

EARLY ADVERSITY AND MENTAL HEALTH OUTCOMES: LINKING
EXTREMELY LOW BIRTH WEIGHT, NEUROENDOCRINE DYSREGULATION,
AND INTERNALIZING BEHAVIOURS

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BIRTH WEIGHT, NEUROENDOCRINE DYSREGULATION, AND
INTERNALIZING BEHAVIOURS

By

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Abstract

Salivary cortisol and electrocardiogram data was collected at baseline and after a stress-anticipation task in extremely low birth weight (ELBW; < 1000 grams) survivors and normal birth weight (NBW) controls, in order to examine the moderating influence of emotion regulation on the relationship between being born at ELBW and internalizing problems in adulthood. The stress manipulation was an adapted Trier Social Stress Task. The participants were told they would have three minutes to create a speech on one of three predetermined topics (i.e., gun control, same sex marriage, or abortion). After three minutes passed, the participants were told that there would be no speech. All participants showed a decrease in salivary cortisol levels throughout the day, and an increase in heart rate during the stress anticipation task. When a median split was used to create high and low stress reactive cortisol and heart rate groups, an interaction was found between birth status (ELBW vs. NBW) and group (High vs. Low Stress Reactive Cortisol) on self-reported internalizing problems (anxiety, depression, withdrawal). Those born at ELBW who had high stress reactive cortisol self-reported significantly higher levels of internalizing problems compared to ELBWs with low stress reactive cortisol. Those born at NBW did not differ on self-reported internalizing problems based on their stress reactive cortisol levels. When the moderating effect was probed with a linear regression analysis, the ELBW group was driving the relation between stress reactive cortisol levels and internalizing problems.

Taken together, the results suggest that emotion regulation, as indexed by the neuroendocrine system, is moderating the relation between being born at ELBW and internalizing problems in adulthood. This is indicative of a differential susceptibility of risk and

resiliency in ELBW survivors depending on their ability to regulate their emotions, specifically during periods of stress.

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Chapter I:

Introduction

The experience of early adversity can increase one's risk of psychopathology later in life (Franzek, Sprangers, Janssens, Duijn, & Wetering, 2008; Koenen, Moffitt, Poulton, Martin, & Caspi, 2007; Levitan, Rector, Tess, & Goering, 2003). Extremely low birth weight (ELBW; < 1000 grams) provides a unique model of early adversity that affords us the opportunity to understand how prenatal and early postnatal adversity can perturb the normal development of emotional, biological, and behavioural systems (Schmidt, Miskovic, Boyle, & Saigal, 2010).

The functioning of the neuroendocrine and autonomic systems can be adversely affected by exposure to early adversity. Individuals who have been exposed to unusually high and/or prolonged levels of early life stress, also known as toxic stress, (Shonkoff, Boyce, & Mcewen, 2009) frequently manifest dysregulation of hypothalamic-pituitary-adrenal axis (HPA) and the cardiovascular system in responses to stress (Jones, 2012; Nomura et al., 2007). Dysregulation of the neuroendocrine and/or cardiovascular system is also widely believed to contribute to links between early adversity and increased levels of mental health problems later in life, particularly internalizing problems, including major depressive disorder (MDD) and a variety of anxiety disorders (Koenen et al., 2007; Lin, Lin, Lin, & Huang, 2011).

Emerging evidence suggests that various types of psychophysiological reactivity in response to stress are useful markers of emotion regulatory capacity (Lam, Dickerson, Zoccola, & Zaldivar, 2009; Quirin, Kuhl, & Düsing, 2011). Indeed, a growing body of

literature indicates that markers of HPA axis and cardiovascular functioning can serve as useful indices of emotion regulation (Driscoll, Tranel, & Anderson, 2009; Lam et al., 2009). However, the potential mediating and/or moderating effects of emotion regulation, as indexed by these biological systems, on the links between early adversity and later mental health outcomes (See Figures 1 and 2) have not been widely examined to date. These links are important to investigate, as neuroendocrine and cardiovascular reactivity in response to stress are important aspects of a child's emotion regulatory capacity (Quirin et al., 2011).

Although it is clear that individuals born at ELBW are at risk for a range of stress-related and psychiatric problems, we do not know if these difficulties are mediated and/or moderated by problems with emotion regulation and/or if dysregulation of the neuroendocrine and/or cardiovascular system can serve as a useful index of these processes in this population. In this thesis, I argue that problems with emotion regulation mediate and/or moderate associations between extremely low birth weight (early adversity) and later psychopathology, and that these mediating/moderating emotion regulatory factors can be indexed by HPA axis and cardiovascular dysregulation. To this end, I will discuss the following: a) early adversity and its association with psychopathology, b) the link between early adversity and emotion regulation, c) associations between early adversity and the neuroendocrine system d) associations between emotion regulation and the neuroendocrine system, e) associations between early adversity and the autonomic nervous system f) associations between emotion regulation and the autonomic nervous system, f) links among early adversity, emotion regulation, and psychopathology, and g) the present study.

A. Linking early adversity and psychopathology

‘Early adversity’ has been referred to as exposure to single or multiple challenges to emotional or physical well-being that hinders one’s ability to cope and leads to chronic stress (Gunnar & Quevedo, 2007). Common and particularly deleterious types of early adversity include exposure to emotional, sexual, or physical abuse or neglect, maternal depression, and premature birth. Such environments can impact the development of biological, emotional, and behavioural regulatory systems, and lead to a variety of adverse mental and physical outcomes (Hazel, Hammen, Brennan, & Najman, 2008).

The tenets of adaptive developmental programming theory attempt to explain how development in biological, emotional, and behavioural domains are shaped by exposure to specific experiences during sensitive periods of development. Sensitive periods represent developmental epochs during which specific experiences are required for particular brain functions to develop normally (Heim & Binder, 2011). However, early exposure to adverse environmental conditions can cause the brain to adapt in ways that potentially lead to severe deficits in emotion regulation and other types of pathology (Rutter & O’Connor, 2004).

In response to physical or psychosocial stress, activation of stress management systems in the brain result in HPA axis activation, leading to short-term release of cortisol, as well as increased heart rate (Shonkoff, Boyce, & Mcewen, 2012). Early adversity epitomizes stress exposure and can result in the dysregulation of biological systems, including the HPA axis and autonomic nervous system (ANS). This relation has been demonstrated to occur in response to a number of disparate forms of early adversity,

including premature birth (e.g., Crombie, Clark, & Stansfeld, 2011; Spangler & Schieche, 1998).

The early environment is a significant contributor to the development of biological systems and behaviour. Exposure to early adversities can affect the structure and physiology of regulatory systems, such as the HPA axis and ANS. In fact, exposure to these environments can affect the HPA axis and the ANS in ways that can subsequently increase one's risk for developing mental health problems later in life (Franzek et al., 2008; Heim et al., 2012; Koenen et al., 2007; Levitan et al., 2003). In this thesis, I will focus on internalizing-related behaviours, as these are the most common types of problems that tend to result from exposure to early adversity (Koenen et al., 2007).

Abuse, institutionalization in infancy and early childhood, and premature birth are known to be associated with later mental health problems (Hazel et al., 2008; Imanaka, Morinobu, Toki, & Yamawaki, 2006; Raikkonen et al., 2008; Rao, Hammen, Ortiz, Chen, & Poland, 2008; Yehuda et al., 2010). Due to the association between internalizing disorders and dysregulation of the HPA axis, researchers have hypothesized that early life stress can lead to permanent perturbations in this axis which then lead to the development of internalizing disorders later in life (Rao et al., 2008). For example, Essex and colleagues (2002) found that when children were exposed to maternal depression, the earlier the exposure, the stronger the link between maternal stress and children's basal cortisol levels at age four. High basal cortisol levels were also predictive of children's externalizing and internalizing problems in first grade (Essex, Klein, Cho, & Kalin, 2002). Similar conclusions have been made with regards to early adversity and heart rate,

as individuals who experienced early adversity, such as childhood abuse, suffer from persistent changes in stress reactivity (Heim et al., 2012). Heim and colleagues (2012) discovered that depressed women (i.e., 18-45 years of age) who were abused as children had significantly increased heart rate and increased mean maximum heart rate compared to controls (Heim et al., 2012). This finding suggests that increased sympathetic activity is a persistent consequence of early adversity, which may contribute to the diathesis for adulthood psychopathological outcomes (Heim et al., 2012).

Being born prematurely is also associated with development of internalizing disorders throughout the lifespan (Crombie et al., 2011; Hack et al., 2002; Nomura et al., 2007; Schlotz & Phillips, 2009). Birth categories have been created based on morbidity rates (Mayer & Joseph, 2013), which have led to the following categorizations; low birth weight (LBW; <2500 grams), very low birth weight (VLBW; <1500 grams), and ELBW. Decreasing birth weight is linked to an increase in one's risk for psychopathology (Raikkonen et al., 2008). Those born at VLBW, and individuals born small for gestational age (SGA) manifest lower scores on executive functioning and higher on emotional instability scales (Strang-Karlsson et al., 2008) compared to normal birth weight and appropriate for gestational age (AGA) comparison groups. Being born at VLBW is also associated with a variety of other problems, including internalizing disorders, reduced academic achievement, and deficits in executive functioning. VLBW is a strong predictor of internalizing disorders in adulthood, with VLBW status being a significant predictor of both parent- and self-reported measures of internalizing symptoms (Aarnoudse-Moens, Weisglas-Kuperus, van Goudoever, & Oosterlaan, 2009; Bhutta, Cleves, Casey, Cradock, & Anand, 2002; Boyle et al., 2011). Those born at

ELBW tend to have persistent issues with internalizing problems into young adulthood and those born SGA have the most severe problems (Boyle et al., 2011; Raikkonen et al., 2008). Size for gestational age appears to play a significant role in determining the severity of internalizing disorders with these low birth weight groups (e.g., Monfils Gustafsson, Josefsson, Ekholm Selling, & Sydsjö, 2009; Raikkonen, Pesonen, Heinonen, Kajantie, Hovi, Jarvenpaa, Eriksson, & Andersson, 2008)

B. Early adversity and emotion regulation

Emotion regulation has been defined as an individual's active attempts to manage their emotional states (Koole, 2009) and appears to involve an integrated network of biological, social, cognitive, and behavioural domains, which contribute to emotional self-management (Thompson, 2011). These domains work in synchrony to complete the goal-directed processes needed to influence the intensity, duration, and type of emotion experienced (Gross & Thompson, 2007). Through successful emotion regulation, children and adults develop healthy and appropriate social and emotional functioning (Gyurak, Gross, & Etkin, 2011). I will highlight the neuroendocrine and autonomic nervous systems as a biological proxies for emotion regulation in this work because psychophysiological reactivity in response to stress is an important aspect of the child's emotion regulatory capacity (Watamura, Donzella, Kertes, & Gunnar, 2004).

Emotional self-regulation has long been parsed into two distinct systems, referred to as "hot" and "cold" (Metcalf & Mischel, 1999). The "hot" system refers to the emotional and reactive side of self-regulation, while the "cold" system involves more cognitive processes (Metcalf & Mischel, 1999). One's biological starting states, early

experiences, and stress levels determine the degree to which either system dominates emotion regulation (Metcalf & Mischel, 1999). Early adversity may alter the baseline states of the hot/cold system and has implications for emotion regulation (Metcalf & Mischel, 1999).

As children learn to regulate their emotions, choices may be made in favour of immediate coping, which may be effective in the short-term but may result in problems with emotion dysregulation if excessively relied upon (Thompson, 2011). By the same token, children who experience early adversity may adopt deleterious emotion regulatory strategies that protect them against challenges in their immediate environment, but leave them vulnerable to other risks over the long-term (Thompson & Calkins, 1996). In the following section, I will briefly discuss how early adversity impacts emotion regulation.

Exposure to several types of early adversity has been linked to deficits in emotion regulation. This includes institutionalized rearing, maltreatment, and maternal depression (Alink, Cicchetti, Kim, & Rogosch, 2009; Silk, Shaw, Skuban, Oland, & Kovacs, 2006; Tottenham et al., 2010). For example, Tottenham and colleagues (2010) demonstrated that institutionalized rearing led to poorer emotion regulation in children compared to controls, which was illustrated by their difficulty regulating behaviours in an emotional computer task.

Maltreated children and adolescents suffer from the same pervasive emotion dysregulation, with earlier onset of maltreatment leading to lower levels of emotion regulation (Alink et al., 2009). Emotion regulation was found to affect the relation between maltreatment and psychopathology, with lower levels of emotion regulation

being associated with higher internalizing and externalizing symptomatology (Alink et al., 2009; Shields & Cichetti, 1997).

Similar patterns of emotion dysregulation are found in children who experience maternal depression at a young age (Silk et al., 2006). Children of depressed mothers are found to engage in more passive strategies for regulating emotions, which do not effectively down-regulate negative emotions (Silk et al., 2006). These inefficient emotion regulatory strategies could lead to depression in late childhood or adolescence as these individuals have trouble disengaging from distressing stimuli (Silk et al., 2006).

Emotion dysregulation is hypothesized to be due to the HPA axis and ANS becoming dysregulated based on early life stressors, which leads to negative outcomes such as psychopathology. In the following section, I will discuss the negative impacts on the neuroendocrine system due to early adversity.

C. Early adversity, the neuroendocrine system, and emotion regulation

Early adversity and the neuroendocrine system. The neuroendocrine system functions as a result of two inter-related systems, the ANS and the HPA axis. These two systems assist with neuroendocrine and cardiovascular responses to stress, which are aimed at increasing the likelihood of the short-term survival of the organism in the face of adversity (Sanchez, 2006).

The HPA axis is the slower-acting stress response system that controls many bodily processes and is activated by stressors (Rudolph, Troop-Gordon, & Granger, 2011). In humans, this process begins with a stressor triggering the hypothalamus to release the corticotrophin-releasing hormone (CRH) (Schulkin, Gold, & McEwen, 1998).

CRH binds to receptors in the anterior pituitary gland and stimulates secretion of adrenocorticotrophic hormone (ACTH). ACTH then triggers the adrenal cortex to release the glucocorticoid hormone cortisol (McCrory et al., 2010). Cortisol initiates adaptive responses to stress, preparing the body to meet the energy demands associated with stressful events (Rudolph et al., 2011). Dysregulation of the HPA axis is prevented through a negative feedback loop, which normally returns the system to homeostasis in order to protect against the deleterious effects of a chronically activated HPA axis (McCrory et al., 2010; Schulkin et al., 1998). If the HPA axis is chronically activated however, its protective effects are diminished and the system becomes pathogenic (Schulkin et al., 1998).

Disruption of the HPA axis can affect emotional and behavioural functioning, particularly the regulation of emotion. Emotion regulation has been connected to the HPA axis in previous research (Watamura et al., 2004). Emotion and HPA axis dysregulation both contribute to the development of psychopathology (Tarullo & Gunnar, 2006). Since the neuroendocrine system and emotion regulation can both be adversely affected by exposure to early adversity, and dysregulation in these regulatory systems has been linked to various forms of psychopathology, it is possible that these systems would mediate and/or moderate associations between early adversity and later psychopathology.

Children exposed to maladaptive pre- and post-natal environments display variable cortisol levels throughout the lifespan. Prenatal stress has been shown to produce perturbations in the HPA axis (Field et al., 2004; Tollenaar, Beijers, Jansen, Riksen-Walraven, & de Weerth, 2011). Glucocorticoids are capable of passing through the placenta as well as being produced by the placenta itself (Field et al., 2006), which can

lead to increases in fetal HPA activity (Field et al., 2006). Chronic exposure to prenatal stress can cause structural changes in the neuroendocrine system, which in turn can lead to emotion regulation problems (McEwen, 2003).

Baseline and stress-reactive cortisol have been found to be increased in children exposed to early postnatal adversity, and this pattern may be due to early activation of the HPA axis (Gunnar & Donzella, 2002; Gunnar & Vazquez, 2001; Tarullo & Gunnar, 2006). Adversity experienced in later childhood, including maltreatment, neglect, and deprived rearing environments also result in patterns of low early morning cortisol and a blunted diurnal rhythm (Gunnar & Vazquez, 2001; Kliewer, Reid-Quinones, Shields, & Foutz, 2008; MacMillan et al., 2008; Tarullo & Gunnar, 2006). Adolescents who were exposed to insensitive caregiving may acquire sub-optimal coping strategies from their mothers, which may lead to dysregulation in emotion and stress responses (Compas, 2006).

Alterations in the HPA axis due to early adversity can also affect individuals when they are adults. Lower basal cortisol concentrations and higher stress reactive cortisol were experienced in young adults whose mothers experienced negative life events during pregnancy in comparison to a control group (Entringer, Kumsta, Hellhammer, Wadhwa, & Wüst, 2009). Young adults who demonstrated unsuccessful emotion regulatory traits also displayed exaggerated stress reactive cortisol levels (Lam et al., 2009; Laurent & Powers, 2007). The stability of emotion and stress dysregulation in adults exposed to early adversity supports the existence of deleterious outcomes of programming effects and early life stress on the HPA axis (Tarullo & Gunnar, 2006).

Early adversity has also been hypothesized to affect regions of the brain involved in HPA axis and emotion regulation (McCrory et al., 2010). Damage to regions of the brain involved in emotion regulation, such as the medial prefrontal cortex (mPFC), the hippocampus, and the amygdala can lead to disinhibited patterns of stress reactivity in those who experienced early adversity (McCrory et al., 2010). These brain regions appear to allow for feedback and emotion regulation (Buchanan et al., 2010; Compas, 2006; Urry et al., 2006). However, in the case of exposure to early adversity, the HPA axis and other emotion regulation systems are perturbed (Urry et al., 2006).

Those who are exposed to early adversity may experience a programming developmental effect on the HPA axis. For example, Ouellet-Morin and colleagues (2008) found that in twins who experienced higher levels of family adversities, such as smoking during pregnancy, low birth weight, low family income, low maternal educational level, single parenthood, young motherhood, and maternal hostile or reactive behaviours displayed higher levels of cortisol reactivity at 19 months of age. In twins with low levels of family adversities, both genetic and unique, but not shared environmental factors accounted for individual differences in cortisol reactivity, with genes explaining the similarity observed between twins. In twins with high levels of family adversities, variance in cortisol reactivity was accounted for solely by environmental factors, with shared environmental factors explaining the similarity between twin pairs (Ouellet-Morin et al., 2008).

Birth weight and the neuroendocrine system. The level of perturbation in the neuroendocrine system has been demonstrated to worsen with decreasing birth weight, as inverse associations between birth weight and basal cortisol levels have been reported by

several groups (Grunau et al., 2007; Kajantie et al., 2002). Infants who are born at LBW have also been shown to have higher rates of cortisol in the early months of life (Field et al., 2004). Some have argued that LBW individuals manifest changes in the expression of steroid receptors in the limbic system that may be due to specific stressors such as maternal deprivation, exposure to glucocorticoids, and/or infection (Phillips & Jones, 2006). Changes in the HPA axis due to birth weight do not appear to be transient, and may affect individuals well into adulthood (Reynolds et al., 2001).

Individuals born at VLBW also have dysregulated HPA axes. Past studies have found that infants born at VLBW displayed high levels of ACTH and cortisol concentrations at birth, as well as at one month of age compared to controls (De Felice et al., 2008). Those born at ELBW (<1000 grams) have enhanced biological responses to stress regardless of their steroid exposure at birth. This pattern is evidenced by a flattened diurnal cortisol rhythm in early infancy and heightened cortisol production at 8-18 months compared to normal birth weight controls (Aucott, Watterberg, Shaffer, & Donohue, 2010; Aucott, Watterberg, Shaffer, & Donohue, 2008). However, since these individuals are born at the limits of survivability, they frequently receive treatment with corticosteroids in an attempt to prepare them for postnatal life. Corticosteroid treatment can lead to pituitary adrenal suppression. Preterm infants treated with corticosteroids have been found to exhibit suppressed hypothalamic and pituitary functions up to three weeks after treatment, which did not fully recover to pretreatment levels (Ng et al., 2008).

An identical pattern was found in extremely low gestational age (ELGA; <24-28 weeks gestation) babies compared to very low gestational age babies and normal birth weight controls (Brummelte et al., 2011). The results suggest that early maturation of

physiological systems due to shortened gestation is involved in the development of emotion regulation (Brummelte et al., 2011).

Although research demonstrated that the HPA axis becomes perturbed in those who are classified as LBW, and those with LBW have an increased amount of behaviours that could be regarded as failures in emotion-regulatory functioning, there is only a modest amount of research with regards to emotion regulatory problems in this unique population (Davis & Burns, 2001). Past research has demonstrated that emotion regulation is perturbed in those born prematurely (Anderson & Doyle, 2004; Clark, Woodward, Horwood, & Moor, 2008). Clark and colleagues (2008) discovered that those born with ELBW had pervasive problems with emotion regulation at both two and four years of age. A gradient of risk became apparent, as children born extremely preterm were characterized by the most severe deficits in emotion regulation, compared to very preterm and full term children. In a study done by Anderson and Doyle (2004), the authors found that emotion dysregulation was stable across childhood, as ELBW and even very preterm infants had an increased risk for exhibiting clinically significant behaviour regulation problems at school-age, especially in the emotional control domain.

Poehlmann and colleagues (2011) found that infants born preterm or LBW, and who also had low sustained attention, experienced the highest amount of internalizing disorders. It is thus possible that emotion regulation may mediate and/or moderate the relation between birth weight and mental health outcomes (Poehlmann, Schwichtenberg, Schlafer, & Hahn, 2011).

It appears that emotion regulation is impacting the relation between early adversity and psychopathology. However, there is only a modest amount of research investigating the association between emotion regulation and the neuroendocrine system. In the following section, I present how emotion regulation can be indexed by the HPA axis through discussing how the development of emotion regulation and the HPA axis coincide.

Emotion regulation and the neuroendocrine system. It is well established that the HPA axis modulates stress responses in humans and non-human models (Abe et al., 2007; Davis, Glynn, Waffarn, & Sandman, 2011). However, previous research on the biological markers of emotion regulation has focused mainly on other measures of psychophysiological reactivity such as skin conductance and finger pulse amplitude (Gross, 1998). Some evidence suggests that HPA axis responses to stress may be an important aspect of humans' emotion regulatory capacity. Support for the assertion that HPA axis measures can serve as a biological proxy for emotion regulation is illustrated by studies that demonstrate that the development of emotion regulation and the HPA axis systems coincide temporally throughout life.

Early life: Prenatal to preschool. The transition from infancy to early childhood is marked by the development of emotion regulatory competencies, including sustained attention and effortful control, as well as regulation of the HPA axis (Watanabe et al., 2004). In most normally developing humans, the first 4-14 postnatal days are defined as the stress hyporesponsive period (SHRP), because it is difficult for them to produce elevated levels of ACTH and cortisol in response to stressors (Slattery & Neumann, 2008). After postnatal day 14, newborns are found to have significant increases in stress

reactive cortisol levels as well as an emerging diurnal rhythm (Rivkees, 2003). The diurnal rhythm is the normal variation in cortisol levels over typical 24-hour periods. This rhythm becomes increasingly stable in early childhood, with the highest levels of cortisol experienced early in the morning, followed by a sharp decrease at mid-morning, and a gradual decline over the course of the day (Entringer et al., 2009).

During this transition, Watamura and colleagues (2004) also found that infants who exhibited more effortful control produced lower concentrations of basal cortisol, suggesting that lower basal cortisol levels are indicative of adaptive self-regulation strategies. The authors concluded that a better developed capacity for self-regulation is reflected in more regulated patterns of cortisol (Watamura et al., 2004).

Infants of depressed mothers display more negative affect, heightened emotionality and dyregulated aggression than infants born to euthymic mothers (Zahn-Waxler, Cummings, Iannotti, & Radke-Yarrow, 1984). The association observed between postpartum depression and later problems with emotion regulation in offspring are hypothesized to be due to postnatal stressors, such as insensitive caregiving (Zahn-Waxler et al., 1984). The HPA axis and emotion regulatory abilities are thus easily programmed and permanently altered by events occurring in gestation and in early infancy (Zahn-Waxler et al., 1984).

Studies examining temperamental characteristics in toddlers have also provided support for the link between emotion regulation and HPA activity (Zimmermann & Stansbury, 2004). Using measures of emotion dyregulation such as shyness, surgency, and boldness, Zimmermann and Stansbury (2004) found that these predicted greater

cortisol elevations in children, while better emotion regulation predicted lower cortisol levels.

The HPA axis in three year olds is still immature, but there is a distinct daytime rhythm in cortisol production (Watamura et al., 2004). Throughout the toddler and preschool period, everyday stressors fail to lead to significant elevations in cortisol levels (Watamura et al., 2004). The toddler period is marked by the development of personality styles such as shyness and boldness. Personality styles that are linked to low emotion regulation have also been found to produce higher levels of stress reactive cortisol in toddlers as compared to toddlers with good emotion regulation (Zimmermann & Stansbury, 2004).

School-aged children. Emotion regulatory capacities in school-aged children tend to become more complex and integrated during grade school years (Fox, 1994). This parallels the HPA axis in school-aged children, which gradually begins to approximate the adult diurnal rhythm at the age of four, with a clear, adult-like pattern observed in children by the age of six (Dettling, Gunnar, & Donzella, 1999; Gunnar & Donzella, 2002; Watamura et al., 2004).

Adolescence. Adolescents have acquired an adult-like diurnal cortisol rhythm, but still maintain higher levels of basal cortisol and prolonged HPA activation in response to stressors (Lupien, McEwen, Gunnar, & Heim, 2009). This pattern may be due to adolescents trying to regulate affect in adaptive ways without the aid of the adults who provide guidance in childhood (Steinberg et al., 2006).

The link between emotion regulation and HPA axis function is also supported by research investigating the moderating effects of oxytocin, a neuropeptide that counteracts stress-induced activity in the ANS (Quirin et al., 2011). Quirin, Kuhl, and Dusing (2011) showed that cortisol increases were absent after a stress task in young adults with low emotion regulation abilities (ERA) after oxytocin was administered. However, these findings were not present after a placebo application. Individuals with high ERA did not benefit from the oxytocin administration, which was hypothesized to be due to individuals with high ERA regulating their neuroendocrine responses independently (Quirin et al., 2011). Taken together, the above evidence highlights the bidirectional nature of the relation between emotion regulation and the HPA axis and suggests that it may serve as a useful biological proxy of emotion regulation. In the next section, I review evidence that suggests that the autonomic nervous system is also affected by early adversity.

D. Early adversity, the autonomic nervous system, and emotion regulation

Early adversity and the autonomic nervous system. As reviewed above, the neuroendocrine system functions as a result of two interrelated systems, the HPA axis and the ANS. The ANS is comprised of the sympathetic and parasympathetic nervous systems (Rudolph et al., 2011). The sympathetic branch is involved in the fast-acting stress response and is referred to as the “fight-or-flight” system. The sympathetic branch defends against controllable threats (Rudolph et al., 2011). The parasympathetic system is referred to as the “brakes” of the ANS, as it imposes negative feedback control on ANS activation and ensures that the sympathetic response is brief.

There is a long and rich history using ANS in psychological processes. Work by Eppinger and Hess (1915) discussed the notion of *vagotonia*, which is the state of the autonomic nervous system in which homeostasis between the sympathetic and parasympathetic nervous system favours the parasympathetic branch. This autonomic imbalance was said to produce delinquent behaviours (Eppinger & Hess, 1915). Later research by Clifton (1974) suggested that newborn infants may show an orienting response when an expected stimulus does not appear, which is characterized by cardiac decelerations. Due to early life stress, infants may have expected cardiac responses that were beneficial during this stressful period, but are deleterious when stressful events are absent (Clifton, 1974).

Similar to that of the HPA axis, the cardiovascular system can affect individuals' emotional regulatory abilities (Hastings et al., 2009). When the cardiovascular system and emotion regulation are not synchronized, deleterious outcomes may ensue, such as psychopathology (Hastings et al., 2009). This idea is suggestive of a moderating effect of emotion regulation, as indexed by heart rate, on the relation between early adversity and mental health outcomes.

A newborn's cardiovascular system can be significantly affected by maladaptive pre-and post-natal environments, such as maternal depression. Newborns of depressed mothers have reported significantly different basal and stress reactive physiological states compared to newborns of non-depressed mothers (Jones, 2012; Kinsella & Monk, 2009). These physiological differences are characterized by a higher heart rate during a stressful task in infants of depressed mothers compared to control infants (Jones, 2012; Kinsella &

Monk, 2009). Similarly, one-year-olds who have unsupportive caregivers produce elevations in heart rate in response to the strange situation (Spangler & Schieche, 1998)

Early adversity experienced later life, such as child abuse and/or neglect may lead to varied sympathetic reactivity (Koopman et al., 2004; Lovallo, Farag, Sorocco, Cohoon, & Vincent, 2012). Eleven to 16 years olds who were exposed to abuse and/or neglect displayed higher mean heart rate increases during a stressful interview compared to controls, although abused individuals who had increased dissociative symptoms displayed lower heart rate during the stressor (Koopman et al., 2004). These results suggest that emotion regulation may mediate and/or moderate the relation between early adversity and sympathetic reactivity. Other studies, such as the work by Lovallo and colleagues (2012) state that smaller heart rate responses to stress and unaltered tonic heart rate are demonstrated in young adults who experienced adverse life events before the age of 15 compared to controls. These results suggest that varied experiences of stress in early life can have a multitude of effects on the brain systems controlling baseline and stress responsive heart rate (Lovallo et al., 2012).

Birth weight and the autonomic nervous system. When one is born prematurely, it is likely that the fetus has been exposed to stress in utero (Johansson et al., 2007). Past research has suggested that stressful pre- and post-natal environments characterized by inflammation, pain, and separation from mother may cause lasting activation of the syphoadrenal system (Johansson et al., 2007). It has been found that those who were born prematurely experience enhanced autonomic nervous activity throughout the lifespan (Cohen, Brown, & Myers, 2009; IJzerman et al., 2003; Johansson et al., 2007; Miller, Seifer, Stroud, Sheinkopf, & Dickstein, 2006; Phillips & Barker, 1997).

As early as 12 to 96 hours old, babies born at term in the lowest quintile of birth weight exhibited altered physiological activity that is consistent with low energy expenditure (Cohen et al., 2009). Term born infants in the lowest birth weight quintile had lower heart rates prior to feeding but greater increases in heart rate post-feeding compared to the middle and highest quintile birth weight groups (Cohen et al., 2009). This programmed “thrifty” phenotype is expressed in LBW babies, and may be a long term marker for cardiovascular vulnerabilities (Cohen et al., 2009). Indeed, babies born at ELBW at 4 weeks continue to have difficulties modulating their immediate and recovery responses to an acute stressor (Oberlander et al., 2012). Specifically, ELBW infants had a more sustained sympathetic response following blood collection by a heel lance compared to term born infants (Oberlander et al., 2012).

This connection between perinatal stress and sympathoadrenal overactivity is persistent, and continues to affect those born prematurely into childhood. Particularly, those born preterm and/or SGA tend to have higher heart rates after mental stress than control children (Johansson et al., 2007). In adolescence, a similar pattern emerges, with LBW individuals having increased heart rate during a stressor compared to control children (IJzerman et al., 2003). Although there are few studies investigating premature birth and adult autonomic activity, a consistent upregulated heart rate is present into adulthood in LBW individuals. A study by Phillips and Barker (1997) revealed that men and women who had LBW displayed increased resting pulse rates when compared to term controls. These results were independent of current body-mass index, waist-hip ratio, smoking habits, alcohol use, and social class.

Past research in this area is suggestive of elevated autonomic nervous system activity that is established in utero or early post-natally (Phillips & Barker, 1997). Although birth weight and its connection to emotion dysregulation has been touched upon in past research (Anderson & Doyle, 2004; Clark, Caldwell, Power, & Stansfeld, 2010), similar to research investigating the neuroendocrine system and emotion regulation, not much research has been done with regards to this unique population.

In the next section, I present findings regarding heart rate as an index of emotion regulation. This approach will be done by discussing how the development of emotion regulation parallels regulation of the autonomic nervous system, as well as past research that directly connects emotion regulation and heart rate.

Emotion regulation and the autonomic nervous system. Developmental changes in heart rate are present throughout infancy, childhood, and into adolescence. Development of the cardiovascular system coincides with the development of emotion regulation, which has been connected to the cardiovascular system in past research. In the following section, the development of the cardiovascular system will be discussed, emphasizing its connection to the development of emotion regulation.

Early life: Infancy to preschool. There is moderate stability and steady developmental decreases in heart rate across the first year of life, with the greatest decrease in heart rate between four and nine months of age (Bar-Haim, Marshall & Fox, 2000). After nine months of age, there are slight decreases in heart rate until four years of age (Bar-Haim et al., 2000; Porges, Doussard-Roosevelt, Portales, & Suess, 1994). During this period from nine months to four years of age, heart rate remains relatively

stable (Bar-Haim et al., 2000). This stability in heart rate may reflect an maturational increase in activity in areas of the brain stem that control respiratory function (Bar-Haim et al., 2000). As the heart rate begins to stabilize from birth, it is not surprising that basic emotions are linked to heart rate from early infancy. Innate emotions such as anger, fear, and sadness are associated with accelerated heart rate in infants at 4.5 months of age (Levenson, 1992). Heart rate accelerations during anger and fear are posited to be due to its relation to the “fight” system, while heart rate accelerations due to sadness reflect the connections between sadness and stress reactivity (Levenson, 1992).

School-aged children. The cardiovascular system continues to mature into early and middle childhood (Kagan et al., 1988; Marshall & Stevenson-Hinde, 1998). Heart rate significantly decreases and becomes more stable between four and seven years of age, which parallels the continuing development of behavioural regulation throughout childhood (Marshall & Stevenson-Hinde, 1998).

When a child suffers from emotion dysregulation in middle childhood, patterns of stress reactive heart rate differ from the normal population (Hessler & Fainsilber Katz, 2007). In a study done by Hessler and Fainsilber-Katz (2007), increased emotion dysregulation led to increased heart rate during a peer provocation. The results suggest that when one is unable to control emotional responses, emotion dysregulation presents physiologically as well as behaviourally.

Adolescence. Heart rate variability is a sign of normal homeostatic mechanisms of the cardiovascular system, and is highly correlated with heart rate (Finley & Nugent, 1995). Although stability of heart rate in normally developing adolescents is a field of

study that has minimal research, Finley and Nugent (1995) demonstrated that heart rate variability reaches a maximum level in early adolescence. Due to heart rate and heart rate variability being highly correlated, it can be assumed that heart rate is relatively stable by adolescence and into adulthood.

Emotion regulation is associated with heart rate well into adulthood (Driscoll et al., 2009). In a study done by Driscoll and colleagues (2009), the authors demonstrated that conscious and deliberate attempts to regulate emotions are associated with reliable changes in heart rate. Adults were instructed to down regulate emotional responses, which led to reduced heart rate when compared to upregulating emotions (Driscoll et al., 2009).

Individuals who suffer from internalizing and externalizing disorders are known to have emotion regulation problems, which may result in a decreased coherence between emotions and physiological responses (Hastings et al., 2009). Indeed, a study by Hastings and colleagues (2009) confirmed that there was a lack of coherence between emotions and physiological measures in adolescents suffering from internalizing and externalizing problems. The authors found that there was a lack of consistency between heart rate and negative emotions, such as sadness. That is, those who suffered from internalizing or externalizing disorders displayed an increased heart rate in response to sadness compared to controls. These results suggest that those who suffer from emotion dysregulation are not somatically prepared to engage in appropriate actions, as characterized by differing physiological reactions to emotions (Hastings et al., 2009).

Based on the correspondence between emotion regulation and heart rate throughout the lifespan, it can be assumed that the autonomic nervous system can still serve as a useful biological proxy of emotion regulation in adulthood, and in unique populations such as those born at ELBW.

E. Linking early adversity, emotion regulation, and psychopathology

Early adversity can lead to emotion dysregulation, which can be indexed by neuroendocrine and autonomic markers including those of the HPA axis and heart rate, respectively (Driscoll et al., 2009; Hessler & Fainsilber Katz, 2007; Quirin et al., 2011; Watamura et al., 2004). Taken together with evidence that links exist among neuroendocrine and autonomic system dysregulation and psychopathology (Tarullo & Gunnar, 2006), I argue that emotion regulation as indexed by neuroendocrine and autonomic markers could mediate and/or moderate these associations between early adversity and psychopathology.

As birth weight decreases, the HPA axis becomes increasingly perturbed (Schlotz & Phillips, 2009). The HPA axis may be associated with later onset of internalizing problems in individuals born at VLBW, as the significant intrauterine and postnatal stresses they were exposed to, combined with their small size at birth may alter HPA axis activity. These individuals may have been exposed to more stress in-utero than those born at normal birth weight, which may increase their susceptibility to HPA axis dysregulation and later onset of internalizing problems, including depression (Raikkonen et al., 2008). Past studies have investigated the impact of low birth weight on emotion regulation and have found that emotion regulation is poorer in those born prematurely (Anderson &

Doyle, 2004; Clark et al., 2008) which may explain the relation between this unique example of early adversity and psychopathology.

Other examples of early adversity, such as early trauma, have predicted mental health problems later in life. These relations have been shown to be moderated through the ANS. Low sympathetic activity has been shown to be a protective factor in the relation between early trauma and later mental health problems. Oldehinkel, Verhulst, and Ormel (2008) discovered that high exposure to stressors predicted mental health problems in adolescence with intermediate and high heart rate levels, but not low heart rate levels (Oldehinkel, Verhulst, & Ormel, 2008).

These two biological systems, the ANS and the HPA axis, have been shown to dysregulate in synchrony when one experiences early adversity. Smaller cortisol and heart rate responses to stress were exhibited in those who experienced stressful life events before 15 years of age (Lovallo et al., 2012). These stressful experiences in early life can have permanent effects on brain systems controlling stress responsivity (Lovallo et al., 2012), which may lead to an increased risk for psychopathology. Past research has supported this notion, as increased heart rate and cortisol levels in response to stress were only found in abused women with depression, as compared to abused women without depression (Heim et al., 2012).

Schmidt and colleagues (2010) investigated how ELBW status can affect cortisol levels, heart rate, and future psychopathology. Although internalizing behaviour problems increased from adolescence to young adulthood, similar basal cortisol and tonic heart rate levels were found in ELBW individuals and NBW controls. However, there

was no measure of stress related cortisol or heart rate, and only high-functioning ELBW adults were included in this study. Past research has revealed that higher stress reactive cortisol and heart rate is demonstrated in those who experienced early adversity (Entringer et al., 2009; Heim et al., 2012), which suggests that future research is required in order to determine if emotion, autonomic, and/or neuroendocrine dysregulation, could increase the risk of psychiatric morbidity in ELBW survivors in adulthood.

Although the neuroendocrine system is just beginning to be examined as a proxy for emotion regulation, past research suggests that the neuroendocrine system and emotion regulation are linked. A vast amount of research has linked emotion regulation and the ANS. A gradient of risk for deleterious effects, such as internalizing disorders ensues and seems to be based on the degree of HPA axis and ANS alteration. Based on this research, it would be expected that those who are born at ELBW would display increased psychopathology if their HPA axis and/or ANS was dysregulated.

F. The present study

The current study was designed to replicate and extend previous research on mental health outcomes for those born at ELBW. There were two goals of the present study. First, mental health outcomes of ELBW individuals in their 30s was examined. This is the first study to investigate mental health outcomes of those born at ELBW in their 30s. Second, the mediating and moderating influences of biological indices of emotion regulation were examined in relation to ELBW and later internalizing problems. The HPA axis and the ANS were hypothesized to be biological indices of emotion regulation, as past research has linked these biological systems to the development and

stability of emotion regulation (Driscoll et al., 2009; Quirin et al., 2011). Dysregulation in both the HPA axis and the ANS have been found in other populations that have suffered from early adversity (Oldehinkel et al., 2008; Tollenaar et al., 2011). Greater dysregulation in these biological systems is associated with an increased risk for internalizing psychopathology, suggesting a moderating effect of emotion regulation on the relation between ELBW and internalizing problems (Oldehinkel et al., 2008).

The current study involved the administration of a battery of mental health related measures and a structured neuropsychiatric interview (the Mini International Neuropsychiatric Interview) that assessed internalizing problems. During the full day of testing, the cohort of ELBW participants were asked to expectorate three times (morning, afternoon, post-stressor) in order to produce salivary cortisol, which measures HPA axis functioning. Heart rate was measured twice (baseline and during a stressor) in the laboratory, which produced a measure of baseline and stress-reactive heart rate.

I tested the following predictions: First, it was predicted that those born at ELBW would continue to display higher levels of internalizing problems into their 30s compared to NBW controls. Second, it was predicted that salivary cortisol and heart rate responses would moderate the relation between birth status and mental health outcomes. ELBW adults who experienced higher levels of stress-reactive cortisol and heart rate would self-report higher levels of internalizing problems in their 30s compared to ELBW adults with low stress-reactive cortisol and heart rate. Those born at NBW were expected to have the same amount of internalizing problems regardless of their neuroendocrine and autonomic activity.

Chapter II:

Method

A. Overview

Over the past 40 years, there have been vast improvements in the survival of those born at ELBW and VLBW (Doyle, 2006). Although the first generation of ELBW survivors are now well into adulthood, a proportion of these individuals have struggled with problems ranging from neurosensory and cognitive impairments, to behavioural and emotional problems, and poorer general health relative to NBW controls (Allin, Rooney, Cuddy, et al., 2006; Saigal et al., 1994; Saigal et al., 1990).

The present study was part of a larger longitudinal investigation of metabolic, psychological, and physiological outcomes of adults born at ELBW. These ELBW participants have been followed longitudinally since birth, and have previously been reported on at ages 3 years (Saigal, Rosenbaum, Hattersley, & Milner, 1989), 5 years (Saigal et al., 1990), 8 years (Saigal, Szatmari, Rosenbaum, Campbell, & King, 1991; Szatmari, Saigal, Rosenbaum, Campbell, & King, 1993), adolescence (Saigal, Hoult, Streiner, Stoskopf, & Rosenbaum, 2000; Saigal, Lambert, Russ, & Hoult, 2002; Saigal, Pinelli, Hoult, Kim, & Boyle, 2003), and young adulthood (Boyle et al., 2011; Schmidt et al., 2010).

In the following thesis, I focused on particular measures examined in the adult sweep of data collection of the ELBW project. Three classes of personality measures were investigated, which provided a wealth of knowledge on basic personality, emotional well-being, and clinical descriptions of those born at ELBW. The

neuroendocrine and autonomic nervous system were examined as potential moderating factors that influenced the relation between ELBW and personality and psychopathology.

B. Participants

The ELBW cohort comprised 397 predominantly Caucasian infants (birth weight: 501-1000 g) born between 1977-1982 to residents of central-west Ontario, Canada, and were recruited from birth. Of the 397 infants, 179 survived to hospital discharge from the NICU; 166 survived to young adulthood, and in total, 142 participants were tested at the young adult visit. In the current sweep, 20 participants were unable to be located by the study team, 6 participants refused the entire adult study, 15 participants only completed a self-report package, and 18 participants were unable to be recalled to the laboratory. A total of 83 (46%) of the ELBW adults participated in this study (See Table 1 for further details).

The NBW control group comprised 145 individuals who were selected at age 8 to be followed longitudinally, from a random sample of children in the Hamilton Public School Boards who were born at term. The control group was matched for race, gender, and socioeconomic status with the ELBW cohort (Saigal et al., 1991). The control group was not followed from birth. Of the 133 eligible NBW control participants, 18 participants were unable to be located by the study team, 9 participants refused the entire adult study, 9 participants only completed a self-report package, 8 participants were unable to be recalled to the lab, and 1 participant was deceased. A total of 85 (58%) of the NBW adults participated in this study. All participants were tested at the Child

Emotion Laboratory at McMaster University. The participants received \$100.00 compensation for participating in the study, and any travel and/or lodging costs were covered.

C. Procedure

The participants were involved in a two-part experiment that occurred over the span of one day at McMaster University. Prior to their visit to McMaster University, the participant was asked to complete a self-administered questionnaire packet containing a variety of brief self-report measures. In the morning, the participant was escorted to McMaster hospital where they were involved in metabolic testing. Upon arrival at the hospital, the participant was briefed about the experimental procedures and consent was obtained from the participant. Salivary cortisol collection took place in the morning, as well as DNA collection and a variety of metabolic measures.

In the afternoon, the participant was brought back to the Child Emotion Laboratory where they provided a salivary cortisol sample, completed two semi-structured neuropsychiatric interviews (the Mini International Neuropsychiatric Interview and the Family History Screen), and a variety of computer tasks. Upon completion of the interview and computer tasks, the participant was prepared for the EEG and ECG testing. Once EEG and ECG testing concluded, the participant provided a third salivary cortisol sample and was then debriefed.

The present study examined the psychological, personality, cortisol, and ECG measures collected. The other measures were collected as part of the larger study and are not discussed further.

D. Electrocardiogram (ECG) data reduction and analyses

ECG recording. ECG was recorded using two disposable electrodes attached to the participant's forearms and collected simultaneously with EEG. The ECG signal was amplified by an individual SA Instrumentation Bioamplifier. The ECG data were recorded at a sampling rate of 512 Hz and filtered between .1 Hz (high pass) and 1000 Hz (low pass), using software developed by the James Long Company (IBI Analysis Program, Caroga Lake, NY).

ECG data reduction and quantification. The eyes-open and eyes-closed segments of the resting condition were aggregated. A file of interbeat intervals (IBIs) was created on each participant for the 6-minute resting condition and the 3-minute speech anticipation condition. The IBI data were visually edited for artifact (missing or spurious R-waves) and analyzed using the ECG Analysis software. This program also calculated the mean heart period and the standard deviation of the mean heart period (i.e., global heart period variability measures).

E. Salivary cortisol collection and assay determinations

Salivary cortisol collection. Each participant was asked to donate three individual saliva samples during the laboratory visit; Sample A was donated in the morning, Sample B in the afternoon, and Sample C twenty minutes after the speech anticipation condition (mean time of day in minutes: Sample A- 497.89, Sample B- 742.67, Sample C- 830.94). A 50- μ l cryogenic tube was used to collect passive saliva. Approximately 50- μ l of saliva were collected at each sample. Salivary cortisol samples were refrigerated within 30 minutes of collection.

Salivary cortisol assay determinations. Unbound or the biologically active form of serum cortisol enters saliva via intracellular mechanisms and studies consistently report high correlations between serum and salivary cortisol. Salivary cortisol is quantified using a competitive Enzyme Immunoassay kit (Salimetrics, LLC State College, PA, USA). The intra-assay coefficient variation is 3.50%, the inter-assay coefficient of variation is 5.08%, and the sensitivity is 0.08 nmoles/l. Salivary cortisol results were log transformed in order to reduce variation in the samples. Salivary cortisol levels that were three standard deviations above the mean were eliminated from analyses due to potential blood contamination that may skew the results.

F. Baseline and speech anticipation condition

Baseline condition. During a six-minute baseline condition, the participant was asked to remain as still and relaxed as possible, alternating between eyes open and eyes closed every minute.

Speech anticipation condition. Following the six-minute baseline condition, the participant took part in a speech anticipation task. The participant was told that they were going to have three minutes to create a speech on one of three pre-determined topics (i.e., abortion, gun control, same-sex marriage). The participant was informed that they had three minutes to create a speech on whichever topic they would like, which would be recorded and later judged by expert raters. The participant was then handed a sheet with the three speech topics and were told to sit as still as possible while they thought about their speech. After three minutes the experimenter informed the participant that there would not be a speech.

G. Personality Measures: Self-report

Beck Anxiety Inventory (BAI). The BAI is a 21-item questionnaire describing common symptoms of anxiety over the past week (Beck, Epstein, Brown, & Steer, 1988). Sample items include, “Numbness or tingling” “Unable to relax.” The participant is asked to rate how much he or she has been bothered by each symptom over the past week on a four-point scale ranging from 0 (“not at all”) to 3 (“severely—I could barely stand it”). Higher scores on the BAI reflect more severe anxiety symptoms. The BAI is psychometrically sound and has excellent validity and reliability (Beck et al., 1988).

Beck Depression Inventory (BDI). The BDI is a 21-item questionnaire that assesses the intensity of depressive symptoms in both psychiatric and normal populations over the past two weeks (Beck, Steer, & Garbin, 1988). Sample items include, “Sadness” “Pessimism.” The respondents are asked to rate the severity of their depressive symptoms on a four-point scale, ranging from 0 (i.e., “I do not feel sad”) to 3 (i.e., “I am so sad or unhappy that I can’t stand it”). Higher scores on the BDI reflect more severe depressive symptoms. The relevant psychometric information is reported by Beck and colleagues (Beck et al., 1988).

The Short-scale Eysenck Personality Questionnaire-Revised (EPQ-R). The EPQ-R is a 48-item questionnaire that assesses personality dimensions of extraversion, neuroticism, and psychoticism (Eysenck & Eysenck, 1985). Sample questions assessing extraversion (a predisposition to sociability) include, “Are you a talkative person?” “Are you rather lively?”; those tapping neuroticism (a tendency to experience emotions like anxiety and sadness strongly) included, “Does your mood often go up and down?” “Do

you feel ‘just miserable’ for no reason?”; and psychoticism (a predisposition to antisocial behaviour, aggression, and risk taking) was assessed via questions that included “Would you take drugs which may have strange or dangerous effects?” “Is it better to follow society’s rules than go your own way?” The EPQ-R also contains a “lie scale” that measures social desirability, conformity, and risk aversion. Sample items from the lie scale include, “Are *all* of your habits good and desirable ones?” “Do you always practice what you preach?” Each item on the EPQ-R is answered as either 1 (“yes”) or 0 (“no”). The EPQ-R subscales (i.e., extraversion, neuroticism, psychoticism, and lie) are summed separately to produce total scores for each of the four subscales. The EPQ-R is widely used and has been shown to be both reliable and valid (Eysenck & Eysenck, 1985).

Young Adult Self-Report (YASR). The YASR is a 118-item questionnaire that assesses behavioural and emotional problems (Achenbach, 1997). The YASR can be parsed into anxious/depressed, withdrawn, somatic complaints, thought problems, attention problems, intrusive, aggressive behaviour, delinquent behaviour, other problems, and other physical problems. A composite measure of internalizing problems can be created by summing anxious/depressed and withdrawn categories. A composite measure of externalizing problems can be created by summing the intrusive, aggressive behaviour and delinquent behaviour categories. Sample items from the internalizing scale include, “I feel lonely” “I would rather be alone than with others.” Sample items from the externalizing scale include, “I brag” “I argue a lot.” Each item on the YASR is answered as either 0 (“Not True”), 1 (“Somewhat or Sometimes True”), or 3 (“Very True or Often True”). The YASR is widely used and has been shown to be both reliable and valid (Achenbach, 1997).

H. The Mini International Neuropsychiatric Interview (MINI)

The MINI is a brief structured interview for the major Axis 1 psychiatric disorders in the DSM-IV and ICD-10 (Sheehan et al., 1998). Trained interviewers conducted the interview, which required the participants to answer very precise questions about psychological problems with either a “yes” or “no.” The MINI is divided into modules identified by letters, each corresponding to a diagnostic category. The disorders covered in this version of the MINI include major depressive episode, dysthymia, manic episode and hypomanic episode, panic disorder, agoraphobia, social phobia, obsessive compulsive disorder, posttraumatic stress disorder (current and lifetime), alcohol dependence/abuse (current and lifetime), substance dependence/abuse (current and lifetime), generalized anxiety disorder, and adult attention deficit/hyperactivity disorder.

A diagnostic algorithm screened for major depressive disorder (current, lifetime, and recurrent), bipolar I disorder (current, past, recurrent), bipolar II (current, lifetime, and recurrent), and bipolar disorder not otherwise specified (current and past). Sample questions for the major depressive episode include, “Were you ever depressed or down, most of the day, nearly every day, for two weeks?” “Were you ever much less interested in most things or much less able to enjoy the things you used to enjoy most of the of time, for two weeks?” The MINI has excellent validity, interrater reliability, and very good retest reliability. (Sheehan et al., 1998).

I. Missing Data

Personality data was missing from 12 participants (3 ELBW) who did not complete the BAI scale, 13 participants (5 ELBW) who did not complete the BDI scale,

12 participants (4 ELBW) who did not complete the EPQ-R Psychoticism scale, 13 participants (5 ELBW) who did not complete the EPQ-R Extraversion scale, 14 participants (5 ELBW) who did not complete the EPQ-R Neuroticism scale, 12 participants (5 ELBW) who did not complete the EPQ-R Lie scale, 15 participants (5 ELBW) who did not complete the YASR Anxiety/Depression scale, 11 participants (3 ELBW) who did not complete the YASR Withdrawal scale, and 15 (5 ELBW) participants who did not complete the YASR Internalizing scale. Due to issues relating to time and quality of salivary cortisol samples (i.e., inadequate amount of saliva) 11 participants were missing sample A, 4 participants were missing sample B, and 6 participants were missing sample C. Two participants were also excluded due to their cortisol levels exceeding three standard deviations from the mean cortisol value for each sample. Due to equipment failure, motor movement artifact, as well as failure of the individual to participate correctly or vigilantly (e.g., failure to follow proper instructions), baseline ECG data from 9 participants and anticipation ECG data from 11 participants was lost.

Chapter III:

Results

A. Demographics and descriptive statistics

Demographics. The mean birth weight of the ELBW cohort was mean (SD) 830 (133) g and 3401 (482) g for the NBW cohort; the corresponding gestational ages were 27.08 (2.27) weeks and term, respectively (Table 2). There were no significant differences in the parental socioeconomic or educational status of the ELBW and NBW cohort (the P values were $> .05$), although there was a significant difference in income levels for the ELBW and NBW cohort at ages 30-35 ($p < .05$). The mean age at assessment was 32.5 (1.8) years for ELBW and 33.0 (1.5) years for NBW and differed between groups ($p > .05$).

Descriptive statistics: Non-clinical and clinical personality measures. Mental health problems were examined through non-clinical and clinical measures. The Eysenck Personality Questionnaire-Revised, the Beck Depression Inventory, and the Beck Anxiety were used as non-clinical measures of internalizing and externalizing problems. The Young Adult Self-Report and the Mini International Neuropsychiatric Interview were used to examine clinical facets of internalizing and externalizing problems. The mean, standard deviations, and range for all non-clinical and clinical measures are reported in Table 3 and 4, respectively.

Descriptive statistics: Physiological measures. The neuroendocrine and autonomic systems were investigated in this thesis through the use of salivary cortisol and heart period, respectively. The mean, standard deviation, and range were described

for the timing of cortisol samples in minutes and salivary cortisol levels in nMoles/liter (Table 5A); the mean, standard deviation, and range for heart period during baseline and the stressor were also reported (Table 5B).

B. Intercorrelations between self-report and physiological measures

Intercorrelations between non-clinical and clinical measures. The intercorrelations between all self-report measures are described in Table 6. Correlations among subscales of measures were found for all scales and interviews. As expected, the BAI and BDI ($r = .663, p < .001$), the YASR Anxiety/Depression and Withdrawal subscales ($r = .725, p < .001$), and the MINI Total Anxiety and Mood Disorders ($r = .387, p < .001$) were all positively correlated.

A variety of clinical and non-clinical measures were used in order to investigate internalizing problems. The intercorrelations between these non-clinical and clinical scales is reflective of the consistency between measures in reporting internalizing related problems. For example, the BAI was significantly positively correlated with a variety of measures, including the BDI ($r = .663, p < .001$), The YASR Anxiety/Depression subscale ($r = .612, p < .001$), the EPQ-R Neuroticism subscale ($r = .628, p < .001$) the YASR Withdrawal subscale ($r = .422, p < .001$), the MINI Total Mood Disorders ($r = .486, p < .001$), and the MINI Total Anxiety Disorders ($r = .618, p < .001$). Similar intercorrelations can be found between all the abovementioned scales in Table 6.

Intercorrelations between physiological measures. Intercorrelations between physiological measures can be found in Table 7. There were significant positive correlations between the three salivary cortisol samples. The correlations were as follows,

Cortisol sample A and B ($r = .260, p = .003$), Cortisol sample A and C ($r = .303, p = .001$), and Cortisol sample B and C ($r = .435, p < .001$). Significant positive correlations were also found between baseline and stress-reactive heart period ($r = .902, p < .001$). There were no significant intercorrelations between the neuroendocrine and autonomic measures.

C. Between group differences on subjective and physiological measures in the ELBW and NBW groups

Between group differences on non-clinical measures. Independent t tests were performed with group (ELBW and NBW) as the between-subject factor on each of the subjective non-clinical measures. These analyses revealed a significant main effect of group on the EPQ-R Extraversion ($t_{176} = 1.986, p = .041$) and EPQ-R Lie ($t_{177} = 4.287, p < .001$) subscales. The ELBW group self-reported significantly lower levels of extraversion and higher lie scores on the EPQ-R than the NBW group.

Between group differences on clinical measures. Independent t tests were performed with group (ELBW and NBW) as the between-subject factor on each of the subjective clinical measures. These analyses revealed a significant main effect of group on the YASR Anxiety/Depression ($t_{170} = 2.313, p = .022$), Withdrawal ($t_{175} = 2.102, p = .037$), and Internalizing ($t_{166} = 2.533, p = .012$) subscales. The ELBW group self-reported significantly higher levels of anxiety/depression, withdrawal, and internalizing symptoms on the YASR than the NBW group.

Between group differences on physiological measures. Independent t tests were performed with group (ELBW and NBW) as the between-subject factor on each of the

physiological measures. These analyses revealed no significant differences on any of the salivary cortisol levels throughout the day or mean heart period during baseline and the stressor.

In order to further investigate whether there were differences in cortisol levels between groups (ELBW and NBW) across time, a repeated measures ANOVA was performed with group as the between-subjects factor. When an ANOVA with repeated measures was used with a Greenhouse-Geisser correction, the mean salivary cortisol levels were significantly different across time ($F(1.439, 174.163) = 110.01, p < .001$) (See Figure 3), but not between groups. Both groups' salivary cortisol levels decreased across time points, reflecting the normal diurnal cortisol rhythm.

D. Moderation analyses: Linking extremely low birth weight, emotion dysregulation, and internalizing problems

In order to investigate cortisol and heart rate data, we used a median cut-score to make high and low cortisol and heart rate groups. Any participant equal to or above the median cortisol and heart rate levels were considered “High” and anyone below the median cortisol and heart rate levels were considered “Low.”

The data were analyzed with ANOVAs and linear and logistic regressions in order to investigate the moderating influences of emotion regulation, as indexed by the neuroendocrine and autonomic system, on the relation between ELBW and internalizing problems.

Non-clinical measures of internalizing problems. The data were analyzed in an ANOVA with group (ELBW and NBW), stress-reactive cortisol (High and Low), and

stress-reactive heart period (High and Low) as the between subjects factors. Time of sampling, cortisol sample A, baseline heart period, age, and income level were covariates. Analyses revealed a significant Group X Stress-Reactive Cortisol interaction on the BDI [$F(1, 39) = 6.675, p = .014$]. The results indicated that those born at ELBW had the highest scores on the BDI when paired with high stress-reactive cortisol levels, but also the lowest scores on the BDI when paired with low stress-reactive cortisol levels. BDI scores for those born at NBW did not differ depending on their stress-reactive cortisol levels (See Figure 4).

An ANOVA with group (ELBW and NBW), stress-reactive cortisol (High and Low), and stress-reactive heart period (High and Low) as the between subjects factors was performed on the EPQ-R Neuroticism subscale. Analyses revealed a significant Group by Stress-Reactive Cortisol interaction [$F(1, 40) = 6.849, p = .012$]. The results indicated a similar pattern for those born at ELBW displaying the highest scores on the EPQ-R Neuroticism subscale when paired with high stress-reactive cortisol levels, but also the lowest scores on the EPQ-R Neuroticism measure when paired with low stress-reactive cortisol levels (See Figure 5).

A linear regression was performed in order to test the moderation analysis further. Group (ELBW and NBW), the z-scored stress reactive cortisol, and an interaction term (z scored group status X z-scored stress reactive cortisol) were used as predictors for the non-clinical outcomes. The interaction term significantly predicted BAI scores, $\beta = -.227, t(127) = -2.230, p = .028$. The interaction term also explained a significant proportion of variance in BAI scores, $r^2 = .083, F(3, 127) = 3.755, p = .013$. When the participants were split by group status, it became apparent that this relation stemmed

from the ELBW participants. As demonstrated in Figure 6A and 6B, there was a positive relation between z-scored stress reactive cortisol and BAI scores in the ELBW survivors, but there was no relation between z-scored stress reactive cortisol and BAI scores in the NBW group.

Clinical measures of internalizing problems. The data were analyzed in an ANOVA with group (ELBW and NBW), stress-reactive cortisol (High and Low), and stress-reactive heart period (High and Low) as the between subjects factors. Time of sampling, cortisol sample A, baseline heart period, age, and income level were covariates. Analyses revealed a significant Group by Stress-Reactive Cortisol interaction on the YASR Anxiety/Depression [$F(1, 40) = 9.246, p = .004$] (Figure 7), Withdrawal [$F(1, 40) = 6.511, p = .015$] (Figure 8), and Internalizing [$F(1, 40) = 9.371, p = .004$] (Figure 9) subscales. The results indicated that those born at ELBW had the highest scores on the YASR Anxiety/Depression, Withdrawal, and Internalizing subscales when paired with high stress-reactive cortisol levels. Those ELBW participants who had low stress reactive cortisol levels displayed similar scores to the NBW group on all three subscales.

Chapter IV: Discussion

A. Review of the cohort and current study

The present study was an extension of previous research on a cohort of ELBW survivors born between 1978-1982 to residents of central west Ontario, Canada, who have been followed longitudinally since birth, and a NBW control group that has been followed since age 8 (Saigal, Szatmari, Rosenbaum, Campbell, & King, 1991). The ELBW survivors have been tested across the lifespan, specifically at age 3 (Saigal, Rosenbaum, Stoskopf, & Sinclair, 1984), age 5 (Saigal, Szatmari, Rosenbaum, Campbell, & King, 1990), age 8 (Saigal et al., 1991), adolescence (Saigal et al., 1996), and young adulthood (Schmidt, Miskovic, Boyle, & Saigal, 2008; Schmidt, Miskovic, Boyle, & Saigal, 2010).

Although this cohort of ELBW survivors are now well into adulthood, a proportion of these individuals have struggled with problems ranging from neurosensory and cognitive impairments, to behavioral and emotional problems, and poorer general health relative to NBW controls (Boyle et al., 2011; Saigal et al., 1994; Saigal, Pinelli, Hoult, Kim, & Boyle, 2003; Saigal et al., 1990; Schmidt et al., 2008; Schmidt et al., 2010). As the ELBW survivors transitioned into their 30s, it was hypothesized that novel life events, such as full time work, marriage, and children, would lead to an increase in stress that would be apparent both biologically and behaviourally, which may have deleterious psychological effects. During this data collection, we examined the same ELBW survivors and NBW controls during cognitive, behavioural, physiological, and

psychological tasks. In this thesis, we examined psychological and physiological measures (i.e., cortisol and heart period).

In this study, we tested ELBW survivors and NBW controls at age 30-35, where we collected a variety of self-report measures of mental health problems as well as administered a clinical neuropsychiatric structured interview that screened for a variety of mental health problems. By using a broad range of assessments, we were able to gain a complete picture of the mental health of ELBW survivors and NBW controls. We collected salivary cortisol at rest and 20 minutes post-stressor and electrocardiogram data during rest and during the same stressor in order to assess the moderating influences of these physiological measures on the relation between ELBW and mental health.

B. Hypotheses

Two hypotheses were tested. First, it was hypothesized that those born at ELBW would continue to display higher levels of internalizing problems into their 30s compared to NBW controls. Second, it was hypothesized that salivary cortisol and heart rate responses during stress would moderate the relation between birth status and mental health outcomes. ELBW adults who experienced higher levels of stress-reactive cortisol and heart rate would self-report higher levels of internalizing problems in their 30s compared to ELBW adults with low stress-reactive cortisol and heart rate. Those born at NBW were hypothesized to have the same amount of internalizing problems regardless of their neuroendocrine and autonomic activity.

Group differences. In line with the first hypothesis, those born at ELBW displayed significantly lower levels of Extraversion and higher Lie scores on the EPQ-R,

as well as higher levels of Anxiety/Depression, Withdrawal, and Internalizing symptoms on the YASR compared to NBW controls. With regards to the second hypothesis, our predictions were substantiated with the neuroendocrine system. The neuroendocrine system was found to moderate the relation between birth status and mental health problems. Specifically, the relation between birth status and some of the non-clinical (i.e., BDI, BAI, Neuroticism subscale of the EPQ-R) and clinical (Anxiety/Depression, Withdrawal, and Internalizing subscales of the YASR) measures of mental health. Participants born at ELBW who had high stress-reactive cortisol levels displayed the highest amount of internalizing symptoms. However, those ELBWs who displayed low stress-reactive cortisol had equivalent or lower scores on the clinical and non-clinical measures of internalizing problems compared to NBW controls.

Separate moderating analyses revealed that there was an interaction between birth status and stress-reactive cortisol levels. Specifically in the ELBW group, as stress-reactive cortisol levels increased, so did their scores on the BAI. However, there was no relation between stress reactive cortisol levels and scores on the BAI in the NBW control group. These analyses substantiated the moderating influence of the neuroendocrine system on the relation between ELBW and later internalizing problems.

The finding that those born at ELBW display higher self-reported levels of non-clinical and clinical internalizing problems in their 30s replicates and extends past research. Past research on those born at VLBW or very preterm (VPT; <33 weeks' gestation) have reported that these individuals display personality styles characterized by decreased risk taking behaviors (Allin et al., 2006; Hack et al., 2002; Hack et al., 2004). Allin and colleagues (2006) found that 18 to 19 years olds born VPT had significantly

lower extraversion and higher neuroticism and lie (i.e., social desirability) scores on the Eysenck Personality Questionnaire than term controls (those born at 38-42 weeks gestational age). Pesonen and colleagues (2008) also reported lower openness to experience, less assertiveness, higher agreeableness and increased levels of conscientiousness in those born at VLBW. These personality traits are reflective of reduced risk taking and decreased social behavior, and are suggestive of a more cautious and obedient personality style (Pesonen et al., 2008). Schmidt and colleagues (2008) compared our cohort of ELBW survivors to NBW controls on a variety of facets of personality in early adulthood (i.e., 22-26 years of age). The authors found that cognitively and physically non-impaired ELBW survivors had significantly higher self-reported levels of shyness, behavioral inhibition, and cautiousness (Eysenck psychoticism measure reversed score + lie scale) at age 22-26 (Schmidt et al., 2008)

Being born at LBW, VLBW, and ELBW has also been associated with higher rates of internalizing disorders throughout the lifespan (Crombie et al., 2011; Hack et al., 2002; Boyle et al., 2011). Those born at VLBW who were also SGA displayed heightened levels of depression as indexed by the Beck Depression Inventory compared to normal birth weight controls at age 18-27 (Raikkonen et al., 2008). Boyle and colleagues (2011) found that our ELBW cohort manifested higher levels of depressed mood, anxiety, social withdrawal, and poor self-esteem (internalizing problems) compared with NBW controls, but not higher levels of externalizing problems at age 22-26. Those born at VLBW and ELBW have been found to have persistent issues with internalizing disorders into young adulthood (Boyle et al., 2011; Raikkonen et al., 2008),

and our findings extend this research by confirming that these internalizing problems are present in the ELBW group into their 30s.

Moderating influences of the neuroendocrine system. The moderating influence of the neuroendocrine system on the relation between prematurity and mental health problems has been found in two separate studies of children. Research by Bagner, Sheinkopf, Vohr, and Lester (2010) found that in a sample of two to five year olds born at less than 37 weeks gestation, those with increased cortisol reactivity following a stressor had more severe problems with attention, emotional reactivity, anxiety, depression, and overall internalizing behaviour problems compared to children with decreases in cortisol reactivity following a stressor.

Similarly, Brummelte and colleagues (2011) reported a gradient of risk for internalizing behavior problems based on cortisol levels and size for gestational age. In this work, a child's inability to regulate both baseline and stress-reactive cortisol levels contributed to increased levels of anxiety and depressive symptoms at 18 months of age in children born at ELGA (24-28 weeks gestation), and to a lesser degree VLGA (29-32 weeks gestation).

Schmidt and colleagues (2010) investigated how ELBW status can affect cortisol levels, electroencephalographic (EEG) activity, and psychopathology in young adulthood. The authors found that higher basal cortisol levels in the ELBW adults are related to greater relative right frontal electroencephalographic activity, which in turn is related to more internalizing problems (Schmidt et al., 2010). However, there was no measure of stress reactive cortisol, and only high-functioning ELBW adults were included in this study. Therefore, this study is the first to illustrate the moderating

influence of the neuroendocrine system, specifically stress-reactive cortisol, on the relation between ELBW and internalizing problems in adulthood.

C. Possible explanations

Group differences. Researchers in the area of prematurity and developmental psychopathology have posited that there are a variety of environmental and biological factors involved in the diathesis of psychopathology in those born prematurely (Boyle et al., 2011; Pesonen, Raikkonen, Strandberg, Jarvenpaa, 2005; Seckl & Holmes, 2007). Past research has implicated parental monitoring as a potential mediating factor in the relation between premature birth and detrimental personality styles (Allin et al., 2006; Hack et al., 2002; Hack et al., 2004; Heinonen et al., 2010). Some studies have shown that those born prematurely have been exposed to higher behavioral restrictiveness and parental monitoring (Allin et al., 2006; Hack et al., 2005; Hack et al., 2004; Pesonen et al., 2008), which have been found to increase one's risk for withdrawal tendencies and produce lower emotional well-being, and lead to personality traits including cautiousness (Allin et al., 2006; Schmidt et al., 2008). A cautious personality is associated with decreased social engagement, which increases the chance that one will experience loneliness. These characteristics are associated with psychiatric problems, such as depression and anxiety later in life (Hack et al., 2004; Raikkonen et al., 2008; Schmidt et al., 2008). It is possible that early parenting differences may have contributed to personality development in this cohort and the differences observed in internalizing problems.

Birth weight is considered a surrogate marker of fetal environment, which can be impacted by a variety of factors (Boyle et al., 2011). Genetic mechanisms, such as

maternal genes, cannot be overlooked as they have lasting effects on the fetus (Pesonen et al., 2005). Indeed, a study by Pesonen and colleagues (2005) found that depression and depressive symptoms are moderately heritable. Maternal distress during pregnancy has been found to be associated with shorter length of gestation and with less optimal development in the offspring (Pesonen et al., 2005). We did not have the history of parental depression, so we cannot resolve the question of confounding parental depression.

Premature birth can reflect exposure to adverse intrauterine conditions, which may leave the infant at risk for a variety of negative outcomes, such as inadequate time for the meeting of important developmental milestones (Schäffer et al., 2009). Coupled with additional stressful postnatal events such as blood sampling, steroid exposure, suctioning, and routines such as weighing and clustered nursing (Glover, Miles, Matta, Modi, & Stevenson, 2005; Holsti, Weinberg, Whitfield, & Grunau, 2007), it is common that those born prematurely have accelerated HPA axis maturation, which may reset baseline and stress reactive cortisol levels and have long term adverse effects on the HPA axis and these individuals' mental health (Grunau et al., 2007; Schäffer et al., 2009).

A variety of studies investigating mental health outcomes in those born prematurely have proposed intrauterine glucocorticoid programming of the HPA axis as a potential explanation for heightened levels of internalizing problems and cautious personality styles in this unique population (Pesonen et al., 2008; Raikkonen et al., 2008). A substantial amount of research has been conducted on HPA axis activity in those born prematurely, which has found that there is reduced activity in the placental enzyme 11 β hydroxysteroid dehydrogenase type 2 in those born at preterm and term SGA

births, which has been linked to intrauterine growth restriction, increased HPA axis activity and anxiety (Seckl & Meaney, 2007). In addition, small size at preterm and term birth is associated with altered HPA axis activity, which in turn is among the key biological characteristics of depression (Raikkonen et al., 2008).

Moderating influences of the neuroendocrine system. Due to ELBW survivors' increased risk of altered HPA axis activity, it is possible that an individual's capacity to regulate basal or stress reactive cortisol levels may contribute to the higher anxiety and depressive symptoms evident in those born at ELBW in adulthood (Grunau et al., 2005; Levy-Shiff et al., 1994). Those born at ELBW may have HPA function that is differently regulated compared to termborn children, which may lead ELBW's neuroendocrine system to be more sensitive to environmental effects, such as child rearing (Brummelte et al., 2011).

Additionally, cortisol reactivity may be a physiological antecedent of internalizing problems and may suggest that HPA activity is part of the broader behavioural profile of those born prematurely (Bagner et al., 2011). The behavioural profile of those born at ELBW is such that a small but significant portion present with higher levels of internalizing problems throughout the lifespan (Boyle et al., 2011). The results of this study provide a possible explanation for differences in behavioural profiles of those born at ELBW, which suggest that differences in stress reactive cortisol may be a sensitivity factor for later internalizing problems. Those ELBW survivors with disrupted HPA activity may be at an increased risk for internalizing problems, while decreased HPA functioning may be a resiliency factor which protects those born at ELBW from internalizing problems (Bagner et al., 2011).

D. Limitations

The present study is not without limitations. First, as with many longitudinal studies, there was a moderate amount of attrition. Return rates for both groups were slightly lower than our previous studies. As the sample size was relatively small, it may have reduced the power to detect some effects. Second, survivors have ready access to universal health care which may improve their outcomes relative to systems where care is less readily available. Third, some of the personality measures that we used were self-reported and therefore subjective in nature. It is also possible that participants did not fully understand the questions posed in the questionnaires, were limited by the response options, or may not have been completely honest when answering the questions. Fourth, we recorded electrocardiography and salivary cortisol levels on one occasion only. Accordingly, we do not have information on the stability of these measures. It would be advisable to have repeated measures of both physiological samples over time (Schmidt et al., 2010). Lastly, the participants were subject to a battery of physiological tests in the morning as a part of the metabolic component of the ELBW study. Due to stress related to medical procedures, it is possible that the participants were in a heightened state of arousal during the afternoon procedures. This may have affected physiological measures collected in the afternoon, which may have skewed the results. All of these possibilities reflect limits to the reliability of our results.

E. Theoretical and practical applications

The present findings have important theoretical implications for research on personality and mental health outcomes in typical and atypical populations. The discovery that extreme prematurity is associated with the development of behavioral

inhibition and cautious personality styles, as well as internalizing problems suggest that personality dispositions may not only be biologically based or innate, but can be modified through stressful experiences (Fox et al., 2005; Schmidt et al., 2008). Our current study provides further evidence that early life stress, such as extreme prematurity and being born at ELBW can lead to enduring personality differences that remain stable throughout adulthood, and may lead to higher rates of psychiatric morbidity in this unique population. The results of the present study provide further evidence for an alternative hypothesis to genetically determined theories of personality characteristics in that they suggest that exposure to stress prenatally, perinatally, or early postnatally can have enduring effects on social and affective development (Heinonen et al., 2010).

Our second finding that stress reactive cortisol levels moderate the relation between ELBW and some measures of mental health provide support for a differential susceptibility model (Belsky, Bakersmans-Kranenburg & IJzendoorn, 2007). Our results suggest that cortisol levels seem to heighten susceptibility to a wide variety of environmental stressors, with ELBW survivors with low and high stress reactive cortisol promoting, respectively, positive and negative outcomes. NBW controls seem to be producing the same outcome regardless of their cortisol levels during stress. The results suggest that extreme prematurity and early life stress are contextual factors that interact with one's emotion regulatory abilities (i.e. cortisol) to confer risk or resiliency. Emotion regulation can be thought of as a sensitivity factor in the relation between ELBW and later internalizing problems.

These findings highlight the continued importance of health outcomes of those born extremely prematurely, the clinical importance of monitoring growth among high-

risk pregnancies (Boyle et al., 2011), and the need for more research investigating dysregulated cortisol activity in order to understand the behavioural profile of ELBW survivors. Potential intervention programs aimed at reducing the negative psychological impact of being born at ELBW may target stress reduction. Individuals born at ELBW seem to display differences in their ability to regulate stress, so by providing services related to stress reduction, it may provide those ELBW survivors with emotion regulatory problems with the additional support that is necessary for proper socio-emotional development.

F. Conclusions

To summarize, our findings suggest that those born at ELBW display higher levels of internalizing related problems at 30-35 years of age compared to NBW controls. The relation between ELBW and some non-clinical and clinical measures of internalizing problems have been shown to be moderated by stress-reactive cortisol levels. However, NBW controls do not display a moderating effect of stress reactive cortisol levels on the relation between NBW and internalizing related problems.

These results have implications for theory as well as practice, as early life stress has been shown to affect mental health outcomes into adulthood in *some* ELBW survivors. Personality is a multifaceted system which is reflective of both environmental and biological influences. Past research and our current findings have demonstrated that stress early in life may robustly impact the development of personality characteristics, which is illustrated in those born at ELBW displaying stable personality differences and higher internalizing problems throughout adulthood (Boyle et al., 2011; Schmidt et al., 2008). A differential susceptibility of risk model has been utilized as an explanation for

these divergent outcomes, with emotion regulatory abilities, as indexed by stress reactive cortisol, providing the most positive and negative outcomes in those born at ELBW.

Because these results suggest that the neuroendocrine system is a mechanism that may be affecting the development of psychopathology in ELBW survivors, it is important for future research to examine this mechanism in more detail. Future research should include increasing the number of saliva samples throughout the day in order to investigate not only the stress response, but recovery from a stressor. Brummelte and colleagues (2011) found that those premature children who recovered successfully from a stressor fared better in terms of mental health outcomes than those premature children who did not successfully recover from a stressor. Additionally, the HPA axis is coupled with many other hormonal systems, including growth hormone and insulin-like growth factor-I, which are key regulators of growth and brain development and may be involved in the diathesis of depression (Schneider, Pagotto, & Stalla, 2003). In future research, other systems that are associated with the HPA axis should be investigated in order to see if multiple linked systems are affected by this form of early adversity, which might lead to a modified differential susceptibility model.

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Table 1

Extremely Low Birth Weight (ELBW) and Normal Birth Weight (NBW) Adult Sweep (30-35 y.o.) Participation Flow Chart

ELBW	NBW
179 (Survived to Hospital Discharge)	145 (Enrolled at age 8)
↓	
13 Late Deaths	
↓	
166 Survived to Young Adulthood (22-26 y.o.)	
↓	
142 Participated in Young Adult Sweep	133 Participated in Young Adult Sweep
↓	↓
Eligible to Participate in Adult Sweep (30-35 y.o.)	Eligible to Participate in Adult Sweep (30-35 y.o.)
↓	↓
142	133
20 Could not locate	18 Could not locate
6 refused both questionnaire and laboratory components of study	9 refused both questionnaire and laboratory components of study
15 completed questionnaires only	9 completed questionnaires only
18 unable to recall to lab	8 unable to recall to lab
↓	1 deceased
84 completed questionnaire and laboratory components of adult study (46%) ^a	↓
	88 completed questionnaire and laboratory components of adult study (58%)

^a 1 ELBW participant did not participate at the young adult study, but participated in the adult study.

Table 2

Sociodemographic variables for ELBW and NBW groups

Variable	Group	
	ELBW (n = 98)	NBW (n = 91)
Birth weight, G ^a		
Mean	830	3401
SD	133	483
Gestational age, wk ^b		
Maximum	34	Term
Minimum	23	NA
Mean	27.08	NA
SD	2.27	NA
Gender, female/male	61/37	57/34
Parental social class ^c		
Highest	10	16
Middle/High	32	19
Middle	29	30
Low/Middle	14	14
Lowest	2	5
Total household income ^d		
<50 000	44	20
<100 000	20	33
>100 000	15	21
Current highest education, % ^e		
Less than high school	0	0
High school	12	12
Partial post-secondary	21	14

Post-secondary completion	43	44
Post-graduate degree	9	13
Age at adult assessment, y		
Mean	32.5	33.0
SD	1.8	1.5

NA: not applicable

^a Data were missing for 8 ELBW and 2 NBW participants.

^b Data were missing for 10 ELBW participants.

^c Data are based on Hollingshead classification. Data were missing for 9 ELBW and 7 NBW participants.

^d Data were missing for 19 ELBW and 17 NBW participants.

^e Data were missing for 14 ELBW and 15 NBW participants.

Table 3

Descriptive Statistics for Non-clinical Measures

3A. Mean, standard deviation, and range for the Eysenck Personality Questionnaire-Revised (EPQ-R)

	Mean	Standard Deviation	Range
EPQ-R Psychoticism (N = 177)	.11	.10	1
EPQ-R Neuroticism (N = 175)	.40	.31	1
EPQ-R Extraversion (N = 176)	.61	.31	1
EPQ-R Lie (N = 177)	.45	.23	1

3B. Mean, standard deviations, and range for the Beck Anxiety Inventory (BAI) and Beck Depression Inventory (BDI)

	Mean	Standard Deviation	Range
BAI (N = 177)	.41	.46	2.48
BDI (N = 176)	.43	.55	2.55

Table 4

Descriptive Statistics for Clinical Measures

4A. Mean, standard deviation, and range for the Young Adult Self Report (YASR)

	Mean	Standard Deviation	Range
YASR Anxiety/Depression (N = 176)	.49	.43	1.81
YASR Withdrawal (N = 178)	.40	.36	1.86
YASR Intrusive (N = 178)	.26	.29	1.57
YASR Aggressive (N = 177)	.24	.24	1.25
YASR Delinquent (N = 178)	.15	.26	1.33
YASR Internalizing Problems (N = 174)	.44	.37	1.71
YASR Externalizing Problems (N = 177)	.22	.21	1.23

4B. Mean, standard deviation, and range for the Mini International Neuropsychiatric Interview (MINI)

	Mean	Standard Deviation	Range
MINI Mood Problems (N = 161)	.80	1.23	4
MINI Anxiety Problems	.48	1.26	8

(N = 161)

MINI Total Problems	2.32	3.30	18
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(N = 161)

Table 5

Descriptive Statistics for Physiological Measures

5A. Mean, standard deviation, and range for timing of cortisol samples (minutes) and salivary cortisol levels (nMoles/liter)

	Mean	Standard Deviation	Range
Time- Cortisol Sample A	497.89	20.94	125.00
Time- Cortisol Sample B	742.67	49.01	450.00
Time-Cortisol Sample C	830.44	51.84	418.00
Cortisol Sample A (N = 127)	10.30	6.29	31.50
Cortisol Sample B (N = 133)	4.41	3.53	19.39
Cortisol Sample C (N = 131)	3.47	2.50	14.08

5B. Mean, standard deviation, and range for heart period (IBI)

	Mean	Standard Deviation	Range
Baseline (N = 123)	814.13	120.86	682.41
Stressor (N = 121)	776.52	110.69	546.77

Table 6
Intercorrelations among clinical and non-clinical measures

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
YASR Anx/Dep	-															
YASR With	.725 ^a	-														
YASR Intrus	.342 ^a	.217 ^b	-													
YASR Aggr	.631 ^a	.528 ^a	.556 ^a	-												
YASR Delinq	.490 ^a	.450 ^a	.466 ^a	.507 ^a	-											
YASR Intern	.940 ^a	.917 ^a	.308 ^a	.629 ^a	.511 ^a	-										
YASR Extern	.584 ^a	.473 ^a	.842 ^a	.821 ^a	.797 ^a	.576 ^a	-									
BAI	.610 ^a	.419 ^a	.215 ^b	.496 ^a	.390 ^a	.565 ^a	.436 ^a	-								
BDI	.722 ^a	.481 ^a	.223 ^b	.480 ^a	.460 ^a	.660 ^a	.460 ^a	.663 ^a	-							
EPQ Psychot	.369 ^a	.517 ^a	.346 ^a	.433 ^a	.523 ^a	.471 ^a	.525 ^a	.286 ^a	.251 ^b	-						
EPQ Neurot	.808 ^a	.584 ^a	.316 ^a	.569 ^a	.379 ^a	.765 ^a	.501 ^a	.613 ^a	.679 ^a	.372 ^a	-					
EPQ Extra	-.347 ^a	-.541 ^a	.257 ^b	-.102	-.018	-.473 ^a	.072	-.115	-.214 ^b	-.237 ^a	-.325 ^a	-				
EPQ Lie	-.132	-.136	-.161 ^b	-.273 ^a	-.384	-.143	-.326 ^a	-.215 ^a	-.221 ^a	-.329 ^a	-.163 ^b	.070	-			
MINI Mood	.500 ^a	.373 ^a	.193 ^b	.326 ^a	.296 ^a	.481 ^a	.320 ^a	.486 ^a	.461 ^a	.208 ^a	.511 ^a	-.116	-.139	-		
MINI Anx	.646 ^a	.417 ^a	.197 ^b	.420 ^a	.473 ^a	.582 ^a	.426 ^a	.617 ^a	.719 ^a	.205 ^a	.540 ^a	-.162 ^b	-.193 ^b	.387 ^a	-	
MINI Total	.675 ^a	.496 ^a	.339 ^a	.526 ^a	.625 ^a	.636 ^a	.588 ^a	.629 ^a	.726 ^a	.374 ^a	.606 ^a	-.131	-.310 ^a	.620 ^a	.853 ^a	-

Table 7

Intercorrelations among physiological measures

	1	2	3	4	5
Cortisol Sample A	-				
Cortisol Sample B	.260 ^b	-			
Cortisol Sample C	.303 ^b	.435 ^a	-		
Baseline Heart Period	.556	.056	.073	-	
Stressor Heart Period	.720	.299	.331	.902 ^a	-

Table 8

8A. Between group differences on non-clinical measures

	Birth Status		<i>t</i>	<i>df</i>
	ELBW	NBW		
BAI	.46 (.53)	.34 (.34)	1.752	159
BDI	.46 (.61)	.40 (.49)	.728	175
EPQ Psychoticism	.09 (.09)	.12 (.10)	-1.636	170
EPQ Neuroticism	.44 (.30)	.36 (.31)	1.681	175
EPQ Extraversion	.56 (.30)	.66 (.31)	-2.063*	176
EPQ Lie	.52 (.24)	.38 (.20)	4.287***	177

Note. * = $p < .05$, *** = $p < .001$. Standard deviations appear in parentheses.

8B. Between group differences on clinical measures

	Birth Status		<i>t</i>	<i>df</i>
	ELBW	NBW		
YASR Anx/Dep	.56 (.46)	.41 (.39)	2.313*	170
YASR Withdrawal	.45 (.41)	.34 (.30)	2.102	175
YASR Intrusive	.24 (.30)	.28 (.28)	-.885	175
YASR Aggressive	.24 (.25)	.23 (.22)	.431	174
YASR Delinquent	.13 (.24)	.17 (.27)	-1.146	166
YASR Intern	.51 (.41)	.37 (.31)	2.533*	166
YASR Extern	.21 (.22)	.23 (.21)	-.708	174
MINI Mood	.88 (1.25)	.73 (1.21)	.775	167
MINI Anxiety	.60 (1.42)	.37 (1.09)	1.186	167
MINI Total	2.22 (3.31)	2.39 (3.31)	-.351	167

Note. * = $p < .05$, *** = $p < .001$. Standard deviations appear in parentheses.

Table 9

Between group differences on physiological measures

	Birth Status		<i>t</i>	<i>df</i>
	ELBW	NBW		
Cortisol Sample A (nMoles/liter)	9.91 (5.78)	10.60 (6.78)	-.615	125
Cortisol Sample B (nMoles/liter)	3.95 (3.16)	4.87 (3.82)	-1.510	131
Cortisol Sample C (nMoles/liter)	3.52 (2.86)	3.46 (2.19)	.130	129
Stressor IBI	778.86 (108.98)	774.95 (113.85)	.193	119
Baseline IBI	805.99 (108.65)	821.68 (132.73)	-.716	121

Note. Standard deviations appear in parentheses.

Figure 1

The following figure illustrates the moderating effect of emotion regulation on the relation between ELBW and psychopathology. As HPA axis/ANS dysregulation increase, the deleterious effects of ELBW amplify and lead to increased risk for psychopathology

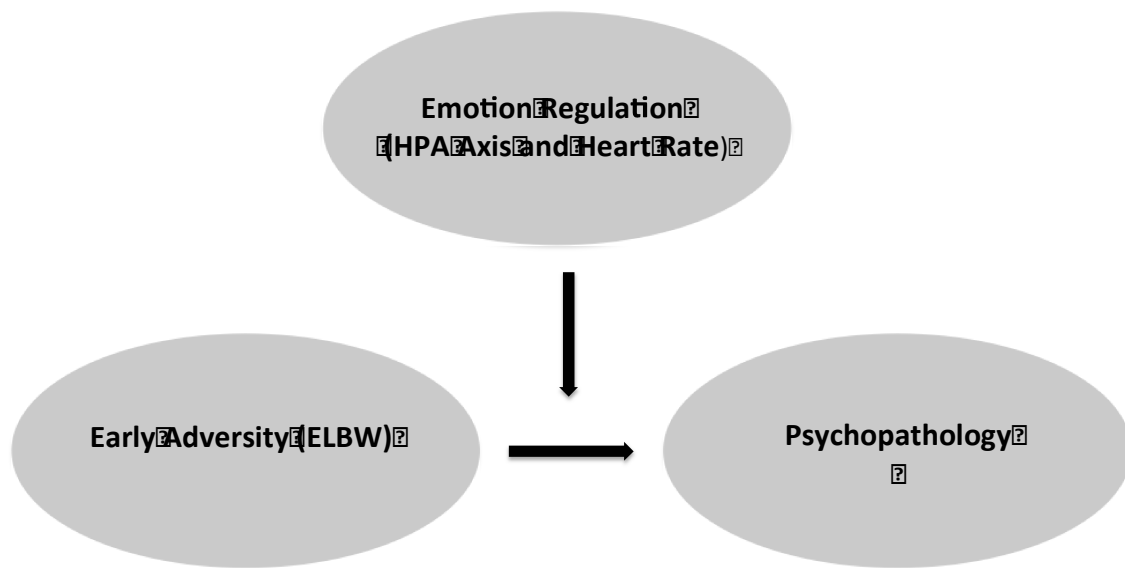


Figure 2

The mediating effect of emotion regulation on the relation between early adversity and psychopathology is illustrated through displaying how early adversity is linked to both psychopathology and emotion regulation, and how emotion regulation is linked to psychopathology

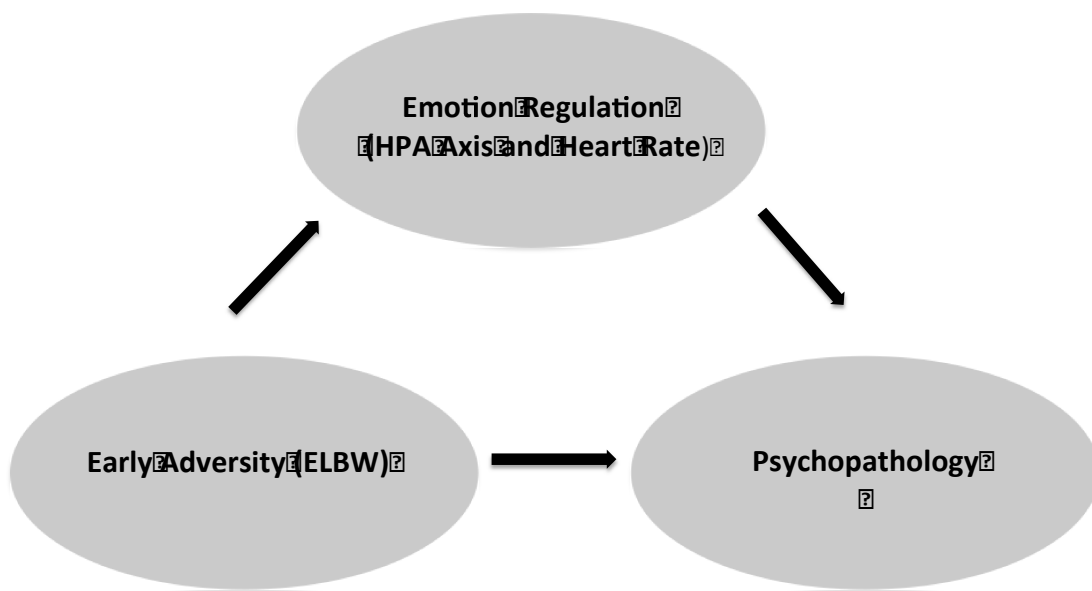


Figure 3

Mean cortisol levels in ELBW and NBW group across three time points

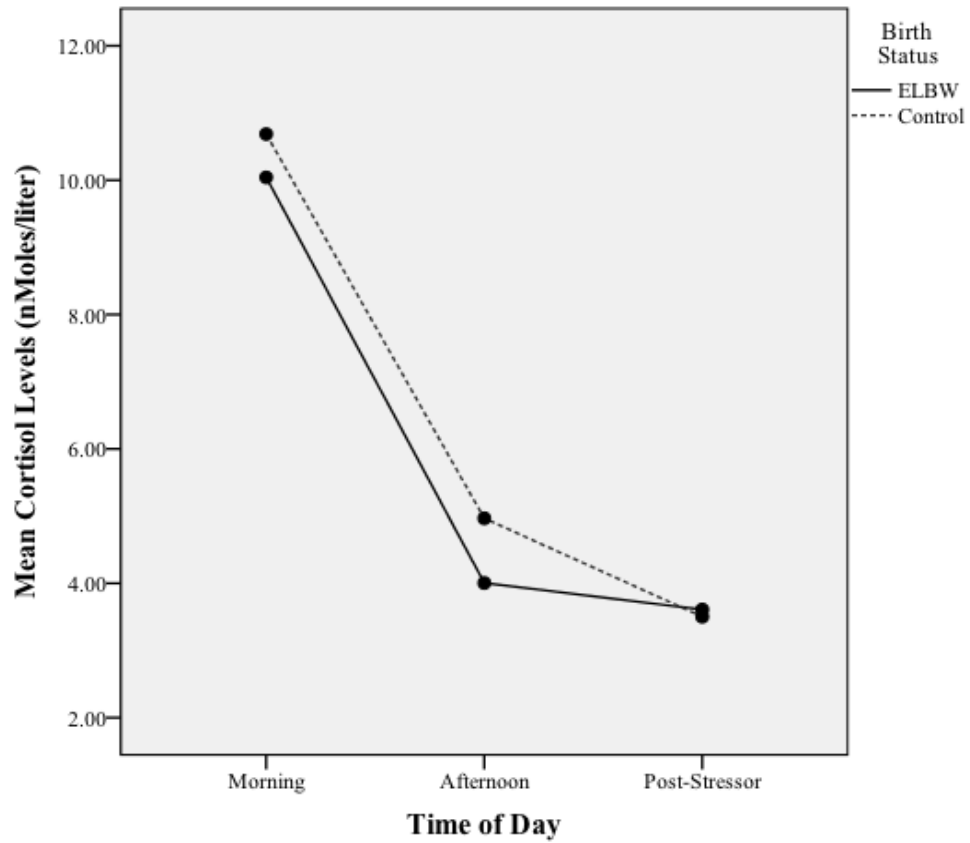


Figure 4

Mean Beck Depression Inventory score based on birth status and stress reactive cortisol levels

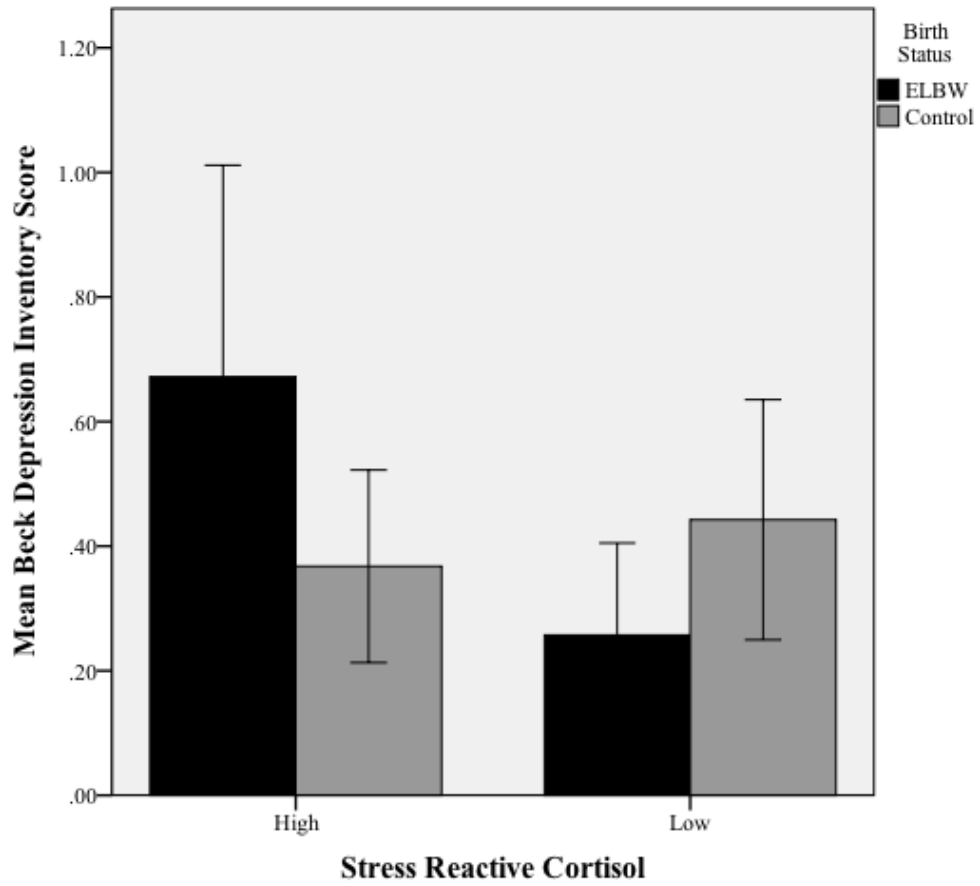


Figure 5

Mean Eysenck Personality Questionnaire-Revised Neuroticism score based on birth status and stress reactive cortisol levels

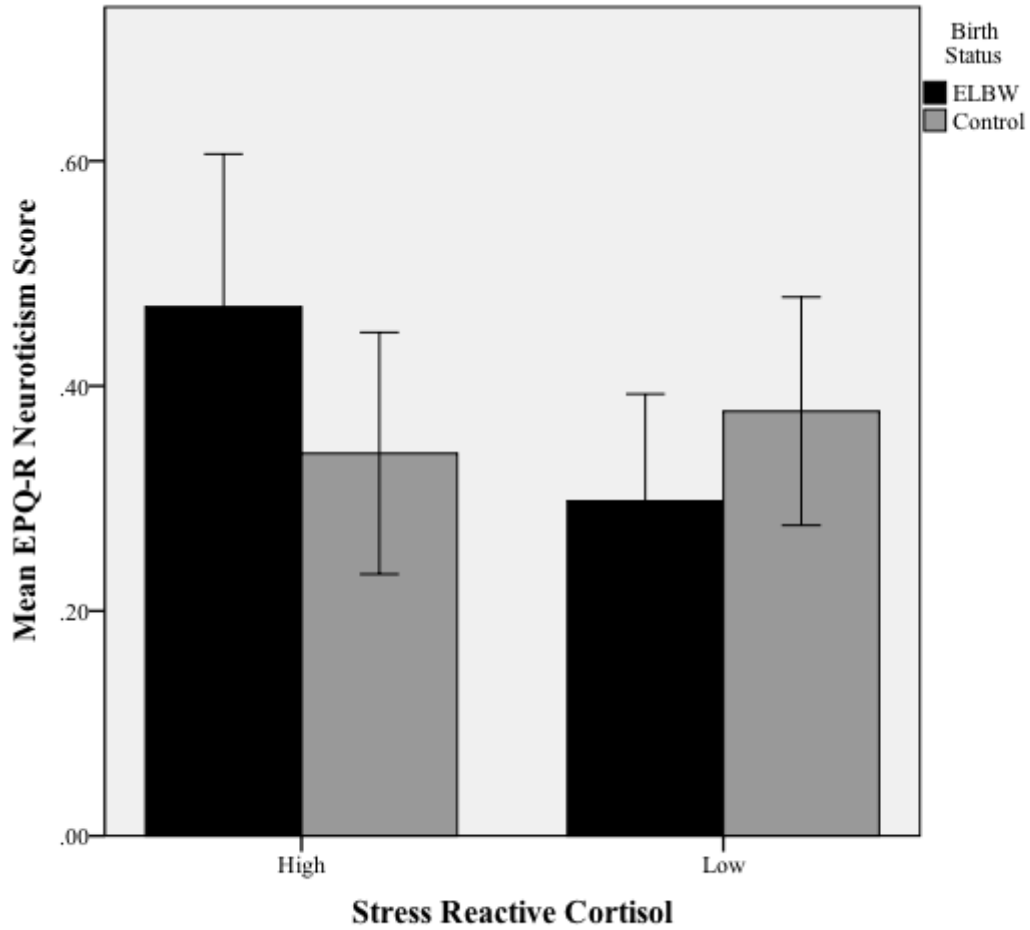


Figure 6

Scatterplots separated by birth status. Displaying the correlation between stress reactive cortisol levels (z-scored) and Beck Anxiety Inventory score.

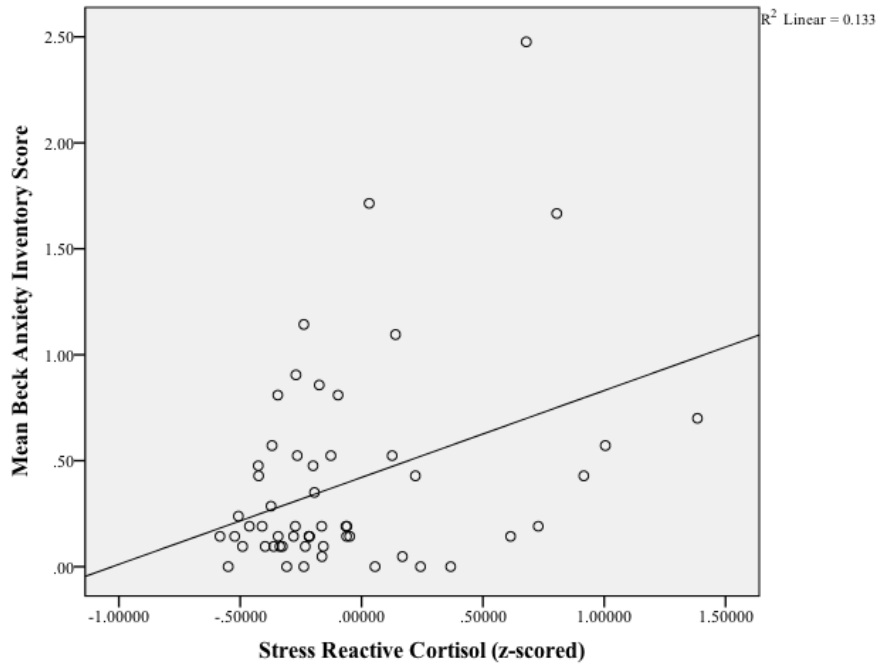
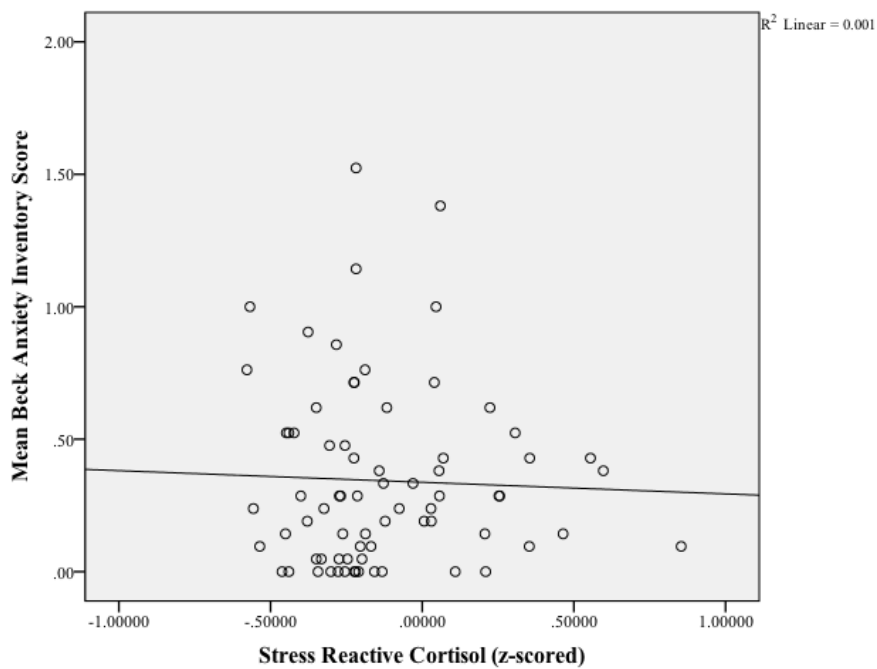
6A. Extremely Low Birth Weight**6B. Normal Birth Weight**

Figure 7

Mean Young Adult Self Report Anxiety/Depression score based on birth status and stress reactive cortisol levels

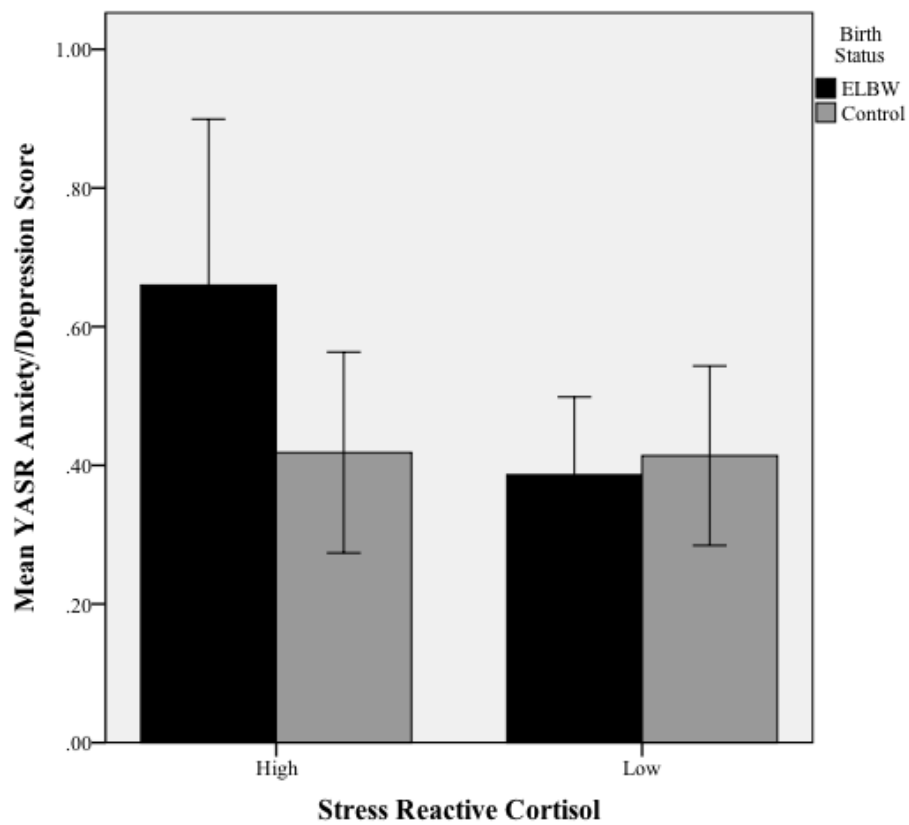


Figure 8

Mean Young Adult Self Report Withdrawal score based on birth status and stress reactive cortisol levels

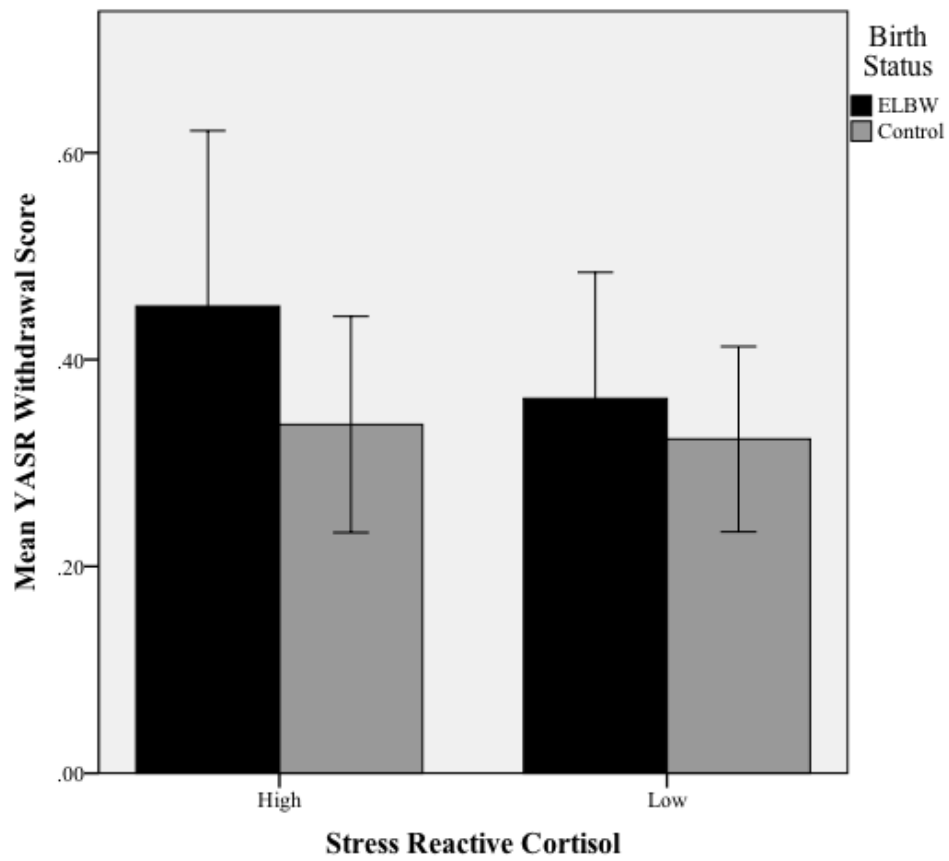
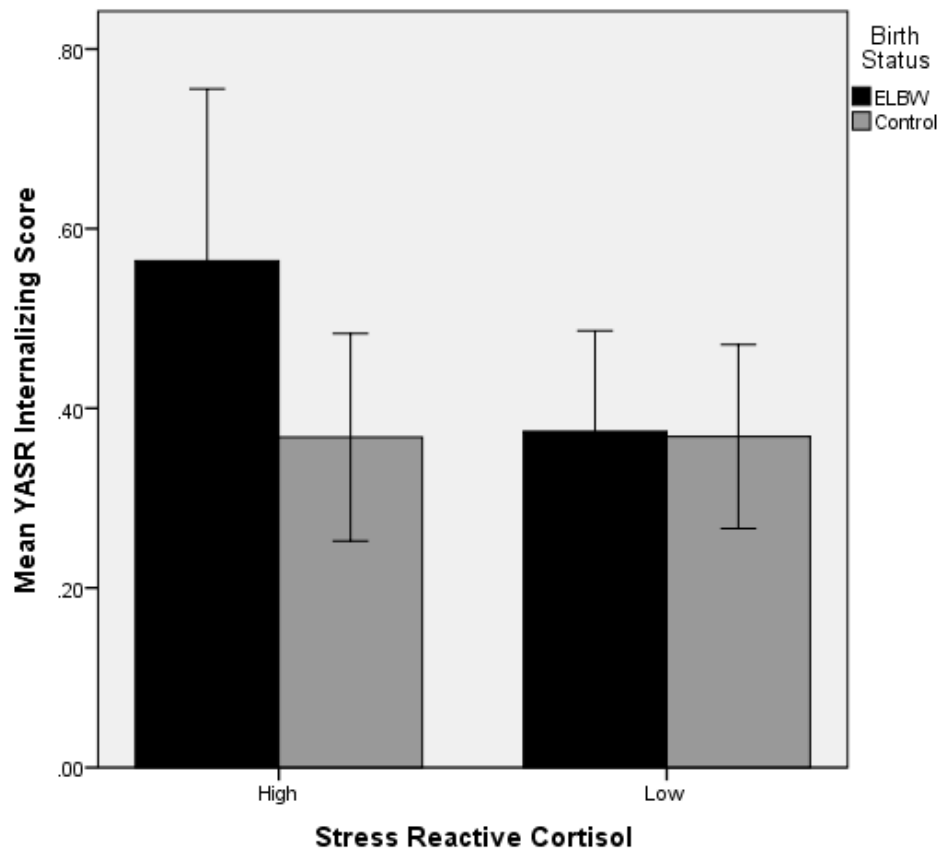


Figure 9

Mean Young Adult Self Report Internalizing score based on birth status and stress reactive cortisol levels



APPENDIX 1



CONSENT FORM

**PLEASE NOTE THAT THERE ARE TWO PARTS TO THE STUDY:
MORNING AND AFTERNOON**

STUDY TITLE: *NEUROPSYCHIATRIC AND MENTAL HEALTH OUTCOMES OF EXTREMELY LOW BIRTH WEIGHT SURVIVORS AND NORMAL BIRTHWEIGHT CONTROLS FROM CHILDHOOD TO ADULTHOOD*

PI: Louis A. Schmidt, Ph.D.

GRANTING AGENCY: Canadian Institutes of Health Research

MORNING PROCEDURES: METABOLIC MEASURES

Overview

There is some evidence in the medical literature to suggest that smaller size at birth is associated with an increased chance of abnormalities in the handling of glucose by the body resulting in a higher incidence of Type 2 diabetes (high blood sugar levels), and for somewhat higher blood pressure in adult life. These problems occur in a small proportion of individuals who were small at birth and may be related to changes in body fat and rapid growth during infancy and childhood. *Very little information is available in infants who were born prematurely.*

We need more accurate information to find out if this is also a problem in infants who were very premature at birth. Although we expect that these problems are not very common, they do require monitoring, and possibly treatment, if they are present. *We think it is important to find out about this at an early age before any problems become obvious.*

Procedure

We ask that you fast for 8 hours overnight. You are encouraged to drink water during this fast, and we will schedule an appointment at McMaster in the morning. At the visit, you will be examined briefly for height, weight, waist circumference and blood pressure. You will then have a test called an “Oral glucose tolerance test (OGTT)”. For this test, you will have 30 ml (1oz, or 2 tablespoons) of blood drawn. After that, you will drink a bottle of sweet liquid containing 75 g (2½ oz) of glucose. Another 10 ml (2 teaspoons) of blood will be drawn after 2 hours. The blood that will be drawn is to measure blood glucose, insulin, lipids (fats), fat cell markers and some markers of inflammation. You may have access to a cream to reduce any discomfort at the site where the blood sample will be taken if you request that.

During the waiting period between blood sampling, two other tests will be done. An ultrasound of your carotid artery (in your neck) will be done. This test measures the thickness of the lining of the artery. This measurement has been shown to reflect ‘atherosclerosis’ or hardening of the arteries in adults. This test takes about half an hour, and although you are required to lie down during this period, it is not at all painful. A scan to measure the amount of muscle, bone and fat in your body (called dual energy x-ray absorptiometry) will require you to lie still for about 3 minutes. This method includes a small x-ray dose which is less than 1/100th of a standard chest x-ray or similar to the natural exposure when flying in an airplane from Toronto to Calgary. (You will recall that you participated in this test on the last visit and we gave you your body scan picture!)

In the last section of the morning procedures, your heart rate and blood pressure will be continuously recorded as you rest while lying down, and while you participate in two short, standardized procedures, 1) blowing through a very small tube for several seconds (twice, with rest in between) and 2) standing comfortably for several minutes. For continuous ECG recording, 3 self-sticking removable electrodes will be applied to your right clavicle (near your upper right shoulder), and your left and right sides at the lower rib level. For continuous blood pressure recording, a standard blood pressure cuff will be wrapped around the upper part of your (non-dominant) arm, and a Velcro-covered finger cuff will be wrapped around the middle section of the middle finger of your hand, connected to a small box that rests on your forearm. Following these two tests, the blood pressure recording apparatus will be removed while ECG recording is continued during your performance of a simple, computerized button-pressing task.

Finally, the research staff will ask you to complete a questionnaire. The questionnaire reviews some aspects of your family medical history, and collects information about where you live, your activities, and what you eat. The questions focus on medical history that relates to atherosclerosis (heart disease), diabetes and obesity. As you leave this visit, you will be asked to wear a small (1” x 1”) monitor on your waist for one week to record your activities, such as walking etc. You will need to record the time when you put it on and when you take it off on a sheet of paper. After one week, we would like you to mail the sheet and the monitor back to us in the prepaid envelope we have provided.

Risks and Benefits

There are no risks involved other than minimal pain of taking a blood sample intravenously and rarely some bruising. The blood pressure recording procedure involves minimal to no discomfort to you, except for some temporary congestion and blush discoloration in the tip of the finger to which the finger cuff is applied. This disappears on removal of the finger cuff. The benefits include providing you with reassurance that there are no problems with your blood glucose levels or your blood pressure and blood vessels. Should there be some evidence of higher than normal blood sugar or cholesterol levels, if you like, we will inform you and your designated family physician so you can receive the appropriate management and subsequent monitoring. The information on the overall study results will be published in the medical literature without identifying your name, and will assist us in advising future young adult preemies of the risks, if any.

Person Responsible for the Morning Procedures

Katherine Morrison, M.D.

Co-Principal Investigator

Associate Professor

Department of Pediatrics

McMaster University

905-525-9140 ext. 73716

Email: morriso@mcmaster.ca

AFTERNOON PROCEDURES:

MENTAL HEALTH AND PSYCHOPHYSIOLOGY MEASURES

Overview

This part of the study involves how your brain processes emotion and how you feel about yourself in general and in particular situations.

Procedure

Your brain electrical activity (EEG) will be recorded using a stretchable cap and heart rate by attaching electrodes to the surface of your skin while you perform computer tasks that measure your response to novelty. (You will recall that you participated in a similar activity at your last visit). Brain electrical activity and heart rate will be recorded continuously during performance of the novelty tasks, including a speech task. After completing these two tasks, the EEG cap and heart rate electrodes will be removed and you will perform a third experiment that assesses attention for emotional facial expressions and attention to nonsocial objects (e.g., houses). We will also have you donate three saliva samples at the beginning, middle, and end of this study so that we can examine a stress hormone known as cortisol and see if this is related to how you process

emotion and feel. Finally, you will be asked to complete some self-administered and interview-administered measures that ask you questions about your general health, family background, emotional well-being, mental health, and adjustment. The whole study will take approximately three hours to complete.

Risks and Benefits

It is possible that some of the items included in the self and interview administered questionnaires might make you uncomfortable. You may skip any question that you do not want to answer or you can withdraw from the study, without penalty, at any time. The placement of an EEG cap and ECG electrodes may feel a little uncomfortable but there are no known risks involved with these procedures.

The results will not benefit you directly, but will help scientists understand more about how the brain processes emotion and how the brain and mental health are linked. Your results will be combined with those from other participants and a summary of the group results will be made available to you in a newsletter.

Person responsible for the afternoon procedures

Louis A. Schmidt, PhD.

Principal Investigator

Professor

Director, Child Emotion Laboratory

Department of Psychology, Neuroscience & Behaviour

McMaster University

905-525-9140 ext. 23028

Email: schmidt1@mcmaster.ca

Confidentiality

Confidentiality will be respected and no information that discloses your identity will be released or published. The data will be stored without identifiers on a password-protected computer. Hard copies of any materials will also be coded with unique identifiers and stored in locked cabinets in the laboratory.

Participation

Participation in research is voluntary. If you choose to participate in this study, you can withdraw from the study at any time. If you decide to withdraw, your data will be destroyed unless you indicate otherwise.

Reimbursement

You will receive \$100.00 as compensation for completing all of the procedures. If you decide to withdrawal from any of the procedures, we will pro-rate your compensation for the total hours participated.

CONSENT STATEMENT**SIGNATURE OF RESEARCH PARTICIPANT**

Consent: I acknowledge that the research procedures described above have been explained to me and that any questions that I have asked have been answered to my satisfaction. I have been informed about the right not to participate and the right to withdraw. As well, the potential harms and discomforts have been explained to me, and I also understand the benefits of participating in the research study. I know that I may ask now, or in the future, any questions I have about the study or the research procedures. I have been assured that records relating to me will be kept confidential and that no information will be released or printed that would disclose personal identity without my permission. Please note that both the morning and afternoon sessions have been approved by the Ethics Review Board of Hamilton Health Sciences. McMaster University and the investigators are under contract with the Sponsor of this study (Canadian Institute of Health Research) and are receiving compensation to cover the costs of conducting the study.

YOU MAY CONTACT THE OFFICE OF THE CHAIR OF THE HAMILTON HEALTH SCIENCES/FACULTY OF HEALTH SCIENCES RESEARCH ETHICS BOARD AT 905-521-2100, EXT. 42013 IF YOU HAVE ANY QUESTIONS REGARDING THE PRESENT STUDY.

Name of Participant

Signature of Participant

Date

Consent form administered and explained in person by:

Name and title

Signature

Date

SIGNATURE OF INVESTIGATOR

In my judgement, the participant is voluntarily and knowingly giving informed consent and possesses the legal capacity to give informed consent to participate in this research study.

Signature of Investigator

Date

Investigative Team

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Principal Investigator

Professor

Director, Child Emotion Laboratory

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