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Neonatal Toxic Stress and Long-Term Neurodevelopment in Premature Infants

Rachelle Sey
University of San Diego

UNIVERSITY OF SAN DIEGO
Hahn School of Nursing and Health Science

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NEONATAL TOXIC STRESS AND LONG-TERM NEURODEVELOPMENT IN PREMATURE INFANTS

by

Rachelle R. Sey

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Dissertation Committee
Cynthia D. Connelly, PhD, RN, FAAN, Chairperson
Jane M. Georges, PhD, RN
Gabriella Malagon-Maldonado, PhD, DNP, RN, NEA-BC

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CANDIDATE'S NAME: Rachelle R. Sey

TITLE OF DISSERTATION: Neonatal Toxic Stress and Long-term Neurodevelopment in Premature Infants

DISSERTATION COMMITTEE:

_____

Cynthia D. Connelly, PhD, RN, FAAN
Chairperson

_____

Jane M. Georges, PhD, RN
Committee Member

_____

Gabriella Malagon-Maldonado, PhD, DNP, RN, NEA-BC
Committee Member

Abstract

Background: Evidence suggests the presence of complex biologic connections between the social environment, neurologic development, and long-term health. Premature infants spend many months in the Neonatal Intensive Care Unit (NICU) often separated from their parent(s). Decrease in the age of viability threshold allows more extremely preterm infants to benefit from lifesaving therapies; however, they are frequently exposed to significant stressors that increase their risk for adverse neurodevelopmental outcomes.

Purpose: The purpose of this study is to examine the relationship among socio-demographic factors, exposure to stressors in the NICU environment, stress modifiers/buffers, neonatal morbidities at discharge, and 1. 2-year neurodevelopmental outcomes and 2. risk for autism in infants born less than 32 weeks gestational age cared for in a large, urban, tertiary NICU.

Conceptual Basis: The study design was guided by Mefford's Theory of Health Promotion for Preterm Infants and D'Agata's Infant Medical Trauma in the NICU.

Methods: A retrospective cohort design was conducted to identify predictors leading to variation in long-term neurodevelopment.

Findings: Final models were computed for Bayley III cognitive, language, and motor composite scores. All significant predictors at the $p < 0.05$ level were included in the model while controlling for gestational age. Sociodemographic factors influenced long-term neurodevelopment at 2 years of age. Parent presence in the NICU was an important predictor for cognitive outcomes at 2 years of age. The multivariable regression model explained 23.7% of the variance in Bayley III cognitive composite scores at 2 years of age: $R^2 = 0.237$, R^2 adj. $= 0.148$, $F(26, 225) = 2.681$, $p < .001$. The final multivariable

regression model explained 26.1% of the variance in Bayley III language composite scores at 2 years of age: $R^2 = 0.261$, R^2 adj. = 0.187, $F(23, 228) = 3.504$, $p < 0.001$. The multivariable regression model explained 26.1% of the variance in Bayley III motor composite scores at 2 years of age: $R^2 = 0.175$, R^2 adj. = 0.108, $F(19, 232) = 2.599$, $p < 0.001$.

Research Implications: Identification of modifying factors that influence negative effects of prolonged stress in preterm neonates may lead to identification of interventions that alter the trajectory of long-term neurodevelopmental outcomes for infants discharged from the NICU.

Further research is needed to identify the impact parent presence, nurse-guided family centered developmental care interventions, staffing models, and pain/stress exposure have on short and long-term neonatal outcomes.

Dedication

I would like to dedicate this dissertation to my family. To my loving, kind, and devoted husband, Ryan, thank you for your support in making this doctoral degree a reality and for your never-ending patience and unwavering encouragement that motivated me to complete this work. To my children, Jonas and Morgan, thank you for cheering me on along the way and always rooting for me. I love you both so much and pray that I have set a positive example for you to achieve your dreams to your fullest potential. To my supportive parents who have always led by example and encouraged me to do my best in achieving my goals. I am where I am today because of the unconditional love and support you have provided to me.

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Chapter I

Introduction

The rate of premature infants born, less than 37 weeks gestational age (GA), in the United States continues to rise. In 2017, nearly one in ten infants was born before 37 weeks GA (Centers for Disease Control & Prevention, 2019). A decrease in the age of viability threshold down to 22-23 weeks GA allows more extremely premature infants to benefit from lifesaving therapies in the neonatal intensive care unit (NICU) (Weiner & Zaichkin, 2016). Consequently, these infants are at increased risk of developing significant morbidities including intraventricular hemorrhage, retinopathy of prematurity, and chronic lung disease that may predispose them to cerebral palsy, developmental delay, or vision disturbances (Marcellus & Cross, 2016; Rogers & Hintz, 2016). These alone have a profound impact on the neurodevelopment of premature infants.

Scientific advances continue to demonstrate the complex biologic connection between the social environment, neurologic development, and long-term health. Recently, this has been explored within the context of infants admitted to the NICU. The NICU environment is one that is stressful and traumatic with noise, lights, procedures, and separation from parents. Yet, it is an environment in which premature infants must grow and thrive. Premature infants discharged from the NICU experience varying degrees of neurobehavioral sequelae at follow-up (Church et al., 2012; Montirosso & Provenzi, 2015; Provenzi, Guida, et al., 2018).

Despite advances in care for premature and hospitalized infants, there remain remarkable disparities in long-term neurodevelopment between premature hospitalized neonates and healthy, term infants. In addition to common morbidities, researchers delineate a high

prevalence of low severity morbidities often referred to as the “preemie phenotype” comprised of mental illness including anxiety and depression; behavioral issues; and alterations in the hypothalamic-pituitary-adrenal axis (Church et al., 2012). A review of the literature ascertains this phenomenon may be explained by neonatal exposure to toxic stress as a result of epigenetic changes within the brain (Montirosso & Provenzi, 2015; Provenzi, Guida, et al., 2018).

Problem and Background

Toxic Stress and Brain Development

Research suggests a maladaptive response to stress during early infancy and childhood, also known as toxic stress response, plays an important role in neuronal pathway development (Casavant et al., 2019; Provenzi, Guida, et al., 2018). The concept of toxic stress was introduced with the groundbreaking research conducted by Filetti and colleagues (1998), who explored the relationship between childhood experiences, adult risk behaviors, and mortality. Their research, the largest of its kind, enrolled over 17,000 adult participants. They concluded individuals who had experienced four or more stressful adverse childhood experiences (ACE’s) were more likely to exhibit multiple risk factors related to leading causes of death in adults.

Toxic stress refers to the body’s response to trauma, not to the traumatic, stressful situation. It is characterized by an altered, dysregulated, and prolonged stress response that occurs in relation to severe early life adversity exposure (Bucci et al., 2016). Toxic stress alters the developing brain and impairs functions required for sustained attention, emotional regulation, problem solving, and learning (D'Agata et al., 2017). The extent to which stressful events have detrimental effects on the infant and child are determined by

duration, intensity, and timing of the exposure (Montirosso & Provenzi, 2015). Toxic stress may be mitigated by an individual's level of resilience expressed by a biologic response (genetic predisposition) and/or access to supportive relationships which help to moderate the stress response (D'Agata et al., 2017).

For over a decade, the National Scientific Council on the Developing Child at Harvard has raised awareness on the relationship of toxic stress from early life adversity, exposures to ACE's, and the impact on the developing brain. In a working paper, the council described the impact of environmental influences on gene expression through the study of epigenetics. The changes in gene expression resulting from early prenatal and postnatal experiences, including lack of social connectedness with a supportive caregiver, have been linked to poor long-term health outcomes (National Scientific Council on the Developing Child, 2010).

Neonatal Toxic Stress

Infants born prematurely may spend up to four to five months in the Neonatal Intensive Care Unit separated from their parent(s) or support person. It is well established infants admitted to the NICU experience significant pain and stress over the course of the NICU stay; at times neonates may experience as up to 70 stressful events per day (Cong et al., 2017; Weber & Harrison, 2019). Prolonged exposure to stress in the NICU increases the risk for adverse neurodevelopment (Bucci et al., 2016; Smith et al., 2011). However, uncertainty remains regarding the threshold of exposure to pain and stress, which leads to adverse developmental outcomes. Furthermore, deprivation of the social connection with a caring adult disrupts the homeostasis of the normal biologic stress response. This ultimately undermines the infant's habituation towards attachment, alters

gene expression, and disorganizes healthy development pathways (Marcellus & Cross, 2016). Studies have linked exposure to repeated pain and stress to decreased brain size and function specifically in the frontal and parietal areas on magnetic resonance imaging, as well as altered temporal microstructure and functional connectivity (Smith et al., 2011; Vinall et al., 2012). Smith et al. (2011) concluded early exposure to multiple stressors was related to altered neurobehavior for infants when assessed prior to NICU discharge.

Purpose

The purpose of this study was to examine the relationship among socio-demographic factors, exposure to stressors in the NICU environment, stress modifiers/buffers, neonatal morbidities at discharge from the NICU and 1. 2-year neurodevelopmental outcomes using Bayley Scales of Infant Development (3rd Edition) (Bayley III), and 2. risk for autism in infants born less than 32 weeks gestational age using the Modified Checklist for Autism in Toddlers (M-CHAT), for infants cared for in a large, urban, tertiary NICU in Southern California. Using a retrospective cohort design, this study was designed to answer the following general research questions:

1. What are the defining characteristics of maternal infant dyads within this large, urban tertiary NICU?

2. What are the associations among socio-demographic factors, exposure to NICU environment, stress modifiers, neonatal morbidities, and 2-year neurodevelopmental outcomes in infants born less than 32 weeks gestational age?

Specific Aims

- AIM 1: To describe the maternal-neonatal demographics and clinical stressors, environmental stressors and stress modifiers, neonatal morbidities, and 2-year

neurodevelopmental outcomes (Bayley III: motor, language, and cognitive scales and M-CHAT autism screen) among neonates receiving care in a large tertiary NICU in Southern California.

- AIM 2: To examine the relationships among maternal/neonatal demographics, environmental stressors, stress modifiers, neonatal morbidities, neurodevelopmental outcomes (Bayley III: motor, language & cognitive scales, and M-CHAT autism screen) at two years of age.
- AIM 3: To identify the amount of variance in neurodevelopmental outcomes (Bayley III: motor, language, & cognitive scales) at 2 years of age accounted for by maternal/neonatal demographics, environmental stressors, stress modifiers, and neonatal morbidities.
- AIM 4: To identify the odds of positive autism screen on the M-CHAT at 2 years of age as determined by maternal/neonatal demographics, environmental stressors, stress modifiers, and neonatal morbidities.

Introduction to Research Conceptual Framework

The study conceptual framework is informed by components of the toxic stress framework, Mefford's Theory of Health Promotion for Preterm Infants, and D'Agata's Infant Medical Trauma in the NICU (IMTN) conceptual model that conveys the neonatal stress experience on health outcomes (D'Agata et al., 2016; Mefford & Alligood, 2011). The IMTN model encompasses three life experiences unique to the NICU that D'Agata proposes may influence long-term health in neonates: stress, parental separation, and pain. All three of these experiences are modifiable according to D'Agata allowing potential for increased resilience, while minimizing detrimental effects related to

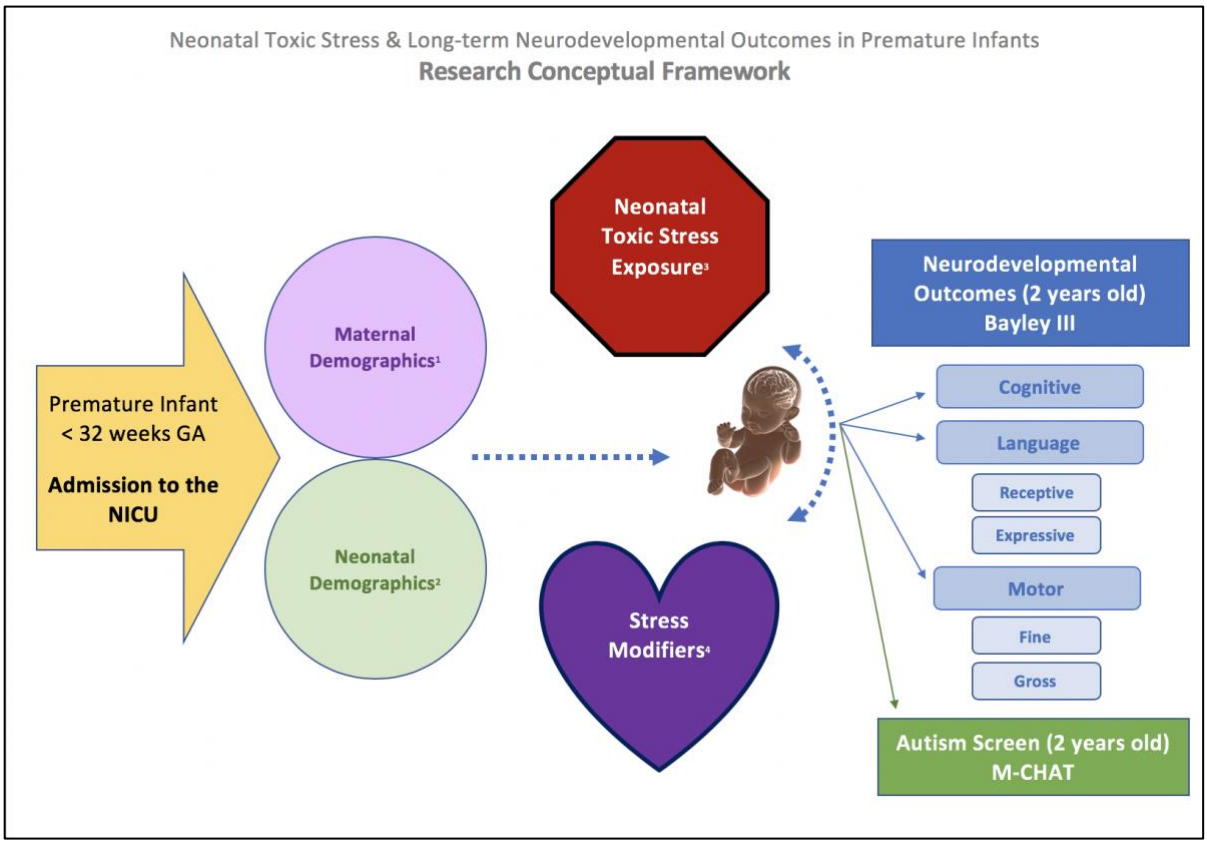
increased allostatic stress burden on the neonate (D'Agata & McGrath, 2016; D'Agata et al., 2017).

Toxic stress is the prolonged activation of the brain's response (*threat*) to trauma in the absence of a protective, nurturing adult relationship buffer (*deprivation*) that results in a complex alteration of brain development exhibited by poor long-term health outcomes. Neonatal intensive care is an early life adverse experience that includes experiences of both threat (exposure to pain and sensory input that changes the response to fear) and deprivation (absence of maternal care/socioemotional experience). These concepts are interwoven within the research conceptual framework.

The research conceptual framework depicted below illustrates the potential relationships independent variables (neonatal/maternal demographics, stressors, and stress modifiers) for infants born less than 32 weeks gestational age have on the variation of dependent variables (cognition, language development, motor development, and autism screen) at 2 years of age. The selected independent variables listed in the conceptual research framework in Figure 1 and Appendix A are proxies for parent presence/separation and stress/pain experienced by the neonate. Both neonatal and maternal demographics have the potential to directly influence long-term patient outcomes such as the dependent variables. The curved dotted line between "neonatal toxic stress exposure" and "stress modifiers" indicates the potential relationship that exists between stress exposure and parent presence or other buffers to influence the variance in long-term neurodevelopmental outcomes and/or the risk for autism.

Figure 1

Research Conceptual Framework



Implications for Nursing

The NICU admission, regardless of diagnosis, exemplifies an early life adverse experience for the neonate that has a profound impact on future neurodevelopment. Identification of modifying factors influencing negative effects of prolonged stress in preterm neonates may lead to identification of interventions that alter the trajectory of long-term neurodevelopment for infants discharged from the NICU. This would allow clinicians to target specific, individualized, preventative, and neuroprotective strategies to improve neonatal neurodevelopmental outcomes for a lifetime. This study will add to the growing research related to parent presence, developmental interventions, nurse staffing models, stress exposure, and the impact on neonatal outcomes.

Chapter II

Review of the Literature

The purpose of this chapter is to present the current, relevant literature related to toxic stress, neonatal stress, the role parent/family presence in stress modification, and preterm infant neurodevelopment. This chapter also contains an in-depth overview of the theoretical and research conceptual framework used to guide the development of this study.

Toxic Stress

Toxic stress occurs when a substantial, prolonged stress response follows exposure to sustained adversity without adequate buffering support from an adult caregiver (National Scientific Council on the Developing Child, 2005). There are varying degrees of stress; it is important to note not all stress has negative consequences for the individual. To further define toxic stress, it must be differentiated from positive and tolerable stress. Positive stress is the result of normal development and results in a natural biologic response to a stressor. An example includes an infant or child who encounters a brief, stressful episode such as an injection. There is a temporary autonomic response, as well as brief visible distress signals. Tolerable stress is slightly more exaggerated and involves an elevated stress response as a result of more severe stressors. A suitable example of tolerable stress is separation anxiety where a parent is absent for several hours, then returns, resulting in a slightly longer period of anxiety and stress response in the child before returning to baseline. These three levels are not quantifiable due to the complexity of the stress response; however, they do allow the ability to categorize stress

based on the relative severity of the infant's response to a stressful condition (Ash & Williams, 2016).

The Adverse Childhood Experiences Study

The concept of toxic stress originated from the groundbreaking research of Filetti and colleagues (1998); they explored the relationship between childhood experiences, adult risk behaviors, and mortality. Their research enrolled over 17,000 adult participants and established individuals who had experienced four or more stressful adverse childhood experiences (ACEs) were more likely to exhibit multiple risk factors related to leading causes of death in adults. According to the authors, ACEs include physical, emotional, or sexual abuse; mental illness exposure; substance abuse; observed violence; and criminal behavior (Felitti et al., 1998).

National Scientific Council on the Developing Child

In 2004, the National Scientific Council on the Developing Child at Harvard University published their first working paper on early childhood development and the influence of relationships. Later in 2005, they published another working paper on the effects of excessive stress and the developing brain. For over a decade, this council has raised awareness of the relationship of toxic stress from early life adversity, exposures to ACEs, and the impact on the developing brain. In a more recent working paper, the council describes the impact of environmental influences on gene expression through the study of epigenetics. The changes in gene expression resulting from early prenatal and postnatal experiences, including lack of social connectedness with a supportive caregiver, have been linked to poor long-term health outcomes (National Scientific Council on the Developing Child, 2010).

American Academy of Pediatrics & American Academy of Nurses

Both the American Academy of Pediatrics (AAP) and the American Academy of Nurses (AAN) have published policy statements regarding the harmful effects of toxic stress on the developing infant and the brain (Garner et al., 2012; Gross et al., 2016). The AAP technical paper proposes many chronic illnesses may be diminished if the underlying mechanisms of toxic stress are addressed (Garner et al., 2012). The AAN's published policy statement labels toxic stress as a top priority and calls for interventions to protect the infant from the devasting consequences of toxic stress, especially in the first 5 years of life (Gross et al., 2016).

Trauma Informed Care Model in the NICU

In 2014, Coughlin published a book entitled, *Transformative Nursing in the NICU: Trauma-Informed Age Appropriate Care*. This book provides a developmental framework to minimize and prevent the adverse outcomes related to neonatal toxic stress. Coughlin emphasizes the importance of providing responsive, genuine caring to premature and chronically ill, hospitalized neonates who are exposed to toxic stress in the NICU. Coughlin (2017) published clinical practice guidelines for trauma informed care in the NICU. These guidelines provide a care delivery model guided by core measures to minimize the impact of the trauma experience on the neonate-family dyad.

Neonatal Toxic Stress

A concept's defining attributes are the core element of concept analysis. The defining attributes are the characteristics most frequently associated with the concept, which distinguish it from other related concepts (Walker & Avant, 2019). The essential attributes of toxic stress can be categorized into two main themes: threat and deprivation.

Within the context of the NICU, both of these are present, since the infant is exposed to pain and stressors from sensory inputs culminating in elevated stress levels (*threat*) and the absence of a consistent, responsive connection with a parent or primary caregiver (*deprivation*) (Coughlin, 2014).

Threat

The first attribute for toxic stress acknowledged collectively in the literature is described as a prolonged stress exposure leading to a dysregulation of the physiologic stress response (Ash & Williams, 2016; Bucci et al., 2016; D'Agata et al., 2017; National Scientific Council on the Developing Child, 2005).

Deprivation

In order for the body to respond naturally to a stress response, there must be protective factors present to buffer the effects of exposure to prolonged stress. Deprivation of the social connection with a caring adult disrupts the homeostasis of the normal biologic stress response. This ultimately undermines the infant's habituation towards attachment, alters gene expression, and disorganizes healthy development pathways (Marcellus & Cross, 2016). Neonates are sensitive to maternal presence. When this supportive, responsive relationship with a caring adult early in life is non-existent or minimal, the stress response remains elevated leading to dysregulation of the stress response system resulting in toxic stress. Consequently, the second attribute of toxic stress is absence of a constant, loving adult relationship to buffer the prolonged, elevated stress response.

Antecedents

Antecedents are the events that must be present prior to the occurrence of the concept (Walker & Avant, 2019). The antecedents for neonatal toxic stress include trauma and exposure to adversity or ACE's that occurs during a sensitive period of neurodevelopmental growth.

Trauma

Exposure to trauma early in life is associated with long term health outcomes and is an important determinant of health. Early life adversity, also referred to as adverse childhood experiences as described by Felitti and colleagues (1998), includes stressful or traumatic experiences in childhood including abuse, neglect, and household dysfunction. Hospitalization of an infant or child is also considered an ACE that may precipitate toxic stress (Shah et al., 2016). Admission to the NICU is a traumatic experience, which is marked by unexpected, prolonged maternal separation coupled with a potential life-threatening diagnosis involving medical interventions and invasive procedures to sustain life (Coughlin, 2014).

Sensitive period of neurodevelopmental growth

Critical periods of brain growth and development occur in utero, after the infant is born, and continue through early childhood into adolescence. During this time of rapid brain growth, the brain organization is influenced by experiences in the environment. Synaptogenesis, pruning, and myelination are all critical for the development of neural pathways during early childhood (Volpe et al., 2018). Premature neonates have a lower threshold to pain and stressors due to their immature brain structure and ability to respond to stressful and painful encounters. Several studies have attributed exposure to pain

during vulnerable brain growth and organization as detrimental to later growth and development due to rewiring of the neuronal pathways. Furthermore, some studies have linked exposure to repeated pain to decreased brain size and function (Smith et al., 2011; Vinall et al., 2012).

Exposure to adversity

The infant in the NICU is exposed to a variety of environmental stressors in addition to those imposed by their primary and secondary diagnoses. The primary stressor is *maternal separation*. In addition, neonates in the NICU are exposed to *pain* from medical devices, procedures, and care. The *environment* also presents several stressors, which include bright lights, excessive noise, sleep deprivation, and isolation. Research indicates environmental stressors activate the stress response involving the hypothalamic-pituitary-adrenal (HPA) axis (Coughlin, 2014).

Consequences

Consequences are the outcomes that occur as a result of the concept. Exploring consequences is useful in determining additional variables or relationships that may be useful in developing future research (Walker & Avant, 2019). Current literature suggests a maladaptive response to stress during early childhood, also known as toxic stress response, plays an important role in the neuronal pathway development. There is a link between exposure to early adversity to later developmental of illness (Bucci et al., 2016). Exposure to toxic stress in early childhood is associated with physiologic maladaptation across various systems including immune, metabolic, and nervous systems (Slopen et al., 2014). As a result, consequences of a prolonged, activated stress response are associated

with negative long-term health outcomes including cardiovascular disease, obesity, diabetes, asthma, immune disorders, and premature death (Garner et al., 2012).

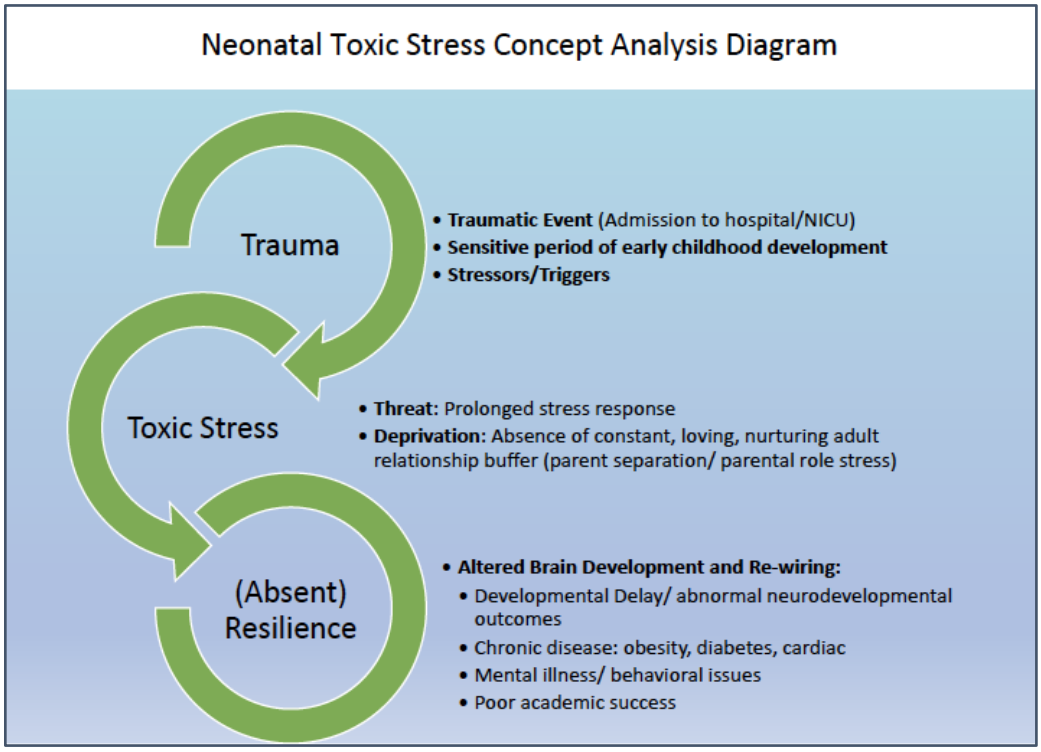
In addition to the health outcomes described above, extensive evidence of the effects of negative early life experiences and altered mental and behavioral health outcomes have been presented including anxiety, depression, and mood disorders (Sanders & Hall, 2018). Associations between toxic stress and poor academic success have also been described in the literature. Toxic Stress alters the developing brain and impairs functions required for sustained attention, emotional regulation, problem solving, and learning (D'Agata et al., 2017). The extent to which stressful events have detrimental effects on the infant and child may be determined by duration, intensity, and timing of the exposure. Toxic stress may be mitigated by an individual's level of resilience expressed by a biologic response (genetic predisposition) and/or access to supportive relationships, which help to moderate the stress response (National Scientific Council on the Developing Child, 2010).

The derived operational definition for toxic stress is the prolonged activation of the brain's response (*threat*) to trauma in the absence of a protective, nurturing adult relationship buffer (*deprivation*) that results in a complex alteration of brain development exhibited by poor long-term health outcomes. A pictorial diagram depicting the antecedents, defining attributes, and consequences for the concept of neonatal toxic stress is located in Figure 2. The image illustrates a linear connection between the antecedents (traumatic event, sensitive period of early childhood development, and stressors) and the defining attributes of toxic stress (threat and deprivation). The connection between the defining attributes of toxic stress and the consequences represent a circular relationship

dependent on the presence or absence of resilience to buffer the prolonged stress response.

Figure 2

Neonatal Toxic Stress Concept Analysis Diagram



NICU Environment and Stressors

There are many sources of stress within the NICU environment including excess noise, lighting, maternal separation, social isolation, invasive procedures, and excessive handling (Santos et al., 2015). These stressors are associated with early life exposure that adversely impact premature infants. Cong and colleagues (2017) conducted a prospective exploratory study following 50 preterm infants 28 to 33 weeks GA to investigate the impact of early life painful/stressful experiences on neurobehavioral outcomes of preterm infants once they reached 36 to 37 weeks GA, while still in the NICU. In this study, preterm infants in the first 4 weeks of life experienced a total of 643±64.5 acute

procedures with a daily average of approximately 23 acute procedures per day. These authors also looked at hours of parent contact in the NICU (holding, breastfeeding, skin to skin care). They concluded preterm infants experience high numbers of daily acute events, as well as cumulative stress exposure over time. The increased exposure to pain and cumulative stress contributed significantly to short-term neurobehavioral outcomes using the NICU Network Neurobehavioral Scale (NNNS) at 36 to 37 weeks GA. Parent contact, specifically skin to skin care (SSC), and breastfeeding also positively influenced NNNS habituation scores (Cong et al., 2017).

Provinzi and his team of researchers (2018) completed a prospective study looking at the impact of early stress exposure in the NICU and its association to telomere length changes within the genomic DNA from cord blood at birth and peripheral blood samples at discharge. NICU related stress was calculated from the number of skin breaking procedures (heel punctures, peripheral venous line insertion, and arterial and venous punctures) and amount of exposure to mechanical ventilation. These authors identified telomere length erosion occurred in very preterm infants in response to pain and stress exposure (Provenzi, Giorda, et al., 2018).

Furthermore, Smith et al. (2011) assessed cumulative exposure and concluded early exposure to multiple stressors correlated with altered neurobehavior for infants when assessed at their term equivalent prior to NICU discharge. This prospective cohort study evaluated 44 preterm infants less than 30 weeks GA at birth. Cumulative stress was measured using the Neonatal Infant Stress Scale (NISS). Stressful exposures were captured from enrollment at birth until discharge from the NICU or until the infants reached term equivalent age. The researchers assessed short-term neurobehavior at

discharge using the NNNS, as well as MRI scans to measure brain injury and diffusion tensor imaging. They identified the average daily exposure to stressors was greatest in the first 14 days of life, consistent with other study findings. These exposures were highly variable among infants in the study. However, they found infants with greater exposure to stressors was associated with decreased frontal and parietal brain width, altered diffusion measures and functional connectivity in the temporal lobes based on MRI results. They also noted abnormal motor behavior assessed using the NNNS (Smith et al., 2011). Additional studies are necessary to examine the impact of stress on long-term neurodevelopment in premature infants.

Modifiers for Neonatal Stress Exposure

Parent Presence

For the most part, when an infant is admitted to the NICU, the primary care of the infant is transferred from the parent to the NICU caregivers, even though the NICU strives for a family-centered care environment. As a result, there is an altered parental role and subsequent infant-parent separation that disrupts the nurturing adult relationship buffer required to mitigate the effects of toxic stress exposure. Maternal-infant separation is a considerable stressor for neonates receiving care in the NICU (Coughlin, 2017; Marcellus & Cross, 2016; Weber et al., 2018). Typical models in NICUs don't allow for parents to room in next to their infant; some NICUs even have limitations to visitation hours for family members. Although, this paradigm has begun to change with the heightened awareness of the importance of family centered care, it may not be enough to mitigate the stress caused by parent-infant separation, critical for normal infant growth

and development (Cong et al., 2017). In order for adequate social connection and attachment to occur, this separation needs to be minimized.

The second attribute of toxic stress is the absence of a loving, stable adult relationship to buffer prolonged stress responses. Research supports the importance of parent presence and early interaction with the infant (Bergman, 2019; Bergman et al., 2019; Gonya et al., 2017; Weber et al., 2018; Weber et al., 2012). According to Bergman (2019), parent separation is routine in many NICUs for a variety of reasons and is considered a source of toxic stress. There currently is no specific instrument available to measure this attribute. However, this can be measured by logging parent presence (frequency and duration) and cataloging interactions with the infant including skin to skin kangaroo care, holding, breastfeeding, hand swaddling, singing, reading, touching, and participating in infant care (Cong et al., 2017).

Attachment and bonding may be altered by a variety of factors. Some of these factors are out of the control of both practitioners and parents, including the parent's own role stress or difficulty coping in the NICU. The environment is often overwhelming and there are many obstacles to promoting attachment, including high propensity for post-partum depression, stress, and anxiety. The quality of the relationship infants have with their caregivers plays an integral role in regulating the infant's stress response. Relationships that convey safety, security, and love aid in cultivating resilience (Coughlin, 2017).

Parent presence is an important component to mitigate the consequences of overall toxic stress exposure in neonates. But parents may not always be able to visit their infant consistently in the NICU. They may have other obligations, such as other siblings

at home to care for. When the length of stay (LOS) in the NICU is long, some parents have to return to work before the infant is discharged home. Distance from the hospital may be a barrier to visitation, as well as transportation difficulties. Parents who suffer from post-traumatic stress disorder from prior experiences in the NICU or mothers who struggle with postpartum depression may find it difficult to visit their infant in the NICU and build attachment. Neonates' emotional and behavioral development is dependent on early social connections. Therefore, sustained parental engagement is a key component of family centered developmental care interventions. Alternative strategies, when the parents are absent, are necessary to form this early socialization of the newborn while in the NICU (Sanders & Hall, 2018).

In a prospective cohort study, Reynolds et al. (2013) concluded infants who had increased parent visitation and were held more often demonstrated improved short-term neurobehavior measured by the NNNS at term equivalent by NICU Discharge. These authors did not study the longitudinal impact on later long-term neurodevelopment. In their study, they found as the infant spent time in the NICU the number of visitation hours decreased, but the number of times the infants were held increased. Increased holding demonstrated less stress and less arousal at the term age equivalent on the NNNS. Motor developmental also improved with increased holding and increased parental visitation (Reynolds et al., 2013).

Developmental Care Interventions

Weber and colleagues (2018) completed a secondary analysis of data from a larger prospective, longitudinal study of infants born less than 29 weeks gestational age. The aim of the secondary analysis was to examine whether human milk, touch, or stress

exposure was related to plasma oxytocin trajectories (OT) in premature infants. OT is important for attachment and bonding. The OT system also interacts with the hypothalamic-pituitary-adrenal axis that is responsible for the stress response and the autonomic nervous system (Weisman et al., 2013). Plasma oxytocin is a social hormone marker that has the potential to assess relationship of nurse-guided interventions, i.e. human touch, provision of human milk, and reducing infants' exposure to stress in the NICU environment. Weber and her team looked at a subset of 33 infants ranging from 25 to 29 weeks GA from three midwestern level III NICUs. In addition to maternal and neonatal demographics, the independent variables of interest included nurse guided interventions, for example volume of mother's milk consumed by the infant, skin to skin care, parent holding, and neonatal infant stressor scale (NISS) scores. Linear mixed models tested associations between these nurse guided variables and the dependent variable, plasma oxytocin trajectories. The authors concluded the volume of human milk consumed was not related to infant plasma OT levels nor was there an increase in OT levels with increased NISS scores. They identified a decline in plasma OT levels with increasing GA. However, they did find skin to skin care (SSC) is associated with the steepness of decline, indicating SSC enhances a natural decline in OT levels. This study highlights the potential interactions of parents and nurses that may impact the developing premature infant; however, additional, larger studies are needed to support this finding.

Gonya and his team (2017) conducted a retrospective cohort study looking at 97 premature infants born less than 27 weeks gestation age, admitted to the small baby intensive care unit (SBICU). The SBICU maintained specialized guidelines for all infants less than 27 weeks gestation age, which included SSC. In their study, they used

correlations and logistic regression to examine relationships between high and low amounts of SSC and Bayley Scales of Infant and Toddler Development Third Edition (Bayley-III) composite cognitive scores at 6 and 12 months of age. SSC varies among families; patterns were evident and appeared to have an impact on early cognitive and language outcomes in their study.

A systematic review of developmental care interventions in NICUs found positive effects related to variations in language, motor, and cognitive development up to 18 months of age (Burke, 2018). This systematic review identified kangaroo SSC and infant massage were significant and concluded holding and touch should be included in any routine developmental care programs. A primary indicator for many developmental care interventions is parent involvement; however, while the majority of the studies included in this systematic review measure parent involvement, they did not capture parent's ability to provide interventions. Due to the variation in developmental care practices across NICU settings, it is difficult to identify which interventions in this systematic review had the most impact on developmental care outcomes.

Nurse Staffing Models

It is clear parent-infant bonding and social connection are critical for natural growth and development of the newborn and infant. However, in the absence of parent presence, this may be unavoidable, additional alternative NICU caregiving models need to be evaluated that provide protective neurodevelopment. One such model may be a consistent caregiver model where the number of care providers in the NICU is minimized to create a more stable environment for the infant in the NICU. Neonatal nurses have a profound impact on the developing neonate and promoting parent-infant interactions

(Weber et al., 2018). They spend considerably more amounts of time interacting with the neonates than other healthcare providers.

Nurse work environments are correlated with parent presence in the NICU (Hallowell et al., 2019). Hallowell and colleagues (2019) conducted a cross-sectional, observational secondary analysis to examine relationships between subscale items on the Practice Environment Scale of Nurse Work Index (PES-NWI) and the proportion of time parents spent in the NICU during a nurse's shift. The composite PES-NWI score and subscale scores for Nurses Participation with Hospital Affairs and Manager Leadership and Support were moderately correlated with increased parent presence during the nurse's shift. According to this study, the elements of a positive nurse work environments that lead to increased parent presence include having effective nurse manager support, and sufficient staffing and resources available to provide additional nursing support encouraging family presence and participation.

Premature Infant Neurodevelopment

The rate of premature infants born less than 37 weeks GA in the United States continues to rise. With the largest percentage of premature infants in the 34 to 37 weeks GA range and nearly 2% born less than 32 weeks GA (Rogers & Hintz, 2016). According to the Centers for Disease Control & Prevention, in 2017 the rate of premature births was one in ten infants, born before 37 weeks GA. Changes in resuscitation of infants less than 26 weeks has led to a decrease in the age of viability threshold down to 22-23 weeks GA (Weiner & Zaichkin, 2016). This allows more extremely premature infants to benefit from lifesaving therapies in the NICU. Advances in technology have resulted in increased survivability of these extremely preterm infants, but not without risk of developing

significant morbidities such as hearing and vision impairment, neurologic deficits, and chronic lung disease (Marcellus & Cross, 2016; Rogers & Hintz, 2016) . Premature infants discharged from the NICU experience varying degrees of neurobehavioral sequelae at follow-up (Church et al., 2012; Montirosso & Provenzi, 2015; Provenzi, Guida, et al., 2018; Rogers & Hintz, 2016).

Neurodevelopmental impairment is inversely proportional to GA at birth; therefore, GA is a primary contributing variable in the degree of impairment seen at follow-up from the NICU. However, early developmental care interventions have demonstrated improvements in long-term neurodevelopment of preterm infants (Orton et al., 2009; Santos et al., 2015). A Cochrane review evaluating early developmental interventions in preterm infants' post-discharge in the first year of life exhibited improvements in both motor and cognitive outcomes. The cognitive benefits extended into the preschool age for these preterm infants. The authors noted interventions focusing on the parent-child relationship as a whole, versus the infant or the parent alone, were more beneficial (Spittle et al., 2015).

Epigenetics and Neurodevelopment

Epigenetics describes the interaction between genes and the environment (Maddalena, 2013). While interactions with the environment cannot physically change the gene, it changes how gene's phenotypes are expressed. This may account for the "preemie phenotype" that clinicians refer to when describing behavioral characteristics of preterm infants (Church et al., 2012). Epigenetics reinforces the concepts of toxic stress and may elucidate how early experiences for preterm infants both prenatally and postnatally in the NICU environment and beyond impact long term neurodevelopment

outcomes. How clinicians work to minimize stress/pain exposure and implement buffers is critical to altering the trajectory for long term outcomes.

Theoretical Model and Research Conceptual Framework

Mefford's Health Promotion in Preterm Infants Theory is a middle-range theory guided by Levine's (1964) *Four Conservation Principles in Nursing Theory* that encompasses four conservation principles guiding nursing practice: conservation of energy, conservation of structural integrity, conservation of personal integrity, and conservation of social integrity. A key component in Levine's theory is adaptation from one environment to another, which the individuals "fit' the environments in which they live" (Levine, 1996). Mefford builds on these principles within the context of the premature infant in the NICU. Admission to the NICU's stressful environment requires the preterm neonate to adapt early and quickly to the extrauterine environment. According the Mefford, the nurse is central to this adaptation process for both the neonate and the parents (Mefford & Alligood, 2011).

Mefford identifies corresponding concepts to Levine's four conservation principles: physiologic immaturity at birth (principle of energy conservation), structural immaturity at birth (principle of structural integrity), neurologic immaturity at birth (conservation of personal integrity), and family system characteristics at birth (conservation of social integrity). Mefford and Alligood (2011) tested the middle range theory examining the consistency of nursing caregivers and the intensity of nursing care on upholding these four principles while achieving the intended outcome of health or wholeness at discharge. The effect of consistency in nursing aligns with the literature presented above and demonstrates the influence the nurse has on minimizing stress,

promoting development and attachment while encouraging family presence and connection to promote health outcomes.

D'Agata and McGrath (2016) convey the neonatal stress experience on outcomes in the Infant Medical Trauma in the NICU (IMTN) conceptual model. Within this model, there are three life experiences unique to the NICU she proposes may influence long-term health in neonates: stress, parental separation, and pain. All three of these experiences are modifiable according to D'Agata allowing potential for increased resilience, while minimizing detrimental effects related to increased allostatic stress burden on the neonate (D'Agata & McGrath, 2016; D'Agata et al., 2017).

There are 5 primary assumptions within the IMTN model proposed by D'Agata and McGrth (2016). One, an infant admitted to the NICU is exposed to an enhanced level of care as a result of a compromised health status. Two, the primary care of the infant is transferred from the parent(s) to the NICU caregivers such as the nurse. Three, the NICU experience is different than that experienced by a healthy term neonate. Four, the NICU infant experiences increased stress, parental separation, and pain compared to the healthy infant. Finally, the combined experience of stress, separation from parent(s), and pain exposure may contribute negatively to the infant's overall long-term health resulting from increased allostatic stress load. These assumptions are interwoven throughout the research conceptual framework for the current study as described below.

There are similarities that run parallel within both the Health Promotion for Preterm Infant Theory and the Infant Medical Trauma in the NICU Model. First, the experience of early, unanticipated delivery, and admission to the NICU is foremost. Second, parent attachment/presence and social interaction are important for healthy

outcomes. Third, the nurse and staffing models contribute to promoting healthy neurodevelopment through nurse guided interventions aimed at increasing parent-infant interactions and minimizing stress.

As mentioned previously, toxic stress is the prolonged activation of the brain's response (*threat*) to trauma in the absence of a protective, nurturing adult relationship buffer (*deprivation*) that results in a complex alteration of brain development exhibited by poor long-term health outcomes. Neonatal intensive care is an early life adverse experience including experiences of both threat (exposure to pain and sensory input that changes the response to fear) and deprivation (absence of maternal care/socioemotional experience). The concept of neonatal toxic stress is supported by both the INMT model and the Mefford's Health Promotion Model and underpins the research conceptual framework for this study as described below.

The research conceptual framework depicted in Figure 1 maps the potential relationships independent variables (neonatal/maternal demographics, stressors, and stress modifiers) for infants born less than 32 weeks gestational age have on the variation of dependent variables (cognition, language development, motor development and autism screen) at 2 years of age. The selected independent variables listed in conceptual research framework are proxies for parent presence/separation and stress/pain experienced by the neonate. Both neonatal and maternal demographics have the potential to directly influence long-term patient outcomes such as the dependent variables (Fuller et al., 2019; Ko et al., 2013). Therefore, there is a straight dotted line indicating that relationship in the conceptual framework. The curved dotted line between "neonatal toxic stress exposure" and "stress modifiers" indicates the potential relationship that exists between

stress exposure and parent presence or other buffers to influence the variance in long-term neurodevelopmental outcomes and/or the risk for autism.

Health Implications and Summary

Toxic stress is a potentially treatable mental health problem in childhood; however, it is one of the most underrecognized public health concerns. In addition to minimizing a neonate's exposure to stressors and pain while in the NICU, providers can identify the parent or adult caregiver and the infant's propensity towards recovery and resilience to improve long-term consequences of elevated stress exposure. Additional research is needed to develop a clearer understanding of the mechanisms of early life experience and toxic stress in the NICU and neurodevelopmental outcomes. This will allow clinicians to target specific, individualized, preventative, and neuroprotective strategies to improve neonatal neurodevelopmental outcomes for a lifetime. Therefore, the purpose of this study was to explore the relationship among socio-demographic factors, exposure to stressors in the NICU environment, stress modifiers/buffers, neonatal morbidities at discharge from the NICU, and 2-year neurodevelopmental outcomes, as well as risk for autism in infants born less than 32 weeks gestational age cared for in a large, urban, tertiary NICU.

Chapter III

Methodology

The purpose of this study was to examine 1. the relationship among socio-demographic factors, exposure to stressors in the NICU environment, stress modifiers and buffers, neonatal morbidities at discharge from the NICU and 2-year neurodevelopmental outcomes, and 2. risk for autism using the M-CHAT at 2 years of age in infants born less than 32 weeks gestational age cared for in a large, urban, tertiary NICU. Within this chapter, the research design, sample and sample characteristics, procedures for study conduct including data collection, and data analysis techniques are described. The protection of human subjects is also presented.

The specific aims for this study include:

- AIM 1: To describe the maternal-neonatal demographics and clinical stressors, environmental stressors and stress modifiers, neonatal morbidities, and 2-year neurodevelopmental outcomes (Bayley III motor, language, and cognitive scales and M-CHAT autism screen) among neonates receiving care in a large tertiary NICU in Southern California.
- AIM 2: To examine the relationships among maternal/neonatal demographics, environmental stressors, stress modifiers, neonatal morbidities, neurodevelopmental outcomes (Bayley III: motor, language & cognitive scales, and M-CHAT autism screen) at two years of age.
- AIM 3: To identify the amount of variance in neurodevelopmental outcomes (Bayley III: Motor, Language, & Cognitive scales) at 2 years of age accounted for

by maternal/neonatal demographics, environmental stressors, stress modifiers, and neonatal morbidities.

- AIM 4: To identify the odds of positive autism screen on the M-CHAT at 2 years of age as determined by maternal/neonatal demographics, environmental stressors, stress modifiers, and neonatal morbidities.

Study Design

This study employed a retrospective cohort design. All variables including outcome measures were previously assembled for the purpose of developing a clinical and administrative database at the organization level. This data was analyzed in order to define the study sample by examining prevalence and distributions of both predictors and outcomes within the select population and by characterizing associations between variables.

Retrospective cohort study designs are relatively inexpensive and less time-consuming to conduct because all data has already been collected. However, this leads to the potential disadvantage of less control over the measurement and subject selection (Hulley et al., 2013). The researcher is limited to existing variables within the database or those that can be adequately extracted from an electronic record. The result may mean there is incomplete, inaccurate, or miss-aligned measurement data. For example, the nature of a retrospective cohort design using a preexisting database lends itself to subjects from the primary cohort potentially being lost to follow-up. Furthermore, another potential disadvantage is interpretation may be blurred by the presence of multiple confounding variables (Hulley et al., 2013). Nevertheless, the use of a retrospective

cohort design provides a feasible, cost-effect method to explore and address the study aims for this proposed study.

Study Sample and Setting

A convenience sample of patients who met inclusion criteria were included in this study. The existing institution's high-risk infant follow-up electronic REDCap database was reviewed from January 2012 through April 2020 to identify infants who met inclusion criteria as detailed below. This database consists of neonates who were admitted and received NICU care in a large, tertiary 84-bed, Magnet® Program recognized NICU in Southern California and who completed their two-year follow-up at a California Children's Services approved high risk infant follow-up (HRIF) program. This hospital is the largest health care center dedicated to women and newborns in Southern California delivering roughly 8,000 infants annually including both high-risk and premature infant deliveries, thus, providing a large, diverse sample population.

Inclusion criteria. Preterm infants born less than 32 weeks GA and admitted to the NICU with LOS greater than 30 days were included in this study. Additionally, these infants completed the Bayley III developmental assessment and the M-CHAT autism screening at 2 years of age in a HRIF program.

Exclusion criteria. Infants who had known major congenital anomalies; severe neurologic deficits including cerebral palsy, seizures, or seizure disorders; did not survive to discharge; or who were born as a result of a surrogate pregnancy were excluded from data analysis.

Sample Size

There were approximately 650 infants in the follow-up REDCap database who had completed a 2-year HRIF visit. It was estimated that roughly 20% of the infants in this database would not meet the inclusion criteria leaving approximately 480 eligible infants for inclusion in the data analysis. An a priori power-analysis to determine adequate sample size was conducted using G*Power 3.1; a sample size of approximately 305 is needed to achieve an 95% power with a medium effect size (f^2=0.15) given a two-sided alpha level of 0.05 given the current number of predictor variables (44) for a linear multivariable regression. Additionally, according to Tabachnick and Fidell (2012), the formula used to calculate the N for a multiple regression is: N should be greater than 50 plus 8 times the number of predictor variables. Using this calculation, a minimum sample size of 402 is needed. For this study, all eligible infants who met the inclusion and exclusion criteria were included in the study.

Independent Variables

Independent variables were limited to documentation extracted from the electronic health record (EHR). Independent variables consisted of both nurse guided interventions (modifiers) and environmental factors, as well as variables that aided the researcher in quantifying both stress exposure and parent presence/activity. The complete list of variables and operational definitions is located in the Variable Table located in Appendix B. Descriptive statistics using both maternal and neonatal demographic variables were used to describe the study sample. These variables were used as both independent variables and/or confounders contributing to the overall regression models. All variables were derived and supported by the literature and the principal investigator's

clinical experience to have a potential effect on the dependent variables. Items meeting statistical assumptions and significance were included in the final models. Proxies from the EHR were selected to represent parent presence (time from birth to first hold, time from birth to first skin to skin, time to first breastfeeding, some breastmilk at discharge, and parent visitation).

There are inherent limitations in using data extracted from the EHR because the primary intent of the documentation was not for the intended retrospective research use. Literature supports the importance of parent presence and early interaction with the infant (Bergman, 2019; Bergman et al., 2019; Gonya et al., 2017; Weber et al., 2018; Weber et al., 2012). Therefore, collecting data that reflects these interactions (holding, breastfeeding, parent visitation) were included as predictors in the overall regression models. For the most part, when an infant is admitted to the NICU, the primary care of the infant is transferred from the parent to the NICU caregivers, even though the NICU strives for a family-centered care environment. As a result, there is an altered parental role and subsequent infant-parent separation that disrupts the nurturing adult relationship buffer required to mitigate the effects of toxic stress exposure.

Given the structure of nurse staffing in modern NICUs, there is the potential premature infants also are deprived of infant-nurse relationships that could mitigate toxic stress and its effects. In the absence of parent presence, that may be unavoidable, additional alternative NICU caregiving models need to be evaluated that provide protective neurodevelopment and increase social interaction with premature infants (Coughlin, 2017). Data was available within the EHR providing the total number of nurse

caregivers for each patient in the first week, first month, and total LOS. This data was used as a proxy for nurse staffing models in this NICU.

Dependent Variables

Bayley-III is a widely used developmental assessment for preterm infants during follow-up appointments post NICU discharge. It is a comprehensive instrument used to detect developmental issues in early childhood; it provides a standardized mechanism to assess developmental outcomes for preterm infants in five categories: cognitive, language, motor, social-behavioral, and adaptive skills (Bayley, 2006; Bayley, 2006). For the purposes of this study, cognitive, language and motor development domains were used as the primary dependent variables. This is consistent with other studies assessing similar outcomes (Gonya et al., 2017; Weber et al., 2018; Welch et al., 2015). This data exists in the current high-risk follow-up REDCap database. According to Bayley (2006), the Bayley–III is a technically sound instrument, with strong internal consistency (Cronbach's alpha coefficients ranging from 0.86-0.93 for each domain), as well as test–retest stability. Raw scores are converted into a standardized 100-point scale with SD of 15 with an abnormal score below 85, indicating developmental impairment (Bayley, 2006). Refer to the Instrument Table in Appendix C for additional details regarding the Bayley instrument. For the purposes of this study, these three dependent variables were measured at the continuous level of data. The Bayley instrument is administered by the provider at the time of the high-risk infant follow up visit. All practitioners who administer the exam have received education and completed proctored observations.

Studies have identified premature infants are also at increased risk of developing autism spectrum disorders (Kuzniewicz et al., 2014; Wong et al., 2014). Therefore,

another dependent variable of interest is the autism screen using M-CHAT. M-CHAT is a free, easy to use instrument for screening autism. It consists of a 20-item questionnaire completed by the parent. Each question is answered yes or no by the parent; then the number of yes answers are totaled to provide the total score. Scores of 0-2 equal minimal risk and are labeled negative. Scores of 3-6 suggests child should be followed and reassessed and are labeled suspect. Scores of 7-20 equals high risk and are labeled a positive screen (Robins et al., 2014). M-CHAT has an internal consistency with Cronbach's alpha equal to 0.79 (Robins et al., 2014). Use of this screening instrument increases the likelihood of early detection of autism spectrum disorders. It is a highly sensitive test and predictive of autism spectrum disorders when there is a positive screen (Robins et al., 2014; Robins et al., 2001). The M-CHAT was recorded in the follow-up database as a dichotomous variable, screening either positive or negative. A positive autism screen score is 3 to 20 (Kim et al., 2016).

Study Conduct

Data Collection

After completion of IRB approval, all data was downloaded into data management software using Excel. Data was primarily extracted from two database sources. The first was the pre-existing high-risk follow-up REDCap database containing infants who received follow-up at two years of age from 2007 to 2020. This database currently contained approximately 650 infants born less than 32 weeks GA at birth. This database was reviewed from January 2012 through April 2020 to identify infants who met inclusion criteria. This database contained the majority of the demographic variables and dependent variables.

The second database was constructed to collect the independent variables of interest for this study from the EHR. The two databases were merged and matched by patient identification. The researcher evaluated the extracted data for errors and omissions. All data was finalized, de-identified, and recoded using sequential numbering prior to uploading into SPSS for statistical analysis.

Analytic Approach

Data analysis was completed using SPSS version 26. To address aim one**,** descriptive statistics including means, percentages, and standard deviations (SD) were conducted in order to describe the study sample. For the second aim: to examine the relationships between independent and dependent variables inferential statistics were used to identify relationships among study variables. Chi-squares were used for categorical measures. Correlations were completed for continuous variables. Variables found to be significantly associated with dependent variables at the 0.05 level were included in model development. All *p* values were two-tailed, and a 0.05 significance level were used in final models. To address aim three, multivariable linear regression was used to describe variance in Bayley III outcomes (cognitive, language & motor) related to the independent variables. Aim four was analyzed using multivariable logistic regression to identify the odds of a positive autism screen related to the independent variables. Given a large sample size, normality was assumed for all continuous variables; representativeness of the sample was maintained by running parametric tests and non-parametric tests with continuous variables that had significant outliers for comparison.

Protection of Human Subjects

Approval was obtained by the healthcare entity and University of San Diego Institutional Review Boards (IRB) with a waiver of consent due to the retrospective nature of this study. The principal investigator completed both the entity and CITI Human Subjects' Protection training programs. All data accessed, collected, and used was downloaded directly into data management software (Excel) and stored on a secure drive on a password protected personal computer.

Limitations

While retrospective cohort study designs are relatively inexpensive and less time-consuming to conduct, there were some identified limitations to this study. First, the researcher was limited to what was documented and easily extracted from the EHR; these variables are not generally documented for the purpose of research. Likewise, by using a pre-existing database, the researcher was limited to variables within the database. This can lead to the potential disadvantage of less control over the measurement and subject selection. Another limitation is general attendance rate for the HRIF is about 60-70% of infants who meet criteria, consequently, the outcome data from the HRIF database may not be reflective of all infants discharged from the NICU and may skew some of the findings. Additionally, this study was a single site, non-randomized study not allowing for generalizability of study findings.

Summary

The use of a retrospective cohort design using a purposive sample allowed the researcher to describe the study sample and identify relationships between the study

variables. Using this research approach allowed the researcher to address the study purpose and each of the four study aims.

Chapter IV

Results

The purpose of this study was to examine the relationship among socio-demographic factors, exposure to stressors in the NICU environment, stress modifiers and buffers, neonatal morbidities at discharge from the NICU, and 1. 2 year neurodevelopmental outcomes and 2. risk for autism in infants born less than 32 weeks gestational age cared for in a large, urban, tertiary NICU in Southern California. Within this chapter, the research findings will be presented. Data analysis was completed using Statistical Package for the Social Sciences (SPSS) version 26 to obtain frequencies, correlations, one-way analysis of variances (ANOVA), crosstabs, multiple linear regression, and logistic regression.

Study Sample and Defining Characteristics

Aim 1. To describe the maternal-neonatal demographics and clinical stressors, environmental

stressors and stress modifiers, neonatal morbidities, and 2-year neurodevelopmental outcomes (Bayley III motor, language, and cognitive scales and M-CHAT autism screen) among neonates receiving care in a large tertiary NICU in Southern California.

To address the first aim, descriptive analysis was used to define characteristics of the maternal-infant dyads within this study sample. Complete sociodemographic and clinical characteristics of the study sample are presented in Table 1.

Maternal Characteristics

The sample (N = 340) was ethnically/racially diverse, with slightly less than half of the mothers (44.7%, n = 152) reported Hispanic/Latino origin, (32.1%, n= 109) White, not of Hispanic origin; 11.8% (n = 40) Asian, Pacific Islanders, or Hawaiian Natives; and 7.6 % (n = 26) Black, African American. Approximately 90% (87.8%, n = 179) of the mothers' primary language was English; Seventy-one percent of the mothers had either some college or completed college degree, 52.6%, (n = 179) had private insurance (and 46.2% (n =157) had public insurance.

Neonatal Characteristics

As presented in Table 1, there was equal representation of male (50.9%, n = 173) and female (49.1%, n = 167) infants, mean birth weight of 1.12kg (*SD* = 1.78). The mean gestational age at birth for the overall sample was 28.2 weeks (*SD* =2.29), 18% (n = 63) born less than 26 weeks GA. The overall average LOS in the NICU was 73.5 days (*SD* =32.07). NICU LOS was significantly longer for infants in the 22 to 25 weeks GA at birth group (*M* = 113.13, *SD* 20.04, Welch *F* (2, 149) = 328.30, $p < 0.001$) when compared to those in the 26 to 28 weeks group (*M*= 81.64, *SD* = 26.86), and those in the 29 to 32 weeks group (*M* = 47.51, *SD* = 12.89). A decrease in infant LOS in the NICU as GA at birth increased with a large effect size ($\eta^2 = 0.579$); refer to Table 5.

Two hundred and sixteen infants were screened for autism at 2 years of age, 88.4% (n = 191) screened negative; 4.2% (n = 9) screened positive, and 7.4% (n=16) screened suspect for autism. The positive and suspect autism screen accounted for 11.6 % (n=25). The autism screen did not yield significant differences between GA at birth groups (refer to Table 5). The findings from the Bayley III assessment at 2 years of age

was as follows: mean composite cognitive score 95.56 (*SD* = 14.92), mean composite language score 89.28 (*SD* = 16.83), and mean composite motor score 96.03 (*SD* = 13.82) (see Table 1). There were significant differences between GA at birth groups in Bayley III outcomes: cognitive composite scale score, x^2 (2) = 12.88, p = 0.002; language composite scale score, x^2 (2)= 7.46, p = 0.024; and motor composite scale score, x^2 (2), p = 0.004 as presented in Table 5.

Table 1 *Sociodemographic and Clinical Characteristics of Study Population (N = 340)*

	Total	
Maternal Characteristics	***M***	***SD***
Maternal Age	30.72	6.13
Maternal Gravida	2.64	1.78
Maternal Parity	0.97	1.23
	n	***%***
Maternal Race/Ethnicity		
White, not of Hispanic origin	109	32.1
Hispanic, Latino	152	44.7
Black, African American	26	7.6
Asian, Pacific Islander, Hawaiian Native	40	11.8
Another Race	13	3.8
Maternal Primary Language		
English	296	87.8
Spanish	23	6.8
English and: Spanish, Chinese, Japanese, Other	18	5.3
Maternal Marital Status		
Married	206	61.3
Separated, divorced	16	4.8
Single	114	33.9
Maternal Education Level		
Less than High School	10	10.9
High School Diploma	16	17.4
Partial College	29	31.5
College Degree	37	40.2
Maternal Health Insurance		
No insurance	4	1.2
Private insurance	179	52.6
Public insurance	157	46.2
Prenatal Care		
Yes (≥ one visit)	329	96.8
No	11	3.2
Maternal History of Depression		
Yes	8	2.4
No	332	97.6
Maternal History of Drug Use		
Yes	8	3.1
No	253	96.9

	Total	
Neonatal Characteristics	***M***	***SD***
Gestational Age at Birth, Weeks	28.17	2.29
Infant Weight, kg	1.12	0.35
No. of Fetuses	1.32	0.55
LOS at NICU	73.52	32.07
	n	***%***
Infant Gender		
Male	173	50.9
Female	167	49.1
GA at Birth		
< 26 weeks	63	18.5
26-28 weeks	138	40.6
≥ 29 weeks	139	40.9
Birth Hospital		
Inborn (SMBHWN)	330	97.6
Outborn (all others)	8	2.4
Mode of Delivery		
Primary c-section	202	59.9
Repeat c-section	60	17.8
Spontaneous vaginal	75	22.3
Multiple Delivery		
Yes	96	28.2
No	244	71.8
No. of Fetuses		
1	244	71.8
2	82	24.1
3	14	4.1
Apgar 1 minute		
1	32	9.4
2	20	5.9
3	32	9.4
4	27	7.9
5	39	11.5
6	49	14.4
7	84	24.7
8	52	15.3
9	5	1.5
10	0	0.0

	Total	
Neonatal Characteristics (cont.)	***n***	***%***
Apgar 5 minute		
1	2	0.6
2	2	0.6
3	5	1.5
4	5	1.5
5	9	2.6
6	23	6.8
7	74	21.8
8	169	49.7
9	49	14.4
10	2	0.6
Breastmilk at Discharge		
Yes	62	18.2
No	278	81.8
Infant Blood Transfusion[a]		
Yes	178	52.5
No	161	47.5
Infant High Flow Nasal Cannula[b]		
Yes	30	9.1
No	299	90.9
Infant CPAP at 36 Corrected Weeks		
Yes	30	8.9
No	307	91.1
Infant Intubated at 36 Corrected Weeks		
Yes	7	2.1
No	329	97.9
Infant on Oxygen at Discharge		
Yes	16	4.7
No	324	95.3
Early Onset Sepsis		
Yes	11	3.2
No	328	96.8
Late Onset Sepsis		
Yes	32	9.4
No	307	90.6

	Total	
Neonatal Characteristics (cont.)	***n***	***%***
ROP Requiring Treatment[c]		
Yes	20	6.0
No	315	94.0
Highest Grade IVH[d]		
None	297	87.4
Grade I	16	4.7
Grade II	18	5.3
Grade III	4	1.2
Grade IV	3	0.9
Periventricular Leukomalacia on any HUS		
Yes	4	1.2
No	336	98.8
Rehospitalization since NICU Discharge		
Yes	69	20.5
No	267	79.5
Autism Screen		
Yes	216	63.5
No	124	36.5
Autism Screen Results		
Positive	9	4.2
Suspect	16	7.4
Negative	191	88.4
Autism Screen Results		
Positive/Suspect Combined	25	11.6
Negative	191	88.4

Characteristic	***M***	***SD***
No. days birth to being held	9.77	10.50
No. days birth to skin-to-skin	9.90	11.24
No. days birth to breastfeeding	36.48	20.53
No. days birth to enteral feeding volume	10.30	6.56
Breastmilk volume during LOS, L	16.03	8.08
Gestation age at discharge, weeks	38.23	2.79
No. parent visits per day, LOS	1.03	0.66
No. parent visits per week, LOS	6.46	0.80
No. RNs cared for infant, week 1	12.41	2.15
No. RNs cared for infant, month 1	40.72	5.56

Characteristic	Total	
	M	***SD***
No. RNs cared for infant, LOS	71.97	21.55
No. lab tests, LOS	57.61	46.29
No. blood transfusion, LOS	2.23	3.15
No. days infant on supplemental O_2, LOS	30.52	2.16
No. days intubated, LOS	7.10	11.25
Gestational age at follow-up visit	24.46	2.43
Bayley III: Cognitive score	95.56	14.92
Bayley III: Language score	89.28	16.83
Bayley III: Motor score	96.03	13.82

Note. CPAP = continuous positive airway pressure, HUS = head ultrasounds, IVH = Intraventricular hemorrhage, LOS = length of stay, NICU = neonatal intensive care unit, SMBHWN = Sharp Mary Birth for Women and Newborns. χ^2 = Pearson's Chi-square unless otherwise specified.

[a] Transfusions of Packed Red Blood Cells (PRBCs).

[b] High flow nasal cannula, 2 liters per minute or more at 36 corrected weeks.

[c] Retinopathy of Prematurity (ROP) requiring treatment (Avastin or laser surgery).

[d] Highest Grade IVH, any ultrasound before or on day 28.

[e] Fisher's Exact Test, Monte Carlo Sig. (2-sided).

Relationships Among Study Characteristics

Aim 2. To examine the relationships among maternal-neonatal demographics, environmental stressors, stress modifiers, neonatal morbidities, neurodevelopmental outcomes (Bayley III: motor, language & cognitive scales, and M-CHAT autism screen) at two years of age.

Inferential statistics including one-way ANOVAs, Kruskal-Wallis, crosstabs, and correlations were used to examine relationships among the independent and dependent variables. This analysis was also used to identify significant variables with moderate to

large effect size to include in the final regression models. Additional sub-analysis was done to identify differences between variables based on GA at birth groups.

Analysis of Variance and Kruskal-Wallis

One-way ANOVAs were conducted to identify if neonatal-maternal sociodemographic and clinical characteristics, NICU environmental stressors and stress modifiers, neonatal morbidities, and neurodevelopmental outcomes were significantly different in terms of the Bayley III outcome measures (cognitive, language, and motor scales) among neonates within this study population. Homogeneity of variances was assessed by Levene's test of homogeneity of variances; Welch robust test for equality of means is reported for those ANOVA results that did not meet the homogeneity of variance assumption. Criteria for effect size for the one-way ANOVAs was determined using Cohen's (1988) criteria. Eta squared can range from 0 to 1 and represents the proportion of variance in the dependent variable is explained by the independent variable. Cohen proposes the following values to classify effect size: 0.01 = small effect, 0.06 = moderate effect size, and 0.14 = large effect.

The Kruskal-Wallis H test is a rank-based non-parametric test used to identify significant differences between two or more groups of an independent variable on a continuous or ordinal dependent variable. This test was used to evaluate the Bayley III outcome measures for cognitive, language, and motor scales in terms of neonatal-maternal sociodemographic and clinical characteristics, NICU environmental stressors, stress modifiers, and neonatal morbidities for those variables that violated any of the one-way ANOVA assumptions.

ANOVA and Kruskal-Wallis Analysis for Bayley III Cognitive Composite Scale

The Bayley III cognitive composite scores were significantly different for infants in terms of mother's prenatal care, $F(1,338) = 6.84$, $p=.009$. Bayley III cognitive scores significantly increased for those infants whose mothers received prenatal care (greater than or equal to one visit, $M = 95.95$, $SD = 14.86$) when compared to those who did not receive any prenatal care ($M= 84.09$, $SD = 12.61$). Analysis indicated the increase in cognitive score for infants whose mothers received prenatal care was significant with a small effect ($\eta^2 = 0.02$). Bayley III cognitive composite scores were significantly different in terms of race and ethnicity, $F (4, 335) = 5.25$, $p < 0.001$ with a small effect ($\eta^2 =0.05$), breastmilk at discharge $F (1, 338) = 11.19$, $p = 0.001$, $\eta^2 = 0.045$; infant blood transfusion $F (1, 337) = 11.72$, $p = 0.001$; $\eta^2 = 0.034$; and infant remained on high flow nasal cannula at 36 weeks GA $F (1, 327) = 9.43$, $p = 0.002$; $\eta^2 = 0.028$ (see Table 2).

Kruskal-Wallis H test was conducted to identify significant differences in infant cognitive composite scale scores in terms of maternal history of drug use: yes (n = 8) and no (n=253). Values are mean ranks unless otherwise stated. Distributions of infant cognitive scale scores were not similar for both groups, as assessed by visual inspection of a boxplot. The mean ranks of infant cognitive scale scores were significantly different between groups with a relatively strong effect, $x^2 (2) = 5.20$, $p = 0.023$, $\varepsilon^2 = 0.020$. The ANOVAs and Kruskal-Wallis H findings for sociodemographic and clinical characteristics for the Bayley III cognitive composite score is located in Table 2.

Table 2

*One-Way ANOVAs and Kruskal-Wallis H: Bayley III **Cognitive** Composite Score at 2 Years of Age (N = 340)*

Characteristic	***M***	***SD***	***F***	***p***	η^2
Maternal Race/Ethnicity			5.25	< .001	.059
White, not of Hispanic origin	100.48	15.69			
Hispanic, Latino	93.42	13.29			
Black, African American	93.65	14.46			
Asian, Pacific Islander, Hawaiian Native	94.38	16.18			
Other Race	86.92	14.80			
	n	***Md.***	***H (df)***	***p***	ε^2
Maternal Primary Language			5.31 (2)	.070	--
English	296	95.00			
Spanish	23	95.00			
English and: Spanish, Chinese, Japanese, Other	18	100.00			
Characteristic	***M***	***SD***	***F***	***p***	η^2
Maternal Marital Status			5.88	.003	.034
Married	97.91	15.96			
Separated, divorced	92.19	13.16			
Single	92.30	12.17			
Education Level			1.58	.201	--
Less than High School	83.00	16.53			
High School Diploma	94.69	12.58			
Partial College	93.79	16.02			
College Degree	97.03	21.71			
Maternal Health Insurance			8.13[a]	.011	.041
No insurance	101.25	7.50			
Private insurance	98.27	17.05			
Public insurance	92.34	11.48			
	n	***Md.***	***H (df)***	***p***	ε^2
Maternal History of Depression			0.46 (1)	.497	--
Yes	8	97.50			
No	332	95.00			

	n	***Mean Rank***	***H (df)***	***p***	ε^2
Maternal History of Drug Use			5.20 (1)	.023	.020
Yes	8	71.69			
No	253	132.88			
Characteristic	***M***	***SD***	***F***	***p***	η^2
Prenatal Care			6.84	.009	.020
Yes (≥ one visit)	95.95	14.86			
No	84.09	12.61			
Infant Gender			2.63	.106	--
Male	94.28	15.73			
Female	96.90	13.97			
Birth Hospital			1.69	.195	--
Inborn (SMBHWN)	95.54	14.96			
Outborn (all others)	95.70	14.91			
	n	***Md.***	***H (df)***	***p***	ε^2
Mode of Delivery			1.14 (2)	.566	--
Primary c-section	202	95.00			
Repeat c-section	60	95.00			
Spontaneous vaginal	75	95.00			
Multiple Delivery			1.85 (1)	.174	--
Yes	96	95.00			
No	244	95.00			
No. of Fetuses			1.90 (2)	.387	--
1	244	95.00			
2	82	95.00			
3	14	95.00			
Apgar 1 minute			6.64 (8)	.576	--
1	32	92.50			
2	20	100.00			
3	32	95.00			
4	27	95.00			
5	39	95.00			
6	49	95.00			
7	84	97.50			
8	52	95.00			
9	5	100.00			

	n	***Md.***	***H (df)***	***p***	ε^2
Apgar 5 minute			4.10 (9)	.905	--
1	2	95.00			
2	2	102.50			
3	5	100.00			
4	5	90.00			
5	9	90.00			
6	23	95.00			
7	74	95.00			
8	169	95.00			
9	49	95.00			
10	2	100.00			
	M	***SD***	***F***	***p***	η^2
Breastmilk at Discharge			11.19[a]	.001	.045
Yes	102.29	18.25			
No	94.06	13.67			
Infant Blood Transfusion[b]			11.72	.001	.034
Yes	92.95	14.34			
No	98.43	15.12			
Infant High Flow Nasal Cannula[c]			9.43	.002	.028
Yes	87.50	17.36			
No	96.23	14.53			
	n	***Md.***	***H (df)***	***p***	ε^2
Infant CPAP at 36 Corrected Weeks			0.61 (1)	.436	--
Yes	30	95.00			
No	307	95.00			
	M	***SD***	***F***	***p***	η^2
Infant Intubated at 36 Corrected Weeks			1.86	.174	--
Yes	87.86	19.33			
No	95.61	14.80			
Infant on Oxygen at Discharge			1.41	.237	--
Yes	91.25	17.46			
No	95.78	14.79			
	n	***Md.***	***H (df)***	***p***	ε^2
Early Onset Sepsis			0.41	.522 (1)	--
Yes	11	95.00			
No	328	95.00			

	M	***SD***	***F***	***p***	η^2
Late Onset Sepsis			1.83	.177	--
Yes	92.19	16.56			
No	95.93	14.75			
ROP Requiring Treatment[d]			1.08	.299	--
Yes	92.00	18.95			
No	95.56	14.56			
Highest Grade IVH[e]			2.75	.028	.032
None	96.19	14.84			
Grade I	93.44	14.91			
Grade II	93.33	14.65			
Grade III	75.00	15.81			
Grade IV	83.33	7.64			
	n	***Md.***	***H (df)***	***p***	ε^2
Periventricular Leukomalacia on any HUS			2.67	.102	--
Yes	4	65.00			
No	336	95.00			
Characteristic	***n***	***Mean Rank***	***H (df)***	***P***	ε^2
Rehospitalization since NICU Discharge			6.42 (1)	.011	.019
Yes	69	142.38			
No	267	175.25			
	M	***SD***	***F***	***P***	η^2
Autism Screen			0.00	.988	--
Yes	95.56	15.88			
No	95.58	13.15			
Autism Screen Results			35.28	< .001	.249
Positive	66.67	12.75			
Suspect	78.75	13.10			
Negative	98.32	13.93			

Note. CPAP = continuous positive air pressure, HFNC = high flow nasal cannula, HUS = head ultrasound, IVH = intraventricular hemorrhage, LOS = length of stay.

[a] Welch ANOVA; robust test of equality of means.

[b]Infant blood transfusion during LOS.

[c]Infant on HFNC; 2 liters per minute or more at 36 corrected weeks during LOS.

[d]Retinopathy of Prematurity (ROP) requiring treatment; Avastin or laser surgery.

[e]Highest Grade IVH; any Ultrasound before or on Day 28.

ANOVA and Kruskal-Wallis Analysis for Bayley III Language Composite Scale

Bayley III language composite scores were also significantly different for infants in terms of their mothers' race and ethnicity with a moderate effect size, Welch $F(4, 61) = 6.40$, $p < 0.001$, $\eta^2 = 0.085$. Bayley III language score significantly decreased for infants with a Hispanic mother ($M = 85.63$, $SD = 14.93$). Games- Howell post-hoc analysis identified the significant decrease in language score from the White mother group to Hispanic (110.52, 95% CI (-16.59 to -4.44, $p < 0.001$) and Asian, Pacific Islander, or Hawaiian Native (-11.37, 95% CI (-19.86 to -2.89), $p = 0.003$). The ANOVAs and Kruskal-Wallis H findings for sociodemographic and clinical characteristics for the Bayley III language composite score are located in Table 3.

Table 3

*One-Way ANOVAs and Kruskal-Wallis H: Bayley III **Language** Composite Score at 2 Years of Age (N = 340)*

Characteristic	***M***	***SD***	***F***	***p***	η^2
Maternal Race/Ethnicity			6.40[a]	< .001	.085
White, not of Hispanic origin	96.15	19.22			
Hispanic, Latino	85.63	14.93			
Black, African American	90.35	11.16			
Asian, Pacific Islander, Hawaiian Native	84.78	15.34			
Other Race	85.85	12.85			
	n	***Md.***	***H (df)***	***p***	ε^2
Maternal Primary Language			5.81 (2)	.055	--
English	295	91.00			
Spanish	23	86.00			
English and: Spanish, Chinese, Japanese, Other	18	90.00			
	M	***SD***	***F***	***p***	η^2
Maternal Marital Status			10.87	< .001	.061
Married	92.67	17.32			
Separated, divorced	89.19	11.89			
Single	83.79	14.73			
Education Level			3.11[a]	.040	.111
Less than High School	71.60	19.14			
High School Diploma	88.13	13.09			
Partial College	86.14	14.79			
College Degree	93.76	23.58			
Maternal Health Insurance			18.68[a]	.001	.100
No insurance	95.25	9.47			
Private insurance	94.16	17.98			
Public insurance	83.53	13.54			
Maternal History of Depression			1.46	.228	--
Yes	96.38	12.24			
No	89.11	16.91			

Characteristic	***M***	***SD***	***F***	***p***	η^2
Maternal History of Drug Use			4.87	.028	.018
Yes	75.63	11.87			
No	89.42	17.54			
Prenatal Care			9.49	.002	.027
Yes (≥ one visit)	89.79	16.47			
No	74.09	21.21			
Infant Gender			3.41	.066	--
Male	87.62	17.68			
Female	90.99	15.79			
Birth Hospital			0.30	.588	--
Inborn (SMBHWN)	95.70	14.91			
Outborn (all others)	88.75	16.64			
Mode of Delivery			1.06	.346	--
Primary c-section	90.41	18.20			
Repeat c-section	88.53	14.47			
Spontaneous vaginal	87.24	14.47			
	n	***Md.***	***H (df)***	***p***	ε^2
Multiple Delivery			0.41 (1)	.524	--
Yes	96	89.00			
No	243	91.00			
	M	***SD***	***F***	***p***	η^2
No. of Fetuses			0.63	.533	--
1	89.56	17.29			
2	89.30	15.72			
3	84.36	15.29			
	n	***Md.***	***H (df)***	***p***	ε^2
Apgar 1 minute			8.17 (8)	.417	--
1	32	86.00			
2	20	87.50			
3	32	91.00			
4	27	89.00			
5	39	86.00			
6	49	91.00			
7	84	94.00			
8	51	89.00			
9	5	91.00			

	n	***Md.***	***H (df)***	***p***	ε^2
Apgar 5 minute			4.16 (9)	.900	--
1	2	87.50			
2	2	94.00			
3	5	85.00			
4	5	86.00			
5	9	89.00			
6	23	86.00			
7	74	91.00			
8	169	91.00			
9	48	89.00			
10	2	97.00			
	M	***SD***	***F***	***p***	η^2
Breastmilk at Discharge			14.31	< .001	.041
Yes	96.45	15.93			
No	87.68	16.64			
Infant Blood Transfusion, LOS			8.26	.004	.024
Yes	86.78	15.47			
No	92.00	17.92			
Infant High Flow Nasal Cannula[a]			6.43	.012	.019
Yes	81.70	19.28			
No	89.79	16.38			
	n	***Md.***	***H (df)***	***p***	ε^2
Infant CPAP at 36 Corrected Weeks			0.78	.078 (1)	--
Yes	29	91.00			
No	307	89.00			
	M	***SD***	***F***	***p***	η^2
Infant Intubated at 36 Corrected Weeks			0.14	.705	--
Yes	86.71	16.72			
No	89.08	16.67			
Infant on Oxygen at Discharge			0.01	.909	--
Yes	89.75	20.17			
No	89.26	16.69			
Early Onset Sepsis			2.30	.131	--
Yes	81.73	18.88			
No	89.54	16.76			

Characteristic	***M***	***SD***	***F***	***p***	η^2
Late Onset Sepsis			4.40	.037	.013
Yes	83.38	15.55			
No	89.91	16.89			
ROP Requiring Treatment[b]			0.28	.600	--
Yes	87.15	16.98			
No	89.16	16.57			
Highest Grade IVH[c]			1.03	.393	--
None	89.78	17.25			
Grade I	85.31	12.74			
Grade II	87.56	14.26			
Grade III	75.25	12.50			
Grade IV	90.00	9.64			
Periventricular Leukomalacia on any HUS			3.02	.928	--
Yes	87.50	36.63			
No	89.30	16.57			
	n	***Mean Rank***	***H (df)***	***p***	ε^2
Rehospitalization since NICU Discharge			7.81 (1)	.005	.023
Yes	69	139.02			
No	266	175.52			
	M	***SD***	***F***	***p***	η^2
Autism Screen			0.00	.951	--
Yes	89.32	18.06			
No	89.21	14.52			
Autism Screen Results			43.47	< .001	.291
Positive	66.67	12.75			
Suspect	78.75	13.10			
Negative	98.32	13.93			

Note. CPAP = continuous positive air pressure, HFNC = high flow nasal cannula, HUS = head ultrasound, IVH = intraventricular hemorrhage, LOS = length of stay.

[a] Welch ANOVA; robust test of equality of means.

[b]Infant on HFNC; 2 liters per minute or more at 36 corrected weeks during LOS.

[c]Retinopathy of Prematurity (ROP) requiring treatment; Avastin or laser surgery.

[d]Highest Grade IVH; any Ultrasound before or on Day 28.

ANOVA and Kruskal-Wallis Analysis for Bayley III Motor Scale

Kruskal-Wallis H test was conducted to identify if there were significant differences in infant motor composite scale scores in terms of maternal marital status: Married (n = 206), Separated, divorced (n= 16), and single (n=114). Values are mean ranks unless otherwise stated. Distributions of infant motor scale scores were not similar for all groups, as assessed by visual inspection of a boxplot. The mean ranks of infant motor scale scores were significantly different between groups with a relatively strong effect, x^2 (2) = 6.88, p = 0.032, ε^2 = 0.020. Pairwise comparisons were performed using Dunn's (1964) procedure with a Bonferroni correction for multiple comparison. Adjusted p-values are presented. The post hoc analysis revealed significant differences in infant motor scores between Single (Mean rank = 149.31) and Married Mothers (Mean rank = 178.92), p = 0.032; no other group combination was significantly different. The ANOVAs and Kruskal-Wallis H findings for sociodemographic and clinical characteristics for the Bayley III motor composite score are located in Table 4.

Table 4

*One-Way ANOVAs and Kruskal-Wallis H: Bayley III **Motor** Composite Score at 2 Years of Age (N = 340)*

Characteristic	***M***	***SD***	***F***	***p***	η^2
Maternal Race/Ethnicity			1.86	.118	--
White, not of Hispanic origin	98.61	13.19			
Hispanic, Latino	95.50	14.30			
Black, African American	95.00	12.34			
Asian, Pacific Islander, Hawaiian Native	93.18	14.29			
Other Race	91.38	12.80			
	n	***Md.***	***H (df)***	***p***	ε^2
Maternal Primary Language			1.90 (2)	.386	--
English	296	97.00			
Spanish	23	97.00			
English and: Spanish, Chinese, Japanese, Other	18	100.00			
	n	***Mean Rank***	***H (df)***	***p***	ε^2
Maternal Marital Status			6.88 (2)	.032	.020
Married	206	178.92			
Separated, divorced	16	171.09			
Single	114	149.31			
	M	***SD***	***F***	***p***	η^2
Education Level			3.01	.034	.093
Less than High School	83.30	15.28			
High School Diploma	101.13	12.74			
Partial College	97.00	13.13			
College Degree	97.51	17.79			
Maternal Health Insurance			4.80	.009	.028
No insurance	106.00	4.24			
Private insurance	97.82	14.58			
Public insurance	93.74	12.69			
Maternal History of Depression			1.66	.198	--
Yes	102	12.60			
No	95.88	13.84			

Characteristic	***n***	***Mean Rank***	***H (df)***	***p***	ε^2
Maternal History of Drug Use			6.79 (1)	.009	.025
Yes	8	62.75			
No	253	133.16			
	M	***SD***	***F***	***p***	η^2
Prenatal Care			3.69	.056	--
Yes (≥ one visit)	96.29	13.76			
No	88.18	14.16			
Infant Gender			1.01	.316	--
Male	95.29	14.75			
Female	96.80	12.79			
Birth Hospital			.01	.923	--
Inborn (SMBHWN)	95.90	13.74			
Outborn (all others)	96.38	16.19			
	n	***Md.***	***H (df)***	***p***	ε^2
Mode of Delivery			1.14 (2)	.566	--
Primary c-section	202	97.00			
Repeat c-section	60	100.00			
Spontaneous vaginal	75	94.00			
	M	***SD***	***F***	***p***	η^2
Multiple Delivery			0.07	.793	--
Yes	96.34	11.79			
No	95.91	14.57			
No. of Fetuses			1.33	.266	--
1	95.91	14.57			
2	97.28	11.78			
3	90.86	10.60			
	n	***Md.***	***H (df)***	***p***	ε^2
Apgar 1 minute			9.39 (8)	.311	--
1	32	100.00			
2	20	95.50			
3	32	97.00			
4	27	97.00			
5	39	94.00			
6	49	97.00			
7	84	100			
8	52	94.00			
9	5	94.00			

Characteristic	***n***	***Md.***	***H (df)***	***p***	ε^2
Apgar 5 minute			15.01 (9)	.091	--
1	2	106.00			
2	2	103.50			
3	5	97.00			
4	5	88.00			
5	9	94.00			
6	23	97.00			
7	74	94.00			
8	169	100.00			
9	49	94.00			
10	2	95.50			
	M	***SD***	***F***	***p***	η^2
Breastmilk at Discharge			14.31	< .001	.041
Yes	101.92	11.68			
No	94.72	13.94			
Infant Blood Transfusion[a]			16.47	< .001	.047
Yes	93.18	14.03			
No	96.02	13.84			
Infant High Flow Nasal Cannula[b]			6.75[a]	.014	.032
Yes	88.13	17.73			
No	96.78	13.37			
Infant CPAP at 36 Corrected Weeks			2.04	.154	--
Yes	92.50	14.09			
No	96.28	13.79			
Infant Intubated at 36 Corrected Weeks					
Yes	91.00	22.85			
No	96.08	13.63	0.92	.338	--
Infant on Oxygen at Discharge			4.46	.035	.013
Yes	88.94	16.51			
No	96.38	13.61			
	n	***Md.***	***H (df)***	***p***	ε^2
Early Onset Sepsis			0.04 (1)	.840	--
Yes	11	100.00			
No	328	97.00			

	M	*SD*	*F*	*p*	η^2
Late Onset Sepsis			10.93	.001	.031
Yes	88.44	16.85			
No	96.82	13.28			
	n	*Md.*	*H (df)*	*p*	ε^2
ROP Requiring Treatment[c]			2.10	.148	--
Yes	20	94.00			
No	315	97.00			
	M	*SD*	*F*	*p*	η^2
Highest Grade IVH[d]			2.34	.055	--
None	96.88	13.61			
Grade I	91.75	11.93			
Grade II	89.28	17.07			
Grade III	86.50	16.70			
Grade IV	91.00	9.00			
Periventricular Leukomalacia on any HUS			3.02[a]	.204	
Yes	73.75	27.86			
No	96.29	13.43			
Rehospitalization since NICU Discharge			2.77	.097	--
Yes	93.67	14.32			
No	96.77	13.67			
Autism Screen			0.10	.749	--
Yes	95.85	14.36			
No	96.35	12.90			
Autism Screen Results			17.88[a]	< .001	.256
Positive	70.11	18.15			
Suspect	79.81	17.78			
Negative	98.40	11.61			

Note. CPAP = continuous positive air pressure, HFNC = high flow nasal cannula, HUS = head ultrasound, IVH = intraventricular hemorrhage, LOS = length of stay.

[a] Welch ANOVA; robust test of equality of means.

[b]Infant blood transfusion during LOS.

[c]Infant on HFNC; 2 liters per minute or more at 36 corrected weeks during LOS.

[d]Retinopathy of Prematurity (ROP) requiring treatment; Avastin or laser surgery.

[e]Highest Grade IVH; any Ultrasound before or on Day 28.

Correlations

Pearson's product moment or Spearman's Rho correlations were computed to assess the relationship between (1) cognitive scale, (2) language scale, and (3) motor scale scores respectively and: maternal age, gravida, and parity; infant gestation age and weight at birth; LOS in the NICU; number of days from infant's birth to being held, to skin-to-skin, to breastfeeding and to enteral feeding; breastmilk volume during LOS; gestation age at discharge; number of parent visits per day and per week during LOS; number of lab tests and blood transfusions during infant's LOS; number of days infant was intubated or received supplemental oxygen during LOS; and gestational age at follow-up visit when Bayley III was administered. To determine the strength of the relationship, Cohen's (1988) criteria was used; a small association the correlation coefficient r = 0.1-0.29, a medium association if r = 0.3-0.49, and a large association if r = 0.5 to 1.

Correlations for Bayley III Cognitive Composite Scale

The correlation results for Bayley III cognitive composite scale scores included positive associations between maternal age (r= 0.166, p =.002), infant gestation age at birth (r = 0.184, p =0.001), birth weight (r = 0.207, p < 0.001) increase, and cognitive scores increase. Additionally, as parent visits per day during LOS increase (r = 0.303, p < 0.001) so do the cognitive scores at 2 years of age explaining 9.18% of the variation. In contrast, as the LOS in the NICU (r = -0.221, p < 0.001), the number of days from birth to first hold (r = -0.236, p < 0.001), the number of days to first skin to skin (r = -0.215, p < 0.001), days to first breastfeeding (r = -0.217, p < 0.001), and days to full enteral feeding volume (r = -0.198, p < 0.001) increase, the cognitive scores decreased. As the

number of RNs caring for the infant during the total LOS (r = -0.213, p < 0.001), number of lab tests(r = -0.252, p < 0.001), the total number of blood transfusions (r = -0.264, p < 0.001), number of days intubated (r = -0.207, p < 0.001), and number of days of supplemental oxygen (r = -0.213, p < 0.001) increase, the cognitive scores decreased.

Correlations for Bayley III Language Scale

The correlation results for Bayley III language composite scale scores indicated as maternal age (r= 0.174, p =.001), infant gestation age at birth (r = 0.146, p =0.007) and birth weight (r = 0.182, p = 0.001) number of parent visits per day during the LOS (r = .261, p <0.001) increase, the language score increases. In contrast, as LOS in the NICU (r = -0.176, p = 0.001), number of days to first held (r = - 0.202, p < 0.001), number of days to first skin to skin (r = - 0.194, p < 0.001), number of days to first breastfeeding (r = - 0.204, p = 0.001) total number of nurses caring for the patient over the LOS (r = - 0.187, p = 0.001) total number of lab tests (r = - 0.206, p < 0.001), number of blood transfusions (r = - 0.214, p < 0.001), number of days intubated (r = - 0.142, p = 0.009), and number of days of supplemental oxygen (r = - 0.165, p = 0.007) increase, the language score decreases.

Correlations for Bayley III Motor Composite Scale

Similar to correlations for the cognitive and language scores, as maternal age (r= 0.139, p =.010), infant gestation age at birth (r = 0.194, p < 0.001) and birth weight (r = 0.247, p < 0.001) increase, motor scores increase. There was also a significant, but small relationship between the number of nurses caring for the infant during the first week (r = 0.118, p =0.03), first month (r = 0.122, p = 0.025), and total LOS (r = - 0.175, p =0.001) and the motor score at 2 years of age. The largest variance in language scores were

present with stressors including total number of lab tests (r = - 0.301, $p < 0.001$), total number of blood transfusions (r = - 0.294, $p < 0.001$), number of days the infant was intubated (r = - 0.258, $p < 0.001$), and the total number of days the infant received supplemental oxygen (r = - 0.255, $p < 0.001$). As these variables increase, the motor scores decrease. Finally, the total number of parents visits per day during the LOS also demonstrated a significant relationship with Bayley composite motor scores at 2 years of age. As the total number of parent visits per day (r = 0.255, $p < 0.001$) increase, motor scores increase accounting for 6.5% variation in the motor score.

Sub-analysis by GA at Birth

Crosstabs for GA at Birth

After differences in demographics were identified between infants of varying gestational age groups, a sub-analysis was completed examining GA at birth in 3 groups: 22 to 25 weeks GA at birth, 26 to 28 weeks GA at birth, and 29 to 32 weeks GA at birth. A chi-square test of independence was completed between neonatal-maternal sociodemographic and clinical characteristics, NICU environmental stressors and stress modifiers, neonatal morbidities, neurodevelopmental outcomes, and GA at birth. Not all expected cell frequencies were greater than five; Fisher's Exact Tests were reported for all variables. There were significant associations between GA at birth, primarily with each variable yielding a small effect, and maternal marital status, Fisher's χ^2 = 9.81, p = .039, *Cramer's V* = .118; birth hospital, Fisher's χ^2 = 6.76, p = .025, *Cramer's V* = .133; apgar 1 minute, Fisher's χ^2 = 48.16, $p < .001$ (Monte Carlo Sig.), *Cramer's V* = .269; apgar 5 minute, Fisher's χ^2 = 54.79, $p < .001$ (Monte Carlo Sig.), *Cramer's V* = .288; breastmilk at discharge, Fisher's χ^2 = 7.63, p = .021, *Cramer's V* = .147; infant high flow

nasal cannula, Fisher's $\chi^2 = 32.62$, $p < .001$, *Cramer's V* = .289; infant CPAP at 36 corrected weeks, Fisher's $\chi^2 = 23.44$, $p < .001$, *Cramer's V* = .263; infant intubated at 36 corrected weeks, Fisher's $\chi^2 = 10.40$, $p = .002$, *Cramer's V* = .202; infant on oxygen at discharge, Fisher's $\chi^2 = 21.93$, $p < .001$, *Cramer's V* = .260; highest grade IVH, Fisher's $\chi^2 = 27.63$, $p < .001$, *Cramer's V* = .224; and rehospitalization since NICU discharge, Fisher's $\chi^2 = 11.70$, $p = .003$, *Cramer's V* = .192. There was a significant association with moderate effect between GA groups and late onset sepsis, Fisher's $\chi^2 = 30.98$, $p < .001$, *Cramer's V* = .345. Of note, the most significant differences in GA at birth groups is in terms of the environmental stressor variables. The largest significant association based on effect sizes are between GA at birth and infant blood transfusion, Fisher's $\chi^2 = 156.89$, $p < .001$, *Cramer's V* = .644 with the largest adjusted residual for the 29 to 32 week GA group = 11.4. Additionally, another significant association with large effect was noted between GA groups and ROP requiring treatment, Fisher's $\chi^2 = 66.39$, $p < .001$, *Cramer's V* = .524 with the largest adjusted residual for the 22 to 25 week group (refer to Table 5).

Table 5

Crosstabulation: Sociodemographic and Clinical Characteristics by ***Gestation age at Birth*** *(N = 340)*

	Total	**22 to 25 Weeks**	**26 to 28 Weeks**	**29 to 32 Weeks**		
Characteristic	***n (%)***	***n (%)***	***n (%)***	***n (%)***	X^2	***p***
Maternal Race/Ethnicity					4.03	.862
White, not of Hispanic origin	109 (32.1)	19 (17.4)	39 (35.8)	51 (46.8)		
Hispanic, Latino	152 (44.7)	29 (19.1)	63 (41.4)	60 (39.5)		
Black, African American	26 (7.6)	4 (15.4)	13 (50.0)	9 (34.6)		
Asian, Pacific Islander, Hawaiian Native	40 (11.8)	9 (22.5)	16 (40.0)	15 (37.5)		
Other Race	13 (3.8)	2 (15.4)	7 (53.8)	4 (30.8)		
Maternal Primary Language					1.86	.769
English	296 (87.8)	53 (17.9)	119 (40.2)	124 (41.9)		
Spanish	23 (6.8)	5 (21.7)	10 (43.5)	8 (34.8)		
English and: Spanish, Chinese, Japanese, Other	18 (5.3)	5 (27.8)	7 (38.9)	6 (33.3)		
Maternal Marital Status					9.81	.039
Married	206 (61.3)	32 (15.5)	81 (39.3)	93 (45.1)		
Separated, divorced	16 (4.8)	4 (25.0)	3 (18.8)	9 (56.3)		
Single	114 (33.9)	26 (22.8)	52 (45.6)	36 (31.6)		
Education Level					8.14	.221
Less than High School	10 (10.9)	3 (30.0)	6 (60.0)	1 (10.0)		
High School Diploma	16 (17.4)	2 (12.5)	5 (31.3)	9 (56.3)		
Partial College	29 (31.5)	6 (20.7)	15 (51.7)	8 (27.6)		
College Degree	37 (40.2)	12 (32.4)	14 (37.8)	11 (29.7)		
Maternal Health Insurance					2.14	.704
No insurance	4 (1.2)	0 (0.0)	3 (75.0)	1 (25.0)		
Private insurance	179 (52.6)	33 (18.4)	69 (38.5)	77 (43.0)		
Public insurance	157 (46.2)	30 (19.1)	66 (42.0)	61 (28.9)		
Maternal History of Depression					2.95	.246
Yes	8 (2.4)	2 (25.0)	1 (12.5)	5 (62.5)		
No	332 (97.6)	61 (18.4)	137 (41.3)	134 (40.4)		

	Total	**22 to 25 Weeks**	**26 to 28 Weeks**	**29 to 32 Weeks**		
Characteristic	***n (%)***	***n (%)***	***n (%)***	***n (%)***	X^2	***p***
Maternal History of Drug Use					2.32	.292
Yes	8 (3.1)	0 (0.0)	5 (62.5)	3 (37.5)		
No	253 (96.9)	52 (20.6)	99 (39.1)	102 (40.3)		
Prenatal Care					3.50	.134
Yes (≥ one visit)	329 (96.8)	59 (17.9)	133 (40.4)	137 (41.6)		
No	11 (3.2)	4 (36.4)	5 (45.5)	2 (18.2)		
Infant Gender					0.39	.826
Male	173 (50.9)	31 (17.9)	73 (42.2)	69 (39.9)		
Female	167 (49.1)	32 (19.2)	65 (38.9)	70 (41.9)		
Birth Hospital					6.76	.025
Inborn (SMBHWN)	330 (97.6)	61 (18.5)	130 (39.4)	139 (42.1)		
Outborn (all others)	8 (2.4)	2 (25.0)	6 (75.0)	0 (0.0)		
Mode of Delivery					2.60	.631
Planned c-section	202 (59.9)	36 (17.8)	83 (41.1)	83 (41.1)		
Recurrent c-section	60 (17.8)	9 (15.0)	23 (38.3)	28 (46.7)		
Spontaneous vaginal	75 (22.3)	18 (24.0)	30 (40.0)	27 (36.0)		
Multiple Delivery					1.20	.555
Yes	96 (28.2)	15 (15.6)	43 (44.8)	38 (39.6)		
No	244 (71.8)	48 (19.7)	95 (38.9)	101 (41.4)		
No. of Fetuses					2.02	.739
1	244 (71.8)	48 (19.7)	95 (38.9)	101 (41.4)		
2	82 (24.1)	12 (14.6)	38 (46.3)	32 (39.0)		
3	14 (4.1)	3 (21.4)	5 (35.7)	6 (42.9)		
Apgar 1 minute					48.16[b]	< .001
1	32 (9.4)	12 (37.5)	14 (43.8)	6 (18.8)		
2	20 (5.9)	8 (40.0)	5 (25.0)	7 (35.0)		
3	32 (9.4)	8 (25.0)	13 (40.6)	11 (34.4)		
4	27 (7.9)	7 (25.9)	13 (48.1)	7 (25.9)		
5	39 (11.5)	11 (28.2)	19 (48.7)	9 (31.1)		
6	49 (14.4)	6 (12.2)	25 (51.0)	18 (36.7)		
7	84 (24.7)	6 (7.1)	28 (33.3)	50 (29.5)		
8	52 (15.3)	5 (9.6)	18 (34.6)	29 (55.8)		

	Total	22 to 25 Weeks	26 to 28 Weeks	29 to 32 Weeks		
Characteristic	***n (%)***	***n (%)***	***n (%)***	***n (%)***	X^2	***p***
9	5 (1.5)	0 (0.0)	3 (60.0)	2 (40.0)		
Apgar 5 minute					54.79[b]	< .001
1	2 (0.6)	1 (50.0)	1 (50.0)	0 (0.0)		
2	2 (0.6)	1 (50.0)	0 (0.0)	1 (50.0)		
3	5 (1.5)	1 (20.0)	4 (80.0)	0 (0.0)		
4	5 (1.5)	2 (40.0)	3 (60.0)	0 (0.0)		
5	9 (2.6)	6 (66.7)	2 (22.2)	1 (11.1)		
6	23 (6.8)	8 (34.8)	11 (47.8)	4 (17.4)		
7	74 (21.8)	19 (25.7)	36 (48.6)	19 (25.7)		
8	169 (49.7)	23 (13.6)	63 (37.3)	83 (49.1)		
9	49 (14.4)	2 (4.1)	17 (34.7)	30 (61.2)		
10	2 (0.6)	0 (0.0)	1 (50.0)	1 (50.0)		
Breastmilk at Discharge					7.63	.021
Yes	62 (18.2)	5 (8.1)	24 (38.7)	33 (53.2)		
No	278 (81.8)	58 (20.9)	114 (41.0)	106 (38.1)		
Infant Blood Transfusion[b]					156.89	< .001
Yes	178 (52.25)	60 (33.7)	97 (54.5)	21 (11.8)		
No	161 (47.5)	3 (1.9)	41 (25.5)	117 (72.7)		
Infant High Flow Nasal Cannula[c]					32.62	< .001
Yes	30 (9.1)	14 (46.7)	16 (53.3)	0 (0.0)		
No	299 (90.9)	49 (16.4)	119 (39.8)	131 (43 .8)		
Infant CPAP at 36 Corrected Weeks					23.44	< .001
Yes	307 (91.1)	14 (46.7)	14 (46.7)	2 (6.7)		
No	30 (8.9)	49 (16.0)	124 (40.4)	134 (43.6)		
Infant Intubated at 36 Corrected Weeks					10.40	.002
Yes	7 (2.1)	5 (71.4)	2 (28.6)	0 (0.0)		
No	329 (97.9)	58 (17.6)	135 (41.0)	136 (41.3)		
Infant on Oxygen at Discharge					21.93	< .001
Yes	16 (4.7)	10 (62.5)	6 (37.5)	9 (0.0)		
No	324 (95.3)	53 (16.4)	132 (40.7)	139 (42.9)		
Early Onset Sepsis					2.51	.339
Yes	11 (3.2)	4 (36.4)	4 (36.4)	3 (27.3)		

	Total	22 to 25 Weeks	26 to 28 Weeks	29 to 32 Weeks		
Characteristic	***n (%)***	***n (%)***	***n (%)***	***n (%)***	X^2	***p***
No	328 (96.8)	58 (17.7)	134 (40.9)	136 (41.5)		
Late Onset Sepsis					30.98	< .001
Yes	32 (9.4)	19 (59.4)	8 (25.0)	5 (15.6)		
No	307 (90.6)	43 (14.0)	130 (42.3)	134 (43.6)		
ROP Requiring Treatment[d]					66.39	< .001
Yes	20 (6.0)	20 (100.0)	0 (0.00)	0 (0.0)		
No	315 (94.0)	43 (13.7)	136 (43.2)	136 (43.2)		
Highest Grade IVH[e]					27.63	< .001
None	297 (87.4)	45 (15.2)	124 (41.8)	128 (43.1)		
Grade I	16 (4.7)	3 (18.8)	5 (31.1)	8 (50.0)		
Grade II	18 (5.3)	11 (61.6)	5 (27.8)	2 (11.1)		
Grade III	4 (1.2)	2 (50.0)	2 (50.0)	0 (0.0)		
Grade IV	3 (0.9)	2 (66.7)	1 (33.3)	0 (0.0)		
Periventricular Leukomalacia on any HUS					0.83	.682
Yes	4 (1.2)	1 (25.0)	2 (50.0)	1 (25.0)		
No	336 (98.8)	62 (18.5)	136 (40.5)	138 (41.1)		
Rehospitalization since NICU Discharge					11.70	.003
Yes	69 (20.5)	22 (31.9)	28 (40.6)	19 (27.5)		
No	267 (79.5)	40 (15.0)	108 (40.4)	119 (44.6)		
Autism Screen					3.34	.183
Yes	216 (63.5)	46 (21.3)	87 (40.3)	83 (38.4)		
No	124 (36.5)	17 (13.7)	51 (41.1)	56 (45.2)		
Autism Screen Results					6.42	.150
Positive	9 (4.2)	3 (33.3)	5 (55.6)	1 (11.1)		
Suspect	16 (7.4)	6 (37.5)	6 (37.5)	4 (25.0)		
Negative	191 (88.4)	37 (19.4)	76 (39.8)	78 (40.8)		

Note. CPAP = continuous positive air pressure, HFNC = high flow nasal cannula, HUS = head ultrasound, IVH = intraventricular hemorrhage, LOS = length of stay. χ^2 = Fisher's Exact unless otherwise specified. [a] Welch ANOVA (2-sided). [b] Monte Carlo Sig. (2-sided). [b]Infant blood transfusion during LOS. [c]Infant on HFNC; 2 liters per minute or more at 36 corrected weeks during LOS. [d]Retinopathy of Prematurity (ROP) requiring treatment; Avastin or laser surgery. [e]Highest Grade IVH; any Ultrasound before or on Day 28.

ANOVAs by GA at Birth

One-way ANOVAs were conducted to identify if neonatal-maternal sociodemographic and clinical characteristics, NICU environmental stressors and stress modifiers, neonatal morbidities, and neurodevelopmental outcomes were significantly different in terms of infants' gestational age at birth. Homogeneity of variances was assessed by Leven's test of homogeneity of variances; Welch robust test for equality of means is reported for those ANOVA results that do not meet the homogeneity of variance assumption. Infant weight, LOS in the NICU, GA at discharge ,number of days from birth to breastfeeding, total breastmilk volume during LOS, number of nurses who care for the infant during the first month and total LOS, and the number of lab tests during LOS were significantly different for infants in terms of their gestational age at birth (Table 6).

Infant weight was significantly lower for those in the 22 to 25 weeks group (M = 0.72, SD = 0.13, *Welch* $F(2, 216) = 287.54$, $p < .001$) when compared to those in the 26 to 28 weeks group (M = 1.03, SD = 0.24), and those in the 29 to 32 weeks group (M = 1.39, SD = 0.26). Analysis indicated an increase in infant weight with increasing gestation age at birth, large effect size ($\eta^2 = .527$). LOS in the NICU was significantly longer for those infants in the smaller gestational age group 22 to 25 weeks (M=113.13, SD = 20.04, *Welch* F (2, 149) = 328.30, $p < 0.001$) when compared to those in the 26 to 28 weeks group (M = 81.64, SD = 26.86), and those in the 29 to 32 weeks group (M = 47.15, SD = 12.89). A decrease in the infant LOS was found with increasing GA at birth with a large effect ($\eta^2 = 0.579$). Gestation age at discharge was significantly higher for those in the 22 to 25 weeks group (M = 40.34, SD = 3.24, *Welch* $F(2, 146) = 37.02$, $p <$

.001) when compared to those in the 26 to 28 weeks group (M = 38.51, SD = 2.77), and those in the 29 to 32 weeks group (M = 37.01, SD = 1.80). Analysis revealed a decrease in gestation age at discharge with increasing gestation age at birth, large effect size (η^2 = .189).

Total number of days from birth to breastfeeding was significantly higher for those in the 22 to 25 weeks group (M = 69.84, SD = 12.78, *Welch* $F(2, 95) = 294.15$, $p <$ .001) when compared to those in the 26 to 28 weeks group (M = 42.56, SD = 13.37), and those in the 29 to 32 weeks group (M = 20.47, SD = 9.17). Analysis indicated a decrease in No. of days from birth to breastfeeding with increasing gestation age at birth, large effect size (η^2 = .685). Total volume of breastmilk during LOS was significantly higher for those in the 22 to 25 weeks group (M = 23.20, SD = 8.91, *Welch* $F(2, 142) = 75.28$, p < .001) when compared to those in the 26 to 28 weeks group (M = 17.58, SD = 7.55), and those in the 29 to 32 weeks group (M = 11.25, SD = 4.40). Analysis revealed a decrease in total volume (L) of breastmilk during LOS with increasing gestation age at birth, large effect size (η^2 = .305). This is likely related to the longer LOS for the infants in the smallest GA at birth group.

The total number of nurses who cared for infant during first month of life was significantly lower for those in the 22 to 25 weeks group (M = 37.49, SD = 5.68, *Welch* $F(2, 163) = 22.17$, $p < .001$) when compared to those in the 26 to 28 weeks group (M = 40.14, SD = 5.21), and those in the 29 to 32 weeks group (M = 42.76, SD = 5.03). Analysis revealed an increase in the total number of nurses who cared for the infant during the first month of life with increasing gestation age at birth with a moderate effect size (η^2 = .067). Additionally, the total number of nurses who cared for infant during total

LOS was significantly higher for those in the 22 to 25 weeks group (M = 94.89, SD = 18.87, *Welch* $F(2, 153) = 146.62$, $p < .001$) when compared to those in the 26 to 28 weeks group (M = 77.57, SD = 17.22), and those in the 29 to 32 weeks group (M = 56.04, SD = 12.61). Analysis revealed a decrease in the total number of nurses who cared for the infant during the LOS with increasing gestation age at birth, large effect size ($\eta^2 = .462$). The total number of lab tests during LOS was significantly higher for those in the 22 to 25 weeks group (M = 127.37, SD = 42.50, *Welch* $F(2, 127) = 208.00$, $p < .001$) when compared to those in the 26 to 28 weeks group (M = 56.92, SD = 33.57), and those in the 29 to 32 weeks group (M = 26.68, SD = 12.16). Analysis revealed a decrease in the total number of lab tests during LOS with increasing gestation age at birth, large effect size ($\eta^2 = .605$) (see Table 6).

Kruskal-Wallis H and GA at Birth

Several Kruskal-Wallis H tests were conducted to identify if there were significant differences in neonatal-maternal sociodemographic and clinical characteristics, NICU environmental stressors and stress modifiers, neonatal morbidities, and neurodevelopmental outcomes in terms of gestation age at the time of birth: 22 to 25 Weeks (n = 63), 26 to 28 Weeks (n = 138), and 29 to 32 Weeks (n = 139). Values are mean ranks unless otherwise stated. Distributions for maternal gravida, parity, and gestation age at the time of the neurodevelopmental assessment were similar for all groups, as assessed by visual inspection of boxplots. The mean ranks for maternal gravida, $\chi^2(2) = 1.269$, $p = .530$, maternal parity, $\chi^2(2) = 0.296$, $p = .862$, and GA at neurodevelopmental assessment, $\chi^2(2) = 4.018$, $p = .134$, were not significantly different between the groups.

Distributions for the number of days from birth to first hold, number of days birth to first skin-to-skin, number of days birth-full enteral feeding volume, number of parent visits per day during LOS number of parent visits per week during LOS, number of nurses who cared for infant during the first week, number of blood transfusions during LOS, number of days infant was intubated during LOS, number of days infant received supplemental oxygen during LOS, and cognitive, language and motor scores were not similar for all groups, as assessed by visual inspection of boxplots. The means for number of days birth-being held, $\chi^2(2) = 144.43$, $p < 0.001$; number of days birth-skin-to-skin, $\chi^2(2) = 143.67$, $p < 0.001$; number of days birth-full enteral feeding volume, $\chi^2(2) = 140.02$, $p < .001$; number of parent daily visits during LOS, $\chi^2(2) = 144.08$, $p < 0.001$; number of parent weekly visits during LOS, $\chi^2(2) = 14.54$, $p = 0.001$; number of nurses who cared for infant during the first week, $\chi^2(2) = 25.45$, $p < 0.001$; number of PRBC transfusions during LOS, $\chi^2(2) = 183.60$, $p < 0.001$; number of days infant was intubated during LOS, $\chi^2(2) = 141.52$, $p > 0.001$; number of days infant received supplemental oxygen during LOS, $\chi^2(2) = 148.87$, $p < 0.001$; cognitive score, $\chi^2(2) = 12.88$, $p = 0.002$; language score, $\chi^2(2) = 7.46$, $p = .024$; and motor score, $\chi^2(2) = 10.98$, $p = .004$ were significantly different between the groups (see Table 6).

Pairwise comparisons were performed using Dunn's (1964) procedure with a Bonferroni correction for multiple comparisons. This post-hoc analysis identified significant differences in the number of days from birth to first hold among the 22 to 25 weeks gestation age group (*Md.* = 26.00), the 26 to 28 weeks gestation age group (*Md.* = 8.00), and the 29 to 32 weeks gestation age group (*Md.* = 3.00, $p < .001$). Significant differences were found in the number of days from birth to first skin-to-skin among the

22 to 25 weeks gestation age group (*Md.* = 26.0), the 26 to 28 weeks gestation age group (*Md.* = 7.00), and the 29 to 32 weeks gestation age group (*Md.* = 3.00, $p < .001$). Significant differences were found in the number of days from birth to full enteral breastfeeding volume among the 22 to 25 weeks gestation age group (*Md.* = 16.00), the 26 to 28 weeks gestation age group (*Md.* = 10.00), and the 29 to 32 weeks gestation age group (*Md.* = 5.50, $p < .001$).

Significant differences were found in the total number of parent daily visits between the 22 to 25 weeks gestation age group (*Md.* = 0.33) and the 26 to 28 Weeks gestation age group (*Md.* = 0.76), and between the 22 to 25 weeks gestation age group and the 29 to 32 weeks gestation age group (*Md.* = 1.47, $p < .001$); significant differences were not found between the 26 to 28 weeks and 29 to 32 weeks groups. Additionally, significant differences were found in the total number of parent weekly visits among the 22 to 25 weeks gestation age group (*Md.* = 6.50), the 26 to 28 weeks gestation age group (*Md.* = 6.62), and the 29 to 32 weeks gestation age group (*Md.* = 6.71, $p < .001$). Significant differences were also identified in the total number of nurses who cared for the infant in the first week of life between the 22 to 25 weeks gestation age group (*Md.* = 12.00) and the 29 to 32 weeks gestation age group (*Md.* = 13.00, $p < .001$), and between the 26 to 28 weeks gestation age group (*Md.* = 12.00) and the 29 to 32 weeks gestation ($p < .001$); significant differences were not found between the 22 to 25 weeks and the 26 to 28 weeks groups.

Significant differences were found in the number of PRBC transfusions during LOS among the 22 to 25 weeks gestation age group (*Md.* = 7.00), the 26 to 28 weeks gestation age group (*Md.* = 1.00), and the 29 to 32 weeks gestation age group (*Md.* =

0.00, $p < .001$). Significant differences were found in the number of days the infant was intubated among the 22 to 25 weeks gestation age group (*Md.* = 25.00), the 26 to 28 weeks gestation age group (*Md.* = 2.00), and the 29 to 32 weeks gestation age group (*Md.* = 0.00, $p < .001$). Significant differences were found in the number of days infant was on supplemental oxygen among the 22 to 25 weeks gestation age group (*Md.* = 47.00), the 26 to 28 weeks gestation age group (*Md.* = 101.00), and the 29 to 32 weeks gestation age group (*Md.* = 2.00, $p < .001$).

Finally, significant differences were found in the cognitive scale scores between the 22 to 25 weeks gestation age group (*Md.* = 90.00) and the 29 to 32 Weeks gestation age group (*Md.* = 95.00, $p = .002$). Significant differences were also identified in the language scale scores between the 22 to 25 weeks gestation age group (*Md.* = 89.00) and the 29 to 32 weeks gestation age group (*Md.* = 91.00, $p = .024$). Significant differences were found in the motor scale scores between the 22 to 25 weeks gestation age group (*Md.* = 94.00) and the 29 to 32 Weeks gestation age group (*Md.* = 100.00, $p = .004$) (see Table 6).

Table 6

*One-Way ANOVAs and Kruskal Wallis H: Sociodemographic and Clinical Characteristics by **Gestation age at Birth** (N = 340)*

	Total	**22 to 25 Weeks**	**26 to 28 Weeks**	**29 to 32 Weeks**			
Characteristic	***M (SD)***	***M (SD)***	***M (SD)***	***M (SD)***	***F***	***p***	η^2
Maternal age	30.72 (6.13)	29.78 (5.58)	30.41 (6.30)	31.45 (6.15)	1.93	.147	--
Infant weight, kg	1.12 (0.35)	0.72 (0.13)	1.03 (0.24)	1.39 (0.26)	287.54[a]	< .001	.527
LOS at NICU	73.52 (1.74)	113.13 (20.04)	81.64 (26.86)	47.51 (12.89)	328.30[a]	< .001	.579
No. days birth to breastfeeding	36.48 (20.53)	69.84 (12.78)	42.56 (13.37)	20.47 (9.17)	294.15[a]	< .001	.685
Breastmilk volume LOS, L	16.03 (80.83)	23.20 (8.91)	17.58 (7.55)	11.25 (4.40)	75.28[a]	< .001	.305
Gestation age at discharge, weeks	38.23 (2.79)	40.34 (3.24)	38.51 (2.77)	37.01 (1.80)	37.02[a]	< .001	.189
No. RNs cared for infant, month 1	40.72 (5.56)	37.49 (5.68)	40.14 (5.21)	42.76 (5.03)	22.17[a]	< .001	.067
No. RNs cared for infant, LOS	71.97 (21.55)	94.89 (18.87)	77.57 (17.22)	56.04 (12.61)	146.62[a]	< .001	.462
No. lab tests, LOS	57.61 (46.29)	127.37 (42.50)	56.92 (33.57)	26.68 (12.16)	208.00[a]	< .001	.605
	n (Mean Rank)	***n (Mean Rank)***	***n (Mean Rank)***	***n (Mean Rank)***	***H (df)***	***P***	ε^2
Maternal gravida	340 (--)	63 (160.44)	138 (169.11)	139 (176.45)	1.27 (2)	.530	--
Maternal parity	340 (--)	63 (170.67)	138 (167.45)	139 (173.45)	0.30 (2)	.862	--
Gestational age at follow-up	340 (--)	63 (149.66)	138 (170.88)	139 (179.57)	4.02 (2)	.134	--
	n (Md.)	***n (Md.)***	***n (Md.)***	***n (Md.)***	***H (df)***	***P***	ε^2
No. days birth to being held	340 (5.50)	63 (26.00)	138 (8.00)	139 (3.00)	144.43 (2)	< .001	.426
No. days birth to skin-to-skin	338 (5.00)	63 (26.00)	137 (7.00)	138 (3.00)	143.67 (2)	< .001	.426
No. days birth to enteral feeding	335 (8.00)	62 (16.00)	135 (10.00)	138 (5.50)	140.02 (2)	< .001	.419
No. parent visits per day, LOS	340 (0.98)	63 (0.33)	138 (0.76)	139 (1.47)	144.00 (2)	< .001	.425
No. parent visits per wk, LOS	340 (6.66)	63 (6.50)	138 (6.62)	139 (6.71)	14.54 (2)	< .001	.043
No. RNs cared for infant, week 1	340 (12.00)	63 (12.00)	138 (12.00)	139 (13.00)	25.45 (2)	< .001	.075
No. PRCB transfusion, LOS	340 (1.00)	63 (7.00)	138 (1.00)	139 (0.00)	183.60 (2)	< .001	.542

	Total	22 to 25 Weeks	26 to 28 Weeks	29 to 32 Weeks			
Characteristic	***n (Md.)***	***n (Md.)***	***n (Md.)***	***n (Md.)***	***H (df)***	***P***	ε^2
No. days intubated, LOS	336 (2.00)	63 (25.00)	136 (2.00)	139 (0.00)	141.52 (2)	< .001	.422
No. days infant on supplemental O_2, LOS	263 (14.00)	47 (83.00)	101 (33.00)	115 (2.00)	148.87 (2)	< .001	.568
Bayley III: cognitive scale	340 (95.00)	63 (90.00)	138 (95.00)	139 (95.00)	12.88 (2)	.002	.038
Bayley III: language scale	339 (89.00)	63 (89.00)	137 (89.00)	139 (91.00)	7.46 (2)	.024	.022
Bayley III: motor scale	340 (97.00)	63 (94.00)	138 (97.00)	139 (100.00	10.98 (2)	.004	.032

Regression Analysis

Multiple Linear Regression

Aim 3: To identify the amount of variance in Bayley III neurodevelopmental assessment (Motor, Language, & Cognitive scales) at 2 years of age accounted for by maternal/neonatal demographics, environmental stressors, stress modifiers, and neonatal morbidities.

Cognitive Scale

A multivariable regression was run to identify which factors (maternal age, race/ethnicity, marital status, insurance, maternal history of drug use, prenatal care, gestation age at birth, birth weight, number of days from birth to first skin-to-skin, number of day from birth to full enteral feeding, some breastmilk at discharge, average number of parents' daily visits during LOS, number of nurses caring for infant during LOS, PRBC infant transfusions, HFNC at 36 weeks, highest grade IVH, and rehospitalization since discharge) predict infant cognitive scores at 2 years of age. There was linearity as assessed by partial regression plots and a plot of studentized residuals

against the predicted values. There was independence of residuals, as assessed by a Durbin-Watson statistic of 1.964. There was homoscedasticity, as assessed by visual inspection of a plot of studentized residuals versus unstandardized predicted values. There was no evidence of multicollinearity, as assessed by tolerance values less than 0.1 (VIF < 10). There were several studentized deleted residuals greater than ±3 standard deviations (about 5%), one leverage values were greater than 0.2, and no values for Cook's distance above 1. The assumption of normality was met, as assessed by a Q-Q Plot. The multivariable regression model explained 23.7% of the variance in Bayley III cognitive composite scores at 2 years of age: R^2 = 0.237, R^2 adj. = 0.148, $F(26, 225)$ = 2.681, $p < .001$. Six parameters: maternal race-ethnicity: Hispanic, Latino ($t = -2.01$, p = .046); Asian, Pacific Islander, Hawaiian Native ($t = -2.11$, p = .036); Other race, Native American, Alaska Native ($t = -2.30$, p = .022); marital status: separated, divorced ($t = -1.98$, p = .049); some breastmilk at discharge ($t = 2.12$, p = .035); and the average number of parent visits per day during the LOS ($t = 2.42$, p = .016) added significantly to the prediction. There is a decrease in cognitive scores for Hispanic/Latino; Asian, Pacific Islander, and Hawaiian; and other races, Native American, and Alaska Native; but not for Black, African American mothers when compared to White mothers as the reference category. Predicted infant cognitive scores were higher for infants whose parents visit them more per day during their LOS in the NICU (B = 4.38, 95% CI 0.82 to 7.95). Regression coefficients and standard errors can be found in Table 7.

Table 7

*Multivariable Regression for Predicting Bayley III **Cognitive** Composite Score at 2 Years of Age (N = 340)*

		95% CI for B				
Variable	***B***	**LL**	**UL**	**Beta**	***t***	***p***
Maternal age	0.17	-0.16	0.50	0.07	1.01	.312
Maternal race-ethnicity:						
White, Caucasian						Ref
Hispanic, Latino	-4.33	-8.57	-0.08	-0.14	-2.01	**.046**
Black, African American	-3.28	-10.56	4.00	-0.06	-0.89	.375
Asian, Pacific Islander, Hawaiian Native	-6.40	-12.37	-0.43	-0.14	-2.11	**.036**
Other, Native American, Alaska Native	-11.32	-21.00	-1.63	-0.15	-2.30	**.022**
Maternal marital status:						
Married						Ref
Separated, divorced	-8.55	-17.04	-0.06	-0.12	-1.98	**.049**
Single	-2.28	-6.73	2.17	-0.07	-1.01	.313
Maternal insurance:						
Private						Ref
No insurance, self-pay	1.32	-15.01	17.64	0.01	0.16	.874
Public	-1.23	-5.42	2.97	-0.04	-0.58	.565
Maternal history of drug use: Yes	-5.25	-15.97	5.47	-0.06	-0.96	.336
Prenatal care: Yes	9.40	-0.63	19.44	0.11	1.85	.066
Gestational age at birth:						
22 to 25 Weeks						Ref
26 to 28 Weeks	-0.85	-7.10	5.39	-0.03	-0.27	.788
29 to 32 Weeks	-4.62	-13.25	4.02	-0.15	-1.05	.293
Infant weight at birth, kg	1.62	-6.44	9.69	0.04	0.40	.692
No. of days birth to 1st skin-to-skin	-0.06	-0.28	0.16	-0.04	-0.51	.610
No. of days birth to full enteral feeding volume, 160 ml/kg/day	-0.15	-0.54	0.24	-0.07	-0.76	.450
Some breastmilk at discharge	5.10	0.36	9.84	0.13	2.12	**.035**
No. of parents' daily visits during NICU LOS, average	4.38	0.82	7.95	0.20	2.42	**.016**
No. of nurses caring for infant during NICI LOS	-0.02	-0.14	0.11	-0.03	-0.29	.771
Infant PRBC transfusion during LOS at NICU	0.63	-4.61	5.87	0.02	0.24	.812

		95% CI for B				
Variable	***B***	**LL**	**UL**	**Beta**	***t***	***p***
Infant on HFNC, ≥ 2 L/min at 36 corrected weeks	-4.54	-11.10	2.01	-0.09	-1.37	.174
Highest grade IVH:						
None						Ref
Grade I	-0.09	-8.39	8.22	0.00	-0.02	.983
Grade II	1.45	-6.77	9.68	0.02	0.35	.728
Grade III	-15.54	-31.99	0.91	-0.11	-1.86	.064
Grade IV	-8.41	-27.34	10.52	-0.05	-0.88	.382
Infant rehospitalization since NICU discharge	-0.25	-4.81	4.31	-0.01	-0.11	.914

Note. B = unstandardized regression coefficient; *CI* = confidence interval; *LL* = lower limit; HFNC = High flow nasal canula; IVH = Intraventricular hemorrhage; LOS = length of stay; NICU = Neonatal intensive care unit; *UL* = upper limit; β = standardized coefficient. ***Reference categories:*** Maternal race-ethnicity, White; Maternal marital status, Married; Maternal insurance, No insurance; Maternal history of drug use, No drug use; Prenatal care, No prenatal care; Some breastmilk at discharge, No breastmilk; Infant PRBC transfusion during LOS at NICU, No PRBC transfusion; Infant on HFNC, No HFNC; Highest grade IVH, None; Infant rehospitalization since NICU discharge, No.

Language Scale

A multiple regression was run to identify which factors (maternal age, race/ethnicity, marital status, insurance, maternal history of drug use, prenatal care, gestation age at birth, birth weight, number of days from birth to first skin-to-skin, number of day from birth to full enteral feeding, some breastmilk at discharge, average number of parents' daily visits during LOS, number of nurses caring for infant during LOS, PRBC infant transfusions, HFNC at 36 weeks, late onset sepsis, and rehospitalization since discharge) predict infant language scores at 2 years of age. There was linearity as assessed by partial regression plots and a plot of studentized residuals against the predicted values. There was independence of residuals, as determined by the

model design. There was homoscedasticity, as assessed by visual inspection of a plot of studentized residuals versus unstandardized predicted values. There was no evidence of multicollinearity, as assessed by tolerance values less than 0.1 (VIF < 10). There were several studentized deleted residuals greater than ±3 standard deviations (< 5%), several leverage values greater than 0.2 (also < 5%), and no values for Cook's distance above 1. The assumption of normality was met, as assessed by a Q-Q Plot. The final multivariable regression model explained 26.1% of the variance in Bayley III language composite scores at 2 years of age: R^2 = 0.261, R^2 adj. = 0.187, $F(23, 228) = 3.504$, $p < 0.001$. Three parameters: maternal race-ethnicity: Hispanic, Latino ($t = -2.77$, $p = .006$); maternal race-ethnicity: Asian, Pacific Islander, Hawaiian Native ($t = -3.43$, $p = .001$); and maternal insurance: public ($t = -2.41$, $p = .017$) added significantly to the prediction. There was a significant decrease in language scores for Hispanic/Latino; and Asian, Pacific Islander, and Hawaiian; but not for Black, African American; and other races, Native American, and Alaska Native mothers when compared to White mothers as the reference category. Predicted infant language scores were lower for infants whose mother had public insurance (B = -5.64, 95% CI = -10.25 to -1.02). Regression coefficients and standard errors can be found in Table 8.

Table 8

*Multivariable Regression for Predicting Bayley III **Language** Composite Score at 2 Years of Age (N = 340)*

		95% CI for B				
Variable	***B***	**LL**	**UL**	**Beta**	***t***	***p***
Maternal age	0.10	-0.26	0.46	0.04	0.55	.581
Maternal race-ethnicity:						
White, Caucasian						Ref
Hispanic, Latino	-6.57	-11.24	-1.90	-0.19	-2.77	**.006**
Black, African American	-0.57	-8.57	7.43	-0.10	-0.14	.888
Asian, Pacific Islander, Hawaiian Native	-11.45	-18.02	-4.87	-0.22	-3.43	**.001**
Other, Native American, Alaska Native	-8.04	-18.62	2.53	-0.09	-1.50	.135
Maternal marital status:						
Married						Ref
Separated, divorced	-4.81	-14.17	4.56	-0.06	-1.01	.313
Single	-3.16	-8.04	1.73	-0.09	-1.27	.205
Maternal insurance:						
Private						Ref
No insurance, self-pay	0.12	-17.87	18.10	0.01	0.01	.990
Public	-5.64	-10.25	-1.02	-0.17	-2.41	**.017**
Maternal history of drug use: Yes	-7.47	-19.38	4.45	-0.08	-1.24	.218
Prenatal care: Yes	10.57	-0.49	21.62	0.11	1.88	.061
Gestational age at birth:						
22-25 Weeks						Ref
26 to 28 Weeks	-1.48	-8.39	5.43	-0.04	-0.42	.673
29 to 32 Weeks	-5.11	-14.59	4.36	-0.15	-1.06	.289
Infant weight at birth, kg	1.57	-7.31	10.45	0.03	0.35	.728
No. of days birth to 1st skin-to-skin	-0.03	-0.27	0.21	-0.02	-0.25	.803
No. of days birth to full enteral feeding volume, 160 ml/kg/day	-0.13	-0.56	0.29	-0.05	-0.62	.536
Some breastmilk at discharge	4.66	-0.55	9.86	0.11	1.76	.079
No. of parents' daily visits during NICU LOS, average	3.73	-0.19	7.64	0.15	1.88	.062
No. of nurses caring for infant during NICI LOS	-0.04	-0.17	0.10	-0.05	-0.55	.582
Infant PRBC transfusion during LOS at NICU	0.94	-4.78	6.67	0.03	0.32	.746

		95% CI for B				
Variable	***B***	**LL**	**UL**	**Beta**	***t***	***p***
Infant on HFNC, ≥ 2 L/min at 36 corrected weeks	-5.05	-12.26	2.17	-0.09	-1.38	.169
Late onset sepsis, culture positive blood or CSF > 72h of life	-2.04	-9.12	5.04	-0.04	-0.57	.571
Infant rehospitalization since NICU discharge	-2.29	-7.31	2.72	-0.06	-0.90	.369

Note. B = unstandardized regression coefficient; *CI* = confidence interval; *LL* = lower limit; HFNC = High flow nasal canula; IVH = Intraventricular hemorrhage; LOS = length of stay; NICU = Neonatal intensive care unit; *UL* = upper limit; β = standardized coefficient. ***Reference categories:*** Maternal race-ethnicity, White; Maternal marital status, Married; Maternal insurance, No insurance; Maternal history of drug use, No drug use; Prenatal care, No prenatal care; Some breastmilk at discharge, No breastmilk; Infant PRBC transfusion during LOS at NICU, No PRBC transfusion; Infant on HFNC, No HFNC; Late onset sepsis, No; Infant rehospitalization since NICU discharge, No.

Motor Scale

A multiple regression was run to identify which factors (maternal age, marital status, insurance, history of drug use, gestation age at birth, birth weight, number of days from birth to 1st skin-to-skin, number of days from birth to full enteral feed, some breastmilk at discharge, number of average parent daily visits during LOS, number of nurses caring for infant during 1st week, number of nurses caring for infant during 1st month, PRBC infant transfusions, HFNC at 36 weeks, oxygen at discharge, and late onset sepsis.) predict infant motor scores at 2 years of age. There was linearity as assessed by partial regression plots and a plot of studentized residuals against the predicted values. There was independence of residuals, as assessed by a Durbin-Watson statistic of 1.756. There was homoscedasticity, as assessed by visual inspection of a plot of studentized residuals versus unstandardized predicted values. There was no evidence of multicollinearity, as assessed by tolerance values less than 0.1 (VIF < 10). There were several studentized deleted residuals greater than ±3 standard deviations (< 5%), nine

leverage values greater than 0.2, and no values for Cook's distance above 1. The assumption of normality was met, as assessed by a Q-Q Plot. The multivariable regression model explained 26.1% of the variance in Bayley III motor composite scores at 2 years of age: $R^2 = 0.175$, R^2 adj. = 0.108, $F(19, 232) = 2.599$, $p < 0.001$. One parameter: some breastmilk at discharge ($t = 2.05$, $p = .041$) added significantly to the prediction. Regression coefficients and standard errors can be found in Table 9.

Table 9

*Multivariable Regression for Predicting Bayley III **Motor** Composite Score at 2 Years of Age (N = 340)*

		95% CI for B				
Variable	***B***	**LL**	**UL**	**Beta**	***t***	***P***
Maternal age	0.11	-0.19	0.42	0.05	0.73	.467
Maternal marital status:						
Married						Ref
Separated, divorced	-3.20	-11.18	4.78	-0.05	-0.79	.430
Single	-0.06	-4.21	4.08	-0.01	-0.03	.976
Maternal Insurance:						
Private						Ref
No insurance, self-pay	4.79	-10.66	20.25	0.04	0.61	.542
Public	-2.17	-6.01	1.66	-0.08	-1.12	.266
Maternal history of drug use:	-7.12	-17.09	2.84	-0.09	-1.41	.160
Gestational age at birth:						
22-25 Weeks						Ref
26 to 28 Weeks	-0.52	-6.43	5.40	-0.02	-0.17	.864
29 to 32 Weeks	-5.66	-13.78	2.46	-0.20	-1.37	.171
Infant weight at birth, kg	6.02	-1.47	13.50	0.15	1.59	.114
No. of days birth to 1st skin-to-skin	-0.03	-0.23	0.18	-0.02	-0.24	.814
No. of days birth to full enteral feeding volume, 160 ml/kg/day	-0.04	-0.40	0.32	-0.02	-0.22	.826
Some breastmilk at discharge	4.67	0.19	9.16	0.13	2.05	**.041**
No. of parents' daily visits during NICU LOS, average	2.20	-1.13	5.54	0.11	1.30	.194
No. of nurses caring for infant during NICU 1st week	0.32	-0.60	1.24	0.05	0.69	.489
No. of nurses caring for infant during NICU 1st month	0.08	-0.29	0.45	0.03	0.44	.662
Infant PRBC transfusion during LOS at NICU	-1.68	-6.46	3.10	-0.06	-0.69	.489
Infant on HFNC, ≥ 2 L/min at 36 corrected weeks	-5.72	-11.87	0.44	-0.12	-1.83	.069
Infant on supplemental oxygen at discharge	-3.32	-11.52	4.89	-0.05	-0.80	.427
Late onset sepsis, culture positive blood or CSF > 72h of life	-4.40	-10.47	1.67	-0.09	-1.43	.154

Note. B = unstandardized regression coefficient; *CI* = confidence interval; *LL* = lower limit; HFNC = High flow nasal canula; IVH = Intraventricular hemorrhage; LOS = length of stay; NICU = Neonatal intensive care unit; *UL* = upper limit; β = standardized coefficient. ***Reference categories:*** Maternal marital status, Married; Maternal insurance, Private; Maternal history of drug use, No drug use; Gestation age at birth, 22 to 25 Weeks; Some breastmilk at discharge, No breastmilk; Infant PRBC transfusion during LOS at NICU, No PRBC transfusion; Infant on HFNC, No HFNC; Infant on supplemental oxygen at discharge, No; Late onset sepsis, No; Infant rehospitalization since NICU discharge, No.

Autism Screen

Aim 4: To identify the predictors that increase or decrease the odds of positive autism screen as

> measured with M-CHAT at 2 years of age as determined by maternal/neonatal demographics, environmental stressors, stress modifiers, and neonatal morbidities.

Crosstabs and T-tests for Autism Screen

A chi-square test of independence was conducted between neonatal-maternal sociodemographic and clinical characteristics, NICU environmental stressors and stress modifiers, neonatal morbidities, neurodevelopmental outcomes (Bayley III: cognitive, language, and motor scales), and the autism screening using M-CHAT at approximately 2 years of age. Not all expected cell frequencies were greater than five; Fisher's Exact Tests were reported for all variables except otherwise noted. Due to the small sample size for infants who screened positive and suspect, these variables were combined for the purposes of running the inferential statistics. There were significant associations between infants' autism screen and: maternal marital status, Fisher's $x^2 = 9.08$, p=0.11; maternal education level, Fisher's $x^2 = 8.11$, p =0.27; infant high flow nasal canula at 36 weeks, Fisher's $x^2 = 5.41$, p =0.36, early onset of sepsis, Fishers $x^2 = 11.66$, $p = 0.012$; periventricular leukomalacia, Fisher's $x^2 = 9.02$, p= 0.036; and infant rehospitalization since discharge, Fisher's x^2 =15.65, $p < 0.001$ (see Table 10). The largest significant association as demonstrated by effect size was between autism screen and maternal education level (Cramer's V =0.328, moderate effect). The largest adjusted residuals are for the less than high school diploma category and positive autism screen group

(Adjusted residual = -2.6). The second largest significant association is between autism screen and infant rehospitalization after NICU discharge (Phi = 0.270, small, almost reaching moderate effect). Adjusted residuals of 4.0 for re-hospitalized infant with a positive autism screen.

Table 10

*Crosstabulation: M-CHAT **Autism** Screen at 2 years of age (N = 216)*

	Total		**Positive**		**Negative**			
Characteristic	***n***	***%***	***n***	***%***	***n***	***%***	χ^2	***p***
Maternal Race/Ethnicity							5.09	.240
White, not of Hispanic origin	109	32.1	5	7.7	60	92.3		
Hispanic, Latino	152	44.7	17	17.1	79	82.3		
Black, African American	26	7.6	1	5.3	18	94.7		
Asian, Pacific Islander, Hawaiian Native	40	11.8	2	6.9	27	93.1		
Other Race	13	3.8	0	0.0	7	100.0		
Maternal Primary Language							1.92	.401
English	296	87.8	21	10.9	171	89.1		
Spanish	23	6.8	2	15.4	11	84.6		
English and: Spanish, Chinese, Japanese, Other	18	5.3	2	22.2	7	77.8		
Maternal Marital Status							9.08	**.011**
Married	206	61.3	9	6.7	126	93.3		
Separated, divorced	16	4.8	1	14.3	6	85.7		
Single	114	33.9	15	20.8	57	79.2		
Education Level							8.11	**.027**
Less than High School	10	10.9	4	40.0	6	60.0		
High School Diploma	16	17.4	0	0.0	15	100.0		
Partial College	29	31.5	2	7.1	26	92.9		
College Degree	37	40.2	6	16.2	31	83.8		
Maternal Health Insurance							4.79	.081
No insurance	4	1.2	0	0.0	3	100.00		
Private insurance	179	52.6	9	7.5	111	92.5		

	Total		Positive		Negative			
Characteristic	***n***	***%***	***n***	***%***	***n***	***%***	χ^2	***p***
Public insurance	157	46.2	16	17.2	77	82.8		
Maternal History of Depression							0.53[a]	.465
Yes	8	2.4	0	0.0	4	100.00		
No	332	97.6	25	11.8	187	88.2		
Maternal History of Drug Use							1.83	.204
Yes	8	3.1	2	28.6	5	71.4		
No	253	96.9	21	11.5	161	88.5		
Prenatal Care							3.48	.095
Yes (≥ one visit)	329	96.8	3	30.0	7	70.0		
No	11	3.2	22	10.7	184	89.3		
Gestation age at birth							5.48	.060
22 to 25 weeks	63	18.5	9	19.6	37	80.4		
26 to 28 weeks	138	40.6	11	12.6	76	87.4		
29 to 32 weeks	139	40.9	5	6.0	78	94.0		
Infant Gender							1.93	.203
Male	173	50.9	16	14.5	94	85.5		
Female	167	49.1	9	8.5	97	91.5		
Birth Hospital							0.68[a]	.639
Inborn (SMBHWN)	330	97.6	25	12.0	184	88.0		
Outborn (all others)	8	2.4	0	0.0	5	100.00		
Mode of Delivery							1.67	.428
Primary c-section	202	59.9	16	11.7	121	88.3		
Repeat c-section	60	17.6	2	6.1	31	93.9		
Spontaneous vaginal	75	22.3	7	15.9	37	84.1		
Multiple Delivery							0.31	.805
Yes	96	28.3	5	9.4	48	90.6		
No	244	71.8	20	12.3	143	87.7		
No. of Fetuses							1.33	.487
1	244	71.8	20	12.3	143	87.7		
2	82	24.1	4	8.3	44	91.7		
3	14	4.1	1	20.0	4	80.0		

	Total		Positive		Negative			
Characteristic	***n***	***%***	***n***	***%***	***n***	***%***	χ^2	***p***
Apgar 1 minute							7.46	.440
1	32	9.4	5	25.0	15	75.0		
2	20	5.9	1	7.7	12	92.3		
3	32	9.4	2	11.1	16	88.9		
4	27	7.9	2	10.0	18	90.0		
5	39	11.5	3	12.0	22	88.0		
6	49	14.4	6	16.2	31	83.8		
7	84	24.7	2	4.1	47	95.9		
8	52	15.3	4	13.3	26	86.7		
9	5	1.5	0	0.0	4	100.0		
Apgar 5 minute							6.06	.591
1	2	0.6	0	0.0	1	100.0		
2	2	0.6	0	0.0	0	0.0		
3	5	1.5	1	25.0	3	75.0		
4	5	1.5	1	33.3	2	66.7		
5	9	2.6	1	16.7	5	83.3		
6	23	6.8	2	14.3	12	85.7		
7	74	21.8	7	14.0	43	86.0		
8	169	49.7	10	9.3	98	90.7		
9	49	14.4	3	10.7	25	89.3		
10	2	0.6	0	0.0	2	100.0		
Breastmilk at Discharge							3.60	.089
Yes	62	18.2	1	2.6	37	97.4		
No	278	81.8	24	13.5	154	86.5		
Infant Blood Transfusion during NICU Stay							2.40	.139
Yes	178	52.5	17	14.8	98	85.2		
No	161	47.5	8	8.0	92	92.0		
Infant High Flow Nasal Cannula[b]							5.41	**.036**
Yes	30	9.1	5	29.4	12	70.6		
No	299	90.9	20	10.4	173	89.6		
Infant CPAP at 36 Corrected Weeks							0.30[a]	.864
Yes	30	8.9	1	5.3	17	89.5		
No	307	91.1	8	4.1	171	88.1		

	Total		Positive		Negative			
Characteristic	***n***	***%***	***n***	***%***	***n***	***%***	χ^2	***p***
Infant Intubated at 36 Corrected Weeks							0.69[a]	.408
Yes	7	2.1	0	0.0	5	100.00		
No	329	97.9	25	12.1	182	87.9		
Infant on Oxygen at Discharge							0.32	.635
Yes	16	4.7	2	16.7	10	83.3		
No	324	95.3	23	11.3	181	88.7		
Early Onset Sepsis							11.66	**.012**
Yes	11	3.2	3	60.0	2	40.0		
No	328	96.8	22	10.5	188	89.5		
Late Onset Sepsis							2.56	.158
Yes	32	9.4	5	21.7	18	78.3		
No	307	90.6	20	10.4	172	89.6		
ROP Requiring Treatment[c]							0.09	.674
Yes	20	6.0	2	14.3	12	85.7		
No	315	94.0	23	11.7	174	88.3		
Highest Grade IVH[d]							4.45	.273
None	297	87.9	20	10.6	168	89.4		
Grade I	16	4.7	3	27.3	8	72.7		
Grade II	18	5.3	1	10.0	9	90.0		
Grade III	4	1.2	1	25.0	3	75.0		
Grade IV	3	0.9	0	0.0	2	100.0		
Periventricular Leukomalacia on any HUS							9.02	**.036**
Yes	4	1.2	2	66.7	1	33.3		
No	336	98.8	23	10.8	190	89.2		
Rehospitalization since NICU Discharge							15.65	< **.001**
Yes	69	20.5	13	27.1	35	72.9		
No	267	79.5	11	6.6	155	93.4		

Note. CPAP = continuous positive air pressure, HFNC = high flow nasal cannula, HUS = head ultrasound, IVH = intraventricular hemorrhage, LOS = length of stay, NICU = neonatal intensive care unit, ROP = retinopathy of prematurity, SMBHWN = Sharp Mary Birch Hospital for Women and Newborns.

Fisher's Exact Test, unless otherwise specified.

[a] Pearson-product or Monte Carlo Sig. (2-sided).

[b] High flow nasal cannula: 2 liters per minute or more at 36 corrected weeks.

[c] ROP requiring treatment: Avastin or laser surgery.

[d] Highest Grade IVH: any ultrasound before or on day 28.

An independent samples t-test was computed to identify if there were differences in autism screen (negative vs. positive) in terms of the neonatal-maternal sociodemographic and clinical characteristics, NICU environmental stressors and stress modifiers, and neonatal morbidities. There were 191 negative autism screens and 25 positive autism screens. Maternal age, infant weight, and the total number of nurses who care for the infant during the first week of life, first month of life, and the total LOS for each level. Of autism scores were normally distributed, as assessed by histograms and normal Q-Q plots, and there was homogeneity of variances, as assessed by Levene's test for equality of variances ($p > 0.05$). Infants with a positive (including suspect) autism screen score had lower birth weights ($M = 0.97$, $SD = 0.33$) than those who had a negative autism score ($M = 1.11$, $SD = 0.34$), a significant difference of 1.14 kg (95% CI 0.01, 0.29), $t(214) = 2.06$, $p = 0.041$. Infants with a positive (including suspect) autism screen score were cared for by more nurses during their LOS in the NICU ($M = 83.08$, $SD = 18.55$) than those who had a negative autism screen score ($M = 73.11$, $SD = 21.99$), a significant difference of almost 10 nurses (95% CI -19.04, -0.09), $t(214) = -2.17$, $p = 0.031$.

A Mann-Whitney U test was run to examine differences in neonatal-maternal sociodemographic and clinical characteristics; NICU environmental stressors and stress modifiers; and neonatal morbidities between infants with a positive versus negative autism screen. Distributions for positive and negative autism screen were similar and median scored demonstrated significant differences for days birth to first skin to skin ($U = 3110$, $z = 2.552$ $p = 0.011$), days to first breastfeeding ($U = 1548$, $z = 2.476$, $p = 0.013$), total breastmilk during NICU LOS ($U = 3210$, $z = 2.799$, $p = 0.005$), total number of lab

tests (U = 3143, z = 2.571, p = 0.010), total number of blood transfusions (U = 3225, z = 3.016, p = 0.003), total number of days intubated (U = 2985, z = 2.558, p = 0.011), total number of days requiring supplemental oxygen (U = 1869.5, z = 2.940, p = 0.003), and GA at time of autism screen (U = 1548, z = 2.476, p = 0.013). There was a significant difference for the variables listed above between infants with a positive and negative autism screen using an Asymptotic sampling distribution for U (for Median scores see Table 11). Distributions for total LOS NICU, days birth to first hold, gestational age at discharge, and total number parent visits per day were not similar as assessed by visual inspection; however, there were significant differences noted between infants with a positive and negative autism screen (for mean rank scores refer to Table 11).

Table 11

*Independent Samples T-test: M-CHAT **Autism** Screen at 2 years of age (N = 216)*

	Total	**Positive**	**Negative**		
Characteristic	***M(SD)***	***M (SD)***	***M (SD)***	***t***	***p***
Maternal age	30.72 (6.13)	29.28 (7.31)	31.22 (6.09)	1.46	.145
Infant Weight, kg	1.12 (0.35)	0.97 (0.33)	1.12 (0.34)	2.06	**.041**
No. RNs cared for infant, week 1	12.41 (2.15)	11.92 (2.64)	12.46 (2.19)	1.13	.259
No. RNs cared for infant, month 1	40.72 (5.56)	39.52 (6.68)	40.59 (5.32)	0.92	.359
No. RNs cared for infant, LOS	71.97 (21.55)	83.08 (18.55)	73.11 (21.99)	-2.17	**.031**
	n (Med.)	***n (Med.)***	***n (Med.)***	***U***	***p***
No. days birth to skin-to-skin	215 (9.90)	25 (11.00)	190 (5.00)	3110	**.011**
No. days birth to breastfeeding	172 (36.48)	14 (52.00)	158 (31.00)	1548	**.013**
No. days birth to enteral feeding vol.	213 (10.30)	25 (10.00)	188 (8.00)	2601.5	.384
Breastmilk volume during LOS, L	216 (16.03)	25 (21.52)	191 (14.30	3210	**.005**
No. parent visits per week, LOS	216 (6.46)	25 (6.60)	191 (6.64)	2084.5	.302
No. lab tests, LOS	216 (57.61)	25 (97.00)	191 (39.00)	3143	**.010**
No. blood transfusion, LOS	216 (2.23)	25 (6.00)	191 (1.00)	3225	**.003**
No. days intubated, LOS	213 (7.10)	24 (12.50)	189 (2.00)	2985	**.011**
No. days infant on suppl. O_2, LOS	158 (30.52)	19 (12.50)	139 (2.00)	1869	**.003**
Gestational age at follow-up visit	216 (24.46)	25 (22.92)	191 (24.07)	1668	**.014**
	M (Mean Rank)	***M (Mean Rank)***	***M (Mean Rank)***	***U***	***p***
Maternal gravida	216 (--)	25 (96.68)	191 (110.05)	2092	.299
Maternal parity	216 (--)	25 (101.54)	191 (109.41)	2213.5	.522
LOS at NICU, days	216 (--)	25 (141.08)	191 (104.24)	3202	**.006**
No. days birth to being held	216 (--)	25 (132.68)	191 (105.34)	2992	**.010**
Gestation age at discharge, weeks	216 (--)	25 (140.84)	191 (104.27)	3196	**.006**
No. parent visits per day, LOS	216 (--)	25 (78.14)	191 (112.47)	1628.5	**.010**

Note. LOS = length of stay, NICU = neonatal intensive care unit.

Logistic Regression

Two hundred and sixteen infants were screened for autism at 2 years of age, 88.4% (n = 191) screened negative; 4.2% (n = 9) screened positive, and 7.4% (n=16) screened suspect for autism. The positive and suspect autism screen accounted for 11.6 % (n=25). The autism screen did not yield significant differences between GA at birth groups. A logistic regression for autism outcome could not be computed due to the low frequency in the autism screen results for suspect and positive.

Chapter V

Discussion

The purpose of this study was to examine the relationship among sociodemographic factors, exposure to stressors in the NICU environment, stress modifiers/buffers, neonatal morbidities at discharge from the NICU, and 1. 2-year neurodevelopmental outcomes and 2. risk for autism in infants born less than 32 weeks GA cared for in a large, urban, tertiary NICU in Southern California. Specifically, this study sought to answer the following questions: 1. What are the defining characteristics of maternal infant dyads within this large, urban tertiary NICU? 2. What are the associations between socio-demographic factors, exposure to NICU environment, stress modifiers, neonatal morbidities, and 2-year neurodevelopmental outcomes in infants born less than 32 weeks gestational age? This study was guided by Mefford's Theory of Health Promotion for Preterm Infants and D'Agata's IMTN conceptual model (D'Agata et al., 2016; Mefford & Alligood, 2011). In this chapter the significance of the research findings, limitations and strengths of the study, suggested direction for future research, and implications for nursing practice are presented.

Significance of Research Findings

Scientific advances continue to support the complex biologic connection between the social environment, neurologic development, and long-term health. The NICU environment is stressful and traumatic with noise, lights, procedures, and parental separation. Yet, it is an environment in which premature infants must grow and thrive. Despite advances in care for premature and hospitalized infants, there remain remarkable disparities in long-term neurodevelopment between premature hospitalized neonates and

healthy, term infants. This study sought to examine contributing stressors, as well as modifiers over the course of the NICU hospitalization that may contribute to 2-year neurodevelopmental outcomes including cognition, language, and motor. In addition, this study also sought to identify contributing predictors for a positive autism screen at 2-years of age. The significance of the research findings for each study aim are discussed below.

Aim 1: Study Demographics and Characteristics

The first aim of this study was to describe the maternal-neonatal demographics and clinical stressors, environmental stressors and stress modifiers, neonatal morbidities, and 2-year neurodevelopmental outcomes (Bayley III motor, language, and cognitive scales and M-CHAT autism screen) among neonates receiving care in a large tertiary NICU in Southern California.

Overall, the study sample was diverse and representative of the overall community with the largest percentage of mothers reported Hispanic/Latino origin (44.7%), followed by white , not of Hispanic origin (32%); Asian, Pacific Islanders, or Hawaiian Natives; (11.8%) and Black, African American (7.6 %). The majority of the mothers' primary language was English. A large percentage of the mothers had either some college or completed college degree. Maternal health insurance was evenly distributed between private insurance and public insurance. When evaluating insurance by race and ethnicity, 61.1% of Hispanics vs. 18.5% of White, not of Hispanic origin had public insurance. Approximately two thirds of the infants were delivered via cesarean section with 60% delivered by primary cesarean section.

In this study, the mean birth weight (M = 1.12kg, *SD* = 1.78) and mean gestational age at birth (M = 28.2 weeks, *SD* =2.29) with 18% (n = 63) born less than 26 weeks GA is representative of the overall NICU demographics. Infants generally spend 2 to 3 months in the NICU depending on their gestational age at birth; this is similar to findings in this study with the average length of stay reported (73.5 days, *SD* =32.07). Not surprisingly, NICU length of stay was significantly longer for the smaller, younger infants in the 22 to 25 weeks GA at birth group (*M* = 113.13, *SD* 20.04) when compared to those in the 26 to 28 weeks group (*M*= 81.64, *SD* = 26.86), and those in the 29 to 32 weeks group (*M* = 47.51, *SD* = 12.89). A decrease in infant length of stay in the NICU as GA at birth increased was noted. Similarly, exposure to stressor variables was less for babies of larger GA at birth than those with smaller GA.

Raw scores on the Bayley III assessment are converted into a standardized 100-point scale with SD of 15 with an abnormal score below 85 indicating developmental impairment (Bayley 2006). The overall study sample means for the Bayley III outcomes for cognition, language, and motor were all above the cut score of 85. However, when Bayley III scores were assessed by GA at birth groups, there were significant differences in the identified median scores for all three of Bayley III outcomes with the lowest median scores in the 22-to-26-week GA at birth group; however, median scores were still above a cut score of 85; Sixty three percent of the study sample was screened for autism using M-CHAT; M-CHAT was not a standard assessment for infants born earlier in the study population. A very small percentage of infants screened positive or suspect for autism (12%) at 2-years of age with the majority screening negative (88%). Infants who

screened positive or suspect on the autism screen also scored lower and below 85 on Bayley's III neurobehavior assessment for cognition, language, and motor

Aim 2: Study Relationships Among Variables

The second aim of this study was to examine the relationships among maternal/neonatal demographics, environmental stressors, stress modifiers, neonatal morbidities, neurodevelopmental outcomes (Bayley III: motor, language & cognitive scales, and M-CHAT autism screen) at two years of age.

Bayley III Neurodevelopmental Outcomes

There were several small to medium yet significant correlations between maternal/neonatal characteristics, environmental stressors, stress modifiers, neonatal morbidities, and Bayley III neurodevelopmental outcomes. As maternal age, infant GA at birth, birth weight increase and parent visits per day during LOS increase, cognitive scores increase. In contrast, as the LOS in NICU, number of days from birth to first held, number of days from birth to first skin to skin, number of days to first breastfeeding increase, cognitive scores decrease. This may be associated with gestational age at birth. When these variables were evaluated by GA groups, smaller GA infants had longer lengths of stay and generally longer number of days before the first hold, first skin to skin and first breastfeeding. Furthermore, there were large correlations between among lower GA at birth and increased number of tests/labs, blood transfusions, number of days intubated, and total number of days requiring supplemental oxygen.

As maternal age, infant gestation age at birth, and birth weight increase, language scores at 2 years of age increased. As the number of parent visits per day during the LOS increase, the language score also increases accounting for nearly 7% of the variation in

the language score with a small correlation. In contrast, as LOS in the NICU, number of days to first held, number of days to first skin to skin, number of days to first breastfeeding increased, the language score decreased. As the total number of nurses caring for the patient over the LOS increased, the Bayley III cognitive, language, and motor scores at 2 years of age decreased. Notably, as parent visits per day during total LOS increased, so did cognitive, language, and motor scores.

Maternal race/ethnicity, marital status, type of insurance, and prenatal care were all significantly associated with cognitive and language outcomes at 2 years of age in this study sample. Type of insurance, as well as marital status, were associated with lower scores across all 3 domains: cognitive, language, and motor. Infants with private insurance generally had slightly higher mean composite scores. Likewise, infants had high composite scores when their mother was married versus single. Maternal history of drug use was associated with lower cognitive and motor scores. Maternal education level impacted language and motor scores. Maternal primary language was not significantly associated with the infant's language score at 2 years. However, mothers whose primary language was Spanish had a lower median language score compared to mothers who spoke English only or English and a second language.

Autism Screen

It is estimated infants born prematurely have an increased incidence of autism spectrum disorder. A recent meta-analysis reported approximately 7% of premature infants have autism spectrum disorder compared to 1.8% in the general population (Agrawal et al., 2018). Prior studies have identified relationships between autism spectrum disorders and low birth weight, gestational age, male gender, chronic lung

disease, maternal chorioamnionitis, duration of supplemental oxygen (Chen et al., 2020). Consistent with what has been published in the literature, the current study identified associations between infants with a positive or suspect autism screen and early onset sepsis, lower birthweight, longer length of stay, nasal cannula at 36 weeks GA, periventricular leukomalacia, and re-hospitalization post NICU discharge.

Several modifiers had associations with a negative autism screen including total days from birth to skin to skin, breastfeeding, and first hold. The total number of nurses caring for the infant during the infants' length of stay was associated with the M-CHAT results. Infants with fewer total number of nurses were more likely to screen negative. The total number of parent visits over the length of stay was associated with the autism screen results; infants whose parents visited more often were more likely to screen negative on the M-CHAT autism screen. While these are potential modifiable factors during the infants stay in the NICU, many of the differences in these variables were related to GA age at birth; for example, when looking at demographics by GA age at birth groups, the older infants were generally held earlier and had more parent visits per day. It is interesting to note GA at birth did not lead to significant differences in the autism screen results in this study.

Infants who had increased exposure to stressors (lab tests, number of blood transfusions, number of days intubated, and overall days of supplemental oxygen) indicating higher acuity were associated with positive autism screen. The increased exposure to stressors was also correlated with decreasing GA at birth. While GA at birth did not have a significant association with the infants' autism screen results, it is likely GA at birth influenced the stressor variables and therefore is indirectly associated with

the autism screen results. This is consistent with reports in the literature of increase incidence of autism spectrum disorders in preterm infants.

Aim 3: Predictors of Cognition, Language & Motor Neurodevelopment Outcomes

The third aim of this study was to identify the amount of variance in neurodevelopmental outcomes (Bayley III: Motor, Language, & Cognitive scales) at 2 years of age accounted for by maternal/neonatal demographics, environmental stressors, stress modifiers, and neonatal morbidities. Premature infants discharged from the NICU experience varying degrees of neurobehavioral sequelae at follow-up (Church et al., 2012; Montirosso & Provenzi, 2015; Provenzi, Guida, et al., 2018). Factors influencing long-term neurodevelopmental outcomes are multifactorial. While the findings in these models were significant, they yielded a small effect and account for a small percentage of the overall outcome.

Bayley III Cognitive Composite Score Regression

A multiple regression was run to predict infant cognitive scores at 2 years of age accounted for by maternal age, race/ethnicity, marital status, insurance, maternal history of drug use, prenatal care, gestation age at birth, birth weight, number of days from birth to first skin-to-skin, number of day from birth to full enteral feeding, some breastmilk at discharge, average number of parents' daily visits during LOS, number of nurses caring for infant during LOS, PRBC infant transfusions, HFNC at 36 weeks, highest grade IVH, and rehospitalization since discharge. The multiple regression model significantly predicted infant cognitive scores at 2 years of age, $F(26, 225) = 2.681$, $p < .001$, adj. $R^2 = .148$ accounting for 23.7% of the variability in cognitive scores compared to the mean model. Six of the variables add significantly to the prediction of cognitive scores:

maternal race-ethnicity: Hispanic, Latino; maternal race-ethnicity: Asian, Pacific Islander, Hawaiian Native; maternal race-ethnicity: Other race, Native American, Alaska Native; marital status: separated, divorced; some breastmilk during LOS; and average number of parent visits per day during the LOS. Hispanic race/ethnicity was associated with a decrease in cognitive scores when compared to White mothers as the reference category. A similar association was found for Asian, Pacific Islander, Hawaiian mothers; and other race, native American and Alaska native mothers; but not for black, African American mothers. Furthermore, predicted infant cognitive scores were higher for infants whose parents visit them more per day during their length of stay in the signaling the importance of parent presence in the NICU.

Bayley III Language Composite Score Regression

A multiple regression was run to predict infant language scores at 2 years of age accounted for by maternal age, race/ethnicity, marital status, insurance, maternal history of drug use, prenatal care, gestation age at birth, birth weight, number of days from birth to first skin-to-skin, number of days from birth to full enteral feeding, some breastmilk at discharge, average number of parents' daily visits during LOS, total number of nurses caring for infant during LOS, PRBC infant transfusions, HFNC at 36 weeks, late onset sepsis, and rehospitalization since discharge. The final model for language composite score ($F(23, 228) = 3.504$, $p < 0.001$, adj. $R^2 = 0.187$) accounted for 26.1% of the variability in language scores compared to the mean model. Three variables contributed significantly to the prediction of language scores including maternal race-ethnicity: Hispanic, Latino; maternal race-ethnicity: Asian, Pacific Islander, Hawaiian Native; and maternal insurance: public. Hispanic race/ethnicity is associated with a decrease in

language scores when compared to White mothers. A similar association is found. For Asian, Pacific Islander, Hawaiian Native mothers; but not for other race/ethnicities. Furthermore, predicted infant language scores were lower for infants whose mothers had public insurance as compared to those with private insurance.

Bayley III Motor Composite Score Regression

A multiple regression was run to predict infant motor scores at 2 years of age accounted for by maternal age, marital status, insurance, history of drug use, gestation age at birth, birth weight, number of days from birth to 1st skin-to-skin, number of days from birth to full enteral feed, some breastmilk at discharge, number of average parent daily visits during LOS, number of nurses caring for infant during 1st week, number of nurses caring for infant during 1st month, PRBC infant transfusions, HFNC at 36 weeks, oxygen at discharge, and late onset sepsis. The final model for motor composite scores was significant ($F(19, 232) = 2.599$, $p < 0.001$, adj. $R^2 = 0.108$) accounting for 17.5% of the variability in cognitive scores compared to the mean model. One parameter: some breastmilk at discharge added significantly to the prediction.

Aim 4: Predictors of Positive Autism Screen

The fourth aim of this study was to identify the odds of positive autism screen on the M-CHAT at 2 years of age as accounted of by maternal/neonatal demographics, environmental stressors, stress modifiers, and neonatal morbidities. In the bivariate analysis, the largest significant association in terms of effect size was between autism screen and early onset sepsis. Specifically, for positive autism screen and presence of early onset sepsis. As described above, several variables were associated with the autism screen. A logistic regression for autism screen could not be computed due to the low

frequency in the autism screen results for suspect and positive. Considering the rare event of positive screen for autism in this sample, results must be interpreted with caution.

Implications for Nursing Practice

Both maternal and infant health outcomes continue to be a major concern in the United States (US). Studies have concluded maternal-infant bonding is a key determinant of infant health outcomes especially when admitted to the neonatal intensive care unit (NICU) where there is often disruption in parent presence and engagement. Bonding and subsequent attachment are critical for developing optimal growth and development for healthy, thriving newborns, and minimizing health disparity gaps.

Parents as Caregivers and Support for Family-Centered Care in the NICU

Deprivation of the social connection with a caring adult disrupts the homeostasis of the normal biologic stress response. This ultimately undermines the infant's habituation towards attachment, alters gene expression, and disorganizes healthy development pathways (Marcellus & Cross, 2016). Therefore, the importance of parent presence and bonding/attachment are critical. Maternal-infant separation is a considerable stressor for neonates receiving care in the NICU (Coughlin, 2017; Marcellus & Cross, 2016; Weber et al., 2018). Nurses and healthcare providers in the NICU must find ways to address inequities in the care provided to all patients. When engaging with families and their newborn on a daily basis in the NICU, healthcare providers must strive to identify ways to consistently deliver care equality for all patients regardless of barriers related to language, ethnicity, race, finances, or access to limited resources. Every parent in the NICU should have the same opportunities to engage with their infants, participate

in care, and speak with a provider. As some recent studies have shown, this is not always the reality and is not actualized in practice (Sigurdsen et al., 2018).

Reynolds et al. (2013) concluded infants who had increased parent visitation and were held more often demonstrated improved short-term neurobehavior as measured by the NNNS at term equivalent by NICU Discharge. The findings from this current study support parent presence as a key buffer and mitigating factor to improve long-term neurodevelopmental outcomes at 2 years of age for cognition, language, and motor scores. These findings support both theoretical frameworks used to guide this study: Mefford's Theory of Health Promotion for Preterm Infants and D'Agata's Infant Medical Trauma in the NICU.

Several evidence-based strategies already exist to mitigate stress exposure in the NICU. However, they are not consistently implemented in all NICUs due to a variety of barriers including staff resistance, parent's inability to visit in the NICU, and language barriers between families and staff. There are many potential barriers to parent and family visitation including lack of transportation, working parents with limited time off, young siblings at home to care for, presence of mental illness or substance use, and significant post-partum depression (Weber & Harrison, 2019). Nonetheless, NICUs should universally implement family centered care within a trauma-informed care approach to mitigate stress and improve outcomes.

Health Equity

This study identified race/ethnicity disparities in both cognitive and language outcomes at 2 years of age. In addition, access to resources such as private insurance, social support, and prenatal care were associated with neurodevelopmental outcomes.

Prior studies have identified white, educated parents visit their infants more often and for longer lengths of time compared to minority parents (Greene et al., 2015; Pindeda et al., 2018; Sigurdson et al., 2018). Similar to the findings by Sigurdson and colleagues, Pineda et al. (2018) found parent presence and increased holding was higher with mothers who were Caucasian, married, older , employed, maintained family support, and provided breastmilk to their infant. The amount of holding was also influenced by the acuity of the patient and the number of medical interventions the infant experienced. Pineda and his colleagues demonstrated both social and medical factors impact parent presence, holding, and skin to skin care while infants are cared for in the NICU.

Nurse Staffing Models

Consistent caregiver models with fewer nurses caring for the infant over the NICU LOS support improved outcomes. As identified in this study, as the total number of nurses caring for the infant over the LOS increased, the Bayley III cognitive, language, and motor scores at 2 years of age decreased. Therefore, babies who had fewer nurses, had increased cognitive, language, and motor scores. Nurse work environments are correlated with increased parent presence in the NICU also improving outcomes (Hallowell et al., 2019).

Strengths and Limitations of Study

While retrospective cohort study designs are relatively inexpensive and less time-consuming to conduct, there were some identified limitations to this study. This study was a single center, non-randomized study; therefore, results are not generalizable. The retrospective study design, although cost-effective and less time-consuming was limited to documentation easily extracted from the EHR; these variables are not generally

documented for the purpose of research. Likewise, by using a pre-existing database, the study was limited to variables within the database. This can lead to the potential disadvantage of less control over the measurement and subject selection.

Another limitation is general attendance rate for the HRIF is about 60-70% of infants met criteria. Therefore, the outcome data from the HRIF database may not be reflective of all infants discharged from the NICU and may skew some of the findings. It is also important to note, the study sample was selected from an existing database of neonates followed up in a CCS HRIF clinic; therefore, it is anticipated a large percentage of the patients may have public insurance leading to additional skewness of the study sample reducing generalizability of study findings.

Despite these limitations, findings from this study helped further clarify the relationships among parent presence in the NICU and long-term outcomes. Many prior studies have explored similar variables (parent presence, nursing care, and stressors) and early neurodevelopmental outcomes at the time of the discharge from the NICU; this study identified important variables that may influence long-term neurodevelopment and should be explored further in future research.

Future Research

Until recently, there was a paucity of research examining the relationship of racial and ethnic influence on health disparities in the NICU. In a recent systematic review, Sigurdson and colleagues (2019) identified racial and ethnic disparities in structure, process, and outcomes across NICUs; African American infants were more disadvantaged. Additional studies have focused on process measures such as rates of breastfeeding and found higher rates of breastfeeding occurred in hospitals that had more

white mothers (Lee et al., 2011; Profit et al., 2014). There has been a recent shift to focus on the impact of racial and ethnic disparities in NICU care, as well as a focus on measuring health equity measures to highlight these disparities at the unit, local, and state levels (Profit el al., 2017).

Further research is needed to identify both individual and cumulative effects of specific risk factors for preterm infants in the NICU resulting in behavioral epigenetics. Specific research topics proposed by Weber and Harrison (2019) include defining levels of neonatal stress response in order to prioritize interventions and identifying barriers to current evidence-based strategies to minimize stress in the neonatal environment (resource allocation, staffing, staff resistance, and team communication). Additionally, Weber and Harrison recommend using implementation science as a framework to apply evidence-based concepts, principles, and theories in a strategic approach as opposed to a sporadic adoption common in most NICUs.

Parent stress, anxiety, and depression may influence parent presence and alter maternal/paternal bonding. Forthcoming studies should explore parent stress, anxiety, and depression including postpartum mood and anxiety disorders using valid instruments and their influence on parent presence and engagement in the NICU. Parenting premature, fragile infants is often unexpected and provides a variety of unique challenges for parents. Parent-infant attachment has been shown to act as a modifying buffer to the experiences of prolonged neonatal stress. However, the processes and parental perspectives of parenting in the NICU are not well described.

Stressful and traumatic experiences are characteristic of the NICU environment not only for the infant, but for the family as well (Loewenstein et al., 2019; Provenzi et

al., 2016). There is a lack of evidence or literature examining the complexities of the parenting role for parents of infants in the NICU. Most studies have focused intently on parental stress and anxiety in addition to post-traumatic stress disorder and postpartum depression (Morey & Gregory, 2012; Discenza, 2016, 2017; Greene et al., 2015). A few qualitative studies have assessed the experience of the NICU parents (Loewenstein et al., 2019). Additional studies exploring the phemonenon and/or experiences of parenting in the NICU will contribute to the overall body of knowledge of barriers for parent presence in the NICU and their unique contribution to the infant's care.

Conclusion

This study identified the significance of parent presence on long-term neurodevelopment within the study population. Additional research is needed to develop a clearer understanding of the mechanisms of early life experience, exposure to toxic stress in the NICU, stress modifiers and neurodevelopmental outcomes. Identification of modifying factors that influence negative effects of prolonged stress in preterm neonates may lead to identification of interventions that alter the trajectory of long-term neurodevelopmental outcomes for infants discharged from the NICU. This will allow clinicians to target specific, individualized, preventative, and neuroprotective strategies to improve neonatal neurodevelopment across the lifespan.

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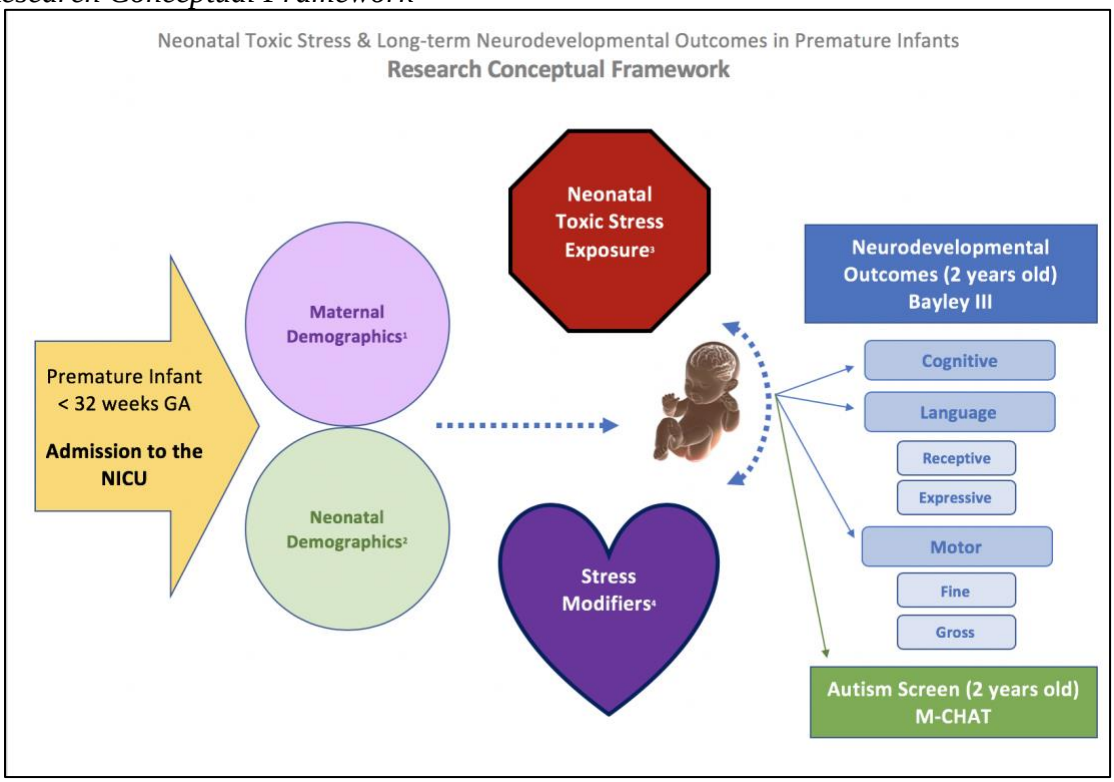
Appendix A

Figure 1

Research Conceptual Framework



Maternal Demographics[1]

- Primary language
- Ethnicity, race
- Highest level of education
- Maternal age
- Gravida/ Para
- Marital status
- Prenatal care at least 1 visit
- Type of insurance
- Maternal ACEs
  - Known hx illicit drug use

Stress Modifiers[4]

- Time from birth to first hold (days)
- Time from birth to first skin to skin (days)
- Time to first breastfeeding (days)
- Time to achieve full enteral feedings (days)
- Some breastmilk at discharge
- Parent visitation (avg. # visits per day, week)
- Constant Caregivers (RN) (1 week, 1 month, LOS)

Neonatal Demographics[2]

- Gestational age at birth
- Length of stay
- Birthweight
- Gender
- Mode of Delivery
- Apgar Score (1, 5 min)
- Birth Hospital (inborn vs. outborn)
- Corrected GA at discharge
- Co-Morbidities (IVH, CLD, ROP, PVL, Infection)

Neonatal Toxic Stress Exsposure[3]

- # lab tests during NICU LOS
- # blood transfusions
- Ventilator Mode (CPAP, vent, HFNC at 36 weeks GA)
  - Total days intubated
- Oxygen at discharge
- Total oxygen days
- Hospitalization since discharge

Appendix B

Variable Table

Variable Name	Operational Definition	Instrument	Level of Measurement	Descriptive Statistics
Maternal Demographics (Primary language, Ethnicity, Race, Highest level of education, Maternal age, Parity, marital status, number prenatal care visits)	Maternal demographics include variables that characterize the attributes of mothers of infants born and admitted to the NICU and who receive follow-up care in the high-risk infant follow-up clinic (HIRF). These demographic variables will be used to provide descriptive statistics of the study sample. These variables may be both independent variables and/or covariates that contribute to the overall model. Maternal demographics were collected both at the time of NICU admission as well as at the time of the 2-year visit in the HIRF clinic.	<u>Hospital EHR</u> ▪ Primary language ▪ Race ▪ Ethnicity ▪ Maternal age ▪ Parity ▪ Marital status ▪ Number of prenatal visits <u>HRIF Redcap Data</u> ▪ Highest level of education ▪ Marital status ▪ Maternal age	Interval Nominal	Number (n)/ Percentages (%) for categorical data, means (M)/ standard deviations (SD) for continuous data
Neonatal Demographics (Primary Insurance, gestational age at birth, LOS, birthweight, gender, mode of delivery, apgar score at 1, 5 and 10 min, birth hospital, CGA at discharge, presence of co-morbidities, re-hospitalization)	Neonatal demographics include variables that characterize the attributes of infants born and admitted to the NICU and who receive follow-up care in the high-risk infant follow-up clinic (HRIF). These demographic variables will be used to provide descriptive statistics of the study sample. They may be both independent variables and/or confounders that contribute to the overall model. Neonatal demographics will be collected both at the time of NICU admission	<u>Hospital EHR</u> ▪ Insurance ▪ Gestational age at birth ▪ LOS ▪ Birthweight ▪ Gender ▪ Mode of delivery ▪ Apgar scores ▪ Birth hospital ▪ CGA at discharge	Interval Nominal	N and % M and SD

Variable Name	Operational Definition	Instrument	Level of Measurement	Descriptive Statistics
	as well as at the time of the 2-year visit in the HIRF clinic.	HRIF Redcap Data ▪ Co-morbidities at discharge		
Time from birth to first hold	Number of days from date of birth to documentation of first hold by parent or significant other (SO).	Calculated from EHR	Interval	M and SD
Time from birth to first skin to skin	Number of days from date of birth to documentation of first skin to skin with mother, father or SO.	Calculated from EHR	Interval	M and SD
Time to first breastfeeding	Number of days from date of birth to documentation of first breastfeeding including dry breastfeeding.	Calculated from EHR	Interval	M and SD
Time to achieve full enteral feedings	Number of days from date of birth to documentation of reaching full enteral feedings of 160ml/kg/day.	Calculated from EHR	Interval	M and SD
Any breastmilk at discharge	Documentation reflects infant was receiving some amount of maternal breastmilk at the time of discharge (within two days of the date of discharge).	EHR	Nominal: Yes = 1 No = 0	N and %
Parent visitation	Documentation of parent or SO visit frequency to the NICU at the patient bedside. This will be collected as average number of visits per day and average number of	Calculated from EHR	Interval	M and SD

Variable Name	Operational Definition	Instrument	Level of Measurement	Descriptive Statistics
	visits per week over the total LOS.			
Constant Caregivers (RN)	Total number of registered nurses who cared for patient as pulled from 1 point in time in each shift during the first week of life, the first month of life and over the entire LOS.	Calculated from EHR	Interval	M and SD
Number of lab tests	Total number of labs tests over the course of the NICU LOS. This provides a representation of the total number tissue breaking procedures which equates to accumulated stress exposure in the neonate.	Calculated from the EHR	Interval	M and SD
Number of blood transfusions	Total number and total volume in milliliters of blood product transfusion administered during the first week of life, the first month of life and total LOS. This is a proxy for patient acuity and associated stress exposure for the infant.	Calculated from the EHR	Interval	M and SD
Ventilator Mode	Ventilator Mode at 36 weeks GA including nasal continuous positive pressure ventilation (NCPAP), high flow nasal cannula (HFNC) includes flows greater than or equal to 2 liters, pr intubated. This represents neonate's exposure to stress.	Calculated from the EHR	Interval Nominal	M and SD
Total Supplemental Oxygen Days	Total number of days infant is exposed to	Calculated from the EHR	Interval	M and SD

Variable Name	Operational Definition	Instrument	Level of Measurement	Descriptive Statistics
	supplemental source of oxygen including ventilator modes above and low flow nasal cannula. This can be a source of stress; it also acts as a proxy to severity of illness when infants require prolonged supplemental oxygen.			
Rehospitalizations since Discharge	Reported rehospitalizations since discharge from the NICU.	HRIF Redcap Data	Nominal	N and %
Dependent Variables				
Cognition	Sensorimotor development including exploration, and manipulation, object relatedness, concept formation, and memory to determine and assess cognitive processing (Bayley, 2006). This is assessed using the Bayley III exam and reflected with a total composite cognitive score based on the infants adjusted chronological age.	Bayley Scales of Infant Development (3rd Ed)	Interval	M and SD
Motor development	Fine motor developmental skills related to perceptual-motor integration, motor speed, prehension and gross motor skills related primarily to limb/torso movement, static positioning and dynamic movement (Bayley, 2006). This is measured using the Bayley III exam and reflected as a total composite motor score derived from the sum of fine and gross	Bayley Scales of Infant Development (3rd Ed)	Interval	M and SD

Variable Name	Operational Definition	Instrument	Level of Measurement	Descriptive Statistics
	motor subscale scaled scores.			
Language development	Primary language skills appropriate for developmental stage and reflect both receptive and expressive communication skills such as preverbal behaviors/ communication, vocabulary development, and verbal comprehension (Bayley, 2006). This is assessed using the Bayley III exam and reflected with a total composite language score derived from the sum of expressive and receptive communication subscale scaled scores.	Bayley Scales of Infant Development (3rd Ed)	Interval	M and SD
Autism Screening	Identified traits predictive of the presence of autism spectrum disorder derived from a parent questionnaire and subsequent provider examination. Results are generally reported as a total score. Scores: 0-2 equal minimal risk 3-6 suggests child should be followed and reassessed 7-23 equals high risk. (Robins et al., 2014)	Modified Checklist for Autism in Toddlers Revised with Follow-up (M-CHAT-R/F)	Nominal: Positive Negative	N and %

Appendix C

Instrument Table

Instrument/ Author (year)	Description Including Subscales	Levels of Measurement	Reliability	Sensitivity and Specificity
Bayley, N. (2006). Bayley Scales of Infant Development (3rd Ed).	The Bayley Scales of Infant Development (3rd Ed) (Bayley III) is a standardized, validated instrument that assesses the developmental functioning of infants and young children ranging from 1 month to 42 months of age. It is widely used for premature infants born less than or equal to 32 weeks gestational age and low birth weight babies born less than or equal to 1500 grams to assess development post-discharge from the NICU. The Bayley III consists of five domains: Cognitive, Language, Motor, Social-Emotional, and Adaptive. Cognitive, Language, and Motor domains are assessed by a trained individual using items that are administered to the infant/child. These three domains will be the primary outcome variables for this study. The other two domains are completed through a caregiver questionnaire. The language domain consists of two subsets: receptive and expressive	Interval - Measurement is based on raw scores from the exam and the infant's/child's corrected age to calculate a scaled score for each subset and the cognitive domain. The scaled score is then used to determine the composite scores, percentile rank and confidence intervals for each domain. For each domain, a composite score is derived and scaled to a mean score of 100 with a standard deviation of 15. Scores less than 70 indicate significant developmental delay and scores less than 85 indicated mild to moderate developmental delay.	Cronbach's alpha: 0.86 to 0.93 for each domain.	Specificity: 0.77-1.00

Instrument/ Author (year)	Description Including Subscales	Levels of Measurement	Reliability	Sensitivity and Specificity
	communication. The sum of the subsets is used to calculate the total composite score for the language domain. The motor domain consists of two subsets: fine and gross motor. The sum of these subsets is used to calculate the total composite score for the motor domain. The number of items in each domain varies based on the corrected gestational age at the time of the exam and determines the raw score used to determine scaled scores and subsequent composite scores in each domain.			
Modified Checklist for Autism in Toddlers Revised with Follow-up (M-CHAT-R/F)	This is a free, easy to use instrument for screening autism. It is a parent report questionnaire used to screen children 16 to 30 months of age for autism traits. The questionnaire contains 20 items related to sensory responsiveness, language, and communication, and non-verbal social communication. Parents complete each item on the questionnaire as yes or no. This tool has demonstrated the likelihood of early detection of autism spectrum disorders when there is a	Nominal - Results are reported as a total score. Scores: 0-2 equal minimal risk 3-6 suggests child should be followed and reassessed 7-20 equals high risk.	Cronbach's alpha = 0.79	Not available for M-CHAT-R/F Original M-CHAT instrument: Sensitivity = 52% Specificity = 84% PPV = 20% NPV = 96%

Instrument/ Author (year)	Description Including Subscales	Levels of Measurement	Reliability	Sensitivity and Specificity
	positive screen (Robins et al., 2014; Robins, Fein, Barton, & Green, 2001). The M-CHAT is currently recorded in the NICU follow-up database as a dichotomous variable screening either positive or negative. For the original M-CHAT instrument, among extremely preterm infants, nearly half were not screened correctly when using the M-CHAT at age 2 (refer to Sensitivity & Specificity column). Sensiorimotor and cognitive impairments, socioeconomic factors, and emotional/behavioral dysregulation contributed to this finding (Kim et al., 2016).			

Note. Validity not available for the Bayley Scale of Infant Development or MCHAT-R/F.

Appendix D

USD IRB

Jul 2, 2020 8:53 AM PDT

Rachelle Sey
Hahn School of Nursing & Health Science

Re: Exempt - Initial - IRB-2020-489, Neonatal Toxic Stress & Long-term Neurodevelopment in Premature Infants

Dear Rachelle Sey:

The Institutional Review Board has rendered the decision below for IRB-2020-489, Neonatal Toxic Stress & Long-term Neurodevelopment in Premature Infants.

Decision: No Human Subjects Research

Selected Category:

Findings: None

Research Notes:

Internal Notes:

Note: We send IRB correspondence regarding student research to the faculty advisor, who bears the ultimate responsibility for the conduct of the research. We request that the faculty advisor share this correspondence with the student researcher.

The next deadline for submitting project proposals to the Provost's Office for full review is N/A. You may submit a project proposal for expedited or exempt review at any time.

Sincerely,

Dr. Thomas R. Herrinton
Administrator, Institutional Review Board

Office of the Vice President and Provost
Hughes Administration Center, Room 214
5998 Alcalá Park, San Diego, CA 92110-2492
Phone (619) 260-4553 • Fax (619) 260-2210 • www.sandiego.edu