The Neurodevelopment Profile and Early Executive Function as a Protective Factor in Developmental Deficits in Young Children with Neonatal Hypoglycaemia and Cumulative Risk

Person- and Variable-Centred Developmental Approaches

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A thesis submitted in partial fulfilment

of the requirements for the degree of Doctor of Philosophy,

Department of Psychological Medicine, the University of Auckland, 2017

Abstract

Background

Maintenance of low blood glucose levels approximately 2.6 mmol/L or 47 mg/dL in newborns showed no adverse effects on the neurodevelopment of young children at 2 years (N = 404) and at 4.5 years of age (N = 355) enrolled in the *Children with Neonatal Hypoglycaemia and their Later Development* (CHYLD) study. However, recent evidence suggests that primary risks of neonatal hypoglycaemia such as gestational diabetes, prematurity, born small or born large might increase the chance of developmental deficits in young children. Guided by the bio-ecological framework, this doctoral thesis evaluates the effect of early cumulative risk and its effect on the neurocognitive and neurobehavioral development in preschool children. Integrative 'person-focused' and 'variable-focused' strategies were found useful in the evaluation of child neurodevelopment.

Methods

Six studies were performed in order to determine a) the impact of cumulative risk on child development and b) the developmental trajectory of cognitive constructs in at-risk young children.

1. A cluster analysis of risk factors and outcomes at 2-year and 4.5-year follow-ups in the CHYLD cohort, and validation of the 5-cluster solution.

2. A multivariate analysis to identify group differences in neurodevelopment of at-risk young children at 2 years and at 4.5 years of age.

3. A validation of the 2-cluster solution; the identification of risk predictors and profile of children in more at-risk and less at-risk groups at 4.5 years.

4. Factor analysis of two measures of executive function at 2 years and at 4.5 years of age, and comparison of factor loadings in 'less at-risk' children versus 'more at-risk' children.

5. A path analytic model to estimate the relationship between general intelligence and executive function, and the cascade impact of cumulative risk on working memory, processing speed, reasoning abilities, and motor development at 4.5 years of age.

6. A path analytic model to estimate the impact of cumulative risk on neurobehaviour and the relationship between 'parent-rated' executive function and measures of child psychopathology at 4.5 years of age.

Results

1. The use of child risk factors (birth characteristics, primary risk factors of neonatal hypoglycaemia, parent substance use history, socioeconomic status, maternal education) were useful to aggregate patterns of neurodevelopment in at-risk young children at 2 years and at 4.5 years.

2. Significant differences were observed among groups. Neurodevelopmental deficits were observed in groups 1, 2 and 3. These groups of at-risk young children are more likely living in poor family household, lower maternal education, most likely Māori or Pacific ethnicity, and most likely born IDM and/or SGA.

3. Risk status ('less at-risk' versus 'more at-risk') was validated. Risk status was found related to deprivation, ethnic affiliation, SGA, and head circumference. Risk factors that predicted group membership were: a) prenatal substance exposure, b) postnatal substance exposure, c) SGA and ethnicity, and d) maternal education and SES.

4. 'More at-risk' young children had immature inhibition of prepotent responses compared to 'less at-risk' children at 2 years, and more immature cognitive flexibility skills at 4.5 years. In the 'parent-rated' measure of executive function, 'more at-risk' young children have lesser inhibitory skills than 'less at-risk' children observed at 2 and at 4.5 years of age. Hypothesised parent-beliefs of child development were significantly influential in the evaluation of executive function in young children at 2 years and at 4.5 years.

5. Intelligence was strongly associated with executive function. However, this relationship was compromised by the effect of cumulative risk. Effects of cumulative risk on verbal reasoning were mediated by working memory, whereas effects of

cumulative risk on non-verbal reasoning were mediated by processing speed. Effects of cumulative risk on motor development were mediated by executive function and visuomotor integration. Therefore, the protective role of 'observed' executive function in reasoning abilities and motor development were established.

6. Parent-rated executive function was highly correlated with parent reports of child psychopathology. Externalising behaviour was related to inhibitory self-control index, whereas internalising behaviour was related to flexibility and metacognitive indices. Everyday executive function mediated the effects of cumulative risk on child psychopathology. However, executive function only partially mediated the impact of cumulative risk on autism-like behaviours. Therefore, the compensatory role of everyday executive function in child social adjustment was tenable.

Conclusions and recommendations

Cumulative risk compromises the neural integrity of young children, through a weakening of the global brain efficiency. Subtle traces of neurodevelopmental deficits were observed in areas of language development, inhibition, cognitive flexibility, visuomotor integration and motor development and higher parent reports of hyperactivity, aggressive behaviour, inattention problems and even autism-like behaviours. Moderate neonatal hypoglycaemia was not related to the established risk status in children. However, primary risks such as born small-for-gestation was related to risk status. These findings should be taken in light of the socio-ecological context of risk configuration (SES, maternal education, parent substance use, and ethnicity). Therefore, follow-up assessments and early intervention for the 'more at-risk' young children in the CHYLD cohort is highly recommended.

Dedication

To my loving and very supportive parents in the Philippines, ***Marilyn (mommy)*** *and* ***Jaime (daddy)****, who had to tolerate and endure my long-term absence in order for me to study a doctorate in New Zealand, they are my source of inspiration and motivation.*

I offer my sleepless nights and hard work to all the suffering ***Children*** *in different parts of the world; stricken by war, violence, poverty, and inequalities.*

May ***YOU*** *find Peace, Love and Kindness!*

Acknowledgments

I would like to express my heart-felt thanks to the key people whose contribution made this enormous doctoral journey possible; their time, effort, expertise and motivation were highly appreciated:

- *Associate Professor Trecia A. Wouldes, PhD* (Department of Psychological Medicine, The University of Auckland) my primary supervisor, for your endless guidance, patience and motherly approach as well as your academic advises on developmental psychology.

- *Distinguished Professor Jane E. Harding, MBChB, FRACP, DPhil* (Liggins Institute, The University of Auckland, New Zealand) my secondary supervisor, PI for CHYLD study, for your research support, and for allowing me to work with the CHYLD data.

- *University Fellows and Lecturers Nicolas Chevalier, PhD*, and *Bonnie Auyueng, PhD* (Wee Science Lab, School of Philosophy, Psychology, and Language Sciences, The University of Edinburgh, United Kingdom) and *Associate Professor Yusuke Moriguchi, PhD* (Moriguchi Child Development Lab, Graduate School of Education, Kyoto University, Japan) for their inspiration, guidance, and academic encouragements as well as fellowships.

I am grateful to meet and work with the following people whose roles, services, and support were vital in each stage of my doctoral work:

- *Jenny Rogers* and *Heather Stewart* (our lovely research nurses) for their company and wise tips and tricks on the assessment of young children. *Ranjeeni Ram* (our lovely administrative staff) for your prompt and supportive and friendly advises on doctoral forms, press account details, and enrolment information.

- *Barbara Darragh* for the guidance and support in revising, editing, and style.
  Without her it would be very hard for an ESL (English as Second Language) international student like me to write at least a readable thesis. The *CHYLD study committee and staffs* for making this study possible, and to *the CHYLD study participants and parents* who have travelled from different parts of New Zealand and abroad for our data collection and assessment.

Lastly, I would like to thank several institutions that made my doctoral experience very nurturing by supporting my academic and professional development through academic conferences, doctoral internship, and travels. I am grateful to the *University Scholarship Committee* for the doctoral scholarship and doctoral extension grants, the university press account, the *Universitas 21 fellowship* (Edinburgh, UK), and to the *Cognitive Development Society and Jacobs Foundation* (CDS, USA) for the international fellowship and grants*, the university libraries* at the University of Auckland, University of Waikato, Victoria University of Wellington, and The University of Edinburgh for allowing me to stay long tedious hours, also to the *Filipino families (Hilario family) and community in Hamilton*, New Zealand for taking good care of me. Thank you very much for all your graces and Love!!!

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List of Abbreviations

ADHD	Attention Deficit Hyperactivity Disorder
AIC	Akaike Information Criterion
ASD	Autism Spectrum Disorder
ANOVA	Analysis of Variance
BRIEF - P	Behaviour Rating Inventory of Executive Function - Preschool
CBCL	Child Behaviour Checklist
CF	Cognitive Flexibility
CFI	Comparative Fit Index
CR	Cumulative Risk
DCCS	Dimension Change Card Sorting
EF	Executive Function
EMI	Emerging Metacognitive Index
FI	Flexibility Index
GEC	Global Executive Control
IDM	Infant of Diabetic Mother
IN	Inhibition
IQ	Intelligence Quotient
ISCI	Inhibitory Self Control Index
L	Wards
LGA	Large for Gestational Age
MABC-2	Movement Assessment Battery for Children - 2nd Ed.
MANOVA	Multivariate Analysis of Variance
mmol/L	Millimoles per Litre
MSML	Multisearch Multilocation
NH	Neonatal Hypoglycaemia
NZ	New Zealand
OR	Odds Ratio
RMSEA	Root Mean Square Error of Approximation
SCQ	Social Communication Questionnaire
SDQ	Strengths and Difficulties Questionnaire
SE	Standard Error
SEM	Structural Equation Modelling
SES	Socioeconomic Status
SGA	Small for Gestational Age
VMI	Visuo-Motor Integration
WM	Working Memory
WPPSI-III	Wechsler Preschool and Primary Scale of Intelligence - 3rd Ed.

Structure of the Thesis

Chapter 1: Introduction and Background provides the focal point of the doctoral thesis, which is the underlying impact of cumulative risk, and presents the theoretical frameworks for the subsequent chapters. This chapter provides an overview of the study context (CHYLD Study) as well as the research aims. It also explicitly states the position of this doctoral thesis as an important investigation *complementing* previous CHYLD doctoral theses and building on the previous research outcomes.

Chapter 2: Review of Related Literature is written to discuss, review and provide foundations for neurodevelopment literatures in three areas: 1) outcomes of primary risks of neonatal hypoglycaemia, 2) aspects of developmental outcomes and 3) overview of early environmental risks and their association with neurodevelopment in young children.

Chapter 3: General Methodology, describe the CHYLD study and the findings to date. Materials and tools from the 2-year and 4.5-year follow-up assessments were presented along with the statistical and research orientation. Main analytical orientations, such as, a) 'person-centred approach' and b) 'variable-centred approach' were discussed.

Chapters 4: Cumulative Risk in the CHYLD Cohort, presents a series of studies conducted to determine whether the proposed research objectives and aims are a substantial pursuit of new knowledge and understanding of atypical development in young children. These chapters provide explanations and causal associations or confirmation of previous hypotheses regarding cumulative risk studies, primary risks of neonatal hypoglycaemia, neurocognitive profiles of young children, and development of early executive function in at-risk preschool children. In addition, neurocognitive and neurobehaviour mechanisms are covered to determine the emerging role of cumulative risk and executive function in cognition and well-being in young children.

Chapters 5: General Synthesis and Implication provides an overall summary, and synthesis of the findings. It will also provide a discussion of the implications of this research for developmental psychologists, child neuropsychologists, preschool teachers, policy makers, and future developmental/clinical trial researchers for CHYLD study or similar cohort study, on child research themes such as: a) follow-up suggestions, b) neuro-imaging study, b) research methods in cumulative risk and child poverty, d) tools and strategies for intervention, and e) measurement development and validation.

CHAPTER I: INTRODUCTION AND BACKGROUND

This section provides the theoretical perspective that is used in this thesis to evaluate developmental outcomes in clinical trials of children at risk of perinatal insults. Firstly, cumulative risk and methods in designing risk research are presented in order to position this doctoral thesis in an interactive bio-ecological context. A number of theoretical frameworks are presented in order to support cumulative risk as a central intervening variable (covariate), Evidence of the influence of cumulative risk has had on several developmental outcome studies is presented. Overview of the Children with Neonatal Hypoglycaemia and their Later Development (CHYLD) study; published findings to date are presented to introduce this doctoral work and provide a context for the cumulative risk perspective in a longitudinal clinical cohort study. Lastly, research objectives and aims are presented.

Cumulative risk in developmental research

Risk in several developmental studies is often defined in general terms as any predictor/s of adverse outcomes in infants and young children. Risk may be in the form of biological illness, prenatal exposure to toxins and substances, adverse life experiences, or as a consequence of maternal birth complications. Its impact is measured according to neurodevelopmental indicators by measures of child behaviour. Infants and young children exposed to risks may have an increased chance of developing neurological problems ranging from severe, such as cerebral palsy, to more subtle deficit in the form of learning problems. Early assessment of risks among infants and young children is necessary to ameliorate the effects of these risks through the identification and application of appropriate developmental interventions (Aylward & Aylward, 2011; Hooper, Burchinal, Roberts, Zeisel, & Neebe, 1998).

Early follow-up studies of infants and young children at-risk looked at a single risk factor (biological/medical) and its relationship with developmental outcomes (Evans, Li, & Whipple, 2013). This causal approach may have originated from the concept of "*reproductive casualty*" (Ounsted, 1987) stating that problematic pregnancy or childbirth may result in neurological damage to the foetus and/ or the newborns. This early causal hypothesis evolved from four propositions predicting negative outcomes in pregnancy: First, prematurity and pregnancy complications may cause infantile death due to cerebral damage, although, some will survive. Second, depending on the location of the damage in the brain, survivors will develop possible neurodevelopmental problems. Third, pregnancy-related problems and abnormalities are associated with life adversities, and as such pregnancy or birth problems are situated most

likely in the poorer areas of the society. Finally, maternal endocrine problems, birth complications, birth prematurity, prenatal infections all may aggravate each other resulting in more severe outcomes in infants and young children (Pasamanick & Knobloch, 1966). However, this perspective was contested by a "*caregiving casualty*" framework, which provided a more balanced view of risk from an environmental context. Therefore, instead of '*single risk analysis'*, a contextual form of analysis was proposed that looked into individual developmental progress or regress within the environmental setting (Sameroff & Chandler, 1975; Sameroff, Seifer, Zax, & Barocas, 1987). Socioeconomic status, birth complications and cognitive development in young children are interconnected and it was suggested that one element cannot function without the other, such that an assessment of cognitive development without the social factors may not be the most clinically appropriate way to describe the consequent ability or disability of a child (Aylward, 1992; Sanson, Oberklaid, Pedlow, & Prior, 1991). Such a claim was supported when socioeconomic status was included in the analysis of young children; those children from lower socioeconomic environments. For instance, those children from more deprived economic strata were found to have more exposure to perinatal complications, which in turn were associated with poorer scores on cognitive tests. Perinatal status alone was found to have poor predictive validity when measured in later outcomes (Sameroff et al., 1987). Sameroff et al,. (1987) argued this contextual approach or "transactional model" was a viable explanation for several paediatric clinical trials and clinical developmental studies, owing to its emphasis on the critical role of the environment in child development rather than the medical history alone.

Several questions were explored through Sameroff's (1987) transactional framework of environment and child plasticity. Within this framework, Aylward, (1992) conceived the term *"risk route"* and suggested three domains of developmental assessment (bio/medical, social, and behavioural/developmental) that fit with the transactional model. Within this framework, several developmental hypotheses for follow-up studies were proposed, including: a.) Cumulative risk affects developmental outcomes, b) environmental factors exert an effect on child development from two years old onwards, c) environmental risks may influence later language and cognitive development in early childhood more than biological risks, d) environmental risks aggravate the effects of biological risks in child development, and e) an interaction exists between genetics and the environment The question of predictive validity of follow-up studies was addressed by looking at several influences such as person factors (brain plasticity), time factors (timing of the insult), and social factors (home, school environment).For instance, severe developmental outcomes associated with early brain insults may be ameliorated by the development of new neural connections that come about through more optimal cognitive and social stimulation available in families where there are

more resources. However, timing of the insult and its impact on later development may also be important, as some perinatal problems may have no observable effects in early childhood, but have latent effects that occur when higher order cognitive processes are required later in childhood (Aylward & Kenny, 1979; Aylward, 1990; Aylward, 1992).

Cumulative risk model

Therefore, because it is unlikely that a single factor may cause a severe developmental outcome it has been arqued that examination of multiple risk factors during pregnancy and early childhood is needed and many studies have adopted a “cumulative risk” model can be argued in infants and young children (Greenberg, Speltz, DeKlyen, & Jones, 2001; Sanson et al., 1991). Using this model Cumulative Risk (CR) is constructed from dichotomising each risk as 0 = no risk and 1 = risk and risk is evaluated by the number of risks rather than the frequency or pattern. For example in a study of Sanson (1991), the interactions between low socioeconomic status and a child with a difficult temperament as well as the interaction of male sex and perinatal stress were associated with overall parent-rated evaluation of child problem behaviour. In a study that examined domains of ecological risk (child, parent, attachment and family), child behaviour problems were better predicted with a combination of these factors. Sensitivity and specificity of clinical status increased when three or more factors were present, and specific combinations were differentially associated with conduct problems (Greenberg et al., 2001). Finally, accumulated risks that have been shown to have an effect on early cognitive development and well-being have also been shown to have differential effects with slower rates of acquisition of language and cognitive skills over time (Burchinal, Roberts, Hooper, & Zeisel, 2000; Masten, 2001). Vulnerable children can be identified and proper intervention can be given (Evans et al., 2013).

More recently, *cumulative risk models* (CR) were examined in 196 published articles (Evans et al., 2013). Overall, CR was consistently derived from the accumulation (additive) of adversities from the biological to the physical environment in a non-aggregated manner. The most common variables were gender, household income, parent educational attainment, single parent household, teenage pregnancy and indigenous or minority affiliation.CR was also reviewed in cross-domain studies where risk factors in different domains were aggregated and the question of whether developmental outcomes were worse when risk was present across a number of domains was addressed. For instance, similar risk predictors might be aggregated in the family domain (child-parent relationship, crowding and parent rearing practices), the neighbourhood domain (community violence, community pollution, and

community interaction), and educational domain (hours in early childcare, teacher-student activities, and early childcare practices). CR in cross-domain studies was found to predict outcome depending on the number of different domains of risk exposure (Evans et al., 2013).

A number of metric approaches to cumulative risk have been explored to test whether several alternative statistical modelling of CR could be more potent than the additive CR model (Evans et al., 2013; Hooper et al., 1998). A review of *multiple regression method* (OLS method) with the additive method of analysing CR showed that the multiple regression method was better in 58 out of 95 studies, 7 studies found that CR method was superior and 30 studies found the two different metrics were comparable (Evans et al., 2013). A further comparative study of different multiple risk developmental models found the CR index was superior in prospective prediction (Flouri & Kallis, 2007). A further approach for examining multiple risks is the *additive approach*. In this method, risk factors are standardised (converted to Z score) and then summed (*summary score method*), this method was found to be almost identical to the additive CR method. Finally a factor analytic approach was evaluated and found to be beneficial in reducing several risk predictors into uncorrelated factor scores to be used as predictor variables. *Factor scores* derived from factor analyses can be used for further analysis without the problems of variable overlap. This technique was better in nine out of 11 studies than additive CR. The only disadvantage in the factor score method is the possible removal of uncorrelated risk predictor variables that may be important in subsequent analyses.

Profiling or clustering risks into meaningful constellations was a further method that Evans et al., (2013) reported was underutilised, but may address the trade-offs and limitations identified in other methods. The *cluster analytic method* creates a profile or cluster of risks that are hypothesised related, based on configuration and the magnitude of risks more than the accumulation. Therefore, this technique is useful to test whether certain meaningful combinations of risks may explain variance in developmental outcomes. It is also possible to invert the cluster solution from risk to resilience and vice versa. The cluster approach has been shown to be more tenable with Masten's model of resilience (2001). A theoretically informed clustering approach is known as the '*Person-centred approach';* this approach uses the inter-correlations of risks, aggregating these for the purpose of creating a group profile (Laursen & Hoff, 2006). This approach challenges the additivity hypothesis of risks - which is that the 'quantity' of risk is associated with more adverse developmental outcomes. A more complicated approach to understanding interconnections of risks can be determined through the use of *structural equation modelling* (*SEM approach*), here latent variables can be

evaluated, as to whether or not similar magnitude is invariant among groups, and interaction of risks can be tested with a larger sample size (Evans, 2003; Evans et al., 2013; Hooper et al., 1998). In sum, both cumulative risk (additive) and statistical risk models (aggregated) were helpful in determining the environmental risk interactions with child outcomes. However, cumulative risk models were generally more readily interpretable and more parsimonious (Burchinal et al., 2000; Hooper et al., 1998).

Clustering risks

The *risk designation approach* was previously applied to test developmental outcomes. However, in these models CR was often assigned arbitrarily and included only a small exposed group (upper quartile) or those children who were most likely exposed to severe adversities. Therefore, to avoid the chance of evaluating only a small portion of the sample in an outcome studies, a 'recursive partitioning' method has been utilised. In this method, child participants were grouped according to specific criteria: a) homogeneity of risk exposures and c) tests showing significant difference of outcome variables among groups (Evans et al., 2013) Therefore, this method can be handled by a cluster analytic approach whereby child samples are grouped together according to their pattern of responses among risk measures and predictors. A cluster solution can be used to determine subgroups that in turn can be used for further tests of significant differences. It also captures similar propositions that actual associations of risk variables and developmental outcomes should be explored, significant differences should be tested among subgroups, and emergence of risk patterns should reveal configuration of risks. However, the cluster analytic/risk designation approach and the additive cluster risk model both lack substantial theoretical explanation to support their claim (Evans et al., 2013).

More refined methods of cluster analysis are currently employed in child risk studies (*Latent Class Analysis*) with a focus on the '*person-centred approach'* perspective. Latent Class Analysis is a variant of cluster analysis and is a measurement approach to estimate risks (ecological or social) as predictor of outcomes. Several studies opted for LCA due to its intuitive results rather than the traditional CR model. Longitudinal studies in large sample data used LCA to determine multiple risks and unobserved subgroups that impact child or later development. Current research with LCA as the main analysis span several areas: a) predictors of childhood poverty (Roy & Raver, 2014), b) culture and caregiving quality (Lanza, Rhoades, Greenberg, Cox, & The Family Life Project Key Investigators., 2011), c) family risk profiles and early executive function (Rhoades, Greenberg, Lanza, & Blair, 2011), d)

cumulative childhood stress (Bjorkenstam et al., 2015) and e) gene markers in youth resilience (Brody et al., 2013) among others.

Theoretical framework to explain cumulative risk

The literature on theoretical frameworks to support cumulative risk is scarce and explanation for its predictive power may be dependent on the careful analogy of the risk configuration. However, developments in the field of biological stress have provided an explanation of why people may be sensitive to high levels of risk exposure – allostatic load. The term *Allostatic load*, is an index of the organism's ability to withstand the effects of the stress and strain from repeated exposures to various threats, demands and challenges (McEwen, 1998).This model proposes that a number of physical response system interact with each other and the prolonged exposure to wear and tear will inevitably result in the slowing down of the system and inability to achieve a resting state (Ganzel, Morris, & Wethington, 2010). This analogy is similar to an individual exposed to multiple risks compared to a single risk factor. The use of statistical mediation analysis to determine the potency of cumulative risk in a longitudinal study can be utilised. Results support the claim that long term CR overwhelms the developmental trajectory of an outcome (Evans et al., 2013). Four similar frameworks from the fields of developmental psychology, paediatrics, behavioural ecology and integrationist could be used to support cumulative risk in young children:

Developmental – Bronfenbrenner's bio-ecological framework

Cumulative risk impacts developmental outcomes more than the expected single risk factor. The theory expands on the idea that the energy system that exists to support an organism is interchangeably flowing between living, non-living as well as geographical sources. Cumulative risk may interfere in this flow of energy that supports the organism. As a consequence, it results in greater energy requirement to support the normal progress and development of life (Bronfenbrenner, 1979; Evans et al., 2013). The bio-ecological perspective allows room to support risk domains that can be distal (micro level) and proximal (macro level) to outcomes are significant in infancy, early childhood and middle childhood stages (Bronfenbrenner, 1986). In this model, influences surrounding the child were represented as a concentric circles, spiralling outwards from child-centred to micro-level (family processes) to the macro-level (school environment and culture). Interactions and inter-connections of influences can be described in the following nested systems: a) microsystem – refers to the proximal influences the child is exposed to (for example, parents and siblings), b) mesosystem – refers to the interconnections of proximal influences such as in the case of family unit and early childhood day centres, where relationships and literacies can be

explored, c) exosystem – refers social and more indirect influences such as the mass media, and local communities. Children learn values and social processes from reading books, watching televisions, technologies and the internet and from their parents' socialisation (church, school organisations, and social projects), d) macrosystem – refers to the larger socio-cultural activities and traditions that permeates in a society or economic-political events that might be relevant to human development policies affecting living conditions (household, education, and health), and e) chronosystem – refers to the 'time and timing' of child development along the rapid changes in tools and technologies, parenting practices, housing conditions, environmental changes, and social legislations and human development policies (Bronfenbrenner, 1979; Bronfenbrenner, 1986).

Paediatric – EBD framework

Developmental-paediatric theoretical frameworks evolved through the development of basic sciences: epigenetics, neuroscience, and biomedical sciences. Three growing principles supported the EBD framework (Ecology – Biology – Health/Development) in understanding lifelong effects of early childhood stress and experience of deprivation: a) early experiences are built into the human system, b) early adverse experiences can influence the human system and in turn the body's stress response, and c) early human system disruption may persist into lifespan and lead to impairments and/or disability (Shonkoff, Garner, & The Committee on Psychosocial Aspects of Child and Family Health, Committee on Early Childhood, Adoption, and Dependent Care, and Section on Developmental and Behavioral Pediatrics., 2012).

Integrative adaptive framework

The adaptive framework is the behavioural ecologist's view of early stress response that influences subsequent human development. Early stresses complicate physiological and neuroendocrine systems, re-wire neural networks and affect brain growth trajectory. This framework identifies several complex mechanisms in the early stages that predict adverse development, starting with the mother as an early environment they are: a) maternal corticosterone, b) other maternal biochemical, c) maternal behaviour affecting offspring hormones, d) maternal behaviour affecting child gene expression, e) maternal behaviour affecting child nutrition, f) maternal attachment and separation. Early stress experiences are multi-layered (social, biotic and abiotic) and may have possible *stress carryover effects* which can be enhancing (survival purposes) or debilitating (disability or deficit). Substantial effects of early stress could influence a spectrum of child development from sensitivity (limiting developmental windows) to personality (adaptive response to environment) (Sih, 2011).

Early life stress framework

Early Life Stress (ELS) is the exposure to single or multiple adverse experiences (early trauma, antenatal/prenatal stress, child birth complications, substances, household deprivation, neglect, lack of stimulation) which aggravate negative coping styles and may lead to poorer outcomes. ELS framework is flexible and adheres to the behavioural and biological markers of developmental outcomes. ELS is deemed related to several parts of the neural system such as prefrontal cortex, superior temporal gyrus, corpus callosum and the cerebellum, which are then associated with global cognitive skills that predict intellectual capacity, achievement, language development/acquisition and executive function skills. ELS are also related to basal ganglia and the amygdala, which are then responsible for reward-processing behaviour and emotional reactivity to negative experiences. Therefore, ELS can account for a significant variance in child development and well-being (Pechtel & Pizzagalli, 2011).

Overview: CHYLD Study

The *Children with Neonatal Hypoglycemia and their Later Development* (CHYLD) Study is a cohort of infants enrolled in one of two parallel studies: The Babies and Blood Sugar's Influence on EEG (BABIES) study, (N = 102 infants), and the Sugar Babies study (N = 514 infants) from 2006 to 2010, born at Waikato Hospital, in Hamilton, New Zealand. The general aim of the CHYLD study was to prevent the adverse outcomes of neonatal hypoglycaemia by looking at the neurodevelopment of young children aged 2 and 4.5 years. Neonatal Hypoglycaemia is defined as low blood glucose less than 2.6 mmol/L or 47 mg/dL. A portion of the infants (N = 237) were enrolled in a randomised placebo-controlled trial to investigate the effectiveness of buccal dextrose gel. Children were assessed at 24 months (N = 404) and at 54 months (N = 355) for motor development, visual processing, and cognitive and social and emotional development (Mckinlay et al., (nd); Mckinlay et al., 2015).

Outcomes

Doctoral theses and publications related to the CHYLD study identified that early treatment of neonatal hypoglycemia and the maintenance of blood glucose level approximately, 2.6 mmol/L or 47 mg/dL was effective preventing adverse neurosensory outcomes and developmental delays in young children (see Table 1). However, at the ecological level, some children assessed at 2 and 4.5 years showed signs of poor performance in tests of cognition, executive function, and parent-rated behaviour. These could be related to social predictors that may aggravate the effects of primary risk factors (IDM, born large, born small, late

preterm, neonatal hypoglycemia or maternal substance use). Therefore, the use of any integrated bio-ecological paradigm to account for cumulative risk is worth investigating.

Table 1 : Doctoral theses and published/submitted studies related to the CHYLD study

Author/s	Study	Theme	Outcome
Mckinlay (2015) (Research Fellow) and the CHYLD study Investigators	2-year follow-up (published article) (Interdisciplinary Scope)	Neurodevelopmental outcome (Cross-section)	Results showed that neonatal hypoglycemia was not associated with neurosensory development of toddlers; maintaining blood glucose level at least 2.6 mmol/L or 47 mg/dL is not related to any adverse outcomes.
Ansell (2014) (Doctoral Research)	2- year follow-up (doctoral thesis) (Liggins Institute)	Neurodevelopmental outcome (Cross-section)	Primary risks such as being born small for gestation, infant of diabetic mother, feeding problems, less breastfeeding, predisposes a child for poorer developmental outcomes. Interactions among socio-environmental variables such as low socioeconomic status, sex (male), and gestational diabetes are related to poorer developmental outcomes.
Sandy Yu (2014) (Doctoral Research)	2-year follow-up (doctoral thesis) (Optometry and Vision Science)	Vision outcome (Cross-section, Instrument validation)	Results showed that there were no differences between euglycaemic group and neonatal hypoglycemic group when vision measures were compared. Visual deficit score was found not significant when compared among groups (hypoglycaemic vs euglycaemic) Toddlers who experienced episodes of low blood glucose level (less than 2.6 mmol/L or 47 mg/dL) did not result in statistical difference in vision measures compared to euglycaemic group.
Chakraborty (2015) (Doctoral Research	4.5 year follow-up (doctoral thesis) (Optometry and Vision Science)	Vision outcome (Comparative, Cross-section)	The threshold used (2.6 mmol/L or 47 mg/dL) for the treatment of neonatal hypoglycemia is an effective cut-off in preventing adverse visual impairment in young children. Global motion perception is poorer for children with cumulative risks (primary risk factors) compared to those with

			only one risk factor.
Paudel (2016) (Doctoral Research)	2 and 4.5-year follow-up (doctoral thesis) (Optometry and Vision Science)	Vision outcome (Longitudinal)	Early intervention and maintaining blood glucose at 2.6 mmol/L or 47 mg/dL is a preventive approach to avoid visual impairment associated with adverse outcomes in severe neonatal hypoglycemia in young children. The frequency of low blood glucose (less than 2.6 mmol/L or 47 mg/dL) after birth is not associated with visual difficulties at 4.5 year of age. Visual outcome measures at 2 years are weakly associated with visual outcome measures at 4.5 years of age.
Mckinlay (2017) (Research Fellow) and the CHYLD study Investigators	4.5 year follow-up (in press, article) (Interdisciplinary Scope)	Neurodevelopmental outcome (Cross-section)	Maintaining blood glucose level at least 2.6 mmol/L or 47 mg/dL is not related to any neurosensory difficulties. However, dose-response relationship is associated with executive function and visual measure outcomes.
Burakevych (2016) (Doctoral Research)	2 and 4.5 year follow-up study (Neonatology/ Paediatrics)	Growth, development and paediatric assessment (Longitudinal, paediatric assessment validation)	Children in the CHYLD follow-up study were mostly socioeconomically deprived. A portion of this cohort experienced neurosensory deficit to at 2 and at 4.5 years of age. Treatment of neonatal hypoglycaemia is associated with the glycaemic responses after six hours of low blood sugar concentration

Study objectives and aims

This thesis is part of a larger follow-up study of children at risk of neonatal hypoglycemia, the *Children with Neonatal Hypoglycaemia and their Later Development* (CHYLD) study. The main objective of this study was to investigate neurodevelopment and health at 2 and again at 4.5 years of young children who were at a risk of low blood glucose level (<2.6 mmol/L) at birth. Five doctoral students and a research fellow have used the data from this study to investigate the heath and development of this cohort using cross-sectional data. Ansell (2014) using the 2-year data and Chakraborty (2015) using the 4.5-year data both found a relationship between CR and neurodevelopmental outcomes. This thesis will contribute to these findings by investigating CR in both the 2-year and 4.5-year CHYLD study data using Bronfenbrenner's bio-ecological model of development and by exploring CR using both a "person-centred approach" and a "variable-centred approach"

A "Person-Centred' approach to neurodevelopment in young children

Much research in the area of neurodevelopment and higher cognitive processes focuses on the relationships and associations using a 'variable-centred' strategy to identify relationships between single risk factor and health, neurodevelopment, and behavioural outcomes. This perspective assumes that associations between variables are homogenous. In contrast the 'person-centred' strategy predicated on the heterogeneity of participants' characteristics, distinct group qualities and categories of behaviour (Laursen & Hoff, 2006). This integrated approach can provide a more thorough explanation of the CHYLD data and a means of analytical strategy through which the evaluation of the following general assumptions can be examined:

1. Primary risks of neonatal hypoglycaemia, paediatric data, sociodemographic variables (social deprivation, maternal education, sex, and ethnicity), parent substance use predict group memberships; and
2. Cumulative risk (risk status) predict all of the following developmental outcomes at 2 years and at 4.5 years: a) cognitive, b) visuomotor integration, c) motor development, e) examiner administered and parent-rated executive function, and f.) parent-rated measure of child psychopathology.

The overall aims of this study is to determine whether a combined person-centred and a variable-centred approach can provide a more in-depth explanation of the various processes

and relationships that describe the neurodevelopment of children born at risk of neonatal hypoglycaemia at 2 years and at 4.5 years of age. The specific aims of this thesis are the following: a) to explore mechanisms of risk and neurodevelopment in children born at risk of neonatal hypoglycaemia; and b) examine the impact of cumulative risk and its interaction with the social/environmental context in order to determine child neurodevelopmental outcomes. The following research questions will address these aims:

- Can distinct subgroups (risk profiles) of children be identified using the CHYLD 2-year and 4.5 year data; and are these risk profiles tenable for exploring theoretical models of CR, and for identifying the risk profile if groups who are more likely to require clinical intervention.
- Assuming valid risk profiles can be identified for the children in the 2 and 4.5 year follow-up, are these risk profiles associated with neurodevelopment at 2 and 4.5 years of age.
- Are risk factors predictive of established risk clusters ('more at-risk' versus 'less at risk')?
- What is the configuration and development of early executive function in at-risk children at 2 years of age and at 4.5 years of age?
- Does risk status (more at-risk versus less at-risk children) differ in the parent report BRIEF-P factor structure at 2 years and at 4.5 years of age?
- Does risk status (more at-risk versus less at-risk children) differ in EF skills as observed in examiner administered tasks at 2 years and at 4.5 years of age?
- What is the role of "observed" executive function on the effects of cumulative risk on cognition?
- What is the role of "everyday" executive function on the effect of cumulative risk on parent-reported childhood problem behaviours?

Rationale

As we have evaluated the neurodevelopment of children born at risk of neonatal hypoglycaemia through the cohort sample at 2 years and at 4.5 years of age (CHYLD study), our understanding of the risk implied by treating neonatal hypoglycaemia and maintaining blood glucose level at 2.6 mmol/L or 27 mg/dL is clinically significant (neurosensory and neurocognition). However, findings with regards to socio-ecological risks and their associations with the primary risks of neonatal hypoglycaemia are not well understood and needing more clarification in this regard. Therefore, after achieving the objectives and aims of the thesis it is prudent that:

- This doctoral thesis will contribute to the *theoretical understanding* of cumulative risk, its nature, mechanisms, and relationship with primary risk factors of neonatal hypoglycaemia as well as its influence on the neurodevelopment of young children. This study may provide additional breadth and depth to the progressive field of *Developmental Science*, through evaluation of conceptual and theoretical models of cognitive-emotional processes in a cohort of atypical young children.

- This doctoral thesis contributes to the *clinical assessment* of young children at risk of neonatal hypoglycaemia. It provides basic clinical information regarding the progress of neurodevelopment in at-risk children through a) the use of statistical profiles of cognitive abilities in the context of cumulative risk; b) identification of risk status ('more at-risk' versus 'less at-risk') in children; and c) configuration of early executive function in at-risk young children.

My doctoral contribution to the CHYLD study

Developmental assessment and Training provides the focal point of the doctoral thesis, which is the underlying impact of cumulative risk, and presents the theoretical frameworks for the subsequent chapters. This chapter provides an overview of the study context (CHYLD Study) as well as the research aims. It also explicitly states the position of this doctoral thesis as an important investigation *complementing* previous CHYLD doctoral theses and building on the previous research outcomes.

Assessment Interpretation and Management is written to discuss, review and provide foundations for neurodevelopment literatures in three areas: 1) outcomes of primary risks of neonatal hypoglycaemia, 2) aspects of developmental outcomes and 3) overview of early environmental risks and their association with neurodevelopment in young children.

Study planning; describe the CHYLD study and the findings to date. Materials and tools from the 2-year and 4.5-year follow-up assessments were presented along with the statistical and research orientation. Main analytical orientations, such as, a) 'person-centred approach' and b) 'variable-centred approach' were discussed.

Data management and analysis, presents a series of studies conducted to determine whether the proposed research objectives and aims are a substantial pursuit of new knowledge and understanding of atypical development in young children. These chapters provide explanations and causal associations or confirmation of previous hypotheses regarding cumulative risk studies, primary risks of neonatal hypoglycaemia, neurocognitive profiles of young children, and development of early executive function in at- risk preschool children. In addition, neurocognitive and neurobehaviour mechanisms are covered to determine the emerging role of cumulative risk and executive function in cognition and well-being in young children.

Results dissemination provides an overall summary, and synthesis of the findings. It will also provide a discussion of the implications of this research for developmental psychologists, child neuropsychologists, preschool teachers, policy makers, and future developmental/clinical trial researchers for CHYLD study or similar cohort study, on child research themes such as: a) follow-up suggestions, b) Neuro-imaging study, d) research methods in cumulative risk and child poverty, d) tools and strategies for intervention, and e) measurement development and validation.

CHAPTER 2: REVIEW OF RELATED LITERATURE

This section explores and reviews a significant body of empirical research to determine the state of knowledge on the neurodevelopmental outcomes of common risk factors (IDM, Large, Small, Preterm) for neonatal hypoglycaemia. This section also reviews the association between socio-ecological risks: (household income, deprivation, parent characteristics, and parent substance use) and neurodevelopment in young children. In addition, literature overview on social deprivation and cognitive development (intelligence and executive function) are presented to provide a theoretical foundation for subsequent analyses of the data.

Neurodevelopmental Outcomes of Common Risk Factors of Neonatal Hypoglycaemia

Neonatal hypoglycaemia and neurodevelopment

Hypoglycaemia is a common metabolic problem in newborns. Achieving a balance of blood glucose is one of the biochemical requirements in the *fetal-to-neonatal transition* (Tin, 2014). It is expected that full-term newborns adjust to the transition by undergoing both metabolic and hormonal changes (Chadran, Rajadurai, Abdul Haium, & Hussain, 2015; Hawdon, 2014). During fetal life, glucose along with other substrates necessary for fetal growth are transported across the placenta. As pregnancy progresses, the amount of glucose transported increases; leading to significant deposits of glycogen and fat storage in the adipose tissue. At birth, when the neonate is separated from its continuous intrauterine supply of glucose, metabolic changes occur that preserve fat stores for vital organ function. At this time the newborn must adapt to a drop in blood glucose and the *fast-feed cycle* by utilising fat released from adipose tissue stores and ingested with milk feeding. Hormonal changes after birth that support the drop in glucose and the transition to the fast-feed cycle allow the release of glucose stored from different sources: glycogen in the liver, cardiac muscle and the brain (glycogenolysis); glucose produced by the liver (gluconeogenesis); and released from adipose tissue stores (lipolysis).

Certain groups of infants either fail to mount the normal metabolic responses in the fetal-to-neonatal transition or are at risk of a more severe or prolonged drop in blood glucose resulting in neonatal hypoglycaemia. Groups that have been found to be at risk are infants who have hyperinsulinism (born to mothers with poorly controlled diabetes during pregnancy),

infants with intrauterine growth restriction (IUGR), or infants born large, preterm or with other pathological conditions at birth (Arya, Senniapan, Guemes, & Hussain, 2014).

Neonatal hypoglycaemia that is symptomatic and prolonged has been shown to be associated with brain injury (Burns, Rutherford, Boardman, & Cowan, 2008). However, the effect of moderate or “transient” hypoglycaemia on the neurodevelopment and behaviour of the developing fetus and child requires further investigation (Hay, Raju, Higgins, Kalhan, & Devaskar, 2009). One of the challenges for establishing the association between neonatal hypoglycaemia and developmental outcomes has been the lack of understanding around the level of blood glucose at which neurodevelopment may be impaired, or whether the frequency and/or duration of low levels of glucose are related. The plasma glucose concentration that has generally been adopted is < 47 mg/dL or < 2.6 mmol/L and is the level used in identifying hypoglycaemia in the CHYLD study (Adamkin & Committee on Fetus and Newborn., 2011; Mckinlay et al., 2015) using this guidelines, it has been estimated that up to 30% of neonates are thought to be at risk for hypoglycaemia and 15% receive a diagnosis (Harris, Weston, & Harding, 2012). However, different guidelines have been suggested for populations where there are high rates of malnutrition or where children are unwell (Achoki, Opiyo, & English, 2010).

Methodological issues have also hampered our understanding of neonatal hypoglycaemia and development. Boluyt, Van Kempen, and Offringa (2006) reviewed 18 studies investigating neonatal hypoglycaemia and evaluated the methodological standards used. They classified 16 studies poor in quality and only two studies were classified as high in quality. Likewise, not a single study mentioned strong neurodevelopmental deficits as a consequence of neonatal hypoglycaemia. Given this outcome the researchers suggested that appropriate guidelines were needed for studying neonatal hypoglycaemia in newborns and infants. They recommended prospective cohort studies and nested randomised trials were needed to test the effects of varying glucose levels or to test the effects of treatments. They also suggested investigating primary risks factors associated with gestational age and maternal metabolic problems. Finally, they recommended measurements of blood glucose should be standardised using continuous monitoring or identifying body fuels such as ketones, fatty acids or other hormones that can regulate glucose in the blood and neurodevelopment outcome measures should be standardised tests with sound psychometric properties. The CHYLD study was designed to address these recommendations and similar recommendations from the Eunice Kennedy Shriver National Institute of Child Health and Human Development workshop that was held to determine the gaps in knowledge on

neonatal hypoglycaemia (Hay et al., 2009). The results from this study to date have shown that maintaining blood glucose level < 2.6 mmol/L is a preventive approach to the adverse neurodevelopmental effects of neonatal hypoglycaemia in newborns and infants (Mckinlay et al., 2015). Neurodevelopmental outcomes at 2 years showed no significant sensory impairments (visual perception) and no neurocognitive deficits (Bayley-III and Executive Function) (Ansell, 2014; Yu, 2014). Subsequent analyses showed that even when compared to children prenatally exposed to substances, children with neonatal hypoglycaemia did not show any sensory processing deficits (visual acuity, global motion perception and visual perception) at 4.5 years (Chakraborty, 2015). A 2-year and 4.5-year follow-up showed similar sensory findings (visual acuity, stereopsis, and global motion perception) (Paudel, 2016). Neurodevelopment outcomes and paediatric health were evaluated at 4.5 years and found no significant impairments (motor development and physical health) (Burakevych, 2016). However, a dose-dependent risk was found associated with poorer executive function and poorer visuo-motor function was hypothesised (Mckinlay et al., 2017).

Infant of diabetic mother and neurodevelopment

Diabetes is a metabolic problem of the pancreas resulting in the inability to balance glucose and the maintenance of insulin in the body. One type of diabetes is gestational in nature, wherein there is an impairment of maternal glucose during pregnancy. Risk factors related to gestational diabetes are: a) family history of diabetes, b) sedentary lifestyle, c) obesity and d) maternal age during pregnancy. Gestational diabetes occurs in about five percent (5%) of all pregnant women. This may cause problems with fetal development affecting neurodevelopment, and even influence the child's ongoing development. Consequences of being born to a diabetic mother are *macrosomia* or *Large-for-Gestation* (LGA); too much glucose or hyperglycemia; and the most common fetal-neonatal transition, neonatal hypoglycaemia. Finally, preterm births are also linked to gestational diabetes (American Diabetic Association., 2004; Martin & Dombrowski, 2008). Regardless of the type of diabetes (Type 1 or Type 2), maternal blood glucose concentration is considered one of the main metabolic markers in predicting child development outcomes (Ben-Haroush, Yovev, & Hod, 2003; Lawrence, Chen, Contreras, & Sacks, 2008; Persaud, 2007; Weindling, 2009). Despite the established knowledge about gestational diabetes there is little research published about the neurodevelopment of infants born to diabetic mothers (IDM). Long-term studies are lacking which can explain whether or not gestational diabetes predisposes children to brain insults and eventually leads to poorer behavioural and educational outcomes (Martin & Dombrowski, 2008).

Two models can be used for evaluating neurodevelopmental outcomes in IDM. The first is *directly through the alteration of maternal glucose level resulting in behavioural teratology and impacting child development*; and the second is *indirectly through the mediating role of perinatal complications* (for example neonatal hypoglycaemia and respiratory distress at birth). These two models can be analysed individually or in combination, to examine how each process and mechanism can influence developmental outcomes. (Cornblath & Schwartz, 1976; Freinkel & Metzger, 1979; Rizzo et al., 1995).

Previous studies evaluating the psychomotor development of IDM showed no significant correlations between motor proficiency and perinatal complications; similarly no significant findings were seen among the relationship between gestational diabetes, neonatal hypoglycaemia and psychomotor development (Rizzo et al., 1995). Nevertheless this study evaluated only one domain of neurodevelopment. In a prospective, controlled three-year follow-up study, several developmental domains where evaluated to look at delays or deficits. Results showed that only language development was significant to IDM who entered the study late and whose maternal diabetes was less well controlled. Head circumference was associated with mental and developmental motor scores at 6 months and 3 years of age. Head circumference alone was associated with both average (mean) length of utterance and verbal reasoning scores (Sells, Robinson, Brown, & Knopp, 1994). To support the claim, that language development is impaired in IDM, Dionne, Boivin, Seguin, Perusse and Tremblay (2008) carried out a case controlled, longitudinal study (from 18-months to 7 years of age) of 105 singletons and 116 twins, subgroups of two large Canadian follow-up studies. Infants born less than 32 weeks gestation were excluded. After controlling for child gender, gestation duration, birth weight, Apgar score, gestational hypertension and alcohol/cigarette consumption, IDMs scored between .27 to .42 SD below controls on expressive vocabulary and expressive grammar at 18 and 30 months. At 42 and 60 months, there were no differences between IDMs and controls on expressive and receptive language development. At follow-up of 72/84 months IDMs performed .35 SD below controls, but they did not differ between reading and math. Subsequent analyses examining the moderating effects of genes and educational level showed genes were strongly associated with the risk of delays infants of diabetic mothers, and offspring of educated mothers were less affected (Dionne et al., 2008). A further study of neurodevelopment outcomes compared 57 children born to 48 mothers with well-controlled diabetes to 57 control children matched for age, birth order and parental socioeconomic status. An extensive battery of physical and neurodevelopmental tests examined the neurobehavioral function of school-aged children from 5 years to 12 years

of age. Results showed that IDM were heavier than controls, had significantly lower motor scores, and significantly higher soft neurological signs compared to control group. In behavioural outcomes, IDM were associated with increased hyperactivity. Severity of maternal diabetes was tested through correlating biochemical data (blood glucose, urine, glycosylated haemoglobin) with developmental outcomes. Sensory-motor function of IDM was associated with severity of maternal diabetes. However, IDM children scored in the normal range for cognition and did not differ from controls (Ornoy et al., 1998). A similar study were carried out in 32 IDM children at an earlier school age who were compared to 57 matched controls and showed similar outcomes. Children of diabetic mothers before 9 years of age were prone to attention problems, lower gross and fine motor scores and in turn lower cognition scores. Weight was associated with gross motor scores. Findings also showed that differences observed at earlier ages tend to disappear by early adolescence (Ornoy, Wolf, Razon, Greenbaum, & Dulitzky, 1999).

Earlier studies of IDM suggest that the development of attention problems and hyperactive behaviour may appear during early childhood years but these behavioural manifestations in IDM were never a focus of these studies. A more recent study focused on the risks for ADHD and aimed to analyse the data within the context of family household income (Nomura et al., 2012). Participants were young preschool-age children from three to four years. Neuropsychological tests, temperament measures and sociodemographic data were used in the subsequent analyses. Results support previous findings of IDM exhibiting more problems of inattention compared to controls. However, results also showed that being born in low socioeconomic status (SES) puts the child at a higher risk of developing attention deficit hyperactivity disorder even at 2-year follow-up. Children exposed to combined gestational diabetes and low socioeconomic status showed higher scores for inhibition problems, activity level, poor persistence, and impulsive behaviour. Behavioural functioning at six years of age showed that combined gestational diabetes and low socioeconomic status was associated with a 14-fold increased risk for ADHD (Nomura et al., 2012).

More recent study of school-aged children found that compared to a control group, school aged children IDM scored lower for general IQ, however, not outside the average range and a higher prevalence of soft neurological signs (Bolanos, Matute, Ramirez-Duenas, & Zarabozo, 2015). This study also showed that working memory scores were poorer for IDM compared to controls as working memory is largely associated with the hippocampal-prefrontal networks, a part of the brain that is sensitive to metabolic abnormalities, the researchers suggested that an early insult to this region may have downstream effects such as impairing more complex

behaviours associated with executive function (EF). However, to date few studies had investigated the association of IDM with these more complex cognitive processes. As deficits in EF processes could be associated with the outcomes on poor language processing where the IDM group show problems in reading non-words which is a representation of phonological processing and is associated with reading problems (dyslexia), while on the other hand, the group's performance in digit-ordering tasks may be similar to early numeracy problems (dyscalculia) (Rosselli, Matute, Pinto, & Ardilla, 2006). This study supports early findings (Ornoy et al., 1999) that children exposed to gestational diabetes have poorer bimanual, graphic and spatial performance (Bolanos et al., 2015). Mild cognitive impairment seen in this group of children were not evaluated for school achievement so further assessment is required to test whether subtle e deficits will impact literacy and numeracy among preschool children and whether learning difficulties can be predicted.

In summary, gestational diabetes is a risk factor in developing subtle developmental deficits in children. Behavioural manifestations such as inattention and hyperactivity were associated to low socioeconomic status and IDM. Further cognitive correlates showed lower language and cognitive scores and problems in inhibition and working memory from infancy to early childhood. Hypothesised developmental deficits could impact early literacy and numeracy development in children.

Small for Gestational Age (SGA) and premature birth

Small-for-gestational-age can be defined in different ways in medical contexts but the most common definition is a birth weight <10th population centile. A review of several studies showed that maternal risks include maternal height (being short), maternal weight, ethnicity (Asian), nulliparity, cigarette (smoking), and cocaine exposure. Maternal complications such as hypertension, liver problems and malaria are contributory to SGA births. Some risk factors commonly identified are frequent bleeding during the early stage of pregnancy, placental problems, pre-eclampsia, and maternal hypertension (McCowan & Horgan, 2009).

Fetal growth restriction (FGR) is the inability to reach full fetal development conditions due to several maternal and intrauterine problems. A meta-analysis showed that SGA children are prone to suboptimal neurodevelopmental scores, regardless whether they are term-born or with growth restrictions. It has been hypothesised that poorer neurodevelopmental scores are related to the mechanisms of SGA and placental dysfunction. However, placental dysfunction

alone does not explain poor neurodevelopment outcomes (Arcangeli, Thilaganathan, Hooper, Khan, & Bhide, 2012).

A prospective cohort study of infants from Brazil comparing SGA births and appropriate-for-gestational-age AGA births in the first year of life showed a significant trend of poorer performance for motor scores from 2-months through 12-months on the Bayley Scales of Infant Development-II (BSID-II) among SGA infants (Mello, Gagliardo, & Goncalves, 2014). The SGA infants were observed to have more irritable and less engaging behaviours on the Behaviour Rating Scale (BRS) of the BSID-II compared to AGA infants. Findings on the BRS also showed that motivational or interactive processes were also poorer for SGA. These deficits and delays were attributed to early insults from being born SGA. The hypothesis was that the limbic system, which governs emotion and motivational regulation, were affected by SGA while motor deficits in the second month after birth may be a marker to detect motor and behavioural problems (Mello et al., 2014)

Factors associated with SGA and preterm birth

McCowan, Pryor and Harding (2002) conducted a study in the mid-1990s in Auckland, New Zealand looking at a range of perinatal variables and their association with neurodevelopment and behavioural ratings using the BSID-II in 282 SGA children at 18 months. They found no significant direct association if SGA and cognitive and motor scores. They concluded that being born SGA was only one factor of the many that may contribute to poorer neurodevelopmental and behavioural outcomes (McCowan et al., 2002).

Restricted fetal growth may result from various complications. Thus, being born very preterm with an accompanying SGA is hypothesised to have poorer developmental outcomes compared to being born preterm but appropriate-for-gestational-age (AGA). Research has shown that weight at birth, birth length and head circumferences are associated with SGA (Gortner et al., 2003). However, there were no differences in eye-hand coordination, creeping, crawling, sitting, first words, and walking alone within specific developmental milestones when compared to AGA controls (Gortner et al., 2003).

Prematurity and intrauterine growth restrictions were found to be common among infants with complicated maternal conditions and pregnancy, and to be associated with poorer

neurodevelopmental outcomes. In a sample comparing SGA-born, extremely premature and term-born, an 18- and 22- month follow-up showed that being born SGA group was associated with mothers who frequently received maternal care and antenatal corticosteroids, had pregnancy-related hypertension, and had lower educational attainment. Their infants were most likely delivered by caesarean and had lower Apgar scores (De Jesus et al., 2013).

A recent study that aimed to investigate cognitive development of very low birth weight (VLBW) preterm SGA and AGA babies in Great Britain followed-up 107 infants born between 24 and 35 weeks of gestational age with birth weights less than 1500g (Nogel, Deiters, Stemmler, Rascher, & Trollman, 2015). When children were followed up at 2-years of age results showed that 17% of the cognitive development in children could be predicted by gestational age. Those with lower gestational age between 26 to 29 weeks had a poorer mental development index (MDI) on the BSID-II than those born at 30 weeks or higher. Despite these differences SGA and AGA-born did not differ significantly in their cognitive function. Neonatal risks associated with cognitive functions were gestational age, bronchopolmunary dysplasia, intracranial bleeding, retinopathy and sepsis. In addition, a strong association was found between the parents' profession and cognitive development. This model predicted 21% of the variance in cognitive development at 2 years of age (Nogel et al., 2015).

Neurodevelopmental and behavioural were examined in a population based study of 5-year olds born SGA abd before 32 weeks (Graz, Tolsa, & Fischer, 2015). The Kaufman Assessment Battery for Children (K-ABC) measured cognitive development and the Strengths and Difficulties Questionnaire (SDQ) measured behavioural outcomes. SGA was significantly associated with behavioural scores but not with cognition or neurodevelopment impairment. Predictors of cognitive outcomes were gestational age, major brain lesions, and poor socioeconomic status (SES). Severe impairment was associated with birth asphyxia, major brain lesions and maternal smoking (Graz et al., 2015).

The effect of growth trajectories on neurodevelopment in children born SGA

The dilemma of different patterns of "catch-up" growth on postnatal health and development among SGA infants was investigated in a study carried out by Lei et al., (2015). Rapid postnatal catch-up growth in some studies has been related to a number of metabolic

disorders (Lei et al., 2015). In contrasts, persistent poor postnatal growth has been associated with impaired cognitive development (Varella & Moss, 2015).

Lei et al. (2015) examined 5 trajectories of growth and found catch up was not necessarily protective for neurodevelopment or infection, but rather may be predictive of high blood pressure and/or obesity. Those who have appropriate catch-up are the ones who had decreased risks. The optimal 4-month catch-up was observed to be an indicator of good performance for those SGA-born. Optimal catch-up growth for SGA was described as an increased birth weight and birth length ratio to about the 30th percentile during the first few months after birth followed by a moderate catch-up of around the 50th percentile later on (Lei et al., 2015). A similar study evaluated early catch-up and associated cognitive performance in 4-year olds. Results showed that infant weight gain within four months was predictive of its intelligence score at 4-years of age. Children with early appropriate catch-up have slightly higher intelligence scores compared to the steady growth children and those who have developmentally regressive growth (Varella & Moss, 2015).

Catch-up in head growth patterns were investigated in school-aged children aged 7 to 9 years of age (Frisk, Amsel, & Whyte, 2002), SGA children (N = 71) were divided into groups based on head circumference at birth and at 9 months and compared to 16 full-term AGA control children of similar SES. Children completed a battery of developmental tests that included: cognition, language, working memory, problem solving, visuomotor, phonological awareness, and literacy. Results showed different patterns of growth trajectories were associated with different levels of impairment. Children with poor prenatal and postnatal growth at 9 months had the worst outcome, with significantly lower verbal and nonverbal IQ ratings relative to full-term controls and SGA without brain growth compromise. Phonological awareness, problem solving and visuomotor integration, and copying tasks were also poorer. SGA that initially had a brain growth compromise in utero but experienced catch-up at 9 months (head circumference >9th percentile) also had verbal and verbal IQ ratings that were significantly lower than SGA without growth impairment and controls, but no impairment in visuomotor or problem solving. The SGA children with not growth impairment had the best outcomes and did not differ from controls with the exception of spelling. One explanation put forward by the authors of this study for the SGA group with not catch-up being at particular risk was that problem solving ability characterising this group may be a marker for sub-optimal frontal lobe function. As the frontal lobe is one area of the brain that does not reach full synaptic density until 2 to 3 years, the prolonged impairment if growth of this group which extended well into

the first year and beyond may lead to impairment in frontal lobe functions such as executive function (Frisk et al., 2002).

To date most studies examining neurodevelopment outcomes of SGA focus on infants born very premature or with associated maternal complications. However, most SGA children are born only moderately premature or term-born rather than very premature. To address the effects of moderate prematurity of SGA on neurodevelopment, Tanis et al., (2015) investigated the neurodevelopmental function of 7-year old children. They found that cognitive outcomes were not statistically lower nor was visuomotor integration than a control group of AGA. However, attention control problems were associated with SGA. The odds of SGA to have abnormal scores on attention control were 4 times greater than that of AGA peers (Tanis et al., 2015). A further study in moderately preterm SGA focused solely on attention problems and whether they were related to gestational age and being born SGA in 6- to 8-year old children. Results showed that there was an inverse relationship between intensity of reported attention problems and weeks of gestation (Eryigit-Madzwamuse & Wolke, 2015). This means attention problems were higher for every week less than 37 weeks of gestation. Further analyses showed there were no observed interaction effects from the combination of prematurity and SGA indicating that the impact of being SGA was similar across the whole gestation spectrum. However, the effects were attenuation once adjusted for head circumference at 5 months and its impact disappeared by 8 years when adjusted was made for child sex and family SES (Eryigit-Madzwamuse & Wolke, 2015).

Previous studies have shown that prematurity is common among SGA, but the separate effects of being born premature and SGA on the developmental outcomes have only been investigated in one longitudinal study to date that examined emotional problems in early adolescence (Hall & Wolke, 2012) Results showed that children who were more likely to develop emotional problems in early adolescents are more likely to be born premature than SGA and to have parents from low SES backgrounds(Hall & Wolke, 2012). This study supports the fetal programming hypothesis, which states that intrauterine problems most likely influence the development of the central nervous system, however, outcomes are altered by several mediating factors such as developmental changes and socioeconomic experiences to the conceptualisation that intrauterine problems are most likely to influence the development of the central nervous system. However, outcomes are altered by several mediating factors such as developmental changes and socioeconomic experiences (Raikkonen & Pesonen, 2009).

In summary, SGA as a form of intrauterine growth problem is associated to early poorer neurodevelopment. Associated risks such as preterm birth, birth characteristics (head circumference), complicated maternal conditions, and social deprivation (SES) were related to adverse outcomes. SGA in early childhood was correlated with more with increasing inattention problems in children born premature than cognitive scores.

Large for gestational age (LGA) and neurodevelopment

Infants' born to mothers with gestational diabetes mellitus (GDM) are known to be at risk for increased birth size and often develop macrosomia (citation). An infant with a birth weight between 4000 and 4500 grams is considered macrosomic. On the basis of gestation, birth weight and gender, infants are categorised as large-for gestational-age (LGA) when they have a birth weight >90th percentile for gestational age. LGA in 1-year olds is related to maternal anthropometric status such as maternal adiposity or being overweight and an increase of abdominal skin fold thickness and waist circumference. Associated maternal diabetes and LGA cases in children are related to childhood obesity. Post-meal glucose assessment among mothers with gestational diabetes is associated with upper arm circumference and skinfolds in 1-year old infants. These physiological processes observed in mother and offspring may explain the *Fuel Mediated Model of Teratogenesis* in newborns. This model states that maternal intrauterine complications as the immediate environment for the growing fetus are associated with adverse developmental outcomes (Vohr & McGarvey, 1997). One complication of GDM at birth is hypoglycaemia; however, hypoglycaemia has also been shown to occur in 16% of LGA infants born to non-diabetic mothers (Schaefer-Graf et al., 2002).

Few studies are available that investigate the neurodevelopment of being born LGA with and without neonatal hypoglycaemia. However, one study that investigated the neurodevelopment outcomes of 4-year-old children born LGA to non-diabetic mothers found no differences between normoglycaemic children (N = 15) compared to hypoglycaemic children (N=60) (plasma glucose, 2.2 mmol/L at 1 hour post birth or 2.5 mmol/L, later on) on standardised measures of neurodevelopment, non-verbal IQ or child behaviour. Infants were healthy, full-term and were only allowed up for the first day of postnatal life (Brand, Molenaar, Kaaijk, & Wierenga, 2005).

More recently, a retrospective national cohort study in the United States investigated whether SGA or LGA birth weights were associated with increased odds of children with an Autism Spectrum Disorder (ASD). Different risk factors and pathways were identified for SGA-born and LGA-born. ASD risk was higher when a child was born SGA and premature while LGA was observed to be a proxy for maternal diabetes and other maternal complications. This study identified that separate pathways for ASD risk may arise from brain insults from the combination of prematurity and SGA, while maternal inflammation, intrauterine growths and maternal diabetes were the central factors for LGA-born at risk of ASD (Moore, Kneitel, Walker, Gilbert, & Xing, 2012). Despite the association between of LGA and maternal diabetes, more neuropsychological and developmental outcome research is needed to determine the impact of cumulated risks in young children born LGA.

Cumulative Risk and Neurodevelopment

Early language differences among infants from two levels of family income showed that there were considerable differences from infancy to toddlerhood but there was a noticeable 6-month gap in between for developmental processes. In addition, at infancy stage, those from low income families showed less quality real time processing compared to high income families. Infants from high income parents were hypothesised to have enough resources for cognitive stimulation and these infants were more likely to use more resources for resiliency and positive development (Fernald, Marchman, & Weisleder, 2013).

In support of this study a structural analysis (statistical) showed that SES was associated with the successful performance of children in administered executive function tasks. In fact, correlations of SES, cognitive abilities and executive function in children suggest that children in the low SES group have deficits in reasoning abilities and language development. Previous studies have shown that language development drove executive function. Cognitive impulsivity was observed among children in the low SES group compared to children classified under the middle class group. This study indicated that poor housing, which means fewer resources for cognitive stimulation and more felt distress, played a significant role in the development of executive function in children. A SEM analysis showed that cognitive impulsivity can be a mediating factor that influenced the executive function → SES in children (Aran-Filippetti & Minzi, 2012).

In a sample of Argentine children, researchers evaluated childhood poverty levels and cognition. Results showed that children in a less stimulating home environment have lower quality of performance in administered cognitive tasks, which was then related to the prefrontal region of the brain. There were no differences among performances in EF tasks, when compared to SES status (Lipina et al., 2013). This then suggests that poverty has varying effects on the brain system and the different neural resources. This study advocated the use of imaging paradigms to view SES → brain system association in a biosocial perspective. In addition, health care privileges coupled with environmental cognitive stimulation were the best environmental mediating factors for further cognitive development in children. Other specified mediators such as frequent reading of books and access to computer technology and connection to internet had varied effects to SES → cognitive development relationship (Lipina et al., 2013). Several findings from early childhood and middle school children have expanded knowledge on the effects of environmental quality and adverse experiences on the development of executive function. Research showed that executive function in very young children was strongly correlated with attentional control, information acquisition and information processing as observed by their school teachers. A composite measure of executive function difficulties in very young children predicted 0.12 standard deviation decrease in cognitive processing at middle childhood. In addition, accounting for family income in the equation, over the 4-year period was predictive of more difficulties in middle childhood schooling (Raver, McCoy, Lowenstein, & Pess, 2013).

The interaction of problematic SES and parenting style were taken into account in investigating executive function in young children. Cross-cultural differences showed that poverty was sensitive to African American children, but this was only true for poor families with a single parent. In addition, felt-distress alone was not predictive of executive function in children. Instead, *distress and its interaction with maternal low income status and being a single mother* was a sufficient predictor for poorer executive function in young children. Overall, this study pointed out that the quality of maternal-child interaction predisposed executive function and its consequences. In fact, White American children's poverty status → EF skills association was mediated by maternal-child relationships, while on the other hand African American children's single parent → EF relations was mediated by maternal-child relationships (Rhoades et al., 2011).

Findings from the Millennium Cohort Study (MCS), a large scale longitudinal study of 18,818 child participants from 18, 552 families in United Kingdom revealed that cumulative risks were related to neurodevelopmental outcomes in the early years. Parent psychopathology, prenatal

smoking and poor life skills were related to poorer cognitive development outcomes at 3- to 5-years of age (Mensah & Kiernan, 2010). Changes in cognitive development were related to the quality of the home environment such as parent long-term alcohol use, unemployment, overcrowded house and teenage pregnancy. Parent psychopathology (depression and disability) was associated with adverse Socioemotional adjustments at 3- to 5-years of age. An increased number of cumulative risks predicted more hyperactivity and conduct problems in young children (Mensah & Kiernan, 2010).

In summary, there is strong evidence that socioeconomic status along with parent lifestyle, maternal substance use, and child and parent relationships is associated with various neural developments. Effects were known to have an impact when risk interactions or cumulative risk were present. Cortical thickness is shown to be related to the quality of environmental stimulation and experience. Considerable differences can be seen among children's language development relative to economic status. Environmental quality is very important in the development of executive function at preschool years. In addition, childhood poverty generally, is a predictor of poorer performance in cognitive tasks; while, infant distress, maternal characteristics and single parenting predict low executive function scores.

Neurocognition in children

Intelligence can predict neuropsychological profiles for groups (clusters) of children. Children evaluated as "below average" in IQ tests may show some deficits in encoding as well as deficits in some memory tasks. On the other hand, children under the label "average" revealed some variability in information subtests (Foley, Garcia, Shaw, & Golden, 2009). Therefore, clustering may enhance observations of IQ in children, and be better than qualitative labelling. Subtests of intelligence tests not only predict developmental abilities (when clustered) but also can predict higher cognition (executive function). A study showed that verbal intelligence predicted executive strategies (problem solving techniques) as compared to performance intelligence. The executive strategy pertains to solving mathematical problems which may tap into arithmetic fluency. On the other hand performance intelligence may account for significant variance in the speed of processing but not in the quality of the strategy output. This study pointed out that executive strategy use may not solely focus on intelligence but there are other links to some areas of cognitive function, such as the child's ability to reflect (metacognition) and the ability to regulate one's behaviour (self-regulation) (Luwel, Foustana, Onghena, & Verschaffel, 2013). Likewise, a canonical relation study showed that WAIS-III subtests are strongly linked to D-KEFS, which is a good test of

executive function. WAIS-III, being highly regarded as a test of crystallized intelligence, showed that this may be helpful in solving novel problems when performing executive tasks. 54% of the variance in this model can be attributed to the executive function → speed of processing association (Davis, Pierson, & Finch, 2011).

Executive function in young children

The ability to learn and retain information (*Working Memory*), how to adjust and make decisions from previous information (*Cognitive Flexibility*), how to control one's thoughts or actions in order to achieve the desired goal (*Inhibition*) are considered valuable cognitive processes in order to survive and thrive. Factor analysis was used to describe the interrelated componential skills of executive function. In this study, Miyake and his colleagues (2000) found that the ability to take control and synchronise higher mental processes indicated three distinct and yet separable constructs. These are based on administered experimental tasks, which are identified as: *shift, update and inhibit*. A replication of this study on children, the construct validity of EF was tested on a sample group of 3-year old children and it supported the unidimentional feature of EF. Other factors such as gender showed no differences in EF structure, while children who are considered living in poor socioeconomic conditions have lower levels of executive function (Wiebe et al., 2011).

In another study of executive function (parent and teacher-rated measures in young children), results revealed five factors, namely: inhibition, emotion modulation, flexibility, working memory, and planning/organization. It is also possible to integrate teacher and parent ratings of children's executive function to create more informative factors. Follow-up studies showed that a three-factor solution best describes executive function, wherein inhibitory self-control, flexibility and emerging metacognition were fully supported (Isquith, Gioia, & Espy, 2004). Empirical evidence of an 8- and 9-factor model of executive function was analysed, comparing teacher and parent ratings. Confirmatory factor analysis supported the 9-scale partition, measuring three separable factors of executive function among children (Egeland & Fallmyr, 2010). At present, the developmental perspective supports "observed" executive function as unitary for young children with each skill mature on its phase. However, in "parent-rated" measures, a 3-factor model with subscales was reported to be tenable for young children.

Configurations and exploration of EF constructs were taken into consideration, in particular skills that are more active and related to young children's cognitive organization. A path

analysis study of Senn, Espy and Kaufmann (2004) showed that inhibition is influential on young children's problem-solving performance, while in older children, working memory seems to be more prominent. In addition, emotion regulation is said to be related to inhibition and flexibility constructs, which may lead to the understanding that emotional responses develop alongside the two and may provide ample support for better emotion regulation research in the future (Isquith et al., 2004). On the other hand, developmental gains in working memory peak with age. Performance in neuropsychological tests results showed visuospatial and verbal working memory both peak at age 11 while working memory processing peaks in the 20s (Lehto, Juujarvi, Kooistra, & Pulkkinen, 2003).

Assessment of executive function in children

Executive function is conceptualised as a multifaceted construct coming from unitary but distinctive factors. There is no single measure of executive function that covers the wide and contested variety of factors which up to now are still undergoing some construct validation and clarification. Suchy (2009) devised a guideline for careful use of EF constructs in assessment and researches. This involves the development of the construct, understanding, cautious definition of executive function skills, careful treatment of EF constructs as there is no uniform definition for each, and careful selection of assessment instruments for the study.

Because of the ongoing studies of executive function in children, the assessment relies heavily on performance tasks with questionable psychometric properties, and the suggestions of scale development are advocated specifically for developing children with intraindividual differences (Willoughby, Wirth, & Blair, 2011). Earlier suggestions were made (Henry & Bettenay, 2010; Silver, 2014; Toplak, Bucciarelli, Jain, & Tannock, 2009) such that EF should be measured using both performance and rating scales based on a neuropsychological model. Reynolds and Horton (2008) suggested *multiple executive function abilities* using this model. They recommended both *observed tasks* and *behavioural (parent-rated) measures*, specifically measures which are not heavily dependent on perceptual-motor abilities, as well as a verbal measure that is purely cognitive, while the behavioural (parent-rated) measure is used for the ecological (everyday) behaviour. However, there seems to be a problem in using both performance and behavioural measures. Recent problems have risen regarding disagreements over two measures among researchers and over the outcomes of their research. Silver (2014) explained that EF rating scales are used by teachers and parents to assess a different level of behavioural EF, compared to a laboratory cognitive-type EF. Each measure assumes that executive function can be viewed in the socio-emotional and cognitive

aspects. This explanation supports the earlier claim of Henry and Bettenay (2010) in their assumptions that assessors are encouraged to use alternative EF measures to understand multifaceted structures of executive function in everyday living. In addition, Toplak, West and Stanovich (2013) expanded the explanation by stating that performance on EF tasks evaluates cognitive efficiency in a more structured way, as compared to EF rating scales which evaluate unstructured situations. In addition, the different information revealed by the two different measures will identify goal achievement in both structured (with supervision) and unstructured (without supervision) environments. Research showed that the use of behavioural rating scale to assess executive function provides some prediction of daily living quality (Karzmark, Llanes, Tan, Deutsch, & Zeifert, 2012).

CHAPTER 3: GENERAL METHODOLOGY

This section presents a detailed description of the CHYLD Study and its follow-up developmental assessment procedures. Background statistics are presented to describe the sample of children for each follow-up period. Recruitment summary, study ethics, and research design and processes are included. Only materials used in the developmental assessment of children at 2 years and at 4.5 years are presented, with corresponding psychometric properties and developmental domains. Lastly, a general overview of statistical treatment of the data is described.

Children with Neonatal Hypoglycaemia an their Later Development (CHYLD) Study

Participants

Babies recruited for the CHYLD study were previously part of two clinical studies, *the Babies and Blood Sugar's Influence on EEG Study* (BABIES) that was conducted at Waikato Hospital, New Zealand from December 2006 to February 2009, and the *Sugar Babies study*, that was conducted from November 2008 to November 2010. The general aim of the BABIES study was to evaluate a *Continuous Glucose Monitoring System* (CGMS) and its association with physiological measures of brain activity (EEG). The aim of the randomised controlled Sugar Babies study was to look at the effectiveness of administering oral dextrose gel for the management of neonatal hypoglycaemia postnatally. Blood concentration samples for both studies were done through heel prick procedures and analysed by a blood oxidase method. A glucose monitor was attached subcutaneously to the thigh of the neonates to determine the continuous blood sugar concentration for about two to seven days. Most babies were breast-fed and clinical standards and guidelines were used in most procedures (Harris, Battin, Weston, & Harding, 2010; Harris et al., 2011; Harris, Weston, Signal, Chase, & Harding, 2013).

Risk factors for neonatal hypoglycaemia (see Table 2) in the CHYLD study were assigned based on hierarchical allocation. Primary risk factors were: *infant of diabetic mother* (IDM), *born large* (≥ 90th percentile or ≥ 4500g), *born small* (≤10th percentile or ≤ 2500g), *preterm* (< 37 weeks gestation), *other complications* (feeding difficulties, sepsis, pre-eclampsia, and others). *Neonatal hypoglycaemia* is a common risk among neonates within several hours after birth. Infants were excluded if they were deemed by the attending physician not to survive or were born with congenital anomalies. The incidence of low blood glucose

concentration may have detrimental effects on the early brain development in turn adverse neurodevelopmental outcomes in later childhood. Blood glucose levels in the CHYLD study were maintained at 2.6 mmol/L or 47 mg/dL (Mckinlay et al., 2015).

Infants recruited from both neonatal clinical studies, were assessed at 2 years ± 1 month of age and 4.5 years ± 2 months (52 to 56 months). Those who were born < 37 weeks at gestation were examined at their corrected gestational age. Toddlers born < 35 weeks of gestation or who were older than 2 years ± 1 month at follow-up; were excluded from the study. A letter and an information pack were sent to the family explaining the follow-up study. Families were contacted by phone and the CHYLD study was discussed and parents were given opportunities to ask questions about the study process as well as its risk. For cultural sensitivity purposes, the CHYLD team had a Māori research nurse who provided cultural support and was a liaison between family and other examiners during the follow-up process. A questionnaire titled the *Home and Family Survey* was posted to the parents to be completed prior to their toddler's assessment (Ansell, 2014)

Table 2: ***Characteristics of participants at the CHYLD study 2-year and 4.5-year follow-up***

	Participants at 2-Year			Participants at 4.5-Year		
Characteristics	Total	Glycaemic	Euglycaemic	Total	Glycaemic	Euglycaemic
No. of Participants	404	216	188	477	280	197
Female *n* (%)	192 (48%)	116 (54%)	76 (40%)	228 (48%)	145 (52%)	83 (42%)
Ethnicity *n* (%)						
European	206 (51%)	118 (55%)	88 (47%)	253 (53%)	150 (54%)	103 (53%)
Maori	115 (28%)	60 (28%)	55 (29%)	180 (38%)	103 (37%)	77 (39%)
Pacific	14 (3%)	7 (3%)	7 (4%)	18 (4%)	11 (4%)	7 (4%)
Other	69 (17%)	31 (14%)	38 (20%)	22 (5%)	13 (5%)	9 (5%)
SES decile	4.5	4.5	4.5	4	4	4
Gestational age in - wks	37.8	37.7	37.8	37.3	37.1	37.6
Birth weight - g	3134	3089	3187	2997	2932	3089
Birth Weight z score	0.19	0.13	0.25	0.07	0.02	0.14
Primary risks for neonatal hypoglycaemia *n* (%)						
Maternal diabetes	161 (40%)	80 (37%)	81 (43%)	180 (38%)	91 (33%)	89 (45%)
Late Preterm	129 (32%)	71 (33%)	58 (31%)	164 (34%)	105 (37%)	59 (30%)
Small	60 (15%)	39 (18%)	21 (11%)	73 (15%)	50 (18%)	23 (12%)
Large	42 (10%)	17 (8%)	25 (13%)	39 (8%)	19 (7%)	20 (10%)
Other	12 (3%)	9 (4%)	3 (2%)	21 (4%)	15 (5%)	6 (3%)
No. of Mothers	376	201	175	438	257	181
Age - yr	29.9	29.9	30	30	30	30

Note g = grams

CHYLD study ethics

The CHYLD study 2-year follow-up received ethics approval from the Northern Y Health and Disability Ethics Committee (NTY/10/03/021) of the Ministry of Health (New Zealand). To extend the study for the 4.5-year follow-up, an amendment was submitted, which was approved by the same ethics committee on the 24th of June 2011. (Ansell, 2014; Burakevych, 2016; Chakraborty, 2015; Mckinlay et al., 2015; Paudel, 2016; Yu, 2014).

Follow-up assessment

Assessments at 2 years and at 4.5 years follow-up were conducted either at a local hospital in Hamilton, New Zealand, or at a research house, set up to accommodate the child and an accompanying family members. The research house (Kahikatea Research House) was equipped with materials, computers, and supplies needed for the follow-up assessment. Separate rooms were provided to assess vision, paediatric health, and child behaviour and neurodevelopment and a reception space that was used for family breaks during the assessment and for obtaining informed consent from the primary caregiver. The neurodevelopmental assessments were divided into paediatric, vision, and developmental sessions and were carried out by assigned New Zealand registered professionals and/or PhD students who were blind to the clinical status of the child. In special cases, where children could not travel for assessment, a special arrangement was made to do these at a home visit. Examiners were trained to reliability on all developmental assessments and feedback of their performance was provided periodically. Skills in scoring and administration were introduced first, while issues of assessment procedures for difficult cases were discussed at monthly meetings. Consensus between examiners on alternative strategies and scoring were agreed on to ensure standard assessment practices. Assessments were videotaped and reviewed to ensure the consistency of scoring and that administration protocols were maintained. Assessment packs were sent to Auckland (Liggins Institute) for sorting, encoding, and storing in a database. Red flags were identified for each case where a child performed below a set criterion on the psychological assessments. These children's developmental assessments were then reviewed by developmental psychologist to determine whether they required a specialist referral for follow-up (Ansell, 2014; Burakevych, 2016; Chakraborty, 2015; Paudel, 2016; Yu, 2014).

Research process and design at 2 years

Figure 1 shows the research process and recruitment at the 2-year follow-up study. This prospective cohort study enrolled 528 neonates, who were assessed at 2 years ± 1 month. The neonates were treated for neonatal hypoglycaemia, and blood glucose levels were maintained at 2.6 mmol/l or 47 mg/dl. Neurodevelopmental assessments at 2 years included neurodevelopment tests for cognitive and motor abilities, executive function skills, and visual acuity and function (Ansell, 2014; Mckinlay et al., 2015; Paudel, 2016).

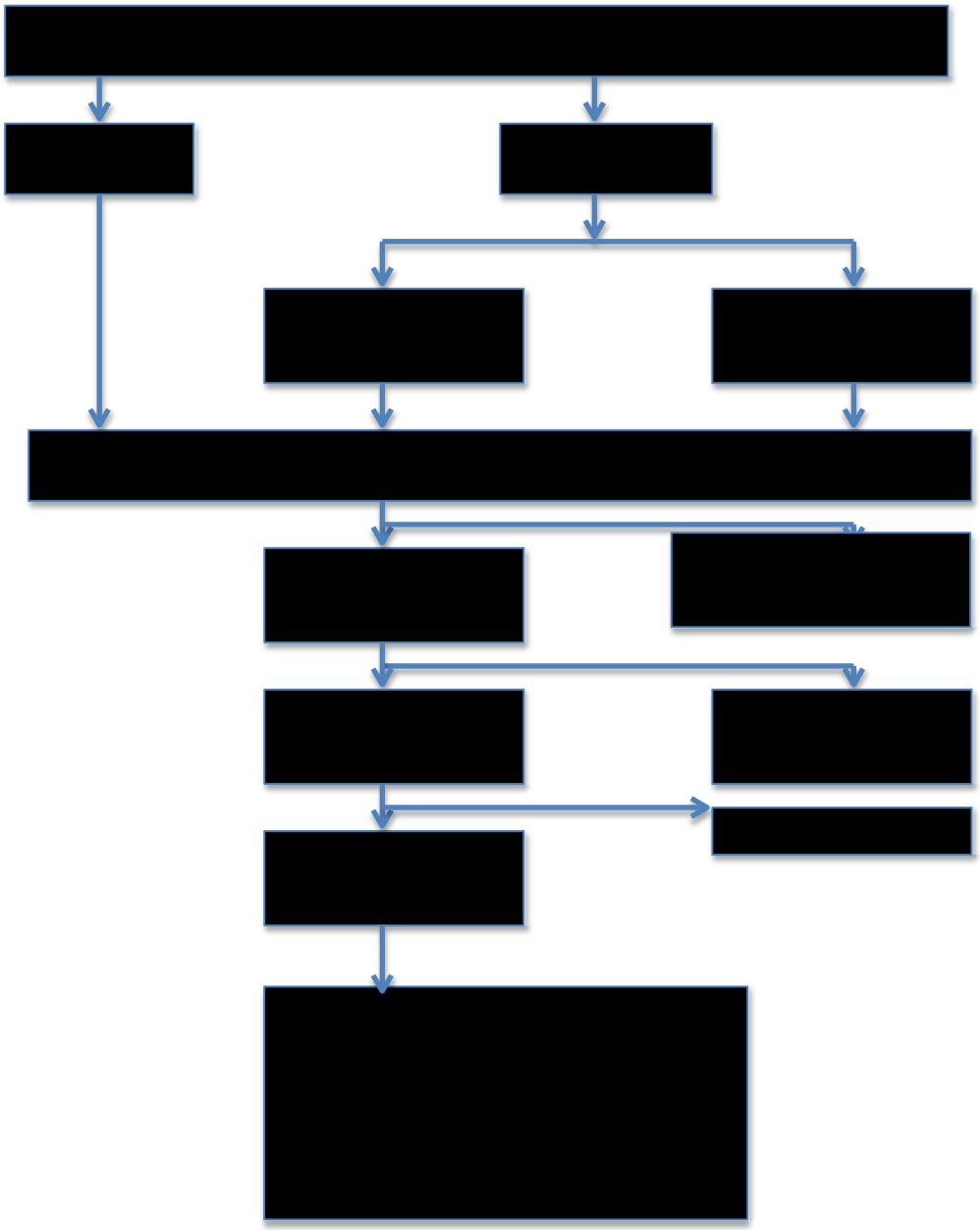

Figure 1: Recruitment at 2-year follow-up

CHYLD study follow-up at 2 years

Of the final sample 62 babies (15%) experienced a blood glucose concentration of 2.0 mmol/L, and 78 babies (19%) were considered *recurrent*, as they had more than one occurrence of less than 2.6 mmol/L concentration of blood glucose. The cumulative primary risks (IDM, SGA, LGA, Preterm, and Others) for neonatal hypoglycaemia were the following: 275 neonates had one primary risk (68.1%), 116 neonates had two primary risks (28.7%) and 13 neonates had three risks (3.2%). Follow-up at 2 years involved 213 toddlers (53.7%) who had experienced neonatal hypoglycaemia. In this cohort of toddlers, females (59.9%) had more episodes of neonatal hypoglycaemia than males (46.2%). Records showed no infants had recognised symptoms of neonatal hypoglycaemia. There was significant association between sex and ethnic affiliation. Being born female and Māori meant a higher incidence of neonatal hypoglycaemia in this cohort (61.8%). Across socioeconomic (deprivation index, household income, maternal education) and lifestyle patterns (parent substance use), similar distributions were observed for both euglycaemic and hypoglycaemic groups (Ansell, 2014; Mckinlay et al., 2015).

Examiner administered test of behaviour and development at 2 years

Bayley Scales of Infant and Toddler Development – 3rd Edition (Bayley-III)

The Bayley Scales of Infant Development (BSID) was designed to assess developmental milestones in infants and young children between the ages of 1 and 42 months of age. The purpose of this battery of tests was to identify developmental delays among young children. Bayley-III is a revised version, which includes parent-rated measures of child social emotional functioning and adaptive skills as well as subtests of cognitive ability, language (receptive and expressive) and motor skills (fine and gross motor). The updated Bayley-III also included norms for clinical populations such as Down's syndrome, pervasive developmental disorder (PDD), cerebral palsy, specific language impairment (SLI), infants at-risk of developmental delays, intrapartum asphyxia, fetal alcohol syndrome, small-for-gestation (SGA), and children born premature. The *cognitive domain* of Bayley-III includes information processing, processing speed, and problem solving and activities that test early fantasy play. The

language domain measures a child's communication through gestures such as gaze, facial expressions and pointing, and through vocalization (number of words, and the combination of words to form sentences). The *motor domain* evaluates the child's control of trunk, head and planned movement of large body parts (gross motor) as well as the use of hands and fingers for object manipulation (fine motor). Parent-rated domains (*Socioemotional* and *adaptive function*) evaluate the child's behaviour in natural settings. Bayley-III is a norm-referenced test, which can be scored manually or through computer software. It has Index (composite) scores (Mean = 100 ± 15) and subtest scaled scores. (Bayley, 2006).

Snack Delay – Delay task

The Snack Delay task is a measure of inhibitory behaviour. A bell is placed next to a mat on the table and a lolly (raisin, M&M, popcorn) is placed under a transparent cup in the middle of the mat. In this task the child was instructed (and reminded of the rule for each trial) to put his/her hands on the mat resting on top of the table and *"to wait until I ring the bell before you take the lolly"*. Trials were arranged with increasing delays of 5 second increments beginning with 5 seconds, then 10, 15, 30, and 45 seconds. Scoring includes, *Failed trial (0 point)* if the child retrieved the treat before the bell was rung; or child ringing the bell, *Partial wait (1 point)* if the child did not retrieved treat but touched the glass during the wait, *Full wait (2 points)* if the child waited to retrieve treat without touching the glass until the bell was rung. The task finishes when a failed response is made. The Snack Delay task has been found to have a strong Kappa reliability coefficient (.97 to 1.00 for touching and hand codes). (S. Carlson, 2005; Kochanska, Murray, & Harlan, 2000).

Fruit Stroop (Shape Task)

The Fruit Stroop task tests more complex inhibitory function or the ability to resist making a prepotent or learned response. In the instruction phase children were shown two sets of individual photos of (three large and three small photos of an apple, orange and banana). They are asked to name or point to each fruit as the individual picture is presented. For instance, *"point (or name) the big apple*" and then "*point (or name) the little banana"*, During the trials the examiner shows the same fruit pictures (apple, orange, banana) with a different picture of a smaller fruit embedded in the large picture of the fruit. The examiner then asks the child to point to the little fruits ("show me the little orange"). Scoring includes: 2 points for pointing to the correct little fruit (not the big orange) embedded in each large picture, 1 point

for partially correct (self-correct) and 0 points for failure to respond correctly (S. Carlson, 2005; Kochanska et al., 2000). Original tasks have strong Kappa reliability.

Ducks and Buckets (Reverse Categorisation)

The Ducks and Buckets reverse categorisation task also measures complex inhibitory behaviour. The Ducks & Buckets task is a two-part task requiring categorisation (sorting) of large and small ducks followed by a reverse categorisation task. In the training trial of the task the child was taught to put the big duck in the big bucket and the little duck in the little bucket. Following this there were two rule-check trials, one each for big and small, with feedback. In the categorisation task the child was asked to sort a pseudorandom assortment of three large and three small ducks. Responses were recorded. The criterion for proceeding to the reverse categorisation was for the child to correctly sort at least five ducks in the categorisation task. Reverse categorisation was introduced as a “silly game” in which the big ducks are to go into the little bucket and little ducks into the big bucket. There were two rule-check trials, during which feedback was provided. The child was asked to reverse-sort the pseudorandom assortment of three big and three little ducks. The scoring for the CHYLD study at 2-year follow-up assigned 1 for each duck correctly sorted in each part of the assessment (S. Carlson, Mandell, & Williams, 2004; S. Carlson, 2005).

Multisearch Multilocation (MSML)

In the CHYLD study 2-year follow-up task, a 3-step phase is introduced rather than the original 4-phase trial. The apparatus for this task was constructed of three drawers positioned in a row on a black square. A large piece of black felt was attached to the back of the square so that it could be used to cover the drawers between trials. The examiner started the task with a training phase where a treat (M&M, popcorn, raisin) is put in the center drawer and a black diamond shape is attached to the handle. The examiner asked the child to get the treat and demonstrated by lifting the cover, pulling the drawer out by the diamond shape, pointing to the treat and asking the child to get the treat. There were three test trials and 2 points given when the child successfully removed the cover, pulled back the diamond, and retrieved the treat without assistance; 1 point was given when the child completed some but not all the steps; 0 points were given when the child did not attempt any of the steps. In the next phase (pre-switch trials) a yellow circle, blue triangle, and a green square were then attached to the handles of the drawers. In the pre-switch trial, a food treat was placed and always hidden in the (middle) blue triangle drawer. The child watched the treat being hidden and then the black

felt cover was placed over the drawers and a 10 second interval passed before the child was then asked to retrieve the food. If the child opens a wrong drawer, the box was withdrawn and the trial scored as a fail. The correct drawer was then shown to the child and the instruction was then repeated to the child. Three consecutive correct trials were required before the child could progress to the post-switch phase, or a minimum of six trials attempted. Failure to respond after 30 seconds was scored as a failed trial. In the post-switch phase, the child was told they were going to play "a silly game"; the food treat is hidden in the green square drawer. The black felt cover was placed over the apparatus and a 10-second delay was given before the child was asked to find the food treat. Outcomes were: post-switch success (getting the treat from the green square drawer, perseverative error (incorrect search in the blue triangle drawer); or non-perseverative error (incorrect search in the yellow circle drawer). There are two consecutive trials until the correct response is achieved or until eight set trials are (S. Carlson, 2005; Zelazo, Reznick, & Spinazzola, 1998).

Parent reports of child behaviour and development at 2 years

The *Behaviour Rating Inventory of Executive Function, Preschool Version* (BRIEF-P) which is described under the 4.5 year measures and the *Social-Emotional and Adaptive Questionnaire* of the Bayley-III were used to obtain parents' perception of their child's everyday executive function (BRIEF-P) and development of social relationships and interaction with peers and adults.

Research Process and Design at 4.5 years

Participants for the 4.5-year follow-up included a total of 477 preschool children. Of this sample 355 children were also followed up at 2 years of age. Neurodevelopmental assessment of cognitive abilities, motor tests, executive function tests, and measures of visual acuity and function were again administered.

CHYLD study follow-up at 4.5 years

Figure 2 shows the recruitment and follow-up studies at 4.5 years. Among the sample of 477 children available for follow-up at 4.5 years of age, 288 (48%) were female, 253 (53%) were of New Zealand European ethnicity and 180 (38%) self-identified as Māori. Paediatric data revealed the average gestation for this cohort was 37.3 weeks (SD = 2.1) and 240 (50%)

were admitted to the neonatal intensive care unit (NICU). The primary risks for neonatal hypoglycaemia were as follows: 180 (38%) were an infant of a diabetic mother (IDM), 164 (34%) were born preterm (32 to 36 weeks), 73 (15%) were born small (<10th centile or <2.5 kg), and 39 (8%) were born large (>90th centile or >4.5 kg); More than half of the newborns had neonatal hypoglycaemia, 280 (59%) had hypoglycaemia during the first week of birth, 377 (79%) underwent interstitial glucose monitoring, 126 (26%) received neonatal dextrose gel and the remaining 45 (9%) and 48 (10%) had intravenous or a combination of intravenous and buccal gel treatment (Burakevych, 2016; Mckinlay et al., 2017). Of the total follow-up sample, 280 children were hypoglycaemic and 197 euglycaemic. More euglycaemic children were born to mothers with diabetes compared to hypoglycaemic children. However, more hypoglycaemic children were born preterm (32 to 36 weeks) and small-for-gestation compared to euglycaemic children. Standard protocols and breastfeeding were followed; in the hypoglycaemic group there were 178 children (64%) and in the euglycaemic group were 99 (50%) had breast-fed and used formula milk (Burakevych, 2016; Mckinlay et al., 2017).

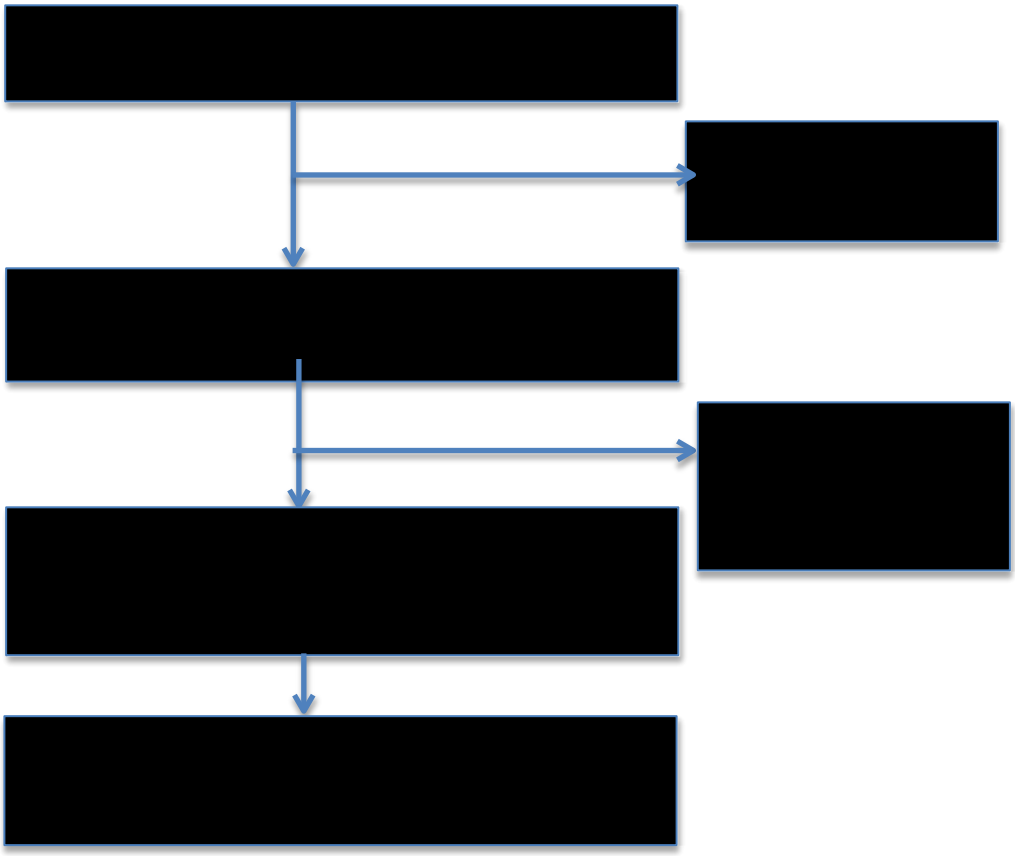

Figure 2: Recruitment at 4.5-year follow-up

Examiner administered test of behaviour and development at 4.5 years

Wechsler Preschool and Primary Scale of Intelligence – 3rd. Edition, Australian Version, (WPPSI-III)

Cognitive ability at the 4.5 year follow-up was measured with the WPPSI-III Australian Version. The WPPSI-III is a norm referenced intelligence test that measures overall cognitive ability in preschool children (ages 2 years 6 months to 7 years and 3 months) with different core subtests for ages 2 years 6 months to 3 years 11 months and 4 years to 7 years and 3 months. The seven core subtests (Table 3) included in the 4 to 7 years and 3 months assessments include: Information, Vocabulary, Word Reasoning, Block Design, Matrix Reasoning, Picture Concepts and Coding. Based on these measures of 5 composite scores can be calculated including: Verbal IQ (VIQ), Performance IQ (PIQ), General Language Composite (GLC), Processing Speed Composite and Full Scale IQ (FSIQ). The WPPSI-III was standardized from 1,700 children in the United States. The ethnicity of the sample was predominantly European American Ethnic (60.9%). Psychometric features: Internal consistency reliability was considered good with Cronbach Alpha's for VIQ (0.94 to 0.96), PIQ (0.89 to 0.95), and FSIQ (0.86 to 0.92). Criterion validity showed a modest correlation with the Bayley-III (Cognitive Scale: r = .79, and Motor Scale: r = .55) counter-balanced 2 to 25-day periods. A factor analytic method supported the three-factor structure (verbal, performance, processing speed) in the 4 to 7 years and 3 months. Subtests that are more associated with general intelligence (*g*) were: Word Reasoning, Information, and Vocabulary subtests. Verbal Composite accounted for 62%, Performance Composite accounted for 42%, and Processing Speed accounted for 33% of the general intelligence (*g*) in the 4 to 7 years and 3 months age group. Composite scores have a mean of 100 and standard deviation of 15, subtests has a mean of 10 and standard deviation of 3. Qualitative interpretation of composite scores: extremely low (below 70), borderline (70 – 79), low average (80 – 89), average (90 – 109), high average (110 – 119), superior (120 – 129), and very superior (130 +) (Sattler, 2008; Wechsler, 2002).

Table 3: The Wechsler Preschool and Primary Scale of Intelligence - 3rd Edition

General IQ	**Composites**	**Subtests**	**Function**
WPPSI Full Scale IQ	Verbal Composite (*Gc*)	Information	Measures long-term memory for factual information (shows richness of environment, quality of early education, and cultural exposures)
		Vocabulary	Fund of knowledge, verbal fluency, lexical knowledge, verbal comprehension, and language development
		Word Reasoning	Verbal reasoning, alternative concepts, capacity for associative thinking, and language development
	Performance Composite (*Gf*)	Block Design (*Visual processing*)	Nonverbal reasoning and visual spatial organization, analysis-synthesis (visual motor coordination and visual organization)
		Matrix Reasoning (*Visual processing*)	Visual-spatial analogical reasoning, visual processing, classification ability, and analogies
		Picture Concepts	Abstract, categorical reasoning based on visual-perceptual recognition processes
	Processing Speed	Symbol Search	Visual-perceptual discrimination, psychomotor speed, attention and concentration, visual short-term memory
		Coding	Processing speed, dexterity, scanning ability, visual short-term memory, fine-motor coordination

Beery Visual Motor Integration, (BVMI)

The Beery-VMI was used to evaluate the child's visual-motor function (hypothesised to be located in the motor cortex opposite the dominant hand area and including areas of the corpus callosum and the cortex). The Beery-VMI is a norm referenced neuropsychological test designed to identify deficits in visual perception, fine motor skills, and hand-eye coordination. The Beery-VMI was normed on a sample of 1,737 children 2 to 18 years of age in 2010 and 1,021 adults in 2006. It can be administered to individuals from 2 years of age through adulthood. Visual motor integration (VMI) is measured by the ability of an individual to copy a sequence of increasingly complex geometric set of drawings (30 in total). Separate tests for visual perception and motor coordination (fine motor skills) can be administered to determine if deficits are related to problems with visual perception or fine motor skills. It is administered in about 10 to 15 minutes and designed to integrate visual and motor abilities in children and adults. There is a strong correlation between chronological age and Beery-VMI (r = .80 to r = .95). This measure is sensitive to learning disorders, reading disabilities and other perinatal conditions such as exposure to industrial toxins and low birth weight. It has also been shown to be a predictor of academic achievement and environmental quality (SES). Administration is conducted in the following sequence: Beery-VMI, visual perception, and motor coordination scales. Administration for young children (or suspected intellectual disability) has alternative tests that require identification of body parts, picture outlines, and parts of the pictures. Within the three-minute period the child is required to match (by pointing to) the 27 geometric shapes. The motor coordination task is to trace a pathway or road without going "off the road" (staying between the lines of the road) and takes about five minutes for administration. Alternative administration for the motor coordination subtest requires very young children to climb on a chair, hold a pencil and hold a paper while making a mark with the pencil. Rasch analysis of Beery-VMI items among 400 Australian children and 314 Taiwanese children reached unitary dimension agreement. The Beery-VMI internal consistency reliability (Cronbach's Alpha) is 0.96, and concurrent validity with other visual-motor integration measure is about r = .52 to r =.75 (Beery & Beery, 2010).

Movement Assessment Battery for Children, (MABC-2)

MABC-2 is a standardised measure of motor development in children. It consists of 3 core tests (manual dexterity, aiming & catching, and balance). The MABC-2 is designed for clinical, research and developmental evaluation purposes. This measure is designed for clinical groups such as developmental coordination disorder, motor difficulties, developmentally at-risk, and genetic disorders. Manual dexterity is measured from a

composite of posting coins, threading beads, and drawing trails. Aiming and catching is composed of catching beanbags, and throwing them onto a mat. Balance is evaluated with tasks where the individual is required to balance on one-leg balance, walk with heels raised, and hop from one mat to another and jumps over a rope. Psychometric properties show strong inter-rater reliability .95, and a test-retest reliability of .48 (aiming and catching) to .89 (manual dexterity). Convergence with other similar measures is moderate to strong .53 to .86 (Henderson, Sugden, & Barnett, 2007).

Bear and Dragon (Simon-says task)

This task is a measure of complex response inhibition. It requires holding a rule in mind, responding according to the rule and inhibiting a prepotent response. In this task the child must *"do what the nice bear says"* and *"not do what the naughty dragon says"* Two stuffed hand puppets, a bear and a dragon, are used in this task. The examiner introduces the instruction in a light friendly voice for the nice teddy bear, and a strong deep, fierce voice for the naughty dragon. Bear trials (activation) must be followed, while Dragon trials (inhibition) must be avoided. There is a practice trial, and two blocks/sets of 20 trials are then administered. Each block has 10 inhibition and 10 activation-alternating tasks. Children were seated on chairs throughout the task. Expected responses were hand gestures or movements as requested by the examiner. Performance on the Dragon trials indicates high self-control. A score of 1 was given for a correct response (not doing what the dragon says), and 0 was given for an incorrect response. (S. Carlson, 2005; Reed, Pien, & Rothbart, 1984).

Day and Night

This task is also a measure of complex response inhibition. In this task a set of cards is presented that have an illustration of either the sun or the moon and stars. The child must respond to a picture of the Moon by saying "Day" and a picture of the Sun by saying "Night". There is a training phase and 15 testing cards for the trial phase. The child is shown the moon and told "*when you see this card, I want you to say day*" and then the examiner waits for the child to respond "day"; then the examiner presents the sun-card, "*if you see this card, I want you to say night*" and waits for the child to say "night". If the child responds incorrectly the examiner corrects them. A fixed pseudorandom order is presented to the child, and there are no rule reminders after the practice trial. Accuracy is recorded for the total of 16 trials. (S. Carlson, 2005; Gerstadt, Hong, & Diamond, 1994).

Auditory Processing Tasks

This is a subtest of the *Phelps Kindergarten Readiness Scale* (PKRS-II) and was designed to evaluate the academic readiness of young children entering the preschool stage. The PKRS-II is composed of three core tests namely: a) verbal processing domain, b) perceptual processing domain, and c) auditory processing domain. In the CHYLD 4.5-year follow-up, the *auditory processing* domain is used as a measure of working memory. The auditory processing domain is divided into three sets of tasks. 1) In the *auditory discrimination task* two words that either sound similar or are the same are presented and the child is asked to determine if they are the same word. (For example chair – chair response is *same*, boy – toy, response is different). 2) In the *memory for sentences and stories* task a set of sentences of increasing length are presented by the examiner and the child is instructed to repeat the sentence. In the memory for stories a short story is read by the examiner and then the child is asked questions about the story. 3.) In the auditory digit memory numbers are presented and the child is asked to repeat the numbers in the same sequence. The numbers start with one number and increase by one on subsequent trials. The auditory processing domain has good concurrent validity and predictive validity coefficients. PKRS-II has reliability values of .75 to .93 (Duncan & Rafter, 2005).

Dimension Change Card Sorting Advanced (DCCS Advanced)

DCCS is used with typically developing young children age 3.0 to 5.0 years. The task is to sort target cards according to colour, shape, or border. The standard version of the DCCS is known to be a good index of the development of executive control in young children. It is correlated with other tasks of cognitive control as well as tasks predicting social understanding (Theory-of-Mind). The *standard version* can be administered from 2.5 to 5.0 years of age. The *border version* (advanced phase) is suitable for children age 5.0 to 7.0 years of age. Both versions can be used to assess executive function at the preschool age

to 7.0 years). The standard version is composed of a practice phase with two trials and pre-switch trials (rabbits and boats) and post-switch trials (red and blue), both having six trials each. Trays and display panels are placed in front of the child. The instruction is to sort the cards face down, placing them on each tray “according to colour” (pre-switch trial). After six trials, the experimenter will instruct the child to play a new game where cards need be sorted “according to shape” (post-switch trial). A child needs to sort five correct cards out of six in order to pass the post-switch phase. After passing the post-switch trial, the child may proceed to the border version (red rabbit and blue boat). In Advanced version, the experimenter carefully instructs the

child to sort the cards according to a rule, whereby if there is a “border” the child needs to sort the card “according to colour” and if there is “no border” the child needs to sort the card “according to shape”. The border phase consists of 12 trials and in each trial the experimenter needs to remind the child (“If there’s a border, play the colour game. If there’s no border, play the shape game”). A child needs to sort nine correct cards out of 12 trials in order to pass the border version. DCCS is known to be sensitive to the child’s reflective ability, planning skills and goal representation to sort the cards and take into account the rules of the game (S. Carlson, 2005; Zelazo, 2006).

Gift Wrap Delay

The Gift Wrap Delay measures simple response inhibition and requires withholding/delay of prepotent or automatic response to “peek”. The examiner tells the

the child that he/she did a great job and will receive a prize. However, that he/she “forgot” to wrap the prize. The child is instructed to turn his/her back to the examiner so that they can’t see what is being wrapped. The examiner purposely makes a great deal of noise such as cutting pieces of paper, crumpling paper, and putting tape on the gift to appear to be wrapping the gift and says, “This will be a big surprise”. This task lasts for 60 seconds and latency to peek as well as peeking behaviours was recorded as well as the number of times and whether head or trunk movements were fully used to peek (S. Carlson, 2005; Kochanska, Murray, Jacques, Koenig, & Vandegeest, 1996).

Table 4: Examiner administered EF tasks at 4.5 years follow-up

EF Measure	Function	Representative Skill
Bear & Dragon	Activation & Inhibition	Conflict Inhibition
Day & Night	Inhibition	
Digit Span (Phelps, Auditory Processing: Auditory Discrimination, Sentence Recall, Digit Span, and Stories)	Memory	Working memory
DCCS	Shifting / Flexibility	Cognitive flexibility
Gift Delay	Inhibition	Delay Inhibition

Parent report measures of child behaviour and development at 4.5 years

Behaviour Rating Inventory of Executive Function – Preschool, (BRIEF-P)

This is a 63-item measure designed to assess the broad, everyday executive function skills in young children age between 2 years and 5 years and 11 months. Rating forms are available for parents or teachers. In the CHYLD study only the parent-report was obtained. The items are rated on a likert-type scale (1 = Never, 2 = Sometimes, and 3 = Always) to identify multiple aspects of executive functioning observed over the previous six months. Test developers reported a 3-factor model for both teachers and parents, which were used as a basis for the 3 indices of BRIEF-P. This measure has 5 clinical scales: *Inhibit* (16 items; measures child's ability to control prepotent behavioural responses in different situations), *Shift* (10 items; measures the child's ability to appropriately shift from one task, new environment, or problem), *Emotion Control* (10 items; measures the child's ability to handle emotion reactions in a specific situations), *Working Memory* (17 items; measures the child's ability to hold information in memory in order to achieve appropriate or desirable behaviour, follow instructions, or accomplish a task) and *Plan / Organise* (10 items; measures the child's ability to anticipate future goals in response to present situation) and three composite indexes: *Inhibitory Self-Control Index* (ISCI), *Flexibility Index* (FI), and *Emergent Metacognition Index* (EMI). There is an overall composite score known as the *Global Executive Composite* (GEC) and additional scores to determine valid responses. Psychometric properties of each clinical scale reported high (parent, r = .80 to r = .90) to very high (teacher, r = .90 to r = .97). *T* scores above 65 are considered clinically significant (Gioia, Espy, & Isquith, 2003).

Strengths and Difficulties Questionnaire, (SDQ)

The Strengths and Difficulties Questionnaire (SDQ) is a brief behavioural screening norm referenced questionnaire for children and adolescents 3 – 16 years of age. It is a 25-item questionnaire which asks about 25 attributes, some positive and some negative. Five scales have 5 items each, which corresponds to negative symptom behaviour (Hyperactivity,

Emotional, Conduct, Peer problem) and a positive dimension (Prosocial). Psychometric properties show high concurrent validity and good discriminant/diagnostic validity among samples of preschool children and adolescents. A 5-factor model was confirmed achievable for preschool children and adolescents. Convergent validity was good and its discriminant validity was shown to be useful to identify more externalizing problems (conduct and hyperactivity) and some internalizing problems (depression and anxiety) (Goodman, Ford, Simmons, Gatward, & Meltzer, 2000; Goodman, Renfrew, & Mullick, 2000).

Child Behaviour Checklist 1.5 – 5, (CBCL 1.5 – 5 years)

This is a 99-item measure to evaluate the child's internalizing and externalizing problems over the previous two months. There are separate parent report and teacher report forms. The CHYLD study used the parent report forms only. The CBCL has six subscales that represent common emotional problems in children (Emotional Reactive, Anxious/Depressed, Somatic Complaints, Withdrawn, Attention Problems, and Aggressive Behavior). *T*-scores are derived and converted from the summed subscales. Psychometric properties show that the internal consistencies are moderate to very high (r = .68 to r = .92). *T*-scores above 70 are considered within the clinical range. CBCL are administered together with the BRIEF-P at the subsequent assessment schedule, when the child reaches 4.5 years of age (Achenbach & Rescorla, 2000).

Social Communication Questionnaire, (SCQ)

The SCQ is a parent-report screener of behaviours associated with autism spectrum disorder (ASD). It is intended for clinical and research purposes. Administration takes 10 to 15 minutes and involves items of yes/no response. The raw scores are added for a total score. SCQ has three subtests: *reciprocal, communication*, and *repetitive behaviour*. Psychometric property for a cut-off of 15 for the total score includes a sensitivity of .85 and specificity of .75. Internal consistency reveals strong coefficients (.81 to .93)(Rutter, Bailey, Berument, Lord, & Pickels, 2003).

Home and Family Questionnaire

The *Home and Family Questionnaire* was designed specifically for the CHYLD study and parents answered this questionnaire at both the 2-year and 4.5-year follow-up assessments. This questionnaire provided data about the demographics of the family (parental income, age and educational level attained), the home and family environment (number of siblings, number of people living in the household, and parental substance abuse), child health and medical history. The *New Zealand Deprivation Index* (NZDEP) was used to determine the socioeconomic status (1 = least deprived and 10 = most deprived). This national index is divided according to social index among 18 to 64-year-olds according to income, house ownership, social support, employment, qualifications, living space, access to communication and access to transportation (Ansell, 2014).

Data collection, scoring and management

Data collection

Data collection packs were prepared at the Liggins Institute that included the forms for standardised measures, executive function scoring sheets, and parent-report forms. Each assessment pack also included an examiner signed cover sheet with child ID number, parent consent form, paediatric health data, vision acuity and perception data. The Home and Family Questionnaire was mailed to the family for completion prior to the assessment. After completion of the assessments, the completed data packs were stored in locked cabinets until they were transported to the Liggins Institute. In addition to all measures the pack contained a cover sheet that was filled out by the respective examiners and the assessments completed recorded.

Data scoring and management

Examiner administered assessments were scored immediately after each assessment. Raw scores for the Bayley-III and the WPPSI-III were calculated by the examiner and any concerns noted by affixing a red flag to the assessment pack. These packs were reviewed by a developmental psychologist to determine whether the “flagged” child needed further follow-up. After the assessment packs were sent to the Liggins Institute, they were checked for completeness and accuracy, and composite scores for the Bayley-III and the WPPSI-III and scores for the social-emotional and adaptive questionnaires were calculated and a report generated using the respective Scoring Assistant Software. Parent-report questionnaires (Home and Family survey, SCQ, BRIEF-P, CBCL, and SDQ) were checked for completeness

before being entered into the CHYLD database. Algorithms for scoring were used to obtain summary scores after double entry of the data was completed. Videotaped of the developmental assessments were transferred to a CD-ROM to ensure administration standards and further review of scored materials. After data entry each pack was stored in locked filing cabinets at the Liggins Institute. Each examiner completed a child summary report online in a secure database (paediatric, vision, and developmental) and reported overall impression of the child. CHYLD study coordinator reviewed each section of this report for missing details, and follow-up. Letters were then sent to the family that provided an overview of their child's health and development.

Exploratory data analysis

The data analysis in this doctoral thesis included 355 children who were available for follow-up at both 2 years and 4.5 years and 477 children who completed just the 4.5-year follow-up. The data were transferred from *MS Excel* spreadsheets to *IBM SPSS* data analysis and multivariate analysis. *Mplus* and *IBM AMOS* software were used for latent analysis of the data. Exploratory data analysis was done manually and through statistical software. Normal distributions of the data were evaluated. Frequencies and descriptive statistics were inspected for range, missing data and normality. Missing data were treated depending on the nature of the *missing-ness*. Outliers were tested through the use of regression *mahalanobis distance*. If outliers were significant enough to affect the scores, they were deleted. Outliers identified far from the mean as suggested by boxplots and mahalanobis distance were deleted (Tabachnick & Fidell, 2013).

Some variables were converted to summary scores for ease of use, however, the theoretical and practical nature of this method was considered first. The scores for examiner administered executive function at the 2-year follow-up and at the 4.5-year follow-up were each converted into a composite score. Executive function scores at 2-year follow-up (ducks and buckets, fruit stroop, snack delay and multisearch multilocation) were log transformed and each score were summed to produce composite score for 2-years follow-up. Similar transformed scores were applied to Executive function scores at 4.5-year follow-up (bear & dragon, dimension card sorting test, day & night, digit span, and gift wrap delay). Executive function is considered one-dimensional in young children. Executive function tasks were also scored separately as they were found to be weak to moderately related to each other, supporting the theoretical and neural hypothesis that executive function skills are interdependent.

Analysis progressed in the following way: The increasing measurement and hypothesis-testing approach were done, from measuring group clusters, to validation of risk clusters, and to a more complex latent variable analysis. This strategy was cautious and also underwent a rigorous of first testing the practicality of the results prior to subsequent data analysis. Based on the suggestion of Evans and colleagues (2013) a prospective, longitudinal study complimenting the clinical trials of CHYLD study was employed in this doctoral thesis.

Overarching analytical strategies

The individual statistical procedures used to address each research question will be described in the result section. The following is a description of the overall strategies that guided the statistical analyses. Two *analytical strategies* were used to analyse the 2-year and 4.5-year CHYLD data in this doctoral thesis. The 'person- centred approach' and the 'variable-centred approach' using both strategies enabled a more integrated exploration of the neurodevelopment of children in the CHYLD cohort data. Using these strategies both intraindividual and interindividual differences in neurodevelopment in children who were at risk of neonatal hypoglycaemia could be examined.

The *'Person-centred approach'* used clustering techniques to identify subgroups of this cohort. Two-and five-cluster models were calculated from the combined 2-year and 4.5-year data. Validation of these subgroups will be established using discriminant function analysis (for group membership) and multivariate analysis of variance (for group differences). The following research questions were addressed using the *'person-centred approach'*:

- Can distinct subgroups (risk profiles) of children be identified using the CHYLD 2-year and 4.5 year data; and are these risk profiles tenable for exploring theoretical models of CR, and for identifying the risk profile of groups who are more likely to require clinical intervention.
- Assuming valid risk profiles can be identified for the children in the 2 and 4.5 year follow-up, are these risk profiles associated with neurodevelopment at 2 and 4.5 years of age.

On the other hand, *'variable-centred approach'* explores the magnitude of the construct through estimating its relationship with other variables. Therefore, correlations, factor

analysis, multiple regressions and structural equation modelling were all employed for this approach. The following research questions were addressed:

- Are risk factors predictive of established risk clusters (‘more at-risk’ versus ‘less at risk’)?
- What is the configuration and development of early executive function in at-risk children at 2 years of age and at 4.5 years of age?
- Does risk status (more at-risk versus less at-risk children) differ in the parent report BRIEF-P factor structure at 2 years and at 4.5 years of age?
- Does risk status (more at-risk versus less at-risk children) differ in EF skills as observed in examiner administered tasks at 2 years and at 4.5 years of age?
- What is the role of “observed” executive function on the effects of cumulative risk on cognition?
- What is the role of “everyday” executive function on the effect of cumulative risk on parent-reported childhood problem behaviours?

CHAPTER 4: CUMULATIVE RISK IN THE CHYLD COHORT

STUDY 1: Cumulative Risk in the CHYLD Cohort: Cluster Analysis

Introduction

Published and findings from the doctoral theses of the CHYLD cohort suggest that young children from deprived social strata with several birth risks (SGA, LGA, Maternal substance use and male gender) might have adverse neurodevelopment (Ansell, 2014; Burakevych, 2016; Chakraborty, 2015; Mckinlay et al., 2017). The goal of the present study is to identify whether the use of a multivariate classification technique (cluster analysis) in preschool children born exposed to subtle cumulative prenatal and postnatal risks produces valid and reproducible subtypes of neurodevelopment profile that can be used as a basis for further follow-up evaluation of young children. Therefore, the outcomes are cumulative 'risk clusters' derived from the 2-year follow-up and 4.5-year follow-up studies, based on the metric, "cluster analysis" proposed by Evans et al., (2013).

Method

CHYLD Data

Refer to Chapter 3 for the detailed description of the measures used for this study. Variables entered into the equation were based on the risk route and risk domains of cumulative risk, wherein sociodemographic domains, health and birth characteristic domains, and behavioural/neurocognitive domains were utilised (Aylward, 1992; Sameroff et al., 1987). These include socioeconomic status (New Zealand Deprivation status at birth, at the 2-year follow-up and at 4.5 year follow-up), and maternal education, health and clinical outcomes at birth data (gestational age, birth weight, weight at 2 years, and weight at 4.5 years, birth head circumference, head circumference at 2 years and head circumference at 4.5 years). Data were log-transformed to *Z* score to minimise measurement errors prior to cluster analysis.

Data Analysis

Cluster analysis groups together cases in order to uncover homogenous groups while maximising possible heterogeneity among subgroups. Therefore, typologies or classes can be identified in a large set of data. Cluster analysis is descriptive and atheoretical, thus a careful validation of subgroups to test for heterogeneity is required (Hair, Black, Babin,

Anderson, & Tatham, 2006). A *K-means* cluster technique was used for large set of variables (characteristics), and clustering was based on *Ward's Method* wherein variables were treated in an algorithm cycle (iterative) to form a group of characteristics (agglomerative). Once a final solution was reached, both cluster centres and group membership could then be used to describe the characteristics of each group (Tabachnick & Fidell, 2013). Subsequent analyses such as descriptive statistics (Means, SD, and/or percentages) and discriminant functional analysis were employed to look at significant group heterogeneity and group membership. IBM SPSS version 23 was used in all statistical analyses in this study.

Results and Findings

Cluster Analysis

Results of *K-means* cluster analysis supported five and two cluster solutions, which can be utilised for subsequent analyses for validation. Both 5 and 2-cluster solutions reached significant iteration. Results for the 2-cluster solution are discussed in Study 3. Results for the 5-cluster solution revealed that 22 iterations achieved a maximum absolute coordinate change of .000. Sociodemographic data and paediatric data were significantly clustered (p < .001). An appropriate number of participants in each cluster was achieved, Cluster 1 (n = 50), Cluster 2 (n = 65), Cluster 3 (n = 73), Cluster 4 (n = 111), and Cluster 5 (n = 56). Table 5 and 6 show the percent of infants that characterised the five clusters in the following categories: sociodemographic, paediatric health, primary risk of neonatal hypoglycaemia and parent substance use.

Table 5: ***Sociodemographic characteristics of 5 clustered groups (N = 355)***

Characteristics		Group n (%)				
		G1 (n = 50)	G2 (n = 65)	G3 (n = 73)	G4 (n = 111)	G5 (n = 56)
Sex						
	Male	35 (70%)	36 (55%)	28 (38%)	54 (49%)	32 (57%)
Ethnic Affiliation						
	European	15 (30%)	27 (42%)	39 (53%)	85 (77%)	27 (48%)
	Maori	29 (58%)	32 (49%)	26 (36%)	20 (18%)	24 (43%)
	Pacific	6 (12%)	5 (8%)	3 (4%)	1 (1%)	2 (4%)
	Asian	0	1 (2%)	5 (7%)	5 (5%)	3 (5%)
	Others	0	0	0	0	0
SES at 4.5 Yrs						
	Deprived	41 (82%)	54 (83%)	44 (60%)	41 (37%)	38 (68%)
Maternal Education						
	Low	21 (42%)	29 (45%)	30 (41%)	11 (10%)	21 (38%)

Characteristics		Group n (%)				
		G1 (n = 50)	G2 (n = 65)	G3 (n = 73)	G4 (n = 111)	G5 (n = 56)
Smoking						
Antenatal	mother (yes)	18 (36%)	23 (35%)	25 (34%)	8 (7%)	18 (32%)
	father (yes)	20 (40%)	21 (32%)	21 (29%)	19 (17%)	22 (39%)
2 Yrs.	mother (yes)	16 (32%)	19 (29%)	24 (39%)	16 (14%)	17 (30%)
	father (yes)	17 (34%)	18 (28%)	17 (23%)	15 (14%)	17 (30%)
4.5 Yrs.	mother (yes)	22 (44%)	17 (26%)	19 (26%)	12 (11%)	16 (29%)
	father (yes)	16 (32%)	17 (26%)	19 (26%)	15 (14%)	12 (21%)
Alcohol						
Antenatal	mother (yes)	8 (16%)	3 (5%)	8 (11%)	13 (12%)	4 (7%)
	father (yes)	25 (50%)	27 (42%)	38 (52%)	88 (79%)	38 (68%)
2 Yrs.	mother (yes)	21 (42%)	29 (45%)	25 (34%)	71 (64%)	34 (61%)
	father (yes)	31 (62%)	28 (43%)	36 (49%)	90 (81%)	37 (66%)
4.5 Yrs.	mother (yes)	23 (46%)	31 (48%)	40 (55%)	78 (70%)	35 (63%)
	father (yes)	21 (42%)	27 (42%)	37 (51%)	90 (81%)	34 (61%)
Marijuana						
Antenatal	mother (yes)	8 (16%)	7 (11%)	10 (14%)	5 (5%)	9 (16%)
	father (yes)	7 (14%)	6 (9%)	7 (10%)	5 (5%)	7 (13%)
2 Yrs.	mother (yes)	0	2 (3%)	2 (3%)	1 (1%)	2 (4%)

Characteristics		Group n (%)				
		G1 (n = 50)	G2 (n = 65)	G3 (n = 73)	G4 (n = 111)	G5 (n = 56)
	father (yes)	5 (10%)	4 (6%)	3 (4%)	4 (4%)	4 (7%)
4.5 Yrs.	mother (yes)	2 (4%)	4 (6%)	1 (1%)	0	3 (5%)
	father (yes)	2 (4%)	2 (3%)	3 (3%)	2 (2%)	3 (5%)

Table 6: ***Birth characteristics and risk status of 5 clustered groups (N = 355)***

Characteristics		Group *M* (*SD*) or n (%)				
		G1 (n = 50)	G2 (n = 65)	G3 (n = 73)	G4 (n = 111)	G5 (n = 56)
Neonatal Hypoglycaemia						
Yes		27 (54%)	36 (55%)	41 (56%)	67 (60%)	30 (54%)
Primary Risk Factor						
IDM	Yes	27 (54%)	27 (42%)	24 (33%)	42 (38%)	24 (43%)
Preterm	Yes	19 (35%)	23 (35%)	26 (36%)	47 (42%)	13 (23%)
Small	Yes	9 (18%)	22 (34%)	46 (63%)	23 (21%)	0
Large	Yes	16 (32%)	14 (22%)	3 (4%)	21 (19%)	41 (73%)
Others	Yes	2 (4%)	1 (2%)	2 (3%)	4 (4%)	3 (4%)
Risk Status						
More at-risk		50 (100%)	46 (71%)	41 (56%)	0	18 (32%)
Gestational Age		37 (1.39)	38 (1.70)	38 (1.36)	38 (1.73)	39 (1.79)
Birth Weight		3, 211 (711.7)	3,067 (810)	2,526 (508)	3,073 (672)	4,081 (761)
Birth Length		49 (4.89)	51 (6.04)	49 (2.55)	51 (3.22)	54 (3.39)
Birth Head Circumference		35 (1.78)	34 (1.94)	32 (1.99)	34 (1.79)	36 (2.06)

Note: IDM = Infant of Diabetic Mother

Discriminant Function Analysis for 5-Cluster Solution

Significant function models accounted for each measure of developmental outcomes to identify whether variables (sociodemographic data, paediatric health data, and primary risk of neonatal hypoglycaemia, parent substance use, and developmental outcomes) could discriminate group membership in the CHYLD cohort data. *Refer to supplementary statistical analysis for study 1 at the end of this study*. Using the 2-year and 4.5-year follow-up data, the following variables were revealed as significantly predicting the 5-clusters, these variables are summarised in Table 7.

Table 7: ***Summary of significant discriminant models in predicting group membership for 5-cluster solution***

	Discriminant Model Values			
	No. of Models	Walds	X^2	*p*
Child Risk				
Parent alcohol use	1	0.847	37.15	0.042
Parent smoking	1	0.807	49.82	0.001
Primary risk for neonatal hypoglycaemia	2	0.621	165.83	< .001
		0.893	39.61	0.001
Paediatric health	2	0.817	46.79	< .001
		0.35	243.7	< .001
Sociodemographic data	2	0.685	119.21	< .001
		0.946	16.6	0.04

Sociodemographic data revealed a 2-function model ($p < .001$) with deprivation index at 4.5 years; maternal education and male sex were significant. Deprivation index at 4.5 years was the highly loaded discriminating variable. Among parent substance use history, both smoking ($p = .001$) and alcohol drinking ($p = .042$) categories derived a single significant function. Fathers who had a history of alcohol drinking at 4.5 years and mothers who smoked during pregnancy were significant highly loaded discriminating variables.

Paediatric and birth characteristics data showed significant 2-function variates for both sets. Large for gestational age (LGA) and small-for-gestational age (SGA) and prematurity were accounted for ($p = .001$), while head circumference at birth and at 2 years, as well as weight at 2 years and 4.5 years, were significant ($p < .001$). Primary risks of neonatal hypoglycaemia

such as LGA and SGA were highly loaded and head circumference at 2 years was all considered significant variables for group membership.

Neurocognitive data showed that at 2 years Bayley-III subtests for language, cognition, motor and parent-rated socio-emotion was significant (p = .012). Cognition scores were highly loaded. Among the Wechsler subtests (WPPSI) at 4.5 years, Word Reasoning, Information, Vocabulary, Coding, Block Design, Matrix Reasoning, and Picture Concepts were significant ($p < .001$). Word Reasoning and Information were highly loaded compared to other subtests. Administered tests of executive function showed that Dimension Change Card Sorting (DCCS), Bear & Dragon, Gift Wrap and Ducks& Buckets at 2 years were significant ($p <$ .001); only tasks requiring inhibition of prepotent responses at 2 years (Ducks & Buckets) and at 4.5 years (DCCS) were highly loaded. Among the parent-rated executive function (BRIEF-P), Global Executive Control at 4.5 years (GEC), Inhibitory Self Control (ISCI), Emergent Metacognition (EMI) and Flexibility (FI) were found to be significant ($p < .001$). Among the parent-rated skills, ISCI was highly loaded ($p < .001$). Tests of visual-perception showed a 1-function model, wherein Visual Motor Integration scores (VMI) was significant ($p < .001$) and highly loaded.

Behavioural data showed a significant 2-function model (p = .015). Externalising problems, such as attention problems, aggressive behaviour, and conduct problems were correlated highly on the variate compared to internalising problems. Aggressive behaviour was also found to be highly loaded. Among the subtests of Social Communication Questionnaire (SCQ), a 3-function model was significant (p = .036), both Reciprocal-Social and Repetitive behaviour were loaded on the same variate, while Communication was loaded on the second variate. Stereotypy (Repetitive) behaviour was highly loaded.

Five clusters were validated through discriminant function analysis. Cluster 1 (n = 50, 14.1%) appeared to be the group that had the poorest developmental outcomes among the five groups (Table 7) However, observed developmental scores profiles showed that Cluster 1, 2 and 3 represented a continuum of developmentally lower outcomes. Cluster 4, (n = 111, 31.3%) appeared to be the least at-risk for developmental problems with most children living in higher SES group and most were of NZ European ethnicity. Cluster 5, (n = 56, 15.8%) was made up of a high proportion of infants born seen to be another group which needed more observations because in comparison this group was considered heavy (mostly born Large). Clusters 1 – 3 were mostly from deprived social strata, lower maternal education, mostly of

male sex and of Māori and Pacific ethnicity. Cluster 3 was smaller (born mostly SGA) than other groups. Almost 50% of the 355 followed-up at 4.5 years were considered at-risk and were from clusters 1 – 3. Because this study cannot ascertain significant differences from the proportions of risks, a subsequent study will determine if there were significant group differences as suggested by the final cluster centres (profile) and represent groups that are valid and predictive of child outcomes.

Discussion

Are subgroups tenable for the CHYLD cohort?

The aim of study 1 was to identify whether subgroups of participants can be aggregated from a cohort of children at risk of neonatal hypoglycaemia. Both 5-cluster and 2-cluster solutions were revealed useful for further analyses. Further cluster adjustments were made and then validated: Wherein, the 5-cluster was found more suitable for profiling discrete groups. The strength of this method was considered innovative in the sense that a typically developing child at risk of neonatal hypoglycaemia can be analysed by aggregating child qualities and characteristics. As compared to the traditional test of group differences, one reason could be that a straightforward test of group differences among categorical variables (glycaemic versus euglycaemic), may have offered less sensitivity for detecting simple main effects when these variables were not configured based on socio-ecological context. In this regard, a person-centred approach to identify risks was supported and its impact evaluated through the use of group profiles. These initial findings supported the cumulative risk hypothesis, that risk effect was not merely additive by nature but individual outcomes were associated with different combinations of risk (Evans et al., 2013). Therefore, group differences may be discriminated through the quality of lifestyle, birth characteristics, socioeconomic status, parent characteristics and exposure to parent substance use.

Are group effects suggestive of general or subtle deficits in neurodevelopment?

Observed discrimination of neurocognitive variables showed that Bayley-III scales (Cognitive, Language, and Motor) were significant in discriminating groups, with a small proportion attributed to parent-rated socio-emotion. Similarly Bayley Language scores at 2 years were largely contributory, compared to other Bayley-III scales. This finding supported the argument that language performance at 2 years among children at risk of neonatal hypoglycaemia may have shown a context-specific difference (Ansell, 2014). Similarly, verbal IQ subtests: Word Reasoning and Information were observed contributory to discriminating group differences at

4.5 years. It seems that longitudinally, language development may have been an issue among these groups of children. Hand-eye coordination also discriminated group differences with a large proportion attributed to Beery VMI score. The combined hand-eye coordination, which taps into visuospatial processing, is considered a basic neural system function (Colzato, Wouwe, & Hommel, 2007) associated with pre-academic achievement (Cameron et al., 2012). In observed executive function tasks, inhibition (Bear & Dragon, Day & Night, and Gift Delay), cognitive flexibility (Card Sorting) at 4.5 years, and a categorisation task (Ducks & Buckets) at 2 years were significant predictors for group memberships. A large contribution was attributed to cognitive flexibility. This suggests that group differences are tenable as a function of this higher order cognitive shifting. Among the parent-rated measures of executive function, discriminating functions of GEC and ISCI were contributory to group differences. Compared to the observed measures, parent-rated measures at 4.5 years only contributed to the discriminating function. Overall, these findings suggest that there is a discrepancy between the two measures of executive function.

With regard to behavioural outcomes, the findings suggest that externalising behaviours, specifically attention problems and aggressive behaviour were more likely to be used as discriminating variables among groups. Although the contribution of internalising behaviours was not enough to differentiate group membership, nevertheless externalising behaviours were suggested to be more prominent. Among domains of autism-like behaviour, compared to CBCL, a 3-function variate was suggested in discriminating group differences. Repetitive behaviour and communication domains seemed tenable, with repetitive behaviour more endorsed as discriminating than other domains. This finding was unexpected because the CHYLD cohort participants were neurologically healthy and exclusion criteria were strict. However, this should be taken in light of the cumulative risk configuration supported in the study.

What does the profile suggest?

This thesis is the first in the author's knowledge to use a person-focused approach to analyse children at risk of neonatal hypoglycaemia. Although the findings are preliminary, they suggest that a number of children in the cohort needed a follow-up evaluation. For instance, looking at the risk profiles (percentages) of Groups 1, 2 and 3, it is more likely that these children may have had some behavioural and cognitive deficits. The tenability of the 5-cluster solution suggests that the cohort can be described as part of a spectrum of developmental qualities which features the group of children with most likely poorer performance (group 1),

poorer physical qualities (group 3), larger size and measures (group 5), more likely to have neonatal hypoglycaemia but in good social strata (group 4), or combined primary risks and poor social strata (group 2). Data must be interpreted with caution because a number of children for this cohort may have had one or more primary risks of neonatal hypoglycaemia, which could not be controlled statistically.

The important issue that emerged in these analyses are a) primary risk effects, though it may have been hard to determine the individual effects of these primary risks of neonatal hypoglycaemia, this study was able to identify, at least, how each primary risk group along with the early environment were predictive of developmental outcomes. Therefore, group clusters were discriminated based on the spread of being small for gestation (SGA) among groups 1, 2 and 3. Born large (LGA) and IDM were significantly discriminated, while cases of neonatal hypoglycaemia together with “other medical conditions” along with IDM were classified but found not significant. Similarly, significant discrimination was observed among child characteristics. A bigger proportion of group differences were attributed to the combination of child weight at 2 years and 4.5 years and head circumference at birth and 2 years. In summary, both child characteristics and primary risks contributed to the grouping of children with significant attention to the magnitude of SGA, preterm, children’s weight and head circumference.

Is group clustering sensitive to the effect of neonatal hypoglycaemia?

In contrast to earlier findings from the CHYLD data that suggested a child at risk of moderate neonatal hypoglycaemia living in poor social conditions may have adverse neurodevelopment (Ansell, 2014; Burakevych, 2016), this study did not reveal any such findings. Based on risk discrimination, there was no evidence that moderate neonatal hypoglycaemia may have interacted with the poor early environments, compared to being born small-for-gestation (SGA). However, discriminating among primary risks, neonatal hypoglycaemia was found loaded together with “Other medical condition”, which means moderate hypoglycaemia may have had an interaction with medical conditions, which required more immediate medical support. However, this hypothesis needs further investigation in future research. It may be the case that this cohort of children was treated with dextrose oral gel, which is an effective treatment to support the needed level of blood sugar among newborns. Thus, the subtle or trace effect of moderate neonatal hypoglycaemia was not enough to discriminate group differences when it failed to load on the groups hypothesised as ‘more at-risk’.

Supplemental Statistical Analysis for Study 1

Discriminant Function Analysis for Parent Alcohol Use

Analysis revealed four discriminant functions: Function 1 explained 66.2% of the variance, R^2 = .32. Function 2 explained 24.3% of the variance, R^2 = .20. Function 3 explained 6.1% of the variance, R^2 = .10, and Function 4 explained 3.4% of the variance, R^2 = .08. A single function model was significant, L = .847, X^2 (24) = 37.149, p = .042. Correlations between outcomes and the discriminant functions revealed that paternal alcohol use during pregnancy (r = .73), maternal alcohol use at 2 years (r = .54), paternal alcohol use at 2 years (r = .69), and paternal alcohol use at 4.5 years was highly loaded on function 1. Maternal alcohol use at pregnancy was loaded at function 3 (r = .48) while maternal alcohol use at 4.5 years was loaded at function 4 (r = .67). Patterns of alcohol use among parents were discriminated among groups. Original grouped cases were correctly classified at 35%. Refer to Table 8 for correlations and coefficients.

Discriminant Function Analysis for Parent Tobacco Use

Analysis revealed four discriminant functions: Function 1 explained 67.1% of the variance, R^2 = .36, Function 2 explained 22.7%, R^2 = .22, Function 3 explained 7.5%, R^2 = .13 and Function 4 explained 2.6%, R^2 = .08. A single function model was significant, L = .807, X^2 (24) = 49.817, p = .001. Correlations between outcomes and the discriminant functions revealed that maternal smoking at pregnancy (r = .81), paternal smoking at 4.5 years (r = .76), maternal smoking at 4.5 years (r = .75), paternal smoking at pregnancy (r = .66), paternal smoking at 2 years (r = .63), and maternal smoking at 2 years (r = .44). Patterns of parental smoking did not vary widely among groups. Original grouped cases were correctly classified at 45%. Refer to Table 9 for correlations and coefficients.

Table 8: ***Correlation of Predictor Variables with Discriminant Functions and Standardised Discriminant Function Coefficients of Parent Alcohol Use at Pregnancy, at 2 Years and at 4.5 Years.***

	Standardized Canonical Discriminant Function Coefficients				Structure Matrix			
Predictor Variable	1	2	3	4	1	2	3	4
Maternal Alcohol Use at Pregnancy	0.174	0.442	0.461	0.097	0.326	0.403	.479*	0.219
Maternal Alcohol Use at 2 Yrs	0.35	-0.635	-0.534	0.478	.541*	-0.408	0.031	0.495
Maternal Alcohol Use at 4.5 Yrs	-0.41	0.369	0.582	0.845	0.396	0.066	0.422	.671*
Paternal Alcohol Use at Pregnancy	0.291	1.435	-0.908	-0.002	.726*	0.279	0.169	-0.179
Paternal Alcohol Use at 2 Yrs	-0.177	-1.142	1.581	-0.835	.695*	-0.121	0.492	-0.215
Paternal Alcohol Use at 4.5 Yrs	0.924	-0.217	-0.593	-0.047	.895*	-0.003	0.126	0.085

*Note: * Largest relationship*

Table 9: ***Correlation of Predictor Variables with Discriminant Functions and Standardised Discriminant Function Coefficients of Parent Smoking at Pregnancy, at 2 Years and at 4.5 Years.***

	Standardized Canonical Discriminant Function Coefficients				Structure Matrix			
Predictor Variable	1	2	3	4	1	2	3	4
Maternal Smoking at Pregnancy	0.654	-0.996	-0.196	-0.233	.809*	-0.235	-0.095	-0.092
Maternal Smoking at 2 Yrs	-0.656	0.016	0.619	0.53	.443*	0.103	0.111	0.058
Maternal Smoking at 4.5 Yrs	0.429	1.146	-1.227	-0.019	.747*	0.339	-0.278	0.212
Paternal Smoking at Pregnancy	0.174	1.265	0.644	-0.935	.663*	0.287	0.497	-0.373
Paternal Smoking at 2 Yrs	0.174	-1.092	-0.474	-0.563	.634*	-0.04	0.268	-0.219
Paternal Smoking at 4.5 Yrs	0.285	-0.268	0.89	1.246	.758*	0.115	0.425	0.385

*Note: * Largest relationship*

Discriminant Function Analysis for Primary Risk Factors

Analysis revealed four discriminant functions: Function 1 explained 79% of the variance, R^2 = .55. Function 2 explained 15.1%, R^2 = .28, Function 3 explained 3.8%, R^2 = .14 and Function 4 explained 2.3% with R^2 = .11. A 2-function model was significant. L = .621, X^2 (24) = 165.830, p < .001 and L = .893, X^2 (15) = 39.606, p = .001. Correlations between outcomes and the discriminant functions revealed that being born large for gestation (r = -.83), and being born small for gestation (r = .72) significantly loaded in function 1. Prematurity (r = -.36) loaded in function 2, Infant of diabetic mother (IDM) loaded in function 3 (r = .77), while hypoglycemia (r = .88) and Other medical conditions (r = .36) loaded on function 4. Patterns of primary risk factor discriminate groups. Original grouped cases were correctly classified at 43%. Refer to Table 10 for correlations and coefficients.

Discriminant Function Analysis for Paediatric Data

Analysis revealed four discriminant functions: Function 1 explained 86.3% of the variance, R^2 = .76, Function 2 explained 9.2 % of the variance, R^2 = .35, Function 3 explained 2.7%, R^2 = .20 and Function 4 explained 1.8%, R^2 = .17. A 2-function model is significant, L = .350, X^2 (28) = 243.704, p < .001 and L = .817, X^2 (18) = 46.791, p < .001. Correlations between outcomes and the discriminant functions revealed that head circumference at 2 years (r = .69), weight at 4.5 years (r = .64), head circumference at birth (r = .53) and weight at 2 years (r = .51) significantly loaded in function 1. Head circumference at 4.5 years (r = -.64) loaded at function 2. Birth weight (r = -.61) loaded at function 3, and gestational age (r = .74) loaded in function 4. Paediatric data were discriminated among groups. The original grouped cases were classified 54.4% correctly. Refer to table 11 for correlations and coefficients.

Table 10: ***Correlation of Predictor Variables with Discriminant Functions and Standardised Discriminant Function Coefficients of Primary Risk Factors.***

	Standardized Canonical Discriminant Function Coefficients				Structure Matrix			
Predictor Variable	1	2	3	4	1	2	3	4
IDM	0.249	0.232	1.224	0.384	-0.105	-0.047	.765*	-0.02
Preterm	0.096	-0.255	0.667	0.28	0.117	-.363*	0.09	0.075
Small	0.657	0.911	0.313	0.312	.721*	0.579	-0.264	0.077
Large	-0.657	0.723	0.196	0.252	-.825*	0.511	0.044	0.069
Other	0.007	0.15	0.381	0.467	-0.031	-0.06	0.03	.356*
Neonatal Hypoglycemia	-0.011	-0.17	-0.225	0.882	0.006	-0.184	-0.296	.883*

*Note: * Largest relationship, IDM = Infant of Diabetic Mother*

Table 11: ***Correlation of Predictor Variables with Discriminant Functions and Standardised Discriminant Function Coefficients of Paediatric Data at Birth, at 2 Years and at 4.5 Years.***

	Standardized Canonical Discriminant Function Coefficients				Structure Matrix			
Predictor Variable	1	2	3	4	1	2	3	4
Gestational Age	0.084	1.603	0.494	1.209	0.201	0.34	-0.141	.735*
Birth Weight	0.497	0.191	-0.716	-0.091	0.61	0.271	-.612*	0.282
Weight at 2 Yrs	0.467	2.711	-0.013	0.58	.506*	0.086	-0.418	-0.182
Weight at 4.5 Yrs	0.417	0.153	0.734	0.115	.639*	-0.03	0.63	-0.039
Birth Head Circumference	-0.355	-3.177	-0.301	-0.975	.527*	0.118	-0.411	0.101
Head Circumference at 2 Yrs	0.441	0.514	0.214	-0.641	.688*	-0.189	0.223	-0.219
Head Circumference at 4.5 Yrs	0.104	-1.02	-0.197	0.69	0.578	-.635*	0.04	0.296

*Note: * Largest relationship*

Discriminant Function Analysis of Sociodemographic Data

Analysis revealed three discriminant functions: Function 1 explained 87% of the variance, R^2 = .53, Function 2 explained 11.2%, R^2 = .22, Function 3 explained 1.8%, R^2 = .09. A two-function model is significant, L = .685, X^2 (16) = 119.211, p < .001, and L = .946, X^2 (9) = 16.601, p = .040. Correlations between outcomes and the discriminant functions revealed that deprivation at 4.5 years (r = .70), maternal educational status (r = .61) loaded on function 1. Sex (r = .74) loaded on function 2. Ethnicity (European versus Non-European) loaded on function 4 (r = .67). Sociodemographic data varied according to group. The original grouped cases were classified 40% correctly. Refer to Table 12 for correlations and coefficients.

Table 12: ***Correlation of Predictor Variables with Discriminant Functions and Standardised Discriminant Function Coefficients of Sociodemographic Data.***

	Standardized Canonical Discriminant Function Coefficients				Structure Matrix			
Predictor Variable	1	2	3	4	1	2	3	4

STUDY 2: Cumulative Risk in the CHYLD Cohort: Validation and Prediction of 5 Groups

Introduction

Findings to date from the CHYLD study only suggests possible deficits in neurocognition (visual motor integration and executive function) from the comparison of limited categories (e.g., euglycaemic versus glycaemic) (Ansell, 2014; Burakevych, 2016; Chakraborty, 2015; Mckinlay et al., 2015). However, an alternative approach can be utilised to determine whether a bottom-up process of agglomerating similar person-ecological characteristics predicts patterns, rather than a comparison of categories (Chiarello, Welcome, & Leonard, 2012). A person-centred approach aims to maximise the clarity of the statistical impact of multiple risks (person-environment) and minimise the occurrence of a single factor as the determinant of outcomes (Rhoades et al., 2011). As this approach draws on the identification of group differences in neurocognition and behavioural outcomes, there is an advantage in looking at a spectrum, subgroups of at-risk young children, in order to identify the proportion of risk requiring immediate intervention. In this particular study there is an emphasis on the use of a person-centered approach to estimate the impact of cumulative risks, before and after birth (at 2 years and at 4.5 years) on the neurodevelopment of young children. Study 1 validated the 5-cluster solution as tenable for subsequent tests of group differences. It was hypothesised (based on the final cluster centres) that Groups 1, 2 and 3 form a spectrum-like typology for at-risk young children, while Groups 4 (mostly neonatal hypoglycaemia) and 5 (mostly born-large) form as independent and yet significant members of the cluster solution.

Method

CHYLD Data

Data used for this study were from the 2-year and 4.5-year follow-up developmental data. Neurodevelopmental outcomes were categorised into: neurocognitive results (measures of cognitive abilities) and behavioural results (parent-rated measures of child behaviour problems). Chapter 3 provides the complete description and/or psychometric properties of each measure. Analysis included general cognitive tests at 2 years (Bayley-III) and at 4.5 years (Wechsler Test), executive function tasks at 2 years (Duck & Buckets, Snack Delay, Fruit Stroop, and Multisearch Multilocation), and also at 4.5 years (Bear & Dragon, Day and Night, Gift Wrap, Forward Digit Span, and Card Sorting). Practice trial and answer sets (e.g., pre-switch, post-switch, border) were included to determine phase group differences. Parent-

rated executive function at 2 years and 4.5 years were included, wherein T scores of each subtest were utilised instead of indices. In addition, Global Executive (GEC) scores from both time points were utilised. Behavioural data included syndrome scores from the Child Behaviour Checklist from 4.5-year data (CBCL); likewise, clinical subtest scores from Strengths and Difficulty Questionnaire (SDQ) and from Social Communication Questionnaire (SCQ) were utilised.

Data Analysis

A multivariate analysis of variance (MANOVA with Bonferroni adjusted alpha) was used to examine group differences in neurodevelopment (neurocognition and behavioural outcomes) at 2 years and 4.5 years, among five groups of at-risk preschool children (n = 355). Data cleaning was conducted prior to MANOVA. The data was analysed with SPSS Statistics to look at whether assumptions were met. Univariate normality was assessed with Shapiro-Wilk tests and boxplots. Multivariate outliers were detected through Mahalanobis distance. *Deletion* or *value changes towards the group mean* were the two strategies used. Games-Howell was used where sample size differences and homogeneity of variance could not be assumed. Correlations among variables were linear and their magnitude showed moderate to low relationships, which was an indication that there was no multicollinearity issue. Univariate analysis of variance/ covariance were utilised to determine individual variable group differences. Descriptive statistics were presented for each group (refer to *supplementary statistical analysis for study 2* at the end of this study for Means and SDs). All statistics were entered and analysed in IBM SPSS Version 23.

Results and Findings

Neurocognitive outcomes

Discrete cognitive abilities (intelligence subtests) and measures of higher cognitive skills supported the preliminary hypotheses of Study 1 for Bayley-III, F (20, 1300) = 12.07, p < .001, ηp^2 = .157; WPPSI-III, F (32, 1332) = 6.896, p < .001, ηp^2 = .142; Beery VMI score, F (12, 1026) = 7.632, p < .001, ηp^2 = .082; 'Observed' EF tasks at 2 years showed significant differences in snack delay, F (4, 330) = 12.81, p < .001; fruit stroop, F (4, 276) = 4.56, p = .001; ducks and buckets, F (4, 274) = 5.58, p < .001, and for the 4.5 year administered EF tasks in bear & dragon, F (12, 319) = 14.97, p < .001, ηp^2 = .157; gift wrap delay, F (4, 315) = 3.95, p < .001, = .047; digit span, F (3, 323) = 10.11, p < .001, ηp^2 = .111; and DCCS on the following: practice trial, F (4, 334) = 4.978, p = .001, eta^2 = 0.06; pre-switch colour trial, F (4, 334) = 4.797, p = .001, eta^2 = 0.05; and post switch shape trial, F (4, 334) = 11.326, p < .001,

eta^2 = 0.12, and 'everyday' executive function at 2 years, F (5, 337) = 5.236, p < .001, ηp^2 = .071 and at 4.5 years F (5, 335) = 12.825, p < .001, ηp^2 = .159. Subsequent analyses identified that the 5-cluster solution was more sensitive to the parent-rated executive function, at 2 years than observed executive function. On the other hand, parent-rated EF endorsed more deficits in the ISCI index compared to observed EF skills (cognitive flexibility). Also, the impact of cumulative risk was considered larger for parent-rated EF at 4.5 years than at 2 years, while a very small effect size difference was seen between 2 years and 4.5 years composite scores for observed EF. See Figure 3 – 5 for neurodevelopmental profiles at 3 and at 4.5 years. Refer to supplementary statistical analysis for study 2 at the end of this study.

Behavioural outcomes

In the behavioural domain, the results supported the final cluster centre from Study 1. There were observed significant and substantial differences among syndrome scores of CBCL, F (7, 322) = 8.899, p < .001, ηp^2 = .161 (externalizing behaviour, aggressive behaviour and attention problem) that were then further supported by the SDQ, F (5, 328) = 13.147, p < .001, ηp^2 = .166 (conduct problems and hyperactive/inattention problem). In addition, Autism-like behaviour, F (4, 346) = 64.438, p < .001, eta^2 = .429 was supported. See Figure 3 and Figure 6 for the behavioural profile of CHYLD cohort at 2 years and at 4.5 years. Refer to supplementary statistical analysis for study 2 for further analytics and tables.

In summary, Groups 1, 2 and 3 appeared to be tenable description of developmental continuum of groups for at-risk young children. Groups 4 and 5 were considered to be groups needing more investigation owing to the proportion of risks such as LGA and neonatal hypoglycaemia and possible occurrences of late risk impact. Therefore, the rate of 53% at risk was supported based on the group differences. Follow-up assessments and/or referrals are suggested for this group of children.

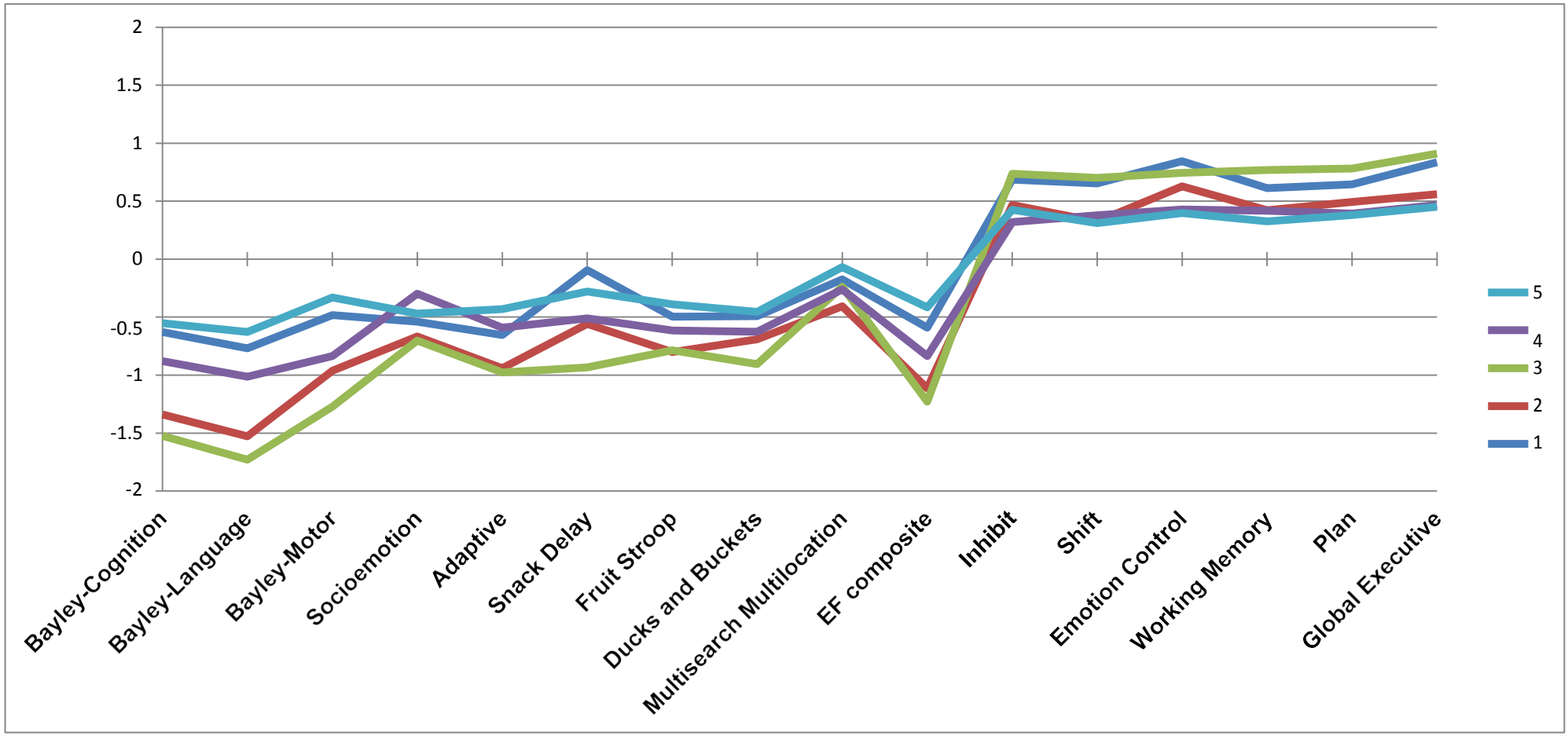

Figure 3: ***Profile of Neurodevelopment Standardised (Means) Scores at 2 Years***

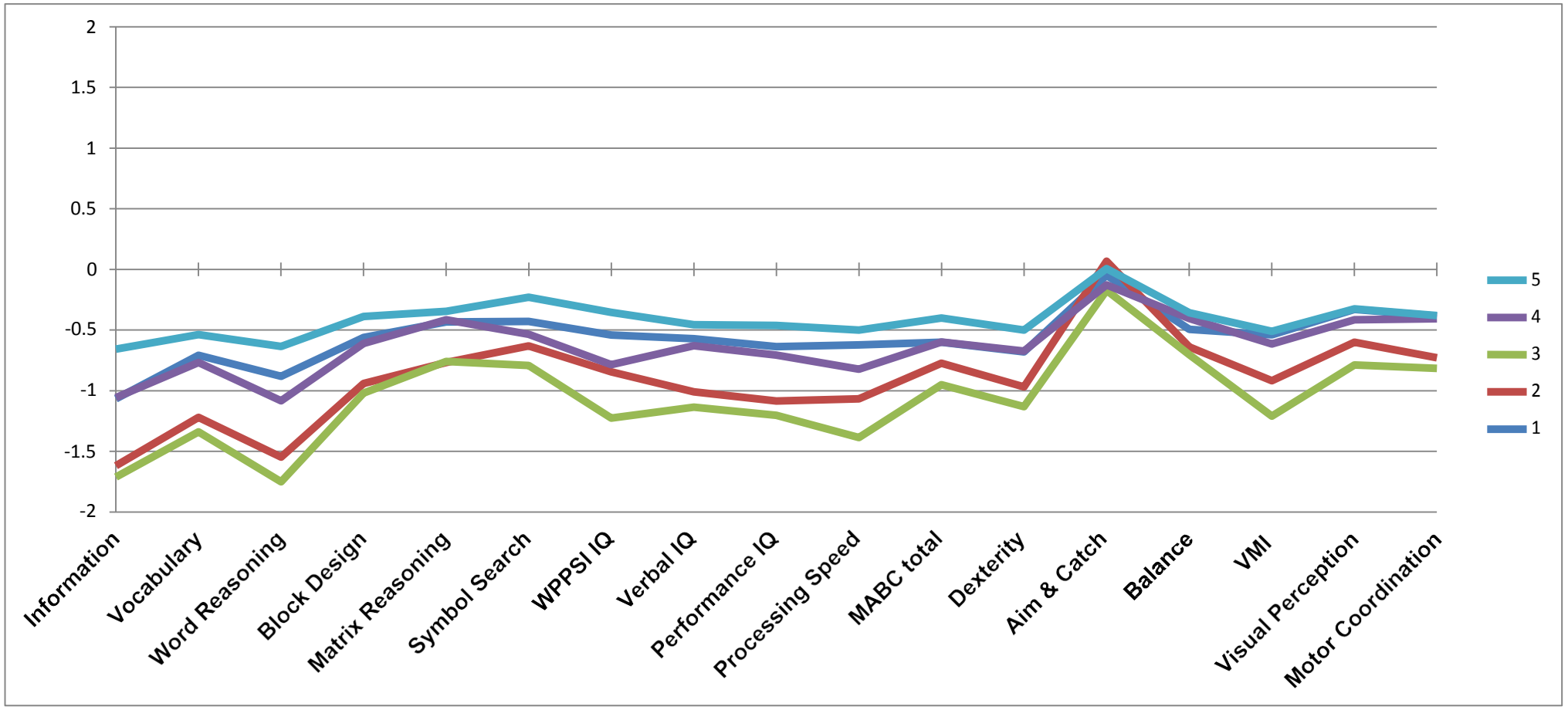

Figure 4: ***Profile of Neurodevelopment Standardised (Means) Scores at 4.5 Years (Neurocognition)***

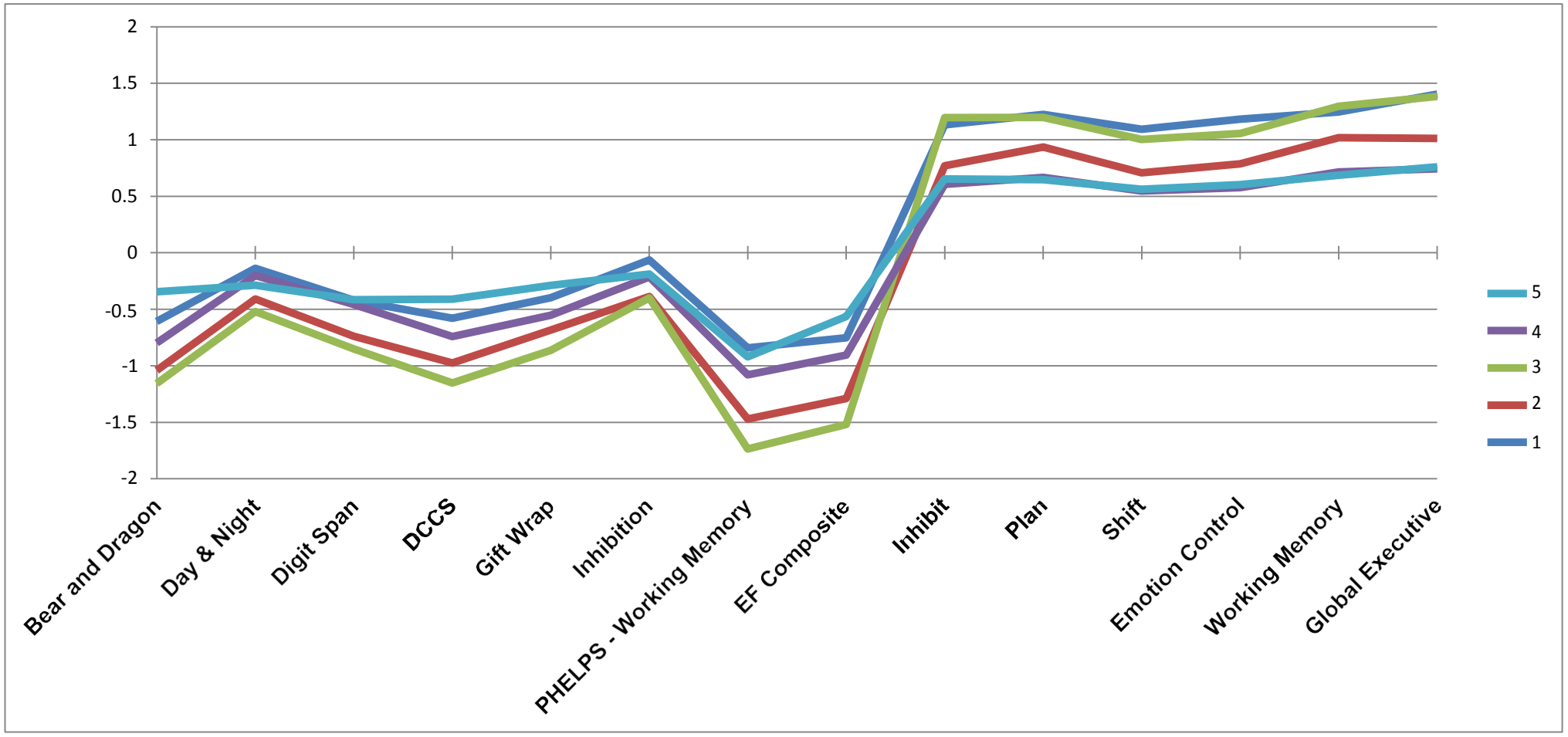

Figure 5: ***Profile of Neurodevelopment Standardised (Means) Scores at 4.5 Years (Executive Function)***

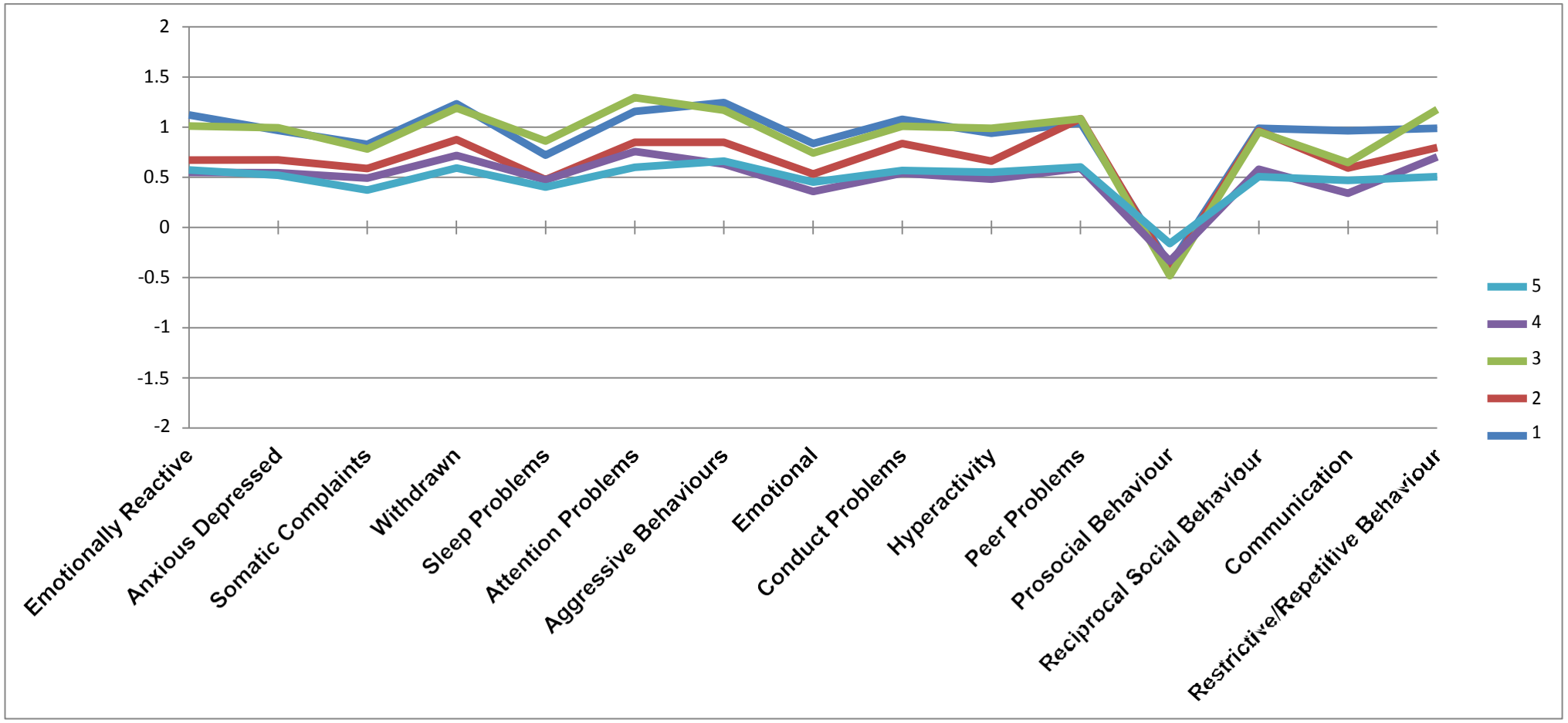

Figure 6: ***Profile of Neurodevelopment Standardised (Means) Scores at 4.5 Years (Behaviour)***

Discussion

What are the trends observed in the neurodevelopment of these at-risk children?

The aim of study 2 was to complement study 1 by validating group differences. Findings in this study were consistent with the preliminary results from discriminant function analysis and cluster centres. Effects observed in Bayley-III language scores validate the initial hypothesis. Information and word reasoning are mostly affected among at-risk groups. Subtests such as information are found to be more sensitive to quality early environment and stimulation, while verbal reasoning is related to language development and making connections from past learning experiences (Sattler, 2008). Thus, this subtest (Information) may highlight that a deprived early environment may have had an effect on children's performance on these subtests. The Beery visual-motor integration score (VMI) was found significantly different among groups and was poorer in most at-risk group (Group 3).

In contrast to the initial study at 2 years (Ansell, 2014), there were no group differences seen among composite scores. However, task unit scores showed significant group differences. Phase or stage analysis of the task unit is important because it may suggest whether a certain group of children are homogenous in their executive function performance. For instance, responses on delayed inhibition (Snack Delay sets) showed significant differences at set 2 and set 3 – longer waiting time (in seconds); therefore, delaying of behavioural responses might be an issue for this cohort of children. The initial task set for Fruit Stroop, which is a part known where the child builds a concept representation and task set 2 (sorting and categorisation) for Ducks and Buckets were identified issues. Therefore, this suggests that children in this cohort have less cognitive control (goal representation, rule shifting and inhibition). Groups from poorer social environments and/ or with primary risks such as SGA were exhibited poorer performance at 2 years. These findings were supported in the follow-up data at 4.5 years, wherein inhibition (Dragon trials of the Bear & Dragon Task) was found significantly different among groups. However, in a similar inhibition task where inhibition of responses was easier (Day & Night), group differences were not observed. This may suggest that there is a ceiling-effect for children at 4.5 whereby the Day & Night may be too easy for this age group and is no longer discriminative of complex inhibition in this age group. The same may be true for the Gift Wrap Delay task as the effect sizes were small. This task measures simple inhibition whereas the Fruit Stroop used at the 2 year follow-up and the Bear and Dragon used at 4.5 year follow-up are meant to test more complex inhibition. The Digit-Span (working memory) task showed between group differences in the subtest of Digit

Sequences, a separate test of working memory was estimated to include the three subtests of Phelps Auditory Processing, groups 1, 2 and 3 scored lower suggesting poorer working memory. Performance in the Dimension Change Card Sorting (DCCS) task showed that those who were in the groups (1,2 and 3) that were most at risk tended not to pass the post-switch trial. This is consistent with research that has shown that typically developing children between ages 4.5 to 6 years could pass the post-switch (Zelazo, 2006). Therefore, more at-risk groups (1,2, and 3) showed more tendencies of cognitive control errors in flexibility and working memory compared to less at-risk groups (4 and 5).

In regards to parent-rated executive function, emotion control was observed more endorsed at 2 years and inhibit at 4.5 years. In contrast to the result of the parent-rated EF at 2 years, the group effect was observed larger at 4.5 years. Therefore, these findings may suggest that group effects were revealing their impact in preschool years and not as much in the toddler years. This study also supported the initial findings that 'observed measure' of EF endorsed a different higher cognitive skill (cognitive flexibility and working memory) more than 'parent-rated' EF (inhibition and emotion control). Trends observed between 2 years and 4.5 years of parent-rated EF data showed that Group 1 increased errors in everyday executive function from 2 years to 4.5 years, while group 4 decreased; other groups also decreased at 4.5 years. These observations may be supported by the increase of composite scores of 'observed' EF from 2 years to 4.5 years. Observed EF composite scores for Group 1 showed small increases compared to other groups, each with at least two to three mean scores increase. Overall, the pattern of executive function among at-risk children was identified as poorer but non-clinical; only group 1 showed an increased error and slow developmental trajectory of 'observed' EF performance. Group effects showed that children from the most deprived backgrounds and with cumulative risk were the ones who lag behind in higher cognitive skills, while group 3 (poor and mostly SGA) were slowly catching-up compared to group 1 (poor and mostly IDM and Non-European).

In contrast to the findings in the neurocognitive variables, behavioural outcome variables had larger group effects. Consistent with the initial findings, peer problems, hyperactivity, and aggressive behaviour differed largely among groups. Contrary to the expectations, group differences in prosocial behaviour were very small. This could be an issue, because children perceived as socially competent were more likely to be reported positively by their parents. Thus, the presence of a small effect size could mean that the presence of good prosocial behaviour may mask the real perception of problem behaviour among at-risk children (see Figure 6). Also, consistent with the initial findings, restrictive/repetitive domain group effects

were larger. These findings suggest that increased cumulative risk in young children may explain the features of stereotypy. However, as the sample of this cohort was not neurologically damaged, careful interpretation is needed. The findings only allow for possible exploration of the hypothesis among at-risk children. Cumulative risk is associated with higher chance of sensory processing similar to stereotypy behaviours seen among children diagnosed with autism spectrum disorder (ASD).

What are the patterns of child behaviours and cognitive deficits that can be deduced from the CHYLD cohort data?

Overall these findings suggest that the 5-cluster solution is valid for subgroups of children from the CHYLD cohort, however features of neurodevelopment were similar for each group. The only differences observed were the socioeconomic data, maternal education, ethnicity, parent substance history and SGA. The most at-risk children (Groups 1, 2 and 3) among the groups showed poorer language development, errors in tasks requiring visuospatial processing, aggressiveness, hostile bouts of behaviour, some attention problems, perseverative errors in tasks requiring previous rules to be overridden, and some possible sensory processing deficits. This study does not support any evidence of neurological damage in this sample of at-risk children or where damage is attributed to a single risk effect. Children in this CHYLD cohort were perceived by their parents with average prosocial behaviour. These findings have implications for further child assessment looking into how cumulative risk may influence their pre-academic development at preschool and middle school (literacy and numeracy). Child characteristics that are more likely to be associated with cognitive deficits and parent or teacher reports of problem behaviour may have come from mostly deprived households, with mothers having less than university degrees, affiliated with New Zealand Maori and Pacific, most likely of male sex, exposed to prenatal and/or prolonged parent substance use (alcohol and smoking), and more likely combination of IDM and born small (SGA). Overall, SES was a potent predictor of child developmental outcomes. Based on the longitudinal profile at 2 years and 4.5 years (see Figure 4 – 6), Groups 1, 2 and 3 showed more developmental deficits. However, Group 1 showed developmental regression on everyday executive function and behaviour measures, whereas, Group 3 showed consistent poorer neurocognition scores from 2 to 4.5-year follow-up. Therefore, because Group 1 was identified as more socially deprived group in the cohort, the effect was seen on the behaviour domains. On the other hand, the combination of IDM and SGA were consistently identified marker for Group 3 being consistently poor for neurocognition domains.

Supplemental Statistical Analysis for Study 2

Neurocognitive Outcomes

One-way MANOVA for Bayley-III at 2 years

Table 13 shows the descriptive statistics (Means and Standard deviations) for each group. Controlling for family-wise error, a Bonferroni-adjusted alpha level (0.01) was used as an indicator of statistical significance. For multivariate test statistics Pillai's Trace was used. Results showed that there were significant group differences in Bayley-III performances at 2 years. F (20, 1300) = 12.07, $p < .001$, $\eta p^2 = .157$. Analysis of dependent variables individually showed group differences in *cognitive scores*, F (4, 326) = 41.44, $p < .001$, $\eta p^2 = .337$; *language scores*, F (4, 326) = 56.71, $p < .001$, $\eta p^2 = .410$; *motor scores*, F (4, 326) = .306, $p < .001$, $\eta p^2 = .306$; *socio-emotional scores*, F (4, 326) = 7.73, $p < .001$, $\eta p^2 = .087$; and *general adaptive scores*, F (4, 326) = 18.05, $p < .001$, $\eta p^2 = .181$. Groups which represent children mostly from deprived socio-economic status, male sex, more likely to be affiliated with Maori or Pacific groups, born from mothers with gestational diabetes and with accompanying prenatal risks such as born preterm or small-for-gestation where all likely to have lower scores in Bayley-III. Language scores were seen statistically and largely differing among groups. Parent-rated components of Bayley-III such as socio-emotion and general adaptive functioning scores were seen as statistically significant but of small effect sizes.

Table 13: ***Mean Scores and Standard Deviations for Bayley-III Subtests at 2 Years.***

Group	*n*	Cognition Score		Language Score		Motor Score		Socio-emotional Score		General Adaptive Function Score	
		M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
1	46	88.33	6.83	85.07	9.99	93.61	4.33	95.43	15.41	90.52	13.01
2	57	87.58	4.47	84.54	8.07	93.96	4.41	101.49	16.31	93.91	12.43
3	69	92.25	8.25	91.35	8.73	96.28	6.21	102.14	13.21	102.59	6.73
4	107	99.39	7.82	104.79	11.73	103.48	8.07	107.8	12.49	104.58	13.01
5	52	97.83	4.92	100.46	10.72	103.13	7.54	100.77	8.99	103.04	10.16

Note: M = Mean and SD = Standard Deviation

One-way MANOVA for WPPSI at 4.5 years

Controlling for family-wise error, a Bonferroni-adjusted alpha level (0.00) was used as an indicator of statistical significance. For multivariate test statistics Pillai's Trace was used. Results showed that there were significant group differences in Wechsler Primary and Preschool Scale of Intelligence (WPPSI) subtests at 4.5 years.

Tables 14 – 16 show the descriptive statistics (Means and Standard deviations) for each group. The MANOVA was statistically significant, F (32, 1332) = 6.896, p < .001, ηp^2 = .142, in combined dependent variables. Inspection of individual dependent variables revealed that scores in *information*; F (4, 337) = 51.812, p < .001, ηp^2 = .381, *vocabulary*; F (4, 337) = 30.611, p < .001, ηp^2 = .267 and *word reasoning*; F (4, 337) = 49.849, p < .001, ηp^2 = .372, have larger group differences compared to *block design*; F (4, 337) = 15.844, p < .001, ηp^2 = .158, *symbol search*; F (4, 337) = 17.952, p < .001, ηp^2 = .176 and *coding*, F (4, 337) = 15.078, p < .001, ηp^2 = .152. Smaller effects were seen in *matrix reasoning*, F (4, 337) = 8.442, p < .001, ηp^2 = .091 and *picture concepts*, F (4, 337) = 9.303, p < .001, ηp^2 = .099.

A univariate analysis of variance (ANOVA) was conducted for each WPPSI scale to avoid multicollinearity. There were statistically significant differences at p <. 001 levels in WPPSI *full scale IQ*: F (4, 343) = 55.65, p < .001; *verbal IQ*: F (4, 344) = 59.92, p < .001; *performance IQ*: F (4, 345) = 19.49, p < .001; and *processing speed*: F (4, 335) = 25.49, p < .001.

Table 14: ***Means and Standard Deviations of WPPSI-III Verbal Components at 4.5 Years.***

		Verbal Components					
		Information		Vocabulary		Word Reasoning	
Group	*n*	*M*	*SD*	*M*	*SD*	*M*	*SD*
1	46	6.78	2.91	7.59	2.33	6.54	2.47
2	62	8.02	2.39	7.98	2.27	7.27	2.07
3	72	9.79	2.47	9.35	2.69	8.86	3.2
4	107	11.71	1.88	11.57	2.7	11.61	2.41
5	55	10.87	1.89	10.35	2.5	10.84	2.5

Note: M = Mean and SD = Standard Deviation

Table 15: ***Means and Standard Deviations of WPPSI-III Performance Components at 4.5 Years.***

		Performance Components					
		Block Design		Matrix Reasoning		Picture Concepts	
Group	*n*	*M*	*SD*	*M*	*SD*	*M*	*SD*
1	46	8.24	3.32	9.04	1.75	8.41	2.52
2	62	8.32	2.49	8.84	1.73	8.77	1.99
3	72	9.86	3.47	9.76	1.87	9.15	2.5
4	107	11.6	3.14	10.54	2.36	10.35	2.74
5	55	10.76	3.16	9.73	2.17	10.64	2.74

Note: M = Mean and SD = Standard Deviation

Table 16: ***Means and Standard Deviations of WPPSI-III Processing Speed Components at 4.5 Years.***

		Processing Speed Components			
		Symbol Search		Coding	
Group	*n*	*M*	*SD*	*M*	*SD*
1	46	7.04	2.91	8.28	1.92
2	62	7.81	2.79	8.47	2.43
3	72	7.56	2.84	9.24	2.64
4	107	10.21	3.16	10.64	1.95
5	55	10.09	2.76	10.02	1.97

Note: M = Mean and SD = Standard Deviation

One-way MANOVA for Beery Visual-Motor Integration at 4.5 years

Controlling for family-wise error, a Bonferroni-adjusted alpha level (0.02) was used as an indicator of statistical significance. For multivariate test statistics Pillai's Trace was used. Results showed that there were significant group differences in Beery Visual-Motor Integration performances at 4.5 years.

Table 17 shows the descriptive statistics (Means and SDs) for each group. The MANOVA was statistically significant, F (12, 1026) = 7.632, $p < .001$, $\eta p^2 = .082$. Individual inspection of independent variables revealed group differences in *Beery visual-motor integration*, F (4, 342) = 22.981, $p < .001$, $\eta p^2 = .212$, compared to *visual perception*, F (4, 342) = 8.576, $p < .001$, $\eta p^2 = .091$ and *motor coordination*, F (4, 342) = 8.705, $p < .001$, $\eta p^2 = .091$.

Table 17: Mean Scores and Standard Deviations of Beery Visual-Motor Integration at 4.5 Years.

		Visual-Motor Integration Score		Visual Score		Motor Score	
Group	*n*	*M*	*SD*	*M*	*SD*	*M*	*SD*
1	47	96.04	6.95	92.55	16.41	88.96	10.35
2	62	97.44	6.59	93.44	14.88	88.08	11.97
3	73	98.67	6.51	94.75	11.42	91.63	10.95
4	110	105.73	7.99	103.18	12.81	96.91	10.48
5	55	101.6	7.45	98.82	13.84	92.73	9.62

Note: M = Mean and SD = Standard Deviation

Univariate Analyses of Variance for Executive Function Tasks at 2 years

A univariate analysis of variance (ANOVA) was conducted for each executive function task administered at the 2 year follow-up. Group comparison was done with the task scores followed by each task set administered to identify group differences at the level of set units.

Table 18 shows the descriptive statistics (Means and Standard deviations) for each group. There were statistically significant differences in the executive function task such as in the *snack delay*, F (4, 330) = 12.81, $p < .001$; *fruit stroop*, F (4, 276) = 4.56, $p = .001$; *ducks and buckets*, F (4, 274) = 5.58, $p < .001$. However, no significant difference was observed in *multisearch multilocation*, F (4, 318) = 2.12, $p = .078$. Group comparison in the task set unit showed group differences in snack delay sets: *snack delay set 2*, F (4, 330) = 9.16, $p < .001$, and *snack delay set 3*, F (4, 330) = 10.93, $p < .001$. No significant group differences were found in *snack delay set 1*, F (4, 330) = 1.17, $p = .325$. In the *fruit stroop sets* only *set 1* showed significant group difference, F (4, 276) = 7.39, $p < .001$. But no significant differences were found for *fruit stroop set 2*, F (4, 276) = 2.09, $p = .081$, and *fruit stroop set 3*, F (4, 276) = 2.22, $p = .067$. In *ducks and buckets set* only *set 2* was found to be significant, F (4, 274) = 5.47, $p < .001$, while there were no significant group differences for *set 1*, F (4, 274) = 1.21, $p = .306$, and *set 3*, F (4, 274) = 1.65, $p = .163$. No significant group differences were seen in *multisearch multilocation set*. *Set 1*, F (4, 318) = .294, $p = .882$; *Set 2*, F (4, 318) = 1.30, $p = .269$, and marginal significance for *Set 3*, F (4, 318) = 2.27, $p = .061$.

Table 18: ***Means and Standard Deviations of Examiner Administered Executive Function Tasks at 4.5 Years.***

	Group 1	Group 2	Group 3	Group 4	Group 5	Total
Tasks (range of scores)	*M(SD)*	*M(SD)*	*M(SD)*	*M(SD)*	*M(SD)*	*M(SD)*
Ducks and Buckets						
Set 1 (0-1)	0.4(0.50)	0.56(0.50)	0.54(0.50)	0.61(0.49)	0.63(0.49)	0.57(0.50)
Set 2 (0-2)	0(0)	0.2(0.60)	0.2(0.60)	0.59(0.92)	0.46(0.85)	0.36(0.77)
Set 3 (0-3)	0(0)	0(0)	0(0)	0.15(0.66)	0.13(0.61)	0.08(0.47)
Snack Delay						
Set 1 (0-1)	0.98(0.15)	0.98(0.13)	1(0)	1(0)	1(0)	0.99(0.08)
Set 2 (0-2)	0.82(0.99)	0.41(0.81)	0.6(0.92)	1.23(0.98)	1.04(1.00)	0.87(0.99)
Set 3 (0-3)	0.55(1.17)	0.2(0.76)	0.17(0.70)	1.16(1.47)	0.96(1.41)	0.67(1.25)
Fruit Stroop						
Set 1 (0-1)	0.84(0.37)	0.76(0.44)	0.96(0.19)	0.98(0.14)	0.96(0.19)	0.92(0.27)
Set 2 (0-2)	0.65(0.95)	1.11(1.01)	0.91(1.01)	1.1(1)	1.23(0.98)	1.04(1)
Set 3 (0-3)	0.29(0.90)	0.2(0.76)	0.68(1.27)	0.72(1.29)	0.69(1.28)	0.58(1.18)

Tasks (range of scores)	Group 1 *M(SD)*	Group 2 *M(SD)*	Group 3 *M(SD)*	Group 4 *M(SD)*	Group 5 *M(SD)*	Total *M(SD)*
Multisearch						
Multilocation						
Set 1 (0-1)	0.97(0.16)	0.96(0.19)	0.99(0.12)	0.96(0.19)	0.98(0.14)	0.97(0.17)
Set 2 (0-2)	1.68(0.74)	1.65(0.77)	1.86(0.52)	1.71(0.71)	1.85(0.52)	1.75(0.66)
Set 3 (0-3)	2.37(1.24)	2.32(1.27)	2.74(0.85)	2.6(1.03)	2.78(0.79)	2.58(1.04)

Note: M = Mean and SD = Standard Deviation

One-way MANOVA for Bear and Dragon at 4.5 years

Table 19 shows the descriptive statistics (Means and Standard deviations) for each group. Bonferroni-adjusted was Alpha = 0.017. Multivariate analysis of variance was conducted for the three task units of Bear and Dragon. Findings showed that there was a significant group difference in the combined dependent variables, F (12, 319) = 14.97, p < .001, ηp^2 = .157. Inspection of the individual dependent variables showed significant differences in three task units: *bear and dragon practice*, F (4, 321) = 38.45, p < .001, ηp^2 = .324; *bear totals*, F (4, 321) = 27.10, p < .001, ηp^2 = .252; and *dragon trials total* = F (4, 321) = 30.06, p < .001, ηp^2 = .273.

Table 19: ***Mean Scores and Standard Deviations of Bear and Dragon at 4.5 Years.***

		Practice		Bear Totals		Dragon Totals	
Group	*n*	*M*	*SD*	*M*	*SD*	*M*	*SD*
1	37	3.84	1.26	16.7	1.39	10.97	7.77
2	58	4.02	1.1	17.24	1.09	10.97	7.45
3	68	4.44	1.37	17.5	0.87	12.4	7.62
4	109	5.53	0.68	18	0	18	0
5	54	5.39	0.69	18	0	18	0

M = Mean and SD = Standard Deviation

One-way MANOVA for Day and Night at 4.5 years

Table 20 shows the descriptive statistics (Means and Standard deviations) for each group. Bonferroni-adjusted for this analysis was alpha = 0.017. Multivariate analysis of variance was computed for the three task units of Day and Night. Findings showed that there was no significant group difference on the combined dependent variables, F (3, 315) = 1.41, p = .155, ηp^2 = .017. Independent inspections of dependent variable showed only marginal significance for *total score* (Sum), F (4, 317), = 2.99, p = .019, ηp^2 = .036, while no group differences were seen at the *night trials*, F (4, 317) = 1.69, p = 1.51, ηp^2 = .021 and *day trials*, F (4, 317) = 2.198, p = .069, ηp^2 = .027.

Table 20: ***Mean Scores and Standard Deviations of Day and Night at 4.5 Years.***

		Night Trial		Day Trial		Total (Sum)	
Group	*n*	*M*	*SD*	*M*	*SD*	*M*	*SD*
1	36	1.97	1.18	1.64	1.31	16	12.02
2	60	1.67	1.22	1.47	1.32	13.52	11.91
3	66	1.77	1.26	1.68	1.39	15.24	12.14
4	108	2.05	1.23	2	1.26	19.41	12.29
5	52	1.6	1.3	1.5	1.31	14.25	12.95

Note: M = Mean and SD = Standard Deviation

One-way MANOVA for Gift Wrap Delay at 4.5 years

Table 21 shows the descriptive statistics (Means and Standard deviations) for each group. Bonferroni-adjusted for this analysis was alpha = 0.013. Multivariate analysis of variance was computed for the four task units of Gift Wrap Delay. Findings showed that there was a significant group difference in the combined dependent variables, F (4, 315) = 3.95, $p < .001$, = .047. Post-hoc evaluation of individual dependent variables showed significant group differences in the four task units. *Latency*, F (4, 318) = 5.756, $p < .001$, $\eta p^2 = .068$; *peeks*, F (4, 318) = 10.697, $p < .001$, $\eta p^2 = .119$; *total duration*, F (4,318) = 7.264, $p < .001$, $\eta p^2 = .084$, and *resistance*, F (4, 318) = 4.421, $p = .002$, $\eta p^2 = .053$.

Table 21: ***Mean Scores and Standard Deviations of Gift Wrap Delay at 4.5 Years.***

		Latency		Peek		Duration		Resistance	
Group	*n*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
1	39	30.62	22.89	1.69	1.58	3.85	4.04	1.08	0.84
2	55	33.8	22.51	1.64	1.78	3.02	3.39	1.04	0.86
3	65	34.94	22.79	1.62	1.66	3.45	3.85	0.92	0.82
4	109	45.06	19.92	0.51	0.63	1.6	2.18	0.62	0.78
5	55	43.8	20.39	1.2	1.54	1.69	2.12	0.65	0.78

Note: M = Mean and SD = Standard Deviation

One-way MANOVA for Digit Span at 4.5 years

Table 22 shows the descriptive statistics (Means and Standard deviations) for each group. Bonferroni-adjusted for this analysis was alpha = 0.017. Multivariate analysis of variance was computed for the three task units of Digit Span. Analyses showed that there was a significant group difference in the combined dependent variables, F (3, 323) = 10.11, $p < .001$, ηp^2 = .111. Inspection of individual dependent variables confirmed group differences, wherein all the three task units were shown to differ among groups. *Digit sequence A*, F (4, 325) = 18.291, $p < .001$, ηp^2 = .184; *digit sequence B*, F (4, 325) = 4.711, $p < .001$, ηp^2 = .148 and *overall digit memory*, F (4, 325) = 26. 230, $p < .001$, ηp^2 = .244.

Table 22: ***Mean Scores and Standard Deviations of Digit Span at 4.5 Years.***

		Sequence A		Sequence B		Total Digit Memory	
Group	*n*	*M*	*SD*	*M*	*SD*	*M*	*SD*
1	42	1	0	0.67	0.48	6.05	1.25
2	60	1	0	0.83	0.59	6.37	1.64
3	68	1.18	0.77	1	0	6.76	1.47
4	108	1.57	0.63	1.53	0.83	7.72	1.26
5	52	1.4	0.72	1	0	7.37	0.86

M = Mean and SD = Standard Deviation

One-way MANOVA for Behaviour Rating Inventory of Executive Function (BRIEF-P) at 2 years

Table 23 shows the descriptive statistics (Means and Standard deviations) for each group. Bonferroni-adjusted for this analysis used alpha = 0.01. Multivariate analysis of variance was computed to identify group effects on five clinical subscales of BRIEF-P at 2 years. Results showed that the combined variable was significant, F (5, 337) = 5.236, $p < .001$, $\eta p^2 = .071$. Individual inspection of dependent variables showed significant group differences for *inhibit*, F (4, 341) = 13.194, $p < .001$, $\eta p^2 = .134$; *shift*, F (4, 341) = 18.611, $p < .001$, $\eta p^2 = .179$; *emotion*, F (4, 341) = 16.655, $p < .001$, $\eta p^2 = .163$; *working memory*, F (4, 341) = 11.486, $p < .001$, $\eta p^2 = .119$; and *plan/organise*, F (4, 341) = 13.797, $p < .001$, $\eta p^2 = .139$.

Table 23: ***Mean Scores and Standard Deviations for Five Clinical Subscales of BRIEF-P at 2 Years.***

		Inhibit		Shift		Emotion		Working Memory		Plan/Organize	
Group	*n*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
1	46	62.78	13.27	58.61	10.54	59.33	10.04	68.39	13.14	63	10.73
2	63	53.67	8.98	48.86	6.99	48.89	7.12	59	9.12	53.87	8.59
3	73	59	9.79	54.59	7.85	52.52	9.14	63.96	10.73	58.25	10.51
4	109	51.94	8.06	48.09	7.39	48.13	7.61	57.15	10.41	51.27	9.78
5	55	57.64	10.42	51.45	7.78	50.98	7.76	60.18	9.25	54.8	9.18

Note: M = Mean and SD = Standard Deviation

One-way MANOVA for Behaviour Rating Inventory of Executive Function (BRIEF-P) at 4.5 years

Table 24 shows the descriptive statistics (Means and Standard deviations) for each group. Bonferroni-adjusted alpha of 0.01 was used in the analysis. Multivariate analysis of variance was computed to identify group effects on five clinical subscales of BRIEF-P at 53 months. Results revealed significant group effects on the combined dependent variables, F (5, 335) = 12.825, $p < .001$, $\eta p^2 = .159$. Inspection of individual dependent variables showed that the five clinical scales were different among groups: *inhibit*, F (4, 339) = 58.771, $p < .001$, $\eta p^2 = .409$; *shift*, F (4, 339) = 54.955, $p < .001$, $\eta p^2 = .393$; *emotion*, F (4, 339) = 53.258, $p < .001$, $\eta p^2 = .386$; *working memory*, F (4, 339) = $p < .001$, $\eta p^2 = .326$, *plan/organise*, F (4, 339) = 40.097, $p < .001$, $\eta p^2 = .321$.

Table 24: ***Mean Scores and Standard Deviations for Five Clinical Subscales of BRIEF-P at 4.5 Years.***

		Inhibit		Shift		Emotion		Working Memory		Plan/Organize	
Group	*n*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
1	44	61.61	8.44	58.57	8.38	62.98	10.21	67.27	8.08	64.14	8.87
2	63	46.78	5.44	44.35	4.15	43.33	4.87	52	10.02	48.81	9.09
3	72	56.13	8.29	52	7.98	51.83	7.48	57.9	8.98	54.96	8.94
4	110	44.52	5.52	43.7	4.58	44.06	6.99	47.61	8.22	45.64	7.84
5	55	52.22	9.78	49.25	7.41	50.56	11.42	54.33	10.52	51.82	9.39

Note: M = Mean and SD = Standard Deviation

Univariate Analysis of Variance for Dimension Change Card Sorting Task (DCCS) at 4.5 years

Univariate analysis of variance for the three unit tasks for DCCS was statistically significant. Group performances differ in *practice trial*, F (4, 334) = 4.978, p = .001, eta^2 = 0.06; *pre-switch (colour trial)*, F (4, 334) = 4.797, p = .001, eta^2 = 0.05; *post-switch (shape trial)*, F (4, 334) = 11.326, p < .001, eta^2 = 0.12. However, no significant difference was seen in Advanced (*border trial)*, F (4, 188) = 2.177, p = .073, eta^2 = 0.04. Refer to Table 25 for the descriptive statistics.

Table 25: ***Mean Scores and Standard Deviations for Dimension Change Card Sorting Task (DCCS) at 4.5 Years.***

		Practice		Pre-switch (Color)		Post-switch (Shape)		Advanced (Border)	
Group	*n*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
1	46	1.74	0.61	5.6	1.03	2.59	2.6	6.5	0.91
2	61	1.87	0.34	5.93	0.4	2.72	2.71	6.43	0.93
3	70	1.93	0.35	5.89	0.75	3.53	2.78	5.95	0.32
4	108	1.98	0.14	5.99	0.09	4.6	2.43	6.1	0.89
5	54	1.96	0.19	6	0	5	1.99	6.29	0.81

Note: M = Mean and SD = Standard Deviations

Univariate Analyses of Covariance for BRIEF-P Global Executive Score (GEC) at 2 years and at 4.5 years

Univariate analysis of covariance for the two parent-rated global executive control scores showed statistically significant difference among groups at *time 1*, F (4, 342) = 20.369, p < .001, ηp^2 = .192, even after accounting for Bayley-III cognitive Score, F (1, 342) = .103, p = .748, ηp^2 = .000 and sex, F (1, 342) = 8.59, p = .004, ηp^2 = .024. At *time 2*, F (4, 339) = 88.591, p < .001, ηp^2 = .511, after controlling for Bayley-III cognitive score, F (4, 339) = .113, p = .737, ηp^2 = .000 and Sex, F (4, 339) = 2.836, p = .093, ηp^2 = .008 at 4.5 years. Refer to Table 26 for the descriptive statistics.

Table 26: ***Means and Standard Deviations of BRIEF-P Global Executive Control at 2 Years and at 4.5 Years.***

		GEC (2 Years)			GEC (4.5 Years)	
Group	*n*	*M*	*SD*	*n*	*M*	*SD*
1	49	65.51	11.59	47	67.38	3.52
2	63	54.3	8.22	62	47.56	7.47
3	73	60.89	10.73	72	56.6	8.14
4	109	51.89	7.93	110	43.66	5.95
5	55	57.22	9.61	55	52.44	10.49

Note: GEC = Global Executive Control; M = Mean and SD = Standard Deviation

Univariate Analysis of Covariance for Executive Function Composite Score at 2 years and 4.5 years

Univariate analysis of covariance of the two composite scores from executive function tasks administered at two time points showed significant difference among groups. At *time 1*, F (4, 327) = 6.717, $p < .001$, $\eta p^2 = .076$, even after accounting for cognitive score, F (4, 327) = 7.976, $p = .005$, $\eta p^2 = .024$, and sex, F (4, 327) = .108, p = .743, $\eta p^2 = .000$. At *time 2*, F (4, 338) = 6.217, $p < .001$, $\eta p^2 = .069$, even after controlling for Bayley-III cognitive score, F (4, 338) = 62.525, $p < .001$, $\eta p^2 = .156$, and sex, F (4, 338) = 2.221, $p = .137$, $\eta p^2 = .007$. Refer to Table 27 for the descriptive statistics.

Table 27*: Means and Standard Deviations of EF Composite Scores at 2 Years and at 4.5 Years.*

		EF Composite (2 Years)			EF Composite (4.5 Years)	
Group	*n*	*M*	*SD*	*n*	*M*	*SD*
1	44	8.2	3.96	48	9.21	4.99
2	57	8.19	3.19	62	10.4	4.25
3	70	10	2.99	71	12.14	5.16
4	107	12.11	4.24	109	16.87	4.6
5	56	12.23	4.14	55	15.33	5.02

Note: EF = Executive Function; M = Mean and SD = Standard Deviation

Behavioural Outcomes

One-way MANOVA for Syndrome Scores of Child Behaviour Checklist (CBCL) at 4.5 years

Table 28 shows the descriptive statistics (Means and Standard deviations) for each group. Bonferroni-adjusted alpha of 0.007 was used in this analysis. A one-way multivariate analysis of variance was used to identify whether group variations among syndrome in CBCL was significantly different. MANOVA revealed that combined dependent variables were statistically significant, F (7, 322) = 8.899, $p < .001$, $\eta p^2 = .161$. Inspection of individual dependent variables showed that all syndromes scale scores of CBCL were statistically significant: *emotional/reactive*, F (4, 328) = 42.163, $p < .001$, $\eta p^2 = .340$; *anxious/depressed*, F (4, 328) = 29.943, $p < .001$, $\eta p^2 = .267$; *somatic complaints*, F (4, 328) = 15.009, $p < .001$, $\eta p^2 = .155$; *withdrawn*, F (4, 328) = 48.692, $p < .001$, $\eta p^2 = .373$; *sleep problems*, F (4, 328) = 48.692, $p < .001$, $\eta p^2 = .261$; *attention problems*, F (4, 328) = 39.156, $p < .001$, $\eta p^2 = .323$; and *aggressive behaviour*, F (4, 328) = 54.233, $p < .001$, $\eta p^2 = .398$.

Table 28: Means and Standard Deviations of Syndrome Scale Scores of CBCL at 4.5 Years.

		ER		AD		SC		WI		SP		AP		AB	
Group	*n*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
1	37	5.05	2.707	4.68	2.506	2.78	1.685	3.49	2.103	3.95	2.134	4.43	1.741	14.59	4.822
2	63	1.38	1.313	1.94	1.749	1.19	1.33	0.65	0.676	1.29	0.941	1.7	1.613	5.29	3.594
3	68	3.47	2.202	3.15	1.814	1.84	1.532	2.1	1.712	3.29	2.186	3	1.745	9.88	5.355
4	110	1.24	1.285	1.32	1.354	0.98	1.141	0.54	0.7	1.34	1.429	1.19	1.267	3.67	3.343
5	55	2.4	1.911	2.45	1.834	1.18	1.219	1.27	1.269	2.27	1.769	1.91	1.378	7.75	5.204

Note: M = Mean; SD = Standard Deviation; ER = Emotional/Reactive; AD = Anxious/Depressed; SC = Somatic Complaints; WI = Withdrawn; SP = Sleep Problems; AP = Attention Problems; and AB = Aggressive Behaviour

Univariate Analysis of Variance for Clinical Subscales of CBCL at 4.5 years

Table 29 shows the descriptive statistics (Means and Standard deviations) for each group. A series of univariate analysis of variance were employed to test whether there were group differences on CBCL's externalising behaviour, internalising behaviour and total problem scores. Significant group effects were achieved on the three clinical scales: *externalising behaviour*, F (4, 346) = 70.772, $p < .001$, $eta^2 = .453$; *internalising behaviour*, F (4, 346) = 54.537, $p < .001$, $eta^2 = .389$; and *total score*, F (4, 346) = 86.467, $p < .001$, $eta^2 = .503$.

Table 29: Mean Scores and Standard Deviations of Three Clinical Subscales of CBCL at 4.5 Years.

		Externalising Behaviour		Internalising Behaviour		Total Score	
Group	*n*	*M*	*SD*	*M*	*SD*	*M*	*SD*
1	48	57.71	5.41	62.21	7.19	62.54	6.67
2	63	42.06	4.13	44.62	4.92	43.25	6.29
3	71	50.68	8.46	54.32	10.13	53.11	8.56
4	110	39.16	6.97	42.44	9.1	39.97	7.47
5	55	46.31	9.09	49.35	10.06	47.93	9.12

Note: M = Mean and SD = Standard Deviation

One-way MANOVA for Subscales of Strengths and Difficulty Questionnaire (SDQ) at 4.5 years

Table 30 shows descriptive statistics (Means and Standard deviations) for each group. Bonferroni-adjusted alpha was 0.01. A one-way multivariate analysis of variance was used to identify whether group variations among subscales of SDQ were significantly different. MANOVA showed statistically significant group difference in combined dependent variables, F (5, 328) = 13.147, $p < .001$, $\eta p^2 = .166$. Inspection of individual dependent variables showed significant group differences: *emotional symptoms*, F (4, 332) = 18.932, $p < .001$, $\eta p^2 = .186$; *conduct problems*, F (4, 332) = 52.100, $p < .001$, $\eta p^2 = .386$; *hyperactivity/inattention*, F (4, 332) = 26.775, $p < .001$, $\eta p^2 = .244$; *peer problem*, F (4, 332) = 51.058, $p < .001$, $\eta p^2 = .381$; and *prosocial behaviour*, F (4, 332) = 2.389, $p = .001$, $\eta p^2 = .057$.

Table 30: ***Mean Scores and Standard Deviations for Subscales of Strengths and Difficulties Questionnaire (SDQ) at 4.5 Years.***

		EM		**CO**		**HY**		**PE**		**PR**	
Group	*n*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
1	44	3.02	1.47	3.31	1.32	5.95	2.27	3.23	1.57	5.48	0.88
2	57	1.12	1.05	1.34	1.16	3.26	1.95	1.39	1.14	5.77	0.91
3	71	2.1	1.42	1.96	1.33	4.42	1.83	1.27	0.93	5.72	0.85
4	110	1.21	1.36	0.71	0.68	2.73	1.64	0.63	0.73	6	0
5	55	1.98	1.41	1.42	0.88	3.97	1.95	1.36	0.97	5.84	0.71

M = Mean; SD = Standard Deviation; EM = Emotional Symptoms; CO = Conduct Problems; HY = Hyperactivity/Inattention; PE = Peer Problems; PR = Prosocial Behaviour

Univariate Analysis of Variance for Scales of Social Communication Questionnaire (SCQ) at 4.5 years

Table 31 shows the descriptive statistics and series of univariate analyses of variance that were employed to identify significant group differences in the subscales of SCQ. ANOVA revealed significant group differences in the three scales of SCQ. *Total score*, F (4, 346) = 64.438, $p < .001$, $eta^2 = .429$; *reciprocal social domain*, F (4, 346) = 21.040, $p < .001$, $eta^2 = .197$; *communication domain*, F (4, 346) = 20.854, $p < .001$, $eta^2 = .196$; and *restrictive-repetitive domain*, F (4, 346) = 40.895, $p < .001$, $eta^2 = .324$.

Table 31: ***Mean Scores and Standard Deviations for Subscales of Social Communication Questionnaire (SCQ) at 4.5 Years.***

		Total Score		Reciprocal-Social		Communication		Restrictive-Repetitive	
Group	*n*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
1	48	12.31	2.26	2.06	1.45	4.33	1.67	4.75	2.38
2	63	5.62	2.93	1.08	1.02	2.17	1.44	1.94	1.66
3	72	7.39	3.56	0.88	0.63	2.86	1.43	3.33	2.35
4	110	4.31	2.85	0.63	0.68	2.24	1.39	1.05	1.15
5	54	6.09	2.89	1.02	0.94	2.98	1.37	1.89	1.87

Note: M = Mean and SD = Standard Deviation

STUDY 3: Profile and Predictors of Risk Status (2-cluster solution)

Introduction

Study 1 endorsed both 5-cluster and 2-cluster solutions to account for a 'person-approach' to cumulative risk. This particular study addressed the validation of the 2-cluster solution as an alternative to 5-cluster (subgroups) of at-risk young children. The 2-cluster solution was subjected to subsequent statistical analysis and found to be tenable and useful as a classification of risk status in the CHYLD cohort. Cluster analysis for a 2-cluster solution revealed that among participants at the 4.5-year follow-up (n = 355), cluster 1 had 164 members and cluster 2 had 191 members. Sociodemographic data significantly accounted for the 2-cluster solution. Paediatric and child characteristics data did not hold up. Only head circumference at 4.5 years significantly accounted for the 2-cluster (p = .006). Discriminant function analysis results from study 1 reinforced the 2-cluster solution as an alternative and parsimonious model (Table 7).

Method

CHYLD Data

Both 2-year and 4.5-year follow-up data were used; this included major neurocognitive domains: a) Wechsler tests (verbal, performance and processing speed), b) Beery VMI, c) composite scores for 'observed' EF and 'parent-rated' EF (BRIEF-P), and the behavioural domains: d) Strengths and Difficulty Questionnaire (SDQ total score), e) CBCL scores (Externalising, Internalising, and Total Problem scores); a derived-CBCL subtest known as Callous-Unemotional (CU) behaviour was also included in order to test for trait-like behaviours in problems of lack-of-sympathy and non-remorseful attitudes among young children; and f) SCQ for test of autism-like behaviour. Refer to Chapter 3 for a detailed description of each measure.

Data Analysis

A series of tests of mean differences and regressions were employed to validate the endorsed 2-cluster solution from previous cluster analysis. IBM SPSS version 23 was used to analyse the data for this study. The data from the 4.5-year follow-up was utilised and subjected to univariate analysis of covariance (ANCOVA), to look at group differences between 'more at-risk' and 'less at-risk' young children. Variables such as ethnic affiliation,

sex, SES, and maternal education were used as covariates. *Logistic regression* was used to identify which developmental data from the 2-year and 4.5-year follow-ups was associated with the established 2-cluster solution ('more at-risk' and 'less at-risk'). Lastly, *Chi-square test of contingencies* was used to analyse associations between the 2-cluster solution and dichotomous risk factors. Refer to the *supplementary statistical analysis for study 3* at the end of this study, for more tables and interpretation.

Results and Findings

Group differences in neurocognition at 4.5 years

Cognitive outcomes at the 4.5-year follow-up were used for group comparisons controlling for sociodemographic variables (Table 32). Overall, "more at-risk" children were performed below average in a test of general cognition (Wechsler) compared to "less at-risk children". More likely, "more at-risk" children were poorer in acquisition and development of language. They are more likely to have difficulties in hand-eye coordination, errors in inhibiting responses and organising purposive behaviour, accompanied by higher reports of self-regulatory difficulties. These observations were significant even after adjusting for the effects of socioeconomic status (SES), ethnicity, maternal education, and sex.

Group differences in behavioural outcomes at 4.5 years

Behavioural outcomes at 4.5-year follow-up were used for group comparison controlling for sociodemographic variables (Table 32). Parent rated measures of child psychopathology showed that higher tendencies of child problems were observed among "more at-risk" children, externalising behaviours (inattention, hyperactivity, conduct problems, and aggressiveness). Hypothesised features of sensory processing maybe present in some children. Therefore, children with "more at-risk" status are prone to a variety of problem behaviours that is related to their inability to regulate their emotion, responses, and inability to organise oneself.

Table 32: ***Summary of Neurodevelopment Scores at 4.5 Years in 2-cluster Solution (Risk Status)***

	More at-risk (N = 164)		Less at-risk (N = 191)			
Measure	*M*	*SD*	*M*	*SD*	*p*	ES (ηp^2)
WPPSI IQ	89.77	11.71	106.59	11.57	< .001	0.229
WPPSI Verbal	89.51	14.37	107.26	12.24	<.001	0.199
WPPSI Performance	93.1	11.95	105.11	12.83	<.001	0.115
WPPSI Processing Speed	90.78	11.54	101.76	11.6	<.001	0.09
Beery VMI	96.82	8.3	103.78	7.93	<.001	0.162
MABC	7.65	3.22	9.52	2.73	<.001	0.322
EF Composite	10.61	4.99	15.99	4.58	<.001	0.18
BRIEF-P GEC	59.97	10.94	46.1	7.99	<.001	0.3
SDQ Total Difficulty	12.17	4.75	6.64	3.65	<.001	0.266
CBCL Externalising	14.8	8.48	6.55	5.42	<.001	0.217
CBCL Internalising	12.66	8.31	5.55	4.83	<.001	0.183
CBCL Total	42.69	22.16	19.74	13.75	<.001	0.237
SCQ Total	8.88	4.58	4.85	3.01	<.001	0.186

Note: M = Means, SD = Standard Deviations, ES = Effect Size; adjusted for ethnicity, sex, maternal education and SES. Refer to Appendix C for individual analysis. MABC = Movement, WPPSI = Wechsler Test, SDQ = Strengths and Difficulties Questionnaire, VMI = Visuo-Motor Integration, SCQ = Social Communication Questionnaire, CBCL = Child Behaviour Checklist, BRIEF – P = Behaviour Rating Inventory of Executive Function – Preschool.

Neurodevelopmental factors predictive of risk status in young children

In order to identify relevant neurodevelopment that could predict risk status in children (more at-risk versus less at-risk children) series of logistic regression were performed, result showed that in behavioural outcome measures, SCQ total score (*B* = 0.19, OR = 1.22, *p* < .001), as well as SDQ total score (*B* = 0.19, OR = 0.04, *p* < .001) were significant. Cognitive subtests which highly predicted risk status were Bayley-III cognitive score (*B* = -0.09, OR = 0.92, *p* = .001), Bayley-III language score (*B* = - 0.06, OR = 0.94, *p* = .003), and WPPSI-III verbal composite score (*B* = - 0.05, OR = 0.96, *p* = 0.005). Among the administered executive function tasks at 2-years follow-up; only fruit stroop (*B* = -0.27, OR = 0.76, *p* = 0.023) was significant. At 4.5- year follow-up; dimension change card sorting test (*B* = -0.52, OR = 0.59, *p* = 0.001), and digit span (*B* = -0.50, OR = 0.59, *p* = 0.001). Whereas in parent-rated measure of executive function. BRIEF-P GEC at 2-year follow-up (*B* = 0.03, OR = 1.03, *p* = 0.028) was significant. Higher association were found in EMI T score (*B* = 0.08, OR = 1.08, *p* < .001) and ISCI T score (*B* = 0.03, OR = 1.07, *p* = 0.012) for 4.5-year follow-up data. Therefore, higher reports of problem behaviour, poor performance in Bayley-III subtests at 2-year follow-up, lower WPPSI-III verbal composite score at 4.5-year follow-up and poor cognitive flexibility at 2 and 4.5-year and higher inhibition problems at 2 and 4.5 year follow-up were predictive of risk status in children. The administration of a battery of tests to measure cognition, executive function, and parent-rated measures of behaviour were helpful in predicting risk status in the CHYLD cohort.

Table 33: ***Percentages, Chi Squares and Factor Loadings of Child Risks***

Child Risk f (%)		More at-risk (N = 161)	Less at-risk (N = 194)	*p*	Factor Loading (KMO = .711, Var = 67.03%)				*nh*
					F1 (29.1%)	F2 -17.30%	F3 (10.4%)	F4 (10.3%)	
Sex				ns					
	Male	92 (57.1%)	93 (47.9%)						
	Female	69 (42.9%)	101 (52.1%)						
Ethnicity				< .001	0.345	-0.385	0.539		0.604
	European	61 (37.9%)	132 (68%)						
	Non-Euro	100 (62.1%)	62 (32%)						
SES				< .001	-0.328	0.372	-0.365	0.463	
	Low	128 (79.5%)	90 (46.4%)						
Maternal Education				< .001	-0.436			0.504	
	Low	75 (46.6%)	37 (19.1%)						
Maternal substance use									
Marijuana at pregnancy	Yes	26 (16.1%)	13 (6.7%)	< .001	0.552				0.372
Marijuana at 2 years	Yes	3 (1.9%)	4 (2.1%)	ns					
Marijuana at 4.5 years	Yes	7 (4.3%)	3 (1.5%)	ns					
Smoking at pregnancy	Yes	60 (37.3%)	32 (16.5%)	< .001	0.818				0.731
Smoking at 2 years	Yes	58 (36%)	34 (17.5%)	< .001	0.844				0.78
Smoking at 4.5 years	Yes	56 (34.8%)	30 (15.5%)	< .001	0.896				0.845
Alcohol at pregnancy	Yes	17 (10.6%)	19 (9.8%)	ns					
Alcohol at 2 years	Yes	66 (41%)	114 (58.8%)	< .001		0.821			0.754
Alcohol at 4.5 years	Yes	74 (46%)	133 (68.6%)	0.004		0.831			0.772

Primary risks for NH								
IDM	Yes	69 (42.9%)	75 (38.7%)	ns				
Small	Yes	56 (34.8%)	44 (22.7%)	0.012		0.695	0.536	0.804
Large	Yes	44 (27.3%)	51 (26.3%)	ns				
Preterm	Yes	55 (34.2%)	73 (37.6%)	ns				
Neonatal Hypoglycaemia	Yes	83 (51.6%)	110 (56.7%)	ns				

Note: IDM = Infant of Diabetic Mother, KMO = Kaiser-Meyer-Olkin Measure of Sampling Adequacy, nh = Communalities. This table shows the summary of significant child risks associated with risk status and risk constellation from factor loadings (factor analysis), F = factor and (percent of variance).

Risk factors associated with risk status in the CHYLD study cohort

Chi-square test of contingencies was used (Table 33) to look at association of risks: a) primary risks of neonatal hypoglycaemia, b) sociodemographic and c) parent substance use with risk status in young children. Results showed that among primary risks of neonatal hypoglycaemia, small-for-gestation (SGA) was significant, X^2 (1, 355) = 6.37, p = .012. Sociodemographic data showed maternal education, X^2 (1, 355) = 39.22, p < .001; SES deprivation, X^2 (1, 355) = 39.81, p < .001 and ethnicity, X^2 (1, 355) = 32.24, p < .001, were correlated with risk status. History of maternal substance use revealed: marijuana use during pregnancy, X^2 (1, 355) = 14.05, p < .001; maternal alcohol drinking at 2 years, X^2 (1, 355) = 21.99, p < .001; maternal alcohol drinking at 4.5 years, X^2 (1, 355) = 8.26, p = .004; smoking during pregnancy, X^2 (1, 355) = 23.73, p < .001; smoking at 2 years, X^2 (1, 355) = 19.92, p < .001; and smoking at 4.5 years, X^2 (1, 355) = 24.45, p < .001 were significant. Therefore, more at-risk children are more likely born small, living in poor social condition, lower maternal education, Non-European ethnicity, and more likely exposed to prenatal marijuana and cigarette smoking, and long term maternal alcohol drinking. Domains identified in Figure 7.

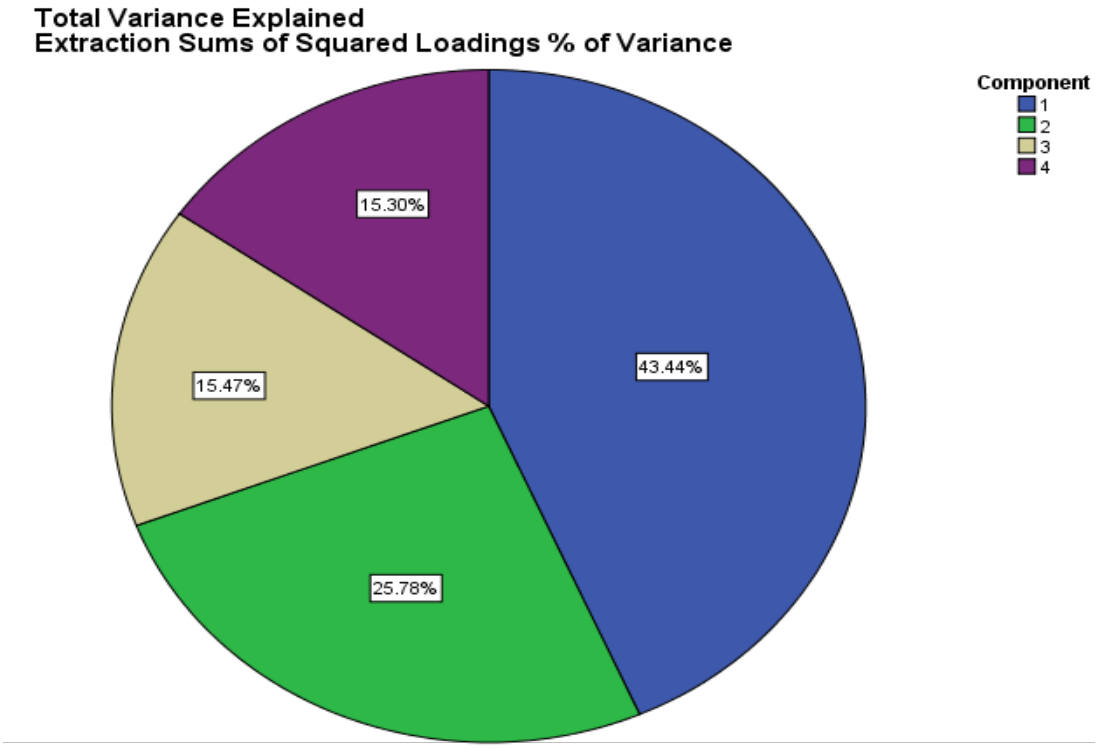

Figure 7: ***Components of Cumulative Risk in CHYLD Cohort (1:*** *Prenatal Exposures,* ***2:*** *Maternal Long-Term Substance Use,* ***3:*** *SGA and Ethnicity,* ***4:*** *SES and Maternal Education****)***

Discussion

What is the purpose of a 2-cluster solution in the CHYLD cohort data?

The aim of study 3 was to validate the non-spectrum typology of groups, which was found tenable from study 1 and study 2. This 2-cluster solution was identified as useful to categorise children as either belonging to 'less at-risk' or 'more at-risk' children. The strength of this 2-cluster approach is its parsimony. Children classified as 'more at-risk' may require immediate attention. Future plans for follow-up assessment would target these children with the intention of increasing the follow-up rate. Statistically, it is easier to use dichotomous variables and use them for multivariate analysis rather than the 5-cluster solution whereby converting each group into a continuous variable may result in unforeseen statistical issues. Variables that are dichotomous can be handled in most standard statistical software programs and statistical techniques such as structural equation modelling is amenable for a dichotomous independent variable.

The emerging issue that is considered unexpected was the sensitivity of the spread of children into groups. When collapsed into several groups (5-cluster solution) the primary risks effects were significant, compared to when groups were adjusted into limited spread (2-cluster solution). Birth characteristics and primary risks were discriminated more in the 5-cluster solution.

Findings in the present study support the 5-cluster solution even though it is not as sensitive to the effects of birth characteristics. However, SGA is still tenable. This suggests that the strong discriminating ability of this specific variable is independently predicting developmental outcomes. Another possible explanation is that the association of SGA and the presence of higher cumulative risk in children can be supported by further analysis. Observed risk association identified four domains: a) prenatal smoking and marijuana use, b) maternal alcohol drinking, c) SGA and ethnicity, and d) SES and maternal education.

What are the neurodevelopmental characteristics of children classified as 'more at-risk' compared to 'less at-risk'?

Findings in the present study are consistent with the 5-cluster solution wherein 'most at-risk' groups tend to show poorer behavioural outcomes and be prone to cognitive errors. However, in this study, because children in the cohort were categorised into two groups therefore

general characteristics can be identified. ‘More at-risk children’ had a general cognitive mean score that is considered below average level at 4.5 years (WPPSI-III). In addition, children that were ‘more at-risk’ was more prone to errors in tasks requiring hand-eye coordination (Beery-VMI), and more likely to fail tasks requiring them to: a) inhibit prepotent responses, b) process information, c) and use rules. Parents rated them as more prone to errors of everyday executive control. Whereas in the behavioural outcomes, ‘more at-risk’ children were more likely to experience being reported by their parents as having problem behaviours compared to ‘less at-risk’ children. These behaviours span from conduct problems, truancy, hostile or aggressive behaviours, attention problems, lack of sympathy or remorse, and instances of autism-like behaviours (Social Communication Questionnaire, Strengths and Difficulties Questionnaire, and Child Behaviour Checklist). These neurodevelopmental characteristics were significantly predicted by the measures of child behaviour (Social Communication Questionnaire, Strengths and Difficulties Questionnaire, and Child Behaviour Checklist) as well as measures of cognitive abilities (Bayley-III and WPPSI-III).

What are the neurodevelopmental trends observed?

An important finding of Study 3 was the validation of the initial results from the CHYLD study 2-year follow-up. More specifically, language development was found to be an emerging issue among at-risk children. Higher cognitive skills such as inhibiting behavioural responses and flexible rule use, which are important in pre-academic development, were prone more to perseverative responses. Externalising behaviours and possible autism-like behaviours were observed. These findings can be attributed to the large contribution of early environmental risks such as SES, maternal education, SGA, parent substance use and ethnic affiliation in ‘more at-risk’ children. In reference to the components of cumulative risk identified, maternal lifestyle (prenatal exposures and long term substance use) largely contributed to cumulative risk. Risk status showed about 53% of the participants were considered ‘more at-risk’ and might need additional follow-up assessment.

Supplemental Statistical Analysis for Study 3

Analysis of Covariance for WPPSI-III – Full Composite Score at 4.5 years

Univariate analysis of variance was used to identify the effects of risk status on WPPSI IQ composite scores at 4.5 years. Ethnicity, sex, socioeconomic status, and maternal education were used as covariates. Significant differences in the WPPSI IQ composite scores between groups were seen such that 'less at-risk' children performed better on average (M = 106.59, SD = 11.57) than 'more at-risk' children (M = 89.77, SD = 11.71), F (1, 313) = 93.06, $p < .001$, $\eta p^2 = .229$. Among the covariates, only the ethnicity showed significance (European vs Non-European), F (1, 313) = 10.73, p = .001, $\eta p^2 = .033$.

Analysis of Covariance for WPPSI-III – Verbal Composite Score at 4.5 years

Univariate analysis of variance was used to identify the effects of risk status in WPPSI verbal composite scores at 4.5 years. Variables such as ethnicity, sex, socioeconomic status, and maternal education were used as covariates. Significant differences in the verbal composite scores between groups were observed, such that 'less at-risk' children performed better on the average, (M = 107.26, SD = 12.24) than 'more at-risk' children (M = 89.51, SD = 14.37), F (1, 301) = 77.86, $p < .001$, $\eta p^2 = .199$. Among the covariates, only the ethnicity showed significance (European vs Non-European), F (1, 313) = 11.86, p = .001, $\eta p^2 = .036$.

Analysis of Covariance for WPPSI-III – Performance Composite Score at 4.5 years

Univariate analysis of variance was used to identify the effects of risk status in WPPSI performance composite scores at 4.5 years. Variables such as ethnicity, sex, socioeconomic status, and maternal education were used as covariates. Significant differences in the performance composite scores between groups were observed, such that 'less at-risk' children performed better on the average (M = 105.11, SD = 12.83) than 'more at-risk children' (M = 93.10, SD = 11.95), F (1, 314) = 40.85, $p < .001$, $\eta p^2 = .115$. There were no significant effects seen among covariates.

Analysis of Covariance for WPPSI-III – Processing Speed Composite Score

Univariate analysis of variance was used to identify the effects of risk status in WPSSI processing speed composite scores at 4.5 years. Variables such as ethnicity, sex, socioeconomic status, and maternal education were used as covariates. Significant differences in the composite scores between groups were observed, such that 'less at-risk' children performed better on the average (M = 101.76, SD = 11.60) than 'more at-risk' children (M = 90.78, SD = 11.54), F (1, 308) = 30.62, $p < .001$, $\eta p^2 = .090$. There were no significant effects seen among covariates.

Analysis of Covariance for Beery VMI Score at 4.5 years

Univariate analysis of variance was used to identify the effects of risk status in VMI scores at 4.5 years. Variables such as ethnicity, sex, socioeconomic status, and maternal education were used as covariates. Significant differences in the VMI scores between groups were observed, such that 'less at-risk' children were observed performing better on the average (M = 103.78, SD = 7.93) than 'more at-risk' children (M = 96.82, SD = 8.30), F (1, 313) = 12.12, $p < .001$, $\eta p^2 = .162$. There were no significant effects seen among covariates.

Analysis of Covariance for Motor Development (MABC-2) Total Score at 4.5 years

Univariate analysis of variance was used to identify the effects of risk status in movement total score at 4.5 years. Variables such as ethnicity, sex, socioeconomic status, and maternal education were used as covariates. Significant differences in the total scores between groups were observed, such that 'less at-risk' children were observed performing better on the average (M = 9.52, SD = 2.73) than 'more at-risk' children (M = 7.65, SD = 3.22), F (1, 303) = 6.94, $p < .001$, $\eta p^2 = .322$. There were no significant effects seen among covariates.

Analysis of Covariance for Composite measure of Observed Executive Function at 4.5 years

Univariate analysis of variance was used to identify the effects of risk status in composite executive function scores at 4.5 years. Variables such as ethnicity, sex, socioeconomic status, and maternal education were identified as covariates. Significant differences in the composite scores between groups were observed such that 'less at-risk' children perform better on the average (M = 15.99, SD = 4.58) than 'more at-risk children' (M = 10.61, SD =

4.99), F (1. 312) = 68.26, p < .001, ηp^2 = .180. There were no significant effects seen among covariates.

Analysis of Covariance for BRIEF-P GEC at 4.5 years

Univariate analysis of variance was used for parent-rated global executive function at 4.5 years (BRIEF-P GEC). Variables such as ethnicity, sex, socioeconomic status, and maternal education were used as covariates. Results reached statistical significance, F (1, 308) = 134.21, p < .001, ηp^2 = .30, even after controlling for covariates. 'Less at-risk' children scored lower: M = 46.10, SD = 7.99 than 'more at-risk' children: M = 59.97, SD = 10.94. Only the sex was the significant covariate: F (1, 308) = 4.48, p = .035, ηp^2 = .014.

Analysis of Covariance for SDQ Total Difficulty Score

Univariate analysis of variance was conducted; ethnicity, maternal education, sex, and socioeconomic status were used as covariates. Risk status was significant, F (1, 307) = 111.15, p < .001, ηp^2 = .266. After controlling for covariates, 'less at-risk' children have lower total difficulty scores, M = 6.64, SD = 3.65, compared to 'more at-risk' children, M = 12.17, SD = 4.75. Significant covariates were the sex, F (1, 307) = 9.42, p = .002, ηp^2 = .030, and socioeconomic status, F (1, 307) = 5.69, p = .018, ηp^2 = .018.

Analysis of Covariance for CBCL Externalising Behaviour at 4.5 years

Univariate analysis of variance was conducted for parent-rated child behaviour measures at 4.5 years (CBCL externalising score). Ethnicity, sex, socioeconomic status, and maternal education were used as covariates. Results reached statistical significance for risk status, F (1, 307) = 85.05, p < .001, ηp^2 = .217, even after controlling for covariates, 'less at-risk' children showed lower externalising scores, M = 6.55, SD = 5.42, compared to 'more at-risk' children with M = 14.80, SD = 8.48. No covariates were found to be statistically significant.

Analysis of Covariance for CBCL Internalising Behaviour at 4.5 years

Univariate analysis of variance was conducted for parent-rated child behaviour measure at 4.5 years (CBCL internalising score). Ethnicity, sex, socioeconomic status, and maternal education were used as covariates. Results showed statistical significance for risk status, F

(1, 307) = 68.59, $p < .001$, $\eta p^2 = .183$, even after controlling for covariates, 'less at-risk' children showed lower internalising scores, $M = 5.55$, $SD = 4.83$, compared to 'more at-risk' children, $M = 12.66$, $SD = 8.31$. No covariates were found to be statistically significant.

Analysis of Covariance for CBCL Total Problem Scores at 4.5 years

Univariate analysis of variance was conducted for parent-rated child behaviour measures at 4.5 years (CBCL total problem score). Ethnicity, sex, socioeconomic status, and maternal education were used as covariates. Results showed statistical significance for risk status, F (1, 307), $p < .001$, $\eta p^2 = .237$. Even after controlling for covariates, 'less at-risk' children showed lower total problem scores, $M = 19.74$, $SD = 13.75$, compared to 'more at-risk' children, $M = 42.69$, $SD = 22.16$. No covariates were found to be statistically significant.

Analysis of Covariance for Callous Unemotional Behaviour at 4.5 years

Univariate analysis of variance was conducted for parent-rated child behaviour measures at 4.5 years (callous-unemotional behaviour). Ethnicity, sex, socioeconomic status, and maternal education were used as covariates. Results showed statistical significance for risk status, F (1, 307) = 44.68, $p < .001$, $\eta p^2 = .127$. Even after controlling for covariates, 'less at-risk' children showed less callous-unemotional behaviour, $M = .82$, $SD = 1.08$, compared to 'more at-risk' children, $M = 2.18$, $SD = 1.85$. No covariates were found to be statistically significant.

Analysis of Covariance for Social Communication Questionnaire (SCQ) at 4.5 years

Univariate analysis of variance was conducted to identify whether group status of risk ('less at-risk' versus 'more at-risk') were significantly different among samples of follow-up children. Ethnicity, maternal education, sex and socioeconomic status were used as covariates. Results showed that there was a statistical difference between risk groups, F (1, 307) = 70.35, $p < .001$, $\eta p^2 = .186$. 'More at-risk' children had higher SCQ total scores, $M = 8.88$, $SD = 4.58$ than 'less at-risk' children, $M = 4.85$, $SD = 3.01$. The sex was the only significant covariate, F (1, 307) = 4.29, $p = .039$, $\eta p^2 = .014$.

Logistic Regression Predicting Likelihood of Reporting Problem Behaviour at 4.5 years

Direct logistic regression was performed (see Table 34) to assess risk status ('less at-risk' versus 'more at-risk') among children. Parent-rated measures of child emotional and behavioural problems validated whether 'more at-risk' children were reported with more general behaviour and emotional problems. The model included a difficulty screening score (SDQ), a global score for autism behaviour (SCQ) and total score for general childhood psychopathology (CBCL). The full model containing all predictors was statistically significant, X^2 (3, N = 355) = 171.69, $p < .001$. This indicated that parent-reports on the three measures could be used to determine whether a child can be classified as 'less at-risk' or 'more at-risk'. The model as a whole explained 39.2% (Cox and Snell R square) and 52.5% (Nagelkerke R squared) of the variance in children's risk status; this correctly classified 81.7% of the cases. All three predictors made unique contributions to the model. The strongest predictor of reporting risk status among children was the parent-rated measure of autism behaviour recording an odds ratio of 1.22, followed by a screening measure of behaviour with an odds ratio of 1.22 and a general parent report of child psychopathology with an odds ratio of 1.03. Therefore, an increase of approximately one standard deviation in each child behaviour measure is most likely predictive of a child being more at-risk.

Table 34: ***Logistic Regression Analysis Predicting Risk Status with Child Behaviour Measures at 4.5 Years.***

Variable	*B*	SE	Wald	df	*p*	OR	95% CI
SCQ Total Score	0.19	0.04	20.02	1	< .001	1.22	[1.12, 1.32]
SDQ Total Score	0.19	0.04	16.55	1	< .001	1.22	[1.11, 1.34]
CBCL Total Score	0.03	0.01	8.39	1	0.004	1.03	[1.01, 1.06]

*Note: Beta (B), Standard Error (SE), Degrees of Freedom (*df*), Odds Ratio (OR), Social Communication Questionnaire (SCQ), Strengths and Difficulty Questionnaire (SDQ), Child Behaviour Checklist (CBCL)*

Logistic Regression Predicting Risk Status in Cognitive Scores at 2 years and 4.5 years

Direct logistic regression was performed (see Table 35) to assess risk status ('less at-risk' versus 'more at-risk') among children. Administered measures of cognitive abilities validated whether 'more at-risk' children were more likely to have lower cognitive performance. The

model included subscales from the Bayley Scales of Infant and Toddler Development (Bayley-III) measured at 2 years and the subscales of Wechsler Preschool and Primary Scale of Intelligence-III (WPPSI) measured at 4.5 years. The full model including all predictors was statistically significant, X^2 (8, N = 355) = 201.36, $p < .001$. This indicated that cognitive scores could be used to determine whether a child could be classified as 'less at-risk' or 'more at-risk'. The model as a whole explained 46.7% (Cox and Snell R square) and 62.5% (Nagelkerke R squared) of the variance in children's risk status; this correctly classified 83.1% of the cases. Only five out of eight predictors made a unique contribution to the model. The strongest predictor for reporting risk status was the children's Bayley cognitive scores recording an odds ratio of .92, followed by Bayley scale for parent-rated measures of socio-emotional functioning with an odds ratio of .96, Bayley language scores with an odds ratio of .94 and the WPPSI verbal scores with an odds ratio of .96. Therefore, a decrease of approximately one standard deviation in each cognitive performance at 2 years (cognitive, language, emotional, and motor) and at 4.5 years (verbal composite scores) is most likely predictive of a child being more at-risk at 4.5 years.

Table 35: ***Logistic Regression Analysis Predicting Risk Status with Cognitive Measures (Bayley-III and WPPSI-III) at 2 Years and at 4.5 Years.***

Variable	*B*	SE	Wald	df	*p*	OR	95% CI
Bayley Cognitive	-0.09	0.03	11.66	1	0.001	0.92	[.87, .96]
Bayley Language	-0.06	0.02	8.87	1	0.003	0.94	[.91, .98]
Bayley Motor	-0.06	0.02	6.23	1	0.013	0.95	[.90, .99]
Bayley Socio-emotional	-0.04	0.01	9.89	1	0.002	0.96	[.93, .98]
Bayley General Adaptive	0.03	0.01	3.43	1	0.064	1.03	[.99, 1.06]
WPPSI Verbal	-0.05	0.02	7.72	1	0.005	0.96	[.92, .99]
WPPSI Performance	-0.03	0.02	3.41	1	0.065	0.97	[.94, 1.00]
WPPSI Processing Speed	-0.03	0.02	2.96	1	0.085	0.97	[.94, 1.00]

Note: Beta (B), Standard Error (SE), Degrees of Freedom (df), Odds Ratio (OR), Wechsler Test (WPPSI).

Logistic Regression Predicting Risk Status in Executive Function Scores at 2 years and 4.5 years

Direct logistic regression was performed (see Table 36) to assess risk status ('less at-risk' versus 'more at-risk') among children. Administered measures of executive function tasks validated whether 'more at-risk' children were reported as more likely to have lower executive

function task performance. The model included tasks from administered 2-year EF tasks (ducks and buckets, fruit stroop, snack delay and multisearch multilocation) and 4.5-year EF tasks (dimension change card sort, bear and dragon, day and night, digit span and gift wrap). The choice of individual tasks rather than a composite score was based on the previous analyses that each task was moderately associated with each other. The full model including all predictors was statistically significant, X^2 (9, N = 355) = 76.10, $p < .001$. This indicated that 'observed' executive function scores could be used to determine whether a child can be classified as 'less at-risk' or 'more at-risk'. The model as a whole explained 29% (Cox and Snell R square) and 40.2% (Nagelkerke R squared) of the variance in children's risk status; this correctly classified 77.9% of the cases. Only five out of nine predictors made a unique contribution to the model. The strongest predictor for reporting risk status was the child's Dimension Change Card Sort performance recording an odds ratio of .59, followed by Digit Span with an odds ratio of .61, Fruit Stroop with an odds ratio of .76, Bear and Dragon with an odds ratio of .85, and Ducks and Buckets with an odds ratio of .69. Therefore, a decreasing performance in each observed executive function task at 2 years (Fruit Stroop and Ducks and Buckets) and at 4.5 years (Dimension Change Card Sort, Digit Span and Bear and Dragon) is most likely predictive of a child being more at-risk at 4.5 years.

Table 36: ***Logistic Regression Analysis Predicting Risk Status with Examiner Administered Executive Function Tasks at 2 Years and at 4.5 Years.***

Variable	*B*	SE	Wald	df	*p*	OR	95% CI
Snack Delay 2y	-0.19	0.09	3.72	1	0.054	0.83	[0.69, 1.00]
Fruit Stroop 2y	-0.27	0.12	5.15	1	0.023	0.76	[0.60, 0.96]
Ducks & Buckets 2y	-0.37	0.19	3.86	1	0.050	0.69	[0.48, 0.99]
Multisearch Multilocation 2y	-0.02	0.12	0.03	1	0.875	0.98	[0.78, 1.24]
Bear and Dragon 4.5 y	-0.16	0.08	4.03	1	0.045	0.85	[0.73, 0.99]
Day and Night 4.5 y	-0.14	0.08	3.24	1	0.072	0.87	[0.75, 1.01]
Digit Span 4.5 y	-0.50	0.19	7.09	1	0.008	0.61	[0.42, 0.88]
Card Sorting 4.5 y	-0.52	0.16	11.32	1	0.001	0.59	[0.44, 0.80]
Gift Wrap 4.5 y	-0.15	0.08	3.72	1	0.054	0.86	[0.73, 1.00]

Note: Beta (B), Standard Error (SE), Degrees of Freedom (df), Odds Ratio (OR)

Logistic Regression Predicting Risk Status in (parent-rated) BRIEF-P Scores at 2 years and 4.5 years

Direct logistic regression was performed (see Table 37) to assess risk status ('less at-risk' versus 'more at-risk') among children. Administered parent-rated measures of executive function, deemed to reflect behavioural aspects of cognitive control, validated that 'more at-risk' children were reported as more likely to exhibit more everyday executive function (EF errors). The model included global measure of Executive Control (GEC) from the BRIEF-P administered at 2 years and three indices of BRIEF-P: Inhibitory Self Control Index (ISCI), Flexibility Index (FI) and Emerging Metacognition Index (EMI) at 4.5 years. The choice of variables in the model was dependent on the available literature of executive function for toddlers and young children. The full model containing all predictors was statistically significant, X^2 (4, N = 355) = 159.41, $p < .001$. This indicated that 'parent-rated' executive function scores could be used to determine whether a child can be classified as 'less at-risk' or 'more at-risk'. The model as a whole explained 37.3% (Cox and Snell R square) and 49.9% (Nagelkerke R squared) of the variance in children's risk status; this correctly classified 78.7% of the cases. Three out of four predictors made a unique contribution to the model. The strongest predictors of reporting risk status were the parent-rated Emerging Metacognitive Index (EMI) recording an odds ratio of 1.08, followed by Inhibitory Self Control Index (ISCI) with an odds ratio of 1.07, and lastly, the Global Executive Control with an odds ratio of 1.03. Therefore, an increase of one standard deviation in each parent-rated executive function at 2 years (GEC) and at 4.5 years (EMI and ISCI) is most likely predictive of a child being more at-risk at 4.5 years.

Table 37: ***Logistic Regression Analysis Predicting Risk Status with Parent-Rated Executive Function at 2 Years and at 4.5 Years.***

Variable	*B*	SE	Wald	df	*p*	OR	95% CI
GEC at 2 y	0.03	0.02	4.81	1	0.028	1.03	[1.00, 1.07]
ISCI 4.5y	0.03	0.03	6.36	1	0.012	1.07	[1.02, 1.13]
FI 4.5y	0.02	0.02	0.61	1	0.435	1.02	[0.97, 1.07]
EMI 4.5y	0.08	0.02	15.99	1	<.001	1.08	[1.04, 1.12]

Note: Beta (B), Standard Error (SE), Degrees of Freedom (df), Odds Ratio (OR), Global Executive Control (GEC), Inhibitory Self Control Index (ISCI), Flexibility Index (FI), Emergent Metacognitive Index (EMI)

Logistic Regression Predicting Risk Status in Demographic Profile

Direct logistic regression was performed (see Table 38) to assess risk status (less at-risk versus more at-risk) among children. Administered home and family questionnaire validated that 'more at-risk' children reported more likely to have deprived resources and poor environmental experience. The model included socioeconomic status, sex, ethnic affiliation, and maternal education status. The full model containing all predictors was statistically significant, X^2 (4, N = 355) = 83.56, $p < .001$. This indicated that a demographic profile could be used to determine whether a child can be classified as 'less at-risk' or 'more at-risk'. The model as a whole explained 23% (Cox and Snell R square) and 30.8% (Nagelkerke R squared) of the variance in children's risk status; this correctly classified 73.4% of the cases. Each of the four predictors made a unique contribution to the model. The strongest predictors of reporting risk status were the socioeconomic status recording an odds ratio of .27, closely followed by maternal educational status with an odds ratio of .29. Ethnic affiliation contributed with an odds ratio of 2.45 and sex with an odds ratio of 1.69. Therefore, a decrease in socioeconomic status and maternal education are most likely predictive of poorer outcomes in children. Indigenous affiliation and male gender are most likely to receive 'more at-risk' labels.

Table 38: ***Logistic Regression Analysis Predicting Risk Status with Sociodemographic Data.***

Variable	*B*	SE	Wald	df	*p*	OR	95% CI
Socioeconomic Status	-1.31	0.29	20.85	1	< .001	0.27	[0.16, 0.48]
Sex	0.52	0.26	3.99	1	0.046	1.69	[1.01, 2.81]
Ethnicity	0.89	0.26	11.6	1	0.001	2.45	[1.46, 4.11]
Maternal Education	-1.22	0.27	20.06	1	< .001	0.29	[0.17, 0.50]

Note: Beta (B), Standard Error (SE), Degrees of Freedom (df), Odds Ratio (OR)

STUDY 4: Configuration of Early Executive Function in At-Risk Preschool Children: Longitudinal Evidence from Two Measures of Executive Function

Introduction

The regulation of thought processes and accompanying behavioural responses require the maturity of several higher cognitive skills. These skills are known to be interrelated and integrative (Miyake et al., 2000), thus enhancing the smooth flow of higher cognition that results in relative efficiency in reflection, decision-making, action regulation, and self-monitoring (Hughes, 2011) to achieve desirable outcomes. Development of cognitive control (executive function) in children was understood from the earlier adult models of executive function. Evidence for a 2-factor rather than a unitary model was argued, showing that EF skills were actively developing in the preschool years (Mantyla, Ronnlund, & Kliegel, 2010; Van Der Ven, Kroesbergen, Boom, & Leseman, 2012; Wiebe et al., 2011). However, a unitary dimension was favoured by cognitive and developmental psychologists; whereas 'parent-rated' executive function supported the 9-construct/subtest of the BRIEF measure. This reflected the 3-factor indices which were argued to be sensitive to an ecological "everyday behaviour" manifestation of executive function (Egeland & Fallmyr, 2010; Isquith et al., 2004). Among the most recent published studies in the assessment of EF, it appears that *the use of both "observed" and "parent-rated" EF is considered a holistic approach* to determine EF in young children (Karzmark et al., 2012; Toplak et al., 2013). EF was shown to be associated with child behaviour (internalising and externalising behaviours) and academic achievement (Hughes & Ensor, 2011; Vuontela et al., 2013). However, as participants in these studies were 'typically' developing children, it was thought appropriate to conduct a study to test whether 'cumulative risk' impacted configuration of EF skills. Therefore, the aim of Study 4 was to look at the impact of cumulative risk and to identify the configuration of EF in 'more at-risk' and 'less at-risk' preschool children.

Method

CHYLD Data

Data for this study included the sociodemographic profile (maternal education, sex, ethnicity), risk status, and executive measures at 2 years and at 4.5 years ('observed' and 'parent-rated'). Dichotomous variables were coded for: maternal education (high versus low), sex (male versus female), and risk status (less versus more) and ethnicity (European versus Non-

European). BRIEF-P T scores, clinical indices, and GECs were included in the subsequent data as well as 'observed' EF scores (composite scores), and derived scores for each EF task at 2 years and at 4.5 years. Refer to chapter 3 for detailed description and psychometric properties of each measure.

Data Analysis

Pearson correlations were used to identify magnitude of association within variables (intra-correlations) and between variables (inter-correlations). These test convergent and divergent validities among scores. *Hierarchical linear regressions* (HLM) were utilised to determine whether risk status, sociodemographic data, and cognitive skills accounted for measures of executive function (observed and parent-rated). *Exploratory factor analyses* (EFA) were used to determine the configuration of each EF skill at 2 years and at a 4.5-year follow-ups among 'less at-risk' and 'more at-risk' young children. The hypothesis was that variables were assumed correlated and allowed to load within the preset cluster for typical EF (3-factor structure). In-depth measurement analysis of BRIEF-P was further analysed in a separate paper by the author.

Results and Findings

Inter-correlation of 'observed' and 'parent-rated' executive function at 2 years

Positive and significant correlations were observed among examiner administered tasks (observed) at 2 years. Individual correlations showed weak but positive relationships (ranging from r = .18 to r = .22) suggesting that tasks moderately influence each other. However, correlation with the executive function composite score showed individually moderate and positive associations (ranging from r = .49 to r = .62). Therefore, this magnitude showed that each administered task reflects a cognitive skill that can be measured and combined together with other executive function tasks to create a unitary cognitive control construct. Results also suggest that analysis can be done at the individual level (task score) and at the construct level (composite score).

Parent-rated subscales from BRIEF-P showed moderate to strong, positive associations ranging from r = .41 to r = .77 and strong, positive associations with the global composite score (GEC) ranging from r = .66 to r = .87. The following relationship suggests that

behavioural aspects of executive function can be assessed in the combined unitary construct (GEC), or at the level of clinical indices, owing to the moderate to strong inter-correlations of each of the subscales.

Correlations of 'parent-rated' and 'observed executive' function tasks showed negative, weak but significant relationships with magnitudes ranging from r = -.14 to r = -.15; similarly, associations between 'parent-rated composite score' and 'observed executive function composite score' showed a weak, negative but significant relationship (r = -.16).

Inter-correlation of observed and parent-rated executive function at 4.5 years

Correlations among examiner administered 'observed' executive function tasks showed positive, significant but weak relationships. Magnitude ranges from r = .13 to r = .26, suggesting that each tasks individually reflect a cognitive task. These magnitudes are similar to the associations from the 'observed' tasks at 2 years. Therefore, similar levels of analysis can be taken for the 'observed' tasks at 4.5 years. Correlations with the composite score showed moderate magnitudes ranging from r = .45 to r =. 68.

Inter-correlations of 'parent-rated' subscales (BRIEF-P) showed magnitudes ranging from r = .51 to r = .73, and similar findings of moderate to strong relationships were identified from 'parent-rated' subscales at 2 years. Correlations of subscales with the composite score showed magnitudes ranging from r = .72 to r = .88. The relationship between 'parent-rated' composite score and 'observed' executive function composite score at 4.5 years showed similar negative but weak relationship to that of the 2 years (r = -.30).

Sociodemographic and Neurocognitive Predictors of 'Parent-Rated' Executive Function (GEC T score) at 4.5 years

To test the hypothesis that both social and cognitive variables can predict 'behavioural' aspects of executive function, four models were tested through hierarchical multiple regression analysis (Table 39). In step 1, maternal education, sex, socioeconomic status and risk status accounted for 35.8% of the variance, R^2 = .358, F (5, 290) = 32.40, p < .001. In step 2, cognitive predictors such as Bayley-III language score, WPPS-III verbal composite score, and WPPSI-III processing speed scored were added into the regression equation, and

an additional 2% added to the variance, F change (3, 287) = 2.91, $p < .001$. 'Parent-rated' global scores (GEC) at 2 years and 'observed' executive function composite scores at 2 years were added into step 3, and accounted for 11% of the variance, F change (2, 285) = 30.26, $p < .001$. In the last step, 'observed' executive function composite scores at 4.5 years were added into the model, and contributed .02% to variance, F change (1, 284) = .898, $p < .001$. In combination, the model explained at least 49% of the variance and the variables significantly predicted 'parent-rated' executive function at 4.5 years. Significant predictors in the final model were sex, risk status, Bayley-III language score and Global Executive Control score (GEC) at 2 years, $R^2 = .488$, adjusted $R^2 = .468$, F (11, 284) = 24.61, $p < .001$.

Table 39: ***Hierarchical Regression Analysis for Sociodemographic, Risk Status, and Cognitive Scores Predicting Parent-Rated Executive Function at 4.5 Years.***

Step and Predictor Variable		B	SE B	*B*	R^2	ΔR^2	*p*
Step 1					0.358		< .001
	Maternal Education	0.37	1.23	0.02			0.761
	Sex	2.06	1.11	0.09			0.063
	Ethnicity	0.07	1.18	0.01			0.951
	Socioeconomic Status	1.33	1.24	0.06			0.283
	Risk Status	-14.15	1.26	-0.6			< .001
Step 2					0.377	0.019	< .001
	Maternal Education	0.62	1.23	0.03			0.618
	Sex	2.23	1.11	0.1			0.045
	Ethnicity	-0.17	1.18	-0.01			0.884
	Socioeconomic Status	1.35	1.23	0.06			0.271
	Risk Status	-15.4	1.45	-0.66			< .001
	Bayley III Language Score	0.16	0.05	0.19			0.004
	WPPSI Verbal Score	-0.06	0.05	-0.08			0.264
	WPPSI Processing Speed Score	-0.02	0.05	-0.02			0.727
Step 3							

Step and Predictor		B	SE B	*B*	R^2	ΔR^2	*p*
	Ethnicity	-0.47	1.08	-0.02			0.665
	Socioeconomic Status	1.4	1.13	0.06			0.212
	Risk Status	-11.73	1.41	-0.5			< .001
	Bayley III Language Score	0.15	0.05	0.18			0.003
	WPPSI Verbal Score	-0.07	0.05	-0.1			0.136
	WPPSI Processing Speed Score	-0.06	0.05	-0.06			0.248
	GEC T Score at 24 Months	0.41	0.05	0.37			< .001
	EF Composite Score at 24 Months	0.12	0.14	0.04			0.4
Step 4					0.488	0.002	< .001
	Maternal Education	1.11	1.13	0.05			0.327
	Sex	3.87	1.04	0.17			< .001
	Ethnicity	-0.4	1.08	-0.02			0.71
	Socioeconomic Status	1.44	1.12	0.06			0.198
	Risk Status	-11.46	1.44	-0.49			< .001
	Bayley III Language Score	0.16	0.05	0.19			0.002
	WPPSI Verbal Score	-0.06	0.05	-0.08			0.224
	WPPSI Processing Speed Score	-0.05	0.05	-0.05			0.308
	GEC T Score at 24 Months	0.41	0.05	0.37			< .001
	EF Composite Score at 24 Months	0.12	0.14	0.04			0.383
	EF Composite Score at 53 Months	-0.11	0.12	-0.05			0.344

Note: *Wechsler Preschool and Primary Scale of Intelligence (WPPSI), Global Executive Control (GEC), Executive Function (EF)*

Sociodemographic and Neurocognitive Predictors of 'Observed' Executive Function (EF 4.5 composite score) at 4.5 years

To test the hypotheses that both social and cognitive variables could predict 'cognitive' aspects of executive function, four models were tested through hierarchical multiple regression analysis (see Table 40). In step 1, maternal education, sex, socioeconomic status and risk status accounted for 25.7% of the variance, R^2 = .257, F (5, 290) = 20.02, p < .001. In step 2, cognitive predictors were added into the regression equation; Bayley-III language score, WPPSI-III verbal composite score, WPPSI-III processing speed score accounted for an additional 15.9 %, F change (3, 287) = 25.29, p < .001. In step 3, 'observed' and 'parent-rated' executive function at 2 years were included and contributed .03% of the variance, F change (2, 285) = .733, p < .001. In the final model, 'parent-rated' executive function GEC scores were included; this addition contributed .02% of the variance. Taken together, the model explained 42% of the variance. Significant predictors were risk status, Bayley-III language score, WPPSI-III verbal composite score, and WPPSI-III processing speed score, R^2 = .420, Adjusted R^2 = .397, F (11, 285) = 18.69, p < .001.

Table 40: ***Hierarchical Regression Analysis of Sociodemographic Data, Risk Status, and Cognitive Scores Predicting Examiner Administered EF Tasks at 4.5 Years.***

Step and Predictor Variable		B	SE B	*B*	R^2	ΔR^2	*p*
Step 1					0.257		< .001
	Maternal Education	0.03	0.61	0			0.055
	Sex	-0.97	0.55	-0.09			-1.764
	Ethnicity	-0.03	0.58	0			-0.056
	Socioeconomic Status	0.75	0.61	0.07			1.222
	Risk Status	4.97	0.63	0.46			7.962
Step 2					0.415	0.159	< .001
	Maternal Education	-0.5	0.55	-0.04			0.367
	Sex	-0.78	0.5	-0.07			0.115
	Ethnicity	0.58	0.53	0.05			0.278
	Socioeconomic Status	0.38	0.55	0.03			0.489
	Risk Status	2.12	0.65	0.2			0.001
	Bayley III Language Score	0.07	0.02	0.18			0.003
	WPPSI Verbal Score	0.1	0.02	0.29			< .001
	WPPSI Processing Speed Score	0.06	0.02	0.13			0.015
Step 3					0.418	0.003	< .001
	Maternal Education	-0.46	0.55	-0.04			0.406
	Sex	-0.67	0.51	-0.06			0.19
	Ethnicity	0.57	0.53	0.05			0.283

Step and Predictor Variable		B	SE B	*B*	R^2	ΔR^2	*p*
	Socioeconomic Status	0.38	0.55	0.03			0.485
	Risk Status	2.34	0.69	0.22			0.001
	Bayley III Language Score	0.07	0.03	0.17			0.01
	WPPSI Verbal Score	0.1	0.02	0.29			< .001
	WPPSI Processing Speed Score	0.05	0.02	0.13			0.024
	GEC T Score at 24 Months	0.03	0.03	0.05			0.288
	EF Composite Score at 24 Months	0.04	0.07	0.03			0.555
Step 4					0.42	0.002	< .001
	Maternal Education	-0.43	0.55	-0.04			0.44
	Sex	-0.56	0.52	-0.05			0.285
	Ethnicity	0.56	0.53	0.05			0.294
	Socioeconomic Status	0.42	0.55	0.04			0.444
	Risk Status	2.02	0.77	0.19			0.009
	Bayley III Language Score	0.07	0.03	0.18			0.007
	WPPSI Verbal Score	0.1	0.02	0.28			< .001
	WPPSI Processing Speed Score	0.05	0.02	0.12			0.029
	GEC T Score at 24 Months	0.04	0.03	0.08			0.174
	EF Composite Score at 24 Months	0.04	0.07	0.03			0.524
	EF Composite Score at 53 Months	-0.03	0.29	-0.06			0.344

Note: Wechsler Preschool and Primary Scale of Intelligence (WPPSI), Global Executive Control (GEC), Executive Function (EF)

Investigating configuration of parent-rated executive function skills in at-risk preschool children at 2 years and 4.5 years

Exploratory factor analyses (EFA) were conducted on the five subscales of 'parent-rated' executive function (BRIEF-P) at 2 years (Table 41 - 42). Oblique rotation (promax) was chosen to allow scores to correlate with each other. The Kaiser-Meyer-Olkin reached sampling adequacy for both analysis of 'more at-risk' and 'less at-risk' groups, (KMO more at-risk = .755, and KMO less at-risk = .753).

The purpose of the EFA was to give emphasis to the configuration more than the factor structure; therefore, loadings of .30 and above were used as a basis. Likewise, loadings of less than .30 were considered non-loading. Three hypothesised factors, which support the original theoretical framework of BRIEF-P (ISCI, EMI, and FI) were forced into the analyses for both the 2-year and 4.5-year data.

EFA at 2 years, for the 'more at-risk' group resulted in a cumulative 60.36% of the variance and was explained by Factor 1 (Plan/Organise T scores, Working Memory T score, and Inhibit T scores). The remaining variances were explained by Factor 2 (Shift T scores and Emotion Control T scores), and cross loadings for Factor 3 (Emotion T scores, and Inhibit T scores). Configuration of the five subscales of BRIEF-P showed similar configuration to the original model of BRIEF-P. However, the cross loadings of Inhibit T scores and Emotion T scores should be considered as a variant of the original model of BRIEF-P. However, in the 'less at-risk' group, a cumulative 52.17% of the variance was explained by Factor 1 (Working Memory T scores and Plan/Organise T scores) alone, followed by Factor 2 (Emotion Control T scores and Shift T scores) and Factor 3 (Inhibit T scores). Comparing group configurations showed that the 'more at-risk' group loaded Inhibit T scores and Emotion Control T scores as auxiliary loadings more than the 'less at-risk' group without any cross loadings.

Factor analyses (EFA) were employed to identify configurations of 'parent-rated' subscales of BRIEF-P at 4.5 years (see Table 42). Sampling appropriateness was evaluated; Kaiser-Meyer-Olkin reached adequacies (KMO more at-risk = .743, KMO less at-risk = .756) at 4.5 years. Similar to the 2-year data for 'more at-risk' group factor structure, the 4.5 year 'more at-risk' structure displayed a similar configuration to Factor 1 (Working Memory T score, Plan/Organise T score, and Inhibit T score) having a cumulative 57.58% of the variance,

Factor 2 (Shift T score and Emotion Control T score) and Factor 3 (Inhibit T score and Emotion Control T score). A similar configuration was observed in the 2 year ‘less at-risk’ group. The 4.5-year ‘less at-risk’ factor structure explained lower variance with Factor 1 (Working Memory T score and Plan/Organise T score) explaining 52.02% of the variance alone. The variance explained (Factor 1) for the ‘less at-risk’ group did not change from 2 years to 4.5 years. Similar configurations for Factor 2 (Emotion Control T score and Shift T score) and Factor 3 (Inhibit T score) were observed.

Table 41: ***Factor Loadings, Communalities and Percent of Variances of Parent-Rated Executive Function at 2 Years.***

	More At-Risk Children				Less At-Risk Children			
	Factor				Factor			
Subscale	1	2	3	h2	1	2	3	h2
Plan/Organize T score	0.872			0.802	0.699			0.594
Working Memory T score	0.739			0.715	0.926			0.925
Shift T score		0.768		0.612		0.569		0.305
Inhibit T score	0.456		0.649	0.863			0.749	0.73
Emotion T score		0.536	0.553	0.816		0.682		0.644
Percent of Variance	60.36	11.56	4.25	76.17	52.17	8.77	3.01	63.95

Note: Factor 1 (Metacognitive), Factor 2 (Flexibility), Factor 3 (Inhibitory Self Control), h2 (communalities)

Table 42: ***Factor Loadings, Communalities and Percent of Variances for Parent-Rated Executive Function at 4.5 Years.***

	More At-Risk Children				Less At-Risk Children			
	Factor				Factor			
Subscale	1	2	3	h2	1	2	3	h2
Plan/Organize T score	0.805			0.828	0.731			0.554
Working Memory T score	0.829			0.728	0.847			0.867
Shift T score		0.785		0.584		0.687		0.518
Inhibit T score	0.311		0.729	0.774			0.682	0.677
Emotion T score		0.537	0.534	0.801		0.7		0.648
Percent of Variance	57.58	12.14	4.6	74.32	52.02	9.82	3.45	65.29

Note: Factor 1 (Metacognitive), Factor 2 (Flexibility), Factor 3 (Inhibitory Self Control), h2 (communalities)

Investigating configuration of observed executive function skills in at-risk preschool children at 2 years and 4.5 years

Exploratory factor analyses were conducted to identify configurations of observed executive function skills (examiner administered) at 2 years and at 4.5 years (see Tables 43 – 44). Hypothesised theoretical frameworks endorsed the three-factor structure of executive function (inhibition, working memory and cognitive flexibility). Oblique rotation (Promax) was used to allow correlations among EF scores.

At 2 years, sampling adequacies for both the 'more at-risk' group (KMO = .573) and the 'less at-risk' group (KMO = .484) reached poor values. The 'more at-risk' group yielded 11.57% of the variance from Factor 1 (Snack Delay), Factor 2 (Multisearch Multilocation), and Factor 3 (Fruit Stroop). Gift Wrap failed to load strongly in either of the factor structures. For the 'less at-risk' group, Factor 1 (Snack Delay and Ducks & Buckets) contributed at least 16.21% of the variance, followed by Factor 2 (Multisearch Multilocation) with 9.14% variance explained, and 3.18% for Factor 3 (Fruit Stroop). Compared to the 'more at-risk' group with one endorsed factor structure, the 'less at-risk' group endorsed a 2-factor model. Therefore, the neural mechanisms of the 'less at-risk' group seem to suggest a more componential cognitive control than the 'more at-risk' group at 2 years. The 'more at-risk' group endorsed more combined delay inhibition/working memory than any other executive task, while the 'less at-risk' group endorsed a 2-factor structure from combined delay inhibition/cognitive flexibility and working memory/conflict inhibition.

At 4.5 years, sampling adequacies for both the 'more at-risk' group (KMO = .544) and the 'less at-risk' group (KMO = .538) were of poor values. The 'more at-risk' group accounted for 20.62% of the variance for an endorsed 2-factor structure. Factor 1 (Dimension Change Card Sort) and Factor 2 (Bear & Dragon and Day & Night) were endorsed. Factor 3 (Digit Span) accounted for a small portion with 4% of the variance. In this regard, flexibility and attention as well as inhibition dimension can be suggested active at 4.5 years even for 'more at-risk' preschool children. Gift Wrap, which is a measure of delay inhibition, did not load strongly in any factor, suggesting that this measure may not have shared variances with other EF tasks. At the conceptual level, this may also reflect that the 'more at-risk' group may have had low cognitive priority in this domain. However, in the 'less at-risk' group a cumulative 17% of the variance can be explained by a 2-factor model whereby Factor 1 (Bear & Dragon) and Factor

2 (Day & Night and Gift Wrap) were endorsed, and a small amount of variance was contributed by Factor 3 (Digit Span). Compared with the 'more at-risk' group, endorsement of the 2-factor structure for this group showed inhibition (delay and conflict) and working memory, compared to an attention/inhibition and working memory structure.

Discussion

Correlations among 'parent-rated' and 'observed' executive function showed that each measure of executive function may reflect a different dimension of higher cognitive control. The 'observed' tasks depicted pure cognitive skills, whereas, the 'parent-rated' measure may capture the behavioural manifestations of executive function. However, as executive function skills are known to be more cognitive than behavioural, multiple regressions can be utilised to identify whether social (demographics, risks) and cognitive predictors (language and processing speed) can be used to explain the differences among parent-rated and observed executive function measures.

Risk status and Bayley-III language scores at 2 years significantly predicted both 'observed' and 'parent-rated' composite scores at 4.5 years. GEC T scores at 2 years predicted GEC T scores at 4.5 years. Between 40% and 50% of the variance can be explained in combined social and cognitive predictors for 'parent-rated' and 'observed' executive function at 4.5 years. The 'parent-rated' measure of executive function is not entirely "behavioural" because the Bayley-III language score, which is a cognitive domain, contributed a significant variance in GEC T scores at 4.5 years.

Findings showed that in longitudinal observation of the data, factor structure for the purely 'cognitive' tasks seems to endorse evidence of componential cognitive control at 2 years and at 4.5 years for 'less at-risk' preschool children. The 'more at-risk' group tends to endorse a unitary model at 2 years, catching up at 4.5 years with a variant of skills configuration. DCCS (cognitive flexibility) was observed, loaded highly ('more at-risk' group) and differently ('less at-risk' group) in the cross analysis. However, in general, due to the low variance explained in the analysis, it is therefore suggested that EF at 4.5 years is considered unitary and actively developing.

In the ‘behavioural’ aspects of cognitive control, both models from 2 years and at 4.5 years were found to be similar to the theoretical model of BRIEF-P. However, the ‘less at-risk’ group tends to have no cross loadings of inhibit T score and emotion control T scores suggesting that this group of children may differ in their self-regulatory functioning compared to the ‘more at-risk’ group of preschool children.

Lastly, risk status (‘less at-risk’ vs ‘more at-risk’) independently predicted observed executive function (25%) and parent-rated executive function (35%). Therefore, risk status is an influential factor in the development and configuration of early executive function in young children. Similarly, the use of both executive function measures is useful in the identification of behavioural risks in young children.

Table 43: ***Factor Loadings, Communalities and Percent of Variances of Examiner Administered Executive Function Tasks at 2 Years.***

	More At-Risk Children				Less At-Risk Children			
	Factor				Factor			
Subscale	1	2	3	h2	1	2	3	h2
Snack Delay	0.423			0.131	0.35			0.389
Fruit Stroop			0.353	0.083			0.535	0.189
Ducks and Buckets				0.203	0.625			0.308
Multisearch Multilocation		0.426		0.144		0.544		0.256
Percent of Variance	11.57	1.63	0.844	14.04	16.21	9.14	3.18	28.53

Note: h2 (communalities)

Table 44: ***Factor Loadings, Communalities and Percent of Variances of Examiner Administered Executive Function Tasks at 4.5 Years***

	More At-Risk Children				Less At-Risk Children			
	Factor				Factor			
Subscale	1	2	3	h2	1	2	3	h2
Bear and Dragon		0.459		0.403	0.59			0.291
Day and Night		0.453		0.176		0.417		0.108
Digit Span			0.416	0.229			0.439	0.159
DCCS	0.639			0.348				0.042
Gift Wrap				0.055		0.473		0.356
Percent of Variance	14.67	5.96	3.56	24.19	12.64	3.91	2.55	19.1

Note: h2 (communalities), DCCS = Dimension Change Card Sorting Task

STUDY 5: Executive Function and Neurocognition: The Impact of Cumulative Risk and the Role of Observed Executive Function at 4.5 Years

Introduction

Cumulative risk has proved to be a tenable and significant predictor of developmental outcomes in the CHYLD cohort. This approach was validated in 5-cluster and 2-cluster solutions described in previous chapters of this thesis. In review, both cluster solutions were associated with risks found in the CHYLD (Children with Neonatal Hypoglycaemia and their Later Development) CHYLD study data (deprived social strata, low maternal education, parent substance use, small for gestation among others), factors that are considered strong predictors of neurodevelopment and which support the impact of person-environment risks in child development.

Deprived social status (SES) was associated with deficits in neurocognitive and behavioural outcomes, for instance, working memory that is related to the hippocampus; emotion regulation that is related to the amygdala; reasoning abilities; language development (Aran-Filippetti & Minzi, 2012; Fernald et al., 2013; Lawson, Duda, Avants, Wu, & Farah, 2013; Noble, Norman, & Farah, 2005; Noble, Houston, Kan, & Sowell, 2012) and executive function skills, which are related to the prefrontal cortex (Dahlman, Backstrom, Bohlin, & Frans, 2013; Lipina et al., 2013; Rhoades et al., 2011; Sarsour et al., 2011). Accompanying primary risks, such as small for gestation (SGA) (McCowan et al., 2002) and/or prematurity, suggested sensitivity to: task orientation, general cognitive abilities and executive function (Eryigit-Madzwamuse & Wolke, 2015; Graz et al., 2015; Nogel et al., 2015; Tanis et al., 2015), as well as behavioural aspects (Mello et al., 2014). Lastly, parent characteristics (Conway & Stifter, 2012; Sheridan, How, Araujo, Schamberg, & Nelson, 2013; Turner, Wittkowski, & Dougal, 2008; Von Der Lippe, Eilertsen, Hartmann, & Killen, 2010) and parent substance use (Burden, Jacobson, & Jacobson, 2005; Jacobson, Fein, Jacobson, Schwartz, & Dowler, 1984; Jacobson, Jacobson, Sokol, Martier, & Ager, 1993; Jacobson, Jacobson, Sokol, Martier, & Chiodo, 1996; Jacobson, Jacobson, Sokol, Chiodo, & Corobana, 2004) were found to be associated with executive function and other cognitive processes among infants and young children.

Relationships among neurocognitive variables showed that processing speed is strongly related to executive function owing to its substantial neural brain wiring (Ferrer et al., 2013). It also may extensively mask performance in observed EF tasks administered (Cepeda, Blackwell, & Munakata, 2013). Processing speed is an important cognitive ability (global efficiency) that helps in the performance of various cognitive-related tasks (Kail & Salthouse, 1994; Kail & Ferrer, 2007; Kail, 2007; Kail, 1992). A substantial proportion of this neural association supports working memory and inhibitory responses among children and adults (McAuley & White, 2011). However, some developmental psychologists pointed out that these neural associations with processing speed and executive function skills are sensitive to primary risks at birth, for instance, premature birth among others, which in turn lead to a poor learning and pre-academic development in literacy and numeracy (Rose & Feldman, 1996; Rose, Feldman, & Jankowski, 2011).

The roles of processing speed and executive functioning as higher order cognitive processes were tested in several studies and found to be supported, for instance, in the development of reasoning in children. Inhibitory control and composite executive function were found associated with analogical reasoning (Richland & Burchinal, 2013). Age-based improvement in processing speed is directly related to improved reasoning in young children as well as possibly having an indirect relationship through working memory (Kail, 2007; Kail, Lervag, & Hulme, 2016). Working memory was found related to processing speed in a longitudinal study, and was predictive of preschool academic achievement (Stevenson, Bergwerff, Heiser, & Resing, 2014).

The association between cognitive processes such as general cognition, executive function, and visual-motor and motor development were not thoroughly investigated until recently. Previous findings showed that cognition, especially fluid intelligence, was related to ‘copy and design’, a visuo-motor task (Decker, Englund, Carboni, & Brooks, 2011). Both ‘copy and design’ tasks and the ability to draw geometric shapes were predictive of early language development (reading, writing and forming sentences) (Cameron et al., 2012). However, the integration and cascade influences of higher cognition (EF) were in their infancy; only findings from atypical children were investigated (AD/HD, intellectual disabilities, William syndromes). The study revealed that atypically developing children tend to have deficits in both executive function and motor control. Visuomotor processing was found sensitive to primary risks at birth such as low birth weight and prematurity (Rider, Weiss, McDermott, Hopp, & Baron, 2016). Clumsy motor behaviours and inattention were found among atypically developing children who were hypothesised to have deficits in overlapping neural areas covered by

motor area and executive function (Hartman, Houwen, Scherder, & Visscher, 2010; Hocking et al., 2013; Ozonoff et al., 2008). It was hypothesised that motor function deficits were related to EF deficits in young children (Michel, Roethlisberger, Neunschwander, & Roebers, 2011). Motor difficulties and executive function skills deficits were associated with developmental coordination problems or DCD (Bernardi, Leonard, Hill, & Henry, 2016; Leonard & Hill, 2015; Leonard, Bernardi, Hill, & Henry, 2015; Sumner, Pratt, & Hill, 2016).

Based on the literature presented, associations of variables can be tested in two ways: a) effects of cumulative risk predict cognition / higher cognition and in turn predict reasoning abilities and b) effect of cumulative risk predicts higher cognition and visual processing and in turn predicts motor development. These impact of cumulative risk on developmental outcomes needed more clarity and research support. Therefore, the following hypotheses aim to contribute to the understanding of these mechanisms and their associations:

In analysis 1: *Hypothesis 1:* Cumulative Risk (CR) predicts executive function and general cognitive ability (IQ) at 4.5 years of age; *Hypothesis 2*: The effects of CR on executive function are mediated by the direct effect of CR on general cognitive ability (IQ).

In analysis 2: *Hypothesis 1:* Processing speed predicts working memory and in turn predicts verbal reasoning; *Hypothesis 2:* CR has direct and indirect effects on reasoning abilities (verbal and non-verbal reasoning) and is even mediated by working memory and processing speed.

In analysis 3: *Hypothesis 1:* Visuomotor integration and executive function predict movement at 4.5 years of age. *Hypothesis 2:* CR has direct and indirect effects on movement and is even mediated by Visuomotor integration, processing speed and/or working memory.

Method

CHYLD Data

Five sets of data were used for these analyses (n = 477) were 1) the metric-based cumulative risk (2-clustered solution), 2) observed executive function tasks at 4.5 years: a) the Inhibition

score was a derivation from Bear & Dragon, Gift delay, and Day & Night tasks, b) Working Memory score was a composite of Phelps auditory processing subtests, which included Forward Digit Span, Memory for Sentences and Stories and Word Discrimination, c) Cognitive Flexibility score was derived from the Dimension Change Card Sorting Test (DCCS). 3) Cognitive abilities taken from the examiner administered WPPSI-III and indices for Verbal (VIQ), Performance (PIQ), and Processing Speed (PSI) were used. Similarly, WPPSI-III subtests were utilised for verbal reasoning (Word Reasoning) and non-verbal reasoning (Block Design). 4) Beery-VMI represented visual processing and integration variables, while 5) Movement ABC-2 total score was used as a measure of motor development at 4.5 years. Refer to Chapter 3 for detailed description of measures and participants of this study.

Data Analysis

Mediation analyses were used to estimate both direct and indirect effects of independent variables on outcome variables. *Mediation* is defined as a statistical mechanism, whereby the impact of an independent variable is estimated on the dependent variable. The original regression mediation model adheres to the following: Step 1. where variable X (independent variable) predicts variable Y (dependent variable), Step 2, where variable X predicts Variable M (mediating variable), and Step 3, where Variables X and M both predict Variable Y (Baron & Kenny, 1986). A *mediating variable* is defined as a third intervening variable between an independent variable and an outcome or dependent variable; often, these causal (association) relationships rely on theories and empirical findings (Hoyle, 2012). The use of linear *structural equations* instead of a series of linear regressions improves the estimation of direct and indirect effects (Hoyle, 2012; Jose, 2013). *Direct effect* is the estimated influence of an independent variable on a dependent variable and is represented by a path diagram, while *the indirect effect* is the result of an additional variable, usually an intervening variable, being added into the equation, which may result in a change of direct effect (Sobel, 1987). The mediation is estimated through *structural equation modelling* (SEM), therefore, several characteristics and procedures in reporting SEM need to be discussed. SEM is a series of statistical regressions, and estimates substantial variables related to phenomena. It also evaluates parameter and test model fitness (Schumacher & Lomax, 2010). This statistical model testing is considered confirmatory in nature. Therefore, causal inference through statistical means has features such as a) association, b) direction, and c) isolation (Hoyle, 2012). Therefore, as this study aims to provide statistical inference, it also seeks models that are parsimonious, data-driven, theory-driven and practical, based on suggested best practice in statistical model building (Thompson, 2000). Assessment of the model fit for structural

equation modelling follows several fit indices for evaluation. Non-significant X^2 shows model fitness and the ratio of X^2 to degrees of freedom (*df*) should be less than 2. Comparative Fit Index (CFI) should be greater than .95 as indicative of good fitting model, and Root Mean Square Error of Approximation (RMSEA), which tests the non-significance of the data, should be less than .10, or a minimum of .06 can be acceptable depending on the sample size. Model parsimony can be identified by comparing values (smaller) of Akaike Information Criterion (AIC) among models tested (Marsh, Hau, & Wen, 2004; Tabachnick & Fidell, 2013).

Results and Findings

Analysis 1: *Hypothesis 1:* Cumulative Risk (CR) predicts executive function and general cognitive ability (IQ) at 4.5 years of age; *Hypothesis 2*: The effects of CR on executive function are mediated by the direct effect of CR on general cognitive ability (IQ).

To test whether general cognitive ability (IQ) and executive function (EF) are significantly and substantially correlated, correlational and path analytic approaches were used (see Figure 3). Descriptive statistics and correlation coefficients showed that the study variables WPPSI full scale IQ (M = 98.04, SD = 14.82), and executive function composite score at 4.5 years (M = 13.52, SD = 5.74), and CR (M = .45, SD = .50) were significantly and moderately related: EF → IQ (r = .59, p < .05), EF → CR (r = -.52, p < .05), and CR → IQ (r = .62, p < .05).

Initial standardised regression coefficients (Figure 8) revealed that general cognitive ability highly predicted EF (β = .96, p = < .05), while CR negatively and significantly predicted EF (β = - .79, p = < .05), Therefore, these associations suggested that there was an overlap between IQ and EF in young children and that CR influenced both higher cognitive processes and general cognitive abilities. Mediation analysis showed (Figure 9) that the effect of CR on EF was decreased by half (partially mediated) when IQ was added into the equation; which means, the effect of CR on young children's EF could be explained by its effect on IQ (indirect effect). CR → EF decreased (β = - .30, p = < .05). This model achieved acceptable fit (parameter =16, minimum x^2 = 1.20, df = 4, x^2/df = .299, CFI = 1.02, RMSEA = .000, 90% CI [000 - .034], AIC = 33.20).

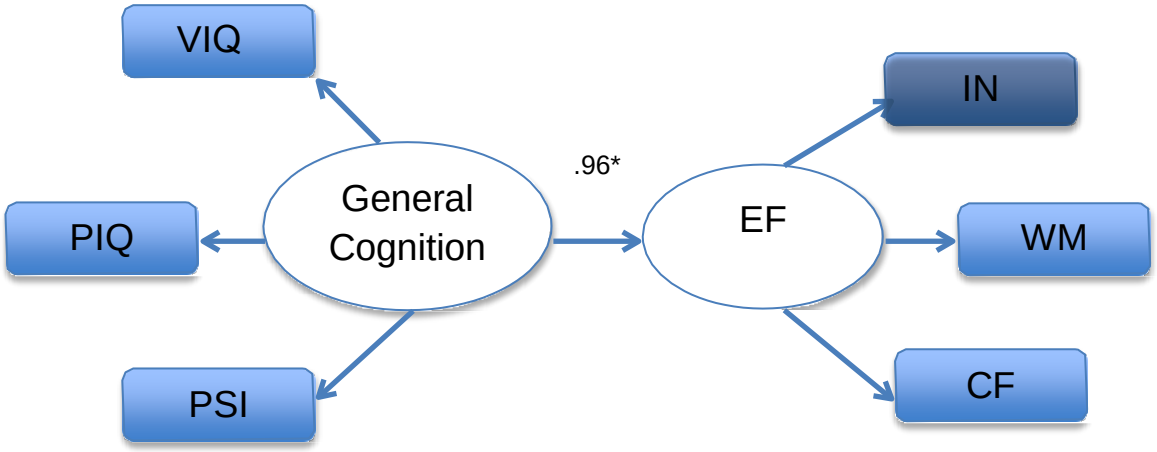

Figure 8: ***Path model estimating association between Intelligence and Executive Function.***

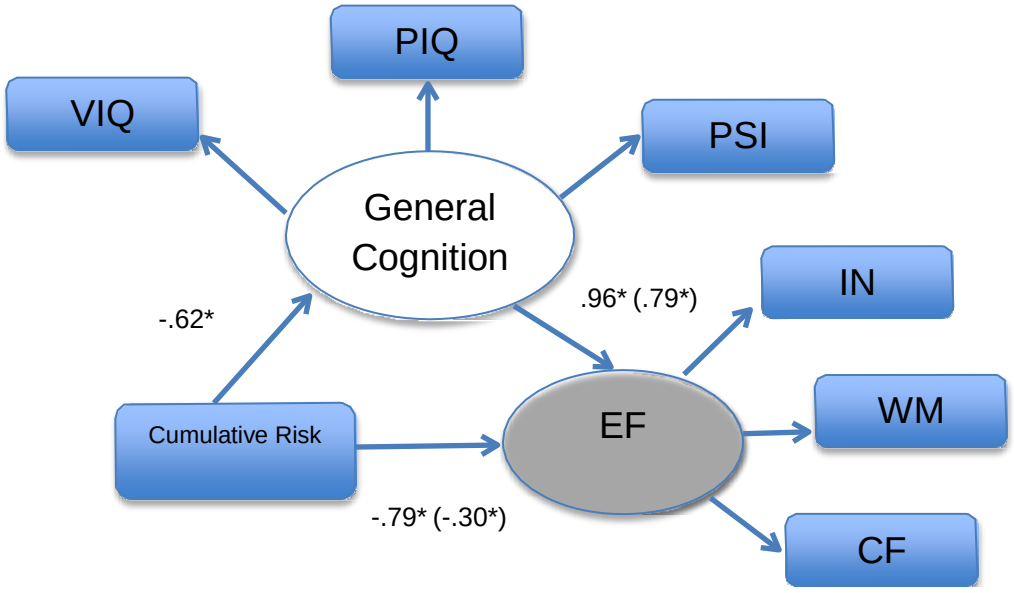

Figure 9: ***Mediation Analysis Estimating Impact of Cumulative Risk on IQ and Examiner Administered Executive Function Tasks at 4.5 Years.***

*Full model: a) general cognition (WPPSI-IQ) significantly predicted executive function; b) cumulative risk mediated the association between general cognition and executive function. Standardized coefficients, Latent constructs are shown in ellipses and observed variables are shown in rectangles. Solid-lines denote significant path, and (mediated effect). EF = Executive Function, IN = Inhibitory, WM = Working Memory, CF = Cognitive Flexibility, VIQ = Verbal Intelligence Quotient, PIQ = Performance Intelligence Quotient, PSI = Processing Speed Index, *p < .05.*

Analysis 2: *Hypothesis 1:* Processing speed predicts working memory and in turn predicts verbal reasoning; *Hypothesis 2:* CR has direct and indirect effects on reasoning abilities (verbal and non-verbal reasoning) and is even mediated by working memory and processing speed.

Correlational analysis showed that processing speed (PS) was significantly and moderately associated with verbal reasoning (WR) and working memory (WM). Cumulative Risk (CR) was significantly and moderately associated with neurocognitive variables in the study. Panel model showed that the standardised coefficients were significantly larger: PS → WM (β = .70, p = < .05), PS → WR (β = .67, p = < .05) and WM → WR (β = .88, p = < .05). Direct effects of CR on study variables were substantial: CR → WM (β = - .69, p = < .05), CR → WR (β = - .57, p = < .05) and CR → PS (β = - .52, p = < .05).

In a path analysis, three variables predicting WR, the model failed to achieve acceptable fit (x^2/df = 15.02, CFI = .767, RMSEA = .720). In Model 2, where WM was the mediator and PS the predictor, the model showed an increase in some fit index (x^2/df = 7.60, CFI = .895, RMSEA = .118, AIC, 236.73). In this model, WM substantially reduced the association of CR on WR.

A multiple mediation model (Figure 10) was tested and found decreased the direct effect of CR on verbal reasoning. The model showed unacceptable fit (x^2/df = 3.87, CFI = .956, RMSEA = .078, AIC = 149.13). However, CFI and RMSEA suggested that reconfiguration of the model with theoretical support could lead to model fit. A mediated mediation model (see Figure 4) was evaluated where PS was the main mediator and hypothesised to influence the mediated relationship of CR → WM → WR. This model achieved acceptable fit, (x^2/df = 1.586, CFI = .991, RMSEA = .035, AIC = 99.31).

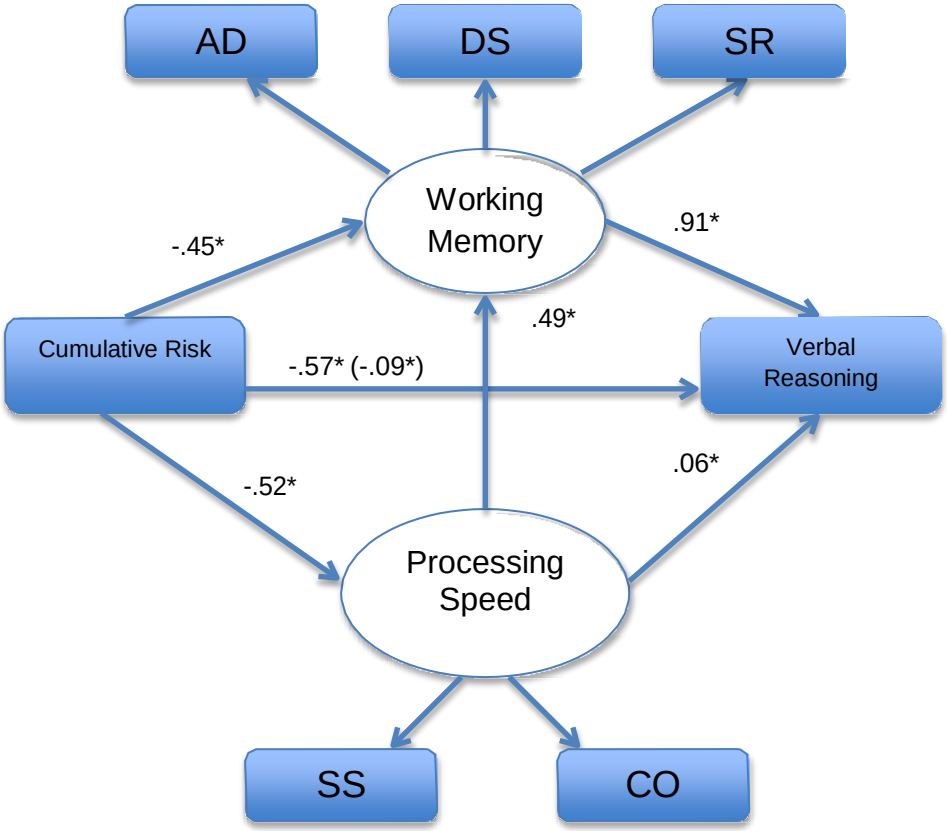

Figure 10: ***Mediation Analysis Estimating the Impact of Cumulative Risk on Working Memory, Processing Speed and Verbal Reasoning at 4.5 Years.***

*Full model: a) cumulative risk significantly predicted outcome (verbal reasoning, b) multiple mediators (working memory and processing speed) mediated effects of cumulative risk on outcome (verbal reasoning). Standardized coefficients, Latent constructs are shown in ellipses and observed variables are shown in rectangles. Solid-lines denote significant path, and (mediated effect). AD = Auditory Discrimination, DS = Digit Span, SR = Sentence/ Story Recall, SS = Symbol Search, CO = Coding, *p < .05.*

The path model showed that the direct effect of CR → WR through WM was highly reduced when PS → WR through WM was introduced from β = - .57 to β = - .09 p < .05. Therefore, this model suggests that there is a complex neural processing for verbal reasoning, which accounts for both executive function and processing speed. In addition, the impact of CR on verbal reasoning could be explained by its influence on basic level neural processing.

To test whether a similar path provides causal association for non-verbal reasoning (see Figure 11), block design (BD) was used as an outcome variable *(M* = 9.72, *SD* = 3.41). Associations among non-verbal reasoning (BD) showed significantly modest results, with WM (*r* = .34, *p* < .05), with PS (*r* = .50, *p* < .05) and with CR (*r* = -.38, *p* < .05), CR → BD was hypothesised with substantial coefficient (*β* = - .37, *p* = < .05). A mediated mediation model (x^2/df = 1.74, CFI = .997, RMSEA = .039, AIC = .39.48) showed (Figure 11) a significant decrease in the direct effects of CR on BD (*β* = - .37 to *β* = - .04, *p* = < .05) when PS and WM were considered in the equation. Therefore both verbal and non-verbal reasoning have somewhat different neural pathways as suggested by the model testing, but the direct effect of CR was larger in WR than BD.

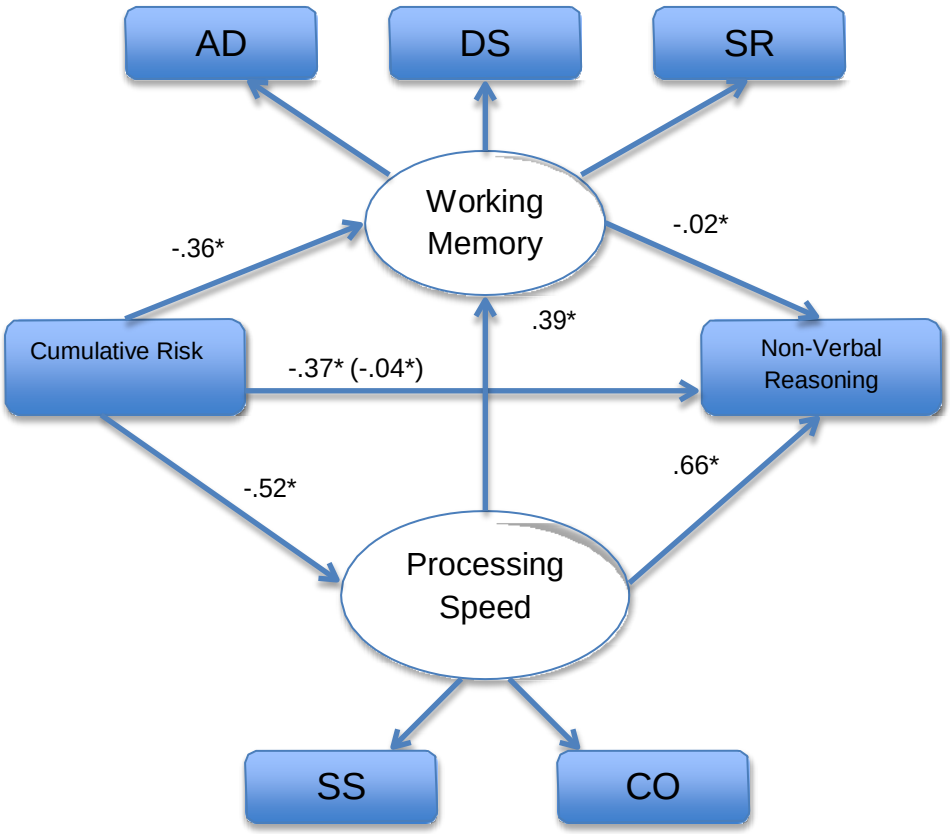

Figure 11: ***Mediation Analysis Estimating the Impact of Cumulative Risk on Working Memory, Processing Speed, and Non-Verbal Reasoning Ability at 4.5 Years.***

*Full Model: a) cumulative risk significantly predicted outcome (non-verbal reasoning), b) multiple mediators (working memory and processing speed) mediated effects of cumulative risk on outcome (non-verbal reasoning). Standardized coefficients, Latent constructs are shown in ellipses and observed variables are shown in rectangles. Solid-lines denote significant path, and (mediated effect). AD = Auditory Discrimination, DS = Digit Span, SR = Sentence/ Story Recall, SS = Symbol Search, CO = Coding, *p < .05.*

Analysis 3: *Hypothesis 1:* Visuomotor integration and executive function predict movement at 4.5 years of age. *Hypothesis 2:* CR has direct and indirect effects on movement and is even mediated by visuomotor integration, processing speed and/or working memory.

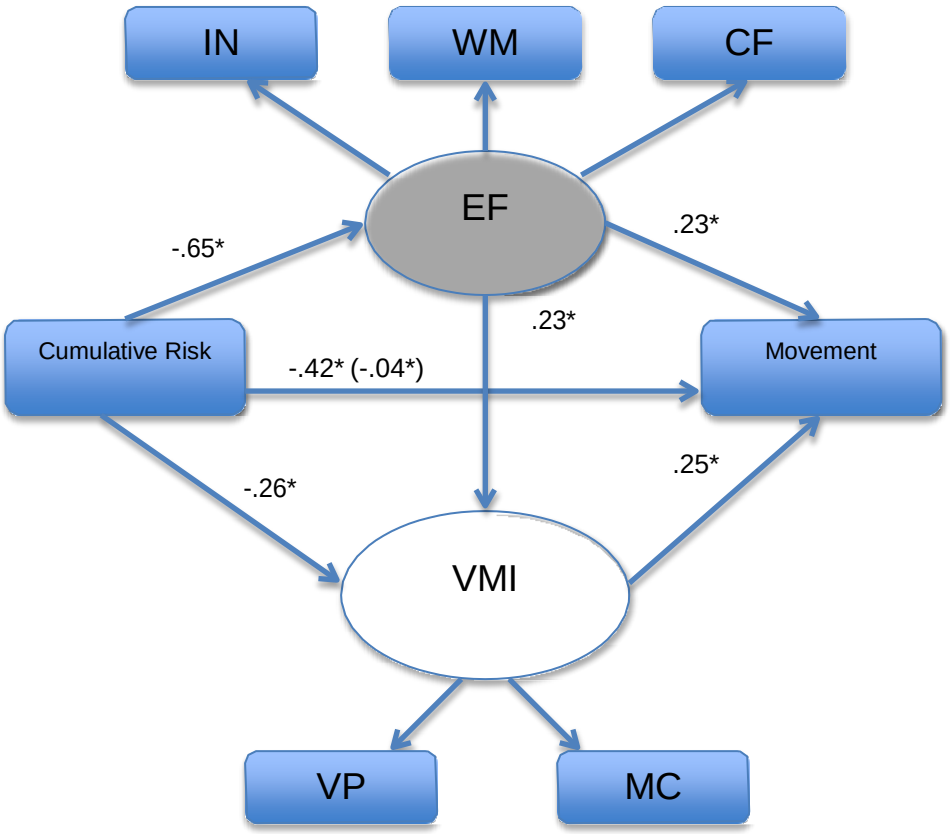

Figure 12: ***Mediation Analysis Estimating the Impact of Cumulative Risk on Examiner Administered Executive Function Tasks, Visuo-Motor Integration and Motor Development at 4.5 Years.***

*Full model: Cumulative risk significantly predicted outcome (Motor), multiple mediators (EF and VMI) decreased the effect of cumulative risk on outcome (Motor). Standardized coefficients, Latent constructs are shown in ellipses and observed variables are shown in rectangles. Solid-lines denote significant path, and (mediated effect). EF = Executive Function, IN = Inhibitory, WM = Working Memory, CF = Cognitive Flexibility, VMI = Visuo-Motor Integration, VP = Visual Perception, MC = Motor Coordination, *p < .05.*

Correlations showed that visuomotor integration (VMI) is significantly and modestly associated with movement (MO). CR significantly and negatively related to both VMI and MO.

To test the mediator, models were evaluated among hypothesised variables known to mediate effects of CR on MO: (VMI, PS, and EF or WM). Standardised regression coefficients revealed substantial causal association among CR → MO (β = - .42, p = < .05), CR → PS (β = - .40, p = < .05) and PS → MO (β = .50, p = < .05).

In model 1 (PS as mediator), direct effects of CR on MO showed a substantial decrease from β = - .42 to β = - .15, p = < .05 (partial mediation) when PS was added as a mediator. This model achieved acceptable fit (x^2/df = 1.46, CFI = .997, RMSEA = .031, AIC = 38.93). In model 2 (EF as mediator), direct effects of CR on MO showed substantial decrease from β = - .42 to β = - .08, p = < .05. This model was acceptable (x^2/df = 1.50, CFI = .991, RMSEA = .033, AIC = 66.03). In model 3 (VMI as mediator), direct effects of CR on MO showed decrease from β = - .42 to β = - .18, p = < .05. This model failed to provide acceptable model fit (x^2/df = 3.99, CFI = .984, RMSEA = .079, AIC = 43.98).

Two mediated mediations were identified (Figure 12) as a possible solution to whether a series of basic level neural processing (PS or EF) and visual processing (VMI) could significantly mediate the CR → MO relationship. When PS was added as the main mediator predicting the VMI → MO relation, the direct effect of CR → MO dropped to β = - .08, p = < .05 with a good model fit (x^2/df = 2.63, CFI = .976, RMSEA = .059, AIC = 76.35). Another mediated mediation model with EF as main mediator was tested (see Figure 6). When EF was added into the equation the CR → MO direct effect was reduced β = - .04, p = < .05, with a better model fit (x^2/df = 2.09, CFI = .979, RMSEA = .048, AIC = 89.17).

Discussion

Several key findings supported cognitive development literature. General intelligence and executive function show a strong association. However, in this study, cumulative risk compromises the association between the two cognitive constructs. The impact of CR is strongly linked with general intelligence rather than with executive function. Therefore, this finding supports the previous studies on the effect of cumulative risk on neural development and basic cognitive processing in young children, general cognitive abilities mediated the impact of cumulative risk on executive function. This is the first exploration to date on the impact of cumulative risk on neurodevelopment in perinatal outcome research taking into consideration the associated developmental variables, for instance, Intelligence in the processing of higher-order thinking (Inhibition, Working Memory, and Flexibility). This global

effects of cumulative risk on the child cognitive development were similar to the findings where language development, self-regulation and emotion processing were largely affected by low SES (Tomalski et al., 2013), and poorer development of executive function in social context (Rhoades et al., 2011).

Cumulative risk accounts for a significant variance in verbal reasoning. However, this direct effect is mediated when working memory is added into the equation. In the estimation of multiple mediator variables, it shows that the effect of processing speed on verbal reasoning is accounted for by working memory. Therefore, this multiple mediation model showed that significant variance can be mediated by the presence of working memory in verbal reasoning. On the other hand, the impact of cumulative risk on non-verbal reasoning is smaller, but the effect of processing speed is not mediated by the presence of working memory. In this model, separate cognitive processes are influential in two types of reasoning, where verbal reasoning is more associated with working memory, and non-verbal reasoning is associated with processing speed. Findings supported literature on the hypothesised longitudinal support of processing speed and working memory on reasoning abilities (Kail, 2007) and quality of neural interconnections between processing speed, executive function and reasoning abilities in young children (Ferrer et al., 2013).

Motor development at 4.5 years is predicted by cumulative risk, but the direct effect is highly mediated when executive function predicts visuomotor processing. Both executive function and visuomotor processing substantially predict motor development; the effect of cumulative risk on motor development is reduced when higher cognitive processes and visual-spatial construction are taken into consideration. This findings supports the future directions of executive function difficulties and accompanying neurocognitive constructs in evaluating development coordination problems or DCD in young children (Bernardi et al., 2016; Leonard et al., 2015; Leonard & Hill, 2015)

STUDY 6: Executive Function and Behavioural Outcomes: The Impact of Cumulative Risk and The Role of Everyday Executive Function at 4.5 years

Introduction

Study 5 supports previous studies about the association of executive function and general intelligence, as well as the strong association of processing speed with observed executive function, especially working memory. Models were tested to justify the hypothesis that cumulative risk may have influenced developmental outcomes in young children. Findings showed that the effects of cumulative risk on reasoning abilities and motor development were mediated by an intervening variable (executive function and/or processing speed). In this study, a similar approach is used to identify the association of cumulative risk on young children's behavioural outcomes at 4.5 years; likewise, whether a similar association can be observed in parent-rated executive function.

Social functioning in the form of communication skills, play, engagement in school activities, and making friends are some of the adaptive processes related to executive function among young children. These activities require higher cognitive processing which are dependent on behaviour regulations and emotion control in order to achieve and maintain smooth interpersonal functioning through efficient expression of emotion, careful responses, and self-monitoring. *Proactive control* of executive function is being able to adjust to social cues and develop efficient coordination of self-control strategies to achieve goals (behavioural responses). It is also related to adaptive function in young children (Chevalier, 2015a). Young children are prone to reactive behaviours owing to immature emotion regulation and inattention to environmental cues (Chevalier, 2015b). This perspective of poor behavioural regulation in young children is supported by previous research (Hughes, White, Sharpen, & Dunn, 2000; Isquith et al., 2004). "Hard-to-manage" children have deficits in inhibitory control (Brophy, Taylor, & Hughes, 2002). Latent modelling of executive function and child problem behaviours among non-referred child-participants reveal four dimensions: hyperactive behaviour, attention problems, disinhibition, and emotional dysregulation (Espy, Sheffield, Wiebe, Clark, & Moehr, 2011).

In atypical groups of children, executive function is associated with attention deficit hyperactivity disorder (ADHD), autism, Tourette and conduct problems. Logical and distinct EF characteristics were observed among individual diagnoses. An EF pattern among child behaviour diagnoses is known as “executive fingerprint” (Ozonoff & Jensen, 1999; Pennington & Ozonoff, 1996), and is supported by a subsequent profiling with the use of parent-rated executive function (BRIEF) (Gioia, Isquith, Kenworthy, & Barton, 2002). A form of externalizing behaviour such as aggression is found related to brain regions responsible for impulse control (orbito-frontal cortex), and attention and planning behaviour (dorsolateral cortex) (Giancola, 1995). Significant change in cognitive flexibility is associated with hostile behaviour, while change in inhibition is sensitive to impulse control behaviour (Hancock, Tapscott, & Hoaken, 2010). Working memory is associated with complex aggression, while inhibition and shifting are related to relational and reactive aggressive type (Granvald & Marciszko, 2016). A type of non-empathic and lack-of-remorse behaviour in young children, known as callous unemotional behaviour (CU) is predictive of aggressive behaviour in middle childhood. Executive function interacted with CU in later aggressive behaviour (Waller, Hyde, & Baskin-Sommers, 2016). Problematic temperament and poor executive function predicted subsequent antisocial behaviour, while quality of executive function moderates the aggressive behaviour in conduct/antisocial features (Giancola, Martin, Tarter, Pelham, & Moss, 1996; Giancola, Mezzich, & Tarter, 1998; Giancola, Roth, & Parrott, 2006). On the other hand, AD/HD symptoms in children are more likely associated with disinhibition (Berlin, Bohlin, & Rydell, 2003; Karalunas & Huang-Pollock, 2011; Martel, Roberts, & Gremillion, 2013; Toplak et al., 2009). Comorbid aggressive behaviour is found associated with hyperactive compared to non-hyperactive type, while inattentive type and poor executive function is related to social adjustment (Diamantopoulou, Rydell, Thorell, & Bohlin, 2007). Both cognitive and emotional aspects of EF are related to the development of AD/HD in children (Martel et al., 2013). Based on the reviewed literature, externalising behaviours are explicitly associated with inhibition problems compared to internalising behaviours. Neural explanation pointed to the unique neurophysiology networks associated with internalising behaviour (Tucker, Poulsen, & Luu, 2015).

In comparison with externalising problems in children, autism behaviour is hypothesised to have a different neural deficit. Therefore, prefrontal cortex insult is not considered a sufficient issue. This is based on several studies pointing out that executive function is only partly responsible for the behaviour (Ozonoff, Pennington, & Rogers, 1991). Most research focused on metacognitive/cognitive flexibility(Didden et al., 2008; Gilotty, Kenworthy, Sirian, Black, & Wagner, 2002; Granader et al., 2014; Leung, Vogan, Powell, Anagnostou, & Taylor, 2016; Liss et al., 2001; Winsler, Abar, Feder, Schunn, & Rubio, 2007) which was shown to be

related to poor social and adaptive functioning, as well as poor verbal fluency among others (Verte, Geurts, Roeyers, Oosterlaan, & Sergeant, 2006; Winsler et al., 2007). Hypothesised sensory deficits, problems with knowledge acquisition and stereotypy are predicted by parent-rated executive function (Kenworthy, Black, Harrison, Rosa, & Wallace, 2009; Mcgonigle-Chalmers & Alderson-Day, 2010).

Associations among cumulative risk (CR) and problem behaviour in children were estimated through a structural model. CR and emotional dysregulation was found higher in children with high emotional negativity and this in turn was reflected in their poor social adjustments (Chang, Shelleby, Cheong, & Shaw, 2012). Familial risks (poor and disadvantaged families) are associated with higher conduct problems (Schonberg & Shaw, 2007), as well as in composite internalising and externalising scores (Trentacosta et al., 2008).

Cumulative risk (person-environment) and executive function skills: inhibitory self-control, emerging metacognition, and flexibility (higher cognitive processing) on child behaviour problems (internalising, externalising, and autism-like behaviour), were estimated in a structural model to support claims. Previous studies showed the mediating role of executive function. For instance, temperament was mediated by executive function in anxiety disorder in children (Affrunti & Woodruff-Borden, 2015), while executive function skill (working memory) mediated the effect of AD/HD symptoms on pre-academic (language and mathematics) development (Sjowall & Thorell, 2014). This thesis aims to test whether executive function mediates the cumulative risk → behavioural outcomes at 4.5 years. The following hypotheses guide the study.

In analysis 1, *Hypothesis 1:* Executive function skills (ISCI, FI, and EMI) predict childhood emotional and behavioural problems at 4.5 years. *Hypothesis 2:* CR has direct and indirect effects on childhood emotional and behavioural problems and these effects are reduced when mediated by executive function skills (ISCI, FI, and EMI).

In analysis 2, *Hypothesis 1:* Executive function skills (ISCI, FI, and EMI) predict childhood autism-like behaviours at 4.5 years. *Hypothesis 2:* CR has direct and indirect effects on childhood autism-like behaviours when mediated (partially) by executive function skills (ISCI, FI, EMI).

Method

CHYLD Data

Data used for these two-part analyses (*n* = 477) were the cumulative risk (2-clustered solution, dichotomous variable), the parent-rated everyday executive function (BRIEF-P) at 4.5 years and a measure of child psychopathology at 54 months: Child Behaviour Checklist (CBCL) and Social Communication Questionnaire (SCQ). In addition, BRIEF-P clinical indices: Inhibitory Self-Control Index (ISCI T score), Emerging Metacognitive Index (EMI T score), and Flexibility Index (FI T score) were utilised to identify micro-skills of everyday executive function, compared to the macro skill (GEC T score). Two clinical syndromes were utilised in CBCL: internalising T score and externalising T score. In SCQ, three behaviour domains were utilised: reciprocal domain, communication domain, and the restrictive/repetitive domain. Detailed descriptions of child-participants recruited for this longitudinal, cohort study is covered at length as well as the psychometric description of each measure mentioned in this study in Chapter 3.

Data Analysis

Similar statistical techniques and principles used in Study 5.

Results and Findings

Cumulative Risk, Parent-rated Executive Function, and Child Problem Behaviours

Analysis 1, *Hypothesis 1:* Executive function skills (ISCI, FI, and EMI) predict childhood emotional and behavioural problems at 4.5 years. *Hypothesis 2:* CR has direct and indirect effects on childhood emotional and behavioural problems and these effects are reduced when mediated by executive function skills (ISCI, FI, and EMI).

Results revealed that cumulative risk (CR) was significantly and moderately associated with parent-rated executive function (BRIEF-P) at 4.5 years and significantly and moderately to strongly associated with childhood emotional and behaviour outcomes at 4.5 years. Initial path analysis (Figure 13) showed that Inhibitory Self Control Index (ISCI) predicted Child Behaviour Checklist subscales (CBCL) for anxious/depressed, sleep problems, attention

problems and aggressive behaviour. Flexibility Index (FI) predicted CBCL subscales for 'emotional/reactive', 'anxious/depressed', somatic complaints and withdrawn. Emergent Metacognitive Index (EMI) predicted CBCL subscale withdrawn. However, this model did not comply with the acceptable fit requirements (x^2/df = 19.60, CFI = .96, RMSEA = .198). After reconceptualization, individual CBCL subscales were replaced with internalising and externalising latent variables. The specified model was identified as more parsimonious (with two latent variables). The model achieved acceptable fitness (x^2/df = .565, CFI = 1.00, RMSEA = .000). ISCI predicted externalising problems (β = .80, p = < .05), while FI (β = *.64, p* = < .05) and EMI (β = *.15, p* = < .05) predicted internalising problem. Cumulative risk (CR) was evaluated whether it would influence childhood problems at 4.5 years.

A mediation model was designed (Figure 14) to identify the direct and indirect effects of CR on childhood problems. Model fitness was achieved (x^2/df = .565, CFI = 1.00, RMSEA = .000). Significantly large predicted values were observed, CR → ISCI (β = *.54, p* = < .05), CR → FI (β = *.48, p* = < .05), and CR → EMI (β = *.56, p* = < .05). The initial direct effects of CR on internalising (β = *.47, p* = < .05) and externalising problems (β = *.50, p* = < .05) were significantly reduced CR → internalising problem (β = *.12, p* = < .05) and CR → externalising problem (β = *.09, p* = < .05) after EF skills (ISCI, FI, and MI) mediated the CR → problem behaviour relationship.

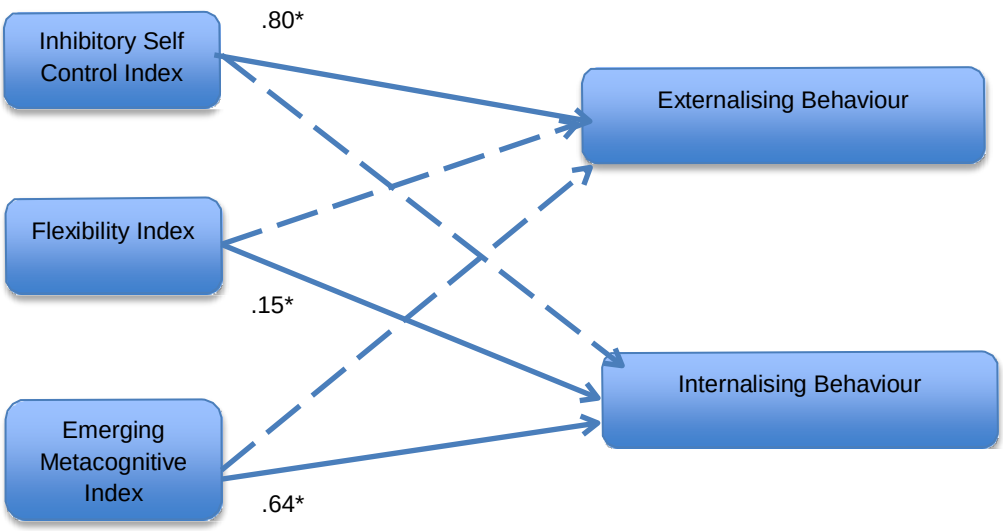

Figure 13: ***Panel Model Estimating Associations between Everyday Executive Function Skills (BRIEF-P Indices) on Child Problem Syndromes (CBCL) at 4.5 Years.***

*Path model results: The significant relationship identified between the three indices of everyday executive function and the child behaviour syndromes (externalising and internalising). Standardized coefficients for Model 2, Observed variables are shown in rectangles. Solid-lines denote significant predictor and dashed lines for not significant predictor, *p < .05.*

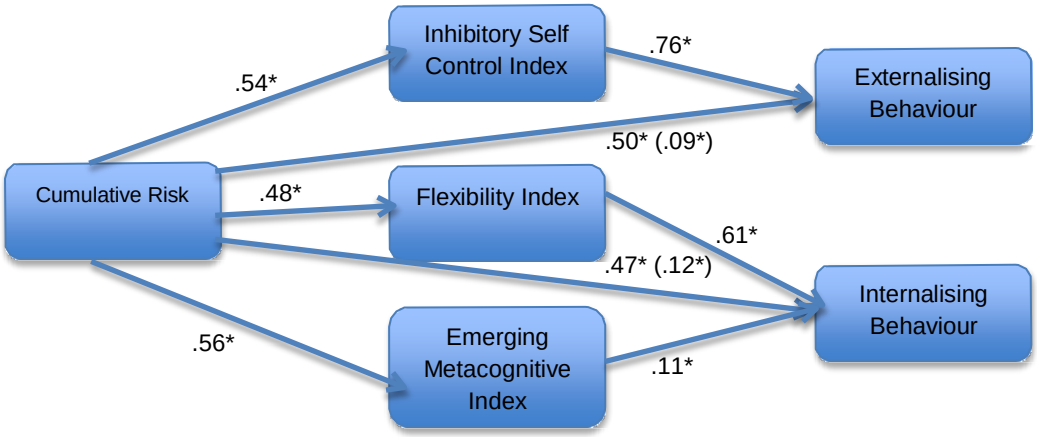

Figure 14: ***Mediation Analysis Estimating the Impact of Cumulative Risk on Indices of***

*Path model: a) cumulative risk significantly predicted outcomes (child behaviour syndromes) and mediating variables (three indices of everyday executive function), b) mediating variable significantly predicted outcome variables and c) effects of cumulative risk on outcomes were reduced. Standardized coefficients for Model 3, Observed variables are shown in rectangles, solid-lines denote significant predictor, and (mediated effect), *p < .05.*

The A path model showed that ISCI only facilitated externalising problems while FI and EMI were associated with internalising problems, which suggested a different Neuro-behavioural network, such that the ability to suppress desires and control oneself were predictive of externalising behaviour (attention problem and aggressive behaviour). The ability to reflect, plan, as well as find alternative solutions to a problem were related to internalising behaviour (emotional/reactive, anxious/depressed). The direct effects of CR on problem behaviours were largely inhibited by executive function. Therefore, interventions should be directed to improving executive function skills, which may help in the reduction of problematic behaviours in children.

Cumulative Risk, Parent-rated Executive Function, and Autism-like Behaviours

Analysis 2, *Hypothesis 1:* Executive function skills (ISCI, FI, and EMI) predict childhood autism-like behaviours at 4.5 years*. Hypothesis 2:* CR has direct and indirect effects on childhood autism-like behaviours when mediated (partially) by executive function skills (ISCI, FI, EMI).

The associations among study variables showed significantly moderate results. CR was moderately associated with executive function skills (ISCI, FI, and EMI) and moderately associated with domains of autism-like behaviours (reciprocal, communication, and restrictive/repetitive) at 4.5 years. Initial path analysis (Figure 15) showed that clinical subscales of BRIEF-P predicted each domain of autism-like behaviours, with FI → Reciprocal domain (β = *.34, p* = < .05) and EMI → Communication domain (β = *.33, p* = < .05) accounting for higher standardised coefficients. This model achieved a desirable model fit (x^2/df = .345, CFI = 1.00, RMSEA = .000). Therefore, executive function skills, compared to the internalising-externalising behaviours, were not the core issue in the domains of autism-like behaviours. In model 2, results revealed that CR contributed to the domains of autism-like behaviours but executive function skills did not fully mediate the direct effects of CR on each domain of autism-like behaviour (Figure 16). This model suggested a good fit (x^2/df = .652, CFI = 1.00, RMSEA = .000). Initial direct effects of CR on autism-like behaviours were modest but significant: CR → Reciprocal domain (β = *.37, p* = < .05), CR → Communication domain (β = *.30, p* = < .05) and CR → Restrictive/Repetitive domain (β = *.45, p* = < .05).

Direct effects of CR on executive function skills were large: CR → ISCI (*β = .54, p* = < .05), CR → FI (*β = .48, p* = < .05), and CR → EMI (*β = .50, p* = < .05). There were reductions of direct effects of CR on autism-like behaviour after executive function skills mediated the relationship (CR → Autism): CR → Reciprocal domain (*β = .25, p* = < .05), CR → Communication domain (*β = .12, p* = < .05) and CR → Restrictive/Repetitive domain (*β = .29, p* = < .05).

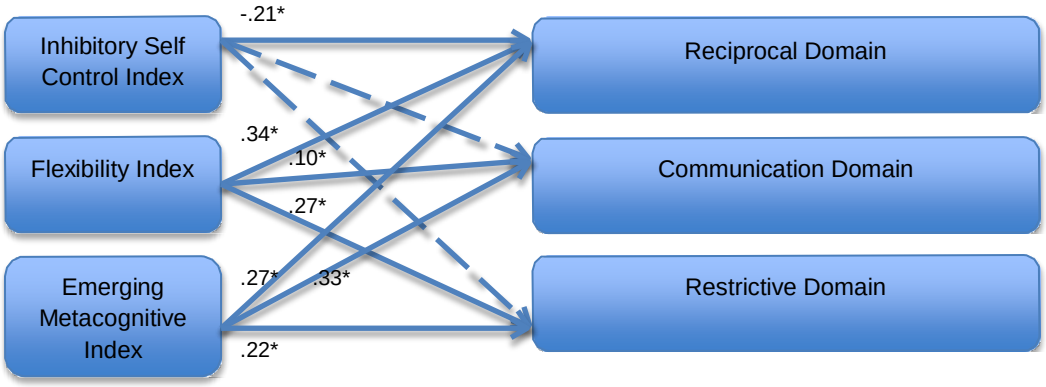

Figure 15: ***Panel Model Estimating Associations between Indices of Everyday Executive Function (BRIEF-P) on Domains of Autistic-like Behaviours (SCQ) at 4.5 Years.***

*Path model results: The significant relationship identified between the three indices of everyday executive function and domains of autistic-like behaviours. Standardized coefficients for Model 2, Observed variables are shown in rectangles. Solid-lines denote significant path and dashed lines for non-significant path, *p < .05.*

The modest impact of CR on stereotypy and social domains did not decrease substantially. Therefore, autism-like behaviour may have had different neural insults compared to common emotional and behaviour problems in young children, although, in part, autism-like behaviours are mediated by executive function skills. In addition, children with autism-like behaviour may require a different intervention, which could tap into different neuropsychological stimulation and be more complicated than common behavioural problems in children. The path model is also suggestive that CR predicted autism-like behaviour but this influence should explore interactions with biological or genetic markers.

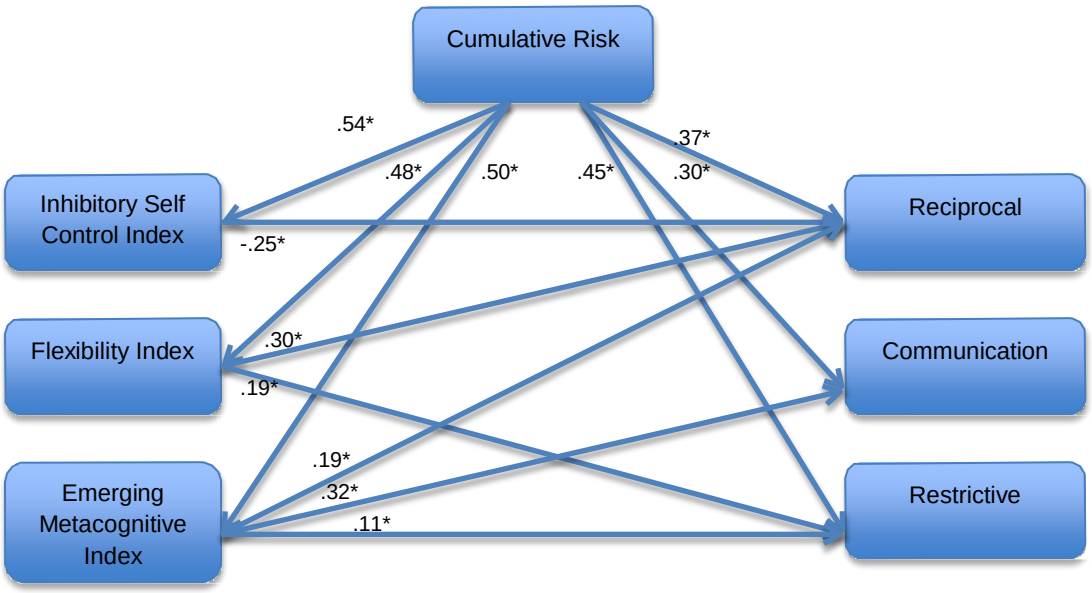

Figure 16: ***Mediation Analysis Estimating the Impact of Cumulative Risk on the Indices of Everyday Executive Function (BRIEF-P) and Domains of Autistic-like Behaviours (SCQ) at 4.5 Years.***

*Path model: a) cumulative risk significantly predicting outcomes (domains of autistic-like behaviours) and three indices of everyday executive function, b) three indices of everyday executive function predicting domains of autistic-like behaviour and c) mediating effect of cumulative risk on outcomes. Standardized coefficients for Model 2, Observed variables are shown in rectangles. Solid-lines denote significant predictor, and (mediated effect), *p < .05.*

Discussion

Previous findings from atypical samples of children are supported by this study. Executive function predicted child problem behaviour at 4.5 years (Cassidy, 2016). However, the association was tenable for inhibitory control and externalising problems, whereas, emergent metacognition and flexibility are linked with internalising problems. These findings suggest an explanation that validates the disinhibition behaviour observed among children with hostile, aggressive and hyperactive tendencies (E. Carlson, Jacobvitz, & Sroufe, 1995; Espy et al., 2011; Utendale, Hubert, Saint-Pierre, & Hastings, 2011). In addition, the association between internalising syndrome and the more reflective and evaluative skills of executive function only

proves that poor problem-solving, the inability to adjust perspectives, and the inability to find solutions are all tenable for emotional problems (e.g., depression, anxiety, withdrawn behaviours) (Feifer & Rattan, 2007). The mediating role of executive function showed that the impact of cumulative risk on the development of child problem behaviours is fully mediated in externalising syndromes but only partially in internalising syndromes. A neurophysiological model suggested that these syndromes may have overlapping but different biological pathways that may tap into different cortical areas of the brain responsible for emotion regulation and control of impulses (Hinshaw, 2003).

Autism-like behaviours in a cohort of at-risk young children were measured and evaluated in a linear structural model to identify strengths of associations between executive function and domains of autism-like behaviours. Results showed that three clinical indices of BRIEF-P predict the reciprocal domain, while inhibitory behaviour has an inverse relation. This means that activation of behaviour through appropriate behavioural response was observed related to executive function. Communication domain was associated with EMI and FI, which suggests that verbal fluency and social behaviour require reflective and evaluative skills. This finding is supported by previous research that has shown that children with autism were associated in these skills and domains (Kenworthy et al., 2009; Ozonoff et al., 1991). Stereotypy (restrictive and repetitive domain) was found sensitive to EMI and FI. Children with autism-like behaviours may have sensory deficits and problems in information acquisition, which are the foundation for appropriate cognitive control. Although speculative at this point, more neural areas responsible for self-monitoring, metacognition, and sensory information processing are problematic for children showing autism-like behaviours (Gilotty et al., 2002). The mediating role of executive function skills appears to only partially mediate the impact of cumulative risk on each autism behaviour domain. These findings also support previous research that executive function is not directly involved in the development and expression of autism-like behaviours (Liss et al., 2001).

CHAPTER 5: GENERAL SYNTHESIS AND IMPLICATIONS

This section presents the summary of the doctoral thesis, and includes main points, support for empirical research, emerging issues as well as suggestions for further research. Furthermore, the research contribution reflects the sequence of studies performed in this thesis. It is hoped that the notion of cumulative risk and its impact on neurodevelopment in young children is substantiated and extends the findings of the CHYLD study.

Synthesis

Cumulative Risk (CR) in the CHYLD Cohort

The present study is the first to use a "person-centred" approach to investigate the neurodevelopment and behaviour of children who had one or more risk factors associated with neonatal hypoglycaemia (IDM, SGA, LGA, and Preterm), in the context of CHYLD study. Theoretically this research was informed by Bronfenbrenner's Bio-ecological theory and Sameroff's Transactional model of development (Bronfenbrenner, 1979; Bronfenbrenner, 1986; Sameroff & Chandler, 1975; Sameroff et al., 1987). Both models emphasise the importance of the context or the environment to development, but also the interactive processes "transactions" that occur between the child and their environment. The statistical design of the study was informed by Evans et al., (2003; 2013), they suggested that aggregate models may be more informative than additive models in studies of children at risk from multiple context and individual risk factors.

The benefits of examining a 5-cluster and 2-cluster solution

Two models were identified that proved to be theoretically and statistically valid, and predictive (associated with) neurodevelopment and behavioural outcomes. The 5-cluster solution served as a descriptive continuum of developmental deficits in subgroups of at-risk children. Group 1 was identified as mostly at-risk, mostly Maori and Pacific, mostly born large, of poorer SES and lower maternal education. Group 3 was identified mostly SGA and poor SES. Group 4 was mostly living in better SES but most likely with neonatal hypoglycaemia, while Group 5 was mostly born large living in better SES. Groups 1, 2 and 3 were the worst group on the continuum. The 5-cluster solution provided a good spread of subgroups where both birth characteristics and primary risks of neonatal hypoglycaemia were evenly distributed. Observed nested interactions between birth risks, primary risks and

sociodemographic data were predictive of developmental outcome. Group 3 was observed consistently poorer in neurodevelopment at 2-years and at 4.5-year follow-up, while group 2 was observed poorer in parent-reports of problem behaviour at 4.5-year follow-up. In comparison, the 2-cluster solution was found more parsimonious and an alternative model to the 5-cluster solution. However, in this solution, only head circumference and SGA were significant primary risks predictive of developmental outcomes along with the 4 domains of cumulative risk (prenatal exposure, long term alcohol use, SGA and ethnicity, maternal education and SES). This solution, however, can be used to classify children according to 'most at-risk' and 'less at-risk' and suitable for further multivariate analysis of the CHYLD data.

This author's research has investigated the use of a 'person-centred approach' in a cohort of children who were at risk of neonatal hypoglycaemia. The study has shown that the clustering of sociodemographic variables, parent substance use, primary risks of neonatal hypoglycaemia and maternal education was an effective strategy in the investigation of neurodevelopment in young children. The 'person- and variable-centred' approaches provided an in depth analysis to perinatal cohort study in the case of CHYLD by providing both substantial information on the "context' and 'correlates' of developmental outcomes in young children.

The results are significant in clarifying three aspects of the study: a) cumulative risk is better indicator than risk additivity, b) the estimation of risk aggregation is dependent on the risk effects, c) a metric approach to risk constellation extends the definition of *cumulative risk as a series of negative events / exposures / deprivations / and restrictions that are interrelated, transactional, and nested. They are either distal or proximal to the child's immediate environment and detrimental to growth and neurodevelopment.*

The At-Risk Children

This research confirms previous findings (Rhoades et al., 2011) and extends the understanding of at-risk young children and their neurodevelopment and self-regulation (Blair, Berry, Mills-Koonce, Granger, & FLP Investigators., 2013; Blair, 2016; Blair & Raver, 2016; Raver, 2012; Raver, Blair, Willoughby, & The Family Life Project Key., 2013; Rhoades et al., 2011) . 'More at-risk' children were observed performing below average in general cognitive

measures and showed tendencies to a wide range of behaviours and deficits: poor hand-eye coordination; reactive response to inhibitory tasks; problems in goal representation necessary to pass rule-based tasks; motor clumsiness; and poor in language development. This was accompanied by a higher frequency of parent-reported problem behaviours including aggressiveness, emotional outburst, hyperactivity, inattention, and autistic-like features. These findings supported research describing neuropsychological abilities of children with below average intelligence (Foley et al., 2009), with disruptive behaviour (Cole, Usher, & Cargo, 1993), with poorer working memory (Alloway, 2010), and with poorer language abilities (Henry, Messer, & Nash, 2012; Pons, Lawson, Harris, & Rosnay, 2003).

Risks predictive of risk status in young children

Although this thesis did not show effects of neonatal hypoglycaemia at 2-year and 4.5- year outcomes, primary risks such as *born small-for-gestation* was considered the main birth risk predictor for neurodevelopment at 2 years and at 4.5 years. These primary risk effects were observed potent among young children who were living in more deprived conditions, of NZ Maori ethnicity, and with mothers having low educational achievement. Poorer socioeconomic status was observed as the foundation for subsequent risk which can be divided into a) *prenatal exposures*, b) *parent long term substance use*, c) *development of primary birth risks*, and d) *social inequalities* (cultural affiliations and lower maternal education). Contrary to expectations, in this doctoral thesis, parent substance use was not hypothesized to correlate with risk status more than primary risks of neonatal hypoglycaemia. Though previous research supported effects of prenatal exposure on neurodevelopment in young children (Burden et al., 2005; Day et al., 1992; Fried & Watkinson, 1988; Fried & Watkinson, 1990; Fried, O'Connell, & Watkison, 1992; Huizink & Mulder, 2006; Linnet et al., 2003; Monuteaux, Blacker, Biederman, Fitzmaurice, & Buka, 2006; Shankaran et al., 2007), studies on postnatal and long term exposure to parent substance use are scarce. These results were in support of the Dunedin longitudinal study on the identification of child risks and the need for immediate early intervention of at-risk young children in New Zealand (Caspi et al., 2016).

This research conforms to several empirical studies on the effect of early environment experience and deprivation on the following aspects of child development:

a) *Neural integrity and early brain development*, for example, the suspected effects of deprived social conditions on the timing of gene expression (Fox, Levitt, & Nelson,

2010), neurophysiological correlates and whole brain architecture (Noble et al., 2012), specifically, prefrontal cortex volume in the left superior frontal gyrus and right anterior cingulate (Lawson et al., 2013), and reduced brain gamma power (Tomalski et al., 2013) which was identified as critical for language development, higher cognitive skills, and emotional processing.

b) *Self-regulation*, for instance, inhibition and externalizing behaviour and poor emotional competence (Garner, Jones, Gaddy, & Rennie, 1997; Hardaway, Wilson, Shaw, & Dishion, 2012), lower cognitive control (Raver et al., 2013) poorer executive skills (Bernier, Carlson, Deschenes, & Matte-Gagne, 2012; Hackman et al., 2014; Hardaway et al., 2012; Sarsour et al., 2011) and poor development of executive function (Rhoades et al., 2011).

c) *Crystallised and fluid intelligence*, for example, poor general cognitive ability (Aran-Filippetti & Minzi, 2012), poor early language development (Fernald et al., 2013), poor preschool language performance (Noble et al., 2005), low verbal fluency test (Ardilla, Rosselli, Matute, & Guajardo, 2005) and difficulties in visual-processing and visuospatial tasks (Noble et al., 2005).

Early Executive Function Development in At-Risk Children

Exposure to poor early environments and social deprivation in at-risk children increases the likelihood of more cognitive errors and poorer task outcomes associated with a compromised neural integrity (Blair, 2016; Booth et al., 2004).

This author's thesis has investigated the configuration of executive function comparing 'less at-risk' children with 'more at-risk' children. The purpose of the research was to determine the trajectory of executive function at 2 years and at 4.5 years, and to estimate whether unitary but interdependent relationships were tenable for at-risk group of children. The results of this thesis are significant in many respects and extend previous research in the following areas:

a) 'Observed executive' function at 2 years and 4.5 years are both *unitary and interdependent* in both 'less at-risk' as well as 'more at-risk' children, which support earlier studies on the unitary and interdependent trajectory of executive function skills in young, typically developing children (P. Anderson, 2002; Lehto et al., 2003; Wiebe,

Espy, & Charak, 2008; Wiebe et al., 2011). Moderate correlations among tasks administered at the two time points show that there are *stable age-related changes* in the quality of executive function in the preschool years (Davidson, Amso, Anderson, & Diamond, 2006; Garon, Bryson, & Smith, 2008; Klenberg, Korkman, & Lahti-Nuutila, 2001; McGuigan & Nunez, 2006; Riggs, Blair, & Greenberg, 2003; Stuss, 1992).

b) 'Parent-rated' executive function skills at 2 years are different from 4.5 years, when a similar measure (BRIEF-P) was administered to both 'less at-risk' and 'more at-risk' children. This is the first study to date that looked at the variance between scores of the same measure at two time points in CHYLD cohort. This extends the literature on age-related factors in the assessment of everyday executive function but in the context of parent perception of child development. It also supports earlier studies on *maternal expectations* of normal development in children (Murphey, 1992; Pachter & Dworkin, 1997), and *parent beliefs* and child thinking (S. Miller, 1988; Ninio, 1988). However, high inter-item correlations show that behavioural manifestations of executive function at 2 years predict EF manifestations at 4.5 years.

c) The 3-factor structure (ISCI, EMI, and FI) of BRIEF-P at 2 years and 4.5 years among at-risk children supported the original BRIEF-P framework among typically developing children and diagnosed children (Isquith et al., 2004; Isquith, Crawford, Espy, & Gioia, 2005).

d) 'More at-risk' children have more errors in inhibiting prepotent responses at 2 years and poorer cognitive flexibility at 4.5 years in observed tasks, and more parent-endorsed problems in inhibitory self-control at 2 years and 4.5 years. This is the first study to date to identify longitudinal deficits of children with risk related to neonatal hypoglycaemia in two measures of executive function. These results support previous studies on the continuity of self- regulatory deficits in the childhood years (Feifer & Rattan, 2007).

e) *Observed* (more cognitive) and *parent-rated* (more behavioural) measure of executive function appraise different but important neuropsychological facets of young children, and are complementary to other child measures. This observation adheres to the views of several researchers looking at the holistic function and trajectory of executive function in clinical and non-clinical groups of children (V. Anderson, 1998; Espy et al., 2011; Isquith et al., 2005; Silver, 2014).

Neurocognition in At-Risk Children

This thesis has shown that discrete cognitive structures such as intelligence and executive function are strongly related at 4.5 years. No evidence of severe neurodevelopmental impairment was seen among at-risk children, however *scant traces of developmental deficits* were observed based on the results of group comparisons and typology of children.

Theoretical models of cognitive structures for at-risk children were found tenable in this study and supported previous studies:

a) *Intelligence and executive function* (Brydges, Reid, Fox, & Anderson, 2012; Davis et al., 2011; Friedman et al., 2006; Nisbett et al., 2012; Salthouse, 2005).

b) *Processing speed, working memory and intelligence* (Cepeda et al., 2013; Ferguson & Bowey, 2005; Fry & Hale, 1996; Fry & Hale, 2000; McAuley & White, 2011; L. Miller & Vernon, 1997; Rijsdijk, Vernon, & Boomsma, 1998; Rose et al., 2011; Walhovd et al., 2005; Weiler, Forbes, Kirkwood, & Waber, 2003).

c) *Processing speed, executive function, and reasoning abilities* (Ferrer et al., 2013; Kail, 2007; Luwel et al., 2013; Richland & Burchinal, 2013).

d) *Executive function and motor development* (Bernardi et al., 2016; Hartman et al., 2010; Hocking et al., 2013; Leonard & Hill, 2015; Leonard et al., 2015; Michel et al., 2011; Ozonoff et al., 2008).

Important findings to emerge in this study are: a) *executive function is strongly related but different to intelligence*, b) *executive function mediates effects of cumulative risk on verbal reasoning*, c) *processing speed mediates effects of cumulative risk on non-verbal reasoning*, and d) *executive function mediates the effects of cumulative risk on motor development*. These results extend the literature on cognitive development, by estimating causal relations of cognitive skills (EF, visuomotor, and motor) in an at-risk but undiagnosed cohort of young children.

Overall, the effect of cumulative risk is considered diffuse and globalised rather than domain-specific. However, *these effects compromise the global efficiency of the neural system.* These neural connections represented by child performance in measures of cognitive abilities and executive function domains are weakened due to the detrimental effects of cumulative risk. Processing speed and executive function serve as protective factors (mediators) to lessen the whole-brain effect of cumulative risk.

Neurobehaviour in At-Risk Children

This thesis adds to the body of knowledge around the association between everyday executive function and child socioemotional adjustments. The present study has investigated behavioural correlates of executive functions skills, and evaluated the mediating role of executive function in cumulative risk and problem behaviour relationship. Results support the relationship between executive function and social adjustments from heterogeneous samples of healthy children (Cassidy, 2016). Problem behaviours can be less severe but still prevalent among 'more at-risk' young children.

Statistical panel models show that everyday executive function predicts behavioural adjustments at 4.5 years. However, behavioural syndromes (internalising, externalising, autistic-like behaviours) correlate differently among executive function skills (inhibitory self-control, flexibility, and emerging metacognition). The following associations found in this thesis support previous studies:

a) *Inhibition and externalising behaviour (Aggression, Hostile, Attention, Callous-Unemotional, Conduct)* (E. Carlson et al., 1995; Espy et al., 2011; Ozonoff & Jensen, 1999; Riccio, Hewitt, & Blake, 2011; Seguin, Parent, Tremblay, & Zelazo, 2009; Silverman & Ragusa, 1992; Utendale et al., 2011)

b) *Early environment, self-regulation and internalising behaviour* (Feifer & Rattan, 2007; Southam-Gerow & Kendall, 2002; Vuontela et al., 2013)

c) *Executive function and Autism-like behaviour* (Gilotty et al., 2002; Gioia et al., 2002; Granader et al., 2014; Kenworthy et al., 2009; Landa & Goldberg, 2005; Xiao et al., 2012)

d) *Compensatory role of executive function skills in at-risk young children* (McClelland, Leve, & Pears, 2016; Raver, 2012).

Important findings that emerge in this thesis are: *a) parent-rated measure of everyday executive function is associated with preschool problem behaviours b) Inhibitory skill is associated with externalising problem, whereas c) flexibility and metacognition are related to internalising problem, d) EF skills are protective factors in decreasing the impact of cumulative risk in the development of child problem behaviours. However, e) executive function skills are found not to be the core cognitive construct responsible for autism behaviour.* These results extend the literature based on the hypothesised different neural pathways in the development of externalising and internalising behaviour, and the complexity of autism behaviour.

In conclusion, 'real-life' manifestation of executive function mediates the ongoing transaction between the environment and child well-being. Therefore, executive function to some extent is responsible for the modulation of behavioural symptoms dependent on the detrimental effects of early environment deprivation and exposures.

Research strengths and limitations

One of the strengths of this body of research is that it was based on well-validated models of early child development (Bronfenbrenner, 1979; Bronfenbrenner, 1986; Sameroff & Chandler, 1975; Sameroff et al., 1987) and presented an integrated 'person-centred' and 'variable-centred' approach to examining the neurodevelopmental and behavioural outcomes of young children with multiple risks. Therefore both 'context' and 'correlates' of neurodevelopment were explored. Second, using the combined data from the 2-year and 4.5-year follow-up mean developmental change across early childhood could be examined and any progress or regress and their related mechanisms could be determined. In addition, this is the first doctoral thesis to estimate the effect of cumulative risk in the CHYLD study, looking at the impact of aggregated risks on neurodevelopment in children from toddlerhood to early childhood.

However, a number of limitations need to be considered. The following limitations were observed and appropriate steps and strategies in handling and interpreting the data were cautiously applied: the CHYLD study did not have a control group and a disproportionate number of the children in the study were Maori, therefore, as a whole the sample was not representative of the general NZ population. This means these results may not be generalizable. The examiner administered tests for executive function at the 2-year and at 4.5-year follow-up were not similar. This is a common limitation identified by developmental psychologists for the lack of EF measures which can be administered among toddlers and preschool children. Some limitations were also observed on the scale of data and the lack of multi-informant variables to compare reliability of parent reports, this doctoral thesis did not employ continuous data to represent primary risk factor for neonatal hypoglycaemia. Dichotomous variables (yes/no) were used as the only available data for the study. There is the tendency to lose a significant amount of statistical value from the use of dichotomous data compared to continuous data. In addition the blood glucose values data which may have further informed our profiles was not available to this doctoral candidate. Lastly, interactions among environmental risk variables did not show any associations with neonatal hypoglycaemia and found that dichotomous variable is not a good alternative for continuous data.

Implications and recommendations

Based on the above-mentioned synthesis, this doctoral thesis extends the literature in developmental science specifically through the investigation of a large, funded cohort of at-risk children (CHYLD study); however, further research is suggested in order to understand the complexity of cognitive development and its association with social adjustments in the CHYLD cohort. Future doctoral students, developmental researchers and clinicians can extend the present findings guided by the following themes:

- ***Follow-up assessment and evaluation of academic achievement*** at middle school. This doctoral work shows that 'more at-risk' preschool children are prone to cognitive and behavioural problems, therefore, it is hypothesised that pre-academic achievement in literacy, reading comprehension and numeracy could be impacted by the cumulative risk. Therefore, this study may inform future research and statistical design of the CHYLD study cohort.

- ***Brain imaging of at-risk children***, and comparison of cortical volumes of CHYLD cohort against children with mild traumatic brain injury. Findings from this doctoral

thesis suggest subtle deficits that can be located in different parts of the neural system. Therefore, an imaging study could answer some hypotheses regarding the impact of long-term deprivation on the child's brain and its similarities to children withmild traumatic brain injuries (TBI). Although it is known that TBI has a specific focal brain insult, the question is whether the manifestations of cognitive deficits and behavioural problems are similar to children from a deprived background. This study may inform developmental paediatricians and child neuropsychologists of the neural effects of cumulative risks on young children. Another reason why CHYLD cohort needs to compare with mTBI cohort is to identify whether neurochemical deficits is similar to the physical insult to the brain, when factors such as environment, ethnicity, and related risks are present

- ***Risk mobility analysis*** can ascertain whether children from the CHYLD cohort who gained positive social experience and higher in household income show improvement in cognitive performance. This can be done through statistical modeling of risk mobility from several time points. The result of this study may guide social analysts regarding measurement of child poverty and adversity prediction in child development.

- Executive function mediates both cognitive and behavioural processes, therefore identification of an ***early childhood curriculum*** sensitive to executive function growth, as well as ***development of tools or technologies*** are both highly recommended. Along with this suggestion is the ***identification of developmental skills*** or strategies needed in order to successfully pass executive function tasks. This study may inform teachers, curriculum developers and developmental psychologists of the contribution of each profession to provide evidence-based educational interventions and a developmentally appropriate curriculum for at-risk group in the CHYLD cohort.

- ***Development of executive function measures*** that are both reliable and ecologically valid measures of 'cognitive' and 'behavioural' aspects of self-regulation and is sensitive to the manifestations of cognitive errors and behavioural symptoms in young children. This study will greatly help both child psychologists and educators to determine specific EF skills needing intervention specially among groups with poorer EF in the CHYLD cohort

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