

The Long-term Effects of Neonatal Abstinence Syndrome on Neurodevelopmental Health
Outcomes

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Dedication

This dissertation is dedicated to my wonderful husband Joe, our daughters Lillie and Maryjane, my parents, Marilyn Maxwell and Ken Maxwell, and my friends Trisha Braxton, Julie Thornton Johnson, and Gina Brown. Joe, thank you for your 100% support during this PhD journey. You never let me give up and provided me with everything I needed to be successful. Thank you for allowing me the opportunity to focus on my education by taking on a huge load at home and work. You are the love of my life and I am grateful for you. Lillie and Maryjane, thank you for being my cheerleaders and for helping out around the house to allow me the time to focus on this work. It is a privilege to be in your life. I thank you for accepting me into your lives and for letting me to be a mother to you. Mom, thank you from the bottom of my heart for your willingness to help me over the years and for your un-wavering support as I pursued this and every dream I have ever attempted. Dad, thank you for instilling in me the work ethic to complete this journey. Rish, thank you for being my person! There are no words to explain what your friendship means to me. Julie, thank you for your constant support. I will never be able to put into words what it means to have you as a “younger” sister. Gina, thank you for ensuring that I took necessary breaks over the past four years, I would not have succeeded without you.

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Abstract

Every 25 minutes in the United States, a newborn is born experiencing neonatal abstinence syndrome. Neonatal abstinence syndrome is a withdrawal syndrome caused by exposure to medications or drugs *in utero* that leads to symptoms of withdrawal leading to extensive, high cost hospital stays. Little is known about the neurodevelopmental effects of neonatal abstinence syndrome beyond the age of five. The purpose of this study was to 1) describe the neurodevelopmental health of children with NAS at 10 years of age, 2) examine the relationship between NAS and neurodevelopment (i.e. abnormal behavioral, cognitive, and motor development) at the ages of 1, 5, and 10 years, and 3) examine the longitudinal effect of NAS on neurodevelopment (i.e., learning disorders and language delays) from birth to 10 years. This work extended that knowledge by analyzing data on children who presented, during the newborn period, with the clinical signs and symptoms of NAS to examine the effect of NAS on neurodevelopmental outcomes through the age of ten. This work identified that at the age of ten ($n=234$) children with a history of NAS experienced learning disorders, language delays, abnormal behavioral development, and abnormal cognitive development. At the age of ten ($N=727$), NAS significantly predicted abnormal behavioral development in children with a history of NAS ($p<.01$). Findings did not significantly predict abnormal cognitive or motor development. Further, over the first ten years of life children ($N=727$) with a history of NAS had a significantly different pattern of language delay than those without NAS ($p<.01$). There was no significant difference in patterns of learning disorders. Implications for practice, research, and policy are presented.

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Definitions

NAS	A withdrawal syndrome experienced by newborns exposed to opioids in utero (Bailey, 2015).
Children	A person under the age of 18 (HHS, 2016)
Neurodevelopment	The growth and development of the brain and nervous system (Spear, 2013)
Neurodevelopmental disorders	Neurodevelopmental disorders are those that affect physical movement, learning, language, and behavior emerging in childhood and affecting behaviors of everyday functioning. They include intellectual disabilities, communication disorders, autism spectrum disorder, learning disabilities, specific learning disorder, and attention-deficit/hyperactivity disorder (ADHD) (APA, 2013).
Opioids	Opioids are a class of drugs naturally found in the opium poppy plant, including heroin, oxycodone, codeine, methadone, and buprenorphine (NIDA, 2018b).
Hyperactive Moro reflex	Prolonged infantile reflex exhibited with the sudden loss of support characterized by the arms extended for greater than 3 seconds with or without tremors (Meyer and Phillips, 2015).
Hypertonicity	Difficulty or inability to straighten arms or legs when an infant is lying supine (Meyer and Phillips, 2015).
Excoriation	Red or broken skin from excessive rubbing (Meyer and Phillips, 2015).
Low birth weight	A birth weight less than 2500 grams (Cutland et al., 2017).
ADHD	A brain-based neurodevelopmental disorder characterized by developmentally inappropriate levels of inattention and/or hyperactivity and impulsivity (McGough, 2014).
Learning disability	A neurodevelopmental disorder that involves ongoing problems learning key academic skills, including reading, writing and math (APA, 2013).
Intellectual Disability	A neurodevelopmental disorder begins in childhood and includes intellectual difficulties, as well as difficulties in conceptual, social, and practical areas of living.
Developmental Disability	A severe, long term disability that may affect cognitive ability, physical functioning, or both occurring before the age of 22 and likely to be life-long (NIH, 2018).
Seizure	Disorganized or abnormal electrical activity in the brain (Sugerman, 2013).

Introduction

In more than a decade, the United States (US) has experienced a 300% increase in diagnoses of Neonatal Abstinence Syndrome (NAS) (Ko, Patrick, Patel, Lind & Barfield, 2016). This equates to one newborn being diagnosed with NAS every 25 minutes (Patrick, Davis, Lehmann, & Cooper, 2015). NAS, a newborn withdrawal syndrome, is a national health epidemic (Bauer & Li, 2013). In 2014, nearly 32,000 newborns were diagnosed with NAS (Winkelman, Villapiano, Kozhimannil, Davis, & Patrick, 2018). Despite the staggering numbers of infants born with NAS, little is known about the long-term effects on child health, specifically the effects on neurodevelopment. Understanding how a history of NAS affects infants and children over time will guide the development of screening tools, early interventions, and policy to ensure access to needed health care.

Maternal substance use during pregnancy causes documented negative effects on newborns and is the precursor to NAS, leading to low birth weight, neurological excitability, gastrointestinal distress, and autonomic reactivity (Lee, 2015; Maguire et al., 2016; McQueen & Murphy-Oikonen, 2016). NAS is most commonly associated with the use of opioids, however NAS may occur with exposure to methamphetamines, anti-depressants, and benzodiazepines, by the mother during pregnancy leading to dependency in the infant (Hudak et al., 2012; Jones, et al., 2010; Jansson et al., 2017; Klinger et al., 2011; Lee, 2015; Raffaelli et al., 2017). Dependence occurs when the infant functions normally only during exposure to the drug, thus they present with physical disturbances of withdrawal when the drug is removed (National Institute on Drug Abuse, 2018).

The onset of symptoms is associated with the half-life of elimination of the drug (Hudak et al., 2012). NAS attributed to heroin withdrawal generally presents around 24 hours post-delivery, while withdrawal from methadone appears by 24 to 72 hours (Hudak et al., 2012;

Jones, et al., 2010; Lee, 2015). Buprenorphine has an onset of withdrawal around 40 hours after delivery (Hudak & Tan, 2012; Jones et al., 2010; Lee, 2015). The severity of the symptoms varies based on the type of drug taken (Hudak et al., 2021). NAS due to methadone exposure is associated with higher treatment doses of morphine to manage withdrawal symptoms, longer hospital stays, and longer duration of treatment versus buprenorphine or heroin (Jones et al., 2010). Symptoms of NAS include, but are not limited to, mottled skin, inconsolable and high-pitched crying, hypertonicity, hyperactive moro reflex, difficulty eating, poor weight gain, and seizures (Lee, 2015; McQueen & Murphy-Oikonen, 2016). Diagnosis of NAS usually occurs by the fifth day of life (Maguire, et al., 2016; Lee, 2015) lasting up to six months of age (Desmond & Wilson, 1975).

The negative impact of NAS on health care utilization and costs is substantial and projected to increase. NAS-related admissions to neonatal intensive care units (NICUs) increased from 7:1000 to 27:1000 from 2004 to 2013 (Tolia et al., 2015). In states with the highest incidence of NAS, such as Tennessee, at least 92% of children born with NAS were on Medicaid and 15% had social service involvement with out-of-home placement (TDHCFA, 2017). In 2015, the average cost per NAS newborn, during the initial hospitalization (at birth), was \$44,314, approximately 10 times higher than the costs for a normal birth-weight, non-NAS birth (TDHCFA, 2017). Additionally, there is a significant association between diagnosis of NAS and hospital readmission (Patrick, Burke, Biel, Auger, Goyal, & Cooper, 2015). The cost of care for newborns with NAS increased from \$732 million in 2009 to \$1.5 billion in 2012 (Patrick, Davis, et al., 2015). The estimated lifetime costs associated with NAS are expected to exceed \$100,000 per year per child (O'Brien & Phillips, 2011). In some states, such as Massachusetts, it is estimated that 2.5% of the total yearly state budget or \$4.3 million will be spent on social

services for children with NAS (Franca, Mustafa, & McManus, 2016). Thus, there is an increased cost of care associated with newborns diagnosed with NAS. Therefore, a better understanding of the long-term health effects may capture a better understanding of the long-term associated costs.

Early evidence suggests exposure to opioids *in utero* leads to increased risk for adverse neurodevelopmental health outcomes in early childhood; however, there is a lack of empirical evidence on the effects of a history of NAS as children age (Hudak et al., 2012; Bunikowski, Grimmer, Heiser, Metze, Schafer, & Obladen, 1998; Hunt, et al., 2008; McGlone & Mactier, 2015). Neurodevelopmental health outcomes include disorders that affect physical movement, learning, language, and behavior. Neurodevelopmental disorders emerge in childhood and affect behaviors of everyday functioning, ranging from intellectual disabilities, communication disorders, autism spectrum disorder, learning disabilities, specific learning disorder, and attention-deficit/hyperactivity disorder (ADHD) (American Psychiatric Association [APA], 2013).

Maternal opioid use during pregnancy has a direct impact on development (McGlone & Mactier, 2015; Sirnes et al., 2017) by decreasing fetal/newborn brain volume (Sirnes et al., 2017), reducing newborn motor function (Bunikowski et al., 1998), and increasing the risk of adverse intellectual and developmental effects among exposed newborns (Hunt et al., 2008). Research conducted before the age of five suggests that children with a history of opioid exposure *in utero* have poorer neurodevelopmental health than those who were not exposed (Bunikowski et al., 1998; Hudak, et al., 2012; Hunt et al., 2008; McGlone & Mactier, 2015; Wang & Han, 2009). Thus, the impact of NAS on the central nervous system of the developing fetus may significantly increase the risk of neurodevelopmental disorders.

A study of three-year old children found those exposed to opioids *in utero* showed a significant decrease in developmental outcomes, such as cognition and verbal communication as measured by the Bayley Scales of Infant Development-Mental Development Index (Bayley, 1993), along with significantly lower scores in communication and behavior as measured with the Vineland Social Maturity Scale (Sparrow, 2011) versus the control group at both 18 months and 3 years of age (Hunt et al., 2008). Children exposed to opioids *in utero* have a significant positive association with a diagnosis of ADHD (Sirnes et al., 2017). Magnetic resonance imaging of newborns with a history of *in utero* opioid exposure showed decreased brain volumes (basal ganglia and cerebellar white matter) in those exposed compared with those without exposure, after controlling for a diagnosis of ADHD and birth weight (Sirnes et al., 2017). Thus, exposure to opioids *in utero* may negatively influence neurodevelopment in young childhood, yet this is only part of the story as information on the long-term effect of NAS is missing.

In summary, the current literature provides compelling evidence that maternal opioid exposure and the health conditions associated with NAS influence neurodevelopment. However, there is still a significant gap in our understanding of the direct role of NAS on neurodevelopment, given few studies were identified that examined this relationship. In addition, minimal studies have explored this relationship as a child matures and develops neurologically. The purpose of the proposed study was to address these gaps and generate evidence about the effect of NAS on neurodevelopment between the ages of birth and 10 years, with additional analysis at specific ages of 1, 5, and 10 years.

Several researchers have shown a relationship between NAS and adverse neurodevelopmental outcomes in early childhood, however, there has been lack of research as children age. Newborns with NAS due to *in utero* methadone exposure experienced lower

language and hearing, hand/eye coordination, and developmental performance as measured with the Griffith's Developmental Quotient Scale (DQ) (McGlone & Mactier, 2015). Children, ages three to eight, with a history of NAS had more evaluation for, diagnosis of, and accommodations for educational disabilities than children without a history of NAS (Fill, Miller, Wilkinson, Warren, Dunn, Schaffner, & Jones, 2018). In addition, children with a history of NAS had more behavioral, emotional, and developmental diagnoses at 24 months of age than those who experienced *in utero* opioid exposure but without a diagnosis of NAS (Hall, McAllister, & Wexelblatt, 2018). Using the research performed during early childhood (i.e. birth to 8 years [World Health Organization, 2016]), it is hypothesized that NAS would have a negative effect on children throughout childhood (1 – 10 years).

AIM 1: To describe the neurodevelopmental health of children with NAS at 10 years of age.

AIM 2: To examine the relationship between NAS and neurodevelopment (i.e., abnormal behavioral, cognitive, and motor development) at the ages of 1, 5, and 10 years. Based on previous research (Hunt et al., 2008; Hudak & Tan, 2012; McGlone & Mactier, 2015; Sirnes, 2017; Fill et al. 2018) and using the SEM as a guide, the following hypotheses are proposed:

- *Hypothesis 2:* NAS will be associated with abnormal behavioral, cognitive, and motor development at the ages of 1, 5, and 10 years, while controlling for interpersonal, intrapersonal, community, organizational, and public policy factors.

Hypothesis 2A: NAS will be associated with abnormal behavioral, cognitive, and motor development at 1 year.

Hypothesis 2B: NAS will be associated with abnormal behavioral, cognitive, and motor development at 5 years.

Hypothesis 2C: NAS will be associated with abnormal behavioral, cognitive, and motor development at 10 years.

AIM 3: To examine the longitudinal effect of NAS on neurodevelopment (i.e., learning disorders and language delays) from birth to 10 years. Based on the literature relating NAS to adverse neurodevelopmental findings (Hall et al., 2018; Fill et al. 2018), the following hypothesis is proposed:

- *Hypothesis 3:* NAS will be associated with learning and language disorders over 10 years.

Significance of the Study

A review of the literature indicates that this study was the first to examine the long-term effect of NAS on neurodevelopmental health of children through the age of 10 years, while controlling for child, family, community, and societal characteristics. This study examined the long-term impact on children over a 10 year time span, as well as examining the age-specific relationship between NAS and neurodevelopmental outcomes at 1, 5, and 10 years. Previous studies have addressed the effects of opioid exposure or NAS on developmental outcomes through the age of four. In addition, prior research has not included fully-specified models that include potential confounding variables such as child, family, community, and societal characteristics.

Understanding the influence of NAS on neurodevelopment is important clinically for nurses. Evidence from this study may inform clinicians about the role of NAS in neurodevelopment and provide insight into potential clinical practices, such as NAS screening; a key component of early intervention. Most importantly, the findings may influence clinical care with evidence about a national health problem that may ultimately improve the quality of care

for children with a history NAS and their families. Researchers can use the findings to allocate limited resources either to develop age-specific interventions to lessen the effects of disability or to ensure availability of adequate resources for the population of children with a history of NAS. In addition, research on the long-term effects of NAS is policy relevant. As policies are being enacted at the state and federal levels, it is critical to understand the potential effects of NAS on long-term neurodevelopmental health outcomes, both to assist in developing age-specific interventions, as well as to inform policy to support the affected children. The lack of evidence on the long-term effect of NAS impairs the ability of the state and federal government to understand the societal cost of NAS across the lifespan. Thus, this study can provide insight of the potential outcomes and expected expenses over the course of the child's life.

Theoretical Framework

The Social-Ecological Model (SEM) was used to conceptualize the relationship between NAS and neurodevelopmental health outcomes (McLeroy, Bibeau, Streckler, & Glanz, 1988). The main assumption of the SEM is intrapersonal, interpersonal, organizational, community, and public policy factors influence health (Figure 1). Intrapersonal factors include biological make-up, knowledge, attitudes, and behaviors (McLeroy et al., 1988). Interpersonal factors are relationships with family, friends, and peer groups that influence an individual's health. Organizational factors are rules, regulations, and policies that may promote or hinder health. Community factors are neighborhoods in which an individual belongs. The public policy factors include local, state, and national policies and laws that may directly or indirectly affect health. For this study, I focused on the intrapersonal factors of NAS, which are factors that occur within the individual. The model also included interpersonal (i.e., maternal prenatal care and

socioeconomic status), organizational (i.e., CPS referral), community (i.e., region and type of housing), and public policy (i.e., insurance status) factors as covariate variables.

Summary

This dissertation is divided into five chapters, or manuscripts, and a conclusion section. Chapter 1 presents a literature review of the current state of knowledge of the long-term effects of NAS on neurodevelopmental health outcomes and includes a discussion of gaps in the literature and implications. Chapters 2, 3, and 4 report the findings of the three aims of the dissertation study describing the theoretical model and methodology of each study, including research design, sampling, measures, data sources, data analysis, and analytical issues. Chapter 5 presents a policy analysis of the impact of Tennessee opioid legislation on neonatal abstinence syndrome.

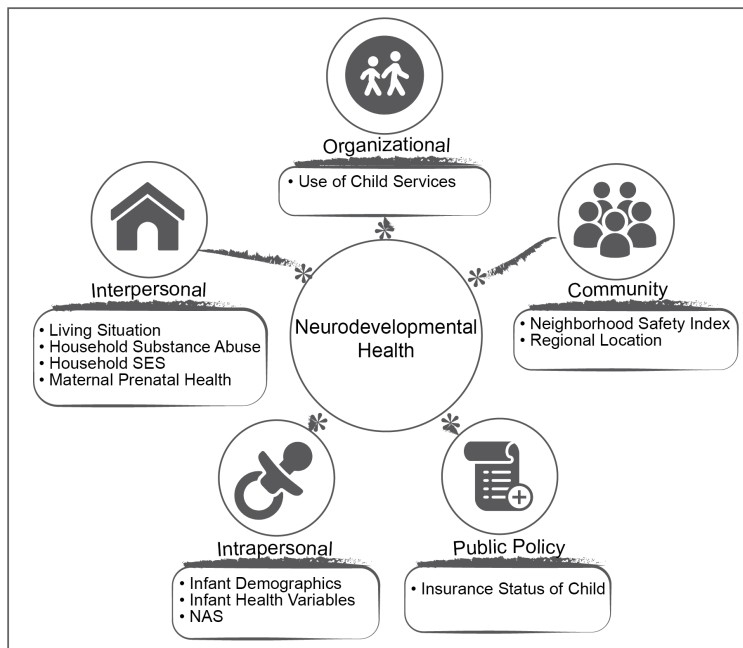


Figure 1. Conceptual Model of Neurodevelopmental Health. Note. Adapted from “An Ecological Perspective on Health Promotion.” K. McLeroy, D. Bibeau, A. Steckler, & K. Glanz, 1988, Health Education Quarterly.

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Chapter 1

Neonatal Abstinence Syndrome and Neurodevelopmental Health Outcomes: A State of the Science

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Abstract

Despite the alarming increase in the numbers of infants born with neonatal abstinence syndrome (NAS), little is known about the effect on the children past the age of four. Clinical findings associated with NAS are found in the literature to have a negative effect on neurodevelopmental health outcomes. The purpose of this review is to examine the current evidence regarding NAS and neurodevelopmental outcomes, identify gaps in the literature, and discuss the possible association between NAS symptoms and neurodevelopmental disorders. A comprehensive literature review of quantitative research and review articles identified human and animal studies to clarify the current knowledge on the long-term effects of opioid exposure and NAS on neurodevelopmental outcomes. The analysis found that infants exposed to opioids *in utero* are at risk for poorer neurodevelopmental outcomes in early childhood; however, there is a lack of empirical evidence on the effect of NAS as children age.

Key Words: Neonatal Abstinence Syndrome, Intellectual Outcomes, Developmental Outcomes, Neurodevelopmental Disorders, NAS

Neonatal abstinence syndrome (NAS), a withdrawal syndrome that occurs in infants exposed to opioids *in utero*, is a national health epidemic (Bauer & Li, 2013). Maternal use of opioids during pregnancy causes documented negative effects on neonates and is the precursor to NAS, which leads to low birth weight, neurological excitability, gastrointestinal distress, and autonomic reactivity (Lee, 2015; Maguire et al., 2016; McQueen & Murphy-Oikonen, 2016). The United States experienced a 380% increase in diagnoses of NAS from 1999 to 2013, leading to an estimated 28,000 infants diagnosed in 2013 alone (Ko et al., 2016; Patrick et al., 2015). NAS-related admissions to neonatal intensive care units (NICUs) increased from 7:1000 to 27:1000 from 2004 to 2013 (Tolia et al., 2015). Additionally, the cost of care for infants with NAS increased from \$732 million in 2009 to \$1.5 billion in 2012 (Patrick et al., 2015).

NAS occurs in infants following the use of opioids by the mother during pregnancy (Hudak et al., 2012; Jones, et al., 2010; Lee, 2015). Opioids, both legal and illegal, including heroin, oxycodone, codeine, methadone, and buprenorphine, cross the placenta, leading to dependency in the infant (Lee, 2015). Dependence occurs when the infant functions normally only during exposure to the drug, thus they present with physical disturbances of withdrawal when the drug is removed (NIDA, 2007). Symptoms of NAS are in Table 1.1 and include, but are not limited to, mottled skin, inconsolable and high-pitched crying, hypertonicity, hyperreactive reflexes, difficulty eating, poor weight gain, and seizures (Lee, 2015; McQueen & Murphy-Oikonen, 2016).

Table 1.1.

Symptoms Associated with NAS

Neurological Excitability	Gastrointestinal Distress	Autonomic Reactivity
Exaggerated moro reflex	Dehydration	Increased sweating
Frequent yawning	Diarrhea	Mottled skin
High-pitched crying	Excoriation	Nasal stuffiness
Hyperactive reflexes	Poor feeding	Temperature instability
Hypertonicity	Poor suck reflex	
Increased respiratory rate	Poor weight gain	
Irritability	Vomiting	
Seizures		
Sneezing		
Tremors		
Trouble sleeping		

Note. Adapted from “Neonatal abstinence syndrome” by K. Lee; “Neonatal abstinence syndrome” by J. McQueen & K. Murphy-Oikonen; and “Long-term outcomes of infants with neonatal abstinence syndrome” by D. McGuire et al.

Diagnosis of NAS usually occurs by the fifth day of life with onset of symptoms dependent on the type of drug taken by the mother (Maguire, et al., 2016; Lee, 2015) and lasting up to six months of age (Desmond & Wilson, 1975). Although the clinical findings of NAS in the period following birth have been well documented, minimal research is available regarding the effects of NAS on neurodevelopmental health, particularly the association between NAS and incidences of neurodevelopmental disorders during childhood. Neurodevelopmental disorders emerge in childhood and affect behaviors of everyday functioning, ranging from intellectual disabilities, communication disorders, autism spectrum disorder, learning disabilities, specific learning disorder, and attention-deficit/hyperactivity disorder (ADHD) (American Psychiatric Association, 2013). Clinical findings associated with NAS can be linked to decreased neurodevelopmental health, thus a review of current empirical findings is necessary to determine the current state of knowledge. Understanding the current state of the science can assist with development of clinical interventions, such as early NAS screening, targeted to the appropriate age group and assist policy makers and advocates understand how the opioid epidemic affects the most vulnerable population in our society. The purpose of this review is to examine the current evidence regarding NAS and neurodevelopmental outcomes, identify gaps in the literature, and discuss the possible association between NAS symptoms and neurodevelopmental disorders.

Methods

A comprehensive literature review identified articles related to the topics of NAS and neurodevelopmental outcomes through a search of PubMed, PsychINFO, and CINAHL with multiple combinations of keywords including “Neonatal Abstinence Syndrome,” OR “NAS,” AND “long-term outcomes,” OR “intellectual outcomes,” OR “developmental outcomes,” OR

“developmental disabilities,” OR “intellectual disabilities”, OR “neurodevelopment.” The search was limited to peer-reviewed journal articles and literature review articles with no limit on publication dates. Initial literature searches identified 222 articles. After reviewing titles for duplicate and non-related content, abstracts for 96 articles were reviewed further. Twenty-five articles were chosen for inclusion and extensive critique (Figure 1.1). A review matrix was organized for synthesis of the findings. The review of the literature identified human and animal studies to clarify the current knowledge on the long-term effects of opioid exposure and NAS on neurodevelopmental outcomes.

Results

Infants exposed to opioids *in utero* are at risk for poorer neurodevelopmental outcomes in early childhood; however, there is a lack of empirical evidence on the effect of NAS as children age (Bunikowski et al., 1998; Hudak, et al., 2012; Hunt et al., 2008; McGlone & Mactier, 2015; Wang & Han, 2009). Current research focuses primarily on children under the age of five, often without a diagnosis of NAS, but with maternal exposure to opioids *in utero*. Research performed during early childhood indicates that children exposed to opioids during pregnancy have poorer neurodevelopmental outcomes than those who were not exposed. Neurodevelopmental outcomes are measured with specific indicators of health and development using standardized scales tested for reliability and validity (CDC, 2014). Findings related to neurodevelopmental outcomes vary in the available literature.

In the detailed review and synthesis of 25 articles, four themes emerged regarding the association between NAS and neurodevelopmental outcomes: (a) developmental outcomes, (b) intellectual outcomes, (c) behavioral outcomes, and (d) neurophysiological outcomes. We provide an overview of the findings below.

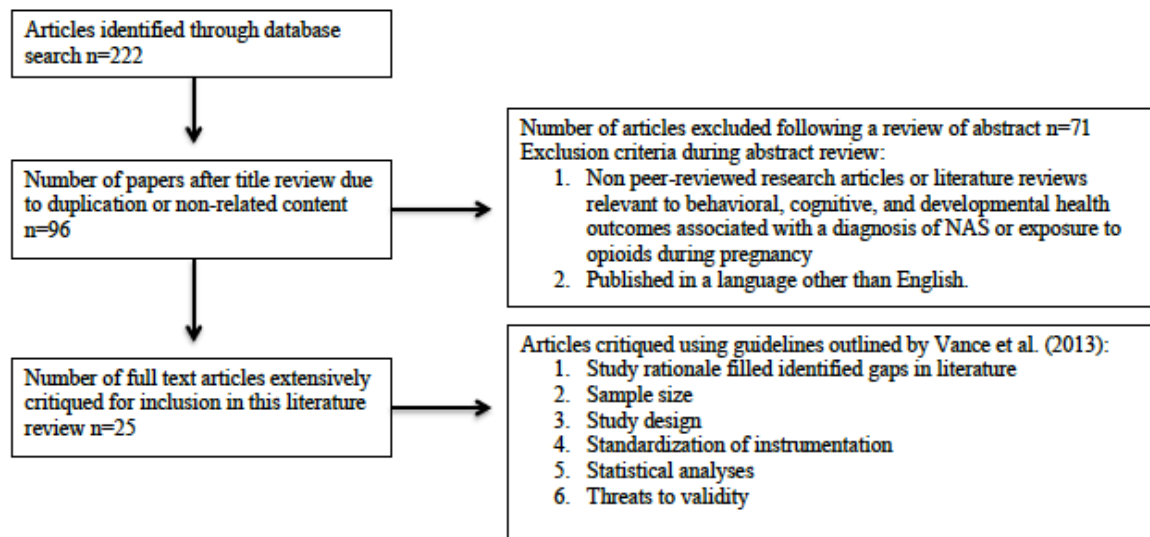


Figure 1.1. *Inclusion and Exclusion Criteria*

Developmental Outcomes

Infants born to mothers using prescribed methadone during pregnancy scored significantly lower on the Griffith's Developmental Quotient (DQ) scale, even when taking into account smoking and alcohol consumption during pregnancy (McGlone & Mactier, 2015). The Griffith's DQ scale measures the development of infants and young children from birth to 2 years of age measuring locomotor skills, personal-social measures, hearing and language, eye and hand coordination, and performance (Griffiths, 1996). Bunikowski and colleagues (1998) also found that children at one year of age exposed to opioids *in utero* showed a significant decrease on the Griffith's DQ scale by having poorer ability to move from one place to another and worse intellectual performance compared with children not exposed. Additionally, a study of three-year old children found those exposed to opioids *in utero* showed a significant decrease in developmental outcomes on the Bayley Scales of Infant Development-Mental Development Index (MDI), along with significantly lower scores on the Vineland Social Maturity Scale versus

the control group at both 18 months and 3 years of age (Hunt et al., 2008). Infants exposed to opioids *in utero* who were raised in their biological home scored lower, though not significantly, on the MDI than those children raised in adopted homes and the control group, while those exposed and living in a lower socioeconomic status home showed significantly lower developmental test scores (Ornoy, 2003).

Intellectual Outcomes

Exposure to opioids *in utero* is associated with significant decreases on intellectual tests. At one year of age, children exposed to opioids during pregnancy demonstrated a significant increase in mild retardation and neurological deviations versus unexposed children (Bunikowski, et al., 1998). In a longitudinal, case-control study of methadone-exposed versus non-exposed children measured at 18 months and 3 years of age, children exposed to methadone *in utero* were significantly more likely to score lower on intelligence scales, including the Stanford-Binet Intelligence Scale, Reynell Expressive Language Scale, and the Reynell Verbal Comprehension Scale at both time points. Among seventh graders with a previous diagnosis of NAS, 37.7% did not meet the National Minimum Standard on one or more sections of national standardized tests compared with 18.4% who did not meet the national standard in the control group (Oei et al., 2017). Additionally, in 7th grade, children with NAS scored lower than children in 5th grade on standardized testing (Oei, et al., 2017).

Behavioral Outcomes

Prenatal exposure to opioids is associated with lower scores on behavioral scales, as well as a significant increase in the diagnosis of ADHD. Children between the ages of 10 and 14 years with exposure to opioids *in utero* are significantly more likely to have a diagnosis of ADHD (Sirnes, 2017). Similarly, a finding of a suspected ADHD diagnosis during early childhood was

significantly associated with the use of opioids during pregnancy, despite controlling for living in a biological home versus living in an adoptive home (Ornoy, 2003).

Neurophysiological Outcomes

Research has varied regarding the association of infant head circumference (HC) with *in utero* opioid exposure or NAS. Exposed two-year-olds followed in a prospective, cohort study had significantly smaller HC than the control group (Hans, 1989). Additionally, studies by Hunt and colleagues (2008) and Moe (2002) identified significantly smaller HC for exposed infants. Similarly, a retrospective study of birth outcomes found a significant decrease in HC in infants exposed to methadone *in utero* versus naltrexone, buprenorphine, and the control group (Kelty & Hulse, 2017). Furthermore, findings of significantly smaller HC differences were identified in infants exposed to high-dose methadone management versus low-dose methadone and buprenorphine exposure (Bier et al., 2015). However, additional studies have provided inconsistent findings, with no significant difference in HC in exposed infants (Kaltenbach et al., 2017; McGlone & Mactier, 2015; Sirnes, 2017; Wiegand et al. 2015).

Sirnes (2017) completed a study of magnetic resonance imaging (MRI) in children ages 10–14 years with previous *in utero* opioid exposure and found decreased brain volumes (basal ganglia and cerebellar white matter) in those exposed compared with those without *in utero* opioid exposure, after controlling for a diagnosis of ADHD and birth weight. Additionally, a study of *in utero* heroin exposure in rats measured the effects of heroin on the hippocampus, which plays a role in learning and memory (Wang & Han, 2009). Wang and Han (2009) showed that *in utero* heroin exposure enhances apoptosis, or cell death, of hippocampal neurons, leading to neurobehavioral deficits in learning and memory in adolescent rats.

Discussion

The increase in the number of infants diagnosed with NAS raises concerns about associated long-term health outcomes, specifically neurodevelopment. There are currently no clear empirical findings of the long-term effects of NAS on neurodevelopmental outcomes. The clinical findings of NAS during the newborn period may explain the potential long-term findings, though not all withdrawal symptoms have a relationship with potential negative long-term effects. Although the long-term impacts specific to NAS are not yet fully understood, there is ample evidence of the impact of clinical findings associated with NAS on neurodevelopmental outcomes, including low birth weight (LBW), poor feeding, poor weight gain, and seizures. We provide a description of such outcomes in the following paragraphs.

Low Birth Weight

Low birth weight (LBW), or a birth weight of less than 2500 grams, is associated with decreased academic performance and diagnosed neurodevelopmental disorders. A study of children ages 6–15 years born at less than 2500 grams showed a significant likelihood to repeat a grade and attend special education classes compared with children born at normal birth weight (Cormana & Chaikind, 1998). Boardman and colleagues (2002) found significantly lower scores on the Peabody individual achievement test in mathematics and reading recognition (PIAT-M, PIAT-RR) for LBW infants, while controlling for social risk factors (i.e., race/ethnicity, gender, maternal level of education, poverty status, maternal marital status). In addition, a secondary analysis of data from the National Health Interview Survey Sample Child Core from 1997–2005 found a correlation between LBW and diagnoses of one developmental delay (DD), 3+ DD, learning disability without intellectual disability (ID), ID, ADHD, and other developmental delay

(Boule et al., 2011). Thus, there is an association between LBW infants and neurodevelopmental disorders.

Poor Feeding and Weight Gain

Clinical findings of NAS include poor feeding and poor weight gain, which can lead to malnutrition (Lee, 2015). Poor feeding and poor weight gain in NAS infants is related to an uncoordinated suck and swallow pattern leading to an inability to effectively feed from a bottle or nipple (Finnegan et al., 1975). Malnutrition and failure to thrive (FTT) occur when the child ranks below the fifth percentile on a standard growth chart (Corbett & Drewett, 2004). A systematic review of the literature indicated that infants with FTT demonstrate adverse intellectual outcomes as evidenced by lower intelligent quotient (IQ) scores and lower scores on the McCarthy Scales and Bayley Developmental Index Scales (Corbett & Drewett, 2004). A conceptual framework looking at the circular relationship between nutrition and disability demonstrated that malnourished children, or those children at low weight for age, are more likely to screen positive for a developmental disability (Groce et al., 2014). Furthermore, macro- and micronutrition are risk factors for physical, sensory, and cognitive impairments (Groce et al., 2014).

Seizures

Infants with NAS may experience seizures (Lee, 2015, McQueen & Murphy-Oikonen, 2016). Seizures, or a sudden surge of electrical activity in the brain (Falco-Walter et al., 2018), are associated with adverse developmental and intellectual effects, although there are inconsistent findings within the literature. Garfinkle and Shevell (2011) have identified predictors of adverse developmental outcomes regarding neonatal seizures. These include seizures on the first day of life, after the third day of life, and types of seizures including subtle

seizures, multifocal clonic seizures, tonic seizures, and myoclonic seizures. Seizures in neonates can affect the brain given that the associated hypoxic event leads to neurological disability and worse motor and cognitive outcomes (Nardou et al., 2013). Additionally, Nardou and colleagues (2013) identified that during a seizure, damage may occur as the cells are dividing to create new pathways and synapses, leading to deleterious effects. There are significant correlations between seizures associated with abnormal electroencephalogram (EEG) findings and impaired developmental outcomes beyond learning disabilities (Ronen et al., 2007). Likewise, clonic behavior with facial involvement significantly correlates with adverse developmental outcomes versus clonic seizures without facial involvement (Ronen et al., 2007). Holmes (1991), on the other hand, found no significant association with neonatal seizures, which equated to unknown protective mechanisms within the infant brain.

Infants born with LBW, difficulty eating and gaining weight, and seizures have shown significantly decreased scores on intellectual and developmental tests. These symptoms are found in children with NAS; therefore, the literature findings warrant further exploration.

In summary, a review of the literature identified inconsistent findings related to developmental, intellectual, behavioral, and neurophysiological outcomes. The majority of research does not focus on a diagnosis of NAS, but on opioid exposure during pregnancy. Moreover, the current literature primarily applies to children at the age of five years or younger. There is scant research on the health outcomes of NAS beyond early childhood. Furthermore, current research has minimal control for variables beyond the diagnosis of NAS that can have an effect on neurodevelopmental outcomes, including maternal alcohol and tobacco use, maternal educational level, current drug use by caregivers, medical diagnoses, diet, and prenatal control variables. The paucity of research addressing the long-term effects of NAS, along with the

significant increase in NAS cases, hastens the need for an understanding of long-term health outcomes.

Conclusion

The increased trend in diagnoses of NAS is rising at an alarming rate nationally. The current available research provides inconsistent findings related to neurodevelopmental health outcomes associated with NAS and/or exposure to opioids during pregnancy. Evidence available on the short-term effects of NAS raises concerns as to long-term effects. For this reason, research must explore the long-term developmental and intellectual health of children with a diagnosis of NAS to ensure an understanding of the outcomes for these affected children.

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Chapter 2

Neurodevelopmental Health of Children with a History of Neonatal Abstinence Syndrome at Ten Years of Age

This manuscript has not been submitted for publication at this time.

Abstract

Purpose: To describe the neurodevelopmental health of children with a history of neonatal abstinence syndrome (NAS) at 10 years of age.

Design and Methods: This study used a retrospective, descriptive design to examine the demographics and neurodevelopmental health characteristics at 10 years in children with a history of NAS using the 1993–2011 Maternal Lifestyle Study.

Results: Of the 234 children in this study at 10 years, the most common neurodevelopment health problems were abnormal cognitive development (26%), followed by language disorders (24%), learning disorders (23%), and abnormal behavioral development (16%). It was less common in our study for children to be with CP (3%), ASD (0.4%), or motor development abnormalities (4%).

Conclusions: This is the first study to extend the description of NAS children beyond five years. From these results, approximately a quarter of children with a history of NAS have a developmental health problem, which is significantly higher than the general population of US school-age children (7%).

Practice Implications: The study findings have practice implications for primary care nurses related to neurodevelopmental screening and for school nurses as they monitor the health of these children in the school environment.

Keywords: neonatal abstinence syndrome, opioid-related disorders, neurodevelopment

In 2014, over 32,000 newborns in the United States were born with neonatal abstinence syndrome (NAS), a 300% increase in the past decade (Ko, Patrick, Patel, Lind & Barfield, 2016; Patrick, Davis, Lehmann, & Cooper, 2015; Winkelman, Villapiano, Kozhimannil, Davis, & Patrick, 2018). NAS is a withdrawal syndrome experienced by newborns that includes low birth weight and signs of neurological excitability, gastrointestinal distress, and autonomic reactivity (Lee, 2015; Maguire et al., 2016; McQueen & Murphy-Oikonen, 2016). NAS occurs following exposure to substances *in utero* leading to development of dependence in the infant most commonly associated with opioid exposure, although it also may occur with exposure to methamphetamines and psychotropic medications, such as antidepressants and benzodiazepines (Hudak et al., 2012; Jansson et al., 2017; Jones, et al., 2010; Klingner et al., 2011; Raffaelli et al., 2017). The physical signs of withdrawal occur when the exposure to the substance is removed (National Institute of Drug Abuse [NIDA], 2018).

There is emerging evidence that NAS influences neurodevelopment among children. Neurodevelopmental health includes disorders affecting physical movement, learning, language, and behavior that alter everyday functioning (American Psychiatric Association [APA], 2013). Research to date indicates that NAS may impair neurodevelopment. At two years of age, a study found that NAS was associated with significantly more behavioral disorders, developmental delay, and speech disorders than those without NAS (Hall et al., 2018). Further, children with a history of NAS showed a significant increase in special educational services eligibility for speech and language impairment between the ages of three and eight (Fill et al., 2018). Additionally, children with a history of NAS received more speech therapy than those without NAS (Fill et al., 2018). Although these studies provide important initial evidence about the link between NAS and neurodevelopmental health, there is a notable gap in the literature describing

the neurodevelopmental health of children with a history of NAS during middle childhood (i.e., ages 8-12) (Cooper, Garcia, Bartko, & Davis, 2005).

The evidence to date has primarily focused on children under five years, and little is known about the neurodevelopmental health of children with a history of NAS in middle childhood. There is no information on the types of neurodevelopmental disorders or the prevalence among this population. Middle childhood is a critical time for development with important milestones, such as synapse development affecting cognitive, behavioral, and social development (Mah & Ford-Jones, 2012). During middle childhood, the brain grows to approximately 95% of adult size with increasing white matter volume and neuron growth (Muftuler, Davis, Buss, Head, Hasso, & Sandman, 2011). However, studies have shown an association between prenatal methadone and buprenorphine exposure and structural changes to white matter in the brain (Monnelly et al., 2018; Pujol, Soriano-Mas, Sebastian-Galles, Losilla, & Deus, 2006). Although we have no knowledge on how NAS may influence neurodevelopment, it is plausible that NAS might cause age-related changes in neurodevelopment.

Understanding the prevalence of neurodevelopmental disorders in middle childhood is timely and relevant to pediatric nurses since neurodevelopment changes dramatically between fetal development and young adulthood (Muftuler, Davis, Buss, Head, Hasso, & Sandman, 2011). Information about their health might provide critical information about the need for surveillance beyond the age of five, the maximum age for early intervention (Tennessee Department of Education [TDE], 2019). Understanding the child's health may also assist school-based nurses and counselors to ensure appropriate interventions and accommodations aimed at improving educational outcomes. From a policy perspective, knowledge about neurodevelopmental outcomes in children with a history of NAS might inform public policies

are enacted to ensure necessary medical, social, and educational support. Therefore, the purpose of this study was to describe the demographics, prenatal, family, and neurodevelopmental health characteristics of children with a history of NAS at 10 years of age.

Methods

Design and Data Source

This retrospective, descriptive study used the 1993–2011 Maternal Lifestyle Study (MLS) dataset. The original MLS collected data on mother-infant dyads as part of a multi-site investigation into the effects of prenatal cocaine and opiate use on a child’s physical, social, and behavioral development over 16 years (Lester et al., 2016). These data include information on maternal drug exposure, infant/child health, and demographic characteristics. The original MLS had an initial enrollment between May 1993 and May 1995 at four participating centers in Rhode Island (Providence), Florida (Miami), Tennessee (Memphis), and Michigan (Detroit), with follow-up monthly for one year and yearly for 16 years.

Enrollment and follow-up of the mother-infant dyads occurred at one of the four centers. Inclusion criteria for the original MLS study included exposed dyads at participating centers matched with those with non-exposure. Original maternal MLS exclusion criteria included: age under 18 years, institutionalization for retardation or emotional disorders, and evidence of psychosis. Original newborn MLS exclusion criteria included the following: unlikely to survive, multiple gestation, born at outlying facilities, greater than 43 weeks gestation, congenital anomaly, chromosomal anomaly, and overt TORCH infection. The present study analyzed MLS data collected at birth and 10 years. The Institutional Review Board at the University of Tennessee, Knoxville approved this study.

Study Population

The study sample was limited to children during middle childhood at 10 years with or without a history of *in utero* opioid exposure who presented with symptoms of NAS at birth using the MLS data. Children with missing data were excluded. After applying the inclusion and exclusion criteria, the final sample included 234 newborns diagnosed with NAS.

Measures

The study included demographics, prenatal, family, and neurodevelopmental health characteristics of ten-year olds with a history of NAS. Measures were derived from the MLS files and prior NAS research. The variable for NAS was created using available variables of newborn clinical signs using the modified Finnegan NAS scoring tool (Finnegan & Kaltenbach, 1992). A history of NAS was assigned with a score of ≥ 8 (Finnegan & Kaltenbach, 1992; McGuire et al., 2013).

Demographics. Race was measured as a group of newborns with a common ancestry specified here as African American compared with all other races. Sex was measured as whether or not the child is male or female by physical examination (Lester, 1998). Birth weight in kg was a continuous variable of weight at birth obtained from chart review. Preterm birth was operationalized as a categorical variable specified as ‘yes’ for children born before 37 weeks gestation and ‘no’ if born at ≥ 37 weeks gestation (ACOG, 2013).

Prenatal Characteristics. Prenatal care was measured as a continuous variable identifying the number of maternal visits to prenatal health care services. Prenatal tobacco exposure was operationalized using a continuous variable to identify the number of packs per day the mother smoked during pregnancy (Lester, 1998). Prenatal exposure to alcohol, cocaine, marijuana, opiates, and combined cocaine/opiates were measured by admission of substance use

during this pregnancy based on the hospital interview or positive laboratory confirmation of exposure (Lester, 1998). A variable for polysubstance exposure was created as children with an exposure to two or more of the substances *in utero*.

Family Characteristics. Living situation was based on with whom the child lived at 10 years of age, either biological parent(s), extended family, foster family, adopted family, or no stable living situation (Lester, 1998). A binary variable was created as living situation, biological parent(s), or other (a combined variable for children living with extended family, foster family, adopted family, or no stable living situation). Household substance use was measured as the use of alcohol or illicit substances in the home where the child lived during the previous study year (Lester, 1998). Poverty was measured using the Hollingshead Four Factor Index (Hollingshead, 1975). A binary variable was created, using the continuous Hollingshead Index, measuring the family's current socioeconomic status (SES) as either low (a score between 8 and 30) or average (a score greater than 30) (Cirino, Chinn, Sevcik, Wolf, Lovett, & Morris 2002).

A neighborhood safety index variable was created as a summed variable based on a literature review of neighborhood safety and neurodevelopment (Milam, Furr-Holden, & Leaf, 2010; O'Campo, Wheaton, Nisenbaum, Glazier, Dunn, & Chambers, 2015; Webb et al., 2017). The original MLS variables of neighborhood gang activity, crimes, shootings, and rundown condition were summed for a value of 0–4, with a higher number indicating worse neighborhood safety. The clinic location was measured as the regional location of the clinic in which the dyad was recruited and followed during the MLS: Providence (RI), Miami (FL), Memphis (TN), or Detroit (MI) (Lester, 1998). Use of child services was operationalized as a dichotomous variable (yes/no) on the use of child services (e.g., home health care, mental health counseling, developmental assessment/testing, early intervention, residential treatment, or special education)

during the previous study year (Lester et al., 2016). Insurance was operationalized as the child's current insurance status using the values Medicaid insurance versus other forms of payment (i.e., private insurance, HMO, or self-pay).

Neurodevelopmental Health. For this study, neurodevelopmental health is defined by medical disorders and identification of abnormal neurodevelopment. Two groups of neurodevelopmental health were created: neurodevelopmental disorders and abnormalities. Neurodevelopmental disorders included cerebral palsy (CP), autism spectrum disorder (ASD), attention-deficit hyperactivity disorder (ADHD), learning disorder, and language delay. CP, ASD, ADHD, learning disorder, and language delay were measured as dichotomous (yes/no) variables indicating presence of a medical diagnosis by chart review (Lester, 1998).

The abnormal neurodevelopmental health (i.e., motor, behavioral, and cognitive) variables were based on an examiner's independent assessment of the development of the child, completed each year during the medical data collection in the original study (Lester et al. 2016). Children were assessed to determine if development was normal, suspect, or abnormal in three categories of development (i.e., motor, behavioral, and cognitive). Licensed and trained health care professionals performed the developmental assessments. For the purposes of the current study, abnormal development was operationalized as dichotomous (yes/no) variables.

Data Analysis

The aim of this study was to describe demographics and neurodevelopmental health characteristics of 10-year old children with a history of NAS. Standard descriptive statistics of all study variables were calculated including frequencies and means/standard deviations. Results are presented 10 years of age. All analyses were completed using SPSS v. 25 (IBM Corp., 2016), with the level of significance set at $p < 0.05$.

Results

Descriptive statistics are displayed in Table 2.1. Most children in the sample were African American (74%) and male (53%). More than 40% were born preterm and the average birth weight was 2.6 kg. Among children in the study, prenatal substance exposure included alcohol (62%), cocaine (51%), marijuana (24%), opioids (11%), and combined cocaine and opioids (56%). The majority (80%) of children experienced prenatal polysubstance exposure of two or more substances. During the prenatal period, mothers of NAS children smoked an average of 0.28 packs per day and had an average of 8.5 prenatal visits. Most of the children were from Detroit (50%).

It was common for children at 10 years to reside with their biological parent (71%), while less than a quarter lived in poverty. The majority (68%) of children were exposed to substance use in the home. Among the children in the study, 43% used child services and 69% were enrolled in Medicaid insurance. Average neighborhood safety index was 1.45 – suggesting a relatively safe neighborhood environment.

The neurodevelopmental health disorders of children with a history of NAS at 10 years are shown in Figure 2.1. Relatively few children at 10 years had cerebral palsy. In our sample, 3% of children were diagnosed with CP. Less than 1% of children were diagnosed with an autism spectrum disorder. The proportion of children with ADHD was 15%. Learning disorders were prevalent among 23% of children in the sample, while language delays were diagnosed in 24% of children.

Abnormal neurodevelopmental conditions were frequent among 10-year old children with a history of NAS (Figure 2.2). Less than 5% of children had abnormal motor development, or continuous, age-related change resulting in abnormal movement (Kremer, Moran, Walker, &

Table 2.1.

Characteristics of Study Sample at 10 years of Age (n=234)

Variable Name	<i>Freq</i>	<i>mean(SD) or %</i>
African American	174	74.4%
Male	148	63.2%
Female	86	36.8%
Preterm birth	102	43.6%
Birth weight in Kg		2.58(.78)
Number of prenatal care visits		8.54(6.27)
Prenatal tobacco exposure (p/d)		0.28 (.41)
Prenatal alcohol exposure	144	61.5%
Prenatal cocaine exposure	119	50.9%
Prenatal marijuana exposure	57	24.4%
Prenatal opioid exposure	26	11.1%
Prenatal cocaine and opioid exposure	130	55.6%
Prenatal polysubstance exposure	186	79.5%
Clinic		
Detroit	117	50.0%
Memphis	39	16.7%
Miami	7	3.0%
Providence	71	30.3%
Lives with biological parent(s)	166	70.9%
Poverty	47	20.1%
Substance use in house	158	67.8%
Use of child services	100	42.7%
Neighborhood safety index		1.45(.81)
Medicaid insurance at 10 years	158	69.3%

Note. Freq = frequency; SD= standard deviation; Preterm birth = less than 37 weeks gestation; p/d = packs per day; Neighborhood safety index=measurement of safety from 0-4 with lower number indicating safer neighborhood

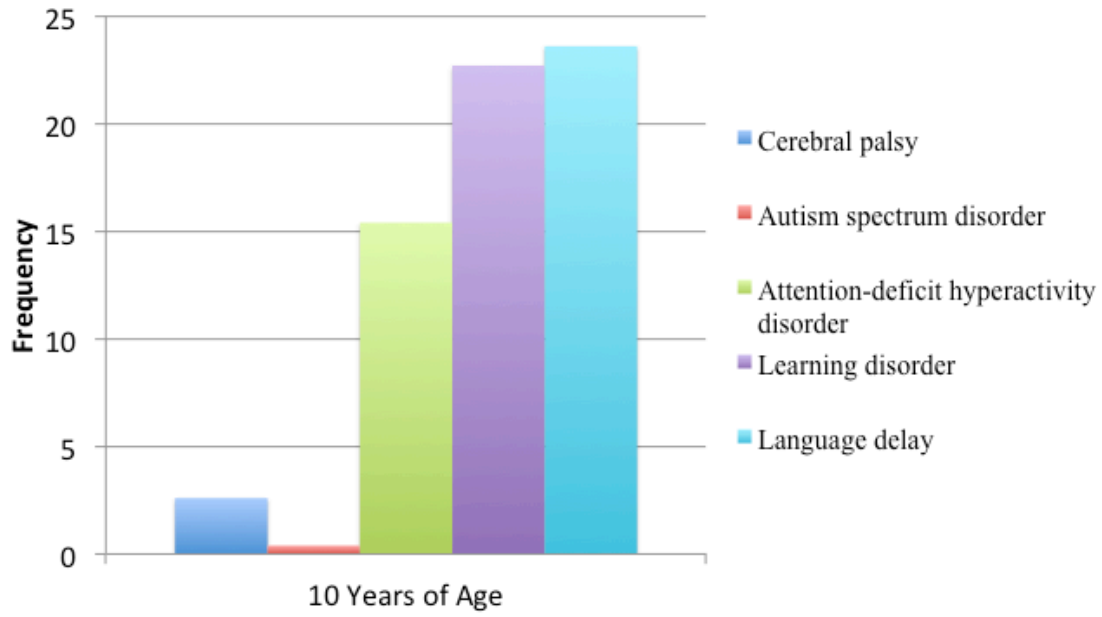


Figure 2.1. *Neurodevelopmental Disorders in Children with a History of NAS at 10 Years of Age*

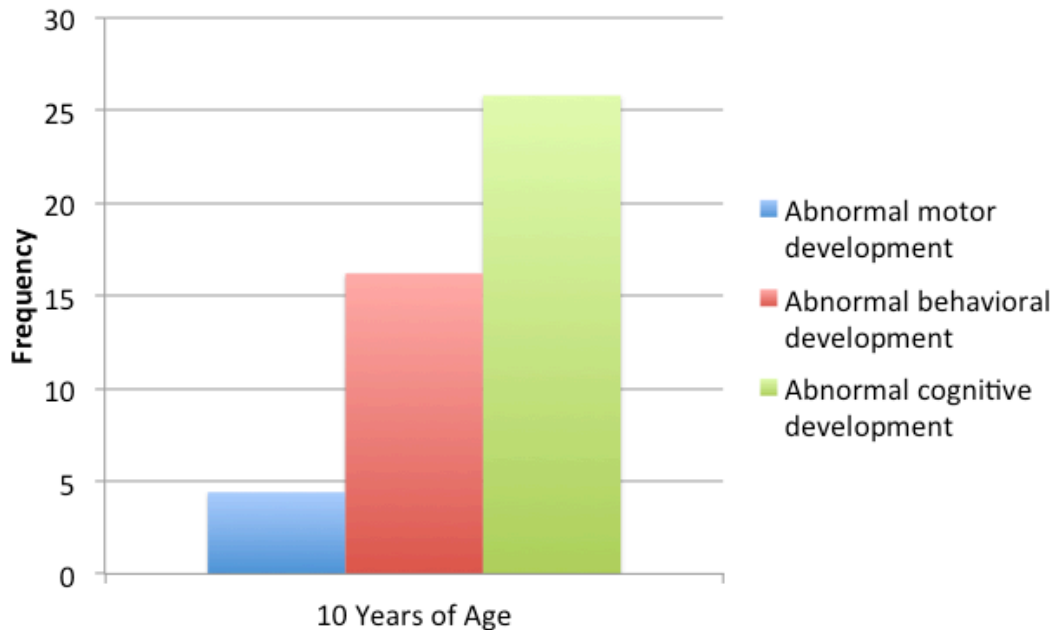


Figure 2.2. *Abnormal Neurodevelopmental Conditions in Children with a History of NAS at 10 Years of Age*

Craig, 2011). Among the children in the sample, 16% had abnormal behavioral development, such that they present with disruptive social and emotional processes (Schlinger, 2002). The most common neurodevelopment issue among this population was abnormal cognitive development. These children had impaired mental functioning affecting thought processes and learning, such as remembering, reasoning, and problem solving (Sullivan, 2009).

Discussion

The aim of this study was to describe the characteristics of children with a history of NAS at 10 years of age using data from the MLS. Few studies were identified that examined the characteristics of children with a history of NAS beyond the age of five. Therefore, these findings provide a baseline description to begin to fill this gap. The majority of children in this study were African American males from Detroit, MI. Most lived with a biological parent and were exposed to substance use in the home. Children with a history of NAS had diagnoses of

ADHD, learning disorders, language delays, as well as, abnormal behavioral and cognitive development. Based on these findings, children with a history of NAS have a higher prevalence of adverse neurodevelopmental health compared to the children in the general population at this age (i.e., 6.9%) (Zablotsky, Black, & Blumberg, 2017).

These findings revealed that children at 10 years with a history of NAS suffered with neurodevelopmental disorders. In the analysis, learning disorders, language delays, and abnormal cognitive development occurred in more than 20% of children with a history of NAS. The findings are consistent with the literature regarding NAS (Konijnenberg & Melinder, 2015; McGlone & Mactier, 2015); yet, contrasted with Fill and colleagues (2018) who found only 5.3% of children with a history of NAS were eligible for educational services because of developmental delays between the ages of three and eight. It is possible that NAS may indirectly affect cognitive functioning in the developing brain of an NAS child. Although our data did not allow for an in-depth, biological examination of brain functioning, we do know many medications and drugs react in the brain similar to NAS and that these medications and drug can cause treatment-induced white-matter injury. White matter is the largest part of the brain and is made up of myelin-coated axons that are involved in cognitive functioning and language development (Filley, 2012; Ross, et al., 2015; Simmonds, Hallquist, Asato, & Luna, 2014; Pujol, Soriano-Mas, Sebastian-Galles, Losilla, & Deus, 2006). Studies have identified an association between prenatal methadone and buprenorphine exposure (e.g. a cause of NAS) and structural changes to the white matter and myelination in the newborn brain (Monnelly et al., 2018; Sanchez, Bigbee, Fobbs, Robinson, & Sato-Bigbee, 2008). In addition, emerging evidence suggest that white-matter injury may have a direct impact on frontal lobe cognitive processing resulting in executive dysfunction. Executive dysfunction broadly includes a range of cognitive,

emotional and behavioral difficulties. Thus, NAS may contribute to white-matter injury that affects learning and language abilities in children. Future research might explore the development and myelination of white matter in children with a history of NAS.

Another interesting finding of the analysis was related to polysubstance exposure among NAS children at 10 years. The finding on prenatal substance exposure revealed that 80% of children with a history NAS had polysubstance (i.e. two or more substances) exposure (including tobacco), which was consistent with other studies (Hall et al., 2014; Wachman et al., 2018). One explanation may be that a significant number of individuals report use of one or more substances in addition to opioid use or heroin use (Winkelman, Chang, & Binswanger, 2018). Findings indicate that co-occurring substance use varies as opioid use increases (Winkelman, Chang, & Binswanger, 2018). Individuals with prescription opioid use disorders report co-occurring substance use 50% of the time and those using heroin report co-occurring substance use 88.5% of the time. Polysubstance exposure often occurs more frequently than single substance use, yet the literature does not provide an explanation. Further, polysubstance exposure (including methadone, buprenorphine, other opioids, amphetamines, benzodiazepines) is significantly associated with pharmacologically managed NAS (Isemann, Stoeckle, Taleghano, & Mueller, 2017; Jansson et al., 2017). Research shows that individual substances (i.e., tobacco, alcohol, cocaine, opioids, and benzodiazepines) have differing effects on NAS (Erol, Ozcan, Celik, Bas, & Demirel, 2017; Hudak et al., 2012; Jones, et al., 2010; Klinger & Merlob, 2008; Raffaelli et al., 2017). However, little is known about the interaction effects of combinations of substances on newborns (Lester et al., 2004; Jansson, DiPetro, Elko, Williams, Milio, & Velez, 2012). Future research could focus on understanding the role of polysubstance exposure in fetal development, newborn withdrawal, and long-term outcomes, especially in middle childhood.

Limitations

There were several limitations to note in this study. The primary limitation is that it is not generalizable outside of the MLS. A second limitation is the subjectivity of the abnormal development measures. Although the same professional (as much as possible) assessed the children at each visit, there was a possibility of bias related to inter-rater reliability. Another limitation is the lack of differentiation between substances that led to the diagnosis of NAS given that this variable was created based on clinical signs and not exposure. This allowed us to capture all newborns with clinical signs of NAS because not all substances associated with the diagnosis were considered in the original study (i.e., selective serotonin reuptake inhibitors, methamphetamines, and benzodiazepines). An additional limitation is the age of the data. The original MLS study enrollment occurred between 1993 and 1995, before the current opioid epidemic. Despite these limitations, this study used a comprehensive, longitudinal dataset of *in utero* substance exposure with detailed demographic, prenatal, and postnatal characteristics, along with family, medical, and social follow-up. These findings provide critical information on characteristics of children with a history of NAS and have implications for their care.

Implications

Despite these limitations, this study has important implications for nurses. First, the information on disorders is critical for registered nurses in primary care and school-based settings. For advanced practice registered nurses (APRNs), these findings suggest that primary care could ensure that children with a history of NAS continue to receive neurodevelopmental screening up to and beyond 10. Currently, federal and state policies offer early intervention services to children with *in utero* substance exposure through the age of five (Centers for Disease Control [CDC], 2018; TDE, 2019). Nurses may need to work with state policy makers to ensure

understanding of the potential risks to neurodevelopment in middle childhood in order to develop policies aimed at continuing surveillance to ensure access to needed interventions.

Second, this study has important implication for school-based nurses. There is potential for partnerships and coordination between primary care and school-based nurses to ensure that the neurodevelopmental health of these children is effectively monitored during this critical development phase. School-based nurses could use the BASC-3 Behavioral and Emotional Screening System (BESS) to monitor children with a history of NAS during middle childhood (Kamphaus & Reynolds, 2015). The BESS screens behavioral and emotional functioning to assess strengths and weaknesses providing a risk index that predicts behavioral, emotional, and academic problems (DiStefano, Greer, & Dowdy, 2017).

In conclusion, this study provides an important contribution to the knowledge of the effect of NAS on children as they age by describing the characteristics of these children at 10 years of age, as it is the first study to extend the description of children with a history of NAS to 10 years. From these results, children with a history of NAS suffered significantly with neurodevelopmental disorders and abnormalities. In addition, the study showed that the majority of children with a history of NAS had prenatal polysubstance exposure with continued exposure to substance use by people living in their home. For these children, continued surveillance may be an important component of neurodevelopmental health management.

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Chapter 3

The Effects of Neonatal Abstinence Syndrome on Neurodevelopmental Health in Children from 1 Year to 10 Years of Age

This manuscript has not been submitted for publication at this time.

Abstract

Introduction: To examine the effects of neonatal abstinence syndrome (NAS) on age-specific neurodevelopment at ages 1, 5, and 10 years.

Method: A retrospective, longitudinal design to examine the effects of NAS on neurodevelopmental health outcomes, while controlling for intrapersonal, interpersonal, community, organizational, and public policy characteristics. A hierarchical multivariate logistic regression model was used to evaluate the influence of NAS on neurodevelopmental health outcomes.

Results: NAS was a statistically significant predictor of adverse neurodevelopmental outcomes at 10 years of age. NAS was positively associated with abnormal behavioral development (OR 2.17, $p < .01$).

Discussion: Our findings identified that by the time children reach age 10, those with a history of NAS were at increased risk of having abnormal behavioral development. These findings provide a rationale for pediatric, mental health, and school-based health care providers to implement early and continued neurodevelopmental evaluation of children with a history of NAS.

Keywords: neonatal abstinence syndrome, opioid-related disorders, neurodevelopment

Neonatal abstinence syndrome (NAS) is an increasing problem in the United States (U.S.). NAS occurs following substance exposure, both legal and illicit, during pregnancy, leading to dependency in the infant (Hudak et al., 2012; Jones, et al., 2010; Lee, 2015). NAS is most commonly associated with opioid exposure, although NAS may also occur with exposure to methamphetamines and psychotropic medications, such as antidepressants and benzodiazepines (Hudak et al., 2012; Jansson et al., 2017; Jones, et al., 2010; Klinger et al., 2011; Raffaelli et al., 2017). Over the past decade, the U.S. has experienced a 300% increase in diagnoses of NAS, equating to one infant born with NAS every 25 minutes (Ko, Patrick, Patel, Lind & Barfield, 2016; Patrick, Davis, Lehmann, & Cooper, 2015; Tolia et al., 2015). In 2014 alone, nearly 32,000 infants were diagnosed with NAS (Winkelman, Villapiano, Kozhimannil, Davis, & Patrick, 2018), making NAS a national health emergency.

As newborns with NAS age and develop, there is the potential for adverse neurodevelopmental health outcomes, including disorders that affect physical movement, learning, language, and behavior emerging in childhood and affecting everyday functioning (American Psychiatric Association [APA], 2013). Endogenous opioid receptors are believed to mature throughout childhood and adolescence influencing brain development (Kolb & Gibb, 2011; Simmonds et al., 2017). Prenatal opioid exposure may alter white matter development leading to structural abnormalities in the newborn brain (Monnelly et al., 2018). The evidence to date has focused almost exclusively on exposure to opioids *in utero*. From this work, we know that prenatal opioid exposure increases the risk for smaller overall brain volume (Sirnes et al., 2017), reduced motor function (Bunikowski et al., 1998), and increased risk of adverse intellectual and developmental effects (Hunt et al., 2008). Among children at 5 years of age, research suggests that children with a history of *in utero* opioid exposure have poorer

neurodevelopmental health than those without exposure (Bunikowski et al., 1998; Hudak, et al., 2012; Hunt et al., 2008; McGlone & Mactier, 2015). Therefore, there is compelling evidence that *in utero* opioid exposure may influence neurodevelopment in early childhood.

Despite findings related to opioid exposure, there is still a significant gap in the understanding of the impact of NAS on neurodevelopment throughout childhood and adolescence, given few studies were identified in which this relationship was examined. Newborns diagnosed with NAS, born to mothers using prescribed methadone, scored significantly lower on the Griffith's Developmental Quotient Scale (DQ), demonstrating developmental delay and abnormal visual acuity at six months (McGlone & Mactier, 2015). Children with a history of NAS had a higher proportion of evaluation for and diagnosis of educational disabilities between the ages 3 and 8 and were more likely to have classroom educational accommodations than children without a history of NAS (Fill, Miller, Wilkinson, Warren, Dunn, Schaffner, & Jones, 2018). In addition, Hall et al., showed that newborns diagnosed with NAS had more behavioral, emotional, and developmental diagnoses at 24 months of age than those who experienced *in utero* opioid exposure but without a diagnosis of NAS (Hall, McAllister, & Wexelblatt, 2018).

Understanding the long-term effects of NAS on neurodevelopment is timely and relevant. Neurodevelopmental disorders have a lasting impact on children, their families, and society, as health care, social services, and educational support is often necessary to assist these children in leading successful, independent lives. The care of newborns with NAS is significantly more expensive than infants without NAS; in fact, in 2014 total hospital costs for NAS births covered by Medicaid was \$462 million (Patrick, Burke, et al., 2015; O'Brien & Phillips, 2011). And we know that long-term care of children with neurodevelopmental disorders from other causes

results in enormous costs (literally and figuratively) to families, communities, social and healthcare services, and society. It stands to reason, then, that with the continued increase in NAS, it is imperative to understand the possible neurodevelopmental effects in later childhood and adolescence, in order show the likely future costs. As state and federal opioid-related policies continue to be developed and implemented (Shearer, Erwin, Davis, Anderson, Lindley, 2019), information on NAS and neurodevelopment may inform policy makers and key stakeholders. Thus, the purpose of this study was to examine these gaps and generate evidence about the effects of NAS on neurodevelopmental health outcomes at ages 1, 5, and 10 years.

Theoretical Model

The Socio-Ecological Model (SEM) was used to guide and conceptualize this study. Five levels of factors (i.e., intrapersonal, interpersonal, organizational, community, and public policy) form a reciprocal relationship that shapes behavior in the individual (McLeroy et al., 1988). The intrapersonal level includes factors specific to the individual, including biological make-up, knowledge, attitudes, and behaviors (McLeroy et al., 1988). The interpersonal level accounts for the effects of relationships, such as family, friends, and peer groups, on behavior. The organizational level details the regulations and policies that may promote or negate behaviors. Community factors include organizations and networks within defined boundaries or geographic areas (McLeroy et al., 1988). The public policy factors include local, state, and national policies that may have direct or indirect effects on the child.

Conceptual Model

Multiple factors are known to have adverse effects on neurodevelopmental health. Intrapersonal factors in our conceptual model included NAS and infant demographic characteristics. NAS might influence the neurodevelopment of children by decreasing brain

volume in those affected (Sirnes et al., 2017). Additionally, low birth weight (LBW) has a direct association with adverse neurodevelopmental outcomes (Boulet, Schieve, & Boyle, 2011; Islam, 2015); infants with NAS are 3 times more likely to be LBW compared with non-NAS infants (Fill et al., 2018). Interpersonal factors included maternal prenatal health, household socioeconomic status (SES), current drug use in the household, and current living situation given potentially negative influences on neurodevelopment (Bitsko et al., 2016; Maggi, Irwin, Siddiqi, & Hertzman, 2010). For example, a significant body of evidence suggests that maternal tobacco use is significantly associated with adverse neurodevelopment in children (Huang, Zhu, Qu, & Mu, 2016). Furthermore, there is strong evidence that SES has an association with neurodevelopment, for example as SES decreases, so does cognitive and language development (Webb et al., 2016).

Organizational factors in the model included the use of child services, such as home health care, mental health counseling, residential treatment, or special education. Child services were included because of the association between neurodevelopmental disorders and referral for services (Shonkoff, Boyce, & McEwen, 2009). For example, early intervention services are associated with a minimized risk of long-term health and developmental problems (Levine & Schanzenbach, 2009; Islam, 2015). Community factors included region of residence and safety of the neighborhood, both potential influencers of adverse neurodevelopmental outcomes given that children living in high crime areas often exhibit signs of toxic stress, which is associated with adverse neurodevelopmental outcomes (O'Campo, Wheaton, Nisenbaum, Glazier, Dunn, & Chambers, 2015). Additionally, research indicated that living in a neighborhood that is in poor repair might negatively affect neurodevelopmental outcomes (Bitsko et al., 2016). Finally, public policy factors included child insurance status because of the association between a lack of

insurance and adverse neurodevelopmental outcomes (Levine & Schanzenbach, 2009; Bitsko et al., 2016).

Methods

Design and Sample

This study used a retrospective, longitudinal, non-experimental design to examine the effects of NAS on neurodevelopmental health outcomes, while controlling for child, maternal, and other SEM characteristics as described above (McLeroy et al., 1988). Using data originally collected between 1993 and 2011 for the Maternal Lifestyle Study (MLS) (see below) (Lester et al., 2014), the unit of analysis was the child. The sampling frame included children who originally participated in the MLS study. The sample was limited to children ≤ 10 years of age with or without *in utero* opioid exposure to ensure inclusion of all children with potential NAS. Exclusion criteria included any children missing an entire time point of observation (i.e., years 1, 5, or 10). Missing data were assessed for missing completely at random (MCAR) using Little's MCAR test (McKnight et al., 2007). The chi-square test was identified as non-significant ($p=.833$), thus the missingness was MCAR. Therefore, multiple imputations were used on the continuous variables (i.e., neighborhood safety index) and the categorical variables (all missing less than 5%) were treated with case-wise deletion.

An *a priori* power analysis was conducted to determine the minimum sample size necessary to detect the effects of NAS on neurodevelopment, if such effects exist. The calculation was based on widely accepted conventions of statistical power (0.80), Type II error rate ($\beta=0.20$), and level of significance ($\alpha=0.05$). Based on prior literature (Hunt et al., 2008), a conservative effect size of 0.15 was used in calculating the sample size. G*Power (Faul, Erdfelder, Lang, & Bucher, 2007) was used for the overall dataset and at each time point. For an

analysis with 36 regressors, a sample size of 201 children was needed. For this project, the total sample size was 727 children. There was sufficient power to detect variation in outcomes at the 0.05 level of significance.

Data Source

The data source for this study was the 1993–2011 MLS dataset maintained and available through the Inter-University Consortium for Political and Social Research. The original MLS collected data on children, mothers, families, and communities as part of a multi-site investigation into the effects of maternal drug use on children’s physical and mental health over 16 years. These data included information on prenatal drug exposure, maternal and infant demographics, newborn health, and longitudinal physical health, social, behavioral and neurodevelopmental outcomes in children. For the original MLS study, the initial enrollment occurred between May 1993 and May 1995 and continued until 2011 at four participating centers in Rhode Island (Providence), Florida (Miami), Tennessee (Memphis), and Michigan (Detroit). Inclusion criteria for the original MLS study included drug exposed dyads (n=658) from participating centers group matched with those with non-exposure (n=730), which provides a large cohort of children in the original study exposed to drugs *in utero*. Mother-infant dyads were enrolled at one of the four centers and longitudinal follow-up occurred monthly for the first 12 months and yearly until children reached 16 years. The current study used data from birth, 1, 5, 10, and 15 years. The data from 15 years were not used in analysis because of the percentage of missing cases. The Institutional Review Board at the University of Tennessee, Knoxville approved this study.

Measures

Dependent Variables. The main outcome was neurodevelopmental health using separate measures for abnormal motor, behavioral, and cognitive development. Motor development is the

continuous, age-related change that results in a movement outcome (Kremer, Moran, Walker, & Craig, 2011). Behavioral development includes the progress of social and emotional processes (Schlinger, 2002). Cognitive development is the expansion of thought processes and learning structures, such as remembering, reasoning, and problem solving (Sullivan, 2009). A member of the original MLS team, a certified health care provider, performed independent assessments of these outcomes at 1, 5, and 10 years. Each measure was the report of an examiner's independent assessment of the child's neurodevelopment (motor, behavioral, or cognitive) (Lester, 1998; Lester et al., 2014). The measures were dichotomized as abnormal (no/yes).

Independent Variable. The independent variable was NAS. A measure of NAS was created based on the Modified Finnegan Neonatal Abstinence Syndrome (MFNAS) scoring tool, a widely used tool to diagnose NAS (Finnegan & Kaltenbach, 1992; McGuire, Cline, & Parnell, 2013). The MFNAS tool uses clinical signs, which in varying combinations lead to a diagnosis of NAS. For this study, 18 clinical findings related to NAS (i.e. high-pitched cry, sleeping after eating, hyperactive moro reflex, tremors, hypertonia, excoriation, myoclonic jerks, general convulsions, sweating, frequent yawning, mottled skin, nasal stuffiness, sneezing, nasal flaring, tachypnea, excessive sucking, poor feeding, and loose stools) were identified in the MLS and used to generate a measure of whether an infant had NAS at birth. Four clinical findings (hyperthermia, regurgitation/projectile vomiting, watery stool, and tachypnea with retractions) were unavailable in the MLS dataset. Using the available symptom variables, an initial score was computed to create an NAS score. Each symptom variable was assigned the minimum score as identified on the MFNAS. This computed variable provided a composite score between 0 (min) and 35 (max). NAS was identified with a score of eight or greater, a standard clinical score used to determine the necessity of pharmacological treatment of NAS (Finnegan & Kaltenbach, 1992;

McGuire et al., 2013). The variable was then recoded into a dichotomous variable with 0 = less than 8 (no NAS) and 1 = \geq 8 (NAS).

Covariate Variables. A group of covariates were created for this study *a priori* based on the SEM (Lester, 1998; Hollingshead, 1975, Cirino, Chinn, Sevcik, Wolf, Lovett, & Morris 2002; Milam, Furr-Holden, & Leaf, 2010; O'Campo, Wheaton, Nisenbaum, Glazier, Dunn, & Chambers, 2015; Webb et al., 2017; Lester et al., 2014). Covariate variables were used in the statistical models to control for factors that may influence neurodevelopmental outcomes (Polit & Beck, 2004). Covariate variables included, race (African American or other race), sex (male or female), birth weight (kg), preterm birth (< 37 weeks gestation [ACOG, 2013]), living situation (biological parents or non-biological parents), household substance use, socioeconomic status (SES), prenatal care visits, prenatal substance exposure (alcohol, opioid, cocaine, or marijuana) and polysubstance exposure (e.g. tobacco, alcohol, opioid, cocaine, marijuana), prenatal smoking, use of child services (i.e., home health care, mental health counseling, developmental assessment/testing, early intervention, residential treatment, or special education), neighborhood safety index (score 0–4 with high score less safe), location (Detroit, Providence, Memphis, Miami), and insurance status (Medicaid or other).

Statistical Analysis

Standard descriptive statistics, including means and percentages, of study variables at baseline and at each time point were calculated. Bivariate comparisons were made using Mann-Whitney U tests for continuous variables and Pearson's chi-square for categorical variables at birth. A hierarchical multivariate logistic regression model was used to evaluate the influence of NAS on each neurodevelopmental outcome, while controlling for covariates. The model fit indices included log likelihood and Nagelkerke R^2 . The assumptions of logistic regression were tested. Multicollinearity was identified with correlations greater than 0.70 (Tabachanik & Fidell,

2007). Variance inflation factors (VIF) were used for confirmation. Variables identified as collinear were substituted to improve the model. Separate regressions were conducted for each age group and each measure of neurodevelopmental health. Results of the logistic regression are presented as odds ratio and 95% confidence intervals with p -values. All analyses were completed using SPSS v. 25 (IBM Corp., 2016). Statistical significance was assessed at $p = 0.05$.

Results

Baseline child characteristics among the study sample at birth are displayed in Table 3.1. The sample included 727 newborns, of which 32% had a diagnosis of NAS. The majority of children in the study were African American (79%). Males and females were represented equally. Of the sample, 43% of newborns were preterm (less than 37 weeks gestation) [ACOG, 2013] with an average birth weight of 2.63 kg. The average number of prenatal visits was 8.4. The mothers smoked an average of 0.28 packs of cigarettes per day. Newborns were exposed *in utero* to alcohol (58%), opioids (7.6%), cocaine (43%), combined cocaine and opioids (75%), and marijuana (22%). More than 75% of children had polysubstance exposure. Detroit (41%) was the most common clinic location, followed by Memphis (26%), Miami (17%), and Providence (16%). Over 80% of the study sample had Medicaid coverage. In comparing newborns with and without a diagnosis of NAS, newborns with NAS were more commonly male (63%) compared with those without NAS (48%). Most newborns with NAS were from Providence (62%) and Detroit (39%). The majority were on Medicaid, 76.5% and 82.6% with and without NAS, respectively.

Table 3.1.

Descriptive Statistics of Study Sample at Birth

	<i>All children (n=727)</i>	<i>NAS (n=234)</i>	<i>No NAS (n=493)</i>	<i>p-value</i>
	<i>mean or %</i>	<i>mean or %</i>	<i>mean or %</i>	
Intrapersonal Factors				
African American (N)	78.7%	74.4%	80.7%	0.05
Female (N)	47.0%	36.8%	51.9%	0.000
Preterm Birth	43.2%	43.6%	43%	0.88
Birthweight in Kg	2.63	2.5	2.66	0.21
Interpersonal Factors				
Number of Prenatal Care Visits	8.4	8.7	8.34	0.84
Prenatal smoking (packs/d)	0.28	0.27	0.28	0.15
Prenatal Alcohol Exposure	58.6%	61.5%	57.2%	0.27
Prenatal Opioid Exposure	7.6%	11.1%	5.9%	0.01
Prenatal Cocaine and Opioid Exposure	62.0%	55.6%	65.1%	0.01
Prenatal Cocaine Exposure	42.6%	50.4%	42.8%	0.00
Prenatal Marijuana Exposure	21.6%	24.4%	20.3%	0.21
Polysubstance Exposure	75.2%	79.5%	73.6%	0.07
Community Factors				
Clinic				0.00
Detroit	41.3%	50.0%	37.1%	
Memphis	26.3%	16.7%	30.8%	
Miami	16.8%	3.0%	23.3%	
Providence	15.7%	30.3%	8.7%	
Public Policy Factors				
Medicaid at birth	80.6%	75.6%	82.6%	0.05

Note. N= newborn; a < 37 weeks gestation, b packs per day. Source: Maternal Lifestyle Study (1993-2011).

The descriptive statistics of sample characteristics at 1 year, 5 years, and 10 years of all children in the study are listed in Table 3.2. At 1 year, 28% of children had a history of NAS. Nearly 90% of children lived with a biological parent. More than 10% of infants resided in low SES households. The majority of those children 1 year old (63%) were exposed to substance use in the home. Many infants resided in safe neighborhoods with an average neighborhood safety index of 1.4 and 14% of infants used a form of child services. At 5 years, 32% of the sample had a history of NAS. The majority of children (82%) resided with a biological parent with 16% of families in low SES and the average neighborhood safety score was 1.41. The majority of children at 5 years used child services (87%) and Medicaid (70%). At 10 years, children continued to mostly reside with a biological parent (77%) in a low SES household (18%). By 10 years, children were exposed to substances use in the home (66%) and resided in neighborhoods with a safety index of 1.39. More than a third of children had child services involvement and a majority (70%) had Medicaid insurance.

Trends in neurodevelopmental outcomes among all children in the study at 1 year, 5 years, and 10 years are shown in Figure 3.1. At 1 year, 21% of children had abnormal motor development, 8% abnormal behavioral development, and 13% abnormal cognitive development. At 5 years, 5% of children had abnormal motor development, 22% abnormal behavioral development, and 22% abnormal cognitive development. At 10 years, 3% of children had abnormal motor development, 18% abnormal behavioral development, and 27% abnormal cognitive development. Abnormal cognitive development increased steadily from 1 to 10 years, while abnormal motor development declined. Abnormal behavioral development trended upwards during the first 5 years with a slight decline at 10 years.

Table 3.2.

Descriptive Statistics of Study Sample at 1 year, 5 years, and 10 years

	1 year <i>n</i> =655 mean/ %	5 years <i>n</i> =653 mean/ %	10 years <i>n</i> =666 mean/ %	<i>p</i> -value
NAS	27.6%	32.4%	31.9%	
Interpersonal Factors				
Living situation (biological)	89.8%	82.4%	76.8%	.008
Low socioeconomic status	13.7%	16.3%	17.5%	.59
Substance use in house	63.1%	49.4%	65.8%	.000
Community Factors				
Neighborhood safety index	1.41	1.41	1.39	.73
Organizational Factors				
Use of child services	13.8%	87.8%	37.6%	.07
Public Policy Factors				
Medicaid insurance (birth)		70.3%	70.3%	.94

Note. ^a living with biological family; ^b safety of neighborhood ranked 0 - 4 with low score indicating safer neighborhood. Source: Maternal Lifestyle Study (1993-2011)

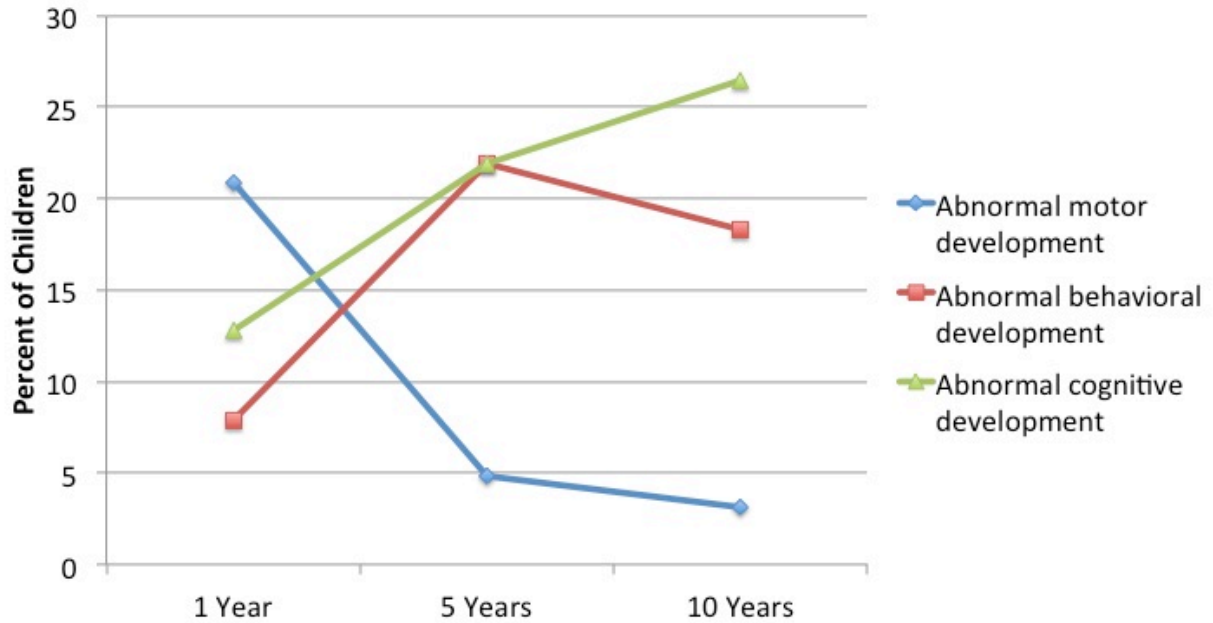


Figure 3.1. *Neurodevelopmental Trends among All Children in the Sample Over Time.*

Multivariate regression results examining the relationship between NAS and neurodevelopmental health outcomes at 1 year are displayed in Table 3.3. NAS was not associated with any of the neurodevelopmental outcomes at year 1. However, several covariates were related to neurodevelopmental health. Race (OR 2.0, $p < .001$), weight (OR .36, $p < .05$), location (Detroit [OR 7.8, $p < .001$], Memphis [OR 8.4, $p < .001$], Miami [OR 4.6 $p < .05$]), and Medicaid insurance at birth (OR .44, $p < .05$) were associated with abnormal motor development. Predictors of abnormal behavioral development included race (OR 2.8, $p < .05$), weight (OR .44, $p < .01$), and location (Detroit [OR 9.7, $p < .01$], Miami [OR 11.6, $p < .01$]). Abnormal cognitive development was influenced by weight (OR .54, $p < .01$), prenatal smoking (OR 1.76, $p < .05$), and location (Detroit [OR 11.5, $p < .01$]).

Table 3.3.

Regression Analysis at 1 Year.

Variable Name	Abnormal Motor Development		Abnormal Behavioral Development		Abnormal Cognitive Development	
	OR	95% CI	OR	95% CI	OR	95% CI
NAS	0.83	.506-1.364	0.77	.386-1.553	1.79	1.291-2.390
Race (African American)	2.00*	1.016-3.936	2.79*	1.174-6.630	2.12	.940-4.775
Sex	0.70	.462-1.064	1.27	.684-2.348	0.64	.384-1.054
Preterm birth	1.21	.676-2.149	1.12	.469-2.653	1.20	.590-2.449
Weight (kg)	.36***	.250-.522	.44**	.253-.772	.54**	.348-.841
Maternal prenatal visits	0.99	.949-1.025	1.03	.980-1.080	0.98	.930-1.022
Prenatal smoking	1.23	.762-1.992	1.55	.822-2.904	1.76*	1.021-3.020
Prenatal exposure to alcohol	1.13	.664-1.923	0.70	.326-1.514	0.65	.469-.904
Prenatal exposure to cocaine	1.17	.833-1.647	0.68	.273-1.677	0.53	.234-1.207
Prenatal exposure to marijuana	0.94	.794-1.115	1.52	.636-3.638	0.86	.454-1.608
Polysubstance exposure	0.65	.292-1.464	1.44	.476-4.325	1.77	1.084-2.873
Living situation (Biological)	0.81	.382-1.733	0.39	.135-1.146	1.18	.730-1.899
Low socioeconomic status	0.99	.472-2.077	1.41	.429-4.633	2.02	1.139-3.584
Household substance use	1.00	.760-1.322	0.46	.193-1.078	1.65	.862-3.159
Location						
Providence	Ref		Ref		Ref	
Detroit	7.83***	2.433-25.227	9.74**	2.377-39.897	11.54**	5.002-26.608
Memphis	8.54***	2.906-25.079	1.13	.192-6.599	3.91	1.632-9.386
Miami	4.56*	2.448-8.490	11.62**	2.404-56.189	3.23	.579-18.030
Neighborhood safety index	1.03	.804-1.316	1.26	.891-1.772	0.82	.610-1.108
Use of child services	1.21	.691-2.121	0.43	.279-.673	1.04	.494-2.195
Medicaid insurance (birth)	.44*	.219-.885	0.79	.308-2.050	0.40	.241-.647

Note. Source: Maternal Lifestyle Study. OR= odds ratio; CI = confidence interval; Ref = reference group; * $p < .05$; ** $p < .01$; *** $p < .001$

Regression results examining the relationship between NAS and neurodevelopmental health outcomes at 5 years are displayed in Table 3.4. NAS was not related to any of the neurodevelopmental outcomes at year 5. There were several covariates related to neurodevelopmental health. Predictors of abnormal motor development included weight (OR .36, $p < .01$), prenatal smoking (OR 3.33, $p < .01$), and Medicaid insurance at 5 years (OR .21, $p < .05$). Abnormal behavioral development was associated with race (OR 2.11, $p < .05$), sex (2.11, $p < .001$), living situation (OR 2.05, $p < .001$), and Medicaid insurance at birth (OR .44, $p < .05$). Sex (OR .41, $p < .001$), weight (OR .50, $p < .001$), location (Detroit [OR 3.18, $p < .05$], Memphis [OR 9.18, $p < .001$]), Medicaid insurance at birth (OR .44, $p < .05$), and Medicaid insurance at 5 years (OR .48, $p < .05$) were related to abnormal cognitive development.

The relationship between NAS and neurodevelopmental health outcomes at 10 years are displayed in Table 3.5. NAS was associated with adverse neurodevelopmental outcomes at 10 years, specifically abnormal behavioral development (OR 2.17, $p < .01$). Additionally, several covariates were related to neurodevelopmental health. Race (OR 5.67, $p < .05$), prenatal exposure to alcohol (OR 5.2, $p < .05$), and use of child services (OR .02, $p < .001$) were related to abnormal motor development. Predictors of abnormal behavioral development included sex (OR .48, $p < .01$), prenatal exposure to cocaine (OR 2.42, $p < .05$), low SES (OR 2.49, $p < .05$), location (Detroit [OR 5.7, $p < .01$]), neighborhood safety index (OR 1.3, $p < .001$), and use of child services (OR .22, $p < .001$). Abnormal cognitive development was influenced by race (OR .4, $p < .05$), sex (OR .63, $p < .05$), low SES (OR 2.86, $p < .01$), location (Detroit [OR 5.4, $p < .01$], Miami [OR 4.47, $p < .01$]), use of child services (OR .18, $p < .001$), and Medicaid insurance at 10 years (OR .53, $p < .05$).

Table 3.4.

Regression Analysis at 5 Years

Variable	Abnormal Motor Development		Abnormal Behavioral Development		Abnormal Cognitive Development	
	OR	95% CI	OR	95% CI	OR	95% CI
NAS	.768	.316-1.865	.773	.491-1.218	.808	.498-1.309
Race (African American)	1.527	.391-5.966	2.112*	1.134-3.396	.913	.436-1.910
Sex	.486	.201-1.174	.384***	.250-.590	.412***	.266-.637
Preterm birth	.844	.250-2.852	.801	.456-1.406	1.507	.843-2.694
Weight (kg)	.360**	.178-.728	.800	.566-1.131	.504***	.350-.726
Maternal prenatal visits	1.038	.969-1.113	1.027	.990-1.065	1.025	.987-1.064
Prenatal smoking	3.333**	1.507-7.352	1.003	.606-1.661	1.298	.772-2.182
Prenatal exposure to alcohol	1.639	.571-4.706	1.351	.807-2.260	.969	.564-1.665
Prenatal exposure to cocaine	1.586	.454-5.531	1.304	.668-2.543	1.250	.624-2.507
Prenatal exposure to marijuana	1.067	.269-4.235	1.578	.861-2.889	1.333	.725-2.451
Polysubstance exposure	1.327	.252-6.981	.712	.320-1.582	.895	.383-2.092
Living situation (Biological)	.958	.294-3.115	.486*	.272-.867	.644	.352-1.178
Low socioeconomic status	.507	.181-1.418	1.751	.918-3.341	1.590	.793-3.192
Household substance use	1.319	.549-3.169	.930	.603-1.435	.784	.500-1.229
Location						
Providence	Ref		Ref		Ref	
Detroit	.726	.166-3.172	1.740	.821-3.686	3.178*	1.154-8.753
Memphis	.730	.150-3.550	2.223	.989-4.999	9.174***	3.220-26.136
Miami	.287	.041-2.019	.635	.246-1.591	1.923	.605-6.112
Neighborhood safety index	.821	.483-1.394	1.099	.868-1.391	1.085	.858-1.372
Use of child services	.000		.536	.261-1.103	.735	.386-1.400
Medicaid insurance (birth)	.859	.243-3.306	.442*	.224-.875	.439*	.202-.956
Medicaid insurance (5 years)	.210*	.059-.748	.723	.433-1.207	.479*	.269-.856

Note. Source: Maternal Lifestyle Study. OR= odds ratio; CI = confidence interval; Ref = reference group. * $p < .05$; ** $p < .01$; $p < .001$

Table 3.5.

Regression Analysis at 10 Years

Variable	Abnormal Motor Development		Abnormal Behavioral Development		Abnormal Cognitive Development	
	OR	95% CI	OR	95% CI	OR	95% CI
NAS	.853	.263-2.768	2.173**	1.295-3.645	1.228	.770-1.958
Race (African American)	5.662*	1.402-22.876	1.032	.497-2.144	.397*	.195-.808
Sex	.844	.282-2.522	.479**	.302-.759	.632*	.421-.948
Preterm birth	1.181	.266-5.238	.716	.382-1.339	1.048	.600-1.829
Weight (kg)	.541	.227-1.287	1.212	.822-1.787	.768	.545-1.082
Maternal prenatal visits	.978	.888-1.078	1.025	.984-1.067	.985	.948-1.022
Prenatal smoking	.850	.308-2.350	1.230	.730-2.073	1.246	.760-2.041
Prenatal exposure to alcohol	5.200*	1.064-25.423	1.409	.802-2.476	1.467	.865-2.488
Prenatal exposure to cocaine	.687	.143-3.309	2.425*	1.157-5.084	1.564	.810-3.022
Prenatal exposure to marijuana	.324	.061-1.713	1.250	.644-2.426	.812	.453-1.455
Polysubstance exposure	1.639	.167-16.094	.454	.192-1.073	.767	.346-1.698
Living situation (Biological)	1.303	.350-4.858	.698	.373-1.307	1.093	.633-1.888
Low socioeconomic status	3.875	.343-43.808	2.486*	1.144-5.402	2.862**	1.384-5.918
Household substance use	1.171	.367-3.735	1.586	.940-2.676	.923	.578-1.474
Location						
Providence	Ref		Ref		Ref	
Detroit	.426	.079-2.290	5.697**	2.140-15.166	5.410**	1.979-14.791
Memphis	1.346	.245-7.389	.646	.211-1.981	1.236	.421-3.631
Miami	.155	.012-2.084	1.175	.390-3.536	4.469**	1.520-13.141
Neighborhood safety index	.982	.531-1.814	1.298***	1.116-1.510	.962	.749-1.237
Use of child services	.021***	.003-.175	.224***	.140-.358	.181***	.118-.276
Medicaid insurance (birth)	1.611	.312-8.305	.971	.474-1.989	.518	.254-1.055
Medicaid insurance (10 years)	.114*	.017-.765	.897	.505-1.595	.529*	.311-.898

Note. Source: Maternal Lifestyle Study. OR= odds ratio; CI = confidence interval; Ref = reference group; * $p < .05$; ** $p < .01$; *** $p < .001$

Discussion

To our knowledge, this is the first study of the impact of a diagnosis of NAS on neurodevelopmental health over time with controls for SEM characteristics. In the present study, 32% of children had a history of NAS. NAS was not found to be a significant predictor of neurodevelopment at one and 5 years, but was a significant predictor of abnormal behavioral development at 10 years of age.

It was surprising that a history of NAS had no effect on neurodevelopmental health during the first 5 years of childhood. Our analysis indicated that NAS was not a statistically significant predictor of any neurodevelopment indicators at ages 1 and 5. Our findings contrast with those of Fill and colleagues (2018) who found that children, between the ages 3 and 8, born with NAS had a higher proportion of evaluation and diagnosis of educational disabilities, as well as a greater likelihood of educational accommodations. A possible explanation for this difference might be different definitions of neurodevelopment health. In this study, we defined neurodevelopmental health as abnormal motor, behavioral, or cognitive development as identified by a licensed health care practitioner per medical chart review; whereas, Fill and colleagues (2018) operationalized it as referral for evaluation of educational disability, eligibility for educational disability services, or receipt of therapy for an educational disability. Therefore, the specificity of measurement may have contributed to the difference in findings.

Our findings identified that by the time children reached age 10, children with a history of NAS were at increased risk of developing abnormal behavioral development. Our results align with Bada and colleagues' abnormal behavioral findings. These researchers found that children exposed to opioids *in utero* scored significantly higher than those without exposure on the childhood behavioral checklist (CBCL), indicating externalizing behaviors (such as aggressive

behaviors), internalizing behaviors (i.e., social withdrawal and anxiety), and significant trends for worsening attention scores as rated by teachers in longitudinal follow-up (Bada et al., 2007; Bada et al., 2011). One explanation for the abnormal behavioral development presenting later in life might be that NAS exposure in the developing brain may cause longitudinal changes in brain development (Kolb & Gibb, 2011; Monnelly et al., 2018). It is possible that NAS exposure may influence brain structure, specifically white brain matter (Monnelly et al., 2018). Studies have shown an association between prenatal methadone exposure and structural changes to the newborn brain's white matter identified by MRI (Monnelly et al., 2018). White matter is involved in cognitive and behavioral development and is believed to mature between teenage years or young adulthood. Further research is needed to understand the role of NAS on brain structure among children.

Alternatively, NAS may influence brain chemistry in children causing long-term neurodevelopment problems. Although our data did not allow for exploration to brain chemistry, there is a possibility that NAS might influence serotonin levels later in childhood. Studies have shown that intense and prolonged exposure to opioids may increase serotonin (5-HT) levels (Baldo, 2018). NAS is an intense and prolonged exposure to opioids. Serotonin is a neurotransmitter that communicates between neurons and the central nervous system, which affects the parts of the brain involved with depression, memory, and aggression (Davidson, 2011). It is possible that NAS also may activate the level of serotonin. Increased serotonin is associated with changes during brain development manifesting through regulation of cognition, attention, and emotion (Brummelte, Glanaghy, Bonnin, & Oberlander, 2017). Further study of changes in serotonin metabolism in children with NAS is needed to understand the relationships to the abnormal behavioral development noted in adolescence.

Limitations

This study expanded our knowledge on the effects of NAS on neurodevelopment; however, there are several limitations. The first limitation was variable measurement. The NAS variable was created using a valid and reliable measurement tool (Modified Finnegan Neonatal Abstinence Syndrome tool), which uses 22 identified clinical signs to assess the presence of NAS. In the available data, there were 18 of the 22 clinical signs identified as variables. This was a limitation because of the risk of underscoring infants for NAS; thus, the sample of infants with NAS may have been larger if all variables were available. Despite this limitation, the NAS variable was created using a valid tool and the presence of clinical signs that identify NAS, thus providing a clinically meaningful variable.

A second limitation was the possibility of omitted variable bias. A thorough review of the literature identified possible confounders, allowing for inclusion in the study. An example of a possible omitted variable was rural versus urban living status. Although, rural/urban was not included in the dataset, we were able to capture location by the study site location. A third limitation was the age of the data. The original MLS enrolled subjects with exposure between 1993 and 1995, which was before the current opioid epidemic. This could affect current outcomes, as the substances children are exposed to now differ from those >20 years ago. Additional prospective studies are warranted. Despite these limitations, the MLS provided rigorous medical and social follow-up, which allowed for control of socio-economic factors that influence neurodevelopment.

Implications

The study findings have important practice implications. For pediatric, mental health, and school-based clinicians, the findings provide a rationale for implementation of early and

continued neurodevelopmental evaluation of children with a history of NAS. The BASC-3 Behavioral and Emotional Screening System (BESS) could be implemented in the clinical setting for children between the ages of 3 and 18 (Kamphaus & Reynolds, 2015). The BESS tool provides an overview of behavioral and emotional functioning through a brief interview with children, families, or teachers to assess both behavioral problems and strengths, including internalizing and externalizing behaviors. The results provide a risk index, which predicts behavioral, emotional, and academic problems (DiStefano, Greer, & Dowdy, 2017). This risk index could be used to determine the need for intervention. .

Additionally, the study results have policy implications. The finding that use of child services were inversely associated with abnormal neurodevelopmental outcomes (i.e., use of child services decreased risk of abnormal outcomes) supports ensuring that children with a history of NAS have access to support, such as developmental assessment, counseling, and early intervention. While not all clinicians may be familiar with regulations, pediatric health care providers should be informed on ways to initiate child services for these children. Efforts to improve access to care might include the training of NAS caseworkers to have expertise in the clinical and administrative management of care for children with a history of NAS.

Finally, this NAS study on neurodevelopmental health has implications for health care research. Although this study examined the effects of NAS on neurodevelopmental health outcomes, further research should continue to examine specific neurodevelopmental disorders that may present in NAS children, such as internalizing (e.g. anxiety and depression) and externalizing behavior disorders (e.g. aggression and antisocial behavior). Additionally, future research should focus on understanding biological changes to provide critical insight into neurodevelopmental outcomes. The possible link between NAS and serotonin should be

examined because of the risk of NAS on the child. Further, it is important to understand the etiology of changes to brain structure in NAS, as this may provide valuable insight into NAS management.

In summary, the findings of this study establish a starting point for management of care for children affected by the opioid epidemic. By providing an understanding of potential outcomes, we can design future research and develop interventions aimed at reducing the behavioral risk for this vulnerable population. Through continued work, we have the potential to improve lives and promote access necessary to ensure children born with NAS have the best opportunity for success in the future.

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Chapter 4

The Effect of Neonatal Abstinence Syndrome on Learning Disorders and Language Delay over Time

This manuscript has not been submitted for publication at this time.

Abstract

Purpose: To examine the longitudinal effects of a history of NAS on learning and language development over the first 10 years of life.

Design and Methods: This study used a retrospective longitudinal design. The data were analyzed using generalized linear mixed models (GLMM) to examine the effect of NAS on learning disorders and language delay over time.

Results: There was a significant interaction between children with a history of NAS and language delays over time. At the age of 1 and 5, children with a history of NAS had a significantly greater probability of language delay than those without NAS. At the age of 10, those with NAS had a lower probability of having a language delay than those without NAS. Learning disorders were not significantly different between NAS and no NAS groups over time.

Conclusions: Children with a history of NAS had higher rates of language delays at the age of 1 and 5 with lower rates at age 10.

Practice Implications: There is a need to increase surveillance, along with referrals for specialized services, for children with a history of NAS before they enter the school system.

Keywords: neonatal abstinence syndrome, opioid-related disorders, learning disorders, language delays

Cases of neonatal abstinence syndrome (NAS), also known as newborn drug withdrawal, have increased dramatically over the past decade (Ko, Patrick, Patel, Lind & Barfield, 2016; Patrick, Davis, Lehmann, & Cooper, 2015). NAS occurs when a newborn exposed to substances prenatally develops signs of withdrawal with removal of the substance. These substances are most commonly opioids; however, methamphetamines, antidepressants, and benzodiazepines are also linked to NAS (Hudak et al., 2012; Jansson et al., 2017; Jones, et al., 2010; Klinger et al., 2011; Raffaelli et al., 2017). NAS presents within the first five days of life with signs of poor feeding, tremors, uncontrollable crying, seizures, respiratory distress, and low birth weight (Lee, 2015; McQueen & Murphy-Oikonen, 2016). In 2014, there were over 32,000 cases of NAS in the United States, a five-fold increase from 2004 (Winkelman, Villapiano, Kozhimannil, Davis, & Patrick, 2018).

Research is emerging on the learning and language development of children with a history of NAS. Learning disorders lead to ongoing difficulty with reading, writing, and math (American Psychiatric Association [APA], 2013). Language disorders are deficits despite normal hearing, normal visual/nonverbal abilities, and at least low cognitive functioning (Riccio, 2013). Children with a history of NAS had a higher proportion of special education for speech and language disabilities between the ages three and eight and were more likely to speech therapy than children without a history of NAS (Fill, Miller, Wilkinson, Warren, Dunn, Schaffner, & Jones, 2018). Furthermore, Hall and colleagues (2018) showed that children with a history of NAS had significantly more speech disorders at 24 months of age than those with a history of *in utero* opioid exposure but without a diagnosis of NAS. These findings suggest that NAS may produce adverse effects on learning and language development.

Given the potential link between NAS and language/learning development, little is known about the effect of NAS on these disorders. During fetal development, brain organization begins early in gestation, however regional brain growth continues into adulthood (Dubois, Dehaene-Lambertz, Kulikova, Poupon, Huppi, Hertz-Pannier, 2014). Although there are no studies linking NAS to abnormal brain development, studies have identified an association between *in utero* methadone and buprenorphine exposure and abnormal white matter development and myelination in the newborn brain (Monnelly et al., 2018; Sanchez, Bigbee, Fobbs, Robinson, & Sato-Bigbee, 2008). *In utero* methadone and buprenorphine exposure is directly associated with a diagnosis of NAS (Lee, 2015). Abnormal brain development might affect cognition and language processing, as this is the primary role of white matter (Walhovd, et al., 2010). Therefore, the potential changes to the brain matter and myelination due to prenatal exposure to opioids (e.g. a cause of NAS) might affect learning and language development in children with a history of NAS.

Understanding how NAS affects learning and language development is both timely and relevant. Learning and language disorders can affect children throughout their lifetime and may increase the need for medical services and educational support. The long-term care of children with learning and language disorders from other causes results in high costs to families, communities, and society (Popova, Lange, Burd, Shield, & Rehm, 2013). With the continued increase in cases of NAS, there is a necessity to understand the potential effects on learning and language that may present in late childhood and adolescence, if for no other reason than to estimate future medical need and costs. Thus, the purpose of this study was to examine the longitudinal effects of a history of NAS on learning and language development over the first 10 years of life.

Conceptual Model

The Socio-Ecological Model (SEM) was used to conceptualize this study. The SEM suggests that biology and the environment (i.e., intrapersonal, interpersonal, organizational, community, and public policy) integrate to influence development (McLeroy et al., 1988). The intrapersonal level includes personal factors such as biological make-up, knowledge, and behaviors (McLeroy et al., 1988). The interpersonal level involves the effects of different types of relationships, such as family, friends, and peer groups, on behavior. Regulations and policies that may either promote or negate development comprise the organizational level. For example, organizations may influence child health, including access to child health services. Community factors are those within defined boundaries or geographic area that may affect development, such as neighborhood safety (McLeroy et al., 1988). The public policy factors include policies and legislation that may directly, or indirectly, affect child development. All levels of the SEM were used to organize covariate variables in the development of this model to ensure success in examining the longitudinal effects of a history of NAS on learning and language disorders.

Methods

Design and Sample

This study used a retrospective, longitudinal design to examine the effects of a diagnosis of NAS at birth on learning and language disorders over a ten-year period. Using data originally collected for the Maternal Lifestyle Study (MLS) (Lester et al., 2016), the unit of analysis was the child. The sampling frame included children who originally participated in the MLS. To capture all children with a potential diagnosis of NAS in the dataset, the sample was limited to children 10 years of age or under with or without *in utero* opioid exposure. Children missing an entire time point of observation (i.e., years 1, 5, or 10) were excluded.

G*Power (Faul, Erdfelder, Lang, and Bucher, 2007) was used to conduct an *a priori* power analysis to determine the minimum necessary sample size needed to detect the effects of NAS on learning and language disorders, if such effects exist. The calculation was based on widely accepted conventions of statistical power (0.80), Type II error rate ($\beta=0.20$), and level of significance ($\alpha=0.05$). Based on prior literature (Hunt et al., 2008), an effect size of 0.15 was used in calculating the sample size. For an analysis with 36 regressors, a sample size of 201 children was needed. For this study, the total sample size was 727 children. Power was sufficient to detect outcome variation at the 0.05 level of significance.

Data Source

This study used the MLS (1993–2011) dataset. The MLS is a restricted dataset maintained and available through the Inter-University Consortium for Political and Social Research. The original MLS, funded by the National Institutes of Health, investigated the longitudinal effects of maternal drug use on child health over 16 years. For the original study, initial enrollment occurred from May 1993 to May 1995 with longitudinal follow-up until 2011 at four centers: Rhode Island (Providence), Florida (Miami), Tennessee (Memphis), and Michigan (Detroit). The original MLS inclusion criteria included drug-exposed dyads ($n=658$) from participating centers group-matched with non-exposed dyads ($n=730$) to provide a large cohort of *in utero* substance exposed children. These data included information on prenatal drug exposure, maternal and infant demographics, newborn health, and longitudinal physical health, social, behavioral and neurodevelopmental outcomes in the children. Mother-infant dyads were examined monthly for the first 12 months and yearly until children reached 16 years. The current study used data from birth with follow-up at 1, 5, and 10 years. The Institutional Review Board at the University of Tennessee, Knoxville approved this study.

Measures

Outcome Variables. The outcome variables of learning disorders and language delay were measured at 1, 5, and 10 years of age. At 1 year, learning disorders and language delay was measured using the *Bayley Development Scale-Mental Development Index (MDI)* (Bayley, 1993). The MDI includes items that assess memory, problem solving, early number concepts, generalization, and vocalization to generate a standard score, the Mental Development Index. A binary variable will measure the MDI using a cut off score of 85, with less than 85 being defined as at risk/delayed and 85 or greater being defined as normal (Gauthier, Bauer, Messinger, & Closius, 1999). At 5 years and 10 years, learning disorders and language delay were measured as a medical diagnosis per chart review conducted by original MLS investigator (Lester, 1998).

Independent Variable. The independent variable was a diagnosis of NAS. The NAS variable was built using the Modified Finnegan Neonatal Abstinence Syndrome (MFNAS) scoring tool, a commonly used tool to diagnose NAS (Finnegan & Kaltenbach, 1992; McGuire, Cline, & Parnell, 2013). The MFNAS tool uses physical assessment findings to identify NAS. For the current study, variables within the MLS were identified that matched clinical findings of NAS (i.e., high-pitched cry, sleeping after eating, hyperactive moro reflex, tremors, hypertonia, excoriation, myoclonic jerks, general convulsions, sweating, frequent yawning, mottled skin, nasal stuffiness, sneezing, nasal flaring, tachypnea, excessive sucking, poor feeding, and loose stools). Each identified variable was assigned the minimum score per the MFNAS. Using the compute variable function in SPSS, an overall NAS score was created. This computed variable provided a score between 0 (min) and 35 (max). NAS was identified using the cutoff score of eight or greater, an accepted score in determining the necessity of pharmacological treatment of

NAS (Finnegan & Kaltenbach, 1992; McGuire et al., 2013). The score was recoded into a dichotomous variable indicating a diagnosis of NAS.

Covariate Variables. Covariates were selected *a priori* based on the SEM (Polit & Beck, 2004)). Based on a review of literature (Lester, 1998; Hollingshead, 1975, Cirino, Chinn, Sevcik, Wolf, Lovett, & Morris 2002; Milam, Furr-Holden, & Leaf, 2010; O’Campo, Wheaton, Nisenbaum, Glazier, Dunn, & Chambers, 2015; Webb et al., 2017; Lester et al., 2014), covariates included race (African American or all other races), sex (female or male), birth weight (kg), preterm birth (gestational age < 37 weeks [ACOG, 2013]), living situation (biological parents or non-biological parents), household substance (alcohol or drug) use, low socioeconomic status (SES), prenatal care visits, prenatal polysubstance exposure (e.g., varying combinations of tobacco, alcohol, opioid, cocaine, marijuana), prenatal smoking, use of child services, neighborhood safety index (score 0–4 with low scores indicating neighborhoods more safe), location (Detroit, Providence, Memphis, Miami), and insurance status at birth (Medicaid or other).

Analysis

Data from study variables were summarized as means and standard deviations for continuous measures and frequencies for categorical measures. For each outcome measure, the data were analyzed using generalized linear mixed models (GLMM) to examine the longitudinal impact of a diagnosis of NAS, the interaction of NAS and time, and covariate variables on learning disorders and language delay. The mixed model allowed for analysis of data gathered from individuals with repeated observations (Tabachnick & Fidell, 2011). GLMM includes fixed predictor variables, as well as random effects for repeated measurements (i.e. time) and clinic location (Stroup, 2013). GLMM was chosen for the ability to model categorical outcome

variables with non-normal distributions (Heck, 2012). The assumptions of GLMM were tested: multicollinearity, normally distributed random effects and link function. Multicollinearity was identified with tolerance $< .10$ and variance inflation factor (VIF) < 10 (Tabachanik & Fidell, 2013). The outcome variable was binary and assumed to have a binomial distribution, thus a logit link function was used (Stroup, 2013).

For each outcome measure, models were analyzed in a sequence of increasing complexity (Tabachanick & Fidell, 2013). The initial model of each outcome variable included only fixed variables to determine the significant variables in the model (Tabachanick & Fidell, 2013). The second model included fixed effects for time, NAS, time * NAS interaction, and significant covariate variables, along with random effects for time and clinic location. Non-significant model terms were removed from the final model to ensure parsimony (Tabachanick & Fiddell, 2013). Separate models were conducted for each outcome measure. The covariance structures of compound symmetry (CS), autoregressive covariance (AR1), and unstructured were analyzed. AR1 structure assumes that correlation decreases over time (IDRE, n.d.). CS assumes equal correlation over time (IDRE, n.d.). Akaike's Information Criterion (AIC) was used to assess model fit (Tabachanik & Fidell, 2007). All analyses were completed using SPSS v. 25 (IBM Corp., 2016). Statistical significance was assessed at $p < 0.05$.

Results

The descriptive data for the fixed variables of the sample are displayed in Table 4.1. The total sample included 727 children, in which 32% of the sample met the criteria of NAS. The majority of the sample were male (53%), African American (78%), and were not born preterm (57%). The average birth weight was 2.63 kg. Mothers had an average of 8.4 prenatal visits and smoked an average of 0.28 packs of cigarettes per day. The majority of the children in the

sample were from Detroit (41%) and on Medicaid (81%). Over 70% of the sample had polysubstance exposure.

The results for the GLMM examining the effects of NAS and time on learning disorders are displayed in Table 4.2. There was not a significantly different pattern of learning disorders between the NAS and no NAS groups over time. However, children with a history of NAS did have a significantly lower probability of learning disorders ($p < .01$) as they aged.

The results for the covariate variables effect on learning disorders are displayed in Table 4.2. Females had a lower probability ($p < .001$) of learning disorders. As birth weight increased by one unit, there was a higher probability of learning disorders ($p < .001$). Among children with exposure to alcohol *in utero*, there was a higher probability of learning disorders ($p < .05$). Children living with non-biological families ($p < .001$) and those using child services ($p < .001$) had a decreased probability of learning disorders. SES had an inverse relationship with learning disorders; as SES decreased the risk of learning disorders increased significantly ($p < .001$). Neighborhood safety index ($p < .001$) was positively associated with learning disorder; as neighborhood safety index increased (indicating a less safe neighborhood), the risk of learning disorders increased. There were significant differences in learning disorders over the 3 time points that were likely to be related to a change in time or clinic.

The results for the GLMM examining the effects of NAS on language delays are displayed in Table 4.3. There was a significant interaction between children with a history of NAS and language delays over time. NAS and no NAS groups had significantly different patterns of language delays change over at 1, 5, and 10 years. At the age of 1 and 5, children with a history of NAS had a significantly greater probability of language delay than those without

Table 4.1.

Descriptive Statistics of Study Sample (N=727)

Variable	<i>M</i>	<i>SD</i>	%
NAS			32.2
African American			78.7
Female			47
Male			53
Birth weight (kg)	2.63	0.83	
Preterm			43.2
Prenatal care visits	8.4	6.02	
Polysubstance exposure ()			75.2
Prenatal smoking (pk/day)	0.28	0.43	
Location			41.3
Detroit			26.3
Memphis			16.8
Miami			15.7
Providence)			
Medicaid			80.6

Note. pk = packs; NAS =neonatal abstinence syndrome

Table 4.2.

Generalized Linear Mixed Model Results of Learning Disorder (N=727)

Variable	Year 1	Year 5	Year 10
<i>Fixed Effects</i>			
NAS x Time interaction	1.58(21.1)	.37 (.20)	.22 (.12)
NAS			-.22 (.08)**
Time	5.58 (20.97)	4.44 (.47)***	1.78 (.64)**
Female sex			-.58 (.06)***
Birth weight (kg)			.30 (.03)***
Prenatal alcohol exposure			.13 (.05)*
Living with non-biological parent(s)			-.45 (.07)***
Use of child services			-1.51 (.07)***
Low socioeconomic status			.54 (.08)***
Neighborhood Safety Index			.16 (.03)***
<i>Random Effect Covariance</i>			
Variance (Time and Clinic)			.99 (10.41)***

* $<.05$; ** $<.01$; *** $<.001$; *a* = coefficient (standard error); *b* = estimate (Z score)

NAS. At the age of 10, those with NAS had a lower probability of having a language delay than those without NAS. African American children had a lower probability ($p<.001$) of having language delays. Among children who were born preterm ($p<.01$) and those using child services ($p<.001$), there was a lower probability of language delay. Low SES ($p<.01$) was inversely associated with language delay; as SES decreased the probability of language delay increased. Neighborhood safety index ($p<.001$) was positively associated with language delay. Less safe the neighborhood the greater the risk of language delay. There were no significant differences in language delays over the 3 time points that were likely random from change over time or change in clinic.

Table 4.3.

Generalized Linear Mixed Model Results of Language Delay (N=727)

Variable	Year 1	Year 5	Year 10
<i>Fixed Effects</i>			
NAS x Time interaction	.65 (.45)**	.67 (.11)***	-.288 (.11)**
NAS			-.31 (.08)***
Time	-.87 (.22)**	-1.82 (.54)**	1.29 (.41)**
African American			-.18 (.07)**
Preterm birth			-.32 (.05)***
Use of child services			-.72 (.06)***
Low socioeconomic status			.13 (.07) *
Neighborhood Safety Index			.12 (.03)***
<i>Random Effect Covariance</i>			
Variance (Time and Clinic)			.13 (1.14)

* $<.05$; ** $<.01$; *** $<.001$; *a* = coefficient (standard error); *b* = estimate (Z score)

Discussion

In the present study, children with a history of NAS had higher rates of language delays at the age of 1 and 5 with lower rates at age 10. Learning disorders were not significantly different between NAS and no NAS groups.

In this study, NAS was associated with language delays. Higher rates of language delays in children with a history of NAS were found at the ages of 1 and 5 with lower rates at the age of 10 versus those without a history of NAS. The findings align with those of Fill et al. (2018) and Hall et al. (2018), who found increased language delays in children with a history of NAS between 24 months and 8 years of age. Higher rates of language delay in children with a history of NAS suggest that there may be a mechanism leading to this change. It is possible that NAS affects myelin development during the prenatal period (Sanchez, Bigbee, Fobbs, Robinson, & Sato-Bigbee, 2008). Although this study did not biologically examine brain development, it is

known that the medications and drugs that result in NAS can lead to abnormal white-matter development. During normal prenatal development, myelin sheaths form around axons in the brain white matter (Pujol, Soriano-Mas, Sebastian-Galles, Losilla, & Deus, 2006). Myelin sheaths facilitate communication between neurons and are related to expressive and receptive language (O’Muircheartaigh, et al., 2014). Studies have shown that exposure to buprenorphine *in utero* (i.e. a known case of NAS) led to disproportionately thinner myelin sheaths during the fetal and early newborn period (Vestal-Laborde, Eschenroeder, Bigbee, Robinson, & Sato-Bigbee, 2014). The thin myelin sheaths are thought to result in abnormal language development in early childhood (i.e. birth to eight years) (Walhovd, et al., 2010). The improvements at the age of ten could be associated with “late” myelination that occurs during adolescence and young adulthood (Vestal-Laborde et al., 2014). Further research is needed to better understand the role of NAS on brain development.

Our study results revealed an association between neighborhood safety and neurodevelopment. This study found that neighborhood safety was positively associated with learning disorders and language delays over a ten-year period. This finding was consistent with other studies (O’Campo, Wheaton, Nisenbaum, Glazier, Dunn, & Chambers, 2015; Bitsko et al., 2016) showing positive associations between the neighborhood safety and neurodevelopment. Children living in a high crime area often exhibit signs of toxic stress, which is associated with adverse neurodevelopmental outcomes (O’Campo et al., 2015). Toxic stress is thought to stimulate cortisol production through the neuroendocrine network leading to a persistent state of inflammation and disrupting brain development (Center for Developing Child, 2007). Further research is needed to understand the role of toxic stress on neurodevelopment.

This study expanded our knowledge on the effect of a history of NAS on learning disorders and language delays, however there were limitations. The primary limitation was the age of the data. The original MLS enrolled subjects with exposure between 1993 and 1995, before the current opioid epidemic. A second limitation was variable measurement. In the current study, the NAS variable was created using the Modified Finnegan Neonatal Abstinence Syndrome tool, rather than using an ICD-9 code. The NAS variable was created using a valid tool and the presence of clinical signs that identify NAS, thus it provides a clinically meaningful variable. Despite these limitations, the MLS provided data with longitudinal medical and social follow-up.

Implications

This study has important implications for practice. For advanced practice registered nurses (APRNs), these findings suggest language delays in children with a history of NAS from birth to five years. APRNs may monitor these children for abnormalities in language development and provide referrals for speech therapy, as needed. Currently, children with NAS can receive early intervention until the ages of 3 and 5, depending on the state (Centers for Disease Control [CDC], 2018; TDE, 2019), although it is not required. APRNs have an opportunity to assess these NAS children, who may not be using early intervention, and provide education to families to the impact of speech therapy on language delays.

This study had important policy implications. Under the Individuals with Disabilities Education Act [IDEA] (Lipkin & Okamoto, 2015), children through the age of 2 receive early intervention with the presence of developmental delay and/or disability under section C. Section B of IDEA (Lipkin & Okamoto, 2015), provides special education for certain disabilities as defined by the state, including speech and language impairment. Pediatric nurses could work

with state and federal policy makers to ensure NAS children can access speech and language evaluation through the age of 10, regardless of diagnosed disability.

In conclusion, rates of language delay were significantly higher at the ages of one and five and significantly lower at the age of 10 among children with a history of NAS than those without NAS. This suggests that screening for language delays are warranted throughout childhood and adolescence for children with a history of NAS. Children with a history of NAS used significantly more child services at the time of the study, suggesting that despite the use of child services there are still risks. Pediatric nurse practitioners and public health nurses need to increase surveillance, and needed referrals for specialized services, for children with a history of NAS. The current study findings provide a preliminary understanding of potential learning and language delays in children with a history of NAS and provide a starting point for improvement of outcomes.

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Chapter 5

Implications of Tennessee's Opioid Legislation for Neonatal Abstinence Syndrome

This chapter was submitted for publication by Jennifer N. Shearer, Paul Campbell Erwin, Sharon K. Davis, Joel G. Anderson, and Lisa C. Lindley:

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Abstract

Opioid use during pregnancy is on the rise in the United States. Neonatal abstinence syndrome (NAS), also known as newborn drug withdrawal, is a public health epidemic. Between 1999 and 2011, Tennessee experienced a 11-fold increase in NAS hospitalizations, from 0.7 to 8.5 per 1000 live births. Soaring increases in the number of newborns with NAS nationwide have caught the attention of many federal and state lawmakers, especially given the unknown burdens associated with medical and social services needed by those affected over time. Tennessee opioid-related regulations and laws enacted between 2000 to 2018 were systematically reviewed and analyzed to identify each law's purpose, effects on families and individuals, pros and cons in terms of social, practical, and legal factors, and implications for nursing practice. Our findings were that Tennessee's laws are intended to decrease the number of opioids prescribed, ensure access to continued prenatal care and substance abuse management for mothers with substance use disorders, and reduce the ease of obtaining opioids. We also found that Tennessee lawmakers have enacted laws and regulations aimed at decreasing the abuse of opioids, but not reducing the incidence of NAS. As new laws are considered, it is critical that health care providers and lawmakers work together to ensure that the developed and enacted laws strike a balance between safely managing the care of both pregnant women and their newborns without producing negative outcomes.

Keywords: policy making, opioid-related disorders, neonatal abstinence syndrome, infant, Tennessee

Opioid use during pregnancy is on the rise in the United States (Patrick et al., 2015). Neonatal abstinence syndrome (NAS), also known as newborn drug withdrawal, is a public health epidemic (Bauer & Li, 2013). Between 1999 and 2011, Tennessee experienced an 11-fold increase in NAS hospitalizations, from 0.7 to 8.5 per 1000 live births (Bauer & Li, 2013). In 2013, nearly 28,000 newborns in the United States were born with NAS (Ko et al., 2016; Patrick, Davis, et al., 2015). Soaring increases in the number of newborns with NAS nationwide have caught the attention of many federal and state lawmakers, especially given the unknown burdens associated with medical and social services needed over time. Tennessee has enacted several opioid-related laws and regulations between 2000 and 2018, yet there have been limited systematic reviews of these policies, specifically related to how these policies affect NAS, which is at epidemic levels in the state. The research question we sought to answer is: To what extent do Tennessee's opioid-related laws and regulations impact newborns with NAS and their families. After an overview of the epidemiological factors pertaining to opioid use and NAS in TN, this article has three main sections: (a) an overview of the Tennessee opioid-related laws and regulations enacted since 2000, (b) an analysis of the impact on NAS, and (c) implications for nurses, including why and how nurses can influence the legislative outcomes and inform policymakers of actual and potential consequences of laws, both positive and negative, and whether intended or unintended.

Background of Opioid Use in Tennessee

In 1999, 342 residents of Tennessee, age 15 and older, died from prescription medication overdose and 5% of Tennessee residents in publicly funded addiction treatment were receiving treatment for pain management addiction (Tennessee Department of Mental Health and Substance Abuse Services [TDMHSAS], 2014). By 2012, Tennessee had the second highest

rates of opioid use among all states, reaching over 1,000 overdose deaths annually (Center for Disease Control [CDC], 2014). Prescription opioids surpassed alcohol as the primary abused substance (Substance Abuse and Mental Health Services Administration [SAMHSA], 2012). More Tennesseans died in 2014 from opioid overdoses than motor vehicle accidents (TDMHSAS, 2014). Furthermore, between 2012 and 2014, 4% of Tennessee residents who were 18-25 years of age, roughly 207,000 individuals, used opioids without a prescription (Tennessee Department of Mental Health and Substance Abuse Services [TDMHSAS], 2016). Additionally, 24,000 high school students reported using opioids for non-medical use in their lifetime between 2012 and 2014 alone (TDMHSAS, 2016). Despite the reduction in the number of opioid prescriptions dispensed in Tennessee between 2013 and 2017 (Centers for Disease Control [CDC], 2018), there is an increase in overall opioid deaths in Tennessee associated with the use of heroin and synthetic opioids, such as fentanyl (Melton & Pellegrin, 2018). Between 2015 and 2016, Tennessee saw a 14% increase in overdose deaths with a 58% increase in deaths associated with heroin and fentanyl (Melton & Pellegrin, 2018).

Overview of NAS

The significant rise in opioid abuse in Tennessee has led to an increase in the number of newborns with NAS. NAS leads to low birth weight, neurological excitability, gastrointestinal distress, and autonomic reactivity manifesting as signs including inconsolable and high-pitched crying, increased muscle tone, difficulty eating, poor weight gain, and seizures beginning within five days of life (Lee, 2015; Maguire et al., 2016; McQueen & Murphy-Oikonen, 2016). The research on the long-term effect of NAS on development is still emerging throughout childhood and adolescence, however findings indicate an adverse effect on neurodevelopment. For example, newborns with NAS scored significantly lower on the Griffith's Developmental

Quotient Scale by demonstrating developmental delay and abnormal vision at the age of six months (McGlone & Mactier, 2015). Children, ages 3 and 8, born with NAS were more likely to have a diagnosis of educational disabilities and educational accommodations in the classroom than those without NAS (Fill, Miller, Wilkinson, Warren, Dunn, Schaffner, & Jones, 2018). In addition, a study of children with NAS found more behavioral, emotional, and developmental diagnoses than those opioid exposed with no NAS (Hall, McAllister, & Wexelblatt, 2018). Therefore, ongoing research indicates a positive association between NAS and abnormal development.

States in the southeastern part of the country, including Tennessee, Kentucky, Mississippi, and Alabama, have NAS rates nearly three times higher than the national average (Patrick et al., 2015). Some counties in Tennessee, especially in northeastern Tennessee, have rates of NAS of 60 per 1,000 live births, roughly 10 times the national average (Brown, Doshi, Pauly, & Talbert, 2016; Miller, McDonald, & Warren, 2018). The type of opioid associated with cases of NAS in Tennessee varied by region (Erwin, Meschke, Ehrlich, & Lindley, 2017). Overall, NAS in Tennessee is associated with maternal prescription opioid misuse (Miller & Warren, 2014; Erwin et al., 2017). However, NAS specific to Eastern Tennessee is associated with maternal illicit use of opioids, including heroin and diverted-prescription opioids. Hence, pregnant women in Eastern Tennessee were less likely to obtain opioids as part of a prescribed treatment than mothers in other parts of Tennessee.

In 2013, Tennessee Department of Health (TDH) made NAS a mandatory reportable condition and established the Tennessee Surveillance System for Neonatal Abstinence Syndrome, which requires hospitals and treating physicians to report all cases of NAS to TDH, for all inpatient and outpatient diagnoses respectively (Warren, Miller, Traylor, Bauer, & Patrick,

2015). Instating mandatory reporting of NAS enhanced understanding of the incidence and prevalence of NAS in the state (Warren et al., 2015). By understanding the incidence of NAS, the state of Tennessee was able to compare NAS births with other factors, such as total births, to have a better overall understanding of the effect of NAS on state resources. One example of a trend the state was able to monitor was total births in contrast to NAS births. Between 2013 and 2014, there was a 1% decrease in total births in Tennessee, while cases of NAS increased almost 13% (Tennessee Division of Health Care Finance & Administration [TNDHCFA], 2016). In 2014, the incidence of NAS among newborns with Medicaid was 21.3 per 1000 live births, up from 5.3 per 1000 live births in 2008. The total health care expenditures during the first year of life for all live births in Tennessee covered by Medicaid in 2014 totaled over \$384 million for 45,824 births; over \$51 million of that total was for the 1,063 babies born with NAS (TNDHCFA, 2016). In other words, the Medicaid expenditures for a newborn with NAS was 10 times higher than the cost for a normal weight newborn, and 1.3 times higher than the average cost for low birth weight newborns (TNDFFCA, 2016). Additionally, in 2014, the average length of hospital stay for a Tennessee newborn with NAS was 24.1 days compared to a 3.3-day average for all live births (TNDHFCA, 2016). Therefore, the epidemic of opioid abuse and misuse in Tennessee, along with the increasing number of newborns experiencing NAS, prompted state policymakers to address and control the problem.

What is Known and Unknown About Laws Affecting NAS

Laws that have an impact on NAS in the United States vary in purpose and severity of litigation. Between 1974 and 2016, the number of states that developed policies focused on drug use during pregnancy increased from 1 to 43 (Thomas, Treffers, Berglas, Drabble, & Roberts, 2018). Policies range from supportive (i.e. focused on treatment) to punitive, with punitive being

most frequent (Thomas et al., 2018). In 2015, three states (Tennessee, Alabama, and South Carolina) considered substance abuse during pregnancy a crime (Krans & Patrick, 2016). Tennessee was the only state to have a law specifying that drug use in pregnancy is a crime, although it has since been rescinded due to lack of legislative support for the law (Krans & Patrick, 2016). Alabama and South Carolina interpret child endangerment laws to include drug-using pregnant women and new mothers (Krans & Patrick, 2016).

Eighteen states define drug use during pregnancy as child abuse: Alabama, Arkansas, Colorado, Florida, Illinois, Indiana, Iowa, Louisiana, Minnesota, Nevada, Oklahoma, Rhode Island, South Carolina, South Dakota, Tennessee, Texas, Virginia, and Wisconsin (Krans & Patrick, 2016). Three (Minnesota, South Dakota, and Wisconsin) states view drug use during pregnancy as grounds for involuntary civil commitment to a treatment program. For example, Wisconsin provides the fetus a court-appointed lawyer and there is a risk of the mother losing custody after delivery (Krans & Patrick, 2016). Additionally, 15 states (i.e., Alaska, Arizona, Illinois, Iowa, Louisiana, Maryland, Massachusetts, Michigan, Minnesota, Montana, North Dakota, Oklahoma, Rhode Island, Utah, and Virginia) require health care workers to report women who they suspect are using drugs during pregnancy.

Although some states are enacting laws aimed at penalizing pregnant women for the use of opioids during pregnancy, the legal ramifications of such laws often deter women from seeking prenatal health care and create an adversarial relationship between the women and their health care clinicians (Kremer & Arora, 2015). Additionally, evidence does not indicate improvement in maternal health outcomes with incarceration. To the contrary, obstetrical emergencies are common among incarcerated women because of acute opioid withdrawal (Kremer & Arora, 2015). States vary in how they handle substance use during pregnancy, from

increasing the requirement for obtaining opioids to assisting women to receive needed support; thus, critical analysis of individual state laws is vital to understand the effects of the laws on newborns with NAS in order to best assist the legislature with evidence to guide policy development.

Methods

We used a systematic approach for this policy analysis (Teitelbaum & Wilensky, 2017). Searches of the state of Tennessee website (TN.gov) and PUBMED identified state legislative laws and regulations related to opioid use, misuse, and abuse using the key words “health policy” AND “opioids” OR “neonatal abstinence syndrome.” The search was limited to legislative opioid laws and regulations in the state of Tennessee between the years 1999 and 2018 and excluded federal opioid policies, thus, identifying seven Tennessee laws and regulations. We analyzed the opioid laws to identify the purpose of the enacted law, effects of the law on newborns and families, and the pros and cons of the policy using social, practical, and legal factors.

Conceptual Framework

In this policy analysis, we systematically analyzed Tennessee’s opioid-related laws and regulations to understand the impact on the NAS epidemic using the process outlined by Teitelbaum and Wilensky (2017). Table 5.1 includes the constructs of the process and includes identification of the policy problem, provision of evidence to understand the significance of the problem, and identification of policies and key factors related to the problem. Key factors refer to the social, practical, and legal aspects of the opioid-related policies (Teitelbaum & Wilensky, 2017). An understanding of the key factors is necessary to make informed decisions regarding the impact of the policies.

Table 5.1.

Policy Analysis Constructs

Construct	Definition
Problem Statement	Defining the policy problem being analyzed
Background	Provision of information and evidence needed to understand the problem
Landscape	Provision of the overall context of the problem, including identification of key stakeholders and their positions and examination of key factors (i.e. social, practical, and legal) related to the problem.
Options	Identification and analysis of policies with inclusion of pros and cons

Note. Adaptation of the analysis process outlined by Teitelbaum and Wilensky (2017)

The *social factors* pertain to the fairness of the policies for those affected by the problem. The *practical factors* explore to what extent the policies solve the problem. The *legal factors* concern the legal implications of the policies, such as legal restrictions, legal uncertainty, and potential for future litigation with policy implementation (Teitelbaum & Wilensky, 2017). The key stakeholders are those people who have a significant interest in the outcomes of these policies, such as newborns, mothers, nurses and other health care professionals, state legislature, taxpayers, and social services. The policy analysis concludes with a discussion of the potential impact of these policies on key stakeholders and future research (Teitelbaum & Wilensky, 2017). Thus, examining Tennessee opioid-related laws and regulations provides critical insight into the effects of these laws, particularly the affected neonates and families in Tennessee.

Results

Overview of Laws and Regulations

There were seven opioid-related laws and regulations enacted in Tennessee between 2000 and 2018 (Table 5.2). Among these laws, two (Intractable Pain Treatment Act and Public

Chapter 820) are no longer in effect. Opioid-related laws in Tennessee addressed varying aspects of opioid use including ensuring pain management per the patient's wishes, monitoring how frequently patients are obtaining opioids, and managing the licensure of directors of private pain management clinics.

The Intractable Pain Treatment Act (IPTA) of 2001, known as the pain patient's bill of rights, identified the need to use a team of medical professionals to address pain and the associated issues, including psychological, social, and vocational concerns (Public Chapter 327 [PC327], 2001). The IPTA was one of the first Tennessee opioid-related laws and set the tone for the expectation of the management of pain, per the patient's wishes. The IPTA provided patients with the option to request or reject any or all methods of relieving chronic pain and to choose opioid medications to relieve intractable pain, as they saw fit (PC327, 2001). Intractable pain is incurable, extreme pain that has failed treatment with methods such as non-steroidal anti-inflammatory drugs, physical therapy, and mild opioid medications (Tennant & Hermann, 2000). The IPTA allowed physicians to refuse to prescribe opioids for intractable pain; however, the prescribing physicians were to notify the patient that there are specific physicians who primarily treat chronic pain (i.e., pain management clinics). The IPTA required physicians to notify patients of alternative means of obtaining opioids if the physicians, themselves, refused to prescribe the medication (PC327, 2001). The bill was repealed in April 2015 due to concerns of significant increase in opioid use, the increase in private pain management clinics, and rising incidence of NAS (McMillan, 2015).

The Controlled Substance Monitoring Act of 2002, Public Chapter 840, created the Controlled Substance Monitoring Database to assist in research, investigations, enforcement of

Table 5.2.

Overview of Tennessee Opioid-Related Laws from 2000-2018

Law	Date	Tennessee Code Annotated (TCA)	Overview
Intractable Pain Treatment Act	2001 - 2015	63-6-1104	Ensures pain patient's bill of rights
Controlled Substance Monitoring Act	2002	53-10-301	Monitors patient's receiving controlled substances and dispensers prescribing controlled substances
Public Chapter 820	2014 - 2016	39-13-107	Allows for criminal prosecution of mothers for the use of an illegal narcotic during pregnancy if the child was born dependent to the narcotic
Tennessee Prescription Safety Act	2012	53-10-301	Requires dispensers and dispenser agents to report to the Controlled Substances Monitoring Database
Tennessee Safe Harbor Act	2013	33-10-104	Ensures pregnant women access to publically funded drug treatment centers and prohibits termination of parental rights if mother's seek and continue treatment by the 20th week of pregnancy
Addison Sharp Act	2013	63-1-401	Ensures that current regulations are enforced, creates protocols for managing the controlled substances used to treat chronic pain, and establishes restrictions on the quantities and combinations of controlled substances that may be prescribed
NAS Mandatory Reporting	2013	N/A	Requires mandatory reporting of cases of NAS through a real-time, statewide surveillance system

Note: N/A = not applicable

federal and state laws, and education of health care professionals to monitor patients acquiring controlled substances (Public Chapter 840 [PC840], 2002). All health care professionals legally authorized to dispense controlled substances are required to submit the required information to the Controlled Substance Monitoring Database (Public Chapter 1002 [PC1002], 2016). In 2016, amendments to this law required dispensers to upload a list of the day's controlled substance prescriptions to the database every day (Public Chapter 1011 [PC1011], 2014).

Public Chapter 820 (PC 820) of the Public Acts of 2014, also known as Tennessee's fetal assault law, allowed Tennessee District Attorneys to prosecute women who used illegal narcotics during pregnancy, if the newborn was born dependent to the opioids (Public Chapter 820 [PC820], 2014). PC820 allowed for charges of assault against mothers and, if convicted, they could serve time in jail (Salter, Ridley, & Cummings, 2015). The intent of PC 820 was to address illicit drug use during pregnancy and allow pregnant women to receive help through treatment programs and drug courts, thus reducing the numbers of newborns with NAS. Due to concern regarding potential unintended effects of PC 820, a provision was added to the statute, allowing lawmakers to assess the impact of the law on maternal and newborn outcomes (Salter et al., 2015) and then let it sunset (meaning lapse) in two years without further legislative action. Lawmakers did not have support to extend PC 820 and it ended on July 1, 2016.

The Tennessee Prescription Safety Act of 2012 (amended in 2016) aimed to curb the opioid epidemic by requiring all dispensers (pharmacists) and dispenser agents (health care practitioners with the authority to dispense controlled substances) to report to the Controlled Substance Monitoring Database (Public Chapter 880 [PC880], 2012). The amendment in 2016, Public Chapter 1002, made the law permanent (PC1002, 2016). It also included the requirement that all health care practitioners check the Controlled Substance Monitoring Database for all new

prescriptions, or new pharmacy dispensing, and, at a minimum, annually for all patients. The Prescription Safety Act of 2016 increased the required frequency of reporting to the Controlled Substance Monitoring Database from every seven days to daily (PC1002, 2016). Additionally, the 2016 amendment clarified that an “unusually high pattern of prescribing, distributing, or dispensing” that is not otherwise explainable, will trigger a referral for investigation by the appropriate health care board (PC1002, 2016). A goal of the revised law was to increase patient quality of care by providing real time information to practitioners in an effort to determine the need for counseling and/or intervention for substance abuse (PC1002, 2016).

The Tennessee Safe Harbor Act of 2013 was an effort to reduce the number of pregnant women who misuse controlled substances with the intent to reduce the number of newborns with NAS (Public Chapter 398 [PC398], 2013). Under PC 398, pregnant women referred for substance abuse treatment receive priority treatment from publicly funded drug treatment centers (PC398, 2013). The Safe Harbor Act ensures that women seeking treatment from a center offering management for substance use disorders do not get treatment refused. The bill ensures that the Tennessee Department of Mental Health and Substance Abuse Services provide family-oriented drug abuse and dependence treatment. Obstetrical providers encourage pregnant women who use opioids to obtain substance abuse treatment. Assuming the pregnant woman seeks treatment by the 20th week of pregnancy, maintains treatment compliance throughout pregnancy, and receives prenatal care, then the Department of Children’s Services will be prohibited from petitioning for termination of the mother’s parental rights on the sole account of the use of prescription drugs for non-medicinal purposes (PC398, 2013).

The Addison Sharp Prescription Regulatory Act of 2013, Public Chapter 430 (PC 430), ensures that current regulations are enforced, creates protocols for managing the controlled

substances used to treat chronic pain, and establishes restrictions on the quantities and combinations of controlled substances that may be prescribed (Public Chapter 430 [PC430], 2013). Additionally, PC 430 requires mandatory training on prescriptive protocols with the purpose of regulating pain medication dispensing within pain management clinics, including a limit on dispensing of medication to a 30-day supply at one time. PC 430 provides regulation of pain management clinics or any privately owned facility that provides pain management services for opioids, benzodiazepines, barbiturates, or carisoprodol. The regulations require clinic licensure and mandate that patients have current and valid government identification, be referred to the clinic by a licensed physician, submit to drug screening, and have current diagnostic testing for the basis of the prescription (PC430, 2013). In addition, pain management clinics must have a medical director who is a physician with an unrestricted and unencumbered medical license, with a presence of no less than 50% of weekly hours.

In 2013, the TDH made NAS reporting mandatory through a real-time, statewide surveillance system known as the Tennessee Surveillance System for Neonatal Abstinence Syndrome (Warren, et al., 2015). Previous data collection occurred through a delayed technique of reviewing hospital discharge documentation. Using an online reporting platform, facilities report newborns with a diagnosis of NAS based on clinical symptoms, as well as history of exposure, supporting evidence (such as positive urine or meconium drug screens) and source of substances causing the NAS, if known. The online reporting allows for rapid, secure collection of data. Thus, providing the opportunity for Tennessee to gather information on the number of newborns affected by the disorder, thereby informing efforts to improve outcomes through targeted intervention strategies for those areas at greatest risk (Warren et al., 2015).

Discussion

Between 2000 and 2017, Tennessee, located in the epicenter of the US opioid epidemic, enacted laws that directly and indirectly affected newborns with NAS. The purpose of this policy analysis was to understand these state-level, opioid-related laws and their effects on the statewide NAS epidemic in terms of social, practical, and legal factors (Teitelbaum & Wilensky, 2017). The laws had weak, moderate, or high effects on NAS (see Table 5.3). A weak assessment indicates a policy that negatively affects the outcomes for each factor. Moderate demonstrates a fair, positive effect on outcomes. A high assessment indicates a positive or favorable effect on outcomes associated with NAS.

Social Factors

We reviewed the laws to determine their effect on the societal problem, as well as their fairness to the people and groups affected. The escalation of opioid use following the IPTA led to the need for enactment of policies aimed at controlling and improving the opioid epidemic. Tennessee saw a ten-fold increase in the diagnosis of NAS after enactment of the IPTA (Miller, McDonald, & Warren, 2018). Cases of NAS have increased in Tennessee every year since 1999 (Miller et al., 2018).

The Tennessee Surveillance System for Neonatal Abstinence Syndrome provides an opportunity to understand the demographics of newborns affected by NAS, thus rationalizing the provision of necessary social services for the population. Accurately counting the number of Tennessee newborns affected by NAS and knowing the percentages of newborns diagnosed with NAS per region, provides newborn healthcare providers, advocates and lawmakers

Table 5.3.

Analysis of Effect of Opioid Laws on NAS

	Social Perspective	Practical Perspective	Legal Perspective
Intractable Pain Treatment Act	weak	weak	weak
Controlled Substance Monitoring Act	moderate	moderate	high
Public Charter 820	weak	weak	weak
Tennessee Prescription Safety Act	moderate	moderate	high
Tennessee Safe Harbor Act	high	high	high
Addison Sharp Act	weak	moderate	moderate
NAS Mandatory Reporting	high	high	high

Note: Author's assessment of effect of Tennessee's laws on NAS. A weak assessment indicates a negative effect on outcomes. Moderate indicates a fair, positive effect. A high assessment indicates a positive or favorable effect

with an opportunity to identify state policies needed for their care, development, and optimal health outcomes. The United States reached \$12 billion in hospital charges for NAS in 2012 (Patrick et al., 2015). In Tennessee, Medicaid covered over \$53 million in health care for babies with NAS in 2015 (Tennessee Division of Health Care Finance & Administration [TDHCFA], (2017). By decreasing access to and use of opioids by women during pregnancy, there is a potential to decrease the number of cases of NAS, thus decreasing overall federal and state taxpayer burden.

The Safe Harbor Act empowers mothers to obtain the necessary support for substance use disorders (SUD) and dependency during pregnancy by removing the fear of loss of parental rights in the process. Thus, the Safe Harbor Act potentially increases the number of pregnant women receiving needed substance use treatment; thus, potentially reducing the number of

newborns with NAS. Conversely, PC 820 may have led mothers not to pursue the standard care for substance use disorders during pregnancy given the fear of prosecution (Erwin, et al., 2017). This fear of prosecution, in turn, may have increased the number of cases of NAS. Between May 2013 and May 2014, there was a 1.9% increase in the number of pregnant women entering treatment for SUD; from July 2014 and January 2015, there was a 2% drop (Tennessee Department of Mental Health and Substance Abuse Services [TDMHSAS], 2016). These trends coincided with the enactment of both the Safe Harbor Act of 2013 and PC820. Thus, Tennessee policies may have had indirect positive effects (increase in SUD treatment with the Safe Harbor Act) and negative societal effects (decreased SUD treatment with PC 820) on NAS.

Practical Factors

We assessed the laws and regulations for their practical health care effect on NAS. The Controlled Substance Monitoring Act of 2002 can provide information, as needed, to determine if the mother of a child with NAS was prescribed opioids during pregnancy, as well as the associated morphine milligram equivalents. Understanding the associated morphine milligram equivalents provides the potential for development of scoring tools using the relationship between maternal morphine milligram equivalents and diagnosis of NAS (Tennessee Department of Health [TDH], 2017). Additionally, women in Tennessee receive relief of concern regarding social services intervention because of the Safe Harbor Act. Women can now safely visit obstetrical services without fear of their newborn being placed in an alternative home (PC398, 2013), thus potentially increasing the number of women receiving prenatal care and substance use therapy throughout pregnancy. The data provided through the mandatory reporting of NAS can identify regions of Tennessee most affected by NAS and assist in developing location-specific primary prevention strategies, such as education or interventions for responsible

prescriptive practices (Warren et al., 2013). The Addison Sharp Act provides oversight to communities in which pain management clinics exist. This Act has the potential to affect the number of newborns diagnosed with NAS by reducing the ease of obtaining large quantities of opioid pain medications.

The Tennessee Prescription Safety Act may decrease the number of newborns affected with NAS by decreasing the number of pregnant women who use opioids, along with the dosage of opioids taken by the mother. Of the more than 2,000 cases of NAS in 2013 and 2014, 588 newborns (around 30% of cases) were born to mothers in the Controlled Substance Monitoring Database (TDH, 2017). In 2013, the Tennessee Surveillance System for Neonatal Abstinence Syndrome reported that 27.3% of NAS cases in Tennessee were attributed to supervised pain management, psychiatric, or neurologic therapies, 46.7% were associated with medical replacement therapy, and an additional 26% were associated with illegal substance use (Miller & Warren, 2014). These numbers support the findings of the Controlled Substance Monitoring Database. Although Tennessee has not seen a decrease in the number of NAS diagnoses since the introduction of the Tennessee Prescription Safety Act in 2012, there have been improvements in other areas. Specifically, there has been a 32% decrease in morphine milligram equivalents dispensed between 2012 and 2017 and a 14% decrease in opioid prescriptions between 2105 and 2017 (Tennessee Department of Health [TDH], 2018). Additionally, the rate of increase of new cases of NAS in Tennessee slowed to 2% between 2016 and 2017, although further analysis is necessary to establish whether there is a direct association to the Controlled Substance Monitoring Database.

Not all opioid-related policies have a positive impact on patient outcomes in Tennessee. For example, the IPTA allowed patients to self-determine the need for opioids to treat their pain

(PC327, 2001). By allowing patients to decide if they needed opioids, the IPTA provided a loophole for patients to bypass the opinion of their primary health care provider, allowing patients to continue to receive opioids (McMillan, 2015). Additionally, PC 820 may have deterred women from seeking prenatal care for fear of prosecution, thus impeding access to care for pregnant drug-using women (Burke, 2016; Krans & Patrick, 2016; Erwin et al., 2017). Furthermore, the change in processes for obtaining opioids made necessary by these laws could lead to women obtaining opioids through illegal channels, thus negating the potential decrease in opioid usage. Thus, opioid-related policies in Tennessee may have both positive and negative effects on the incidence and prevalence of NAS.

Legal Factors

We reviewed Tennessee laws and regulations to understand the legal implications. The use of the Controlled Substance Monitoring Database has resulted in a significant decrease in morphine milligram equivalents (Goodin, 2014). Additionally, Tennessee has seen a 63% decrease in potential “doctor and pharmacy shopping” between the years 2011 and 2016 (TDH, 2017). The Tennessee Prescription Safety Act of 2016 may affect the incidence of mothers accessing prescription opioids, as the law requires health care practitioners to check the database before writing or dispensing a new prescription, or once every 12 months (PC1002, 2016).

There were negative legal impacts of the opioid-related laws as well. The enforcement of the IPTA led to a proliferation of pain management clinics in the state (McMillan, 2015). The increase in the number of these private pain management clinics eventually required legislation aimed at managing the types and amounts of controlled substances prescribed, leading to passage of the Addison Sharp Act (PC430, 2013). In PC 820, women receiving medically managed care during pregnancy had the potential to be prosecuted despite receiving care aimed at reducing the

risk to the newborns, thus fewer women may have sought assistance during pregnancy leading to an increase in newborns with NAS (Erwin et al., 2017). Additionally, there is a potential impact on the burden placed on the judicial system through the increased use of drug courts and lawsuits stemming from the enacted laws. Conversely, the Safe Harbor Act may lead to decreased prosecution of mothers receiving necessary care, increasing the number of pregnant women receiving drug treatment. Therefore, legal ramifications of the opioid-related policies in Tennessee regarding NAS demonstrate both positive and negative effects with a positive decline in morphine milligram equivalents and a negative effect on prosecution of pregnant women.

Limitations

We identified limitations of this policy analysis. First, because of a lack of mandatory reporting before 2013, it is difficult to understand fully the impact of state legislation on diagnoses of NAS: how much of the increase is real versus how much is artifact because of mandatory reporting? Before 2013, chart review at discharge identified cases of NAS, which has the potential for loss of cases. Second, the standard of care for maternal treatment for opioid addiction does not prevent NAS. The current standard of treatment is the use of medication-assisted therapy (MAT) using either buprenorphine or methadone (ACOG, 2017). Despite the use of MAT to reduce the licit or illicit use of opioids, both buprenorphine and methadone may lead to NAS (Hudak & Tan, 2012; Jones et al., 2010; Lee, 2015). Thus, the Safe Haven Law may not result in a change in outcomes until the standard of care is changed. Third, the complicated but continual increase in cases of NAS makes it extremely difficult to conclude any direct cause and effect of the opioid-related laws on cases of NAS. Fourth, without data collection relevant to all legislation it will be difficult to pinpoint which individual laws affect changes in incidence of NAS.

Another limitation of this study is the generalizability. This policy analysis is specific to the state of Tennessee, thus the findings are not generalizable to other states. However, Tennessee is one of the states with the most cases of NAS and Tennessee was the first to enact laws directly aimed at prosecuting mothers for the use of opioids during pregnancy. Thus, the results may not be generalizable, but they may provide vital information to policymakers in other states seeking ways to improve the incidence of NAS.

Implications for Nursing Practice, Policy, and Research

Our policy analysis has implications for nursing practice and advocacy of NAS-related policies. Given the profound effects of the opioid epidemic on newborns, it is important for maternal child, OB, and pediatric nurses, along with midwives and women's health nurse practitioners to be aware of the opioid-related legislation affecting newborns and their families. Collaboration between primary care providers and obstetricians can help encourage safe management of pregnancies affected by SUD and nurses may provide necessary education to prospective parents, as well as pregnant women, on the potential risk of *in utero* opioid use on the newborn. The unique position of public health nurses allows for the development of educational programs to ensure that the community understands the effect of opioids on newborns, as well as to inform the public of regulatory changes related to the care of these newborns. Nurses need to be involved in critical conversations regarding healthcare policy through involvement with local, state, and federal organizations ensuring a collective voice regarding the care of newborns with NAS. Nurses must be involved with state and federal nursing organizations, such as the Tennessee Nurses Association (TNA) and American Nurses Association (ANA), respectively. State and federal nursing organizations provide the opportunity to discuss important topics, such as NAS, with the legislature and get directly involved with

policy making. Thus, nurses have a significant role in ensuring legislation that meets the needs of children with NAS.

Our policy analysis has implications for nursing research. Through the analysis of current laws and regulations, our findings demonstrated the importance of examination of Tennessee laws in well-designed research studies. For example, research could examine the influence of Public Chapter 820 on NAS births in Tennessee. Providing more evidence about the impact of laws on NAS better informs policymakers; thus, improving the health of newborns affected by the opioid epidemic. Research is underway regarding the safe detoxification of mothers during pregnancy and resulting decrease in negative outcomes in the neonate, including reduced NAS (Nelson, 2017). Findings from Bell's (2016) maternal detoxification study could affect the American Colleges of Obstetricians and Gynecologists (ACOG) regulations and change the standard of care for detoxification of pregnant mothers, leading to the need for the development of appropriate detoxification procedures (Bell, Towers, Hennessey, Heitzman, Smith, & Chattin, 2016). Current ACOG lists MAT as the standard of care for managing opioid use during pregnancy (American Colleges of Obstetricians and Gynecologists [ACOG], 2017). A change in the ACOG recommendations would create the necessity to determine if the Safe Harbor Act of 2013 has a direct effect on NAS. Future research could explore how morphine milligram equivalents affect diagnosis of NAS, thus, potentially providing new prescribing practices of health care professionals.

In summary, our policy analysis provided an overview of Tennessee's laws and regulations pertaining to opioid use. This analysis provided critical information regarding how opioid laws might affect NAS. Tennessee provides a unique look at governmental intervention to reduce NAS, due to the high number of NAS cases and implementation of strict opioid-related

regulations and laws. Future policy analyses could focus on comparing the policies of two or more states. Specifically, comparing the policies of states with strict opioid laws against those with minimal opioid laws may provide a well-rounded look at how policy intervention affects newborn outcomes. As new laws are considered, it is critical that health care providers and lawmakers work together to ensure that the developed and enacted laws strike a balance between safely managing the care of both pregnant women and their newborns without producing negative outcomes.

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Conclusion

This dissertation consists on five manuscripts exploring the effect of NAS on the neurodevelopmental health over a ten-year period. Research to date focused primarily on children under the age of five with prenatal exposure to opioids, rather than a diagnosis of NAS. This work extended that knowledge by analyzing data on children who presented, during the newborn period, with the clinical signs and symptoms of NAS to examine the effect of NAS on neurodevelopmental outcomes through the age of ten. These studies identified that at the age of ten children with a history of NAS experienced learning disorders, language delays, abnormal behavioral development, and abnormal cognitive development. At the age of ten, NAS significantly predicted abnormal behavioral development. Further, over the first ten years of life children with a history of NAS had a significantly different risk of language delay than those without NAS.

The first manuscript, a systemic review of the literature, was completed to describe the current state of the science related to the effect of NAS on neurodevelopmental health to identify gaps in the literature and to discuss the possible association between the symptoms of NAS and neurodevelopmental disorders. The current research shows inconsistent findings on neurodevelopmental outcomes in children with a history of NAS, as most research focuses on outcomes associated with exposure to opioids *in utero* rather than a diagnosis of NAS. This review revealed a need for further research to explore the long-term developmental health in children with a history of NAS.

The second manuscript described the demographics and neurodevelopmental health characteristics of children with a history of NAS at 10 years. Data on children (n=234) from year 10 of the MLS (Lester, 1998) were analyzed. Children in this study included children with and without *in utero* substance exposure to ensure capturing all children with a history of NAS. This

was the first known study describing these children at 10 years of age. Children with a history of NAS were found to have learning disorders (23%), language delays (24%), abnormal behavioral development (16%), and abnormal cognitive development (26%). Few children in the study were found to have cerebral palsy, autism spectrum disorder, or abnormal motor development. The study revealed that a quarter of children with a history of NAS had abnormal neurodevelopment. This study supports further research aimed at understanding the effect of a history of NAS on neurodevelopment over time.

The third manuscript examined the effect of a history of NAS at 1, 5, and 10 years of age. Ten years of data on children included in the MLS (Lester, 1998) from children with a history of NAS ($n=727$) were analyzed. The socio-ecological model (SEM) was the theoretical perspective for this study (McLeroy et al., 1988). NAS was not found to be a significant predictor of neurodevelopment at 1 and 5 years, but was a significant predictor of abnormal behavioral development at 10 years of age ($p<.01$). Additional significant predictors of abnormal behavioral development based on the SEM were identified, including African American race, sex, prenatal exposure to cocaine, living with the biological family, low socioeconomic status, use of child services, and neighborhood safety. This study revealed a need for further research examining the role of NAS in development of brain structure and serotonin metabolism.

The fourth manuscript examined the longitudinal effect of NAS on learning disorders and language delays in children through the age of 10. Data from the MLS (Lester, 1998) was examined using a generalized linear mixed model to examine the longitudinal effect of NAS on learning and language. The socio-ecological model (SEM) was the theoretical perspective that guided this study (McLeroy et al., 1988). There was a significant change in learning disorders over time. At year one, children with a history of NAS had significantly lower learning than

those without a history of NAS. At years 5 and 10, there was a significant change although the change was not significantly different between groups. Further, there was a difference between children with a history of NAS and language delays, such that the pattern of language delay changed at 1, 5, and 10 years was significantly different for the NAS and no NAS groups. At the age of 1 and 5, children with a history of NAS had a significantly risk of language delay than those without NAS. At the age of 10, those with NAS had a lower risk of language delay than those without NAS. This study expanded our knowledge on the effect of a history of NAS on learning disorders and language delays suggesting the use of continued screening for language delays throughout childhood and adolescence for children with a history of NAS.

The fifth manuscript was a policy analysis that analyzed the Tennessee opioid-related policies enacted between 2000 to 2018 were systematically reviewed and analyzed to identify each law's purpose, effect on families and individuals, social, practical, and legal factors, and implications for nurses. This policy analysis used a systematic approach outlined by Teitelbaum and Wilensky to identify the problem, identify the policies and factors related to the problem, and discussed the impact of the policies (2017). Seven opioid-related laws and regulations were reviewed for social, practical, and legal context. While Tennessee has enacted policies aimed at reducing the opioid epidemic, few have been enacted that result in reduction in NAS. Currently, the standard management of pregnant women with substance use disorders involves medication-assisted therapy (MAT) using methadone or buprenorphine (ACOG, 2017). The substances used in MAT are known to result in cases of NAS (Hudak & Tan, 2012; Jones et al., 2010; Lee, 2015). Thus, until prenatal substance use disorder management changes, it will be difficult to significantly reduce the number of newborns with NAS. The cumulative results of these studies have important implications for practice, research, and policies.

Implications for Practice

There are important implications for clinical practice derived from this work. First, this work identifies opportunities for advanced practice registered nurses (APRNs). Pediatric and family APRNs are in a position to ensure that children with a history of NAS receive continued monitoring and screening for abnormal neurodevelopment, specifically abnormal behavioral development and language delay. Since the majority of research to date focuses on children up to the age of five, this work suggests that children through middle childhood could benefit from evaluation. This work also has implications for school-based nurses, as they are in the position to work closely with teachers and administrators to ensure that children with a history of NAS receive the necessary surveillance for behavioral, cognitive, and language disorders.

Implications for Research

There are many implications for research from this work. The exploration of the effect of NAS on long-term neurodevelopment has provided ample areas for follow-up. This work focused on a group of children identified as having a history of NAS by newborn clinical signs and symptoms to provide preliminary findings on this population of children. To continue to build upon the knowledge, future research is recommended. This work used a group of children born between 1993 and 1995, and future research should focus on children with NAS born during the current opioid epidemic, as well including children with exposure to methamphetamines, selective-serotonin reuptake inhibitors, and benzodiazepines. First, it is important to continue the study on the developmental effect of NAS on brain structures during prenatal and postnatal life. Additionally, it is possible that NAS affects serotonin metabolism during fetal development and this has important research implications both in the newborn period and as these children age. Third, it is important to examine how polysubstance exposure

in utero affects NAS. This research topic can be extended to examine the effect of polysubstance exposure on fetal brain development, as well as the longitudinal neurodevelopmental outcomes.

Implications for Policy

This dissertation work has important policy implications. The findings from this work demonstrated that children who use child services (e.g., home health care, mental health counseling, developmental assessment/testing, early intervention, residential treatment, or special education) are at a decreased risk for abnormal behavioral development. The findings support the development and enactment of policies aimed at ensuring children with a history of NAS have access to needed monitoring and evaluation of abnormal neurodevelopment through middle childhood. Clinicians may not have current knowledge of the available services, thus the creation of NAS caseworkers specially-trained in the management of these children could improve access to care. Further, without a diagnosis of disability children may not receive access to early intervention and special education services. Thus, nurses could work with policy makers to ensure they have an understanding of the effect of NAS on long-term neurodevelopment to develop policies aimed at improving the health of these children.

In conclusion, this study has extended to knowledge of neurodevelopmental outcomes in children with a history of NAS. To date, research primarily focused on children through the age of five with prenatal opioid exposure. This study identified that through the age of 10, these children present with learning disorders, language delays, and abnormal behavioral and cognitive development. Continued monitoring and evaluation may provide an opportunity for implementation of age-specific interventions aimed at improving outcomes for these children.

Vita

Jennifer Shearer Miller earned her Bachelor's of Science in Nursing from the University of Tennessee, Knoxville in 2001 and began her career as a Registered Nurse in the neonatal intensive care unit at The University of Tennessee Medical Center Knoxville. After two years, Ms. Shearer Miler moved to Wilmington NC. In 2004, Ms. Shearer Miller transitioned into a travel nursing career and completed assignments in Redlands, CA and Palm Springs, CA. Ms. Shearer Miller moved to Chattanooga, TN in 2005 and accepted a position as the Clinical Education Coordinator in the NICU at Children's Hospital at Erlanger.

Ms. Shearer Miller took her first academic appointment in 2010 at in a Registered Nursing program. She has worked in various faculty and adjunct faculty positions in nursing education. Currently, Ms. Shearer Miller is a graduate teaching assistant at the University of Tennessee, Knoxville in the College of Nursing.

In 2009, Ms. Shearer Miller earned her Master's Degree in nursing education at Tennessee State University. In August 2015, she enrolled in the PhD program at the University of Tennessee, Knoxville. As a doctoral student, Ms. Shearer Miller was first author in two manuscripts. The first was published by *Journal of Nursing Education* and focused on anxiety in nursing students during simulation. The second manuscript was published by the *Journal of Neonatal Nursing* and was a literature review on neonatal abstinence syndrome and neurodevelopmental health outcomes.

Ms. Shearer Miller is a recipient of the Jonas Philanthropies' American Association of Colleges of Nursing Jonas Nurse Leader Scholar award. She is a member of several professional organizations including Sigma, National League for Nursing, Southern Nursing Research Society, and Academy Health. She has graciously received funding to support her research from the

Office of Research in the Graduate School at the University of Tennessee, Knoxville. She has received additional support as the recipient of the Martha E. Rogers Memorial Dissertation Award from the UTK College of Nursing, a Sigma Gamma Chi Chapter Research Award, and the Knoxville Neonatal Associates student scholarship. Ms. Shearer Miller was a Three Minute Thesis Finalist and was invited to the National Addiction & HIV Data Archive Program secondary data analysis workshop.