years 18% of assessed families and at 4.5 years 24% of families had moved to other parts of New Zealand or overseas, which had implications for follow-up strategy and created challenges for a follow-up team. Follow-up assessments are costly, time consuming, require many trained specialists and incur other additional costs associated with tracking participants, managing data, and travel costs (Doyle, Clucas, Roberts et al., 2015). Contacting, tracking and assessing children whose families have relocated was even more challenging. First of all, extra effort, time and resources had to be allocated to find children which included phone or email contact with parents, extended family, general practitioner or even neighbours. Second, if tracking was successful and a family agreed to participate, another
challenge was to organise the assessment space, assessment team and provision of transportation for a family to attend assessment. Such assessments are particularly complex and expensive in remote areas. Third, re-assessments had to be organised if a child could not complete an assessment during one session or if a family did not attend on the day of a scheduled assessment. And finally, home visits were organised if a family chose this option. Giving an option of home follow-up visits was described as a useful approach to decrease follow-up losses and retain participants with complications (Peterson, Pirraglia, Wells et al., 2012) or circumstances that would otherwise prevent them from attending follow-up assessment.

Children who were very difficult to find or did not attend often lived in remote areas or were from low socio-economic backgrounds. Retaining these children in a cohort is very important for a cohort to be representative of a general population and for study results to be valid. If the cohort assessed at follow-up is different to the initially recruited cohort or the general population, the outcomes of the study cannot be applied to general population. There may be a reason for not attending a follow-up, participants who are lost may have poor outcome and then study results may not be valid (Gray, 2016). In a follow-up study of low birth weight or preterm neonates, prevalence of adverse health outcomes was reported to be higher in children who did not respond to follow-up invitation or responded late after a few reminders and contact attempts compared to those who did respond, which may lead to underestimation of certain conditions (Hille, Den Ouden, Stuifbergen et al., 2005).

Further, children who are difficult to find are very likely to miss out on regular health care visits and may be in need of health assessment and referral (Ministry of Health, New Zealand Health Survey, 2015). Finally, collecting questionnaires from parents who could not complete these before or on the day of assessment was also challenging as this required additional contacts and arrangements.

4.5.3 Factors associated with loss to follow-up

Losses from follow-up studies can be random or not random and this can define if results of the study are likely to be biased. The acceptable follow-up rate has been reported at 80% and this number demonstrates good quality cohort retention rate (Fewtrell, Kennedy, Singhal et al., 2008; Launes, Hokkanen, Laasonen et al., 2014). However, when the data lost to follow-up is missing completely at random or at random it was shown that even follow-up rate of less than 50% did not affect results of the study (Kristman, Manno, & Côté, 2004). In the same
simulation study, when data was missing not at random the loss to follow-up of 20% led to biased results (Kristman, Manno & Cote, 2004).

Factors like age of follow-up, accessibility of places where participants live, benefits of assessment tests, incentives used in the study, the nature of intervention or condition of follow-up interest will influence the follow-up rate. For example, some nutritional or lifestyle changes are difficult to follow-up especially over long follow-up times. Further, for different age groups loss to follow-up is associated with different factors. For example, young women tend to move more often than women in middle and older age groups (Young, Powers, & Bell, 2006), therefore young women and their children might be difficult to track and establish a contact. Moreover, being born in a non-English speaking country and low educational level were associated with high rates of loss (Young, Powers, & Bell, 2006).

Children born preterm and followed up in a national survey from birth to 8 years were more likely to be lost to follow-up if their parents had low educational level or mothers were young (Diez, Yorifuji, Kado et al., 2016). However, maternal age was not different between children who were followed up and those lost to follow-up in a Paris birth cohort study (Clarisse, Nikasinovic, Poinsard et al., 2007). The main reason for not participating in this study was relocation due to change of work. All of the factors associated with loss to follow-up comprise an obstacle that researchers try to overcome (Lee, Dobson, Brown et al., 2000). If researchers know about the reasons for non-participation in follow-up, accurate planning of a follow-up strategy and provision of resources might help minimise the number of lost participants (Savitz, 2009). For example, contacting women by mail or phone did not work for many of the participants of the Australian Longitudinal Study on Women’s Health, even if eight attempts were made (Young, Powers, & Bell, 2006). Therefore, extensive resources are often required for tracking participants, which may involve many types of contact. In the CHYLD study, we contacted families via post, phone, in person visits and visits to members of the extended family.

In a study investigating rates of loss to follow-up in a cohort born at risk of adverse neurodevelopmental outcomes, 16% of participants were lost at 5 years, 24% at 9 years, 35% at 16 years and almost a half (46%) at 30 years (Launes, Hokkanen, Laasonen et al., 2014). In another follow-up study that investigated development of children from the general population, at 15 years 56% of participants were lost and educational level of mothers who were lost was lower compared to those who participated (Gustavson, Von Soest, Karevold et al., 2012).
Further, response to questionnaires administered over the phone was 80% and physical examination was accepted by 90% of families at 18m months follow-up (Clarisse, Nikasinovic, Poinsard et al., 2007). Prospective cohort studies of chronic conditions have also reported high retention rates (93%) at 2 years, most likely due to regular follow-up visits and chronic nature of a disease that manifests often (Bisgaard, 2004). Retention rate of 84.9% was reported at 5 year follow-up of very preterm neonates (Schmidt, Anderson, Doyle et al., 2012).

The retention rate of 95% at 9 months and 92% at 2 years in the Growing Up in New Zealand population study could be due to larger number of contacts made with families prior to follow-up and involvement of community and media (Morton, Atatoa Carr, Berry et al., 2014). The follow-up rate in the CHYLD study was 77% at 2 years and 79% at 4.5 years, which is only slightly below the suggested 80% rate. Although the CHYLD study cohort assessed at 2 years was ethnically different and at 4.5 years was less deprived compared to children who were not assessed, none of the neonatal factors were different. Therefore we can assume that our findings are reasonably representative of the population of Waikato children born at risk of neonatal hypoglycaemia.

4.5.4 Impairment rates

Approximately a quarter of the cohort assessed at 2 years had cognitive and language scores at least 1 SD below the mean. At 4.5 years, close to a fifth of the assessed children had cognitive, language and processing speed scores 1 SD below the mean and a quarter had motor difficulties. Rates of impairment therefore were similar to 2 year rates and were higher than the reference norms of 15.8% (1 SD below the test mean).

The rates of impairment were similar to those reported from preterm and very low birth weight children when assessed at 2 years (Orton, McGinley, Fox et al., 2015). The rate of impairment in the CHYLD 2 year cohort was also similar to that reported from a cohort of intrauterine growth restricted children when assessed at 2 years using Bayley-II (Von Beckerath, Kollmann, Rotky-Fast et al., 2013). However, caution is needed when interpreting these results due to different tests used for the assessment. Bayley-III has a separate cognitive and language scales that replaced the mental developmental index of the Bayley-II (Bayley, 2006), and led to confusion in score interpretations. Bayley second and third editions have been reported to result in different impairment rates when administered to the same group of children (Johnson, Moore, & Marlow, 2014). The recommended Bayley-III cut-offs were reported to underestimate developmental delays (Acton, Biggs, Creighton et al., 2011; Johnson et al.,
2014; Lowe, Erickson, Schrader et al., 2012). In our case, if Bayley-III underestimates developmental delays, it is likely that even more children in our cohort would have been categorised as impaired if Bayley-II had been used. Cognitive impairment rates in the CHYLD study (25%) were 4 times higher than reported rates in late and moderately preterm children (6.3%) and 10 times higher than controls (2.4%) at 2 years (Johnson, Moore, & Marlow, 2015). Developmental delay rates were also higher for the CHYLD 4.5 year cohort compared with 4 year olds born moderately preterm (5-12%) and born at term (2-7%) (Potijk, Kerstjens, Bos et al., 2013). Therefore, children assessed in the CHYLD Study have similar impairment rates to other high risk children, and might need close monitoring and extra services to ensure their successful development.

4.5.5 Obesity and overweight rates.

Because children assessed at 2 and 4.5 years were different cohorts who had slightly different inclusion criteria. Therefore, we will not compare the change in rates over time based on our data, but will compare it to rates reported in New Zealand and other countries.

The rate of overweight (including obese) and obesity was 16% and 2% at 2 years, and 10% and 3% at 4.5 years, respectively, in our study. These rates are lower than findings of New Zealand Health Survey 2014/2015, where 20% of 2 to 4 year olds were overweight and another 9.5% were obese when using International Obesity Task Force (IOTF) guidelines that allow calculation of predicted BMI at 18 years using current BMI (Ministry of Health, New Zealand Health Survey, 2015). The difference in rates could be due to different references used. However, WHO reference guidelines were reported to overestimate the prevalence of overweight and obesity compared to IOTF in other countries (Hassapidou, Daskalou, Tsofliou et al., 2015; Kēkē, Samouda, Jacobs et al., 2015) as well as New Zealand (Rajput, Tuohy, Mishra et al., 2015). In the latter study of New Zealand preschool children who underwent the B4SC at 4 years, rates of overweight and obesity using WHO standards were 18.3% and 16.3%, respectively (Rajput, Touhy, Mishra et al., 2015).

Rates of childhood obesity calculated for 9 different countries using survey data and individual studies were reported at 23-25% in Australia in 2008, 15% in China and 12.1% in France in 2006 (Olds, Maher, Zumin et al., 2011). However, these rates are from different studies that did not have the same standardised protocol and included children from different age groups. Further, a stabilising trend in overweight/obesity rates in all countries was observed from around 2000. Overall, rates of overweight and obesity in our cohort are slightly lower than
those recently found in the New Zealand survey (Ministry of Health, New Zealand Health Survey, 2015). This could be explained by a difference between the general population and our cohort. All children recruited to our study were at risk, born preterm, small or large, or infants of diabetic mothers, all of whom might have a slightly altered growth trajectory from birth. However, children born small, large or average for gestational age have been described to have similar weight status by 12 months of age (Çamurdan, Çamurdan, Polat et al., 2011).

4.6 Summary

The CHYLD study cohort is comprised of children born at risk of neonatal hypoglycaemia who have high impairment rates at 2 and 4.5 years. This confirms that these children are a high risk population that might require additional services and close monitoring. Therefore, this cohort is not representative of the general population of New Zealand due to the inclusion criteria of the study. Further, socio-demographic characteristics are different from the whole New Zealand population, but are representative of the Waikato region where this cohort was recruited and most of the cohort lived up to 4.5 years.

Cohorts born at risk might be difficult to retain in follow-up studies. Nevertheless, the follow-up rate we achieved was only slightly below the most widely accepted 80% goal, increasing confidence that the findings are likely reflect those of the cohort as a whole.
Chapter 5. Growth and motor performance.
5.1 Introduction

Birth weight and rate of growth during infancy are associated with the risk of obesity, cardiovascular and metabolic disorders in later life (Brisbois, Farmer, & McCargar, 2012; Weng, Redsell, Swift et al., 2012). Individuals born small for gestational age (SGA) have both a tendency to rapid postnatal weight gain and increased risk of metabolic disease (Milovanovic, Njuieyon, Deghmoun et al., 2014; Ong, 2007). Children born to diabetic mothers had greater weight, height and BMI than controls at 5 to 8 years, and also had higher total body fat mass measured using dual-energy-x-ray absorptiometry (DEXA) (Mughal, Eelloo, Roberts et al., 2010). Further, head circumference was smaller in 3-year-old children born to diabetic mothers with worse glycaemic control during pregnancy compared to children of mothers with better controlled diabetes and a control group (Sells, Robinson, Brown et al., 1994). In addition, babies born at risk of neonatal hypoglycaemia are considered to have an impaired metabolic adaptation to the postnatal environment immediately after birth, which might be associated with programming of future metabolic disorders (Calkins & Devaskar, 2011). Multiple episodes of neonatal hypoglycaemia (≥6 episodes) were associated with lower BMI at birth, but not with weight and length measurements between 6 months to 5 years. Further, multiple episodes of hypoglycaemia were also associated with consistently smaller head circumference at all follow-up visits: 12 and 18 months, and 5 years, but not growth of head from 6 months to 5 years in SGA preterm children (Duvanel, Fawer, Cotting et al., 1999).

There are different methods to analyse body size and growth of children. Each method has its own applications and is chosen depending on the study question and hypothesis (Johnson, 2015). Some of the most common ways to describe and analyse growth are using internal or external Z (standard deviation) scores, standardised indices, growth curves analysis and conditional regression models (Argyle, 2003). While Z scores are used to determine body sizes of the cohort either in comparison to the mean (SD) of the whole cohort itself (internal Z scores, if the sample is large) or mean (SD) of the reference cohort (external Z scores). External Z scores are useful in comparison of data derived from different populations, and are also commonly used to assess body size in clinical settings. Compared to using Z scores plotted on a cross-sectional chart at the particular time point (body size), conditional growth analysis helps to identify if the growth parameter has deviated from the expected trajectory, given a child’s previous size (Cole, 1995). When longitudinal data are available, compared to previous measurements, the subsequent ones tend to be closer to the population mean, which is called the regression to the mean (Barnett, van der Pols, & Dobson, 2005). Conditional growth
analysis takes into account this phenomenon when including previous measurement in the analysis, and is useful in assessing growth of an individual or the specified subgroup. Therefore, the choice of the method for the analysis of body size or growth depends on the number of measurements available, size of the cohort, and aims of the study.

Moreover, body size has been associated with motor function in children. Children born extremely preterm, low birth weight (Brown, Burns, Watter et al., 2015) or who were admitted to NICU (Hemgren & Persson, 2009) have impaired motor function compared to controls. Further, physical fitness and motor scores as well as body size parameters (weight, height, BMI and head circumference) were significantly lower in very low birth weight children at 13 years compared to controls (Burns, Danks, O'Callaghan et al., 2009). Therefore, associations between neonatal risk factors, motor function and growth has been reported, but the causality is difficult to establish.

The link between anthropometric measurements, physical activity and motor performance has also been established for overweight or obese children. For example, motor coordination scores of overweight and obese children were lower than those of normal weight 6 to 14-year-old children, and the correlation between BMI and motor coordination scores was strongest at 11 years (Lopes, Stodden, Bianchi et al., 2012). Moreover, children with motor problems had higher BMI and waist circumference than children with no difficulties at both the baseline (9-10 years) and at 5-year follow up, with the difference between the two groups increasing between assessments (Joshi, Missiuna, Hanna et al., 2015). Children with higher BMI and waist circumference also had lower physical activity levels measured by Participation Questionnaire (Joshi, Missiuna, Hanna et al., 2015).

Therefore, both short and light children as well as overweight children tend to have decreased motor performance, which might impact social life, academic performance and emotional wellbeing (Cairney, Rigoli, & Piek, 2013). However, most literature reports associations between body size, growth and motor performance and other health outcomes in school aged children. It is unclear what factors are associated with poor motor performance, and if such associations can be identified in young children.

The aims of this chapter are to (1) describe the growth of children born with different risk factors for neonatal hypoglycaemia from birth till 4.5 years; (2) compare overweight and obesity status at 2 and 4.5 years; and (3) assess associations between growth and motor performance at preschool age.
5.2 Methods

5.2.1 Study design
Children were born at Waikato Women’s Hospital, Hamilton, with one or more of the following risk factors for neonatal hypoglycaemia: being an infant of a diabetic mother, preterm (32 to 36 weeks’ gestation), small (<2500g or <10th centile), large (>4500g or >10th centile) or other conditions (Harris, Battin, Weston et al., 2010; Harris, Weston, Signal et al., 2013). Neonates had intermittent blood glucose concentrations measured and hypoglycaemia was defined as one or more consecutive measurements <2.6 mmol/l. Children were invited to participate in a neurodevelopmental assessment at 2 and 4.5 years’ corrected age, including assessment of growth. The 4.5-year assessment also included a test of motor performance. The results reported in this chapter are limited to children who were assessed at both 2 and 4.5 years.

5.2.2 Anthropometric measurements
Children had weight, height, BMI and head circumference measured at 2 and 4.5 years (Chapter 3. Methods). Birth measurements were obtained from clinical records and were not part of the research protocol. Measurements were converted to Z scores using Beeby charts for birth measurements (Beeby, Bhutap, & Taylor, 1996) and WHO reference charts for 2 and 4.5 year measurements (WHO Multicentre Growth Reference Study Group & de Onis, 2006) (Chapter 3. Methods).

5.2.3 Motor assessment
Motor skills at 4.5 years were assessed using Movement Assessment Battery for Children, second edition (MABC-2), which tests manual dexterity, aiming and catching, and balance skills (Henderson, Sugden, & Barnett, 2007). Total motor score ≤15th percentile indicates that a child is at risk for motor difficulty (Chapter 3. Methods).

5.2.4 Statistical analysis
Data were analysed using JMP software Version 11.2.0 (SAS Institute Inc., Cary, NC, 2013). Risk factors were prioritised in the following order: neonates born to diabetic mothers, preterm, small, large and other. Characteristics of children included in the analyses and those who were not assessed, and children who had motor difficulty at 4.5 years and those who did not were compared using one-way analysis of variance (ANOVA), a Chi-squared test or Wilcoxon rank-sum test, as appropriate.
Birth, 2- and 4.5-year Z scores for measures of body size, and conditional growth were compared between different neonatal risk groups, and children who did and did not have hypoglycaemia using t-tests. Conditional growth Z scores were calculated according to method described by Cole to identify if the parameters have deviated from the expected trajectory based on the previous measurement (Cole, 1995).

Linear regression analysis was also conducted to assess associations between total motor score at 4.5 years and Z scores for body size at 2 years and 4.5 years, and conditional growth from 2 to 4.5 years. The regression of MABC-2 scores on body size parameters, and conditional growth was adjusted for NZ Deprivation index, and also for previous Z score.

Children were assigned to three BMI categories: normal weight range, overweight (2 SD above the mean) and obese (3 SD above the mean) (Training course in child growth assessment. WHO child growth standards, 2008). Logistic regression analyses adjusted for NZ Deprivation index and birth weight Z score were used to determine the odds of being overweight or obese at 4.5 years in children who were overweight or obese at 2 years.

5.3 Results
A total of 355 children were assessed at both the 2- and 4.5-year CHYLD follow-up visits. Mean (SD) corrected age at assessments was 24 (1.7) and 53 (1.8) months. In this cohort 185 (52%) were boys, the median (IQR) gestational age was 38 (36; 39) weeks and 193 (54%) had at least one episode of hypoglycaemia in the first 48 hours (Table 5.3). Compared to children who were not assessed at both follow-up visits, children who were assessed at both ages had higher gestational age and birth weight, and also lived in less deprived areas (Table 5.3).

5.3.1 Body size and growth of children born at risk of neonatal hypoglycaemia
Weight Z score at birth was significantly different among neonatal risk groups except between preterm and other. Children whose primary risk factor was small size at birth continued to have the low Z scores for body size parameters at 2 and 4.5 years, whereas children who were large at birth had the highest Z scores for body size parameters at 2 and 4.5 years (Table 5.3.1.1). Z scores for body size parameters did not differ between children who had at least one episode of hypoglycaemia and those who did not (Table 5.3.1.1).
### Table 5.3 Characteristics of children who were assessed at 2 and 4.5 years

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Neonatal cohort N=614</th>
<th>Assessed at 2 and 4.5 years N=355</th>
<th>No N=259</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary risk factor:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDM</td>
<td>232 (38)</td>
<td>144 (41)</td>
<td>88 (34)</td>
<td>0.16</td>
</tr>
<tr>
<td>Preterm</td>
<td>216 (35)</td>
<td>112 (32)</td>
<td>104 (40)</td>
<td></td>
</tr>
<tr>
<td>Small</td>
<td>87 (14)</td>
<td>53 (15)</td>
<td>34 (13)</td>
<td></td>
</tr>
<tr>
<td>Large</td>
<td>56 (9)</td>
<td>35 (10)</td>
<td>21 (8)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>23 (4)</td>
<td>11 (3)</td>
<td>12 (5)</td>
<td></td>
</tr>
<tr>
<td><strong>Boys</strong></td>
<td>327 (53)</td>
<td>185 (52)</td>
<td>142 (55)</td>
<td>0.51</td>
</tr>
<tr>
<td><strong>Ethnicity:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New Zealand</td>
<td>325 (54)</td>
<td>193 (54)</td>
<td>132 (54)</td>
<td></td>
</tr>
<tr>
<td>European</td>
<td>215 (36)</td>
<td>131 (37)</td>
<td>84 (34)</td>
<td></td>
</tr>
<tr>
<td>Maori</td>
<td>23 (4)</td>
<td>17 (5)</td>
<td>6 (2)</td>
<td></td>
</tr>
<tr>
<td>Pacific Islanders</td>
<td>37 (6)</td>
<td>14 (4)</td>
<td>23 (9)</td>
<td></td>
</tr>
<tr>
<td><strong>Gestational age, weeks:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New Zealand Deprivation Index</td>
<td>7 (4, 9)</td>
<td>7 (4, 9)</td>
<td>8 (7, 10)</td>
<td></td>
</tr>
<tr>
<td><strong>Birthweight, grams:</strong></td>
<td>3022 (880)</td>
<td>3138 (832)</td>
<td>2862 (920)</td>
<td>0.002</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>339 (55)</td>
<td>193 (54)</td>
<td>146 (56)</td>
<td>0.62</td>
</tr>
</tbody>
</table>

Data are number (percent), mean (standard deviation) or median (interquartile range). IDM, infant of a diabetic mother. Hypoglycaemia, blood glucose concentration <2.6 mmol/l.

### Table 5.3.1.1 Body size parameters of children assessed at 2 and 4.5 years

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Birth (N=355)</th>
<th>Preterm (N=239)</th>
<th>Small (N=345)</th>
<th>Large (N=348)</th>
<th>Other (N=347)</th>
<th>Hypoglycaemia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Weight</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Birth</td>
<td>0.2 (1.7)</td>
<td>0.7 (1.4)</td>
<td>-0.2 (1.0)</td>
<td>2.7 (0.8)</td>
<td>-0.2 (1.0)</td>
</tr>
<tr>
<td></td>
<td>2y</td>
<td>0.7 (1.0)</td>
<td>0.6 (1.0)</td>
<td>0.8 (0.9)</td>
<td>-0.0 (1.0)</td>
<td>1.4 (0.8)</td>
</tr>
<tr>
<td></td>
<td>4.5y</td>
<td>0.5 (1.0)</td>
<td>0.6 (1.1)</td>
<td>0.5 (0.9)</td>
<td>-0.2 (0.9)</td>
<td>1.0 (0.8)</td>
</tr>
<tr>
<td><strong>Length/height</strong></td>
<td>Birth</td>
<td>-0.1 (1.1)</td>
<td>-0.2 (1.0)</td>
<td>0.1 (1.2)</td>
<td>-0.1 (1.2)</td>
<td>0.6 (0.9)</td>
</tr>
<tr>
<td></td>
<td>2y</td>
<td>-0.1 (1.1)</td>
<td>-0.2 (1.0)</td>
<td>0.1 (1.2)</td>
<td>-0.1 (1.2)</td>
<td>0.6 (0.9)</td>
</tr>
<tr>
<td></td>
<td>4.5y</td>
<td>0.1 (1.1)</td>
<td>0.1 (1.0)</td>
<td>0.2 (1.0)</td>
<td>-0.5 (1.1)</td>
<td>0.6 (0.9)</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td>Birth</td>
<td>1.0 (1.0)</td>
<td>1.0 (1.0)</td>
<td>1.0 (1.0)</td>
<td>0.5 (0.9)</td>
<td>1.5 (0.8)</td>
</tr>
<tr>
<td></td>
<td>2y</td>
<td>0.6 (1.0)</td>
<td>0.8 (1.2)</td>
<td>0.6 (0.9)</td>
<td>0.1 (0.8)</td>
<td>1.1 (0.9)</td>
</tr>
<tr>
<td></td>
<td>4.5y</td>
<td>0.6 (1.0)</td>
<td>0.8 (1.2)</td>
<td>0.6 (0.9)</td>
<td>0.1 (0.8)</td>
<td>1.1 (0.9)</td>
</tr>
<tr>
<td><strong>Head circumference</strong></td>
<td>Birth</td>
<td>0.2 (1.5)</td>
<td>0.5 (1.2)</td>
<td>0.1 (1.3)</td>
<td>-1.3 (1.2)</td>
<td>2.0 (1.1)</td>
</tr>
<tr>
<td></td>
<td>2y</td>
<td>0.9 (1.2)</td>
<td>0.8 (1.1)</td>
<td>0.9 (1.1)</td>
<td>0.3 (1.1)</td>
<td>1.7 (1.2)</td>
</tr>
</tbody>
</table>

Data are mean Z score (standard deviation). Hypoglycaemia, blood glucose concentration <2.6 mmol/l. Cells marked with the same letters are not significantly different on post hoc pairwise comparisons.

From birth to 2 years, weight and height gain of preterm babies was greater compared to small and IDM babies (Table 5.3.1.2). From 2 to 4.5 years compared to small babies, gain in weight and BMI was greater in IDM babies, and gain in head circumference was greater in IDM, preterm and large babies. No other differences were found in conditional growth among children with different risk factors. Conditional growth in length/height, BMI and head...
circumference did not differ between children with and without neonatal hypoglycaemia (Table 5.3.1.2).

Table 5.3.1.2 Conditional growth of children assessed at 2 and 4.5 years

<table>
<thead>
<tr>
<th>Conditional parameters</th>
<th>Cohort</th>
<th>Primary risk factor</th>
<th>Hypoglycaemia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2y</td>
<td>4.5y</td>
<td>IDM</td>
</tr>
<tr>
<td>Weight</td>
<td>N=349</td>
<td>N=340</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.6 (0.9)</td>
<td>-0.1 (1.0)</td>
<td>0.5 (1.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- (0.9)</td>
<td>0.2 (0.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- (0.9)</td>
<td>-0.3 (0.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- (0.9)</td>
<td>0.0 (1.0)</td>
</tr>
<tr>
<td>Length/height</td>
<td>N=341</td>
<td>N=341</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.3 (0.9)</td>
<td>-0.1 (1.1)</td>
<td>0.3 (1.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- (0.9)</td>
<td>-0.3 (0.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- (0.9)</td>
<td>0.0 (1.0)</td>
</tr>
<tr>
<td>BMI</td>
<td>N=338</td>
<td>N=338</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.3 (0.9)</td>
<td>-0.1 (1.1)</td>
<td>0.3 (1.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- (0.9)</td>
<td>-0.3 (0.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- (0.9)</td>
<td>0.0 (1.0)</td>
</tr>
<tr>
<td>Head circumference</td>
<td>N=237</td>
<td>N=341</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.8 (1.1)</td>
<td>-0.1 (1.1)</td>
<td>0.7 (1.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- (0.9)</td>
<td>-0.3 (0.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- (0.9)</td>
<td>0.0 (1.0)</td>
</tr>
<tr>
<td></td>
<td>N=304</td>
<td>N=337</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.2 (0.3)</td>
<td>0.2 (0.3)</td>
<td>1.4 (1.1)</td>
</tr>
</tbody>
</table>

Data are mean (standard deviation). *Weight, height, BMI and head circumference at 4.5 years conditional on the corresponding parameters at 2 years; and weight, height, BMI and head circumference at 2 years conditional on corresponding parameters at birth. Hypoglycaemia, blood glucose concentration <2.6 mmol/l. Same letters indicate no significant pairwise differences.

5.3.2 Stability of BMI category from 2 to 4.5 years

Of 337 children who had BMI measurements at both 2 and 4.5 years, 287 (85%) remained in the same BMI category at 2 and 4.5 years, with 271 (94%) in the normal range, 14 (5%) overweight and 2 (1%) obese at both ages (Table 5.3.2). Of 304 children categorised as having normal BMI at 4.5 years, 32 (11%) were overweight at 2 years; of 24 children categorised as overweight at 4.5 years, 9 (38%) were in the normal BMI range at 2 years, and of 9 children categorised as obese at 4.5 years, 5 (56%) were in the normal BMI range and 2 (22%) were overweight at 2 years (Table 5.3.2). Therefore, 33/337 (10%) overweight or obese 2-year-olds were in the normal BMI range at 4.5 years and 14/337 (4%) 2-year-olds with normal BMI became overweight or obese by 4.5 years. Of 35 children born large 4/35 (14%) moved into the normal range BMI category from 2 to 4.5 years, as did 12/102 (12%) children born preterm. Of children with other risk factor, 2/11 (18%) moved into overweight category from 2 to 4.5 years.

Table 5.3.2 BMI category at 2 and 4.5 years

<table>
<thead>
<tr>
<th>2 year BMI category</th>
<th>4.5 year BMI category</th>
<th>Normal</th>
<th>Overweight</th>
<th>Obese</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>N=304</td>
<td>N=24</td>
<td>N=9</td>
<td>N=43</td>
</tr>
<tr>
<td></td>
<td>271 (89) [-0.4]</td>
<td>9 (38) [1.0]</td>
<td>5 (56) [2.3]</td>
<td>285 (85)</td>
</tr>
<tr>
<td>Overweight</td>
<td>32 (11) [-1.1]</td>
<td>14 (58) [-0.01]</td>
<td>2 (22) [1.0]</td>
<td>48 (14)</td>
</tr>
<tr>
<td>Obese</td>
<td></td>
<td>1 (0.3) [-3.1]</td>
<td>1 (4) [-2.2]</td>
<td>2 (22) [0.9]</td>
</tr>
</tbody>
</table>

Data are number (percent) of children in each BMI category at 2 and 4.5 years; and mean change in BMI Z score (4.5 years – 2 years). BMI, body mass index; BMI Z scores: overweight, 2 SD above the mean; obese, >3 SD above the mean. *One child was underweight (3 SD below the mean), excluded from the analysis.
Children who were overweight or obese at 4.5 years had higher BMI Z score at 2 years than those with normal BMI at 4.5 years (mean difference 1.7 Z score [95% CI 0.8; 1.5], P<0.0001). The odds ratio (95% CI) for being overweight or obese at 4.5 years for children who were overweight or obese at 2 years relative to children who were in the normal BMI range at 2 years adjusted for neonatal risk factor and NZ Deprivation index was 10 (4; 24), P <0.0001.

5.3.3 Motor performance, body size and growth

Children with motor difficulty at 4.5 years (total MABC-2 score ≤15th centile) were more likely to be Maori and live in more deprived areas than children who did not have a motor difficulty (Table 5.3.3.1). Other neonatal characteristics were not different between the two groups.

Table 5.3.3.1 Characteristics of children with and without motor difficulty at 4.5 years

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>MABC-2 total score ≤15th centile</th>
<th></th>
<th></th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes N=91</td>
<td>No N=246</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary risk factor:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDM</td>
<td>42 (46)</td>
<td>95 (39)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preterm</td>
<td>28 (31)</td>
<td>75 (30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small</td>
<td>11 (12)</td>
<td>40 (16)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large</td>
<td>8 (9)</td>
<td>27 (11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>2 (2)</td>
<td>9 (4)</td>
<td></td>
<td>0.65</td>
</tr>
<tr>
<td>Boys</td>
<td>51 (56)</td>
<td>123 (50)</td>
<td></td>
<td>0.32</td>
</tr>
<tr>
<td>Ethnicity:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New Zealand European</td>
<td>36 (41)</td>
<td>131 (56)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maori</td>
<td>42 (48)</td>
<td>73 (31)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pasific Islander</td>
<td>4 (5)</td>
<td>8 (3)</td>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td>Other</td>
<td>5 (6)</td>
<td>24 (10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestational age</td>
<td>38 (36; 38)</td>
<td>38 (36; 39)</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>Birth weight Z score</td>
<td>0.3 (1.6)</td>
<td>0.2 (1.7)</td>
<td></td>
<td>0.50</td>
</tr>
<tr>
<td>NZ Deprivation index</td>
<td>7 (5; 9)</td>
<td>6 (4; 9)</td>
<td></td>
<td>0.02</td>
</tr>
</tbody>
</table>

Data are number (percent), mean (standard deviation) or median (interquartile range).
Data missing: ethnicity, 14; NZ Deprivation index, 5.

Height and head circumference at 4.5 years were positively associated with the MABC-2 total score at 4.5 years (Table 5.3.3.2). This association remained significant when adjusted for NZ Deprivation index. Body size measurements at 2 years and conditional growth from 2 to 4.5 years were not associated with the total MABC-2 score at 4.5 years (Table 5.3.3.2).
Table 5.3.3.2 Relationship between MABC-2 total score and body size and growth parameters

<table>
<thead>
<tr>
<th>Regression coefficient</th>
<th>Unadjusted</th>
<th>Adjusted for NZ Deprivation index</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2 year measurements:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight Z score</td>
<td>1.47 (-1.57; 4.52)</td>
<td>1.49 (-1.55; 4.53)</td>
</tr>
<tr>
<td>Height Z score</td>
<td>2.67 (-0.04; 5.39)</td>
<td>2.64 (-0.07; 5.36)</td>
</tr>
<tr>
<td>BMI Z score</td>
<td>-1.19 (-4.43; 2.06)</td>
<td>-1.12 (-4.37; 2.12)</td>
</tr>
<tr>
<td>Head circumference Z score</td>
<td>1.91 (-0.68; 4.49)</td>
<td>1.81 (-0.77; 4.40)</td>
</tr>
<tr>
<td><strong>4.5 years measurements:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight Z score</td>
<td>1.85 (-1.13; 4.84)</td>
<td>1.90 (-1.07; 4.88)</td>
</tr>
<tr>
<td>Height Z score</td>
<td>3.15 (0.22; 6.08)*</td>
<td>3.08 (0.15; 6.00)*</td>
</tr>
<tr>
<td>BMI Z score</td>
<td>-0.47 (-3.43; 2.49)</td>
<td>-0.32 (-3.28; 2.64)</td>
</tr>
<tr>
<td>Head circumference Z score</td>
<td>3.25 (0.63; 5.87)*</td>
<td>3.27 (0.65; 5.89)*</td>
</tr>
<tr>
<td><strong>Conditional growth (4.5 year parameters conditional on 2 year)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td>0.71 (-2.27; 3.69)</td>
<td>0.81 (-2.16; 3.79)</td>
</tr>
<tr>
<td>Height</td>
<td>1.15 (-2.26; 4.56)</td>
<td>1.09 (-2.31; 4.50)</td>
</tr>
<tr>
<td>BMI</td>
<td>-0.13 (-2.96; 2.70)</td>
<td>0.02 (-2.81; 2.85)</td>
</tr>
<tr>
<td>Head circumference</td>
<td>2.48 (-0.32; 5.28)</td>
<td>2.68 (-0.13; 5.48)</td>
</tr>
</tbody>
</table>

Data are regression coefficients (95% confidence intervals). BMI, body mass index. Data missing: birth length, 252; birth head circumference, 100; 2 year weight, 6; 2 year height, 7; 2 year BMI, 7; 2 year head circumference, 6; 4.5 year weight, 10; 4.5 year height, 8; 4.5 year BMI, 10; 4.5 year head circumference, 9; MABC-2 total score, 17. *P <0.005.

5.4 Discussion

Body size at birth was different among children with different risk factors. At 2 and 4.5 years, children born small and large stayed in the lower and upper ranges, respectively. Further, children born small had the smallest gain in head circumference from 2 to 4.5 years, while children born preterm had the smallest gain in weight and height from birth to 2 years.

Further, children who were overweight or obese at 2 years had a very high risk of being overweight or obese at 4.5 years. Height and head circumference at 4.5 years was positively related with motor performance.

5.4.1 Neonatal factors and growth

Our results are similar to those reported by other studies investigating growth in children born SGA, AGA and LGA (Hediger, Overpeck, McGlynn et al., 1999). Further, children born to diabetic mothers were born large and remained larger than children born to non-diabetic mothers when measured at 7 years, even after adjustment for birth weight, maternal BMI status and socio-economic factors (Baptiste-Roberts, Nicholson, Wang et al., 2012). Children born LGA remained heavier than their AGA peers at age 9 to 10 and 23 to 25 years (Renom Espineira, Fernandes-Rosa, Bueno et al., 2011). Moreover, among children born SGA compared to AGA, weight and height Z scores remained in the -1.3 to -2.6 range at all ages (multiple measurements from birth to 4 years) (Bocca-Tjeertes, Reijneveld, Kerstjens et al.,
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and head circumference was smaller at 3 months and 5 years (Bardin, Piuze, & Papageorgiou, 2004).

Body size and growth are usually monitored because they are indicators of health status. Body size in childhood has been linked with health in later life (Thurber, Dobbins, Kirk et al., 2015; Williams & Holmes, 2004). Growth from birth to 2 years was not found to be associated with systolic blood pressure, fasting insulin concentrations and cognitive function (Krishnaveni, Veena, Srinivasan et al., 2015), but greater fat gain from 5 to 9.5 years was associated with greater body fat content and insulin resistance at 13.5 years. The risk of type 2 diabetes in adulthood was associated with low weight gain from birth to 2 years, especially in children born with low birth weight (Eriksson, Osmond, Kajantie et al., 2006), which means that children born small and preterm in our study might be at high risk of developing diabetes in later life. As for head circumference from birth to 2 years and later neurodevelopment, studies have been mixed showing no association with neurodevelopmental problems at 8 years (Wright & Emond, 2015) or negative association with 4-year IQ which no longer remained at 8 years (Gale, O'Callaghan, Bredow et al., 2006).

Therefore, it is important to monitor how children grow and how neonatal risk factors may contribute to prediction of later growth and health. In this study we only reported on the associations between risk factors and body size and growth from birth to 4.5 years, but the association with later metabolic disease in this cohort of children is unknown.

5.4.2 Stability of BMI

This study confirms previous reports that children who are overweight in early childhood are likely to remain overweight later on (Evensen, Wilsgaard, Furberg et al., 2016). More children who were overweight or obese at 2 years were in the normal BMI category by 4.5 years than children who were in the normal BMI category at 2 years and became overweight or obese by 4.5 years. This contrasts with findings of school age children in an Australian cohort when more children became overweight than the reverse between baseline assessment (age 5-10 years) and a follow-up assessment 3 years later (Hesketh, Wake, Waters et al., 2004). Nevertheless, in our study children were 10 times more likely to be overweight or obese at 4.5 years if they were overweight at 2 years, and this finding was similar to that of Australian school age children who were 25 times more likely to be overweight or obese at follow-up if overweight at baseline (Hesketh et al., 2004). In another study, the relative risk of being overweight at 4 years was 4.3 and 3.5 for children overweight at 1 year and 2 years, respectively.
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(Mei, Grummer-Strawn, & Scanlon, 2003). Moreover, tracking of overweight from birth to 8 years has been reported, when change in BMI scores during consecutive one year intervals from birth to 8 years was associated with obesity at 8 years (Willers, Brunekreef, Smit et al., 2012). In addition, rapid growth up to 1 year is often associated with high risk of overweight or obesity in later childhood (Glavin, Roelants, Strand et al., 2014), and very early BMI gain, from term corrected age to 4 months, in children born preterm and low birth weight was associated with higher odds of overweight or obesity at 8 and 18 years (Belfort, Gillman, Buka et al., 2013). However, another study found that the correlation between birth weight and weight at 5 years was poor while correlation between 5-year and 9-year weight was strong (Gardner, Hosking, Metcalf et al., 2009).

We did not have information on growth measurements up to 1 year, and therefore we could not explore associations between timing of body size changes and risk of overweight at 4.5 years. Differences in findings of different studies might be due to different methodologies and chosen outcomes for the analysis of associations between weight gain and the risk of obesity later on. Nevertheless, all of the above findings suggest that the development of overweight begins from birth and continues throughout childhood. Our study confirms that provision of screening and intervention at very young age in New Zealand children might be advised instead of monitoring at school age and beyond.

Interventions to reduce weight usually require a family input and lifestyle changes, and do not always work for all children, although some children might benefit from it (Reinehr, 2013). For example, school based intervention for 9-10-year old children had no effect on BMI in a study that provided education about nutrition, three weekly 30-minute physical activity sessions and reduced energy and fat lunches (Donnelly, Jacobsen, Whatley et al., 1996). At the same time in another study in which intervention included education about television viewing times, BMI decreased post-intervention (Robinson, 1999). However, when a similar approach was undertaken for 4 to 6-year old children and intervention was home based, it had no effect on BMI (Yilmaz, Caylan, & Karacan, 2015). Therefore, individual approaches to intervention may be undertaken in the light of mixed evidence in this area.

Our findings suggest that some infants are likely to resolve to normal weight from infancy to preschool age, but the risk of staying overweight at 4.5 years was high in children who were overweight at 2 years. Effective interventions are required for overweight and obesity in very young children.
5.4.3 Associations between growth parameters, risk factors and motor performance in preschool children

Poorer motor performance had been previously linked to obesity even as early as 4 years of age. However, results of different studies were not consistent in different cohorts of children and for different motor tests. For example, obese 4 to 6-year-old children had lower scores for hopping and obese girls could not jump as far as normal weight peers, but no other motor tasks were associated with obesity (Castetbon & Andreyeva, 2012). In another study, overweight children performed significantly worse than normal weight children in locomotor (running, hopping, skipping and jumping) and object control (catch, kick, overhand throw) tasks (Morano, Colella, & Caroli, 2011). BMI was also negatively correlated with motor coordination in a cross sectional study of 6 to 14 year olds (Lopes, Stodden, Bianchi et al., 2012). The correlation coefficient increased from 6 till 11 years when it was the strongest and then decreased from 11 till 14 years. Further, overweight or obese children performed worse on motor tests than normal weight peers at 8 years, and the gap in motor performance between the two groups increased at a follow-up two years later (10 years) (D'Hondt, Deforche, Gentier et al., 2013).

Contrary to these studies, we found no association with body size at 2 years, and weight and BMI at 4.5 years, and motor scores at 4.5 years. However, we did find a positive association between height and head circumference at 4.5 years and motor scores. In very preterm children, small head circumference was also associated with poor motor performance at 6 to 12 years (Hebestreit, Schrank, Schrod et al., 2003), and in another study 2-year and 8-year head circumference measurements were inversely related to the risk of motor difficulty but not other neurodevelopmental outcomes (Kan, Roberts, Anderson et al., 2008). Hack et al. also found no association between birth or infant head circumference and cognitive and academic performance (Hack, Breslau, Weissman et al., 1991; Lipper, Lee, Gartner et al., 1981).

Our study in a cohort of at risk preschool children did not confirm the commonly reported association between weight or BMI and motor performance. It might be that such associations appear later in life, which is in part supported by our finding of the relation between 4.5-year height and head circumference and 4.5-year score.

5.4.4 Limitations

We used BMI as a measure of overweight and obesity. BMI is the most widely used measure of body composition that does not require extra testing, is easy to calculate, can be easily used
for repeated assessments, and is included in reference data from many populations. However, BMI or other anthropometric indices may not reflect total body fat and lean body mass (Jensen, Mølgaard, Ejlerskov et al., 2015). Other tools to measure body composition, such as whole body air displacement plethysmography or dual-energy-x-ray absorptiometry (Bolanowski & Nilsson, 2001) provide a better assessment of growth and body composition.

Other factors that we did not explore in our study might be associated with body size, growth and motor function. Weight might be associated with sedentary behaviour and overeating. In our study we did not investigate these factors using, for example, activity monitoring devices and food frequency questionnaires. At the same time overeating might be caused by fetal intrauterine environment. For example, in animal models of maternal diabetes, increased appetite and overeating were linked to the fetal programming of the hypothalamus (Plagemann, 2006). Therefore, we can establish an association between different factors but not explore the mechanism because of a complexity of metabolic and environmental interactions.

**5.4.5 Conclusions**

Neonatal risk factors influenced birth, 2 and 4.5-year body size, and growth from birth to 4.5 years, but were not related to motor difficulties at 4.5 years. Children who were overweight at 2 years were ten times more likely to stay overweight at 4.5 years, suggesting that childhood interventions may need to start as early as 2 years.
Chapter 6. Accuracy of caregivers’ recall of hospital admissions: implications for research.

Content of this chapter was published in Acta Paediatrica (Burakevych, McKinlay, Alsweiler, & Harding, 2015).
6.1 Abstract

Aim: To determine the accuracy of caregivers’ recall of hospital admissions in early childhood.

Methods: Prospective cohort study of babies born at risk of neonatal hypoglycaemia at Waikato Hospital, New Zealand, a regional public hospital and sole provider of acute inpatient care to over 100,000 children.

Caregivers’ recall of children’s hospital admissions up to 4.5 years was compared with medical records. Accuracy of recall was related to neonatal and socio-demographic characteristics.

Results: Of 267 children, 179 (67%) visited hospital and 106 (40%) were admitted at least once. The most frequent reasons for admission were for respiratory (29%) and gastrointestinal (18%) problems. Of 106 children admitted to hospital, 27 (25%) caregivers did not recall the admission and only 37 (35%) accurately recalled the number of admissions. The accuracy of recall was lower for gastrointestinal (38%) and surgical (40%) problems, while recall of respiratory (64%) and ear, nose and throat (60%) admissions was more accurate. Low socio-economic status and multiple admissions were associated with less accurate recall of number of admissions.

Conclusions: Caregivers do not accurately report hospital admissions. Questionnaire data about use of hospital facilities should be interpreted cautiously and may not be sufficiently accurate for use in research studies.
6.2 Introduction

The use of and access to health care services, especially hospital facilities, is an important indicator of childhood health and is often used as an outcome in research. It is particularly important for low-income families and those living in rural areas who might have difficulty accessing medical care (Cloutier, Hall, Wakefield et al., 2005; Gadomski, Jenkins, & Nichols, 1998). History of healthcare visits is often collected in research, audits and surveys via extraction from medical records or self-report in questionnaires. Although extracting data from healthcare provider files is considered the most accurate method (Miller, Gaboda, & Davis, 2001; Roberts, Bergstrahl, Schmidt et al., 1996), it is problematic in large research studies because of the time and cost involved (Jordan, Jinks, & Croft, 2006). Medical events of infants and children in younger age groups are often recorded from recall by a caregiver. Therefore, the accuracy of caregivers’ recall is an important factor to consider when choosing study methodology.

Previous studies of caregiver recall have been inconsistent, with some studies showing reasonably accurate recall of a child’s medical history (Pleas & Pless, 1995) and others showing poor recall (Daly, Lindgren, & Giebink, 1994). Furthermore, accuracy of caregiver recall has been both positively (Fendrich, Johnson, Wislar et al., 1999) and negatively (Daly, Lindgren & Giebink, 1994) related to the number of illness episodes.

There are no recent studies on the recall of hospital visits and factors associated with accuracy of recall in preschool children. Therefore, we aimed to assess the agreement between caregivers’ reports of hospital admissions and hospital medical records in a cohort of preschool children born at risk of poor health outcomes and enrolled in a prospective cohort study from birth.

6.3 Methods

This study was part of a larger prospective cohort study of babies born at risk of neonatal hypoglycaemia, the CHYLD Study, which is investigating the impact of neonatal hypoglycaemia on later neurodevelopment. All babies in the cohort were born at Waikato Women’s Hospital, Hamilton, New Zealand, and recruited to one of two studies, BABIES (Harris, Battin, Weston et al., 2010) and Sugar Babies (Harris, Weston, Signal et al., 2013). Eligible babies were born late preterm (32-36 completed weeks’ gestation), small ($\leq 2500$g or $\leq 10^{th}$ percentile), large ($\geq 4500$g or $\geq 90^{th}$ percentile), of diabetic mothers, or with other
conditions potentially increasing the risk of hypoglycaemia. Babies were excluded from these studies if they had congenital or life-threatening disorders, had been previously treated for hypoglycaemia or had other medical conditions that would interfere with the study protocol. Children included in the analysis were born between December 2006 and February 2010.

Follow-up assessment was completed at 4.5 years ± 2 months’ corrected age. Children were examined by the research team according to standardised protocols. Assessment included developmental, vision examination, neurologic status and general health assessment. A questionnaire was also completed by caregivers that included questions on ethnicity, household income, parental education, and hospital admissions (age at admission, reasons for and duration of each admission and name of the hospital). Socio-economic status was assessed using household income and New Zealand Deprivation Index decile (Salmond, Crampton, King et al., 2006), where 1 indicates the least deprived and 10 the most deprived population decile. Details were collected from Waikato District Health Board medical records from birth up to 4.5 years of age, including outpatient and Emergency Department (ED) visits, hospital admissions (admission to inpatient ward of any duration), number of nights in hospital (both inpatient admissions and ED overnight stays), and date and reason for visit or admission. Waikato Hospital services a population of 400,000 in the upper central North Island of New Zealand and is the sole provider of secondary and tertiary acute medical services for children in the region.

For children whose caregivers indicated that there had been hospitalisations outside Waikato District Health Board, medical records were obtained from the hospital indicated.

Data were analysed using JMP Statistical Software, version 10.0.2, SAS Institute Inc., Cary, NC, 2012, and are presented as number (percent) or median (range). Differences between risk groups and associated socio-demographic factors were analysed using Chi-squared test. Agreement between caregivers’ recall and confirmed admissions in hospital records were analysed using kappa coefficients (95% Confidence Interval) and interpreted as described by Landis and Koch (Landis & Koch, 1977). The study was approved by the Northern Y Health and Disability Ethics committee (approval number NTY/10/03/021). Parents provided written consent to the assessment, and also to the study team accessing the medical records of their children.
6.4 Results

Medical records were extracted for 267 children who were assessed at 4.5 years ± 2 months. Over a third (101/267, 38%) were born pre-term and about a third (91/267, 34%) were born to diabetic mothers (Table 6.4). Approximately one half of the cohort were New Zealand European (139, 54%) and a third were Maori (83, 32%). More children (97, 37%) in this cohort lived in high deprivation areas (worst three deciles) when compared to national data.

### Table 6.4 Characteristics of the cohort

<table>
<thead>
<tr>
<th>Characteristic†</th>
<th>Total cohort N=267</th>
<th>≥1 Hospital visit by hospital records</th>
<th>≥ Hospital admission by hospital records</th>
<th>Number of admissions accurately recalled by caregiver</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes N=179</td>
<td>No N=88</td>
<td>Yes N=106</td>
<td>No N=161</td>
</tr>
<tr>
<td>Neonatal risk factors, prioritised IDM</td>
<td>91 (34)</td>
<td>72 (30)</td>
<td>66 (35)</td>
<td>12 (7)</td>
</tr>
<tr>
<td>Pre-term</td>
<td>101 (38)</td>
<td>72 (28)</td>
<td>66 (28)</td>
<td>12 (4)</td>
</tr>
<tr>
<td>Small</td>
<td>37 (14)</td>
<td>27 (14)</td>
<td>64 (34)</td>
<td>10 (6)</td>
</tr>
<tr>
<td>Large</td>
<td>24 (9)</td>
<td>17 (7)</td>
<td>60 (33)</td>
<td>7 (3)</td>
</tr>
<tr>
<td>Other</td>
<td>14 (5)</td>
<td>11 (6)</td>
<td>60 (34)</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Boys</td>
<td>136 (51)</td>
<td>91 (54)</td>
<td>60 (37)</td>
<td>12 (8)</td>
</tr>
<tr>
<td>Ethnicity:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maori</td>
<td>83 (32)</td>
<td>53 (31)</td>
<td>60 (32)</td>
<td>10 (6)</td>
</tr>
<tr>
<td>Other</td>
<td>37 (14)</td>
<td>20 (12)</td>
<td>60 (35)</td>
<td>7 (4)</td>
</tr>
<tr>
<td>New Zealand European</td>
<td>139 (54)</td>
<td>99 (58)</td>
<td>60 (36)</td>
<td>12 (8)</td>
</tr>
<tr>
<td>Household income:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥$70,000</td>
<td>91 (42)</td>
<td>61 (42)</td>
<td>60 (39)</td>
<td>10 (6)</td>
</tr>
<tr>
<td>$40,001 – 70,000</td>
<td>62 (29)</td>
<td>40 (28)</td>
<td>60 (39)</td>
<td>10 (6)</td>
</tr>
<tr>
<td>&lt;$40,001</td>
<td>62 (29)</td>
<td>43 (30)</td>
<td>60 (39)</td>
<td>10 (6)</td>
</tr>
<tr>
<td>NZ Deprivation Index:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Most derived (8-10)</td>
<td>97 (37)</td>
<td>67 (38)</td>
<td>60 (38)</td>
<td>10 (6)</td>
</tr>
<tr>
<td>Less deprived (&lt;8)</td>
<td>168 (63)</td>
<td>111 (62)</td>
<td>65 (40)</td>
<td>10 (6)</td>
</tr>
<tr>
<td>Mother’s education, highest level:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>School</td>
<td>73 (29)</td>
<td>47 (28)</td>
<td>60 (38)</td>
<td>10 (6)</td>
</tr>
<tr>
<td>Tertiary</td>
<td>178 (71)</td>
<td>119 (72)</td>
<td>65 (40)</td>
<td>10 (6)</td>
</tr>
<tr>
<td>Father’s education, highest level:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>School</td>
<td>57 (26)</td>
<td>33 (23)</td>
<td>60 (37)</td>
<td>10 (6)</td>
</tr>
<tr>
<td>Tertiary</td>
<td>166 (74)</td>
<td>111 (72)</td>
<td>60 (37)</td>
<td>10 (6)</td>
</tr>
<tr>
<td>Number of siblings in the household:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1</td>
<td>145 (57)</td>
<td>96 (36)</td>
<td>60 (37)</td>
<td>10 (6)</td>
</tr>
<tr>
<td>2-3</td>
<td>95 (37)</td>
<td>63 (37)</td>
<td>60 (37)</td>
<td>10 (6)</td>
</tr>
<tr>
<td>≥4</td>
<td>17 (7)</td>
<td>12 (7)</td>
<td>60 (37)</td>
<td>10 (6)</td>
</tr>
<tr>
<td>Admission in hospital records:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>161 (60)</td>
<td>73 (41)</td>
<td>80 (47)</td>
<td>10 (6)</td>
</tr>
<tr>
<td>1</td>
<td>58 (22)</td>
<td>58 (32)</td>
<td>60 (37)</td>
<td>10 (6)</td>
</tr>
<tr>
<td>2-3</td>
<td>34 (13)</td>
<td>34 (19)</td>
<td>60 (37)</td>
<td>10 (6)</td>
</tr>
<tr>
<td>≥4</td>
<td>14 (5)</td>
<td>14 (8)</td>
<td>60 (37)</td>
<td>10 (6)</td>
</tr>
</tbody>
</table>

Data are number (percent); IDM, infant of a diabetic mother; †Total number of children with and without hospital admissions differ for each demographic factor due to missing data: ethnicity, 8; household income, 52; deprivation index, 2; mother’s education, 16; number of siblings, 10; *p=0.03; ‡p=0.04 using Chi-squared test comparing children whose caregivers accurately vs. inaccurately recalled the number of admissions.

Two thirds of children (179/267, 67%) had at least one hospital visit and over a third (106/267, 40%) had at least one hospital admission confirmed in hospital records by 4.5 years of age. For children who had at least one admission, the median (interquartile range) number of overnight stays up to 4.5 years was 2 (1; 5). Neonatal and socio-demographic factors were not significantly different between children who had visited the hospital or were admitted and those who had not (Table 6.4).
Of 106 children who had been admitted according to hospital records, caregivers of 27 (27/106, 25%) reported no admissions. Caregivers of children who lived in more deprived areas (deprivation index 8 to 10 vs <8) were less accurate in recall of their children ever being admitted (Table 6.4). The accuracy of caregiver recall for admissions lasting ≥2 nights was not significantly different compared to admissions of only one night (67% of caregivers were accurate vs 42%, P=0.74). Overall, there was a total of 945 visits to the hospital and 208 hospital admissions for the entire cohort (Table 6.4.2). Most hospital admissions were for respiratory (60/208, 29%) and gastrointestinal (GIT) (38/208, 18%) problems, followed by ENT (32/208, 15%) and surgical (20/208, 10%) problems.

### 6.4.1 Number of hospital admissions

Complete questionnaire data were available for 100 of the 106 children who were admitted to hospital. Of these, only 37 (37%) caregivers were accurate in their recall of the number of hospital admissions (Table 6.4), indicating only slight agreement with hospital records (kappa coefficient [95% CI] 0.13[0.02; 0.25]). Caregivers who lived in more deprived areas were less accurate in their recall of number of hospital admissions. Recall was also less accurate with increasing number of hospital admissions. Fifty-six children had one hospital admission confirmed in medical records; caregivers of 25 (45%) of them recalled it accurately. Of 13 children with four or more admissions, only two (15%) caregivers were accurate in their recall. Other socio-demographic factors were not significantly different between children whose caregivers had accurate and inaccurate recall of the number of admissions (Table 6.4). The proportion of caregivers who accurately recalled the number of hospital admissions was similar for admissions that occurred before the age of 2 years and for admissions from 2 to 4.5 years (57% vs 52%, P=0.42), and for admissions that lasted one night and ≥2 nights (50% vs 53%, P=0.55).

### 6.4.2 Reasons for hospital admissions

Since the number of admissions was often inaccurately recalled, it was difficult to match the reported reason for admission with the relevant hospital record. We therefore assessed recall of reason for admission in two ways. First, we compared caregivers’ recall of the reason for admission with the hospital record for those children with accurate report of the number of admissions (n=37) and for all other children with only one hospital admission (n=31) (Table 6.4.2). The accuracy of caregivers’ recall of the reasons for hospital admission ranged from 82% for gastrointestinal problems to 96% for surgical admissions (Table 6.4.2).
Second, we included all children in the analysis, and determined how accurately caregivers reported that their children had been admitted for common health problems at least once. Gastrointestinal (11/29, 38%; kappa 0.40 [0.21; 0.58]) and surgical (6/15, 40%; kappa 0.48 [0.23; 0.73]) problems were less likely to be reported than respiratory (21/33, 64%; kappa 0.53 [0.38; 0.67]) and ENT (15/25, 60%; kappa 0.58 [0.40; 0.76]) problems (Table 6.4.2).

Table 6.4.2 Reasons for hospital admissions

<table>
<thead>
<tr>
<th>Reason</th>
<th>Hospital admissions N=208</th>
<th>Children whose caregiver accurately reported reasons for admissions(^1) (total N of admissions = 87)</th>
<th>Confirmed by hospital records N=100</th>
<th>Recalled by a caregiver N=100</th>
<th>Agreement, kappa coefficient (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory</td>
<td>60 (29)</td>
<td>60 (88)</td>
<td>33 (33)</td>
<td>21 (21)</td>
<td>0.53 (0.38; 0.67)</td>
</tr>
<tr>
<td>GIT, feeding problems</td>
<td>38 (18)</td>
<td>56 (82)</td>
<td>29 (29)</td>
<td>11 (11)</td>
<td>0.40 (0.21; 0.58)</td>
</tr>
<tr>
<td>ENT</td>
<td>32 (15)</td>
<td>59 (87)</td>
<td>23 (23)</td>
<td>15 (15)</td>
<td>0.58 (0.40; 0.76)</td>
</tr>
<tr>
<td>Surgical</td>
<td>20 (10)</td>
<td>65 (96)</td>
<td>13 (15)</td>
<td>6 (6)</td>
<td>0.48 (0.23; 0.73)</td>
</tr>
<tr>
<td>Other</td>
<td>58 (28)</td>
<td>50 (74)</td>
<td>38 (38)</td>
<td>26 (26)</td>
<td>0.38 (0.23; 0.54)</td>
</tr>
</tbody>
</table>

\(^1\)For children whose caregivers accurately reported number of hospital admissions or who had only one admission. \(^2\)Of 106 children who had \(\geq 1\) admission confirmed by hospital record.

6.5 Discussion

We aimed to determine if caregivers accurately recalled hospital admissions of their children from primary neonatal discharge up to 4.5 years when using a questionnaire, and the factors that influence this recall.

Of concern, we found that a quarter of caregivers did not recall their children ever being admitted to hospital and only a third accurately recalled the number of admissions, with lower socio-economic status and higher number of admissions associated with poorer recall. Similar results were shown by D’Souza-Vazirani et al. (D’Souza-Vazirani, Minkovitz, & Strobino, 2005) who reported that mothers with higher income reported recent admissions more accurately than those with lower incomes. This suggests that researchers should carefully consider the method of collecting data about use of hospital facilities, especially in low socio-economic settings.

Although accuracy of recall was positively related to socio-economic status, we did not find any association with parental education level. In other studies, the relationship between accuracy of recall and parental education has not been consistent. For example, Pleas et al. found no relation between recall accuracy and education of parents (Pleas & Pless, 1995). Conversely, Hoekelman et al. found that maternal education was correlated with accuracy of recall of immunisations, but not the recall of clinic visits (Hoekelman, Kelly, & Zimmer, 1976).
Recall of hospital admissions

It is possible that low socio-economic status might be associated with poorer recall because of its association with poorer health and higher admission rates. However, we did not find evidence that this applied in our cohort, as there were no differences in socio-economic status of children who had at least one admission and those who did not. We also found no association between the number of children in the household and the accuracy of recall. Reports in the literature have variously shown that having other children in the family was associated with poor recall (Daly, Lindgren, Giebnik et al., 1994), improved recall (D'Souza-Vazirani, Minkovitz, & Strobino, 2005), or no effect on recall (Hoekelman, Kelly, & Zimmer, 1976; Pleas & Pless, 1995).

We also aimed to investigate if caregivers could accurately identify reasons for being admitted. Most hospital admissions were for respiratory, GIT, surgical and ENT problems, which is consistent with other reports (Cameron, Shibl, McClure et al., 2014; Witt, Weiss, & Elixhauser, 2012). For the subgroup of children where the reason for admission could be matched with caregivers’ report, reasons for admissions were reported reasonably accurately. However, this might be because children who had no admissions for a specific reason and no report of that problem by a caregiver would be counted as agreement for this analysis. Thus, surgical problems, which contributed to the least number of admissions (20/208, 10%), were associated with the highest recall rate (96%). However, when considering any admission for a particular problem up to 4.5 years, only 38% and 40% of caregivers whose children had been admitted for GIT and surgical reasons recalled this, although recall was better for respiratory (64%) and ENT (60%) admissions. Other studies have also shown that accuracy of parental recall depends on the reason for the visit, with respiratory problems being reported more accurately than ENT problems in a Canadian study of 1 to 13 year olds (Pleas & Pless, 1995).

We analysed only hospital admissions, which we expected would be more likely to be remembered, as they would be perceived as serious events. Others have reported that hospitalisations were better recalled than ED visits when mothers were interviewed by telephone at 2 to 4 and 30 to 33 months after the birth of their children (D'Souza-Vazirani, Minkovitz, & Strobino, 2005). However, in our study, caregivers of only 6 of 15 children who were admitted for surgical problems, which are most likely to be perceived as serious event, accurately reported this. Similarly, poor agreement has been reported when comparing maternal reports and medical records for other relatively severe conditions such as acute asthma (Miller, Gaboda, & Davis, 2001).
One possible factor that could influence our results was that the recall period was relatively long. Participants enrolled in a study with relatively short intervals between recall questionnaires or interviews may be more likely to pay attention and remember hospital visits, as they expect to be approached by the research team. Some previous studies used relatively short recall periods, but a longer time interval is advised for collection of hospital admission data as admissions are relatively rare events (Kjellsson, Clarke, & Gerdtham, 2014). Although the CHYLD Study team examined children at 2 years, and some caregivers would expect to be contacted later with similar questions about hospitalisation details, it is highly unlikely to have had an effect on the recall results due to the long time interval between assessments and the fact that recall was not the main focus of the study. Indeed, we found no differences in accuracy of recall of early hospital visits (before 2 years) and those that occurred more recently (2-4.5 years). However, others have reported that recall is poor even over short time periods. Low-income mothers could not accurately identify the reason for seeing a doctor when they were interviewed three times at 4 month intervals (Murray, El-Mohandes, El-Khorazaty et al., 2007). In addition, Grover et al. found that parents could not accurately identify the reasons for an ED visit, even within a few minutes after discharge (Grover, Berkowitz, & Lewis, 1994). Asthma and otitis media were recalled more accurately than GIT or skin conditions. Many parents could not recall the diagnosis, but stated the complaints children presented to ED with.

A potential limitation of our study is that we may have missed some hospitalisations if children were admitted outside the Waikato Hospital area or to private hospitals and parents did not recall that admission. However, the New Zealand health care system is mainly public and few private hospitals admit children, especially in the Waikato area. Moreover, we compared parental recall with known admissions and reasons, so the under-reporting that we found is likely to be a minimum estimate, with any missed admissions only increasing the extent of parental under-report.

Our data show that hospital visits and admissions are very common in children born at risk of neonatal hypoglycaemia. Previous reports from both Australia (Cameron, Shibl, McClure et al., 2014) and New Zealand (Growing up in New Zealand. Now we are two) found that up to 20% of children were admitted to hospital during the preschool years. Thus, there was a two-fold greater rate of admission in our cohort. This may relate to the long-term health effects of risk factors for neonatal hypoglycaemia, such as prematurity and fetal growth restriction, and also to socio-demographic factors. Indeed, there was greater social deprivation in this cohort compared with the general New Zealand population.
Recall of hospital admissions

Researchers should carefully choose methods for data collection on use of hospital facilities. This includes recall period, administration approach and data source. A suitable approach will depend on the cohort characteristics, including literacy level, but also study research questions. Recall bias may be lower when reporting events in an interview than in a self-administered format, but sensitive information may be more accurately collected via a self-administered questionnaire (Bowling, 2005). Diaries completed by parents can provide accurate information on visits to medical specialists, but are most useful in a cohort with high literacy levels (Bruijnzeels, Van Der Wouden, Foets et al., 1998). Therefore, if a study requires accurate data on health care utilisation, medical records are likely to provide the most complete information.

6.6 Conclusions

Caregivers often do not accurately recall details of hospital admission of their pre-school children. Data collected on use of hospital facilities obtained from caregiver questionnaires should be interpreted cautiously, especially in low socio-economic environments and when use of hospital facilities is high. For accurate assessment of hospital admissions, researchers should consult medical records.

Content of this chapter was published in the Journal of Paediatrics and Child Health (Burakevych, McKinlay, Alsweiler, Woulde, & Harding, 2016). We would like to acknowledge Ministry of Health of New Zealand for providing the Before School Check data.
7.1 Abstract

Aim: The study aim was to compare detection of and referral for developmental and emotional problems in a school readiness screening programme (New Zealand Before School Check, B4SC) with that of a comprehensive neurodevelopmental assessment.

Methods: This is a prospective cohort study of children (n=274) born at risk of neonatal hypoglycaemia and recruited to a follow-up study of neurodevelopmental outcomes at 4.5 years (Children with Hypoglycaemia and their later development (CHYLD) Study). Children identified as of significant concern for developmental and emotional problems, and referrals made, were compared in the B4SC and CHYLD Study. Scores of the parent-completed Strengths and Difficulties Questionnaire used in both assessments were compared.

Results: Of the 274 children who underwent clinical neurodevelopmental assessment at a mean (standard deviation) age of 53.3 (1.8) months, 237 had the B4SC developmental and emotional health screening. Of these, 44 (19%) children met B4SC referral criteria, and 15 (6%) were referred, but only 21 (9%) children met CHYLD referral criteria, and 10 (4%) were referred. Twelve children (5%) met both the B4SC and CHYLD referral criteria, and two were referred by both. When assessed twice, 39 (17%) children changed parent-completed Strengths and Difficulties Questionnaire category. Children who did not have B4SC screening had higher mean total difficulties score (10.5 vs 8.2, P=0.009) and were more likely to have cognitive delay than those who were screened (19% vs 8%, P=0.04).

Conclusions: More children met referral criteria for the B4SC screening programme than for a more comprehensive neurodevelopmental assessment. Children who did not have screening had higher incidence of cognitive and behaviour problems than those who did.
**What is already known on this topic**

- Parent questionnaires are often used to screen young children for developmental and emotional health problems as part of routine child health surveillance.
- Screening is intended to identify children who may benefit from further assessment and intervention where appropriate.
- Clinical neurodevelopmental tests are costly and time-consuming but may detect different problems from those identified by screening questionnaires.

**What this study adds**

- Screening for developmental and emotional problems using questionnaires results in a different referral pattern compared to clinical neurodevelopmental assessment, and referral criteria were inconsistently applied.
- Repeated screening using the same parental questionnaire in different settings and for different purposes may give different screening outcomes.
- Children who were not screened for developmental and emotional health had a higher incidence of cognitive delay and behavioural problems than children who were screened.
7.2 Introduction

Developmental and emotional health problems are common in young children, with an incidence of up to 18% in the general population (Boyle, Boulet, Schieve et al., 2011; Egger & Angold, 2006; Holtz, Fox, & Meurer, 2014), and may lead to social and academic difficulties in later childhood and beyond (Canino, Shrout, Rubio-Stipec et al., 2004; Caspi, Moffitt, Newman et al., 1996). Early intervention in children with developmental and emotional problems has been shown to improve outcomes (Campbell, Pungello, Burchinal et al., 2012; Manning, Homel, & Smith, 2010). However, these problems are difficult to detect during regular health check visits. Low sensitivity and specificity have been reported when identifying these problems based solely on clinical judgement (Sheldrick, Merchant, & Perrin, 2011). As a result, children are often only identified as having a difficulty after they enter school, when they have missed the opportunity for early intervention (Manning, homel, & Smith, 2010). Therefore, many countries have implemented screening for developmental and emotional problems as part of routine child health surveillance to enable early detection and referral to child development services (Alexander, Brijnath, & Mazza, 2013; Bradley, Jadaa, Brody et al., 2003; Dishion, Shaw, Connell et al., 2008; Hedley, Thompson, Morris Matthews et al., 2012; Webster-Stratton, 1998).

While the value of parent evaluation of children’s developmental and emotional status remains controversial (Chung, Liu, Chang et al., 2011; Dixon, Badawi, French et al., 2009; Wake, Gerner, & Gallagher, 2005), most screening programmes use brief parental questionnaires to identify children with problems. Clinical assessment by a psychologist is usually not included because of cost and time constraints. However, an assessment using cognitive tests and a multidisciplinary clinical approach would be expected to provide a more comprehensive understanding of a child’s abilities and problems (Lichtenberger, 2005).

The Before School Check (B4SC) is a school readiness screening programme available for all 4-year-olds in New Zealand. It includes screening for developmental and emotional health problems using questionnaires completed by parents and preschool teachers (B4 School Check, Ministry of Health NZ), and results are used to initiate referral for additional assessment and intervention where required.

The aims of this study were threefold: first, to compare the frequency of identification of developmental and emotional problems and of referrals made as a result of parent reports obtained for the B4SC with those as a result of a comprehensive neurodevelopmental
Preschool screening

assessment obtained by trained examiners, second, to determine whether parent-reported behavioural assessments give similar results when administered in different environments and for different purposes (screening vs research) and, third, to compare the developmental characteristics of children who did and did not participate in B4SC screening.

7.3 Methods

7.3.1 Design
This study was part of a larger prospective cohort study of babies born at risk of neonatal hypoglycaemia, the Children with hypoglycaemia and their Later Development (CHYLD) Study (McKinlay, Alsweiler, Ansell et al., 2015). Children were enrolled at birth (2006-2010) to either the BABIES (Harris, Battin, Weston et al., 2010) or Sugar Babies (Harris, Weston, Signal et al., 2013) studies at Waikato Women’s Hospital, Hamilton, New Zealand. Babies were born with one or more risk factors for neonatal hypoglycaemia: diabetic mother, late preterm (32 to 36 completed weeks’ gestation), small (<2500g or <10th centile), large (>4500g or >90th centile) or other risk (feeding difficulties or respiratory distress). From 614 babies recruited to neonatal studies, 604 were eligible for 4.5-year follow-up. A cohort of 274 children born between 2006 and 2010 and assessed at 4.5 years in the CHYLD Study before August 2014 is reported here.

Families were invited to participate in this follow-up study when the child was 4.5 years’ corrected age. Children underwent a detailed assessment of neurodevelopment, vision, and general health status. Data were collected by questionnaire on household demographics, including income, education and number of children. New Zealand deprivation index, based on the place of residence, was used as a measure of socio-economic status, where decile one is the least deprived and ten is the most deprived (Salmond, Crampton, King et al., 2006).

The study was approved by the Northern Y Health and Disability Ethics Committee (reference number NTY/10/03/021). Parents provided written consent for the assessment and to access the B4SC information.

7.3.2 Neurodevelopmental assessment
Neurodevelopmental assessment for the CHYLD Study was undertaken by trained examiners who were blinded to perinatal history. Each assessment was videoed to standardise assessment administration and scoring. Neurodevelopmental tests included the Wechsler Preschool and
Primary Scale of Intelligence, third edition (WPPSI-III) (Lichtenberger, 2005); Beery-Buktenica Developmental Test of Visual Motor Integration, sixth Edition; Phelps Kindergarten Readiness Scale (Items 6-8); Strengths and Difficulties Questionnaire (SDQ) for 4 to 10-year-olds; Child Behaviour Checklist for ages 1.5-5 years; Social Communication Questionnaire; and tests of executive function. Parents completed paper-pencil questionnaires at the time of assessment or took it home for completion and posted them back.

Children who had WPPSI full Scale IQ (FSIQ) composite score or two or more subset scores ≤79 or who did not complete the neurodevelopmental assessment because of behavioural problems, or when an examiner or a parent had significant concerns about the child’s development or social-emotional status, were considered ‘of concern’. For these children, results of all assessments (WPPSI, Beery, Phelps, SDQ, Child Behaviour Checklist and Social Communication Questionnaire) and video recording of WPPSI assessment were reviewed by a developmental psychologist who made a clinical judgement whether the child met clinical criteria for referral. Parents were informed about the need for referral, and referral was made when they agreed to it. Children were not excluded from the analysis if they had vision, neurological or other deficits identified during the neurodevelopmental assessments.

### 7.3.3 Preschool screening assessment

All children in New Zealand are encouraged to have a screening assessment of school readiness after their fourth birthday, the B4SC (B4 School Check, Ministry of Health NZ). Development and emotional health are assessed using the Parental Evaluation of Developmental Status (PEDS) questionnaire and SDQ completed by parents (SDQ-P) and preschool teachers (SDQ-T). We accessed PEDS and SDQ scores from the B4SC national information system using the National Health Index number assigned to each child at birth.

PEDS assigns children to pathways (A, B, C, D, E) according to parental concerns about cognitive development, language, motor skills, emotional health and self-help (Glascoe, 2003). Reported sensitivity is 86%, and specificity is 83% to predict any developmental and emotional health problems (Glascoe, Marks, Poon, Macias (PEDS training).

SDQ is a behavioural screening questionnaire that has 25 questions divided into five subscales (Goodman, 2001). Four of the subscales, emotional symptoms, conduct problems, hyperactivity and peer problems, are combined to give a total difficulties score. Children are classified as ‘normal’, ‘borderline’ and ‘abnormal’ based on the total SDQ score. The fifth subscale, the strengths of a child, is not used in the B4SC referral process. SDQ completed by
multiple informants was reported to predict disorders with a sensitivity of 63.3% and a specificity of 94.6% in a community sample of 5- to 15-year-olds (Goodman, Ford, Simmons et al., 2000). For the subgroup of 5- to 10-year-old children, SDQ-P predicted problems with sensitivity of 30%, and this figure increased to 62% when SDQ-T scores were added. Similar findings were reported for 3-year-olds when SDQ-P abnormal cut-offs predicted problems with 30% sensitivity and 96% specificity (Ezpeleta, Granero, La Osa et al., 2013). Test-retest reliability within 4- to 6-months assessments was 0.62 (Goodman, 2001).

The B4SC referral criteria are an abnormal score on SDQ-P (≥17) or SDQ-T (≥16) or PEDS pathway A (two or more significant predictive concerns) or B (one significant predictive concern), and these children are classified ‘of significant concern’. Children who do not meet referral criteria but have borderline SDQ-P (14-16) or SDQ-T (12-15) scores or are in PEDS pathway C (non-significant concerns) or D (difficulties communicating) are classified as ‘of some concern’.

7.3.4 Statistical analysis
Analyses were performed using JMP Software, version 11.2.0 (SAS Institute Inc., Cary, NC, 2013). SDQ-P scores were compared from the B4SC and CHYLD assessment and between first and second assessments, using paired t-tests. Agreement between the first and second assessments was compared by change in clinical category (chi-square test) and by kappa agreement coefficient (Landis & Koch, 1977). Referral outcomes of the B4SC and CHYLD assessment were compared using χ²-tests and analysis of variance. Data are presented as number (percent), mean (standard deviation (SD)), median (interquartile range) and mean difference (95% confidence interval).

7.4 Results
For the 274 children included in the analysis mean (SD) age at assessment was 53.3 (1.8) months. Of these, 237 children underwent B4SC screening at 49.8 (2.8) months. The subgroup of included children was not different from the rest of the study children eligible for the 4.5-year follow-up in ethnicity and neonatal risk factors (data not shown) but lived in less deprived areas (NZ DEP 6 (4; 9) vs 7 (5; 9) for the rest of study children).

Half of the cohort were boys, and one-third were Māori (Table 7.4). The majority of households had two children. Over two-thirds of mothers had attended a tertiary education institution.
### Table 7.4 Characteristics of the cohort

<table>
<thead>
<tr>
<th></th>
<th>Cohort†</th>
<th>Had B4SC screening</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=274</td>
<td>Yes N=237</td>
</tr>
<tr>
<td>Boys</td>
<td>138 (50)</td>
<td>118 (50)</td>
</tr>
<tr>
<td>Ethnicity:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>New Zealand European</td>
<td>144 (54)</td>
<td>126 (55)</td>
</tr>
<tr>
<td>Māori</td>
<td>86 (32)</td>
<td>72 (31)</td>
</tr>
<tr>
<td>Other</td>
<td>36 (14)</td>
<td>32 (14)</td>
</tr>
<tr>
<td>Neonatal risk factor‡:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-term</td>
<td>124 (45)</td>
<td>109 (46)</td>
</tr>
<tr>
<td>IDM</td>
<td>91 (33)</td>
<td>82 (35)</td>
</tr>
<tr>
<td>Small</td>
<td>84 (31)</td>
<td>68 (29)</td>
</tr>
<tr>
<td>Large</td>
<td>56 (20)</td>
<td>55 (23)</td>
</tr>
<tr>
<td>Other</td>
<td>13 (5)</td>
<td>9 (4)</td>
</tr>
<tr>
<td>Gestational age, weeks</td>
<td>37 (36; 39)</td>
<td>37 (36; 39)</td>
</tr>
<tr>
<td>Number of siblings:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>38 (14)</td>
<td>32 (14)</td>
</tr>
<tr>
<td>1</td>
<td>107 (41)</td>
<td>95 (42)</td>
</tr>
<tr>
<td>2</td>
<td>76 (29)</td>
<td>65 (29)</td>
</tr>
<tr>
<td>≥3</td>
<td>43 (16)</td>
<td>36 (16)</td>
</tr>
<tr>
<td>Mother’s education' highest level:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>School</td>
<td>75 (29)</td>
<td>66 (29)</td>
</tr>
<tr>
<td>Tertiary</td>
<td>187 (71)</td>
<td>161 (71)</td>
</tr>
<tr>
<td>Household income:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ $30,000</td>
<td>36 (16)</td>
<td>30 (16)</td>
</tr>
<tr>
<td>$30,001 – 70,000</td>
<td>80 (36)</td>
<td>67 (35)</td>
</tr>
<tr>
<td>≥ $70,001</td>
<td>104 (47)</td>
<td>95 (49)</td>
</tr>
<tr>
<td>New Zealand deprivation index</td>
<td>6 (4; 9)</td>
<td>6 (4; 9)</td>
</tr>
</tbody>
</table>

† Characteristics of children who did and did not have the B4SC are not significantly different. Data missing for some variables: ethnicity, 8; number of siblings, 10; mother’s education, 12; household income, 54; deprivation index, 1. ‡ Risk factors not mutually exclusive. Data are number (percent) or median (interquartile range). B4SC, Before School Check; IDM, infant of a diabetic mother.

### 7.4.1 Preschool screening versus clinical neurodevelopmental assessment

At the B4SC 44/237 (19%) children were rated as of significant concern, of whom 15 (34%) were referred (Figure 7.4.1). Six children not meeting criteria were also referred (Figure 7.4.1). PEDS identified more children of parental concern than SDQ, but more were referred because of SDQ results (Table 7.4.1). In the CHYLD Study, 21/237 children (9%) were of significant concern after review of all assessments by psychologist, and 10/21 (48%) of these children were referred (Figure 7.4.1). Twelve (5%) children met both the B4SC and CHYLD Study referral criteria, two of whom were referred after both assessments. Five of 29 children who met the B4SC criteria and were not referred met CHYLD referral criteria and were all referred after that assessment. Similarly, of 11 children that met CHYLD referral criteria and were not referred, five met the B4SC referral criteria, and two of them were referred by the B4SC programme (Figure 7.4.1).
Figure 7.4.1 B4SC and CHYLD Study referrals

Table 7.4.1 The B4SC outcome categories and referrals.

<table>
<thead>
<tr>
<th>SDQ-P</th>
<th>SDQ-T</th>
<th>SDQ: P or T†</th>
<th>PEDS</th>
<th>Any test‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=234</td>
<td>N=152</td>
<td>N=237</td>
<td>Referred N=14</td>
</tr>
<tr>
<td>No concern</td>
<td>214 (91)</td>
<td>146 (96)</td>
<td>213 (90)</td>
<td>4 (29)</td>
</tr>
<tr>
<td>Of some concern</td>
<td>3 (2)</td>
<td>2 (1)</td>
<td>9 (4)</td>
<td>2 (14)</td>
</tr>
<tr>
<td>Of significant concern</td>
<td>13 (6)</td>
<td>3 (2)</td>
<td>15 (6)</td>
<td>8 (57)</td>
</tr>
</tbody>
</table>

†Categorised by the worst score category and referral outcome of all tests. Data are number (percent). P, parent version; PEDS, Parental Evaluation of Developmental Status; SDQ, the Strengths and Difficulties Questionnaire; T, teacher version.

7.4.2 Screening outcomes using SDQ-P in different settings

The mean (SD) SDQ-P total difficulties score was 6.5 (4.7) at the B4SC and 8.2 (4.7) in the CHYLD Study, with a mean difference (95% confidence interval) of 1.7 (1.2, 2.3, P=0.0001). The median (interquartile range) interval between the B4SC and CHYLD SDQ-P assessments was 111 (43; 149) days, and 206 (89%) children completed the B4SC before the CHYLD Study assessment. Mean (SD) total difficulties score was 6.7 (4.7) at the first assessment and 8.0 (4.8) at the second assessment, with a mean difference (95% confidence interval) of 1.3 (0.7, 1.9; P=0.0001) and fair overall agreement between assessments (kappa 0.26). More children had borderline scores at the second than the first assessment. Almost a fifth of the cohort changed...
category between assessments, but the interval between assessments did not appear to affect this (Table 7.4.2).

Table 7.4.2 SDQ-P category outcomes for first and second assessments and for short and long time intervals between assessments.

<table>
<thead>
<tr>
<th>Assessment order</th>
<th>First assessment</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Abnormal</td>
<td>Borderline</td>
<td>Normal</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>Abnormal</td>
<td>4 (2)</td>
<td>1 (0)</td>
<td>7 (3)</td>
<td>12 (5)</td>
<td></td>
</tr>
<tr>
<td>Borderline</td>
<td>5 (2)</td>
<td>2 (1)</td>
<td>18 (8)</td>
<td>25 (11)</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>4 (2)</td>
<td>4 (2)</td>
<td>189 (81)</td>
<td>197 (84)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>13 (6)</td>
<td>7 (3)</td>
<td>214 (91)</td>
<td>234 (100)</td>
<td></td>
</tr>
</tbody>
</table>

Agreement between assessments 0.26 (0.12; 0.39)

<table>
<thead>
<tr>
<th>Time between assessments</th>
<th>&lt;4 months N=123</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First</td>
<td>Second</td>
<td>First</td>
<td>Second</td>
<td></td>
</tr>
<tr>
<td>Abnormal</td>
<td>6 (5)</td>
<td>8 (7)</td>
<td>7 (6)</td>
<td>4 (4)</td>
<td></td>
</tr>
<tr>
<td>Borderline</td>
<td>5 (4)</td>
<td>8 (7)</td>
<td>2 (2)</td>
<td>17 (15)</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>112 (91)</td>
<td>107 (87)</td>
<td>102 (92)</td>
<td>90 (81)</td>
<td></td>
</tr>
</tbody>
</table>

Changed category between assessments 19 (15) 20 (18)

Normal at first but abnormal at second assessment 4 (3) 3 (3)

Agreement between assessments 0.24 (0.02; 0.45) 0.28 (0.10; 0.46)

Data are number (percent) or kappa coefficient (95% confidence interval). *Children changing categories from or to borderline between first and second assessments not included. SDQ-P, the Strengths and Difficulties Questionnaire (parent).

7.4.3 Developmental and emotional health of children who did not have the B4SC

Thirty-seven children (14%) in the CHYLD Study cohort did not have the B4SC. Demographic and neonatal characteristics of these children were not significantly different from those who did have the B4SC (Table 7.4). However, children who did not have the B4SC were twice as likely to have concerning cognitive scores, had significantly lower FSIQ and had higher mean SDQ-P score than children who did have B4SC screening (Table 7.4.3).

Table 7.4.3 CHYLD assessment outcomes and referral status for children who did and did not have B4SC screening.

<table>
<thead>
<tr>
<th>Category</th>
<th>Cohort N=274</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B4SC screening</td>
<td>Yes N=237</td>
<td>No N=37</td>
<td>P</td>
<td></td>
</tr>
<tr>
<td>Mean (SD) SDQ-P score</td>
<td>8.5 (4.9)</td>
<td>8.2 (4.7)</td>
<td>10.5 (5.6)</td>
<td>0.009</td>
<td></td>
</tr>
<tr>
<td>No concern SDQ-P</td>
<td>226 (82)</td>
<td>200 (84)</td>
<td>26 (70)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Of some concern SDQ-P</td>
<td>30 (11)</td>
<td>25 (11)</td>
<td>5 (14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Of significant concern SDQ-P</td>
<td>18 (7)</td>
<td>12 (5)</td>
<td>6 (16)</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td>Low WPPSI scores†</td>
<td>25 (9)</td>
<td>18 (8)</td>
<td>7 (19)</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>WPPSI Full Scale IQ</td>
<td>99 (15)</td>
<td>100 (14)</td>
<td>93 (16)</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>Referred</td>
<td>11 (4)</td>
<td>10 (4)</td>
<td>1 (3)</td>
<td>0.6</td>
<td></td>
</tr>
</tbody>
</table>

Data are mean (SD) or number (percent). B4SC, Before School Check; CHYLD, Children with Hypoglycaemia and their Later Development; SD, standard deviation; SDQ-P, the Strengths and Difficulties Questionnaire (parent); WPPSI, Wechsler Preschool and Primary Scale of Intelligence.
7.5 Discussion

This study compared detection of and referral for developmental and emotional problems in the New Zealand preschool screening programme with that of a comprehensive neurodevelopmental assessment. More children were identified as of significant concern in the B4SC, based on parent-completed questionnaires, than in the CHYLD neurodevelopmental assessment. However, 14% of our cohort did not have the B4SC, and these children had higher incidence of cognitive delay and developmental and emotional problems than children who did have B4SC screening. Furthermore, our findings show that using SDQ-P as a single assessment screening tool can lead to different outcomes when completed in different settings and for different purposes.

7.5.1 Preschool screening tests vs clinical neurodevelopmental assessment

In the B4SC, almost one-fifth of children were identified as being of significant concern, thus meeting criteria for referral for additional assessment. In contrast, in the CHYLD neurodevelopmental assessment, only 9% of children were considered of significant concern.

Parent-completed questionnaires identified around 15-20% of concerning children in other screening programmes; referral rates ranged from less than a third (Talmi, Bunik, Asherin et al., 2014) to over half (Guevara, Gerdes, Localio et al., 2013) of these children. Similar to our results, not all children identified as concerning by a questionnaire have a cognitive problem when tested using examiner-administered cognitive tests (Ek, Holmberg, De Geer et al., 2004). This is appropriate, as screening programmes are designed to identify children with possible health problems who may benefit from further assessment, some of whom will then be found not to have a significant difficulty. Parental questionnaires may also over-identify children with problems, as parents may not understand what normal development is for age (Cox, Huntington, Saada et al., 2010).

Many children who met criteria for referral were not referred: 29 (66%) in the B4SC and 11 (52%) in CHYLD. These non-referral rates are similar to that previously reported for the B4SC in a single region of New Zealand, where 129 of 199 children (65%) who met referral criteria were not actually referred (Hedley, Thompson, Morris Matthews et al., 2012). In the CHYLD Study, some children were not referred because their low WPPSI scores were judged to be due to limited English language rather than cognitive delay. Conversely, some children who had low language scores were referred at parental request. The B4SC expects to refer all children in PEDS pathway A and rate of referral for other pathways to be lower. Discussion with parents
regarding the need for referral is included in the B4SC screening, and this can help clarify additional concerns that may reflect inappropriate expectations of some parents. We have no information about why some children who met B4SC criteria in our cohort were not referred, but of 199 children who met the B4SC referral criteria in one region of New Zealand in 2010-2011, 57 (29%) were judged by clinicians as not in need of a referral, 36 (18%) were already under care and parents of another 36 (18%) children declined referral (Hedley, Thompson, Morris Matthews et al., 2012). An internal review of the B4SC also reported in 2014 that there was wide variation in referral processes and inconsistent recording of examiners’ decisions about referrals (Litmus, 2013. The well child / tamariki ora programme quality reviews. Ministry of Health NZ).

Our results show that using different tools (clinical assessment vs. parent-completed questionnaire) that test different domains result in different referral outcomes for the same group of children (Mackrides & Ryherd, 2011). This is consistent with other studies that have shown that implementation of screening programmes is challenging and that children who fail screening have variable referral outcomes (King, Tandon, Macias et al., 2010). This may be due to many factors such as parental view of the need for services and availability of services that could accept the referral. Therefore, clear referral criteria and pathways are essential to ensure that those identified by screening programmes as having problems do indeed receive the additional assessment and interventions intended.

7.5.2 Screening outcomes using SDQ-P in different settings

Overall, the mean total difficulties score in our cohort was similar to those obtained in other studies (SDQ norms). However, scores were higher at the second assessment, which in most cases was the CHYLD Study assessment. Importantly, the agreement between first and second assessment was only fair, and outcome category differed in 39 (17%) children, independent of the time between assessments.

Such differences in outcome categories might be due to changes in a child’s behaviour over time or changes in parental perception. For example, it is possible that parents may be more critical in their evaluation of a child’s behaviour or have accepted the presence of a problem when completing the SDQ a second time (Angold & Costello, 1995).

The change in a category between assessments could also be due to the change in the setting where the SDQ was completed. Almost 90% of first assessments were part of the B4SC, which included examination of several other aspects of health such as hearing and vision. CHYLD
assessments included an in-depth assessment of neurodevelopment in a home-like setting, which may give the impression to parents that their answers had greater value.

The same screening tools are often used to detect the need for and then measure the effect of interventions. One evaluation of children referred to mental health services showed a decrease of 3.2 SDQ points at 6-month follow-up (Mathai, Anderson, & Bourne, 2003). In a New Zealand evaluation of a 4- to 6-week mental health camp intervention, SDQ scores decreased by 2.9 points in the high-risk population, and the number of children categorised as abnormal decreased by 13%, but several children previously categorised as normal changed category to borderline or abnormal (Gibbs, Moor, Frampton et al., 2008). Our findings suggest that changes in SDQ scores of this magnitude may occur with repeated administration of the questionnaire even in the absence of interventions when the setting where assessment is carried out changes. Thus, in children requiring repeated assessment to evaluate the effect of an intervention, use of additional tools such as the SDQ added value score (Ford, Hutchings, Bywater et al., 2009) or follow-up questions on behavioural change since the last visit might be a more appropriate approach than repeated administration of the same SDQ.

7.5.3 Developmental and emotional health of children who did not have preschool screening

Children who did not have developmental and emotional health screening at the B4SC were more likely to have borderline cognitive scores, lower FSIQ and higher SDQ scores than those who were screened. This is of concern, as these children have missed the opportunity to receive support before school entry, the primary purpose of the B4SC programme. Other studies have also reported that children with significant concerns are less likely to attend surveillance programmes (Lever & Moore, 2005). However, although low socio-economic status has been associated with high rate of emotional problems (Holtz, Fox, & Meurer, 2014) and low utilisation of free health services (Søndergaard, Biering-Sørensen, Michelsen et al., 2008), we did not find any difference in socio-economic status between those who did and did not have the B4SC screening.

7.5.4 Study limitations

We did not have information about the reasons for the B4SC referral decisions and could not investigate variation between test scores and referral outcomes in more detail. For example, advice may have been offered on the day of screening instead of referral.
In addition, we did not control for the time interval between SDQ-P administrations, and could not be sure that interventions of which we were not aware between the two assessments may have contributed to the different scores. It is also possible that a different parent or caregiver completed the SDQ on each occasion, although this was likely to have occurred infrequently as the mother accompanied the child for the majority of assessments.

This cohort of children may not be representative of New Zealand general preschool population, since they were all born with risk factors at a single hospital. However, it is a unique cohort of children with diverse neonatal and socio-demographic characteristics and therefore it is particularly important to provide effective screening and interventions in a timely manner to this group of children.

7.6 Conclusions

The B4SC preschool screening assessment identified more children with developmental and emotional health problems than did clinical neurodevelopmental assessment. However, the majority of children meeting referral criteria for either assessment were not actually referred. Repeated administration of the SDQ-P in different settings and for different purposes may not be a reliable approach to evaluate behavioural interventions in preschool children. Finally, children who miss out on preschool screening have higher rates of cognitive delay and behavioural difficulties. Preschool screening programmes may be more effective if every effort is made to screen all children and referral processes are clear and consistently applied. Further investigation of the reasons for failure to attend the B4SC may help improve the effectiveness of this programme.
Chapter 8. Bayley-III motor scale and neurological examination at two years do not predict motor skills at 4.5 years.

Content of this chapter was accepted for publication in Developmental Medicine and Child Neurology (Burakevych, McKinlay, Alsweiler, Woulde, & Harding).
8.1 Abstract

Aims: To determine if Bayley Scales of Infant and Toddler Development, 3rd edition (Bayley-III) motor scores and neurological examination at 2 years’ corrected age predict motor difficulties at 4.5 years’ corrected age.

Methods: Prospective cohort study of children born at risk of neonatal hypoglycaemia in Waikato Hospital, Hamilton, New Zealand. Assessment at 2 years was performed using the Bayley-III motor scale and neurological examination, and at 4.5 years using the Movement Assessment Battery for Children, 2nd edition (MABC-2).

Results: Of 333 children, 8 (2%) had Bayley-III motor scores <85 and 50 (15%) had minor deficits on neurological assessment at 2 years; 89 (27%) scored ≤15th and 54 (16%) ≤5th centile on MABC-2 at 4.5 years. Motor score, fine and gross motor subtest scores and neurological assessments at 2 years were poorly predictive of motor difficulties at 4.5 years, explaining 0 to 7% of variance in MABC-2 scores. A Bayley-III motor score <85 predicted MABC-2 scores ≤15th centile with positive predictive value of 30% and negative predictive value of 74% (7% sensitivity and 94% specificity).

Interpretation: Bayley-III motor scale and neurological exam at 2 years were poorly predictive of motor difficulties at 4.5 years.

What this paper adds:

- 2 year Bayley-III motor scores were poorly predictive of motor difficulties at 4.5 years.
- Minor deficits on neurological examination at 2 years also did not predict motor difficulties at 4.5 years.
8.2 Introduction

Movement and motor competence are essential in every-day tasks and participation in social life (Bart, Jarus, Erez et al., 2011). Motor competence in early childhood is positively associated with the duration and intensity of physical activity in adolescence (Barnett, van Beurden, Morgan et al., 2009). Motor difficulties that cause low participation in physical activities in turn may lead to poor muscle strength, poor bone health and obesity (Boreham & Riddoch, 2001).

Early screening for motor difficulties using assessment tools and routine neurological examination is performed regularly, especially in children born at risk of adverse outcomes (Bolaños, Matute, Ramírez-Dueñas et al., 2015; Goyen & Lui, 2009) to guide the requirement for early supportive interventions. Bayley Scales of Infant and Toddler Development (Bayley) have been widely used to assess neurodevelopment of children from 1 to 42 months of age (Bayley, 2006). The third edition of the Bayley Scales (Bayley-III) includes a motor scale, which is commonly used as a test of motor function in research and clinical settings (Duncan, Bann, Boatman et al., 2015), although it has been reported to underestimate rates of later motor difficulties in a cohort of 96 children born very preterm (Spittle, Spencer-Smith, Eeles et al., 2013). Demands of tasks increase as children grow. Therefore, neurodevelopmental problems might become more evident as children get older (Kaiser, Bai, Gibson et al., 2015), as has been demonstrated for cognitive function (Elgen, Sommerfelt, & Ellertsen, 2003). Moreover, it is unclear if general neurological examination that is often part of assessment protocols in research and clinical settings at 2 years is itself predictive of later motor difficulties.

Therefore, we aimed to determine whether (1) Bayley-III motor score, and fine and gross motor subtest scores and (2) routine neurological examination at 2 years predict motor difficulties at 4.5 years’ corrected age in a large cohort of children born late preterm or at term and at risk of neonatal hypoglycaemia.

8.3 Methods

8.3.1 Participants

Participants were part of the CHYLD Study, a prospective cohort of children born at risk of neonatal hypoglycaemia at Waikato Women’s Hospital, Hamilton, New Zealand between 2006 and 2010 (McKinlay, Alsweiler, Ansell et al., 2015). Infants were recruited to one of two
neonatal studies, BABIES (Harris, Battin, Williams et al., 2009) or Sugar Babies (Harris, Weston, Signal et al., 2013), due to the presence of one or more of the following risk factors for neonatal hypoglycaemia: preterm (32-36 completed weeks’ gestation), small (<2500 g or <10th centile), large (>4500 g or >90th centile), born to diabetic mothers, or other (poor feeding or sepsis). This study was limited to children born at ≥35 weeks’ gestation and seen for follow-up at 2 and 4.5 years.

8.3.2 Neurodevelopmental assessments

Children and their families were invited to take part in a follow-up assessment at 2 years ± 4 weeks’ (McKinlay, Alsweiler, Ansell et al., 2015) and 4.5 years ± 2 months’ corrected age. The assessment consisted of developmental tests administered by a trained examiner, vision assessment by an optometrist, and neurological, motor skills and general health examinations by a trained doctor. All assessors were blinded to neonatal history and glycaemic status of children.

At 2 years ± 4 weeks’ corrected age, children underwent Bayley-III and structured neurological examination, as previously described (McKinlay, Alsweiler, Ansell et al., 2015). Assessment at 4.5 years ± 2 months’ corrected age included neurological examination and standardised tests of cognitive function (Wechsler Preschool and Primary Scale of Intelligence, 3rd edition), visual-motor integration (Beery-Buktenica Developmental Test of Visual-Motor Integration, 6th edition) and motor function (Movement Assessment Battery for Children, 2nd edition [MABC-2]).

Bayley-III includes a motor score, and fine and gross motor subtest scores. The standardised mean motor score is 100 (Standard deviation [SD] 15), with scores <85 indicating mild impairment and <70 indicating moderate or severe impairment. MABC-2 results include a total score and three subtest scores: Manual Dexterity, Aiming and Catching, and Balance. Standardised mean MABC-2 standard score is 10 (SD 3), and recommended MABC-2 cut-offs are ≤15th centile, indicating a child is at risk of motor difficulty, and ≤5th centile, indicating the presence of significant motor difficulty (Henderson, Sugden, & Barnett, 2007).

Neurological examination included assessment of tone, deep tendon reflexes, gait and level of disability in children with cerebral palsy using the Gross Motor Function Classification System (Palisano, Rosenbaum, Bartlett et al., 2008). Abnormal findings were defined as one or more of the following: decreased or increased tone or deep tendon reflexes, ankle clonus more than 5 beats, limited movements of hip abductors and extensors, toe walking (heels off the ground),
asymmetrical gait. All abnormal findings were reviewed by a panel of study paediatricians (JMA, JEH, CJDMcK). Children with abnormal findings but judged by the examiner and the study paediatricians to not have cerebral palsy were classified as having minor neurological abnormalities.

Children were excluded from analysis if they had experienced significant head trauma that could have had an effect on neurodevelopment, or cerebral palsy diagnosed prior to or at the 2 year assessment.

8.3.3 Statistical analysis
Analyses were performed using JMP Software, Version 11.2.0 (SAS Institute Inc., Cary, NC, 2013). Data are presented as mean (standard deviation), median (interquartile range) or number (percent).

Characteristics of children with MABC-2 scores above and below 15th centile were compared using χ² tests and one-way analysis of variance.

Linear regression was used to explore the relationship between Bayley-III motor score and MABC-2 total score, Bayley-III fine motor subtest score and MABC-2 Manual Dexterity score, and Bayley-III gross motor subtest score and MABC-2 Aiming and Catching and Balance scores. Receiver operating characteristic (ROC) curves were used to assess the predictive value of Bayley-III motor scores for MABC-2 scores ≤15th and ≤5th centiles.

Logistic regression was used to assess the relationship between neurological examination at 2 years and MABC-2 scores ≤15th centile at 4.5 years. Agreement between outcomes of 2 and 4.5 year examinations was assessed using kappa agreement statistics.

Because it is possible that the assessment tasks for the Bayley-III motor scale involve cognitive and visual-motor integration skills as well as motor skills at 2 years, we also explored the association between Bayley-III motor scores and measures of cognitive function and visual-motor skills at 4.5 years using linear regression analysis.

8.3.4 Ethics
The study was approved by the Northern Y Health and Disability Ethics Committee (reference number NTY/10/03/021). Caregivers of children gave written informed consent prior to assessment at both 2 and 4.5 years.
8.4 Results

Of 614 children recruited to the neonatal studies, 86 were not eligible for 2 year follow-up, most because they were already older than 2 years when the study started, or because they were born <35 weeks’ gestation (Figure 8.4.1). Compared with children who were eligible for 2 year follow-up, ineligible children had lower birth weight (2485 g (852) vs 3109 (854) g, P< 0.0001 and gestational age (35.1 (2.6) vs 37.8 (1.7) weeks, P< 0.0001) but had similar sex distribution and socio-economic status (data not shown). Socio-demographic and neonatal characteristics of children eligible and not eligible for 4.5 year follow-up were similar. Characteristics of children recruited and not recruited to 2 year follow-up did not differ, while at 4.5 year follow-up children not recruited were from more deprived areas than those recruited (New Zealand Deprivation index (Salmond et al., 2006) decile 7.2 (2.3) vs 6.4 (2.8), P= 0.002).

The median (IQR) WPPSI Full Scale IQ was lower in children who did not complete Bayley-III motor test (IQ 88 [74; 97], n=3) or MABC-2 (IQ 86 [67; 96], n=21) compared to those who did complete motor tests (IQ 98 [89; 109]) at 4.5 years.

Of 355 children who were assessed at 2 and 4.5 years, 352 completed 2 year Bayley-III motor assessments, 339 completed 4.5 year MABC-2, and 336 children completed both assessments (Figure 8.4.1). Two children with cerebral palsy and one child who had experienced significant head trauma were excluded, leaving 333 children for analysis. The mean corrected age at assessments was 24 (1.8) and 53 (1.8) months, respectively. Children with MABC-2 scores above and below the 15th centile at 4.5 years were similar in sex ratio, gestational age, birth weight, and neonatal risk factors for hypoglycaemia (Table 8.4.1).

The mean Bayley-III motor score was 99 (9.1). No child had a Bayley-III motor score < 70 and 8/333 (2%) had a score < 85 at 2 years. The mean MABC-2 total score at 4.5 years was 72 (14.4) and standard score 9 (3). A total of 89/333 (27%) children had MABC-2 total scores ≤15th centile and 54/333 (16%) had total scores ≤5th centile. A mean difference (95% Confidence Interval) of 3.5 (1.3; 5.7; p= 0.002) in Bayley-III motor score was found for children with MABC-2 total scores >15th and ≤15th centile (Table 8.4.1).

Of the 89 children who had MABC-2 total scores ≤15th centile, 62 (70%) had scores ≤15th centile on manual dexterity, 23 (26%) on aiming and catching and 69 (78%) on balance. Almost half of these children (43/89, 48%) had low scores on two subtests and 11/89 (12%) on all three
subtests of MABC-2. Minor neurological abnormalities were identified at neurological examination in 50/331 (15%) children at 2 years and in 99/315 (31%) children at 4.5 years.

Figure 8.4.1 Flow-chart of CHYLD study participants who completed motor assessment at 2 and 4.5 years

Recruited to neonatal studies (BABIES and Sugar Babies)
N=614 (2 babies in both studies)

For 2 year follow-up:
Not eligible N=86
Died N=2
>2 years old N=65
<35 weeks’ gestation N=19
Eligible N=528
Recruited N=405

For 2 and 4.5 year follow-up:
Eligible N=520

For 4.5 year follow-up:
Not eligible N=10
Died N=3
Withdrawn N=7
Eligible N=604

Recruited to 2 and 4.5 year follow-up
N=355

Did not complete
Bayley-III motor N=4
Died N=1
Reluctant to follow instructions N=1
Not administered† N=2

Completed both 2 year
Bayley-III motor
assessment:
N=401

Completed both Bayley-III and MABC-2 motor assessments
N=336

Included in the analysis
N=333

Completed all components of 4.5 year
MABC-2 assessment:
N=456

Excluded from the analysis N=3
Cerebral palsy N=2
Head trauma N=1

Did not complete
MABC-2 N=21
Reluctant to follow instructions N=14
Not administered† N=7

For 4.5 year follow-up:
Not recruited N=127
Declined N=92
Lost contact N=8
Overseas N=27
Recruited N=477

For 2 year follow-up:
Not recruited N=123
Declined N=79
Lost contact N=11
Overseas N=33
Recruited N=405

Did not complete
Bayley-III motor N=4
Died N=1
Reluctant to follow instructions N=1
Not administered† N=2

Completed 2 year
Bayley-III motor assessment:
N=401

Figure 8.4.1 Flow-chart of study participants. MABC-2, Movement Assessment Battery for Children, second edition; Bayley-III, Bayley Scales of Infant and Toddler Development, third edition. †The test was not administered because trained assessors were unable to assess the child in person (only questionnaire data obtained).
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Table 8.4.1 Characteristics of the study cohort

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cohort N=333</th>
<th>MABC-2 ≤ 15th centile at 4.5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes N=89</td>
<td>No N=244</td>
</tr>
<tr>
<td>Boys</td>
<td>171(51)</td>
<td>49(55)</td>
</tr>
<tr>
<td>Ethnicity( § ):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>New Zealand European</td>
<td>165(52)</td>
<td>35(41)</td>
</tr>
<tr>
<td>Maori</td>
<td>115(36)</td>
<td>42(49)</td>
</tr>
<tr>
<td>Pacific Islander</td>
<td>11(3)</td>
<td>3(4)</td>
</tr>
<tr>
<td>Other</td>
<td>28(9)</td>
<td>5(6)</td>
</tr>
<tr>
<td>Neutnatal risk factor: ( \bullet ):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-term</td>
<td>116(35)</td>
<td>33(37)</td>
</tr>
<tr>
<td>IDM</td>
<td>134(40)</td>
<td>40(45)</td>
</tr>
<tr>
<td>Small</td>
<td>92(28)</td>
<td>22(25)</td>
</tr>
<tr>
<td>Large</td>
<td>91(27)</td>
<td>28(31)</td>
</tr>
<tr>
<td>Other</td>
<td>11(3)</td>
<td>2(2)</td>
</tr>
<tr>
<td>Gestational age, weeks</td>
<td>38 (36, 39)</td>
<td>38 (36, 39)</td>
</tr>
<tr>
<td>Birth weight, grams</td>
<td>3006 (2485; 3673)</td>
<td>3010 (2500; 3640)</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>141 (42)</td>
<td>44 (49)</td>
</tr>
<tr>
<td>Bayley-III motor score</td>
<td>99 (9)</td>
<td>97 (8)</td>
</tr>
<tr>
<td>WPPSI-III Full Scale IQ</td>
<td>98 (89; 109)</td>
<td>92 (81; 102)</td>
</tr>
<tr>
<td>New Zealand Deprivation index</td>
<td>7 (5; 9)</td>
<td>7 (5; 9)</td>
</tr>
<tr>
<td>Maternal education: ( \bullet ):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary school</td>
<td>95 (30)</td>
<td>29 (36)</td>
</tr>
<tr>
<td>Tertiary</td>
<td>218 (70)</td>
<td>51 (64)</td>
</tr>
</tbody>
</table>

Data are number (percent), mean (standard deviation) or median (Interquartile Range). IDM, infant of a diabetic mother. MABC-2, Movement Assessment Battery for Children, second edition; Bayley-III, Bayley Scales of Infant and Toddler Development, third edition; WPPSI, Wechsler Preschool and Primary Scale of Intelligence, 3rd edition. \( \bullet \) Data missing for 20 children. \( \bullet \) Neonatal risk factors not mutually exclusive. \( \bullet \) Comparing characteristics of children ≤15th and >15th centile on MABC-2.

Of the 89 children with MABC-2 total scores ≤15th centile at 4.5 years only three (2%) had a Bayley III motor score < 85 at 2 years. Similarly, of 54 children with total scores ≤5th centile at 4.5 years only two (1%) had a Bayley III motor score < 85 at 2 years. Bayley-III motor scores at 2 years were significantly but weakly related to total MABC-2 scores at 4.5 years (\( \beta = 0.4 \) [95% CI 0.3, 0.6]; \( R^2 = 0.07; p < 0.0001 \); Figure 8.4.2).

There was also a weak association between Bayley-III motor scores and MABC-2 Manual Dexterity scores (\( \beta = 0.8 \) [0.5, 1.1]; \( R^2 = 0.06; p < 0.0001 \)) and Balance scores (\( \beta = 0.7 \) [0.4, 1.0]; \( R^2 = 0.05; p < 0.0001 \)), but no association with Aiming and Catching scores (\( \beta = 0.2 \) [-0.1, 0.6]; \( R^2 = 0.00; p = 0.197 \)). Bayley-III fine motor subtest scores were only weakly associated with MABC-2 Manual Dexterity scores at 4.5 years (\( \beta = 2.7 \) [1.5, 4.0]; \( R^2 = 0.05; p < 0.0001 \)). Similarly, Bayley III gross motor subtest scores were only weakly associated with MABC-2 Aiming and Catching scores (\( \beta = 1.8 \) [0.6, 3.1]; \( R^2 = 0.02; p = 0.003 \)) and Balance scores (\( \beta = 2.4 \) [1.2, 3.5]; \( R^2 = 0.04; p < 0.0001 \)) at 4.5 years.
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Figure 8.4.2 Relationship between 4.5 year MABC-2 total score and 2 year Bayley-III motor composite score

The area under the Bayley III motor score receiver operating characteristic curve for MABC-2 score ≤15th centile was 0.62 (95% CI 0.56, 0.67) and 0.62 (95% CI 0.57, 0.67) for MABC-2 score ≤5th centile. A Bayley-III motor score <85 identified children with MABC-2 total score ≤15th centile with a positive predictive value of 30% and negative predictive value of 74% (sensitivity of 7% and specificity 94%). The best combination of sensitivity (79%) and specificity (39%) was for a Bayley-III motor score cut-off <100, which is the standardised test mean (Table 8.4.2). The specificity and sensitivity of <85 Bayley-III motor cut-off was similar in children with different risk factors for hypoglycaemia (data not shown).

Bayley-III motor scores were only weakly associated with full scale IQ (FSIQ) at 4.5 years (β=0.5 [95% CI 0.3, 0.6]; R²=0.09; p<0.0001). Similarly, Bayley-III fine motor subset scores were only weakly associated with FSIQ at 4.5 years (β=1.8 [1.2, 2.4]; R²=0.09; p<0.0001), and there was no association between Bayley-III gross motor subset score and FSIQ (β=0.6 [-0.1, 1.2]; R²=0.01; p=0.078). There was also no association between Bayley-III motor scores, or fine and gross motor subset scores, and Beery-Buktenica Visual Motor Integration scores at 4.5 years (motor score; β=0.2 [-0.4, 0.8]; R²=-0.01; p=0.540).
Table 8.4.2 Characteristics of Bayley-III motor score cut-off values to predict motor impairment at 4.5 years

<table>
<thead>
<tr>
<th>4.5 year motor outcome</th>
<th>Bayley-III motor composite cut-off</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive predictive value</th>
<th>Negative predictive value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤15th centile on MABC-2</td>
<td>79</td>
<td>2 (0; 8)</td>
<td>99 (97; 100)</td>
<td>30 (7; 93)</td>
<td>74 (68; 78)</td>
</tr>
<tr>
<td></td>
<td>85</td>
<td>7 (3; 14)</td>
<td>94 (91; 97)</td>
<td>30 (12; 54)</td>
<td>74 (68; 78)</td>
</tr>
<tr>
<td></td>
<td>100†</td>
<td>79 (69; 87)</td>
<td>39 (33; 45)</td>
<td>32 (26; 39)</td>
<td>83 (75; 90)</td>
</tr>
<tr>
<td>≤5th centile on MABC-2</td>
<td>79</td>
<td>2 (0; 10)</td>
<td>99 (97; 100)</td>
<td>25 (11; 81)</td>
<td>84 (80; 88)</td>
</tr>
<tr>
<td></td>
<td>85</td>
<td>6 (1; 15)</td>
<td>94 (90; 96)</td>
<td>15 (3; 38)</td>
<td>84 (79; 88)</td>
</tr>
<tr>
<td></td>
<td>100†</td>
<td>83 (71; 92)</td>
<td>38 (32; 44)</td>
<td>21 (15; 27)</td>
<td>92 (86; 96)</td>
</tr>
</tbody>
</table>

Data are composite scores and percentages (95% Confidence Intervals). †Cut-off with the optimal sensitivity and specificity to predict MABC-2 motor scores ≤15th centile and ≤5th centile at 4.5 years’ corrected age. There were no children with motor scores <70 on Bayley-III at 2 years. MABC-2, Movement Assessment Battery for Children, second edition; Bayley-III, Bayley Scales of Infant and Toddler Development, third edition. CI, Confidence Intervals.

Children with minor neurological abnormality at 2 years had similar MABC-2 scores to those who had a normal neurological examination, and were not at increased risk of MABC-2 scores ≤15th centile at 4.5 years (OR=1.7; 95% CI 0.9, 3.12; p=0.124). Further, there was only slight agreement between the outcomes of 2 and 4.5 year neurological examinations (kappa=0.10 [95% CI 0.00, 0.21]). Of 313 children who had neurological examination at 2 and 4.5 years, 21 (7%) had minor abnormalities at both assessments, 26 of 47 (55%) children with minor abnormalities at 2 years had no abnormalities at 4.5 years, and 78 of 99 (79%) with minor abnormalities at 4.5 years had none at the 2 year assessment. At 2 years, the presence of a minor neurological abnormality had a positive and negative predictive values (95% confidence interval) for a neurological abnormality at 4.5 years of 45% (30; 60) and 71% (65; 76), respectively.

8.5 Discussion

We found that Bayley-III motor scores, including fine and gross motor subtest scores, at 2 years are poorly predictive of motor difficulties at 4.5 years, as detected by MABC-2, in children born at risk of neonatal hypoglycaemia. Routine neurological examination at 2 years also did not predict motor difficulties at 4.5 years. More children were identified at risk of motor difficulty at 4.5 years than at 2 years.

Possible explanations of our results are inability of Bayley-III to assess skilled motor function, appearance of motor problems only later in childhood, or variability of motor skills as children grow. Serial assessments of motor performance up to 2 years of age using Bayley-III or II have shown relatively stable or decreasing rates of motor difficulties (Greene, Patra, Silvestri et al., 2013; Koseck & Harris, 2004). However, few studies have followed children beyond 2 years,
and in studies where motor function is assessed in later life a different motor test is required after the age of 42 months.

It is possible that the Bayley-III motor score measures functions that are part of overall development rather than specific motor function defined as a motor competence or skilled movement (Henderson, Sugden, & Barnett, 2007). The fine motor subtest evaluates ocular-motor control, hand and finger movements, reaching and grasping, pre-writing skills, and use of tools (blocks, scissors etc.). The gross motor subtest evaluates skills that are important for movement and play: head control, rolling, sitting, walking and balance. All of these skills are essential for future skilled motor performance, but many are not purposeful at 2 years, whereas MABC-2 includes timed and graded tasks that require accurate and skilled movement and the ability to plan actions and correct errors to achieve a goal. Therefore, as test demands increase, motor difficulties may become more evident.

It is also possible that motor difficulties are not apparent until a later stage of development. In one prospective study of 50 children born <29 weeks’ gestation or <1000g who did not have cognitive or neurological deficits, or vision and hearing problems at 12 months’ corrected age, the prevalence of gross motor impairment assessed using the Peabody Developmental Motor Scale increased from 14% at 18 months to 33% at 3 years and 81% at 5 years, while impairment in fine motor function was found in 54%, 47% and 64% of children, respectively (Goyen & Lui, 2002). Our results show that Bayley-III motor scores and fine motor subtest scores explained a similar proportion of the variance in cognitive score at 4.5 years (9%) and in MABC-2 motor scores (7%), suggesting that the Bayley-III motor scale is not assessing skills that relate specifically to either later cognitive or motor function. In studies assessing predictive validity of Bayley-III cognitive and language scales, both were related to 4 year IQ (correlation coefficient 0.81 and 0.78 respectively), but Bayley-III cut-offs <85 did not have strong sensitivity and specificity to detect developmental delay at 4 years (Bode, D'Eugenio, Mettelman et al., 2014; Spencer-Smith, Spittle, Lee et al., 2015).

The variability of a child’s motor development has been described in many studies of high risk children born preterm or with low birth weight, but the direction of these changes is not clear. For example, the prevalence of motor difficulties increased from 3 to 5 years of age (Goyen & Lui, 2002), while in another study motor impairment improved from 6 to 8 years and then was relatively stable at 12 to 13 years (Powls, Botting, Cooke et al., 1995). Furthermore, in full-term low risk children, gross motor scores were more stable between 21 months and 4 years.
using Peabody Developmental Motor Scale (70% of children remained in the same category) compared to fine motor scores (36% of children had stable scores) (Darrah, Magill-Evans, Volden et al., 2007). Similarly, meta-analysis of reports of motor development of very preterm and very low birth weight children found that up to 2 years children catch up to comparison groups in motor development measured by Bayley Scales, but then motor proficiency declines during elementary school and adolescence when measured by MABC (De Kieviet, Piek, Aarnoudse-Moens et al., 2009). Therefore, it is not clear if the reported changes are because of variability of children’s motor development, or are due to different requirements of the tests used at different ages.

In previous studies, the predictive value of early motor testing for later motor outcomes has been mixed. An Australian study showed that motor difficulties on MABC-2 at 4 years were accurately predicted by two tests administered at 4, 8, and 12 months to children born preterm (Spittle et al., 2015). The Alberta Infant Motor Scale scores at 4 months most accurately predicted MABC-2 scores ≤15th and ≤5th centile at 4 years (accuracy 79%), while Neuro-Sensory Motor Developmental Assessment at 12 months most accurately predicted cerebral palsy at 4 years (accuracy 77%) (Spittle, Lee, Spencer-Smith et al., 2015). However, in a prospective study of healthy term-born children, scores of motor function tests administered at a mean age of 10 days, 12 weeks and 18 months were not associated with motor outcomes at school age (mean 6 years 1 month) (Roze, Meijer, Van Braeckel et al., 2010). Therefore, accuracy of prediction of preschool and school motor performance may depend on the tests used in assessments and the study population.

Both positive and negative predictive values were poor for the cut-off of a Bayley-III score <85, although there were only 8 children with scores below this at two years. Therefore, we investigated if a different cut-off for Bayley-III motor scores would better predict later motor difficulties. We found that the sum of sensitivity and specificity for predicting motor difficulties at 4.5 years was maximal at a cut-off of <100 which is the test mean, but predictive value was still poor. Recent studies have found that Bayley-III underestimated developmental delay compared to the previous edition, Bayley-II (Anderson, De Luca, Hutchinson et al., 2010). Further, Bayley-II has also been reported to have poor predictive validity for later developmental delays (Hack, Taylor, Drotar et al., 2005). An alternative cut-off of <73 was suggested for Bayley-III motor score instead of <85 to improve sensitivity and specificity for identifying motor difficulties at 18-22 months’ corrected age in babies born <27 weeks’ gestation (Duncan, Bann, Boatman et al., 2015). In another study that used the same motor
tests as our study, 2 year Bayley-III motor score cut-offs of <97 and <94 were considered optimal to identify at risk and significant movement difficulty respectively in 4 year old children born very preterm (Spittle, Spencer-Smith, Eeles et al., 2013). Those proposed motor cut-offs had slightly lower sensitivity (74% for ≤15th and 78% for ≤5th MABC-2 centiles) but higher specificity (77% for both) compared to that found for the <100 cut-off in our study (sensitivity 79% for ≤15th and 83% for ≤5th MABC-2 centiles, specificity 39% and 38%).

Routine neurologic examination has been shown to predict major neurological deficits such as cerebral palsy (Heineman & Hadders-Algra, 2008). However, data on the ability of neurological examination to predict mild and moderate motor impairment is limited. We found that neurological examination at 2 years was not predictive of motor outcomes at 4.5 years. In a study of 5 year olds, similar results were found for paediatric overall judgement (at risk, abnormal or optimal categories) with a sensitivity of paediatric examination to detect motor difficulties of 19% and specificity of 98% (De Kleine, Nijhuis-Van Der Sanden, & Den Ouden, 2006). Moreover, in our study there was only slight agreement between 2 and 4.5 year neurological examinations. Our data suggest that, although routine neurological examination at 2 years may be useful in detecting major neurological deficits, it is not a useful tool to predict skilled motor performance or minor neurological abnormalities in children at 4.5 years.

8.5.1 Study limitations
We do not have MABC-2 reference values for New Zealand children. Moreover, the CHYLD cohort is comprised of children born at risk of hypoglycaemia and our findings might not be applicable to the general population. We also do not know the incidence of MABC-2 scores ≤15th and ≤5th centiles in children born without risk factors for hypoglycaemia. Further research is needed to understand motor function and assessment of motor difficulties in typically developing children.

The reference population on which MABC-2 norms are based comprises 1172 children from United Kingdom (Henderson, Sugden, & Barnett, 2007), and may differ from the population in our study. For example, Dutch children performed better on the MABC-2 than the reference population (Niemeijer, van Waelvelde, & Smits-Engelsman, 2015), although total scores of 3-6 year old children were similar to the reference population. Further, the prevalence of children with MABC-2 scores ≤15th centile were greater than the reference norms for 3-6 year-olds and lower for 7-10 and 11-16 year-olds. Nevertheless, MABC-2 is the most widely used test of motor performance in children (Wuang, Su, & Su, 2012), and other studies have reported good
intraclass correlation coefficient, test-retest reliability and internal consistency, and to be able to discriminate typically developing children from those with motor difficulties (Ellinoudis, Evaggelinou, Kourtessis et al., 2011; Valentini, Ramalho, & Oliveira, 2014; Wuang, Su, & Su, 2012).

The poor agreement in neurological status between 2 and 4.5 years could be partly due to examination by different assessors. However, all examiners were experienced in assessment of young children and followed a common examination protocol.

8.6 Conclusions
Bayley-III motor scores at 2 years were poorly predictive of MABC-2 motor scores at 4.5 years in this cohort of children at risk, even if alternative cut-off values were used. Neurological examination at 2 years also did not predict later motor difficulties. Bayley-III motor scale and neurological examination at 2 years may be of limited utility in routine follow-up assessments of children at risk of adverse long-term neurological and skilled motor performance outcomes.

Content of this chapter was submitted for consideration of publication in the Journal of Clinical Endocrinology and Metabolism (Burakevych, McKinlay, Alsweiler, Harris & Harding).
9.1 Abstract

**Context:** Higher and unstable glucose concentrations in the first 48 hours in babies at risk of neonatal hypoglycemia have been associated with neurosensory impairment at 2 years, but it is unclear what defines and contributes to instability.

**Objective:** To determine the relationship between glycemic responses after neonatal hypoglycemia and risk factors, feeding, treatment and neurodevelopmental outcome.

**Design:** Prospective cohort study of term and late preterm babies born at risk of neonatal hypoglycemia. Masked interstitial glucose (IG) parameters were analyzed for 6 hour epochs after each hypoglycemic episode (blood glucose concentration <2.6 mmol/l).

**Participants:** Babies (N=139) with interstitial monitoring and ≥1 hypoglycemic episode in the first 48 hours after birth.

**Main Outcome Measure:** Glycemic parameters and neurosensory impairment at 2 and 4.5 years’ corrected age.

**Results:** Glycemic instability in the first 48 hours was related to instability after hypoglycemia. IG parameters were not related to risk factors for hypoglycemia. Treatment with IV dextrose was associated with higher IG maximum and range and lower minimum compared to treatment with dextrose gel plus breast milk, breast milk alone or formula alone. The risk of neurosensory impairment was increased with both long and short time to reach IG maximum (middle vs upper tertile OR 3.33 [95% CI 1.44; 7.70] and lower tertile OR 2.94 [95% CI 1.31; 6.59].

**Conclusions:** Glycemic response was not related to risk factors, but was related to treatment. The rate of change in glucose concentration was associated with neurosensory impairment. Interventions that stabilize glucose parameters after hypoglycemia may improve neurosensory outcomes.
9.2 Introduction

Neonatal hypoglycaemia is a common condition described as a failure of metabolic adaptation to the postnatal environment (Hawdon, 2012; Platt & Deshpande, 2005; Swanson & Sinkin, 2015). At birth the continuous supply of glucose is interrupted and successful transition to neonatal life requires adequate fuel stores, mature glycogenolytic and gluconeogenic pathways and hormonal homeostatic systems (Hawdon, 2008; Hawdon, 2016). Babies born to diabetic mothers, or who are born preterm, small or large often have impaired metabolic adaptation and are at risk of neonatal hypoglycaemia.

Severe or symptomatic neonatal hypoglycaemia is a known cause of brain injury, but thresholds for diagnosis and treatment of asymptomatic neonatal hypoglycaemia are controversial (Tin, 2014). We have previously shown in a large prospective cohort that neonatal hypoglycaemia, when treated to maintain blood glucose at or above 2.6 mmol/l (47 mg/dl), was not associated with neurosensory impairment at 2 years’ corrected age (McKinlay, Alsweiler, Ansell et al., 2015). However, babies with higher or less stable blood glucose concentrations in the first 48 hours had higher risk of neurosensory impairment. These associations were strongest in babies who had experienced hypoglycaemia and were treated with dextrose, raising concern that glycaemic responses to treatment may influence long-term neurodevelopmental outcome after hypoglycaemia. However, it was not clear if the instability and adverse outcome were related to different responses of babies who were treated similarly, or to different treatments, and which of the parameters that define instability were related to the outcome.

Therefore, we undertook a detailed analysis of interstitial glucose (IG) concentrations following episodes of neonatal hypoglycaemia. Data were collected using continuous glucose monitoring, which is not used in routine care, but provides blinded readings of IG concentrations every five minutes (Beardsall, Ogilvy-Stuart, Ahluwalia et al., 2005; Beardsall, 2010) allowing in-depth investigation of glycaemic responses. The aim of this study was to investigate [1] the association between stability of blood glucose in the first 48 hours and interstitial glucose parameters following hypoglycaemia; [2] the effects of neonatal risk factors, feeding and dextrose treatment on changes in glucose parameters following hypoglycaemia; [3] the association between interstitial glucose parameters following hypoglycaemia and neurosensory impairment at 2 or 4.5 years.
9.3 Materials and Methods

9.3.1 Study design
This was a prospective cohort study of babies born at risk of neonatal hypoglycaemia at Waikato Women’s Hospital, Hamilton, New Zealand between 2006 and 2010. Babies were recruited to two neonatal studies, BABIES (Harris, Battin, Weston et al., 2010) and Sugar Babies (Harris, Weston, Signal et al., 2013) if they had one or more risk factor for neonatal hypoglycaemia: born to diabetic mother, preterm (32-36 completed weeks’ gestation), small (<2500g or <10th centile), large (>4500g or >90th centile) or other conditions (eg poor feeding, respiratory distress). Hypoglycaemia was defined as blood glucose concentration <2.6 mmol/l (<47 mg/dl).

9.3.2 Neonatal management
Breast feeding was encouraged, and infant formula or expressed breast milk was given until adequate breast milk was available according to maternal preference. All babies born <35 weeks’ were routinely admitted to the NICU.

Babies who became hypoglycaemic were treated according to clinician preference with feeding (breast milk or formula according to mother’s preference), 40% dextrose gel massaged into the buccal mucosa followed by feeding (if hypoglycaemia persisted, another dose of gel was given with a maximum of six doses over 48 hours) or intravenous 10% dextrose (2 ml/kg bolus over 10 minutes and infusion 60-90 ml/kg/day [4-6 mg/kg/min]).

9.3.3 Measures
Blood glucose concentration was measured by heel-prick at one hour of age, then every 2-4 hours before feeding for 24 hours, and every 6-8 hours for the next 24 hours, or until stable. In babies who received gel, blood glucose concentration was also measured 30 minutes after treatment. In babies who received intravenous dextrose, blood glucose concentration was measured every 4 hours for 12 hours, and then as clinically indicated. All blood glucose measurements were analysed using glucose oxidase (Radiometer, ABL800 FLEX, Copenhagen, Denmark). A continuous interstitial glucose monitor (CGMS® system gold™ Medtronic, MiniMed, Northridge, CA, USA) was inserted in the lateral thigh soon after birth (Harris, Battin, Weston et al., 2010), and monitoring continued for at least 48 hours. Data from the continuous glucose monitors were downloaded at the end of the monitoring period and were not available to clinical staff, so did not affect clinical management. These data were
recalibrated to true blood glucose concentrations, as previously described (Signal, Le Compte, Harris et al., 2012).

9.3.4 Assessment at 2 and 4.5 years
Children underwent comprehensive neuropsychometric testing of cognitive ability, language, executive function, visual and motor function, and social emotional status at 2 and 4.5 years’ corrected age. Parents completed questionnaires on socio-demographic characteristics of their households.

Neurosensory impairment at 2 years (Harris, Alsweiler, Ansell et al., 2016; McKinlay, Alsweiler, Ansell et al., 2015) was defined as one or more of: developmental delay (Bayley Scales of Infant and Toddler Development, third edition (Bayley, 2006) cognitive or language composite score <85), motor difficulty (Bayley motor composite score <85 or cerebral palsy), visual impairment or hearing impairment requiring hearing aids, executive function score or motion coherence threshold worse than 1.5 SD from the cohort mean (Yu, Jacobs, Anstice et al., 2013).

Neurosensory impairment at 4.5 years was defined as one or more of: cognitive delay (Wechsler Preschool and Primary Scale of Intelligence, 3rd edition full scale IQ <85), motor difficulty (Movement Assessment Battery for Children, second edition total score <15th centile or cerebral palsy), visual impairment (best visual acuity >0.5 logMAR), visual-motor difficulty (Beery-Buktenica Developmental Test of Visual-Motor Integration, sixth edition VMI score <85), hearing impairment (requiring hearing aids), executive function score or motion coherence threshold worse than 1.5 SD from the cohort mean.

9.3.5 Statistical analysis
Analysis was performed using SAS version 9.4 (SAS Institute). An episode of hypoglycaemia was defined as one or more consecutive blood glucose concentrations <2.6 mmol/l (<47 mg/dl). The analysis reported here was restricted to babies who experienced at least one episode of hypoglycaemia in the first 48 h after birth and who had CGM in situ from the onset of the episode.

We analysed IG concentrations for 6 hours after the onset of a hypoglycaemic episode, termed an epoch. For each epoch, the following parameters were defined: number of blood glucose measurements <2.6 mmol/l (<47 mg/dl); time to reach maximum IG concentration (hours); range, average, maximum and minimum IG concentrations, proportion of IG measurements
outside the 3 to 4 mmol/l (54 to 72 mg/dl) central band (McKinlay, Alsweiler, Ansell et al., 2015); and total duration (hours) of IG concentrations <2.6 mmol/l (<47 mg/dl).

The primary risk factor for neonatal hypoglycaemia was defined using the following hierarchical order: infants of diabetic mothers, preterm, small, large and other. Epochs were classified according to dextrose treatment received during the 6 hour period, prioritized as intravenous dextrose, buccal dextrose gel or no dextrose, and by feed received, prioritized as formula and breast milk (expressed or breastfeed). Characteristics of babies who received different treatments were compared. Babies were divided into tertiles of proportion of blood glucose concentrations outside the central range of 3-4 mmol/l (54-72 mg/dl) and babies with the greatest proportion of time outside the central band were defined as unstable. Neurosensory impairment was based on the most recent assessment.

Associations between epoch IG parameters and neonatal risk factors, gestational age, feeding and treatment were analysed using generalized mixed linear models, accounting for multiple epochs per child (random effect). Additional multivariate analysis was performed for epochs with IV dextrose treatment to assess associations between IG parameters and IV bolus, glucose delivery rate (GDR, mg/kg/min) and buccal gel, with adjustment for time of onset of IV dextrose. Models for neurosensory impairment were adjusted for socio-economic status, gestation, birth weight Z score and blood glucose concentration at the beginning of the epoch. Effects are presented as odds ratios with 95% confidence intervals (CI).

9.3.6 Ethics

The Study was approved by the Northern Y Ethics Committee. Caregivers provided written informed consent for the neonatal and follow-up studies.

9.4 Results

A total of 614 babies were recruited to the two neonatal studies (2 babies were in both). Cohort and neonatal outcomes have been reported previously (Harris, Battin, Williams et al., 2009; Harris, Battin, Weston et al., 2010; Harris, Weston, Signal et al., 2013; Harris, Weston, & Harding, 2015). A total of 404 children were assessed at 2 years’ corrected age (77% of those eligible) and 477 (79% of eligible) at 4.5 years. There were 201 6 hour hypoglycemic epochs with complete IG monitoring available for analysis from 139 babies, of whom 66 (47%) were boys, 11 were born at 32-34 weeks’ gestation, 49 at 35-36 weeks’ and 79 at term (Table 9.4).
**Table 9.4 Cohort Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cohort</th>
<th>Gestational age groups, weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>32-34</td>
</tr>
<tr>
<td>Number of 6 hour epochs</td>
<td>201</td>
<td>14</td>
</tr>
<tr>
<td>Number of babies</td>
<td>139</td>
<td>11</td>
</tr>
<tr>
<td>Primary risk factor:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDM</td>
<td>46 (33)</td>
<td>4 (36)</td>
</tr>
<tr>
<td>Preterm</td>
<td>48 (35)</td>
<td>7 (64)</td>
</tr>
<tr>
<td>Small</td>
<td>28 (20)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Large</td>
<td>8 (6)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Other</td>
<td>9 (6)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Boys</td>
<td>66 (47)</td>
<td>5 (45)</td>
</tr>
<tr>
<td>Ethnicity:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>New Zealand European</td>
<td>76 (55)</td>
<td>8 (73)</td>
</tr>
<tr>
<td>Maori</td>
<td>54 (39)</td>
<td>2 (18)</td>
</tr>
<tr>
<td>Pacific Islander</td>
<td>3 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Asian</td>
<td>6 (4)</td>
<td>1 (9)</td>
</tr>
<tr>
<td>Admitted to Neonatal Intensive Care Unit</td>
<td>82 (59)</td>
<td>11 (100)</td>
</tr>
<tr>
<td>Feeding/treatment:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast milk</td>
<td>25 (18)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Formula</td>
<td>24 (17)</td>
<td>1 (9)</td>
</tr>
<tr>
<td>Dextrose gel + breast milk</td>
<td>32 (23)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Dextrose gel + formula</td>
<td>30 (22)</td>
<td>1 (9)</td>
</tr>
<tr>
<td>IV dextrose</td>
<td>28 (20)</td>
<td>9 (82)</td>
</tr>
<tr>
<td>Neurosensory impairmentf</td>
<td>49 (41)</td>
<td>3 (33)</td>
</tr>
</tbody>
</table>

Data are number (percent). IDM, infant of a diabetic mother, IV, intravenous; fOutcome prioritised in order: 4.5 years and 2 years; for description of neurosensory impairment see methods.

### 9.4.1 Blood glucose stability

Babies with more unstable blood glucose concentrations (outside central range of 3–4 mmol/l) in the first 48 hours had lower blood glucose concentrations at the onset of the epoch (tertile 3 vs 1 mean difference [MD] -0.2 mmol/l [95% CI -0.4; -0.08], P= 0.002; and tertile 2 vs 1 MD -0.2 mmol/l; [-0.3; -0.02], P= 0.02). They also had more variable interstitial glucose parameters after hypoglycemia, with lower epoch IG minimum (tertile 3 vs 1 mean difference [MD] -0.2 mmol/l [95% CI -0.4; -0.03], P= 0.02; and tertile 2 vs 1 MD -0.2 mmol/l; [-0.4; -0.05], P= 0.01), and higher epoch IG maximum (tertile 3 vs 2: MD 0.5 mmol/l [0.04; 1.1], P=0.03) and range (tertile 3 vs 1 MD 0.7 mmol/l [0.1; 1.2], P= 0.01, and tertile 3 vs 2 MD 0.6 mmol/l [0.02; 1.1], P=0.04) (Table 9.4.1). They also had a higher proportion of epoch IG concentrations outside the central band of 3 to 4 mmol/l (tertile 3 vs 1 MD 0.29 [0.17; 0.41], P< 0.0001; tertile 2 vs 1 MD 0.18 [0.06; 0.30], P= 0.03) and more time with epoch IG below 2.6 mmol/l (tertile 3 vs 1 MD 0.57 hours [0.17; 0.97], P= 0.003; tertile 2 vs 1 MD 0.62 hours [0.22; 1.02], P= 0.002) (Table 9.4.1).
Table 9.4.1 Interstitial glucose parameters in a 6 hour epoch following hypoglycaemia and blood glucose stability in the first 48 hours after birth

<table>
<thead>
<tr>
<th>Tertile</th>
<th>Proportion of blood glucose concentrations outside central band (3-4 mmol/l) in first 48 hours</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tertile 1</td>
<td>(0.50)²</td>
<td>57 (49)</td>
</tr>
<tr>
<td>Tertile 2</td>
<td>(0.64)²</td>
<td>53 (41)</td>
</tr>
<tr>
<td>Tertile 3</td>
<td>(1.00)²</td>
<td>58 (41)</td>
</tr>
</tbody>
</table>

P = 0.002

Table 9.4.2.1 Primary neonatal risk groups and interstitial glucose parameters following hypoglycaemia

<table>
<thead>
<tr>
<th>Total</th>
<th>IDM</th>
<th>Preterm</th>
<th>Small</th>
<th>Large</th>
<th>Other</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of 6h epochs</td>
<td>201</td>
<td>56</td>
<td>73</td>
<td>49</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>Number of babies</td>
<td>139</td>
<td>46</td>
<td>48</td>
<td>28</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Blood glucose concentration at the onset of the epoch</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of babies</td>
<td>2.2 (0.3)</td>
<td>2.3 [2.1; 2.5]</td>
<td>2.3 [2.1; 2.5]</td>
<td>2.2 (0.3)</td>
<td>2.2 (0.3)</td>
<td>2.2 (0.3)</td>
</tr>
<tr>
<td>Hours to maximum IG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average IG</td>
<td>3.2 (0.6)</td>
<td>3.2 [2.8; 3.5]</td>
<td>3.2 [2.8; 3.5]</td>
<td>3.2 [2.8; 3.5]</td>
<td>3.2 [2.8; 3.5]</td>
<td>3.2 [2.8; 3.5]</td>
</tr>
<tr>
<td>Maximum IG</td>
<td>4.1 (1.1)</td>
<td>3.7 [3.4; 4.5]</td>
<td>3.7 [3.4; 4.5]</td>
<td>3.7 [3.4; 4.5]</td>
<td>3.7 [3.4; 4.5]</td>
<td>3.7 [3.4; 4.5]</td>
</tr>
<tr>
<td>Minimum IG</td>
<td>2.2 (0.4)</td>
<td>2.2 [1.9; 2.4]</td>
<td>2.2 [1.9; 2.4]</td>
<td>2.2 [1.9; 2.4]</td>
<td>2.2 [1.9; 2.4]</td>
<td>2.2 [1.9; 2.4]</td>
</tr>
<tr>
<td>IG range</td>
<td>1.9 (1.2)</td>
<td>1.8 [1.2; 2.2]</td>
<td>1.9 (1.2)</td>
<td>1.6 [1.2; 2.2]</td>
<td>2.1 (1.5)</td>
<td>1.6 [1.2; 2.2]</td>
</tr>
<tr>
<td>Duration (hours) IG &lt; 2.6 mmol/l</td>
<td>0.88 [0.41; 1.76]</td>
<td>0.88 [0.40; 1.85]</td>
<td>0.81 [0.41; 1.42]</td>
<td>0.88 [0.40; 2.16]</td>
<td>1.28 [0.88; 2.05]</td>
<td>1.16 [0.79; 2.08]</td>
</tr>
</tbody>
</table>

Data are number, median [interquartile range] or mean (standard deviation). Values in brackets represent the highest value for each tertile. IG, interstitial glucose concentration. Glucose concentrations are expressed as mmol/l. *P<0.05. Same letters indicate no pairwise significant differences.

9.4.2 Neonatal risk factors and gestational age

Epoch IG parameters were similar among neonatal risk groups (Table 9.4.2.1). Sex distributions were similar in different risk and gestational age groups.

Table 9.4.2.1 Primary neonatal risk groups and interstitial glucose parameters following hypoglycaemia

Glycaemic response to hypoglycaemia
Babies born at 32-34 weeks’ gestation had lower blood glucose concentrations at epoch onset than babies born at 35-36 weeks’ gestation (MD -0.38 mmol/l [95% CI -0.60; -0.15], \( P=0.0003 \)) or term babies (MD -0.34 mmol/l [95% CI -0.56; -0.12], \( P= 0.0008 \)) (Table 9.4.2.2). They also had significantly lower epoch IG minimum (MD -0.25 mmol/l [95% CI -0.49; -0.01], \( P=0.04 \)), shorter time to reach IG maximum (MD -1.32 hrs [95% CI -2.45; -0.19], \( P=0.02 \)) and greater IG range (MD 0.94 mmol/l [95% CI 0.09; 1.79], \( P= 0.03 \)) than babies born at 35-36 weeks’ gestation. They also had significantly higher epoch IG average (MD 0.59 mmol/l [95% CI 0.18; 1.00], \( P=0.0003 \)), maximum (MD 0.86 mmol/l [95% CI 0.08; 1.65], \( P= 0.03 \)) and range (MD 1.02 mmol/l [95% CI 0.20; 1.84], \( P= 0.01 \)) than term babies. IG parameters were similar in babies born at 35-36 and \( \geq 37 \) weeks’ gestation (Table 9.4.2.2).

### Table 9.4.2.2 Gestational age groups and interstitial glucose parameters following hypoglycaemia

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>32-34</th>
<th>35-36</th>
<th>( \geq 37 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of 6h epochs</td>
<td>201</td>
<td>14</td>
<td>71</td>
<td>116</td>
</tr>
<tr>
<td>Number of babies</td>
<td>139</td>
<td>11</td>
<td>49</td>
<td>70</td>
</tr>
<tr>
<td>Blood glucose at the onset of the epoch</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.2 [0.3]</td>
<td>2.3 [2.1; 2.5]</td>
<td>1.9 [0.7]</td>
<td>2.1 [1.7; 2.2]</td>
<td>2.3 [0.2]</td>
</tr>
<tr>
<td>Blood glucose concentrations &lt; 2.6mmol/l</td>
<td>1 [1; 2]</td>
<td>1 [1; 2]</td>
<td>1 [1; 2]</td>
<td>1 [1; 2]</td>
</tr>
<tr>
<td>Hours to maximum IG</td>
<td>3.3 [1.7]</td>
<td>3.0 [2.0; 4.9]</td>
<td>2.4 [1.1]</td>
<td>2.2 [1.7; 2.5]</td>
</tr>
<tr>
<td>Average IG</td>
<td>3.2 [0.6]</td>
<td>3.1 [2.8; 3.5]</td>
<td>3.7 [0.9]</td>
<td>3.7 [3.0; 4.4]</td>
</tr>
<tr>
<td>Maximum IG</td>
<td>4.1 [1.1]</td>
<td>3.7 [3.4; 4.5]</td>
<td>5.0 [1.6]</td>
<td>4.8 [3.7; 5.6]</td>
</tr>
<tr>
<td>Minimum IG</td>
<td>2.2 [0.4]</td>
<td>2.2 [2.0; 2.4]</td>
<td>2.0 [0.7]</td>
<td>2.2 [1.7; 2.5]</td>
</tr>
<tr>
<td>IG range</td>
<td>1.9 [1.2]</td>
<td>1.6 [1.2; 2.2]</td>
<td>3.1 [1.7]</td>
<td>2.5 [2.0; 4.3]</td>
</tr>
<tr>
<td>Proportion IG outside central band of 3–4mmol/l</td>
<td>0.81</td>
<td>0.73 [0.46; 0.85]</td>
<td>0.73 [0.46; 0.85]</td>
<td>0.58 [0.27; 0.82]</td>
</tr>
<tr>
<td>Duration (hours) IG &lt; 2.6 mmol/l</td>
<td>0.88</td>
<td>0.52 [0.32; 1.34]</td>
<td>0.87 [0.41; 1.52]</td>
<td>1.04 [0.41; 2.04]</td>
</tr>
</tbody>
</table>

Data are number, median [interquartile range] or mean (standard deviation). IG, interstitial glucose concentration. Glucose concentrations are expressed as mmol/l. Same letters indicate no pairwise significant differences.

### 9.4.3 IG response to feeding and treatment

Intravenous dextrose was given to 9/11 (82%) babies born at 32-34 weeks’, 6/49 (12%) at 35-36 weeks’ and 13/79 (16%) at term (Table 9.4). Analysis of the effect of feeding and treatment was therefore restricted to babies born at \( \geq 35 \) weeks’ gestation (187 epochs in 128 babies). Epochs were compared among 5 hierarchical feeding and treatment groups: breast milk only, formula, breast milk plus buccal dextrose gel, formula plus buccal dextrose gel, and IV dextrose. Baby sex, ethnicity, socio-economic status, primary neonatal risk factor and size at birth did not differ among these groups (data not shown). However, babies treated with formula
plus dextrose gel, and those treated with IV dextrose were more likely than other treatment groups to be admitted NICU (76% and 100% of babies, respectively, P<0.0001).

Blood glucose concentration at onset was significantly lower in epochs in which IV dextrose was administered than in epochs treated with breast milk alone (MD -0.22 [95% CI -0.41; -0.02], P= 0.02, Table 9.4.3).

**Table 9.4.3 Effect of feeding and treatment on interstitial glucose parameters in a 6 hour epoch following hypoglycaemia**

<table>
<thead>
<tr>
<th></th>
<th>Breast milk</th>
<th>Formula</th>
<th>Dextrose gel and breast milk</th>
<th>Dextrose gel and formula</th>
<th>IV dextrose</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of 6 h epochs</td>
<td>30</td>
<td>39</td>
<td>44</td>
<td>38</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Number of babies</td>
<td>25</td>
<td>23</td>
<td>32</td>
<td>29</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Blood glucose at the onset of the epoch</td>
<td>2.3 (0.2)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.4 [2.3; 2.5]</td>
<td>2.3 (0.3)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2.3 [2.1; 2.5]</td>
<td>2.2 (0.3)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2.3 [2.1; 2.5]</td>
</tr>
<tr>
<td>Number of blood glucose concentrations &lt; 2.6 mmol/L</td>
<td>1 [1; 1]</td>
<td>1 [1; 2]</td>
<td>1 [1; 2]</td>
<td>1 [1; 2]</td>
<td>2 [1; 2]</td>
<td>0.40</td>
</tr>
<tr>
<td>Hours to maximum IG</td>
<td>3.5 (1.8)</td>
<td>3.0 [2.1; 3.5]</td>
<td>3.4 (1.6)</td>
<td>3.0 [2.0; 4.1]</td>
<td>3.7 (1.8)</td>
<td>4.1 [2.2; 5.5]</td>
</tr>
<tr>
<td>Average IG</td>
<td>3.0 (0.3)</td>
<td>2.9 [2.8; 3.2]</td>
<td>3.1 (0.5)</td>
<td>3.0 [2.7; 3.3]</td>
<td>3.2 (0.5)</td>
<td>3.2 [2.8; 3.6]</td>
</tr>
<tr>
<td>Maximum IG</td>
<td>3.3 (0.4)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3.4 [3.2; 3.6]</td>
<td>3.8 (1.0)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3.6 [3.3; 4.2]</td>
<td>3.7 (3.4)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3.7 [3.4; 4.3]</td>
</tr>
<tr>
<td>Minimum IG</td>
<td>2.3 (0.2)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.3 [2.1; 2.4]</td>
<td>2.2 (0.3)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.2 [2.1; 2.5]</td>
<td>2.2 (0.3)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.2 [2.1; 2.4]</td>
</tr>
<tr>
<td>IG range</td>
<td>1.2 (0.5)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.1 [0.8; 1.4]</td>
<td>1.6 (1.0)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.3 [1.1; 1.9]</td>
<td>1.6 (0.7)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.5 [1.1; 1.9]</td>
</tr>
<tr>
<td>Proportion IG outside central band of 3-4 mmol/l</td>
<td>0.37 [0.22; 0.57]</td>
<td>0.60 [0.40; 0.77]</td>
<td>0.55 [0.27; 0.72]</td>
<td>0.49 [0.27; 0.76]</td>
<td>0.75 [0.51; 0.92]</td>
<td>0.08</td>
</tr>
<tr>
<td>Duration (hours) IG &lt; 2.6 mmol/l</td>
<td>0.64 [0.41; 1.30]</td>
<td>1.14 [0.49; 1.92]</td>
<td>0.72 [0.36; 1.50]</td>
<td>0.87 [0.41; 1.38]</td>
<td>1.43 [0.75; 2.80]</td>
<td>0.04&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Data are number, median [interquartile range] or mean (standard deviation). IG, interstitial glucose concentration. Glucose concentrations are expressed as mmol/l. <sup>a</sup>Adjusted pairwise comparisons not statistically significant.

Breast milk alone was provided in 30/187 (16%) epochs, formula alone in 39/187 (21%) and breast milk plus gel in 44/187 (24%) epochs (Table 9.4.3). IG parameters were similar among these groups.

Epochs in which IV dextrose was administered had higher IG maximum compared with those treated with breast milk alone (MD 1.18 mmol/l [95% CI 0.70; 1.66], P<0.0001), breast milk plus dextrose gel (MD 0.78 mmol/l [95% CI 0.34; 1.21], P=0.004) and formula alone (MD 0.79 mmol/l [95% CI 0.34; 1.24], P=0.006, Table 9.4.3). Similarly, epochs treated with formula plus dextrose gel had higher IG maximum than those treated with breast milk alone (MD 0.71 mmol/l [95% CI 0.24; 1.18], P=0.03; Table 9.4.3).

Epochs in which IV dextrose was administered also had lower IG minimum compared to those treated with breast milk alone (MD -0.23 mmol/l [95% CI -0.37; -0.07], P=0.02) or breast milk plus dextrose gel (MD -0.20 mmol/l [95% CI -0.34; -0.07], P=0.03, Table 9.4.3).
Epochs in which IV dextrose was administered had a higher IG range compared to those treated with breast milk alone (MD 1.40 mmol/l [95% CI 0.91; 1.89], P<0.0001), with breast milk plus dextrose gel (MD 0.98 mmol/l [95% CI 0.54; 1.43], P=0.0002) or with formula alone (MD 0.94 mmol/l [95% CI 0.48; 1.40], P=0.0007; Table 9.4.3). Similarly, epochs treated with formula plus dextrose gel had a higher IG range than breast milk alone (MD 0.79 mmol/l [95% CI 0.31; 1.28], P=0.01).

9.4.4 Dextrose gel dose

Babies born ≥35 weeks’ gestation who received >200 mg/kg of dextrose gel (≥2 doses) per epoch were not different from babies who received ≤200 mg/kg (1 dose) in socio-demographic and neonatal variables (data not shown). Blood glucose concentration at onset was significantly lower in epochs in which 2 or more dextrose gel doses were administered than epochs treated with one dextrose gel dose (Table 9.4.4). Administration of ≥2 dextrose gel doses compared with 1 dose was also associated with lower epoch IG average and minimum, higher proportion of time spent outside central 3-4 mmol/l glucose band and more time with IG < 2.6 mmol/l (Table 9.4.4).

Table 9.4.4 Effect of dextrose gel dose on interstitial glucose parameters in a 6 hour epoch following hypoglycaemia

<table>
<thead>
<tr>
<th>Dextrose gel dose</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 (&gt;200 mg/kg)</td>
<td>1 (≤200 mg/kg)</td>
</tr>
<tr>
<td>Number of 6 h epochs</td>
<td>32</td>
</tr>
<tr>
<td>Number of babies</td>
<td>22</td>
</tr>
<tr>
<td>Blood glucose at the onset of the epoch</td>
<td>2.1 (0.3)</td>
</tr>
<tr>
<td>2.2 [1.9; 2.3]</td>
<td>2.3 [2.1; 2.5]</td>
</tr>
<tr>
<td>Number of blood glucose concentration &lt;2.6 mmol/l</td>
<td>2 [2; 3]</td>
</tr>
<tr>
<td>Hours to maximum IG</td>
<td>3.8 (1.7)</td>
</tr>
<tr>
<td>3.7 [2.4; 5.4]</td>
<td>3.0 [2.0; 4.4]</td>
</tr>
<tr>
<td>Average IG</td>
<td>3.0 (0.5)</td>
</tr>
<tr>
<td>3.0 [2.6; 3.3]</td>
<td>3.3 [3.0; 3.7]</td>
</tr>
<tr>
<td>Maximum IG</td>
<td>4.1 (1.3)</td>
</tr>
<tr>
<td>3.8 [3.4; 4.3]</td>
<td>4.0 [3.4; 4.6]</td>
</tr>
<tr>
<td>Minimum IG</td>
<td>2.1 (0.4)</td>
</tr>
<tr>
<td>2.2 [1.8; 2.3]</td>
<td>2.3 [2.1; 2.5]</td>
</tr>
<tr>
<td>IG range</td>
<td>2.0 (1.3)</td>
</tr>
<tr>
<td>1.6 [1.2; 2.1]</td>
<td>1.6 [1.3; 2.4]</td>
</tr>
<tr>
<td>Proportion IG outside central band of 3-4mmol/l</td>
<td>0.68 [0.37; 0.90]</td>
</tr>
<tr>
<td>Duration (hours) IG &lt;2.6 mmol/l</td>
<td>1.91 [1.18; 3.63]</td>
</tr>
</tbody>
</table>

Data are number, median [interquartile range] or mean (standard deviation), or mean difference (95% confidence intervals); IG, interstitial glucose concentration. Glucose concentrations are expressed as mmol/l.

9.4.5 IV dextrose

Of 46 epochs where IV dextrose was administered, a bolus as well as a continuous infusion was administered in 29 (63%), a bolus was administered without ongoing infusion in 3 (7%), and dextrose gel was administered in 19 (41%). In 19 (44%), IV dextrose was already being
infused prior to the onset of the epoch. In the remaining 24 (56%), the IV dextrose was administered at a median of 0.70 [0.37; 1.00] hours from the onset of the epoch.

Among babies born at 32-34 weeks’ gestation receiving IV dextrose, there was no relationship between epoch IG parameters and GDR (mg/kg/min), use of IV bolus or dextrose gel (Table 9.4.5). In babies born at ≥35 weeks’ gestation treated with IV dextrose, there was also no relationship between epoch IG parameters and GDR. Use of IV bolus was associated with lower epoch IG minimum (MD -0.33 mmol/l [95% CI -0.60; -0.07], P< 0.05) but not any other epoch IG parameters. Dextrose gel administration was associated with lower epoch IG average (MD -0.76 mmol/l [95% CI -1.46; -0.06], P< 0.05) and IG minimum (MD -0.39 mmol/l [95% CI -0.69; -0.08], P< 0.05), and increased proportion of time outside central band of 3-4 mmol/l (MD 0.25 [95 % CI 0.02; 0.48], P< 0.05) and time <2.6 mmol/l (MD 1.03 hours [95% CI 0.34; 1.72], P< 0.01) (Table 9.4.5).

Table 9.4.5 Interstitial glucose parameters in 6 hour epochs treated with intravenous dextrose

<table>
<thead>
<tr>
<th>Epochs N=10</th>
<th>Bolus, yes vs no</th>
<th>GDR, mg/kg/min</th>
<th>Dextrose gel, yes vs no</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hours to maximum IG</td>
<td>0.44 [-1.70; 2.58]</td>
<td>-0.12 [-0.44; 0.19]</td>
<td>-1.25 [-3.85; 1.34]</td>
</tr>
<tr>
<td>Average IG</td>
<td>-0.08 [-2.98; 2.82]</td>
<td>-0.09 [-0.53; 0.35]</td>
<td>0.33 [-3.10; 3.76]</td>
</tr>
<tr>
<td>Maximum IG</td>
<td>0.05 [-5.68; 5.78]</td>
<td>0.00 [-0.83; 0.84]</td>
<td>0.15 [-6.80; 7.12]</td>
</tr>
<tr>
<td>Minimum IG</td>
<td>-0.50 [-2.28; 1.28]</td>
<td>-0.17 [-0.50; 0.10]</td>
<td>-0.12 [-2.21; 1.96]</td>
</tr>
<tr>
<td>IG range</td>
<td>0.85 [-4.70; 6.39]</td>
<td>0.11 [-0.70; 0.91]</td>
<td>0.45 [-6.27; 7.17]</td>
</tr>
<tr>
<td>Proportion IG outside central band of 3-4 mmol/l</td>
<td>0.30 [-0.36; 0.97]</td>
<td>0.07 [-0.03; 0.17]</td>
<td>0.67 [-0.12; 1.46]</td>
</tr>
<tr>
<td>Duration (hours) IG &lt;2.6 mmol/l</td>
<td>1.46 [-0.52; 3.44]</td>
<td>0.21 [-0.10; 0.51]</td>
<td>0.02 [-1.49; 3.14]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Epochs N=36</th>
<th>Bolus, yes vs no</th>
<th>GDR, mg/kg/min</th>
<th>Dextrose gel, yes vs no</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hours to maximum IG</td>
<td>-0.53 [-1.87; 0.82]</td>
<td>-0.08 [-0.35; 0.20]</td>
<td>-0.16 [-1.71; 1.39]</td>
</tr>
<tr>
<td>Average IG</td>
<td>-0.23 [-0.83; 0.36]</td>
<td>0.00 [-0.12; 0.13]</td>
<td>-0.76 [-1.46; -0.06]</td>
</tr>
<tr>
<td>Maximum IG</td>
<td>0.04 [-1.12; 1.19]</td>
<td>-0.05 [-0.29; 0.19]</td>
<td>-0.38 [-1.74; 0.97]</td>
</tr>
<tr>
<td>Minimum IG</td>
<td>-0.33 [-0.60; -0.07]</td>
<td>0.00 [-0.05; 0.06]</td>
<td>-0.39 [-0.69; -0.08]</td>
</tr>
<tr>
<td>IG range</td>
<td>0.37 [-0.82; 1.56]</td>
<td>-0.06 [-0.31; 0.19]</td>
<td>0.00 [-1.39; 1.39]</td>
</tr>
<tr>
<td>Proportion IG outside central band of 3-4 mmol/l</td>
<td>0.09 [-0.11; 0.28]</td>
<td>0.02 [-0.02; 0.06]</td>
<td>0.25 [0.02; 0.48]</td>
</tr>
<tr>
<td>Duration (hours) IG &lt;2.6 mmol/l</td>
<td>0.39 [-0.21; 0.99]</td>
<td>-0.02 [-0.14; 0.10]</td>
<td>1.03 [0.34; 1.72]**</td>
</tr>
</tbody>
</table>

Data are regression coefficient [95% Confidence Interval]; Adjusted for time when IV was started; *P <0.05; **P <0.01; IG, interstitial glucose concentration. Glucose concentrations are expressed as mmol/l. GDR, glucose delivery rate.

9.4.6 Neurosensory impairment

Compared to the middle tertile for each epoch IG parameter, the risk of neurosensory impairment was increased in both the higher (OR 3.33 [95% CI 1.44; 7.70]) and lower (OR 2.94; [95% CI 1.31; 6.59], P= 0.01) tertiles of time to reach maximum epoch IG (Figure 9.4.6). A similar but non-significant association was seen with epoch average IG. Neurosensory impairment was not associated with other IG parameters. In a sensitivity analysis, exclusion of babies born at 32-34 weeks’ gestation did not alter results. The risk of neurosensory impairment...
remained increased in both higher (OR 3.55 [95% CI 1.46; 8.64]) and lower (OR 3.84; [95% CI 1.61; 9.18], P= 0.005) tertiles of time to reach maximum epoch IG, with a similar but non-significant association for epoch average IG.

**Figure 9.4.6** Effect of interstitial profile in epochs following neonatal hypoglycaemia on the primary outcome

![Adjusted Odds Ratio (95% CI) of Neurosensory Impairment](image)

**Figure 9.4.6 Primary outcome prioritized in order: 4.5 year, 2 year outcome. IG, interstitial glucose concentration. Glucose concentrations are expressed as mmol/l. Hypoglycaemia was defined as blood glucose measurement <2.6 mmol/l. 6 hour epoch was defined as a 6 hour interval of interstitial glucose monitoring following blood glucose concentration < 2.6 mmol/l. The odds of neurosensory impairment was compared according to the tertile of interstitial glucose parameter in a 6 hour epoch. Results adjusted for socio-economic status, gestation, birth weight Z score and blood glucose concentration at the beginning of the epoch. Triangles denote tertile 1, circles tertile 2 (reference) and squares tertile 3.**

**9.5 Discussion**

In this study we found that parameters reflecting glucose stability in 6 hour epochs following hypoglycaemia in the first 48 hours were not related to neonatal risk factors, but were related to treatment. However, only the rate of change in glucose concentrations was related to adverse neurodevelopmental outcome.
Results of the CHYLD study showed that higher glucose concentrations, even within the normal range, and also less stable glucose concentrations, indicated by increasing proportion of measurements outside the central band of 3 to 4 mmol/l (54 to 72 mg/dl) were associated with higher risk of neurosensory impairment at 2 years (McKinlay, Alsweiler, Ansell et al., 2015). This finding is consistent with animal studies showing that brain injury is more severe when low blood glucose concentrations are followed by hyperglycaemia (Ennis, Dotterman, Stein et al., 2015). However, in our previous study, while babies who experienced hypoglycaemia had a greater proportion of blood glucose concentrations outside the central band, the extent to which instability was temporally related to hypoglycaemia and also to the subsequent higher glucose concentrations after hypoglycaemia was unclear (McKinlay, Alsweiler, Ansell et al., 2015).

In this detailed analysis we found that among babies with hypoglycaemia, those with the most unstable blood glucose concentrations in the first 48 hours also had less stable glucose concentrations in the period immediately after hypoglycaemia. Further, this instability was due not only to low but also to high glucose concentrations. Although we did not find an association between the proportion of epoch IG outside the central band and neurosensory impairment up to 4.5 years, we did find that glycaemic responses immediately following hypoglycaemia were associated with overall stability of blood glucose concentrations. This suggests that to achieve greater stability of neonatal blood glucose concentrations, attention needs to be directed to the period after the onset of hypoglycaemia.

Variation in glucose stability among babies at risk of hypoglycaemia may reflect differences in underlying pathophysiology of hypoglycaemia in different risk groups. For example, babies born to diabetic mothers are thought to have an increased transfer of fuels across placenta due to maternal hyperglycaemia, resulting in hyperinsulinism (de Rooy & Hawdon, 2002; Persson, 2009). Another mechanism is described in preterm babies, who have not have sufficient intrauterine time to deposit fat and glycogen or have accompanying conditions that affect glucose production (Hawdon, 2016). However, we found no association between primary neonatal risk factor and epoch IG parameters. Thus among at-risk infants, glycaemic response to hypoglycaemia does not appear to be related to underlying risk.

Nevertheless, the most immature babies born at 32-34 weeks’ gestation had the least stable epoch IG parameters (average, maximum, minimum and range) despite the fact that most received IV dextrose which might have been expected to stabilize IG concentrations. Preterm
babies have been previously reported to have poor adaptation mechanisms to postnatal life and therefore have low blood glucose concentrations after birth (Platt & Deshpande, 2005). Immaturity of metabolic systems makes the management of glucose concentrations in these babies difficult, and treatment of hypoglycaemia often results in hyperglycaemia (Mitanchez, 2007). Very preterm babies were found to have unstable IG concentrations even after they were clinically stable and receiving full enteral feeds, with the instability more pronounced in less mature babies (Mola-Schenzle, Staffler, Klemme et al., 2015). Therefore, babies born <35 weeks’ gestation seem to be at high risk for glycaemic instability and require close monitoring.

We wanted to establish if the instability was related to different responses of babies who were treated similarly or to different treatments. We found no differences in epoch IG parameters treated with breast milk alone or formula alone, in contrast to a previous report that babies born to mothers with gestational diabetes had higher blood glucose concentrations after receiving formula than after breast feeding (Chertok, Raz, Shoham et al., 2009). Moreover, we found that treatment with dextrose gel plus breast milk was not associated with glucose instability, whereas treatment with formula plus dextrose gel or IV dextrose was.

Epochs in which IV dextrose was administered had low blood glucose concentrations at the onset of the epoch, which might explain why babies received a more aggressive treatment, possibly to increase glucose concentrations fast and achieve stabilization. However, IG parameters for these epochs were more unstable than other treatment group epochs, and were characterized by both low and high glucose concentrations and more time outside central band and time below IG 2.6 mmol/l. Again, it is possible that babies who spent more time below 2.6 mmol/l received more aggressive treatment and in different forms. Another possible explanation might be individual variation in metabolic response to treatment of hypoglycaemia, whereby babies with blood glucose concentrations in the lowest range have less developed homeostatic systems that are not able to maintain stable glucose concentrations when dextrose is administered rapidly.

Among epochs where dextrose gel was administered, two or more dextrose gel doses were associated with lower blood glucose concentration at the start of the epoch, lower average, minimum and more time spent outside the central band and below IG 2.6 mmol/l, but similar maximum IG. This suggests that instability in these epochs was due to low glucose concentrations and treatment with multiple doses of dextrose gel did not result in high glucose concentrations. Similar to IV dextrose treatment, a more aggressive treatment might have been
chosen for babies whose glucose concentration was low at the start of the epoch and remained low.

Literature on the associations between feeding, dextrose treatment and glucose concentrations is limited, and factors that might identify babies who have different metabolic responses to different treatments are unclear. In very preterm babies studied at term equivalent age, IG concentrations fluctuated (both hypo- and hyperglycaemic), with no differences between breast fed and formula fed babies, and no association with specific risk factors (Pertierra-Cortada, Ramon-Krauel, Iriondo-Sanz et al., 2014). Moreover, blood glucose concentrations were not different between breast and formula fed small-for-gestational-age babies, but the concentration of ketone bodies was higher in breast fed babies (de Rooy & Hawdon, 2002). Further, blood glucose response to mini-bolus followed by intravenous infusion was different in babies who were average or small for gestational age, or large/infants of diabetics, but variation within each group was also described (Lilien, Pildes, Srinivasan et al., 1980). Similar to these reports, our data suggests that IG parameters and treatment of hypoglycaemia are related, but we cannot establish the sequence of events to determine causality. This study does not allow us to predict which babies are most at risk of glycaemic instability or predict their response to treatment. However, we can suggest that if oral treatment of hypoglycaemia is planned, preference might be given to giving breast milk alone or breast milk plus dextrose gel over formula plus dextrose gel, which was associated with greater instability as well as lacking the other benefits of breast feeding (Le Hurou-Luron, Blat, & Boudry, 2010).

Our previous report of the increased rate of neurosensory impairment in babies with higher and less stable glucose concentrations is consistent with other reports that glucose instability was associated with adverse health outcomes and increased mortality rates in very low birth weight babies (Fendler, Walencik, Mlynarski et al., 2012) and adults (Bagshaw, Bellomo, Jacka et al., 2009; Wintergerst, Buckingham, Gandrud et al., 2006). Although in this subgroup analysis, glucose stability, as represented by the proportion of epoch IG within the central band, was not related to outcome, we found an association between the rate of change in IG after hypoglycaemia (time to IG maximum) and neurosensory impairment. Further, this relationship appeared U-shaped which suggests that close monitoring is needed at the time of treatment to ensure the appropriate rate of change in glucose concentrations. However, time to IG maximum was not itself associated with neonatal risk factors or different types of feeding and treatment.
An important strength of our study is the use of interstitial glucose monitoring that records glucose concentrations continuously and provides readings every five minutes, but these were not used for the management of neonatal hypoglycaemia. Therefore, we could analyse associations between treatment and IG parameters in epochs of babies treated according to clinical guidelines and not influenced by our findings. One limitation of CGM is the delay in obtaining data after birth, resulting from the practical difficulties of inserting the monitor immediately after birth, and the delay between insertion of the glucose monitor and obtaining the first readings. This means that few data are available in the first critical 1-3 hours after birth, which is a time when blood glucose concentrations are most commonly low (Juthani, Kumar, & Williams, 2013).

In this study we have demonstrated that babies who have unstable blood glucose concentrations in the 48 hours after birth also have unstable glucose concentrations in the period immediately after the onset of hypoglycaemia. Glycaemic responses after hypoglycaemia were not related to neonatal risk factors, but were related to treatment. Intravenous dextrose administration was associated with both low and high glucose concentrations after hypoglycaemia, whereas multiple dextrose gel doses were associated with low but not high concentrations. Rate of change in glucose concentrations, both fast and slow, was associated with neurosensory impairment. These findings suggest that interventions that help stabilize glucose parameters in the period after the onset of hypoglycaemia may be associated with improved neurosensory outcomes after neonatal hypoglycaemia.
Chapter 10. Discussion.
We investigated growth and development of children born at risk of neonatal hypoglycaemia in Waikato hospital and recruited to the follow-up study of later neurodevelopmental outcomes, the CHYLD study. Although families were difficult to track and assess, lived in more deprived areas compared to national average, and moved to other parts of New Zealand and overseas by 4.5 years, the follow-up rate in the study was reasonably high and the cohort was representative of the Waikato population. High neurodevelopmental impairment rates were found at both 2 and 4.5 years.

We found that there were a number of potential problems with the methods that we and many others use for routine follow-up of at risk children. Parental questionnaires provided inaccurate data about early childhood illness, national preschool screening was less likely to be taken up for children with developmental and social-emotional problems, referral pathways were inconsistent, and early standard assessment of motor function was not predictive of later motor difficulty.

The main aim of the CHYLD study was to determine the relationship between measures of neonatal glycaemia and neurodevelopmental outcome in later childhood. The primary analysis of these relationships will be reported elsewhere. In this thesis, we reported some specific aspects of those relationships. In particular, we found that although children were born with different risk factors for neonatal hypoglycaemia, risk factors did not appear to be associated with any differences in measured outcomes. For example, risk factors did not affect growth rate from birth to 4.5 years, accuracy of data collection at 4.5 year follow-up, attendance of preschool screening, motor difficulties at 4.5 years and glycaemic response to hypoglycaemia in the neonatal period. Further, detailed analysis of continuous glucose monitoring data showed that different treatments in the neonatal period were associated with different glycaemic responses to hypoglycaemia, but only the rate of change in glucose concentrations was related to the risk of later neurosensory impairment.

10.1 CHYLD cohort
The CHYLD study cohort comprised children born at risk of neonatal hypoglycaemia in a single tertiary hospital and had higher deprivation rates than the national average. The follow-up rate in our study was 77% of eligible children at 2 years and 79% at 4.5 years, which is lower than the 98% follow-up rate of a cohort of 4 year old children born very preterm in New Zealand (Woodward, Moor, Hood et al., 2009), but similar to that of other studies of at risk
children. For example, in a longitudinal case-control study of New Zealand neonates born small for gestational age, follow-up rate was 85%, 63% and 68% at 1, 3.5 and 7 years, respectively. However, only New Zealand European families were included because of low response rate of non-European mothers (19% at 3.5 years) (Theodore, Thompson, Waldie et al., 2009). In another New Zealand study of high risk children born to Pacific Islander mothers with psychological problems, the follow-up rate was 77% at 2 years (Gao, Paterson, Abbott et al., 2007), which is similar to our follow-up rate.

Although many families in the CHYLD study stayed in the same area by the 4.5 year follow-up, about 20% of them moved to other regions of New Zealand or overseas, which made it difficult to find them. Moreover, families may stay in the same region, but they are likely to move to another town or house over that time. The Growing Up in New Zealand study found that between pregnancy and when child was nine months old 26% of families moved to a different house at least once (12% moved twice), and from 9 months to 2 years 32% of families moved (16% moved twice) (Morton, Atatoa Carr, Berry et al., 2014). However, using NHI number assigned to each child at birth makes it easier to find families and contact their GP if needed.

When the babies who were included in this cohort were recruited to neonatal studies, the follow-up assessment was not planned. That is why the 2 year follow-up started when some of the children in the cohort were older than 2 years and therefore were not eligible, and these were mainly neonates recruited to BABIES study who were born ≥32 weeks’ gestation and were all admitted to NICU (Harris, Battin, Weston et al., 2010). If the follow-up study was planned at the same time as the neonatal studies, the methodology chosen might have been different. More attention may have been directed to collecting data that would be useful for later analysis like complete growth measurements, many of which were missing at birth in our study, and also maternal pre-pregnancy weight and pregnancy weight gain, which have been associated with the trajectory of children’s growth after birth until school age (Giles, Whitrow, Davies et al., 2015; Suzuki, Sato, Zheng et al., 2015). Further, informing parents about future contact may have helped with the follow-up rates. We also might have considered short follow-up visits at 6 and 12 months to keep these families in the study and also to record some of the socio-demographic, nutrition, growth and developmental milestones data. The 2 year follow-up would then include children born at ≥32 weeks’ gestation which would make 2 and 4.5 year CHYLD cohorts more comparable.
The strength of the study was inclusion of assessment of different domains: cognitive, visual processing, language, social-emotional, growth, executive function and neurological function, which provides a comprehensive understanding of a child’s abilities and problems. However, one limitation was the absence of a control group and therefore we could not compare rates of impairment between control children and those at risk of neonatal hypoglycaemia. We also could not establish associations between neonatal glycaemia and later neurodevelopmental outcomes in a control group. Most published studies were done in children born at risk and little is known about glucose concentrations and glycaemic responses to treatment and feeding in apparently normal neonates. However, ethical and practical issues regarding regular blood testing of neonates in a control group would make such studies difficult.

Assessing multiple domains of a child’s function might lead to detection of increase impairment rates compared to studies that focus on a single domain or overall development. High impairment rates were found in the CHYLD study cohort at both 2 and 4.5 years. We used recommended cut-offs where these were available for assessment tests. However, there were no nationally representative norms for most tests and we could not compare the rate of abnormal findings to that of the New Zealand general population. Many of the recommended cut-offs provide different results when validated in counties different to the reference population on which the test was developed. For example, suggested SDQ total difficulties score cut-offs for Australian 4-6 year olds were lower than those of the recommended cut-offs based on the United Kingdom data (Kremer, De Silva, Cleary et al., 2015). Further, lower norms indicative of movement difficulty for 3 years old and higher norms for children in older age groups compared to MABC-2 norms were advised for Dutch and Flemish children (Niemeijer, van Waelvelde, & Smits-Engelsman, 2015). Moreover, using Bayley-III norms based on an American sample in a Danish population led to high rates of delayed receptive language at 4,7,10 and 13 months of age which was explained by differences in sound structures between English and Danish languages (Krogh, Væver, Harder et al., 2012). Children in the CHYLD study were also from different ethnic and cultural backgrounds and tests scores might have been affected by cultural and ethnic differences.

**10.2 Methodology**

Accuracy of data collection is very important to avoid biased findings in any study, including follow-up studies. However, every method has strengths and limitations, and the level of
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accuracy needed for a study will also depend on the research questions and objectives of the study. Other factors need to be considered including time, cost, availability of tools, how easy they are to use, and how much involvement of the team is required, especially in large studies. That is why questionnaires that can be quickly filled by parents are often used in research. Further, linking to information collected by other organisations or routine processes, such as in our case the B4 School Check, might be an efficient use of time and resources in research.

Since parents are often asked to report their children’s medical histories, behaviours or milestones, we wanted to investigate if the information caregivers provided about their children was accurate and could reliably be used for data analysis. We therefore compared parental reports of child health to hospital records. Further, we wanted to investigate if using parental questionnaire data from other sources (the B4SC) is a useful and accurate method of data collection. We found that parents could not accurately recall hospital admissions of their preschool children (Burakevych, McKinlay, Alsweiler et al., 2015), and the data on child behaviour obtained using parental questionnaires in different settings and for different purposes provided different results (Burakevych, McKinlay, Alsweiler et al., 2016).

This suggests that these commonly used approaches to data collection in follow-up studies may not be very accurate, and alternative methods of data collection should be considered if accurate data on health care utilisation of children is required. Use of diaries where caregivers fill in details of all admissions, medical visits etc. might be an alternative (Wiseman, Conteh, & Matovu, 2005). However, having diaries that are kept in a family and are filled in regularly from birth until the follow-up assessment seems unlikely (Thomas, Ramanujam, Velusamy et al., 2015), especially in families with literacy difficulties (Bruijnzeels, Van Der Wouden, Foets et al., 1998), and this is unlikely to be feasible in a predominantly low socioeconomic cohort such as ours. Electronic diaries have been tested in some studies and provided accurate data (Langan & Williams, 2009), and also an 80% reduction in time needed for data handling (Palmblad & Tiplady, 2004; Tiplady, Jamieson, & Crompton, 2000). However, technical problems with electronic questionnaires or diaries may cause data loss (Lauritsen, DeGi'Innocenti, Hendel et al., 2004; Palermo, Valenzuela, & Stork, 2004). Electronic diaries would be suitable for cohorts with good levels of literacy, who don’t need assistance when completing questionnaires, and also are confident users of technology. Computer assisted telephone interviews have also been reported to be accurate in collecting data on health histories, early life experiences and also socio-demographic characteristics in adults (Kendig, Byles, O'Loughlin et al., 2014). This method and also a life history calendar has proved to be
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cost-effective in a population that was geographically widespread and allowed completion of data collection at any time suitable for participants. Computer assisted telephone interviews were also used to collect data using parents as respondents about early childhood health in the National Survey in US. Such interviews reduced time of data processing and allowed the data to be checked for any mismatch with the previous interviews (Blumberg, Olson, Osborn et al., 2002).

Another alternative is regular contact with the family, for example 6 monthly telephone or email questionnaires. Such regular contact with the family (including newsletters, reminders and birthday cards) could also improve the tracking process and willingness of families to come to the follow-up assessment (Lee, Dobson, Brown et al., 2000). At the same time, costs associated with maintaining regular contact may not be justified if the information provided in the questionnaires is not the main outcome measure. Our findings suggest that available funds might better be directed to collection of medical records from health care providers as these would be more detailed and accurate than information provided by caregivers. Therefore, seeking ethical approval to ask for consent to access medical records might be an important approach when planning prospective studies. In addition, assessing accuracy of data collected via questionnaires compared to medical records for a small subgroup in the beginning of the study might be a useful approach for large studies for which use of questionnaires is justified.

Multiple methods of data collection should be considered depending on family preferences, socio-demographic characteristics and availability of tools.

Since the B4SC is the national screening programme aimed at children when they are four and includes assessment of development and health, obtaining data from the B4SC seemed a potentially useful approach. Some of the tools used for the assessment in the B4SC were similar to those used for CHYLD assessments (SDQ, growth measurements, immunisations) while other tools that assessed similar domains were different (PEDS in the B4SC vs WPPSI and executive function in the CHYLD) or not done at all during CHYLD assessments (hearing screening). Therefore, we obtained a lot of additional data from the B4SC for children whose caregivers gave consent.

Parents not only recall information about their children, but also are often asked to evaluate their children’s health, development, behaviour or emotional state. This approach was used in both the B4SC and CHYLD study. However, when we compared SDQ data from the B4SC and CHYLD, we found that scores were different. This could be because of the time difference
between the assessments, but we found that the difference in scores was not significantly influenced by the time between assessments. Of the factors that might contribute to such differences we considered the fluctuating nature of child’s social-emotional and behavioural status, the different purpose for which the data was collected and in different environments, and also the effect the repeat of the test might have on parental perception. Moreover, parents sometimes do not know what is appropriate for a child at that particular age and therefore their concerns are often ungrounded but reported in the questionnaire (Cox, Huntington, Saada et al., 2010). It has been reported that parents were able to accurately detect language, motor and behavioural development, but not cognitive and global development (Chen, Lee, Yeh et al., 2004). Therefore, a selective approach to use parents as informants might be a better option, when parental report is used as additional tool. Examiner assessment in addition to parental report is challenging in national screening programs. Nevertheless, parents observe their children in different situations and can provide overall evaluation over a long period of time whereas the examiner is usually observing a child once during the assessment. Therefore, there is no perfect method and the method of data collection should be suited for study aims with careful consideration of assessment procedures (including setting, timing, etc.).

One strength of the CHYLD study was the setting where the assessment was done, the Research House in Hamilton. It was a standardised testing facility with minimal distractions during neurodevelopmental assessment. It provided privacy and space for families, ability to arrange breaks, and also to accommodate siblings and extended family if needed. Such an environment is beneficial for assessment of young children and engagement of their parents in the assessment process. This might also affect the scores obtained from the parent-completed questionnaires.

Another advantage of collecting additional data from other sources is the receipt of data that would not otherwise have been collected. In our study, the B4SC allowed us to obtain information about behavioural evaluation of children by their teachers. Multiple informant approaches using both parent and teacher reports had better predictive ability for emotional and conduct disorders, and also attention deficit hyperactivity disorder compared to parent rating alone or teacher rating alone, but parents could more accurately identify ASD while teachers better identified conduct problems (Johnson, Hollis, Marlow et al., 2014). This does not mean that the perception of these informants is correct, and quite often the agreement between parents and teachers is poor (Stokes, Mellor, Yeow et al., 2014; Stone, Otten, Engels et al., 2010). A multi-informant approach may also be difficult in studies of young children, because children
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might not have attended a preschool or teachers might not know them well enough or be unwilling to fill in the questionnaire. Missing data for the SDQ teacher report was common in the B4SC dataset. Moreover, preschool screening criteria were not applied consistently. Careful documentation of additional information provided by the assessor and internal audit of examination processes and referrals in the future might help improve consistency in both preschool screening and research studies. Further, our finding of high rates of developmental delay and social-emotional problems in children who miss out on preschool screening is very important. It suggests that aim of the preschool screening (to provide help to children who most need it to ensure their successful performance at school and later in life) is not achieved.

In addition, we found that early assessment of motor function was not predictive of later motor difficulty. This raises a question about whether early assessments should be done, particularly if they are used to determine provision of early intervention which is very common practice in many countries. Mixed findings about effect of early intervention to improve development have been described: positive effect on emotion regulation (Wu, Hsieh, Hsu et al., 2016), improved executive function (Traverso, Viterbori, & Usai, 2015) or no effect on cognitive function (Hauglann, Handegaard, Ulvund et al., 2014). Similarly, mixed findings about the effect of early intervention were found for motor function (Kaaresen, Ronning, Tunby et al., 2008; Lekskulchai & Cole, 2001; Piper, Kunos, Willis et al., 1986). However, even if the intervention is effective, when the test of early motor performance is not predictive of later motor difficulties, then provision of intervention to those who need it most is questionable. Contrary to our findings for the Bayley-III motor scale, the cognitive and language scales of Bayley-III at 2 years have been reported to correlate well with IQ at 4 years in children born preterm (Bode, D'Eugenio, Mettelman et al., 2014). In our study Bayley motor scores explained about the same amount of variability in 4.5 year cognitive scores as motor scores. Our data suggest that early motor performance might be more usefully interpreted as a test of overall development rather than skilled motor function.

Despite our results, we need to choose an age when the assessment is done and 2 years seems to be an optimal time. We need to keep children in the study and it is more difficult to find families after long periods of no contact. Moreover, major neurological difficulties and severe developmental delays can be detected at this age. Furthermore, even if early developmental tests do not predict future development, collection of data on socio-economic characteristics, growth problems and developmental milestones and trajectory up to that age is useful. Development assessment questionnaires instead of examiner-administered assessment might
be the optimal choice for early assessment as they provide a proxy measure of child’s development as reported by a parent, do not take much time to complete and involve parents in the assessment process.

10.3 Hypoglycaemia and adverse neurodevelopmental outcomes

Neonatal hypoglycaemia is a common condition and is associated with adverse neurodevelopmental outcomes (Koh, Aynsley-Green, Tarbit et al., 1988; Lucas, Morley, & Cole, 1988; Tam, Widjaja, Blaser et al., 2008). Previously it was reported that within the CHYLD study cohort over half of neonates born at risk of neonatal hypoglycaemia became hypoglycaemic and about a fifth had more than one episode (Harris, Weston, & Harding, 2012). Moreover, treatment of hypoglycaemia with dextrose gel proved to be effective, cheap, easy to administer, well tolerated and decreased separation of mother and neonate (Harris, Weston, Signal et al., 2013). However, definition of hypoglycaemia, thresholds used for monitoring and treatment of hypoglycaemia remain controversial (Hay, Raju, Higgins et al., 2009; Rozance & Hay, 2010; Tin, 2014). Further, any association between asymptomatic and undetected hypoglycaemia (not detected by intermittent blood measurements, but detected using CGM) and adverse outcomes later in life is not clear. The CHYLD study aimed to address these knowledge gaps.

10.3.1 Hypoglycaemia and outcomes at 2 years’ corrected age

The results of 2 year outcomes in relation to duration, frequency and severity of neonatal hypoglycaemia and treatment with dextrose were previously published by CHYLD research team (Harris, Alsweiler, Ansell et al., 2016; McKinlay, Alsweiler, Ansell et al., 2015). We found no association between hypoglycaemia defined as glucose concentration <2.6 mmol/l and adverse neurodevelopmental outcome at 2 years’ corrected age, both detected using intermittent blood glucose measurements and undetected by intermittent but detected by blinded IG monitoring (McKinlay, Alsweiler, Ansell et al., 2015). However, we found that higher blood and interstitial glucose concentrations and greater time outside the central band of 3-4 mmol/l were associated with higher risk of adverse outcome. In addition, children with adverse outcome at 2 years who became hypoglycaemic had higher glucose concentrations in the first 12 hours after birth and also had faster rise in glucose concentrations. This fast rise was observed in neonates treated with dextrose in any form. This finding raised concern that interventions to rapidly raise blood glucose concentrations might lead to worse outcome. However, two year outcomes of children treated with dextrose gel vs placebo found no
difference in rates of adverse outcomes or any difference in growth parameters between the two treatment groups (Harris, Alsweiler, Ansell et al., 2016).

10.3.2 Hypoglycaemia and outcomes at 4.5 years’ corrected age
The cohort of children included in the analysis at 4.5 years is different from that at 2 years because of different inclusion criteria. Children included at 4.5 years were born at ≥32 weeks’ gestation and this included neonates recruited to BABIES study (Harris, Battin, Weston et al., 2010) all of whom were admitted to NICU, and most of whom were not included in the 2 year follow-up cohort.

Although we did not report associations between duration, frequency and severity of hypoglycaemic episodes in the neonatal period and neurodevelopmental outcomes at 4.5 years as those will be reported elsewhere, we reported the in-depth analysis of glycaemic response after neonatal hypoglycaemia, factors associated with this response, and its relation to neurodevelopmental outcome later in life. We found at 2 years that children who had unstable glucose concentrations, spent more time outside central band, and were treated for hypoglycaemia might be at greater risk of adverse outcome, but we did not know which factors contributed to instability and the relationship between multiple neonatal and management factors and outcome.

10.3.3 Investigating stability of glucose
Data collected in the neonatal period included intermittent blood glucose measurements that are routinely collected in all at risk neonates. However, additionally continuous interstitial glucose measurements were collected which is not a routine hospital procedure. Continuous glucose monitoring detected additional episodes of hypoglycaemia that were not detected by intermittent blood glucose measurements (Harris, Weston, Signal et al., 2013; McKinlay, Alsweiler, Ansell et al., 2015), and provided a better understanding of frequency, severity and duration of hypoglycaemic episodes in the first 48 hours. It also allowed us to explore the association between hypoglycaemia and later neurodevelopmental outcomes, and response to different treatments for hypoglycaemia. Therefore, the CHYLD study cohort is a unique cohort of at risk children who were monitored closely at birth, and who had an extensive data collected in the neonatal period, infant and preschool ages.

Literature reporting factors associated with glycaemic instability and outcomes is scarce. Research in rats that were subjected to hypoglycaemia and then treated with 50% dextrose showed that hyperglycaemia following hypoglycaemia worsened injury (Ennis, Dotterman,
Stein et al., 2015). In very low birth weight neonates admitted to NICU, fluctuating glucose concentrations were associated with increased risk of lethal outcome (Fendler, Walenciak, Mlynarski et al., 2012).

Further, there were no continuous glucose data in the neonatal period that could explain different metabolic responses of neonates to hypoglycaemia. Therefore, we had a unique opportunity to investigate associations between glycaemic response to neonatal hypoglycaemia and neonatal risk factors, treatment and later outcome. We used the 4.5 year neurodevelopmental outcome and then if not available the 2 year outcome. We decided to prioritise outcomes in this order because of our findings of predictive validity of some tests at early ages. Most of children included in this analysis were assessed at 4.5 years, but we did not wish to exclude data from children who were not assessed at this age.

We found no association between glycaemic responses and neonatal risk factors. Similarly, neonatal risk factors were not related to any of the outcomes described in this thesis. However, neonates born before 35 weeks’ gestation were most unstable and were treated differently from those born at later gestations. It might be that their metabolic and homeostatic systems are most immature. Similar to our findings, others have reported that in very low birth weight neonates born at ≤32 weeks’ gestation, 57.9% experienced hyperglycaemia and 36.8% hypoglycaemia detected by CGM that was in place for an average of 7.8 days after insertion within 24 hours after birth (Platas, Thio Lluch, Pociello Alminana et al., 2009). Neonates born very preterm were also likely to experience hyperglycaemia (23.3%), hypoglycaemia (10%) or both (13.3%) when measured using CGM at term equivalent age (Pertierra-Cortada, Ramon-Krauel, Iriondo-Sanz et al., 2014). Moreover, in the study by Hawdon et al. blood glucose concentration varied more in preterm than in term neonates (Hawdon, Ward Platt, & Aysnley-Green, 1992). In our study the division of neonates into three gestational age groups was arbitrary and was mainly based on the difference between inclusion criteria of BABIES (≥32 weeks’ gestation, admitted to NICU) and Sugar Babies studies (≥35 weeks’ gestation) and limited number of subjects with complete IG data who experienced hypoglycaemia. Having a sample of neonates large enough to include those who experienced hypoglycaemia and had complete IG data after hypoglycaemic episodes would allow us to separate the neonates into more gestational age groups, and provide a better understanding of the relationships between neonatal risk factors and glycaemic responses as well as treatment. Missing data is a limitation that is difficult to avoid because of the time needed for the continuous glucose monitor insertion and initiation. As a result we missed continuous interstitial glucose concentration data in the first hours after
birth, when most hypoglycaemia occurs. Another limitation of CGM is the time lag between calibration and obtaining accurate glucose measurements (Wackernagel, Dube, Blennow et al., 2016).

We found that the treatment administered was associated with the glycaemic response after neonatal hypoglycaemia, but could not determine causality. The treatment was administered by a clinician as they thought appropriate. Therefore it was difficult to analyse reasons behind those decisions and it was not controlled by the study protocol. To determine causality a more rigorous research protocol is needed when (1) the same treatment is provided to neonates with the same baseline characteristics and glucose concentrations prior to provision of treatment, (2) different treatments are administered to neonates with the same baseline characteristics and glucose concentrations (3) and same and different treatments are provided to neonates who belong to different defined risk groups. This kind of research would be difficult in human studies, and animal studies might be an alternative approach to better understand these complex associations. Finally, further research is needed to investigate if our finding of the association between rate of glucose change after neonatal hypoglycaemia and adverse neurodevelopmental outcome can be replicated in other large cohorts of neonates.

10.4 Conclusion

Our cohort of children born at risk of neonatal hypoglycaemia is a high risk group with high impairment rates. Follow-up of these children required extra resources and effort to retain them in the study, and to administer complex neurodevelopmental assessment. Studies described in this thesis have increased our understanding of methodology problems when conducting longitudinal studies in children born at risk. These findings will help researchers and clinicians in planning of the future follow-up studies and draw attention to the potential for improvement of the preschool screening programme. Moreover, our study of glycaemic responses after neonatal hypoglycaemia addressed the complex associations between glycaemic stability, neonatal risk factors and treatment and later neurodevelopmental outcomes. Our findings raise important questions in management and treatment of neonates who experienced hypoglycaemia, and we believe will guide future research needed in this field.
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