CHILDHOOD COGNITION & ADULT OUTCOMES OF ELBW SURVIVORS

THE INFLUENCE OF CHILDHOOD COGNITION ON ADULT HEALTH AND SOCIOECONOMIC OUTCOMES IN EXTREMELY LOW BIRTH WEIGHT SURVIVORS

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TITLE: The Influence of Childhood Cognitive Abilities on Adult Health and Socioeconomic Outcomes in Extremely Low Birth Weight Survivors

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LAY ABSTRACT

The following thesis explores the predictive role of childhood cognitive abilities on adult health and socioeconomic outcomes in extremely low birth weight survivors at age 29-36. Study 1 explores the influence of overall intelligence, fluid intelligence, and language abilities assessed at age 8 on the prevalence of lifetime major depressive disorder in extremely low birth weight survivors and normal birth weight comparison participants. Study 2 examines the mediating role of overall intelligence, fluid intelligence, language abilities, quantitative reasoning, and academic achievement on the association between being born at extremely low birth weight and socioeconomic outcomes at age 29-36. The final study examines the moderating role of childhood cognition on the association between postnatal psychosocial adversity and personal income attainment at age 30 in extremely low birth weight survivors. Overall, this body of work suggests that childhood cognitive abilities are an important contributor to adult outcomes in preterm survivors.

ABSTRACT

Objectives: The purpose of this thesis is to explore the associations between childhood cognitive abilities assessed at age 8 and health and socioeconomic outcomes at age 29-36 in extremely low birth weight survivors (ELBW, <1000g).

Methods: Using data from the *McMaster Extremely Low Birth Weight Cohort Study*, Study 1 explores the influence of overall intelligence, fluid intelligence, and language abilities on the prevalence of lifetime major depressive disorder in ELBW survivors and normal birth weight comparison subjects. Study 2 examines the mediating role of overall intelligence, fluid intelligence, language abilities, quantitative reasoning, and academic achievement on the association between being born at ELBW and socioeconomic outcomes at age 29-36. The final study examines the moderating role of childhood cognitive functioning on links between postnatal psychosocial adversity and adult personal earnings in ELBW survivors.

Results: Results from Study 1 suggest that childhood cognitive abilities do not influence the onset of major depressive disorder in ELBW survivors, but are protective against depression in normal birth weight individuals. Study 2 suggests that childhood cognitive abilities partially mediate the association between being born at ELBW and income attainment in adulthood, but not full time employment. Further, Study 2 suggests that this association is stronger in ELBW survivors who have neurosensory impairments. Results of Study 3 suggest that enhanced childhood cognitive functioning is not protective against postnatal psychological adversity in influencing income attainment, as those

ELBW survivors with *higher* childhood intelligence and who suffered psychological adversity reported *lower* annual income at age 30.

Conclusions: This thesis suggests that overall and specific cognitive abilities significantly influence adult outcomes in ELBW survivors and normal birth weight individuals. However, while cognitive reserve may not be protective against psychological adversity in ELBW survivors, early cognitive abilities are a critical indicator of socioeconomic attainment in this vulnerable population.

Keywords: extremely low birth weight, cognition, cognitive reserve, cognitive abilities, IQ, depression, mental health, income, socioeconomic attainment

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LIST OF ABBREVIATIONS AND SYMBOLS

α: alpha
a: pathway between independent variable and mediator
ab: indirect effect
ADD: attention deficit disorder
AGA: average for gestational age
β: unstandardized regression coefficient
b: pathway between mediator and dependent variable
c': direct effect
c: total effect
CSA: childhood sexual abuse
DOHaD: developmental origins of health and disease
DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
ELBW: extremely low birth weight (<1,000g)
EPI: Eysenck Personality Inventory
HPA: hypothalamic-pituitary-axis
g: general intelligence
IQ: intelligence quotient
Κ: Kappa
M: mean
MINI: Mini International Neuropsychiatric Interview
N or n: number of participants
NBW: normal birth weight (≥2,500g)
NICU: neonatal intensive care unit
NSI: neurosensory impairment
OR: odds ratio
p: probability
R^2: coefficient of determination
SD: standard deviation
SE: standard error
SES: socioeconomic status
SGA: small for gestational age
SPSS: Statistical Package for the Social Sciences
VLBW: very low birth weight (<1,500g)
WISC-R: Wechsler Intelligence Scale for Children Revised
WJ: Woodcock-Johnson Psychoeducational Battery
WRAT-R: Wide Range Achievement Test Revised
95% CI: 95% confidence interval

DECLARATION OF ACADEMIC ACHIEVEMENT

This "sandwich" thesis consists of three studies conceived of and written by the student. She developed their premises, objectives, hypotheses, conducted their data analyses, and prepared the chapters in keeping with suggestions of her supervisory committee and co-authors. All of this work was completed between September 2014 and June 2016. As such, the work herein adequately meets the requirements for inclusion in the main text of this thesis. As per the requirements of a "sandwich" thesis, the following highlights the contributions made to each study by my co-authors.

Study 1 examined the association between childhood cognition and lifetime major depression disorder in extremely low birth weight survivors and normal birth weight comparisons from Ontario, Canada. It was co-authored by my thesis supervisor, Dr. Ryan Van Lieshout, as well as Drs. Louis Schmidt, Michael Boyle, and Saroj Saigal. Drs. Schmidt and Saigal were the principal investigators who collected the data on mental health of the cohort. All co-authors critically reviewed the manuscript and made suggestions to improve it prior to submission for publication.

Study 2 examined the mediating role of childhood cognitive function and socioeconomic attainment (defined by personal income attainment and full time employment) in the same cohort as Study 1. This study was co-authored by my supervisory committee Drs. Ryan Van Lieshout, Michael Boyle, Mark Ferro who provided critical review of the manuscript, as well as the principal investigators of the study Drs. Louis Schmidt and Saroj Saigal.

Study 3 examined the moderating influence of cognitive reserve (defined by childhood IQ) on the association between psychosocial adversity and income attainment in extremely low birth weight survivors. Again, this study used the data of extremely low birth weight survivors that was collected by Drs. Louis Schmidt and Saroj Saigal and therefore they are co-authors on this study. As my thesis supervisory committee, Drs. Van Lieshout, Boyle, and Ferro, provided critical guidance of the theoretical and statistical aspects of the paper, they are also co-authors on this work.

CHAPTER ONE

BACKGROUND

When does an individual's health begin? This question underpins clinical and public health practice and guides epidemiological research examining the determinants and distribution of health in general and vulnerable populations. Many clinicians and epidemiologists argue that our health begins before we are even born. The idea that health and risk of chronic illness may have genetic heritability and be passed along generations has been studied by biologists, physicians, and ecologists for centuries (Gluckman, Hanson, & Buklijas, 2010). However, in recent decades by studying not only the genetic heritability of disease, but the influence of perinatal environments has this question gained traction in human populations, owing to work done by scientists who study the developmental origins of health and disease (DOHaD). The DOHaD hypothesis posits that environmental exposures in pre- and early postnatal life can have implications for an individual's health and risk of disease across the lifespan.

Overview of the Developmental Origins of Health and Disease Framework

In the 1930s, scientists examining British and Swedish mortality data hypothesized that poor childhood conditions may be a predictor of later mortality (Kermack, McKendrick, & McKinlay, 1934). During the 1970s and 1980s, research began to suggest that lower birth weight, maternal metabolic state in pregnancy, and poor socioeconomic and environmental conditions in early postnatal life influenced the risk of cardiovascular disorders in adulthood (e.g., Forsdahl, 1977; Freinkel, 1980; Notkola, Punsar, Karvonen, & Haapakoski, 1985; Wadsworth, Cripps, Midwinter, & Colley,

1985). In the late 1980s, a landmark study conducted by Barker and Osmond showed that the areas of England and Wales with the highest rates of neonatal and post neonatal mortality in 1921-1925 also had the highest rates of cardiovascular disease in later decades (Barker & Osmond, 1986). This finding was hypothesized to be a result of the poor neonatal and early life nutrition these individuals were exposed to in-utero (Barker & Osmond, 1986). These studies sparked the idea that adversity faced in prenatal and early postnatal life (particularly relating to nutrition) may result in permanent physiological challenges and negatively influence an individual's later health status (Barker, 2004; De Boo & Harding, 2006).

To explain this association, the *thrifty phenotype hypothesis* was put forward by Barker and Hales. This hypothesis suggested that if a fetus is faced with challenging *in utero* circumstances, it may sacrifice normal growth for survival, which may have adverse health consequences in later life (Hales & Barker, 1992). However, the *thrifty phenotype hypothesis* was scrutinized by some as it did not properly account for confounding factors, which when adjusted for in later studies failed to support the hypothesis (Gluckman et al., 2010; Huxley, Neil, & Collins, 2002). In particular, Barker and Hales' original hypothesis did not account for socioeconomic and environmental factors which may have influenced the pregnancy before conception, nor did it consider the combined influence of pre- and postnatal biopsychosocial factors (Gluckman et al., 2010).

After highlighting the limitations in Barker and Hale's hypothesis, the DOHaD field was shifted by Bateson, Gluckman, and Hanson who proposed that *developmental*

plasticity may be operative in the prediction of later health and risk of disease. Developmental plasticity refers to how the development of an organism is influenced by their environment (Bateson, 2001; Bateson et al., 2004; Gluckman, Hanson, Cooper, & Thornburg, 2008). Within the DOHaD context, pre- and postnatal insults up to the third year of life may lead an individual to negatively adjust their development of specific organs and physiological processes to attempt to adapt to their environment (Gluckman et al., 2010). Adapting to these early adversities may result in immediate and later effects on health trajectories (Gluckman et al., 2010). According to Gluckman and Hanson (2004, 2010), early life insults can have *immediate* effects, as are seen with those that are so severe that they lead to immediate developmental consequences, and/or *predictive*, insults that would guide the trajectory of development through later epochs and may ultimately lead to chronic disease.

When an insult (also referred to as a stressor) occurs in prenatal life, it is thought to alter the cellular development and the epigenotype of an infant, "programming" their increased health risk in later life (Entringer, Buss, & Wadhwa, 2015; Gluckman et al., 2010). One of the most studied mechanisms of prenatal programming posits that poor nutrition or maternal stress during pregnancy elicits physiological responses in the mother which are then passed through the placenta to the fetus (Fowden, Forhead, Coan, & Burton, 2008). When these pass across the placenta, the fetus is exposed to physiological stress biomarkers and their development may be altered, potentially resulting in both immediate developmental impairments and greater risk of disease in later life. For example, when a mother faces stress during pregnancy (particularly during

the first trimester) a common response is for her to produce the stress hormone cortisol (Glover, 2015). This excess cortisol is thought to then be passed across the placenta where it can negatively affect the development of the fetus' hypothalamic-pituitary-adrenal (HPA) axis (Glover, 2015). The HPA axis is a part of the brain that is associated with neuroendocrine system functioning and regulating responses to stress (Glover, O'Connor, & O'Donnell, 2010). An altered HPA axis may predispose an individual to physiological vulnerability to stressors in later life which can increase their susceptibility to disease. It has also been hypothesized that maternal stress occurring in pregnancy may lead to higher levels of pro-inflammatory cytokines that may cross the placenta and further negatively affect the neurodevelopment of the fetus (Glover, 2015).

These intrauterine physiological insults *and* the environmental stressors that an infant may face in the first few years of its life are thought to have the potential to cause epigenetic changes in the individual (Gluckman et al., 2010). For example, exposure to adverse biological or environmental stressors may induce epigenetic changes that include DNA methylation, RNA repression or activation, or histone modifications, which in turn alter how genes are expressed (Bale, 2011). These alterations can then result in downstream phenotypic changes in organ structure and function including in the central nervous system (Cartier, Zeng, & Drake, 2016; Martino & Prescott, 2011; Vo & Hardy, 2012). This can result in cognitive, social, and behavioural changes that may predispose them to disease later in life (Entringer et al., 2015; Monk, Spicer, & Champagne, 2012). Due to the negative biological, physiological, and behavioural outcomes associated with

these early life stressors, it is important to understand how these can affect an individual's development so that interventions can be applied in early life to mitigate risk.

Low Birth Weight as a Proxy of Perinatal Adversity

The ability to study developmental plasticity and later health outcomes in a DOHaD framework is dependent on having a measure of in-utero or early life environmental insults. One of the most studied proxies of intrauterine adversity in humans is low birth weight (<2,500g). Of the 132,882,000 infants born worldwide each year, approximately 17% will be born at a low birth weight (United Nations Children's Fund and World Health Organization, 2004). Low birth weight is thought to be the result of shortened gestational duration/ preterm birth or intrauterine growth restriction. Birth weight is thought to be influenced by a combination of genetic, biological, psychological, and socioenvironmental factors (Kramer, 1987; Valero De Bernabé et al., 2004). Maternal exposures are the most prominent risk factors for low birth weight and include smoking, poor nutrition, very young or old reproductive age, presence of a chronic illness or psychiatric disorder, and socioeconomic disadvantage (Ashdown-Lambert, 2005; Valero De Bernabé et al., 2004).

Extremely Low Birth Weight Survivors: The Most Vulnerable Infants

Despite advances in neonatal care, low birth weight is still one of the world's most significant contributors to neonatal morbidity and mortality (Behrman & Butler, 2007; Martin, Kochanek, Strobino, Guyer, & MacDorman, 2005). The association between birth weight and adverse outcomes later in life is thought to follow a gradient effect: the lower the birth weight, the worse the outcome. The most vulnerable and

smallest low birth weight infants are those born at extremely low birth weight. Extremely low birth weight (ELBW) is defined as a birth weight less than 1,000 grams or 2.2 lbs (United Nations Children's Fund and World Health Organization, 2004). Of the 381,869 live births in Canada in 2012, 380 babies were born less than 500 g and 3,799 babies were born between 500 and 1,499 g (Statistics Canada, 2016). Although ELBW babies account for a relatively small proportion of all live births, they contribute the most to neonatal health care costs. On average, an infant without complications will spend 2 days in hospital, costing the health care system $600; in contrast, an ELBW infant will spend 13 days in the hospital, costing approximately $15,100 (Russell et al., 2007). Due to advances in neonatal care, such as the introduction of neonatal corticosteroids and surfactant, the mortality of ELBW infants is declining (Hamilton et al., 2007). However, the incidence of babies born at ELBW is not (Hamilton, Martin, Osterman, Curtin, & Mathews, 2015), and so it is important to understand how ELBW influences later health and development. Further, studying ELBW survivors may have implications for other, less vulnerable infants. Research findings from this small group of infants usually are generalizable to very low birth weight (VLBW, <1,500 g), low birth weight, preterm (born before 36 weeks gestational age), or even in some instances normal birth weight populations.

Over the past three decades, studies have explored the physical and psychological differences between ELBW survivors and normal birth weight (NBW, ≥2,500g) individuals. The majority of this research has focused on differences in childhood and adolescence. Indeed, in childhood (ages 5-12) ELBW survivors have been seen to have

higher rates of asthma and neurosensory impairments such as blindness, deafness, and cerebral palsy (Hack et al., 2005; Patel, Flisher, Hetrick, & McGorry, 2007). Pulmonary issues such as bronchopulmonary dysplasia are also common among ELBW and VLBW infants; it has been suggested that up to 40% of ELBW survivors suffer from bronchopulmonary dysplasia (Darlow, Cust, & Donoghue, 2003; Saigal & Doyle, 2008). A recent meta-analysis exploring the association between ELBW and later psychopathology suggests that ELBW children exhibit more externalizing behaviours, internalizing behaviours, and attention deficit disorder (ADD) symptoms than NBW children (Mathewson et al., 2016).

Extremely low birth weight survivors also continue to have higher rates of ill-heath and impairment in adolescence (ages 13-17). Generally, ELBW survivors have shorter stature and lower body weight during this developmental epoch (Ford, Doyle, Davis, & Callanan, 2000; Saigal et al., 2001; Saigal & Doyle, 2008). During this time ELBW survivors may have similar rates of allergies, asthma, or cardiac issues as those born at NBW, but are more likely to have multiple conditions compared to NBW teens (Saigal et al., 2001). During adolescence, parents of ELBW survivors report that their children have higher levels of ADD and internalizing problems (Mathewson et al., 2016). Further, this developmental era is also where clumsiness, shyness, and social problems begin to be recognized in ELBW survivors (Saigal et al., 2001).

As the first generations of ELBW infants are now surviving into adulthood, evidence is beginning to accrue suggesting that the physical and mental problems seen in childhood and adolescence persist. It has been reported that adult ELBW survivors are at

increased risk of cardiovascular problems (such as hypertension and type 2 diabetes mellitus), asthma, and impaired pulmonary functioning compared to their NBW counterparts (Doyle & Anderson, 2010; Kajantie & Hovi, 2014). Further, evidence suggests that ELBW survivors may have higher levels of anxiety and depressive disorders and lower levels of substance-related disorders compared to NBW individuals (Boyle et al., 2011; Van Lieshout, Boyle, Saigal, Morrison, & Schmidt, 2015). It has been reported that the impaired motor coordination and shyness seen in ELBW survivors during earlier developmental epochs also persist into the third and fourth decades of life (Poole et al., 2015; Schmidt, Miskovic, Boyle, & Saigal, 2008). Lastly, literature is beginning to explore socioeconomic outcomes (i.e., income, education, occupational attainment) in ELBW survivors. Evidence suggests that ELBW survivors may have poorer socioeconomic outcomes, including less full time employment and lower incomes in their early to mid-30s, compared to their NBW contemporaries (Saigal et al., 2016).

Cognitive Function of Extremely Low Birth Weight Survivors

One of the greatest challenges that ELBW survivors face are impairments in cognitive functioning. Cognition, defined as the mental functions that influence the organization, storage, and manipulation of information (Deary & Batty, 2007), is a critical factor influencing our health and socioeconomic attainment as it affects our behaviours and how we perceive and interact with the world around us. Cognitive abilities are often conceptualized as consisting of three types of intelligence: general intelligence, fluid intelligence, and crystallised intelligence. General intelligence (*g*) is thought to comprise all of our cognitive abilities and encompasses the ability to learn,

reason, problem solve, and think abstractly (Deary & Batty, 2007). Crystallized intelligence comprises our cognitive abilities that are used in solidifying knowledge, such as our memory and language abilities (Cattell, 1963). In comparison, fluid intelligence comprises the cognitive abilities associated with abstract reasoning, problem solving, information processing, and executive functions (Cattell, 1963; Deary & Batty, 2007).

Over the past 25 years, multiple studies and reviews have provided evidence that ELBW survivors are at increased risk of impairments in general, fluid, and crystallized cognitive abilities (Bhutta, Cleves, Casey, Cradock, & Anand, 2002; Jarjour, 2015; Saigal, Szatmari, Rosenbaum, Campbell, & King, 1991). A recent review of the neurodevelopmental outcomes of ELBW infants suggested that between 5-36% of ELBW infants will be affected by intellectual disability (Jarjour, 2015). A study of Australian ELBW survivors born in the early 1990s showed that ELBW survivors scored approximately 6-10 points lower on tests of overall intelligence (IQ), as well as having impaired performance on verbal comprehension, processing speed, reading, and mathematics at age 8 compared to their NBW counterparts (Anderson, Doyle, & The Victorian Infant Collaborative Study Group, 2003). Similar trends were seen in a cohort of Canadian ELBW survivors born in the late 1970s and early 1980s (Saigal et al., 1991). Further, evidence suggests that the association between ELBW and cognitive difficulties may persist into adulthood (Aarnoudse-Moens, Weisglas-Kuperus, van Goudoever, & Oosterlaan, 2009; Eryigit Madzwamuse, Baumann, Jaekel, Bartmann, & Wolke, 2015; Vohr et al., 2000).

Although the mechanisms that link ELBW to intellectual impairments are complex, research suggests that this is due to a combination of fetal and early postnatal adversities and their accompanying brain changes. ELBW survivors are known to be at greater risk of periventricular leukomalacia, a form of white matter injury thought to affect the thalamus, basal ganglia, cerebral cortex, and cerebellum regions of the brain (Volpe, 2009). This white matter injury is thought to affect neurological function, including synapse formation, myelination, maturation of brain cells, and the development of cell membrane ion channels (Jarjour, 2015; Volpe, 2009). Further, compared to those born at NBW, ELBW survivors may have decreased frontal and parietal lobe size due to their shortened gestational duration (Jarjour, 2015; Smith et al., 2011).

It also thought that some maternal risk factors during pregnancy that are linked to low birth weight may also be associated with impaired cognitive abilities in their offspring. For example, a study exploring the predictors of developmental delay in preschool children who were born at low birth weight or preterm found that childhood IQ was most strongly associated with poverty level (Msall, Bier, Lagasse, Tremont, & Lester, 1998). It has also been suggested that the myriad social and behavioural adversities associated with poverty during pregnancy (e.g., smoking, crowded household, low income, low educational attainment, drug use, etc.) may also contribute to the lower cognitive scores seen in ELBW children (Gilman, Gardener, & Buka, 2008).

Lastly, literature suggests that cognitive impairments in ELBW survivors may be a result of biological and environmental adversities faced in neonatal intensive care units (NICU). Due to their vulnerable state at birth, the majority of ELBW survivors will spend

time in the NICU. In these units, ELBW or extremely premature infants may be at risk for suffering neonatal seizures which has lasting consequences for their mental abilities (Smith et al., 2011). Further, the stress of medical interventions may have lasting effects on cognitive function. In a study conducted by Smith et al. (2011) that examined the association between neonatal stress associated with NICU treatments (e.g., IV insertions, intubation, pneumothorax chest drain, eye examination, surgery, heel pricks, etc.) and neurological outcomes in preterm infants, higher neonatal stress was correlated with cerebral hemorrhage, reduced white matter, and transcerebellar diameter.

It is clear that the perinatal adversities that ELBW survivors face are associated with a plethora of health and social challenges across the first four decades of their life. However, little is known about the mechanisms that place ELBW individuals at risk for these physical, mental, and socioeconomic challenges, particularly in adulthood. It is important to understand the mechanisms that influence these health and socioeconomic outcomes in ELBW survivors so that interventions and policies may be created and implemented to target modifiable risk factors that may improve their health, functioning, and quality of life. As many ELBW individuals will face cognitive impairments, cognitive function may be an important modifiable mechanism linking ELBW to later health and socioeconomic outcomes. Cognitive impairments in this population may lead to underachievement and behavioural problems during the school-age years, which may have health and socioeconomic consequences in later life (Aarnoudse-Moens et al., 2009). Due to the ability to detect cognitive impairments in early life, the ease with which cognitive interventions can be applied in childhood, and the impact these interventions

may have on the later functioning and quality of life in individuals facing cognitive challenges, it is important to determine if cognitive abilities contribute to the increased risk of poor health seen in ELBW adults.

Is Cognitive Function A Determinant of Later Health and Socioeconomic Outcomes?

Over the past 15 years, a subset of social epidemiology has emerged that has examined how intelligence and mental abilities influence later health and disease outcomes (Singh-Manoux, 2010). This field, coined "cognitive epidemiology", has focused on how intelligence assessed in childhood, adolescence, or young adulthood may protect against the risk of premature mortality, cardiovascular disease, psychiatric illness, and increase opportunities for socioeconomic attainment in later adulthood (Deary & Batty, 2007). As enhanced early life intelligence has been associated with decreased risk of mortality, disease presence, and poverty in later life, multiple studies have now suggested that there is a link between cognition as a predictor, and later health and socioeconomic outcomes (Batty, Deary, & Gottfredson, 2007; Batty, Mortensen, & Osler, 2005; Hart et al., 2004; Hart, Taylor, et al., 2005; Osler et al., 2003).

Figure 1 highlights the mechanisms hypothesized to link early cognition to later health and socioeconomic attainment. It is thought that our early premorbid cognitive function influences our later health behaviours (e.g., smoking, alcohol use, use of the health care system, exercise, diet, etc.), educational attainment, and socioeconomic success, all of which influence our risk of illness and death (Deary & Batty, 2007; Hart et al., 2003; Taylor, 2003; Whalley, Fox, Deary, & Starr, 2005). It is also thought that our

early cognitive function may be a proxy for bodily integrity (i.e., better functioning of our organs and organ systems) which is associated with better health (Deary & Der, 2005; Deary, 2012; Whalley & Deary, 2001).

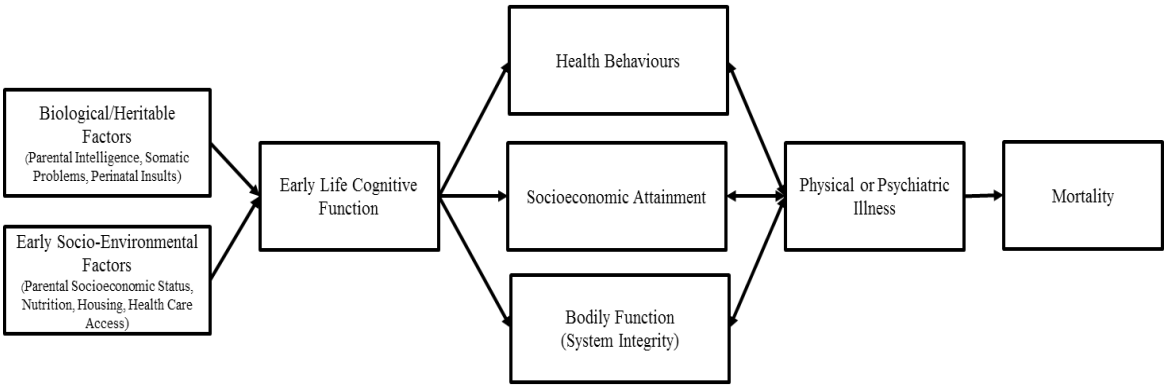

Figure 1. Causal Pathway Linking Early Life Cognition to Later Disease and Mortality (Adapted from Batty, Deary & Gottfredson, 2007)

Research has typically examined early cognitive function as a direct predictor of health, socioeconomic attainment, and/or mortality. It is hypothesized that favourable health outcomes mostly occur at *higher* levels of early cognitive function, while adverse health outcomes typically occur at *lower* levels of cognitive ability. Cognition is usually studied using standardized tests of general intelligence such as the *Moray House Tests* or the *Wechsler Intelligence Scales* (Deary & Batty, 2007). In studies, cognitive ability is typically reported as a continuous variable, or defined per every standard deviation increase or decrease in test score. However, there are some instances where cognitive function may be studied as a dichotomous variable. For example, a study comparing the mortality rates of British individuals with an intellectual disability (IQ score <50) versus the mortality rates of the general population found that all-cause and disease specific

mortality rates were approximately three times higher in individuals with an intellectual disability (Tyrer, Smith, & Mcgrother, 2007).

As seen in Figure 1, cognitive function is thought to be a result of biological, socioeconomic, and environmental factors in early life and that it may be an indirect predictor, or a mediator, of later outcomes (Batty et al., 2007). For example, the Columbia Country Longitudinal Study reported that the association between parental educational level and the occupational success at of their offspring at age 40 was mediated partially by childhood intelligence at age 11 (Dubow, Boxer, & Huesmann, 2009). Further, a study by Basten and colleagues (2015) found that overall intelligence and mathematical abilities partially mediated the association between preterm birth (a marker of perinatal insults) and wealth at age 42. Although cognition may be studied as a predictor of later outcomes in multiple ways, it is important to utilize and test theories as they provide frameworks to explain hypothesized mechanisms and guide analyses.

Theoretical Frameworks

Different theoretical frameworks have been put forward to explain the association between early cognition and later health and socioeconomic outcomes. When exploring the link between cognition and *health*, the most notable extant theory is the *cognitive reserve hypothesis*. When exploring the link between early cognition and *socioeconomic attainment,* studies typically are guided by the *cumulative advantage framework.*

The Cognitive Reserve Hypothesis

The most accepted theory explaining the mechanisms linking early IQ and later health (particularly psychiatric disorders) is the cognitive reserve hypothesis (Batty et al.,

2005; Koenen et al., 2009). Posited by Stern, this hypothesis emerged in the dementia literature and was put forward to explain why some individuals better cope with age-related brain decline than others. Cognitive reserve refers to the ability of our brains to cope with physical or psychological adversity and to protect us from developing disease (Stern, 2002). When faced with neurological adversity, our brains adapt by recruiting and implementing alternate neural and cognitive networks (Stern, 2002). By activating these networks, an individual can continue to function normally despite neurological damage (Cosentino & Stern, 2012). As such, cognitive reserve is thought to act as a "buffer" against later disease.

Those with greater cognitive reserve have a greater ability to activate different cognitive pathways; this results in a bigger buffer against the onset of disease symptoms. Conversely, those with less reserve have less of a buffer and are at greater risk (Stern, 2003). Cognitive reserve has previously been defined by brain size or synapse count (Lee, 2003; Satz, 1993), but is now more frequently defined by the strength of brain networks, cognitive function (typically using IQ or cognitive ability assessments), and/or other markers of neuroplasticity (Cosentino & Stern, 2012; Stern, 2003).

Although seemingly simple, studying cognitive reserve is quite complex due to the vast heterogeneity and compensatory abilities seen in human brain functioning. It is thought that cognitive reserve may be partially heritable (Lee, 2003), but may also be influenced by educational attainment and interventions aimed to improve cognitive function in early life (Richards & Sacker, 2003). Additionally, life experiences, physical exercise, and alterations in physiological development (such as perinatal adversity or

physical damage to the head) may alter our cognitive reserve, resulting in cognitive "compensation" mechanisms (Cosentino & Stern, 2012). According to Stern (2003), compensation in context of the cognitive reserve hypothesis is defined as:

> ...Alternate recruitment in a population with a condition that can disrupt normal cognitive function. This alternate recruitment is considered compensatory in that is adopted as a consequence of this disruption. In some cases differential use of this compensatory network is associated with improved performance, while in other cases it may be associated with best possible maintenance of function in the face of age-related neural challenges. (p.591)

As such, it is important to account for the influence of early adversity and the life experiences of an individual when studying cognitive reserve.

The Cumulative Advantage Framework

When examining the association between early life intelligence and later *socioeconomic attainment*, most research has been framed using the cumulative advantage framework. This theory suggests that more advantages in early life are associated with greater socioeconomic advantage in later life (Judge, Klinger, & Simon, 2010). In this framework, enhanced cognitive abilities (i.e., great IQ, verbal abilities, mathematical abilities, etc.) are considered an early life advantage. Individuals with greater cognitive abilities may be recognized by their parents, teachers, and employers, who in turn may provide these individuals with additional educational and leadership opportunities, resulting in more prestigious post-secondary education or employment, increasing socioeconomic attainment (Judge et al., 2010; Ng, Eby, Sorensen, & Feldman,

2005; Turner, 1960). Further, an individual with enhanced cognitive function may be able to capitalize on specific abilities (i.e., abstract reasoning or communication abilities) within their educational or employment environments, which may result in increased networking skills and performance ability in the workplace that may be beneficial in increasing occupational and socioeconomic prestige (Judge et al., 2010; Turner, 1960). Lastly, an individual with greater cognition may also be privy to other early life advantages, such as higher parental socioeconomic status or better early education, which may jointly lead to opportunities for later socioeconomic gains (Judge et al., 2010; Strenze, 2007).

Methodological Considerations in Cognitive Epidemiology

Regardless of how the role of cognition is conceptualized in epidemiological studies, there are methodological factors that must be considered when studying the contribution of cognition on later life outcomes. First and foremost, temporal ambiguity and reverse causality must be addressed. Determining cognitive function before the onset disease is critical to determine the temporal association between the two factors (Gordis, 2009). As such, cognitive epidemiology research is typically longitudinal in nature, where cognition is assessed between childhood and adolescence and the disease or socioeconomic outcome of interest is assessed in adulthood. However, studying cognition in early adulthood or even adolescence may be problematic as some chronic physical and psychiatric illnesses may begin to manifest during this time (Kessler et al., 2007). This raises the question of reverse causality – is impaired intelligence leading to disease, or is disease lowering intelligence? Secondly, the influence of peers and health behaviours on

an individual's health starts to become more prominent in these developmental periods (Hay & Ashman, 2003), potentially confounding the association between cognition and later health. As such, it has been recommended that when examining cognition as an indicator of later health or socioeconomic attainment, it is best to use an assessment of childhood cognition or intelligence as it is the earliest pre-morbid measure (Strenze, 2007).

A second critical consideration when exploring the link between early cognition and later health is the influence of confounding factors. Without appropriate assessment and acknowledgement of confounding factors, the association between childhood intelligence and later health may not be interpreted correctly (Gordis, 2009). The most prominent confounding factor is childhood socioeconomic status as it is known to be associated with both cognitive ability and health and socioeconomic attainment in adulthood (Breen & Goldthorpe, 2001; Deary et al., 2005; Rowe, Vesterdal, & Rodgers, 1998). Other common confounding factors include educational attainment, birth weight, smoking status, and years of educational attainment (Batty, Der, Macintyre, & Deary, 2006; Hart, Taylor, et al., 2005; Koenen et al., 2009). To account for these confounding factors, generally cognitive epidemiologists adjust for these factors in their logistic regression, linear regression, survival analyses, or structural equation models (Deary & Batty, 2007).

A third methodological aspect to consider is the influence of attrition. As the vast majority of studies exploring the association between early IQ and adult health or socioeconomic status are longitudinal and span many decades, it is inevitable that some

original cohort members will drop out of the study or become loss-to-follow up. This may result in either under or overestimating the association between cognition and later health (Gordis, 2009). However, studies have attempted to avoid or correct for this bias in one of three ways. First, a retrospective cohort design may be used linking hospital, economic, and disease registries with previous population cognitive studies. This may reduce the likelihood of not being able to link participants' health data with their earlier cognitive scores. Secondly, studies commonly adjust their analyses for factors typically associated with attrition such as childhood socioeconomic status, sex, and age. Lastly, assuming that their data is missing at random, studies may perform multiple imputation analyses to account for the influence of missing participants or missing data.

Limitations of the Current Literature Studying the Association between Cognitive Abilities and Later Outcomes

Although the field of cognitive epidemiology has made great advances in understanding how cognitive function influences later health and socioeconomic attainment over the past 15 years, a number of limitations still exist. First, many studies have examined male-only military conscript samples, limiting their generalizability to women. Second, many of the common cohorts studied – such as the Scottish Midspan Studies, the British Birth Cohort, and the Aberdeen Children Study – were born in the early part of the 20th century (Hart, MacKinnon, et al., 2005; Leon, Lawlor, Clark, & Macintyre, 2006; Power & Elliott, 2006). Societal and educational differences since the 1930–1950s may also limit the applicability of these results to later generations. Further,

many of these cohorts are of European, New Zealand, and American origin, potentially limiting their generalizability to Canadian populations.

Third, retrospective studies that rely on registry records for the presence/absence of an outcome measure (particularly for health status) may be affected by ascertainment biases (Koenen et al., 2009). Generally, individuals only receive medical help or hospitalization for the most severe forms of illness which may not be representative of all individuals with a certain disease; this is particularly true when examining psychiatric disorders (Koenen et al., 2009). This may not only overestimate the association between early cognition and disease, but also may not account for those individuals who may not seek help for their conditions.

As stated previously, the cumulative advantage framework posits that the more early life advantages an individual possesses, the more likely they are to have greater social mobility. However, the fourth limitation of current cognitive epidemiological literature is that it has not examined how early cognition moderates the association between psychosocial advantage/disadvantage and later health or socioeconomic attainment. As the majority of studies in the field are retrospective in nature, their data have not allowed this question to be explored. Exploring the joint influence of cognition and early life developmental factors will not only advance knowledge of chronic disease onset and socioeconomic attainment, but provide opportunities to develop specialized cognitive interventions for vulnerable populations.

The last, and perhaps most important limitation is that majority of literature within the cognitive epidemiology field has been studied in general population samples.

Examining how childhood cognitive function influences important health and socioeconomic outcomes in populations that are vulnerable to cognitive dysfunction provides a chance to determine how early biopsychosocial circumstance may influence later disease.

Exploring the Association between Childhood Cognition and Adult Outcomes in Extremely Low Birth Weight Survivors

The perinatal adversity to which ELBW survivors are exposed can result in lasting physical, mental, and neurological consequences for many survivors. In particular, the much higher risk of cognitive impairment in ELBW versus normal birth weight children makes one wonder if the influence of early life cognition on later health and socioeconomic standing is similar for the two groups. To our knowledge, no studies have explored the associations between childhood cognition and later health outcomes in a preterm/low birth weight population, and only one study has explored how early cognition influences later socioeconomic attainment in a high risk pediatric population. Using data from the National Child Development Study and the British Birth Cohort, this study found that in both cohorts overall intelligence and mathematical abilities partially mediated the association between preterm birth and wealth at age 42 (Basten, Jaekel, Johnson, Gilmore, & Wolke, 2015). However, these cohorts were born in 1958 and 1970 (Basten et al., 2015), a period when very few ELBW infants survived.

As recent low birth weight and preterm survivors still continue to suffer with impaired cognitive function (Marlow, Wolke, Bracewell, & Samara, 2005; Mikkola et al., 2005; Wolke et al., 2015), studying the role of childhood cognition as a risk and

protective factor for later outcomes in a low birth weight sample is timely and important. Exploring early cognition as a mediator, moderator, and direct predictor of later outcomes associated with quality of life can provide robust evidence for clinical, psychological, and educational professionals to potentially develop cognitive interventions for low birth weight survivors or similar vulnerable populations. Secondly, more ELBW and preterm survivors are living into adulthood than ever before. At a population level, it is important to explore this association to model human capital. Within the health economics literature, human capital is defined as a function of the current health and its depreciation rate in the labor force (Almond & Currie, 2011). As the incidence of low birth weight and preterm birth survivors is increasing, a significant proportion of the population will have faced perinatal adversity. Understanding the predictive influence of childhood cognition on health and socioeconomic outcomes may be extrapolated and used to guide economic policy. Lastly, studying the association between childhood cognition and adult outcomes in ELBW survivors is important to further the DOHaD and cognitive epidemiology fields. Understanding this association can help clinical professionals, psychologists, and epidemiologists understand if the theories of developmental plasticity, cognitive reserve, and the cumulative advantage framework hold true in one of the most vulnerable populations in the world.

Thesis Overview

To explore the role of childhood cognitive abilities on adult outcomes in ELBW survivors, I have completed three different studies using the same Canadian cohort of ELBW survivors. These three studies fill a gap in cognitive epidemiology by studying

this association in a population who have faced significant perinatal adversity. The collection of these studies examines early cognitive function as a direct predictor, mediator, and moderator of later health and socioeconomic attainment. By assessing cognition using different frameworks, statistical techniques, and by measuring different aspects of early cognitive function (i.e., general, crystalized, and fluid intelligence), these studies are among the first studies to explain mechanisms linking ELBW to later health in adulthood within the DOHaD literature.

Study 1 explores the influence of childhood cognitive abilities (assessed at age 8) on the development of major depressive disorder in ELBW survivors and NBW individuals up to age 29-36. This study was completed to explore if cognitive reserve acts similarly in ELBW and NBW individuals in protecting against later psychopathology. The results of this study indicated that early life cognition did not influence the onset of depression in ELBW survivors, but did protect against depression onset in NBW comparison individuals. This study has been accepted for publication in the *Journal of Developmental Origins of Health and Disease*.

The second study of this thesis explores the mediating role of childhood cognitive abilities at age 8 on personal income attainment and employment outcomes in ELBW survivors in the fourth decade of life. This study was completed to examine if the cumulative advantage framework explaining the association between early intelligence and socioeconomic attainment applies to a vulnerable population. Our results suggest that first, cognitive abilities in early life partially mediate the association between being born

at ELBW and later income attainment, and secondly, that there is a stronger mediating association in those ELBW participants with neurosensory impairments.

Study 3 explores the moderating influence of childhood IQ on the association between postnatal psychosocial adversity and personal income attainment at age 30 in ELBW survivors. This study aimed to explore if early cognitive reserve protected against early adversity in an ELBW sample. Results from study 3 suggest that ELBW survivors who faced psychological adversity with *higher* childhood IQ reported lower incomes in adulthood, suggesting that cognitive reserve does not provide the protective influence against adversity typically seen in general populations.

Since each of these studies uses the same cohort, the three studies are inter-related and may have some replication of the cohort profile in their method sections. As two studies explore how cognitive abilities influence later personal income attainment, there was some duplication of information in Study 2 and 3.

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CHAPTER TWO

STUDY 1

TITLE: Childhood Cognition and Lifetime Risk of Major Depressive Disorder in Extremely Low Birth Weight and Normal Birth Weight Adults

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CONTEXT AND IMPLCATIONS OF THIS STUDY: The first study of the 'sandwich' thesis examines the association between early cognitive function and risk of lifetime major depressive disorder in the fourth decade of life in extremely low birth weight survivors and normal birth weight comparisons. As the introduction section of this chapter suggests, the cognitive reserve hypothesis posits that those individuals with higher pre-morbid cognitive functioning should be protected (i.e., have lower risk) of psychiatric disorders in later life. However, to our knowledge, this association has never been examined in a sample of low birth weight survivors, a population known to be at risk of impaired cognitive function.

Using multivariable logistic regression, the results of this study suggest that childhood cognitive function did not predict lifetime depression in extremely low birth weight survivors, but it did predict depression in normal birth weight comparisons. Specifically, higher levels of overall intelligence, fluid intelligence, and receptive language abilities in childhood were associated with lower depression risk in individuals born at normal birth weight.

To our knowledge, this is the first study that examines cognitive ability as a predictor of later health in extremely low birth weight survivors. As such, it may be used to guide other studies that wish to examine how the cognitive abilities of low birth weight/preterm survivors influence later physical or psychiatric health.

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Abstract

In general population samples, better childhood cognitive functioning is associated with decreased risk of depression in adulthood. However, this link has not been examined in extremely low birth weight survivors (ELBW, <1000g), a group known to have poorer cognition and greater depression risk. This study assessed associations between cognition at age 8 and lifetime risk of major depressive disorder in 84 ELBW survivors and 90 normal birth weight (NBW, ≥2500g) individuals up to age 29-36. The *Wechsler Scale for Children-Revised* (WISC-R), *Raven's Coloured Progressive Matrices,* and the *Token Test* assessed general, fluid, and verbal intelligence, respectively, at age 8. Lifetime major depressive disorder was assessed using the *Mini International Neuropsychiatric Interview* at age 29-36. Associations were examined using logistic regression adjusted for childhood socioeconomic status, educational attainment, age, sex, and marital status. Neither overall IQ (WISC-R Full Scale IQ, OR=0.87, 95%CI=0.43-1.77), fluid intelligence (WISC-R Performance IQ, OR=0.98, 95%CI =0.48-2.00), nor verbal intelligence (WISC-R Verbal IQ, OR=0.81, 95%CI=0.40-1.63) predicted lifetime major depression in ELBW survivors. However, every standard deviation increase in WISC-R Full Scale IQ (OR=0.43, 95% CI=0.20-0.92) and Performance IQ (OR=0.46, 95% CI=0.21-0.97), and each one point increase on the Token Test (OR=0.80, 95%CI=0.67-0.94) at age 8 was associated with a reduced risk of lifetime depression in NBW participants. Higher childhood IQ, better fluid intelligence, and greater verbal comprehension in childhood predicted reduced depression risk in NBW adults. Our

findings suggest that ELBW survivors may be less protected by superior cognition than NBW individuals.

Introduction

Globally, depressive disorders affect approximately 5% of the population.[1] The burden of depression on individuals, societies, and health systems is staggering. Depressive disorders are one of the leading causes of disability adjusted life years and years of life lost due to premature mortality.[2,3] Further, depression is a significant contributor to the global burden of mental illness, one that is estimated to result in a $16 trillion loss in global GDP over the next 20 years.[4,5] As such, there is a need to examine early factors that mitigate risk, improve course of illness, and reduce healthcare costs.[6,7] Research in general population samples suggests that better cognitive functioning during childhood may serve as a protective factor, reducing the risk of mood and anxiety disorders in adult life.[8–14] Cognitive abilities include overall intelligence, commonly measured as intelligence quotient (IQ); fluid intelligence, encompassing processing, problem solving and abstract reasoning abilities; and verbal intelligence, including language comprehension.[11]

In these general population samples, it has been estimated that for every standard deviation increase (i.e., 15 points) in IQ, the odds of developing depression decreases by approximately 20%.[10] This area of epidemiological research suggests that more cognitive reserve, marked by superior cognitive functioning and performance, may decrease susceptibility to later psychopathology.[10,15] Cognitive reserve may be protective against mental disorders via biological pathways, influenced by genetics and physiological integrity; social pathways, via safe familial environment, early socioeconomic advantage,

and educational attainment; and behavioral pathways through the consequences of good health choices.[11,15]

However, most studies that have examined associations between early cognition and adult psychopathology rely on IQ as the primary indicator of cognitive ability, even though overall intelligence may mask dysfunction in other, more specific cognitive areas that could influence the onset of psychiatric disorders.[16,17] As well, a number of studies have relied on male-only samples of military conscripts, and few prospective, population-based cohorts exist to study these links.[10] Due to their retrospective nature, work in this area typically uses hospital records to define depression, which introduces a selection bias toward inclusion of the small sub-sample of individuals with the most severe forms of depression. Lastly, the majority of the literature to date has only focused on general population samples; comprehensively studying the influence of childhood cognition in less typical developing and more vulnerable populations provides an opportunity to determine how early biology, social circumstance, and health behaviors may be protective against depression onset and improve course of illness.

Every year, approximately 10% of all infants are born preterm or at low birth weight, known risk factors for developing depression later in life.[18] Advances in neonatal care have increased survival rates among those born at extremely low birth weight (ELBW, <1000g), the birth weight group most at-risk for psychiatric disorders.[19] It is well established that ELBW survivors suffer from poorer childhood cognitive abilities than their normal birth weight counterparts, (NBW, $\geq$2500g);[20–22] however, it is unclear if ELBW individuals also benefit from the protective effects of cognitive reserve as this has

never been studied. Accordingly, we examined the influence of cognition at age 8 on the development of depression in Canadian ELBW survivors and NBW comparisons up to the fourth decade of life. It was hypothesized that given their exposure to significant perinatal adversity, ELBW survivors would not benefit from the protective influence of cognitive reserve and that greater childhood cognitive ability would not protect against major depression in this group.

Method

Sample

The study sample was comprised of primarily Caucasian ELBW survivors and NBW individuals born between 1977 and 1982 in central west Ontario, Canada. Three-hundred and ninety-seven ELBW infants were recruited at birth, with 179 infants surviving to hospital discharge. The ELBW group had longitudinal assessments of physical, mental, and social health outcomes at ages 3, 5, 8, 14, 22-26, and 29-36 years. Ten additional children subsequently died, resulting in 169 survivors at age 8. At age 8, 143 of the 169 ELBW survivors participated in data collection which included the assessment of cognitive skills. At ages 22-26, 142 survivors participated in data collection and were eligible to participate in the current adult sweep (age 29-36). Eighty-four of the 142 ELBW participants (59.2%) participated in the current data sweep and provided information on depression risk. Six eligible ELBW individuals refused to partake in the current assessment and the remaining non-participants could not be contacted or were unable to attend the psychiatric diagnostic interview.

At age 8, 145 NBW individuals group-matched for age, sex, and parental socioeconomic status (SES) were recruited from a random sample of students in the Hamilton Ontario Public School System. These comparison participants have also been followed at ages 14, 22-26, and 29-36. At age 22-26, 133 NBW individuals participated in data collection and were eligible. Of these 133 NBW individuals, 90 (67.7%) participated in the current (29-36 year old) assessment and provided information on lifetime depression risk. Nine eligible NBW individuals refused to participate in the current assessment and the remaining non-participants could not be contacted or were unable to attend. Written informed consent was received from all participants in adulthood and from their parents during childhood assessments.

Assessment of Childhood Cognition

At age 8, cognition was assessed using the *Wechsler Intelligence Scale for Children-Revised* (WISC-R), *Raven's Coloured Progressive Matrices*, and the *Token Test*. These tests were selected as they measure general, fluid, and verbal intelligence, respectively, and have been validated in children. Details on assessment procedures in the cohort have been described previously.[23]

The WISC-R consists of ten subtests, each with a mean of 10 and standard deviation of three. Combining these subtests creates a Performance IQ, an assessment of fluid intelligence evaluating visuospatial abilities, alertness to detail, and processing speed; and a Verbal IQ, an assessment of verbal intelligence. These two IQ scores are then combined to calculate a Full Scale IQ (mean 100 and standard deviation of 15), an assessment of overall intelligence.[24]

Raven's Coloured Progressive Matrices is a test of fluid intelligence and problem solving abilities that assess nonverbal reasoning, visual spatial abilities, and information recall in children ages 5-11.[25] The test consists of 36 questions asking the child to select a pattern which completes a picture. The test consists of three sets of 12 questions, increasing in difficulty.[26]

The final test administered was the *Token Test*, a measure of receptive language ability. This test consists of tokens in different colours, shapes, and sizes, in which the child is instructed to touch the appropriate token. The test consists of 62 questions, divided into 5 sections that increase in difficulty with a mean of 500 and standard deviation of 5.[27]

Assessment of Lifetime Major Depressive Disorder

Lifetime major depressive disorder was assessed at age 29-36 using the *Mini International Neuropsychiatric Interview* (MINI), a validated structured psychiatric diagnostic interview.[28] The psychiatric assessment provided by the MINI aligns with the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) and the *International Classification of Diseases, 10th Revision*. Each participant was interviewed privately in a room within the Psychology Department at McMaster University. The MINI was administered by two trained graduate student interviewers blind to participant birth weight status.

Covariates

Variables known to be associated with poor cognitive function, low birth weight, adult depression, and attrition in our sample were included in statistical models. These

variables included childhood SES, educational attainment, age, sex, and marital status.[13,19,29] Childhood SES was assessed using Hollingshead classification criteria and self-reported by participants' parents at age 8. At the current assessment, educational attainment was assessed via self-report and calculated by summing the years of education each cohort member had successfully completed up to the time of testing. Marital status was also self-reported by participants at the 29-36 year old sweep and was defined as those who were married or living common-law with a partner versus those who were not.

Statistical Analysis

All data analyses were performed using *IBM SPSS v20*. Descriptive statistics of ELBW and NBW groups including cognitive measures and depression prevalence were computed and compared using Chi square and independent sample t tests.

Given their exposure to significant perinatal adversity, we expected that ELBW survivors would be less protected by their cognitive abilities, and so decided *a priori* to analyze data separately for ELBW and NBW groups. Using logistic regression stratified by birth weight, we examined whether each cognitive measure at age 8 predicted major depressive disorder at age 29-36. Cognitive predictors were defined as each standard deviation increase in Full Scale IQ, Performance IQ, and Verbal IQ, and each one point increase on Raven's percentile and Token score, as this is how these tests are commonly reported in literature.[10,25,30] Lastly, logistic regressions were then adjusted for all covariates mentioned above. We examined our findings for those with complete data and also performed a multiple imputation analysis to account for missing covariate data. As no significant differences in results were seen in multiple imputation regressions, we

report results only for participants with complete data. Results from logistic regressions are presented with odds ratios and 95% confidence intervals (CIs). All statistical tests were 2-tailed with a 0.05 significance level.

Results

The characteristics of the 84 ELBW survivors and 90 NBW participants can be found in Table 1. The average age of both groups was approximately 32 years. Birth weight ($p<0.0001$) and the number of participants that were married or in common-law relationships ($p=0.01$) was greater in the NBW group. No differences were seen between ELBW and NBW participants in their educational attainment, childhood SES, or sex. ELBW participants scored significantly lower on all cognitive tests in childhood compared to NBW participants at age 8. Twenty-one ELBW survivors and 23 NBW participants met diagnostic criteria for lifetime major depressive disorder as per the MINI ($p=0.95$).

Table 2 highlights the results of unadjusted associations between childhood cognitive test scores and lifetime major depressive disorder in both the ELBW and NBW groups. In unadjusted models, no childhood cognitive measure was associated with lifetime major depressive disorder in ELBW survivors. However, among NBW individuals, for every standard deviation increase in WISC-R full scale IQ, the odds of having a lifetime major depressive episode was reduced by 51% (95% CI=0.25-0.95). This was nearly identical for WISC-R Performance IQ score (OR=0.50, 95% CI=0.26-0.98). Moreover, for every one point increase on the Token Test, the odds of developing depression in the NBW group decreased by 18% (95% CI=0.75-0.97). The WISC-R

Verbal IQ and Raven's Matrices score were not significant predictors of lifetime depression.

Table 1. Sample Characteristics

	ELBW (n=84)		**NBW** (n=90)		
	M	*SD*	*M*	*SD*	*p*
Age, years	32	1.6	32.5	1.3	0.055
Birth Weight, g	829.0	132.2	3410.6	473.3	<0.0001
Gestational Age, weeks	27	2.3	40	0	<0.0001
Total Years of Education	16.2	2.8	16.6	3.2	0.417
Parental SES (n, %)					0.515
I: Highest SES Level	5	6.2	8	8.9	
II	11	13.8	20	22.2	
III: Middle SES Level	38	47.5	33	36.7	
IV	23	28.8	26	28.9	
V: Lowest SES Level	3	3.8	3	3.3	
Sex (Female, %)	53	63.1	54	60.0	0.675
Married (n, %)	34	42	52	61.2	0.013
Cognitive Tests (Age 8)					
WISC-R Full Scale IQ Score	93.4	15.2	106.4	12.1	<0.0001
WISC-R Performance IQ Score	95.0	16.6	108.4	12.7	<0.0001
WISC-R Verbal IQ Score	93.3	14.7	103.7	12.6	<0.0001
Raven's Matrices Percentile	45.1	25.5	57.9	29.1	0.003
Token Test Score	498.6	6.5	500.7	4.1	0.025
Lifetime Major Depressive Disorder at Age 29 – 36 (n, %)	21	25.0	23	25.6	0.952

Table 2. Unadjusted Odds Ratios between Childhood Cognitive Function and Lifetime Depression at Age 29 – 36 in ELBW Survivors and Normal Birth Weight Individuals

	ELBW				**NBW**			
	OR	*95% CI*		*p*	*OR*	*95% CI*		*p*
WISC-R Full Scale IQ	0.84	0.45	1.58	0.60	0.49	0.25	0.95	0.04
WISC-R Performance IQ	0.96	0.52	1.76	0.90	0.50	0.26	0.98	0.04
WISC-R Verbal IQ	0.77	0.41	1.45	0.42	0.60	0.34	1.08	0.90
Raven's Matrices Percentile	0.99	0.97	1.02	0.71	1.00	0.98	1.01	0.58
Token Test Score	0.97	0.89	1.05	0.45	0.85	0.75	0.97	0.01

After adjustment for childhood SES, educational attainment, sex, age, and marital status, no childhood cognitive measure was associated with the presence of a lifetime major depressive episode in ELBW survivors (Table 3). However, the odds of developing depression were 57% less for every standard deviation increase in overall IQ in the NBW cohort (95% CI=0.20-0.92). A similar trend persisted for the WISC-R Performance IQ (OR=0.46, 95% CI=0.21-0.97). The association between the Token Test score and later depression remained in fully adjusted models, in that every point increase on the Token Test was associated with an approximate decrease of 25% in the odds of lifetime major depression (95% CI=0.67-0.94).

Table 3. Adjusted[a] Odds Ratios between Childhood Cognitive Function and Lifetime Depression at Age 29 – 36 in ELBW Survivors and Normal Birth Weight Individuals

	ELBW				NBW			
	OR	*95% CI*		*p*	*OR*	*95% CI*		*p*
WISC-R Full Scale IQ	0.87	0.43	1.77	0.71	0.43	0.20	0.92	0.03
WISC-R Performance IQ	0.98	0.48	2.00	0.96	0.46	0.21	0.97	0.04
WISC-R Verbal IQ	0.81	0.40	1.63	0.55	0.56	0.29	1.06	0.07
Raven's Matrices Percentile	1.00	0.97	1.03	0.90	1.00	0.98	1.02	0.62
Token Test Score	0.89	0.77	1.04	0.14	0.80	0.67	0.94	0.01

[a] Estimates adjusted for parental SES, educational attainment, sex, age, and marital status

Discussion

As depression is one of the most common mental disorders and greatly affects individual functioning and quality of life, there is a need to examine early factors that might mitigate risk, improve course of illness, and reduce healthcare costs in populations known to be at increased risk for mood disorders. This is the first study to examine the influence of childhood cognition on the lifetime risk of major depression in ELBW

survivors through the fourth decade of life. Data supported our hypothesis that better childhood cognitive function was not protective against depression in ELBW survivors. In the NBW comparison group, our results suggest that better cognitive functioning in childhood is associated with reduced depression risk. Specifically, every standard deviation increase in overall intelligence (as measured by the WISC-R Full Scale IQ), and in fluid intelligence (as measured by the WISC-R Performance Scale) at age 8 was associated with 57% and 54% reductions in the odds of lifetime depression. Lastly, receptive language ability defined as a one point increase on the Token Test was associated with a 25% reduction in the odds of lifetime depression. These findings persisted despite adjustment for confounding variables.

Comparison with Other Studies

Our results support previous work that has shown that NBW individuals with greater childhood cognitive abilities are less susceptible to depression later in life.[8–10,12–14] Indeed, data from a large general population sample born in New Zealand in the early 1970s showed that every standard deviation decrease in overall intelligence was associated with roughly a 20% increase in the odds of developing depression.[10] Moreover, Zammit and colleagues showed that a one standard deviation increase in general IQ was associated with a 16% reduction in the odds of depression in Swedish military conscripts.[14] In a study that examined depressive episodes in the British Birth Cohort, it was found that increased childhood intelligence (encompassing reading comprehension, pronunciation, vocabulary, and non-verbal reasoning) was associated with fewer depressive symptoms at age 53 as assessed by the GHQ-28 in women.[12]

Potential Mechanisms

Cognitive abilities are typically classified as overall intelligence (IQ), encompassing specific-domain related abilities including our fluid intelligence (i.e., problem solving) and verbal abilities.[11] As the WISC-R Full Scale IQ is an assessment of overall intelligence and encompasses all cognitive abilities, it is not surprising that higher IQ was a strong predictor of reduced depression risk among NBW participants.[31] However, fluid intelligence is also critical to consider for depressive episodes as it provides us with the ability to solve problems and adapt our behaviors to changing environments. We included two measures of fluid intelligence in our analyses, the Raven's Coloured Progressive Matrices and WISC-R Performance IQ. Although both the Raven's Matrices and WISC-R Performance IQ assess non-verbal reasoning and visual-spatial abilities, the WISC-R Performance IQ may place more emphasis on processing speed, which perhaps is why it was a significant predictor of later depression while the Raven's score was not. In a recent meta-analysis examining the influence of different cognitive domains on the severity of depression, processing speed was found to be associated with depression severity whereas visuospatial abilities were not.[32] Enhanced processing abilities may positively influence how children socially connect with their peers, teachers, and parents as well as successfully adapt to their changing social environments through childhood, adolescence, and young adulthood.

The ability to adapt to new environments beginning in childhood may also be strongly tied to verbal comprehension skills. The Token Test, an assessment of receptive verbal comprehension, was the strongest predictor of depression risk in NBW

participants. This may be because verbal comprehension powerfully influences how we understand and communicate thoughts.[33] Children with the ability to understand their families, teachers, and peers may feel more socially accepted and integrated into their social environment, resulting in better academic performance and the confidence to confide in their social support network about their emotions when they encounter problems. Consequently, individuals with impaired receptive language may struggle throughout childhood with understanding their teachers, peers, and families, which can result in feelings of social isolation or rejection and poorer academic performance.

Although not statistically significant, results of logistic regressions in ELBW survivors were in the same direction as the results for NBW individuals, in that higher cognitive functioning in childhood was associated with decreased lifetime depression risk. Apart from methodological explanations (i.e., reduced statistical power) there may be additional reasons why ELBW survivors' risk for depression may not be as strongly linked to childhood cognitive difficulties. First, as adverse pre- and post-natal environments are known to affect brain development, the neural pathways affecting cognitive functioning in those born at ELBW may differ from those born at NBW. The latter half of gestation is a time when much neural cell differentiation and synapse formation occurs, and early delivery and stresses during this time may lead to differences in the structure and function of neural pathways associated with coping skills and adaptation to different social environments. Altered neural pathways and decreased brain volume in ELBW survivors (e.g., in the prefrontal cortex, subgenual cingulate cortex, hippocampus, and amygdala)[20,34–36] may change how they perceive, process, and recall

negative emotional experiences as compared to those born at NBW, thus weakening the relation between poorer cognition and depression risk.

Second, perhaps ELBW survivors, particularly those with reduced cognitive functioning, had increased access to health and educational services in childhood and adolescence that might have served to improve cognitive functioning and/or reduce the negative influence of poorer cognitive ability. Research on parental bonding in low birth weight cohorts suggest that mothers of ELBW survivors use a more protective and supportive parenting style,[37] and this protective parenting may have helped to buffer the negative effects of cognitive dysfunction. Lastly, apart from poorer cognitive functioning, ELBW survivors are known to be more socially reticent, have more attention difficulties, as well as elevated levels of physical health problems.[20,38] All of these risk factors together may result in increased overall allostatic load and therefore weaken associations between individual risk factors (e.g., cognitive function) and psychiatric risk.[39]

Strengths and Limitations

Our study extends previous research on the protective effects of cognition on psychopathology risk. We assessed multiple domains of cognition, providing a broader examination of how childhood cognition affects depression risk in later life. Unlike many previous studies, we assessed both men and women. Major depressive disorder was assessed in all participants using a structured and validated diagnostic interview, thereby decreasing sampling and classification biases which may arise from using registry data to define depression. Lastly, our cohort of ELBW survivors is the oldest, longitudinally

followed cohort known, which permitted us to examine the influence and strength of cognitive predictors on adult depression in individuals exposed to significant perinatal risk.

Our study is not without limitation. Sample attrition over the past 30 years has reduced our sample size and statistical power, which may have played a role in our ability to detect associations between cognition and depression among ELBW survivors. However, we attempted to minimize the impact of differential attrition by adjusting for predictors of dropout and via a 5 iteration multiple imputation bootstrap analysis which did not differ from the results presented. Due to our small sample size, we did not examine subgroups of ELBW survivors (such as ELBW survivors with and without neurosensory impairments), in which different levels of cognitive function may differentially influence the onset of depression. As such, we recommend that future studies using larger samples examine how early cognitive abilities may influence psychiatric disorders in different subgroups of high risk pediatric populations. Another potential factor to consider is the place and time that our ELBW and NBW samples were born and raised. Both the majority of ELBW and NBW participants are Caucasian and generally grew up in middle SES families in central west Ontario in the 1980s and 1990s. Access to universal healthcare and high quality public education may contribute to associations between childhood cognition and later depression that may differ from other settings with different socioeconomic landscapes. Finally, as a number of neonatal advances have occurred since 1982, our findings will need to be replicated in larger, more

contemporary samples. However, it has been found that ELBW survivors in the 1990s have similar cognitive abilities to those in our cohort.[21]

Conclusions

Our findings suggest that the protective effects of cognition may operate differently in ELBW and NBW adults. This may be due to differences in neurodevelopmental pathways, environmental risk exposure, and how cognitive reserve is affected in each group. Further research is required to replicate our results in other low birth weight cohorts, as well as further explore the influence of problem solving abilities and receptive language abilities on depression risk.

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CHAPTER THREE

STUDY 2

TITLE: The Mediating Role of Childhood Cognitive and Academic Abilities on Socioeconomic Outcomes in Extremely Low Birth Weight Survivors in the 4th Decade of Life

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CONTEXT AND IMPLCATIONS OF THIS STUDY: Study 2 of this thesis further explores the predictive influence of early cognition on later adult outcomes in extremely low birth weight survivors. First, this study examines the mediating role of early cognitive function on another important adult outcome, socioeconomic attainment (defined by personal income attainment and full time employment). This is important to note as only one study to our knowledge has examined the role of cognitive ability as a mediator between preterm birth and later socioeconomic attainment. Secondly, Study 2 examines the role of different cognitive variables compared to the first study of this thesis. In addition to overall IQ, verbal intelligence, and fluid intelligence, in this study we examine the mediating role of childhood mathematical abilities and academic achievement, critical cognitive domains to consider in predicting later socioeconomic status. Thirdly, the present study performed a subgroup mediation analysis to explore the mediating role of different cognitive abilities in those extremely low birth weight survivors with or without neurosensory impairments. The knowledge gained from this subgroup analysis is timely and important since extremely low birth weight survivors are

at increased risk of these impairments which may significantly influence their socioeconomic attainment.

In this study, our results suggest that childhood cognitive abilities (particularly general intelligence and mathematical abilities) are mediators of the extremely low birth weight and income attainment association for both those born with and without neurosensory impairments. However, childhood cognitive abilities did not mediate the association between extremely low birth weight status and full time employment, though this may be due to limited statistical power. Lastly, this study suggests that the mediating role of early cognition is stronger in extremely low birth weight survivors with neurosensory impairments. The findings of this study indicate that early cognitive ability may have serious implications for social mobility in preterm survivors.

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CONFLICTS OF INTEREST: None

Abstract

Background: Evidence from general population samples suggests that cognition is an important predictor of later socioeconomic attainment. This association has not been examined in extremely low birth weight (ELBW) survivors, despite their higher risk of having impaired cognitive function.

Objective: To examine: 1. if childhood cognitive and academic abilities at age 8 mediate the association between being born at ELBW and socioeconomic attainment at age 29-36; 2. which cognitive abilities (e.g., IQ, verbal abilities, fluid intelligence, mathematical abilities, or overall academic achievement) most strongly mediate this association; and 3. if the mediating role of early cognition is stronger in ELBW survivors with serious neurosensory impairment compared to ELBW survivors without neurosensory impairments.

Methods: Data from 189 ELBW survivors and normal birth weight participants from Ontario, Canada, we used to examine the mediating role of childhood cognition using five cognitive mediators (overall IQ, verbal IQ, performance IQ, quantitative ability, and academic achievement) assessed at age 8. We defined socioeconomic attainment using personal annual earnings and full time employment, assessed via self-report at age 29-36. To address our first two objectives, we performed single-mediator models following the method of MacKinnon. For our third objective, we performed mediation models using a multivariable categorical independent variable to examine ELBW survivors with and without neurosensory impairments.

Results: Our results suggest that childhood cognition (particularly overall IQ and arithmetic abilities) mediated the association between ELBW and income attainment, but not for full time employment. Data also suggest that the mediating effect of cognition was stronger for those ELBW survivors who were born with a neurosensory impairment.

Conclusions: This study suggests that early life cognition is a critical mediator of later socioeconomic attainment in high risk preterm survivors. Future research should explore the use of early cognitive interventions in this population to improve cognitive and academic abilities.

Introduction

Socioeconomic status is a key determinant of individual health. Socioeconomic outcomes such as income, employment status, educational attainment, and occupational prestige are vital to quality of life as they influence where we live, who we associate with, and our health status. Two of the most important measures of socioeconomic status are personal income attainment and full time employment. Individuals with low-incomes are more likely to suffer from illness and premature mortality, even when age, sex, and ethnicity are accounted for (Mikkonen & Raphael, 2010). Further, individuals earning low incomes access and utilize health services less frequently, thereby limiting their opportunities to consult medical professionals about improving their health (Stewart et al., 2001). A recent meta-analysis that examined associations between temporary employment and health outcomes suggested that the odds of psychological morbidity (e.g., stress, anxiety, depression) were 25% higher, and the odds of morbidity and mortality due to physical health conditions were 13% higher in individuals with temporary versus full time employment (Virtanen et al., 2005).

It has been recommended that research explore inequities associated with the distribution of economic resources at both macro (i.e., locally, nationally, and globally) and micro levels in an attempt to improve and help mitigate these health risks (Marmot, Friel, Bell, Houweling, & Taylor, 2008). Accordingly, it is important to examine individual-level factors that may enhance the opportunity for gains in stable employment and income attainment.

Decades of research have shown that enhanced cognitive functioning beginning in early life is positively associated with educational attainment, which in turn is linked with superior income attainment and labor stability in adulthood (Judge, Ilies, & Dimotakis, 2010; Rowe, Vesterdal, & Rodgers, 1998; Strenze, 2007). Several theories have been put forward to explain these associations, the most prominent being the cumulative advantage framework, commonly referred to as the *Matthew effect* (Judge, Klinger, & Simon, 2010; Strenze, 2007). The *Matthew effect* was proposed by Robert Merton in the 1960s and is named after a verse from the Gospel of Matthew[1] (Judge et al., 2010; Merton, 1968). The general basis of this framework is that the "rich get richer, while the poor get poorer" (Merton, 1968). Those with greater cognitive abilities are at a greater advantage for educational and occupational opportunities leading to occupational prestige, income, and stable employment, while those with poorer cognitive abilities are at a greater disadvantage. Since impaired cognitive abilities may place individuals at risk for poorer socioeconomic trajectories, it is particularly critical to explore the association between early cognitive function and income and job security in later life in populations known to be at risk of impaired cognitive abilities.

General intelligence (IQ) is thought to encompass all of our cognitive abilities (Deary & Batty, 2007) and has been the most commonly studied cognitive predictor of later socioeconomic attainment. However, it is important to also consider how specific cognitive abilities, such as language comprehension, abstract reasoning, and quantitative abilities influence academic achievement and later socioeconomic attainment. In a recent

[1] "For unto every one that hath shall be given, and he shall have abundance: but from him that hath not shall be taken even that which he hath" – Matthew 25:29, King James Version.

study examining the influence of arithmetic and reading abilities at age 7 on socioeconomic attainment at age 42 in of a representative sample from the United Kingdom, it was found that both of these factors were related to socioeconomic attainment, even when accounting for the influence of early life socioeconomic status (Ritchie & Bates, 2013). Additionally, it has been seen that individuals with better communication abilities are promoted more frequently and obtain higher-level employment opportunities (Sypher & Zorn, 1986). This may be because individuals with enhanced communication and language abilities more easily adapt their communication style and empathize with their employers and colleagues, resulting in the more productive work environments valued by their organizations (Payne, 2005).

Quantitative (mathematical) abilities have also been linked to superior socioeconomic attainment. For example, an assessment of associations between childhood mathematical abilities and annual earnings showed that every standard deviation increase in mathematical abilities at age 10 was associated with a weekly salary 13% greater at age 30 (Crawford & Cribb, 2013). It is thought that individuals with enhanced quantitative reasoning skills pursue quantitatively-focused degrees in post-secondary education where they also learn enhanced abstract-reasoning and problem-solving abilities, skills that are valued and desired in the labor force (Adkins & Noyes, 2016; Cassidy & Lynn, 1991).

It is well established that cognitive dysfunction is among the most common disabilities experienced by extremely low birth weight (ELBW, <1000g) survivors (Voss, Jungmann, Wachtendorf, & Neubauer, 2012). As many as 50% of ELBW survivors

suffer from some form of a neurodevelopmental disability (Farooqi, Hägglöf, Sedin, Gothefors, & Serenius, 2006), and almost 40% suffer from limitations in their cognitive abilities during school age (Johnson, Wolke, Hennessy, & Marlow, 2011). Further, ELBW survivors are at increased risk for poor school performance and their cognitive impairments are thought to be a major contributor to these academic difficulties (Johnson et al., 2011; Taylor, Burant, Holding, Klein, & Hack, 2002).

While an extensive literature has linked childhood cognitive abilities to socioeconomic disadvantage in general populations (Boudreau, Bosell, Judge, & Bretz, 2001; Judge et al., 2010; Strenze, 2007), very little is known about the socioeconomic attainment of ELBW survivors in adulthood or its determinants. Studies utilizing European registry data have recently begun to show that that very low birth weight or very preterm individuals are at greater risk of downward social mobility (i.e., less prestigious occupation, income, and education attainment compared to their parents) and unfavourable employment outcomes in adulthood (Black, Devereux, & Salvanes, 2005; Heinonen et al., 2013; Lindström, Winbladh, Haglund, & Hjern, 2007). Further, a recent publication from a Canadian cohort of ELBW survivors found significant discrepancies in employment and income attainment of ELBW survivors compared to those born at normal birth weight (NBW, >2500g) in the fourth decade of life (Saigal et al., 2016).

Despite the increasing number of ELBW survivors living into adulthood, there still remains a gap in the literature exploring the mechanisms by which they develop socioeconomic disadvantage. To our knowledge only one study has examined the mediating role of cognitive abilities on socioeconomic outcomes in high risk pediatric

survivors. Basten and colleagues examined the roles of overall intelligence, language abilities, and mathematical abilities on wealth attainment at age 40 in preterm individuals (born 28-38 weeks gestation) using two population-based British birth cohorts (Basten, Jaekel, Johnson, Gilmore, & Wolke, 2015). Their work suggests that all of these cognitive factors partially mediated the association between preterm birth and wealth attainment, with poorer mathematical abilities in childhood most strongly predicting poorer socioeconomic outcomes in adulthood (Basten et al., 2015). However, this study aggregated multiple socioeconomic outcomes into a single summary wealth estimate (i.e., family income, social class, housing tenure, employment status, and self-perceived financial situation) (Basten et al., 2015), which may be less strongly related to early life cognition than personal income as it may be dependent on contextual factors such subject sex, as if an individual has a partner, if that partner is currently in the workforce, or if the individual has children. Further, their aggregate outcome may potentially inadvertently obscure some of the intricacies of how different cognitive abilities influence individual socioeconomic outcomes. Additionally, it is unclear if their participants had neurodevelopmental disabilities – a common problem among extremely preterm survivors (Patel, 2016) – or how many very low birth weight ($\leq$1,500 g) or ELBW survivors comprised the cohorts they studied.

When exploring associations between cognitive abilities and socioeconomic attainment in ELBW survivors, another gap exists in our understanding of whether or not preterm survivors are a homogenous group in terms of risk. Specifically, it is critical to account for the high rate of neurosensory impairment (NSI), such as deafness, blindness,

mental retardation, and cerebral palsy in the socioeconomic attainment of this population. Due to their susceptibility to intraventricular hemorrhage, periventricular leukomalacia, and early exposure to medical treatments, ELBW survivors are at greater risk of NSI (Patel, 2016). A significant proportion of individuals with NSI in the general population are marginalized due to their disabilities and are unable to gain employment (Shier, Graham, & Jones, 2009). Therefore, the role of cognitive abilities may act differently in ELBW survivors with NSI due to the additional difficulties they may face.

Due to medical advances in neonatal care, more very preterm and ELBW survivors are living into adulthood than ever before. Despite the fact that an increasing number of studies suggests that preterm survivors may have poorer employment and income attainment in adulthood, the mechanisms underlying these disparities remains unclear. Due to the high prevalence of cognitive and academic challenges in ELBW survivors, the ease with which these can be measured in early life, their pronounced impact on socioeconomic and health outcomes in later life, and the ability to improve cognitive function and academic achievement in early life with adequate educational resources, it is critical that we understand the influence of cognitive abilities on socioeconomic outcomes in ELBW populations (Aarnoudse-Moens, Weisglas-Kuperus, van Goudoever, & Oosterlaan, 2009; Jarjour, 2015; Manley et al., 2015; United Nations Children's Fund and World Health Organization, 2004).

Research Objectives

Using data from the oldest, longitudinal cohort of ELBW survivors in the world, we set out to explore three objectives: 1. to determine if childhood cognitive and

academic abilities at age 8 mediate associations between being born at ELBW and socioeconomic outcomes (personal income attainment and full time employment) at age 29-36; 2. to determine which cognitive or academic ability (e.g., IQ, verbal abilities, fluid intelligence, mathematical abilities, or overall academic achievement) most strongly mediate this link; and 3. to determine if the mediation pathway for ELBW survivors differs for those who were born with or without serious neurosensory impairment.

For our first objective, we hypothesized that childhood cognitive abilities would partially mediate the association for socioeconomic outcomes. For our second objective, we hypothesized that overall intelligence would most strongly mediate the association as it encompasses all aspects of cognitive functioning and strongly influences academic achievement. Due to their impaired intellectual abilities and the potential added challenges of physical disabilities and discrimination that individuals with NSI may face in attempting to secure employment, for our third objective we hypothesized that childhood cognitive abilities would play a more prominent role in mediating the association between ELBW status and socioeconomic outcomes in survivors with NSI.

Methods

Participants

The cohort examined in this study consisted of 100 ELBW survivors and 89 NBW comparison individuals born in central west Ontario, Canada. Between 1977 and 1982, 397 ELBW survivors were recruited at birth in Hamilton, Ontario, Canada. Of these, 179 survived and were discharged from hospital. Ten additional children subsequently died, resulting in 169 survivors eligible to participate in data assessments at

age 8. One-hundred and forty-three ELBW survivors participated in cognitive assessments at 8 years of age. At ages 22-26, 142 survivors participated and were eligible to participate in the latest follow-up (age 29-36). Of these, one hundred (70%) ELBW participants participated at the current data sweep and provided socioeconomic and demographic information.

At age 8, 145 NBW individuals group-matched for age, sex, and parental socioeconomic status (SES) were recruited from a random sample of students in the Hamilton Public School System in Ontario, Canada. At age 22-26, 133 NBW individuals participated in data collection and were eligible for to participate in the latest data assessment. Of these 133 NBW individuals, 89 (67%) provided data on socioeconomic outcomes at ages 29-36. Written informed consent was received from all participants in adulthood and from their parents during childhood assessments. This study received ethics approval from the McMaster University Health Sciences Research Ethics Board.

Mediator Variables: Childhood Cognition

Childhood cognitive and academic abilities were assessed at age 8 in ELBW survivors and NBW controls. Details on cognitive assessment procedures in the cohort have been previously described (Saigal, Szatmari, Rosenbaum, Campbell, & King, 1991). For this study, we examined overall intelligence (IQ), verbal abilities, fluid intelligence, mathematical abilities, and academic achievement as mediators. These cognitive factors were selected as they have been previously studied as mediators of adult wealth in preterm and general population samples (Almond & Currie, 2011; Basten et al., 2015).

Overall IQ, verbal abilities, and fluid intelligence were assessed using the *Wechsler Intelligence Scale for Children-Revised* (WISC-R). The WISC-R consists of ten subtests, each with a mean of 10 and standard deviation of 3. Combining these subtests creates a performance IQ score, an assessment of fluid intelligence evaluating visuospatial abilities, alertness to detail, and processing speed; and a verbal IQ score, an assessment of reading, verbal, and language abilities (Wechsler, 1974). These two IQ scores are then combined to calculate an overall IQ (mean of 100 and standard deviation of 15), an assessment of overall intelligence (Wechsler, 1974). The WISC-R is a common assessment of IQ in the field of cognitive epidemiology (Deary & Batty, 2007), and has been seen to have adequate test-retest reliability in general (α=0.96) and special-need (α=0.85) populations (Covin, 1977; Irwin, 1966; Tuma & Appelbaum, 1980).

Mathematical abilities were assessed using the *Wide Range Achievement Test-Revised* (WRAT-R) arithmetic subscale. The arithmetic subscale is comprised of questions pertaining to counting, reading numerical symbols, and solving mathematical problems through numerical computation and is scored to have a mean of 100 and standard deviation of 15 (Jastak & Wilkinson, 1984; Reid, 1986). The arithmetic subscale of the WRAT-R has been deemed to have adequate test-retest reliability (α=0.79-0.92) (Jastak & Wilkinson, 1984; Witt, 1986)

The *Woodcock-Johnson Psychoeducational Battery* was used to assess academic achievement. Three subscales of reading (letter-word identification, work attack, and passage comprehension) were administered to participants. The subscales are combined into a single score with a mean of 100 and standard deviation of 15 (Woodcock, 1977).

The letter-word identification (α=0.94), word attack (α=0.87), and passage compression (α=0.88) have been deemed to have sufficient test-retest reliability and adequate content, criterion, and construct validity (Schrank, McGrew, & Woodcock, 2001).

Socioeconomic Outcomes: Personal Income Attainment & Full Time Employment

We examined two socioeconomic outcomes within our study: annual personal income and full time employment. These two variables were assessed using standardized questions derived from the Ontario Child Health Study questionnaires (Boyle et al., 1987). Personal annual income was assessed by summing the amount of income earned over the past 12 months from seven different sources: wages and salaries before deductions, self-employment, employment-insurance benefits, federal and provincial child benefits, social assistance, child/spousal support, and any other income sources such as dividends, interests, capital gains, and gratuities. Full time employment was assessed by asking participants if they had been employed 30 hours or more a week for the past 12 months.

Covariates

We included variables associated with poor cognitive function, low birth weight, socioeconomic outcomes, and attrition as covariates within mediation models. These variables included familial SES at age 8, sex, total number of years of educational attainment to date, and current age (Heinonen et al., 2013; Nomura et al., 2009). Childhood SES was assessed via self-reported by participants' parents at age 8 using Hollingshead 2-factor index (parental education and occupational prestige) of social position (Hollingshead, 1969). This index has five values, where 1 indicates highest SES

level and 5 indicates lowest SES level. We chose to only include one assessment of early life SES as a covariate to preserve statistical power and because it has been seen that SES in childhood and adolescence may similarly influence long term outcomes (Chen, Martin, & Matthews, 2006). Educational attainment was assessed via self-report and calculated by summing the years of education each cohort member had successfully completed at the time of testing. We selected to examine education as a covariate rather than an outcome as it is hypothesized to be a critical predictor of socioeconomic attainment (Strenze, 2007).

Statistical Analysis

All statistical analyses were performed using SAS version 9.3. Descriptive statistics of birth characteristics, cognitive abilities at age 8, and socioeconomic outcomes at ages 29-36 were first examined by using independent sample t-tests for continuous variables and chi-square tests for categorical variables. To determine the influence of attrition in our cohort, we compared participants and non-participants on variables that were used to match ELBW and NBW participants at age 8 (age, sex, childhood SES) and childhood cognitive abilities. For these comparisons, we compared these variables for all participants (n=189) and non-participants (n=135) rather than for those participants with information on socioeconomic attainment as each of our mediation models included a different number of participants (n=153-157).

To explore the mediating role of childhood cognitive and academic abilities on socioeconomic outcomes (study objectives 1 and 2), we performed modelling following the product of coefficients method described by MacKinnon (MacKinnon, 2008). We

performed single mediator models to examine the mediating influence of each childhood cognitive factor (overall IQ, verbal IQ, performance IQ, mathematical abilities, and academic achievement) separately. In each model, the independent variable was ELBW status and the dependent variable was either annual personal income (continuous) or full time employment status (dichotomous). Continuous covariates (age and years of education) were centered in regression models to minimize collinearity between predictors.

Figure 1 illustrates an example of the mediation model. To begin, we regressed the dependent variable on the independent variable while controlling for covariates to quantify the **total effect** (*c* coefficient) of the independent variable (i.e., ELBW status) on our outcomes. For each mediation model, we then performed two regressions. In the first regression, the dependent variable was regressed on the independent variable and mediator while controlling for covariates; this regression quantifies how much the total effect is affected by the mediator (*c'* coefficient, or the **direct effect**) and the association between the mediator and dependent variable (*b* coefficient). In the second regression model, the mediator was regressed on the independent variable while controlling for covariates, quantifying the association between the independent variable and mediator (*a* coefficient).

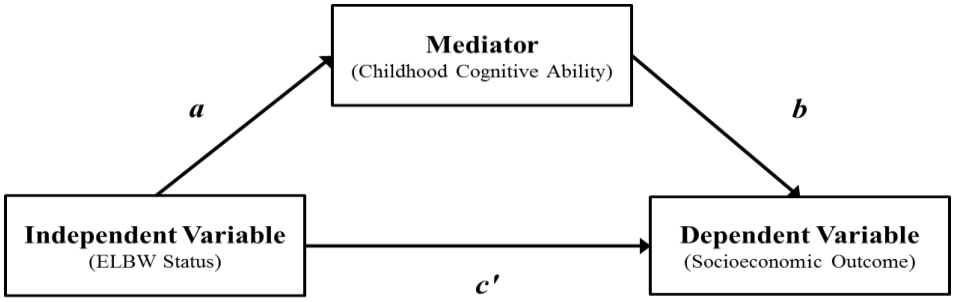

Figure 1. Single-Mediator Model (Adapted from MacKinnon 2008)

In mediation models where annual personal income was the dependent variable, all pathways were assessed using linear regressions (PROC REG). To address our first objective, the **mediated/indirect effect** was calculated by multiplying the *a* and *b* coefficients (*ab*) and computing its 95% confidence interval to determine the statistical significance of the mediated effect. For models in which full time employment was the dependent variable, two of the three pathways (*c*, *c'*, and *b*) were assessed using logistic regression (PROC LOGISTIC). To account for the difference in outcome distribution (i.e., binary versus normal distribution) and to determine the mediated effect, these coefficients were standardized by dividing by the coefficients by their variances. Once standardization was completed, the mediated effect was calculated as described above using the *a* and standardized *b* coefficient. For standardizing equations, please refer to the text by MacKinnon (MacKinnon, 2008).

Subsequently, we performed bootstrap modelling to determine the accuracy and precision of our indirect effects (*ab*). Confidence intervals derived from this random sampling technique may better represent the non-linear sampling distribution of the mediated effect, yielding more accurate effect estimates (Hayes, 2013; MacKinnon,

2008). We performed bootstrap resampling using 10,000 samples (Hayes, 2013) and report the results of these models.

Lastly, to assess the influence of missing data in our models, we performed a multiple imputation analysis (PROC MI) creating 10 imputed datasets. The average value for each continuous predictor from these 10 datasets was used to replace missing data in subsequent analyses. As the results from these mediation analyses did not statistically differ, we report results only for participants with complete data.

To address our second objective and to determine the influence of overall intelligence compared to specific cognitive abilities, we compared the magnitude of each mediated effect for significant models by calculating the proportion mediated (*ab/c x 100*) for each model (MacKinnon, 2008).

Objective 3: Neurosensory Impairment Subgroup Analysis

As a group, ELBW survivors face unique challenges. To explore our third objective, we completed a subgroup analysis to explore the cognition/socioeconomic attainment link in ELBW participants with and without NSI. NSI were diagnosed in childhood by a pediatrician and were defined as any of the following disorders: cerebral palsy, mental retardation, blindness, deafness, or microcephaly. To complete these models, we performed our mediation analyses using a multi-categorical independent variable (**Figure 2**) and compared the magnitude of mediated effects in ELBW survivors with and without NSI impairments (Hayes & Preacher, 2014). As exploring this association was not our primary objective, we did not perform bootstrap modelling or multiple imputation for these analyses.

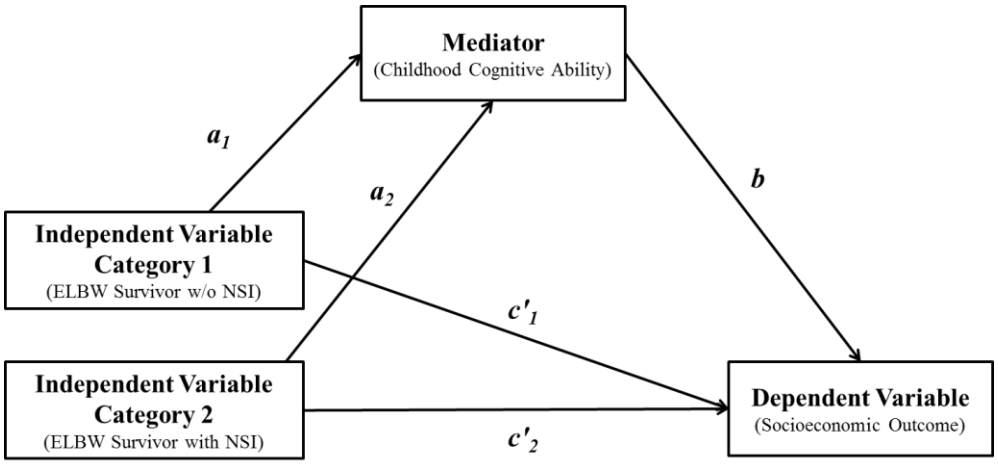

Figure 2. Multi-categorical Independent Variable Mediator Model

Results

Sample Characteristics

The characteristics of the study sample are contained in **Table 1**. No differences were seen in age at the 29-36 year visit, sex, childhood SES, or total years of education between ELBW and NBW participants ($p>0.05$). At age 8, ELBW survivors scored significantly lower in all cognitive domains compared to NBW participants ($p<0.001$). On average, ELBW participants reported personal incomes at ages 29-36 approximately $20,000 lower than NBW participants ($p<0.001$). Roughly 77% of NBW participants and 62% of ELBW participants reported having full time employment over the past year ($p=0.042$). Twenty-six ELBW participants had a NSI.

Table 1. Sample Characteristics

	ELBW (n=100)			NBW (n=89)			
	n	*M*	*SD*	*n*	*M*	*SD*	*p*
Cohort Demographics							
Birth Weight (g)	100	834.9	132.7	89	3388.1	465.6	<0.001
Average for Gestational Age (AGA) n, (%)		71	(71)				
Small for Gestational Age (SGA) n, (%)		29	(29)				
Age (years)	100	32.08	1.69	89	32.47	1.37	0.084
Sex male, (%)	100	39	(39)	89	33	(37)	0.074
Childhood (Parental) SES n, (%)	95			89			0.62
I		5	(5.26)		7	(7.87)	
II		16	(16.84)		20	(22.47)	
III		44	(46.32)		32	(35.96)	
IV		27	(28.42)		26	(29.21)	
V		3	(3.16)		4	(4.49)	
Neurosensory Impairment n, (%)	100	26	(13.76)	89	1	(1.12)	<0.001
Adult SES Variables (Age 29-36)							
Total Years of Education	97	16.00	2.75	88	16.67	3.12	0.126
Personal Annual Income ($)	88	26,484.65	23,721.36	81	46,551.62	31,263.84	<0.001
Total Household Annual Income ($)	91	54,450.55	41,004.41	81	78,148.15	41,985.45	<0.001
Full Time Employment This Year n, (%)	78	48	(61.54)	77	59	(76.62)	0.042
Cognitive Variables (Age 8)							
WISC-R Full Scale IQ	89	93.40	15.77	89	106.20	11.73	<0.001
WISC-R Verbal IQ	89	93.47	15.00	89	103.60	12.35	<0.001
WISC-R Performance IQ	89	94.87	16.94	89	108.10	12.45	<0.001
Woodcock-Johnson Standard Score	89	91.60	15.98	89	99.78	13.86	<0.001
WRAT-R Arithmetic Standard Score	89	83.36	16.16	89	95.28	13.64	<0.001

Table 2. Demographic Factors of Participants and Non-participants at Current Sweep

Characteristics	Group	Participants	Nonparticipants	*p*
Number of Participants	Overall	189	135	
	NBW	89	56	
	ELBW	100	79	
Gender (male, n)	NBW	33	33	0.01
	ELBW	39	45	0.02
Birth Weight, g (SD)	NBW	3388.1 (465.6)	3348.5 (526.5)	0.64
	ELBW	834.9 (132.7)	840.5 (110.0)	0.76
Gestational age, mean (SD), week	NBW	40	40	
	ELBW	26.8 (2.0)	27.1 (2.4)	0.36
NSI	NBW	1	2	0.31
	ELBW	26	25	0.41
SGA	NBW			
	ELBW	29	14	0.08
Childhood SES	NBW	3	3	0.42
	ELBW	3	4	<0.001
WISC-R Full Scale IQ	NBW	106.2 (11.7)	100.1 (12.3)	0.003
	ELBW	93.4 (15.8)	87.2 (15.4)	0.03
WISC-R Performance IQ	NBW	108.1 (12.5)	103.0 (12.4)	0.02
	ELBW	94.9 (16.9)	91.1 (16.6)	0.21
WISC-R Verbal IQ	NBW	103.6 (12.4)	97.6 (13.1)	0.006
	ELBW	93.5 (15.0)	85.8 (15.0)	0.005
Woodcock-Johnson Standard Score	NBW	99.8 (13.9)	95.9 (14.4)	0.11
	ELBW	91.6 (16.0)	85.5 (14.6)	0.03
WRAT-R Arithmetic Standard Score	NBW	95.3 (13.6)	92.5 (13.0)	0.22
	ELBW	83.4 (16.2)	80.3 (17.9)	0.31

When comparing the demographic characteristics of participants and non-participants (**Table 2**), male sex was a predictor of attrition in both ELBW and NBW groups. In ELBW survivors, lower SES was a predictor of increased attrition. It should also be noted that non-participants generally had lower scores on childhood cognitive assessments compared to participants. As such, we further examined differences between

cognitive scores per SES strata in participants and non-participants. It was found that cognitive scores in all groups followed the same trend in that higher socioeconomic participants generally had higher cognition scores compared to those in lower socioeconomic strata, suggesting that non-participants were missing at random.

Personal Income Mediation Models

Of the 189 participants, 157 (83%) had complete data on all variables and were included in mediation models. Results highlighting the total and direct effects of being born at ELBW on personal income, and the mediating (indirect) effect of childhood cognitive or academic abilities on the direct association from bootstrapped analyses are contained in **Table 3**. In each mediation model, ELBW participants scored significantly lower on all cognitive assessments at age 8 compared to NBW participants (*a* coefficient pathway, $p<0.01$). Higher scores on all early life cognitive measures were associated with higher reported personal income at age 30 (*b* pathway, $p<0.01$), except for the WISC-R Performance IQ ($p=0.10$).

Significant indirect effects (*ab*) were seen in all models, supporting the presence of mediation. Our results suggest that ELBW children with lower scores on these cognitive and academic measures in childhood reported lower annual incomes at age 30. However, as ELBW status (*c'* coefficient) was still a significant predictor of income attainment, this indicates that the indirect effect (i.e., the role of cognitive abilities) only partially mediated the association between ELBW status and income attainment.

In examining our second objective, models with overall IQ (WISC-R full scale IQ, *total effect* = -17477, 95%CI = -25,991.97,-8,962.03; *indirect effect* = -4,901, 95%CI = -10,013.48, -986.97) and mathematical abilities (WRAT-R arithmetic score, *total effect* = -17477, 95%CI = -25,991.97, -8,962.03; *indirect effect* = -4,636, 95%CI = - 9,412.11, -1,703.10) as mediators had the largest indirect effects in terms of explaining the association between being born at ELBW and income attainment. The smallest significant indirect effect was seen with the Woodcock-Johnson academic achievement score (*total effect* = -17477, 95%CI = -25,991.97, -8,962.03; *indirect effect*= -3,067, 95%CI= -7,141.89,-856.64).

Full Time Employment Mediation Models

Of the 189 participants, 153 (80%) had complete data and were used in models. Results of the total, direct, and mediated effects from bootstrapped models may be seen in **Table 3**. Our results suggest that childhood cognitive and academic abilities do not mediate the association between ELBW status and full time employment. Similar to the models for personal income attainment, being born at ELBW was associated with lower scores on cognitive and academic achievement tests at age 8 (*a* pathway). However, the indirect effect (*ab*) was not statistically significant, suggesting that no mediation was present. When performing logistic regressions of ELBW status, cognitive mediators, and covariates on full time employment, the most significant predictor of full time employment was sex. Compared to males, the odds of full time employment were three times lower for females.

Table 3. Bootstrapped Direct and Indirect Effects of Childhood Cognition and ELBW on Income Attainment & Full Time Employment

	Overall IQ		Verbal IQ		Performance IQ	
	Effect Estimate	95% CI	Effect Estimate	95% CI	Effect Estimate	95% CI
Annual Personal Income Attainment Models						
Total Effect	-17,477.00	-25991.97, -8,962.03	-17,477.00	-25991.97, -8,962.03	-17,477.00	-25991.97, -8,962.03
Direct Effect of ELBW Status on Personal Income Attainment	-12,575.89	-21,849.15, -3,302.63	-13,665.95	-22,487.74, -4,844.16	-14,002.91	-23,404.73, -4,601.08
Indirect Effect of Cognitive Mediator on Personal Income Attainment	-4,901.11*	-10,013.48, -986.97	-3,811.05*	-8,537.81, -848.09	-3,474.09*	-7,889.93, -166.62
Proportion Mediated (%)[a]	28		22		20	
Full Time Employment Models						
Total Effect	-0.88	-1.64, -0.11	-0.88	-1.64, -0.11	-0.88	-1.64, -0.11
Direct Effect of ELBW on Full Time Employment	-0.57	-1.39, 0.25	-0.68	-1.49, 0.11	-0.62	-1.45, 0.21
Indirect Effect of Mediator on Full Time Employment	-0.35	-0.87, 0.01	-0.25	-0.63, 0.12	-0.27	-0.76, 0.11
Proportion Mediated (%)[a]	40		28		31	

	Mathematical Abilities		Academic Achievement Abilities	
	Effect Estimate	95% CI	Effect Estimate	95% CI
Annual Personal Income Attainment Models				
Total Effect	-17,477.00	-25991.97, -8,962.03	-17,477.00	-25991.97, -8,962.03
Direct Effect of ELBW Status on Personal Income Attainment	-12,840.28	-21,622.72, -4,057.83	-14,410.20	-22,891.78, -5,928.62
Indirect Effect of Cognitive Mediator on Personal Income Attainment	-4,636.72*	-9,412.11, -1,703.10	-3,066.80*	-7,141.89, -856.64
Proportion Mediated (%)[a]	27		18	
Full Time Employment Models				
Total Effect	-0.88	-1.64, -0.11	-0.88	-1.64, -0.11
Direct Effect of ELBW on Full Time Employment	-0.65	-1.46, 0.16	-0.79	-1.57, -0.01
Indirect Effect of Mediator on Full Time Employment	-0.24	-0.67, 0.08	-0.1	-0.40, 0.06
Proportion Mediated (%)[a]	27		11	

[a] *% Mediated = ab/c x 100*

** Significant indirect effect at the α=0.05 level*

Objective 3: NSI Participants

To address our third objective, we performed mediation models using a multi-categorical independent variable separating ELBW survivors with and without neurosensory impairments (**Table 4**). Our results suggest that the mediating role of cognitive abilities on annual income attainment may be stronger in ELBW survivors *with* NSI since this group had larger indirect effects (*ab*) in every model. For example, overall IQ accounted for 25% (*ab* = -4274.11) of the direct effect (*c* = -17,014.00) in ELBW survivors *without* NSI, but accounted for 39% (*ab* = -7,595.51) of the direct effect (*c* = -19,303.00) in ELBW survivors *with* NSI. This trend was seen with every cognitive mediator, with overall IQ and mathematical abilities having the largest indirect effects in both ELBW groups. All indirect effects (*ab*) were statistically significant in both groups, with the exception of the WISC-R Performance IQ mediator. When exploring the mediating role of childhood cognition on full time employment, the indirect effect estimate (*ab*) was not significant for either ELBW group (**Table 4**).

Table 4. Summary of Mediation Effects for NSI Subgroup Models

Mediator	a	b	c'	c	ab	95% CI	% Mediated[a]
ELBW Survivors without NSI Impairments							
Personal Income Models							
Overall IQ (WISC-R Full Scale)	-0.68	6322.53	-12740.00	-17014.00	-4274.41*	-8,172.16, -376.25	25
WISC-R Verbal IQ	-0.53	6462.55	-13606.00	-17014.00	-3408.02*	-6,599.70, -216.32	20
WISC-R Performance IQ	-0.68	4314.79	-14098.00	-17014.00	-2916.54	-6,592.90, 760.39	17
Mathematical Abilities (WRAT-R M)	-8.00	484.26	-13139.00	-17014.00	-3874.90*	7,201.30, -548.60	23
Academic Abilities (WJ)	-4.75	474.88	-14759.00	-17014.00	-2255.54*	-4,941.20, 430.66	13
Full Time Employment Models							
Overall IQ (WISC-R Full Scale)	-0.62	0.49	-0.61	-0.87	-0.09	-0.34, 0.07	34
WISC-R Verbal IQ	-0.50	0.46	-0.72	-0.87	-0.06	-0.18, 0.06	25
WISC-R Performance IQ	-0.61	0.37	-0.65	-0.87	-0.06	-0.22, 0.09	26
Mathematical Abilities (WRAT-R M)	-8.83	0.02	-0.68	-0.87	-0.06	-0.19, 0.07	24
Academic Abilities (WJ)	-4.51	0.02	-0.81	-0.87	-0.02	-0.09, 0.05	9
ELBW Survivors with NSI Impairments							
Personal Income Models							
Overall IQ (WISC-R Full Scale)	-1.20	6322.53	-11708.00	-19303.00	-7595.51*	-14,443.23, - 747.79	39
WISC-R Verbal IQ	-0.83	6462.55	-13930.00	-19303.00	-5373.09*	-10,522.40, -223.81	28
WISC-R Performance IQ	-1.36	4314.79	-13449.00	-19303.00	-5854.22	-13,110.00, 1,401.59	30
Mathematical Abilities (WRAT-R M)	-16.34	484.26	-11391.00	-19303.00	-7912.24*	-14,177.60, -1,646.90	41
Academic Abilities (WJ)	-13.61	474.88	-12839.00	-19303.00	-6463.58*	-12,014.50, -912.71	33
Full Time Employment Models							
Overall IQ (WISC-R Full Scale)	-1.27	0.49	-0.33	-0.91	-0.17	-0.49, 0.14	65
WISC-R Verbal IQ	-1.26	0.46	-0.51	-0.91	-0.16	-0.47, 0.15	60
WISC-R Performance IQ	-1.36	0.37	-0.44	-0.91	-0.14	-0.48, 0.19	53
Mathematical Abilities (WRAT-R M)	-17.15	0.02	-0.52	-0.91	-0.12	-0.37, 0.14	44
Academic Abilities (WJ)	-13.71	0.02	-0.70	-0.91	-0.07	-0.27, 0.13	26

[a] *% Mediated = ab/c x 100*

** Significant indirect effect at the α=0.05 level*

Discussion

In this study, we sought to determine if childhood cognitive abilities mediated the association between being born at ELBW and income attainment and employment status in adulthood; which childhood cognitive factor most strongly mediated this association; and if the mediated association differed for ELBW survivors with and without NSI. Our results suggest that childhood cognitive abilities partially mediate the association between being born at ELBW and income attainment in the fourth decade of life, but not full time employment. Single mediator models suggest overall IQ and arithmetic abilities had the

strongest influence on the association, accounting for 27-28% of the association between being born at ELBW and income attainment.

To our knowledge, this is the first study to examine the mediating role of childhood cognition on employment and income outcomes in a population of ELBW survivors. We completed a detailed and robust mediation analysis by utilizing a well-established mediation method. Further, we cross-referenced our results with bootstrapped estimates to account for any non-linearity which may have been present in our models. Next, our assessments of birth weight and cognitive measures in childhood have high reliability. Studies utilizing general population samples suggest socioeconomic outcomes should be assessed at least 20 years after the assessment of cognition to help ensure a temporal association by reducing the likelihood of educational interventions biasing estimates (Strenze, 2007); since we assessed cognition at age 8 and socioeconomic outcomes at ages 29-36, our study aligns with this recommendation. Thirdly, our mediation models provide enhanced generalizability as we included both men and women in our models and adjusted for known confounders. Additionally, we conducted sensitivity analyses by separating ELBW participants with and without NSI. Lastly, the cohort studied is the oldest and smallest birth weight cohort that has been longitudinally followed for four decades.

Our results align with those previously reported in literature examining the mediating effect of cognition on socioeconomic outcomes in adulthood in preterm born groups. In their work examining associations between preterm birth and wealth in the fifth decade of life, Basten and colleagues (2015) reported a medium-sized effect

estimate for mathematical abilities (accounting for approximately 35-36% of the total effect) and a small effect for general IQ (account for approximately 4-19% of the total effect). Our results were similar in magnitude (roughly 27-28% of the total effect for personal income models).

The small discrepancy seen between our work and that of Basten et al. (2015) may be due to the fact that the present study only examined single mediator models for two different socioeconomic outcomes, compared to the multiple mediator model and aggregate wealth measure they studied. Moreover, the populations they studied were from Britain, were born in 1952 and 1970, and the mean birth weight of their most preterm group (27-36 weeks) was approximately 2,600 grams, over 1,000 grams heavier than our birth cohort. Furthermore, the influence of childhood SES was explored using the Registrar General's Social Classes categories which may act differently within statistical models than our Hollingshead scale. Although ours is the only study that to our knowledge explicitly examines the mediating roles of different aspects of early cognition on adult socioeconomic outcomes in a high risk pediatric sample, multiple general population studies suggest that lower birth weight is associated with poorer income, employment and other adult socioeconomic outcomes, which has hypothesized to be due to the poorer intellectual abilities associated with low birth weight (Almond & Currie, 2011; Black et al., 2005; Case, Fertig, & Paxson, 2005; Nomura et al., 2009).

For our third objective, our findings suggest that the mediation pathway for personal income attainment differs between those ELBW survivors born with and without NSI, in that the mediating influence of childhood cognitive abilities is stronger in

ELBW survivors *with* NSI. Our mediation models suggest that cognitive abilities do not mediate the association between ELBW status and full time employment in survivors with or without NSI. These results are not surprising given the known difficulty of gaining employment for individuals who suffer with NSI (Potts, 2005). For example, the Harris Survey of Americans with Disabilities suggests that only 21% of working-age individuals living with a serious disability report full or part-time employment, compared to 59% of individuals without a disability or NSI (Taylor, Krane, & Orkis, 2010).

Potential Mechanisms

There are multiple ways in which cognitive and academic abilities may influence employment and income attainment in ELBW survivors. When examining socioeconomic attainment using the cumulative advantage framework, contest mobility and sponsored mobility mechanisms provide opposite, yet complementary views about how individuals with greater childhood cognitive abilities have greater upward socioeconomic progression. Sponsored mobility mechanisms suggest that more intelligent individuals are more likely to be acknowledged as candidates for better socioeconomic opportunities such as pay raises and stable employment with benefits (Judge, Klinger, & Simon, 2010; Ng, Eby, Sorensen, & Feldman, 2005; Turner, 1960). As stated by Turner (1960), these individuals can "start the race earlier, gain momentum more quickly, and are more likely to be declared as winners." The contest mobility perspective indicates that those individuals with superior intellectual functioning can better capitalize on their sponsored mobility assets and, as such, gain more occupational prestige and higher income more quickly (Judge et al., 2010; Turner, 1960). Applying the

sponsored mobility perspective, perhaps their poorer cognitive and academic abilities result in ELBW survivors being less integrated into their educational and occupational environments, resulting in fewer opportunities for socioeconomic gains. For example, educators of ELBW survivors with impaired verbal abilities (i.e., reading and public speaking) may not encourage their ELBW students to partake in extracurricular activities such as athletics, arts, or student councils, resulting in smaller social networks and a lost opportunity for these individuals to gain networking skills and socializing skills in early life that may be beneficial in starting their career.

Contest mobility may provide a clearer explanation of the mediating role of specific cognitive abilities. For example, their impairment in fluid intelligence and abstract reasoning may place ELBW survivors at a disadvantage in terms of producing innovative ideas early in their careers, resulting in fewer opportunities for job promotions and pay raises. Further, potentially due to their poorer mathematical abilities, ELBW individuals may not be pursuing quantitatively focused careers, such as those in mathematics, engineering, or sciences, those typically known to have higher entrance incomes. Of their educational attainment up to ages 29-36, 5 ELBW individuals reported having less an a high school education, 37 reported completing high school, 38 reported completing college or university, while 8 reported having a graduate or professional degree (Saigal et al., 2016). Compared to ELBW individuals, more NBW participants reported completing college/university or a graduate degree (Saigal et al., 2016). Or, an additional explanation is that ELBW survivors with poorer verbal or academic abilities may not be inclined to ask for guidance, advice, or mentorship from their teachers or

employers, resulting in less networking and educational opportunities to improve their hard and soft employment skills.

However, longitudinal associations spanning over 20 years are rarely simple; therefore, emphasis must be placed on factors which may influence cognition and academic abilities, and how cognitive abilities may influence factors associated with favourable socioeconomic attainment. The most explored pathway explaining the mediating role of childhood cognition on later socioeconomic outcomes is that poor cognitive abilities in early life are associated with less educational attainment, resulting in limited employment prospects and opportunities for wage increases (Basten et al., 2015; Nomura et al., 2009; Strenze, 2007). Educational attainment was a significant factor in all personal income models, suggesting that each year of education was associated with an increased income of $1,800-2,000. However, within our sample of participants, ELBW survivors had the same number of years of education (approximately the equivalent of an undergraduate post-secondary education) as NBW participants, indicating that educational attainment may not provide the only explanation of how early cognition influences socioeconomic outcomes.

When our cohort was in the third decade of life, it was reported that childhood SES contributed to the variance in income between ELBW and NBW groups (Goddeeris et al., 2010). However, our models examining socioeconomic outcomes in the fourth decade of life indicate that childhood SES did not influence the income attainment of participants, but did impact full time employment. Although this finding may be influenced by our sample composition and attrition, this finding may suggest that higher

childhood SES may help ELBW survivors obtain employment, but that cognitive abilities are a more critical factor in ELBW survivors than early socioeconomic factors in predicting socioeconomic growth.

Apart from cognitive mediators, sex was the strongest predictor of socioeconomic outcomes. Women reported earning less annual income and were less likely to report full time employment compared to our male participants. This result is not surprising and is potentially indicative of normal functioning; our cohort is at reproductive age and many may be having children, and thus perhaps are on maternity leave, working part-time, or supporting their family in the home. Twenty ELBW survivors and 29 NBW participants reported having children at ages 29-36 (Saigal et al., 2016); however, due to our small sample it was out of scope to explore how these variables influenced socioeconomic outcomes in our cohort.

Lastly, it is important to remember that ELBW survivors are known to have a range of impairments apart from of cognitive functioning, including difficulties in motor coordination (Poole et al., 2015), socializing skills (Schmidt, Miskovic, Boyle, & Saigal, 2008), and adverse psychological behaviours (Van Lieshout, Boyle, Saigal, Morrison, & Schmidt, 2015). In keeping with the cumulative advantage framework, an alternative explanation for our results may be that these psychological and physical factors together place ELBW survivors at greater disadvantage in early adulthood, an age when ELBW survivors are first exposed to independence (i.e., finishing their education, moving out of their parent's home, or getting married). As such, the increased physical and neurological disadvantage seen in their late twenties/early thirties may be associated with reduced

productivity or absenteeism at their job (Mauss, Li, Schmidt, Angerer, & Jarczok, 2015), resulting in less favourable income and employment outcomes.

Study Implications

The results of this study and similar studies in the preterm literature provide evidence that early monitoring and perhaps even targeted interventions applied in childhood to improve cognitive functioning or academic functioning may have the potential to enhance socioeconomic outcomes and quality of life for those born prematurely. School interventions, such as additional tutoring (particularly in mathematics), special educational planning, individualized educational plans, and providing educators with knowledge of the cognitive and behavioural challenges ELBW/preterm children may face have been recommended and may provide the training and support that ELBW survivors – particularly for those with NSI – require to enhance their cognitive abilities (Jarjour, 2015; Johnson, Gilmore, Gallimore, Jaekel, & Wolke, 2015).

Limitations

Despite the strengths of the presented study a number of limitations should be mentioned. Our socioeconomic outcomes may have been subject to reporting bias as they were self-reported by participants. However, we attempted to minimize this bias by asking participants clear questions about multiple sources of their annual income and providing clear definitions of full time employment. Secondly, as the cohort has been followed for 30 years, sample attrition has ensued which has limited our statistical power and sample size. In post hoc power analyses using G*Power software, it was seen that

our models with personal income as the dependent variable were sufficiently powered, but our models with full time employment as the dependent variable were not.[2] However, we attempted to minimize any bias caused by this attrition by adjusting for factors associated with differential attrition over time (i.e. male sex, childhood SES). Moreover, we performed and reported on bootstrapped estimates of the mediated effect from 10,000 resampled data sets. Additionally, it was seen that ELBW non-participants had lower childhood cognitive abilities compared to participants, which may be underestimating the true mediating effect of childhood cognitive abilities. As such, future research in larger samples is required to replicate our findings. Lastly, although our cohort is the longest longitudinally followed cohort of ELBW survivors in the world, advances in neonatal care and differences in socioeconomic climates for ELBW infants born after our cohort may reduce the generalizability of our results. However, it is well established that ELBW survivors born since the 1990s also suffer from impaired cognitive abilities (Aarnoudse-Moens et al., 2009; Bhutta, Cleves, Casey, Cradock, & Anand, 2002), and as such, we feel our results are useful to guide interventions for ELBW survivors of all ages. Moreover, given increasing rates of attrition in studies of preterm survivors, our study may present a unique opportunity to address our research question in a group at very high vulnerability to adverse long-term outcomes.

[2] For personal income models, our power level was approximately 0.87, assuming a small-medium effect size (f^2=0.075), α level of 0.05, and sample size of 157 with 6 predictors in the model. For full time employment models, using an odds ratio for full time employment of 2.05 calculated from our sample, a probability of full time employment within ELBW survivors of 0.61 (48/78), α level of 0.05, and total sample size of 153, our power level was approximated to be 0.52.

Conclusions

Our findings suggest that childhood cognition, particularly overall intelligence and mathematical abilities, partially mediates the association between being born at ELBW and income attainment in adulthood. Further, our findings suggest that the mediating role of childhood cognitive abilities may be stronger in survivors born with NSI. Future research should explore the mediating influence of childhood cognitive abilities in larger and more contemporary samples of preterm survivors to establish the robustness of our findings. This work suggests that early cognition can have a lasting impression on socioeconomic outcomes in ELBW survivors. Therefore, clinical and public health interventions aimed at reducing low birth weight/preterm birth and enhancing early cognitive functioning may be important in order to ensure that infants that face perinatal adversity can lead the healthiest and most productive lives possible.

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CHAPTER FOUR

STUDY 3

TITLE: How Does Childhood Intelligence and Early Psychosocial Adversity Influence Earning Attainment among Extremely Low Birth Weight Survivors in the Fourth Decade of Life? A Test of the Cognitive Reserve Hypothesis

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CONTEXT AND IMPLCATIONS OF THIS STUDY: The third and final study of this thesis builds upon Study 1 and Study 2 by testing the cognitive reserve hypothesis while examining socioeconomic outcomes. This study explores the moderating effects of early life intelligence on psychosocial adversities in the prediction of adult income attainment. Under the cognitive reserve hypothesis, it is thought that enhanced early IQ should be protective against physical and psychological insults, reserving cognitive capacity and allowing for an individual to gain upward social mobility.

In this study, we utilize childhood general intelligence (IQ) as our cognitive measure to determine how it moderates the effects of four postnatal psychosocial adversities. We examine two adverse social exposures (low childhood socioeconomic status and childhood sexual abuse), and two psychological adversities (lifetime diagnosis of a non-substance psychiatric disorder and trait neuroticism). The findings of this study suggest that cognitive reserve may not apply to extremely low birth weight survivors as those who had higher IQ and who faced more postnatal adversity reported *lower* annual earnings in adulthood.

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Abstract

Background: Evidence suggests that early psychosocial and perinatal adversity negatively influences individual socioeconomic trajectories, while enhanced early cognitive abilities are known to improve them. While many studies have examined each of these factors separately, little is known about how they jointly influence social mobility. Greater cognitive reserve is thought to act as a buffer against adverse early life exposures which may reduce their impact on socioeconomic trajectories; however, its moderating influence has never been studied, nor studied in a population who have also faced significant perinatal adversity.

Objective: To determine if associations between postnatal psychosocial adversity and socioeconomic attainment (defined by personal annual earnings) in extremely low birth weight (ELBW) survivors at age 29-36 is moderated by cognitive ability (defined by childhood IQ assessed at age 8).

Methods: We examined if childhood IQ (assessed at age 8 via the *Wechsler Intelligence Scale for Children – Revised*) moderated the association between four different types of postnatal adversity – low childhood socioeconomic status, childhood sexual abuse, presence of a psychiatric disorder, and trait neuroticism – and annual earnings at age 29-36 in a sample of 100 ELBW survivors. Moderation effects were tested using multivariable linear regressions adjusted for age, sex, and educational attainment.

Results: ELBW survivors who had faced significant psychological postnatal adversity (psychiatric disorder diagnosis, trait neuroticism, and childhood sexual abuse) with *higher* childhood IQ generally reported *lower* adult annual incomes. No interaction was

seen with childhood cognition and socioeconomic disadvantage on adult income attainment.

Conclusions: The association between postnatal psychological adversity and income attainment was moderated by childhood IQ. However, our findings suggest that ELBW survivors with enhanced cognitive abilities may be more vulnerable to early psychological adversities which may have significant adverse socioeconomic consequences in later life. These findings should be replicated in other preterm samples and future research should continue to explore the early biopsychosocial factors that jointly impact adult functioning to identify target areas for intervention.

Introduction

Income attainment is a critical determinant of health. One's income influences where we live, our behaviours, and our social support networks, all of which greatly impact our risk of disease (Frieden, 2010). Lower personal or household income has been associated with a higher risk of cardiovascular diseases such as hypertension and obesity (Diez-Roux, Link, & Northridge, 2000); depression, anxiety, and substance-related disorders (Sareen, Afifi, McMillan, & Asmundson, 2011); and all-cause mortality (Osler et al., 2002). Individuals with lower incomes are also less likely to access health services, limiting the opportunity to improve their health (Stewart et al., 2001). As such, it is important to examine individual-level factors that impact income and socioeconomic attainment.

One of the strongest predictors of income attainment in general population samples is cognitive ability. Decades of literature have established that cognitive abilities (typically studied using intelligence quotient, IQ) in early life are associated with favourable labor and income outcomes in adulthood, even after adjustment for confounding variables such as childhood socioeconomic status and educational attainment (Strenze, 2007). Research suggests that individuals with better early cognitive abilities are more likely to be offered and pursue more prestigious educational and occupational opportunities (Ceci & Williams, 1997; Ng, Eby, Sorensen, & Feldman, 2005; Turner, 1960), and may be able to better capitalize on their language skills, emotional intelligence, and abstract thinking to network and gain opportunities for social mobility (Judge, Klinger, & Simon, 2010; Rindermann, 2012; Turner, 1960). When

assessing the association between cognitive abilities and socioeconomic attainment, examining these abilities in childhood (i.e., ages 6-12) is preferred since it is less biased by one's educational experiences than assessments at later ages (Strenze, 2007).

Within general population samples, it has been hypothesized that cognitive abilities influence income and socioeconomic attainment in two ways. The first suggests that enhanced childhood cognitive abilities lead to better educational attainment, and that this in turn is associated with higher income, job security, and more prestigious occupation (Ceci & Williams, 1997; Strenze, 2007). The second pathway suggests that cognitive abilities may interact with early life personal and contextual factors to influence an individual's personality, interests, and experiences, and as a result influence later educational aspirations and socioeconomic attainment (Dubow, Boxer, & Huesmann, 2009; Rowe, Vesterdal, & Rodgers, 1998). Compared to the first mechanism, the joint influence of early life cognition and psychosocial context on socioeconomic attainment has rarely been studied (Conger & Donnellan, 2007). As early life psychosocial disadvantage is known to place an individual at risk for poorer socioeconomic attainment (Blanden, Gregg, & Macmillan, 2007; Dubow et al., 2009; Johnston, Propper, Pudney, & Shields, 2014; Zielinski, 2009), it is important to know if or how cognitive abilities mitigate associated risks. This knowledge has the potential to provide a more holistic view of what factors in early life most greatly influence socioeconomic trajectories, which may be used to predict risk and inform policy, as well as the development of early interventions.

One framework that can be used to understand how childhood cognition and early contextual factors jointly influence socioeconomic success is the cognitive reserve hypothesis. Put forward by Stern, it posits that human brains affected by physical or psychological insults can cope and mitigate these risks by activating different neural networks and cognitive processes (Stern, 2002). This theoretically maintains our neurological functioning despite brain alterations caused by adversity, such as trauma, poverty, or illness. Cognitive reserve may be defined in a variety of ways (e.g., brain size, synapse count, or neuroplasticity markers); however cognitive assessments (e.g., IQ assessments) are considered a superior representation of cognitive reserve since they more closely represent cognitive functioning (Deary & Batty, 2007; Stern, 2009).

As cognitive reserve is thought to protect against psychological and physical adversity (Barnett, Salmond, Jones, & Sahakian, 2006), individuals with greater cognitive reserve may be less affected by adversities and be able to pursue higher education and perform adequately in the workforce, leading to socioeconomic success. Conversely, for those individuals with lower cognitive reserve, adversity may disrupt their socioeconomic trajectory, resulting in greater risk of downward social mobility. Accordingly, it is important to test this hypothesis by exploring early adversities that may greatly impact socioeconomic attainment.

The Influence of Early Life Adversity on Socioeconomic Attainment

It has been established that unfavourable social and psychological contexts in childhood, adolescence, and early adulthood are associated with poorer socioeconomic trajectories. For example, the positive correlation between childhood socioeconomic

status (SES) and adult SES has been supported by research since the 1960s (Coleman, 1966). Work in this field suggests that children with lower parental SES receive fewer and poorer educational opportunities, leading to fewer opportunities for social mobility (through education or employment) as adults (Currie, 2008; Sirin, 2005).

Another important factor which may influence socioeconomic attainment is one's propensity to psychological distress and mental illness. For example, trait neuroticism (i.e., sensitivity to emotional stimuli and a tendency to react more strongly to these) is associated with poorer self-efficacy, loss in motivation, and less confidence in the workplace, which may result in fewer opportunities for socioeconomic gains (Judge & Ilies, 2002). It is also associated with lower salaries, fewer promotions, and lower career satisfaction (Ng et al., 2005). Studies have also suggested that there is a negative association between neuroticism in childhood and lower adult earnings (Blanden et al., 2007). Further, higher neuroticism in adulthood has been seen to be a predictor of earning loss associated with workdays missed due to mental or physical illness (Graham, Mroczek, & Elleman, 2015).

Psychiatric disorders including depression, anxiety, and attention deficit disorders have also been linked to poorer educational attainment, income, and socioeconomic mobility in adulthood (Breslau, Lane, Sampson, & Kessler, 2008; Johnston, Propper, Pudney, & Shields, 2014; Kirsh, 2000). Although the individual pathways for each mental disorder may differ, individuals who suffer from a psychiatric disorder in early life are more likely to have lower educational attainment and difficulty maintaining stable employment (Johnston et al., 2014). Further, it is also thought that psychiatric distress

may be associated with poorer social mobility due to its strong association with previous environmental adversity, such as poor home environment, resulting in inadequate emotional skill, material disadvantage associated with poverty, and lack of social support networks (Power, Stansfeld, Matthews, Manor, & Hope, 2002).

Another significant predictor of income attainment is exposure to sexual abuse in childhood or adolescence. Sexual victimization can alter developmental trajectories and lead to long term socioeconomic consequences. Data from the American National Comorbidity Survey suggests that the odds of having an income below the poverty line is 80% greater in victims of child sexual abuse (Zielinski, 2009). Some of the immediate effects of sexual victimization can be symptoms of anxiety, depression, and/or post-traumatic stress disorder (Macmillan, 2000, 2001), which negatively impact the educational aspirations and occupational attainment of survivors (Macmillan & Hagan, 2004). Further, victims of early life physical and sexual abuse have lower self-efficacy and alienate themselves from growing close relationships with individuals in their social support network (Macmillan, 2001). This isolation may result in fewer opportunities to enhance verbal and language abilities, reducing the opportunity to network and build the communication abilities necessary to excel in the work place and gain occupational prestige.

Perinatal Adversity and Socioeconomic Attainment

In addition to the early postnatal psychosocial adversities mentioned above, a field of study is beginning to suggest that unfavourable outcomes resulting from perinatal adversity, often indexed by low birth weight or preterm birth, may be associated with

poorer income and socioeconomic attainment in adulthood (Almond & Currie, 2011). Data from the Helsinki Birth Cohort suggests that those born late preterm (34-36 weeks gestation) are more likely to have lower annual incomes and are at increased risk of downward social mobility compared to those born at term (40 weeks gestation) at ages 56-66 (Heinonen et al., 2013). Within this literature, a gradient effect has been seen suggesting that those born the most preterm or at the lowest birth weights have the lowest earnings in adulthood (Almond & Currie, 2011; Moster, Lie, & Markestad, 2008).

Those born at extremely low birth weight (ELBW, <1000 g) are the tiniest infants and the most vulnerable of any preterm survivor. It is becoming evident that their early biological adversity negatively affects their socioeconomic attainment. Data from the oldest cohort of ELBW survivors in the world suggests that these individuals have lower annual salaries and are less likely to be employed in their early twenties than those born at normal birth weight (NBW, ≥2,500 g) (Goddeeris et al., 2010). Unfortunately these economic discrepancies have persisted into their fourth decade of life. Indeed, at age 29-36, these ELBW survivors were also less likely to work full time and were more likely to receive social assistance compared to individuals born at NBW. Furthermore, ELBW survivors reported annual earnings that were $20,000 less than their NBW counterparts (Saigal et al., 2016). Due to these stark differences in socioeconomic attainment, it is critical to understand potential moderators of ELBW survivors' reduced social mobility.

Apart from their poorer cardiovascular and psychiatric profiles, intellectual impairment is one of the most common and important disabilities faced by ELBW survivors. The poorer cognitive function ELBW survivors face has been recognized in

very early life (Aarnoudse-Moens, Weisglas-Kuperus, van Goudoever, & Oosterlaan, 2009; Bhutta, Cleves, Casey, Cradock, & Anand, 2002) and is thought to persist at least into early adulthood (Eryigit Madzwamuse, Baumann, Jaekel, Bartmann, & Wolke, 2015). Research suggests that the cognitive impairments that ELBW individuals face may arise from cerebral white matter injury in regions such as the thalamus, basal ganglia, cerebral cortex, and cerebellum (Volpe, 2009). Due to their shortened gestational age and exposure to environmental stressors in neonatal intensive care units, it has also been proposed that ELBW individuals have smaller frontal and parietal lobe regions, as well as dysfunctional connectivity in their temporal lobes (Peterson et al., 2003; Smith et al., 2011). These abnormalities are associated with cognitive delays, such as poorer general intelligence, academic abilities, verbal comprehension, and arithmetic abilities (Saigal, Szatmari, Rosenbaum, Campbell, & King, 1991; Wolke et al., 2015). Further, these abnormalities in ELBW and preterm groups may result in language and social difficulties and psychomotor impairments (Melbourne, Murnick, Chang, Glass, & Massaro, 2015; Tich et al., 2011).

Despite the plethora of literature exploring the influence of cognitive abilities on income attainment in general population samples, only one study to our knowledge has directly explored the influence of cognitive abilities on socioeconomic attainment in a preterm group. In a study utilizing data from two British population birth cohorts, childhood intelligence, reading, and mathematical abilities strongly explained wealth attainment at age 42 in individuals born before 36 weeks gestation (Basten, Jaekel, Johnson, Gilmore, & Wolke, 2015). Although this study by Basten and colleagues (2015)

reported that preterm individuals with poorer early cognition and academic abilities may be at risk for poorer educational attainment, their study did not examine any postnatal stressors that may occur in childhood or adolescence which may influence wealth attainment.

Based on the association between early cognition and socioeconomic attainment seen in general populations, it is reasonable to suggest that if an ELBW survivor has enhanced cognitive function, it should help them achieve socioeconomic success and protect them against stress associated with postnatal adversity. As such, further evidence is needed to understand the postnatal mechanisms influencing socioeconomic attainment in high-risk pediatric survivors.

Can the Cognitive Reserve Hypothesis Explain the Socioeconomic Attainment of ELBW Survivors?

It is unclear if cognitive reserve explains the income attainment of ELBW survivors. According to the cognitive reserve principles, ELBW survivors with higher cognitive reserve (represented by their childhood cognitive function) should be able to overcome adversity and pursue stable employment and higher incomes, while those with lower cognitive reserve will not. This is supported by recent findings from a longitudinal sibling-pair study examining the joint influence of neuroplasticity (the ability to overcome adversity from neurologically damaging environments) and birth weight on adult wages at age 53. Using data from the Wisconsin Longitudinal Study, Cook and Fletcher (2015) examined how genes associated with neuroplasticity (defined by the number of favourable alleles of the APOE, BDNF, and COMT genes) interacted with

birth weight (a proxy for prenatal adversity) to influence wage earnings in the sixth decade of life. Their results suggest that the positive association they observed between birth weight and wages at age 53 is upheld in individuals with low-moderate neuroplasticity scores (i.e., low cognitive reserve), but is reduced in individuals with high neuroplasticity scores (i.e., high cognitive reserve) (Cook & Fletcher, 2015).

Although Cook and Fletcher's study extends the literature exploring the mechanisms of how perinatal adversity may affect socioeconomic outcomes in later adulthood, their study has four main limitations. Although the authors make a compelling argument about the "resiliency genes" (APOE, BDNF, and COMT) studied, these genes are also associated with myriad outcomes (such as metabolism, chronic physical conditions, and psychiatric disorders), and so it is unclear if these are specific markers of neuroplasticity/cognitive reserve or general health (Dunning et al., 1999; Jiménez-Jiménez, Alonso-Navarro, García-Martín, & Agúndez, 2014; Mahley, 1988; Maritim, Sanders, & Watkins, 2003). The authors posit that poor intrauterine nutrition is a leading factor of low birth weight and poor cognitive function, which in turn influences poorer earnings. While this may be true, low birth weight is a result of many factors (Kramer, 1987) and cognitive development may be greatly influenced by early postnatal advantages or disadvantages (Strenze, 2007) that the study could not account for. Thirdly, the mean birth weight of their sample was approximately 3,370 g (SD≈635 g) (Cook & Fletcher, 2015). Under the central limit theorem, this suggests that less than 1% of their sample was born at 1,465 g or less, potentially limiting the generalizability of their results to ELBW or very low birth survivors (< 1,500 g). This is important to consider as these

individuals generally face greater perinatal adversity and are at higher risk of poorer cognitive function (United Nations Children's Fund and World Health Organization, 2004). The final limitation is that their cohort was born between 1939 and 1948 (Herd, Carr, & Roan, 2014), potentially limiting these findings to individuals born in later decades. This is particularly important to consider as many very or extremely low birth weight infants would not have survived hospital discharge at this time. Due to these limitations, it is important to extend the work by Cook and Fletcher and explore the influence of cognitive reserve on income attainment in an extremely low birth weight sample.

Although cognitive reserve may aid in preserving cognitive function in light of postnatal adversity, the perinatal adversity associated with ELBW may undermine the usual benefits associated with cognitive reserve (Cosentino & Stern, 2012). The extreme perinatal adversity ELBW survivors face may make them more vulnerable to the effects of postnatal adversities such as poverty, trauma, and poor psychological health, nullifying the protective effects of cognitive reserve on socioeconomic attainment. Further, it is hypothesized that cognitive reserve in populations known to have intellectual impairments may only help to maintain cognitive function, not protect against outside adversity (Stern, 2009). However, it is unclear if this is true within the population of ELBW survivors as the impact of cognitive reserve on socioeconomic attainment in light of postnatal contextual factors has not yet been examined in those experiencing significant perinatal adversity.

It is clear that early biopsychosocial adversity has a lasting impact on socioeconomic attainment in adulthood. Indeed, the influences of cognitive abilities and psychosocial context in early life have been examined separately as predictors of socioeconomic outcomes in general population samples (Basten et al., 2015; Ng & Feldman, 2010; Strenze, 2007). However, socioeconomic trajectories based upon the interaction of cognitive abilities and psychosocial context have not yet been thoroughly studied in the general populations (Conger & Donnellan, 2007), let alone studied in individuals who have faced significant perinatal adversity (e.g., low birth weight survivors). Due to their perinatal vulnerability, it is important to test if the positive influence of cognitive reserve persists in ELBW survivors despite their exposure to other postnatal adversities.

Exploring the complex association between cognitive reserve, psychosocial adversity, and socioeconomic attainment in ELBW survivors is critical to our understanding of what factors most strongly influence socioeconomic attainment and can potentially help us to predict and mitigate socioeconomic disadvantage in this population. Furthermore, understanding these associations is also important at a population level in modelling human capital – a function of the current health and its depreciation rate – of the labor force in developed countries (Almond & Currie, 2011). As roughly 17% of all infants are born at low birth weight/preterm and that the incidence of low birth weight is not decreasing, (United Nations Children's Fund and World Health Organization, 2004) a significant proportion of the labor force will have faced early biological adversity similar to ELBW survivors. Lastly, to our knowledge, the cognitive reserve hypothesis has not

been thoroughly studied in early life, explored as a predictor of socioeconomic success, or in samples that have faced perinatal adversity. Studying cognitive reserve in an ELBW sample would help further the cognitive reserve field by uncovering how cognitive reserve functions in this vulnerable population.

Study Objective

To examine if cognitive reserve protects against postnatal psychosocial adversities that may affect socioeconomic development in those who have already been exposed to perinatal stresses, the present study examined whether childhood cognitive function (assessed at age 8) moderated the association between psychosocial adversity and personal annual earnings in ELBW survivors at age 29-36. We examine childhood SES and childhood sexual abuse as social-environmental adversities, and trait neuroticism and lifetime diagnosis of a psychiatric disorder as psychological adversities. Given previous literature exploring cognitive abilities, psychosocial contexts, and perinatal adversity as predictors of social mobility, we hypothesized that those ELBW survivors with *lower* childhood IQ (i.e., lower cognitive reserve) would be less resistant to the negative effects of these *adverse* psychosocial contexts, resulting in lower income attainment in adulthood.

Methodology

Participants

Our study examined socioeconomic attainment from adults who were born at ELBW. Between 1977 and 1982, 379 ELBW infants born between 501 – 1,000 g were recruited at birth in central west Ontario, Canada. Two-hundred and eighteen of these

infants died before hospital discharge, resulting in a sample of 179. After hospital discharge, ten children subsequently died. At age 8, 143 survivors participated in collection of intellectual and cognitive abilities. At ages 22-26, 149 ELBW participants completed sociodemographic assessments. At ages 29-36, 100 survivors participated in collection of socioeconomic and mental health data.

Outcome Measure: Annual Personal Income

At ages 29-36, all participants completed a standardized sociodemographic questionnaire derived from the *Ontario Child Health Study* questionnaires (Boyle et al., 1987). In this self-reported measure, ELBW participants were asked to report the dollar amount they had received over the past 12 months from seven sources: wages and salaries before deductions, self-employment, employment-insurance benefits, provincial and federal child benefits, social assistance, child/spousal support, and any other income sources such as dividends, interests, capital gains, and gratuities. The amount from each source was summed together to calculate annual earnings. Based on 2013 national estimates, the median total income of individuals in Canada was approximately $32,020 (Statistics Canada, 2015).

Moderator Measure: Cognition at Age 8

Childhood cognitive abilities were assessed via the *Wechsler Intelligence Scale for Children – Revised* (WISC-R) at age 8. Details of this assessment have been previously reported (Saigal, Szatmari, Rosenbaum, Campbell, & King, 1991). The WISC-R cognitive assessment is comprised of 10 subscales that examine a range of cognitive abilities such as processing speed, alertness to detail, visuospatial abilities, fluid

intelligence, verbal comprehension, reading, and language abilities (Wechsler, 1974). Each of these scales are combined to procedure an overall IQ score (M=100, SD=15). The WISC-R Full Scale IQ score is not only seen to have high test-retest reliability in general populations (α=0.98), but high reliability in child populations with learning disabilities (α=0.85) as well (Covin, 1977; Irwin, 1966; Tuma & Appelbaum, 1980).

Postnatal Adversity Measures

We examined the influence of two social and two psychological adversity variables on personal income attainment in ELBW survivors. Childhood SES and childhood sexual abuse were selected to represent social adversities, and diagnosis of a lifetime non-substance psychiatric disorder and trait neuroticism were selected to represent psychological adversities. These factors were assessed at age 8, 22-26, and 26-39, respectively. **Childhood SES** was assessed at age 8 using the Hollingshead 2-factor index. SES was self-reported by the parents of participants by indicating parental education level and occupational prestige (Hollingshead, 1969). This index ranges from 1 (indicating highest SES level) to 5 (indicating lowest SES level).

Childhood sexual abuse (CSA) was reported by participants retrospectively at age 22-26 using questions from an abbreviated version of the *Childhood Experiences of Violence Questionnaire* (Tanaka et al., 2012; Walsh, MacMillan, Trocmé, Jamieson, & Boyle, 2008). Participants were asked "before age 16 when you were growing up, did anyone ever do any of the following things when you did not want them to: touch the private parts of your body or make you touch their private parts, threaten or try to have sex with you, or sexually force themselves on you?" This item has been shown to have

acceptable test-retest reliability (K=0.91), as well as construct and criterion validity (K=0.69) with other abuse measures (Tanaka et al., 2012). Participants had the option to report *never, 1-3 times, 3-5 times, 6-10 times,* or *more than 10 times*. Based on the known skewness of victimization variables (Macmillan, 2000), we chose to dichotomize this variable into *never abused* or *previously abused* for analyses.

At age 29-36, the **lifetime presence of a psychiatric disorder** was assessed using the *Mini International Neuropsychiatric Interview* (MINI). The MINI is a validated, structured psychiatric diagnostic interview (Sheehan et al., 1998) that aligns to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) and the *International Classification of Diseases, 10th Revision* psychiatric diagnoses. The MINI was administered to each ELBW participant in a private room by two trained graduate students at McMaster University. Additional details of this assessment have been previously reported (Van Lieshout, Boyle, Saigal, Morrison, & Schmidt, 2015). This interview assessed the lifetime prevalence of major depression, bipolar, dysthymia, panic, posttraumatic stress disorders, and alcohol/substance disorders. Given our limited sample size and since ELBW survivors are at increased risk for non-substance use disorders, but at *reduced* risk of substance use problems (Van Lieshout et al., 2015; Mathewson et al., 2016), we combined all non-substance disorder into a single summary estimate: *presence* or *absence of a lifetime psychiatric disorder.* Although lifetime psychiatric disorder presence was examined at the same time as income attainment, the MINI assessed the presence of psychiatric disorder *at any point in their lives* up to that point, not just in the present.

Lastly, since personality traits seen in early life are thought to be relatively stable until at least middle age (Caspi & Roberts, 2001; Milojev & Sibley, 2014), we examined **trait neuroticism** using the Eysenck Personality Inventory (EPI) at ages 29-36. The EPI is a 48-item questionnaire that produces four scales of different personality factors: extraversion, psychoticism, neuroticism, and social desirability/conformity (Eysenck, Eysenck, & Barrett, 1985; Lahat, Van Lieshout, Saigal, Boyle, & Schmidt, 2015). The neuroticism scale was calculated by summing the results of 12 questions; this scale has been shown to have adequate reliability in men (α=0.84) and women (α=0.80) (Eysenck et al., 1985).

Covariate Measures

Within our moderation models, we controlled for age, sex, and years of educational attainment since these are either associated with attrition in our sample or are known confounding factors (Basten et al., 2015; Strenze, 2007). The years of education each cohort member had successfully completed at age 29-36 were self-reported by participants. Childhood SES was also used as a covariate in CSA, psychiatric disorder, and trait neuroticism statistical models.

Statistical Analyses

All statistical analyses were performed using SAS version 9.3. We first examined the descriptive statistics of ELBW participants. We then assessed the influence of attrition in our cohort by comparing participants and non-participants on a number of variables, using independent sample t-tests (PROC T TEST) for continuous variables and Chi-square tests (PROC FREQ) for categorical variables.

To explore the moderating influence of childhood cognition on psychosocial context in predicting income attainment at 29-36, we performed hierarchal linear regression modelling (PROC REG). For each moderation model, three steps were performed. The first step regressed personal income attainment on each individual psychosocial adversity variable (i.e., childhood SES, CSA, psychiatric disorder, or neuroticism) and all covariates. The second step regressed personal income attainment on childhood IQ (WISC-R Full Scale IQ score), each individual psychosocial moderator, and all covariates. The third step regressed personal income attainment on all predictors from the second step and an interaction term between child IQ and the psychosocial factor. In models examining childhood SES as the adversity variable, childhood SES was not included in the first step, but was entered in the second and third steps.

To minimize collinearity and improve the accuracy our models, all continuous predictors were centered and childhood IQ was standardized (representing a 15.8 point increase) in our models. After completing regression analyses, any significant interactions were further explored using probing techniques for multiple linear regression (Preacher, Curran, & Bauer, 2006).

To account for the sample attrition in our cohort, we also performed a 10-iteration multiple imputation analysis to account for missing data. As no significant differences were seen in multiple imputation models, we report results only for the participants with complete data. Results of hierarchical linear regressions are reported as regression coefficients (β) and their standard errors. All statistical tests were two tailed using a α=0.05 significance level.

Results

Descriptive Statistics

Table 1. Sample Characteristics

	n	***M***	***SD***
Sociodemographic Characteristics			
Birth Weight (g)	100	834.9	132.74
Average for Gestational Age, AGA (n, %)		71	71
Small for Gestational Age, SGA (n, %)		29	29
Age (years)	100	32.08	1.69
Sex (Male, %)	100	39	39
Neurosensory Impairment (n, %)	100	26	13.76%
Social Predictor Variables			
Childhood (Parental) SES (n, %)	95		
I		5	5.26
II		16	16.84
III		44	46.32
IV		27	28.42
V		3	3.16
Childhood Sexual Abuse (n, %)	98	16	16.33%
Psychological Predictor Variables			
Eysenck Neuroticism Scale Score	96	5.6	3.8
Lifetime Psychiatric Disorder Diagnosis (n, %)	79	29	36.71%
Adult SES Variables (Age 29-36)			
Total Years of Education	97	16	2.75
Personal Annual Income ($)	88	26,484.65	23,721.36
Total Household Annual Income ($)	91	54,450.55	41,004.41
Full Time Employment This Year (n, %)	78	48	61.54
Cognitive Variables (Age 8)			
WISC-R Full Scale IQ	89	93.40	15.77

Table 1 summarizes the demographic characteristics of our 100 ELBW participants. Their average age was 32 years and the mean childhood IQ was 93 (SD=16). The majority of participants had a middle class childhood SES (46%) and 16 participants reported exposure to CSA (1-2 times, n=9; 3-5 times, n=6; and more than 10 times, n=1).

Our sample had a mean score of 5.6 (SD=3.8) on the Eysenck Neuroticism Scale and 37% of participants were identified to have a lifetime non-substance psychiatric disorder. The average reported annual personal income was $26,485 (SD=23,721.36)[3]. Compared to participants in the study, non-participants at the 29-36 year sweep were more likely to be male (p=0.02), have a lower childhood SES (p<0.001), and lower childhood IQ (M=87, SD=15, p=0.03, **Table 2**).

Table 2. Characteristics of Participants and Non-Participants

Characteristics	Participants		Nonparticipants		
	n	***M (SD)***	***n***	***M (SD)***	***p***
Number of Participants	100		79		
Gender (male)	100	39	79	45	0.02
Birth Weight, g	100	834.9 (132.7)	79	840.5 (110.0)	0.76
Gestational age, week	100	26.8 (2.0)	79	27.1 (2.4)	0.36
NSI (n, %)	100	26	79	25	0.41
SGA (n, %)	100	29	79	14	0.08
Childhood SES	95	3	61	4	<0.001
WISC-R Full Scale IQ	89	93.4 (15.8)	48	87.2 (15.4)	0.03
Childhood Sexual Abuse (n, %)	98	16 (6.3)	42	3 (7.1)	0.15

Psychological Adversity Models

To examine the moderating influence of cognitive reserve (represented by childhood IQ) on the association between psychosocial adversity and adult income attainment, we explored the influence of childhood SES, CSA, lifetime psychiatric disorder diagnosis, and trait neuroticism using a three-step hierarchical regression for each predictor (**Table 3**). We considered childhood SES and CSA as social adversity predictors and psychiatric disorder and trait neuroticism as psychological predictors.

[3] The median reported annual income for ELBW survivors was approximately $22,850.00.

Table 3. Social and Psychological Moderation Regression Analyses Predicting Income Attainment at ages 29-36 in ELBW survivors

Moderator Model	Predictor by Step	R^2	β	*SE*	*p*
Lifetime Non-Substance Psychiatric Disorder[1]	***Step 1***	0.22			
	Presence of Psychiatric Disorder		-16,687	5,863.41	0.0062
	Step 2	0.44			
	Presence of Psychiatric Disorder		-16,048	5,037.14	0.0024
	IQ		13,337	2,939.67	<.0001
	Step 3	0.56			
	Presence of Psychiatric Disorder		-14,241	4,524.64	0.0027
	IQ		19,135	3,031.52	<.0001
	IQ x Presence of Psychiatric Disorder		-23,333	6,093.71	0.0003
Trait Neuroticism[1]	***Step 1***	0.15			
	Neuroticism Score		-1,406.98	677.53	0.0416
	Step 2	0.32			
	Neuroticism Score		-1,460.90	608.46	0.0191
	IQ		11,319	2,717.25	<.0001
	Step 3	0.37			
	Neuroticism Score		-1,279.20	599.13	0.0365
	IQ		10,972	2,653.31	0.0001
	IQ x Neuroticism Score		-1,678.80	788.41	0.0370
Childhood SES[2]	***Step 1***	0.10			
	Childhood SES		1,134.01	2,912.54	0.6982
	Step 2	0.26			
	Childhood SES		-70.47	2,677.37	0.9791
	IQ		10,737	2,757.74	0.0002
	Step 3	0.26			
	Childhood SES		-43.98	2,746.11	0.9873
	IQ		10,755	2,800.07	0.0003
	IQ x Childhood SES		131.73	2,580.74	0.9594
Childhood Sexual Abuse[1]	***Step 1***	0.12			
	CSA		-10,708	7,398.33	0.1523
	Step 2	0.33			
	CSA		-15,031	6,572.16	0.0253
	IQ		13,678	2,966.91	<.0001
	Step 3	0.35			
	CSA		-10,509	7,309.02	0.1552
	IQ		15,164	3,138.73	<.0001

Moderator Model	Predictor by Step	R^2	β	*SE*	*p*
	IQ x CSA		-13,796	10,020	0.1731

1 Model covariates for all steps include: childhood SES, current age, educational attainment at age 29-36, and sex
2 Model covariates for all steps include: current age, educational attainment at age 29-36, and sex

In models examining the presence of a lifetime psychiatric disorder as the adversity predictor, the first regression step indicated that participants with a lifetime non-substance psychiatric disorder reported annual earnings $16,687 ($p$=0.006) lower at age 29-36 compared to participants without a psychiatric disorder. In the second step, participants with the presence of a psychiatric disorder reported annual earnings $16,048 ($p$=0.002) lower at age 29-36 compared to participants without a psychiatric disorder. Childhood IQ was a significant predictor of income attainment in this model, in that every standard deviation increase in IQ was associated with a $13,337 increase in reported adult earnings (p<0.0001). When examining the interaction of childhood IQ and presence of a psychiatric disorder (Step 3, **Figure 1**), participants with a psychiatric disorder who had higher childhood IQ reported a *lower* annual personal income (p=0.003). For those without psychiatric disorders, cognition was predictive of increased income.

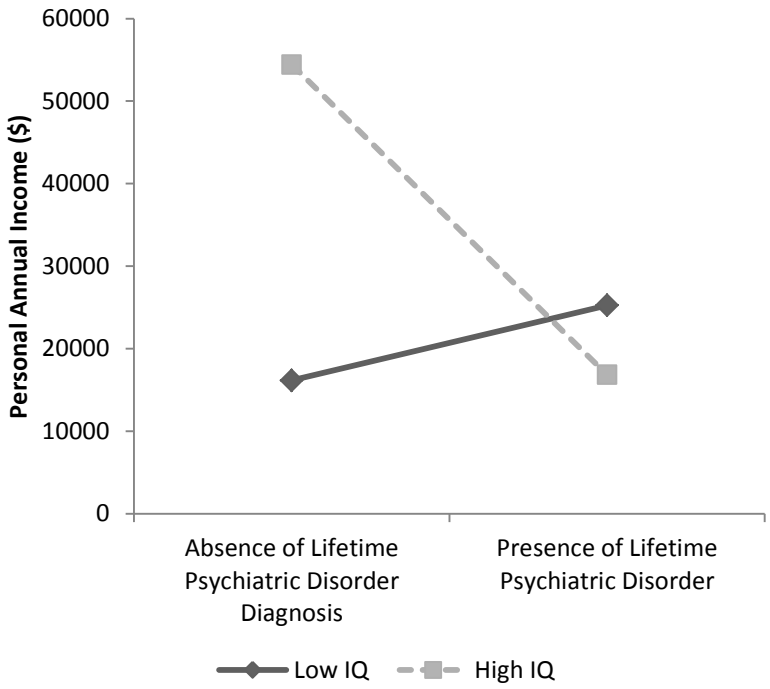

Figure 1. Interaction of Lifetime Psychiatric Disorder and Childhood IQ on Personal Income Attainment at age 29-36

Similar main effects were seen when trait neuroticism was examined. When both IQ and trait neuroticism were examined as predictors of adult income (Step 2), every standard deviation increase in IQ was associated with a $11,319 increase in annual earnings ($p<0.0001$), and every one-point increase in neuroticism score was associated with a $1,461 decrease in annual earnings at age 30 ($p=0.019$). When the interaction of these two predictors was examined (**Figure 2**), our model indicated that those with higher neuroticism scores and higher childhood IQ reported *lower* annual incomes at age 29-36 ($p=0.037$).

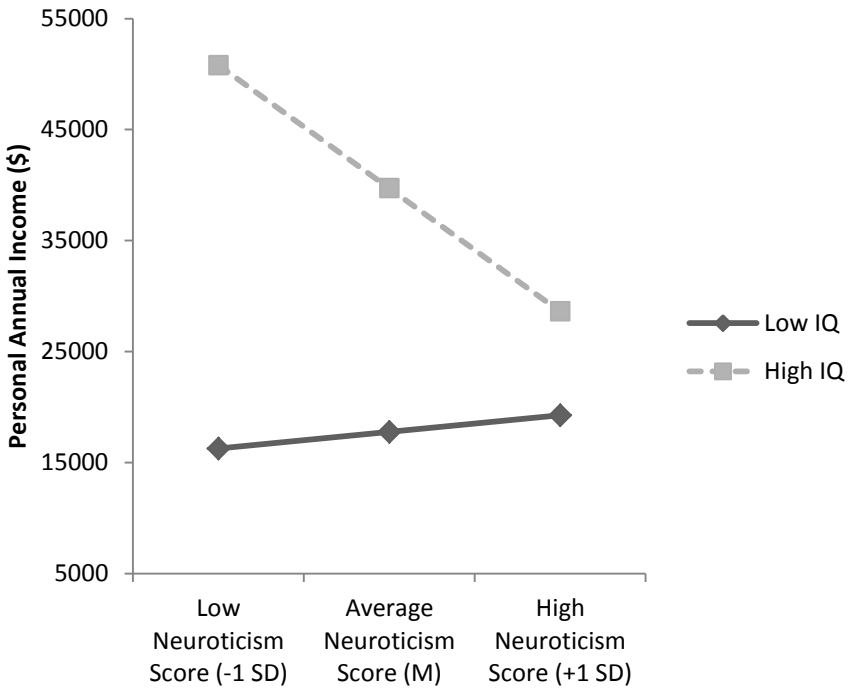

Figure 2. Interaction of Trait Neuroticism by Childhood IQ on Personal Income Attainment at age 29-36

Social Adversity Models

To explore the moderating role of cognitive reserve on the association between socio-environmental adversity and annual earnings at age 30, we explored the influence of childhood SES and CSA. Childhood SES was not a significant predictor of personal income at age 29-36 (Step 2, β=-70.47, p=0.979). This did not change in Step 3 of the model, indicating that there was no statistical moderating effect of childhood cognition on SES in predicting adult income attainment within our ELBW sample.

In our models examining CSA as an adversity factor, when entered in Step 1, there was no association between CSA and later earnings (β=-10,708, p=0.152). However, a significant negative association (β=-15,031, p=0.026) was found between CSA exposure and adult annual earnings in Step 2 when childhood IQ was added to the

equation. Although the coefficient of the interaction between CSA and childhood IQ was similar in magnitude to the findings of our psychological moderators (Step 3, β=-13,796), our model did not indicate the presence of a statistically significant interaction between CSA and childhood IQ on adult income (p=0.173).

As there was only one ELBW participant who reported CSA more than 10 times, we decided to perform a *post hoc* moderation analysis using three categories of the CSA variable (i.e., those who reported CSA 1-2 times compared to never being abused, CSA 3-5 times vs. never being abused, and CSA more than 10 times vs. never being abused) instead of the dichotomous CSA variable used in our original analyses. This *post hoc* regression analysis indicated that the variable for CSA reported more than 10 times did not offer enough information to provide a reliable estimate of income attainment (Austin & Steyerberg, 2015). Therefore, this variable was excluded from the model and no coefficient estimate was provided. However, we did find a significant main effect between CSA reported 1-2 and annual earnings (n=9, β=-17,061, p=0.049) but not for CSA reported 3-5 times (n=6, β=-6,464.61, p=0.546). When examining the interaction between CSA and childhood IQ (**Figure 3**), those who reported being sexually assaulted 1-2 times and who had higher IQ reported lower incomes at age 29-36 (β=-24,038, p=<0.0001).

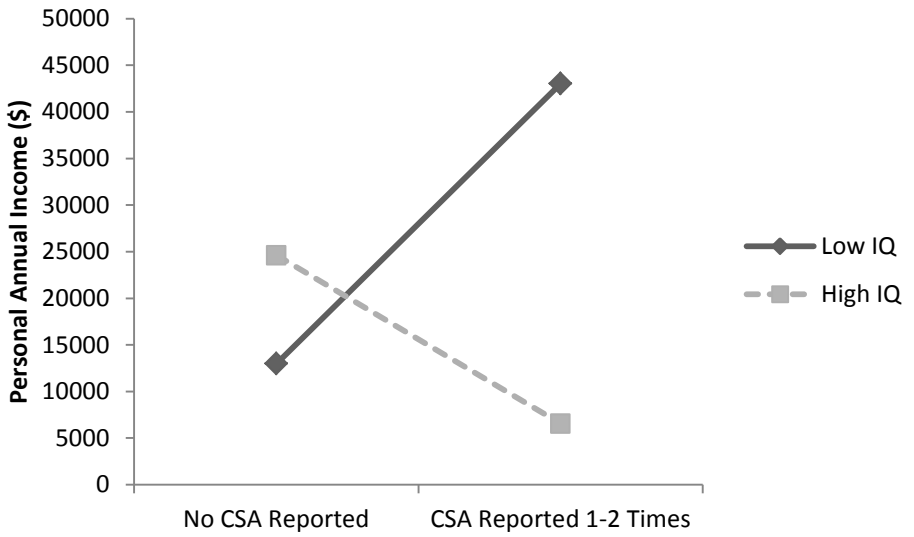

Figure 3. Post-Hoc Interaction of Childhood Sexual Abuse by Childhood IQ on Personal Income Attainment at age 29-36

Discussion

We set out to explore the moderating influence of cognitive function on the association between postnatal psychosocial adversity and personal income attainment in ELBW survivors in the fourth decade of life. Our results suggest that cognitive reserve may not protect against psychological and environmental adversity within ELBW survivors. Contrary to our hypothesis, our results suggest that among those born ELBW and exposed to psychosocial adversity (e.g., lifetime psychiatric disorder, higher trait neuroticism, and perhaps CSA), *higher* childhood IQ was predictive of lower annual earnings in adulthood. These findings suggest that enhanced cognitive abilities and reserve in ELBW survivors may not be protective against adverse contextual factors in the prediction of socioeconomic attainment in adulthood. However, we did not find that that childhood IQ moderated the association between early SES and income in ELBW survivors.

There is a surprisingly scarce amount of literature in general population samples that explore the moderation of adversity factors by childhood cognitive abilities on later income attainment and socioeconomic development. Accordingly, there has been a recommendation for studies to explore the joint influence of early life developmental factors on later health and socioeconomic health (Conger, Conger, & Martin, 2010). Work exploring the genetic and environmental heritability of IQ and educational attainment indicate that there may be an interaction between genetic heritability (i.e., IQ) and the early environment in influencing education and socioeconomic outcomes (Johnson, Deary, & Iacono, 2009; Rowe et al., 1998). However, this work has not yet explored all of the early adversity factors that our study has. As such, it is important to first discuss how the presence of a psychiatric disorder, trait neuroticism, CSA, and childhood SES may have individually influenced income attainment in our ELBW cohort before exploring the mechanisms of cognitive reserve.

Comparison with Previous Literature

It was apparent that the presence of a lifetime non-substance psychiatric disorder was strongly and negatively associated with income attainment in our ELBW cohort. Indeed, it is well established that individuals with mental health problems beginning in early life are less likely to succeed in elementary and secondary school, and less likely to graduate and pursue post-secondary education, negatively influencing their socioeconomic attainment (McLeod & Fettes, 2007). Further, as symptoms of their mental disorder (particularly depression), individuals may experience from lower self-esteem, efficacy, and confidence (American Psychiatric Association, 2013) influencing

their job performance and opportunities for promotional gains in job status and income (Judge & Hurst, 2007). Lastly, it is important to consider that individuals with a mental disorder beginning in early life may suffer episodes in adulthood and may face stigma from their employers, making it difficult to maintain stable and meaningful employment (McLeod & Fettes, 2007; Stuart, 2006; Twenge & Campbell, 2002).

Our results also suggest that there is a negative association between increasing trait neuroticism and income attainment at higher levels of childhood IQ in ELBW survivors. Our personalities strongly influence how we perceive socioeconomic incentives and opportunities (Boyce & Wood, 2011). A study that utilized data from the 1970 British Birth Cohort indicated that parental-reported trait neuroticism at age 5 was associated with higher income at age 33, but this was attenuated by cognitive and other behavioural factors in fully-adjusted models (Blanden et al., 2007). It is thought that neuroticism in later life (such as in young adulthood) may be more strongly linked to poorer socioeconomic attainment as it is more closely associated with emotional instability and anxiety which may decrease job performance, opportunities for advancement, and career satisfaction (Ng et al., 2005). However, literature suggests the negative effects of trait neuroticism on job satisfaction and performance may be mitigated by adequate coping mechanisms (Wei-Tao & Shih-Chen, 2007).

In our original model, income attainment was negatively affected in ELBW survivors who reported CSA. Our results from the second step of our hierarchical regression indicated that ELBW individuals who had experienced CSA reported annual earnings $15,000 less than ELBW survivors who had not experienced CSA. The

magnitude of this effect aligns to those seen in general population literature (Zielinski, 2009). In our original model, CSA did not moderate the association between childhood IQ and income attainment. In our *post hoc* analyses where we explored the CSA variable categorically, a significant interaction between childhood IQ and victimization occurring 1-2 times was present and similar in magnitude to our other psychological moderators. However, as such a small proportion of our sample reported CSA, these findings need to be considered in light of low statistical power and require further replication in other larger, preterm samples.

Contrary to previous literature and our hypothesis, childhood SES did not predict income attainment in adulthood. Although our results may have been influenced by attrition, our participants exhibited a range of childhood SES which may suggest that early life SES may influence income attainment differently in ELBW populations than in general populations. Within general populations, childhood socioeconomic status is typically associated with lower socioeconomic and income attainment in adulthood (Masten et al., 1999; Walker, Greenwood, Hart, & Carta, 1994). However, its influence is thought to be completely *indirect* through enhancing cognitive abilities and providing expectations within the home about educational attainment (Dubow et al., 2009). Lower parental socioeconomic status may influence earnings and social mobility by reducing access to educational opportunities and educational aspirations (Dubow et al., 2009; Masten et al., 1999). Further, it has also been thought that better SES in adolescence may be associated with better family functioning, reducing the risk for unfavourable personality traits, such as neuroticism (Conger et al., 2010; Schofield et al., 2011).

The Influence of Cognition on Income Attainment

Our results clearly indicate that early life cognitive abilities are a critical predictor of income attainment in ELBW survivors. In our models, every standard deviation increase in childhood IQ was associated with at least a $10,000 increase in reported income in the early to mid-30s. Although this finding may be influenced by the composition of our cohort and sample attrition that has ensued over the past 30 years, in studies exploring the association between low birth weight or preterm birth and later socioeconomic attainment (Heinonen et al., 2013; Lindström, Winbladh, Haglund, & Hjern, 2007; Moster et al., 2008), it has been hypothesized that impaired intellectual ability is a critical mechanism linking these two factors. Similar results to our study were seen in a report from Basten and colleagues (2015) that explored the mediating role of childhood cognitive abilities on wealth attainment at age 42 (as defined by family income, social class, housing, and self-perceived financial status) in individuals who were born preterm. Their results suggest that the impaired cognitive abilities (particularly general intelligence and arithmetic abilities) preterm and low birth weight survivors face may place them at risk for learning disabilities, potentially leading to academic and professional underachievement, and may result in lower earnings and socioeconomic attainment (Basten et al., 2015; Heinonen et al., 2013; Lindström et al., 2007; Moster et al., 2008). However, the authors did not explore the interaction of childhood cognition with other postnatal factors on wealth attainment.

The Influence of Cognitive Reserve: Potential Mechanisms

Contrary to our hypothesis, our results suggest that a negative association exists between the presence of a lifetime psychiatric disorder, trait neuroticism, and perhaps CSA and income attainment at *higher* levels of childhood IQ. This suggests that the cognitive reserve hypothesis may not be upheld in ELBW survivors.

The first reason why the cognitive reserve hypothesis may not hold in our ELBW sample was because our sample was comprised of individuals exposed to significant perinatal adversity. The physiological adversity associated with ELBW adversity may alter cognitive development in such a way that cognitive reserve does not apply in these individuals. According to Stern (2009), cognitive reserve under these contexts may only maintain cognitive function and not protect against outside adversity. However, if this was truly the case then ELBW survivors who faced adversity with *lower* childhood IQ should have reported lower incomes; this was not supported by our findings. As such, there may be other mechanisms occurring explaining this association.

Within general populations, developmental trajectories are heavily dependent on adequate psychosocial resources beginning in early life (Conger et al., 2010; Masten et al., 1999). Individuals with access to supportive teachers, parents, peers, and cognitive-enriching environments typically have more opportunities to enhance their cognitive skills and have higher educational and occupational aspirations (Dubow et al., 2009). This in turn typically leads to greater occupational success and higher earnings (Conger & Donnellan, 2007). These resources are usually uncommon in children who face early life adversity (e.g., poor socioeconomic status or family functioning), leading to fewer opportunities for cognitive gains in early life (Dubow et al., 2009). However, many

ELBW survivors receive social, health, and educational assistance in early life from their parents, clinical professionals, and teachers to help improve impairments brought on by their perinatal adversity and to improve their daily functioning. Perhaps due to their more evident developmental delays in childhood, ELBW individuals in our cohort with lower childhood IQ received more assistance than individuals with higher IQ in early life, increasing their cognitive reserve and protecting them against the effects of later psychosocial stress. Further, this additional support may have helped them feel more comfortable in educational environments, positively influencing their educational and occupational aspirations. On the contrary, perhaps ELBW survivors with seemingly "normal" cognitive functioning in childhood received less assistance and support from their parents and teachers, providing them fewer opportunities to enhance their cognitive reserve and leaving them more vulnerable to stress related to postnatal adversity which resulted in economic consequences in adulthood.

A second explanation for our results may be that socioeconomic attainment is not influenced by cognitive reserve, but rather it is influenced by our perception of adversity. ELBW survivors may perceive adversity differently depending on their cognitive abilities. Although it is thought that individuals living with physical or mental disabilities suffer from poorer health and quality of life (Kottke, 1982), many of these individuals actually report high self-rated health, well-being, and satisfaction with life (Albrecht & Devlieger, 1999). This phenomenon known as the "disability paradox" (Albrecht & Devlieger, 1999) may suggest that ELBW survivors with lower cognitive function in childhood do not see their cognitive limitations as an impairment, which could potentially

be advantageous in light of psychological adversity. Although it is suggested that individuals with greater cognitive abilities may have stronger coping mechanisms to deal with psychosocial stressors (Beasley, Thompson, & Davidson, 2003), perhaps ELBW survivors with lower cognitive function do not perceive psychological distress as strongly (perhaps jointly due to their increased access to resources in early life enhancing their coping mechanism), and therefore are less affected by negative psychosocial adversity. Conversely, perhaps when ELBW survivors with enhanced cognitive abilities are faced with adversity they perceive feelings of depression, anxiety, or stress more intensely, which may further influence poor self-esteem and confidence affecting their socioeconomic attainment.

It is also important to remember that ELBW survivors are at an increased risk for many physical, intellectual, and psychological morbidities (Doyle & Anderson, 2010), which may influence their earning potential. A third explanation why the beneficial effects of cognitive reserve were not seen in in light of psychosocial adversity is that the cumulative physical, social, and psychological morbidity ELBW survivors face may suppress its effects, particularly when ELBW individuals are trying to begin their careers. Young adulthood (i.e., early twenties) is thought to be a particularly stressful period for ELBW survivors (Saigal, 2014; Saigal et al., 2006) since it is the first time in their lives that they are beginning to live independently with less support from their parents and childhood caregivers. Perhaps the stress of this transition into adulthood in conjunction with their other morbidities affect how well they perform in their post-secondary education which mitigates the buffer cognitive reserve may provide. Further, those

ELBW survivors with lower childhood IQ may still be receiving support from their parents/caregivers (i.e., living at home, financial support from their families, etc.), helping them successfully get through this transition and obtaining stable employment compared those ELBW survivors with greater childhood IQ.

Lastly, it is also important to remember that cognitive functioning and reserve may diminish in light of psychological stress and adversity (Wilson et al., 2003). A final explanation of why higher cognitive functioning was associated with lower personal income in the presence psychosocial adversity is that these negative contextual factors may have reduced cognitive functioning and mitigated the beneficial buffer that cognitive reserve typically provides within our ELBW survivors. For example, it has been reported that a traumatic experience such as CSA is associated with altered brain structure and function in the frontal and temporal lopes, hippocampus, and corpus callosum (Navalta, Polcari, Webster, Boghossian, & Teicher, 2006). These alterations are thought to influence the impaired memory, inhibitory capacity, language, mathematical, and academic abilities, and general intelligence seen in CSA victims (Koenen, Moffitt, Caspi, Taylor, & Purcell, 2003; Navalta et al., 2006). As these brain regions are also thought to be affected by ELBW (Volpe, 2009), perhaps any compensated cognitive pathways ELBW survivors gained in early life (represented by higher childhood IQ) were neutralized by the psychological stress associated with victimization or psychiatric disorders, negatively affecting their social mobility and earnings in adulthood.

Surprisingly, we did not see an interaction between childhood SES and IQ in predicting later income attainment. Apart from limitations in statistical power, due to its

indirect association with later socioeconomic attainment (Dubow et al., 2009), perhaps the reason why childhood SES did not moderate the association between childhood IQ and income attainment is because the interaction between these two childhood variables is not a multiplicative, but rather additive. A study by Manley and colleagues (2015) recently explored the impact of parental social status on cognitive development in very low birth weight infants from 18 months to 5 years age. Their findings suggest that higher parental education and caregiver employment had additive effects on cognitive gain so much so that when all of these factors were present, the cognitive scores of survivors increased by roughly 11 points (Manley et al., 2015). Applying this knowledge to our results, perhaps the mechanism in which early life social status influences income attainment in adulthood is that those ELBW survivors who were born into higher SES homes had increased access to medical and educational interventions, resulting in cognitive gains in early life. This positive influence on cognitive abilities in turn may have led to more opportunities for educational attainment, occupational opportunities, and income attainment.

Limitations

Although this study furthers our knowledge about the mechanisms by which socioeconomic attainment develops in preterm survivors, its results must be viewed in light of its limitations. The most prominent threat to the generalizability of our results is the sample attrition which has occurred in our cohort over the past 30 years. However, to help mitigate the bias caused by differential attrition, in our models we controlled for predictors of attrition (i.e. sex and childhood SES). We also performed multiple

imputation analyses using 10 imputed samples in which our results did not differ from those presented. Further, non-participants were more likely to have lower childhood IQ, potentially underestimating the impact of early life cognition and how it interacts with psychosocial contexts in our results. As such, additional research in high-risk pediatric survivors is required to replicate our results.

A second limitation of our study is the self-reported nature of our socioeconomic outcome measure. As participants self-reported their income sources, this may have been subject to social desirability bias (i.e., participants indicating values that they believed the research team wanted to see) and may result in under or overestimation of their actual income. However, we attempted to minimize this reporting bias by asking participants clear questions and provided detailed definitions about multiple sources of their annual income.

The third threat present in our study is the potential temporal ambiguity between psychological contextual factors and our socioeconomic outcome as these were both assessed at age 29-36. For example, it is possible that psychiatric disorders and trait neuroticism may occur as a result of poor income attainment rather than cause poor income attainment. However, we chose to examine these measures for two reasons. It has been established that *lifetime* psychiatric disorders, even when reported in adulthood, are likely to begin in childhood (Johnston et al., 2014; Kessler et al., 2007). Secondly, evidence in general populations has suggested that psychological distress (although may begin in childhood) has a stronger effect on socioeconomic outcomes in later adolescence and adulthood (Macmillan, 2000).

Finally, as they were born in the late 1970s, our cohort was not privy to many of the recent medical advances in neonatal care. As such, our results may be less generalizable to new generations of ELBW survivors. Nevertheless, it has been established that ELBW survivors born in the 1990s face similar cognitive challenges to our cohort (Aarnoudse-Moens et al., 2009; Bhutta et al., 2002); therefore, we feel our results are important and may be used to guide cognitive intervention and policy for ELBW survivors at any age.

Conclusions & Future Directions

This study is the first to examine in a high-risk pediatric population how early life cognition moderates the association between early social and psychological adversity and income in adulthood. Our measure of childhood IQ is both reliable and valid (Deary & Batty, 2007), and in keeping with previous recommendations in the field, we assess outcomes more than 20 years after our cognitive assessments as this provides more robust findings and reduces bias (Strenze, 2007). Finally, our cohort includes both men and women with a range of early SES and range of cognitive abilities, which increases the generalizability of our results.

Our study suggests that cognitive reserve in ELBW survivors may not be protective against early psychological adversity resulting in lower income attainment in adulthood. Our findings suggest that ELBW survivors with enhanced cognitive abilities may be more vulnerable to psychological contexts, resulting in socioeconomic consequences in later life. In hopes to further this area of research and provide evidence for interventions and policies to improve the cognitive functioning of low birth weight

survivors, we recommend that future research explore similar associations using other moderators and socioeconomic outcomes during different developmental epochs; examine different cognitive predictors apart from general intelligence; and replicate findings in other atypical developing or high risk populations such as those born preterm or from other developed and developing countries. By doing so, we may help individuals exposed to perinatal adversity lead the most fulfilling and productive lives possible.

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CHAPTER FIVE

CONCLUSIONS

As more and more preterm infants survive beyond delivery, a contemporary reality is that an increasing proportion of the population has been exposed to significant perinatal adversity. Since we are aware that these individuals are at increased risk for poorer physical, mental, and socioeconomic outcomes, identifying the modifiable mechanisms that link perinatal adversity with these adverse outcomes is important and timely. A better understanding of the influence of different risk and protective factors can potentially lead to interventions that can help improve the daily functioning and quality of life of high risk preterm survivors and show that no individual is "doomed from the womb".

Since it is unethical to randomize individuals to extreme perinatal adversity, properly conducted observational studies are critical to identifying these mechanisms. As cognitive function may be improved with early educational interventions and since many low birth weight survivors will face cognitive impairments (Jarjour, 2015), it is important to explore its role in predicting later life outcomes. Accordingly, this thesis examined what impact early life cognitive function had on the adult health and socioeconomic attainment of a cohort of extremely low birth weight survivors and matched normal birth weight controls.

The first study of this thesis examined how early life cognition (assessed at age 8) influenced the risk of lifetime major depressive disorder in the fourth decade of life. Framed using the cognitive reserve hypothesis (that greater cognitive ability should

protect against psychiatric disorders), our findings suggest that greater cognitive reserve may not protect extremely low birth weight survivors against psychopathology, but may protect individuals born at normal birth weight against later depression risk.

Using the cumulative advantage framework (that the more biopsychosocial advantages an individual faces in early life, the greater their chances of later socioeconomic success), the second study of this thesis explored how childhood cognitive function may mediate the association between perinatal adversity and adult socioeconomic attainment. This study suggests that early cognition may have a lasting impression on the socioeconomic outcomes of extremely low birth weight survivors. This study found that cognitive abilities (particularly overall intelligence and mathematical abilities) explain a significant proportion of the discrepancy in income attainment between extremely low birth weight survivors and their normal birth weight counterparts at age 29-36. Our results suggest that this association is particularly important for those survivors who have significant neurosensory impairments. Additionally, the results of this study suggest that extremely low birth weight survivors with greater cognitive skill in childhood earned greater annual incomes in the fourth decade of life, despite adjustments for childhood socioeconomic status and educational attainment.

Taking a different view of how early intelligence may influence socioeconomic attainment, the final study of this thesis examined if cognitive reserve (as defined by overall IQ assessed at age 8) moderated the association between postnatal psychosocial adversity and personal income attainment in extremely low birth weight survivors in the fourth decade of life. Our results again suggest that cognitive reserve may not protect

against postnatal adversities, as extremely low birth weight survivors with *higher* general intelligence who faced adversity reported *lower* personal income in adulthood.

Major Findings of Completed Studies

This thesis highlights three significant issues. First, it suggests that both general intelligence and other cognitive abilities are important predictors of later health and socioeconomic attainment. Most studies in the field of cognitive epidemiology examine general intelligence or overall mental ability as a predictor of later health outcomes (Deary & Batty, 2007); however, this may conceal specific cognitive abilities that are also protective against later adversity. Study 1 and 2 provide evidence that specific cognitive abilities may also be important in the onset of depression and socioeconomic attainment. Study 1 suggests that early receptive language abilities are influential in protecting against later depression in those born at normal birth weight, while Study 2 suggests that early IQ and mathematical abilities may have a significant impact on later earnings in extremely low birth weight survivors. These findings highlight that early interventions aimed to optimize cognition in childhood could be helpful in preventing and reducing later health and socioeconomic problems.

Secondly, this thesis suggests that cognitive function is a critical predictor of socioeconomic attainment in extremely low birth weight survivors. Socioeconomic status is not only an important factor in determining our quality of life, but it is an important risk factor for later disease (Mikkonen & Raphael, 2010).The extremely low birth weight survivors studied in this thesis reported earning an annual income $20,000 less than their normal birth weight contemporaries (Saigal et al., 2016). This is similar to discrepancies

seen in other low birth weight and preterm survivors cohorts (Heinonen et al., 2013; Moster, Lie, & Markestad, 2008). Study 2 of this thesis also uncovered that the impairment in cognitive function that extremely low birth weight survivors face contributes meaningfully to this discrepancy. These results align with the predictions of the cumulative advantage framework: that biological or psychological adversity in early life may reduce the likelihood of opportunities for social mobility in adulthood (Judge, Klinger, & Simon, 2010). Indeed, these findings suggest that targeting early cognitive problems in ELBW survivors may be helpful for optimizing certain adult outcomes.

Due to their known high risk of chronic health conditions, it is important to determine which characteristics of extremely low birth weight survivors may protect or mitigate risk of adverse outcomes, particularly those that are modifiable. In general population samples, it is thought that cognitive reserve (i.e., the ability to activate different cognitive networks under stressful circumstances) may be a protective factor against early adversity (Koenen et al., 2009; Stern, 2009) that may predict ill health or socioeconomic disadvantage. The third major finding of this thesis is that cognitive reserve may not offer the same protection against adverse outcomes in adulthood in extremely low birth weight survivors as it might in those who have not faced significant perinatal adversity. This is supported by the results of Study 1 and Study 3 which suggest that cognitive reserve may not be protective against adversity in our cohort of extremely low birth weight survivors.

Health Outcomes of Extremely Low Birth Weight Survivors: Is their Altered Cognitive Reserve a Marker of System Integrity?

A strong theme emerged from the work of this thesis: that the cognitive reserve hypothesis may not hold in those exposed to significant perinatal adversity when it comes to later mental health and socioeconomic outcomes. In Study 1, our results revealed that enhanced childhood cognition may not protect extremely low birth weight survivors from later depression. Further, the striking results in extremely low birth weight survivors from Study 3 actually suggested that *higher* cognitive function was associated with lower reported adult income in those who faced significant postnatal disadvantage.

One potential reason the cognitive reserve hypothesis may not have been supported in Study 1 and 3 is because the myriad of comorbidities experienced by ELBW survivors combine with exposure to perinatal adversity to overwhelm the ability of cognitive reserve to protect against negative health and socioeconomic outcomes later in life. As described previously, the HPA axis is critical in regulating stress and protecting us from chronic illness (Glover, O'Connor, & O'Donnell, 2010; Pariante & Lightman, 2008; Rosmond & Bjorntorp, 2000). As an extremely low birth weight child is developing, perhaps their impaired cognitive function, poor motor coordination, social difficulties, and attention difficulties are each just a proverbial "drop in the bucket" that lead to inadequate physiological system functioning and increases their allostatic load, which is then what leads to disease onset or trajectories of poor socioeconomic attainment. In other words, the inadequate functioning of multiple physiological systems

is what leads ELBW individuals to have greater risk of later disease and downward social mobility.

This idea of inadequate general physiological function has been previously hypothesized as a mechanism in cognitive epidemiology. The "system integrity hypothesis" posits that early cognitive test scores are a proxy for how efficiently the complex systems within our bodies function (Deary & Batty, 2007). When individuals function well in one system (for example, cognitive function) they tend to have adequate functioning of all of their systems which helps them manage allostatic load and lower their risk of disease (Deary, 2012). However, when one system is not functioning properly, other neurological and physiological systems may be forced to overcompensate which results in an inability to manage allostatic load properly and increase the risk of disease (Gale, Batty, Cooper, & Deary, 2009). Indeed, the findings from Study 1 and 3 and the idea of system integrity warrants more consideration in future research about how cognition functions as a protective factor in this vulnerable population.

Importance of Completed Studies

Apart from their novel findings, this thesis also advances the developmental origins of health and disease and cognitive epidemiology fields. Most notably, this is one of the first collections of work to explore modifiable postnatal mechanisms that link perinatal adversity to adult outcomes. Survivors of perinatal adversity as significant as ELBW are a unique population who face different risks than those general populations do. These postnatal risk factors, such as impaired cognitive function, are usually not collected or unavailable to study in general population or registry-linked cohort studies.

Further, only few prospective cohorts examining preterm survivors exist in the world. The cohort studied in this thesis is the smallest birth weight, and longest longitudinally followed cohort in the world. The findings in this thesis therefore provide the basis for a collection of evidence supporting that maternal health and early cognitive interventions may be critical in determining the later life outcomes of low birth weight and preterm survivors.

Up until this decade, the study of extremely low birth weight survivors has been mostly descriptive, comparing the health and behavioural outcomes of survivors to normal birth weight comparisons up until young adulthood. As the first generation of individuals who faced extreme perinatal adversity are now surviving into adulthood, little is known about their socioeconomic attainment. The second strength of this collection of work is that Study 2 and 3 are among the first studies in the world to not only examine socioeconomic attainment of perinatal survivors, but to explore links between perinatal adversity and socioeconomic attainment. The findings from these two studies are not only important in understanding the outcomes of perinatal survivors, but are also important pieces of evidence for public health research as they suggest that adverse birth outcomes can have lasting health and socioeconomic consequences that may be modified using specific early life interventions.

The second study in this thesis is quite unique. First, it is one of the few studies to utilize mediation analyses to link perinatal adversity and adult outcomes. Secondly, it is one of the first mechanistic studies of extremely low birth weight survivors to be based in theory. By framing its findings using the cumulative advantage framework, it not only

strengthens the argument for the potential importance of early cognitive intervention, but it sets a precedent to consider other early individual, family, and community-level advantages in perinatal research, interventions, and policy development. Third, this study has very practical implications as it explored early cognition as a mediator in extremely low birth weight survivor with and without neurosensory impairments. As many perinatal survivors at risk for neurosensory impairments, it is important for this field to understand the specific challenges these individuals will face as well.

Lastly, the critical theme that this thesis highlights is that human development is very complex. To adequately understand and address the needs of perinatal survivors and general populations, transdisciplinary research is necessary. Although very challenging to complete, this thesis highlights one way in which transdisciplinary research in this field may be accomplished. By utilizing methodological and theoretical principles from epidemiology, pediatric, psychiatry, neuro-psychology, and sociology fields, the ideas in this thesis may be used as a template of how to merge different specialties together to answer important questions about human development.

Limitations

Although the studies included in this thesis greatly advance our understanding of how cognitive function influences health and socioeconomic outcomes, these findings need to be considered in light of their limitations. First, the attrition which has occurred within the studied cohort is one of the greatest limitations of this research. Since these studies only accounted for 60-70% of the original cohort members, this limited our statistical power (particularly for logistic regression analyses and interaction testing).

Further, the loss-to-follow up bias that has occurred over the past 30 years introduces the possibility that our findings may be either over or underestimating the true influence of early life cognitive abilities in extremely low birth weight survivors (Choi & Noseworthy, 1992). However, we attempted to combat the effects of attrition in each study by: 1. comparing participants to non-participants on relevant characteristics; 2. adjusting statistical analyses for variables which may have been associated with attrition; and 3. performing multiple imputation analyses to account for the effects of missing data.

The second limitation pertaining to Study 2 and 3 is that socioeconomic attainment was self-reported. As self-reported measures may introduce recall bias, our findings could be either under of overestimating the true influence of early life cognition (Choi & Noseworthy, 1992). However, the questionnaire used was carefully designed to ensure the most accurate responses possible by making sure that questions were clear, the instrument length was short and simple to complete, the use of leading questions or double-barreled questions were avoided, and the questions were written at an appropriate literacy level (Van den Broeck, Chhagan, & Kauchali, 2013).

Another potential criticism of these three studies is that they did not entirely account for repeated measures of cognition, health, or social functioning from developmental epochs between when childhood cognition was assessed and when psychiatric and socioeconomic outcomes were completed in adulthood. Participant factors such as their socializing ability/relationships, family functioning in early life, physical comorbidities, or self-esteem in adolescence or young adulthood may have also contributed to their depression and socioeconomic risk. Further, by not examining

repeated assessments of their cognitive function (such as in adolescence and young adulthood), we cannot be sure in what developmental epoch cognitive function may most influence disease or when cognitive interventions would be most effective. However, according to the stages of development put forward by Jean Piaget, the most critical stage of cognitive development is when a child is 7-11 years of age since it is when organized, operational thought and problem solving abilities begins to develop (Piaget, Cook, & Norton, 1952; Piaget, 1955, 2006). Since our studies assess cognition during this stage, it is reasonable to suggest that this is an important time to implement cognitive interventions if they are needed.

Future Research

Based on the findings and shortcomings of the studies in this thesis, there are multiple ways in which future research could extend and improve the study of cognition as a predictor of later health in high risk pediatric populations. To attempt to mitigate the shortcomings that the small sample size and attrition in the presented studies, future research could utilize a retrospective population-registry approach, in which birth weight examined via medical records may be linked to provincial cognitive test scores and health and socioeconomic outcomes from provincial hospital and tax records. Incorporating confounding factors could be accomplished by extracting data from the federal census or surveys. However, this linkage may be extremely complex. Therefore, a second alternative could be to set up a prospective arm in the *Canadian Neonatal Network* to explore the cognitive outcomes of low birth weight and preterm survivors and link this data to hospital registry data.

A second area for additional research could be to complete a randomized control trial testing cognitive interventions in extremely low birth weight/preterm children. The randomized control trials to date such as the Infant Health and Development Program, the Abecedarian Project, and Project CARE, have reported mixed results, with cognitive gains seen at ages 1-5, but not at age 8-9 (Hauglann et al., 2015; McCarton et al., 1997; Ramey & Ramey, 1998). However, these trials have limitations. First, the interventions being tested are extremely heterogeneous and seem to focus more on teaching parents signs of negative behaviours, reflexes, and/or social processes in their infants in very early life rather than cognitive verbal and quantitative abilities. Secondly, many of these studies have small sample sizes, ranging from 100-200 and therefore may be underpowered. Only one study to our knowledge has had a large sample size (n≈1,000) which occurred in the late 1990s, almost 20 years ago (McCarton et al., 1997). As such, designing an adequately powered randomized control trial beginning at the time of school entry (or just a little before to be able to see the influence a school has on cognitive development) in a group of low birth weight or preterm survivors that focuses on developing specific cognitive skills is warranted.

A third area of potential research is to explore the system integrity hypothesis by examining the joint influence of cognition with other system integrity markers, such as HPA axis function or telomere length, on health states of extremely low birth weight survivors. Secondly, the combined influence of the comorbidities extremely low birth weight face in early life should jointly be studied as predictors of later psychopathology, chronic illness, and socioeconomic attainment. Both options could be done by combining

multiple cohorts of extremely low birth weight survivors from around the world to increase the sample size required to gain the statistical power necessary to test these interactions using multi-level modelling. Of course, differences in measurement tools used may be a limitation to this approach.

As Study 2 and 3 examined mechanisms of socioeconomic attainment of extremely low birth weight survivors at an individual level, a final area of research could be to explore the economic impact of adverse pediatric outcomes at a population level. As there is a wealth of statistics describing the incidence of low birth weight/preterm birth and the prevalence of certain physical and psychiatric disorders in this population up to adulthood, this knowledge could be used in predictive economic modelling. For example, current prevalence estimates of low birth weight and preterm birth could be used in Markov chain modelling to predict the prevalence of physical and psychiatric disorders in this population in 5, 10, or even 20 years. Although very high-level, this knowledge could inform economists about the health capital of a population, an important factor which affects the working ability of our labour force (Almond & Currie, 2011). Further, this information could inform health policy makers about what health conditions will be the most pressing in this segment of the population to allow for planning and gathering of the medical resources required to support their needs.

Concluding Remarks

Early cognition is a factor that can affect the physical, psychological, and social functioning of extremely low birth weight survivors throughout their lives. To answer the question posed at the beginning of this thesis, the included studies provide evidence that

our health most certainly begins before we are even born. By answering this question however, it raises more difficult and complex questions. For extremely low birth weight survivors, are the insults that occur *in utero* more detrimental to health than those that occur in infancy and childhood? How much risk will actually be mitigated if cognitive and developmental interventions are implemented in this vulnerable population? For epidemiologists, how can we design the best observational studies to come to valid conclusions while mitigating the limitations and biases of previous literature when studying the outcomes of preterm survivors? As our neonatal technologies continue to improve, what are the steps parents of these infants need to take to ensure their child develops in the most optimal way? Who are the trained medical and educational professionals that need to be involved to help improve neurological function in low birth weight children? One can only hope that the developmental origins of health and disease field will continue to answer these questions to help improve the lives of those affected by perinatal adversity.

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