Impact of Parent Presence on Stress in Infants in the Neonatal Intensive Care Unit

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LOYOLA UNIVERSITY CHICAGO

IMPACT OF PARENT PRESENCE ON STRESS IN INFANTS IN THE NEONATAL INTENSIVE CARE UNIT

A DISSERTATION SUBMITTED TO THE FACULTY OF THE GRADUATE SCHOOL IN CANDIDACY FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

PROGRAM IN NURSING

BY

SUSAN M. HORNER

CHICAGO, IL

MAY 2022
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Our lives begin to end the day we become silent about things that matter.
—Martin Luther King Jr.
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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>17-OHP</td>
<td>17-hydroxyprogesterone</td>
</tr>
<tr>
<td>ACE</td>
<td>Adverse Childhood Experience</td>
</tr>
<tr>
<td>ANS</td>
<td>Autonomic nervous system</td>
</tr>
<tr>
<td>APSS</td>
<td>Accumulated Pain/Stressor Scale</td>
</tr>
<tr>
<td>CBCL</td>
<td>Archenbach Child Behavior Checklist</td>
</tr>
<tr>
<td>COVID-19</td>
<td>Coronavirus disease of 2019</td>
</tr>
<tr>
<td>CRH</td>
<td>Corticotrophin releasing hormone</td>
</tr>
<tr>
<td>DSC</td>
<td>Developmentally supportive care</td>
</tr>
<tr>
<td>EEG</td>
<td>Electroencephalogram</td>
</tr>
<tr>
<td>EMR</td>
<td>Electronic medical record</td>
</tr>
<tr>
<td>FNI</td>
<td>Family Nurture Intervention</td>
</tr>
<tr>
<td>GC</td>
<td>Glucocorticoid</td>
</tr>
<tr>
<td>HPA</td>
<td>Hypothalamic-pituitary-adrenal axis</td>
</tr>
<tr>
<td>HRV</td>
<td>Heart rate variability</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional review board</td>
</tr>
<tr>
<td>KS test</td>
<td>Kolmogorov-Smirnov test</td>
</tr>
<tr>
<td>LOD</td>
<td>Limit of detection</td>
</tr>
<tr>
<td>LOS</td>
<td>Length of stay</td>
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<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>Acronym</td>
<td>Description</td>
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<td>---------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>NMI</td>
<td>Neonatal medical index</td>
</tr>
<tr>
<td>NICU</td>
<td>Neonatal intensive care unit</td>
</tr>
<tr>
<td>NISS</td>
<td>Neonatal Infant Stressor Scale</td>
</tr>
<tr>
<td>NNNS</td>
<td>NICU Network Neurobehavioral Scale</td>
</tr>
<tr>
<td>NPE</td>
<td>NICU parent engagement</td>
</tr>
<tr>
<td>PMA</td>
<td>Post menstrual age</td>
</tr>
<tr>
<td>PNS</td>
<td>Parasympathetic nervous system</td>
</tr>
<tr>
<td>RSA</td>
<td>Respiratory sinus arrhythmia</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized controlled trial</td>
</tr>
<tr>
<td>SAM</td>
<td>Sympathetic adrenomedullar axis</td>
</tr>
<tr>
<td>SFR</td>
<td>Single family room</td>
</tr>
<tr>
<td>SNS</td>
<td>Sympathetic nervous system</td>
</tr>
<tr>
<td>SSC</td>
<td>Skin-to-skin care</td>
</tr>
<tr>
<td>VIF</td>
<td>Variance inflation factor</td>
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</table>
ABSTRACT

The purpose of this study was to examine potential relationships between cumulative stress exposure in infants in neonatal intensive care units (NICU), as measured using a resting salivary cortisol level at NICU discharge, and the amount (hours per week) or frequency (days per week) of parent presence and skin-to-skin care (SSC). This descriptive study was conducted via a secondary analysis of a dataset representing 78 NICU families from a tertiary level NICU in the Midwest. Median length of stay was 33 days, and a resting salivary cortisol level collected at one month of age was used for infants not discharged at or before one month of age. Data were examined using correlational, linear regression and hierarchical regression analyses. Cumulative parent presence was not significantly associated with infant stress at NICU discharge, however, significant negative correlations between cumulative SSC and infant stress response at NICU discharge were supported. Results of hierarchical regression analyses examining the timing of parent presence supported a model including admission cortisol, infant level of illness, and hours of parent presence in weeks one through four of life for explaining infant stress at NICU discharge; but, more parent presence in week two was associated with more infant stress. Results of hierarchical regression examining timing of SSC supported a model including cortisol at admission, level of illness and the frequency of SSC in week one for explaining NICU infant stress at discharge. During early weeks of life, parents may require more support from NICU staff to be present and engage with their NICU infants. Further study examining potential
associations between the amount, frequency and timing of parent presence and NICU infant stress response is warranted.
CHAPTER ONE
INTRODUCTION

Challenges faced by critically ill neonates do not end at discharge from the neonatal intensive care unit (NICU). Despite advances in health care that have markedly decreased infant mortality, NICU infants have adverse outcomes that persist into adulthood. Major neurosensory disabilities including cerebral palsy, intellectual disability, and significant vision or hearing impairments, are observed in 15-18% of NICU survivors at school age (Cheong et al., 2017). These rates of significant disability are unchanged from those observed in the 1990s. In addition, NICU infants are at risk of more minor neurodevelopmental disabilities as well as adverse behavioral and mental health outcomes.

At the population level, prematurity is associated with more than 50% of cerebral palsy and 15-20% of intellectual disability diagnoses (Schieve et al., 2016). Significant numbers of term and post-term infants requiring NICU care are also at risk of cerebral palsy and intellectual disabilities (deVries & Jongmans, 2010; Marino et al., 2012; Stavsky et al., 2017), and among NICU infants requiring major surgery for a non-cardiac anomaly, 23% have cognitive and motor delays at 24 months (Stolwijk et al., 2016). Neurosensory impairments including sensorineural hearing loss and visual impairments are also observed in NICU infants in higher rates than those observed in typically-developing infants (American Speech-Language-Hearing Association, 2021; Chang & Borchert, 2020). Greater risks for significant neurodevelopmental morbidities are inversely related to gestational age in NICU infants (Manuck et al., 2016).
In addition to the major neurosensory disabilities observed in NICU survivors, 35-50% experience mild to moderate neurodevelopmental morbidities that may not be identified until school age (Luu et al., 2017). This spectrum of minor neurodevelopmental morbidities includes cognitive deficits, learning disabilities, delays in expressive and receptive language, fine and gross motor delays, and deficits in executive function, processing speed, visual perception, and attention (Coughlin, 2021; Luu et al., 2017). As a result, many NICU infants require early intervention and special education services (Luu et al., 2017; Nist et al., 2020), increasing the family and societal burdens attributable to NICU outcomes.

Behavioral health disorders are observed in survivors of NICU care. Among preterm infants a behavioral phenotype, characterized by introversion, anxiety and risk-aversion, has been described (Johnson & Marlow, 2017). Increased rates of attention-deficit hyperactivity disorder are also observed in prematurely-born school-aged children and preteens (Yates et al., 2020) as well as a 5 to 8% prevalence rate of autism spectrum disorder (Agrawal et al., 2018; Schieve et al., 2016).

Increased risks for mental health disorders including internalizing and externalizing disorders are also observed in NICU survivors (Coughlin, 2021; Yates et al., 2020), and in contrast to healthy cohorts, expected, age-related reductions in depression or anxiety are not observed in NICU survivors as they reach adulthood (Van Lieshout et al., 2018). These behavioral and mental health outcomes have lifelong impacts for NICU infants, and as adults fewer complete higher education, marry or have children (Johnson & Marlow, 2017).

**Nature of the Problem**

NICU care occurs during a critical period of neurodevelopment when more than a million neural connections are formed per second, and infants’ experiences are particularly important in
shaping the architecture of their developing brains. During early development the brain is particularly vulnerable to experiences that activate stress responses (National Scientific Council on the Developing Child, 2020). Exposure to NICU-related stressors is associated with abnormal neurodevelopment (Smith et al., 2011). Unfortunately, stress is inevitable in the NICU.

**Magnitude of the Problem**

NICU admission rates are on the rise, with 10-12% of all infants born in the United States (US) requiring NICU care (Harrison & Goodman, 2015; US Department of Health and Human Services, 2013). Historically, a majority of NICU infants were admitted for problems related to prematurity; and, as preterm birth rates continue to climb, representing 10.02% of live births in the US (National Center for Health Statistics, 2019), significant numbers of preterm infants continue to be seen in NICUs. However, term newborns increasingly require NICU care for a variety of illnesses, and equal numbers of term and preterm infants are currently represented in the NICU population (Harrison & Goodman, 2015). Term NICU infants are frequently hospitalized for medical and surgical care related to birth defects that impact 120,000 babies annually (Centers for Disease Control and Prevention, 2020a). Many NICU infants are hospitalized for long periods of time, ranging from weeks to months.

Costs of caring for NICU infants are high and include expenses related to medical care and special education needs. The March of Dimes estimates that expenditures related to preterm birth were $25.2 billion dollars in 2016 (Waitzman & Jalali, 2019). Expenses related to medical care of preterm infants were $19.1 billion dollars or two-thirds of total costs, while expenses related to special education and lost productivity were 1.3 and 4.8 billion dollars respectively. Estimated costs do not include caregiver expenses or lifelong costs of disabilities. Costs of caring for preterm infants are inversely related to gestational age and birthweight (Beam et al., 2020).
The Developing Brain

Infant development is shaped by the interaction of biology and experiences. Beginning in the second trimester of pregnancy, significant brain development proceeds in overlapping sequential stages that include neural proliferation and migration, neural organization, synaptogenesis, programmed apoptosis, glial proliferation, synaptic pruning and myelination (DeMaster et al., 2019; Ortinau & Neil, 2015). Elevated rates of synaptogenesis and myelination, which are essential for typical brain development, occur during the third trimester of pregnancy and continue through the second year of life (Ortinau & Neil, 2015). Selective pruning of cells and synapses that are rarely used begins prenatally, continues through adolescence, and may be observed via changes in cortical thickness over time that are related to neurodevelopmental outcomes (Kolb & Gibb, 2011). The precocious synaptogenesis and the pruning of cells and synapses in early life are some of the mechanisms by which environmental influences, including stress, impact neurodevelopment (DeMaster et al., 2019; Hodel, 2018). Thus, the extended periods of brain maturation that support neuroplasticity, also contribute to the vulnerability of the developing brain (DeMaster et al., 2019).

Stress and the NICU

The developing brain is particularly vulnerable to stress. NICU-related stressor exposure is associated with reduced frontal and parietal lobe volumes and altered connectivity in temporal lobes (Smith et al., 2011). NICU infants experience multiple acute and chronic daily stressors that are cumulative in nature (Nist et al., 2019) and contribute to infant neurobehavioral outcomes (Cong et al., 2017). Sources of NICU-related stress include pain and distress related to care and procedures, environmental stressors and separation from parents.
Care and Procedures

All painful events are a source of stress, and in the NICU infants may experience up to 17 painful procedures per day (Cruz et al., 2016). Green et al. (2019) suggest that premature infants may be unable to discriminate non-painful from painful touch, making them vulnerable to experiencing pain and stress during routine NICU care. Despite efforts to emphasize the importance of pain prevention and management for NICU infants, pain is inadequately and inconsistently addressed in NICUs (Balice-Bourgios et al., 2020; Young et al., 2017).

Early pain exposures impact brain development. Greater pain exposures in preterm infants are associated with decreased cortical thickness and myelination as well as decreases in cerebellar, amygdala and thalamus volumes (Chau et al., 2019; Vinalli et al., 2014). Increased exposure to painful NICU procedures is also associated with adverse neurodevelopmental outcomes, including poorer cognitive outcomes through school age (Vinalli et al., 2014).

Stressful care routinely experienced by NICU infants includes suctioning, nasogastric tube insertion, and venipuncture. NICU infants are unable to anticipate touch and movement. The lack of predictability that is associated with handling during routine care activities contributes to the stress experienced by NICU infants (D’Agata, 2017). Even benign nursing care procedures such as diaper changes may elicit physiologic and behavioral stress responses in NICU infants (Griffiths et al., 2021). The behavioral signs of stress that are observed in NICU infants during routine care are quite energy consuming (Lin et al., 2014).

NICU infants are exposed to greater numbers of stressors during the first two weeks of life. However, very immature or critically ill infants may have high levels of stressor exposures throughout their NICU stay (Smith et al., 2011). D’Agata et al. (2019) observed 43 stressful events per day among preterm infants over the first six weeks of life in the NICU.
Environmental Stressors

The mismatch between typical intrauterine or newborn environments and the NICU environment is a significant source of stress for infants. NICU infants experience frequent environmental exposures that include bright lights, noise, noxious smells, and unpleasant tastes or oral experiences (Coughlin, 2021). Bright lights and noise disrupt sleep and emerging circadian rhythms in NICU infants and may trigger stress responses that include physiologic dysregulation (Santos et al., 2015; Weber & Harrison, 2019). NICU infants may also respond to noxious tastes and smells such as the scent of alcohol wipes with physiologic and behavioral signs of stress (Kenner et al., 2019). The inability of sick and preterm infants to anticipate stressful sensory exposures may heighten these responses (D’Agata, 2017).

In the NICU, infants are deprived of pleasant, expected sensory exposures. These include parental voice, nurturing forms of touch, and the smell and taste of breastmilk. Thus, NICU infants may simultaneously experience stress related to overwhelming environmental stimuli and sensory deprivation. The neurodevelopmental impacts of NICU infants’ concurrent exposures to sources of sensory overload and deprivation in the NICU are not well understood (Pineda et al., 2017; Santos et al., 2015).

Separation from Parents

Early psychosocial deprivation negatively impacts human development (Bowlby, 1988). The most significant aspects of an infant’s psychosocial environment are relationships with consistent, caring adults, typically the infant’s parents (Franck & O’Brien, 2019; Givrad et al., 2021). Healthy parent-infant relationships support healthy development, protect the infant in times of stress, and are the basis for infant mental health (National Scientific Council on the Developing Child, 2020; Givrad et al., 2021). Separation from parents is a source of stress that
deprives NICU infants of positive sensory experiences such as nurturing touch. These sensory and psychosocial deprivations are sources of stress for NICU infants (Weber & Harrison, 2019).

The neurodevelopmental outcomes of institutionalized children inform our understanding of the adverse outcomes associated with psychosocial deprivation. The outcomes of institutionalized infants and young children are similar to those seen in NICU survivors and include developmental, behavioral and mental health disorders (Bick & Nelson, 2016; Nelson et al., 2019). Long-term follow-up of institutionalized children supports the need for relationships with consistent, caring adults in early infancy to avoid negative neurodevelopmental consequences (Bick & Nelson, 2016).

Social relationships influence the neurodevelopmental outcomes of infants (Burnett et al., 2018). Parent presence has been identified as form of parent engagement in the NICU that is essential to the development and maintenance of parent-infant social relationships in the NICU, as it is during time spent in the NICU that parents interact with their infants (Klawetter et al, 2019; Pineda et al., 2018). This interaction may include caregiving activities such as SSC or in the moment touches and vocalizations in response to infant cues that are not documented or measured. Although the vast majority of NICUs support parent presence 24 hours per day, all NICU infants experience some amount of separation from parents (D’Agata, 2017). Parent presence in the NICU is variable, and researchers reporting parent presence describe multiple issues with parent presence including postpartum depression and stress, as well as the need to return to work or care for siblings at home (Pineda et al., 2018). Thus, the absence of consistent, responsive relationships with caring adults represents a significant source of stress for NICU infants.
Healthy parent-infant relationships protect the infant in times of stress (National Scientific Council on the Developing Child, 2020), yet, few investigators have examined the impact of parent presence on stress in NICU infants. Morelius et al. (2012) observed no significant differences in mothers’ or infants’ cortisol reactivity to a diaper change done by the mother in 152 mother-infant dyads exposed to nearly continuous parent presence compared to 137 mother-infant dyads in exposed to more limited parent presence. However, significant correlations in mother-infant baseline and response cortisol levels were observed in the mother-infant dyads exposed to continuous parent presence. These findings suggest that decreasing NICU parent presence may delay dyadic co-regulation of cortisol (Morelius et al., 2012). Neu et al. (2009) observed a significant increase in the co-regulation of mother-infant salivary cortisol levels following 60 minutes of infant holding in the NICU. Although the underlying mechanisms are not well understood, the co-regulation of the HPA axis in mother-infant dyads is believed to be essential to infant development (Provenzi et al, 2019).

**Lifelong Impacts of Stress**

Although preterm and term NICU infants are at high risk for traumatic brain injuries including cerebral hemorrhages, white matter injuries and encephalopathies, rates of neurodevelopmental morbidities among NICU survivors are not fully explained by brain injuries (D’Agata et a., 2017; Pickler et al., 2010). Throughout their stay in the NICU, infants are exposed daily to toxic stressors that include stressful care and procedures, overwhelming sensory exposures, sensory deprivation and separation from parents. The toxic stress experienced by NICU infants contributes to the adverse outcomes observed in this population.
Toxic Stress

Significant adversity or stress in early childhood is linked to lifelong risks for morbidities in health and development (Felitti et al., 1998), and the Centers for Disease Control and Prevention (2020b) have named the prevention of Adverse Childhood Experiences (ACEs) a public health priority. The American Academy of Pediatrics’ technical report on stress in early childhood identified three levels of stress exposure, positive stress, tolerable stress and toxic stress (Shonkoff et al., 2012). Positive stress experiences are relatively mild and may promote growth. Tolerable stress experiences represent a greater threat, but these are mitigated through protective relationships with caring adults; and relationships with caring adults help a child build resiliency in managing stress. Toxic stress is severe, repeated or prolonged activation of the stress response system during critical periods of development, in the absence of buffering social relationships (Garner & Shonkoff, 2012). The temporal context of exposures to toxic stressors is significant, with increasing evidence identifying early infancy (Shonkoff et al., 2021) or the first 1000 days post-conception (D’Agata et al., 2017; Linner & Almgren 2020) as critical periods for the developing brain, metabolic regulation and the immune system.

The definition of toxic stress proposed by the American Academy of Pediatrics (Shonkoff et al., 2012) is consistent with the stressor exposures of NICU infants that are repeated, severe or prolonged, and may occur in an environment characterized by periods of relative social isolation (Pineda et al. 2018). Prematurity, severe illness and disabilities that are common in NICU infants are beginning to be recognized as sources of toxic stress (National Academies of Sciences, Engineering and Medicine, 2019). Protecting NICU infants from significant early adversity or toxic stress is an essential component of supporting their neurodevelopment. The presence of
supportive relationships to buffer stressors may be central to mitigating toxic stress in infants (Shonkoff et al., 2021).

**Physiology of Stress**

Selye (1976) was the first to describe the biological stress response. Stressors represent real or potential threats that result in a release of mediating molecules that interact with specific receptors in the body and brain, resulting in the stress response. Although they may overlap, different types of stressors are processed differently, with physical stressors processed predominantly by the brainstem and hypothalamus and psychological stressors processed mainly by areas of the brain involved in emotion including the amygdala, prefrontal cortex, and hippocampus (Joels & Baram, 2009). Exposure to a stressor triggers activation of the stress response via the two major components of the stress response system, the autonomic nervous system’s (ANS) sympathetic adrenomedullar axis (SAM) that secretes noradrenaline and norepinephrine, and the hypothalamic-pituitary-adrenal axis (HPA axis) that releases glucocorticoids including cortisol (Godoy et al., 2018). Once activated, coordinated responses of the stress response system activate energy mobilization, the immune system and metabolic changes as well as suppressing digestive and reproductive systems (Godoy et al., 2018). Through physiological and behavioral changes in the ANS and the HPA axis, the stress response typically returns the body to homeostasis and promotes adaptation, however, a stress response may continue for extended periods.

**Autonomic Nervous System.** The ANS is one of the major neural pathways triggered by stressor exposure. The ANS consists of two distinct divisions, the sympathetic and parasympathetic nervous systems. The sympathetic nervous system (SNS) mobilizes the stress response system via SAM: these responses produce noradrenaline and norepinephrine that
induce rapid physiologic changes supportive of reflexive flight or fight responses including increased alertness, cardiovascular changes, and defensive responses (Godoy et al., 2018). The parasympathetic nervous system (PNS) predominates during physiologic resting conditions and is responsible for the downregulation of the SNS’s stress responses via the vagus nerve. This downregulation of stress responses by the PNS results in changes in cardio-respiratory regulation called vagal tone (Godoy et al., 2018).

**Hypothalamic-Pituitary-Adrenal Axis.** The second phase of the stress response involves the activation of neuroendocrine responses from the HPA axis, and while the HPA axis is slower to respond to stressor exposure, its responses are more intense and longer-lasting (Godoy et al., 2018). The paraventricular nucleus (PVN) of the hypothalamus is responsible for triggering HPA axis activity that includes the production of vasopressin, oxytocin and corticotrophin releasing hormone (CRH). In the pituitary CRH stimulates production and release of adrenocorticotropic hormone that stimulates the secretion of glucocorticoids (GCs) including cortisol (Tsigos et al, 2020). GCs mediate cognitive, immune, metabolic and other physiologic processes that support adaptation to stress. GCs also support the regulation of basal HPA activity and termination of stress responses (Tsigos et al., 2020).

**Stress and the Immune System.** The effects of stress on the immune system are mediated by GCs released by the HPA axis. Short-term stressor exposure may increase immune system protections via anti-inflammatory mechanisms that defend against injury (Godoy et al., 2018). These immune system protections are supported by the production of anti-inflammatory cytokines. However, stress exposure may overwhelm protective anti-inflammatory mechanisms and increase levels of pro-inflammatory cytokines (Dhabhar, 2014; Godoy et al., 2018).
**Allostasis and Allostatic Load.** An expanded framework for understanding the responses of physiologic systems to stress, including allostasis and allostatic load, are described by McEwen (2006). Allostasis is defined as the essential process by which the body returns to equilibrium via physiologic feedback mechanisms. Allostatic load or overload is described as maladaptive wear-and-tear on the body and brain that results from chronic dysregulation of physiologic stress systems, including the production of stress hormones via the HPA axis. This chronic dysregulation may result from over-activity or inactivity of physiological stress systems. Thus, allostatic load represents a physiological tipping point in which the body either remains fixed on high alert due to the ongoing production of stress hormones via the HPA axis, or the body fails to respond to threats appropriately due to blunted production of stress hormones or adrenal exhaustion (Herman et al., 2016; McEwen & Gianaros, 2010).

Several different types of allostatic load producing situations are described. These include exposure to frequent stressors, failure to habituate to repetition of the same stressor, chronic exposure to stress, and failure to physiologically respond to stressors (McEwen & Gianaros, 2010). Regardless of the underlying cause of allostatic overload, chronic dysregulation of physiologic stress responses occur, resulting in a cascade of maladaptive metabolic, immune, cardiovascular and neuroendocrine responses.

Allostatic load may be an appropriate framework for considering the cumulative effects of repeated stressor exposures on NICU infants (Grunau et al., 2005). Autonomic nervous system (ANS) responses including typical changes in heart rate and heart rate variability are observed in NICU infants under conditions of stress and relaxation (Porges, 2011). However, alterations in ANS functioning, including the blunting of heart rate changes typically observed during painful stimuli, are observed in NICU survivors exposed to repeated painful procedures (Goffaux et al.,
Repeated HPA axis activation in the NICU may result in long-term changes in HPA responses, and, in contrast to term-born children, former preterm infants are observed to have lower hair cortisol levels at school age (Grunau et al., 2013). Elevations in infant inflammatory markers are observed in preterm infants at birth and when under stress at three months of age (Sesso et al., 2014). Increased inflammation is associated with several conditions reported in NICU infants including necrotizing enterocolitis, bronchopulmonary dysplasia, intraventricular hemorrhage and retinopathy of prematurity, and allostatic load is linked to these complications in a model proposed by Moore et al. (2014). Thus, allostatic load is an appropriate framework for examining effects of toxic stress on NICU infants.

Stress and the Developing Brain

The cascade of physiologic responses resulting from allostatic overload targets the developing brain along with the rest of the body (McEwen & Gianaros, 2010). Consistent with the definition of toxic stress, allostatic overload is associated with toxic stressor exposures that are strong, chronic or repeated, or that occur during critical periods of development (Godoy et al., 2018). The cascade of physiologic responses resulting from allostatic overload may be responsible for the biological embedding of stress-induced developmental alterations observed in NICU infants.

Prenatal Stress. Studies examining animal and human models have increased our understanding of the effects of prenatal stress on neurodevelopment. In animal models, interventions that elevate maternal cortisol levels during gestation are associated with low birth weights (Seckl, 2004), and in a large prospective study Goedhart et al. (2010) observed lower birth weights in human infants born to mothers with elevated early morning serum cortisol. Low
birth weight is associated with neurodevelopmental deficits as well as behavioral and mental health disorders (Miguel et al., 2019).

Although GCs are essential for the developing brain (Lupien et al., 2009), the immature brain is particularly sensitive to prenatal overexposure to GCs (Reynolds, 2013). Exposing prenatal rats to glucocorticoids is associated with significant delays in brain development (Seckl, 2008). In human infants increased prenatal cortisol exposure is associated with impaired cognitive development at 17 months (Bergman et al., 2010); and prenatal stress exposure is associated with increased amygdala volume on magnetic resonance imaging (MRI) and more emotional problems in girls, but not boys, at seven years of age (Buss et al., 2007). The amygdala is involved in the processing of emotional memory, including fear and anxiety (Reynolds, 2013).

Significant life-long elevations in HPA axis activity are observed in prenatal rats exposed to stress (Koehl et al., 1999), and decreased hippocampal volumes at 20 months of age have been observed in monkeys prenatally exposed to glucocorticoids (Uno et al., 1990). HPA axis activity is inhibited by the hippocampus. Consistent with animal studies, in human infants exposed prenatally to stress, increases in basal HPA axis activity may be observed throughout childhood (Lupien et al, 2009) and into adult life (Reynolds, 2013). Thus, prenatal stress may predispose individuals to greater HPA activity, including GC exposure.

**Postnatal Stress.** In both rat and monkey models, stress related to maternal separation in infancy is associated with both HPA axis hypo-reactivity and hyper-reactivity, depending on the timing and length of separation (Levine, 2000). Studies of children in daycare demonstrate elevated cortisol levels, with greater increases observed in young children in less supportive child care environments (Gunnar & Donzella, 2002). In contrast, reduced basal cortisol levels are
observed in young children with more severe stress exposures such as neglect, abuse or institutional care (Gunnar & Donzella, 2002), and these findings are similar to those reported for adults experiencing chronic stress. However, supportive adult care of toddlers in foster care is associated with normalization of previously low basal cortisol levels (Dozier et al., 2008). In preschool children maternal support is associated with greater hippocampal growth; this is significant as the hippocampus supports stress regulation (Luby et al., 2012).

Evidence links early life stress to adverse neurodevelopmental outcomes. For example, the outcomes of institutionalized children are similar to those seen in NICU survivors and include developmental, behavioral and mental health disorders (Bick & Nelson, 2016; Nelson et al., 2019). Studies examining early life stress and neurodevelopmental outcomes infrequently measure GC exposure. Studies reporting associations between increased GC exposure and cognitive issues are reported in adults, and elevated morning cortisol levels are associated with poor cognitive outcomes including issues with memory, mental flexibility, and general cognitive ability as well as reduced hippocampal volume (Lupien et al., 1998; Reynolds, 2010).

Stress may impact HPA axis functioning and neurodevelopment through epigenetic changes that regulate the HPA axis and the developing brain (Fumagalli et al., 2018; Janusek et al., 2019; Provenzi et al., 2018). Maternal care may reduce epigenetic changes that result from early life stress (Janusek et al., 2019). Nist et al (2019) proposes a Neonatal Stress Embedding model that describes the relationships between stress exposure, affected physiologic systems and neurodevelopment. In this model, maternal interaction is depicted as a contributor to the effects of neonatal stress exposure on physiologic systems and neurodevelopment (Nist et al., 2019).

**NICU Stress Exposure.** The cumulative exposure to acute and chronic stressors experienced by NICU infants is consistent with the definitions of toxic stress and chronic stress
and is associated with adverse neuro-developmental outcomes in preterm NICU infants (American Psychological Association, 2020; Shonkoff et al., 2012). Grunau et al. (2007) observed lower basal salivary cortisol levels in extremely preterm infants at three months and higher basal salivary cortisol at eight and 18 months that were associated with cumulative pain and stress in the NICU. Cumulative early pain exposures in preterm infants are associated with thalamic volume loss at term age that is associated with poorer cognitive and motor outcomes at three years (Duerden et al., 2018). Greater NICU pain exposures are also associated with decreased myelination and poorer cognitive outcomes at school age (Vinalli et al., 2014).

Smith et al. (2011) used the Neonatal Infant Stressor Scale (NISS) to measure cumulative stressor exposures throughout the NICU stay. Increased cumulative stressor exposure in the NICU was associated with decreased frontal and parietal size and altered connectivity in temporal lobes on MRI, poorer motor development on Dubowitz exam, and suboptimal reflexes using the NICU Network Neurobehavioral Scales (NNNS) at term-age. Cong et al. (2017) measured cumulative NICU-related stressor exposure over the first month of life using a new version of the NISS, the Accumulated Pain/Stressor Scale (APSS), which was modified to better reflect NICU care in the US (Xu et al., 2016). Increased acute and chronic stressor exposures were significantly associated with poorer neurodevelopment measured using the NNNS at term age that were mediated by increased daily breastfeeding or SSC (Cong et al., 2017). Parent-infant interactions affect the infant’s responses to stressors (Feldman et al., 2014; Lupien et al., 2009), yet, the potential impacts of parental presence are rarely considered in studies reporting associations between cumulative pain and stress in NICU infants and adverse neuro-developmental outcomes.
The Polyvagal Theory

In the Polyvagal theory Porges (1995) describes a revised, evolutionary understanding of the autonomic nervous system, particularly the vagus nerve. He proposes that two distinct branches of the vagus nerve have evolved, with each supporting different responses to stress (Porges, 1995). Working in opposition to the sympathetic nervous system (SNS) that mobilizes physiologic stress responses, the vagus nerve inhibits SNS activity via the parasympathetic nervous system (PNS). An older, unmyelinated branch of the vagus nerve is associated with more primal stress responses that include immobilization, loss of consciousness and severe depression of respiratory and heart rates. These primitive vagal responses are directly observable in the behavior of NICU infants under stressful conditions (Sanders & Hall, 2018).

A basic tenet of the Polyvagal theory is that the myelinated or smart branch of the vagus is linked to social behaviors including facial expression, listening and vocalization. Through an unconscious process termed neuroception, the central nervous system senses safety in the presence of social engagement, signaling the myelinated vagus to down-regulate the SNS, effectively acting as a vagal brake that is consistent with vagal tone (Porges, 2011). A model of the Polyvagal theory is provided in Appendix A.

Porges (2017) views social relationships as a biological imperative for human beings, particularly infants and young children, with self-regulation of stress responses developing through co-regulation with caring adults. Thus, NICU practices that support social relationships may be effective in buffering the toxic stress experienced by NICU infants and may prevent activation of dangerous primitive vagal responses to stress (Sanders & Hall, 2018). One such practice is developmental care.
Developmentally Supportive Care

The goal of developmentally supportive care (DSC) is to integrate neuroprotective practices with the highly technical environment and intensive care practices necessary for the survival of NICU infants. DSC is age-appropriate care that is individualized to meet an infant’s needs, and family-centered in that it promotes family presence and engagement throughout the NICU stay. Care practices that are typically addressed by DSC include protecting sleep, pain and stress assessment and management, developmentally supportive positioning, handling and feeding practices, provision of a healing environment, and family-centered care (Coughlin, 2011). Goals of DSC include preventing and mitigating infant stress, conserving the infant’s energy to promote growth and development, and promoting family development. A growing body of evidence supports DSC, finding that DSC improves the outcomes of NICU infants in ways not observed following typical NICU care (Coughlin, 2011; McAnulty et al., 2012; Montirosso et al., 2016).

Nearly all DSC programs and practices endorse parent presence as critical for improving NICU infant outcomes, but few require parent presence for implementation. DSC programs and practices requiring parent presence for implementation include the Family Nurture Intervention (FNI) (Welch et al., 2020), exposure to live maternal voice (Filippa et al., 2013), and skin-to-skin care (SSC) (Feldman et al., 2014). SSC is often the topic of studies examining the impact of parent presence and engagement on NICU infant outcomes. The improved stress-related outcomes associated with the FNI program (Porges et al., 2019; Welch et al., 2020) and the use of live maternal voice (Filippa et al., 2013) or SSC in the NICU (Feldman & Eidelman, 2003; Feldman et al., 2014) may be related, in part, to parent presence.
DSC practices and programs that require parent presence, including SSC and FNI, are among the most successful in reducing NICU infant stress responses. DSC programs and practices endorse parent presence, and parent presence is considered an essential aspect of parent-infant relationships in the NICU, in that parent presence promotes formal and informal parent-infant interactions (Klawetter et al., 2019; Pineda et al., 2018). Formal parent-infant interactions in the NICU may include caregiving activities described in the developmental care literature, such as SSC. Yet, the impact of informal parent-infant interactions in the NICU that may include in the moment vocalizations or touches are inadequately described or reported.

**Nursing, Developmental Care and Parent Presence**

DSC programs and practices that are implemented to reduce stress and adverse outcomes in NICU infants, such as FNI, live maternal voice, and SSC, may be costly and time-intensive to implement. In addition, investigators studying developmental care programs or practices rarely measure parent presence, which may represent informal aspects of the NICU parent-infant relationship not considered in the DSC literature. Thus, it is not known whether the amount of parent presence alone or in combination with DSC has greater impact on NICU infant stress responses to cumulative stressor exposures that impact neurodevelopmental outcomes.

Nursing’s Social Policy Statement (American Nurses’ Association, 2010) defines a social contract between nurses and society and identifies critical nursing role components that include promoting health and wellness, promoting adaption to physiological processes such as stress, addressing the environment in preventing disease, and supporting research to guide practice. As NICU professionals, nurses are obligated to consider this social contract as it relates to parent presence, a critical component of parent-infant relationships in the NICU and DSC, and the effect of parent presence on toxic stress in NICU infants.
**Rationale for Proposed Study**

Consistent with the Polyvagal theory, the social relationship between parents and their NICU infant, which is supported by parent presence, may be essential for mitigating NICU-related stressors and for preventing the impacts of toxic stress that result from cumulative NICU-related stressor exposures, including psychosocial deprivation. There is a need for further study to examine potential associations between parent presence, a critical component of parent-infant relationships in the NICU and DSC, and stress in NICU infants (Griffiths et al., 2021). Thus, this study is necessary to advance nursing science in DSC and the care of NICU infants.

**Research Questions and Hypotheses**

The purpose of this study is to examine the impact of parent presence on the stress response of NICU infants that results from cumulative NICU-related stressor exposures. The chronic activation of the HPA axis that is associated with cumulative exposure to NICU-related stressors may alter infant cortisol levels (Grunau et al., 2007; Morelius et al., 2016), and NICU infant stress response will be measured using salivary cortisol in this study. The amount and frequency of parent presence in the NICU will be measured as it is considered essential to parent-infant relationships in the DSC literature, and parent presence may represent previously unstudied aspects of the parent-infant social relationship. The amount and frequency of SSC will also be examined as it represents a DSC practice that requires parent presence and is frequently reported as a measure of the parent-infant social relationship in the NICU. The following research questions and corresponding hypotheses will be addressed.

Question 1: Are there significant associations between parent presence, measured in hours per week and days per week, and NICU infant stress response, as measured by salivary cortisol?
Hypothesis 1: Parent presence measured in hours per week is significantly associated with NICU infant stress response, as measured by salivary cortisol.

Hypothesis 2: Parent presence measured in days per week is significantly associated with NICU infant stress response, as measured by salivary cortisol.

Questions 2: Are there significant associations between increased SSC, measured in hours per week and days per week, and reductions in NICU infant stress response, as measured by salivary cortisol?

Hypothesis 3: Increased SSC measured in hours per week is significantly associated with reductions in NICU infant stress response, as measured by salivary cortisol.

Hypothesis 4: Increased SSC measured in days per week is significantly associated with reductions in NICU infant stress response, as measured by salivary cortisol.

Question 3: Do parent presence, SSC, and infant’s level of illness contribute to explaining NICU infant stress response, as measured by salivary cortisol?

Hypothesis 5: Parent presence (hours per week), SSC (hours per week), and infant’s level of illness significantly contribute to explaining NICU infant stress response, as measured by salivary cortisol.

Hypothesis 6: Parent presence (days per week), SSC (days per week), and infant’s level of illness significantly contribute to explaining NICU infant stress response, as measured by salivary cortisol.

Hypothesis 7: Controlling for infant’s level of illness and salivary cortisol at admission, the timing of parent presence in hours per week over the first four weeks of life significantly contributes to explaining NICU infant stress response, as measured by salivary cortisol at NICU discharge.
Hypothesis 8: Controlling for infant’s level of illness and salivary cortisol at admission, the timing of parent presence in days per week over the first four weeks of life significantly contributes to explaining NICU infant stress response, as measured by salivary cortisol at NICU discharge.

Hypothesis 9: Controlling for infant’s level of illness and salivary cortisol at admission, the timing of SSC in hours per week over the first four weeks of life significantly contributes to explaining NICU infant stress response, as measured by salivary cortisol at NICU discharge.

Hypothesis 10: Controlling for infant’s level of illness and salivary cortisol at admission, the timing of SSC in days per week over the first four weeks of life significantly contributes to explaining NICU infant stress response, as measured by salivary cortisol at NICU discharge.

Summary

NICU infants are at lifelong risk for adverse neurodevelopmental outcomes. In the NICU, infants are exposed to toxic stress that results from severe, frequent or prolonged activation of stress responses systems, during periods of separation from their parents. The cascade of physiologic responses resulting from the cumulative stressor exposure experienced by NICU infants targets the developing brain and may contribute to the adverse neurodevelopmental outcomes observed in this population. A basic tenet of the Polyvagal theory is that the human stress response may be down-regulated in the presence of buffering social relationships. The majority of DSC programs and practices endorse parent presence as critical for improving NICU infant outcomes. Parent presence may represent a previously unstudied aspect of the parent-infant social relationship, however, parent presence is rarely measured or considered by investigators of DSC. The current study will address this gap by examining potential
relationships between parent presence and infant stress response. The following chapter will present a review of the Polyvagal theory and literature relevant to parent presence in the NICU.
CHAPTER TWO
LITERATURE REVIEW

Introduction

NICU infants are at significant risk for adverse neurodevelopmental outcomes. In the NICU, infants are exposed to frequent stressors that occur during periods of separation from parents. The cumulative stress experienced by NICU infants occurs during sensitive periods of development that may explain the adverse neurodevelopmental outcomes observed in this population. While programs and practices of developmentally supportive care (DSC) endorse parent presence as critical for improving NICU infant outcomes, parent presence is rarely examined by investigators of DSC. Associations between parent presence and stress in infants hospitalized in neonatal intensive care units (NICUs) were examined in this study.

Theories provide a systematic view of a phenomenon of interest that may be useful in describing, explaining, predicting, or prescribing the phenomenon (Walker & Avant, 2019). Theory informs and guides research. Thus, the Polyvagal theory, the theoretical framework for this study, is described in the first part of this chapter.

Once a research topic is identified, a review of relevant literature is conducted to identify gaps in the literature (Tappen, 2016). The literature review may identify significant conceptual and methodological issues in an area of study (Cone & Foster, 2006). Therefore, the second part of this chapter synthesizes the contemporary literature relevant to parent presence and its impact on NICU infants.
The Polyvagal Theory

Description

The Polyvagal theory (Porges, 1995) served as the theoretical framework for the current study that was designed to examine associations between parent presence and stress in infants in the neonatal intensive care unit (NICU). In this theory Porges (1995) proposes that evolution of the vagus or 10th cranial nerve enables positive social relationships to buffer or down-regulate the stress response system. According to Porges (2017), buffering social relationships are a biological imperative for humans that support the regulation of physiologic and behavioral stress responses by signaling safety and connection.

In the Polyvagal theory, Porges (1995) proposes that two distinct branches of the vagus nerve evolved, each supporting different responses to stress. Working to balance the sympathetic nervous system (SNS) that mobilizes the stress response system in response to stressor exposure, the parasympathetic nervous system (PNS) inhibits SNS activity via the vagus nerve. The myelinated ventral vagal complex or smart vagus supports social relationships through connections to the muscles of the face and neck that innervate facial expression, listening and vocalization (Porges, 2011). Through neuroception, an unconscious process for evaluating safety versus threat, the presence of social relationships may communicate safety and signal the PNS to down-regulate the stress response system, acting as a vagal brake. The ability to self-regulate during times of stress is developed and maintained via social connection and co-regulation with others (Porges, 2017).

Unmyelinated or dorsal vagal responses are associated with exhaustion of the SNS (Sanders & Hall, 2018). The more primitive responses of the unmyelinated vagus include
immobilization, loss of consciousness and severe depression of respiratory and heart rates. These responses include severe apnea and bradycardia that are observed in NICU infants under stress (Porges, 2017).

**Appropriateness for Current Study**

According to Porges (2017) supportive social relationships are a biological imperative for the developing infant, and in early infancy, the primary social relationships are those with parents. The association between social relationships and the regulation of stress responses proposed in the Polyvagal theory is directly related to this study’s questions regarding potential relations between parent presence and infant stress response to chronic NICU-related stressor exposures. A novel application of Polyvagal theory was considered in this study in that associations between the presence of parents, an infant’s primary social (buffering) relationship, and NICU infant stress response were examined. Consistent with the plan for the study, the Polyvagal framework supports the use of biomarkers of stress as dependent variables. In NICU infants, baseline stress, stress reactivity, and relations between DSC and stress have been examined in studies grounded in the Polyvagal theory (DiPietro & Porges, 1991; Feldman et al., 2003; Porges, 1992; Porges & Furman, 2011; Porges et al., 2019). These studies are reviewed in the next section. Therefore, the Polyvagal theory provides an appropriate theoretical framework for examining potential associations between parent presence, which is recommended in DSC programs and practices, and the stress response of NICU infants.

**NICU Infants and Polyvagal Theory**

Measurement of heart rate variability (HRV) at rest reflects baseline vagal tone (Porges & Furman, 2011; Porges, 2011). The human infant is born dependent, without a completely developed ventral vagal complex. Following baselines studies of HRV in preterm and full term
infants, Porges (1992) reported an inverse relationship between resting HRV and gestational age, and he concluded that infants born preterm have reduced vagal tone that may negatively impact their ability to manage stress. Neuroanatomical research supports rapid development of the myelinated vagus from 24 weeks gestation through the teen years, although the greatest increases are seen from approximately 30 weeks gestation to six months post-partum age (Porges & Furman, 2011). Significant correlations between severity of illness and resting HRV are also reported for NICU infants (r=.9), with healthier infants demonstrating higher vagal tone (Porges, 1992). Increases in baseline HRV measured in preterm infants, indicating increased vagal tone, are associated with improvements in mental processing, motor skills and behavioral regulation at three years of age (Doussard-Roosevelt et al., 1997).

Measures of vagal tone in response to stress or a challenge, such as oral feeding, reflect stress reactivity and ANS maturity (Porges, 2011), and the HRV responses of NICU infants to gavage and oral feedings are reported. Preterm infants with increased vagal tone during gavage feeding, and return of vagal tone to baseline after feeding, are discharged home earlier (DiPietro & Porges, 1991). Reduced vagal tone is observed in term and preterm infants during oral feedings, and reduced vagal tone may be necessary to meet the metabolic demands of eating (Porges & Furman, 2011; Suess et al., 2000). A return to baseline vagal tone following oral feeding is observed in older born infants, indicating that vagal regulation may be compromised during oral feeding in more immature infants (Porges & Furman, 2011; Suess et al., 2000).

Several investigators report using the Polyvagal theory to evaluate NICU infant outcomes following implementation of DSC programs and practices. Compared to control group infants, Porges et al. (2019) observed greater increases in respiratory sinus arrhythmia (RSA), a measure of HRV and autonomic maturity, at 35 and 41 weeks post menstrual age (PMA) in NICU infants
receiving the Family Nurture Intervention (F(1, 161.95)=4.72, p=.03, d=0.38), an intervention aimed at facilitating nurturing co-regulation between parents and their NICU infants throughout their NICU stay (Welch, 2012). Feldman et al. (2003) observed significant increases in vagal tone, measured using RSA, at 37 weeks PMA in 35 preterm infants exposed to skin-to-skin care (SSC) in the NICU (M=2.32, SD=0.99) compared to 35 control group infants (M=1.77, SD=1.1) (F=4.98, p=.03). At 10 year follow-up of this cohort Feldman et al., (2014) observed increased vagal tone measured using RSA and reduced stress reactivity measured using salivary cortisol in the group exposed to SSC in the NICU. Although the Polyvagal theory is emerging as a framework for investigating DSC programs and practices, the phenomenon, parent presence, has not been examined using this theoretical lens.

Revisions for Current Study

Polyvagal theory is a relatively complex theory, and Porges (2017) currently defines more than 60 theory-related concepts. However, not all Polyvagal concepts, such as biological rudeness, are relevant to infants, the population of interest in the current study. Other Polyvagal concepts such as dissociation and neural exercise are not relevant to the study of parent presence in the NICU as it relates to infant stress response. Therefore, this framework was simplified for use by limiting the number of Polyvagal concepts to those with relevance to the current study. These concepts are defined in table 1.

Because the heart is directly linked to the vagus nerve, Porges (2011) recommends use of HRV to assess cardiac vagal tone, a biomarker of stress vulnerability and reactivity. Decreases in HRV during times of stress represent the body’s application of the vagal brake (Porges, 2011). However, the stress response system is an integrated system of responses that include vagal influences on the autonomic nervous system (ANS) and the regulation of cortisol through the
hypothalamic-pituitary-adrenal axis (HPA axis) (Godoy et al., 2018). In this study, potential relations between parent presence and NICU infants’ stress response to cumulative stressor exposure were measured using salivary cortisol, thus cortisol was added to the list of relevant concepts. While this modification is consistent with other DSC studies grounded in the Polyvagal theory (Feldman et al., 2014), it is a limitation.

Table 1. Polyvagal Theory Concepts and Definitions Relevant to the Current Study

<table>
<thead>
<tr>
<th>Concept</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Autonomic Nervous System</td>
<td>SNS and PNS including myelinated branch of vagus nerve</td>
</tr>
<tr>
<td>Autonomic State</td>
<td>Interchangeable with physiologic state in Polyvagal theory</td>
</tr>
<tr>
<td>Biological Imperative</td>
<td>Social connectedness is a biological imperative for humans</td>
</tr>
<tr>
<td>Connectedness</td>
<td>Trusting relationships between humans</td>
</tr>
<tr>
<td>Co-regulation</td>
<td>Mutual regulation of autonomic state between individuals</td>
</tr>
<tr>
<td>Cortisol</td>
<td>A glucocorticoid regulated by the HPA axis</td>
</tr>
<tr>
<td>Death feigning/shutdown</td>
<td>Primitive PNS response characterized by immobilization and depressed SNS function (apnea, bradycardia)</td>
</tr>
<tr>
<td>Heart rate variability</td>
<td>The variation in time between heartbeats, mostly determined by vagal influences. Not constant in a healthy heart.</td>
</tr>
<tr>
<td>Neuroception</td>
<td>Unconscious evaluation of safely</td>
</tr>
<tr>
<td>Self-regulation</td>
<td>Skills that allow a person to stay calm under stress</td>
</tr>
<tr>
<td>Social engagement system</td>
<td>Physiologic systems coordinating the heart with muscles of the face and head</td>
</tr>
<tr>
<td>Vagal brake</td>
<td>Inhibitory vagal pathways on heart and stress response system in response to stress; equivalent to vagal tone</td>
</tr>
<tr>
<td>Ventral vagal complex</td>
<td>Myelinated vagus that regulates heart and muscles of the face</td>
</tr>
</tbody>
</table>

Note. Conceptual definitions were derived from the Polyvagal theory (Porges, 2011).
The association between social relationships and the regulation of stress reactivity proposed by Porges (1995) in the Polyvagal theory is directly related to this study’s questions regarding potential relations between parent presence and NICU infant stress response to cumulative or chronic stress exposure. Parent presence in the NICU has been identified as a form of parent-infant engagement that is essential to the development and maintenance of dyadic social relationships, as it is during time spent in the NICU that parents learn to read their infants’ cues and interact with their infants (Klawetter et al., 2019; Pineda et al., 2018). Parent presence encompasses all aspects of the parent-infant relationship in the NICU that include formal relational activities, such as SSC, or previously unstudied relational activities such as in the moment touches and vocalizations in response to infant cues. Thus, parent presence in this study is consistent with Porges’ (1995) concept of buffering relationships.

The Polyvagal theory is complex, including many concepts that are not relevant to NICU infants. However, it was simplified for use with the population of interest in the current study. The Polyvagal theory has been used in research examining the impacts of DSC on NICU infant stress, measured using heart rate variability and salivary cortisol (Feldman et al., 2003; Feldman et al., 2014; Porges et al., 2019). Thus, Polyvagal theory is an appropriate theoretical framework for the current study.

A review of relevant literature relevant to parent presence and NICU infant stress was necessary to identify gaps in the contemporary literature. Therefore, a review of literature relevant to associations between parent presence and NICU infant stress follows.
Literature Review

DSC and Parent Presence

The purpose of DSC is to integrate neuroprotective practices with the intensive care necessary for the survival of NICU infants. Based on the foundational work of Als et al. (2004), the goals of DSC include preventing and mitigating NICU infant stress. Engaging families in their infant’s care is a central tenet of DSC (Coughlin, 2021). DSC consists of a number of different programs and practices, however, few require parent presence for implementation. The Family Nurture Intervention program, SSC and live maternal voice are among the only DSC interventions requiring parent presence, and the only DSC interventions requiring parent presence that have been considered by researchers investigating DSC and infant stress outcomes.

Family Nurture Intervention. The goal of the Family Nurture Intervention (FNI) is to establish emotional connections between NICU infants and their parents throughout their NICU stay (Welch et al., 2013). Nurture specialists assist baby and parent during calming sessions aimed at helping them achieve relaxed, co-regulated physical and emotional states. Activities such as scent cloth exchanges, skin-to-skin care and talking to the baby are facilitated by program specialists. To date only one FNI trial of 134 NICU infants between 31 and 35 weeks gestational age has been reported (Welch et al., 2013). Hours of parent presence above the FNI were not measured, although intervention group infants received the FNI an average of 3.5 times per week, for a mean 6.4 hours per week over an average six weeks in this randomized controlled trial (RCT) (Porges et al., 2019; Welch et al., 2013). Consistent with increased vagal tone and efficiency, from 35 to 41 weeks PMA, the FNI group was observed to have greater increases in respiratory sinus arrhythmia (RSA) (F(1, 161.95)=4.72, p=.03, d=0.38) and greater increases in the slope between RSA and heart rate (F(1, 147.43)=8.02, p=.01, d=0.62) compared
to control group infants, (Porges et al., 2019). At 4- to 5-year follow-up (N=115), children and mothers in the FNI group continued to demonstrate higher levels of RSA (child mean difference=0.6, 95% CI=0.17, 1.03, p=.008) (mother mean difference=0.64, 95% CI=0.07, 1.21, p=.03) than control infants and mothers (Welch et al. 2020).

**Skin-to-skin Care.** Skin-to-skin care (SSC) or kangaroo care is the practice of holding an infant, naked except for a diaper, against the parent’s bare chest. In contrast to the Kangaroo mother care program that encourages SSC for most of the day, Western NICUs tend to promote episodic SSC for one or two hours a day. SSC is among the most studied DSC practices.

Associations between SSC and improvements in NICU infant stress regulation, have been measured using HRV, cortisol and oxytocin (Ionio et al. 2021). Investigators examining stress responses of preterm infants following SSC interventions report impacts of single versus longer SSC interventions. Thus, infant stress-related outcomes reported for single SSC interventions are reported separately from those reported for longer SSC interventions in this review.

**Single SSC Interventions.** Several studies report improvements in HRV following relatively brief, single SSC interventions. Butruille et al. (2017) examined HRV before, during and after a one-hour SSC intervention in 22 preterm infants at a median age of 31 weeks PMA. A subset of infants (N=13) with lower HRV before SSC were observed to have significantly improved HRV during and after SSC (p<.05). Kommers et al. (2017) measured HRV before and during 191 episodes of SSC observed in 11 preterm infants (median PMA=30 1/7 weeks). Six out of eight features of HRV were significantly lower during SSC (p=.015 to p=.0001). Kommers et al. (2018) also observed lower HRV during and after SSC (p<.01) in 182 SSC episodes in another cohort of 20 preterm infants (median PMA=31.3 weeks). Similarly, Vogl et al. (2021) observed significantly lower HRV (r=.88; p=.00009) during SSC over 20, 90-minute
SSC episodes in 10 preterm infants (mean PMA=33 5/7 weeks) with a parent. All investigators observing lower HRV during SSC concluded that reductions in HRV may reflect improved infant stability.

NICU infant stress responses following single SSC interventions have also been examined using salivary cortisol. Mirnia et al. (2017) compared salivary cortisol levels in 23 preterm infants randomized to 45 minutes of SSC with their fathers to 22 preterm infants receiving standard NICU care in the presence of fathers. Salivary cortisol levels sampled over a 60 minute period, before, during and after SSC or standard care were lower in both infant groups over time; and although cortisol levels were lower during and after SSC, these levels did not reach significance. In a randomized crossover study, Vittner et al. (2018) examined salivary cortisol levels in 28 preterm infants before, during and after a one-hour SSC session with mother and father. Infant cortisol levels fell significantly during SSC with mothers (F=5.85; p=.005, η^2=.06) and fathers (F=11.48; p=.001; η^2=.11). In contrast to studies of preterm NICU infants, Lisanti et al. (2020) measured salivary cortisol levels before, during and after one-hour episodes of SSC with mother in full term cardiac infants, once in the pre-operative and once in the post-operative period. At both pre- and post-operative time points, salivary cortisol levels decreased during SSC (not significant) and increased significantly following SSC (p=.001 and p=.02, respectively). Small sample sizes and differences in the methods of analysis used may have influenced the outcomes of studies measuring cortisol to evaluate single SSC interventions.

Salivary oxytocin levels have also been used to examine NICU infant stress regulation during and following single SSC interventions. Vittner et al. (2018) observed significantly higher salivary oxytocin levels during and following SSC for one hour with mothers (F=8.05, p=.002, η^2=.52) and fathers (F=8.21, p=.001, η^2=.14). The variable timing of SSC interventions and
salivary cortisol measures reported by investigators examining relatively brief, single SSC episodes may have impacted stress regulation outcomes using HRV, cortisol and oxytocin.

**Longer SSC Interventions.** Investigators have also examined NICU infant stress responses following longer SSC interventions using HRV and cortisol measures. In a randomized controlled trial (RCT) El-Farrash et al. (2020) compared baseline salivary cortisol level to salivary cortisol levels following seven days of SSC for 60 minutes or 120 minutes versus no SSC in 120 preterm infants. Compared to control infants, after seven days salivary cortisol levels in both SSC cohorts decreased significantly (p<.05).

In an early randomized controlled trial (RCT), Feldman et al. (2003) observed significant improvements in RSA, an indicator of vagal tone, at 37 weeks PMA in 35 preterm infants exposed to one hour of SSC for 14 consecutive days in the NICU compared to 35 control group infants (F=4.98, p=.03). At 10 year follow-up, children in the SSC group continued to demonstrate improvements in baseline RSA, with significant group differences observed (F=6.53, p=.01) (Feldman et al., 2014). In addition, children in the SSC group had significant lower cortisol reactivity in response to a standardized social stress test (F=5.45, p=.02).

In a small study of term infants (N=10) with congenital heart disease, Harrison and Brown (2017) measured HRV prior to and at two-week intervals following a two-week SSC intervention with the mother, once the infant was extubated and started oral feedings post-operatively. Infants received an average of 77 minutes of SSC per day over 14 days, and HRV was measured in response to and with recovery from oral feeding, a significant challenge for sick infants. HRV across feeding improved over the six week period following the SSC intervention (F=4.88, p=.04). At three month follow-up, investigators again observed HRV during a learning task and compared them to HRV during the same task in typically developing infants and similar
cardiac infants. The investigators’ findings suggest that the SSC intervention continued to benefit the ANS maturity in the SSC group (Harrison et al., 2019).

In a secondary analysis, Marvin et al. (2019) examined associations between the frequency of SSC, HRV and NICU infant outcomes in 101 preterm infants (M=31 weeks PMA) who received SSC at least once in the first three weeks of life. HRV was measured weekly until 35 weeks PMA. Frequency of SSC was documented by NICU nurses in the electronic medical record from birth through three weeks of life. Greater SSC during the first week of life was positive correlated with improved HRV (r=.23, p=.02) and a shorter length of stay (r= -.34, p=.001) as well as other improved medical outcomes.

Few investigators have examined the cumulative effects of longer SSC interventions. Among studies reported by investigators examining the effects of longer SSC interventions, associations with improvements in infant stress regulation are more consistently observed. However, the parent-infant relationship measured via SSC in these studies may also reflect differences in parent presence that were not measured.

**Live Maternal Voice.** Although use of maternal voice has been examined as a component of DSC, few investigators have used live maternal voice as an intervention, and only two of these have examined infant stress outcomes. Blumenfeld and Eisenfeld (2006) examined the impacts of live maternal singing on 11 preterm infants during two consecutive oral feedings on two consecutive days. No significant differences in infants’ heart rates or respiratory rates were observed. Filippa et al. (2013) observed the effects of maternal speaking for five minutes and singing for five minutes for three out of six days on behavioral states and physiologic parameters in 18 preterm infants. Infant heart rates and oxygen saturations remained within normal limits and were higher during exposures to maternal voice. Numbers of critical events,
including bradycardia and oxygen desaturations, were significantly lower during maternal voice exposure (14.7%, 95% CI=8.19, 25, p<.0001), and infants were more often in a quiet alert state (Filippa et al., 2013). Inconsistencies in the infants’ PMAs and exposures to maternal voice may explain the differences in infant stress outcomes reported in these two studies.

**Summary of DSC and Parent Presence.** DSC interventions universally endorse parent presence. DSC programs and practices requiring parent presence, including FNI, SSC and live maternal voice interventions, are reported by some investigators to be successful in reducing NICU infant stress responses. However, the improved stress-related outcomes observed may also be associated with greater parent presence, which has been identified as a form of parent engagement and may represent aspects of NICU parent-infant relationships not previously considered. Unfortunately, parent presence is rarely measured in DSC studies. The aim of this literature review is to critically review the state of the science relevant to parent presence and its impacts on NICU infant stress. Thus, parent presence in the NICU is the focus of this review.

**Parent Presence in the NICU**

A systematic literature search was conducted to identify studies of NICU parent presence and its impacts on NICU infants. Searches for relevant published research were conducted using several databases including PubMed, CINAHL and Ovid Medline. Search terms included parent presence, parent visiting, neonatal intensive care, newborn, infant, and preterm infant. The search was limited to papers published in English and peer-reviewed research. Papers published prior to 2000 or reporting data collected prior to 2000 were excluded as an emphasis on DSC and family-centered care increased parent visitation after the year 2000 (Reynolds et al., 2013). Hand searches were also conducted using reference lists of publications related to NICU parent presence.
Following the removal of 145 duplicates, database and hand searches resulted in 557 articles relevant to NICU parent presence or visiting. Study abstracts were screened for eligibility, and studies not measuring NICU parent presence were excluded. For purposes of this study, parent presence was defined as the amount of time a parent is in the NICU with their infant. Studies reporting interventions to increase parent presence were excluded. Where parent presence outcomes for the same cohort of infants were duplicated by an investigator, only one study was retained. Where NICU infant outcomes were reported, only papers reporting infant stress-related outcomes were included. The resulting 52 papers were reviewed, and an additional 28 papers not relevant to this search were eliminated. The remaining 24 papers are included in this review.

A critical review of literature relevant to parent presence and its impacts on NICU infants follows. This literature review begins with an appraisal of papers reporting amounts of and factors related to NICU parent presence. Then, studies reporting associations between parent presence and NICU infant stress-related outcomes are addressed. Finally, conclusions are discussed, including gaps in the literature.

**NICU Parent Presence**

Investigators reporting NICU parent presence primarily describe amounts of parent presence and factors influencing parent presence. However, data related to parent presence in NICUs are generally scarce and inconsistently measured, with investigators using different methods to quantify parent presence (Powers et al., 2020). Additionally, investigators have considered the presence of only mothers, only fathers or both.

Among nations represented in this review, only the United States (US) does not provide paid leave following the birth of a baby (Livingston & Thomas, 2019). Excluding the US, the
lowest amount of postnatal paid leave reported for nations included in this review is eight weeks, thus studies reporting parent presence in the US and internationally are considered separately.

**Parent Presence Internationally.** International investigators have examined parent presence in single-site studies, multisite studies and in studies examining parent presence in single-family rooms. These three study types are reviewed separately below. Variables reported to be related to parent presence are also described.

**Single-setting Studies.** Three international investigators have examined NICU parent presence in single-site studies. Franck et al. (2003) measured parent presence for 110 NICU infants in the United Kingdom. Parent visits were recorded by nurses using bedside logs for 12 days over four months. Mothers were present more frequently than fathers, with 85% (29%) versus 45% (41%) daily presence reported (p<.05). Duration of visits was significantly longer for mothers at 3.02 (1.6) mean hours versus 1.42 (1.08) hours for fathers (p<.05), although data analyses and effect sizes were not reported for frequency or duration of visits. More siblings, increased infant age and less paternal visiting explained 27% of the variance associated with lower maternal presence (F=11.01, p=.001). Younger infant age and more maternal visiting explained 17% of variance associated with more paternal presence (F=6.68, p=.001).

In a related study, parent presence for the first 31 days of life in a Dutch NICU were reported by Kamphorst et al. (2018) for 162 infants. Parent presence data were collected using nursing logs. After the first week of life, median parent presence was one-time per day for 3-4 hours per day per infant. Duration of paternal visits were significantly shorter than maternal visits (95% CI= -43, -24, p<.001). The number of siblings in the home and distance to the hospital were negatively correlated with paternal (r= -.19, r= -.25) and maternal visiting (r= -.28, r= -.31) visiting. Duration of visits for mothers and fathers were positively associated with more
frequent visits (r=.5, r=.65), increased SSC (r=.38, r=.25), and higher infant birth weight (r=.23, r=.22). The duration of parent visits and decreased duration of fathers’ visits reported in this study are consistent with those reported by Franck et al. (2003), as are negative relationships between the number of siblings and parent presence. However, Kamphorst et al. (2018) reported small effect sizes for associations between the number of siblings and parent presence (4-8%), distance to the hospital and parent presence (6-10%), and the duration of mothers’ visits and amounts of SSC (14%).

In Canada, Kim et al. (2021) observed parent presence for 142 NICU infants. Parents logged visitation and skin-to-skin care during the infant’s first 34 days of life. On average mothers were present a mean 8.7 (5.3) hours/day, and fathers were present a mean 4.1 (2.9) hours/day. Daily parent presence decreased over time. In multivariate analysis, maternal presence was positively associated with father’s presence (β=0.3, 95% CI=0.04, 0.57), increasing maternal age (β=4.82, 95% CI=1.04, 8.6), being a first time mother (β=1.96, 95% CI=0.43, 3.49), and greater infant birth weight (β=0.002, 95% CI=0.001, 0.003), and negatively associated with greater distance to home (β=-0.01, 95% CI= -0.01, -0.001), and an increased length of stay (β= -0.04, 95% CI= -0.07, -0.01) (R²=.47). Although longer parent visits were reported in this study, the shorter visits by fathers observed are consistent with previous reports of paternal visiting (Franck et al., 2003; Kamphorst et al., 2018). Results of this study support the negative associations between maternal presence in the NICU and siblings in the home, greater distance to the NICU and less partner visiting previously described (Franck et al., 2003; Kamphorst et al., 2018; Kim et al., 2021).

**Multisite studies.** Papers from three investigative teams reporting NICU parent presence in multisite studies were identified. Visiting patterns of parents of 127 preterm infants from two
German NICUs during the first 28 days of life were reported by Garten et al. (2011). Data were collected via retrospective chart review. Mothers visited a median 133.4 minutes/day (2.22 hours/day), while fathers visited 72.5 minutes/day (1.2 hours/day), 46% less than mothers. Frequency of parent visits declined over time. Frequency and duration of parent presence were associated with increased maternal age ($r=.21$, $r=.35$), decreased infant gestational age ($r=-.27$, $r=-.29$) and decreased infant birth weight ($r=-.28$, $r=-.29$). The duration of parent visits in this study were shorter than those reported in international studies of parent presence. However, the decreased duration of paternal visiting observed is consistent with that reported in other studies (Franck et al., 2003; Kamphorst et al., 2018; Kim et al., 2021). The findings of Garten et al. (2011) also support the decline in parent presence in the NICU over the infant’s length of stay observed by Kim et al. (2021), although this decline is not well defined in either study.

The presence of parents of 328 preterm infants from 11 European NICUs in six countries was examined by Raiskila et al. (2017). Parent presence and skin-to-skin care was recorded using parent logs during the infant’s first two weeks of life. Among study NICUs parent presence varied from a median of 3.3 to 22.3 hours per day. More parent presence, 19.7 (5.3) versus 5.5 (2.6) mean hours ($p<.001$), and skin-to-skin care, 4 (4.51) versus 1.74 (1.54) mean hours ($p<.001$), were observed in six NICUs that provided parents with opportunities to spend the night, although no test statistics or effect sizes were reported. On multivariate analysis, background variables associated with more parent presence included younger maternal age, higher maternal education, and parents living together.

Aija et al. (2019) also examined parent presence in 11 European NICUs in six countries. Families of 241 preterm infants participated in the study. Parent presence data were collected via parental responses to daily texts throughout the NICU stay. Mothers were present 62.5-91% of
NICU days, with fathers present 30.8-77.8% of NICU days. In multivariate analyses, more parent presence was associated with higher infant gestational age, being invited to participate in medical rounds and a more highly educated father. Results of the study are limited in that a range of frequencies for parent presence are reported and effect sizes are not reported.

**Single-family rooms.** Four papers reporting parent presence in single-family rooms (SFRs) internationally were identified. In a descriptive study, Wigert et al., (2010) compared parent presence for 42 NICU infants in two Swedish NICUs based on the availability of SFRs. Parent presence was collected over one week using parent logs. Parents in SFRs spent a mean of 23.1 hours per day in the NICU versus parents staying at home (5.9 hours/day), in a hotel (6.8 hours/day), or in the maternity ward (5.4 hours/day). In interviews parents reported that parental illness, a lack of privacy and comfort in the NICU, and caring for children at home were barriers to presence in the NICU.

Similarly, Tandberg et al. (2019) compared parent presence for 77 preterm infants in a SFR NICU versus an open-bay NICU in Norway. Parent presence and SSC were recorded from birth through 34 weeks PMA using parent logs. The mean presence of mothers in SFRs was 21 (5) hours per day versus 7 (3) hours per day in the open bay NICU. Fathers in SFRs were present a mean 16 (6) hours per day versus 5 (2) hours in the open bay NICU. Infants in SFRs received more SSC per day, 6 (2) hours versus 4 (2) hours per day in the open bay NICU. The increases in parent presence (p<.001) and hours per day of SSC (p<.001) observed in SFRs were reported as statistically significant findings, but test statistics and effect sizes were not reported. Visitation by parents in both the SFR and non-SFR settings were consistent with visitation reported in the Swedish study by Wigert et al. (2010). The shorter visits described for fathers are consistent with the paternal visiting in NICUs previously described in this review.
In an Australian NICU, Jones et al. (2016) compared parent presence following the transition from an open bay NICU (N=31) to a SFR NICU (N=25). Parent presence data were collected using parent logs for the first two weeks the family was in the NICU. Mothers in SFRs logged more presence during their first two weeks in the NICU, a mean 63.3 (59.6) hours compared to 35 (39.6) hours for mothers in the open bay NICU (p=.05, Cohen’s d=0.6). Fathers in SFRs were present a mean of 2.6 (7.2) hours compared to 0.8 (1.7) hours for infants in the open bay NICU for the first two weeks of admission. Hours of parent presence in SFRs reported in this study were relatively low, at 4.5 mean hours per day, compared to the more than 20 hours per day of parent presence reported in SFR NICUs in Scandinavian countries (Wigert et al., 2010; Tandberg et al., 2019). These differences may reflect differences in paid family leave.

In a related study, parent presence and SSC were compared before and after an open bay NICU’s transition to all SFRs in Australia (Broom & Kecskes, 2020). Parents of 93 infants recorded visitation and SSC in parent diaries, 46 in the open bay NICU and 47 after the transition to all SFRs. Frequency of parent visits per day were not significantly different in SFRs (2.6/day) versus the open bay NICU (3/day) (p=.33). However, mean duration of parent presence in SFRs was significantly longer at 329.36 (17) minutes/day versus 229.78 (18) minutes per day in the open bay NICU (p<.001). Mean minutes of SSC per infant per day were 70.85 (12) for infants in SFR versus 9.5 (4.8) for infants in the open bay unit (p<.001). Results of parent surveys before and after the change to SFRs indicate that parents viewed SFR as more private (94% versus 45%, p=.01), and supportive of parent involvement (98% versus 89%, p<.001). Although significant increases in parent presence and SSC are reported in this study, test statistics and effect sizes are not reported. Parent presence in hours per day (5.4) reported in the study are consistent with amounts reported in Australia and lower than amounts reported in Scandinavia.
Summary of parent presence measured internationally. Ten investigative teams have examined NICU parent presence internationally. There is a lack of standardization in measuring parent presence, and these ten investigators report frequency of visits, duration of visits or both. The presence of both parents was measured in all studies reviewed. Paternal visits were consistently 40-50% shorter than maternal visits, although effect sizes were rarely reported (Franck et al., 2003; Kamphorst et al., 2018; Kim et al., 2021; Garten et al., 2011). Parent presence data were documented using a variety of methods, and the reliability of data collection methods was not assessed in any study reviewed. A decline in parent visiting over time was reported in two studies (Kim et al., 2021; Garten et al., 2011) but, visiting trends were not consistently considered.

Associations between parent presence and infant variables, parent variables or NICU-related variables were reported in all studies, although differences in the type of variables considered by study were observed. Effect sizes for associations between variables related to parent presence, where reported, tended to be small. The presence of siblings and fewer visits by the co-parent were associated with decreased parent presence in three studies (Franck et al., 2003; Kamphorst et al, 2018; Kim et al., 2021). Positive associations between increased parent presence and increased amounts of SSC were reported in several studies (Kamphorst et al., 2018). The presence of parents of preterm infants is reported in the majority of international studies, limiting the generalizability of findings.

Parent presence in SFRs versus open bay NICUs is consistently higher in international studies. Increases in parent presence in SFRs are reported to be significant, however, statistical reporting is often inadequate with effect sizes rarely reported. SSC is increased for infants in SFRs. Factors that influence parent presence are considered less often in studies of SFRs.
Parent Presence in the US. In contrast to international studies, investigators in the US have primarily examined NICU parent presence in single-site studies. Additionally, the presence of mothers and fathers are often considered separately in studies of US NICUs. Thus, results of studies reporting the presence of mothers, fathers or both are reviewed separately, followed by studies reporting parent presence in SFRs.

Mothers’ presence in US NICUs. Three US investigative teams have examined maternal presence in the NICU. In a single-site study Gonya and Nelin (2013) examined maternal presence for 32 preterm infants. Mean frequency of mothers’ presence was 78% of days their infants were in the NICU. Duration of visits were not reported. Regression modeling was used to identify variables associated with decreased maternal presence. These included maternal stress related to infant appearance and behavior ($t=2.78, p=.01$), number of siblings ($t=-4.16, p<.001$), maternal age ($t=2.82, p=.009$), and parent-staff communication score ($t=1.76, p=.09$) ($R^2=.58, p<.001$). Distance to the NICU and socioeconomic status were not related to visitation, however, a small sample size may have limited the study’s power to detect other significant effects. This study is consistent with international studies reporting associations between less maternal presence in the NICU and greater numbers of siblings (Franck et al., 2003; Kamphorst et al., 2018; Kim et al., 2021).

In a related study, Greene et al., 2015 examined maternal presence throughout the NICU stay of 69 preterm infants using hospital visitor logs. Mothers were present 61% of days their infants were hospitalized. More siblings ($B=-0.05, 95\% CI=-0.09, -0.01, p<.05$), more lifetime exposure to traumatic events on the Life Events Checklist ($B=-0.03, 95\% CI=-0.04, -0.01, p<.05$), African American race ($B=-0.18, 95\% CI=-0.28, -0.08, p<.01$) and lower maternal anxiety on the Strait-trait Anxiety Index ($B=0.14, 95\% CI=0.04, 0.24, p<.01$) explained less
maternal presence in the NICU from birth through discharge ($R^2=.49$, $F(4,49)=11.73$, $p<.001$). Findings related to more siblings in the home and less maternal presence are consistent with the findings of Gonya and Nelin (2013) and several international studies. However, this is the first study to describe race and cumulative trauma exposure as variables associated with parent presence.

Harris et al. (2018) also considered the psychosocial distress of mothers in examining maternal presence in the NICU. The presence of 37 mothers of preterm infants was assessed using a structured written questionnaire completed by mothers prior to NICU discharge. Sixty-five percent of mothers reported visiting the NICU every day. Mothers in the high weekly visitation group visited more than 17 hours per week, while mothers in the low visitation group visited less than 16 hours per week. Mothers in the high visitation group reported less parental role alteration ($M=2.61$, $SD=0.58$) than mother in the low visitation group ($M=3.43$, $SD=0.97$, $p=.03$) and less emotionality on an infant care questionnaire ($M=4.15$, $SD=1.03$ versus $M=4.7$, $SD=0.42$, $p=.03$). These findings are consistent with other US investigators that have considered psychosocial distress in examining parent presence (Gonya & Nelin, 2013; Green et al., 2015).

**Fathers’ presence in US NICUs.** One investigator examined paternal presence in the NICU. Patel et al. (2019) conducted a retrospective chart review to examine fathers’ presence in the NICU among 292 preterm infants during week one of life. Fathers were present a median frequency of 3 days during the first week of life. Fathers married to the mother (IRR=2.74, 95% CI=2.33, 3.23, $p<.001$) or living with the mother (IRR=2.05, 95% CI 1.72, 2.45, $p<.001$) visited more often. Father visited less often if the mother lived more than 25 kilometers from the hospital (IRR 0.83, 95% CI=0.72, 0.97, $p=.02$). Results of this study are consistent with those reporting greater distance to the hospital as a barrier to parent presence.
**Parent presence in US NICUs.** Papers from two researchers who focused on parent presence in US NICUs were identified. Saxton et al. (2019) retrospectively examined parent presence for 386 NICU infants from a tertiary-level NICU using data obtained from unit sign-in sheets. Median frequency of parent presence was 75% of NICU days for mothers and 59.2% of days for fathers. Mothers were present a median 10.33% of total minutes in the NICU, while fathers were present 5.14% of total NICU minutes (z=-10.45, p<.001). Frequency and duration of maternal and paternal visits were positively associated, which is consistent with international studies reporting parent presence (Franck et al., 2003; Kim et al., 2021). Duration of parent visiting reported was low in this study, as indicated by percentage of time parents spend in the NICU. Despite the study’s large sample, the study’s retrospective use of unit sign-in logs to document parent presence may have limited the accuracy of the data.

Using a prospective cohort design, Zauche et al. (2020) examined parent presence for 66 preterm infants in two NICUs over a 48 hours period. Parent presence was recorded using unit visitation logs that were verified using electronic medical record (EMR) data. Parent presence was reportedly variable with mean parent presence 32.4% (+/- 28.22%) over 48 hours. Investigators reported significant associations between less parent presence and infants with a neurological diagnosis (F=24.6, p<.001, d=4.92), infants in open-bay NICU beds (F=37.71, p<.001, d=5.54), infants with a surgical history (F=24.45, p<.001, d=10.54), and lower perceived parental stress (F=4.74, p=.03, d=4.35). Using multivariate analysis SFR (β=15.96), infant surgical history (β= -37.66), infant neurological comorbidity (β= -22.19), fewer siblings (β=16.12), lower perceived parent stress (β= -9.98), and a significant interaction effect between SFR and surgery history (β= -28.59) explained 65.8% of NICU parent presence (R²=.66, F=20.23, p<.001). Because parent visiting may vary over time, the short window of time NICU
parent presence was observed in this study limits the generalizability of findings. However, associations observed between fewer siblings and decreased parent presence are consistent with findings reported in other studies. This study was the first to consider relationships between infant diagnoses or surgical history and parent presence in the NICU.

**Single-family rooms.** One investigative team reporting parent presence relative to use of SFRs in US NICUs was identified for this review. Using a longitudinal design, Pineda et al. (2012) compared parent presence for 39 preterm infants in SFRs versus 42 preterm infants in open bay NICU beds in the same NICU. Bedside nurses logged parent presence, and data were verified using the EMR. No significant differences in infant or maternal baseline variables were identified. Investigators quantified trends in parent visiting over time, and they documented decreased hours of visiting per week over the first five weeks of life for infants in SFRs (9.6 hours/week decrease) and open bay beds (2.22 hours/week decrease). Over the infant’s NICU stay, parents in SFR were present more, 25.49 (25.41) mean hours per week versus 16.85 (13.47) hours per week, than parents of infants in open bay beds (p=.05). Amounts of skin-to-skin care did not differ by room type. Parent presence in this US NICU was relatively low compared to international studies reporting parent presence in SFRs, and no test statistic or effect size was reported for the difference in parent presence for parents in SFRs and open bay beds.

**Summary of parent presence in the US.** Seven investigators examined parent presence in US NICUs. Four of these investigators considered the presence of mothers or fathers only, and they reported the frequency but not the duration of parent presence, with mothers observed to be present 61-78% of NICU days (Greene et al., 2015; Gonya & Nelin, 2013) and fathers present 43% of days measured (Patel et al., 2019). Two investigators examined the presence of both parents. These two investigators reported duration of visits, although this was reported as a
percent of time versus hours per day or week, making comparisons with international studies of parent presence difficult (Saxton et al., 2019; Zauche et al., 2020). Similar to international studies, fathers’ visits were shorter in duration than mothers’ visits (Saxton et al., 2019; Pineda et al., 2012). A decline in parent visiting was observed over time and quantified, although effect sizes were not reported (Pineda et al., 2012).

In contrast to international studies, US investigators examined associations between parent presence and parental psychological distress including anxiety, trauma history (Greene et al., 2015) and perceived stress (Gonya & Nelin, 2013; Harris et al., 2018). Similar to international studies, numbers of siblings (Greene et al., 2015), distance to the NICU (Patel et al., 2019), and frequency and duration of co-parent visits impacted parent presence, although effect sizes were infrequently reported (Saxton et al., 2019). Parents in the US are present more in SFRs compared to open bay NICU beds, however, amounts of parent presence reported in SFRs are lower than those reported internationally (Pineda et al., 2012). The smaller sample sizes reported for studies in the US may have impacted study outcomes. The use of single sites for data collection limits the generalizability of study findings.

**Parent Presence and NICU Infant Outcomes**

Papers on parent presence and NICU infant outcomes are scarce, and seven reports of parent presence and NICU infant outcomes for four cohorts of infants were identified. Most investigators compared infant outcomes in SFRs versus open bay NICU beds. These studies are related to this review, because parent presence was measured, and associations between parent presence and infant stress-related outcomes were examined. Investigators have examined associations between parent presence and short or long-term infant outcomes. Two studies were
conducted in Europe. These papers are considered separately due to the availability of paid parental leave outside the US (Livingston & Thomas, 2019).

International studies reporting infant outcomes. Two international investigators have examined parent presence and NICU infant outcomes. In Finland, Latva et al. (2004) measured the frequency of parent visiting for 47 preterm infants using medical record data. Mothers were present a median number of 6.2 days per week, while fathers were present 4.7 days per week. Data collected from parents using the Achenbach Child Behavior Checklist (CBCL) at school age indicated that infants with mothers who visited every day had fewer emotional and behavioral problems. Using multivariate analysis, mother’s daily presence was associated with favorable CBCL scores (OR 0.2, 95% CI=0, 1.2), but NICU stays longer than 30 days were associated with scores indicating emotional or behavioral problems, (OR 5.5, 95% CI=0.8, 46.9). Father’s visiting was not associated with outcomes of NICU graduates. Limitations of the study include use of a small sample from single site and that other variables that may influence behavioral outcomes in children were not considered.

Morelius et al. (2012) compared infant stress outcomes in 152 preterm infants in SFRs to the outcomes of 137 preterm infants in standard open bay rooms in two NICUs in Sweden. Families and their infants were randomly assigned to room types. Parents were expected to be present around the clock in the SFRs. Amounts of parent presence were not recorded for the standard care group. Infant cortisol levels measured in response to a diaper change performed by the mother at 36 weeks PMA increased in 35% of infants in both groups. However, significant associations in baseline and response salivary cortisol levels, unique to infants and mothers in the SFR group were observed (baseline cortisol r=.31, p=.001; response cortisol r=.24, p=.01). Morelius et al. (2012) concluded that decreased parent presence may delay dyadic co-regulation
of cortisol in the NICU. Co-regulation of the HPA axis in mother-infant dyads is believed to be essential to infant development (Provenzi et al, 2019). However, effect sizes reported for associations in mother-infant cortisol in this study are small.

**NICU infant outcomes and parent presence in the US.** Five papers representing two cohorts of NICU infants and reporting associations between parent presence and infant outcomes were identified. Studies for these two infant cohorts are reported separately below.

**Cohort one.** Reynolds et al. (2013) examined infant neurobehavioral outcomes at term-age in a cohort of 81 preterm infants in a single NICU also described by Pineda et al. (2012, 2014, & 2018). Mean hours of parent presence per week were 21.33 (20.88) per week, and mean days of skin-to-skin care were 0.71 (0.94) per week during the infants’ NICU stay. Data were documented using nursing logs that were verified using the EMR. The multivariate analysis conducted included controls for infant covariates including gestational age, cerebral injury, postnatal steroids and days of ventilation. Infant neurodevelopment was examined using the NICU Network Neurobehavioral Scale (NNNS) at term-age. Increased parent presence, holding and SSC were associated with lower infant arousal (β= -0.02) and excitability (β= -0.03) summary scores, which reflect reduced behavioral signs of stress. Lower infant stress scores (β= -0.03) were related to greater amounts of infant holding. Reynolds et al. (2013) did not report mean infant NNNS scores or standard deviations, making study results difficult to interpret.

Pineda et al. (2014) examined the neurodevelopment of infants from this cohort at 34 weeks PMA using the NNNS, at 30 weeks and term-age using electroencephalogram (EEG), at term-age using magnetic resonance imaging (MRI), and at two years using the Bayley Scales of Infant and Toddler Development, third edition (Bayley-III). Controlling for illness scores, insurance type and cerebral injury, more arousal or irritability (β=0.5, 95% CI=0.1, 0.9) was
observed using the NNNS at 34 weeks PMA in SFRs infants compared to open bays infants. At term-age, cerebral maturation scores from EEG trended lower in SFR infants ($R^2=.15$, $\beta=-0.52$, 95% CI=0.1, 0.95), and typical hemispheric asymmetry was decreased on MRI. At two years, SFR infants had significantly lower language scores on the Bayley-III ($M=84.8$, $SD=10.5$) than infants in open-bay NICU beds ($M=91.9$, $SD=11.4$, $p=.005$) (Pineda et al., 2014). More parent presence was documented in SFRs, however, the 21.33 mean hours per week previously recorded for SFR infants in this cohort is equal to only 3.05 hours per day, and parent presence varied between families. Associations between parent presence and infant outcomes were not directly examined in this study.

In a follow-up study, Pineda et al. (2018) examined the neurodevelopment of this same cohort of preterm infants using the Ages and Stages Questionnaires, third edition (ASQ-3) at four to five years of age. The frequency of parent presence for SFR and open bay infants combined was examined. Parents were present a median of 4 days per week over the NICU stay; held their infants in arms a median 2.2 days per week; and participated in skin-to-skin care 0.2 days per week. Data were analyzed using linear regression. Older mothers ($\beta=0.22$), parents of Caucasian race ($\beta=0.3$), married parents ($\beta=0.24$), parents with more extended family support ($\beta=0.47$) and parents providing breastmilk ($\beta=0.4$) visited more; and parents with more siblings ($\beta=-0.39$) visited the NICU less frequently. More skin-to-skin care was associated with better gross motor development at four to five years ($\beta=0.28$). Associations between parent presence and developmental outcomes were not explored. Strengths of studies done using this cohort include the verification of parent presence data using the EMR and the longitudinal follow-up of subjects, however, use of a small sample and single site limit generalizability of findings.
**Cohort two.** Following the transition from an open bay to SFR NICU, Lester et al. (2014) compared the outcomes of 252 preterm infant in SFRs versus 151 in an open bay NICU using a longitudinal, prospective, quasi-experimental design. Maternal presence data were retrieved from the EMR. At term-age, maternal involvement in days per week over the first 12 weeks of life was greater for infants in the SFRs (M=4.5, SD=1.7) compared with infants in open-bay NICU beds (M=3.6, SD=1.5, p<.001) (Lester et al., 2014). At term age SFR infants displayed less stress (M=0.1, SD=0.25 versus M=0.2, SD=0.31, p<.001), less hypertonicity (M=0.05, SD=0.22 versus M=0.12, SD=0.35, p=.02), better attention (M=4.8, SD=1.3 versus M=4.5, SD=1.2, p=.01) and no increases in arousal-irritability scores using the NNNS (Lester et al., 2014). Maternal involvement in SFRs was also associated with lower infant pain scores (M=1.6, SD=0.4 versus M=2, SD=0.4, p<.001).

At 18 months infants in this cohort were evaluated using the Bayley-III and Pervasive Developmental Disorders Screening Test, stage two (PDDST-II) (Lester et al, 2016). Infants with more days per week of maternal involvement in SFRs had better cognitive (M=93.8, SD=13.2 versus M=87.8, SD=11.8, p=0.01, ES=0.4), and language scores (M=93.7, SD=16.5 versus M=82.9, SD=14, p<.001, ES=0.72) on the Bayley-III. The language scores of infants in open-bay NICU beds also favored infants with more days per week of maternal involvement (M=90, SD=18.4 versus M=81.5, SD=13.2, p=.01, ES=0.57). Associations between scores from the PDDST-II indicated that infants with any autism symptom were more likely to be in the open bay, low maternal involvement group (OR=4.91, 95% CI=2.2, 11.1). Maternal involvement in SFRs was associated with increases in cognitive and language outcomes that were supported by moderate to large effect sizes at 18 months. Strengths of the study include the quasi-experiment design and a robust sample size that was supported by an a priori power analysis. Study
limitations include the use of a single site. In addition, the level of maternal involvement from NICU discharge until infants were 18 months of age was not considered.

**Summary.** Few investigators have examined parent presence and its potential impacts on the neurodevelopmental outcomes of NICU infants. Parent presence has been associated with fewer behavioral signs of stress in preterm infants at term-age, although effect sizes are not reported for these behavioral differences (Lester et al., 2014). In studies of SFR, high levels of maternal involvement are related to language development at 18 months of age that is supported by moderate to large effect sizes in one study, regardless of NICU room type (Lester et al., 2016). Increased parent presence is also associated with a reduced risk for autism at 18 months (Lester et al., 2016) and reduced behavioral and emotional problems at school-age (Latva et al., 2004). Increased skin-to-skin care measured alongside parent presence is associated with better gross motor development at four to five years (Pineda et al., 2018), and skin-to-skin care is frequently considered in studies of NICU parent presence.

Significant differences in stress reactivity have not been associated with 24 hour per day parental presence compared to standard NICU care (Morelius et al., 2012). Relations between baseline mother and infant cortisol levels may reflect dyadic co-regulation of HPA axis when examining NICU infant outcomes related to parent presence (Morelius et al., 2012). A similar co-regulatory relationship of cortisol levels between mothers and their preterm NICU infants has been reported by Neu et al. (2009), where lower mean salivary cortisol was observed in mothers and infants post-holding, and co-regulation was operationalized as a lower absolute difference between maternal-infant cortisol measured before and after a 60 minute holding session.

Studies in the US benefitted from longitudinal and quasi-experimental designs. However, small samples with no power analysis were reported in all but one study. Also, only Lester et al.
(2011) based their study of SFRs on a theoretical model of NICU design and infant outcome (Lester et al., 2011; Lester et al., 2016). All studies were limited by use of a single NICU setting.

**Summary of Literature Review**

There is a lack of standardization in measuring parent presence. In addition, the availability of paid parent leave following the birth of a baby in many nations outside the US necessitates discretion when comparing studies measuring parent presence. This review of parent presence in the NICU suggests that parent presence in the US is infrequently measured and generally low in comparison to parent presence in international NICU studies. Even in studies of SFRs where parent presence is more clearly measured, parent presence per day in US NICUs averages between two to four hours per day. In contrast, international studies often report more than 20 hours per day of presence in SFRs and three to four hours of parent presence per day in traditional NICUs.

Variables associated with parent presence are similar in the US and internationally. Fathers visit less often and for shorter durations than mothers. The presence of siblings in the home, longer distance to the NICU and fewer visits by the co-parent have been associated with decreased parent presence in many studies, although effect sizes are rarely reported. In international studies investigators tend to examine associations between infant and family variables and parent presence. In the US, investigators tend to focus on associations between parent psychosocial distress and parent presence. Investigators in the US also consider infant variables including neurologic injury or surgical status that are often associated with term NICU infants. SSC is often included in studies of NICU parent presence in the US and internationally.

Few investigators report the impacts of NICU parent presence on infant neurodevelopmental outcomes, and the results of studies examining the effects of parent
parental presence has been associated with fewer behavioral stress signs in preterm infants at term-age, and a reduced risk for behavioral and emotional issues in NICU graduates at school age. Conversely, significant differences in stress reactivity have not been associated with 24 hours per day of parent presence when compared to standard NICU care. Relations between mother-infant cortisol may reflect co-regulation of stress when examining mother-infant dyads. A similar co-regulatory relationship of cortisol levels between mothers and their preterm NICU infants has been reported by Neu et al. (2009) following a one-hour holding session.

**Gaps in Existing Knowledge**

Mitigating infant stress is a primary goal of DSC, which seeks to improve infant outcomes by integrating neuroprotective interventions with standard NICU care. Most DSC programs and practices consider parent presence critical to NICU infant outcomes. Yet, few DSC programs and practices require or measure parent presence, and the degree to which outcomes attributed to DSC programs and practices are influenced by parent presence is not known.

Potential associations between parent presence and NICU infant stress-related neuro-developmental outcomes are poorly understood. Relationships between mother-infant cortisol that have been observed in two studies may reflect co-regulation of the HPA axis in mother-infant dyads. SSC is often measured in studies examining parent presence and NICU infant outcomes. Studies of parent presence have not considered other aspects of parent-infant relationships in the NICU, such as in the moment touches and vocalizations that may co-occur with parent presence, complicating the interpretation of infant outcomes in these studies.

Whether parent presence alone is effective in reducing stress in NICU infants is not known. There is a scarcity of literature examining the impact of maternal presence on the stress
responses of NICU infants. The potential impact of fathers’ presence on infant stress responses has not been examined.

**Contributions of Current Study**

In the Polyvagal theory, Porges (2011) proposes that social relationships may down-regulate activation of the stress response system via co-regulation during times of stress. This study proposes a novel application of Polyvagal theory to study NICU parent presence, a component of DSC that may represent aspects of the parent-infant relationship not previously considered, and infants’ stress response to cumulative stressor exposures in the NICU. The presence of NICU parents, measured in hours per week and days per week, will be considered an independent variable that may buffer infant stress response, as measured by salivary cortisol, a biomarker of stress. SSC, measured in hours per week and days per week, will also be considered an independent variable that may buffer infant stress. Use of the Polyvagal framework to guide this work supports examining associations between aspects of NICU parent-infant relationships and infant biomarkers of stress as dependent variables. This study may contribute to knowledge related to the importance of parent presence for NICU infants, and it may inform nursing care, research and policy in the future.
CHAPTER THREE

METHODS

Introduction

Each year significant numbers of term and preterm infants are admitted to neonatal intensive care units (NICUs) (Harrison & Goodman, 2015). In the NICU, infants are exposed to toxic stress that results from frequent, severe or prolonged activation of the stress response system, during periods of separation from parents. The toxic stress experienced by NICU infants occurs during critical periods of neurodevelopment and may contribute to the adverse neurodevelopmental outcomes observed in this population. In the Polyvagal theory, Porges (1995) proposes that the stress response system may be down-regulated in the presence of buffering social relationships.

DSC programs and practices aimed at reducing stress in NICU infants universally endorse parent presence, but few require parent presence for implementation. Skin-to-skin care (SSC), a developmentally supportive care (DSC) practice that requires parent presence and supports parent-infant relationships in the NICU, is associated with reductions in stress in NICU infants (Ionio et al., 2021). However, investigators often report the impact of relatively brief SSC interventions. Parent presence is rarely measured in studies reporting infant outcomes related to DSC. Parent presence may represent an aspect of the parent-infant social relationship in the NICU not previously considered. It is not known whether parent presence is related to reductions in the stress response of NICU infants.
The purpose of this study was to examine the impact of parent presence on the stress response of NICU infants that results from cumulative NICU-related stressor exposures. The chronic activation of the HPA axis that is associated with cumulative exposure to NICU-related stressors may alter infant cortisol levels (Grunau et al., 2007; Morelius et al., 2016), and NICU infant stress response was measured using salivary cortisol in this study. The amount and frequency of parent presence in the NICU was measured as it may represent a previously unstudied aspect of the parent-infant social relationship. The amount and frequency of SSC was also examined as it represents a DSC practice that requires parent presence and is frequently reported as a measure of the parent-infant social relationship in the NICU. A description of the research methods used to address this study’s aims and hypotheses are reviewed in this chapter. Study limitations are also addressed.

Specific Aims and Hypotheses

Three research aims were addressed in this study.

Aim 1: Determine whether there are significant associations between parent presence, measured in hours per week and days per week, and NICU infant stress response, as measured by salivary cortisol.

Hypothesis 1: Parent presence measured in hours per week is significantly associated with NICU infant stress response, as measured by salivary cortisol.

Hypothesis 2: Parent presence measured in days per week is significantly associated with NICU infant stress response, as measured by salivary cortisol.
Aim 2: Determine whether there are significant associations between increased SSC, measured in hours per week and days per week, and reductions in NICU infant stress response, as measured by salivary cortisol.

Hypothesis 3: Increased SSC measured in hours per week is significantly associated with reductions in NICU infant stress response, as measured by salivary cortisol.

Hypothesis 4: Increased SSC measured in days per week is significantly associated with reductions in NICU infant stress response, as measured by salivary cortisol.

Aim 3: Determine the independent explanatory contribution of parent presence, SSC, and infant’s level of illness to NICU infant stress response, as measured by salivary cortisol.

Hypothesis 5: Parent presence (hours per week), SSC (hours per week), and infant’s level of illness significantly contribute to explaining NICU infant stress response, as measured by salivary cortisol.

Hypothesis 6: Parent presence (days per week), SSC (days per week), and infant’s level of illness significantly contribute to explaining NICU infant stress response, as measured by salivary cortisol.

Hypothesis 7: Controlling for infant’s level of illness and salivary cortisol at admission, the timing of parent presence in hours per week over the first four weeks of life significantly contributes to explaining NICU infant stress response, as measured by salivary cortisol at NICU discharge.

Hypothesis 8: Controlling for infant’s level of illness and salivary cortisol at admission, the timing of parent presence in days per week over the first four weeks of life significantly contributes to explaining NICU infant stress response, as measured by salivary cortisol at NICU discharge.
Hypothesis 9: Controlling for infant’s level of illness and salivary cortisol at admission, the timing of SSC in hours per week over the first four weeks of life significantly contributes to explaining NICU infant stress response, as measured by salivary cortisol at NICU discharge.

Hypothesis 10: Controlling for infant’s level of illness and salivary cortisol at admission, the timing of SSC in days per week over the first four weeks of life significantly contributes to explaining NICU infant stress response, as measured by salivary cortisol at NICU discharge.

Study Design

The aims and hypotheses for this study were addressed via a descriptive, correlational design using data from an existing dataset to conduct a secondary analysis. The dataset includes data from 78 families collected for a NICU Parent Engagement (NPE) study. The current study used selected data from the NPE study including relevant parent and infant demographic data, the amount and frequency of parent presence in the NICU, the amount and frequency of SSC, and infant level of illness scores. Infant salivary cortisol data collected at NICU admission and discharge from the NPE dataset were also used in this study. The median age at NICU discharge was 33 days (17-56.25) for NPE infant subjects, and infant salivary cortisol data collected at one month of life was used for NPE infant subjects not discharged at or before 33 days of life.

Rationale for Secondary Analysis

By definition a secondary analysis is appropriate when an existing data set can be used to answer a different research question (Tappen, 2016). The primary aim of the NPE study was to determine whether parent and infant stress would be impacted by a NICU-wide intervention aimed at increasing parent presence in the NICU. In this study, data from two independent groups of families enrolled in the NPE study, one enrolled during the pre-intervention period and
a second group enrolled in the post-intervention period, were combined to address new research questions, aims and hypotheses. The NPE study is described in Appendix B.

Benefits of using existing data to answer research questions include maximizing the use of resources, including time and money (Cheng & Phillips, 2014). This was relevant in the current study as laboratory analysis of salivary cortisol levels are expensive, and costs associated with measuring salivary cortisol in the NPE study were several thousand dollars. Use of an existing dataset also eliminated the need to collect salivary cortisol samples from a new cohort of fragile NICU infants.

Databases from smaller studies may also be used for secondary analysis if these contain data relevant to the new study (Tappen, 2016). The sample and setting of the NPE study were appropriate for use in the current study, and the NPE study dataset contained data necessary to address this study’s research questions. In addition, during the coronavirus disease of 2019 (COVID-19) pandemic many NICUs implemented parent visiting restrictions (Mahoney et al. 2020), resulting in reduced parent presence. As the pandemic subsides, hospitals may vary in the timing and degree to which COVID-19 visitor restrictions are lifted, making the collection of new parent presence data that accurately reflect parents’ typical visiting patterns impractical for the current study.

**Setting**

The NPE study data was collected in a tertiary-level NICU in a free-standing, Midwestern children’s hospital. The dataset includes data from families of term and preterm infants with a variety of medical and surgical diagnoses requiring intensive care that were admitted to this setting and enrolled in the NPE study. The hospital did not deliver babies, and all NICU infants represented in the dataset were transferred from outside hospitals.
Sample

The dataset from the NPE study includes parent presence, SSC and infant data from 78 unique NICU families, 40 families in a pre-NPE study intervention group and 38 families in a post-NPE study intervention group. Among the 78 families included in the dataset, 78 NICU infants, 78 mothers and 35 fathers are represented. Data from all of the 78 infants and families enrolled in the NPE study were employed in this study. Parent presence data varied widely in NPE pre- and post-intervention study families, and no significant differences in parent presence in the pre- or post-intervention groups were identified in the original study. However, use of parent presence data from all NPE families remains a limitation in the current study.

The NPE study dataset includes data from families of 41 term (53%) and 37 preterm infants (47%). Preterm infants represented in the data set were born at greater than or equal to 28 weeks gestation. NICU infants in the NPE study were enrolled at or before two weeks of age, were of mixed acuity, and were not screened for variables that may impact cortisol levels; and use of discharge cortisol data was planned to limit the impact of variables such as medications and infections. Although there were no significant differences in gestational age or infant levels of illness in the two NPE study groups that were combined for use in this study, the heterogeneous nature of the sample represented in the NPE dataset and lack of screening for variables that may impact cortisol level are limitations in the current study.

Dataset Characteristics

The NPE study dataset contains data necessary to address this study’s research questions, specific aims and hypotheses. Data available in the NPE dataset include demographic data for enrolled infants and parents. Available demographic data for enrolled NICU infants include sex, gestational age, birthweight, length of stay, breastfeeding status, and a Neonatal Medical Index
(NMI) (Korner et al., 1993) score indicating the infant’s level of illness. Parent demographic data available in the NPE dataset include age, relationship status, number and ages of siblings, level of completed education, employment status and distance from the parent’s residence to the hospital. The dataset also contains parent presence and SSC data recorded in hours per day. Infant salivary cortisol data available in the dataset includes infant salivary cortisol levels collected at NICU admission, at discharge from the NICU, and at each month of age the infant reached prior to NICU discharge. Psychometric evidence and NPE study data collection procedures for data relevant to the current study are described later in this chapter.

**Power Analysis**

A power analysis was conducted to estimate the sample size needed to address study aims. Comparing the sample size required to address study aims in the current study to the NPE study’s sample size provided additional support for use of the NPE study’s dataset for this secondary analysis.

**Aim 1.** The first aim of the study was to determine whether there are associations between parent presence, measured in hours per week and days per week, and NICU infant stress response, as measured using salivary cortisol. There are few studies examining potential relations between NICU parent presence and infant stress to guide power analysis.

Reynolds et al. (2013) measured parent presence in hours per week for a cohort of 81 preterm infants. In this sample more parent presence was associated with lower infant arousal ($\beta = -0.01$) and excitability ($\beta = -0.04$) measured using the NICU Network Neurobehavioral Scale (NNNS) at term-age. Mean infant scores and effect sizes were not reported.

In a study comparing 151 infants in an open-bay NICU with 252 infants in single-family rooms, Lester et al. (2014) observed greater maternal presence in days per week ($M=4.5$,
SD=1.7) in single-family rooms versus (vs.) open-bay NICU rooms (M=3.6, SD=1.5, p<.001). In this sample increased parent presence was associated with less stress (M=0.0.1, SD=0.25 vs. M=0.2, SD=0.31, p<.001), less hypertonicity (M=0.05, SD=0.22 vs. M=0.12, SD=0.35, p=.02), and better attention (M=4.8, SD=1.3 vs. M=4.5, SD=1.2, p=.01), as measured using the NNNS at term age.

Thus, there is a lack of evidence examining parent presence and stress-related outcomes in NICU infants, and no studies reported measuring infant stress response using salivary cortisol. Effect sizes are not reported for behavioral measures of stress, and these outcomes may not be relevant to physiologic measures of stress. As this aim had not been addressed in the literature using similar measures of infant stress, a moderate effect size was selected. Estimating a medium effect size of 0.33, an alpha of 0.05, and a power of 80%, a sample size of 69 was calculated for the first aim using G*Power (Faul et al., 2009). This was within the sample size available in the NPE study.

**Aim 2.** The second aim of the study was to determine whether there are significant associations between SSC, measured in hours per week and days per week, and NICU infant stress response, as measured by salivary cortisol. Correlational analyses were planned for this aim. There are few studies examining the cumulative impact of SSC that may occur over time in the NICU and infant stress response, as measured using salivary cortisol.

In a randomized controlled trial, El-Farrash et al. (2020) observed decreased salivary cortisol levels in 40 preterm infants exposed to 60 minutes of SSC (median=4.2 ng/ml, IQR=2.6-7) and 40 infants exposed to 120 minutes of SSC (median=2.4 ng/ml, IQR=1.2-4.5) for seven consecutive days in the NICU compared to 40 control group infants (median=10.5, IQR=8.7-
Single infant salivary cortisol samples were collected in the morning prior to SSC or feeding. Test statistics and effect sizes were not reported.

In another randomized trial, Morelius et al. (2015) compared salivary cortisol in late preterm infants that received nearly continuous SSC in the NICU (M=19.6 hours/day) compared to standard care infants that received less SSC (M=7 hours/day). Significantly lower infant salivary cortisol reactivity was observed in response to a diaper change performed by the mother at 44 weeks post-menstrual age (PMA) in the high SSC infants (F=7.6, p=.01). Effect sizes were not reported.

There are few studies examining the cumulative effects of SSC that may occur over time in the NICU and infant stress response, as measured by salivary cortisol, and in the two related studies identified, no effect sizes were reported for relations between the amounts of SSC received over time and infant salivary cortisol levels. Therefore, a moderate effect size was selected to examine this aim. Using G*Power (Faul et al., 2009) a sample size of 69 was calculated to address the study’s second aim using a moderate effect size of 0.33, an alpha of 0.05, and a power of 80%. Again, this was well within the limits of the NPE study dataset.

**Aim 3.** The third aim of the study was to determine the independent explanatory contribution of parent presence, SSC, and infant’s level of illness to NICU infant stress response, as measured by salivary cortisol. Multiple regression was planned to examine hypotheses associated with this aim. As this question had not been addressed in the literature, a conservative, moderate effect size was selected (f2=.15) to address the third aim of this study. Using a moderate effect size of 0.15, an alpha of 0.05, and a power of 80%, a sample size of 55 was calculated for aim three using G*Power (Faul et al., 2009).
Because aim one and two of the proposed study required a sample size of 69, a minimum sample of 69 was needed to address all research questions. The NPE study’s dataset was obtained using a sample of 78 NICU families. Due to missing salivary cortisol data at discharge for a small number of infants in the dataset (N=17), the entire NPE dataset of 78 NICU families was needed to address the research questions, specific aims and hypotheses of this study.

**Variables**

The variables of interest in this study included parent presence, infant stress response as measured by salivary cortisol at discharge, SSC and the infant’s level of illness. Conceptual and operational definitions for each variable are described here. Psychometric evidence for variables measured is addressed in the following section.

**Parent Presence**

Parent presence was conceptually defined as a biological imperative of human infants. Parent presence was also defined as the presence of parents, the primary social relationship of infants that supports the mutual regulation of stress between individuals (Porges, 2011). NICU parent presence was identified as a form of parent engagement may represent a previously unstudied aspect of the parent-infant social relationship. In the current study, parent presence was operationally defined as the amount of time parents were with their infant in the NICU in hours per week and days per week as documented in the electronic medical record (EMR).

**Infant Stress Response**

Infant stress response was conceptually defined as cortisol levels that are impacted by stress-related activation of the hypothalamic-pituitary-adrenal axis (HPA axis), that are regulated via interactions with endocrine and neuronal systems, including the autonomic nervous system (Godoy et al., 2018; Porges, 2011; Smith & Vale, 2006); and, that are impacted by the chronic
activation of the HPA axis associated with cumulative acute and chronic exposure in the NICU (Grunau et al., 2007; Morelius et al., 2016). Acute stressor exposures inherent in the NICU may include painful procedures, while chronic stressor exposures inherent in the NICU may include in situ medical equipment or therapies such as nasogastic tubes and mechanical ventilation (Cong et al., 2017).

In the current study, infant stress response was operationally defined as a resting salivary cortisol level measured at discharge from the NICU (median = 33 days of life), or at one month of age for infants not discharged at or before one month of age. Using a one-time resting measure of NICU infant salivary cortisol, El-Farrash et al. (2020) observed decreased salivary cortisol levels in infants exposed to the cumulative effect of SSC for 60 to 120 minutes per day for one week. Cong et al. (2017) measured the cumulative acute and chronic stressor exposures of 40 preterm NICU infants during the first month of life using the Accumulated Pain/Stressor Scale (APSS) (Xu et al., 2016). In this sample, cumulative acute and chronic stressor exposures during the first 28 days of life were significantly associated with infant neurobehavioral stress/abstinence scores measured using the NNNS at term-age.

**Skin-to-skin Care**

SSC was conceptually defined as an activity that supports connectedness in relationships between parents and infants, where parent-infant relationships are a biological imperative for the human infant (Porges, 2011). SSC was operationally defined as the amount of time, in hours per week or days per week, NICU parents held their infant naked except for a diaper and hat against their bare skin, as documented in the EMR.
**Infant Level of Illness**

The infant’s level of illness was conceptually defined as the infant’s physiologic state that reflects infant birthweight, primary illness, co-morbidities and treatments such as mechanical ventilation. According to Porges’ Polyvagal theory (2011), physiologic state is interchangeable with autonomic state. Operationally infant’s level of illness is defined as the infant’s Neonatal Medical Index score (NMI) (Korner et al., 1993). The NMI considers illness-related variables that reflect a NICU infant’s level of illness at baseline and throughout hospitalization.

**Instruments and Psychometric Evidence**

Examining the instruments used to collect data in the NPE study dataset and their psychometric evidence was necessary to ensure the data was of sufficient quality for use in this secondary analysis (Tappen, 2016). Thus, instruments used in the NPE study and psychometric evidence supporting the use of these instruments in research are described below.

**Parent Presence and Skin-to-skin Holding**

In studies examining NICU parent presence and skin-to-skin holding, data have been collected using parent logs, nursing logs, unit sign-in sheets and infant medical records (Gonya & Nelin, 2013; Greene et al., 2015; Reynolds et al., 2013). In the NPE study parent presence and SSC data were obtained from the infants’ EMR. Reliability of EMR data depends on the accurate documentation of parent presence and skin-to-skin holding by NICU nurses. The accuracy of nurses’ documentation of parent presence and skin-to-skin holding data were supported in the NPE study in that EMR flowsheets routinely utilized by NICU nurses prompted documentation of these data points, a flowsheet row prompting nurses to document the amount of time parents were present was added to the EMR prior to the NPE study, and staff were given frequent reminders to record this data in staff meetings, staff emails and unit signage. Parent presence and
skin-to-skin holding data collected from the EMR were double-checked by the study’s principal investigator, and any inaccuracies were corrected.

**Salivary Cortisol**

Cortisol is a biomarker of stress that reflects activation of the hypothalamic-pituitary-adrenal (HPA) axis in response to stressor exposure (Godoy et al., 2018). In utero HPA axis activity is detected between eight to twelve weeks of gestation (Ng, 2000). The collection of cortisol data using saliva is preferable in that it is a non-invasive collection method that is less likely to cause stress to the infant or parent than a blood draw. In addition, salivary cortisol levels represent free or biologically available cortisol in contrast to serum cortisol that measures both free and bound cortisol (Amin et al., 2017). Diurnal cycling of cortisol levels are observed in adults and children, with peak cortisol levels occurring in the morning and the lowest cortisol levels observed at night (Fries et al. 2009). However, this diurnal cortisol cycling is not observed in infants until four to eight weeks post-term (Ivars et al., 2017; Stalder et al., 2013).

**Validity Evidence.** Several small studies have documented associations between pain and stress exposures and cortisol levels in NICU infants (Mitchell et al., 2012). Pourkaviani et al. (2020) examined associations between salivary cortisol levels and stressor exposure, measured using the Neonatal Infant Stressor Scale (NISS), six hours prior to specimen collection. From a sample of 125 preterm infants, 386 salivary cortisol specimens were collected. Acute and chronic stressor exposures were associated with increased salivary cortisol levels ($r=.31, p<.01; r=.24, p<.01$), providing evidence of concurrent validity for salivary cortisol levels. However, results of regression analysis indicated that only acute and total NISS scores were associated with salivary cortisol levels. Stressors categorized as chronic using the NISS may not affect cortisol or may require cumulative assessment. Analysis using a mixed-effects regression model did not detect
significant effects for antenatal or postnatal steroid exposure, but PMA and caffeine treatment were observed to be significant covariates between the NISS and salivary cortisol levels.

Long term associations between NICU stressor exposure and salivary cortisol have also been observed in former preterm infants. Grunau et al. (2007) observed associations between resting or unstimulated salivary cortisol levels and the number of skin breaking procedures in the NICU in 53 preterm infants. At eight months of age, correlations between exposures to more skin breaking procedures in the NICU and higher resting salivary cortisol levels (r=.31) as well as higher salivary cortisol levels after introduction of an unfamiliar experience (r=.29) were observed.

**Reliability Evidence.** Amin et al. (2017) compared the cortisol levels that resulted from 230 paired serum and salivary cortisol specimens from 90 preterm infants. Eighty-eight percent of salivary cortisol specimens contained sufficient volume for analysis. The correlation between serum and salivary cortisol was 0.674. Although this reliability may be considered relatively low, this value reflects inherent differences in measuring salivary and serum cortisol, in that serum cortisol levels reflect free and bound cortisol while salivary cortisol reflect only free cortisol (Amin et al., 2017).

**Salivary Cortisol Instrumentation in NPE Study.** Salivary cortisol samples were collected using SalivaBio® oral swabs. Reliability of salivary cortisol samples obtained using the SalivaBio® oral swabs was established in a study comparing oral swab samples with samples obtained using the passive drool method (r=.98), the gold standard for salivary cortisol collection (Salimetrics, 2018). Although difficulties obtaining sufficient saliva from infants for analysis are reported (Mitchell et al., 2012), 84% (N=131) of the combined admission and discharge infant salivary cortisol samples collected in the NPE study had sufficient quantity for analysis. Analysis
of salivary cortisol specimens was completed using enzyme immunoassay for salivary cortisol. The low limit of detection for salivary cortisol in the NPE study was <0.2 nanograms per milliliter (ng/ml). Coefficients of variation for salivary cortisol reported in studies of preterm infants are less than 12% (Morelius et al., 2016), where a rate of 20% or lower for coefficients of variation are recommended (Calvi et al., 2017). Local reference ranges for salivary cortisol in infants and adults were 0-8.24 ng/ml. Specific data collection procedures for salivary cortisol in the NPE study, including timing of specimen collection, are detailed in the following section.

**Neonatal Medical Index**

The NMI is a morbidity scale that is used to quantify the severity of illness in NICU infants (Korner et. al., 1993). The NMI includes baseline variables such as birth weight and factors related to an infant’s level of illness throughout their NICU stay including days of oxygen therapy, days of mechanical ventilation, selected medication use, surgical history and the presence of neurologic conditions. There are five levels of NMI scores, ranging from one to five. Level I describes an infant with relatively low levels of morbidity, while level V indicates that an infant is among those with the most severe levels of medical morbidities. Data necessary to calculate NMI scores are readily available in the infants’ EMR.

**Predictive Validity.** Korner et al. (1993) examined the predictive validity of the NMI for a sample of 512 NICU infants at 12, 24 and 36 months PMA. Infant cognitive and motor outcomes were observed at 12 and 24 months using the Bayley Scales of Infant Development (BSID) and the Stanford Binet Intelligence Scale, third edition, at 36 months. Multiple regression for infant cognitive and motor outcomes considered NMI scores, maternal education, infant gender, and two variables for ethnic group, black or Hispanic. NMI scores were associated with
infant cognitive development at 12 months ($R^2=.31, \beta=-0.41$), 24 months ($R^2=.38, \beta=-0.27$) and 36 months ($R^2=.44, \beta=-0.24$) in infants born at less than 1500 grams (Korner et al., 1993).

NMI scores at 32 weeks PMA have also been found to be predictive of oral feeding and age at discharge in NICU infants. In a retrospective study, Pickler et al. (1997) examined associations between oral feeding milestones, age at NICU discharge and NMI scores in a convenience sample of 40 preterm infants. NMI scores were related to PMA at first bottle feeding ($r=.34$), PMA at full oral feeding ($r=.65$), and PMA at discharge ($r=.55$). Regression analysis considering NMI, birth weight, gestational age and days of ventilation accounted for 30% of the variance in PMA at discharge and 42% of the variance in PMA at full oral feeding.

In a more recent study, Pickler et al (2005) used a longitudinal design to examine associations between the NMI and NICU infant oral feeding outcomes for 920 bottle feedings in 95 NICU infants. Feeding outcomes considered included volume consumed in the first five minutes of feeding (proficiency), percent of feeding consumed, and total feeding volume over feeding time (efficiency). NMI scores were related to feeding efficiency ($X^2=8.18; \phi=0.27$).

**Study and Data Collection Procedures**

When using secondary data, it is essential to understand the data collection procedures and data management strategies used in the original study (Cheng & Phillips, 2014). This is necessary to verify the data are of sufficient quality for use in the planned secondary analysis. Thus, data collection and management procedures for the variables selected for use from the NPE study are reviewed below. All data were collected following informed consent, and protection of human subjects in the NPE study is discussed later in this chapter.
**Demographic Data and NMI Scores**

In the NPE study infant demographic data were collected from the EMR. This information included sex, gestational age, birthweight, length of stay, weight at discharge, number of days of receiving breastmilk, breastfeeding status at discharge, and information required to calculate the NMI or level of illness score. All infant data were recorded on an infant data sheet that was transcribed to a computer database by the principal investigator. NMI scores were calculated by the principal investigator following infant discharge and documented on the infant data sheet and in the computer database. NMI scores were double checked for accuracy.

Parent demographic data were collected via brief parent interviews conducted by the principal investigator (PI) at study enrollment. These data included age, relationship status, number and ages of siblings, level of education completed, employment status and distance from the parent’s residence to the hospital. Data were documented on a parent information sheet designed for the NPE study and transcribed to the study’s computer database. If parents were unsure of the distance traveled between the hospital and home, this was determined using a computerized map application.

**Parent Presence and Skin-to-Skin Holding**

Parent presence and skin-to-skin holding data in the NPE study were documented in hours per day using data collected from nursing flowsheets contained in the EMR. Nursing flowsheets in the EMR are displayed in one-hour increments, and nurses write comments when parents’ visits or SSC are less than one hour. Where a nurse indicated in an EMR row for a particular hour that a parent was present or participated in SSC, but did not quantify a specific amount of time for these activities, one hour of parent presence or SSC was credited to the study data. If both parents were present during an hour, only one hour of parent presence was credited.
If a parent was present and held their baby skin-to-skin, both parent presence and SSC were credited. Parent presence and SSC data for mothers and fathers were not reported separately, and combining parent presence and SSC data for mothers and fathers is a limitation of this study. Parent presence and SSC data was converted to hours and days per week for use in this study.

**Salivary Cortisol**

In the NPE study, salivary cortisol samples were obtained using SalivaBio® oral swabs designed for this purpose. When collecting salivary cortisol for a group of infants, improved accuracy may be achieved by using a consistent team and by using consistent collection techniques that include screening for oral intake or stressful procedures (Tryphonopoulos, et al., 2014). Salivary cortisol samples were collected by trained NICU nurses that were members of the NPE research team using a consistent collection procedure.

Because breastmilk or formula may contain cortisol and a number of other hormones that may interfere with the accuracy of salivary cortisol results, infant samples must be collected well after feedings and contamination of samples with feeding material must be avoided (Magnano et al., 1989). In addition, samples should be collected at a consistent time of day. In the NPE study, infant salivary cortisol levels were collected between the hours of 5 and 9 am, prior to any anticipated standard of care procedures that might initiate an acute physiologic stress response in the infant. To avoid components that can disturb salivary cortisol analysis, salivary cortisol samples were obtained one hour after oral intake or oral care, and study team nurses inspected the infant’s mouth for formula or breastmilk prior to obtaining the sample. Infant medications that may influence salivary cortisol levels were not considered in the NPE study, however, use of glucocorticoid medications at one month of age in the NICU is rare, and infants are not discharged from the NICU on glucocorticoid medications or with signs of infections. Therefore,
either the infant’s discharge cortisol or one month cortisol level in the NICU were used in this study.

Following an inspection of the oral cavity for milk, the oral swab was placed alongside the buccal mucosa or under the tongue of infant subjects for three to five minutes. This procedure was repeated to provide two saliva samples at each salivary cortisol collection. If insufficient quantities of saliva were reported by the lab, salivary cortisol samples were repeated when possible. After collection, cortisol samples were centrifuged prior to freezing at -20 Centigrade. Batched analysis of specimens was completed locally every one to two weeks using an enzyme immunoassay for salivary cortisol. Eighty-four percent (N=131) of the combined infant salivary cortisol samples collected at admission and at discharge in the NPE study had sufficient quantity for analysis.

**Data Management**

NPE study data were cleaned prior to analysis. Seventeen missing data points were observed in the dataset for salivary cortisol levels in infants at discharge or at one month of age. Missing salivary cortisol levels were the result of unanticipated infant discharge, sample contamination or an insufficient quantity of saliva that was not repeatable, and no patterns were observed in the missing data points. These missing data points were not replaced or imputed, and missing data points were coded to indicate the data point was missing.

Several salivary cortisol levels in the NPE dataset that are relevant for the current study were observed to be at the limit of detection (LOD<0.2 ng/ml). The value of these data is between zero and the LOD. Replacing these values with zero or managing them incorrectly may introduce bias in data analysis (Croghan & Egeghy, 2003; Johnson, 2018). Where the proportion of data below the LOD is less than 10%, a simple imputation may be used without introducing
significant bias (Lubin et al., 2004). Thus, all LOD data in the dataset were replaced with the single value, 0.14, calculated using the formula, LOD/√2. This formula considers the variance of values below the LOD and is recommended (Croghan & Egeghy, 2003; Johnson, 2018).

Data Analysis

The data analysis plan for this study’s aims and hypotheses are described below. In addition to addressing study aims and hypotheses, descriptive analysis were planned to provide a summary of parent and infant subject characteristics. Data were analyzed using the SPSS® 28.0, a statistical software program.

Aim 1: Hypothesis and Analysis

Aim 1: Determine whether there are significant associations between parent presence, measured in hours per week and days per week, and NICU infant stress response, as measured by salivary cortisol.

Hypothesis 1: Parent presence measured in hours per week is significantly associated with NICU infant stress response, as measured by salivary cortisol.

Hypothesis 2: Parent presence measured in days per week is significantly associated with NICU infant stress response, as measured by salivary cortisol.

After confirming normality of the data, aim one was analyzed using correlational statistics. Relationships observed in this analysis were considered descriptive, as these associations do not suggest causality (Tappen, 2016).

Aim 2: Hypothesis and Analysis

Aim 2: Determine whether there are significant associations between increased SSC, measured in hours per week and days per week, and reductions in NICU infant stress response, as measured by salivary cortisol.
Hypothesis 3: Increased SSC measured in hours per week is significantly associated with reductions in NICU infant stress response, as measured by salivary cortisol.

Hypothesis 4: Increased SSC measured in days per week is significantly associated with reductions in NICU infant stress response, as measured by salivary cortisol.

After confirming normality of data, aim two was also analyzed using correlational statistics. Associations observed were considered descriptive and not suggestive of causality.

**Aim 3: Hypothesis and Analysis**

Aim 3: Determine the independent explanatory contribution of parent presence, SSC, and infant’s level of illness to NICU infant stress response, as measured by salivary cortisol.

Hypothesis 5: Parent presence (hours per week), SSC (hours per week), and infant’s level of illness significantly contribute to explaining NICU infant stress response, as measured by salivary cortisol.

Hypothesis 6: Parent presence (days per week), SSC (days per week), and infant’s level of illness significantly contribute to explaining NICU infant stress response, as measured by salivary cortisol.

Hypothesis 7: Controlling for infant’s level of illness and salivary cortisol at admission, the timing of parent presence in hours per week over the first four weeks of life significantly contributes to explaining NICU infant stress response, as measured by salivary cortisol at NICU discharge.

Hypothesis 8: Controlling for infant’s level of illness and salivary cortisol at admission, the timing of parent presence in days per week over the first four weeks of life significantly contributes to explaining NICU infant stress response, as measured by salivary cortisol at NICU discharge.
Hypothesis 9: Controlling for infant’s level of illness and salivary cortisol at admission, the timing of SSC in hours per week over the first four weeks of life significantly contributes to explaining NICU infant stress response, as measured by salivary cortisol at NICU discharge.

Hypothesis 10: Controlling for infant’s level of illness and salivary cortisol at admission, the timing of SSC in days per week over the first four weeks of life significantly contributes to explaining NICU infant stress response, as measured by salivary cortisol at NICU discharge.

Multiple linear regression was used to examine potential relationships between infant stress response and parent presence, skin-to-skin holding, and infant level of illness for hypotheses five and six. Hierarchical multiple linear regression was used to examine hypotheses seven through ten examining potential relationships between infant stress response and parent presence in the NICU for weeks one through four of life, controlling for infant NMI score and salivary cortisol at admission. Where relationships were detected, these were considered descriptive and not indicative of causality (Tappen, 2016).

**Protection of Human Subjects**

**Institutional Review Board Application**

The NPE study was approved by the Ann and Robert H. Lurie Children’s Hospital’s Institutional Review Board (IRB). Human subjects were protected in the NPE study in that written informed consent was obtained for each family member enrolled in the study. All consents were conducted in single-family rooms, which provided privacy for individual families during consent discussions. The NPE study remains open with the Lurie IRB for analysis and publication, and the results of the study remain unpublished.

The current study, consisting of a secondary analysis of an existing dataset, was approved by Loyola University’s IRB. A letter documenting this approval is provided in Appendix C.
Risks

The secondary data analysis conducted in this study did not change the risk level for subjects that completed their participation in the NPE study. However, risks to parent and infant subjects in the NPE study were minimal. Saliva for salivary cortisol levels was collected by placing a small oral swab in the infants’ mouths. This procedure was not observed to be uncomfortable. There were no negative consequences for parents that were not able to or chose not to visit their baby daily.

Although risks of breach of privacy and confidentiality existed in the NPE study, the private room lay-out of the NICU provided privacy for informed consent and parent interviews conducted to obtain parent demographic information. Parents may have been uncomfortable disclosing demographic data such as relationship status or educational level. This was not observed or reported by parents.

All subjects were assigned a study number, allowing study data to be kept confidential. Study numbers were used on all study documents, and a file linking study numbers to subject identifiers is stored separately from study data in a password protected computer file. NPE study data is maintained in a password protected computer database and in a locked file cabinet in a locked office at the original study site.

As I am the principal investigator of the NPE study, permission to use de-identified data from the NPE study was not required. A separate computer database was used for the current study. It contains only de-identified subject data and is maintained in a password protected computer file with no relationship to the original study.
Benefits

There were no benefits for families that participated in the NPE study. The goal of the NPE study was to obtain information that could be helpful to NICU families in the future. There were no benefits of the current study to the de-identified subjects in the dataset.

Limitations

Limitations are inherent to the use of a secondary analysis of an existing dataset to address new research questions, aims and hypotheses (Tappen, 2016). When an existing dataset is used to answer specific research questions, it may lack some information that would be useful in addressing new research questions. This was the case in the current study in that the NPE dataset did not provide information about variables that may have impacted infant cortisol levels, such as medications, and did not include other measures of infant stress or stressor exposure. With the exception of SSC, the quality of parent-infant relationships occurring during times of parent presence was not measured in the NPE study. In addition, parent presence and SSC data for mothers and fathers was combined in the NPE dataset.

In the Polyvagal theory Porges (1995) proposes that social buffering may down-regulate stress via regulation of the autonomic nervous system. While salivary cortisol also reflects the regulation of stress, it is a measure reflecting HPA activity, and its use to measure stress in a study grounded in the Polyvagal theory is a limitation. Also, use of a single resting salivary cortisol measure versus a measure of cortisol reactivity to a specific stressor is a limitation in that one measure may not accurately reflect a NICU infant’s stress response to cumulative stressor exposures over time.

The sample represented in an existing database may also be a disadvantage to performing a secondary analysis (Tappen, 2016). Combining pre-intervention and post-intervention groups
in the current study is a limitation related to the use of the NPE dataset in this study, and although no significant differences in parent presence were observed between groups, parents and infants may have been impacted by the intervention or subtle changes in the setting that occurred over the study period. The potential for selection bias and the heterogeneity of the infants represented in the NPE dataset is also a limitation in the current study in that subtle infant differences not considered in the dataset may have impacted infant stress response. Finally, some NICU infants in the dataset were discharged home earlier than one month of life, and their discharge cortisol levels did not reflect NICU stressor exposures for one month.

**Summary**

The purpose of this study was to examine the impact of parent presence on the stress response of NICU infants that results from cumulative NICU-related stressor exposures. A secondary analysis of an existing dataset was conducted to address this study’s research questions and hypotheses. Results of this secondary analysis included a summary of sample characteristics and detailed results for each research question, aim and hypothesis. These results are reported in the following chapter.
CHAPTER FOUR

RESULTS

Introduction

Infants in neonatal intensive care units (NICUs) are at significant risk for adverse neurodevelopmental outcomes (Cheong et al., 2017; Schieve et al., 2016). In the NICU, infants are exposed to frequent stressors, including separation from parents, during sensitive periods in development. These cumulative stressor exposures contribute to the adverse neurodevelopmental outcomes observed in this population (Cong et al., 2017; Smith et al., 2011). Developmentally supportive care (DSC) programs and practices emphasize infant stress reduction and endorse parent presence as critical for improving NICU infant outcomes (Coughlin, 2021), and in the Polyvagal theory Porges (1995) proposed that stress responses may be down-regulated in the presence of buffering social relationships. While skin-to-skin care (SSC) is often measured in DSC studies, parent presence is infrequently considered by investigators of DSC. NICU parent presence may represent aspects of the parent-infant social relationship not previously considered.

The results of a descriptive, correlational study examining the impact of parent presence and SSC on the stress response of infants to cumulative NICU-related stressor exposures are presented in this chapter. A secondary analysis of data from an existing dataset was conducted to address study aims. Data analyses were conducted using Statistical Package for the Social Sciences 28.0 software. Following a description of sample demographics, descriptive statistics are presented for each study variable. Results for the following three study aims and
associated hypotheses are also presented. The aims and associated hypotheses for this study were:

Aim 1: Determine whether there are significant associations between parent presence, measured in hours per week and days per week, and NICU infant stress response, as measured by salivary cortisol.

Hypothesis 1: Parent presence measured in hours per week is significantly associated with NICU infant stress response, as measured by salivary cortisol.

Hypothesis 2: Parent presence measured in days per week is significantly associated with NICU infant stress response, as measured by salivary cortisol.

Aim 2: Determine whether there are significant associations between increased SSC, measured in hours per week and days per week, and reductions in NICU infant stress response, as measured by salivary cortisol.

Hypothesis 3: Increased SSC measured in hours per week is significantly associated with reductions in NICU infant stress response, as measured by salivary cortisol.

Hypothesis 4: Increased SSC measured in days per week is significantly associated with reductions in NICU infant stress response, as measured by salivary cortisol.

Aim 3: Determine the independent explanatory contribution of parent presence, SSC, and infant’s level of illness to NICU infant stress response, as measured by salivary cortisol.

Hypothesis 5: Parent presence (hours per week), SSC (hours per week), and infant’s level of illness significantly contribute to explaining NICU infant stress response, as measured by salivary cortisol.
Hypothesis 6: Parent presence (days per week), SSC (days per week), and infant’s level of illness significantly contribute to explaining NICU infant stress response, as measured by salivary cortisol.

Hypothesis 7: Controlling for infant’s level of illness and salivary cortisol at admission, the timing of parent presence in hours per week over the first four weeks of life significantly contributes to explaining NICU infant stress response, as measured by salivary cortisol at NICU discharge.

Hypothesis 8: Controlling for infant’s level of illness and salivary cortisol at admission, the timing of parent presence in days per week over the first four weeks of life significantly contributes to explaining NICU infant stress response, as measured by salivary cortisol at NICU discharge.

Hypothesis 9: Controlling for infant’s level of illness and salivary cortisol at admission, the timing of SSC in hours per week over the first four weeks of life significantly contributes to explaining infant stress response, as measured by salivary cortisol at NICU discharge.

Hypothesis 10: Controlling for infant’s level of illness and salivary cortisol at admission, the timing of SSC in days per week over the first four weeks of life significantly contributes to explaining NICU infant stress response, as measured by salivary cortisol at NICU discharge.

Sample

The study’s aims and hypotheses were addressed via a secondary analysis of data from an existing dataset, and the sample represented in this dataset is described. The dataset employed includes data from NICU parents and infants collected for a NICU Parent Engagement (NPE) study that was conducted in a tertiary level NICU in a Midwestern children’s hospital. The dataset includes data for 78 NICU infants, their mothers and 35 of their fathers enrolled in the
NPE study. Parent presence data, SSC, infant salivary cortisol levels, and parent and infant
demographic data from all infants and parents enrolled in the NPE study were used in the current
study. The NPE study is summarized in Appendix B.

Sample Characteristics

Infant demographic data from the NPE dataset used in this study included gestational
age, birth weight, gender, age in days at NICU discharge, and Neonatal Medical Index (NMI)
scores that reflected the infant’s level of illness. The NPE study dataset included data from
families of 41 term (53%) and 37 preterm infants (47%) born at greater than or equal to 28 weeks
gestation. The mean (SD) gestational age of NICU infants represented in the dataset was 36.01
(3.5) weeks with a mean (SD) birth weight of 2.69 (0.86) kilograms. More female infants (54%)
than male infants (46%) were represented. The median infant age at discharge was 33 days with
an interquartile range (IQR) of 39.25 days. NMI scale scores ranged from one to five, with a
score of five indicating that an infant was among those with the most severe levels of illness
(Korner et al., 1993). The median NMI score for infants in the NPE dataset was four (IQR=2). A
summary of infant demographic data is provided in Table 2.
Table 2. Characteristics of Infants in Dataset

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SD)</th>
<th>Median (IQR)</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age</td>
<td>36.01 (3.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birthweight</td>
<td>2.69 (0.86)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discharge age</td>
<td>33 (39.25)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neonatal Medical Index</td>
<td>4 (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender Female/Male</td>
<td>54% / 46%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The NPE dataset included data from 40 NICU families from a pre-NPE intervention group and 38 NICU families from a post-NPE study intervention group. Combining the data from all 78 families in the NPE dataset was planned, thus, examining the pre-intervention and post-intervention datasets for significant differences between groups was necessary. No significant differences in infant gestational age (t=0.03, p=.98), birthweight (t= -0.41, p=.69), gender (X²=0.44, p=.51), age in days at discharge (t=0.27, p=.79), and NMI scores (U=687, p=.45) were identified between groups. Significant differences in the hours of parent presence (t= -0.91, p=.37) and hours of SSC (t= -0.07, p=.95) over the first month of life were not identified. The absence of significant differences between pre-intervention and post-intervention groups in the NPE dataset supported use of the combined dataset in this study. Table 3 summarizes comparisons of the NPE groups.
Table 3. Comparison of NPE Pre-intervention and Post-intervention Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SD)</th>
<th>Test Statistic (df)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age (weeks)</td>
<td>Pre 36.03 (3.75)</td>
<td>t(76)=.03</td>
<td>p=.98</td>
</tr>
<tr>
<td></td>
<td>Post 36 (3.28)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birthweight (kilograms)</td>
<td>Pre 2.65 (0.78)</td>
<td>t(76)= -.41</td>
<td>p=.69</td>
</tr>
<tr>
<td></td>
<td>Post 2.73 (0.94)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender female/male</td>
<td>Pre 57.5% / 42.5%</td>
<td>X²(1)=.44</td>
<td>p=.51</td>
</tr>
<tr>
<td></td>
<td>Post 50% / 50%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discharge age (days)</td>
<td>Pre 48.2 (45.4)</td>
<td>t(76)=.27</td>
<td>p=.79</td>
</tr>
<tr>
<td></td>
<td>Post 45.4 (45.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neonatal medical index</td>
<td>Pre 3.73 (1.22)</td>
<td>U=687</td>
<td>p=.45</td>
</tr>
<tr>
<td></td>
<td>Post 3.5 (1.31)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parent presence (hours)</td>
<td>Pre 129.1 (83.1)</td>
<td>t(76)= -.91</td>
<td>p=.37</td>
</tr>
<tr>
<td></td>
<td>Post 145.6 (77.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin-to-skin care (hours)</td>
<td>Pre 5.44 (9.1)</td>
<td>t(76)= -.07</td>
<td>p=.95</td>
</tr>
<tr>
<td></td>
<td>Post 5.59 (10.87)</td>
<td></td>
<td></td>
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</tbody>
</table>

Descriptive Analysis of Study Variables

Descriptive analyses of study variables provide numerical descriptions of study variables that are essential to examining the central tendency, dispersion and normality of study data (Tappen, 2016). Variables of interest in the current study included infant stress response, as measured by salivary cortisol, parent presence, SSC and infant level of illness, as measured by the NMI. Descriptive analyses of these study variables is presented in the following section.
Infant Stress Response

Infant stress response was operationally defined as a resting infant salivary cortisol level measured at one point in time, at discharge from the NICU (median=33 days of age), or at one month of age for infants not discharged at or before one month of age. These salivary cortisol levels are collectively referred to as infant salivary cortisol data at NICU discharge throughout this document. Seventeen (22%) missing data points were identified in the infant salivary cortisol data at NICU discharge. Missing salivary cortisol data resulted from unanticipated infant discharge, sample contamination or insufficient quantities of saliva. These missing data points were not imputed or replaced, resulting in 61 infant salivary cortisol levels available for analysis.

In this study, infant salivary cortisol levels at NICU discharge ranged from 0.14 to 13.16 nanograms per liter (ng/ml) with a mean (SD) 1.83 ng/ml (2.58 ng/ml). Examination of the histogram for infant salivary cortisol data revealed a positively skewed distribution. A review of the Q-Q plot revealed a non-normal distribution, that was confirmed via a Kolmogorov-Smirnov (KS) test (D(61)=0.31, p<.001). An examination of the stem and leaf plot for salivary cortisol levels at discharge identified 9 cases with higher cortisol results. Following a review of the dataset, these cases were retained as they did not disproportionally represent infants discharged after one month of age and represented natural variations in cortisol.

Measurements of infant stress response using salivary cortisol are susceptible to issues with normality, and following an examination of outliers, data transformations are frequently required (Tryphonopoulos et al., 2014). To address normality issues, the salivary cortisol data in this study were log transformed. Transformation resulted in improved normality of salivary cortisol levels measured at NICU discharge, as examined using the KS test (D(61)=.11, p<.08) and inspection of the post-transformation Q-Q plot (see Figure 1).
Infant Level of Illness

Consistent with the NPE dataset, infant level of illness was operationally defined as the infant’s NMI score (Korner et al., 1993). The NMI score reflects an infant’s level of illness at baseline and throughout the NICU stay. NMI scores range from one to five, with higher scores indicating that an infant has more medical morbidities. No missing NMI data were observed. NMI scores ranged from one to five, with a median score of four (IQR=2). Skewness and kurtosis values were within normal limits, and an inspection of the Q-Q plot indicated a normal distribution of NMI data.
Parent Presence

Parent presence was operationally defined as the amount of time one or both parents were with their infant in the NICU in hours per week and in days per week through NICU discharge (median age at discharge=33 day) or over the first month of life for infants discharged later. As parent presence data was operationally defined in hours and days per week, data from the first four weeks of life were used. Some infants in the NPE dataset were discharged prior to one month of age, thus, their data does not include hours or days per week for all four weeks considered in this study. Incomplete parent presence data due to early infant discharge was coded as not applicable, and to preserve power, pair-wise exclusion of cases was considered for data analysis involving parent presence where applicable.

**Hours per Week.** In the NPE dataset, parent presence data were reported as combined data for mothers and fathers. The range of cumulative parent presence in hours over the first four weeks of life, including infants discharged early, ranged from 28 to 466.25 total hours with a mean (SD) 137.11 (80.26) hours. Skewness and kurtosis values were within normal limits (+3 to -3) and inspection of the Q-Q plot for hours per week of parent presence indicated that data were normally distributed.

Parent presence in the NICU in mean hours per week ranged from 34.9 to 44.92 hours in weeks one to four of life. Parent presence increased over the infants’ first two weeks of life from a mean of 38.5 (SD=22.36) hours per week in week one to 44.92 (SD=25.07) hours per week in week two. In the following weeks of the infants’ NICU stay, parent presence decreased from a mean of 40.05 hour per week (SD=23.88) in week three to a mean of 34.9 hours per week (SD=25.18) in week four. This decrease in parent presence over time is consistent with the
findings of several studies reporting parent presence in the NICU (Garten et al., 2011; Kim et al., 2021; Pineda et al., 2012).

**Days per Week.** Parent presence in days per week represented the frequency of parent presence over the first four weeks of life and was measured using the percentage of days parents were present for any amount of time per week. The range of cumulative parent presence in days per week over the first four weeks of life ranged from 35.7% to 100% of days in the NICU with a mean (SD) of 91.1% (13.8%) days. Weekly parent presence in mean days per week ranged from 88% to 93.5% of days for weeks one to four of a NICU infants’ life. The highest mean frequency of parent presence was observed in week two (93.5%), and the lowest mean frequency of parent presence was observed in week four (88%).

Examination of the histogram for parent presence in days per week revealed a negatively skewed distribution that was impacted by a large number of 1.0 percent proportions. Visual inspection of the Q-Q plot for parent presence in days per week and results of a KS test indicated that the data did not follow a normal distribution. In addition, ten outlier cases with low parent presence in days per week were identified, reviewed and retained, in that these low values for parent presence were found to be consistent with normal variations. In multivariate studies using percent proportion data, a prevalence of zero and one scores may make data transformation problematic (Holland, 2017), thus the use of non-parametric tests or robust statistical procedures, such as bootstrapping, was planned.

**Skin-to-skin Care**

SSC was operationally defined as the amount of time parents participated in SSC with their NICU infant in hours per week and in days per week through NICU discharge (median age at discharge=33 day) or during the first month of life for infants discharged later. SSC data from
the first four weeks of life was used in this study. Because some infants in the NPE dataset were discharged prior to one month of age, their SSC data does not include hours or days per week for all four weeks considered in this study. Incomplete SSC data due to early infant discharge were coded as not applicable, and a pair-wise exclusion of cases was employed where appropriate.

**Hours per Week.** In the NPE dataset SSC data were reported as combined data for mothers and fathers. Cumulative SSC hours over the first four weeks of life, including infants discharged early, ranged from zero to 52 total hours with a mean (SD) 5.52 hours (9.93). Due to large numbers of infants not receiving SSC in the NICU (N=39), inspection of the histogram for SSC in hours per week revealed a positively skewed distribution. Examination of the Q-Q plot and KS test indicated that the data did not follow a normal distribution. Thus, the use of non-parametric or robust statistical procedures was planned.

Seven outlier cases representing infants with more hours of SSC were reviewed and retained as they were found to represent normal variations in the amount SSC. No significant trends in cumulative hours of SSC over time were identified. Mean hours of SSC per week ranged from 1.29 to 1.81 hours in weeks one to four of life.

**Days per Week.** SSC in days per week was measured using the percent of days parents were involved in SSC with their infants for any amount of time per week. The range of cumulative SSC in days per week over the first four weeks of life ranged from zero to 67.9% of days in the NICU with a mean (SD) of 8.63% (13.5%). Due to the large number of infants with no reported SSC (SSC=0), examination of the histogram for SSC in days per week revealed a positively skewed distribution. A KS test of cumulative frequency of parent presence in days per week indicated that the data did not follow a normal distribution. This was confirmed via
examination of the Q-Q plot. Therefore, the use of non-parametric or robust statistical procedures such as bootstrapping was planned.

Three outlier cases with more days of SSC were identified using the stem and leaf plot. These cases were found to represent normal variations in SSC frequency and were retained. No significant trends in SSC in days per week over time were identified.

**Results of Analyses of Study Aims**

The purpose of this study was to examine the impact of parent presence and SSC on the stress response of NICU infants that results from cumulative NICU-related stressor exposures. Correlational and regression analyses were employed to address study aims. Where appropriate, parametric tests were employed. To address violations of assumptions, including the non-normality of some study variables, bootstrapping was applied to parametric analyses to provide more robust statistical testing, and in some analyses non-parametric tests were used. A review of results of hypothesis testing for each study aim follows.

**Aim 1**

The first aim was to examine potential relationships between parent presence, measured in hours per week and days per week, and NICU infant stress response, as measured by salivary cortisol. Two hypotheses were established for this aim. The focus of one hypothesis was the potential relationship between NICU infant stress response and parent presence in hours per week, while the focus of the second hypothesis was the potential relationship between infant stress response and parent presence in days per week.

**Hypothesis 1.** The first hypothesis was: parent presence measured in hours per week is significantly associated with NICU infant stress response, as measured by salivary cortisol. As the log transformed salivary cortisol data and parent present data met the assumptions of linearity
and normality, a Pearson’s correlation with a two-tailed test of significance was selected to test this hypothesis. The small positive correlation resulting from this analysis did not support a significant association between hours of parent presence per week and infant stress, as measured by salivary cortisol at NICU discharge (r=.11, 95% CI= -0.15, 0.35, p=.39).

**Hypothesis 2.** The second hypothesis was: parent presence measured in days per week is significantly associated with NICU infant stress response, as measured by salivary cortisol. Upon inspection, a linear relationship between these variables was observed. However, the dataset for parent presence in days per week was not normally distributed, and there was a prevalence of percent proportion data equal to one for parent presence data. Therefore, both a Pearson correlation with bootstrapping and a Spearman correlation were assessed at a two-tailed level of significance. Neither the results of the Pearson correlation with bootstrapping (r=.06, 95% CI= -0.15, .23, p=.63), nor results of the Spearman correlation (r_s=.03, p=.8), supported a significant association between parent presence in days per week and NICU infant stress at discharge.

**Aim 2**

In the second aim potential relationships between SSC and stress in NICU infants, as measured by salivary cortisol at NICU discharge were examined. Two hypotheses were addressed in this aim. The first hypothesis addressed a potential association between increased SSC in hours per week and reductions in NICU infant stress response, and the second addressed a potential association between more SSC measured in days per week and reductions in infant stress response.

**Hypothesis 3.** The third hypothesis was: increased SSC measured in hours per week is significantly associated with reductions in NICU infant stress response, as measured by salivary cortisol. Due to a non-normal distribution with a large number of zero values for SSC in hours
per week, a one-tailed test of significance using Pearson correlation with bootstrapping and Spearman’s rho correlation were conducted to address this hypothesis. Cumulative hours of SSC over the first four weeks of life in the NICU were negatively correlated with infant stress response at discharge assessed using the Pearson correlation with bootstrapping (r = -0.15, 95% CI= -0.31, 0.05, p= .13) and Spearman’s rho (rs = -0.25, p= .03), however, only the Spearman’s rho correlation supports a significant association between more SSC and lower levels of infant stress at discharge.

**Hypothesis 4.** The fourth hypothesis was: SSC measured in days per week is significantly associated with NICU infant stress response, as measured by salivary cortisol. To address the lack of normality with a large number of zero values in the SSC data, a one-tailed test of significance using the Pearson correlation with bootstrapping and Spearman’s rho were selected to address this hypothesis. A significant negative correlation between cumulative SSC measured in days per week and infant stress response at NICU discharge was identified using Spearman’s rho (rs = -0.21, p= .05). A small negative association identified using the Pearson correlation with bootstrapping was not significant (r = -0.12, 95% CI= -0.307, 0.12, p= .18). Results of the Spearman correlational analysis supports an association between increased SSC measured in days per week and reduced infant stress response at NICU discharge.

**Aim 3**

The third aim of this study was to determine the independently explanatory contribution of parent presence, SSC, and infant’s level of illness to NICU infant stress response, as measured by salivary cortisol. Six hypotheses were addressed for this aim. In the first two hypotheses, the independent explanatory contribution of cumulative parent presence and SSC, measured by hours per week or days per week, and infant’s level of illness to NICU infant stress response at
discharge was examined. The last four hypotheses focused on whether the timing of parent presence or SSC over weeks one to four of life explains NICU infant stress response at discharge, controlling for infant’s level of illness and infant salivary cortisol on admission.

Multiple linear regression was used to test these hypotheses. This analysis began with an examination of assumptions for each regression analyses. A summary of linear regression assumptions for each hypothesis in aim three is provided in table 4. Scatterplots between variables of interest for each hypothesis were examined to assess linearity.

**Table 4. Summary of Linear Regression Tests of Assumptions by Hypothesis**

<table>
<thead>
<tr>
<th>Hypothesis</th>
<th>Variance Inflation Factor</th>
<th>Tolerance</th>
<th>Autocorrelation</th>
<th>Standardized Residuals for Outliers (# of cases)</th>
<th>Normality/Homoscedasticity</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>1.05-1.09</td>
<td>.91-.96</td>
<td>2.03</td>
<td>2.2 (1)</td>
<td>No/No</td>
</tr>
<tr>
<td>6</td>
<td>1.03-1.06</td>
<td>.94-.97</td>
<td>2.03</td>
<td>2.15 (1)</td>
<td>No/No</td>
</tr>
<tr>
<td>7</td>
<td>1.1-4.95</td>
<td>.20-.91</td>
<td>2.13</td>
<td>2.49 (1)</td>
<td>Yes/Yes</td>
</tr>
<tr>
<td>8</td>
<td>1.23-4.45</td>
<td>.23-.8</td>
<td>2.03</td>
<td>2.1-2.2 (2)</td>
<td>No/No</td>
</tr>
<tr>
<td>9</td>
<td>1.11-3.9</td>
<td>.26-.9</td>
<td>1.79</td>
<td>2.31 (1)</td>
<td>No/No</td>
</tr>
<tr>
<td>10</td>
<td>1.14-3.15</td>
<td>.32-.88</td>
<td>1.95</td>
<td>2.32 (1)</td>
<td>No/No</td>
</tr>
</tbody>
</table>

Note. Assessment of normality and homoscedasticity for all variables in hypothesis regression model represented in column 6.

Each regression analysis was assessed for multicollinearity using variance inflation factor (VIF) and tolerance statistics for every variable pair. A VIF greater than 10 or a tolerance statistic less than 0.2 indicate potential multicollinearity issues (Field, 2016). The ranges of VIF
and tolerance statistics for the six hypotheses tested for this aim were 1.03 to 4.95 and 0.20 to 0.97 respectively, indicating that there were no significant multicollinearity issues.

Independence of errors, or autocorrelation, was assessed using the Durbin-Watson test. Durbin-Watson values near two indicate that residuals are not correlated (Field, 2016). The range of Durbin-Watson values for all hypotheses examined for this aim were 1.8 to 2.03, indicating no significant autocorrelation of residuals.

The potential impact of outliers in the regression analyses were assessed using standardized residuals. Per Field (2016) less than five percent of cases should have a standardized residual greater than two. The percent of cases per hypothesis with standardized residual values greater than two ranged from 1.6% to 5.1%, indicating that the models resulting from the regression analyses were not significantly impacted by outliers.

The lack of normality for independent variables including parent presence and SSC measured in days per week, as well as SSC measured in hours per week, was previously described. Homoscedasticity was examined using scatterplots of residuals against the dependent variable. Scatterplots indicated that some independent variables may be in violation of the assumption of homoscedasticity. Thus, with one exception bootstrapping was applied to each regression analysis, because bootstrapped significance values and confidence intervals do not rely on normality and homoscedasticity assumptions. Bootstrapping was not employed in analyzing hypothesis seven as normality and homoscedasticity assumptions were met for all variables included.

**Hypothesis 5.** The fifth hypothesis was: parent presence (hours per week), SSC (hours per week), and infant’s level of illness significantly contribute to explaining NICU infant stress response, as measured by salivary cortisol. This hypothesis was assessed using multiple linear
regression with pairwise deletion. Due to missing cortisol infant data, the sample size for this hypothesis was 61.

Results of regression analysis indicated that a model including cumulative parent presence and SSC, measured in hours per week across the first four weeks of life, and infant’s level of illness, measured using the NMI, did not significant contribute to explaining infant stress response at NICU discharge, as measured by salivary cortisol ($R^2=.05$, $F(3,57)=0.99$, $p=.4$). As detailed in table 5, none of the variables in this model explained infant stress at discharge. Thus, the fifth study hypothesis was not supported.

Table 5. Linear Regression: Infant Stress and Cumulative Hours per Week of Presence and SSC

<table>
<thead>
<tr>
<th>Model</th>
<th>Unstandardized Beta</th>
<th>Standardized Beta</th>
<th>p value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>-.25</td>
<td></td>
<td>.32</td>
<td>-.71, .21</td>
</tr>
<tr>
<td>NMI</td>
<td>.04</td>
<td>.1</td>
<td>.48</td>
<td>-.07, .16</td>
</tr>
<tr>
<td>Parent presence</td>
<td>.001</td>
<td>.12</td>
<td>.41</td>
<td>-.001, .002</td>
</tr>
<tr>
<td>SSC</td>
<td>-.01</td>
<td>-.18</td>
<td>.03</td>
<td>-.02, .001</td>
</tr>
</tbody>
</table>

Note. Confidence intervals and p values based on 1000 bootstrap samples. NMI = Neonatal Medical Index, SSC = Skin-to-skin care.

**Hypothesis 6.** The sixth hypothesis was: parent presence (days per week), SSC (days per week), and infant’s level of illness significantly contribute to explaining NICU infant stress response, as measured by salivary cortisol. This hypothesis was examined using multiple linear regression with pairwise deletion. The sample size of infants for this hypothesis was 61.

Results of the analysis indicated that a model including cumulative parent presence and SSC, measured in days per week across the first four weeks of life, and infant’s NMI score, did
not significant contribute to explaining infant stress response at NICU discharge ($R^2=.03$, $F(3,57)=0.62$, $p=.61$). As presented in table 6, no variables were significant in explaining infant stress response at discharge. Therefore, hypothesis six was not supported.

Table 6. Linear Regression: Infant Stress and Cumulative Days per Week of Presence and SSC

<table>
<thead>
<tr>
<th>Model</th>
<th>Unstandardized Beta</th>
<th>Standardized Beta</th>
<th>p value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>-.3</td>
<td></td>
<td>p=.43</td>
<td>-1.11, .47</td>
</tr>
<tr>
<td>NMI</td>
<td>.05</td>
<td>.12</td>
<td>p=.42</td>
<td>-.06, .17</td>
</tr>
<tr>
<td>Parent presence</td>
<td>.12</td>
<td>.04</td>
<td>p=.74</td>
<td>-.79, .90</td>
</tr>
<tr>
<td>SSC</td>
<td>-.52</td>
<td>-.14</td>
<td>p=.19</td>
<td>-1.37, .45</td>
</tr>
</tbody>
</table>

Note. Confidence intervals and p values based on 1000 bootstrap samples. NMI = Neonatal Medical Index, SSC = Skin-to-skin care.

**Hypothesis 7.** Hypothesis seven was: controlling for infant’s level of illness and salivary cortisol at admission, the timing of parent presence in hours per week over the first four weeks of life significantly contributes to explaining NICU infant stress response, as measured by salivary cortisol. A hierarchical multiple linear regression was selected to address this hypothesis. List-wise deletion was selected to include only those cases with recorded parent presence over each of the four weeks to be examined in the analysis. The sample size of 39 cases available for this analysis was impacted by missing salivary cortisol data at admission and infants discharged prior to four weeks of life.

In the first step of this analysis the covariates, level of illness (NMI scores) and salivary cortisol levels at admission, were analyzed. To maintain consistency of cortisol data, admission
salivary cortisol levels were log transformed. Analysis of this first model revealed a non-significant model (p=.07) explaining 14% of the variance in infant stress response at discharge.

In step two of the analysis parent presence in hours per week for the first week of life was added. This analysis also resulted in a non-significant model (p=.11) explaining 16% of the variance in infant stress response at discharge, indicating that 84% of the variance in resting infant cortisol level at discharge was not explained by the variables included in this model.

During the third step of analysis parent presence in hours per week for week two of life was added to the model. This model was significant (p=.01) with a 17% increase in R² indicating that the model explained 33% of the variance in infant salivary cortisol at NICU discharge (R²=.33, F(4,34)=4.14, p=.008). One significant variable, parent presence in hours per week during week two of life, was identified in this model (β=0.81, 95% CI=0.01, 0.03, p=.01).

In step four, parent presence during week three was added to the model. Analysis revealed a significant model that improved the R² by 10% (R²=.43, F(5,33)=4.95, p=.002). Three model variables were significant including infant’s level of illness (β=0.35, 95% CI= 0.03, 0.33, p=.02), parent presence during week two (β=1.15, 95% CI= 0.01, 0.04, p<.001), and parent presence during week three (β= -0.56, 95% CI= -0.02, -0.002, p=.02).

Parent presence for week four was added in step five of the regression. Results of this model were also significant and were similar to those in step four. Week four parent presence was not a significant variable. This analysis supports the hypothesis that infant’s level of illness and the timing of parent presence contribute to explaining NICU infant stress response at discharge, although more parent presence in week two explained greater stress at discharge, and more presence in week three explained reduced stress response at NICU discharge. This analysis is summarized in table 7.
Table 7. Hierarchical Linear Regression: Infant Stress and Parent Presence in Hours per Week

<table>
<thead>
<tr>
<th>Model Step/Variable</th>
<th>B</th>
<th>SE</th>
<th>B</th>
<th>p</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1: R²=.14, F=2.87, p=.07</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constant</td>
<td>-.64</td>
<td>.32</td>
<td>.05</td>
<td>-1.30, .01</td>
<td></td>
</tr>
<tr>
<td>Admission cortisol</td>
<td>.15</td>
<td>.13</td>
<td>.18</td>
<td>.27</td>
<td>-.12, .41</td>
</tr>
<tr>
<td>Neonatal medical index</td>
<td>.15</td>
<td>.08</td>
<td>.29</td>
<td>.08</td>
<td>-.02, .31</td>
</tr>
<tr>
<td>Step 2: R²=.16, F=2.156, p=.11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constant</td>
<td>-.72</td>
<td>.34</td>
<td>.04</td>
<td>-1.41, -.04</td>
<td></td>
</tr>
<tr>
<td>Admission cortisol</td>
<td>.15</td>
<td>.13</td>
<td>.19</td>
<td>.24</td>
<td>-.11, .42</td>
</tr>
<tr>
<td>Neonatal medical index</td>
<td>.14</td>
<td>.08</td>
<td>.26</td>
<td>.11</td>
<td>-.03, .31</td>
</tr>
<tr>
<td>Week 1 parent hours/week</td>
<td>.003</td>
<td>.004</td>
<td>.14</td>
<td>.39</td>
<td>-.004, .01</td>
</tr>
<tr>
<td>Step 3: R²=.33, F=4.14, p=.008</td>
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<td></td>
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<tr>
<td>Constant</td>
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<td>.31</td>
<td>.01</td>
<td>-1.42, -.18</td>
<td></td>
</tr>
<tr>
<td>Admission cortisol</td>
<td>.20</td>
<td>.12</td>
<td>.24</td>
<td>.11</td>
<td>-.04, .44</td>
</tr>
<tr>
<td>Neonatal medical index</td>
<td>.13</td>
<td>.08</td>
<td>.24</td>
<td>.11</td>
<td>-.03, .28</td>
</tr>
<tr>
<td>Week 1 parent hours/week</td>
<td>-.01</td>
<td>.01</td>
<td>.55</td>
<td>.05</td>
<td>-.03, .00</td>
</tr>
<tr>
<td>Week 2 parent hours/week</td>
<td>.02</td>
<td>.01</td>
<td>.81</td>
<td>.01</td>
<td>.01, .03</td>
</tr>
<tr>
<td>Step 4: R²=.43, F=4.95, p=.002</td>
<td></td>
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<td></td>
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<tr>
<td>Constant</td>
<td>-.95</td>
<td>.29</td>
<td>.003</td>
<td>-1.55, -.35</td>
<td></td>
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<tr>
<td>Admission cortisol</td>
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<td>.11</td>
<td>.21</td>
<td>.14</td>
<td>-.06, .39</td>
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<tr>
<td>Neonatal medical index</td>
<td>.18</td>
<td>.08</td>
<td>.35</td>
<td>.02</td>
<td>.03, .33</td>
</tr>
<tr>
<td>Week 1 parent hours/week</td>
<td>-.01</td>
<td>.01</td>
<td>-.44</td>
<td>.10</td>
<td>-.02, .002</td>
</tr>
<tr>
<td>Week 2 parent hours/week</td>
<td>.02</td>
<td>.01</td>
<td>1.15 &lt;.001</td>
<td>.01</td>
<td>.01, .04</td>
</tr>
<tr>
<td>Week 3 parent hours/week</td>
<td>-.01</td>
<td>.01</td>
<td>-.56</td>
<td>.02</td>
<td>-.02, -.002</td>
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<tr>
<td>Step 5: R²=.44, F=4.11, p=.004</td>
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<tr>
<td>Constant</td>
<td>-.92</td>
<td>.30</td>
<td>.004</td>
<td>-1.53, -.31</td>
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<tr>
<td>Admission cortisol</td>
<td>.16</td>
<td>.11</td>
<td>.20</td>
<td>.16</td>
<td>-.07, .39</td>
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<tr>
<td>Neonatal medical index</td>
<td>.17</td>
<td>.08</td>
<td>.34</td>
<td>.03</td>
<td>.02, .33</td>
</tr>
<tr>
<td>Week 1 parent hours/week</td>
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<td>.01</td>
<td>-.46</td>
<td>.09</td>
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<tr>
<td>Week 2 parent hours/week</td>
<td>.02</td>
<td>.01</td>
<td>1.15 &lt;.001</td>
<td>.01</td>
<td>.01, .04</td>
</tr>
<tr>
<td>Week 3 parent hours/week</td>
<td>-.01</td>
<td>.01</td>
<td>-.66</td>
<td>.03</td>
<td>-.03, -.002</td>
</tr>
<tr>
<td>Week 4 parent hours/week</td>
<td>.003</td>
<td>.004</td>
<td>.14</td>
<td>.54</td>
<td>-.01, .01</td>
</tr>
</tbody>
</table>
**Hypothesis 8.** Hypothesis eight was: controlling for infant’s level of illness and salivary cortisol at admission, the timing of parent presence in days per week over the first four weeks of life significantly contributes to explaining NICU infant stress response, as measured by salivary cortisol at discharge. This hypothesis was examined using hierarchical multiple linear regression with list-wise deletion of cases. Bootstrapping was used to address non-normality and heteroscedasticity observed in independent variables. The sample size for this analysis was 39.

In the first step of this analysis the covariates, level of illness and salivary cortisol levels at admission, were analyzed: results were unchanged from those obtained in step one of the analysis for hypothesis seven ($R^2=.14$, $p=.07$). Parent presence for weeks one, two, three and four of life were added in a sequential steps in this regression analysis. While the models including parent presence in weeks one through four in days per week explained from 17% to 26% of the variance in infant stress response at NICU discharge, none of the models were significant. In addition, the only significant variable identified in any model was infants’ level of illness. Thus, the results of this analysis do not support the hypothesis that controlling for infant’s level of illness and salivary cortisol at admission, the timing of parent presence in days per week over the first four weeks of life explains infant stress response at NICU discharge. A full description of each model in the hierarchical analysis are reviewed in table 8.
Table 8. Hierarchical Linear Regression: Infant Stress and Parent Presence in Days per Week

<table>
<thead>
<tr>
<th>Variable</th>
<th>b</th>
<th>SE</th>
<th>β</th>
<th>p</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1: $R^2 = .14$, $F=2.87$, $p=.07$</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Constant</td>
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<tr>
<td>Admission cortisol</td>
<td>.15</td>
<td>.13</td>
<td>.25</td>
<td>.25</td>
<td>-12, .36</td>
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<tr>
<td>Neonatal medical index</td>
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<td>.06</td>
<td>.29</td>
<td>.02</td>
<td>.05, .27</td>
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</table>

Note. Standard errors (SE) and 95% Confidence intervals (CI) based on 1000 bootstrap samples.
**Hypothesis 9.** The ninth hypothesis was: controlling for infant’s level of illness and salivary cortisol at admission, the timing of SSC in hours per week over the first four weeks of life significantly contributes to explaining NICU infant stress response, as measured by salivary cortisol. Hierarchical linear regression with list-wise deletion of cases and bootstrapping was used. The sample size for this analysis was 39.

In the first step of this analysis the covariates, level of illness and salivary cortisol at admission, were analyzed. To maintain consistency, log-transformed admission salivary cortisol levels were used. Analysis of this first model revealed a non-significant model (p=.07) explaining 14% of the variance in infant stress at discharge.

In step two of the analysis, SSC in hours per week for week one of life was added. This analysis resulted in a non-significant model (p=.08) explaining 17% of the variance in infant stress at discharge. The model that resulted from step three, adding SSC for week two, was not significant ($R^2=.18$, $p=.15$). Infant illness level was significant in this model ($\beta=0.26$, $p=.03$).

In the fourth step of the regression, SSC in hours per week for week three of life was added. This model was not significant (p=.08), although a seven percent increase in $R^2$ was observed, indicating that the model explained 25% of the variance in infant stress response at discharge. Lower level of illness and more SSC ($\beta=-0.03$, 95% CI= -0.08, -0.01, $p=.04$) during week three were significant variables in this model.

SSC for week four was added in step five. The resulting model was not significant, and only infant illness level remained a significant variable. Thus, this analysis did not support the hypothesis that the timing of SSC in hours per week significantly contributes to explaining infant stress response at NICU discharge. This analysis is summarized in table 9.
Table 9. Hierarchical Linear Regression: Infant Stress and Skin-to-Skin Care in Hours per Week

<table>
<thead>
<tr>
<th>Variable</th>
<th>$b$</th>
<th>SE</th>
<th>B</th>
<th>p</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
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<td></td>
</tr>
<tr>
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<td>.23</td>
<td>.01</td>
<td>-1.08, -30</td>
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</tr>
<tr>
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<td>.12</td>
<td>.18</td>
<td>.24</td>
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<td>.03, .33</td>
</tr>
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<td>.03</td>
<td>.02, .30</td>
</tr>
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<td>.02</td>
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<td>.12</td>
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<td>.03</td>
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<td>.26</td>
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<td>.02, .28</td>
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<td>Week 1 SSC hours/week</td>
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<td>.03</td>
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<td>.37</td>
<td>-.08, .001</td>
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<tr>
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<td>-.07</td>
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<td>.21</td>
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<td>.07, .30</td>
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</table>

Note. Standard errors (SE) and 95% Confidence Intervals (CI) based on 1000 bootstrap samples.
**Hypothesis 10.** The final hypothesis was: controlling for the infant’s level of illness and salivary cortisol at admission, the timing of SSC in days per week over the first four weeks of life significantly contributes to explaining NICU infant stress response, as measured by salivary cortisol. Hierarchical linear regression with bootstrapping and list-wise deletion of cases was employed. The sample size for this analysis was 39.

Analysis of the covariates, infant’s level of illness and salivary cortisol at admission, in the first step again revealed a non-significant model (p=.07) explaining 14% of the variance in infant stress at discharge. In step two SSC in days per week for week one of life was added, resulting in a significant model explaining 21% of the variance in infant stress at discharge ($R^2=.21$, $F(1,35)=3.08$, $p=.04$). One significant variable, SSC in days per week during week one of life, was identified in this model ($\beta=-0.28$, 95% CI= -1.74, -0.3, $p=.01$).

In steps three through five of hierarchical regression, SSC in days per week for weeks two through four were added sequentially to the analysis. None of the resulting models were significant (p=.06 to p=.11). A six percent increase in $R^2$ was observed in model four and retained in model five, indicating that the models explained 27% of the variance in infant stress at NICU discharge. Similar coefficients and 95% confidence intervals for SSC during week one were retained in models resulting from steps two through five, however, these were not significant after step two as described above. In models resulting from steps three to five, infant’s level of illness emerged as a significant covariate.

The results of this analysis identified a significant model in step two of the hierarchical analysis, supporting the hypothesis that the timing of SSC in days per week contributes to explaining infant stress response at discharge. This analysis is summarized in table 10.
Table 10. Hierarchical Linear Regression: Infant Stress and Skin-to-skin Care in Days per Week

<table>
<thead>
<tr>
<th>Variable</th>
<th>$b$</th>
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<th>$\beta$</th>
<th>p</th>
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<td>.05, .24</td>
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<td>-.27</td>
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<td>-1.44, .13</td>
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<td>-.56</td>
<td>.27</td>
<td>.03</td>
<td>.06</td>
<td>-1.26, .34</td>
</tr>
<tr>
<td>Admission cortisol</td>
<td>.20</td>
<td>.15</td>
<td>.24</td>
<td>.19</td>
<td>-.06, .29</td>
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<tr>
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<td>.03</td>
<td>.05, .25</td>
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<td>.84</td>
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<td>-.27</td>
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<td>.95</td>
<td>-.001</td>
<td>.99</td>
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Note. Standard errors (SE) and 95% Confidence Intervals (CI) based on 1000 bootstrap samples.
Summary

The purpose of this study was to examine the impact of parent presence and SSC on the stress response of NICU infants that results from cumulative NICU-related stressor exposures. Three aims with ten corresponding hypotheses were addressed in the study. Correlational and regression analyses were used to address study aims. The following is a summary of the results described throughout this chapter.

The first aim was to determine whether there were significant associations between cumulative parent presence, measured in hours per week and days per week, and NICU infant stress response, as measured by salivary cortisol at discharge. Small positive correlations between cumulative parent presence measured in hours per week and cumulative parent presence measured in days per week and infant’s salivary cortisol at discharge were identified, however these correlations were not significant. Thus, the first study aim was not supported by the results of this study.

The second aim was to determine whether there were significant associations between increased SSC, measured in hours per week or days per week, and reductions in NICU infant stress response, as measured by salivary cortisol at discharge. Results of Spearman correlational analyses supported significant associations between more SSC, measured in hours per week or days per week, and reduced infant stress response at NICU discharge with small negative correlations, \( r = -.25 \) and \( r = -.21 \), respectively. Thus, results of the study support the second aim.

The third aim in this study was to determine the independently explanatory contribution of parent presence, SSC, and infant’s level of illness to NICU infant stress response, as measured by salivary cortisol. Six hypotheses were examined for this aim. Two hypotheses addressed
infant level of illness as well as cumulative parent presence and SSC. Four hypotheses addressed the timing of parent presence and SSC during the first four weeks of life.

Results of multiple linear regression analyses conducted to address the two hypotheses concerned with infant’s level of illness, cumulative parent presence, and cumulative SSC did not support aim three. Results of the analyses for the two hypotheses, one examining cumulative parent presence and SSC measured in hours per week and another examining cumulative parent presence and SSC measured in days per week, explained only 5% and 3% of the variance respectively in NICU infant stress response at NICU discharge with no significant independent variables observed. Thus, the results of these analyses do not support a model including infant’s level of illness, cumulative parent presence and cumulative SSC for explaining NICU infant stress response at discharge, as measured by salivary cortisol.

The four hypotheses examining the timing of parent presence and SSC during the first four weeks of life were examined using hierarchical analyses. Results of the analyses of these four hypotheses for aim three were mixed and are described below.

Models examining parent presence measured in hours per week over the first four weeks of life explained up to 43% of the variance in infant stress at NICU discharge, with three significant variables supported, including infant’s level of illness. These results support the hypothesis that the timing of parent presence contributes to explaining infant stress response at NICU discharge, although more presence in week two explains higher cortisol at discharge, and more presence in week three explains lower stress at NICU discharge.

A model examining SSC measured in days per week during the first week of life with covariates considering infant’s level of illness and salivary cortisol on admission explained 21% of the variance in infant stress response at NICU discharge. One significant independent variable
was observed, days per week of SSC during the first week of life. Results of the analysis support the hypothesis that the timing of SSC in days per week contributes to explaining infant stress response at discharge, with more SSC in week one of life explaining lower stress at NICU discharge in support of aim three.

Hierarchical linear regression analyses for NICU infant stress response, as measured by salivary cortisol at discharge, and parent presence measured in days per week or SSC measured in hours per week did not yield any significant models. The only significant independent variable consistently observed in these analyses was the covariate, infant’s level of illness. Thus, the third aim of this study was partially supported by the results of analyses for two of six hypotheses for aim three.

A secondary analysis was conducted to address study aims and hypotheses for a study designed to examine potential associations between parent presence, SSC and NICU infant stress response at discharge. Results of the study supported associations between SSC and infant stress response at NICU discharge and partially supported the timing of parent presence and SSC as contributors to explaining NICU infant stress response at discharge. A discussion of study findings in the context of the extant literature are reported in the following chapter.
CHAPTER FIVE

DISCUSSION

Programs and practices of developmentally supportive care (DSC) are implemented to address the adverse neurodevelopmental outcomes observed in neonatal intensive care unit (NICU) survivors that may persist into adulthood. The toxic stress experienced by NICU infants, which occurs during critical periods of development and often occurs in the absence of the infant’s parents, contributes to these adverse outcomes. As a result, an overarching goal of DSC programs and practices is mitigating infant stress, and parent presence in the NICU is universally endorsed as critical to improving infant outcomes. However, few DSC programs or practices require parent presence for their implementation, and parent presence is rarely measured in DSC studies.

The purpose of this descriptive, correlational study was to examine the impact of parent presence and SSC on the stress response of NICU infants resulting from cumulative NICU-related stressor exposures. In this chapter, study findings will be discussed. This discussion will include the relationship of key findings to the extant literature, strengths and limitations of the study, implications of the study for nursing practice and research, and recommendations for future research.

The Polyvagal theory (Porges, 1995) served as the theoretical framework for the study. In this theory Porges proposed that human evolution of the vagus nerve enables positive social
relationships to down-regulate the stress response; and that the ability to regulate stress is developed and maintained via the co-regulation of stress that occurs in buffering social relationships, which are a biological imperative for the developing infant (Porges, 2017). In this study, two relevant constructs, buffering social relationships and stress, were examined. The variables, parent presence and SSC, were used to represent the construct, buffering social relationships. SSC represented a DSC practice that requires parent presence and is a frequently reported measure of the parent-infant relationship in the NICU. Parent presence represented a component of buffering social relationships between NICU parents and infants that is considered critical for the developing infant but is rarely measured in DSC studies. The construct of infant stress response was represented by a resting infant salivary cortisol collected at NICU discharge. Measurement of heart rate variability is more directly related to the construct of infant stress response in the Polyvagal theory, and although previous research grounded in the theory supported use of salivary cortisol to measure stress (Feldman et al., 2014), the use of cortisol was a modification of the theory.

In this study, relationships between the amount and frequency of parent presence and SSC in the NICU and infant stress response, as measured by salivary cortisol at NICU discharge, were examined. Associations between cumulative parent presence and SSC were considered as well as the timing of parent presence and SSC. In the following sections demographic data for the study sample and descriptive data for the study variables will be described as well as their relevance to the existing literature.

**Study Sample**

The study was conducted via a secondary analysis of an existing dataset collected for a NICU Parent Engagement (NPE) study, including data from 78 enrolled NICU infants, their
mothers and 35 of their fathers. The study was conducted in a tertiary level NICU in a Midwestern children’s hospital. The NPE database includes data for 41 term (53%) and 37 (47%) preterm infants with a mean gestational age of 36.01 weeks (SD=3.5 weeks) and a mean birth weight of 2.69 (SD=0.86) kilograms. Despite the fact that 50% of NICU infants are born at term (Harrison & Goodman, 2015), studies of SSC and parent presence in the NICU typically focus on premature or low birth weight infants. Among the few investigators examining parent presence for a mixed sample of preterm and term NICU infants, only one conducted research in the US (Saxton et al., 2019), and all reported parent presence data collected in tertiary level settings (Franck et al., 2003; Kamphorst et al., 2018; Saxton et al., 2019). The variety and range of gestational ages, birth weights and infant acuities in this study is a limitation that may impact the generalizability of findings.

The median length of stay (LOS) for infants in the NPE dataset was 33 days. The mean LOS for NICU infants reportedly ranges from 13.2 to 27 days, with longer LOS reported for infants born earlier or with more medical morbidities (DiRienzo et al., 2016; March of Dimes, 2011). Consistent with LOS in this study, Kim et al. (2021) reported an average LOS of 34.4 days for a sample of preterm infants from a tertiary level NICU in Canada. The longer LOS for infants in this study may reflect differences in gestational ages or infant acuity and are a limitation that may also impact the generalizability of study findings.

**Study Variables**

**Infant Salivary Cortisol.** Infant stress response was operationally defined as a resting salivary cortisol level measured in the morning at NICU discharge, or at one month of age for infants not discharged at or before one month of age. Infant salivary cortisol levels at discharge ranged from 0.14 to 13.16 nanograms per liter (ng/l) with a median 0.73 ng/ml (IQR=1.72 ng/l).
While no other investigator has examined infant salivary cortisol at NICU discharge, salivary cortisol is reported as a biomarker of infant stress in increasing numbers of NICU studies (Tryphonopoulos et al., 2013). Use of single cortisol measures to assess the stress response of NICU infants resulting from cumulative stressor or parent exposures over time have been reported (D’Agata et al., 2019; El-Farrash et al., 2020; Pourkaviani et al., 2020; Rohan, 2016).

Following a seven day SSC intervention, El-Farrash et al. (2020) measured resting, morning salivary cortisol levels in 120 preterm infants, 40 each in one-hour or two-hour per day SSC intervention groups and 40 control group infants. Results of the study indicated that median salivary cortisol levels for infants in the SSC groups ranged from 2.4 to 4.2 ng/l (IQR=1.2-7 ng/l) with median morning salivary cortisol levels of 10.5 ng/l (IQR=8.7-12.2 ng/l) for infants in the control group. While different ranges of morning salivary cortisol levels were reported by El-Farrash et al. (2020), the differences reported between control and SSC group infants following a one-week exposure to NICU stressors and parent presence lends support to the use of a one-time resting salivary cortisol level to measure the interaction of cumulative NICU stressor exposures and exposures to parents.

**Parent Presence.** In this study, parent presence was defined as the amount of time one or both parents were in the NICU with their infant, measured in hours per week and in days per week, over the first four weeks of life. Cumulative hours over the first four weeks of life ranged from 28 to 466.25 hours with a mean 137.11 hours (SD=80.26). Per week mean parent presence ranged from 34.9 to 42.35 hours. Parent presence in international NICUs may be greater due to paid family leave (Livingston & Thomas, 2019), therefore, it is essential to compare the parent presence results for this study to studies from other NICUs in the US. However, there are a
paucity of studies conducted in the US reporting parent presence, and among studies reporting parent presence, few report parent presence in hours per week or days per week.

Pineda et al. (2012) compared parent presence in hours per week for NICU infants over their first five weeks of life in single-family rooms (SFRs) versus open-bay NICU beds, reporting means of 25.49 (SD=25.41) and 16.85 (SD=13.47) hours per week respectively. Reynolds et al. (2013) reported mean hours of parent presence at 21.33 (SD=20.88) hours per week. Thus, lower mean parent presence in hours per week than that observed in the current study has previously been reported in studies of parent presence in the US. The limited number of investigators measuring parent presence in hours per week may explain these differences.

A trend toward increased mean parent presence in hours per week over the first two weeks of life, followed by a decrease in mean parent presence was observed in this study. Trends in parent presence in the US are rarely reported. Pineda et al. (2012) observed a decline in maternal presence in the NICU over the infant’s first month of life. After week two, mother’s presence was a mean 4.26 hours per week lower for infants in open bay NICU beds (p=.02) and 5.5 hours lower for infants in SFRs (p=.04). Investigators in two international papers have also reported decreased parent presence over the first weeks of life, however, differences in parent presence over time were not well described (Garten et al., 2011; Kim et al., 2021). Thus, findings of this study will contribute to research focused on trends in NICU parent presence over time.

Parent presence in days per week was measured to assess the frequency of parent presence. The range of cumulative parent presence over the first four weeks of life ranged from 35.7% to 100% of days in the NICU, with a mean of 91.1% (SD=13.8%). Weekly parent presence in days per week ranged from 88% to 91.5% of NICU days over the first four weeks of life. In the literature, reported cumulative parent presence frequencies from US studies for NICU
mothers are 61% to 78% of NICU days and (Gonya & Nelin, 2013; Greene et al., 2015; Saxton et al., 2019) 59.2% for fathers (Saxton et al., 2019). Weekly parent presence in days per week has been reported to be 57.14% to 64.29% of NICU days in two studies examining parent presence in SFRs (Lester et al., 2014; Pineda et al., 2018). Cumulative and weekly frequencies of parent presence reported in the literature are lower than the frequency of parent presence observed in this study. The limited findings in this area may explain differences observed.

**Skin-to-skin Care.** SSC was defined as the amount of time a parent participated in SSC with their NICU infant over the first four weeks of life, as measured in hours per week and days per week. These data were combined for mothers and fathers in the NPE dataset. The range of cumulative SSC in hours per week was zero to 52 total hours with a mean 5.52 (9.93) hours. Mean hours of SSC per week ranged from 1.29 to 1.81 hours. The range of cumulative SSC in days per week over the first four weeks of life was zero to 67.9% with a mean of 8.63% of NICU days (SD=13.5%).

Investigators in few studies report longitudinal data for naturally occurring SSC in the NICU. In a US NICU Cong et al. (2017) measured naturally occurring SSC in a study examining infant stress exposures over the first four weeks of life. A mean 13.35 (SD=32.1) minutes per day SSC by mothers was observed. Fathers performed SSC a mean 1.44 (SD=9.4) minutes per day. The combined amount of SSC for mothers and fathers observed by Cong et al. (2017) is equivalent to 1.73 hours per week, which is consistent with amounts of SSC observed in this study. Also consistent with the current study, Kim et al. (2021) reported mean SSC numbers of 8.4 minutes per day, corresponding to 0.98 hours per week of SSC in a Canadian NICU. Pineda et al. (2012) reported mean SSC in hours per week over the LOS for 81 preterm infants ranging from 0.63 to 0.84 days per week. The low numbers reported in these studies are in keeping with
the findings of a March of Dimes family-centered care study that included SSC. In this survey research a majority of NICU nurses reported believing that SSC was valuable for parent and infant outcomes, however, only 8% of nurses reported implementing SSC in their practice (Gooding et al., 2011).

**Covariates**

**Infant Level of Illness.** Consistent with the NPE study database, infant’s level of illness in this study was operationally defined as an infant’s Neonatal Medical Index (NMI) score that reflects an infant’s level of illness at baseline and throughout the NICU stay. NMI scores range from one to five with higher scores reflecting more medical morbidity. In this study, NMI scores ranged from one to five, with a median score of four (IQR=2).

Controlling for maternal education, associations between NMI scores and infant cognitive development at 12 and 36 months have been reported (Korner et al., 1993). Among preterm infants, lower NMI scores are also associated with lower post-menstrual ages (PMA) at first bottle feeding and full oral feeding, lower PMA at NICU discharge (Pickler et al., 1997), and better oral feeding efficiency (Pickler et al., 2005). As expected, the range of NMI scores in a sample varies with the acuity of the sample. In several early studies (Korner et al., 1993; Pickler et al., 1997), among 552 preterm infants the distribution of NMI scores indicated that only 13% to 30% of infant subjects had NMI scores greater than four. In the current study the median NMI score of four indicates this is a higher acuity sample, which is typical in tertiary level NICUs, but may limit the study’s generalizability.

**Infant Salivary Cortisol at Admission.** A second covariate considered in analyses of study aims was an infant resting salivary cortisol level measured at NICU admission. Infant cortisol levels at admission ranged from 0.14 to 33.36 ng/l with a mean 3.6 ng/ml (SD=6.6 ng/l).
Few studies have included infant salivary cortisol levels on admission to the NICU. The use of single salivary cortisol measurements is described above. Admission cortisol may be affected by the stress of delivery and stabilize by two days of life (Morelius, 2005). In the NPE study, infants were transferred from a birth hospital to the study hospital, and the earliest age at admission cortisol was 48 hours.

**Discussion of Findings Related to Study Aims and Hypotheses**

**Aim 1**

The first aim was to examine potential relationships between parent presence, measured in hours per week and days per week, and NICU infant stress response. NICU infant stress response was operationalized as a single resting measure of salivary cortisol at NICU discharge. The results of hypothesis testing for this aim did not support significant associations between parent presence and infant stress levels at NICU discharge.

**Parent Presence and Infant Stress.** The first hypothesis was that parent presence measured in hours per week was significantly associated with NICU infant stress response, as measured by salivary cortisol. Pearson correlation analysis with a two-tailed test of significance was conducted. The small positive correlation resulting from this analysis did not support a significant association between hours of parent presence per week and infant stress, as measured by salivary cortisol at NICU discharge ($r=.11$, 95% CI= -0.15, 0.35, $p=.39$).

The second hypothesis was: parent presence measured in days per week is significantly associated with NICU infant stress response, as measured by salivary cortisol. A Pearson correlation with bootstrapping and a Spearman correlation were assessed at a two-tailed level of significance. The resulting correlations did not support this hypothesis, including results of the Pearson correlation with bootstrapping ($r=.06$, 95% CI= -0.15, 0.23, $p=.63$) and results of the
Spearman correlation (rs=.03; p=.8). Thus, an association between parent presence in days per week and NICU infant stress at discharge, as measured by salivary cortisol was not supported.

In the Polyvagal theory, Porge’s (1995) proposes that stress may be down-regulated in the presence of buffering social relationships. Associations between parent presence in hours per week and NICU infant stress response at discharge were not supported in this study. The amount of parent presence may not adequately reflect NICU parent-infant relationships, or single measures of salivary cortisol may not adequately reflect the stress responses of NICU infants to stressor and parent exposures over time. Previous investigators examining parent presence have not explored relationships between biomarkers of stress and the cumulative exposure to stressors and intermittent parent presence that represents the experience of NICU infants. However, results of studies by investigators examining cumulative stressor exposure suggest that a single measure using a biomarker of stress may be used to assess NICU infant stress response.

Pourkaviani et al. (2020) assessed associations between a single salivary cortisol measure and acute and chronic stress scores on the Neonatal Infant Stressor Scale (NISS) (Newnham et al., 2009), representing the NICU infants’ stressor exposures over the previous six hours. Three hundred eighty-six cortisol levels from 125 NICU infants with PMAs ranging from 28 to term-age were assessed in the study. Positive associations between infant salivary cortisol levels and acute NISS scores (95% CI 0.03, 0.14) and total NISS scores (95% CI .0004, .05) were supported. A similar relationship was not supported between infant cortisol and the chronic NISS score (95% CI -.02, .04). However, the chronic NISS score was tallied for only six hours prior to the salivary cortisol measurement, and while labeled as representing chronic stress, the stressors categorized as chronic using the NISS may not affect cortisol or may require assessment for more than the six hours considered in this study.
Using a modified version of the NISS, titled the Accumulated Pain/Stressor Scale (APSS) that was designed to measure accumulated pain and stressors among NICU infants in the US (Xu et al., 2016), D’Agata et al. (2019) assessed the cumulative stress exposures of 82 preterm NICU infants from birth through six weeks of life. The average number of stressful events per day was 43. For infants of at least 28 weeks gestation, infant stress response, measured using skin cortisol levels, was significantly correlated with stress experienced during the prior seven days (b=.03, 95% CI .02, .04, p<.01). In the current study, stressor exposures were not measured. The shorter length of stressor exposures measured by D’Agata et al. (2019), as well as the use of skin versus salivary cortisol measures may explain differences in study findings.

Rohan (2016) examined the relationship between serum cortisol and a cortisol precursor, 17-hydroxyprogesterone (17-OHP), and the number of pain exposures of 59 preterm infants at 37 weeks PMA. Similar to the current study, the average number of days infants were in the NICU prior to cortisol and 17-OHP measurement was 31. The mean number of pain exposures was 57 with many occurring in the first week of life. A single resting serum cortisol was not significantly associated with pain exposures, however, a significant negative relationship between a single, random 17-OHP level and recurrent pain-associated stressor exposures was supported (r= -.23, p=.04). 17-OHP levels may be a more sensitive measure of infant stress level when considering longitudinal stressor exposures.

Associations between parent presence, measured in hours per week or days per week, and NICU infant stress at discharge, as measured by a single resting salivary cortisol level were not supported in this study. An a priori power analysis indicated that a sample size of 69 would be needed to address the two hypotheses for aim one. However, missing infant salivary cortisol
levels at NICU discharge resulted in a sample size of 61 for these analyses. Low sample size may have contributed to the lack of support for aim one.

**Aim 2**

The second aim in this study addressed potential relationships between amounts of SSC and NICU infant stress response, as measured by salivary cortisol at NICU discharge. There were two hypotheses examined for this aim. In the third hypothesis, a significant association between increased SSC in hours per week and reductions in NICU infant stress response was proposed. In the fourth hypothesis, a significant association between increased SSC measured in days per week and reductions in NICU infant stress response was proposed.

While significant associations were not observed using Pearson correlational analyses, consistent with Porge’s Polyvagal theory, Spearman correlational analyses identified significant associations between more SSC and a lower infant stress response at NICU discharge for both hypotheses in aim 2. Results of the Spearman correlational analyses were accepted over results of the Pearson analyses, because the datasets for SSC in hours per week and days per week were non-normal. The higher Spearman correlational values for both hypotheses indicate that the monotonic trend that was observed using the Spearman test was larger than the linear trend assessed using the Pearson correlation (Lund Research, 2018).

**SSC and Infant Stress.** In the third hypothesis, a significant relationship between SSC measured in hours per week and NICU infant stress response, measured using salivary cortisol, was proposed. Cumulative hours of SSC over the first four weeks of life in the NICU were negatively correlated with infant stress response at discharge assessed using the Pearson correlation with bootstrapping ($r=-.15, 95\% \ CI= -0.31, 0.05, p=.13$) and Spearman’s rho
correlation (rs= -0.25, p=0.03), however, only the Spearman correlation supported a significant association between more SSC and lower levels of infant stress response at discharge.

The fourth hypothesis was: increased SSC measured in days per week is significantly associated with reductions in NICU infant stress response, as measured by salivary cortisol. A significant negative correlation between cumulative SSC measured in days per week and infant stress at NICU discharge was identified using Spearman’s rho (rs= -0.21, p=0.05); and a small negative, non-significant association was identified using the Pearson correlation with bootstrapping (r=-0.12, 95% CI= -0.31, 0.12, p=0.18). Results of the Spearman correlational analysis supported an association between increased SSC measured in days per week and reduced infant stress responses at NICU discharge.

Although DSC programs and practices endorse NICU parent presence, SSC is among the few DSC interventions that require parent presence. Investigators examining SSC and infant stress-related outcomes rarely examine associations between biomarkers of stress and SSC interventions longer than two hours. Among the few investigators reporting associations between longer SSC interventions, only one has examined infant stress related to naturally occurring SSC over time.

In a secondary analysis, Marvin et al. (2019) examined relationships between the frequency of SSC, heart rate variability (HRV) and NICU infant outcomes in 101 preterm infants (M=31 weeks PMA) who received SSC at least once in the first three weeks of life. HRV was measured weekly until 35 weeks PMA. Frequency of SSC was documented by NICU nurses in the electronic medical record from birth through three weeks of life. Marvin et al. (2019) reported that SSC during the first week of life ranged from 0 to 23 sessions with an average SSC
session lasting one hour. SSC during week one of life was positively correlated with improved HRV ($r = .23$, $p = .02$) and a shorter length of stay ($r = -.34$, $p = .001$).

Morelius et al. (2015) compared salivary cortisol in late preterm infants that received nearly continuous SSC in the NICU ($M = 19.6$ hours/day) compared to standard care infants that received less SSC ($M = 7$ hours/day). Significantly lower infant salivary cortisol reactivity was observed in response to a diaper change performed by the mother at 44 weeks post-menstrual age (PMA) in the high SSC infants ($F = 7.6$, $p = .01$).

Consistent with previous studies measuring naturally occurring SSC (Cong et al., 2017; Kim et al., 2021), the amounts of naturally occurring SSC observed over the four weeks of life for infants in this study were quite low, with many infants receiving no SSC in the NICU. In addition, the a priori power analysis indicated that a sample size of 69 would be required to address each of the aim two hypotheses versus the sample of 61 cases available for analysis in this study. Although results of the current study are consistent with the SSC literature, the small effect sizes observed in the current study ($r = -.21$, $r = -.25$) may have been impacted by the low numbers for naturally occurring SSC observed and a lower than required sample size. Despite these issues, the second aim was supported.

**Aim 3**

The third aim of this study was to determine the independent explanatory contribution of parent presence, SSC, and infant’s level of illness to NICU infant stress response, as measured by salivary cortisol at discharge. Six hypotheses were addressed for this aim. In the first two hypotheses, the independent explanatory contribution of cumulative parent presence and SSC, measured by hours per week or days per week, and infant’s level of illness to NICU infant stress response was examined. In the last four hypotheses, the explanatory contributions of the timing
of parent presence or SSC over weeks one to four of life, measured in hours per week or days per week, to infant stress response at NICU discharge were examined, controlling for infant’s level of illness and infant salivary cortisol on admission. Results of regression analyses for aim three hypotheses partially supported this aim. Results of two hypothesis tests for aim 3 that support associations between parent presence and lower infant stress are consistent with Porge’s (1995) Polyvagal theory that proposes buffering social relationships downregulate stress responses.

**Cumulative Parent Presence and SSC.** In the fifth hypothesis, the explanatory contribution of parent presence (hours per week), SSC (hours per week), and infant’s level of illness to NICU infant stress response, as measured by salivary cortisol, was examined. This hypothesis was assessed using multiple linear regression. Results of regression analysis indicated that cumulative parent presence, SSC and infant’s level of illness was not a significant predictor of infant stress response at NICU discharge, as measured by salivary cortisol ($R^2=0.05$, $F(3,57)=0.99$, $p=0.4$). None of the variables in the model explained NICU infant stress response at discharge, and this hypothesis did not support aim three.

The sixth hypothesis was: parent presence (days per week), SSC (days per week), and infant’s level of illness significantly contribute to predicting NICU infant stress response, as measured by salivary cortisol. This hypothesis was also examined using multiple linear regression. Results of the analysis indicated that a model including cumulative parent presence and SSC, measured in days per week during the first four weeks of life, and infant’s NMI score, did not significantly contribute to explaining infant stress response at NICU discharge ($R^2=0.03$, $F(3,57)=0.62$, $p=0.61$). No variables in the model significantly explained infant stress response at discharge. Thus, hypothesis six did not support aim three.
In Sweden, Morelius et al. (2012) compared infant stress outcomes in 152 preterm infants in SFRs to the outcomes of 137 preterm infants in a NICU with open bay rooms. Families and their infants were randomly assigned to room types, and only parents with infants in SFRs were expected to be present 24 hours per day. Amounts of parent presence were not recorded for the standard care group, however, overnight accommodations were limited in the open bay NICU. Infant cortisol levels measured in response to a diaper change done by the mother at 36 weeks PMA increased in 35% of infants in both groups, indicating no difference in stress responses in infants receiving near continuous parent presence. While this outcome may be consistent with parent presence findings in the current study, the lack SSC data in the Morelius study limits comparisons.

In the previously described study by Marvin et al. (2019) relationships between infant outcomes and the frequency of SSC during week one of life, heart rate variability (HRV), and infant morbidity risk were examined using stepwise regression analyses (N=101, mean PMA=31 weeks). Infant morbidity risk at birth was assessed using the Score for Neonatal Acute Physiology (SNAP). Results of these analyses supported that associations between SSC during week one of life and HRV were strongest in a subset of 55 NICU infants with SNAP scores indicating higher levels acuity (r=.38, p=.004). Although the study validates associations between biomarkers of stress in NICU infants, SSC and infant level of illness, parent presence was not considered in the model reported by Marvin et al., (2019).

Studies examining parent presence or SSC over time are rare. In addition, the extant literature does not include studies measuring infant stress outcomes relative to SSC and parent presence over time. In this study, the two hypotheses examining cumulative parent presence, cumulative SSC, and infant’s level of illness did not support aim three.
Timing of Parent Presence. Hypothesis seven was: controlling for infant’s level of illness and salivary cortisol at admission, the timing of parent presence in hours per week over the first four weeks of life significantly contributes to explaining NICU infant stress response, as measured by salivary cortisol. A hierarchical multiple linear regression was selected address this hypothesis. This analysis revealed a significant model that accounted for 43% of the variance in infant salivary cortisol at NICU discharge that included infant salivary cortisol at admission, infant’s level of illness, and parent presence during weeks one, two and three of life. Significant independent variables included infant’s level of illness, parent presence during week two and parent presence during week three.

Results of this hypothesis test supported aim three in that parent presence contributed to predicting infant stress at discharge. However, while the Polyvagal theory would predict lower infant stress related to parent presence, this was not observed for week two of life, and more parent presence in week two was associated with a greater infant stress response at NICU. Consistent with the Polyvagal theory, in the observed model, more parent presence in week three explains lower stress response at NICU discharge.

In a study examining preterm infant stressor exposures using the NISS, Smith et al. (2011) observed higher daily stressor exposures over the first 14 days of life, including painful procedures (N=44). Using the APSS, a modified version of the NISS previously described, Cong et al. (2017) observed that pain/stressors were more prevalent during the first two weeks of life among 50 preterm infants. Zauche et al. (2020) considered relationships between significant infant co-morbidities, and parent presence in the NICU for 66 preterm infants in two NICUs over a 48 hours period. Parent presence was reportedly variable, and using multivariate analysis SFR ($\beta=15.96$), infant surgical history ($\beta=-37.66$), infant neurological comorbidity ($\beta=-22.19$), fewer
siblings (β=16.12), lower perceived parent stress (β= -9.98), and a significant interaction effect between SFR and surgery history (β= -28.59) explained 65.8% of NICU parent presence (R²=.66, F=20.23, p<0.001). The amount of parent presence during the first two weeks of life may represent a parent’s desire to support NICU infants during times of high stressor exposures, such as recovery from procedures or surgeries.

During times of greater infant acuity, well-meaning NICU staff may limit parent-infant interactions such as SSC or vocal interactions in attempts to reduce infant stress. However, during times of high acuity and stress, infants may need buffering social relationships with parents; and parents may need NICU staff support them in safely engaging with their infants. The results of these analysis are exploratory, and underlying mechanisms for findings observed that support associations between more parent presence in week two of life and increases in the infant stress response at NICU discharge are not known.

Hypothesis eight was: controlling for infant’s level of illness and salivary cortisol at admission, the timing of parent presence in days per week over the first four weeks of life significantly contributes to explaining NICU infant stress response, as measured by salivary cortisol. Hierarchical multiple linear regression was also used to examine this hypothesis, and although regression models including weeks one through four in days per week predicted from 17% to 26% of the variance in infant stress at NICU discharge, none of the models were significant. In addition, the only significant predictor variable identified in any model was infants’ level of illness.

Thus, unlike the results of the previous analysis examining the timing of parent presence in hours per week, these results, examining parent presence in days per week, do not support aim three and are not consistent with the buffering of infant stress via the parent-infant relationship.
proposed in the Polyvagal theory (Porges, 1995). It may be that the frequency of parent presence, as measured using days per week of parent presence, is less significant than the amount of parent presence to the parent-infant relationship in the NICU.

**Timing of SSC.** Hypothesis nine was: controlling for infant’s level of illness and salivary cortisol at admission, the timing of SSC in hours per week over the first four weeks of life significantly contributes to explaining NICU infant stress response, as measured by salivary cortisol. Hierarchical linear regression was used to analyze this hypothesis. Results indicated that there were no significant models, although a model including infant salivary cortisol on admission, infant’s level of illness, and SSC in hours per week for weeks one through three accounted for 25% of the variance in infant stress as measured by salivary cortisol at NICU discharge. In this model, infant level of illness and more SSC during week three were associated with lower infant stress at discharge. The low levels of SSC observed in the present study may account for the lack of significant predictor models observed for hypothesis nine.

The tenth and final hypothesis was: controlling for infant’s level of illness and salivary cortisol at admission, the timing of SSC in days per week over the first four weeks of life significantly contributes to explaining NICU infant stress, as measured by salivary cortisol. Hierarchical linear regression was employed. This analysis resulted in one significant model explaining 21% of the variance in infant stress at discharge ($R^2 = .21$, $F(1,35)=3.08$, $p=.04$). Variables in this model included infant salivary cortisol at admission, infant’s level of illness, and SSC in days per week for week one of life. One significant predictor variable, SSC in days per week during week one of life, was identified in this model ($\beta = -0.28$, $p=.01$). Thus, analyses for hypothesis ten, but not hypothesis nine, support aim three. The frequency of SSC in the early days of life may impact the NICU infant stress response more than the amount of SSC in hours.
The results observed for hypothesis ten are consistent with the Polyvagal theory and consistent with previous studies of SSC demonstrating that reductions in infant stress are associated with SSC; and, several investigators have reported reductions in infant stress biomarkers following two week SSC interventions (El-Farrash et al., 2020; Feldman et al., 2003; Harrison & Brown, 2017). However, there are no previous studies examining relationships between biomarkers of stress and the longitudinal, naturally occurring SSC over the first month of life that was measured in this study.

**Summary.** Results of the regression analyses for hypotheses five and six did not support aim three. The results of two of the four hierarchical regression analyses conducted for hypotheses seven through ten, examining the timing of parent presence and SSC, supported aim three. Thus, results of this study partially supported aim three. The number of cases available for these analyses (N=39) were lower than the 55 cases that were identified using an a priori power analysis. Low sample size may have influenced the mixed results observed among the aim three hypotheses.

**Summary of Findings**

In this study cumulative parent presence over the first four weeks of life, measured in hours per week or days per week, was not correlated with infant stress at NICU discharge, as measured using a single resting salivary cortisol. Findings of regression models for infant’s level of illness, cumulative SSC and parent presence, measured in hours per week or days per week, did not explain NICU infant stress response at discharge. Thus, these results do not support associations between cumulative parent presence and infant stress response measured via a single salivary cortisol measure at NICU discharge.
Results of hierarchical regression examining the timing of parent presence supported that a model including salivary cortisol at admission, infant’s level of illness and parent presence during weeks one, two, three and four of life predicted infant stress at NICU discharge. Significant predictor variables in the model included infant’s level of illness and parent presence measured in hours per week during weeks two and three of life. Results of the model suggested that infants with a higher levels of illness had increased stress at discharge. Results of the model also suggest that infants experiencing more parent presence during week two had higher salivary cortisol levels at discharge. In contrast, the model also suggests that infants experiencing more parent presence during week three had lower salivary cortisol at discharge. Interestingly, results of the model suggest that parent presence during week one of life, near the time of NICU admission, or parent presence during week four of life, near the time of NICU discharge, were not significant predictors of infant stress at NICU discharge.

Cumulative SSC, measured in hours per week or days per week, was negatively correlated with infant stress at NICU discharge. These findings suggest that increased cumulative SSC is associated with reduced infant stress, as measured by salivary cortisol at discharge. However, findings of regression models examining infant’s level of illness with cumulative SSC and parent presence, measured in hours per week or days per week, did not explain infant stress at NICU discharge; and cumulative SSC was not identified as a single predictor variable in either model. These results are mixed in supporting associations between cumulative SSC and NICU infant stress response, as measured using a single resting salivary cortisol level at discharge.

Results of hierarchical regression examining the timing of SSC supported that a model including salivary cortisol at admission, infant’s level of illness and SSC measured in days per week during week one explained infant stress at NICU discharge. Significant predictor variables
in the model included infant’s level of illness and SSC during week one of life, suggesting that infants with a higher levels of illness had increased stress at discharge, and infants experiencing more days of SSC during week one had reduced stress at NICU discharge. Results of the hierarchical regression suggest that days of SSC during weeks two, three and four life are not significant predictors of infant stress at NICU discharge. The need for early and frequent SSC in week one of life to address stress in NICU infants was supported in this analysis.

This study explored a novel application of the Polyvagal theory to the experience of infants in the NICU. Relationships between parent presence, an aspect of NICU parent-infant relationships not previously considered, and NICU infant stress response, as measured using salivary cortisol at discharge, were examined in this study; and this study is among the first to examine relationships between parent presence and biomarkers of stress in NICU infants. While relationships between cumulative parent presence and infant stress at discharge were not found, consistent with the Polyvagal theory, relationships between the timing of parent presence and infant stress at NICU discharge were identified. Reports of relationships between cumulative parent presence and infant stress responses are scarce, and relationships between the timing of parent presence and infant stress response at NICU discharge are not reported in the literature.

Investigators examining SSC and stress in NICU infants have conducted studies grounded in the Polyvagal theory (Feldman et al., 2014). However, this study also represented a novel application of the Polyvagal theory in that relationships between cumulative, naturally occurring SSC and infant stress responses were examined at NICU discharge. The current study was also novel in exploring relationships between the timing of SSC over the first month of life and infant stress response at NICU discharge. Previously, only one other investigator has
examined naturally occurring SSC, the timing of SSC and biomarkers of infant stress (Marvin et al., 2019).

**Study Limitations**

When an existing dataset is used to address new research questions, limitations are inherent as the dataset may lack information that would be useful in addressing new research questions (Tappen, 2016). This was the case in the current study, as the NPE dataset did not provide information about variables that may have impacted infant cortisol, including medications. In addition the NPE dataset did not include measures of infant stressor exposures and, with the exception of SSC, did not measure the quality of parent-infant relationships occurring during times of parent presence. Finally, parent presence and SSC data for mothers and fathers was combined in the NPE dataset used in this secondary analysis.

The sample represented in the NPE dataset was a limitation in this study, in that pre-intervention and post-intervention groups were combined. Although no significant differences in infant characteristics, parent presence and SSC were observed between groups, parents and infants may have been impacted by the NPE study intervention or subtle changes in the setting that occurred over the NPE study period. Undetected selection bias and the heterogeneity of the infants represented in the NPE dataset was also a limitation in the current study in that subtle infant differences not considered in the dataset may have impacted infant stress response. In addition, some NICU infants in the dataset were discharged home earlier than one month of life, thus, their discharge cortisol levels did not reflect a full month of NICU stressor exposures. Ongoing illness may have impacted the stress responses of infants in the dataset discharged later than one month of life. Finally, missing data that led to lower sample sizes than indicated by a priori power analyses may have impacted this study’s outcomes.
In the Polyvagal theory Porges (1995) proposes that social relationships may down-regulate stress responses via regulation of the autonomic nervous system. While salivary cortisol also reflects the regulation of stress, it is a measure reflecting hypothalamic–pituitary–adrenal (HPA) axis activity. Thus, use of cortisol to measure stress in a study grounded in the Polyvagal theory is a limitation of this study. Also, use of a single resting salivary cortisol measure versus a measure of cortisol reactivity was a potential limitation, in that a single measure may not accurately reflect infant stress response.

**Implications for Nursing Knowledge and Practice**

Although the exploratory nature of this study limits the generalization of results, this study may add to nursing knowledge related to the importance of parent presence in the NICU. Relationships between the timing of parent presence and infant stress at NICU discharge were identified, suggesting that more parent presence during week two of life was associated with a greater infant stress response, while more parent presence during week three was associated with a lower infant stress response at NICU discharge. These results suggest that NICU nurses may need to provide more support for parent presence and parent-infant relationships during times of presence in the early weeks of life when high levels of infant illness and stress are present. These results also suggest that as infants remain in the NICU beyond two weeks of life, more parent presence should be encouraged by NICU staff.

This study also adds to nursing knowledge relative to the importance of early SSC in the NICU. Relationships between cumulative SSC and SSC during the first week of life were identified, suggesting that more SSC over time, particularly during week one of life are associated with less infant stress at NICU discharge, as measured by salivary cortisol. Early SSC may be challenging due to a higher level of infant acuity and need for supportive therapies such
as mechanical ventilation. However, consistent with the Polyvagal theory, the results of this study indicate that early, frequent SSC may mitigate infant stress in the NICU and should be encouraged by NICU staff.

**Implications for Nursing Research**

Consistent with the American Nurses’ Association Social Policy Statement (2010), the identification of interventions to mitigate NICU infant stress is a critical role of NICU nurses. This study is among the first to address relationships between biomarkers of infant stress and cumulative parent presence. This study is also the first to focus on relationships between the timing of parent presence and infant stress at NICU discharge. Although the importance of parent presence was only partially supported in this study, parent presence is consistent with the Polyvagal theory (Porges, 1995) and parent presence may impact infant stress. Further research is needed to explore these relationships. Future studies should explore cumulative parent presence in prospective, adequately powered studies. In addition to parent presence, parent engagement activities and NICU stressor exposures should be considered as independent variables in future studies. Factors that may impact infant cortisol levels, such as medications, should also be considered in future studies. Finally, NICU infant stress may be better measured using weekly cortisol levels, measures infant of cortisol reactivity versus single measures, or other biomarkers of stress such as skin cortisol or HRV.

This study is among the first to examine relationships between biomarkers of infant stress and cumulative, naturally occurring SSC over time. It is also among the first to consider relationships between the timing of SSC and infant stress at NICU discharge. Consistent with the Polyvagal theory (Porges, 1995), the importance of cumulative SSC and the importance of frequent, early SSC in the first week of life were supported in this study. However, more
research is needed to explore these relationships. Future studies should explore cumulative SSC and the timing of SSC in prospective, adequately powered studies. In addition to SSC, relationships between infant stress and other parent engagement activities, such as holding or bathing, should be considered in future studies. NICU stressor exposures and factors that may impact infant cortisol levels, such as medications, should be considered in future studies as well as the timing and adequacy of measures of infant stress.

Conclusions

Developmentally supportive care is implemented to prevent the adverse neurodevelopmental outcomes observed in NICU survivors. The toxic stress experienced by NICU infants, which often occurs in the absence of parents, contributes to these adverse outcomes. An overarching goal of DSC is mitigating infant stress. Parent presence in the NICU is universally endorsed as critical to improving infant outcomes. This descriptive, correlational study examined infant stress at discharge in a cohort of NICU infants from a single site relative to the amount and timing of parent presence and skin-to-skin care (SSC) received in the NICU.

High levels of stressor exposure over time are reported for NICU infants. More research examining potential relationships between parent presence, SSC, and infant stressor exposure and responses may be critical to mitigating NICU infant stress and improving infant outcomes. Results of future studies may impact nursing practice, nursing and parent education, and health policies related to paid leave for new families.
APPENDIX A

MODEL OF THE POLYVAGAL THEORY
The Movement Paradigm, 2022
APPENDIX B

DESCRIPTION OF THE NICU PARENT ENGAGEMENT STUDY
The NICU Parent Engagement (NPE) study was funded internally by a nursing grant program at the Ann and Robert H. Lurie Children’s Hospital in Chicago and externally supported by the March of Dimes, NICU Family Support program. In the study nurse investigators used an interrupted time series design to compare parent and infant stress outcomes in two separate parent-infant cohorts, one cohort before and one after the implementation of a unit-wide intervention aimed at increasing parent engagement in a single NICU. A diagram of the research design used in the NPE study is provided in figure 1. The NPE study was grounded in the Universe of Developmental Care theory that includes five core measures essential to providing DSC, including family-centered care (Milette et al., 2017).

Figure 1. NPE study design: Interrupted time series

• Pre-group enrollment followed by study procedures through NICU discharge
• Intervention period: Unit-wide implementation of intervention.
• Post-group enrollment followed by study procedures through NICU discharge

Research Questions

The study’s research questions addressed potential impacts of the study intervention on NICU parents and infants as well as on unit visiting, kangaroo care and breastfeeding rates. Research questions included are detailed below.

1) What is the impact of communicating specific expectations for parent presence in the NICU on parent visiting, skin-to-skin care (SSC) and breastfeeding?
2) Does communicating specific expectations for parent presence in the NICU impact maternal and paternal stress?

3) Does communicating expectations for parent presence in the NICU impact infant outcomes including weight gain, length of stay, oral feeding, and stress?

**Study Intervention**

The NPE study intervention was implemented following discharge of parents and infants in the pre-intervention cohort. The intervention consisted of communicating an expectation at NICU admission that parents be present at minimum 4 hours per day versus the usual practice of asking NICU families to “come as much as they want.” As principal investigator of the NPE study, I consented all participating NICU families and can provide assurance that no opinions regarding family presence and parent or infant stress were discussed during the informed consent process. In addition, there were no incentives for families in the post-intervention group to be present four hours per day. Parent presence varied widely between study families, and no significant differences in parent presence in the pre- or post-intervention groups were identified.

**Setting**

The NPE study was conducted in a tertiary-level NICU in a free-standing, Midwestern children’s hospital. At the time of the study the NICU contained 44 intensive care beds in single-family rooms and admitted more than 500 infants per year. Term and preterm infants with a variety of medical and surgical diagnoses requiring intensive care were admitted to this setting. The hospital did not deliver babies, and all NICU infants were transferred from outside hospitals.

Supports for families were in place prior to initiation of NPE study and were not changed during the study period. These supports included free parking, a nearby Ronald McDonald...
house, and additional parent sleep rooms within the hospital. In addition, a breast pump was provided in each single-family NICU room, and lactating mothers were given free meal passes for the hospital cafeteria. A March of Dimes NICU Family Support program, NICU parent-to-parent volunteers, weekly parent groups, and a comprehensive, multidisciplinary family support team provided psychosocial support to inpatient NICU families.

Sample

The NPE study was an exploratory study, and an a priori power analysis was not conducted. The study’s total sample consisted of 78 NICU families, 40 families in the pre-intervention group and 38 different families in the post-intervention group. Among the 78 enrolled families, 78 NICU infants, 78 mothers and 35 fathers were enrolled.

To represent the equal numbers of term and preterm infants observed in NICU populations (Harrison & Goodman, 2015), a non-probability quota sampling technique was employed to select potential subjects for the NPE study. The resulting sample of NICU infants enrolled in the NPE study consisted of 41 term (53%) and 37 (47%) preterm infants. NICU infants enrolled were of mixed acuity, and there were no differences in infant levels of illness in pre- and post-intervention groups.

Infant inclusion criteria included being less than two weeks of age and being born at greater than or equal to 28 weeks gestation. Exclusion criteria included being admitted from home, having a condition typically requiring a prolonged hospitalization of greater than three months, or having a condition typically requiring transfer to another nursing unit or facility prior to discharge home. At the time of the NPE study, less than five percent of NICU families were non-English speaking, therefore, non-English speaking families were excluded from the study.
Study Procedures

Study procedures followed informed consent and are detailed in table 1. Demographic data for infants were collected from the electronic medical record (EMR) including sex, gestational age, and birthweight, length of stay, weight at discharge, breastfeeding status, and data necessary to calculate a Neonatal Medical Index (NMI) (Korner et al., 1993) score indicating the infant’s level of illness. Parent demographic data were collected via brief parent interviews conducted by the principal investigator (PI) at study enrollment. This data included age, relationship status, number and ages of siblings, level of education completed, employment status and distance from the parent’s residence to the hospital. If parents were unsure of the distance traveled between the hospital and home, this was determined using a computerized map application.

Parent presence and SSC data recorded in hours per day using data collected from nursing flowsheets contained in the EMR. Nursing flowsheets in the EMR are displayed in one-hour increments, and nurses comment if the parent visit or SSC is less than one hour.

Parent and infant salivary cortisol samples were collected at NPE study enrollment, at discharge from the NICU, and collected at each month of age the infant reached prior to NICU discharge. Salivary cortisol samples were collected using SalivaBio® oral swabs by trained NICU nurses that were members of the NPE research team using a consistent collection procedure. Infant salivary cortisol levels were collected between the hours of 5 and 9 am, prior to any anticipated standard of care procedures that might initiate a physiologic stress response in the infant. Parent samples were collected when they visited. To avoid components that can disturb salivary cortisol analysis, salivary cortisol samples were obtained one hour after oral
intake or oral care in parents and infants, and study team nurses inspected the infant’s mouth for formula or breastmilk prior to obtaining the sample. Oral swabs were placed alongside the buccal mucosa or under the tongue of infant and parent subjects for three to five minutes. This procedure was repeated to provide two saliva samples at each salivary cortisol collection. If insufficient quantities of saliva were reported by the lab, salivary cortisol samples were repeated when possible. After collection, salivary cortisol samples were centrifuged prior to freezing at -20 Centigrade. Batched analysis of specimens was completed locally every one to two weeks using an enzyme immunoassay for salivary cortisol. Analysis of salivary cortisol specimens was completed using enzyme immunoassay for salivary cortisol. The low limit of detection for salivary cortisol in the NPE study was <0.2 nanograms per milliliter (ng/ml). Eighty-eight of the infant salivary cortisol samples collected in the NPE study had sufficient quantity for analysis.

Table 1. NPE study procedures for pre-intervention and post-intervention groups

<table>
<thead>
<tr>
<th>Study enrollment</th>
<th>Infant age = 1 month</th>
<th>Infant age = 2 months</th>
<th>Infant age = 3 months</th>
<th>NICU discharge</th>
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<tbody>
<tr>
<td>Infant demographic data; infant salivary cortisol</td>
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<td>Enrolled parent(s) demographic data; parent salivary cortisol</td>
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<td>Parent salivary cortisol; parent visiting and SSC over NICU stay collected from EMR</td>
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*Salivary cortisol samples only collected through NICU discharge. Salivary cortisol samples were not collected for parents and infants discharged prior to monthly sampling.

**Data Management**

Parent and infant data were recorded on parent-infant data sheets that were transcribed to
a computer database by the principal investigator. NMI scores were calculated by the principal investigator following infant discharge and documented on the infant data sheet and in the computer database. Data were assessed for accuracy by a second member of the study team.

Several missing data points were observed in the database for salivary cortisol levels in infants at discharge or at one month of age. Missing salivary cortisol levels were the result of unanticipated infant discharge, sample contamination or an insufficient quantity of saliva that was not repeatable. These missing data points were not replaced or imputed, and missing data points were coded to indicate the data point was missing.

Several salivary cortisol levels in the NPE database that are relevant for the current study were observed to be at the limit of detection (LOD<0.2 ng/ml). LOD data in the dataset were replaced with the single value, 0.14, calculated using the formula, LOD/$\sqrt{2}$. This formula considers the variance of values below the LOD and is recommended in the literature (Croghan & Egeghy, 2003; Johnson, 2018).

**Data Analysis**

The NPE study remains open for additional data analysis. Although preliminary results have been presented at conferences, study results have not been published.
APPENDIX C
LOYOLA UNIVERSITY CHICAGO IRB APPROVAL LETTER
NOTICE OF EXPEDITED APPROVAL OF A RESEARCH PROJECT

Investigator: Rodriguez, Loo

Title: The Effect of Parent Presence in the NICU on Infant Outcomes

Date of Initial Review: 11/18/2021

Type of Review: Expedited

Institutional Review Board: LUP 215462

You have full approval. Your project may begin.

The following is for your information and will help you meet local and federal IRB requirements.

1. You must send the final IRB-approved version of the Consent Document, stating all procedural changes that are not also necessary, but any other changes require prior review and approval.

2. You should monitor the study's enrollment and the consent process and maintain records for IRB approval. The report of the approval will only be sent to the investigator's email.

3. The study's consent checklist should be maintained for reference. The inclusion of any data from this study will require documentation in a written protocol prior to the scheduled date of review.

4. You must include information regarding the status of the project. If the information is not received, the project will be suspended.

5. It is important that you not have any ongoing studies.

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https://portal.uic.edu/template/docs/irb/approvalletter.xmhtml
REFERENCE LIST


VITA

Susan Horner was born and raised in Chicago, Illinois. Before attending Loyola University Chicago, she attended the Northern Illinois University, where she earned a Bachelor of Science in Nursing in 1979. Horner also attended Northwestern University in Chicago, Illinois where she earned a Master of Science in Nursing in 1986.

Horner has been a nurse in the Neonatal Intensive Care Unit (NICU) at the Ann & Robert H. Lurie Children’s Hospital in Chicago (formerly Children’s Memorial Hospital of Chicago) since 1979. Since 2001, Horner has been an advanced practice nurse and the developmental specialist in the NICU at Lurie. She was also on the faculty at Northwestern University’s school of nursing from 1986 through 1987.