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An Examination of Neurodevelopmental Outcomes, Healthcare Utilization, and Stigmatizing Language in Populations With Neonatal Abstinence Syndrome (NAS)

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AN EXAMINATION OF NEURODEVELOPMENTAL OUTCOMES, HEALTHCARE UTILIZATION, AND STIGMATIZING LANGUAGE IN POPULATIONS WITH NEONATAL ABSTINENCE SYNDROME (NAS)

A Dissertation
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by
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ABSTRACT

Substance use disorder (SUD) during pregnancy, which includes opioid use disorder (OUD), has developed into a significant medical and social concern, as it can cause a range of complications for pregnant women, fetuses, and infants. One common condition resulting from OUD is neonatal abstinence syndrome (NAS), a withdrawal syndrome experienced by infants after being exposed to opioids in the womb. NAS can cause visual physiological or neurodevelopmental complications or outcomes in newborns. Unfortunately, large-scale studies focusing on long-term neurodevelopmental outcomes of infants with NAS are minimal. NAS consists of indications and symptoms that can also affect the autonomic nervous, gastrointestinal, and respiratory systems, often requiring extended hospitalization and extensive pharmacological treatment. Despite the increase in the number of children suffering from NAS and the healthcare utilization consumed by their treatment, little is known about these children' outcomes and diagnoses behind the utilizations after their initial hospitalization. Additionally, pregnant women with SUD and their children are often stigmatized, mainly through the perpetuation of stigmatizing words and inaccurate beliefs. Unfortunately, extensive use of stigmatizing language exists on social media platforms, with Twitter containing a substantive portion of the posts.

This dissertation consists of three manuscripts that provide a comprehensive understanding of neurodevelopmental outcome, healthcare utilization, and stigmatizing language around NAS. The first manuscript compares neurodevelopmental diagnosis and screening of children treated with a NAS innovation program and children treated with traditional NAS care in South Carolina from birth to 4.5 years of age. It applies Kaplan-Meier survival curves to demonstrate and compare the survival (outcome), and Cox Proportional Hazard (PH) survival analysis models to identify how often neurodevelopmental screenings and diagnosis occur for children with NAS treated with and without the innovation program. The second manuscript explores two healthcare utilization outcomes, hospital readmission and hospital length of stay (LOSD), among children with NAS and children born late preterm in South Carolina, with follow-up years from 0–3 years of age. The risk of hospital readmission was examined using logistic regression, and unadjusted and adjusted negative binomial regression analyses were used to model the relationship between hospital LOSD for children with NAS and those born late preterm. Finally, the third manuscript examines social media data around OUD and NAS to expand understanding of the general population's views and the potential unintended impacts of this communication environment on mothers and infants. This study consists of an event analysis of Twitter data, generated by a social media listening platform Sprinklr, to describe the use of stigmatizing language around OUD and NAS. The event was divided into three timeframes and the tests of significance were performed across all three timeframes using chi-square tests. In conclusion, this dissertation synthesized and discussed the results from the three studies. It also provided a broad discussion on the potential policy implications for clinical practice and possible directions for future research. For instance, increase insurance coverage through Medicaid and the state children's health insurance programs, and the need for reaching a consensus on a specially established "addiction-ary," particularly for NAS-related language.

DEDICATION

To my husband, Dr. Tahmid Hassan Talukdar,

my son, Affan Tahsin Talukdar,

and my mother, Rizia Begum

for the values and joys, you add to my life.

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ACRONYMS

AAP	American Academy of Pediatrics
ACT NOW	Advancing Clinical Trials in Neonatal Opioid Withdrawal Syndrome
ADHD	Attention-Deficit/Hyperactivity Disorder
ASD	Autism Spectrum Disorder
ASPE	Office of the Assistant Secretary for Planning and Evaluation
BMC	Boston Medical Center
BSID	Bayley Scales of Infant and Toddler Development
CALM	Cuddling Assists in Lowering Maternal and Infant Stress
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
CPT	Current Procedural Terminology
CSAT	Center for Substance Abuse Treatment
CSV	Comma-separated values
ECHO	Environmental influences on Child Health Outcomes
EDC	Education Development Center
ER	Emergency Room
ESC	Eat, Sleep, Console
FLOTUS	The first lady of the United States
GMH	Greenville Memorial Hospital
HCPCS	Healthcare Common Procedure Coding System
HCUP	Healthcare Cost and Utilization Project
HEAL	Helping to End Addiction Long-term
HHS	Department of Health and Human Services
HIPAA	Health Insurance Portability and Accountability Act
HR	Hazard Ratios
HRSA	Health Resources and Services Administration
ICD-9	International Classification of Diseases, 9th Revision
ICD-10	International Classification of Diseases, 10th Revision

ID	Intellectual Disorder
IDEA	Individuals with Disabilities Education Act
IQR	Interquartile Range
IRB	Institutional Review Board
ISPCTN	IDeA States Pediatric Clinical Trials Network
JMP	John's Macintosh Project
LD	Learning Disability
LOSD	Length of hospital stays in days
MAiN	Managing Abstinence in Newborns
MAT	Medication-Assisted Treatment
MD	Doctor of Medicine
NAS	Neonatal Abstinence Syndrome
NHIS	National Health Interview Survey
NICHD	National Institute of Child Health and Human Development
NICU	Neonatal intensive care unit
NIDA	National Institute on Drug Abuse (NIDA)
NIH	National Institutes of Health
NOWS	Neonatal Opioid Withdrawal Syndrome
ONDCP	Office of National Drug Control Policy
OR	Odds Ratio
OUD	Opioid Use Disorder
PH	Proportional Hazard
POSC	Plan of Safe Care
QI	Quality Improvement
RRI	Recovery Research Institute
SAS	Statistical Analysis Software
SC	South Carolina
SCDC	South Carolina Department of Corrections
SCHIP	State children’s health insurance programs
SCRFA	South Carolina Office of Revenue and Fiscal Affairs

SD	Standard Deviation
SUD	Substance Use Disorder
UNESCO	United Nations Educational, Scientific and Cultural Organization
US	United States
VUMC	Vanderbilt University Medical Center
WIC	Women, Infants, and Children

CHAPTER 1

INTRODUCTION

1.1 Background/Rationale of the Study

Opioid use during pregnancy has become a major medical and social concern over the past few decades (Hunt et al., 2008; O'Brien et al., 2004; Whiteman et al., 2014), as it can cause a range of problems for pregnant women, fetuses, neonates, and infants (Fischer et al., 1999). One common condition resulting from opioid drug use during pregnancy is neonatal abstinence syndrome (NAS), a syndrome experienced by infants with prenatal opioid exposure (Kocherlakota, 2014), typically occur within 48–72 hours after birth (Barfield, 2016.). From 2000 to 2014, the rate of maternal opioid use disorder (OUD) increased from 1.1 to 6.5 per 1,000 delivery hospitalizations, and the rate of NAS increased from 1.2 to 8.0 per 1,000 hospital births (Hirai et al., 2021). The NAS rate was 8.8 per 1,000 births in 2016, showing a continued stable increase (VUMC, 2020). Additionally, according to the CDC, the number of infants born with NAS between 2010 to 2017 increased 82 percent nationally (CDC, 2021). As NAS surveillance has often depended on hospital discharge data, it historically underestimates NAS incidence in real-time (CDC, 2016; Jilani et al., 2019). Therefore, the actual prevalence of NAS among infants in the US is likely much higher.

NAS, caused by prenatal exposure to certain types of illicit drugs, can cause visual physiological or neurodevelopment complications or outcomes in newborns. Literature shows that NAS can be associated with outcomes such as poor interactional capacity and neonatal adaptation process (Jansson & Velez, 2012), autistic disorder (Rubenstein et al., 2019), attention deficit or hyperactivity disorder (Hoover et al., 2015), and development delay such as social or motor performance (O'Leary, 2004). Unfortunately, large-scale studies focusing on long-term neurodevelopment outcomes of infants with NAS are very limited. A 2014 meta-analysis study found only five articles in the literature that evaluated more than two years of outcomes in opioid-exposed infants (Baldacchino et al., 2014). Furthermore, traditional studies have limited focus on comprehensive programs for opioid-dependent mothers and infants with NAS, although such programs are found to be safe and cost effective by several recent studies (Dickes et al., 2017; Hudson et al., 2016; Summey et al., 2018). A larger gap in the literature is the lack of attention on neurodevelopment screening, especially within the population of infants with NAS. The National Health Interview Survey (NHIS) report reveals that between 2009-2017, the US had a 9.5% increase in the prevalence of developmental disabilities among children (Zablotsky et al., 2019). One argument for this is improvement in developmental screening and access to diagnostic and treatment services across the country, which has resulted in more opportunities to diagnose and treat these children (Durkin, 2019). While this conclusion is relevant for the general population, there are no sufficient investigations in the literature of neurodevelopment screening and efforts to explore the relationship between neurodevelopment diagnosis and screening for children with NAS.

Apart from the gaps in the research, knowledge of the long-term neurodevelopmental outcomes is growing for this population (Liu et al., 2019). However, there is a paucity of information regarding the health care utilization outcomes of children with NAS (Liu et al., 2019; Taylor et al., 2020). Furthermore, existing studies largely fail to explore the patterns of health care utilization among Medicaid-insured children, which is the primary insurance coverage for infants diagnosed with NAS (Corr et al., 2021; Patrick, Davis, et al., 2015). In US, the total cost of in-hospital births with a NAS diagnosis was estimated to be $572.7 million in 2016, and Medicaid was responsible for 83% of these, which indicates the unbalanced burden of state and federal budgets as it relates to the opioid crisis (Strahan et al., 2019). The large percentage of Medicaid coverage also reflects that the majority of mothers using opioids during pregnancy belong to lower-income socioeconomic groups (NIH, 2019).

Several other previous studies also indicated that children with NAS have higher admission rates within the first 30 days to 5 years of their lives compared to unexposed controls (Corr et al., 2021; Liu et al., 2018; Witt et al., 2017). Additionally, studies showed that children with NAS generally have extended hospital length of stays (LOSD) compared to those without NAS, especially during the first year of life (Diop et al., 2022; Lee et al., 2015; Wachman et al., 2011; Winkelman et al., 2018). However, only a handful of studies have assessed the risk of hospital readmission and LOSD among children with NAS compared to other high-risk infant groups in the US (Patrick et al., 2015). For example, starting from the late 1990s, pediatricians directed their attention towards late preterm children (gestational age 33-36 weeks), as a population of high-risk children with adverse healthcare utilization outcomes (Escobar et al., 1999; Phillips et al., 2013; Young et al., 2013). Nevertheless, observational studies focusing on and comparing children with NAS and late preterm and still limited in identifying the general trend and differences in healthcare utilization in these populations.

Another challenge that pregnant women with OUD and children with NAS face is stigmatizing language, which is sometimes used to describe this disease and characterize people suffering from these disorders. Stigma is a discriminatory behavior, and in the case of stigma around issues like NAS, there are public health concerns. Unfortunately, stigma is often transferred willingly or unwillingly to the infants of mothers who used opioids during their pregnancy. Researchers see stigmatizing language used extensively on social media platforms, with Twitter covering a substantive portion of the posting volume. Social media research finds positive and negative sentiments on social media platforms like Twitter (Asur & Huberman, 2010). However, it can be argued that using stigmatizing language targeting children with NAS on social media may cause unintended harm to these children and their families by pushing them further into the shadows of our society. Additionally, this type of language may reinforce compromised or weakened trust in the health care system for these families. Many reporters in the media describe infants with NAS using the terms' born addicted,' 'addicted babies,' or 'babies with addiction' (Webster, 2018). However, this is incorrect and arguable stigmatizing language, infants are not born addicted, as addiction implies choice, and infants do not have any choice who their mothers are or the world they are born into. Given this, understanding more about the landscape of potentially stigmatizing language for infants and mothers with NAS is essential for policymakers as well as the medical and research communities that treat these families.

This dissertation aims to analyze and understand issues within the larger landscape of NAS by focusing specifically on three research areas within NAS; examining neurodevelopmental outcome of infants diagnosed with NAS, health care utilization within the same population in comparison with children born late preterm, and the use of stigmatizing language around NAS more broadly but also looking at a specific NAS case. This research will be one of the very first attempts to apply procedure codes for analyzing neurodevelopmental screening, and web-scraping method for understanding the language around NAS. The dissertation is broken down into five chapters, with three distinct but interrelated studies making up Chapters Two through Four. Chapter one provides an introduction, the overall research design of this dissertation, and outline to follow in the next chapters. Chapter two compares neurodevelopment diagnosis and screening of children treated with a NAS innovation program and children treated with traditional NAS care in South Carolina from birth to 4.5 years of age using Medicaid data from 2006-2014. Chapter three examines three years of health care utilization outcomes for South Carolina Medicaid enrolled children diagnosed with NAS and children born late preterm between 2005-2015. This paper specifically focuses on hospital readmission and hospital length of stay after the initial birth hospitalization within these populations from age 0-3 years. Chapter four uses a trend approach, focusing on a singular event where a national public figure visited a large metropolitan hospital treating children with NAS to analyze the language used around NAS on Twitter. This chapter also applies a public policy theory called the "issue-attention-cycle" developed by Anthony Downs in 1972. Finally, Chapter five reviews and compares the study findings and suggest potential policy implications for clinical practice and future research.

1.2 Dissertation Aims

The overall goal of this dissertation is to examine neurodevelopmental outcome, healthcare utilization, and stigmatizing language focusing children with NAS. It compares neurodevelopmental diagnoses and screening of children with NAS who were treated with a comprehensive care model (Managing Abstinence in Newborns – MAiN) and with traditional NAS care in South Carolina. It also compares two healthcare utilization outcomes, hospital readmission and length of stay, between children with NAS and children born late preterm within the same region. Finally, it investigates the use of stigmatizing language around NAS on Twitter focusing a singular event. The specific aims of this dissertation are as follows.

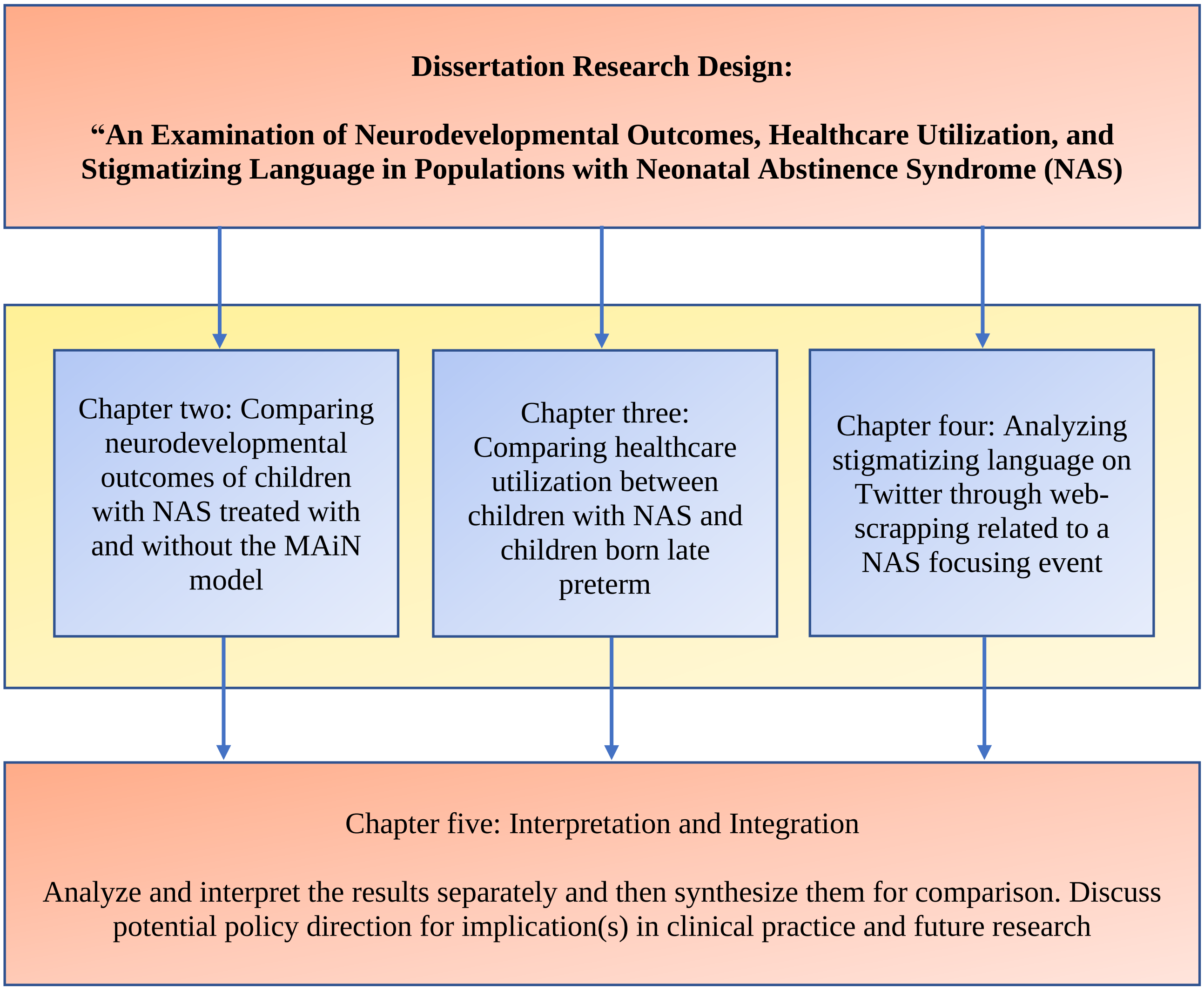
Aim 1: To compare neurodevelopment outcomes (diagnosis and screening) across each year for 4.5 years after birth in children treated with the MAiN program in a large Southeastern regional hospital in South Carolina with a comparable population of children diagnosed with NAS in the state who were treated with traditional care from 2006-2014.

Aim 2: To examine hospital readmission and length of stay across each year for three years after birth of children with NAS and children born late preterm in South Carolina who were born between 2005-2015.

Aim 3: To examine Twitter data around first lady Melania Trump's visit to the Boston Medical Center's pediatric unit of NAS care, which will characterize the language used on Twitter around the event regarding her visit. The timeframe of the visit will be divided into three stages: pre-event, event horizon, and post-event periods, during which, the language used on Twitter will be examined and analyzed.

1.3 Dissertation Organization

This dissertation will analyze neurodevelopment outcome and healthcare utilization in populations of infants diagnosed with NAS and examine the use of stigmatizing language around NAS on Twitter using a specific case for analysis. The dissertation will use three distinct datasets and time periods of analysis. This three-article dissertation will consist of three separate but interrelated studies: two quantitative studies with advanced statistical analysis (Chapters Two and Three), and one descriptive study with portions of qualitative and quantitative analysis (Chapter Four). Therefore, the overall dissertation will draw on the strengths of several statistical analytic methods and descriptive statistics related to both quantitative and qualitative methodologies to fully understand the phenomena of interest. In the last chapter (Chapter Five), findings from the three studies will be reviewed, and a synthesis of findings, discussion of future research, and policy implications will be presented. Especially, a policy discussion to suggest potential policy directions and implication(s) for clinical policy and practice will be explored. By analyzing and comparing dissertation findings, this proposed research will interpret the incidence of neurodevelopment and healthcare utilization outcomes in children with NAS among different comparison groups and the use of language related to NAS on social media platforms like Twitter.



Abbreviation: NAS, Neonatal Abstinence Syndrome; MAiN, Managing Abstinence in Newborns

Figure 1: Chapter summaries of dissertation research design.

1.4 Data Source

The first two studies in this dissertation will be retrospective cohort studies using two Medicaid claims datasets from the South Carolina Revenue and Fiscal Affairs (RFA) office. RFA provides a wide range of fiscal and statistical analysis reports and other services to the Governor, General Assembly, state and local government bodies, private sector, and the residents of the states for various purposes including research and development (SCRFA, 2022). The first study will include Medicaid claims data from RFA from 2006-2014, and the second study will include data from 2005-2015. The rationale for selecting two Medicaid datasets and two timelines is as follows: the first dataset includes information only for children with NAS, while the second dataset encompasses the data of all children in South Carolina, including information on birth hospitalization, inpatient, and outpatient data. Additionally, the first dataset already identified children with NAS who received care through the MAiN model. This dataset covers the birth years from 2006 to 2014, with a follow-up period of 4.5 years. The second dataset, which includes data on all South Carolina children, was ideal for comparing children with NAS and children born late preterm. It spans the birth years from 2000 to 2015, with a follow-up period of 3 years. Moreover, this dataset also contains data on children born until 2018, but to ensure the inclusion of more recent data and maintain consistency with the 3-year follow-up period, year 2000-2015 was selected to analyze the healthcare utilization between children with NAS and children born late preterm.

The data elements in the Medicaid datasets include various diagnosis and billing data that capture all Medicaid enrollee visits to licensed, non-federal healthcare facilities. More specifically, they contain encounter-level demographic, clinical, and non-clinical information (i.e., pharmacy claims, inpatient/outpatient information, birth certificate data, etc.). The two datasets are distinct but similar in terms of the inclusion of diagnostic and procedure codes. The datasets have unique patient identifiers (I.D.) that allow for patient tracking over time and across different care settings. South Carolina RFA routinely performs internal audits to ensure the compliance and accuracy of data elements, which are reported at 99% and 99.5%, respectively, as required by law (SCDC 2014). The datasets were obtained by filing formal applications to RFA and obtaining prior approval from the Clemson University Institutional Review Board (IRB).

Appendix A includes the variables obtained from the Medicaid claims that were used in this dissertation. Most of the variables for the first two studies was ascertained through medical code sets. These types of code sets are applied for encoding data elements, such as international codes for medical diagnosis or procedure, used in the healthcare industry across the world. According to the Health Insurance Portability and Accountability Act (HIPAA) of 1996, code sets for medical data are required in the administrative and financial health care transaction standards for the data elements of diagnosis, procedure, and drugs (VUMC, 2020). This dissertation searched for and applied the following code sets:

- International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)
- International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM)
- Current Procedural Terminology (CPT)
- Healthcare Common Procedure Coding System (HCPCS)

The dataset of the third study contained Twitter data by searching specific NAS-related keywords surrounding an event. The event was chosen after a three-year review (2017-2019) of the NAS-related keywords utilizing the social listening platform Sprinklr (*Sprinklr*, 2009). The researchers first searched for keywords within this period, dividing each year into four-month windows for a total of twelve time periods. Next, each four-month period was evaluated for data outliers; outliers were identified and manually searched to identify potential associated events or issues. From this scan and synthesis, the research team chose the event where First Lady Melania Trump visited the Boston Medical Center's pediatric unit to raise awareness for a new NAS treatment program offered at the hospital. This event also generated the highest frequencies of NAS-related keywords compared to other time periods.

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CHAPTER TWO: NEURODEVELOPMENTAL SCREENING AND DIAGNOSIS IN CHILDREN WITH NEONATAL ABSTINENCE SYNDROME (NAS): A RETROSPECTIVE COMPARISON

2.1 Abstract

Purpose: This study compares neurodevelopmental screening and diagnosis from birth - 4.5 years among South Carolina Medicaid-enrolled children with a history of Neonatal Abstinence Syndrome (NAS) treated with a comprehensive care program and with standard of NAS care.

Method: This retrospective cohort study applied The Cox Proportional Hazard Model (PH) of survival analysis to identify how often neurodevelopmental screenings and diagnosis happen in the exposure group compared to the comparison group over time. It also developed Kaplan-Meier survival curves to compare survival (i.e., smaller risk of outcome) in both groups regarding neurodevelopmental screening and diagnosis and provided a visual tool to evaluate the association between exposure and the risk of outcome.

Result: The initial sample included 110 infants treated with the NAS comprehensive care program (MAiN) and 356 infants treated with standard of NAS care and born between 2006-2014. Statistically significant rates of screening were seen in the MAiN group regarding ASD, developmental delay, and intellectual disability and mental retardation together, and in the standard of care group regarding impairment in vision or hearing in at least one year from birth – 4.5 years. Standard of care group had seen significant increase of two neurodevelopmental diagnosis, ADHD and developmental delay, during the same timeline. According to the Kaplan-Meier survival curves, MAiN group appeared to have a smaller drop in survival at each interval regarding neurodevelopmental screening and diagnosis. The adjusted hazard ratios indicated approximately a 9% higher probability of neurodevelopmental screening, and approximately a 19% lower risk of neurodevelopmental diagnosis in the experimental treatment group than in the comparison group.

Conclusion: Children with NAS treated with the comprehensive care program had higher neurodevelopmental screening and lower neurodevelopmental diagnosis compared to those with standard of NAS care. Recognition and reinforcement of such programs, increase insurance coverage through Medicaid, additional research on neurodevelopmental screening, and necessary modifications to the current general developmental screening guidelines could be some significant strategies to increase screening rates and address neurodevelopmental disorders and in children with NAS.

2.2 Introduction

Opioid use during pregnancy has become a major medical and social concern over the past few decades (Hunt et al., 2008; O’Brien et al., 2004; Whiteman et al., 2014), as it can cause a range of problems for pregnant women, fetuses, neonates, and infants (Fischer et al., 1999). One common condition resulting from opioid drug use during pregnancy is neonatal abstinence syndrome (NAS), a withdrawal syndrome experienced by infants after being exposed to opioids in the womb (CDC, 2016; Kocherlakota, 2014). From 2000 to 2014, the rate of maternal opioid use disorder (OUD) increased from 1.1 to 6.5 per 1,000 delivery hospitalizations, and the rate of NAS increased from 1.2 to 8.0 per 1,000 hospital births (Hirai et al., 2021). The NAS rate was 8.8 per 1,000 births in 2016, showing a continued stable increase (VUMC, 2020). Additionally, according to the CDC, the number of infants born with NAS between 2010 to 2017 increased by 82 percent nationally (CDC, 2021b). As NAS surveillance has often depended on hospital discharge data, it historically underestimates NAS incidence in real-time (CDC, 2018; Jilani et al. 2019). Therefore, the actual prevalence of NAS among infants in the US is likely much higher.

NAS, caused by prenatal exposure to certain types of illicit drugs, can cause visual physiological or neurodevelopmental complications or outcomes in newborns. Literature shows that NAS can be associated with outcomes such as poor interactional capacity and neonatal adaptation process (Jansson & Velez, 2012), autistic disorder (Rubenstein et al., 2019), attention deficit or hyperactivity disorder (Hoover et al., 2015), and developmental delay such as social or motor performance (O’Leary, 2004). Unfortunately, large-scale studies focusing on long-term neurodevelopmental outcomes of infants with NAS are very limited. A 2014 meta-analysis study found only five articles in the literature that evaluated more than two years of outcomes in opioid-exposed infants (Baldacchino et al., 2014). Furthermore, traditional studies have limited focus on comprehensive programs for opioid-dependent mothers and infants with NAS, although such programs are found to be safe and cost-effective by several recent studies (Dickes et al. 2017; Hudson et al. 2016; Summey et al. 2018). A larger gap in the literature is the lack of attention on neurodevelopmental screening, especially within the population of infants with NAS. Periodical screening at recommended ages is an essential strategy as it helps to identify any development concern for a child that can require additional examination or evaluation (CDC 2021b). The National Health Interview Survey (NHIS) report reveals that between 2009-2017, the US had a 9.5% increase in the prevalence of developmental disabilities among children. One argument for this is improvement in developmental screening and access to diagnostic and treatment services across the country, which has resulted in more opportunities to diagnose and treat these children (Durkin, 2019). While this conclusion is relevant for the general population, there are no sufficient investigations in the literature on neurodevelopmental screening along with neurodevelopmental diagnosis for children with NAS.

This dissertation paper examines the neurodevelopmental outcomes of infants diagnosed with NAS. This research will be one of the very first attempts to apply procedure codes for analyzing neurodevelopmental screening. It aims to compare neurodevelopmental diagnosis and screening of children treated with a NAS innovation program and children treated with traditional NAS care in South Carolina from birth to 4.5 years of age using Medicaid data from 2006-2014.

2.3 Overview of NAS

NAS has traditionally been described as an array of signs and symptoms newborns experience after abrupt discontinuation of gestational exposure to opioids (Jansson & Velez, 2012). However, NAS can also be caused by antidepressants, barbiturates, or benzodiazepines, which are used to treat depression and sleeping difficulty (March of Dimes, 2023). Therefore, the causes of NAS are diverse, including in-utero exposure to prescribed or illegal opioids and agents used to treat maternal opioid use or Medication-Assisted Treatment (MAT) (McQueen & Murphy-Oikonen, 2016). NAS is a multisystem disorder that primarily affects the central and autonomic nervous system along with the gastrointestinal tract, creating symptoms such as wakefulness, high-pitched cry, diarrhea, hypertonic muscles, breathing difficulties, impaired weight gain, etc. (Cramton & Gruchala, 2013; Finnegan et al., 1991; Kocherlakota, 2014; Logan et al., 2013; McQueen & Murphy-Oikonen, 2016).

In the US, the average incidence of NAS increased from 1.6 cases per 1000 in-hospital births to 8.8 cases per 1000 births from 2004 to 2014 (Leech et al., 2020). The total hospitalization cost of NAS was $572.7 million in 2016, and Medicaid covered approximately $477.0 million or 83% of the expenditure (Winkelman et al., 2018). The last decade has seen substantive research on NAS risk, treatment, and outcomes, among others but there is much to be learned about the long-term outcomes of NAS in children and families. Research provides preliminary evidence that NAS is associated with adverse neurodevelopmental outcomes in early childhood, but there has been scant research focused on the long-term outcomes of having a NAS diagnosis as an infant. Early childhood is usually defined as the period from birth to eight years old (UNESCO, 2019), but researchers often use conventional lengths (birth- age 3; ages 2-5, etc.) within this period for their specific study purposes (Thatcher, 1992). Given the need for research on this topic, studies focused on early childhood outcomes are well suited for expanding this research stream.

2.4 Managing Abstinence in Newborn (MAiN) model of care

The MAiN or Managing Abstinence in Newborns model of care (2003-2022) was developed by a multidisciplinary team at Greenville Memorial Hospital (GMH) - which is a not-for-profit large regional hospital and a part of a public academic health care delivery system

(Dickes et al., 2017; Summey et al., 2018). It is an early treatment model for infants at high risk for opioid withdrawal or NAS, which is based on the theory that neonates in late gestation and chronically exposed to long-acting opioids need to be considered opioid dependent (Farid et al., 2008). This is caused by a significant transfer of opioids across the placenta that fetuses received from their mothers within the womb. Early low-dose methadone treatment (within 48 hours of birth) can be considered an effective long-acting opioid therapy that can potentially prevent severe opioid withdrawal and its complications (Dickes et al., 2017; Hudson et al., 2016; Summey et al., 2018).

The MAiN model was developed by an array of experts, including pediatric and developmental medical staff representatives, nursing administration, nursing staff, pediatric pharmacy, social work, physical and occupational therapies, and child advocacy (Hudson et al., 2016). The team emphasized ensuring formal screening for vital changes and symptoms of oversedation during hospitalization to decide who should receive the necessary pharmacologic therapy. Therefore, the team believes only the “presumed opioid dependent” at birth after high levels of opioid exposure in late gestation should require or benefit from the MAiN treatment (Summey et al., 2018). This research concludes that a newborn with chronic continuous opioid exposure may be presumed to be opioid dependent whether the source of opioids was an intravenous or placental transfer.

To be eligible to receive the MAiN model of care, a neonate must be born to a mother who has been taking at least 20 mg of methadone or 9 mg of buprenorphine for at least 2 weeks immediately before delivery (Dickes et al., 2017). Additionally, they must complete at least 35 weeks of gestation and exclude no other conditions at birth that require intensive care (Summey et al., 2018). Between 2006 to 2014, approximately 25% of NAS–diagnosed infants met the MAiN eligibility criteria (Dickes et al., 2017; Summey et al., 2018). The MAiN-eligible neonates are admitted to the low-acuity Mother/Baby Unit and offered early methadone treatment (Dickes et al., 2017; Hudson et al., 2016; Summey et al., 2018).

All neonates are managed by a pediatrician and provided low-stimulation supportive care that includes breastfeeding support (unless contraindicated) and extended hospital length of stay from birth hospitalization. Infants exposed to maternal buprenorphine or lower maternal methadone doses are initiated on 0.05 mg/kg/dose, and infants exposed to higher maternal methadone doses (60 mg or higher) are initiated on 0.1 mg/kg/ dose every 6 hours within 6-48 hours of birth. Urine and meconium drug screening, prescription monitoring database queries, and a social work evaluation for all families are routinely performed by the Staff (Summey et al., 2018). A 31-item scale called the Finnegan score, designed to quantify the severity of NAS and to guide treatment, is performed every 4 hours along with providing continuous apnea and bradycardia monitoring in the mother's room (Dickes et al., 2017; Hudson et al., 2016; Summey et al., 2018).

If necessary, dosing adjustments are made, so neonates do not develop signs of poor symptoms or be oversedated. Dosing intervals are monitored and transitioned from 6-12 hours over several days. This process takes considerable caution, which resulted in only 4% oversedation and 2% need for an adjuvant medication of MAiN infants over the study period. In order to be discharged, a neonate needs to show no sign of oversedation for 48 hours, have abstinence scores consistently below 8 on the Finnegan scale (Finnegan et al., 1975), have weight increasing or stable, have adequate feeding pattern/milk intake, stable vital signs for at least 24 hours, and normal voiding and stooling patterns. Social issues related to home disposition are resolved before discharge, and an appointment is established with a medical home. If a neonate meets the discharge criteria, a pediatric pharmacist develops a weaning calendar for them. Neonates are prescribed methadone in prefilled oral syringes at an average out-of-pocket cost of $13 per one-month supply to the family (Summey et al., 2018). In South Carolina, infants do not get the benefit of prescription cost coverage by Medicaid. These prescriptions are filled by caregivers before discharge. Unit staff reconcile the dispensing of all the syringes and educate the caregivers to administer the medication properly (Dickes et al., 2017).

The outpatient weaning process involves gradually reducing the methadone dosage by approximately 15% every Sunday and Wednesday. Regular weekly office visits at an outpatient pediatric medical home are scheduled during this time to monitor the effects of the slow reduction. If the infant shows signs of poor control of NAS, the outpatient physicians may slow down the weaning process. A regional health department office provides one or two home visits, and families are educated about the signs of uncontrolled withdrawal that require additional visits. All newborns are referred for developmental assessment at 3-4 months of age and offered phone-based parenting support and developmental screening services until the child is 8 years old (Summey et al., 2018).

The MAiN innovation program has shown initial evidence of being a safe and effective treatment option for infants with NAS and has been found to result in considerable cost savings when compared to national expenditures (Gareau, Lo`pez-DeFede, and Finney, 2015). A retrospective study was conducted to assess the program's effectiveness, which enrolled 143 patients between 2006 and 2014 at GMH. Of these patients, 26 (18%) were transferred to the NICU due to medical complications, while 117 (82%) completed the inpatient component of the MAiN program. Infants in the program experienced a median peak weight loss of 7% (range: 1% -14%) and a median peak modified Finnegan score of 10 (range: 3–21). The breastfeeding rate among the cohort was 42%. Although 4% of newborns experienced oversedation, there were no medication errors, seizures, or deaths. Outpatient records were available for 115 patients, of which 14% visited an emergency department within 30 days of discharge, and 7% were readmitted, none of which had a primary diagnosis of withdrawal. This indicates that the MAiN program is potentially an effective and cost-efficient alternative to standard treatment for NAS, which typically involves treatment in a NICU setting. Widespread implementation of the program could lead to significant savings in hospital charges and improved patient outcomes for children with NAS (Dickes et al., 2017).

2.5 Previous findings and hypotheses

2.5.1 Association between neurodevelopmental outcomes and NAS

Currently, there are inconclusive evidence available regarding the impact of maternal opioid use during pregnancy and the neurodevelopmental outcomes of their infants (Wachman et al., 2018). Some studies have found development delay or neurodevelopmental complications in children whose mothers used opioids or methadone during pregnancy (Johnson et al., 1984; Nulman et al., 2012; Smith et al., 2008). In contrast, other studies have found no association between prenatal opioid exposure and adverse neurodevelopmental outcomes in early childhood (Bakhireva et al., 2019; Bandstra et al., 2004; Chaplin et al., 2010). No studies to date have attempted to analyze the association between neurodevelopmental diagnosis and neurodevelopmental screening protocols in children with NAS.

Usually, prospective studies investigating the treatment and long-term outcomes of infants with NAS are small-scale and do not extend beyond two years of data to analyze outcomes. (Merhar et al., 2018). Merhar and her associates (2018) retrospectively evaluated developmental outcomes at two years of birth in infants treated for NAS; they found that children with NAS performed lower than the normative sample regarding cognitive, language, and motor development on the Bayley Scales of Infant Development. While instructive, results from a longitudinal sample would provide a more robust analysis of developmental issues in this population. For example, a longitudinal follow-up study on 72 children with prenatal opioid and polysubstance exposure and 58 children without any established prenatal risk examined cognitive functioning at five time points within eight years of age (Nygaard et al., 2015). However, the authors did not find significant differences in cognitive abilities between exposed and control groups over time and highly significant group differences in cognitive abilities at 8½ years of age when considering earlier cognitive abilities.

Several scholars find evidence that infants exposed to opiates in-utero are at risk of neurodevelopmental impairment (Baldacchino et al., 2014; Burke & Beckwith, 2017; Hunt et al., 2008; Konijnenberg & Melinder, 2011). However, a majority of the studies are outdated and lack the inclusion of appropriate comparison groups. An early developmental deficit study showed a significant difference in the language and cognition score distribution between NAS infants and a group of infants without a history of NAS (Beckwith & Burke, 2014). Results from a psychometric assessment at 18 months and three years between opiate-exposed and opiate-free infants showed that the exposed infants had significantly lower scores with most assessment tools, including the Bayley Scales of Infant Development. The authors also found consistent evidence of neurodevelopmental impairment regardless of the assessment tools and age at testing (Hunt et al., 2008). The results of these studies are consistent with several other studies published in the 1980s and '90s, highlighting the need for updated research on outcomes for infants diagnosed with NAS and the inclusion of current, more comparable control groups.

Along with the inclusion of non-homogenous control groups, a substantive number of investigations targetting NAS include case-series and case-control studies with shorter follow-up periods. In contrast to the abovementioned findings, some studies have found no association between prenatal opioid exposure and adverse neurodevelopmental outcomes in early childhood (Bakhireva et al., 2019; Bandstra et al., 2004; Chaplin et al., 2010). For example, results from a 2019 study by Bakhireva et al. showed no development delay in opioid-exposed children treated for NAS compared to a healthy infant control group (Bakhireva et al., 2019)Likewise, several studies examining prenatal cocaine exposure's impact on neurodevelopmental outcomes between 3-7 years old found little or no effect on language and Bayley Scales of Infant Development (BSID) (Bandstra et al., 2004; Kilbride et al., 2000).

Wachman and his colleagues conducted a systematic literature review of NAS diagnosis and management studies including fifty-three studies published between July 1, 2007, to December 31, 2017. Among other things, it examined infant pharmacologic and nonpharmacologic treatments, including neurodevelopmental outcomes. The authors argued that their review found insufficient evidence to support the associations between neurodevelopmental diagnoses and outcomes among infants with NAS (Wachman et al., 2018). Another systematic review and meta-analysis of twenty-six published cohort studies found a negative association between prenatal opioid exposure and neurocognitive and physical development from 6 months of age and persisting until adolescence (Yeoh et al., 2019). Due to the inconclusive and conflicting findings in the current literature, it is crucial to further examine the association between neurodevelopmental outcomes in children with NAS.

2.5.2 Data on neurodevelopmental disorders

The Centers for Disease Control and Prevention (CDC), and National Center for Health Statistics, publish data through The National Health Interview Survey (NHIS) on the percentage of children with neurodevelopmental disorders in the US. However, similar data focused on children with NAS is challenging to find. Data on neurodevelopmental outcomes for the general population can be useful to increase additional insight for the NAS population; however, as evidence shows children with NAS have a higher risk of neurodevelopmental disorders, data explicitly focused on them is a critical need. A recent study used NHIS data and estimated the prevalence of autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), intellectual disorder (ID), and learning disability (LD) among US children and adolescents aged 3–17 years in 2019 and 2020. The summary of the result is shown in Table 1.

Table 1: Prevalence of neurodevelopmental disorders in US children and adolescents aged between 3–17 years, 2019 and 2020

Characteristics	**ASD (%, 95% CI)**	**ADHD (%, 95% CI)**	**ID (%, 95% CI)**	**LD (%, 95% CI)**
Total number of prevalent cases	1.8 million	5.2 million	0.9 million	3.9 million
Current diagnosed	2.9 (2.4, 3.4)	8.5 (7.9, 9.2)	1.4 (1.2, 1.7)	6.4 (5.8, 7.0)
Ever diagnosed	3.1 (2.8, 3.6)	9.5 (8.8, 10.2)	1.9 (1.7, 2.3)	7.6 (7.0, 8.2)

Source: Yang et al., 2022

The analysis included a population of 61.3 million children and adolescents aged 3 to 17 years born between 2019 and 2020. Among this population, 5.2 million individuals were identified with ADHD, 1.8 million with ASD, 0.9 million with ID, and 3.9 million with LD. The weighted prevalence of currently diagnosed neurodevelopmental disorders was found to be 8.5% (95% CI: 7.9–9.2%) for ADHD, 2.9% (95% CI: 2.6–3.4%) for ASD, 1.4% (95% CI: 1.2–1.7%) for ID, and 6.4% (95% CI: 5.8–7.0%) for LD, as shown in Table 1 (Yang et al., 2022). This study is a suitable representation of recent neurodevelopmental prevalence in the US, but it did not account for children before age 3. Neurodevelopmental diagnosis and screening are more common in later years, but symptoms of ASD and ID can be seen as early as 12 months and 2 years (APA, 2023; NIH, 2017).

According to the Centers for Diseases Control and Prevention (CDC), between 1997 and 2017, there were changes in the proportion of children in the age group of 5 to 17 years diagnosed with various developmental and behavioral disorders in the US. The percentage of children diagnosed with ADHD increased from 6.3% in 1993 to 10.7% in 2017. On the other hand, the percentage of children diagnosed with learning disabilities remained stable at 8.8% between 1997 and 2017. Autism diagnosis increased from 0.1% in 1997 to 1.2% in 2013. Similarly, the percentage of children diagnosed with intellectual disability (mental retardation) remained stable between 0.6% and 0.9% from 1997 to 2010 but increased to between 1% and 1.5% from 2011 to 2017 (CDC, 2019). This data shows a continually increasing trend of the most common and known neurodevelopmental disorders, but the portion that children with NAS cover within this statistic is not reported.

State Medicaid data on NAS can be collected by submitting applications to state-level organizations such as SC Revenue and Fiscal Affairs (RFA) office for research purposes, and some of the neurodevelopmental data can be captured from these datasets. Regardless, data focused on neurodevelopmental outcomes in this population are uncommon and particularly salient in the field of neonatal opioid exposure broadly and NAS more specifically. NAS studies have largely focused on the identification and treatment of NAS. However, scholars propose that the global aim needs to focus on introducing access to early intervention programs to improve care for infants with NAS in the short and long run (Maguire et al., 2016). Several studies have addressed the potential and significance of early treatment innovation programs for NAS care (Dickes et al. 2017; Hudson et al. 2016; Summey et al. 2018).

Currently, nationwide data is not available to determine the percentage of children with NAS enrolled in early intervention programs across the US. However, state-level data provides some insights for the children with NAS who require specialized care through such intervention programs. For instance, in Pennsylvania, 21.59% newborns with NAS received referrals to home visiting services 12.66% received assessment of developmental clinics, 2.74% received referrals to medical homes, and 24.6% received referral to Early treatment intervention, reported to the surveillance system in 2020 (Bureau of Family Health and Bureau of Epidemiology, 2022). Another study conducted in Massachusetts found that 61% of infants with moderate to severe NAS were referred to early intervention between 1998 and 2005. Among them, 89% were determined to be eligible for services (Derrington, 2013). However, not all of these infants had a formal NAS diagnosis. Therefore, the discrepancy in eligibility might have occurred due to the non-disclosure of a neonatal drug exposure history during the evaluation process. As the number of infants with NAS is rising all over the US, estimating early intervention referral and improving enrollment rates becomes increasingly essential for planning programs, which are crucial for ensuring access to services for infants and their families affected by NAS and OUD (Peacock-Chambers et al., 2019).

The innovation program MAiN aims to provide multidisciplinary, coordinated, and community-based care for mothers and their infants at high risk for opioid withdrawal (Summey et al. 2018). Existing studies show that MAiN infants had a significant reduction in median charges and lower emergency room (E.R.) use compared to infants receiving traditional NAS care from birth to six months of age (Dickes et al., 2017; Hudson et al., 2016; Summey et al., 2018) Nevertheless, there is a need for further research to analyze the effectiveness of this program focusing on other distinct outcomes, i.e., neurodevelopmental screening and diagnosis, over more extended time periods. Considering the substantive peer-reviewed and validated research on the

MAiN model, the potential for further long-term study of infants treated with this approach is important. In addition, the increasing incidence rate of neurodevelopmental disorders in early childhood leads to the first hypothesis of this study:

Hypothesis 1.1a: *The incidence of neurodevelopmental diagnosis will increase in later years for children with NAS treated with the MAiN program and with standard of care.*

2.5.3 Guidelines for neurodevelopmental screening

As mentioned earlier, numerous studies have found negative, neutral, or little evidence of the association between NAS diagnosis and neurodevelopmental outcomes and diagnosis. However, none analyzed the significance of neurodevelopmental screening in this relationship. The significance of improved screening and identification of children at risk for neurodevelopmental impairment is well-recognized (Sutton & Darmstadt, 2013). According to the American Academy of Pediatrics (AAP), a general developmental screen is recommended at the 9-, 18-, and 30- month well-child visits. At a minimum, screening for behavioral and emotional problems should be performed at the same visits (AAP, 2023). The symptoms of ASD may be identified as early as 12 months of age (Guevara et al., 2013). Therefore, it is recommended that symptomatic children should be screened for ASD at the 18- and 24-month visits (Hyman et al., 2020)

Developmental screening is defined as using standard tools to identify and refine recognized risks in a child’s development (Lipkin & Macias, 2020). According to the US Administration for Families, Office of Planning, Research and Evaluation, screening should start early and be repeated through early childhood in order to be effective (Moodie et al., 2014). Developmental screening does not provide a diagnosis, but it identifies the areas where a child's development differs from the usual regular development. If a child misses any major screening milestone, it may result in late recognition, increasing anxiety, and depriving the child and family of early intervention benefits (Lipkin & Macias, 2020).

Over the past few decades, pediatricians have made significant progress in meeting the goal of early identification and treatment of developmental and behavioral disorders. The American Academy of Pediatrics (AAP) recommends that all children should receive periodic developmental screening using standardized tests, with general developmental screening recommended at the 9-, 18-, and 30-month visits. Screening for behavioral and emotional problems is recommended at the same time points, and screening for ASD is recommended at the 18- and 24-month visits. Children with ASD may experience sleep, eating, and behavioral challenges, which can be managed through appropriate referrals and connections to peer support organizations by pediatric health care professionals. Additionally, if a child misses any visit at 9-, 18-, or 30 months, a developmental screen should be administered at the next opportunity (AAP, 2023). In summary, early identification and intervention for developmental disorders are vital to the well-being of children, especially for vulnerable populations who are at high risk. Children who are screened with developmental disorders are recognized with special healthcare needs and should receive chronic condition management in the pediatric medical home (Hyman et al., 2020).

According to a recent National Health Interview Survey (NHIS) report, the prevalence and trends of developmental disabilities among children in the US increased by 9.5% between 2009-2017. One of the most significant reasons behind this observed increase is related to improvements in developmental screening and access to diagnostic and treatment services (Durkin, 2019). Therefore, an increase in the prevalence and trends of developmental disabilities is not necessarily a negative sign. These results are at least partly an indication that children are being screened and identified more than ever so that these disorders can be diagnosed. Therefore, it is hypothesized that,

Hypothesis 1.1b: *With the increase of the rates of neurodevelopmental screening, the incidence of neurodevelopmental diagnosis will also increase for children treated with the MAiN program and with standard of NAS care.*

2.5.4 Early intervention programs and neurodevelopmental screening and diagnosis

Infants with prenatal opioid exposure often qualify for early intervention treatment programs (Peacock-Chambers et al., 2019). One of the aims of early intervention programs such as MAiN is to educate mothers with opioid disorders about the well-being of their children. According to Carly Draddy, MD, a pediatric Hospitalist, MAiN encourages moms to take care of the baby themselves and start bonding immediately with the infant. It educates, supports, and provides resources to opioid-dependent mothers to practice positive parenting and minimize the risk of health problems for their babies (MAiN, 2022). As development screenings are done at well-child visits, educating parents about the importance of these screenings at the hospital can encourage them to meet the required well-child visits for their children and eventually lead them toward more neurodevelopmental screening. In association with this assumption, this study hypothesized that,

Hypothesis 1.2a: *Children with NAS treated with the MAiN program will be observed with higher rates of having neurodevelopmental screening than children treated with standard of care.*

Evidence shows that early intervention programs and developmental care can potentially be effective for infants' short-term neurodevelopmental outcomes (Blauw-Hospers & Hadders-Algra, 2005; Pa, 1992). Intervention programs like MAiN are available for infants with substance use exposure and who may also be at high risk of neurodevelopmental disorders (Summey et al., 2018). According to a systematic review and meta-analysis by Orton et al. (2009), early intervention programs are significantly effective for a child's cognitive development from birth through preschool age(s) (2-3 years). They also have a minor positive effect on children's motor development (Orton et al., 2009). Intervention programs promote child involvement through positive experiences, such as exposure to language, activity engagement, and environmental stimulation, which can play a vital role in shaping the cognitive development of children (Otsimo Editorial Team, 2023). Therefore, it can be assumed that children diagnosed with NAS who participated in early intervention or comprehensive treatment models might be at a lower risk of having neurodevelopmental disorders than children treated with standard of care. In should be mentioned that, screening plays a vital role here in diagnoses of neurodevelopmental disorders. In relation to Hypothesis 1.2a, we can make the assumption that children enrolled in the MAiN program undergo more frequent screenings, resulting in improved neurodevelopmental outcomes compared to children receiving standard care. Therefore, the final hypothesis of this study is,

Hypothesis 1.2b: *Children with NAS treated with the MAiN program will be observed with a lower risk of neurodevelopmental diagnosis than children treated with standard of care.*

2.6 Methodology

2.6.1 Data Source

This is a retrospective cohort study that compares NAS diagnosed infants treated with the MAiN model of care to NAS infants treated with standard of care in South Carolina. MAiN infants were identified retrospectively from billing records collected from the SC Office of Revenue and Fiscal Affairs (SCRFA). The records contained SC Medicaid data for NAS-diagnosed infants during the birth hospitalization who were born between 2006-2014. Medicaid data include demographic, medical visits and hospital admission, service date and charge, diagnosis and procedure codes for the service received (both in inpatient and outpatient settings), and outpatient prescriptions filled with beneficiaries' information. The study hospital where MAiN infants were treated is a large, regional perinatal referral center with 710 beds with an average annual volume of 5,221 births from 2006 to 2014 (Dickes et al., 2017). This hospital is considered a public and not-for-profit, academic healthcare delivery system in SC (Hudson et al., 2016). An exemption was approved by the Clemson University Institutional Review Board (IRB) prior to the study.

2.6.2 Inclusion and Exclusion Criteria

Live birth from 2006-2014 in SC was identified using *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes V30.00 to V39.01. Infants with NAS were identified by ICD-9-CM code 779.5 (drug withdrawal syndrome in newborn), and 760.72 (narcotics affecting fetus or newborn via placenta or breast milk) in one of the 21 discharge diagnosis fields. The exposed study group includes children with NAS treated by the MAiN model of care. The comparison group was selected from the statewide databases using the aforementioned ICD-9-CM codes and by the MAiN eligibility criteria.

Exposed group (*n*= 110 at the beginning of the study): The number of MAiN infants using the defined eligibility criteria, determined by the frequencies of infants with NAS born between January 2006 – December 2014.

Comparison group *(n* = 356 at the beginning of the study): South Carolina infants diagnosed with NAS, who were potentially eligible for MAiN but received standard of care over the same study period.

According to previous studies, MAiN model eligibility criteria includes infants ≥ 35 weeks gestational age and born to a mother diagnosed with opioid dependence during the pregnancy

(Dickes et al., 2017). Opioid-dependent mothers were identified using ICD-9-CM codes 304.00, 304.01, 304.02, 304.03 and then linked to infants diagnosed with NAS. The exclusion criteria for this study for both groups were infants with the following abnormal condition: (1) assisted ventilation (6 hours), (2) surfactant replacement therapy, (3) and/or seizure. Infants with these conditions were excluded because treatment in a Mother/Baby Unit would not be feasible due to these complications. Infants that meet the inclusion criteria but are treated in neonatal intensive care units (NICUs) were included in this study because infants treated in the Mother/Baby Unit with the MAiN program are likely to be treated in NICUs at other hospitals around that state. (Summey et al., 2018). Previous comparative studies reported that 82% of mothers of MAiN infants received methadone, and 18% received buprenorphine (Hudson et al., 2016). RFA billing records did not include information regarding medication intake for the comparison group.

2.6.3 Demographic and Clinical Characteristics

Demographic information of opioid-dependent mothers and NAS infants included child's sex, child's gestational age, mother's age, race, and education level obtained from state birth certificate data. Clinical information of mothers and infants contained child's birth weight, mother's infection during pregnancy, the Kotelchuck Prenatal Care Index score, tobacco use during and prior to pregnancy, and if the mother was a WIC recipient. Data were collected and generated from the RFA inpatient and outpatient data. Infection during pregnancy was considered having any of the following conditions: gonorrhea, syphilis, herpes, and/or chlamydia. The Kotelchuck Adequacy of Prenatal Care Utilization Index is a measure used to classify prenatal care adequacy (Kotelchuck, 1994), which considers the timing of prenatal care initiation and services received, which is then combined into a single index score.

2.6.4 Outcome measures

The study outcome measures include neurodevelopmental screenings and diagnosis from birth through age 4.5. This study focused on the following five neurodevelopmental disorders: autistic disorder, attention deficit/hyperactivity disorder (ADHD), impairments in vision or hearing, developmental delay, and intellectual disability or mental retardation. The two outcome variables, *neurodevelopmental screening* and *diagnosis* were created by combining these five disorders. In other words, children with NAS who were screened and/or diagnosed with any of these five neurodevelopmental disorders were identified and explicitly labeled into these two respective outcome variables. Neurodevelopmental diagnosis was identified using ICD-9-CM and ICD-10-CM codes, and neurodevelopmental screening was identified using the Current Procedural Terminology (CPT) codes and Healthcare Common Procedure Coding System (HCPCS) (Appendix B). Unfortunately, dates are restricted in SC Medicaid claims data; therefore, it was not possible to calculate the exact age of the participants at each time of the diagnosis and procedure services. Instead, the month when the diagnosis or procedure occurred past the birth month was used as a proxy for age. The approximated years of life were counted as 0-11 months of age as the first year, 12-23 months as the second year, 24-35 months as the third year, 36-47 months as the fourth year, and 48-54 months as the four and half years.

2.6.5 Statistical Analysis

Descriptive analysis of the baseline covariates was demonstrated as mean (standard deviation), median (interquartile range [IQR]), or percentage. To identify the demographic and clinical differences between exposure and comparison group, a *t*-test was used for continuous normally distributed variables, two-sample Wilcoxon rank-sum test was used for continuous skewed variables, and the χ^2 test was used for categorical variables ($\alpha = 0.05$). Frequencies and percentages of neurodevelopmental diagnosis and screenings were calculated for the two groups during the first 4.5 years of life for the primary analyses. The Cox Proportional Hazard Model (PH) of survival analysis was applied to identify how often neurodevelopmental diagnosis and screenings happen in the exposure group compared to the comparison group over time. The results of the PH models were reported as hazard ratios (HR). Additionally, 95% confidence intervals (CIs) were reported for all estimates. The PH models were adjusted for child's sex, mother's age, and mother's race to determine if these variables were potential confounders of these associations. Analysis of outcomes was performed using SAS 9.4 (SAS institute Inc., Cary, NC) and JMP Pro 16 (JMP®, Version <x>. SAS Institute Inc., Cary, NC). Kaplan-Meier survival curves were also developed to compare survival (i.e., smaller risk of outcome) in both groups regarding neurodevelopmental diagnosis and screening and to provide a visual tool to evaluate the association between exposure and the risk of outcome.

2.7 Result

2.7.1 Demographic and Clinical Characteristics

From 2006-2014, 164 infants with NAS were eligible for the MAiN program. Among them, state records were available for 110 infants. Live births between January 2006 - June 2014 identified 536,020 infants, and with ICD-9-CM codes for NAS resulted in specifying 2,496 infants. After matching opioid-dependent mothers with NAS infants and applying all other MAiN eligibility criteria, 356 infants among them were identified as the comparison group (standard of care NAS infants) who were born in other state hospitals during the same timeline. Figure 2 shows the cohort selection flow chart of identifying the analytic sample of this study containing infants with NAS treated with the MAiN model and with standard of care.

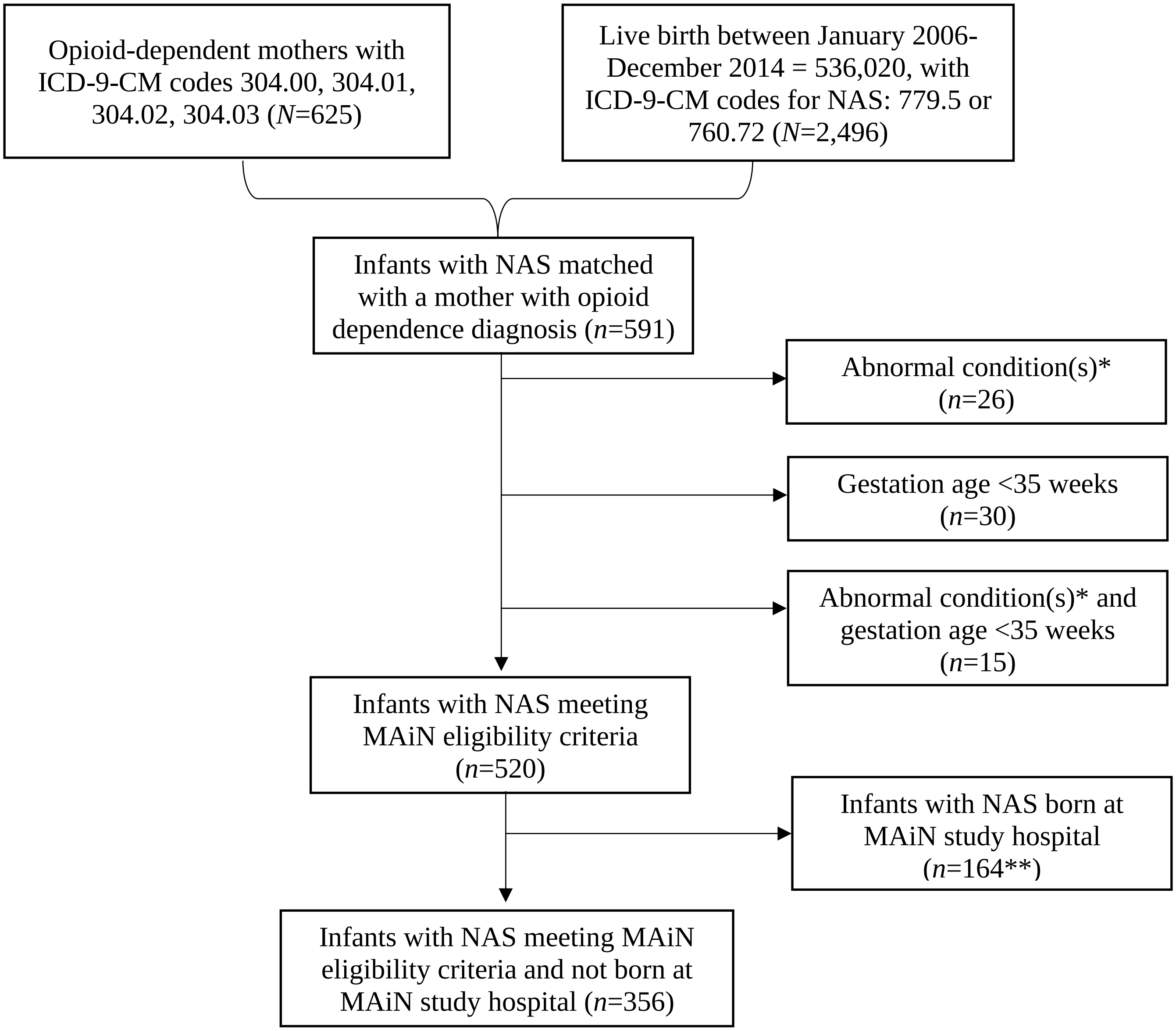

Figure 2: Selection Criteria Based on Managing Abstinence in Newborns (MAiN) Eligibility for Infants with NAS in South Carolina.

Source: *Summey, 2018*

**Abnormal conditions: Assister ventilation (6 hours), Surfactant Replacement Therapy, and/or Seizure*

***State data was available for 110 of the 164 infants with NAS treated with the MAiN program.*

Table 2 demonstrates the baseline covariates, including demographic and clinical characteristics of infants with NAS and their mothers. No difference was found between the MAiN infants and standard of care infants in terms of infant's sex (χ2 [df = 1] = 0.51; p = 0.48), race (χ2 [df = 2] = 0.51; p = 0.29), and weight at birth (t [df = 464] = 0.13; p = 0.90). There was a significant difference between the gestational age of MAiN infants (38.6 (1.6)) and standard of care infants (38.2 (1.6)) (t [df = 463] = 2.54; p = 0.01). Regarding the demographic and clinical characteristics of the mothers, no difference was found in terms of mothers' age (t [df = 464] = −0.51; p = 0.61), educational qualification (χ2 [df = 3] = 6.76; p = 0.08), Kotelchuck Prenatal Care Index (χ2 [df = 3] = 7.82; p = 0.05), and Women, Infants, and Children (WIC) recipient status (χ2 [df = 2] = 4.65; p = 0.10). Significant differences were found regarding infections during pregnancy (χ2 [df = 1] = 11.11; p < 0.001), tobacco use during pregnancy (χ2 [df = 1] = 7.28; p = 0.007), and tobacco use prior to pregnancy (χ2 [df = 1] = 10.76; p = 0.001) where mothers of infants with MAiN had higher rates compared to mothers of standard of care infants with NAS.

Table 2: Demographic and clinical characteristics of children with NAS treated with the MAiN model and with standard of care and their mothers

Variables	**MAiN (*N*=110)**	**Standard of care (*N*=356)**	**p-value**
Sex of the baby *(n, %)*			0.48
• Female	54 (49.1)	161 (45.2)	
• Male	54 (50.94)	183 (53.67)	
Race *(n, %)*			0.29
• White	103 (93.6)	333 (93.5)	
• Black	3 (2.7)	20 (5.6)	
• Hispanic	1 (0.9)	2 (0.6)	
• Other	3 (2.7)	1 (0.3)	
Gestational age, *(mean, SD)*	38.6 (1.6)	38.2 (1.6)	0.001
Weight at birth (grams) *(mean, SD)*	2,953.7 (464.7)	2,946.6 (503.4)	0.90
Mother's age *(mean, SD)*	27.6 (5.1)	27.9 (5.0)	0.61
Mother's education *(n, %)*			0.08
• Less than high school graduate	29 (26)	92 (25.8)	
• High school graduate	38 (35)	34.6 (123)	
• Some college credit or degree	40 (36)	106 (29.5)	
• Bachelor's degree or higher	3 (3)	35 (9.8)	
Tobacco use prior to pregnancy *(n, %)*	80 (75.47)	215 (60.4)	0.001
Tobacco use during pregnancy *(n, %)*	82 (74.5)	215 (60.4)	0.001
Infection during pregnancy *(n, %)*	18 (16.4)	22 (6.2)	<0.001
WIC recipient *(n, %)*	71 (64.5)	238 (66.9)	0.10

Source: Summey, 2018

2.7.2 Incidences of neurodevelopmental screening and diagnosis

Tables 3-5 that include the total frequencies and percentages of neurodevelopmental screening in both groups and also the cases of these screening by year in each group. The total percentage of neurodevelopmental screening in the MAiN group was 57.7% and in the standard of care group was 56.2% from birth to age 4.5. Both groups had the highest percentages of neurodevelopmental screening in year 4 (month 48-54) (MAiN = 30.6%, standard of care = 19.9%). Children treated with the MAiN model had approximately 11% higher rates of neurodevelopmental screening in year 4 (month 48-54) than children treated with standard of care, which can result in the higher incidences of neurodevelopmental diagnosis in the MAiN group than the standard of care group between the same timeline. There were significant differences in the increase of screening in at least one year from birth-4.5 years for autistic disorder, developmental delay, and intellectual disability and mental retardation together for the MAiN group ($p<0.05$), and in the screening rates of impairment in vision or hearing for the standard of care group ($p<0.05$).

Table 3: Frequencies and percentages of Neurodevelopmental screening in infants with NAS treated with the MAiN model and with standard of care.

Neurodevelopmental Screening[1] (Birth – 4.5 years)	**Total number of screening**	**MAiN N = 59**	**State N = 301**	**p-value**
Autistic disorder + developmental delay + intellectual disability or mental retardation (%, n)	34.4 (124)	37.2 (22)	33.8 (102)	0.61
ADHD (%, n)	5.5 (20)	6.7 (4)	5.3 (16)	0.65
Impairment in vision or hearing (%, n)	16.3 (59)	13.5 (8)	16.9 (51)	0.52

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[1] One of the significant limitations of screening/procedure codes is their overlapping. For example, autistic disorder, developmental delay, and intellectual disability or mental retardation fall under the same screening codes. There are ample areas of research focusing on neurodevelopmental diagnosis rather than neurodevelopmental screening, which can partly result from this limitation. Additionally, the Medicaid datasets used in this research did not document all the screening codes. Table 6 shows the total frequency of ADHD is 23 (cumulative for both groups). However, the total screening frequency of ADHD is 20. It is unacceptable that the incidence of a disease will be higher than the screening frequency for the same disease within an identical sample. Therefore, better and complete documentation of the screening codes is needed for future research.

Table 4: Frequencies and percentages of Neurodevelopmental screening in infants with NAS treated with the MAiN model *(N*=59*)* by year.

Neurodevelopmental Screening	Year 0 (Month 0-11)	Year 1 (Month 12-23)	Year 2 (Month 24-35)	Year 3 (Month 36-47)	Year 4 (Month 48-54)	Total	p-value
Autistic disorder + developmental delay + intellectual disability or mental retardation (%, n)	3.3 (2)	1.6 (1)	5.8 (3)	8.4 (5)	18.6 (11)	37.2 (22)	0.02*
ADHD (%, n)	1.6 (1)	0 (0)	0 (0)	3.3 (2)	1.6 (1)	6.7 (4)	0.09
Impairment in vision or hearing (%, n)	1.6 (1)	1.6 (1)	0 (0)	0 (0)	10.1 (6)	13.5 (8)	0.23

*p <0.05

Table 5: Frequencies and percentages of Neurodevelopmental screening in infants with NAS treated with standard of care *(N*=301*)* by year

Neurodevelopmental Screening	Year 0 (Month 0-11)	Year 1 (Month 12-23)	Year 2 (Month 24-35)	Year 3 (Month 36-47)	Year 4 (Month 48-54)	Total	p-value
Autistic disorder + developmental delay + intellectual disability or mental retardation (%, n)	5.9 (18)	5.3 (16)	2.9 (9)	8.3 (25)	11.2 (34)	33.8 (102)	0.32
ADHD (%, n)	0.3 (1)	0.3 (1)	0.6 (2)	1.6 (5)	2.3 (7)	5.3 (16)	0.28
Impairment in vision or hearing (%, n)	0.3 (1)	3.3 (10)	2.6 (8)	4.3 (13)	6.3 (19)	16.9 (51)	0.007*

*p <0.05

Figure 3 demonstrates the increase of neurodevelopmental screening in both groups by year.

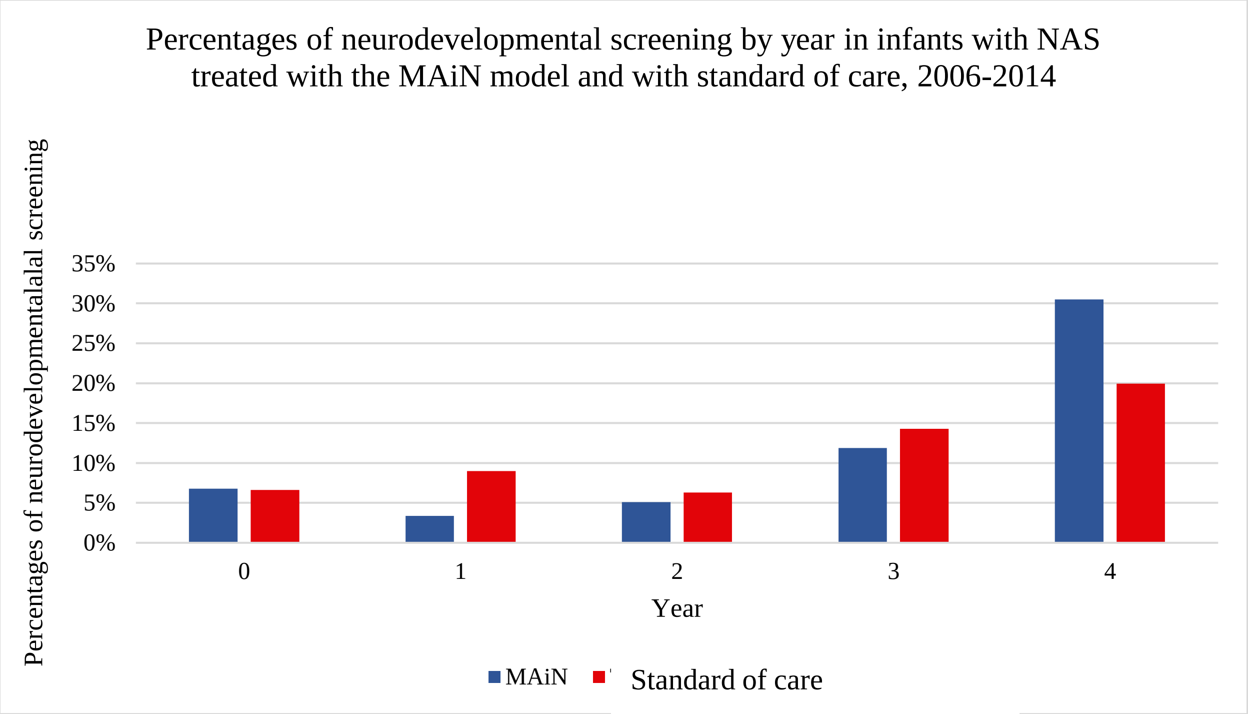

Figure 3: Percentages of neurodevelopmental screening by year in infants with NAS treated with the MAiN model and with standard of care.

According to hypothesis 1.1a, the incidence of neurodevelopmental diagnosis will increase in the later years for children with NAS treated with the MAiN model and with standard of care. Table 6 consist of the frequencies and percentages of neurodevelopmental from birth to 4.5 years in children treated with the MAiN model and with standard of care.

Table 6: Frequencies and percentages of Neurodevelopmental diagnosis in children with NAS treated with the MAiN model and with standard of care, born between 2006-2014.

Neurodevelopmental Disorders (Birth – 4.5 years)	**Number of diagnosis (%, n)**	**MAiN N=59**[2]	**Standard of care N=301**[3]	**p-value**
Autistic disorder (%, n)	1.3 (5)	0.0 (0)	1.6 (5)	0.31
ADHD (%, n)	6.3 (23)	5.0 (3)	6.6 (20)	0.65
Impairment in vision or hearing (%, n)	4.1 (15)	5.0 (3)	3.9 (12)	0.69
Developmental delay (%, n)	20.5 (74)	20.3 (12)	20.5 (62)	0.96
Intellectual disability or mental retardation (%, n)	6.1(22)	3.3 (2)	6.6 (20)	0.33

The total number of incidences of neurodevelopmental diagnosis in both groups was 139 from birth to 4.5 years. Among these, the total number of incidences in children treated with the MAiN model was 20 (33.8%) and with standard of care was 119 (39.5%). Regarding percentages, children treated with the MAiN model had 6% fewer incidences of neurodevelopmental diagnosis than those treated with standard of care from birth to 4.5 years. This analysis was based on five neurodevelopmental disorders, and children treated with the MAiN model had fewer incidences in four out of those five neurodevelopmental disorders than the children treated with standard of care, except for impairment in vision and hearing (Table 6).

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[2] The baseline covariates table (Table 2) was created using a dataset containing demographic and clinical information for children treated with the MAiN model and with standard of care from birth to 6 months. To conduct this study, the MAiN team requested an additional 4 years dataset for the sample born during the same timeframe. Unfortunately, the additional 4 years dataset was incomplete and had many missing IDs. After applying all the MAiN eligibility criteria to the new dataset, information was available for 59 children with NAS treated with the MAiN model who were born between 2006-2014.

[3] The additional 4 years dataset had 1,861 infants with NAS born in SC excluding the study hospital. From them, 301 children with NAS treated with standard of care met the MAiN eligibility criteria.

Table 7 and 8 contains the frequencies of neurodevelopmental diagnosis by year in infants with NAS treated with the MAiN model and with standard of care to show the increase of these incidences in both groups. There were significant differences in the increase of two neurodevelopmental diagnosis in at least one year from birth-4.5 years, ADHD and developmental delay, for the standard of care group ($p<0.05$).

Table 7: Frequencies and percentages of Neurodevelopmental diagnosis in children with NAS treated with the MAiN model *(N*=59*)* by year.

Neurodevelopmental Disorders	Year 0 (Month 0-11)	Year 1 (Month 12-23)	Year 2 (Month 24-35)	Year 3 (Month 36-47)	Year 4 (Month 48-54)	Total	p-value
Autistic disorder (%, n)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	N/A
ADHD (%, n)	0 (0)	0 (0)	0 (0)	1.6 (1)	3.3 (2)	5.1 (3)	0.44
Impairment in vision or hearing (%, n)	0 (0)	0 (0)	0 (0)	0 (0)	5.1 (3)	5.1 (3)	0.32
Developmental delay (%, n)	0 (0)	1.6 (1)	5.1 (3)	1.6 (1)	11.8 (7)	20.3 (12)	0.11
Intellectual disability or mental retardation (%, n)	0 (0)	0 (0)	0 (0)	1.6 (1)	1.6 (1)	3.3 (2)	0.36

Table 8: Frequencies and percentages of neurodevelopmental diagnosis in children with NAS treated with standard of care *(N*=301*)* by year

Neurodevelopmental Disorders	Year 0 (Month 0-11)	Year 1 (Month 12-23)	Year 2 (Month 24-35)	Year 3 (Month 36-47)	Year 4 (Month 48-54)	Total	p-value
Autistic disorder (%, n)	0.3 (1)	0.6 (2)	0.3 (1)	0 (0)	0.3 (1)	1.6 (5)	0.52
ADHD (%, n)	0 (0)	0.9 (3)	0.3 (1)	1.9 (6)	3.3 (10)	6.6 (20)	0.04*
Impairment in vision or hearing (%, n)	0 (0)	1.3 (4)	0.6 (2)	0.3 (1)	1.6 (5)	3.9 (12)	0.15
Developmental delay (%, n)	1.9 (6)	3.3 (10)	1.3 (4)	5.6 (17)	8.3 (25)	20.5 (62)	0.01*
Intellectual disability or mental retardation (%, n)	0 (0)	0.9 (3)	0.6 (2)	1.9 (6)	2.9 (9)	6.6 (20)	0.11

*p <0.05

In most cases, the later years have more frequencies of neurodevelopmental diagnosis than the former years, which shows an increase in these incidences by year for both groups (hypothesis 1.1). To make this statement more evident, figure 4 demonstrates the percentages of neurodevelopmental diagnosis by year in infants with NAS treated with the MAiN model and with standard of care.

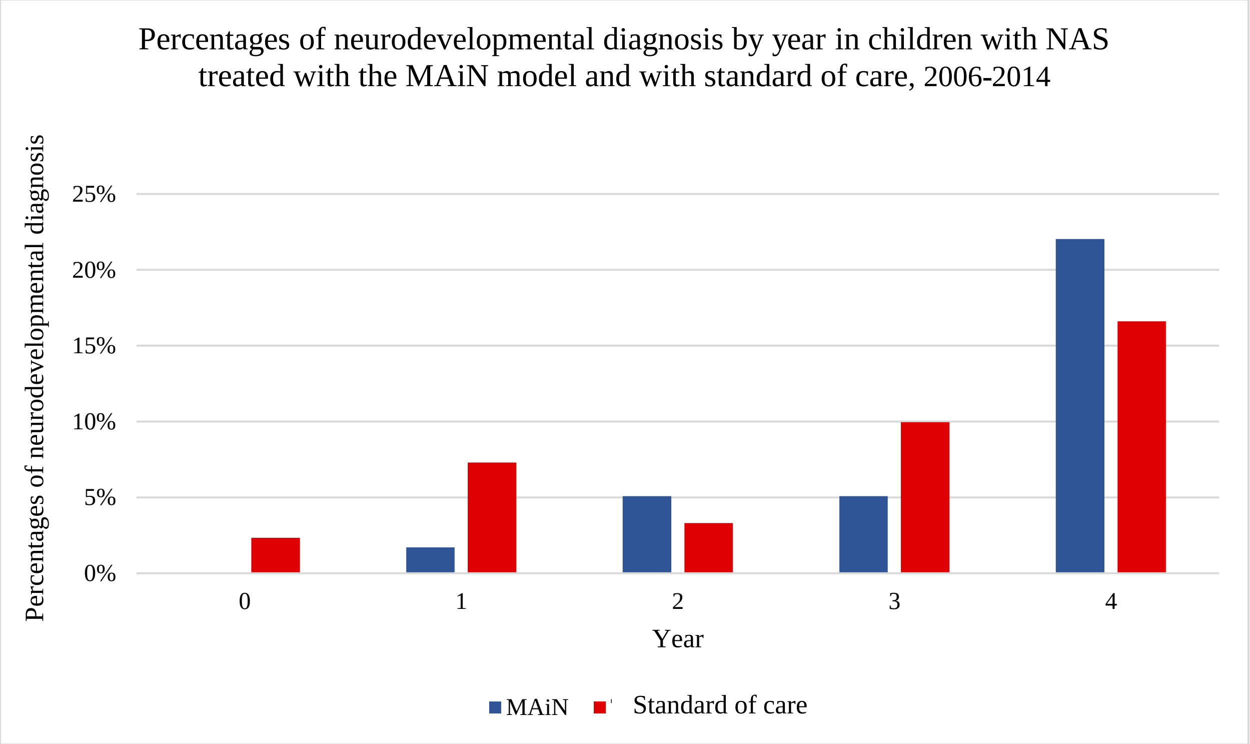

Figure 4: Percentages of neurodevelopmental diagnosis by year in children with NAS treated with the MAiN model and with standard of care

Figure 4 demonstrates the increase of neurodevelopmental diagnosis in both groups by year. The increase is not completely linear, however, year 4 (month 48-54) had the highest percentages of neurodevelopmental diagnosis in children treated with the MAiN model (22.0%), and with standard of care (12.9%) compared to years 0 – 3. This result signifies that children treated with the MAiN model had around 9% higher incidence of neurodevelopmental diagnosis than children treated with standard of care at year 4. However, as mentioned earlier, children treated with the MAiN model also had higher screening rates (30.5%) that children treated with standard of care (19.9%) at the same year.

2.7.3 Correlation between neurodevelopmental screening and diagnosis

According to hypothesis 1.1b, With the increase of the rates of neurodevelopmental screening, the incidence of neurodevelopmental diagnosis will also increase for children treated with the MAiN program and with standard of NAS care. A Spearman correlation test was applied to discover the strength of the linear association between the ordinal variables, neurodevelopmental screening and diagnosis, between these two groups. The MAiN and standard of care group together consisted of 360 children with NAS born between 2006-2014. The mean number of neurodevelopmental screenings was 0.56 (*SD* = 0.71), and the mean incidence of neurodevelopmental diagnosis among those children was 0.39 (*SD* = 0.75). The result of the Spearman correlation identified that the increase of neurodevelopmental diagnosis is significant in correlation to the increases of neurodevelopment screening (r (358) =0.26, $p < .0001$). Therefore, we can reject the null hypothesis 1.1b.

2.7.4 Survival Analysis: Kaplan-Meier Survival Curve and Cox Proportional Hazard (PH) Model

To demonstrate and compare the survival (outcome) of children with NAS belonging to MAiN model and standard of care, Kaplan-Meier survival curves were developed using SAS 9.4. Figure 5 shows a visual assessment of the association between these two groups and the probability of having neurodevelopmental screening from years birth – 4.5 years (0-54 months or 0-4 years for demonstration convenience). In the sample of 360 infants with NAS, 27 of the 59 children belonging to the MAiN model failed and 32 were censored, and 135 of the 301 children belonging to standard of care failed and 166 were censored. In Figure 5 The blue line (MAiN) appears to have a smaller drop in survival at each interval regarding neurodevelopmental screening compared to the red line (standard of care). Similarly, regarding neurodevelopmental diagnosis, the blue line for children belonging to the MAiN model again has a smaller drop in survival at each interval compared to the red line for children belonging to standard of care (Figure 6). In this sample, 17 of the 59 infants belonging to the MAiN model failed and 42 were censored. On the same note, 82 of the 301 infants belonging to standard of care failed and 219 were censored. The total percentage censored was 72.50%. The level of significance from the Log-rank test and Wilcoxon test was *p*=0.55 and *p*=0.39 for neurodevelopmental screening, and *p*=0.70 and *p*=0.43 for neurodevelopmental diagnosis, respectively.

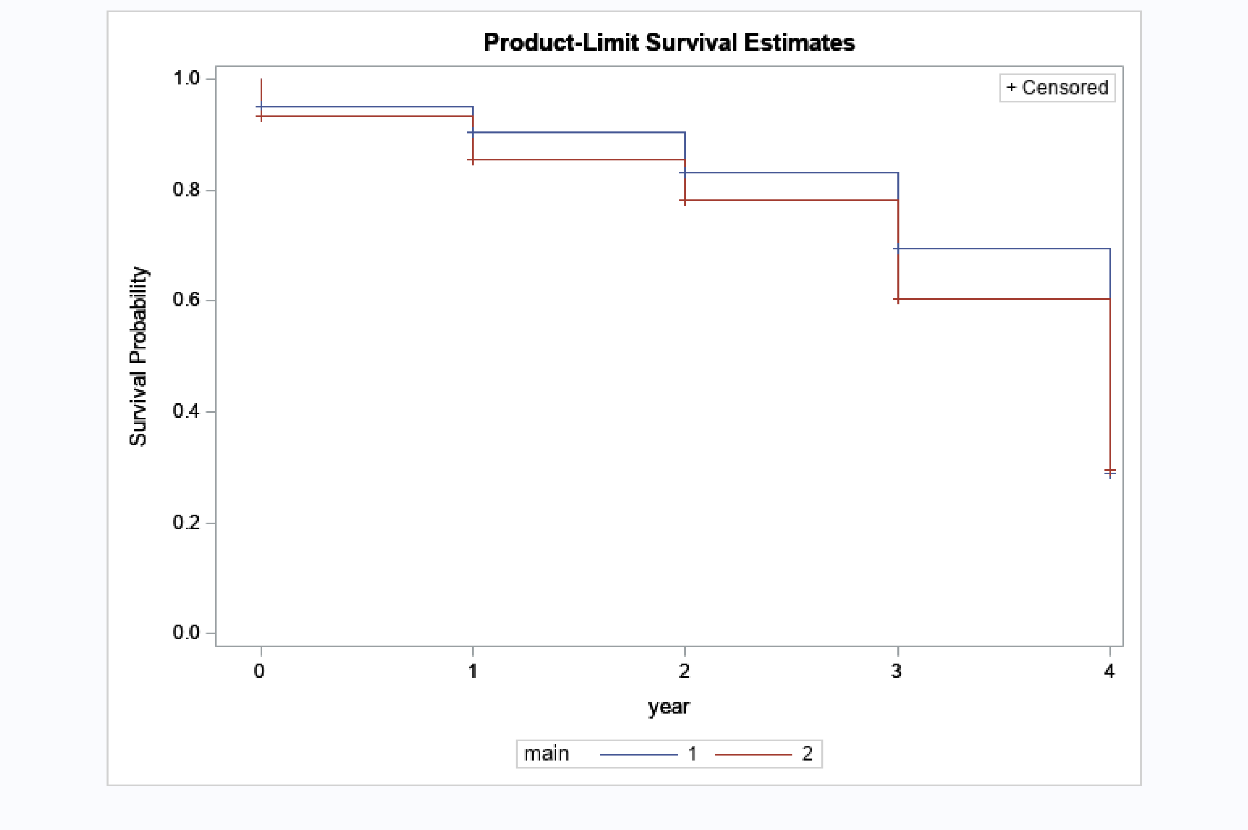

Figure 5: Kaplan-Meier survival estimate for children belonging to the MAiN model and standard of care regarding neurodevelopmental screening from years 0-4

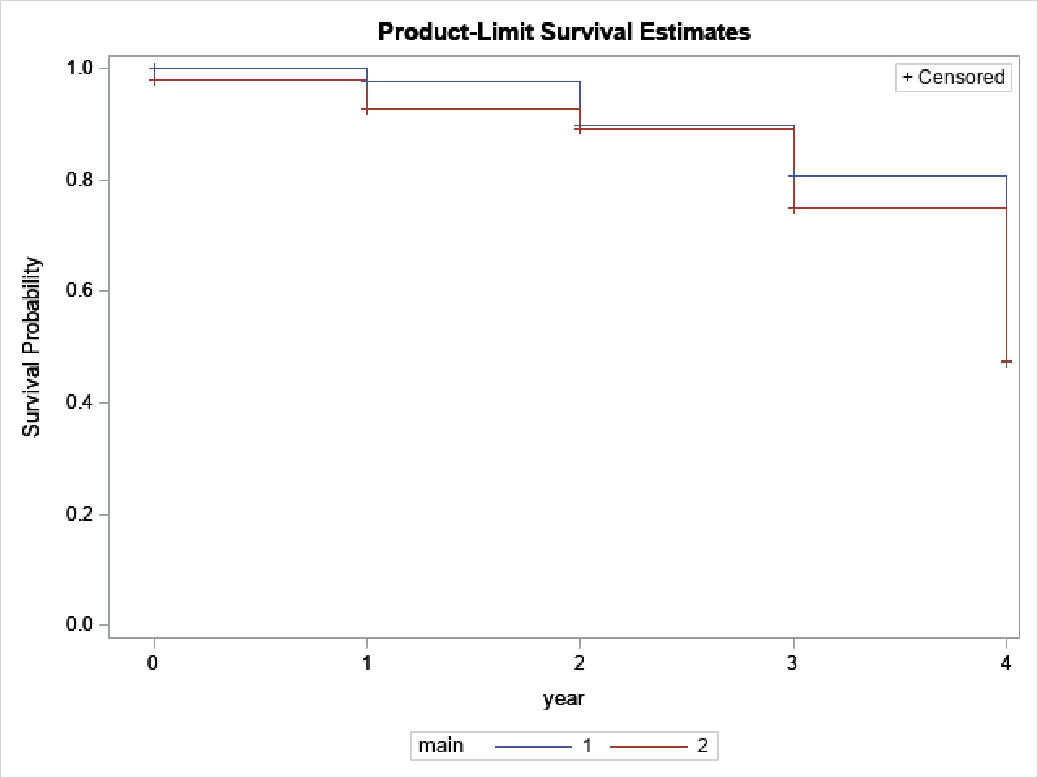

Figure 6: Kaplan-Meier survival estimate for children belonging to the MAiN model and standard of care regarding neurodevelopmental diagnosis from years 0-4

One of the main objectives of this research was to discover the potentiality of MAiN model regarding neurodevelopmental screening and diagnosis compared to standard of care. As a second step of the analysis, this study applied two Cox Proportional Hazard (PH) survival analysis models to identify how often neurodevelopmental screening and diagnosis occur in the MAiN group rather than in the standard of care group (hypotheses 1.2a and 1.2b). The results of the PH models were reported as hazard ratios (HR) and were adjusted for mother's age, race, and infant's sex. Table 9 includes the crude and adjusted hazard ratios of the PH models for neurodevelopmental screening and diagnosis for the MAiN and standard of care group.

Table 9: Results of Cox Proportional Hazard (PH) survival analysis models for neurodevelopmental screening and diagnosis (crude and adjusted)

Model	Hazard Ratio (HR)	95% HR Confidence Limits		p-value
Model 1: Neurodevelopmental screening	1.08	0.82	1.44	0.56
Model 2: Neurodevelopmental screening	1.09	0.82	1.44	0.54
Model 1: Neurodevelopmental diagnosis	0.82	0.59	1.13	0.23
Model 2: Neurodevelopmental diagnosis	0.81	0.59	1.13	0.22

Model 1 = Crude

Model 2 = Adjusted for mother's age, race, and infant's sex

The adjusted hazard ratio of neurodevelopmental screening is 1.09, which implies that children treated with the MAiN model of care had approximately a 9% higher probability of neurodevelopmental screening than children belonging to the traditional model of care. The adjusted hazard ratio of neurodevelopmental diagnosis is 0.81, which indicates on average, approximately a 19% lower risk of neurodevelopmental diagnosis on the experimental treatment group (MAiN) than the comparison group (standard of care). However, the *p*-value for the adjusted hazard ratios ($p = 0.54$ and $p = 0.22$ for neurodevelopmental screening and diagnosis, respectively), were not significant (Table 9).

2.8 Discussion

The recent state of NAS in the US is challenging, with the number of infants exposed to opioids in utero increasing by 333% over the past two decades (Czynski et al., 2020; Haight et al., 1999). According to Health Resources and Services Administration (HRSA), NAS was increased by 4.9 infants per 1,000 birth hospitalizations in South Carolina in 2017; however, infants with

NAS are being underreported in the hospital records of this state (Summey et al., 2018). Although research on neurodevelopmental disorders in infants with NAS is available, it is challenging to locate studies specific to South Carolina or this population. Additionally, due to the overlapping of procedure codes and the quality of billing data, there is an inadequacy of research focusing on neurodevelopmental screening, although administering brief and standardized screening tests are crucial for the early identification of neurodevelopmental disorders (Lipkin & Macias, 2020). One promising piece of evidence is that South Carolina has early treatment innovation programs like MAiN, and research is growing in this field to identify the potentiality of these programs for children with NAS regarding various medical, health care, social, and cost-saving outcomes (Dickes et al., 2017; Hudson et al., 2016; Summey et al., 2018). Along with the current research practices, investigating neurodevelopmental outcomes is also significant not only to confirm the additional advantages of these innovative programs but also to determine the need for their widespread adoption.

This research compared neurodevelopmental outcomes between children with NAS treated by an innovation program (MAiN) and traditional NAS care in SC from birth – 4.5 years. The results indicated that children who were treated with the MAiN model of care had a lower incidence of neurodevelopmental diagnosis and higher rates of neurodevelopmental screening compared to those who received standard of care. The analysis was based on five types of neurodevelopmental disorders, namely, autistic disorder, attention deficit/hyperactivity disorder (ADHD), developmental delay, intellectual disability or mental retardation, and impairments in vision or hearing. Statistically significant rates of screening were seen in the MAiN group regarding ASD, developmental delay, and intellectual disability and mental retardation together, and in the standard of care group regarding impairment in vision or hearing in at least one year from birth – 4.5 years. Furthermore, standard of care group had also seen significant increase of two neurodevelopmental disorders, ADHD and developmental delay, during the same timeline. None of the five neurodevelopmental disorders incidences were statistically significant for the MAiN group.

Children who received the MAiN model of care had a lower incidence of four out of those five neurodevelopmental disorders, except for impairments in vision and hearing, in terms of percentages. Children from both groups had the highest rates of neurodevelopmental diagnosis in year 4 (month 48-54) compared to the preceding three years. The percentage of children with neurodevelopmental disorders in the MAiN group was 22.0%, which was around 10% higher than the standard of care group (12.9%) during this period. However, it is important to note that the higher incidences of neurodevelopmental disorders in the MAiN group might be primarily due to the increased screening measures employed, which was approximately 11% higher than the standard of care group that eventually detected more cases of neurodevelopmental disorders in this group. The Kaplan Meier Survival Curve also demonstrated that children belonging to the MAiN group appear to have a smaller drop in survival at each interval regarding both neurodevelopmental screening and disorder compared to children from the standard of care group. Finally, Cox Proportional Hazard (PH) survival analysis models also indicated higher probability of neurodevelopmental screening and a lower risk of neurodevelopmental diagnosis in the MAiN group compared to the standard of care group.

Currently, there is inadequate evidence to establish a relationship between comprehensive treatment programs and differential neurodevelopmental outcomes in infants with NAS. The evidence available regarding optimal diagnosis and treatment strategies for NAS is primarily derived from small-scale studies focusing on intermediate outcomes such as the need for pharmacologic treatment or hospital length of stay (Wachman et al., 2018). Further research is necessary to assess the health and neurodevelopmental outcomes associated with innovative programs for NAS compared to standard of care. This study has the prospective to add a unique insight regarding the potentiality of early treatment innovation programs like MAiN. Additional research could help to identify targeted and coordinated interventions aimed at increasing the likelihood of neurodevelopmental screening and early identification of neurodevelopmental disorders in children with NAS. These interventions could also help facilitate enrollment in such programs that provide additional benefits to these children.

2.9 Limitations

This study has several limitations related to the quality of Medicaid data used, the availability of procedure codes, and the application of MAiN eligibility criteria. In South Carolina, it is at the discretion of individual physicians to provide treatment for infants with NAS. However, it is not guaranteed that infants identified by their ICD-9-CM code have received such treatment. As this study was conducted retrospectively using Medicaid data from state records, there are some limitations of the data. For instance, the comparison group of infants with NAS (standard of care group) identified as MAiN eligible was determined based on the availability of the ICD-9-CM code in the data, which relied on the accuracy of mothers being coded as opioid-dependent and may have been vulnerable to errors or omissions in terms of the outcomes (Summey et al., 2018).

Furthermore, the MAiN program is designed for infants with NAS who are at high risk for withdrawal due to exposure to long-acting opioids. However, the standard of care cohort includes all infants with NAS, who might have been affected by various medications or prescribed/illegal drugs used by the mother. Some infants may have been diagnosed with NAS due to withdrawal from drugs administered to them during an extended period of critical illness (Dickes et al., 2017).

Cases of NAS can also be linked to supervised opioid replacement therapy, which is a result of mothers only taking prescription drugs during pregnancy (Miller and Warren, 2013). Consequently, the original study population of this research consisted of approximately 25% of NAS–diagnosed infants who met the MAiN eligibility criteria during the study period. However, recent research may suggest that MAiN could have broader applications (Dickes et al. 2017).

Additionally, Medicaid data are primarily generated for billing, not research purposes. It limits the granularity of data and the breadth of questions researchers can draw from. The additional 4 years dataset used in this research had lots of missing IDs both for the children treated with MAiN and standard of care, which could not be recovered. It also did not have all the clinical and demographic variables for children and mothers, so the baseline covariate table presented in this study was created using a previous study. The procedure codes applied in this research for neurodevelopmental screening had overlapping and mismatched issues, and there was a lack of literature to fix these issues. This problem indicates that while children with NAS are underreported in SC, their diagnosis and screening information are also inadequately represented in the Medicaid data. The missing IDs for both groups made the sample sizes smaller, otherwise more accurate and significant results could have been achieved to ensure the differences regarding outcomes between the exposure and comparison groups. Moreover, the study used only birth-4.5-year follow-up data to estimate the cases of neurodevelopmental diagnosis, while the symptoms and behaviors of these disorders often change or evolve as a child grows older (USEPA, 2013). This might be one of the reasons why many researchers and statisticians opt for longer timeframes, typically ranging from 3 to 17 years, to compare or measure the same outcomes. Other limitations of this study include the exclusion of dates in the dataset that hinders the precise determination of children's age, the possibility of coding mistakes within claims data, and an absence of details regarding particular social or demographic traits that could improve the analysis.

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CHAPTER THREE: HOSPITAL READMISSION AND LENGTH OF STAY OF CHILDREN WITH NEONATAL ABSTINENCE SYNDROME (NAS) AND CHILDREN BORN LATE PRETERM: A RETROSPECTIVE COMPARISON

3.1 Abstract

Purpose: This study compares two healthcare utilization outcomes, hospital readmission and hospital length of stay (LOSD), from 0 - 3 years of age among South Carolina Medicaid-enrolled children with a history of Neonatal Abstinence Syndrome (NAS) and children born late preterm (gestation age 33-36 weeks).

Methods: This retrospective cohort study applied simple and multivariable logistic regression models to measure the odds of hospital readmission among two groups from 0 – 3 years of age. Additionally, adjusted and unadjusted negative binomial regression models were developed to examine the association between hospital readmission with hospital LOSD between 0 -3 years of age for the comparison groups.

Results: The sample included 1,054 children with NAS, and 16,048 children born late preterm who were born between 2006-2014. The likelihood of hospital readmission was higher for children with NAS compared to children born late preterm for all three intervals from 0-3 years of age (year 0-1: odds ratio [OR]: 1.33, 95% confidence interval [CI]: 1.12 to 1.58, p = 0.0004; year 2-3: OR: 1.64, 95% CI: 1.20 to 2.23, p = 0.0008; year 2-3: OR: 1.43, 95% CI: 1.01 to 2.03, p=0.02). Children with NAS also had a longer LOSD compared to children born late preterm during all three intervals from age 0-3 years (IRR = 1.71, 95% CI: 1.46 to 1.95, p <0.0001 for 0-1 year; IRR = 1.80, 95% CI: 1.50 to 2.09, p<0.0001 for 1-2 year; and IRR = 1.85, 95% CI: 1.57 to 2.13 for 2-3 year). Furthermore, compared to children born late preterm, children with NAS had more complicated/critical diagnoses for hospital readmission.

Conclusion: Children with NAS had higher likelihood of hospital readmission, longer hospital LOSD, and more complicated diagnoses for hospital readmission compared to children born late preterm. Introduce personalized screening and treatment regimens, practice safer discharge and improved inpatient care, and strengthen social support and child welfare systems can assist in reducing the risk of hospital readmission and hospital length of stay among children with NAS.

3.2 Introduction

Neonatal abstinence syndrome (NAS), resulting from opioid withdrawal, consists of indications and symptoms that affect the autonomic nervous system, gastrointestinal tract, and respiratory system, often requiring extended hospitalization and extensive pharmacological treatment (Finnegan et al., 1991; Wachman et al., 2011). The rates of NAS have increased both in the US and internationally due to the widespread usage of prescription and nonprescription opioids (Corr et al., 2021; Kocherlakota, 2014; Liu et al., 2019; Patrick et al., 2012), with rates in the US escalating from 4/1000 to 7.1/1000 newborn hospitalizations between 2010 and 2018 (Bhatt et al., 2021). The US spent approximately $573 million in 2016 to provide inpatient care for children with NAS (Strahan et al., 2019). Given the ongoing opioid crisis and the persistent increase in rates of NAS, it is crucial to comprehend the long-term healthcare utilization outcomes for children with NAS (Corr et al., 2021).

Between 2008 and 2017, approximately 25% of children with NAS had hospital readmission or ER visit within 90 days of discharge, with the rates being highest in 2012 (25%) and lowest in 2017 (20%) (Ali et al., 2021). Readmission may be occurring for several reasons: for example, infectious and parasitic diseases, neonatal digestive and feeding disorders, respiratory perinatal condition, neonatal cerebral disorders, etc. (Salt et al., 2023). Despite the increase in the number of children suffering from NAS and the healthcare utilization consumed by their treatment, little is known about these children' outcomes and diagnoses behind the utilizations after their initial hospitalization (Patrick et al., 2015).

A single-state investigation by Witt et al. (2017) analyzed hospital readmission in Washington state, and found that children with NAS had an increased risk of readmission during the first five years of life compared to unexposed children. Additionally, studies showed that children with NAS generally have extended hospital length of stay (LOSD) compared to those without NAS, especially during the first year of life (Diop et al., 2022; Lee et al., 2015; Wachman et al., 2011; Winkelman et al., 2018). However, only a handful have assessed the risk of hospital readmission and LOSD among children with NAS compared to other high-risk infant groups in the US (Patrick et al., 2015). For example, starting from the late 1990s, pediatricians directed their attention towards late preterm children (gestation age 33-36 weeks) as a population of high-risk children with adverse healthcare utilization outcomes (Escobar et al., 1999; Kellogg et al., 2011; Phillips et al., 2013). Late preterm children are also considered as high-risk of developing long-term morbidities such as, neurodevelopmental and behavioral disorders, obesity, hypertension, diabetes, and metabolic syndrome (Yoshida-Montezuma et al., 2022). Additionally, late preterm children have increased short-term and long-term hospital readmission rates compared to full term children, especially during the first year of life (Patrick et al., 2015).

The National Institute of Child Health and Human Development recommended replacing the term “near term” with “late preterm” in 2005, which acknowledges their vulnerability and distinguishes them by gestation age between 33 weeks and 0/7 days and 36 weeks and 6/7 days from full term children (gestation age ≥37 weeks) (Raju et al., 2006). The Centers for Disease Control and Prevention (CDC) reported that, in 2021, around 1 in every 10 children born in the US were affected by preterm birth, and this rate increased by 4% to 10.5% in the same year from 10.1% in 2020 (Centers for Disease Control and Prevention, 2022). The US faces an approximate 380,000 preterm births each year, resulting in substantial healthcare utilization costs and a significant burden in the economy (March of Dimes, 2023).

Subsequent hospitalizations and measures to mitigate them are well emphasized in the literature, such as research, interventions, and discharge guidelines for high-risk children (Engle et al., 2007; Phillips et al., 2013). Nevertheless, observational studies focusing on and comparing children with NAS and late preterm and still limited in identifying the general trend and differences in healthcare utilization in these populations. Additionally, existing literature also has a lack of policy direction to suggest a better use of healthcare services among these populations.

This dissertation paper aims to explore healthcare utilization outcomes among children with NAS and born late preterm in South Carolina, using Medicaid data from 2005-2015, with follow-up years from 0 – 3 years of age. Considering the reviewed literature and the need for assessment between the comparison groups, this research analyzes two healthcare utilization outcomes, hospital readmission, and hospital LOSD during this timeframe.

3.3 Previous studies and hypotheses

Several recent single-state research studies revealed that children with NAS have higher admission rates within the first 30 days to 5 years of their lives compared to unexposed controls (Corr et al., 2021; Diop et al., 2022; Liu et al., 2019; Patrick et al., 2015; Salt et al., 2023; Witt et al., 2017). Two notable studies in this area include the research conducted by Diop and colleagues as well as the study by Sant and colleagues. They compared hospital readmission among children with NAS and without NAS, born in Massachusetts during 2011–2017, and in Kentucky during 2016–2020, respectively. The former study indicated that children with NAS did not have significantly higher readmission rates compared to those without NAS within 2-42 days and between 43-182 days after discharge (Diop et al., 2022). Conversely, the second study revealed that children with NAS were 2.7 times higher odds of being readmitted to the hospital (Salt et al., 2023). Despite the differences in findings, another problem arises with the comparison groups utilized in the studies. The majority of control groups employed in these investigations consist of low-risk children who are either unexposed or have no complications at birth, which makes them disparate from children with NAS. In contrast, Patrick and colleagues (2015) conducted a study comparing hospital readmission rates of children with NAS, children born late preterm, and those born uncomplicated term. They discovered increased odds of hospital readmission within the first 30 days and 1-year of life among children with NAS and uncomplicated term children, but not in late preterm children. Interestingly, most of the studies that cited their work only reported the findings comparing children with NAS and uncomplicated term children, but not late preterm children, as the majority of the studies compared a high-risk group (NAS) to a low-risk group (uncomplicated term/unexposed children).

Along with the lack of homogeneity among the comparison groups, several studies that asserted to examine the long-term healthcare utilization of children with NAS only assessed outcomes within a period of 30 days to 1 year. A 2021 study investigated the use of healthcare services in children with NAS after their discharge from the hospital and explored the relationship between the severity of NAS and healthcare utilization through operationalizing pharmacologic treatment, length of hospitalization, and medical conditions (Shrestha et al., 2021). Their results showed that in 3,526 children with NAS (with a gestational age of 33 weeks or more), there was a significant association between the severity of NAS and an increase in the composite one-year utilization. Additionally, in a subset of full-term children (3,008 with NAS and 88,452 uncomplicated births), NAS diagnosis was linked to higher odds of rehospitalization within 30 days and 1-year after discharge. Several other studies used similar comparison groups, outcomes, and timelines and found consistent results.

A 2012 study showed that Medicaid was the primary payer for 80% of hospital charges associated with NAS (Patrick et al., 2012), which was increased to 83% in 2016 (Strahan et al., 2020). Ko and his associates (2016) argued that, given that percentage, it is valuable to analyze the healthcare utilization of children based on their maternal opioid exposure and NAS diagnosis. Such analysis could assist in planning and providing proper healthcare services for affected children who are publicly insured. The studies by Liu et al. (2019) and Corr Xing and Liu (2021) used longer follow-ups periods (8 years and 11 years after birth) to describe and compare healthcare utilization outcomes among privately and publicly insured children with NAS to those without NAS. Liu and his associates (2019) found that children with NAS and those who were privately insured had significantly more inpatient hospitalizations, outpatient encounters, and emergency department visits per year from age 1 to 8 than those without NAS. Their results also showed that the adjusted mean annualized costs for all healthcare services were almost twice as high for children with NAS and over four times as high for inpatient hospitalizations.

Additionally, Corr Xing and Liu (2021) also discovered that children with NAS who were insured by Medicaid had greater healthcare utilization in their early years compared to children without NAS, including higher rates of hospital admissions, for up to three years after birth. Interestingly, the differences resolved by the fourth year, possibly due to developmental health management changes or the complexity of tracking diagnoses in the healthcare database. This research further highlights the importance of analyzing the healthcare utilization of Medicaid-insured children with NAS during early childhood, i.e., the first three years of life. These studies instigate the present research to explore healthcare utilization outcomes among Medicaid-enrolled children and assume the odds of these outcomes will be higher in children with NAS compared to late preterm, which leads to the first hypothesis of this study:

Hypothesis 1 (H1): *Children with NAS will have higher odds of hospital readmission than children born late preterm from 0 – 3 years of age.*

Patrick and his associates (2015) also discovered that children with NAS had significantly longer hospital stays from birth hospitalization, with a median of 15 days, in contrast to late preterm children, who had an average stay of 5 days, and uncomplicated term children, who stayed in hospital after birth for only 2 days. Several other studies also analyzed similar outcomes, i.e., Wachman and his colleagues found the mean hospital length of stay (LOSD) from birth hospitalization in 22.9 days (Wachman et al., 2011), and Summey and her associated found the median LOSD for children with NAS is 9 days from birth hospitalization (Summey et al., 2018). Additionally, the former study identified that maternal use of prescribed methadone and benzodiazepines increased the LOSD for children with NAS by 6 days when compared to methadone alone. However, none of the studies reported the mean and median LOSD from hospital readmission among children with NAS except birth hospitalization. Given the circumstances, the second hypothesis of this study is,

Hypothesis 2 (H2): *Children with NAS will have higher mean hospital length of stay from hospital readmission than children born late preterm from 0 – 3 years of age.*

Ko and his associate's retrospective cohort study of Medicaid-enrolled mothers and term children in Oregon found that almost half of the children with NAS, regardless of maternal opioid exposure, were hospitalized within 4 weeks to 1-year of birth. This rate was higher compared to non-opioid exposed children without NAS (Ko et al., 2016). In their study, children with NAS were more likely to experience feeding issues/dehydration, which are common reasons for hospitalization among all children and considered preventable (Young et al., 2013). Salt and her colleagues also identified the most prevalent diagnoses of hospital readmission among children with NAS: newborns affected by maternal conditions or complications of labor/delivery, other specified and unspecified perinatal conditions, and neonatal digestive and feeding disorders (Salt et al., 2023). These results indicated much more complicated and possibly non-preventable diagnoses of hospital readmission for children with NAS. Some studies assumed that the observed early differences in healthcare utilization might be occurring for several reasons, for example, maternal opioid use can result in placental insufficiency, fetal growth restriction, placental abruption, and preterm labor; each of which can be associated with acute and chronic adverse health can utilization for newborns (Hirai et al., 2021; McQueen & Murphy-Oikonen, 2016; Zedler et al., 2016). Unfortunately, most of these studies only discussed these assumptions along with reporting increased odds of readmission but did not analyze the specificity and severity of diagnoses behind them, making it crucial to identify the reasons for hospital readmission. Considering this issue, the third hypothesis of this study is:

Hypothesis 3 (H3): *Children with NAS will be observed with more severe diagnoses for hospital readmission and hospital length of stay than children born late preterm from 0 – 3 years of age.*

3.4 Methodology

3.4.1 Data source

This retrospective cohort study identified children with NAS and born late preterm retrospectively using billing data from the SC Office of Revenue and Fiscal Affairs (SCRFA). The RFA data contained Medicaid data for all children born in SC between 2005-2015. Later, the data were specified for NAS-diagnosed children and children born late preterm during the birth hospitalization. The data used from Medicaid included information on demographics, medical visits, hospital admissions and readmission, hospital LOSD service dates and charges, diagnosis and procedure codes for services received, and outpatient prescriptions filled with beneficiaries' information from 0 – 3 years of age. The study was deemed exempt by the Clemson University Institutional Review Board (IRB) before initiation.

3.4.2 Identification of Cohort

To conduct a significant comparison of healthcare utilization, this study formed a cohort consisting of two high-risk infant groups: children diagnosed with NAS and children born late preterm. Children with NAS were identified using the *International Classification of Diseases, Ninth and Tenth Revision, Clinical Modification* (ICD-9-CM) and (ICD-10-CM) code 779.5 (drug withdrawal syndrome in newborn), and P96.1 (neonatal withdrawal symptoms from maternal use of drugs of addiction), respectively. In addition, children born late preterm were identified using ICD-9-CM codes 765.27 (33-34 completed weeks of gestation), and 765.28 (35-36 completed weeks of gestation), and ICD-10-CM codes P07.36 (Preterm newborn, gestational age 33 completed weeks), P07.37 (Preterm newborn, gestational age 34 completed weeks), P07.38 (Preterm newborn, gestational age 35 completed weeks), and P07.39 (Preterm newborn, gestational age 36 completed weeks). Live births were identified by using ICD-9-CM codes V30.x-V38.x and ICD-10-CM codes Z38.x at the beginning of the cohort selection.

Exposed group (*n*= 1,054): Children with a history of NAS classified by the corresponding ICD-9-CM and ICD-10-CM codes born between 2005-2015 in SC

Comparison group (n=16,048): Children born late preterm (gestational age 33-36 weeks) classified by the corresponding ICD-9-CM and ICD-10-CM codes between 2005-2015 in SC

For the exclusion criteria, children with presumed iatrogenic withdrawal were excluded from the study since it may result in a prolonged NICU stay due to the presence of comorbidities unrelated to withdrawal symptoms from opioids (Brown et al., 2018; Patrick et al., 2012; Stabler et al., 2017). The iatrogenic withdrawal was identified through a well-cited algorithm, which has been used in several previous studies that focused on Medicaid-insured children with a history of NAS that also examined healthcare utilization in this same population (Hirai et al., 2021; Patrick et al., 2012; Bunn, Ouyang, and Slavova, 2016). The algorithm for identifying children with presumed iatrogenic withdrawal included bronchopulmonary dysplasia (770.7, P27.x), intraventricular hemorrhage (772.1x, P52.x), periventricular leukomalacia (779.7, P91.2), necrotizing enterocolitis (777.5x, P77.x), spontaneous intestinal perforation (777.6, P78.0), and low birth weight of <1500 g (765.x, P07.x). The detailed ICD codes for the algorithm are presented in Appendix C. Additionally, both comparison groups of this study were considered to be mutually exclusive, which means children with NAS were born full term, and children born late preterm did not have NAS.

3.4.3 Demographic and Clinical Characteristics

Demographic information of children with NAS and born late preterm and their mothers included child's sex, child's gestational age, birth year, mother's age, race, and education level that were obtained from state birth certificate data. Clinical information of mothers and children from both comparison groups contained child's birth weight, mother's score in the Kotelchuck Prenatal Care Index, tobacco use before and during pregnancy, and if the mother was a WIC recipient. Clinical information was collected and generated from the RFA inpatient and outpatient data. The Kotelchuck Adequacy of Prenatal Care Utilization Index is a tool utilized to assess the adequacy of prenatal care. It takes into account both the timing of prenatal care initiation and the extent of services received, which are then integrated into a single index score (Kotelchuck, 1994).

3.4.4 Outcome measures

This study examined two healthcare utilization outcomes from 0 – 3 years of age. The primary outcome measure of this study is the risk of hospital readmission after birth hospitalization within 0-1 year, 1-2 years, and 2-3 years of age. As a secondary outcome measure, it also analyzed hospital LOSD from readmission during the defined time periods. Hospital readmission was identified using the variable “age in years at admission” from the Medicaid dataset used in this study, which contained hospital admissions except for birth hospitalization. The Medicaid dataset also had another variable named “length of hospital stays in days (LOSD),” which was used to analyze the secondary outcome measure of this research. Unfortunately, SC Medicaid claims data has restricted dates, which made it impossible to accurately determine the children’s age at the time of diagnoses. Additionally, the variable employed to identify hospital readmission did not have any information on months. As a result, it was not possible to determine the exact month when a child was admitted, and only readmissions that occurred within 0-1, 1-2, and 2-3 years could be identified.

3.4.5 Statistical Analysis

Descriptive analysis of the baseline covariates was calculated by mean (standard deviation, SD, median (interquartile range [IQR]), or frequency and percentage. To identify the demographic and clinical differences between the two comparison groups, *t*-test was used for continuous normally distributed variables, two-sample Wilcoxon rank-sum test was used for continuous skewed variables, and χ^2 test was used for categorical variables ($\alpha = 0.01$). Frequencies and percentages of hospital readmission for the two comparison groups were used for the primary analysis, and the average days of hospital LOSD were calculated as a secondary analysis. Simple and multivariable logistic regression models were developed to measure the odds of hospital readmission among two groups from 0 – 3 years of age. Additionally, adjusted and unadjusted negative binomial regression models were applied to examine the association between hospital readmission with hospital LOSD between 0 -3 years of age for the comparison groups. Statistical analyses were performed by using SAS 9.4 (SAS institute Inc., Cary, NC) and JMP Pro 16 (JMP®, Version <x>. SAS Institute Inc., Cary, NC).

4. Results

4.1 Demographic and Clinical Characteristics

From 2005-2015, there were 651,693 live births in SC. Among them, 19,100 children were either diagnosed with NAS or born late preterm at birth hospitalization. After applying the algorithm for presumed iatrogenic withdrawal, 1,870 children were excluded from the study cohort. Additionally, 128 children were disqualified because they were not mutually exclusive. The final application of inclusion criteria resulted in 17,102 Medicaid-enrolled children in SC. Of them, 1,054 children had a history of NAS, while 16,048 children were born late preterm. The cohort selection flow chart is shown in Figure 7.

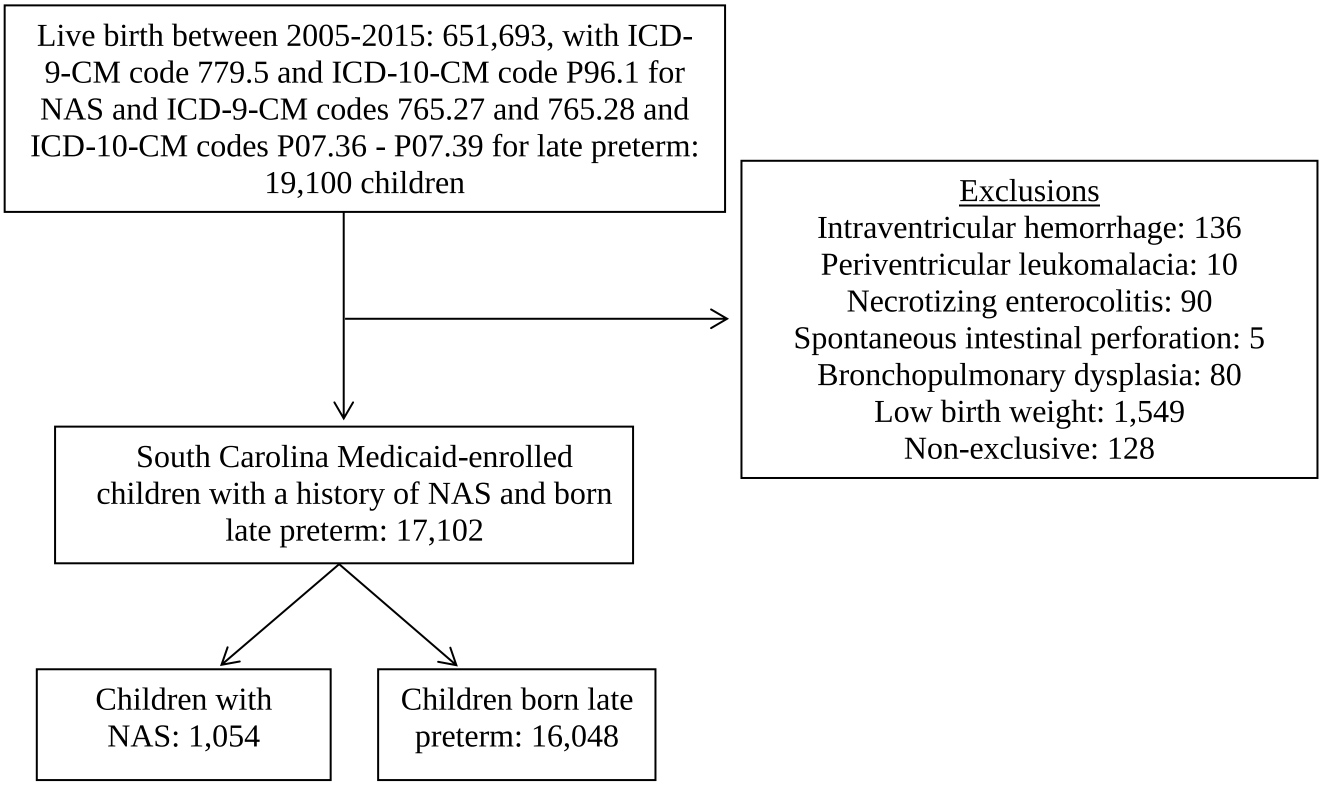

Figure 7. Cohort selection flow chart of South Carolina Medicaid-enrolled children born between 2005-2015 with a diagnosed NAS and born late preterm at birth hospitalization.

The demographic and clinical characteristics of children with NAS and born late preterm in SC between 2005-2015 and their mothers are presented in Table 10. There was no difference regarding the children' sex among the two comparison groups (χ2 [df = 1] = 2.42; p = 0.12). Children with NAS had a significantly higher mean gestational age 38.7 (1.21) and birthweight 3071.6 (500.7), compared to children born late preterm 34.3 (0.73) (t [df = 17100] = 175.89; p = <0.0001), and 2379.8 (419.1) (t [df = 17099] = 51.25; p = <0.0001), respectively. The percentage of children born with NAS increased by 11.2% during the study period; while for children born late preterm, the rate(s) were relatively stable (Figure 8). With regard to mothers' demographics, the majority of mothers of children with NAS identify as white (90.5%), while the majority of mothers of children born late preterm are Black or African American (47.1%) (χ2 [df = 3] = 751.55; p = <0.0001). Mothers of children with NAS had significantly higher average age 27.6 (5.14), lower education levels (in terms of high school and bachelor's degree) (χ2 [df = 8] = 25.62 ; p = 0.001), a lower Kotelchuck prenatal care index (χ2 [df = 4] = 590.66 ; p = <0.0001), higher usage of tobacco before and during pregnancy (χ2 [df = 2] = 1208.22; p = <0.0001) and (χ2 [df = 2] = 1390.92; p = <0.0001), and received lower levels of WIC benefits (χ2 [df = 2] = 20.65; p = 0.01) compared to mothers of children born late preterm.

Table 10: Baseline characteristics of children with NAS and children born late preterm who were born between 2005-2015 in SC and their mothers

Demographics	**NAS (*N*= 1,054)**	**Late preterm (*N*=16,048)**	***P* value**
Children			
Female, % (n)	54.3 (573)	51.8 (8328)	0.12
Gestational age, mean (SD)	38.7 (1.21)	34.3 (0.74)	<0.0001
Birthweight (grams), mean (SD)	3071.6	2379.8	<0.0001
Birth year, % (n)			<0.0001
2005	4.5 (48)	8.9 (1429)	
2006	5.2 (55)	9.7 (1557)	
2007	5.0 (53)	10.5 (1695)	
2008	5.4 (57)	9.6 (1549)	
2009	6.7 (71)	9.7 (1571)	
2010	7.1 (75)	8.4 (1394)	
2011	9.8 (104)	8.6 (1428)	
2012	11.4 (121)	8.5 (1374)	
2013	13.1 (139)	8.4 (1357)	
2014	15.5 (164)	8.5 (1374)	
2015	15.8 (167)	8.2 (1320)	
Mothers			
Age, mean (SD)	27.6 (5.14)	25.3 (5.83)	<0.0001
Education attained, % (n)			0.001
Less than high school graduate	28.1 (297)	25.4 (4087)	
High school graduate or GED	31.7 (335)	32.7 (5261)	
Some college credits	29.6 (312)	27.0 (4347)	
Associate’s or bachelor’s degree	2.7 (29)	4.3 (706)	
Race, % (n)			<0.0001
White	90.5 (954)	47.1 (7549)	
Black or African American	8.5 (90)	51.4 (8256)	
Hispanic or Latino	0.9 (10)	1.4 (230)	
Other	0 (0)	0.08 (13)	
Kotelchuck Prenatal Care Index, % (n)			<0.0001
Inadequate	48.8 (515)	26.1 (4180)	
Intermediate	7.7 (82)	3.8 (613)	
Adequate	18.8 (199)	8.1 (1308)	
Adequate Plus	23.7 (250)	60.4 (9699)	

Tobacco uses prior to pregnancy, % (n)			<0.0001
Yes	68.97 (727)	21.62 (3469)	
No	30.46 (321)	78.20 (12550)	
Tobacco uses during pregnancy, % (n)			<0.0001
Yes	66.32 (699)	18.02 (2892)	
No	33.68 (355)	81.91 (13145)	
WIC recipient, % (n)			0.01
Yes	38.14 (402)	36.73 (5895)	
No	19.63 (207)	14.76 (2368)	

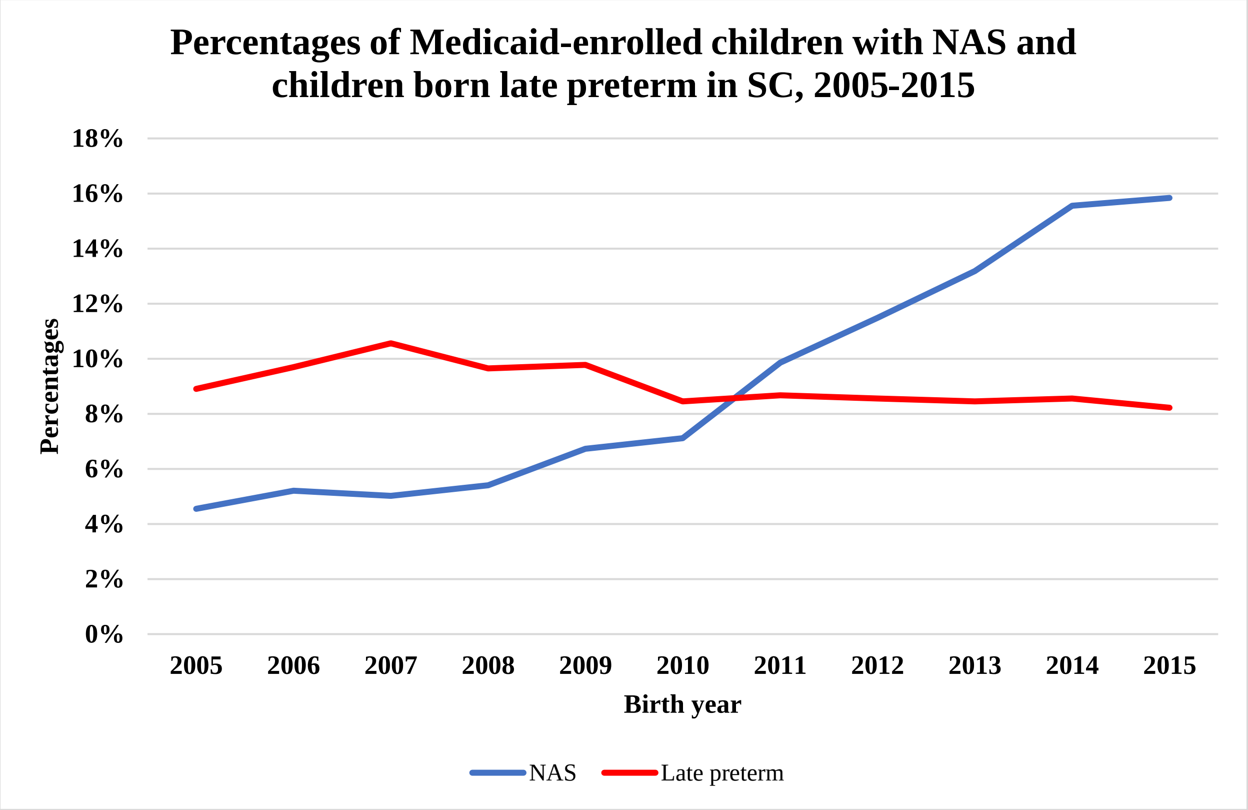

Figure 8: Percentages of Medicaid-enrolled children with NAS and children born late preterm in SC, 2005-2015

4.2 Hospital readmission among children with NAS and children born late preterm

During the first 3 years of life, 203 children with NAS (19.2%) and 2,366 children born late preterm (14.7%) were readmitted to the hospital. Children <1 year of age had the highest percentages of hospital readmission within both groups (12.9% vs 10.8%). In all cases from 0-3 years, children with NAS had higher percentages of hospital readmission compared to children born late preterm, which was 2.9%, 1.5%, and 1.8% for children with NAS, and 1.5%, 1.2%, and 1.1% for children born late preterm for 1 year, 2 years, and 3 years of age. The p-values were significant at the <0.05 level for ages 1 year and 3 years (Table 11).

Table 11: Hospital readmission during the first 3-years of life by study group: results from chi-square test

Age	**Hospital readmission (n)**	**NAS, % (n)**	**Late preterm, % (n)**	***P* value**
<1 year	1871	12.9 (136)	10.8 (1735)	0.24
1 year	277	2.9 (31)	1.5 (246)	0.01*
2 years	214	1.5 (16)	1.2 (198)	0.72
3 years	207	1.8 (20)	1.1 (187)	0.04*

*$p < 0.05$

The risk of hospital readmission between children with NAS and those born late preterm was examined using logistic regression. The simple (unadjusted) and multivariable (adjusted) logistic regression evaluation models are:

Simple Logistic Regression[4]:

$$\log\left(\frac{P(X_i = x, b_i)}{1 - P(X_i = x, b_i)}\right) = \beta_0 + \beta_1 \times x + b_i$$

Or, Z = $= \beta_0 + \beta_1 \times x + b_i$

Where,

Z: Log odds of hospital readmission in ith child where 0 indicates no readmission and 1 indicates readmission

X_i: Comparison group of ith child (1 = NAS, 0 = late preterm)

b_i: Random subject-specific intercept of ith child, taking a value of 0 when examining the typical individual

Multivariable Logistic Regression:

$$\mathrm{Z} = \beta_0 + \beta_1 \times X_1 + \beta_2 \times X_2 + \beta_3 \times X_2 + \cdots \ldots \ldots \ldots \ldots \beta_{13} \times X_{13} + \ b_i$$

$$\begin{aligned} \mathrm{Or}, \mathrm{Z} = {} & \beta_0 + \beta_1 \times group \\ & + \beta_2 \times infant's\ sex + \beta_3 \times gestation + \beta_4 \times birthweight + \ \beta_5 \times birthyear \\ & + \beta_6 \times breastfeeding + \beta_7 \times mother's\ age + \beta_8 \times mother's\ education \\ & + \beta_9 \times mother's\ race + \beta_{10} \times KPCI \ + \beta_{11} \times tobacco \\ & + \beta_{12} \times tobacco_{prepreg} + \beta_{13} \times WIC + \ b_i \end{aligned}$$

Where,

$X_2, \ldots . X_{13}$ = Secondary independent variables

$\beta_2, \ldots . \beta_{13}$ = Random subject-specific intercept for each corresponding independent variable

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[4] The equations only included intercept and group. Time was excluded from the models by following the existing literature. The researcher created separate files for the years and ran the codes individually. The reviewed literature also followed this process to present the results of hospital readmission separately for the follow-up years used.

According to hypothesis 1 (H1), children with NAS will have higher odds of hospital readmission than children born late preterm from 0 – 3 years of age. In unadjusted comparisons, the likelihood of hospital readmission was higher for children with NAS compared to children born late preterm for all three intervals from 0-3 years of age (year 0-1: odds ratio [OR]: 1.33, 95% confidence interval [CI]: 1.12–1.58, p = 0.0004; year 2-3: OR: 1.64, 95% CI: 1.20-2.23, p = 0.0008; year 2-3: OR: 1.43, 95% CI: 1.01-2.03, p=0.02). Therefore, null hypothesis $H1_0$ can be rejected. However, after adjusting for infant's sex, gestational age, birthweight, birth year, breastfeeding status; mother's age, education, race, Kotelchuck prenatal care index, tobacco use prior to and during pregnancy, and WIC recipient, there was no statistically significant difference in readmission risk between the two groups (Table 12).

Table 12: Risk of hospital readmission among children with NAS and children born late preterm for 0-3 years follow-up period: results from logistic regression modeling

Healthcare utilization outcome	**Odds Ratio (OR)**	**95% Confidence Interval**	***P* value**
One-year hospital readmission (0-1 year)			
Unadjusted	1.33	1.12 to 1.58	0.0004**
Adjusted	1.77	0.76 to 4.10	0.18
2-year hospital readmission (1-2 years)			
Unadjusted	1.64	1.20 to 2.23	0.0008**
Adjusted	0.53	0.0.15 to 1.80	0.30
3-year hospital readmission (2-3 years)			
Unadjusted	1.43	1.01 to 2.03	0.02*
Adjusted	1.53	0.41 to 5.72	0.52

**$p < 0.005$

*$p < 0.05$

Unadjusted = Crude model from simple logistic regression

Adjusted = Multiple logistic regression model adjusted for infant's sex, gestational age, birthweight, birth year, breastfeeding status; mother's age, education, race, Kotelchuck prenatal care index, tobacco use prior to and during pregnancy, and WIC recipient

4.3 Length of stay (LOSD) from hospital readmission among children with NAS and children born late preterm

The mean hospital LOSD was higher for children with NAS compared to children born late preterm at each year between age 0-3. Children aged <1 year and 3 years had a significantly higher mean hospital LOSD for both groups, which was 9.9 days (95% CI: 7.51 - 12.36) and 15.0 days (95% CI: -0.44 - 30.44) for children with NAS, and 7.4 days (95% CI: 6.87 - 7.87) and 7.3 days (95% CI: 5.87 - 8.81) for children born late preterm, respectively (p = 0.01 for both years) (Table 13). The median hospital LOSD for children with NAS (5 days) was also higher than for children born late preterm (3 days) from age 0-3 years (Figure 9).

Table 13: Mean hospital length of stay (LOSD) by year for children with NAS and born late preterm.

Age	**Length of stay (LOSD) in days: Children with NAS** Mean (95% CI)	**Length of stay (LOSD) in days: Children born late preterm** Mean (95% CI)	***P* value**
<1 year	9.9 (7.51 to 12.36)	7.4 (6.87 to 7.87)	0.01*
1 year	9.4 (4.52 to 14.31)	7.3 (6.01 to 8.65)	0.31
2 years	5.8 (4.57 to 7.02)	3.1 (1.29 to 4.86)	0.18
3 years	15.0 (-0.44 to 30.44)	7.3 (5.87 to 8.81)	0.01*

*p < 0.05

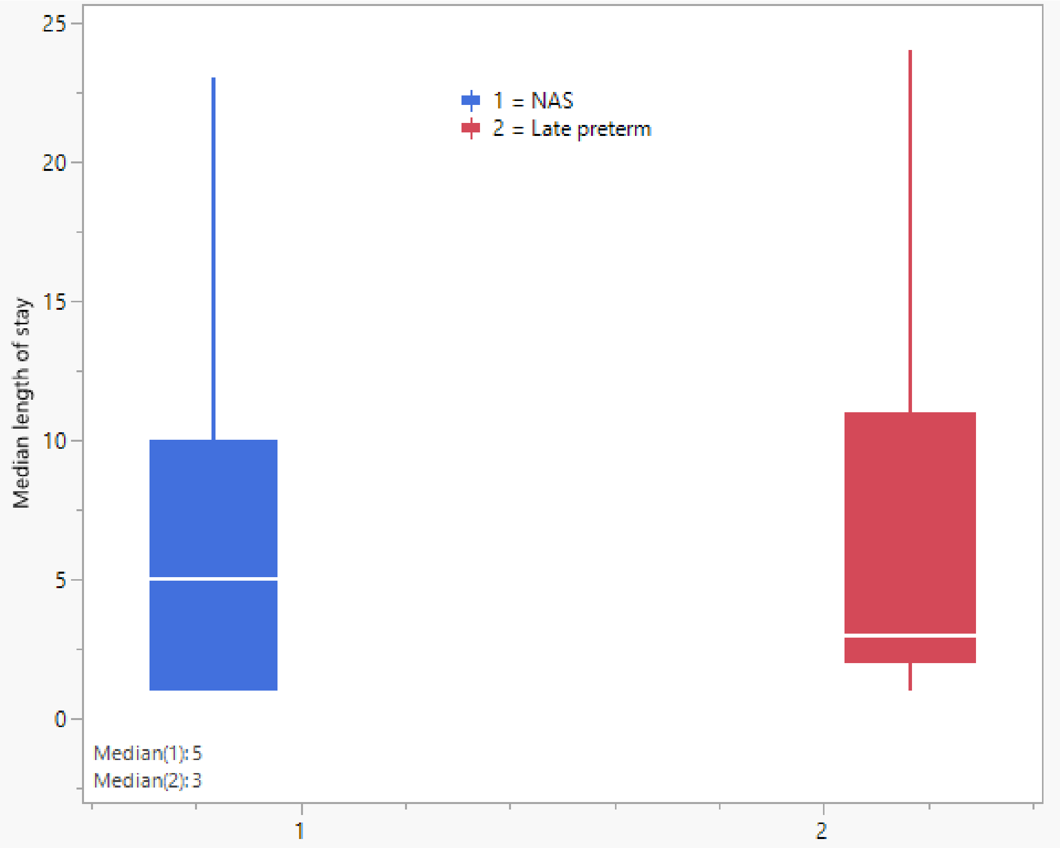

Figure 9: Median hospital length of stay and interquartile range from age 0-3 for children with NAS and born late preterm.

In an attempt to model the relationship between hospital LOSD of the comparison groups, adjusted and unadjusted negative binomial regression analyses were used. The mathematical regression equation models are:

Unadjusted Negative Binomial Regression:

$$\ln(\mu) = \beta_0 + \beta_1 \times X_1 + e$$

Where,

$\ln(\mu)$ = logarithm of the dependent variable (hospital length of stay)

X_1 = Primary independent variable = Group (NAS = 1, Late Preterm = 0)

β_0 = Intercept = The average value of Y when X_1 = 0

β_1 = The average change of Y with a one-unit change of X_1

e = error term

Adjusted Negative Binomial Regression:

$$\ln(\mu) = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \cdots \dots \dots \dots \dots + \beta_{13} X_{13} + e$$

$$Or, \ln(\mu) = \beta_0 + \beta_1 \times group$$

$$+ \beta_2 \times infant's\ sex + \beta_3 \times gestation + \beta_4 \times birthweight + \beta_5 \times birthyear$$

$$+ \beta_6 \times breastfeeding + \beta_7 \times mother's\ age + \beta_8 \times mother's\ education$$

$$+ \beta_9 \times mother's\ race + \beta_{10} \times KPCI + \beta_{11} \times tobacco$$

$$+ \beta_{12} \times tobacco_{prepreg} + \beta_{13} \times WIC + e$$

Where,

$X_2, \dots . X_{13}$ = Secondary independent variables

$\beta_2, \dots . \beta_{13}$ = Regression coefficient for each corresponding independent variable (parameter estimate)

In unadjusted negative binomial analysis, children with NAS had a shorter hospital LOSD (IRR = 0.25, 95% CI: 0.11 to 0.39, p = 0.0004) compared to children born late preterm during age 0-1 year (model 1). Similar effect was found for the later years or age 1-2 and 2-3 years (IRR = 0.21, 95% CI: 0.04 to 0.38, p = 0.01 for age 1-2 year, and IRR = 0.27, 95% CI: 0.10 to 0.44, p = 0.001 for age 2-3 years). However, after applying adjusted negative binomial models (adjusted for infant's sex, gestational age, birthweight, birth year, breastfeeding status; mother's age, education, race, Kotelchuck prenatal care index, tobacco use prior to and during pregnancy, and WIC recipient), the results changed and children with NAS had a longer LOSD compared to children born late preterm during all three intervals from age 0-3 years (IRR = 1.71, 95% CI: 1.46 to 1.95, p<0.0001 for 0-1 year; IRR = 1.80, 95% CI: 1.50 to 2.09, p=<0.0001 for 1-2 year; IRR = 1.85, 95% CI: 1.57 to 2.13, p=<0.0001 for 2-3 year) (Table 14). Hypothesis 2 (H2) stated that children with NAS will have higher mean hospital LOSD from hospital readmission than children born late preterm from 0 – 3 years of age. Therefore, the null hypothesis $H2_0$ can be rejected according to the results of adjusted negative binomial regression modeling.

Table 14: Hospital length of stay (LOSD) among children with NAS and children born late preterm for 0-3 years follow-up period: results from negative binomial regression modeling

*p < 0.05
**p <0.0005

Healthcare utilization outcome	NAS IRR (95% CI)	Late Preterm IRR (95% CI)	*P* value
1-year hospital readmission (0-1 year)			
Unadjusted	0.25 (0.11 to 0.39)	Ref	0.0004**
Adjusted	1.71 (1.46 to 1.95)	Ref	<0.0001***
2-year hospital readmission (1-2 years)			
Unadjusted	0.21 (0.04 to 0.38)	Ref	0.01*
Adjusted	1.80 (1.50 to 2.09)	Ref	<.0001***
3-year hospital readmission (2-3 years)			
Unadjusted	0.27 (0.10 to 0.44)	Ref	0.001**
Adjusted	1.85 (1.57 to 2.13)	Ref	<.0001***

***p < 0.0001
Model 1 = Unadjusted model
Model 2 = Adjusted for infant's sex, gestational age, birthweight, birth year, breastfeeding status; mother's age, education, race, Kotelchuck prenatal care index, tobacco use prior to and during pregnancy, and WIC recipient

4.4 Common diagnoses behind hospital readmission and hospital length of stay (LOSD)

There were both major and minor health issues behind hospital readmission and hospital LOSD during age 0-3 years of life for the study groups (Table 15). Compared to children born late preterm, complicated/critical diagnoses were more common in children with NAS for all years between 0-3 years of age, such as *newborn affected by maternal conditions or complications of labor/delivery* (p < 0.0001 for all years), *other specified and unspecified perinatal conditions* (i.e., congenital hypotonia) ($p < 0.0001$ for years 1 and 3) and *feeding difficulties* ($p < 0.0001$ for years 1 and 2). Only one major diagnosis, *respiratory perinatal condition/distress*, was significant for children born late preterm at $p < 0.005$ level for years <1 and 2. These results suggest that Hypothesis 3 (H3) - children with NAS will be observed with more severe diagnoses for hospital readmission and hospital length of stay than children born late preterm from 0 – 3 years of age - can be supported, while the null hypothesis $H3_0$ can be rejected.

Some less severe conditions like *nasal congestion* ($p < 0.005$ for year 3) and *abnormal weight loss* ($p < 0.005$ for years 1 and 2) were also higher for children with NAS compared to children born late preterm. One minor diagnosis, viral infection, was significant for children born late preterm at $p <0.05$ level for year 2. No significant differences were found between the two groups regarding other major and minor diagnoses behind hospital readmission and hospital length of stay during the first 3-years of life.

Table 15: Common diagnoses behind hospital readmission and hospital length of stay during the first 3-years of life for children diagnosed with NAS and children born late preterm

Diagnoses	Children with NAS (%, n)				Children born late preterm (%, n)			
	<1 year	1 year	2 years	3 years	<1 year	1 year	2 years	3 years
Newborn affected by maternal conditions or complications of labor/delivery	39.5 (83)***	42.4 (53)***	47.1 (64)***	43.3 (65)***	13.1 (377)	14.1 (216)	12.9 (237)	13.2 (293)
Other specified and unspecified perinatal conditions	13.8 (29)**	15.2 (19)***	10.2 (14)*	22.6 (34)***	6.7 (193)	5.8 (89)	5.8 (108)	8.1 (179)
Respiratory perinatal condition/distress	20.9 (44)	32.8 (41)	22.1 (30)	31.3 (47)	33.7 (963)**	31.5 (481)	33.1 (609)**	33.8 (747)
Fluid and electrolyte disorders	1.9 (4)	6.4 (8)	2.9 (4)	5.3 (8)	3.4 (99)	3.6 (56)	3.7 (68)	3.7 (83)
Cough	9.1 (19)	19.2 (24)	22.1 (30)	29.3 (44)	6.1 (176)	15.8 (242)	22.6 (415)	28.5 (630)
Fever	7.6 (16)	24.0 (30)	33.8 (46)	36.6 (55)	6.6 (191)	25.3 (386)	32.6 (599)	38.3 (847)
Viral infection	5.2 (11)	10.4 (13)	9.5 (13)	18.6 (28)	3.9 (113)	13.0 (198)	16.3 (301)*	18.4 (403)
Vomiting	7.1 (15)	13.6 (17)	14.7 (20)	18.6 (28)	5.7 (165)	16.6 (253)	13.7 (252)	20.7 (457)
Nasal congestion	5.7 (12)*	12.0 (15)	10.2 (14)	20.6 (31)**	2.5 (74)	8.0 (122)	10.2 (189)	13.1 (290)
Feeding difficulties	15.2 (31)**	20.8 (26)***	25.0 (34)***	25.3 (38)**	8.7 (250)	8.8 (135)	11.3 (208)	14.4 (320)
Abnormal weight loss	0.4 (1)	5.6 (7)**	3.6 (5)**	4.0 (6)*	0.8 (25)	1.3 (20)	1.0 (20)	1.4 (31)

*p < 0.05

**p < 0.005

***p < 0.0001

4.5 Discussion

The development of a fetus is strongly influenced by the surrounding environment, which can have long-lasting effects on the child's overall health in the future (Liu et al., 2019). In the United States, the opioid epidemic has resulted in a marked increase in the occurrence of NAS over the past two decades (Shrestha et al., 2021). The incidence of NAS-related hospitalizations and rehospitalizations has become a significant healthcare concern, with rates of NAS-related hospitalizations rising from 4/1000 to 7.1/1000 between 2010 and 2018 (Bhatt et al., 2021). It is crucial to identify the risk of readmission to inform safe hospital discharge procedures, promote quality improvement efforts, and enhance health system efficiency for children with NAS (Patrick et al., 2015). Hospital readmissions can result in extensive disruptions, stress, and expenses for patients and their families, although up to a third of unplanned pediatric readmissions is potentially preventable (Brittan et al., 2016; Lapillonne et al., 2012; Leader et al., 2002; Leidy et al., 2005). Further, many recent initiatives have prioritized reducing hospital LOSD from readmission that aimed at improving the care for children affected by NAS and their families (Diop et al., 2022; Patrick et al., 2015; Salt et al., 2023). Shortening LOSD in hospitals for children with NAS can provide substantial benefits to families while also lowering hospital expenses related to the condition and additional diagnoses resulted from it (Diop et al., 2022).

This retrospective study compares two healthcare utilization outcomes, hospital readmission and length of stay, among children with NAS and children born late preterm who were born during 2005-2015 and enrolled by Medicaid in SC using a follow-up period of 0-3 years. Children with NAS and their mothers significantly differed from children born late preterm and their mothers regarding demographic and clinical characteristics. Children with NAS had a significantly higher mean gestational age and birthweight, with an increasing trend in their percentages over the study period (2005-2015). In contrast, a higher proportion of mothers of children with NAS were White, had a higher average age, reported higher tobacco use before and during pregnancy, had lower rates of high school and bachelor's degree, lower scores in the Kotelchuck Prenatal Care Index, and were lower receivers of WIC benefits compared to mothers of children born late preterm. Existing studies also support these differences and may at least partially account for the increasing trend of the number of children with NAS and the poorer condition their mothers (Corr et al., 2021; Liu et al., 2019; Salt et al., 2023).

The unadjusted results of this study indicate that children with NAS had higher odds of hospital readmission compared to children born late preterm during all three intervals from 0-3 years of age. However, the effect became insignificant after adjusting for infant and maternal demographic and clinical characteristics. Additionally, children with NAS had a shorter hospital LOSD from hospital readmission compared to children born late preterm during age 0-3 year, according to the unadjusted negative binomial regression analysis. However, the adjusted negative binomial regression models changed the results and showed a continually significant longer hospital LOSD for children with NAS during all three intervals from age 0-3 years. Regarding common diagnoses, children with NAS were observed with more complicated health issues behind hospital readmission and LOSD from 0-3 years (i.e., *maternal conditions or complications of labor/delivery, other specified and unspecified perinatal conditions* such as congenital hypotonia and *feeding difficulties*) compared to children born late preterm. On the other hand, children born late preterm had a higher observation for only one major diagnoses, *respiratory perinatal condition/distress,* at years <1 and 2.

These findings are similar to other state-level studies from New York, Massachusetts, and Kentucky that found higher readmission rates for children with NAS within 30 days of discharge, between 2 – 42 days and 43 – 182 days of discharge, and 1 year of discharge, respectively (Diop et al., 2022; Patrick et al., 2015; Young et al., 2013). However, these studies analyzed hospital readmission rate within 1 year after birth hospitalization, while the present study applied a follow-up period of 0-3 years. Moreover, most of the studies that examined hospital readmission along with LOSD result from birth hospitalization, rather than hospital readmission. A 2011 study by Wachman and his colleagues discovered that children with NAS who were born at Boston Medical Center had an average LOS from birth hospitalization of 22.9 days between 2003 and 2009 (Wachman et al., 2018). On the other hand, Patrick and his team found that children with NAS born in New York State during 2006-2009 had an average LOS of 15 days (Patrick et al., 2015). The present study has several advantages over previous literature, as it examines outcomes that have been underexplored, such as the LOSD during hospital readmission, longer follow-up periods of 0-3 years for readmissions, and a broader timeframe of 10 years (2005-2015) to analyze these outcomes.

Furthermore, only a limited number of prior studies have explored the common reasons behind hospital readmission for children with NAS. The findings from this research are consistent to those of previous studies that identified a higher incidence of maternal conditions or labor/delivery complications, other specified and unspecified perinatal conditions, and feeding disorders in this population (Salt et al., 2023, Patrick et al., 2015). Also, this study looked into some minor diagnoses, such as nasal congestion and abnormal weight loss, during hospital readmission for children with NAS, providing additional insights to the existing literature. According to some recent studies, there can be several reasons behind the early differences in healthcare utilization. Placental insufficiency and abruption, preterm labor, fetal growth restriction etc. can be resulted from Maternal opioid use, which can cause short-term and long-term health consequences for children (Hirai et al., 2021; McQueen & Murphy-Oikonen, 2016; Zedler et al., 2016). These health consequences can largely be parts of the diagnoses behind hospital readmission later in their lives.

4.6 Limitations

This study has several limitations regarding the nature of Medicaid data and the format of variables used to measure the outcomes. The Medicaid dataset had restricted dates that made it impossible to accurately calculate the children's age. Additionally, the variable "age in years at admission," which was used to examine the risk of hospital readmission did not take admission month into account. Therefore, the exact months when the children were readmitted could not be calculated. Due to this issue, this research was also unable to pinpoint multiple readmissions within a single year. There could be some potential overlapping of readmission with birth hospitalization at year 0 and missing or underreported admission in the later years. There were also possible coding errors within the claims data and the absence of specific social or demographic characteristics such as household income, employment, and information about healthcare providers that could improve the analysis. The "length of stay in days (LOSD)" variable had some potential outliers, which could affect the mean LOSD for both children with NAS and born late preterm. However, median LOSD was calculated and presented for both groups in the analysis to address this issue. The median LOSD also revealed that children with NAS had greater hospital LOSD compared to children born late preterm from 0-3 years of age.

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CHAPTER FOUR: HOW SOCIAL MEDIA STIGMATIZES SUBSTANCE USE: A TREND ANALSYSIS EXAMINING A POLITICIZED VISIT TO A PEDIATRIC HOSPITAL UNIT

4.1 Abstract

Background: Social media has become a ubiquitous platform for language impacting pregnant women with opioid use disorder (OUD) and children with neonatal abstinence syndrome (NAS). This study used the popular social media platform Twitter to investigate stigmatizing language around OUD and NAS by examining NAS-related keywords used around a specific event.

Methods: The researchers gather Twitter data about a renowned political figure's visit to a pediatric hospital unit using the social media management software Sprinklr. Twitter conversations around the event were collected using primary search terms and categorized through a collaborative coding process. The final sample contains N=2,789 tweets posted before, during, and after the event. This study also applied the issue-attention cycle to demonstrate how the public's interest and support for this NAS treatment program changed over the timeframes of the event.

Results: Before the event, the highest number of tweets (56.07%) fell into the *information-sharing* category, suggesting that people were discussing the complex issue of NAS on Twitter prior to a significant event. An increase in the number of *medically divisive* (22.64%) and a high volume of *political* (20.69%) tweets occurred during the event. Tweets coded as *account error* were significantly notable during (37.06%) and after the (32.76%) event. Chi-square analyses revealed that all coded categories were significant, with the *political* category seeing the most significant increase during and after the event. The issue-attention cycle showed that the problem eventually moved into a stage where people's interests became insignificant with lesser attention without any potential to solve it.

Conclusions: Twitter users repeatedly used stigmatizing language to express opinions regarding an event associated with a NAS treatment program. The researchers argue for co-creating an "addiction-ary" for social media platforms, primarily focusing on NAS to monitor stigmatizing language and reshape the current narrative around substance use on social media.

4.2 Background

Substance use disorder (SUD) during pregnancy, which includes Opioid Use Disorder (OUD), has developed into a significant medical and social concern (Hunt et al., 2008; O'Brien et al., 2004; Whiteman et al., 2014). This increase has caused significant medical and social challenges for pregnant women and their infants (Fischer et al., 1999). Pregnant women with SUD and their children are often stigmatized, mainly through the perpetuation of stigmatizing words and inaccurate beliefs. Disease stigmatization is discriminatory and, in the case of issues like SUD, can create significant public health challenges (NIDA, 2021; EDC, 2017). Stigma is often transferred onto the infants of women with SUDs, particularly those who develop Neonatal Abstinence Syndrome (NAS). NAS is a withdrawal disorder that affected 7.3 per 1,000 hospital births in 2017, an increase from 2.9 per 1,000 hospital births in 2009 (HCUP, 2021). Stigmatization amplifies barriers for individuals with SUDs and families with infants with NAS, preventing them from seeking healthcare services and reducing their trust in and communication with healthcare providers.

Unfortunately, extensive use of stigmatizing language exists on social media platforms, with Twitter containing a substantial portion of the posts (Dekeseredy et al., 2021). Stigmatizing language targeting mothers and their children with NAS on social media can harm these children and their families. Social media research methodologies allow us to examine both positive and negative sentiments around specific issues and on specific platforms (Asur & Huberman, 2010). Although some scholars and physicians have recently raised their voices to reduce stigmatizing language by using more accurate and thoughtful language for SUDs-related terminology, stigmatizing language around NAS is a highly underexamined area (Kowalchuk et al., 2018). Most research recommendations appear in research letters or web blogs and have not been directly implemented in existing studies. For example, one physician-authored letter published in 2018 expressed concern regarding the continuing stigmatization of children with NAS and pregnant and postpartum women with SUD; however, many media outlets and reports continue to describe infants with NAS using the terms ‘born addicted,’ ‘addicted babies,’ or ‘babies with addiction’ (Webster, 2018). This type of language directly targets mothers and their infants affected by NAS; therefore, describing the landscape of stigmatizing language around SUDs is essential for policymakers and medical and research communities to effectively characterize the need for change.

Social issues like SUDs and associated stigma have been investigated in several studies, although not specifically within the context of social media (Cleveland & Gill, 2013; Kelly et al., 2010; Stone, 2015a). Social media sites are unique settings for people to seek information and interact with each other, with 72% of US adults reporting using at least one online social media platform (Bishop, 2019; Pew, 2021). Among the social networking platforms, Twitter is one of the largest, with more than 330 million monthly active users who post or share “tweets” to reflect their interests, concerns or relay information in real-time (Jay, 2022). Social media sites like Twitter have also become an increasingly preferred source for information sharing about health issues (Bian et al., 2017; Edo-Osagie et al., 2020; Zhang et al., 2019).

The primary objective of the present study is to examine social media data around OUD and NAS to expand our understanding of the general population's views and the potential unintended impacts of this communication environment on moms and infants. This study consists of Twitter data analysis regarding an event to describe the use of stigmatizing language around OUD and NAS. Because of the comprehensive terminology related to SUD, the analysis focuses specifically on language regarding NAS and maternal OUD. We examine NAS-related Twitter information over two-week and two-day event horizons to understand better how social media's stigmatization of infants with NAS is characterized.

4.3 The Event

On Wednesday, November 6, 2019, First Lady Melania Trump visited the Boston Medical Center (BMC) in Boston, Massachusetts. The center provides a support program focused on swaddling and cuddling infants born dependent on drugs or alcohol—Cuddling Assists in Lowering Maternal and Infant Stress (CALM)—which Boston University School of Medicine designed to provide non-pharmacologic care for infants with NAS and other withdrawal issues. The mission of this program is to train young physicians to improve clinical experiences surrounding this vulnerable population in both inpatient and nursery settings. The program also aims to enhance provider understanding and empathy for these babies, the medical advantages of non-pharmacological care, improved patient-provider communication skills concerning SUDs, and language use around OUD and NAS (Wachman, 2021).

The same day that the First Lady (FLOTUS) visited the unit, Twitter saw a slight increase in NAS-related words, and there was a significant spike on the day after (Thursday, November 7, 2019), with 1,992 tweets mentioning the targeted keywords relating to NAS (see Table 1 for a complete list). Rather than focusing on the mission of CALM, a substantial number of Twitter posts contained news about protests of FLOTUS's visit in front of the hospital. Many people in the protest group were hospital employees denouncing immigration policies of the Trump administration that focused on child-family separation and detention at the US border. Many of the demonstrators thought a visit from FLOTUS ran counter to the hospital's mission: to serve a large population of nonwhite and immigrant patients (Dooling & Chen, 2019). A local news article reported the day before FLOTUS's visit, "Organizers of the protest say they are concerned that a photo opportunity highlighting BMC’s work with a vulnerable population could send the wrong message to patients — especially immigrants who are worried about the Trump administration’s enforcement policies” (Rosen, 2019).

However, even individuals and organizations attempting to counter these arguments by showing support for infants with NAS may have willingly or unwillingly used stigmatizing language in their social media engagement. Considering the issue's social and cultural relevance, examining Twitter data on events like this one deepens our knowledge of the social media universe’s perspectives and understanding of NAS and OUD generally.

4.4 Theoretical Framework

The theoretical framework applied in this research is Downs’s “issue-attention cycle” (1972). Downs introduced the issue-attention cycle as a process that causes some public problems to gain and/or fade from the center of public attention. The first stage, *the pre-problem stage,* is when an undesirable social condition exists but has not received sufficient public attention. In contrast, the second stage, *alarmed discovery and euphoric enthusiasm,* involves sudden episodes or events that cause the public to become aware of and alarmed about the issue. The third stage of the cycle is called *the realization of the cost of significant progress*; this is when people begin to understand the high cost of solving the problem, for example, the time, money, or arrangement they need to sacrifice to provide significant benefits to someone. This cost brings public attention to the fourth stage, or *the gradual decline in the intensity of public interest*, when many become discouraged, others feel threatened, and some become bored and discontinue their interest in the issue. Finally, the issue moves into a “twilight realm” of less attention when public interest becomes insignificant, creating *the post-problem stage* (Downs, 1972).

An issue may not always follow these five stages, as numerous factors can influence the development of public opinion (Nisbet & Huge, 2006). Problems that go through the issue-attention cycle likely possess three qualities to some degree. First, they affect a numerical minority, such as infants with NAS. Second, they involve social arrangements that benefit a majority or a powerful minority, for example in this case, support for first lady Melania Trump and the critiques of the protesting medical professionals. Third, the importance of the event will fade, and as such the event's association with the specific problem will also diminish in attention (Wang & Guo, 2018). This is often the case with focusing events concerning contentious issues like the politics surrounding Melania Trump's visit to the Boston Medical Center in 2019.

This research will apply the issue-attention cycle to demonstrate how the public's interest and support for this NAS treatment program at Boston Medical Center changed over the applied timeframes. The first lady's trip to the Boston Medical Center to visit the medical unit that treats infants born dependent on opioids brought attention and perceived significance to this issue. Her visit also provided imagery to the public that could raise awareness of and attention to this issue as one of potential policy importance. As a result, this research will use this theoretical lens to understand the nature of the attention that this visit drew to the issue of NAS and NAS care and seeks to characterize this visit and the attention it drew to NAS generally.

This issue-attention cycle may illustrate a shift in the understanding of NAS by individuals and organizations on Twitter. It may also exhibit a divergence in power between two groups: (1) those who seek to support the first lady's visit and her interest in this specific cause and (2) those who support improved understanding and models of care for NAS and OUD broadly, but not necessarily FLOTUS and the politics around the visit. The issue of stigma around NAS is too large to understand from one study; however, by using the issue-attention cycle theory, this analysis provides a close examination of Twitter data to better understand the language used around NAS during a sixteen-day timeframe, October 30 – November 14, focusing on Melania Trump's visit to the Boston Medical Center on November 6, 2019.

4.5 Methodology

The event was chosen after a three-year review (2017-2019) of NAS-related keywords on Twitter. We first searched for keywords within this period, dividing each year into four-month windows for a total of twelve time periods. Next, each four-month period was evaluated for data outliers; outliers were identified and manually searched to identify potential associated events or issues. From this scan and synthesis, the research team chose the event where First Lady Melania Trump visited the Boston Medical Center's pediatric unit to raise awareness for a new NAS treatment program offered at the hospital. This event also generated the highest frequencies of NAS-related keywords compared to other time periods.

This study utilized the social listening platform Sprinklr (2009) to gather Twitter data around Mrs. Trump's visit to Boston Medical Center's NAS unit.[5] Sprinklr (2009) collects publicly available social media posts through terminology categories. The researchers divided the Twitter conversation into three groups: before, during, and after the event. The *pre-event period* occurred from October 30 to November 5, 2019, the *event horizon period* occurred on November 6 and 7, 2019; after the event, and the *post-event period* occurred between November 8-14, 2019.

Through a collaborative process and extensive literature review, NAS-related keywords were chosen as primary search terms. Keywords used along with Boolean operators are shown in Table 16. Combining the keywords separated by the Boolean operators and hashtag targeting provided a wide variety of Twitter conversations regarding the topic.

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[5] This study was deemed exempt by the Clemson University Institutional Review Board (IRB).

Table 16. List of keyword groups

Keyword Group 1	**Keyword Group 2**	**Keyword Group 3**
Neonatal Abstinence, Neonatal Opioid Withdrawal AND contains keywords: syndrome	addicted AND babies, addicted AND infants, addiction AND babies, addiction AND infants, babies born addicted, infants born addicted, babies with addiction, infants with addiction	#neonatalabstinencesyndrome, #neonatalopioidwithdrawal, #addictedbabies, #addictedinfants, #babiesbornaddicted, #babieswithaddiction, #infantsbornaddicted, #infantswithaddiction

To focus only on originally authored tweets, the researchers did not collect retweets. Only Twitter mentions, updates, tweets, and replies, as provided through Sprinklr (2009), were collected. The researchers downloaded the CSV file of publicly available tweets, which are visible to anyone with a Twitter account, from October 30 - November 5, 2019 (n = 107), denoted as the *pre-event period*, the 48-hour timeframe of the *event horizon period* from November 6 - 7, 2019 (n = 2,105) and from November 8 - 14, 2019 (n = 577), the *post-event period* (Figure 10).

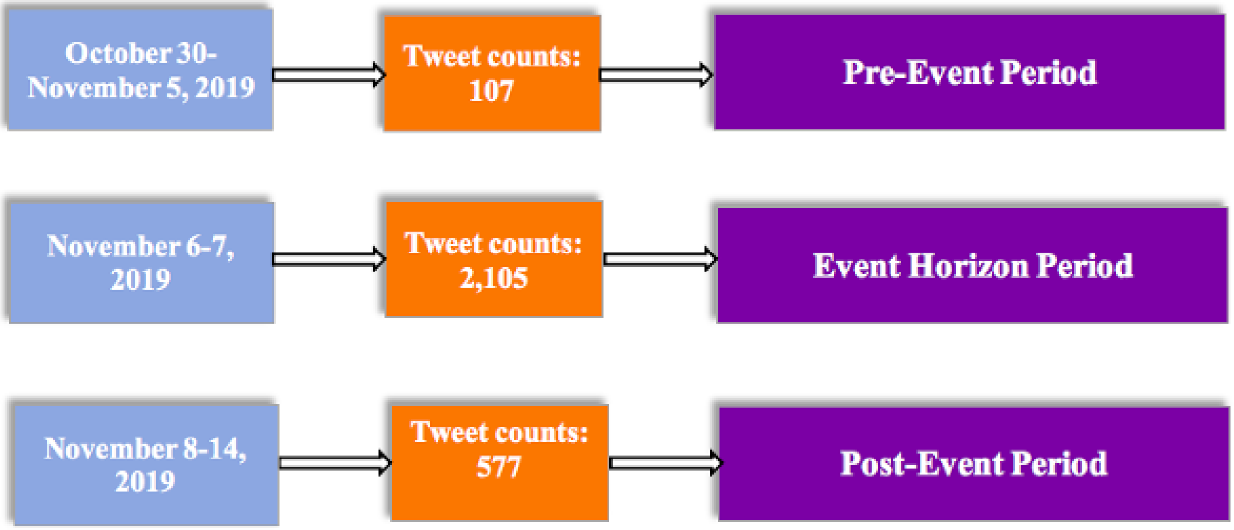

Figure 10: Three groups of the event, surrounding dates, and associated tweets

4.6 Coding Process

Each timeframe was separated into separate CSV files and a coding process was used to co-create and validate thematic codes. There were four members of the research team, with one researcher leading the data gathering and coding process through open coding (using data to generate abstract categories) and selective coding (select and elaborate the core category) (Punch, 2014). There were four stages of the coding process. In the first stage, the research team sampled around 400 tweets from all timeframes. The main topic of the tweet was identified and categorized in various codes such as *medical professionals*, *Trump-focused*, *suspended accounts*, and more. The researchers met to discuss codes and any disagreements on coding were identified and agreed upon before moving forward. The codes were then categorized using selective coding. A second phase consisting of a unique sample of an additional 400 tweets was coded with the previous codes found in phase one.

The team met to discuss, consolidate previous codes, and generate new codes based on phase two coding comparisons. Another 400-tweet sample was conducted under selective coding to ensure 95% coder agreement in phase three. An intercoder agreement was met at the end of phase four, again with 95% agreement on a new sample of 400 tweets. In total, around 1,600 tweets were coded in the four coding phases, ensuring intercoder reliability. As a result of the open coding process, five selective coding categories were chosen to characterize how the stigmatization of infants with NAS is represented on social media. The codes selected for selective coding are as follows: *Medically Divisive, Political, Information Sharing, Account Error,* and *Miscellaneous*. (All sample tweets across each category were kept in the original format, including grammatical errors.)

1. *Medically Divisive*[6]: *Medically divisive* tweets were evaluated based on the main content of the tweet and deemed divisive if they were critical of medical professionals or their actions during the event (e.g., strikes and protests). The more than 100 protestors at the event were mostly Boston Medical Center employees (Dooling & Chen, 2019). As one user tweeted, "They are protesting a Woman caring for addicted babies. Fools indeed!" The main subject of the tweet was focused on the protestors during the former First Lady's visit.
2. *Political:* Tweets were classified as *political* when the main subject was focused on actions of political figures, laws surrounding abortions/NAS, the Trump family, or attacks on the left or right. For example, "Patients aren't doing to well with everyone outside though. That's Dem priorities though. Nothing more important then showing your hatred for POTUS. So a few people die, it's worth it. Bunch of morons."

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[6] The research team actively discussed and clarified the distinction between *medically divisive* and *political* tweets. At times, the team reviewed a tweet that could be coded as both, but re-focused on the main subject of the tweet. For example, the tweet regarding the protesters "... So u "medical professionals" really wanna stand their n protest the First Lady coming to visit newborn babies born addicted to drugs!!! All because ur a buncha cry baby snowflakes that "don't like Trump"!? Y'all r truly a FUCKING DISGRACE! EVERY..SINGLE..ONE..OF..U!!🤬🖕" This tweet still confirmed the presence of medical professionals protesting but the main subject and message was political in nature. While *medically divisive* tweets were identified when they were the main subjects of the protest and creating doubt in medical professionals. "Good for you!! Can you believe the audacity of them!? Of ALL things to protest, Melania cuddling drug addicted babies...."

3. *Information sharing:* These included shared articles, paraphrased statements, or news about Melania Trump's visit. This category primarily aimed to collect more shared information and fewer opinions, especially where implicit bias was visible. For example, "On Wednesday, First Lady Melania Trump visited Boston Medical Center to learn about programs that center on the care of mothers and children affected by opioid addiction and Neonatal Abstinence Syndrome." This news focused on information rather than personal opinion.
4. *Account errors*: *Account error* tweets were deleted tweets, suspended accounts, or tweets unavailable due to privacy restrictions. The decision to code these accordingly was made because the researchers could not determine the full context of the tweet due to Twitter or users' actions. These tweets will be investigated in future research.
5. *Miscellaneous*: *Miscellaneous* is a category for any tweets that focused on *Q-Anon* ideas, *humor/sarcasm*, and/or *no context.*

   5.a) *Q-Anon: Q-Anon* tweets were identified by any ideologies known by the research team to be associated with the Q-Anon conspiracy theory. Key phrases were monitored, such as mentions of George Soros, "The Storm", pizzagate, and more (Roose, 2021). If tweets mentioned these topics, the researchers would code them as miscellaneous. For example: "If Soros had anything that took do with it they probably got at least $1000 each. Maybe more."

   5.b) *Humor*: *Humor* tweets focused on making light of the situation through jokes or sarcasm. Several of these tweets mentioned protestors, but this was communicated through sarcasm. "Good for these protesters. We must put an end to cuddling with drug-addicted babies."

5. c) *No Context*: Through keyword targeting, some tweets that did not mention the event were added to the dataset. By targeting the keywords “Babies” and “addicted”, some of the tweets that mentioned such words were coded as having no context if it was unclear what the tweet was referencing. For example, “Do you even what it means before opening your mouth? We Americans still remember the days when many infants born with drugs addiction and HIV... Does it ring a bell?” In addition, reply-to tweets or quote tweets to another tweet that did not provide context due to tweet accessibility were coded as *no context* because the full context of the discourse was unknown. For example, this tweet was a quote tweet of a video for which the video creator was suspended. “Perfect illustration! Some, never grow out of their small minds.”

The researchers then calculated the frequencies of each category during the pre-event, event horizon, and post-event periods. Polarized word clouds (visual display of most frequently appeared words in a source text)[7] for these three event periods were also generated. The dates surrounding the events and associated tweet counts were identified and then connected to specify different stages of the issue-attention cycle. Finally, a chi-square test was performed to compare the statistical significance across all three timeframes and between the event horizon and post-event period separately.

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[7] https://www.betterevaluation.org/methods-approaches/methods/word-cloud#:~:text=Word%20clouds%20or%20tag%20clouds,in%20the%20document(s).

4.7 Results

4.7.1 *Frequency and percentage of each event*

The three timeframes were organized in a CSV file and imported into "R" statistical software for analysis (R core Team, 2021). Each timeframe was then analyzed for the frequency of tweets in each category, which can be found in Table 17.

The pre-event

Before the event (pre-event period, October 30-November 5), 56.1% (n=60) of tweets shared *information* about the upcoming visit and neonatal abstinence syndrome. In addition, 28.0% (n=28) of tweets were classified as *account error*s. The tweet with the highest number of favorites (31 favorites) discussed improved treatment for babies with NAS. The highest retweeted tweet (n=12) mentioned the frequency of babies born addicted to cocaine.

The event horizon

The second timeframe (November 6-7), which the researchers identified as the event horizon, analyzed tweet frequencies during the 48 hours of the event. *Account errors* increased to 37.1% (n=777) of tweets and were the highest percentage of tweets in the timeframe. A sizable share of the tweets (22.6%; n=477) were *medically divisive*, while 12.5% (n=265) were *political*. Though the conversation was primarily focused on the medical professionals, the most favored (32,329) and retweeted (7,654) tweet was from Melania Trump's tweet: "Wonderful day @The_BMC Medical Center yesterday. Met with incredible doctors, nurses, and families. #BeBest continues to promote programs that help people struggling w/ #opioid addiction."

The post-event

The third timeframe (November 8-14), or the post-event period, saw *political* as the primary coding category, with 20.6% (n=120) of tweets in this period. *Medically divisive* declined to 15.1% (n=89) of tweets compared to the previous timeframe, and a*ccount error* was still substantial with 32.7% (n=198) of the total tweets. The most favorited (4,046) and retweeted (1,308) tweet was from the official White House Twitter account: “On Wednesday, @FLOTUS visited Boston Medical Center to learn about programs that center on the care of mothers and children affected by opioid addiction and Neonatal Abstinence Syndrome. Read more on her visit: http://45.wh.gov/5yKBD8.”

Account errors were also sub-coded as *deleted*, *private,* or *suspended accounts*. In timeframe two (the event-horizon period), there were 729 tweets from *suspended accounts* and 12 *deleted* tweets; timeframe three (the post-event period) consisted of 170 tweets from *suspended accounts* with only five *deleted* tweets.

Table 17. Frequency and percentage of tweets in each category during pre-event, event horizon, and post-event period

Pre-Event				
Tweets from October 30th - November 5th (n = 107)				
Medically Divisive	Political	Information Sharing	No Context Miscellaneous	Account Error
1	10	60	8	28
.93%	9.3%	56.1%	5.6%	28.0%
Event Horizon				
Tweets from November 6th - November 7th (n = 2,105)				
Medically Divisive	Political	Information Sharing	No Context Miscellaneous	Account Error
477	303	265	283	778
22.64%	14.3%	12.5%	13.3%	37.1%
Post-Event				
Tweets from November 8th - 14th (n = 577)				

Medically Divisive	Political	Information Sharing	No Context Miscellaneous	Account Error
89	120	91	79	198
15.1%	20.6%	15.6%	15.6%	32.7%

4.7.2 Comparing the events

Figure 11 and 12 utilize a word cloud approach to compare the type of language used across the three timeframes. The polarized word cloud in Figure 11 highlights the most common terms used. “Volunteer” and “heal” were the most frequently used words during the pre-event period; “protest(ing)”, “addicted”, and “Boston” were the most-used words during the event horizon period; and in the post-event period, “protests”, “first lady” and “Melania” were the most used words. Two terms used over the event horizon period (timeframe 2): “addicted”, and “protest(ing)” were classified as the most significant words based on their higher frequency of mention during the entire timeframe. Figure 12 illustrates the difference in the pattern of language between the pre-and post-event period. During the pre-event period, language emphasizing “neonatal abstinence syndrome”, “heal”, “drug-addicted”, and “volunteer” were highlighted. During the *post-event* period, the language takes on a more political and divisive tone, with words including “Melania”, “First Lady”, “drugs”, “addicted”, and “protests” identified as significant. These word clouds highlight the potential significance of the intersection of divisive politics and the care of newborns impacted by the opioid crisis. Although the intention of Mrs. Trump’s visit was not immigration, there were mixed reactions in the comment section of Twitter posts regarding her visit and the perceived disconnect between her visit and ongoing immigration concerns.

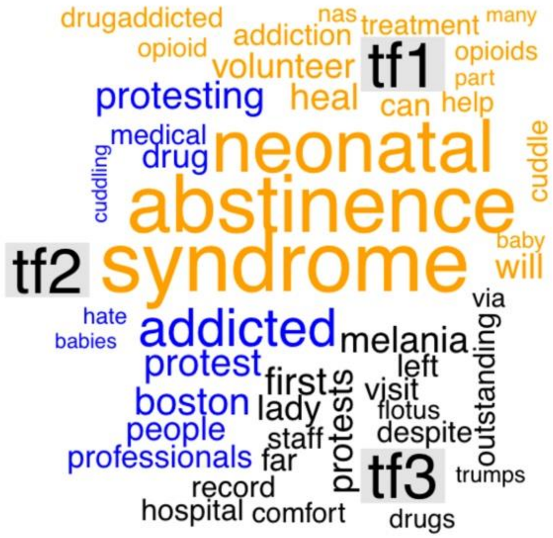

Figure 11. Polarized word cloud for pre-event, event horizon, and post-event timeframes from October 30th - November 14th, 2019.

Figure 12. Differences in language use between the pre- and post-event period (October 30-November 5 and November 8-14, 2019.

4.7.3 Framing the event within the issue-attention cycle

Figure 13 demonstrates the volume trend of tweets containing NAS keywords during the pre-event, event horizon, and the post-event periods over the 16-day timeframe around Trump's visit to Boston Medical Center on November 6, 2019. It also provides an illustration of the three timeframes used in this research and their association with different stages of the issue-attention cycle. From October 30-November 5 (pre-event), the pattern of the tweet counts was mostly flat, without any visible outliers. Therefore, this period can be placed within the *pre-problem stage* of the issue-attention cycle, as a sensitive issue like NAS did not receive substantial public attention according to the lower frequencies of the searched words. The outliers from November 6-7 (event horizon) are strongly visible, including the highest count of NAS keywords within the investigated timeline. It is appropriate to classify this period under the issue-attention stage of *alarmed discovery and euphoric enthusiasm*, which is a convincing example of a sudden episode or event that causes the public to become aware of and alarmed about the issue. The keyword counts from November 8-14 (post-event) again had a relatively flat pattern. According to Nisbet and Huge (2006), an issue may not always follow all five stages of the issue-attention cycle. However, at some point, a phase will arrive when the importance of the event will fade, and its association with the specific problem will diminish in attention (Nisbet & Huge, 2006). Regarding Melania Trump's visit to Boston Medical Center, people might have concluded that the cost (in terms of time and effort) of continuing conversations about NAS and/or FLOTUS' vision on Twitter that outweighed their benefits. Therefore, intensity of interest concerning the issue gradually declined and later became insignificant. The post-event study period (November 8-14) encompasses stages 3-5 of the issue-attention cycle wherein interest in the issue becomes flat and generates little conversation.

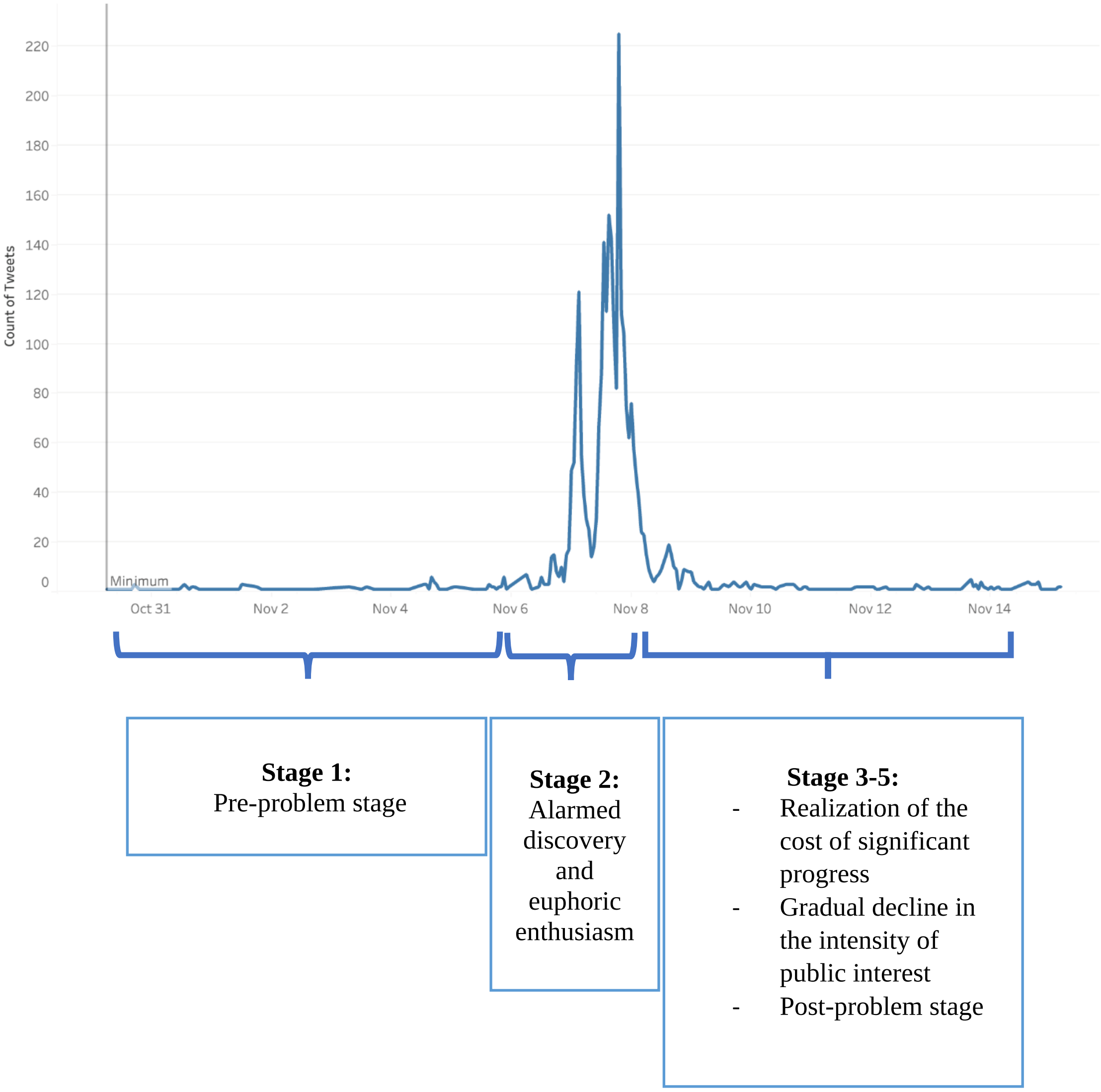

Figure 13: Volume trend of tweets containing NAS keywords during the timeframes of the event, and the stages of the issue-attention cycle in association with the timeframes.

4.7.4 Changes in Frequency

Tables 18 and 19 illustrate the changes in frequency of codes between the timeframes with a specific examination of the *account error* code in Table 18. The most substantial changes occurred between the event horizon and post-event periods. The highest frequency during the event horizon phase was *medically divisive* tweets, while the primary focus during the post-event phase was *politics*. This illustrates the fluidity of social media participation and conversation over an event period.

Table 18. A breakdown of the *account errors* code between pre-event, event-horizon, and post-event periods (October 30 – November 14, 2019)

Frequency Table Codes			
	Pre-event (10/30-11/5)	**Event-horizon (11/6-11/7)**	**Post-event (11/8-11/14)**
Account error	28	777	198
Information Sharing	60	265	91
Medically divisive	1	477	89
No context / Miscellaneous	8	283	79
Political	10	303	120

Table 19. Changes in frequency of the account error codes between pre-event, event-horizon, and post-event periods (October 30 – November 14, 2019).

Frequency Table Account Error			
	Pre-event (10/30-11/5)	**Event-horizon (11/6-11/7)**	**Post-event (11/8-11/14)**
Account found	79	1328	382
Deleted	3	12	5
Private account	5	37	17
Suspended account	18	729	170

A more detailed examination of coded *account error* tweets is notable. The researchers noticed that a large segment of these tweets was from *suspended accounts,* especially for the event horizon period. Table 18 illustrates that the volume of *account error* tweets was highest during this period. Looking more in-depth at this period, *suspended accounts* represented a large share of the *account errors* category. Twitter authorizes the right to suspend any account if reported and deemed to violate Twitter's rules surrounding abuse[8]. This finding is worthy of future research and may add insight into the politicization of this event and issue.

4.7.5 Chi-Square Test

Tests of significance were performed across all three timeframes and between timeframe 2 (tf2) and timeframe 3 (tf3) specifically (Table 20). The results were significant across all tweets, highlighting the perceived importance of this "event." This also highlights the importance of political figures, like the first lady's visit to the Boston Medical Center, as a driver of communication and messaging. The highest score between tf2 and tf3 was for *politically* coded tweets with $x^2(1) = 1966.8$ ($p < .0001$), further reinforcing the potentially divisive nature of the event and issue.

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[8] https://help.twitter.com/en/rules-and-policies/notices-on-twitter#:~:text=When%20we%20permanently%20suspend%20an,believe%20we%20made%20an%20error.

Table 20. Result of chi-square tests between all three timeframes and between timeframe 2 (tf2) and timeframe 3 (tf3)

Chi-Square Test for Given Probabilities (All Three Timeframes)		
	X^2	P-value
Code and timeframe	$\chi 2$ [df = 8] = 183.15	$p < .0001$
Suspended account / tf	$\chi 2$ [df = 4] = 8.23	$p = .08$
Account error	$\chi 2$ [df = 2] = 924.1	$p < .0001$
Information sharing	$\chi 2$ [df = 2] = 176.11	$p < .0001$
Medically divisive	$\chi 2$ [df = 2] = 678.77	$p < .0001$
No context	$\chi 2$ [df = 2] = 330.49	$p < .0001$
Political	$\chi 2$ [df = 2] = 4124.7	$p < .0001$
Chi-Square Test for Given Probabilities (tf2 & tf3)		
	X^2	P-value
Code and timeframe	$\chi 2$ [df = 1] = 867.78	$p < .0001$
Suspended account / tf	$\chi 2$ [df = 1] = 347.59	$p < .0001$
Account error	$\chi 2$ [df = 2] = 344.672	$p < .0001$
Information sharing	$\chi 2$ [df = 1] = 85.045	$p < .0001$
Medically divisive	$\chi 2$ [df = 1] = 265.98	$p < .0001$
No context	$\chi 2$ [df = 1] = 114.96	$p < .0001$
Political	$\chi 2$ [df = 1] = 1966.8	$p < .0001$

4.8 Discussion

Twitter has become a popular social media platform for discussing various issues and opinions (Akram & Kumar, 2017). Examining stigmatizing language used on social media is an essential research area, given that social media discourse can reinforce false stereotypes and narratives around sensitive issues, including those concerning health (Dekeseredy et al., 2021). As one of the largest social networking sites and integrated communication tools, Twitter provides a harbor for thoughts, opinions, and sentiments (Evans et al., 2011). However, more recently, Twitter has been criticized for spreading false information that circulates faster than factual information (Radzikowski et al., 2016; Soroush et al., 2018; Starbird et al., 2014). Malicious language, incorrect information, and the associated stigmatization negatively impact mothers with SUD, OUD, and children diagnosed with NAS. Stigmatizing language may prevent those being stigmatized from seeking appropriate medical care and treatment (Dekeseredy et al., 2021). Our study is essential to the broader body of research about SUDs and NAS because we identify and explore the specific language used around NAS on the popular social networking site Twitter.

This study utilized a unique event focused on a hospital that had recently adopted a new NAS program. We analyzed social media discussion of the event to understand the social media landscape of terminology and opinion sharing, focusing on infants with NAS. The event included a visit by a high-level political figure (the first lady of the US, Melania Trump) to highlight this innovative treatment intervention. We divided our analysis into pre-event, event horizon, and post-event timeframes. Results show that the largest number of tweets (56.07%) fell into the *information-sharing* category during the pre-event period. Before the event, people discussed the complexities and nuances of NAS, further reinforcing the cultural relevance of opioid-related language on social media.

In the event horizon period, an increase in the number of tweets (22.64%) coded as *medically divisive* occurred. The most common critique was a criticism of the medical professionals protesting the FLOTUS's visit to see the NAS palliative care program. The most surprising finding from this period was the high volume of *account error* tweets (37.06%), most of which were from *suspended accounts* (54.89%). Twitter reserves the right to suspend accounts temporarily or permanently based on several factors, with a critical focus on the nature of the violation of Twitter's Rules.[9] Twitter's Rules emphasize the importance of the public commons for open expression free of violence, threats, or other negative behavior that seeks to weaken the public discourse. Thus, the Rules reserve the right for Twitter to constrain speech deemed unsafe, inauthentic, or violate privacy. Given the potential discourse embedded in suspended accounts, future research will explore the content and orientation of these accounts around NAS and SUD issues.

The *account error* tweets were still typical in the post-event period (32.7%). The second-highest number of tweets in the post-event period were coded as *political* (20.6%), and the third highest was *medically divisive* (15.1%). The results reveal that each period had a different public Twitter focus. Chi-square analyses revealed that all coded categories were significant, with the *political* category of tweets seeing the most significant increase during the event horizon and post-event periods.

Issue-centered conversations on social media can often underestimate the more significant issue. The issue-attention cycle applied in this research indicated how a public problem like NAS fades from the center of public attention. It is assumed that most people who used stigmatizing words on Twitter about NAS did not significantly reveal their concerns before the First Lady visited Boston Medical Center's pediatric unit to visit children with NAS. Her visit generated attention and spurred some people to use their social media "voice" on November 6, 2019, and the following day, creating a situation where they became alarmed and enthusiastic about the conversations about NAS. However, the problem subsequently fell from public attention when individuals realized the amount of time and effort they had to put into continuing the conversations on Twitter. Next, intensity of interest further declined, and so did the frequency of the tweet count,

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[9] https://help.twitter.com/en/rules-and-policies/twitter-rules

which showed the diminishment of interest in talking about the problem in a more serious context. Finally, we can assume the problem moved into a “twilight realm” where Twitter users’ interest in it became insignificant as little attention was being paid to the problem without any potential to solve it.

This study demonstrates that people express their opinions differently when focusing on an event, as the larger significance and impacts of the issue at stake are often ignored. It is usually only in hindsight that we understand the positive or negative effects of political or celebrity figures shining a light on a particular issue. For example, First Lady Betty Ford was well known and beloved for her ability to bring attention, and many would argue, reduce the stigma associated with breast cancer treatment and alcohol abuse (Dubriwny, 2008). Conversely, many criticized First Lady Nancy Reagan’s “Just say no” campaign encouraging young people to avoid using any illicit substance for doing the opposite (Short et al., 2005). Both cases highlight the potential impact political figures' platforms may have on healthcare communications.

Overall, the conversation and language used on Twitter during FLOTUS’s visit to the Boston Medical Center failed to highlight the clinical and social challenges associated with NAS, identify potential solutions, or reduce the stigma around it. Understanding the impact of negative stereotypes and false information on mothers and children suffering from SUDs and NAS is vital to professionals working with these patients and consumers of social media generally (Dekeseredy et al., 2021). One strategy for mitigating these risks is to pressure social media platforms like Twitter to share quality information and help minimize stereotypes and stigmatizing language (Ramo et al., 2019).

Previous studies suggest that effective communication can increase public support for comprehensive substance use policies and harm reduction programs (Bachhuber et al., 2015;

McGinty et al., 2017). Social media platforms like Twitter can be practical communication tools to achieve this goal if utilized appropriately. Education programs and social awareness campaigns using social media might have the potential to reduce stigmatizing language use (Chenworth et al., 2021a). Healthcare providers can also work to change the narratives and stigma around NAS (Shapiro et al., 2018). Improved communication between medical staff and mothers with SUDs can be another effective tool to reduce the feelings of stigmatization and unfair treatment surrounding prenatal substance use (Stone, 2015b). Providing compassionate, evidence-based care for mothers and children affected by opioids starts by removing inaccurate and problematic language, such as "infants born addicted to opioids" (Kowalchuk et al., 2018; Shapiro et al., 2018b).

To accomplish this, the Center for Substance Abuse Treatment (CSAT) created a language guide in 2004, which can serve as a foundation for a new approach to reducing stigmatizing language. The Recovery Research Institute recently published an "Addictionary" to draw attention to the terminologies that perpetuate stigma around substance use disorders and promote the use of words that will advance the understanding of this disease (CSAT, 2004; RRI, n.d.). In addition, the Executive Office of the President's Office of National Drug Control policy published a memorandum in 2017 titled *Changing the Language of Addiction*, which addressed terminology related to substance use and substance use disorder (ONDCP, 2017). However, no established addiction terminologies describe children with NAS as we have for adults with SUD (Kowalchuk et al., 2018). Existing language guides are older and more focused on addiction and dependence than they are on NAS. To avoid using stigmatizing terms, there is a need to reach a consensus on a specially established "addiction-ary" focused on NAS-related language. Such a reference document would explicitly exclude stigmatizing language like ‘born addicted’ or ‘addicted babies’ and include a proper definition of NAS and related terminologies.

4.9 Limitations

This study has several limitations, as this research was based on Twitter data, which is not representative of the public at large. Most Twitter users are younger and are more racially diverse than the general population (Chenworth et al., 2021b). The researchers could not measure the sentiments behind the tweets but instead focused on their frequencies. However, while time-consuming, the qualitative coding process ensured 95% accuracy across coders. To further ensure reliability and validity, the example tweets included in this paper had words and grammatical errors that the researchers did not fix or manipulate to maintain integrity. There was a high volume of *account errors*, especially in the event horizon and the post-event periods, for which the researchers could not read the tweets. Among these *account errors*, most of the tweets were from *suspended accounts*. Another limitation is our inability to measure the time of the account suspensions and whether they relate to this event or others. The statistical analyses found that *political* codes were the most significant during the event horizon and post-event periods but could not establish the reasons behind this significance. The researchers plan to further analyze the significance of account errors and the politicization involved in the tweets for the same event.

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CHAPTER FIVE: CONCLUSION, POLICY IMPLICATION, AND FUTURE DIRECTION

5.1 Conclusion

NAS-focused research has observed significant risks, treatments, and outcomes management discovery over the past several decades. However, there is still much to investigate about the long-term effects, such as neurodevelopmental and healthcare utilization, of children with NAS and their families. Additionally, malicious language, spreading misinformation, and the resulting stigmatization also need special consideration to be addressed as it discourages children with NAS and mothers with SUD and OUD from seeking the necessary medical care and treatment they need. The present dissertation identified that children treated with the MAiN model of care had a lower incidence of neurodevelopmental diagnosis and higher rates of neurodevelopmental screening compared to those who received traditional care from birth to 4.5 years. It also found children with NAS had higher odds of hospital readmission and a longer hospital length of stay compared to children born late preterm from 0-3 years of age. Finally, it analyzed an event focusing on first lady Melania Trump's visit to a NAS treatment program, which demonstrated that people express their opinions differently on social media platforms like Twitter when focusing on an event. At the same time, they often ignore the larger significance and impacts related to these conversations.

5.2 Policy implication

There are other innovation programs like MAiN commencing and growing across the country. For example, the Advancing Clinical Trials in Neonatal Opioid Withdrawal Syndrome (ACT NOW) Program in collaboration with the NICHD Neonatal Research Network and the ISPCTN (National Institutes of Health, 2023b), the Eat, Sleep, Console (ESC) approach (National Institutes of Health, 2023a), the Cuddling Assists in Lowering Maternal and Infant Stress (CALM), etc. (Wachman, 2021). For children with NAS to receive long-term physical and psychological care it is crucial that programs supporting them are widely recognized and reinforced.

One government strategy to improve care for infants with NAS and their mothers is to increase insurance coverage through Medicaid and the state children's health insurance programs (SCHIP) (Skinner & Slifkin, 2007). A bill (H.R. 5789) was proposed in 2018 that requires the Secretary of Health and Human Services to provide guidance to states on the best practices for treating these infants under Medicaid and SCHIP. Additionally, the Comptroller General of the US is required to conduct a study on gaps in Medicaid coverage for pregnant and postpartum women with substance use disorder, which would direct the Secretary of HHS to issue guidance to states on best practices under these coverages (115th Congress, 2018). In addition to expanding insurance coverage, the government can augment funding, encourage comprehensive research, and mobilize community resources to raise public awareness about innovative programs aimed at addressing NAS.

As a known fact, early innovation programs can have a significant positive impact on a child's development (Blauw-Hospers & Hadders-Algra, 2005). These programs can help children from birth through 3 years of age (36 months) learn important skills and provide special education services for children aged 3 and older with an identified developmental delay or disability (CDC, 2021a). Program initiatives can include a variety of therapy and other services, based on the child's individual needs, to help the child learn, walk, talk, interact with others, and perform other tasks. Each state offers Child Find programs that evaluate and identify children who require special education services, which should also include children with NAS (Lee, 2023). According to the Individuals with Disabilities Education Act (IDEA), all children diagnosed with a disability must receive special education services. Children under the age of 3 who are at risk of developmental delays due to complex conditions like NAS can also qualify for early intervention treatment services, even if they have not received a formal diagnosis (Peacock-Chambers et al., 2019b). However, there is insufficient data and information available on the number of children with NAS receiving services through Child Find and IDEA.

Although there have been more studies on neurodevelopmental diagnosis in children with NAS compared to studies on neurodevelopmental screening in this population, the current literature is still inadequate. The few studies that have been conducted suggest that children with a history of NAS are more likely to experience behavioral disorders, developmental delay, and speech disorders in early childhood compared to those without NAS (Hall et al., 2018). Additionally, they may require extended speech therapy and special educational services between the ages of 3 and 8 (Fill et al., 2018). These studies highlight the increased incidence of neurodevelopmental diagnosis in children with a history of NAS, further underscoring the need to implement and expand innovative programs like MAiN to support them. Most innovation programs targeting NAS aim to provide pharmacological and non-pharmacological treatment for children with high risk, rather than directly addressing neurodevelopmental disorders (Cook & Fantasia, 2019). Nevertheless, these programs can still create a pathway by potentially contributing to identifying and diagnosing neurodevelopmental disorders in this population.

As mentioned earlier, there is an inadequacy of research and guidelines focusing on neurodevelopmental screening, specifically for children with NAS. Caregivers and innovative programs should make necessary modifications to the current general developmental screening guidelines that are to be followed for these children. Lipkin and Macias (2013) provided some recommendations on how to improve policy and advocacy and research and development to increase neurodevelopmental screening for identifying early developmental disorders. They emphasized early screening and detection rates across healthcare, education, and social service sectors with refinement and coordination among entities. Developing guidance on specific ages for behavioral screening, integrated with developmental and ASD screening is critical. There is also a need to expand and compare the evidence base for the effectiveness of developmental surveillance activities, including the use and validity of developmental milestones. Current research should also identify barriers limiting pediatric healthcare professionals from conducting medical workups for etiology and known associated medical conditions in children with a high risk of developmental disorders, such as those with NAS. Additionally, policy implication by the government needs to encourage ongoing investigation around screening and referral rates to achieve universal screening of all children and the earliest identification of those with developmental disorders (Lipkin & Macias, 2013).

There is a growing national momentum for nurseries to adopt policies and standardized methods of caring for mothers with substance use disorders and children with NAS (Hudak et al., 2012). The MAiN program offers a comprehensive care model for opioid-dependent newborns and their mothers, which can be adapted and implemented broadly at the state level and also in lower-level nurseries throughout the country (Summey et al., 2018). Moreover, as researchers investigate further into this subject, it is crucial to have a better comprehension of the socioeconomic patterns and geographic distribution of mothers and infants with NAS, as well as policy implications across states (Dickes et al., 2017).

In terms of healthcare utilization, Policy implication should focus on the requirement of closer medical attention for children with NAS. With the progress of genetics and epigenetics research, personalized screening and treatment regimens may help direct resources for improving outcomes of children at high-risk (Liu et al., 2019). Regular visits with primary care physicians can also be an effective strategy to monitor their health and wellbeing. In this regard, Medicaid can play a significant role in improving the transition home for the high-risk children by performing home visit and case management (Patrick et al., 2015). Home visit has been observed as a measure to improve some clinical outcomes including neurodevelopmental and healthcare utilization among preterm children (Goyal et al., 2020). Therefore, it can also be significant for early detection and mitigation of withdrawal symptoms after discharge for children with NAS.

Studies found that shorter LOSD of children with NAS from birth hospitalization can trigger higher risk of readmission during the first year of their lives (Diop et al., 2022; Patrick et al., 2015). This indicates the lack of safer discharge practices and a need for improvements in inpatient care to reduce risks of readmission for children with NAS. Standardizing care through Quality Improvement (QI) efforts have the potential to reduce hospital LOSD from birth hospitalization; however, they can also increase the risk of hospital readmission later in life (Sarkar & Donn, 2006). Therefore, QI efforts should aim at both reducing LOSD and hospital readmission as a counterbalancing measure (Patrick et al. 2015).

Mothers of children with NAS also need to be brought under the light of implementing public health and policy changes. The US has several supportive programs controlled by the Health Resources and Service Administration and Maternal and Child Health Bureau, for example, The Healthy Start Program, The Head Start Programs, The Maternal, Infant, and Early Childhood Home Visiting Program, and the Supplemental Nutrition Program for Women, Children, and Children (WIC) can serve as guidelines for implementing such intervention programs that will benefit both children with NAS and their mothers (DHHS, 2015). Since 2003, a section of the Child Abuse and Prevention Treatment Act, which is known as the Plan of Safe Care (POSC) is used to guide the comprehensive service management for children with NAS, required by the child welfare legislation (NCSACW, 2022). The National Center on Substance Abuse and Child Welfare provides some successful practices and general guidelines; however, state level procedures are limited by resources and populations they serve and are heavily dependent on social services (Schroeder et al., 2018). Strengthening social support and child welfare systems is crucial to ensure the adequacy of preventative health maintenance visits (Liu et al, 2019). Recently, social services in some areas have been reinforced due to the increased incidence of NAS (França et al., 2016). However, federal funding for child welfare programs has remained stagnant (Patrick et al., 2017).

Increasing incidence of NAS across the country impose enormous challenges for hospitals and providers. Specific treatment for women with opioid use disorder may decrease the incidence of NAS and its negative health effects if initiate early during their reproductive age and before them becoming pregnant (Lie et al., 2019). Optimizing prenatal care is also essential for them and their children. To ensure this, several postnatal family provisions such as mental health support/substance abuse counseling for mothers, enrollment in healthy parenting classes, and early treatment intervention program for children should be properly stimulated (Sutter et al., 2017).

Finally, stigmatizing language can cause the fear of discrimination, judgment, and punishment for mothers with OUD and their children with NAS, thereby discouraging or preventing them from seeking access to proper care. Policy implications can promote guidelines for better communication between medical staff and these mothers to reduce feelings of stigmatization and unfair treatment (Stone 2015). The practice of stigmatizing language on social media platforms like Twitter, either willingly or unwillingly, can also impose potential harm to children with NAS as they grow up (Webster 2018). Like traditional media, social media can also have significant impacts on politics and policy. Therefore, understanding stigmatizing language is a critical contemporary field of study that needs additional research and investigation. Policy discussions and decisions can often be triggered by increasing recognition and conversation around a specific focusing event. The first lady Melania Trump's visit to the Boston Medical Center on November 6, 2019, and the debate regarding NAS on Twitter during and following the event had the potential to influence this policy environment and create opportunities for policy action in this arena. However, if such issues rise and fall from the agenda due to diminished public interest, policy initiatives can be challenging to begin or follow through on.

Utilizing social media to explore critical health and policy issues related to the opioid crisis is an emerging area of research. Understanding the intersection of health and policy issues through exploring public commentary regarding stigma is instructive and can be leveraged for more effective health communication and policy development. Leveraging public voices, like politicians, for improving public and community health is an essential tool in today’s 24/7 media environment. This study found that people’s comments where information focused, medically divisive, political, and even used humor regarding this event associated with a treatment program related to NAS. However, intentionally or unintentionally many of the tweets used stigmatizing language to express their opinions.

5.3 Future direction

Several studies argued that future research should plan to involve prospective studies using standardized data collection tools to obtain real-time data rather than relying on administrative/billing data (Dickes et al., 2017; Hudson et al., 2016; Summey et al., 2018). It would be ideal for conducting randomized controlled trials to determine the effectiveness of the MAiN model. To encourage further research on neurodevelopmental screening in high-risk infants, it is crucial to address the issue of overlapping procedure codes and ensure their proper inclusion in billing and real-time data. Unification of all current development screenings, including early hearing, motor, behavioral and mental health is needed to simplify the process of screening and benefit affected children, their families, and the pediatric healthcare professional (Lipkin & Macias, 2013). This would facilitate accurate case identification, thereby providing valuable insights into the long-term outcomes of these populations.

Additionally, future research should incorporate larger sample sizes and longer follow-up periods for both MAiN infants and infants with NAS treated with standard of care, which would enable a more comprehensive comparison of neurodevelopmental screening and diagnosis between these two groups. The findings of this study indicated that the higher incidence of neurodevelopmental screening and diagnosis occurred at age 4 (48-54 months) in both groups. Additional follow-up beyond this age range could yield a more comprehensive analysis and demonstrate a better representation of these outcomes in these populations. Furthermore, there is a need for improved data recording that accurately identifies infants with NAS in SC, including detailed information on the specific prescription and illicit drug usage of their mothers that are responsible for their withdrawal symptoms.

Further investigation is necessary to address the necessary outpatient support for children with NAS so their risk of hospital readmission can be reduced (Diop et al., 2022). Efforts for future policy development and research should emphasize on reducing this adverse outcome for vulnerable population, especially for children with NAS, through guaranteeing a secure transition to home (Patrick et al., 2015). Such assurance needs to include investigating strategies to tackle the post discharge complications for children with NAS in both primary care and community-based settings (Patrick et. al., 2015, Diop et al., 2022). Readmission can indicate severe illness, and children with NAS who had shorter LOSDs from birth hospitalization can be more prone to hospital readmission later in their lives (Diop et al., 2022; Witt et al., 2017). Therefore, hospitals and healthcare providers should completely make sure that children with NAS are ready for discharge after a certain time of hospital admission and readmission.

Future research should also investigate if similar patterns apply for children with NAS and born late preterm with private insurance. There is also a need for understanding the complex interplay between biology, society, and environment that affects the health outcomes of children (Corr et al., 2021). To effectively monitor and treat these high-risk children, more research on illnesses related to withdrawal and prematurity, as well as the prescribed medications, should be taken into consideration (Liu et al., 2019). There are several comprehensive research endeavors, for example, the Environmental influences on Child Health Outcomes (ECHO) Program and The Helping to End Addiction Long-term (HEAL) initiative at national level (National Institutes of Health, 2023a, 2023b), the Managing Abstinence in Newborn (MAiN) model of care at state level (Summey et al., 2018) etc. that are ideally designed to direct future approaches for children affected by the opioid epidemic.

More well- matched retrospective studies are needed using improved and quality dataset, which can lead us to promptly obtain knowledge about this vulnerable population (Corr et al., 2021). Hospital billing data like Medicaid datasets should be more user friendly to serve public health research purposes. Months and dates of diagnoses and procedures should be properly inputted so researchers can accurately calculate patients age and duration of services they receive. It is also important to resolve the overlapping and missing data issues and ensure that all the necessary geographical information of the patients is included in the Medicaid dataset.

Finally, in collaboration with medical professionals and those suffering from SUDs, this dissertation argue for the co-creation of a special “addiction-ary” for social media platforms. This tool will include non-stigmatizing terminologies and best practices related to communication around issues of SUD, OUD, NAS, and others and take necessary steps to integrate them into social media platforms like Twitter. Consistent use of agreed-upon terminologies on social media can help reduce the use of stigmatizing language and discriminatory public health and social policies (Kelly et al., 2016). Social media users, authors, reviewers, and readers need to carefully and intentionally consider the language used to describe mothers with SUD and children with NAS to promote their necessary treatment and recovery.

In summary, these three research studies seek to increase our understanding and knowledge of NAS-related outcomes: neurodevelopmental screening and diagnoses, healthcare utilization that includes hospital and community level outcomes, and wider social outcomes with a study focused on the intersection of social media use and NAS. All three of these studies add depth and breadth to the literature on NAS and provide additional opportunities for research in the future.

5.4 References

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APPENDICES

Appendix A: Variables obtained and applied from the Medicaid claims

Category	Variables	Specific Aim	Data Source	Dataset Variable Name
Inclusion Criteria				
	Age	1,2	Birth Certificate	BIRTHDT, YRBTH
	NAS diagnosis	1,2	Medical	PDIAG, SDIAG1-8 PDIAG10, SDIAG10_1-11
	Opioid dependence diagnosis	1	Medical	PDIAG, SDIAG1-8 PDIAG10, SDIAG10_1-11
	Live birth	1,2	Medical	PDIAG, SDIAG1-8 PDIAG10, SDIAG10_1-11
	Late preterm	1		PDIAG, SDIAG1-8 PDIAG10, SDIAG10_1-11
Exclusion Criteria				
	Abnormal conditions	1	Medical	PDIAG, SDIAG1-8 PDIAG10, SDIAG10_1-11
	Gestation age (<35 weeks)	1	Birth Certificate	GEST
	Iatrogenic withdrawal	2	Medical	PDIAG, SDIAG1-8 PDIAG10, SDIAG10_1-11
	Non-exclusive	2		NAS_PRETERM (created)
Demographics				
	Age (mothers)	1,2	Medicaid Eligibility	AGEM
	Education (mothers)	1,2	Medicaid Eligibility	EDUCM
	Sex (infants)	1,2	Birth Certificate	SEX, BABY_SEX
	Race (infants)	1,2	Birth Certificate	RACE, NEW_RACE
Outcome Variables				
	Neurodevelopment disorders	1	Medical	PDIAG, SDIAG1-8 PDIAG10, SDIAG10_1-11
	Neurodevelopment screening	1	Medical	HCPCS, CPT
	Hospital readmission	2	Medical	AGE (age in years at admission)
	Hospital length of stay	2	Medical	LOSD
	Tweets	3	SMLC files	MESSAGES

	Deductive coding	3	SMLC files	CODING (created)
Independent Variables				
	Year of birth	1,2	Birth Certificate	BIRTHDT, YRBTH
	Groups	1,2	Birth Certificate	MAINVAR (created), NAS_PRETERM (created)
	Post type	3	SMLC files	POST_TYPE
Covariates				
	Birth weight	1,2	Birth Certificate	WEIGHT
	Gestation age	1,2	Birth Certificate	GEST
	Infections during pregnancy	1,2	Medical	INFECTION, INFECT
	Kotelchuck Prenatal Care Index	1,2	Medical	KOTELCHUCK
	Tobacco use during pregnancy	1,2	Medical	TOBACCO
	Tobacco use prior to pregnancy	1,2	Medical	TOBACCO_PREPREG
	WIC recipient	1,2	Medical	WIC

Appendix B: Diagnosis and Procedure codes used in this dissertation

Variables	ICD-9 codes	ICD-10 codes	CPT/HCPCS codes
NAS	'7795' '76072'[10]	'P961'	
Opioid-dependent	‘30400’ ‘30401’ ‘30402’ ‘30403’		
Live Birth	'V3000' - 'V3999'	'Z3800' 'Z3801' 'Z381' 'Z3830' 'Z3831' 'Z384' 'Z3861' 'Z3868' 'Z3869' 'Z387'	
ASD	'29900' '29901' '29902' '29903'	'F840'	'96110' '96112' '96113'
ADHD	'314' '3140' '31400' '31401' '3141' '3142' '3148' '3149'	'F900' 'F909' 'F901' 'F902' 'F908'	'90832' '90833' '90834' '90836' '90837' '90838' '90839' '90840' '90845' '90846' '90847' '90848' '90849' '90853' '90875' '90876' '9088' '90880'
Developmental delay	'V400' '3153' '31531' '31532' '31534' '31535' '31539'	'F800' 'F801' 'F802' 'F8081' 'F8082' 'F8089' 'H9325'	'96110' '96112' '96113'
Impairment in vision and hearing	‘3891’ ‘38910’ ‘38911’ ‘38912’ ‘38913’ ‘38914’ ‘38915’ ‘38916’ ‘38917’ ‘38918’ ‘3892’ ‘38920’ ‘38921’ ‘38922’ ‘3897’ ‘3898’ ‘3899’ ‘369’	‘H902’ ‘H9011’ ‘H9012’ ‘H900’ ‘H905’ ‘H904’ ‘H9041’ ‘H9042’ ‘H908’ ‘H9071’ ‘H9072’	‘99174’ ‘99173’ ‘92552’ ‘92553’ ‘92567’

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[10] Periods between the numbers were disregarded due to the nature of value input in the Medicaid datasets.

	‘3690’ ‘36900’ ‘36901’ ‘36902’ ‘36903’ ‘36904’ ‘36905’ ‘36906’ ‘36907’ ‘36908’ ‘3691’ ‘36910’ ‘36911’ ‘36912’ ‘36913’ ‘36914’ ‘36915’ ‘36916’ ‘36917’ ‘36918’ ‘3693’ ‘3694’ ‘3696’ ‘36960’ ‘36961’ ‘36962’ ‘36963’ ‘36964’ ‘36965’ ‘36966’ ‘36967’ ‘36968’ ‘36969’ ‘3697’ ‘36970’ ‘36971’ ‘36972’ ‘36973’ ‘36974’ ‘36975’ ‘36976’ ‘3698’ ‘3699’	‘H906’ ‘H913’ ‘H918X9’ ‘H9190’ ‘H540X33’ ‘H540X55’ ‘H5440’ ‘H540X45’ ‘H540X54’ ‘H540X44’ ‘H540X35’ ‘H540X53’ ‘H540X34’ ‘H540X43’ ‘H5450’ ‘H5410’ ‘H541152’ ‘H541225’ ‘H541142’ ‘H541224’ ‘H541132’ ‘H541223’ ‘H541151’ ‘H541215’ ‘H541141’ ‘H541214’ ‘H541131’ ‘H541213’ ‘H542X12’ ‘H542X21’ ‘H542X22’ ‘H543’ ‘H548’ ‘H54415A’ ‘H5442A5’ ‘H540413A’ ‘H5442A3’ ‘H54512A’ ‘H5452A2’ ‘H54511A’ ‘H5452A1’ ‘H5460’ ‘H547’	
Intellectual disability and mental retardation	'317' '318' '3180' '3181' '3182'	'F70' 'F71' 'F72' 'F73' 'F79'	'96110' '96112' '96113'
Late preterm	'76527' '76528'	'P0736' 'P0737' 'P0738' 'P0739'	
Newborn affected by maternal conditions or complications of labor/delivery	'760' '7600' '7601' '7602' '7603' '7604' '7605' '7606' '76061' '76062' '76063' '76064' '7608' '7609' '761'	'P00' 'P000' 'P001' 'P002' 'P003' 'P004' 'P005' 'P006' 'P007' 'P008' 'P0081' 'P0082' 'P0089'	

	'7610' '7611' '7612' '7613' '7614' '7615' '7616' '7617' '7618' '7619' '762' '7620' '7621' '7622' '7623' '7624' '7625' '7626' '7627' '7628' '7629' '763' '7630' '7631' '7632' '7633' '7634' '7635' '7636' '7637' '7638' '76381' '76382' '76383' '76384' '76389' '7639'	'P009' 'P01' 'P010' 'P011' 'P012' 'P013' 'P014' 'P015' 'P016' 'P017' 'P018' 'P019' 'P02' 'P020' 'P021' 'P022' 'P0220' 'P0229' 'P023' 'P024' 'P025' 'P026' 'P0260' 'P0269' 'P027' 'P0270' 'P0278' 'P028' 'P029' 'P03' 'P030' 'P031' 'P032' 'P033' 'P034' 'P035' 'P036' 'P038' 'P0381' 'P03810' 'P03811' 'P03819' 'P0382' 'P0389' 'P039'	
Other specified and unspecified perinatal conditions	'77989'	'P290' 'P2989' 'P941' 'P942' 'P9689'	
Respiratory perinatal condition/distress	'7706' '7707' '769' '790' '77089' '77087' '77084' '78609'	'P22' 'P220' 'P221' 'P228' 'P229' 'P27' 'P270' 'P271' 'P278' 'P279' 'P2881' 'P285'	
Fluid and electrolyte disorders	'2760' '2761' '2762' '2763' '2764' '2767' '2768' '27661' '27669'	'E87' 'E870' 'E871' 'E872' 'E8720' 'E8721' 'E8722' 'E8729' 'E873' 'E874' 'E875' 'E876' 'E877' 'E8770' 'E8771' 'E8779' 'E878'	
Cough	'7862	'R05'	
Fever	'78060'	'R509'	
Viral infection	'07999'	'B9789'	

Vomiting	'78703'	'R1110'	
Nasal congestion	'47819'	'R0981'	
Feeding difficulties	'7833' '77931' '77934' '7833' '6768'	'R63' 'R633' 'R6330'	
Abnormal weight loss	'78321'	'R634'	

Appendix C: Algorithm for iatrogenic withdrawal

Criteria	ICD-9 codes	ICD-10 Codes
Intraventricular hemorrhage	'7721' '77210' '77211' '77212' '77213' '77214'	'P523' 'P520' 'P521' 'P5221' 'P5222'
Periventricular leukomalacia	'7797'	'P912'
Necrotizing enterocolitis	'7775' '77750' '77751' '77752' '77753'	'P779' 'P771' 'P772' 'P773'
Spontaneous intestinal perforation	'7776'	'P780'
Bronchopulmonary dysplasia	'7707'	'P279'
Low birth weight	‘76501’ ‘76502’ ‘76503’ ‘76504’ ‘76505’ ‘76506’ ‘76511’ ‘76512’ ‘76513’ ‘76514’ ‘76515’ ‘76516’ ‘76521’ ‘76522’ ‘76523’ ‘76524’ ‘76525’ ‘76526’	‘76525’ ‘76526’ ‘P0701’ ‘P0702’ ‘P0703’ ‘P0704’ ‘P0705’ ‘P0706’ ‘P0721’ ‘P0722’ ‘P0723’ ‘P0724’ ‘P0725’ ‘P0726’ ‘P0731’ ‘P0732’ ‘P0733’ ‘P0734’ ‘P0735’