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ASSESSMENT OF POST-DISCHARGE HEALTH CARE UTILIZATION IN INFANTS WITH NEONATAL OPIOID WITHDRAWAL SYNDROME

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BY

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M.S., Pharmaceutical Sciences, The University of New Mexico, 2015

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ABSTRACT

Background/Objectives: Children born to mothers with opioid use disorder often show withdrawal effects characterized by increased stress, hyperirritability, tremors, tachycardia, sleep deprivation, and gastrointestinal discomfort, commonly known as "neonatal opioid withdrawal syndrome" (NOWS). Studies have shown that the effect of NOWS can lead to several health-related disorders later in life leading to increased health care utilization. However, detailed study of post-discharge health care utilization, specifically focusing on encounters with the health care system is currently lacking in the literature. Our objective was to evaluate health care utilization in infants who were diagnosed with NOWS during a one-year follow-up period after their discharge from the hospital. Secondly, we wanted to assess the relationship between NOWS related severity measures and post-discharge health care utilization during a one-year follow-up period.

Methods: Health Facts® data, collected from over 800 contributing CERNER hospitals across the United States, was used to identify infants who were diagnosed with NOWS. Health care utilization during a follow-up period of 365 days after the index period

(discharge date) was evaluated. As comparators, two groups were utilized: late preterm (gestational age: 33 weeks up to 36 6/7 weeks) and uncomplicated birth infants. Outcomes measured were rehospitalization, emergency department visits and outpatient visits. We used logistic regression model to assess the impact of NOWS on health care utilization after discharge. Poisson and Zero-inflated Poisson regression were used to quantify the incidence rates of the health care utilization event. Finally, Cox proportional-hazards regression was used to estimate time to first event related to health care utilization after discharge from the hospital.

Results: We identified our study cohort as infants who had birth related discharges between the period of January 1, 2011, and October 31, 2016 which included 3,526 infants with NOWS, 24,474 infants who had late preterm birth, and 88,452 infants who had uncomplicated births (representing a 25% sample of the births recorded). Mirroring the opioid epidemic in the U.S. there was an increasing trend in the incidence rate of NOWS. Infants with NOWS had significantly longer length of stay (14.9 days vs. 2.1 days, $p<0.001$), and higher cost (Median: $24,944 vs. $3,129, $p<0.001$) compared to uncomplicated birth group. Infants diagnosed with NOWS had significantly higher odds of one-year rehospitalization (Adjusted odds ratio: 1.7, 95% C.I.: 1.3-2.2) and 30-day rehospitalization (Adjusted odds ratio: 1.9, 95% C.I.: 1.3-2.6) compared to uncomplicated birth infants. There was no statistical difference in the risk of emergency department visits in the NOWS group compared to uncomplicated birth group after adjustment for confounders. Infants in the NOWS group had higher odds of any 30-day composite visit (emergency department visit or rehospitalization) compared to the uncomplicated birth group (Adjusted odds ratio: 1.4, 95% C.I.: 1.2-1.6). The results from logistic regression

models closely aligned with the findings from the Poisson, Zero-inflated Poisson, and Cox proportional-hazards regression models. Infants with NOWS had similar rates of post-discharge healthcare utilization when compared to late preterm infants. In examining the impact of NOWS severity measures on post-discharge health care utilization, we found that some of the measures, such as pharmacological management of NOWS, length of stay, receiving medications (e.g., benzodiazepines), and presence of respiratory conditions were associated with higher probability of post-discharge health care utilization. While the results from logistic regression models were inconsistent, results from principal component analysis, which combined NOWS severity measures, showed that NOWS severity was associated with post-discharge health care utilization.

Conclusions/Implications: Our study shows that the higher rates of health care utilization of infants who were diagnosed with NOWS is not just limited to a period of hospitalization for NOWS treatment but can also manifest for an extended period of time post-discharge. Hospital readmissions and emergency department visits could lead to additional physical, mental, and financial stress to the families of the affected infants. Furthermore, they signal presence of an underlying medical condition that could lead to poor health and even infant mortality. The findings of our study suggest that closer follow-up and management of infants may be necessary. Additional support to the infant-maternal dyad may help in improving health outcomes in these infants in the early years of their lives.

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CHAPTER 1: INTRODUCTION

1.1 Opioid use in pregnancy

Opioid use among women of reproductive age has been increasing steadily over the past decade. At least a third of women between the ages of 15-44 years filled a prescription for opioid as an outpatient each year between the years 2008 to 2012.[1] Reflecting the increase in the use of opioids among women of reproductive age, there has been a noteworthy increase in opioid use during pregnancy. A report on Medicaid patients stated that approximately 21.6% of pregnant women on Medicaid had filled a prescription for opioids.[2] The rates had gradually increased from 18.5% in 2000 to 22.8% in 2007.[2] In addition, 2.5% of the pregnant women on Medicaid had received prescription opioids for more than 30 days signifying prolonged exposure to opioids.[2] In commercially insured pregnant women, the prevalence of opioid prescription varied from 6 to 26%.[3] Studies conclude that the rate of prescription opioid use in pregnant women has grown two-folds in the last two decades.[1-5]

Increase in prescription opioid use has led to a surge in the non-medical use of opioids as well as the use of illicit opioids (e.g., heroin) during pregnancy. As the supply of prescription opioids is limited by physicians or as cost becomes a barrier, there is invariably a shift towards cheaper illicit opioids which is facilitated by the ease of availability.[6] The increasing trend in licit and illicit opioid use in women of reproductive age has resulted in a sharp increase in pregnant women who required treatment for opioid abuse. In 1992, approximately 2% of the pregnant women admitted to a substance abuse treatment program reported that opioid was the primary substance that they abused; the

proportion increased to approximately 19% in 2012.[7] Over two-thirds of pregnant women in a substance abuse treatment programs have a history of heroin use suggesting that origins of substance use disorder stem from both illicit drugs and misuse of prescription medications.[8]

1.2 Opioid use disorder in pregnancy

Opioids are any substances, natural or synthetic, which bind to the opioid receptors and modulate the pain, and other neurosensory activities of the body.[9] Prolonged use of opioids causes an imbalance in the activity of these receptors resulting in the patients to show the symptoms of opioid use disorder (OUD). OUD is characterized by craving, tolerance, impulsive, and continued use of opioids regardless of the adverse effects on the individual's health.[10] As with any disorder, OUD is considered a manageable condition that can be treated through medical and behavioral therapy. Medication Assisted Treatment (MAT) has been the cornerstone of treatment of OUD.[11] The treatment focuses on the substitution of illicit opioids by long-acting opioids that addresses the cravings of the individual while preventing adverse events that are associated with illicit opioids. OUD is treated with a drug that is either a full agonist (methadone) or a partial agonist (buprenorphine) of the opioid receptors. Administration of MAT is ideally a part of a broad treatment program that consists of addiction counseling, family therapy, and other social services.[12,13] It is important to note that there are only a limited number of providers in the United States that provide both substance abuse treatment and prenatal care.[14,15] While measures are being undertaken to expand the access to these services in pregnant women with OUD, substantial gaps exist in the perinatal and postnatal care of pregnant women with OUD.[16]

1.3 Outcomes associated with opioid use in pregnancy

1.3.1 Neonatal outcomes

Use of illicit opioids, such as heroin, is associated with increased risk of prematurity and intrauterine growth restriction.[17,18] Compared to infants born to a mother on methadone, infants born to mother who used heroin had lower weight, length, and head circumference at birth.[19,20] Additionally, evidence suggests that opioid use may be associated with birth defects such as congenital heart defects, neural tube defects, and clubfoot. However, these conclusions have been derived primarily from case-control studies and not all studies were adjusted for prenatal environment.[21] A study that analyzed the outcomes of prescription opioid used during pregnancy showed greater odds of preterm labor, premature delivery, fetal growth disorders, longer hospital stays, and maternal-fetal mortality compared to no opioid use.[22] Adverse neonatal outcomes associated with *in-utero* exposure to opioids can substantially increase the risk of adverse health outcomes later in the life of the infant.

1.3.2 Neonatal opioid withdrawal syndrome

More than half of the infants born to pregnant women with OUD develop withdrawal symptoms such as increased stress, hyperirritability, tremors, tachycardia, sleep deprivation, and gastrointestinal discomfort, which are collectively known as neonatal opioid withdrawal syndrome (NOWS), formerly known as neonatal abstinence syndrome (NAS).[23,24] Reflecting the steady growth in OUD during pregnancy, there has been a substantial increase in the incidence of NOWS and other opioid-related adverse events.[21] These infants require considerable amount of pharmacologic and non-

pharmacologic treatments, and have prolonged hospital stays after birth leading to a considerable economic burden to the health system.[25]

1.4 Health care utilization in infants with NOWS

Infants born with NOWS have prolonged hospital stay and higher health care utilization during their hospitalization.[25] Strategies, such as standardizing treatment protocols, management in outpatient settings, or use of adjunctive therapies for treatment of NOWS, have been evaluated to minimize the cost related to management of NOWS.[26-29] These studies aim to decrease the exposure to opioids during withdrawal and/or to decrease the length of stay (LOS) in the hospital and effectively reducing the cost of managing NOWS.[30] However, there is very little consensus on the approaches to treatment in NOWS[31-33] and its impact on long-term health-care utilization. Furthermore, most published research on NOWS is concentrated on the management of withdrawal effects and reducing LOS. Studies that evaluate long-term effects *in-utero* exposure to opioids and resultant health care utilization have been overlooked. A report evaluating health care utilization in a cohort of 499 infants who were diagnosed with NOWS during the first year of their life reported that 15% of the cohort required hospital readmissions and 22% of those who were readmitted required further readmissions.[34] Another study showed that children who had been diagnosed with NOWS/NAS had increased readmission rates in the first five years of life compared to controls.[35] Infants with NOWS who are discharged after less than 7 days of hospital stay have higher rates of hospital readmission compared to those who were discharged after 7 days.[36] Additionally, infants could also be prescribed barbiturates to alleviate their NOWS symptoms.[37] However, the safety and efficacy of prolonged exposure to barbiturates in the newborn period is not well characterized.[38-40]

While the treatment with opioids (with morphine or methadone) or treatment with phenobarbital is effective for the management of the symptom of NOWS, the infants require a gradual decrease in the medication dosing until it can be safely discontinued, resulting in longer hospital stays compared to infants who did not receive these medications. The management of NOWS with these medications early in the life of the infant, combined with the effect of *in-utero* exposure to opioids may lead to poor health outcomes later in life. The rising concerns regarding NOWS in relation to the opioid epidemic in the U.S. warrants a critical evaluation of its long-term consequences. Understanding the various treatment modalities in response to the severity of NOWS and the outcomes associated with these treatments can significantly contribute to improving the health outcomes and lowering the economic burden of the condition.

1.5 Study objectives

The overall goal of this study was to characterize and quantify post-discharge health care utilization in infants with NOWS compared to controls during a one-year follow-up period. The study utilized two control groups: a primary control group that included infants with uncomplicated births and a second control group that included late preterm births (gestational age: 33 weeks to 36 6/7 weeks). Secondary controls served as close comparators to the NOWS group as the condition overall is considered self-limiting, however, late preterm infants are susceptible to poor health and increased health care utilization during early life.[41,42] Post-discharge health care utilization was characterized by hospital readmissions, emergency department visits, and outpatient visits during a period of 365 days after discharge. In addition, this study evaluated the association between the severity of NOWS and how it affected health care utilization post-discharge. This study

utilized the Cerner Health Facts® (HF) database which includes de-identified electronic health records (EHR) from 872 participating CERNER hospital and clinics in the U.S. (years 2011-2017). **We hypothesized that infants who were diagnosed with NOWS at birth would have higher post-discharge health care utilization compared to infants without NOWS. Additionally, we hypothesized that pharmacological management of NOWS, use of adjunctive therapy (indices of NOWS severity) along with LOS and other medical conditions related to NOWS would be associated with overall increased post-discharge health care utilization.** To test these hypotheses we proposed the following Specific Aims:

1.6 Specific Aims

Aim 1: To compare and characterize post-discharge health care utilization of infants born with NOWS compared to controls (uncomplicated births and late preterm births) during a one-year follow-up period.

Hypothesis 1: Infants born with NOWS will show significantly higher post-discharge health care utilization compared to both control groups owing to the exposure to opioids in utero, and during the management of NOWS.

Aim 1 will be evaluated through the following sub-aims:

1.A) To compare the hospital readmissions in infants born with NOWS to controls.

1.B) To compare the emergency department visits in infants born with NOWS to controls.

1.C) To compare the outpatient visits in infants born with NOWS to controls.

Aim 2: To evaluate the relationship between NOWS severity measures (pharmacologic management of NOWS, use of adjunctive therapy, concurrently diagnosed complications associated with NOWS, and hospital length of stay) and post-discharge health care utilization in the one-year follow-up period

Hypothesis 2: Markers of severity of NOWS, including, but not limited to, pharmacologic treatment administered, use of adjunctive therapies (phenobarbital, clonidine), and LOS will be associated with increased health care utilization over the one-year follow-up period.

Aim 2 will be carried out through the following sub-aims:

2.A) To evaluate the relationship between NOWS severity measures and hospital readmissions.

2.B) To evaluate the relationship between NOWS severity measures and emergency department visits

2.C) To evaluate the relationship between NOWS severity measure and outpatient visits.

1.7 Significance

The rates of NOWS in the United States has been constantly rising owing to the opioid epidemic plaguing the country.[43] A majority of the infants diagnosed with NOWS will require treatment and longer hospitalization placing a significant burden on the healthcare system.[37,43] It is also important to note that almost 80% of the births associated with OUD in pregnancy are paid for by Medicaid leading to an immense financial stress on the social welfare system.[25,44] While extensive studies have been conducted to minimize

the burden on the health care system during the initial management of NOWS, the potential long-term impact of such interventions has been relatively overlooked.[26,27,29,39] Only a single prior study used balancing measures such as 30-day all-cause readmission, 30-day readmission related to NOWS, and death or unexpected ICU transfer within 30 days to measure the long-term effectiveness of the intervention.[45] Additionally, there are relatively few studies that evaluated long-term health care utilization in infants born with NOWS. A recent paper by Patrick et al. reported that infants with NOWS had a higher risk of hospital readmissions compared to controls.[36] However, the study did not include any information on the medications that the infants received during their hospital stay. Prior report suggests that variations exist in the treatment of NOWS, hence, detailed examination of treatment received by the infant for NOWS and its association with post-discharge health care utilization are critical.[37]

Our study expands on the work previously done by Patrick et al. by the addition of variables that quantifies the treatment received by the infants for NOWS along with severity measures of the condition. The administrative data used by Patrick et al. lacked clinical data related to the treatment of NOWS which limited the study findings. The availability of clinical information in the HF data overcomes those limitations by elaborating on specific treatment received by the infants during the management of NOWS and its effect on the health care utilization in the future. This study also provides a comprehensive comparative summary of post-discharge health care utilization in infants with and without NOWS. The model assessing the severity of NOWS (based on treatment received, LOS and other variables) and post-discharge health care utilization will be a valuable resource in developing interventions leading to improved health outcomes that do

not merely focus on reducing hospital stay but also minimizing long-term adverse events in infants born with NOWS.

CHAPTER 2: LITERATURE REVIEW

2.1 Introduction

In this chapter, a detailed review of NOWS is presented. In the first section, a description of NOWS will be provided, followed by an account of tools used to assess NOWS. Next, we discuss the management of NOWS. These topics will provide us an insight into the etiology, assessment, and treatment of NOWS in infants. Additionally, further insight into how long-term outcomes may manifest in infants with NOWS is provided. Finally, a detailed literature review of long-term health care utilization in infants with NOWS is presented.

2.2 Neonatal opioid withdrawal syndrome

Opioids are natural, synthetic or semisynthetic compounds that act on the opioid-receptors (mu, kappa, and delta) in the central nervous system (CNS) to produce analgesia.[46] They also produce effects such as euphoria, sedation, and depression of respiratory and gastrointestinal functions. Noradrenaline release is acutely inhibited in the synaptic terminal due to long-term opioid use. However, the rate of noradrenaline release in the synapses returns to normal after prolonged exposure and tolerance to opioid develops in chronic users.[32] Discontinuation of opioid use then results in abnormal release of noradrenaline which produces the signs of withdrawal.

Opioids are lipophilic compounds that can cross the placental and blood-brain barrier. Hence, prenatal opioid use affects the fetus. Active use of illicit opioids in during pregnancy has been associated with adverse birth outcomes in the infant, such as low birth

weight, and put the infant at additional risk because of other risky health behaviors related to active substance use.[47,48]

Treatment with methadone or buprenorphine is a preferred treatment of OUD in pregnancy and is designed to manage cravings, prevent withdrawal symptoms, and minimize stress to the fetus.[49] Pharmacological treatment is often accompanied by a wide variety of prenatal care services that help to maintain physical and mental well-being of the pregnant woman. While treatment with MAT, such as methadone, has substantial benefits compared to illicit opioid use, it does not guarantee successful abstinence and might be associated with significant, prolonged withdrawal effects in the newborn.[32]

A recently published systematic review concluded that the current evidence did not support detoxification as a viable intervention in pregnancy as it increased the risk of relapse.[50] Wang et al. also reported that detoxification during pregnancy increased the risk of relapse and illicit drug use.[51] However, the study also concluded that detoxification treatment did not affect the rates of NOWS or preterm birth.

Approximately 55 to 95% of the newborns with *in-utero* exposure to opioids develop postnatal withdrawal or NOWS.[32,52] NOWS is a complex physiological disorder that involves the nervous system (central and autonomic) and gastrointestinal system of the infant. While NOWS is a preferred term that defines opioid withdrawal in infants, the term Neonatal Abstinence Syndrome (NAS) is also widely used to describe withdrawal in infants. However, the term is not considered technically correct as the term "abstinence" suggests "intention" and infants are not capable of intentional understanding or action.[53] In addition, NAS can refer to withdrawal syndrome associated with other drugs.

Clinical manifestation of NOWS can be broadly classified into three categories: a) metabolic, vasomotor, and respiratory, b) gastrointestinal and c) CNS.[52-55] The first category is associated with symptoms, such as fever, sweating, mottling, and tachypnea. Gastrointestinal expressions are characterized by vomiting/regurgitation, diarrhea, weight loss, and poor feeding. CNS manifestations are characterized by tremors, disturbances in sleep, crying, irritability, and seizures. The symptoms of NOWS develop typically in 24 to 96 hours after birth; however, time of onset, and severity varies depending on multiple factors. While time to onset of NOWS could have multiple predictors, dose and half-life of the opioids that the infant was exposed to *in-utero* play a vital role in explaining the variability. Symptoms may develop later in infants who were exposed to opioids with a longer half-life period (e.g., methadone/buprenorphine) compared to opioids with a shorter half-life period (e.g., heroin). Symptoms attributable to NOWS from heroin use are often seen within 24 hours after birth. In comparison, symptoms of withdrawal from methadone may occur 24 to 72 hours after birth.[18] In buprenorphine exposed infants, the onset of withdrawal is around 40 hours after birth.[56,57] While NOWS is more common in infants exposed to methadone compared to buprenorphine, studies have shown that up to 50% of the infant exposed to buprenorphine develop NOWS.[32,49,57,58] Factors, such as exposure to other drugs, tobacco use, maternal nutrition, stress, opioid metabolism rates, and preterm delivery, may also affect the severity of NOWS.[59-61] Based on such observations, the American Academy of Pediatrics has recommended an in hospital observation period of 3 to 7 days in neonates with *in-utero* exposure to opioids.[32]

2.3 Assessment of NOWS

Assessment of neonates who develop symptoms of NOWS is critical to quantify the severity of withdrawal, thereby providing a guide to its management. Several tools have been developed to help in the assessment of NOWS in newborns. The Finnegan Neonatal Abstinence Scoring Tool (FNAST) was the first tool developed to assess the severity of NOWS.[52] It consists of 21 items and the possible score ranges from 0 to 62. Pharmacologic management of NOWS is usually recommended if the infant scores more than or equal to 8 on three consecutive evaluations or 12 or more on two consecutive evaluations. While it is the first and most widely utilized tool to score the severity of NOWS, it has been criticized for its complexity and length.[62] Additionally, lack of validation and suboptimal inter-rater reliability of the tool are concerning.[63] After the first Finnegan tool was developed, three other scoring tools, i.e., The Lipsitz Neonatal Drug Withdrawal Scoring System, the Neonatal Narcotic Withdrawal Index, and the Neonatal Withdrawal Inventory, were developed between 1975 and 1998.[64-66] They consist of a limited number of items (7-11) for simplicity and rapid administration. In 2010, the FNAST was modified into the MOTHER NAS scale which was utilized in the MOTHER randomized clinical trial study.[49] It is a 19-item scale with scores ranging from 0 to 42; the score required for treatment initiation is 9 or higher. In 2013, a shorter version of the FNAST, called the Finnegan Neonatal Abstinence Syndrome Scale-Short Form, was developed. It allows for faster assessment with fewer items and consists of 7 items with scores ranging from 0 to 16.[67] Treatment initiation with opioids is recommended at a score of 8 or higher. Recently, another approach, called Eat, Sleep, and Console (ESC), was developed by Grossman et al. for evaluation and treatment of infants with NOWS.[26] It utilizes a novel approach that

evaluates three criteria: eating (infant was able to eat ≥ 1 oz. per feed), sleeping (infant was able to sleep undisturbed ≥1 hour), and consoling (infant was able to be consoled within 10 minutes if crying). Infant meeting these criteria is considered "well managed" and requires no further intervention. Evidence from recent studies support ESC method to minimize exposure to pharmacological treatments and decrease the LOS.[68]

Another tool, known as the Neonatal Network Neurobehavioral Scale (NNNS) part II (Stress and abstinence scale) was developed in 2004.[69] The NNNS is a comprehensive instrument developed to examine outcomes in newborn after prenatal exposure to drugs. The stress/abstinence scale of the NNNS consists of 7 categories and consists of fifty items. It is important to note that this tool was not developed to be used as a guide for the treatment of NOWS but rather as a comprehensive newborn evaluation.

2.4 Management of NOWS

The objective of management of NOWS is to promote growth and development of the infant. Particular importance is given towards minimizing distress, improving food intake, and promoting mother-child bonding. While NOWS has been managed for over four decades there is lack of consistency in management protocols across different hospitals. In general, care to infant diagnosed with NOWS should include a multidisciplinary approach that includes non-pharmacologic and pharmacologic management based on the needs of the mother-infant dyad in an environment that is non-judgmental and fosters mother-infant bonding.[70] It is essential to note that the creation of a safe environment for the mother is equally important as there is significant stigma related to opioid use and withdrawal effects in the infants. Also, active participation of mothers in

the healing process by rooming-in and breastfeeding (when appropriate) has shown to benefit the mother-infant dyad.[63,71] Since maternal characteristics (e.g.: polysubstance use, presence of other comorbidities, low socio-economic status, stress, poor nutrition etc.) and environment are considered risk factors for poor health outcomes in those infants, post-partum support mechanism for the mother may be required to ensure the adequacy of care in the newborn.

2.4.1 Non-pharmacologic care

Infants who are prenatally exposed to opioids initially receive supportive care. Such care involves creating a gentle non-stimulating environment to calm the infant and promote rest.[32,53,59,63] It involves minimizing exposure to stimuli, such as light and noise, minimization of handling, promoting feeding to improve weight gain, and resting.[32] While several alternative care methods, such as massage and cuddling, have been utilized in the management of infants with NOWS, those intervention have not been rigorously assessed for their efficacy in reducing severity of NOWS. There is consistent evidence that supports breastfeeding and rooming-in to improve outcomes associated with NOWS.[71,72] Infants who were breastfed were shown to require less treatment with opioids and had a shorter LOS compared to infants who had received formula.[73,74] Unfortunately, rates of breastfeeding in mothers receiving treatment for OUD are low.[75] It is important to note that breastfeeding is contradicted in mother with HIV infection and illicit drug use, and such conditions are common in OUD. Additionally, infant exposure to opioids continues through breast milk, even though in very small amounts. Although the benefits of breastfeeding and rooming-in have been shown consistently, potential barriers to their

implementations, such as differences in the practice setting, unavailability of resources, and reluctance to introduce new practices, exist.[53]

2.4.2 Pharmacologic treatment

More than two-thirds of the infants with NOWS have limited response to non-pharmacologic management and hence require pharmacologic treatment for the management of the symptoms.[23,53] The rationale behind the use of pharmacologic treatment is short-term management of the symptoms, such as seizures, fever, and weight loss associated with NOWS, as drug withdrawal is self-limiting in nature.[32] There is significant variation in the management of NOWS and there is no specific standard of care that is widely accepted in relation to dosing, treatment initiation or use of adjunctive therapies.[37] There is a consensus on the use of oral morphine or methadone as first-line agents for the management of NOWS.[33] Morphine is a short-acting mu-opioid receptor agonist, and methadone is a much longer acting synthetic mu-opioid receptor agonist. While these medications have been consistently shown to be effective in the management of NOWS, their use is often associated with longer hospital stays. Side effects, such as sedation and depression of respiratory functions, are also common.[23,53] Studies also report that regardless of the opioid used for the treatment of NOWS, a structured protocol for treatment is significantly likely to lower treatment days, LOS, and result in lower doses of opioid administered to the infant.[76,77]

Adjunctive agents, such as phenobarbital and clonidine, are used if the infant fails to respond to the first-line agents. There are no specific guidelines for the addition of these second-line agents in the management of NOWS.[38] Studies on long-term safety and efficacy of these agents are also currently lacking.[29]

2.5 Long-term neurobehavioral and clinical outcomes associated with NOWS

There have been several reviews that highlight long-term neurobehavioral and clinical outcomes associated with prolonged *in-utero* opioid exposure in infants.[67,78,79] Studies have reported that problems with vision, such as strabismus, reduction in visual acuity and other impairments, are related to opioid exposure.[80-82] Research on behavioral and cognitive development in infants born to mother with OUD show conflicting results. Two reviews which consisted of studies published prior to 2016 report poor behavioral and cognitive outcomes in infants prenatally exposed to opioids.[78,83] However, recent studies on infants born to women on methadone or buprenorphine therapy showed that these infants had normal neurobehavioral development in early infancy.[84,85]

2.6 Long-term health care utilization in infants diagnosed with NOWS

We conducted a literature review to identify published studies that reported on long-term health care utilization associated with NOWS. We searched PubMed/Medline database using keywords related to long-term health care utilization and neonatal abstinence syndrome/neonatal opioid withdrawal syndrome as stated below:

"((((((((((long-term outcome) OR long-term outcomes)) OR hospital readmissions) OR 30-day hospital readmissions) OR emergency department visits) OR urgent care visits) OR healthcare utilization) OR outpatient visits)) AND ((((((neonatal abstinence syndrome) OR neonatal opioid withdrawal syndrome) OR opioid neonatal abstinence syndrome) OR neonatal abstinence) OR neonatal drug withdrawal syndrome) OR neonatal drug withdrawal)".

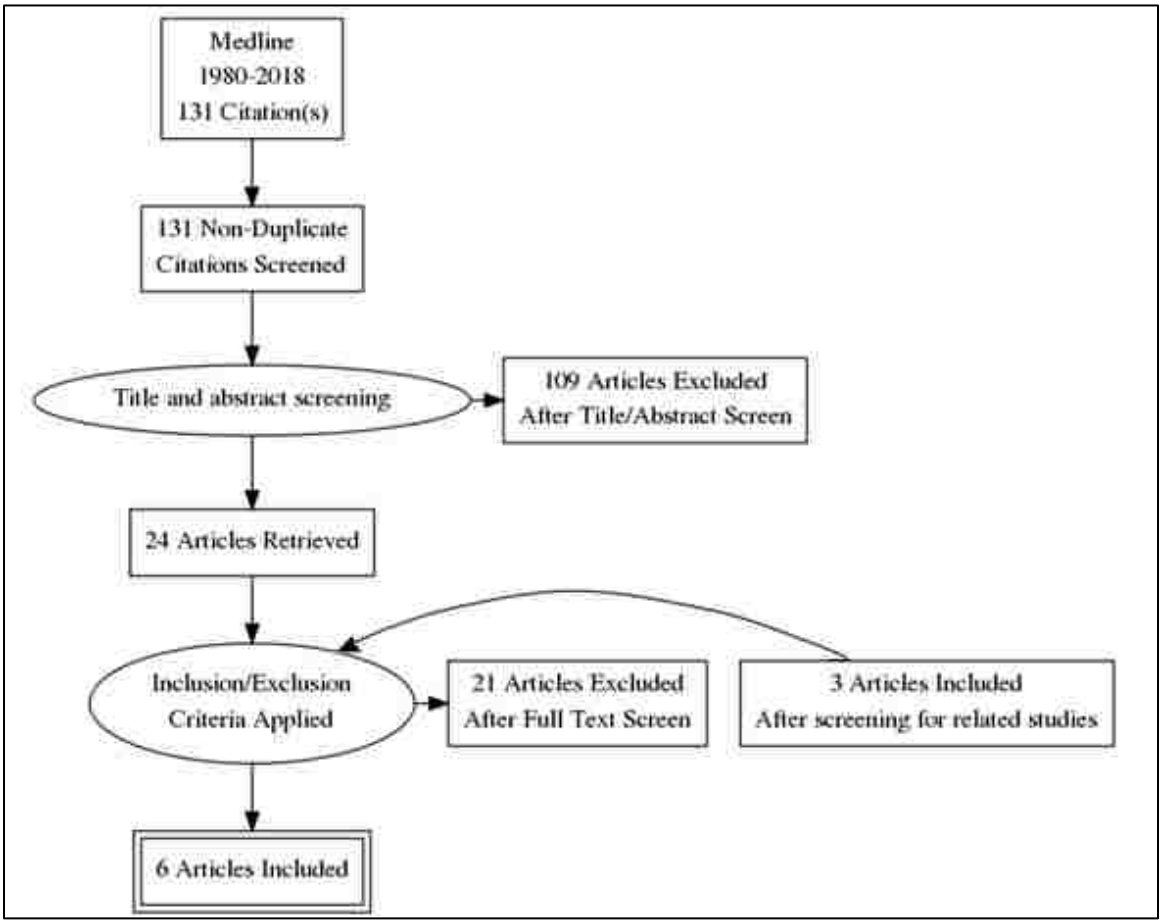
Since there were limited articles that specifically evaluated long-term health outcomes and health care utilization in infants with NOWS, we also included studies that evaluated these outcomes infants with *in-utero* opioid exposure. This allowed for comparison of outcomes in infants with NOWS with infants who had *in-utero* opioid exposure regardless of the diagnosis of NOWS. The inclusion criteria for the literature review included:

1) Study investigating long-term health care utilization associated with NOWS/NAS/maternal opioid exposure
2) Human studies
3) Studies published in English

The exclusion criteria for the review included:

1) Literature review
2) Comment on a published article
3) Withdrawal unrelated to opioids

Figure 1: PRISMA flow diagram for literature review



Based on our search criteria, our initial search led to the identification of 131 studies (Figure 1). Of these studies, 24 studies that were relevant to the literature search were identified and were further screened. Three articles were selected from the 24 studies after evaluation. Three more studies/reports were identified after reviewing the references in selected studies. In the sections below 6 articles that evaluate long-term health care utilization in infants born with NOWS/NAS are described (Table 1).

Cordelie E.W. evaluated the association between NAS and long-term health outcomes.[35] Using a retrospective cohort design, the researchers studied infants born in the

state of Washington between the years 1990 and 2008 evaluating the risk of hospital readmissions in infants with and without NAS. The follow-up period was five years after discharge from the hospital. The study reported that infants diagnosed with NAS were at a significantly higher risk of hospital readmission compared to unexposed infants even after controlling for factors such as maternal age, education, gestational age, and smoking. After adjustment for the confounders, the authors reported that infants diagnosed with NAS had a higher risk of hospital readmission associated with a) infectious and parasitic diseases, b) diseases of the nervous, gastrointestinal and genitourinary system, and c) injury by another person, neglect or abuse.

Stephen W.P. et al. evaluated the risk of hospital readmission in infants who were diagnosed with NAS.[36] The study utilized administrative data for all the births in the state of New York from 2006 to 2009 to identify infants with a NAS diagnosis and two comparison groups - uncomplicated term births and late preterm births. After adjusting for confounders, the study showed that there was a higher risk of 30-day hospital readmission in the infants with NAS compared to infants with uncomplicated term births. They also stated that the readmission rates were similar to late preterm infants. Additionally, infants who received a diagnosis of NAS but were discharged in less than a week since birth had a higher 30-day hospital readmission rate.

Tamara C. et al. reported on the child health services utilization in children born to 119 mother with substance use disorder (self-reported use of methadone, amphetamine or opiates) in the period between 2000 and 2003 in Australia.[86] They reported that approximately 29% of the children who were born to mothers with substance use disorder did not access standard health services in their first two years of life. Additionally, use of

child health services was associated with lower child protection notification for mothers who were on methadone compared to other substances.

Kirsimarja R. et al. conducted a population-based retrospective cohort study in Finland to evaluate hospitalizations and "out-of-home" placements in children whose mothers abused substances.[87] The authors followed 55,369 infants born in Finland in 2002 for the first seven years of their lives. The study reported higher rates of injury, infectious diseases, hospital treatment for other reasons, and out-of-home placement in children of born to women with substance use disorders (n=205) compared to controls (no substance abuse, n=54,291). While these associations (hospitalization) were significant in unadjusted analysis, they remained significant in the adjusted analysis only in subjects who also had concomitant alcohol use. Out-of-home placement was significant (OR: 7.4, 95% C.I.: 5.2-10.5) even after adjustment of confounders. In the adjusted model, the study controlled for factors such as child's sex, mother's psychiatric condition, relationship status, education, and social assistance status.

Hannah U. et al. used a population-based retrospective cohort study to evaluate causes of hospitalization in children who were diagnosed with NAS at birth.[88] The study followed children born between the years 2000 and 2011 in New South Wales for 13 years. They identified 3,842 infants who had received a diagnosis of NAS; the comparison group included 1,018,421 infants who did not have NAS diagnosis. The study reported that infants with NAS had a higher risk of hospitalizations (OR: 1.6, 95% C.I.: 1.5-1.7). The reasons for hospitalization constituted mainly of assault, maltreatment, and poisoning. Physiological reasons for hospital readmission were mental and visual disorders. After accounting for other confounders, NAS was found to be a significant predictor of

readmissions related to maltreatment (OR: 4.5, 95% C.I.: 3.4-6.1), and behavioral disorders (OR: 2.3, 95% C.I.: 1.9-2.9).

A short report by Savin M. described health care utilization during their first year of life in infants who were diagnosed with NAS using the Delaware Medicaid data.[34] Four hundred and ninety-nine infants who received a diagnosis of NAS were identified between the years 2012 and 2014. The study reported that approximately 15% of the infants required hospital readmission. There was a decreasing trend in well-child visits from 38% at six months to 30% at 9 months. Fifty-two percent of the infants had emergency department visits and 7% had urgent care visits. This report, however, lacked a control group for comparison.

Table 1: Summary of articles that evaluate long-term health care utilization in infants with NOWS/NAS or maternal exposure to opioids

Author	Year	Study design	Study population	Database	Exposed group	Control	Outcomes evaluated	Results
Witt CE et al[35]	2017	Retrospective cohort study	Infants born in Washington state (1990-2008)	Comprehensive Hospital Abstract Reporting System in Washington State. Data from both mother and infant was obtained	Infants diagnosed with NAS (n=1,900). Identification by ICD-9-CM code 779.5	Unexposed (n=12,283). Did not receive NAS diagnosis, neither had diagnosis codes that indicated maternal opioid dependence	During the first five years of life after discharge Hospitalizations Infant mortality	Adjusted relative risk All-cause readmission: 1.54 (1.37-1.73) All-cause death: 1.94 (0.99-3.80)
Patrick SWS et al.[36]	2016	Retrospective cohort study	Infants born in New York State (2006-2009)	New York State Inpatient Database from Healthcare Cost and Utilization Project	Infants diagnosed with NAS (n=1643). Identification by ICD-9-CM code 779.5	Uncomplicated term births (n=700,643) and late preterm births (n=51,748)	30-day hospital readmission after discharge	Adjusted relative risk for infants diagnosed with NAS 30-day hospital readmission: 2.49 (1.75-3.55)
Tamara C et al. [86]	2011	Retrospective cohort study	Maternity admissions to Royal Brisbane Women's Hospital (2000-2003)	NA	Mother who self-reported methadone, amphetamine or opiate use (n=119)	NA	During a follow-up of 2 years: Child protection (harm: emotional, physical, neglect) Child health (engagement with any child services)	Approximately twenty nine percent of the children did not have any child health use in first 2 years of life.

Kirsimarja R et al. [87]	2015	Population based retrospective cohort study	Infants born in Finland (2002)	Medical Birth Register (9 additional registers for other detailed information)	Mothers with registry entry related to substance abuse (1998-2009) (n=202 for drug abuse)	Mothers without registry entry substance abuse (n=53,457)	During a follow-up of 7 years: Hospitalizations Out-of-home placements	Significant difference (drug abuse compared to controls) in unadjusted rates of: Injury (8% vs. 4%) Infectious disease (10% vs. 7%) Hospital treatment for other reasons (51% vs. 36%) Out-of-home care (38% vs. 1%)
Hannah U[88]	2015	Population based retrospective cohort study	Infants born in New South Wales (2000-2013)	Linkage of Perinatal Data Collection, Admitted Patient Data Collection, Australian Bureau of Statistics Cause of Death, NICUS Data Collection	Infants diagnosed with NAS (n=3837). Identification by ICD-10 code p96.1.	Infants without NAS (n=1,016,565)	During a follow-up for a maximum of 13 years: Hospitalizations Reasons for hospitalizations	Risk of outcomes compared to controls: Rehospitalization (OR: 1.6, 95% C.I.: 1.5-1.7) Mortality during hospitalization (OR: 3.3, 95% C.I.: 2.1-5.1) Reason for hospitalization: Assaults, maltreatment, poisoning, behavioral health, vision problems.
Savin M[34]	2017	Retrospective study	Infants born in Delaware (2012-2014)	Delaware Medicaid data	Infants diagnosed with NAS (n=499). Identification by ICD-9-CM code	NA	During the first year of life: Emergency department visits Urgent Care visits Primary care provide visits Well child visits	Health care service utilization rates: Inpatient: 15% Emergency department: 52% Urgent Care: 7% No vaccinations: 8% of infants

From the studies above, we can conclude that there is increased health care utilization in infants with a NAS/NOWS diagnosis or those exposed to opioids prenatally. The studies show increased need for care and follow-up services in infants who received such diagnoses. While these studies have shown that withdrawal syndromes can have far-reaching consequences, the results of the studies lack clinical data and are generalized to specific regions. Additionally, most of these studies were not nuanced to capture the specific details of health care utilization, such as emergency department visits and outpatient visits. Inpatient visits are more likely in infants who were diagnosed with NAS/NOWS as noted by those studies, but well-child visits and child care services have been shown to be underutilized. Our study addresses many of these limitations. First, the dataset represents a diverse population. Second, it evaluates a broader range of health care utilization events. Finally, it also incorporates clinical data derived from the electronic health records in the analysis.

Likewise, prior studies have not specifically focused on the treatment received by the infants after birth during their hospital stay and how it could potentially affect health care utilization in the long run. Opioids used for the treatment of withdrawal symptoms and adjunctive therapy may have a long-term effect on the infants that may lead to increased health care utilization. Since a large variability in treatment protocol exists, it is essential to know how such differences might affect long-term health care utilization. Further, studies that focus on the management of NOWS have primarily focused on minimizing the exposure to opioids and LOS in the hospitals without accounting for hospital readmission rates and health care utilization in the future.[35,36] This might lead to increase in rates of hospital readmission in infants who were diagnosed with NOWS. In

some infants, the full symptoms of NOWS could possibly manifest after 4-5 days; any discharge before that period could lead to further health care utilization in terms of emergency department visits. For example, the study by Patrick et al. demonstrated that the rate of emergency department visits are higher in infants with NAS who were discharged before one week since birth compared to those discharge after one week.[36]

Additionally, it is important to be able to compare long-term health care utilization of infants with NOWS to other medical conditions that are known to be self-limiting in nature, but are associated with higher health care utilization. Late preterm infants are born at a gestational age of 33 weeks or higher but less than 37 weeks.[89] These infants are known to be physiologically "immature". They are at a higher risk of morbidity, mortality, and hospital readmission compared to term birth infants.[89] These infants may exhibit symptoms similar to infants with NOWS, such as respiratory distress and feeding difficulties during their birth hospitalization, although the mechanisms vary greatly from infants with NOWS. Late preterm infants can serve as an efficient control group for infants with NOWS. Therefore, it was included in our study as secondary control group

While it is important to note that long-term outcomes are difficult to ascertain given that there are several factors (environmental and social) associated with OUD, the current gap in the literature regarding long-term health care utilization and treatment received during the management of NOWS should be explored. Understanding the differences in health care utilization in infants who were diagnosed with withdrawal syndrome and evaluation of their health care utilization will lead us to better understand the long-term consequences of NOWS. It is imperative that proper follow-up of the mother-infant dyad is maintained to promote child safety and health. In the context of the current opioid

epidemic in the United States, our study will be able to specifically estimate the long-term burden of NOWS which can help in planning intervention or allocation of specific resources for combating the affliction.

CHAPTER 3: METHODS

3.1 Introduction

In this chapter, approach to the analysis of data to test our hypothesis is outlined. This section begins with the description of the data source that was used in the study, followed by the study design, and inclusion and exclusion criteria for sample section. Then the methods for each Specific Aim are described, including methodology for identification of outcome and exposure variables. Finally, statistical methods used in the analysis are described which is followed by power analysis for sample size calculations.

3.2 Data source

The Cerner Health Facts® database was utilized to assess the differences in post-discharge health care utilization in infants born with NOWS compared to controls during a one-year follow-up period. HF is a national database warehouse that collects extensive clinical data across hospitals in the United States that utilize the Cerner EHR System. The database includes encounter data consisting of emergency, outpatient, and inpatient visits. Further, information on provider specialty, hospital procedures, diagnoses, laboratory, and pharmacy data are included in the HF database. Additionally, patient demographic information, such as age, sex, and race, along with hospital characteristics, such as specialty, acute care, number of beds, census region, and location (urban or rural), are available. HF database is de-identified and HIPAA-compliant which allows for protection of both patient's and organization's identity. The database is longitudinal and continuity of patient encounters, if it occurred within the same health system, is preserved. This allows for efficient follow-up of patients after discharge when they seek health care in the same

health system. HF database consists of records from over 500 health facilities in the United States with records dating back over two decades. IRB approval from the University of New Mexico Health Sciences Center Human Research Protection Office was obtained for this study.

For purposes of this analysis, HF data between the January 1, 2011 and September 30, 2017) were used. This time captures the increasing rates of opioid use in the U.S. and subsequent increase in the rate of NOWS.[90]

3.3 Study design

Our study utilized a retrospective cohort study design. The study population consisted of all the births recorded in the HF database between January 1, 2011 and September 30, 2016. Study cohort was sampled from the study population based on inclusion/exclusion criteria listed in the sections below. Retrospective cohort study design allowed for examination of several outcomes in the given sample.

3.4 Study population

3.4.1 Selection criteria for infants diagnosed with NOWS (exposed group)

Inclusion criteria:

Infants diagnosed with NOWS were identified using the International Classification of Diseases, Ninth Revision (ICD-9-CM) diagnostic code 779.5 and ICD-10 diagnostic code P96.1, which denote drug withdrawal syndrome in infants. Encounter identification number (EIN) is a unique identification number assigned to a specific encounter of a patient with the health care system. Based on the EIN, patient number for

that specific visit was determined and traced back to the unique patient identification number (PIN). The unique PIN was used to follow-up the cohort to assess their post-discharge health care utilization. The follow-up assessment period began on the discharge date associated with the encounter that was related to NOWS and ended after 365 days.

Exclusion criteria:

We excluded infants whose initial LOS after birth was less than 3 days. This criterion was used following the rationale that infants with suspected NOWS often have a required observation period of 72 to 96 hours.[32,91,92] Previous studies have also reported that adding an additional criterion regarding LOS could improve the identification of infants with NOWS.[93] We also excluded infants whose age at first encounter was more than 4 days. This period was chosen to account for any infants with NOWS who were transferred into a CERNER facility but not born in that hospital. Critically-ill neonates are often treated with opioids which may result in iatrogenic withdrawal syndrome. Since the objective of the study is to evaluate health care utilization in infants with NOWS subsequent to *in-utero* exposure to opioids, we excluded infants with following conditions: lung disease, intraventricular hemorrhage, periventricular leukomalacia, necrotizing enterocolitis, spontaneous bowel perforation, congenital anomalies, and those that required critical oxygenation (Table 2). These diagnoses are presumed to be linked with iatrogenic NOWS.[25,36,37] Infants with early preterm birth (gestational age at birth less than 33 weeks) were also excluded as they could potentially have a much longer hospital stay and have a large set of comorbidities. Infants with total LOS of more than 60 days were also excluded from this study group as outliers. We also excluded patients whose discharge summary

denoted that the patient had passed away or if they were transferred to a health center/hospital.

3.4.2 Selection of the control groups:

Uncomplicated births:

Uncomplicated births were identified using ICD-9-CM code V30.x and ICD-10 code Z38.0 which apply to "Single liveborn, born in hospital, delivered without mention of cesarean section." We excluded infants with LOS less than 0 days (to account for inaccuracies in information regarding LOS) and infants whose age at first encounter was more than 4 days. Additionally, infants with initial LOS of more than 3 days were also excluded. Prolonged hospital stay after birth is a marker for an underlying condition that could require clinical observation, tests or management. Exclusion of infants with LOS longer than 3 days ensured that such cases were excluded from the uncomplicated birth study group. We also excluded infants who had received additional diagnosis of NOWS, diagnosis codes related to iatrogenic NOWS, or any preterm birth (gestational age less than 37 weeks) from this group. Patients whose discharge summary denoted that the patient had passed away or if they were transferred to a health center were also excluded.

Late preterm births:

Infants with late preterm births served as secondary controls to the exposed group. These infants are susceptible to adverse health outcomes and have increased hospital readmissions compared to term infants, but are not as ill as very preterm infants.[41,42,94] These infants were identified using the ICD-9-CM codes 765.27 and 765.28 (ICD-10: P07.36- P07.39), which represent gestational ages greater than or equal to 33 weeks and less than 37 weeks.[89] Since infants with NOWS are likely to be born preterm, these two

study groups were devised to be mutually exclusive, i.e. infants diagnosed with NOWS were not categorized as late preterm birth. Infants with LOS less than 0 days were excluded from this study group. We also excluded infants whose age at the encounter was more than 4 days. Furthermore, we excluded patients whose LOS was more than 60 days. We also excluded patients whose discharge summary denoted that the patient had passed away or if they were transferred to a health center.

Table 2: Conditions for inclusion and exclusion criteria for sample selection and corresponding diagnostic codes (ICD-9-CM and ICD-10-CM)

Condition	ICD-9-CM	ICD-10-CM
NOWS/NAS	779.5	P96.1
Late preterm births		
Preterm newborn, gestational age 33-34 completed weeks	765.27	P07.36, P07.37
Preterm newborn, gestational age 35-36 completed weeks	765.28	P07.38, P07.38
Single live-born, born in hospital, delivered without mention of cesarean section	V30.00	Z38.0
Exclusionary codes		
Chronic respiratory disease arising in the perinatal period	770.7	P27.X
Intraventricular hemorrhage of fetus or newborn	772.1X	P52.X
Periventricular leukomalacia	779.7	P92.1
Intracranial injury of other and unspecified nature	854.XX	S06.90XA, S06.89XA
Necrotizing enterocolitis in newborn	777.5X	P77.1-3, P77.9
Perinatal intestinal perforation	777.6	P78.0
Early preterm, gestational age less than 33 weeks	765.21-765.26	P07.21- 26, P07.31-35

3.4.3 Detailed description of the sample selection process for the study

HF dataset was accessed using a secure access point at the University of New Mexico Clinical and Translational Sciences Center. The database consists of several data tables linked through a primary encounter identification number. To account for the large number of observations across several years that spans three different cohorts, the initial data cleaning process was divided based on the study group and the year of the encounter. Using Postgres SQL, the first selection criterion was applied to identify the study groups.

For example, infants with NOWS were identified using the type of code (ICD-9 or ICD-10) and the diagnosis code (779.5 or P96.1) from the "diagnosis and procedure specific information table". Additionally, the selection criteria were also restricted to discharge between specific time period (e.g., discharges between 2011 and 2012). For simplicity, the dataset created in this step will be referred to as "base set" in the manuscript.

After the specific EINs were collected for the specific study group and for a specific year (or time period), unique PIN associated with the EIN for each infant in the base set was identified. These PINs were then used to collect all of the encounter related information of an infant for a period of one year starting at the initial index period for the search. For simplicity, the dataset created in this step will be referred to as "complete set" in the manuscript.

The dataset that was created (complete set) contained information on diagnostic codes, age that the specific encounter, hospital information (census region, census division, bed size range, urban-rural status), patient type, care-setting, admit date, discharge date, admission type, discharge description, and information on the infant (race, sex). The

dataset thus created was in a long form, i.e. each encounter along with any number of diagnostic codes or information that varied across that specific encounter were presented in different rows. These individual data files were exported as *.csv file and processed in STATA (version 14, College Station, TX).[95]

The raw dataset extracted from the full HF database was processed in five steps which are described below (illustrated in Figure 2):

a) Preprocessing: Exclusion based on LOS and age at encounter criteria and identification of specific encounter id.

First, raw encounter data (base set) were imported into STATA; the duplicates were removed. Next, LOS variable was created. This variable was calculated by subtracting the date of admission from the date of discharge. Following this step, exclusion criteria were applied based on the study group (Table 3).

Table 3: Exclusion criteria based on age at primary healthcare encounter and LOS

NOWS	Late preterm birth	Uncomplicated birth
Age at encounter more than 4 days	Age at encounter more than 4 days	Age at encounter more than 4 days
LOS less than 3 days	LOS less than 0 days	LOS less than 0 days
-	-	LOS more than 4 days
-	-	Patient care setting: NICU/ICU

After the application of these exclusion criteria any remaining duplicate encounter IDs were excluded and a base encounter ID set was created.

b) Identification of the primary encounter and associated diagnostic codes. Application of diagnostic codes based exclusion criteria.

The base encounter ID set was merged with the "complete set" and matched records were retained. The resulting dataset was in a long form and contained all the primary visit related information. This dataset was converted to a wide form (diagnostic codes from rows to columns). Following the transformation, diagnostic codes based exclusion criteria were applied (Table 4). This set will be referred to as "baseline encounter set" for future reference.

Table 4: Exclusion criteria based on diagnostic codes and LOS

NOWS	Late preterm birth	Uncomplicated birth
Exclusion criteria		
Iatrogenic NOWS	Iatrogenic NOWS	Iatrogenic NOWS
Early preterm (Gestational age <33 weeks)	Early preterm (Gestational age <33 weeks)	Any preterm (Gestational age <37 weeks)
	Diagnostic codes for NOWS	Diagnostic codes for NOWS
LOS more than 60 days	LOS more than 60 days	-

After the application of the exclusion criteria, unique patient identification numbers were selected from the dataset to identify infants who would be eligible for follow-up.

c) Identification of the follow-up visits using the unique patient identification code. Quantification of the outcome variables (post-discharge health care utilization) and the time to events for a specific outcome.

The unique patient identification number set was merged with the "complete set" and the matched records were retained. This dataset consisted of all the encounter related information with the PIN across multiple health related encounters in a long format. The dataset was converted to a wide format accounting for the diagnosis code related to each encounter. Next, the dataset was sorted using the admit date and PIN. Time-to-event variable was created by subtracting unique date of admission/ date of event (post-discharge events) from the date of discharge related to the primary visit. An event counter variable was created to calculate the number of post-discharge health care utilization event. Since the above algorithm would also create a time-to-event for the baseline (which would be equal to the LOS), the value was specified as zero. The value zero for the time-to-event marked the primary/baseline health encounter. Next, the follow-up event or post-discharge health care utilization event were categorized into 3 variables (Inpatient, Emergency, Outpatient) using the patient care-setting and patient type variables originally present in the HF database. These new variables were retained along with EIN and PIN to create a temporary dataset. The temporary dataset was transformed to a wide format. After the conversion, each unique patient (observation unit) had all the health care utilization events in a single row. Following this step, binary variables were created for presence of each event (Inpatient, emergency,

outpatient) for event taking place within 365 days of discharge. This set will be referred to as “outcomes set” in the manuscript.

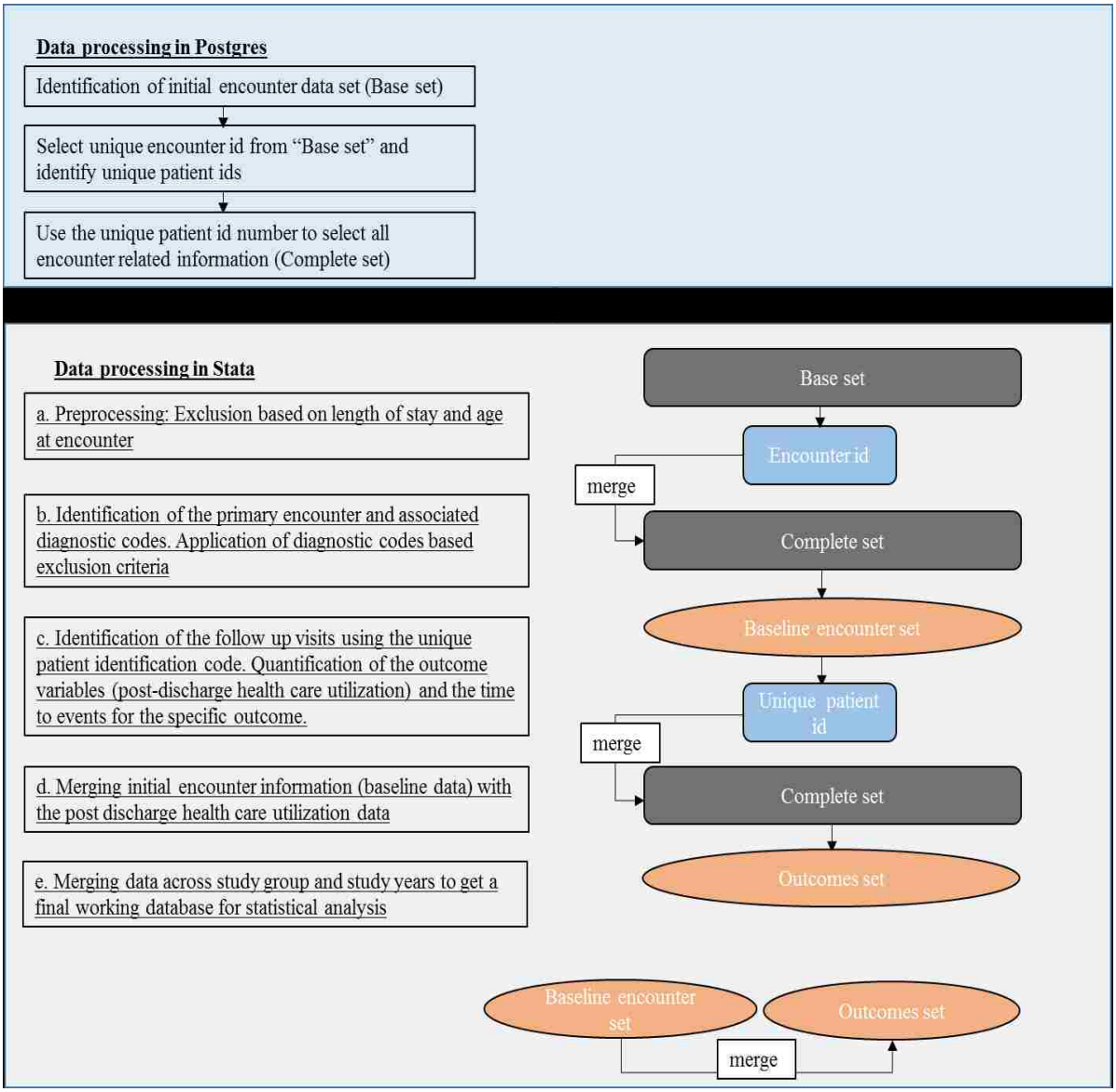
d) Merging initial encounter information (baseline data) with the post-discharge health care utilization data.

The baseline information form “baseline encounter set” was merged with the “outcomes set” using the unique patient identification number. Duplicate matches were excluded.

e) Merging data across study group and study years to get a final working database for statistical analysis.

Data across all the study group for all the study period were appended. The data from the uncomplicated group consisted a 25% random sample (randomly sampled from each year). Additional exclusion criteria for infants who were recorded as “Expired” or “Readmitted” in the initial visit discharge summary was applied during this step. Finally, a second reexamination for duplicate encounters or unique IDs was performed and duplicates were removed.

Figure 2: Graphical illustration of the data cleaning, merging, and modification for the study



3.5 Aim 1: To compare and characterize post-discharge health care utilization of infants born with NOWS compared to controls (uncomplicated births and late preterm births) during a one-year follow-up period.

For Aim I, the study cohort was identified, as previously described. The follow-up period for the cohort began at the time of discharge and ended at 365 days after discharge (Figure 3).

3.5.1 Outcomes

The outcomes of interests are described in the following section (Table 5). For Aim 1.A, the outcome of interest was post-discharge hospital readmission. These visits were assessed using the patient type and patient discharge care setting variable in the HF database. Hospital readmission was operationalized using four different variables. First was an indicator variable for *any readmission within 30 days* of discharge. Second was *any readmission during the total follow-up period of 365 da*ys. Third was the *total number of readmissions* during the study period. Lastly, we calculated *time to first hospital readmission* as the fourth outcome variable.

For Aim 1.B, the outcome of interest was post-discharge emergency department visit. These visits were assessed using the patient type and patient discharge care setting variable. Emergency department visit was operationalized by four different variables. First was an indicator variable for *any emergency department visit within 30 days* of discharge. Second was a*ny emergency department visit during the total follow-up period of 365 days*. Third was the *total number of emergency department visits during the study period*. The fourth was *time to first emergency department visit*.

For Aim 1.C, the outcome of interest was outpatient visits. They were characterized similarly using patient type and patient discharge care setting variable in the HF database. Outpatient visits were operationalized by two variables. The first was *any outpatient visit during the study period* and the second was *total number of outpatient visits*.

Additionally, we constructed "*any composite visit*" (expressed as "any visit" in the tables in result section) variable which was a composite of any emergency department visit or hospital readmission to account for the possibility of one visit affecting other type of visits.

Figure 3: Overview of study design for Aim 1

Table 5: Description of the outcome variables for Aim 1

Sub-aim	Description of the outcome variable	Type of variable
1.A	All cause 30-day hospital readmission	Binary
1.A	All cause hospital readmission during the study period	Binary
1.A	Total number of hospital visits during the study period	Count
1.A	Time to first hospital readmission	Continuous
1.B	All cause 30-day emergency department visits	Binary
1.B	All cause emergency department visit during the study period	Binary
1.B	Total number of emergency department visit during study period	Count
1.B	Time to first emergency department visit	Continuous
1.C	Any outpatient visit during the study period	Binary
1.C	Total number of outpatient visit during study period	Count

3.5.2 Covariates:

We controlled for the infant sex, race, type of insurance, hospital location (urban or rural), hospital census division, year of primary encounter, and the hospital bed size as socio-demographic variables related to initial care. Furthermore, medical conditions, such as respiratory problems, feeding difficulties, jaundice, and sepsis, were also considered as possible covariates. Table 6 and 7 presents the operationalization of these variables.

Table 6: Operationalization of demographics and patient care setting covariates

Variable	Operationalization
Sex	Binary (Male and Female)
Race	Categorical (Caucasian, African American, Hispanic, Native American, Others)
Insurance	Categorical (Medicaid, Commercial, Others)
Census division	Categorical (1,2,3,4,5,6,7,8,9)
Urban rural status	Binary (Urban, Rural)
Bed size	Categorical (Less than 100, 100-299, Greater than 300)

Table 7: Operationalization of medical diagnostic codes present at the primary health encounter

Condition	ICD-9-CM	ICD-10-CM
Respiratory problems		
Respiratory distress syndrome of newborn	769	P22.0
Transient tachypnea of newborn	770.6	P22.1
Respiratory condition of newborn, unspecified	770.9	P28.9
Other specified respiratory conditions of newborn	770.89	P28.89
Feeding difficulties	783.3, 779.31	P92.1-2, P92.8-9
Jaundice	774.XX	P58.XX, P59.XX
Sepsis (Bacterial sepsis of newborn)	771.81	P36.9

3.6 Aim 2: To evaluate the relationship between NOWS severity measures (pharmacologic management of NOWS, use of adjunctive therapy, concurrently diagnosed complications associated with NOWS, and hospital length of stay) and post-discharge health care utilization in the one-year follow-up period

Study sample:

For Specific Aim 2, the sample size was restricted to infants who were diagnosed with NOWS at birth. They were selected based on the inclusion and exclusion criteria described previously in section 3.5. The overview of the study design is presented in Figure 4.

Figure 4: Overview of study design for Aim 2

3.6.1 Measures of NOWS severity as predictors of post-discharge health care utilization

The objective of Aim 2 was to evaluate the impact of pharmacological management of NOWS, LOS, adjunctive therapy, prematurity, other diagnostic codes associated with NOWS associated with hospital stay during the treatment of NOWS on health care utilization during the one-year follow-up period. These variables represented the severity of NOWS in the infant. Pharmacological management of NOWS was described as infant receiving either morphine, methadone, tincture of opium or phenobarbital during the initial hospital stay. Since phenobarbital is also widely used as a second line therapy, its impact on post-discharge health care utilization was also assessed independent of opioid treatment. LOS was calculated as the difference between the infant's date of birth and the discharge date associated with treatment for NOWS. Other medical conditions, such as respiratory problems (presence of any of the conditions listed in Table 7) and feeding difficulties were considered as other factors relating to severity of NOWS. Furthermore, benzodiazepines, administered during the initial hospital stay were also considered as markers of NOWS severity.

3.6.2 Operationalization of NOWS severity factors

i. Identification of infants who received pharmacological treatment for NOWS

As described previously, infants who received morphine, methadone or phenobarbital during their initial stay in the hospital were classified as infants who received pharmacological treatment for NOWS. Medication used during the baseline hospital stay in infants with NOWS was assessed using the medication facts table in the HF database. First, all the encounters related to baseline visits were ascertained. Using those EIN,

medications used during that specific visit was identified. Medication classes were grouped as following: a) medications for treatment of NOWS (methadone, morphine, tincture of opium, phenobarbital) and b) benzodiazepines (lorazepam, alprazolam, clonazepam diazepam or midazolam).

ii. Length of hospital stay

LOS after birth is usually considered a factor that could affect short term post-discharge healthcare utilization.[36] Length of hospital stay is a function of infant health at birth, i.e., presence of any medical conditions at birth can potentially lead to prolonged hospital stay. However, there could also be another mechanism where shorter LOS could lead to increased health care utilization. This could be explained in the case where a medical condition could potentially go undetected during the initial hospital stay which could lead to prompt return to a health care facility following a discharge. Furthermore, it cannot always be assumed that longer hospital stay is associated with poor health. For example, infants treated with methadone or morphine could have different LOS owing to the tapering schedule for the medication they received. Hence, the effect of the LOS on NOWS severity may not be linear. To examine if the effects of LOS are non-linear on short-term post-discharge healthcare utilization (30-day rehospitalization, emergency or composite visit), the following transformation of LOS were examined:

a. LOS in linear form:

   In this model, the LOS was used in its original form.

b. LOS in quadratic form:

   In this model, the LOS was used in a quadratic form, i.e., a normal form and a squared form of LOS were used as covariates.

c. LOS in quantiles:

In this model, LOS was divided into equal quantiles (5 classes) and these quantiles were used as predictors.

d. LOS as cubic splines:

A cubic spline curve is a piecewise cubic curve with continuous second derivative. In our analysis we used a restricted cubic spline with 4 knots. The restriction forces the cubic spline to be linear at the two tails.[96,97]

iii. Medical diagnostic codes assigned during the initial hospital stay:

Medical diagnostic codes assigned to the infants at birth which are described in Table 7 were also considered as severity measures of NOWS. While these conditions are common in infants with NOWS, in the analysis we assumed that the presence of the diagnostic codes would mean that these symptoms were serious enough to warrant assigning of these specific diagnosis codes in the patients chart summary.

3.6.3 Outcomes

Outcomes from Aim 1 were used as the outcome of interest in Aim 2 as the scope of this aim was also to assess post-discharge health care utilization. Time-to-event for the first hospitalization and emergency department visit were not considered as outcomes of interest for this Aim because of the limited sample size in the NOWS group and the small number of events in the group.

3.6.4 Covariates

The covariates described in Aim 1 were used to obtain adjusted estimates in the second Aim. Prematurity, jaundice, sepsis, and use of antibiotics were other medical

covariates that were examined in the analysis. We used the sex of the infant, type of insurance, race, hospital location (urban or rural), hospital census division, and bed size as covariates in multivariable analyses.

3.7 Sensitivity analyses

3.7.1 Examination of the effect of LOS as a selection criterion on post-discharge healthcare utilization.

We excluded late preterm infants whose LOS was less than 3 days to make the study group comparable to the NOWS group. We evaluated the post-discharge health care utilization across these two group after the restriction to assess if the differences in post-discharge health care utilization were a result of the difference in the exclusionary criteria.

3.7.2 Assessment of the difference in rates of pharmacological treatment of NOWS across different hospitals and its impact on post-discharge health care utilization.

We created a binary variable to indicate if an infant was born in a hospital where less than 25% of infants with NOWS received pharmacological treatment for their condition. First, we evaluated the differences in post-discharge health care rate in NOWS group based on the pharmacological treatment rates in the hospitals. We then excluded the infants who were treated in hospitals where pharmaceutical treatment of NOWS was less than 25% and compared post-discharge health care utilization in this restricted group with the control groups. Lastly, we compared the association between pharmacological treatment of NOWS and post-discharge health care utilization stratified by the aforementioned hospital groups.

3.7.3 Propensity score analysis for pharmacological management of NOWS.

A propensity score analysis was performed to account for the unmeasured confounding related to pharmacological treatment of NOWS. Propensity score was calculated for pharmacological treatment for NOWS using the following variables: sex of the infant, cubic form of LOS, prematurity, respiratory conditions, feeding difficulties, jaundice, sepsis, use of benzodiazepines, and use of antibiotics. The balancing property was satisfied with 10 blocks where the mean propensity score in each block was not statistically significant in the pharmacological treatment for NOWS vs. no pharmacological treatment for NOWS groups. The propensity score was used in a linear fixed effects model along with a binary variable for pharmacological treatment for NOWS to predict post-discharge health care utilization (any composite visit, any 30-day composite visit).

3.7.4 Principal component analysis for NOWS severity factors.

To account for the multiple factors related to severity of NOWS, many of which were correlated, we used principal component analysis method. Principal components were derived using the following set of NOWS severity related variables: pharmacological management of NOWS, LOS, respiratory conditions, feeding difficulties, and use of benzodiazepines. Eigen-value >1 was used as a criterion to select components.[98] These components were used as linear predictors to assess post-discharge healthcare utilization (any composite visit, any 30-day composite visit).

3.8 Statistical Analyses

Baseline characteristics of the study population were presented as means for continuous variables, whereas, percentages were used for categorical variables. We used analysis of variance (ANOVA) to assess differences between the baseline characteristics (continuous variables) among the three study groups. For categorical variables, we utilized chi-square test to assess the independence of baseline characteristics across study groups.

Statistical models for each of the Specific Aims were based on the type of outcome variable. For binary outcome variables, we utilized a logistic regression model. The primary predictor for the Specific Aim 1 consisted of the study group, whereas for the Specific Aim 2 the primary predictors were the severity measures for NOWS. First, we used a simple unadjusted binary logistic regression to quantify the association between the predictor variables and the outcome (Model 1). In the second step, a logistic regression model that included all the possible demographic covariates described previously along with the primary independent variable was fitted (Model 2). This step provided an adjusted odds ratio for the association between the predictor and the outcome variables. Finally, in the third step, we added the medical condition as confounders (Model 3).

Post-discharge health care utilization could be triggered by a variety of different factors. Previous studies have reported that factors, such as infant sex, race, and type of insurance (proxy for socio–economic condition), are possible predisposing factors that could affect hospital readmissions or emergency department visits in infants.[99,100] Furthermore, type of hospital, variation in health care utilization across regions and effect of policy changes across an extended period of time could also potentially affect the rates

of post-discharge health care utilization. Model 2 which incorporated these patient specific and hospital related variable was intended to control for these effects.

Model 3 was used to incorporate medical diagnoses present at birth as possible confounders which could affect post-discharge health care utilization in infants. Studies have shown that presence of respiratory problems, jaundice, infection, and feeding difficulties are associated with considerable risk to the infant at birth and could lead to higher post-discharge health care utilization.[101,102] These factors were included in the 3rd model as we anticipated that they could potentially cause an over adjustment as these conditions are very common in NOWS and late preterm infants. In addition, previous studies have incorporated these covariates in their regression models assessing post-discharge health care utilization,[36] thereby providing *a priori* framework for inclusion of these covariates in the regression models.

Area under the receiver operating characteristic curve (AUROC) was used to assess the predictive ability of the logistic regression models. The AUROC measures the ability of the model to correctly classify the outcome (post-discharge health care utilization) based on the predictors included in the model. In a logistic regression model, AUROC of 0.5 or 50% means failed classification (no better than a flip of a coin) and AUROC of 1 or 100% means perfect classification.

For Poisson regression models, we used Akaike Information Criterion (AIC)[103] as the measure for evaluation of relative quality of statistical models. AIC of a model is given by the following:

$$AIC = 2k - 2\ln(L)$$

Where, k= number of parameters or predictors

L= maximum value of the likelihood function.

Given a set of regression models for an outcome, the model with the lowest AIC is preferred. In our study, we present AIC as AIC/N, where N= number of observation to compare the relative quality of Poisson regression models.

Statistical models:

The following equation represents the proposed logistic regression model (adjusted model with all the covariates) for Aim 1:

$$\log\left(\frac{p}{1-p}\right) = \beta_0 + \beta_x \mathrm{I} + \beta_z \mathrm{Z}$$

Where, p = probability of outcome

B_x = categorical variable for study group

I = indicator variable representative of the categories of the study group

$\beta_z Z$ = represents the covariates in the model with their respective beta coefficients

The null hypothesis (H_0) in the model is specified as below,

H_0: $\beta_x = 0$

i.e. there is no difference in the log-odds ratio of outcome in between the control group and the exposed group.

The following equation represents the proposed logistic regression model (adjusted model with all the covariates) for Aim 2:

$$\log\left(\frac{p}{1-p}\right) = \beta_0 + \beta_x \mathrm{X} + \beta_z \mathrm{Z}$$

Where, p= probability of outcome

X= Row vector consisting of all the primary independent variables

β_x= corresponding beta coefficients for the primary independent variables

$\beta_z Z$ = represents the covariates in the model with their respective beta coefficients

The null hypothesis (H_0) in the model is specified as below,

H_0: $\beta_x = 0$

i.e. there is no effect of NOWS severity measures on post-discharge health care utilization.

For count based outcome variables we used Poisson regression models. In the first step, a simple Poisson model with the count outcome variable and the primary predictor variable was fitted. In the second step, a full Poisson model with all the demographic covariates described previously was constructed. Finally, in the third step, a full Poisson log-linear model along with medical conditions as additional confounders was fitted.

A simple Poisson model for Aim 1 is specified as the following:

$\Pr[Y_i = y_i] = \frac{e^{\lambda_i}\lambda_i^{y_i}}{y_i!}$, y_i =0, 1, 2…

The log-linear specification of the model (adjusted model) is given by:

$$\ln \lambda = \beta_0 + \beta_x I + \beta_z Z$$

Where, λ = mean count of the outcome variable.

X = categorical variable for study group

I = indicator variable representative of the categories of the study group

$\beta_z Z$ = represents the covariates in the model with their respective beta coefficients

The null hypothesis (H_0) in the model is specified as below,

H_0: $\beta_x = 0$

i.e. there is no difference in the log ratio of the mean number of outcomes in the control groups to the exposed group (infants with NOWS) after controlling for other covariates.

The log-linear specification of the model (adjusted model) for Aim 2 is given by:

$$\ln \lambda = \beta_0 + \beta_x X + \beta_z Z$$

Where, λ= mean count of outcome variable.

X= Row vector consisting of all the primary independent variables

β_x= corresponding beta coefficients for the primary independent variables

$\beta_z Z$ = represents the covariates in the model with their respective beta coefficients

The null hypothesis (H_0) in the model is specified as below,

H_0: $\beta_x = 0$

i.e. there is no effect of NOWS severity measures on outcomes during the one-year follow-up period post-discharge in infants with NOWS. The results of Poisson regression model are shown as Incidence rate ratio (IRR) which is obtained by exponentiating the Poisson regression coefficient.

One of the limitations of Poisson regression model is that it assumes the variance of the outcome is equal to its mean (or expected value). Since the outcomes consisted of high number of zero values we also constructed a Zero-inflated Poisson regression model as a robustness check to the Poisson regression.

For time-to-event based analysis, we first we used a Kaplan-Meier estimator to estimate the time-to-event (time to first health care utilization event in days).[104] Kaplan-Meier plots for time to first rehospitalization and first emergency department visits across the study groups were created. We then performed log-rank test of equality of time to event function across study groups. Finally, Cox proportional-hazards regression models were used to test the effect of NOWS on time to a hospital readmission or emergency department visits in comparison to the control groups. The following equation represents the proposed Cox proportional-hazards regression model (adjusted model with all the covariates for Aim 1.A:

$$h(t) = h_0(t) + \exp(\beta_x I + \beta_z Z)$$

Where, h(t) = hazard function at time t

$h_0(t)$ =baseline hazard

B_x = categorical variable for study group

I = indicator variable representative of the categories of the study group

$\beta_z Z$ = represents the covariates in the model with their respective beta coefficients

The null hypothesis (H_0) in the model is specified as below,

H_0: $\beta_x = 0$

i.e. there is no difference in the log ratio of hazard function at time t in between the control group and the exposed group.

Clustering to obtain robust standard errors:

Post-discharge care of an infant can take place at any health care centers in the infants surrounding. However, only those encounters that take place at hospitals that utilize CERNER EHRs will be recorded in the HF database. Let us assume that there is a mixture of health care centers (based on the utilization of CERNER EHR) around an infant's initial treatment center (birthing hospital). Furthermore, that the mixture is random across all the different health centers/hospitals where the infant was born/managed. Therefore, the probability that an infant will seek care at a hospital or a health center that utilizes CERNER EHR can be considered a random effect across the hospitals where the initial care takes place. We used the clustered robust standard errors approach, where the observations were clustered across the hospitals where the initial care was provided, to account for the variability in the probability of access of care at a center that uses CERNER EHR.

3.9 Power analysis

Aim 1: Power analysis for Aim 1 was based on the study conducted by Patrick et al. where hospital readmission rates for infants with NOWS was evaluated using New York Inpatient Database.[36] The study reported that 30-day hospital readmission was approximately 3% in infants with NOWS compared to approximately 1.9% in infants with uncomplicated term births. Similarly, almost 7.7% of the infants born with NOWS had one-year hospital readmissions compared to 4% in infants with uncomplicated term births. Additionally, adjusted odds ratio (OR) for 30-day hospital readmissions for infants with NOWS was estimated to be 2.49 (95% C.I.: 1.75-3.55) compared to infants who had uncomplicated term births. While this study reported that the incidence of NOWS was approximately 2 per 1000 births in 2009, we used a recent estimate of 6 per 1,000 births in 2013[105] approximating the time period of our analysis.

For this calculation, the alpha value was set at 0.05 and sample size to achieve a power of 0.8 to 0.85 and was calculated using G*Power software.[106] We used a dichotomous predictor (presence or absence of NOWS) based on the information available for power calculation.

Table 8: Power analysis for Aim 1

Model	**Power**	**Aim**	**Prevalence of NOWS[a]**	**P_0**	**P_1**	**Measure of association[b]**	**Total Sample size**
Logistic regression	.85	1.A	6	0.03	0.019	OR = 1.6	272,916
Logistic regression	0.8	1.A	6	0.03	0.019	OR = 1.6	234,313
Logistic regression	0.85	1.A	6	-	-	aOR = 2.5	55,052
Logistic regression	0.8	1.A	6	-	-	aOR = 2.5	46,396
Logistic regression	.85	1.B	6	0.077	0.04	OR = 2.0	54,033
Logistic regression	0.8	1.B	6	0.077	0.04	OR = 2.0	46,048

[a] per 1000 births

[b] OR = odds ratio, aOR = adjusted odds ratio

Based on the power analysis for Aim 1, with the conservative estimates (OR=1.6 and power =0.85) we would need a sample size of approximately 270,000 total births which reflects at least 1600 encounters of NOWS based on prevalence rates of 6 per 1000 births (Table 8). The constraint in this estimate is primarily the number of births with a diagnosis of NOWS in comparison to total birth. Additionally, if we used a stronger effect size of OR=2.5 and 80% power, then a total sample size of approximately 46,000 will be sufficient for our study. During preliminary analysis we were able to identify approximately 3,000 encounters with diagnosis of NOWS/NAS. Based on these calculation, we achieved

required sample size to be able to detect the effect of diagnosis of NOWS on long-term health care utilization.

Aim 2: Research on the association between severity of NOWS and long-term health care utilization is lacking. Hence, we utilized the concept of event per variable outlined by Peduzzi et al. to estimate the sample size for Aim 2.[107] Based on Peduzzi et al.'s work, the sample size for a logistic regression model can be estimated through the equation below:

$$N = 10*K / P$$

where, N = total sample size

K = number of covariates

P = proportion of events in the population

Assuming that we have a minimum of 5 covariates in the model, and that the probability of 30-day hospital readmission in infants with NOWS is 0.03[36], then the sample size required will be approximately 1,666. Similarly, using the rates of hospital readmission during the one-year follow-up, which is 0.077, the estimated sample size required would be approximately 650. Since our estimated sample size was approximately 3,000, our study was powered sufficiently to detect any effect of NOWS severity measures of post-discharge health care utilization.

CHAPTER 4: RESULTS

In this section we describe the geographic and temporal trends in the incidence of NOWS. It is followed by the results for Aim 1 and Aim 2. We conclude the section by presenting the results of sensitivity analyses for Aim 1 and Aim 2.

4.1 Description of sample selection across the study groups:

A total of 4,874 encounters related to NOWS (study period Jan 1, 2011 – Sep 30, 2016) were identified from the HF database. Of this group, 3,526 were selected for inclusion in the final study cohort after the application of exclusion criteria and removal of duplicates. For the late preterm group, 31,260 infants were identified from the HF database, and 24,472 records were included in the study after the application of exclusion criteria and removal of duplicates. For the uncomplicated birth group, 433,368 infants were initially identified during the same study period from the HF database. Of this group, 355,875 infants were retained after duplicates were removed and exclusion criteria was applied. A random sample of 25% of this group was selected for the final study. Sample section/attrition flowchart for the study is presented in Figures 5, 6, and 7.

Figure 5: Sample selection flowchart for the NOWS group

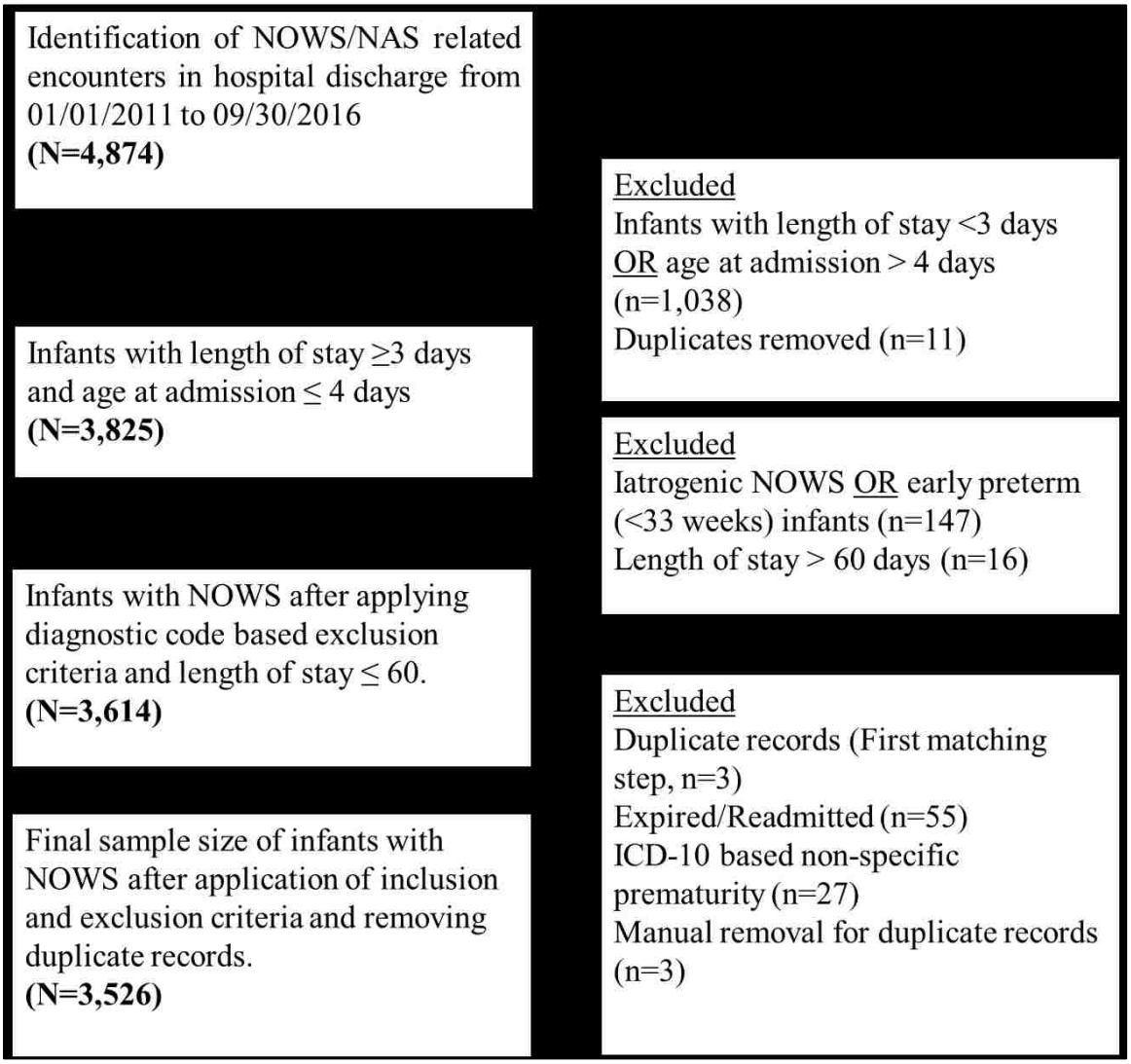


Figure 6: Sample selection flowchart for the late preterm group

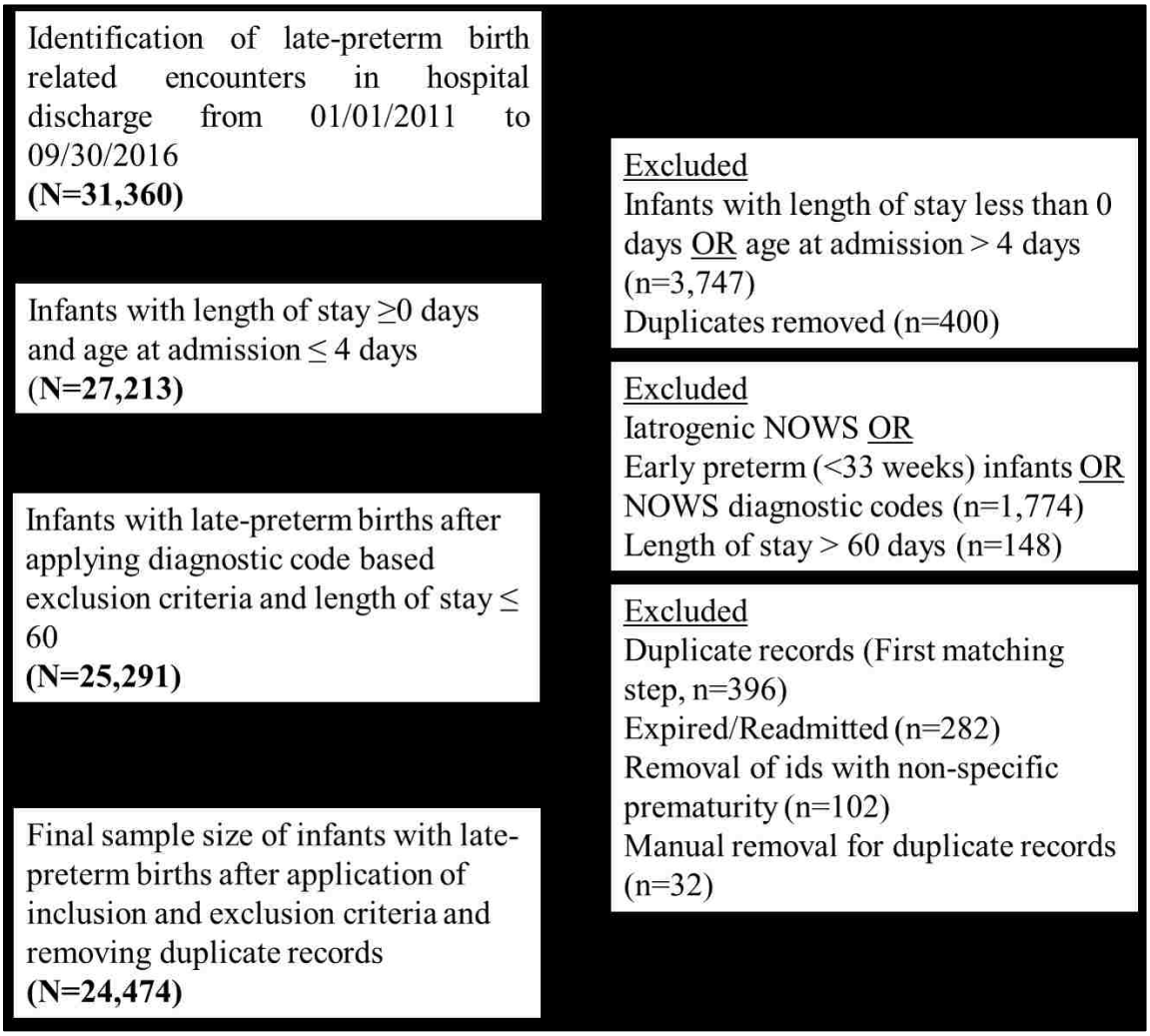
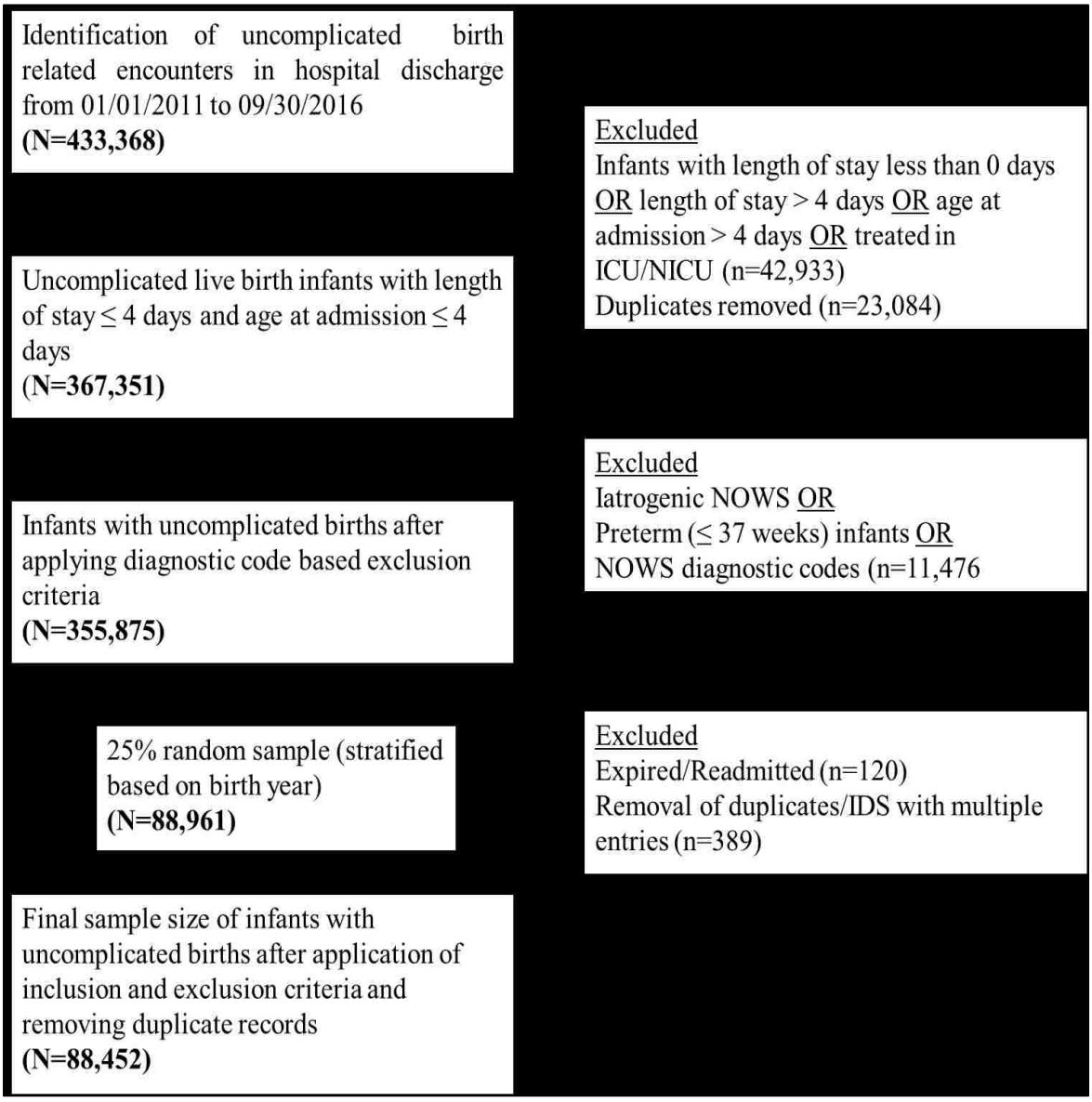


Figure 7: Sample selection flowchart for the uncomplicated birth group



4.1 Geographic and temporal trends in incidence of NOWS

The incidence rate of NOWS in infants born into health systems that utilized CERNER data systems was approximately 5.9 per 1000 births in the year 2011. There was a high degree of variability in the incidence of NOWS across different census divisions. In census division 1 (New England) and 3 (East North Central) the incidence rates of NOWS was over 10 per 1000 births, whereas in census division 4 (West North Central), 5 (South Atlantic), 7 (West South Central), and 9 (Pacific) it was lower than 3 per 1000 births (Table 9). There was an upward trend in the incidence of NOWS between 2011 and 2016. The rates increased from 5.9 per 1000 births in 2011 to 13.1 per 1000 births in 2016 – a 120% increase in 5 years. The variability in incidence of NOWS across census divisions persisted, with a greater number of census divisions reaching incidence rates of more than 10 per 1000 births between 2011 and 2016. We also observed a substantial increase in NOWS in Census Division 1 where the incidence rate peaked at approximately 50 per 1000 births in the year 2014.

While the incidence of NOWS consistently showed an upward trend, the incidence rate of late-preterm birth during the study period remained fairly constant at 63 per 1000 births until 2015 and then increasing to approximately 72.5 per 1000 births in the year 2016. This represents a 20% increase between 2011 and 2016.

Table 9: Incidence rates of NOWS and late preterm per 1000 total live births in infants born into centers that utilized CERNER EHR (Years: 2011-2016)

	2011		2012		2013		2014		2015		2016	
Census division	NOWS	Late preterm	NOWS	Late preterm	NOWS	Late preterm	NOWS	Late preterm	NOWS	Late preterm	NOWS	Late preterm
1	15.5	70.8	22.3	81.3	32.4	78.0	49.7	57.0	21.8	40.1	17.9	32.7
2	8.9	51.6	6.1	46.6	4.4	26.2	7.6	30.0	8.5	37.1	20.0	66.7
3	10.4	76.9	6.6	106.7	5.2	94.2	4.5	98.4	4.8	100.1	6.4	81.4
4	2.3	34.8	4.4	41.7	9.3	66.7	14.7	76.5	14.1	71.3	3.5	82.1
5	2.0	58.7	0.9	84.2	1.8	75.5	2.4	78.2	5.0	68.3	18.5	43.6
6	5.9	81.8	7.9	84.8	5.7	86.9	8.6	73.6	14.1	81.2	18.7	82.6
7	0.7	72.9	3.9	72.8	3.7	84.8	5.5	74.5	4.9	68.0	6.5	75.7
8	4.3	45.6	6.3	45.4	15.6	82.5	18.3	77.8	17.0	79.0	16.5	73.1
9	2.4	65.0	2.8	71.0	1.6	71.8	2.5	67.4	2.2	73.3	6.5	68.4
Total	**5.9**	60.6	**7.4**	65.0	**8.0**	63.7	**11.3**	63.0	**10.3**	64.9	**13.1**	72.5

Table 10 presents the baseline characteristics of the study groups. Statistical significant differences ($p<0.05$) were observed across sex, race, type of insurance, census region of birth, the urban-rural status of the birthing center, and the hospital size (based on the number of beds). Compared to the uncomplicated birth group, NOWS and late preterm groups had significantly higher proportion of males (52.5% and 53.7%, respectively vs 50.6% in uncomplicated birth group). Almost 80% of the infants diagnosed with NOWS were Caucasian compared to 54.0% in the late preterm group, and 57.0% in the uncomplicated birth group. About 69% of the birth-related encounters in the NOWS group were covered by Medicaid; 12% were covered by commercial insurance, and the remaining by other types of insurance (included self-pay, other non-governmental, military dependent, not-reported etc.). In the late preterm group, only 43.8% of birth-related encounters were covered by Medicaid, 18.9% by commercial insurance, and the remaining by other forms of coverage. Commercial insurance covered 44% of the initial birth-related encounters in the uncomplicated birth group, Medicaid covered 34.3%, and 21.5% was covered by other forms of coverage. In the NOWS group, 64% of the births were recorded in hospitals with greater than 300 beds, 29% in hospitals with 100 to 299 beds, and only 7.3% in hospitals with less than 100 beds. Late-preterm and uncomplicated births had fairly similar distribution to each other in regards to the size of the hospital. Fifty percent of late preterm and uncomplicated births were recorded in hospitals with greater than 300 beds, 37% in hospitals with 100 to 299 beds, and 13% in hospitals with less than 100 beds.

Table 10: Description of demographic characteristics and patient care setting by study group

Variable	NOWS (n=3,526)	Late preterm birth (n=24,474)	Uncomplicated births* (n=88,452)	p-value
Sex				<0.001
Male	52.5%	53.7%	50.6%	
Female	47.5%	46.3%	49.4%	
Race				<0.001
Caucasian	79.4%	54.0%	57.0%	
African American	5.9%	18.8%	14.1%	
Hispanic	0.8%	2.7%	2.8%	
Native American	2.7%	2.2%	1.2%	
Other	11.3%	22.4%	24.9%	
Insurance Type				<0.001
Medicaid/Medicaid MC	69.1%	43.8%	34.3%	
Commercial	11.9%	37.3%	44.4%	
Other	18.9%	18.9%	21.4%	
Census region				<0.001
Midwest	16.9%	25.2%	22.9%	
Northeast	44.2%	22.6%	33.1%	
South	23.5%	34.2%	28.1%	
West	15.4%	18.0%	16.0%	
Rural/Urban Status				<0.001
Rural	15.2%	18.2%	17.0%	
Urban	84.8%	81.8%	83.0%	
Bed size range				<0.001
Less than 100	7.4%	13.5%	13.3%	
100-299	28.5%	36.6%	37.6%	
Greater than 300	64.2%	50.0%	49.1%	
Year				-
2011	9.4%	13.9%	15.0%	
2012	11.9%	15.2%	15.2%	
2013	15.3%	17.5%	18.0%	
2014	23.3%	18.8%	19.5%	
2015	20.4%	18.5%	18.4%	
2016	19.3%	16.2%	14.0%	

*Uncomplicated births are 25% sample of the uncomplicated births in each year.

There were 782 unique hospital IDs in the HF database. After selection of the cohort for our study, we identified 186 unique hospital IDs which represented a total of 116,452 births that were included in the study. In Table 11, we present the distribution of these hospitals based on the U.S. census divisions.

Table 11: Distribution of hospitals (included in our final analysis) that utilize CERNER EHR systems across U.S. census divisions

Census divisions	Hospitals/health centers
1 (New England)	9
2 (Mid-Atlantic)	25
3 (East North Central)	22
4 (West North Central)	23
5 (South Atlantic)	11
6 (East South Central)	37
7 (West South Central)	17
8 (Mountain)	24
9 (Pacific)	18
Total	186

In Table 12, we describe the characteristics of the primary medical encounter by study groups. There was a significant difference in the average LOS across the study groups ($p<0.001$). The average LOS was 14.9 days (SD=11.5) in the NOWS group, 8.6 days (SD=8.7) in the late preterm group, and 2.1 days (SD=0.8) in the uncomplicated birth group ($p<0.001$). The median total charges (adjusted to 2016 U.S. dollars) in the NOWS group

was $24,944, $15,970 in the late preterm group, and $3,129 in the uncomplicated birth group ($p<0.001$).

Respiratory problems were common in both the NOWS and late preterm groups. Approximately 20% of the infants in the NOWS group and 34% in the late preterm group had respiratory problems (Respiratory distress syndrome, transient tachypnea of newborn, other respiratory condition). Major differences between these groups were seen in the diagnosis of respiratory distress syndrome (NOWS: 4.7% vs. late preterm: 12.9%, $p<0.001$) and other specified respiratory conditions (NOWS: 7.5% vs. late preterm: 13.8%, $p<0.001$). Respiratory problems in the uncomplicated birth group was less than 3%. In the NOWS group, 1.2% of the infants had a diagnostic code for convulsion compared to 0.4% in the late preterm group, and 0.1% in the uncomplicated birth group ($p<0.001$). Other commonly present diagnostic codes in the NOWS and the late preterm group were feeding difficulties (NOWS: 18.4% vs. late preterm: 22.0%, $p<0.001$), jaundice (NOWS 35.6% vs. late preterm 47.4%, $p<0.001$), and sepsis (NOWS 4.6% vs. late preterm 7.5%, $p<0.001$). Besides jaundice (uncomplicated birth: 10.9%), these conditions were rare in the uncomplicated birth group (less than 2%).

Table 12: Description of the primary medical encounter by study groups

	NOWS (n=3,526)	**Late preterm birth (n=24,474)**	**Uncomplicated births* (n=88,452)**	**p-value**
	Mean (SD)			
LOS (days)	14.9 (11.5)	8.6 (8.7)	2.1 (0.8)	<0.001
Total Charges in dollars* (median)	$24,944	$15,970	$3,129	<0.001
	%			
Gestational age at delivery				<0.001
33 weeks to less than 37 weeks	14.7%	100%	0%	
Any respiratory problems	20.8%	34.0%	2.6%	<0.001
Type of respiratory problems				
Respiratory distress syndrome	4.8%	12.9%	0.2%	
Transient tachypnea of newborn	11.3%	11.8%	1.5%	
Respiratory condition of newborn (unspecified)	0.8%	1.5%	0.1%	
Other specified respiratory condition	7.5%	13.8%	1.1%	
Convulsions	1.2%	0.4%	0.1%	<0.001
Feeding difficulties	18.4%	22.0%	1.0%	<0.001
Jaundice	35.6%	47.4%	10.9%	<0.001
Sepsis	4.6%	7.5%	0.4%	<0.001

4.2: Results for Specific Aim 1

Specific Aim 1 examined post-discharge healthcare utilization during the one-year follow up period in the NOWS group compared to the late preterm, and uncomplicated birth groups. Post-discharge healthcare utilization was measured by emergency department visits, hospital readmissions (inpatient stay), and outpatients visits.

Table 13 shows the rates of post-discharge healthcare utilization during the one-year follow-up period in the three study groups. The NOWS and late preterm groups

showed similar post-discharge health care utilization, such as rates of rehospitalization (~4%) and rates of emergency department visits (~7.5%). In comparison, rehospitalization and emergency department visits were lower in the uncomplicated birth group (1.6%, and 6.1% respectively). The mean number of outpatient visit per person was significantly higher in the late preterm group (0.047) compared to NOWS (0.037) and uncomplicated birth (0.038) groups ($p<0.001$).

We observed differences (range: any composite visit: 8.5%-13.2%; any 30-day composite visit: 2.1%-6.7%) in the post-discharge health care utilization based on the year of discharge (Table 14). Highest rate of post-discharge visits (any composite or any 30-day composite visits) were observed in the year 2013. In comparison the rate of post-discharge health care utilization in the late preterm and uncomplicated birth groups remained fairly constant.

The association between the study groups and hospital readmissions during the one-year follow-up period is shown in Table 15. In the unadjusted model, we observed significantly higher odds of hospital readmission in the NOWS group (OR: 2.5, 95% C.I.: 2.0-3.3) compared to controls (uncomplicated birth). In model 2 (adjusted for sex, race, insurance type, urban-rural status, census region, hospital size and year of discharge), the results still showed a significant association between NOWS and hospital readmission (OR 2.0, 95% C.I.: 1.4-2.7) when compared to uncomplicated birth group. In model 3 (additional adjustment for respiratory conditions, feeding problems, jaundice, sepsis, and convulsions) the odds of rehospitalization in the follow-up period in the NOWS group was 1.7 times the odds in the uncomplicated birth group (95%CI: 1.4-1.9). Similarly, across all

the models, infants who had late preterm births showed higher odds of rehospitalization during the one-year follow-up period when compared to the uncomplicated birth group.

There was a significant association between NOWS and 30-day rehospitalization (OR: 2.7, 95% C.I.: 1.9-3.8). The association persisted after the adjustment for demographic and hospital-related factors in model 2 (OR: 2.1, 95% C.I.: 1.4-3.2) and medical conditions in model 3 (OR: 1.9, 95% C.I.: 1.3-2.6). Similarly, across all the models, infants who had late preterm births also showed higher odds of 30-day rehospitalization compared to uncomplicated birth group.

In the sub-group analysis, we compared the rates of rehospitalization in the NOWS group to the late preterm group. After adjustment of demographics and medical conditions, the odds of any rehospitalization was lower in the NOWS group (OR: 0.8, 95% C.I.: 0.6-0.98) compared to the late preterm group. However, there was no difference in 30-day rehospitalization across these groups (NOWS vs. late preterm group).

Table 16 describes the association between emergency department visits and study groups during the one-year follow-up period. In the unadjusted analysis, we observed that infants in the NOWS group had higher odds of emergency department visits compared to the uncomplicated birth group in the one-year follow-up period (OR: 1.5, 95% C.I.: 1.1-1.9). The results were not statistically significant after adjustment of demographic factors in model 2, and after the addition of medical conditions in model 3. In the unadjusted model, the NOWS group had higher odds of 30-day emergency department visits compared to the uncomplicated birth group (OR: 1.5, 95% C.I.: 1.2-1.9). After adjustments in model 2 and 3, the association was marginally significant (Model 3, OR: 1.3, 95% C.I.: 1.0-1.6). However, compared to the uncomplicated birth group, late preterm group had significantly

higher odds of any emergency department visit and 30-day emergency department visit in all the unadjusted and adjusted models. In the sub-group analysis, we observed no difference in the rates of any emergency department visits (one-year period) or 30-day emergency department visits across all the unadjusted and adjusted logistic regression models between the NOWS group and the late preterm group.

Table 17 describes the differences in composite healthcare utilization (i.e., any emergency department visit or rehospitalization), during the one-year follow-up period between the study groups. In the unadjusted analysis, there were higher odds of composite healthcare utilization in the NOWS group (OR: 1.5, 95% C.I.: 1.4-1.7) compared to the uncomplicated birth group. However, after adjustments, these associations were not statistically significant.

We found higher odds of 30-day composite health care utilization in the NOWS group compared to the uncomplicated birth group across all unadjusted and adjusted logistic regression models. The unadjusted model showed that the odds of composite healthcare utilization in the NOWS group was 1.9 times the odds in the uncomplicated birth group (95% C.I.: 1.6-2.2). After adjusting for demographics and hospital characteristics in model 2 the odds ratio was 1.5 (95% C.I.: 1.3-1.8). In model 3, the odds ratio was 1.4 (95% C.I.: 1.2-1.6).

We found similar association between late preterm birth and composite measures of healthcare utilization. The late preterm group had significantly higher odds of a hospital or emergency room visit, or any 30-day composite visit, compared to the uncomplicated birth group across all unadjusted and adjusted models. In the sub-group analysis, NOWS group had lower odds of any composite visit, compared to the late preterm group, after

adjustment of demographics and medical characteristics (Model 3, OR: 0.8, 95% C.I.: 0.6-0.98). However, there was no difference in any 30-day composite health care utilization across the two groups.

The results of analysis of differences in post-discharge outpatient visits across the study groups is presented in Table 18. In the unadjusted and adjusted logistic regression models, there were no differences in the odds of outpatient visit across the study groups. Similarly, in the sub-group analysis, there were no differences in post-discharge outpatient visit between the NOWS group and the late preterm group.

Model metrics-AUROC for logistic regression models

The unadjusted logistic regression model with the study group as the predictor had an AUROC of 60% or lower across the outcome measures evaluated in the study. Addition of infant demographic covariates in model 2 showed considerable improvement in AUROC (from 60% to approximately 68%). However, addition of other medical condition related covariates in model 3 did not produce major improvements in the AUROC (approximate improvement in AUROC 1.5%) These changes in AUROC showed that adding covariates related to medical condition over the demographic characteristics did not provide additional information in predicting post-discharge health care utilization. This is likely because these conditions were common in the late preterm and NOWS group possibly leading to more collinearity rather than explaining the variability of the outcomes.

Table 13: Post-discharge healthcare utilization by study groups

Variable	NOWS (n=3,526)	Late preterm birth (n=24,474)	Uncomplicated births (n=88,452)	p-value
Rehospitalization				
Mean rehospitalization	0.042	0.049	0.0166	<0.001
Any rehospitalization	3.8%	4.3%	1.6%	<0.001
Any 30-day rehospitalization	2.4%	2.9%	0.9%	<0.001
Emergency Department				
Mean emergency department visit	0.114	0.114	0.86	<0.001
Any emergency department visit	7.5%	7.6%	6.1%	<0.001
Any 30-day emergency department visit	2.0%	1.8%	1.6%	<0.001
Any (Rehospitalization or Emergency Department)				
Total mean visits (Rehospitalization and Emergency Department)	0.156	0.163	0.102	<0.001
Any visit (Rehospitalization and Emergency Department)	10.4%	11.1%	7.3%	<0.001
Any 30-day visit (Rehospitalization and Emergency Department)	4.3%	4.5%	2.4%	<0.001
Outpatient visit				
Mean outpatient visit	0.371	0.470	0.376.	<0.001
Any outpatient	12.4%	16.2%	14.9%	<0.001

Table 14: Yearly variation in post-discharge health care utilization (Composite measures) across study groups

Any e visit			
Year	**NOWS (n=3,526)**	**Late preterm birth (n=24,474)**	**Uncomplicated births (n=88,452)**
2011	8.5%	10.7%	7.3%
2012	12.4%	12.1%	8.4%
2013	13.2%	11.4%	7.6%
2014	8.5%	10.1%	7.7%
2015	10.8%	11.6%	7.0%
2016	9.7%	10.3%	5.5%
Any 30-day visit			
Year			
2011	2.1%	3.9%	1.9%
2012	5.7%	5.1%	2.4%
2013	6.7%	4.7%	2.5%
2014	3.0%	3.9%	2.5%
2015	3.3%	4.8%	2.4%
2016	4.9%	4.8%	2.9%

Table 15: Logistic regression model for rehospitalization during one-year follow-up period

	Model 1	Model 2	Model 3
	Odds Ratio (95% C.I.)		
Any rehospitalization			
Uncomplicated births (Ref) vs. NOWS	2.5 (2.0-3.3)	2.0 (1.4-2.7)	1.7 (1.3-2.2)
Uncomplicated births (Ref) vs. Late preterm births	2.9 (2.3-3.6)	2.7 (2.2-3.3)	2.2 (1.8-2.7)
AUROC	61.5%	68.5%	69.0%
Sub-group analysis			
Late preterm births (Ref) vs. NOWS	0.9 (0.7-1.1)	0.7 (0.6-0.9)	0.8 (0.6-0.98)
AUROC	50.7%	62.4%	63.3%
30-day rehospitalization			
Uncomplicated births (Ref) vs. NOWS	2.7 (1.9-3.8)	2.1 (1.4-3.2)	1.9 (1.3-2.6)
Uncomplicated births (Ref) vs. Late preterm births	3.3 (2.6-4.3)	3.1 (2.4-4.0)	2.6 (2.0-3.3)
AUROC	63.0%	69.0%	69.6%
Sub-group analysis			
Late preterm births (Ref) vs. NOWS	0.8 (0.6-1.0)	0.7 (0.5-1.0)	0.7 (0.5-1.1)
AUROC	51.1%	61.9%	62.2%

Ref: Reference

AUROC: Area under the receiver operating characteristic curve (for the logistic regression models)

Model 1: Unadjusted model

Model 2: Adjusted for sex, race, insurance type, urban-rural status, census division, hospital size, year of discharge

Model 3: Model 2 + respiratory condition, feeding problem, jaundice, sepsis, and convulsions

Table 16: Logistic regression model for emergency department visits during one-year follow-up period

	Model 1	Model 2	Model 3
	Odds Ratio (95% C.I.)		
Any emergency department visit			
Uncomplicated births (Ref) vs. NOWS	1.5 (1.1-1.9)	1.1 (0.9-1.3)	1.0 (0.8-1.2)
Uncomplicated births (Ref) vs. Late preterm births	1.6 (1.4-1.9)	1.4 (1.3-1.6)	1.2 (1.2 -1.5)
AUROC	52.3%	67.7%	67.7%
Sub-group analysis			
Late preterm births (Ref) vs. NOWS	1.0 (0.7-1.4)	0.8 (0.7-1.1)	0.8 (0.6-1.1)
AUROC	50.1%	65.0%	65.0%
30-day emergency department visit			
Uncomplicated births (Ref) vs. NOWS	1.8 (1.7-2.3)	1.4 (1.1-1.8)	1.3 (1.0-1.6)
Uncomplicated births (Ref) vs. Late preterm births	1.9 (1.6-2.3)	1.7 (1.4-2.0)	1.6 (1.3-1.8)
AUROC	51.2%	66.5%	66.5%
Sub-group analysis			
Late preterm births (Ref) vs. NOWS	1.2 (0.8-1.6)	1.1 (0.9-1.5)	1.1 (0.9-1.5)
AUROC	50.9%	64.9%	65.1%

Ref: Reference

AUROC: Area under the receiver operating characteristic curve (for the logistic regression models)

Model 1: Unadjusted model

Model 2: Adjusted for sex, race, insurance type, urban-rural status, census division, hospital size, year of discharge

Model 3: Model 2 + respiratory condition, feeding problem, jaundice, sepsis, and convulsions

Table 17: Logistic regression model for any emergency department visit or rehospitalization during one-year follow-up period

	Model 1	Model 2	Model 3
	Odds Ratio (95% C.I.)		
Any visit (emergency department or rehospitalization)			
Uncomplicated births (Ref) vs. NOWS	1.5 (1.4-1.7)	1.1 (1.0-1.3)	1.1 (0.9-1.2)
Uncomplicated births (Ref) vs. Late preterm births	1.6 (1.6-1.7)	1.5 (1.4-1.6)	1.4 (1.3-1.4)
AUROC	54.6%	66.4%	66.5%
Sub-group analysis			
Late preterm births (Ref) vs. NOWS	0.9 (0.7-1.2)	0.8 (0.6-0.96)	0.8 (0.6-0.98)
AUROC	50.4%	62.7%	62.9%
Any 30-day visit (emergency department or rehospitalization)			
Uncomplicated births (Ref) vs. NOWS	1.9 (1.6-2.2)	1.5 (1.3-1.8)	1.4 (1.2-1.6)
Uncomplicated births (Ref) vs. Late preterm births	2.0 (1.9-2.2)	1.9 (1.7-2.0)	1.7 (1.5-1.8)
AUROC	56.7%	64.9%	65.1%
Sub-group analysis			
Late preterm births (Ref) vs. NOWS	0.9 (0.7-1.2)	0.9 (0.7-1.1)	0.9 (0.7-1.2)
AUROC	50.4%	59.9%	60.0%

Ref: Reference

AUROC: Area under the receiver operating characteristic curve (for the logistic regression models)

Model 1: Unadjusted model

Model 2: Adjusted for sex, race, insurance type, urban-rural status, census division, hospital size, year of discharge

Model 3: Model 2 + respiratory condition, feeding problem, jaundice, sepsis, and convulsions

Table 18: Logistic regression model for any outpatient visit during one-year follow-up period

	Model 1	Model 2	Model 3
	Odds Ratio (95% C.I.)		
Uncomplicated births (Ref) vs. NOWS	0.8 (0.4-1.5)	0.9 (0.6-1.5)	0.9 (0.6-1.4)
Uncomplicated births (Ref) vs. Late preterm births	1.1 (0.9-1.4)	1.0 (0.8-1.2)	1.0 (0.9-1.2)
AUROC	51.2%	69.7%	69.8%
Sub-group analysis			
Late preterm births (Ref) vs. NOWS	0.7 (0.4-1.2)	0.8 (0.6-1.2)	0.8 (0.6-1.2)
AUROC	51.6%	67.9%	68.2%

Ref: Reference

AUROC: Area under the receiver operating characteristic curve (for the logistic regression models)

Model 1: Unadjusted model

Model 2: Adjusted for sex, race, insurance type, urban-rural status, census division, hospital size, year of discharge

Model 3: Model 2 + respiratory condition, feeding problem, jaundice, sepsis, and convulsions

Tables 19 and 20 present the comparison of the incidence rates of post-discharge health care utilization among the study groups, using Poisson and Zero-inflated Poisson regression models. The incidence rates of any composite visit and rehospitalization were significantly higher in the NOWS group compared to the uncomplicated birth group across all unadjusted and adjusted models (any composite visit Model 3: IRR: 1.4, 95% C.I.: 1.2-1.6 and rehospitalization, Model 3: IRR: 2.1, 95% C.I.: 1.6-2.7). For any emergency department visit, the association was marginally significant across all three statistical models (Model 3, IRR: 1.3, 95% C.I.: 1.02-1.6) between NOWS group and uncomplicated birth group. No differences in the rates of outpatient visits were observed across the study groups.

To account for the high number of zero values in the counts of healthcare utilization visits (no use), we used the Zero-inflated Poisson regression model as a robustness check for our previous analysis. The incidence rate of any composite visit in the NOWS group was not significantly different than that in the uncomplicated birth group (Model 3, IRR: 1.1, 95% C.I.: 0.95-1.3). However, the incidence rate of rehospitalization in the NOWS group was statistically significant (Model 3, IRR: 1.8, 95% C.I.: 1.4-2.3) when compared to the uncomplicated birth group. We did not observe significant differences in the rates of emergency department visit or outpatient visit in the NOWS group compared to the uncomplicated birth groups.

In the sub-group analysis (Table 20), there were no differences in any composite visit, emergency department or outpatient visit, in the NOWS group vs. the late preterm group. The rates of rehospitalization, however, were significantly lower in the NOWS group (Model 3, IRR: 0.8, 95% C.I.: 0.6-0.9) compared to the late preterm group.

Model metrics-AIC/N for Poisson regression models

The unadjusted Poisson regression model with the study group as the predictor and any composite visit as outcome had an AIC/N value of 0.798 (lower scores denote better fit). Addition of covariates, such as sex, race, insurance type, urban-rural status, year, hospital id, and census division, in model 2 showed improvement in AIC to 0.777. However, addition of other medical condition related covariate in model 3 did not produce any changes in AIC/N values. Similarly, the AIC/N values for any rehospitalization improved to 0.226 from 0.224 after addition of demographic and hospital characteristics related covariates. There was no improvement in AIC/N in Model 3. The results for the Poisson model for emergency department visits and outpatient visits also showed consistent pattern of improvement in model 2 after addition of demographics and hospital characteristics but no change with the addition of other covariates in Model 3.

Similarly, in the Zero-inflated Poisson regression models, consistent improvement in the model fit was observed after the addition of demographic and hospital related covariates in Model 2 over Model 1. There was limited or almost no improvement in model fit in model 3.

These changes in the AIC/N showed that medical covariates (Model 3) did not add additional information beyond what was provided by demographic characteristics in model 2. As explained previously, this is likely because these conditions were most common in the late preterm and NOWS group possibly leading to more collinearity rather than explaining the variability of the outcomes.

Table 19: Poisson and Zero-inflated Poisson model for post-discharge health care utilization by study groups during one-year follow-up period

	Any visit	Rehospitalization	Emergency department	Outpatient visits
	IRR (95% C.I.)			
Poisson model				
Model 1	-	-	-	-
Uncomplicated births (Ref) vs. NOWS	1.5 (1.2-2.0)	2.5 (2.0-3.2)	1.3 (0.9-1.9)	1.0 (0.5-2.0)
Uncomplicated births (Ref) vs. Late preterm births	1.6 (1.4-1.9)	3.0 (2.3-3.7)	1.3 (1.1-1.6)	1.2 (1.03-1.5)
AIC/N	0.798	0.226	0.679	2.188
Model 2	-	-	-	-
Uncomplicated births (Ref) vs. NOWS	1.5 (1.2-1.8)	2.4 (1.8-3.1)	1.3 (1.04-1.6)	1.0 (0.5-2.0)
Uncomplicated births (Ref) vs. Late preterm births	1.5 (1.3-1.7)	2.9 (2.3-3.6)	1.2 (1.1-1.4)	1.1 (0.9-1.4)
AIC/N	0.777	0.224	0.658	1.989
Model 3	-	-	-	-
Uncomplicated births (Ref) vs. NOWS	1.4 (1.2-1.6)	2.1 (1.6-2.7)	1.3 (1.02-1.6)	1.0 (0.5-2.0)
Uncomplicated births (Ref) vs. Late preterm births	1.4 (1.2-1.6)	2.4 (1.9-3.0)	1.2 (1.0-1.3)	1.1 (0.9-1.3)
AIC/N	0.777	0.224	0.658	1.987
Zero inflated Poisson model				
Model 1	-	-	-	--
Uncomplicated births (Ref) vs. NOWS	1.2 (0.9-1.5)	2.2 (1.8-2.6)	1.0 (0.8-1.4)	1.0 (0.5-2.1)
Uncomplicated births (Ref) vs. Late preterm births	1.3 (1.2-1.5)	2.8 (2.2-3.5)	1.2 (1.1-1.3)	1.2 (1.03-1.5)
AIC/N	0.702	0.220	0.583	1.354
Model 2	-	-	-	-
Uncomplicated births (Ref) vs. NOWS	1.2 (1.1-1.3)	2.0 (1.6-2.6)	1.0 (0.8-1.3)	1.1 (0.7-1.7)

Uncomplicated births (Ref) vs. Late preterm births	1.4 (1.3-1.4)	2.8 (2.2-3.4)	1.2 (1.1-1.3)	1.2 (1.0-1.4)
AIC/N	0.693	0.219	0.576	1.303
Model 3	-	-	-	-
Uncomplicated births (Ref) vs. NOWS	1.1 (0.95-1.3)	1.8 (1.4-2.3)	1.0 (0.8-1.3)	1.1 (0.7-1.6)
Uncomplicated births (Ref) vs. Late preterm births	1.3 (1.2-1.4)	2.4 (1.9-2.9)	1.2 (1.0-1.3)	1.1 (1.0-1.3)
AIC/N	0.693	0.218	0.575	1.303

IRR: Incidence rate ratio

AIC/N: Akaike information coefficient/sample size

Model 1: Unadjusted model

Model 2: Adjusted for sex, race, insurance type, urban-rural status, census division, hospital size, year of discharge

Model 3: Model 2 + respiratory condition, feeding problem, jaundice, sepsis, and convulsions

Table 20: Sub-group analysis: Zero-Inflated Poisson model for post-discharge health care utilization during one-year follow-up period

	Any visit	Rehospitalization	Emergency department	Outpatient visits
	IRR (95% C.I.)			
Zero-inflated Poisson model				
Model 1	-	-	-	--
Late preterm births (Ref) vs. NOWS	0.9 (0.7-1.2)	0.8 (0.6-0.97)	0.9 (0.7-1.2)	0.8 (0.4-1.5)
AIC/N	0.904	0.387	0.684	1.438
Model 2	-	-	-	-
Late preterm births (Ref) vs. NOWS	0.9 (0.7-1.1)	0.7 (0.6-0.9)	0.9 (0.7-1.1)	0.8 (0.6-1.2)
AIC/N	0.893	0.383	0.675	1.390
Model 3	-	-	-	-
Late preterm births (Ref) vs. NOWS	0.9 (0.7-1.1)	0.8 (0.6-0.9)	0.9 (0.7-1.1)	0.8 (0.6-1.1)
AIC/N	0.893	0.382	0.675	1.389

IRR: Incidence rate ratio

AIC/N: Akaike information coefficient/sample size

Model 1: Unadjusted model

Model 2: Adjusted for sex, race, insurance type, urban-rural status, census division, hospital size, year of discharge

Model 3: Model 2 + respiratory condition, feeding problem, jaundice, sepsis, and convulsions

Mean time to the first emergency visit in the NOWS group was 153 (SD: 112) days as opposed to 154 (SD: 113) days in the late preterm group and 157 (SD: 116) days in the uncomplicated birth group ($p=0.53$). The mean time to the first rehospitalization was 71.9 (SD: 105) days in the NOWS group, 52 (SD: 86) days in the late preterm group, and 63.3 (SD: 89.1) days in the uncomplicated birth group ($p<0.05$). These means reflect the average number of days until the first event for infants who had the specific event (emergency department visit or rehospitalization). The Kaplan-Meier curves for rehospitalization and emergency department visits are shown in Figure 8. There were significant differences in the time to event for both emergency department visit and rehospitalization across the study groups based on the log-rank test of equality of survival functions ($p<0.001$).

Using Cox proportional-hazards regression, we estimated the hazard ratios (HR) of outcomes across the study groups (i. emergency visit and ii. rehospitalization, Table 21). There were no significant differences in the hazard ratios for emergency department visits in the NOWS group compared to the uncomplicated birth group across all unadjusted and adjusted Cox proportional-hazards regression models. In the sub-group analysis, comparing NOWS group to the late preterm group, we did not observe any significant difference in the hazard ratio for emergency department visits.

The hazard rate for rehospitalization was significantly higher in the NOWS group compared to the uncomplicated birth group in the unadjusted model (HR: 2.0, 95% C.I.: 1.6-2.5). The association remained significant even after adjustment for demographic characteristics (HR: 1.5, 95% C.I.: 1.2-1.9), and medical conditions (HR: 1.4, 95% C.I.: 1.1-1.8). In the sub-group analysis, the hazard rate for rehospitalization in the NOWS group was not statistically significant when compared to the late preterm group in the unadjusted

analysis. However, after adjusting for other confounders we observed that the HR for rehospitalization was lower in the NOWS group compared to the late preterm group (Model 3, HR: 0.7, 95% C.I.: 0.6-0.8).

Table 21: Survival analysis: Time to first incidence of post-discharge health care utilization across study groups during one-year follow-up period

	Emergency visit	**Rehospitalization**
Cox proportional-hazards regression	HR (95% C.I.)	HR (95% C.I.)
Model 1		
Uncomplicated births (Ref) vs. NOWS	1.2 (0.9-1.7)	2.0 (1.6-2.5)
Uncomplicated births (Ref) vs. Late preterm births	1.3 (1.1-1.5)	2.4 (2.0-2.9)
Model 2		
Uncomplicated births (Ref) vs. NOWS	0.9 (0.7-1.2)	1.5 (1.2-1.9)
Uncomplicated births (Ref) vs. Late preterm births	1.1 (1.0-1.3)	2.2 (1.9-2.7)
Model 3		
Uncomplicated births (Ref) vs. NOWS	0.9 (0.7-1.1)	1.4 (1.1-1.8)
Uncomplicated births (Ref) vs. Late preterm births	1.1 (0.9-1.2)	2.0 (1.7-2.4)
*Sub-group analysis**		
Model 1		
Late preterm births (Ref) vs. NOWS	1.0 (0.7-1.4)	0.8 (0.7-1.1)
Model 2		
Late preterm births (Ref) vs. NOWS	0.8 (0.7-1.1)	0.7 (0.6-0.8)
Model 3		
Late preterm births (Ref) vs. NOWS	0.8 (0.7-1.1)	0.7 (0.6-0.8)

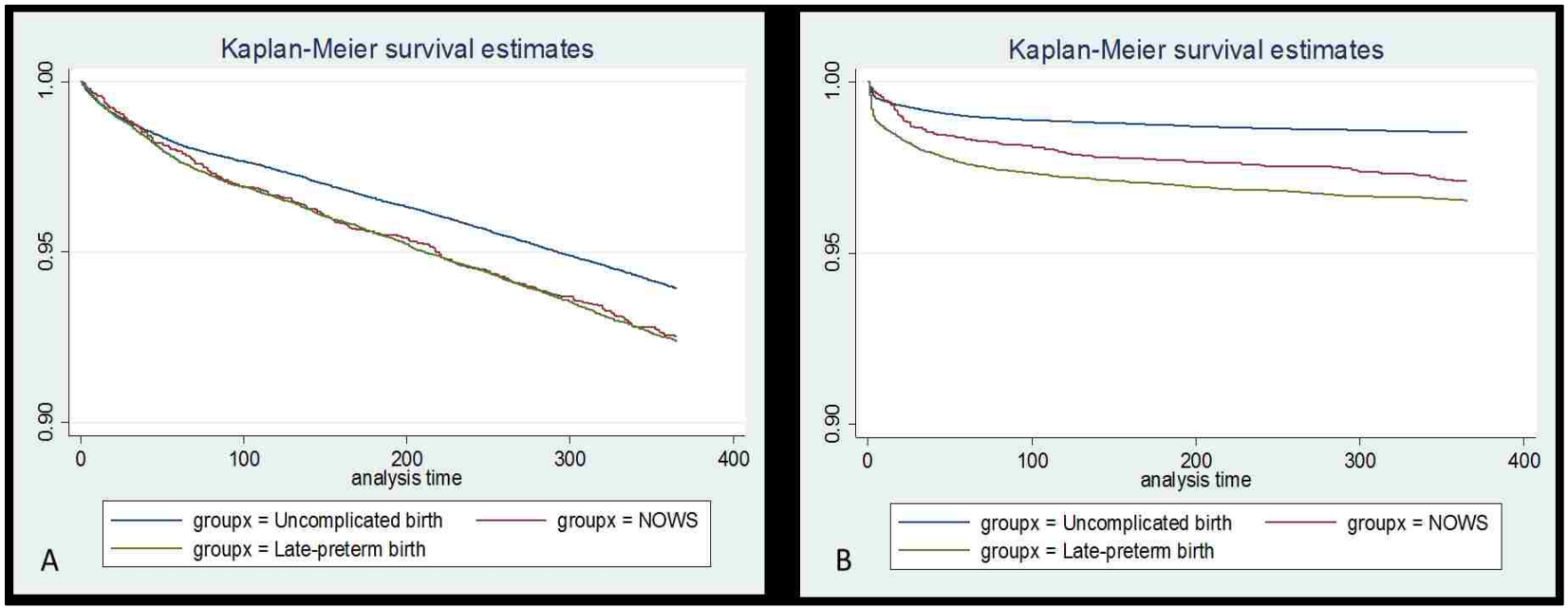
Model 1: Unadjusted model

Model 2: Adjusted for LOS, sex, race, insurance type, urban rural status, census division, hospital size, year of discharge

Model 3: Model 2 + respiratory condition, feeding problem, jaundice, sepsis, and convulsions

*Models 2 and 3 also include initial LOS for the sub-group analysis

Figure 8: Kaplan-Meier survival curves by study groups. A: Emergency department visit B. Rehospitalization



4.3: Results for Specific Aim 2

Table 22 describes the baseline characteristics of the NOWS group divided across infants who received pharmacologic treatment (received methadone, morphine, tincture of opium and/or phenobarbital, henceforth termed "Treated-For-NOWS") and infants who did not receive pharmacological treatment for NOWS (Not-Treated-For-NOWS). This sub-group (Treated-For-NOWS) accounted for 34% of the infants in the NOWS group. There were no significant differences between infants who were Treated-For-NOWS and those who were Not-Treated-For-NOWS with respect to sex, race, or urban-rural status ($p>0.05$). Statistically significant differences were present between these two groups with respect to type of insurance, census region, and hospital size ($p<0.05$).

The differences in characteristics of the primary medical encounter by pharmacological treatment of NOWS is presented in Table 23. Infants in the Treated-For-NOWS group had significantly longer LOS in the hospital following birth, compared to Not-Treated-for-NOWS group (21.9 days vs. 12.2 days, $p<0.001$). Additionally, the median cost for those in the Treated-For-NOWS group was approximately $52,000, compared to $10,000 in the Not-Treated-For-NOWS group.

Overall, a larger proportion of infants in the Treated-For-NOWS group had medical conditions, such as respiratory problems, convulsions, feeding difficulties, and sepsis (all p-values <0.001). Observed respiratory problems within this group included respiratory distress syndrome, transient tachypnea of newborn, and other unspecified respiratory condition. A high proportion of infants in both groups had jaundice (35%, $p=0.74$).

Medications received during the pharmacological treatment are presented in Table 24. Among, infants who were diagnosed with NOWS a majority received either morphine

or methadone (31%) followed by antibiotics (16%) and phenobarbital (6%). Morphine was the most common medication of choice for pharmacologic management treatment of NOWS (72.5%). Infants in the Treated-For-NOWS group were also administered benzodiazepines and antibiotics at significantly higher rates than those in the Not-Treated-For-NOWS group ($p<0.001$).

Table 22: Description of demographic characteristics and patient care setting in infants diagnosed with now based on pharmacologic treatment

	NOWS (n=3,526)	**Treated-For-NOWS (n=1,203)**	**Not-Treated-For-NOWS (n=2,323)**	**p-value**
Sex				0.170
Male	52.5%	54.1%	51.7%	
Female	47.5%	45.9%	48.3%	
Race				0.099
Caucasian	79.4%	78.5%	79.9%	
African American	5.9%	4.9%	6.4%	
Hispanic	0.8%	0.8%	0.8%	
Native American	2.7%	3.1%	2.5%	
Other	11.3%	12.8%	10.5%	
Insurance type				0.001
Medicaid/ Medicaid MC	69.1%	73.2%	67.0%	
Commercial	11.9%	9.8%	13.0%	
Other	18.9%	17.0%	19.9%	
Census region				<0.001
Midwest	16.9%	10.4%	20.3%	
Northeast	44.2%	42.0%	45.3%	
South	23.5%	25.0%	22.8%	
West	15.4%	22.6%	11.6%	
Urban rural status				0.683
Urban	84.8%	84.5%	85.0%	
Rural	15.2%	15.5%	15.0%	
Hospital size (number of beds)				<0.001
Less than 100	7.4%	4.0%	9.2%	
100-299	28.4%	31.3%	27.0%	
Greater than 300	64.2%	64.8%	63.9%	

Table 23: Description of primary medical encounter by status of pharmacologic treatment for NOWS

Variable	NOWS (n=3,526)	Treated-For-NOWS (n=1,203)	Not-Treated-For-NOWS (n=2,323)	p-value
	Mean (SD)			
LOS (days)	14.9 (11.5)	19 (11.6)	11.4 (9.7)	<0.001
Total Charges in dollars* (median)	$24,944	$60,355	$11,989	<0.001
	%			
Gestational age at delivery				0.303
33 weeks to less than 37 weeks	14.7%	15.5%	14.3%	
Any respiratory problems	20.8%	27.5%	17.4%	<0.001
Type of respiratory problems				
Respiratory distress syndrome	4.8%	7.5%	3.4%	<0.001
Transient tachypnea of newborn	11.3%	13.8%	9.9%	<0.001
Respiratory condition of newborn (unspecified)	0.8%	1.2%	0.7%	0.106
Other specified respiratory condition	7.5%	10.2%	6.1%	<0.001
Convulsions	1.2%	1.9%	0.8%	0.005
Feeding difficulties	18.4%	26.2%	14.4%	<0.001
Jaundice	35.6%	36.0%	35.4%	0.740
Sepsis	4.6%	6.9%	3.4%	

Table 24: Description of medication received during primary medical encounter by status of pharmacologic treatment for NOWS

	NOWS (n=3,526)	**Treated-For-NOWS (n=1,203)**	**Not-Treated-For-NOWS (n=2,323)**	**p-value**
Received morphine	24.7%	72.5%	-	
Received methadone	7.9%	23.3%	-	
Received opium	0.2%	0.7%	-	
Received morphine or methadone	31.2%	91.4%	-	
Received phenobarbital	6.4%	18.7%	-	
Received benzodiazepines	1.5%	3.2%	0.6%	<0.001
Received antibiotics	16.3%	25.6%	11.4%	<0.001

4.3.1 Analysis of the association between pharmacological treatment of NOWS and post-discharge health care utilization

A wide variability in post-discharge healthcare utilization (Table 25) across infants who received/did not receive pharmacological treatment for NOWS was found. Any emergency department visit (10.1% vs. 6.2%, $p<0.001$) and the mean number of emergency department visits (0.164 vs. 0.089, $p<0.001$) in the one-year follow-up period were significantly higher in Treated-For-NOWS group when compared to Not-Treated-For-NOWS group. Treated-For-NOWS group also had higher any composite visit (13.0% vs. 9.0%, $p<0.001$) and had higher mean number of composite visits (0.211 vs. 0.129, $p<0.001$) compared to Not-Treated-For-NOWS group. We did not find any significant differences in the mean number of rehospitalization events or any post-discharge rehospitalization based on their pharmacological treatment status. Furthermore, we did not observe any significant differences in the rates of outpatients visits based on the pharmacological treatment status of the infant.

4.3.2 Analysis of the association between NOWS related severity measures and post-discharge healthcare utilization

In the unadjusted logistic regression model (Table 26), medical conditions, such as respiratory conditions (OR: 1.8, 95% C.I.: 1.1-2.9), feeding difficulties (OR: 1.6, 95% C.I.: 1.1-2.5), and receiving antibiotics (OR: 1.4, 95% C.I.: 1.1-1.9) were associated with higher odds of rehospitalization. We did not observe any associations between the pharmacological treatment, LOS, prematurity, medications (phenobarbital, barbiturates), sepsis and rehospitalization. In the adjusted model, these associations were not statistically significant either. In both the unadjusted and adjusted models, there was no association

between odds of any 30-day rehospitalization and medication received, LOS, prematurity, or medical conditions diagnosed at initial hospital stay.

A significant association between pharmacologic treatment for NOWS and emergency department visit was observed (OR: 1.6, 95% C.I.: 1.02-2.8; Table 27). However, in the adjusted models, the association was not statistically significant (OR: 1.4, 95% C.I.: 0.9-2.1). Infants who had a respiratory condition at birth were found to have higher odds of 30-day emergency department visit. However, the association was not significant after controlling for other factors. In the unadjusted logistic regression model, we did not observe any effect of LOS, prematurity, medications (phenobarbital, barbiturates, and antibiotics), and medical conditions on any emergency department visit.

Receiving benzodiazepines (OR: 2.1, 95% C.I.: 1.1-3.8) and having respiratory conditions (OR: 1.5, 95% C.I.: 1.1-2.0) were associated with higher odds of any composite visit during the post-discharge follow-up period (Table 28). Pharmacologic treatment of NOWS, LOS, feeding difficulties, and jaundice showed marginal association with any composite visits. In the full model, these associations were not statistically significant. Respiratory conditions and LOS were associated with higher odds of any 30-day visit. After adjustment, marginal statistical significances was observed for both of these factors.

We did not observe any statistically significant association between majority of the NOWS severity measures and outpatient visits (Table 29). However, in the adjusted model, receiving benzodiazepines was found to be associated with higher odds of outpatient visits (OR: 2.6, 95% C.I.: 1.2-5.2)

Table 25: Description of post-discharge healthcare utilization in infants diagnosed with NOWS by status of pharmacological treatment for NOWS

Variable	NOWS (n=3,526)	Treated-For-NOWS (n=1,203)	Not-Treated-For-NOWS (n=2,323)	p-value
Rehospitalization				
Mean rehospitalization	0.042 (0.22)	0.047 (0.24)	0.040 (0.21)	0.322
Any rehospitalization	3.8%	4.2%	3.7%	0.466
Any 30-day rehospitalization	2.4%	2.2%	2.5%	0.536
Emergency Department				
Mean emergency department	0.114 (0.48)	0.164 (0.60)	0.089 (0.39)	<0.001
Any emergency department visit	7.5%	10.1%	6.2%	<0.001
Any 30-day emergency department visit	2.0%	2.5%	1.8%	0.172
Any (Rehospitalization or Emergency Department)				
Total mean visits (Rehospitalization and Emergency Department)	0.157 (0.56)	0.211 (0.70)	0.129 (0.47)	<0.001
Any visit (Rehospitalization and Emergency Department)	10.4%	13.0%	9.0%	<0.001
Any 30-day visit (Rehospitalization and Emergency Department)	4.3%	4.5%	4.1%	0.619
Outpatient visit				
Mean outpatient visit per 1000	0.371 (1.45)	0.40 (1.56)	0.36 (1.38)	0.372
Any outpatient	12.4%	12.2%	12.5%	0.821

Table 26: Logistic regression model: Examination of factors affecting rehospitalization in infants with NOWS

	Any rehospitalization		**30-day rehospitalization**	
	Unadjusted	Adjusted*	Unadjusted	Adjusted*
	OR (95% C.I.)	OR (95% C.I.)	OR (95% C.I.)	OR (95% C.I.)
Treated-For-NOWS	1.1 (0.7-1.9)	1.0 (0.6-1.7)	0.9 (0.4-1.4)	0.8 (0.4-1.5)
LOS	1.0 (0.99-1.02)	1.0 (0.98-1.0)	1.0 (0.99-1.02)	1.0 (0.97-1.0)
Received phenobarbital	0.4 (0.2-1.2)	-	0.4 (1.0-1.3)	-
Received benzodiazepine	2.1 (0.9-5.2)	2.3 (0.8-6.6)	2.6 (0.9-7.7)	2.9 (0.8-11.2)
Any respiratory condition	1.8 (1.1-2.9)	1.5 (0.8-2.5)	1.7 (0.9-3.2)	1.6 (.0.8-3.2)
Feeding difficulties	1.6 (1.1-2.5)	1.5 (1.0-2.2)	1.6 (0.9-2.8)	1.2 (0.9-1.6)
Prematurity	1.1 (0.7-1.6)	0.8 (0.5-1.2)	1.0 (0.6-1.6)	0.7 (0.4-1.3)
Received antibiotic	1.4 (1.1-1.9)	1.2 (0.8-1.7)	1.1 (0.7-1.8)	0.8 (0.4-1.5)
Jaundice	1.4 (1.0-1.9)	1.3 (0.9-2.0)	1.4 (0.9-2.3)	1.4 (0.8-2.3)
Sepsis	1.1 (0.4-3.6)	0.8 (0.3-2.5)	1.9 (0.7-5.6)	1.5 (0.6-4.0)

*Adjusted for sex, race, insurance type, year, census division, urban rural status

Table 27: Logistic regression model: Examination of factors affecting emergency department visits in infants with NOWS

	Any emergency department visit		**30-day emergency department visit**	
	Unadjusted	Adjusted	Unadjusted	Adjusted
	OR (95% C.I.)	OR (95% C.I.)	OR (95% C.I.)	OR (95% C.I.)
Treated-For-NOWS	1.6 (1.02-2.8)	1.4 (0.9-2.1)	1.4 (0.8-2.4)	1.0 (0.5-2.0)
LOS	1.0 (0.99-1.0)	1.0 (0.98-1.01)	1.01 (1.0-1.03)	1.0 (0.99-1.03)
Received phenobarbital	0.7 (0.4-1.4)	-	0.4 (0.1-1.4)	-
Received benzodiazepine	1.6 (0.6-4.0)	0.2 (0.5-2.9)	0.9 (0.1-6.2)	0.8 (0.2-3.9)
Any respiratory condition	1.4 (0.8-2.2)	1.1 (0.8-1.5)	1.9 (1.1-3.3)	1.6 (0.8-2.9)
Feeding difficulties	1.2 (0.8-1.8)	1.0 (0.7-1.5)	1.2 (0.6-2.2)	0.7 (0.4-1.4)
Prematurity	1.2 (0.8-1.8)	1.0 (0.7-1.5)	1.4 (0.8-2.4)	1.2 (0.7-2.0)
Received antibiotic	1.3 (0.8-2.0)	1.0 (0.7-1.5)	1.4 (0.7-2.5)	0.9 (0.4-2.0)
Jaundice	1.1 (0.7-1.6)	1.0 (0.7-1.4)	1.2 (0.7-2.1)	1.0 (0.6-1.7)
Sepsis	1.3 (0.7-2.3)	1.1 (0.6-2.1)	1.9 (0.6-6.1)	1.5 (0.5-4.7)

*Adjusted for sex, race, insurance type, year, census division, urban rural status

Table 28: Logistic regression model: Examination of factors affecting any composite visit in infants with NOWS

	Any visit (Emergency department or rehospitalization)		**Any 30-day visit (Emergency department or rehospitalization)**	
	Unadjusted	Adjusted	Unadjusted	Adjusted
	OR (95% C.I.)	OR (95% C.I.)	OR (95% C.I.)	OR (95% C.I.)
Treated-For-NOWS	1.4 (0.99-2.3)	1.2 (0.8-1.9)	1.1 (0.7-1.6)	0.9 (0.5-1.6)
LOS	1.0 (1.0-1.02)	0.99 (0.98-1.01)	1.0 (1.0-1.02)	1.0 (0.99-1.02)
Received phenobarbital	0.6 (0.3-1.2)	-	0.4 (0.1-1.1)	-
Received benzodiazepine	2.1 (1.1-3.8)	1.7 (0.8-3.4)	1.9 (0.9-4.1)	1.8 (0.7-4.8)
Any respiratory condition	1.5 (1.1-2.0)	1.2 (0.9-1.6)	1.8 (1.2-2.9)	1.6 (0.96-2.6)
Feeding difficulties	1.3 (0.9-1.8)	1.1 (0.8 -1.5)	1.4 (0.8-2.3)	1.0 (0.7-1.3)
Prematurity	1.2 (0.8-1.6)	0.9 (0.7-1.3)	1.2 (0.8-1.7)	0.9 (0.6-1.4)
Received antibiotic	1.4 (0.9-2.0)	1.1 (0.8-1.5)	1.3 (0.9-1.9)	0.9 (0.6-1.5)
Jaundice	1.1 (0.9-1.5)	1.1 (0.9-1.4)	1.3 (0.9-1.8)	1.1 (0.8-3.2)
Sepsis	1.3 (0.7-2.3)	1.1 (0.6-1.9)	2.1 (0.9-4.6)	1.5 (0.7-3.2)

*Adjusted for sex, race, insurance type, year, census division, urban rural status

Table 29: Logistic regression model: Examination of factors affecting any outpatient visits in infants with NOWS

	Any outpatient visit	
	Unadjusted	Adjusted
	OR (95% C.I.)	OR (95% C.I.)
Treated-For-NOWS	1.0 (0.7-1.4)	1.0 (0.7-1.5)
LOS	1.0 (0.97-1.0)	1.0 (0.98-1.01)
Received phenobarbital	0.6 (0.2-1.1)	-
Received benzodiazepine	1.9 (0.7-5.0)	2.6 (1.2-5.2)
Any respiratory condition	1.1 (0.8-1.5)	1.1 (0.8-1.5)
Feeding difficulties	1.2 (0.8-1.9)	1.1 (0.8-1.5)
Prematurity	1.0 (0.7-1.4)	0.9 (0.7-1.2)
Received antibiotic	1.3 (0.9-1.8)	0.1 (0.7-1.5)
Jaundice	0.7 (0.5-0.97)	1.1 (0.8-1.1)
Sepsis	0.9 (0.5-1.6)	0.7 (0.4-1.3)

*Adjusted for sex, race, insurance type, year, census division, urban rural status

4.3.4 Analysis of the association between NOWS related severity measures and rates of post-discharge health care utilization: Zero-inflated Poisson regression models

In Table 30, the association between NOWS severity measures and rates of post-discharge health care utilization during the one-year follow-up is reported. In the unadjusted model, the infants who received pharmacologic treatment for NOWS (IRR: 1.5, 95% C.I.: 1.01-1.4) and had respiratory condition (IRR: 1.5, 95% C.I.: 1.2-1.8) had higher incidence rates for any composite visit. In the full model, presence of a respiratory condition was associated with a statistically significant increase in incidence of any composite visit (IRR: 1.2, 95% C.I.: 1.04-1.5) compared to those who did not have a respiratory condition. Further, infants who received antibiotics, those who had a diagnosis of a respiratory condition, and feeding difficulties also had higher incidence rates of rehospitalization. In the full model, there was a marginal effect of respiratory condition on increase in incidence of any rehospitalization in the NOWS group (IRR: 1.7, 95% C.I.: 1.0-2.7). In the unadjusted model, infants who had a respiratory condition had higher incidence rates of emergency department visits (IRR: 1.4, 95% C.I.: 1.04-1.8). Infants with feeding difficulties had higher incidence rates of outpatient visits (IRR: 1.5, 95% C.I.: 1.2-1.8). The association remained significant after adjustment for other factors in the full model.

Table 30: Zero-inflated Poisson regression model: Analysis of factors affecting rates of post-discharge health care utilization in infants with NOWS

	Any visit	Rehospitalization	Emergency department	Outpatient visits
	IRR (95% C.I.)			
Zero inflated Poisson model (unadjusted)				
Treated-For-NOWS	1.5 (1.01-1.4)	1.2 (0.7-1.9)	1.7 (1.0-2.7)	1.2 (0.97-1.5)
LOS	1.0 (0.99-1.01)	1.0 (0.99-1.01)	1.0 (0.99-1.02)	1.0 (0.98-1.0)
Received phenobarbital	0.6 (0.3-1.1)	0.4 (0.1-1.1)	0.6 (0.3-1.1)	1.2 (0.8-1.7)
Received benzodiazepine	1.2 (0.7-2.1)	2.3 (0.9-5.6)	1.2 (0.6-2.4)	1.1 (0.5-2.3)
Any respiratory condition	1.5 (1.2-1.8)	1.9 (1.1-3.1)	1.4 (1.04-1.8)	1.0 (0.8-1.4)
Feeding difficulties	1.1 (0.8-1.4)	1.5 (1.1-2.0)	1.0 (0.7-1.2)	1.5 (1.2-1.8)
Prematurity	1.3 (0.99-1.7)	0.2 (0.8-1.9)	1.2 (0.99-1.5)	0.9 (0.7-1.3)
Received antibiotic	1.2 (0.9-1.5)	1.6 (1.1-2.2)	1.1 (0.8-1.5)	0.9 (0.7-1.3)
Jaundice	1.1 (0.9-1.3)	1.4 (1.0-1.8)	1.0 (0.8-1.3)	0.9 (0.7-1.1)
Sepsis	0.9 (0.6-1.5)	1.0 (0.3-2.9)	0.9 (0.6-1.5)	0.5 (0.3-0.9)
Zero inflated Poisson model (adjusted)*				
Treated-For-NOWS	1.2 (0.8-1.7)	0.9 (0.5-1.5)	1.4 (0.9-2.2)	1.1 (0.9-1.5)
LOS	1.0 (0.99-1.01)	1.0 (0.99-1.01)	1.0 (0.98-1.02)	1.0 (0.99-1.0)
Received benzodiazepine	1.5 (0.8-2.8)	2.6 (0.9-7.6)	1.2 (0.5-2.7)	1.2 (0.7-2.1)
Any respiratory condition	1.2 (1.04-1.5)	1.7 (1.0-2.7)	1.1 (0.9-1.4)	1.0 (0.7-1.5)
Feeding difficulties	0.9 (0.7-1.2)	1.3 (0.9-1.6)	0.8 (0.6-1.1)	1.5 (1.2-1.8)
Prematurity	1.1 (0.8-1.4)	1.0 (0.6-1.5)	1.1 (0.8-1.4)	0.9 (0.7-1.3)
Received antibiotic	1.1 (0.8-1.5)	1.3 (0.9-1.9)	1.1 (0.7-1.6)	0.8 (0.6-1.0)
Jaundice	1.1 (0.9-1.4)	1.3 (0.9-1.8)	1.0 (0.8-1.3)	1.0 (0.8-1.2)
Sepsis	0.9 (0.5-1.6)	0.7 (0.2-1.9)	1.0 (0.6-1.9)	0.5 (0.3-0.8)

IRR: Incidence rate ratio

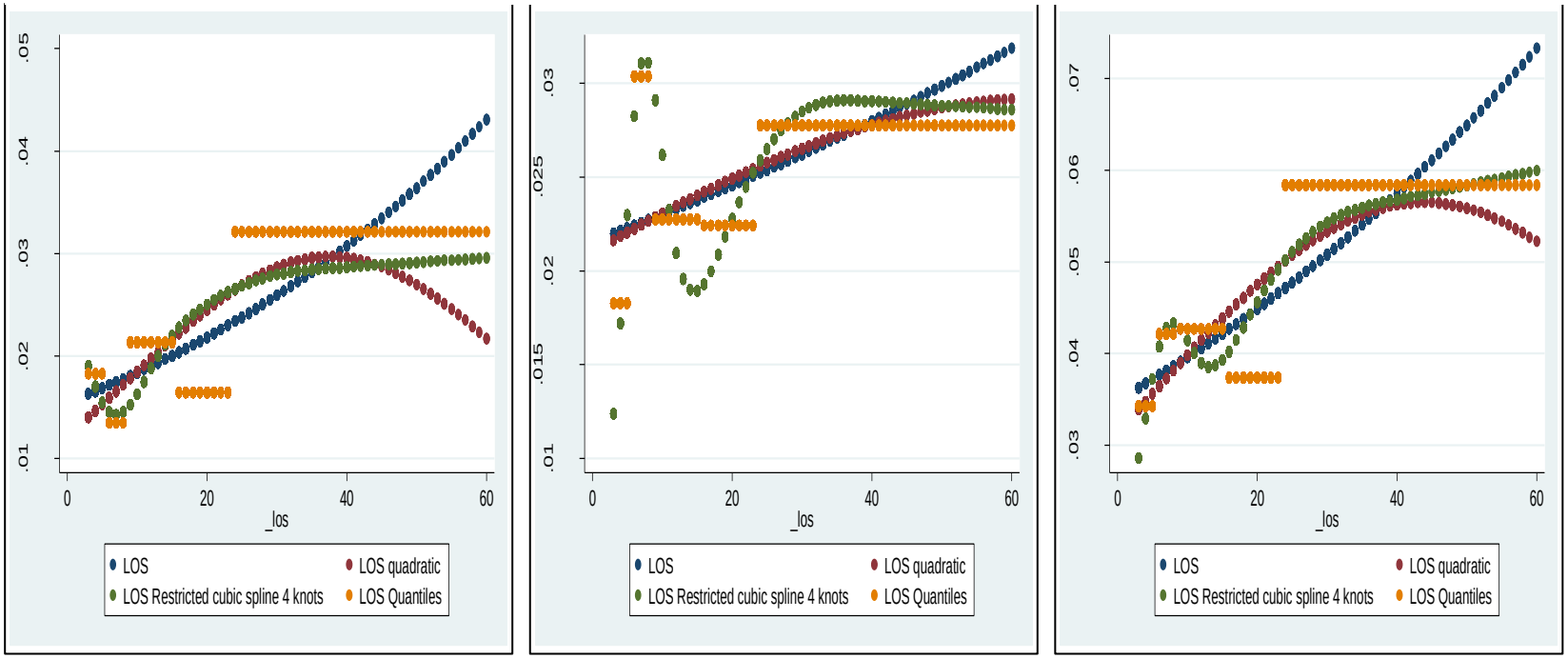
*Adjusted for sex, race, insurance type, urban-rural status, census division, hospital size, year of discharge

4.3.4 Operationalization of LOS: the non-linear effect of LOS on post-discharge healthcare utilization:

LOS was operationalized by four transformations to account for possible non-linear effects on post-discharge healthcare utilization. We observed a non-linear effect of LOS on short-term post-discharge health care utilization. As presented in Figure 9, within the NOWS group, the probability of any event in the 30-day post-discharge period varied for emergency room visits and rehospitalization. The probability of emergency room visits decreases when LOS increases from three to four days to five to six days. This probability increased with increasing LOS. The risk then stabilizes at infants with LOS more than 20 days. For hospital readmission, the risk is significantly higher for infants with short LOS (risk increases exponentially for age at discharge 3 to 7 days. The risk decreases as the LOS increases to at least 10 to 15 days. After 15 days, the risk increases along with LOS. The heterogeneity of non-linear risk for emergency room visit, and rehospitalization limits the interpretation of non-linear association between LOS and composite post-discharge healthcare utilization.

It should also be taken into account that using non-linear transformation for LOS could lead to overfitting. This is more likely in the event that prematurity, pharmacological treatment for NOWS, and other diagnoses are factored into a regression model. With this information available, it is possible that a linear form of LOS could sufficiently describe the variation in post-discharge health care utilization in the NOWS group.

Figure 9: Assessing the non-linear relationship between infant length of stay and short-term post-discharge healthcare utilization



4.4 Sensitivity analysis:

4.4.1 Examination of the effect of LOS as a selection criterion on post-discharge healthcare utilization

Approximately 25% of the infants in the late preterm group had LOS less than three days. We classified the late preterm group into two categories (i.e., LOS less than three days and LOS more than or equal to three days) to compare their post-discharge health care utilization. Besides any emergency visits, the rates of post-discharge health care utilization were higher ($p<0.05$) in the infants with LOS less than three days across all other outcomes (Table 31).

In our selection criteria, we had excluded NOWS infants with LOS less than three days. As the LOS was shown to affect post-discharge healthcare utilization, the inclusion of infants with LOS less than 3 days in the late preterm group could have led to differences in post-discharge health care utilization. We performed a sensitivity analysis to compare the differences in post-discharge health care utilization between NOWS group and the late preterm group after the exclusion of infants in the late preterm group whose LOS was less than three days. The results are shown in Table 32.

Based on the sensitivity analysis, we observed that the exclusion of late preterm infants with LOS less than 3 days did not produce a significant difference in the post-discharge health care utilization across the two study groups. In some of the comparisons (e.g.: 30-day rehospitalization, any rehospitalization) there were substantial changes in the p-value across the sensitivity analysis. These changes were likely due larger change in the proportion of rehospitalization events in the sensitivity analysis.

We performed a multivariable logistic regression to assess if any confounders were affecting the results we observed from the sensitivity analysis (Table 34). In the original analysis (Comparison of post-discharge health care utilization in NOWS group vs. late preterm group: Tables 15, 16, and 17) there were statistically significant differences in post-discharge health care utilization between NOWS and late preterm group after adjustment for confounders. Specifically, NOWS group had lower odds of any rehospitalization and any composite visit. After excluding late preterm infants with LOS less than 3 days, the association was still observed to be statistically significant but the point estimate of the odds ratio was slightly lower (Table 33). Based on these findings we can conclude that there is heterogeneity with respect to post-discharge health care utilization in the late preterm group based on the LOS of the infant. However, the differences did not substantially affect the comparison of post-discharge healthcare utilization between NOWS and late preterm groups.

Table 31: Proportion of late preterm infants who had post-discharge healthcare utilization stratified by LOS (cut-off <3 days)

	Any emergency	Any rehospitalization	Any visit	30-day emergency	30-day rehospitalization	Any 30-day visit
LOS < 3 days	8.1%	4.8%	12.1%	2.3%	3.9%	6.0%
LOS ≥ 3 days	7.7%	3.9%	10.8%	1.7%	2.4%	3.9%
P-value	0.31	0.003	0.008	0.002	<0.001	<0.001

Table 32: Sensitivity analysis: Differences in post-discharge healthcare utilization in NOWS group compared to late preterm group

	Any emergency	Any rehospitalization	Any visit	30-day emergency	30-day rehospitalization	Any 30-day visit
NOWS	7.5%	3.8%	10.4%	2.0%	2.4%	4.3%
Late preterm	7.6%	4.3%	11.1%	1.8%	2.9%	4.5%
P-value	0.86	0.21	0.19	0.23	0.07	0.48
Sensitivity analysis (late preterm LOS ≥ 3 days)						
NOWS	7.5%	3.8%	10.4%	2.0%	2.4%	4.3%
Late preterm	7.7%	3.9%	10.9%	1.7%	2.4%	3.9%
P-value	0.69	0.74	0.36	0.13	0.94	0.36

Table 33: Sensitivity analysis: Logistic regression: Post-discharge healthcare utilization in NOWS group compared to late preterm group

	Any emergency	Any rehospitalization	Any visit
	OR (95% C.I.)		
Late preterm (Ref) vs. NOWS	0.8 (0.7 - 1.1)	0.8 (0.6 - 0.)	0.8 (0.6 – 0.97)
Sensitivity analysis (late preterm LOS ≥ 3 days)			
Late preterm (Ref) vs. NOWS	0.9 (0.7 - 1.1)	0.8 (0.7 - 1.0)	0.8 (0.7 - 0.99)
	Emergency visit (30-day)	Rehospitalization (30-day)	Any visit (30-day)
	OR (95% C.I.)		
Late preterm (Ref) vs. NOWS	1.1 (0.9 - 1.5)	0.7 (0.5 - 1.0)	0.9 (0.7 - 1.1)
Sensitivity analysis (late preterm LOS ≥ 3 days)			
Late preterm (Ref) vs. NOWS	1.1 (0.9 - 1.6)	0.9 (0.7 - 1.2)	1.0 (0.8 - 1.3)

Logistic regression model adjusted for sex, insurance type, race, urban rural status, census division and year.

4.4.2 Assessment of the difference in rates of pharmacological treatment of NOWS across different hospitals and its impact on post-discharge health care utilization

In 55.8% of the hospitals, the rates of pharmacological management of NOWS was less than 25%, which is surprisingly low. We categorized the study sample into two groups: a) infants admitted/born at a hospital where ≥25% of NOWS cases received pharmacological treatment (n=2,029) b) infants admitted/born at a hospital where <25% of NOWS cases received pharmacological treatment (n=1,497). There were no statistical differences in the geographical distribution, urban rural status, and size (number of beds) of these hospital groups.

We conducted a sensitivity analysis to examine the differences in the post-discharge healthcare utilization across between these two hospital groups. The outcome variables that were examined were 30-day composite (emergency department visit or hospital readmission) healthcare utilization and any composite healthcare utilization. We observed significantly higher composite health care utilization (one-year follow-up period) in infants who were admitted/born into a hospital where more than 25% of the NOWS diagnosed infants received pharmacological treatment compared to the group where pharmacological NOWS treatment rate was less than 25% (Any composite visit during one-year follow-up period: 12.7% vs. 7.2%, $p<0.001$). There was no difference in 30-day composite health care utilization across these two hospital groups (Table 34).

We restricted our sample to infants who were admitted to hospitals where the pharmacological treatment rate was ≥25% and compared their post-discharge health care utilization with the uncomplicated birth and late preterm groups. After the application of the exclusion criteria, the remaining NOWS group (infants managed in hospitals where

NOWS treatment rates were more than or equal to 25%) had higher odds of one-year composite health care utilization compared to uncomplicated birth group in the unadjusted analysis (OR: 1.9, 95% C.I.: 1.4-2.5). However, the association was not statistically significant after adjusting for other covariates (Model 2 and Model 3 as explained in the methods section). The NOWS group had higher odds of 30-day composite health care utilization compared to compared to uncomplicated birth group across all the unadjusted and adjusted logistic regression models (Model 3: OR: 1.4, 95% C.I.: 1.02-1.8).

Furthermore, we also evaluated the association between pharmacological treatment and post-discharge health care utilization stratified across these hospital groups (Table 35). There was no difference in the composite healthcare utilization (both 30-day and one-year) based on the pharmacological treatment when stratified by the hospital groups in the unadjusted analysis. However, after controlling for other factors we observed that in hospitals that had lower treatment rates of NOWS, pharmacological treatment of NOWS was associated with lower odds of 30-day composite health care utilization (OR: 0.3, 95% C.I.: 0.1-0.8).

The results from the sensitivity analysis were similar to the findings obtained in the main analysis (Table 17). We do note that there were some differences in the health care utilization in infants based on the hospital they were treated. The regression models in our study utilizes a hospital random effects model (cluster effects of hospital) which would take into account these differences in outcomes.

Table 34: Sensitivity analysis: Proportion of infants in the NOWS group who had any composite healthcare utilization based on NOWS pharmacological treatment rates (<25%) of hospitals

	Facilities with ≥25% of NOWS cases treated	Facilities with <25 of NOWS cases treated	p-value
Any visit	12.7%	7.2%	<0.001
Any 30-day visit	4.7%	3.7%	0.143

Table 35: Sensitivity analysis: Logistic regression model: Association between post-discharge health care utilization and pharmacological treatment of NOWS stratified by NOWS treatment rates (<25%) of hospitals

	Facilities with ≥25% of NOWS cases treated	Facilities with <25 of NOWS cases treated
Variable: Treated-For-NOWS	Any visit OR (95% C.I.)	
Unadjusted model	1.3 (0.86 - 1.9)	0.7 (0.2 - 2.6)
Adjusted model	1.3 (0.83 - 2.1)	0.5 (0.2 - 1.6)
	Any 30-day visit OR (95% C.I.)	
Unadjusted model	1.1 (0.6 - 1.9)	0.5 (0.3 - 1.1)
Adjusted model	1.1 (0.6 - 2.1)	0.3 (0.1 - 0.8)

*Adjusted for sex, race, insurance type, year, census division, urban rural status

4.4.3 Propensity score analysis for pharmacological management of NOWS:

Propensity scores for pharmacological treatment for NOWS were generated by using the process described in the method section. The propensity score was used as a linear covariate along with the pharmacological treatment for NOWS variable as predictor for post-discharge health care utilization (any composite visit, any 30-day composite visit). After adjusting for the propensity score, pharmacological treatment of NOWS was associated with higher odds of any composite visit (OR: 1.4, 95% C.I.: 1.04-1.7) compared to no pharmacological treatment. There was no association between pharmacological treatment for NOWS and any 30-day composite health care utilization after adjusting for propensity scores (OR: 0.9, 95% C.I.: 0.6-3).

4.4.4 Principal component analysis for NOWS severity factors:

The principal component analysis with pharmacological treatment of NOWS, LOS, medications used (benzodiazepines), respiratory conditions, and feeding difficulties as input variables yielded principal components which are listed in Table 36. The Table shows the first three components where the eigenvalues are >1 and the absolute values of factor loadings are >0.3. The first factor is loaded by pharmacological treatment of NOWS, LOS, and feeding problems. The second factor is loaded with pharmacological treatment of NOWS, use of benzodiazepines, respiratory condition of newborn, and feeding problems. The third factor is loaded by transient tachypnea of newborn, respiratory distress syndrome, respiratory condition of newborn, and other specified respiratory conditions. These three components described a total of 49.5% of the variation of in the input variables.

Table 36: Results of principal component analysis: components and factor loadings

Variable	Component 1	Component 2	Component 3
Treated-For-NOWS	0.50	-0.36	
LOS	0.56		
Benzodiazepine use		-0.45	
Respiratory distress syndrome			-0.51
Transient Tachypnea of newborn			0.52
Respiratory condition of newborn (unspecified)		0.49	-0.35
Other specified respiratory condition			-0.58
Feeding problems	0.42	0.31	

These components were considered NOWS severity measures (uncorrelated) and their association with post-discharge health care utilization was examined (Table 37). We observed that the first component was significantly associated with higher odds of any composite visit during the one-year follow-up period (OR: 1.2, 95% C.I.: 1.1-1.3). The same component was significantly associated with any 30-day composite visit (OR: 1.2, 95% C.I.: 1.1-1.3).

Table 37: Logistic regression model: Association between post-discharge health care utilization and principal components as measure of NOWS severity

	Any visit	Any visit*	Any 30-day visit	Any 30-day visit*
	OR (95% C.I.)			
Component 1	1.2 (1.1-1.2)	1.1 (1.04-1.2)	1.2 (1.1-1.3)	1.1 (0.99-1.3)
Component 2	1.0 (0.9-1.1)	1.0 (0.9-1.1)	1.1 (0.98-1.3)	1.1 (0.95-1.2)
Component 3	1.0 (0.9-1.1)	0.9 (0.9-1.03)	1.0 (0.9-1.1)	1.0 (0.8-1.2)

*Adjusted for prematurity, sepsis, jaundice, use of antibiotics, sex, insurance status, race, bed size, year, and census division

CHAPTER 5: DISCUSSION

In this chapter, we discuss the findings of our study. Discussion of the results is presented first and divided based on the specific aims of the study, followed by the limitations of the study, the study's impact and future directions.

5.1: Discussion for Specific Aim 1

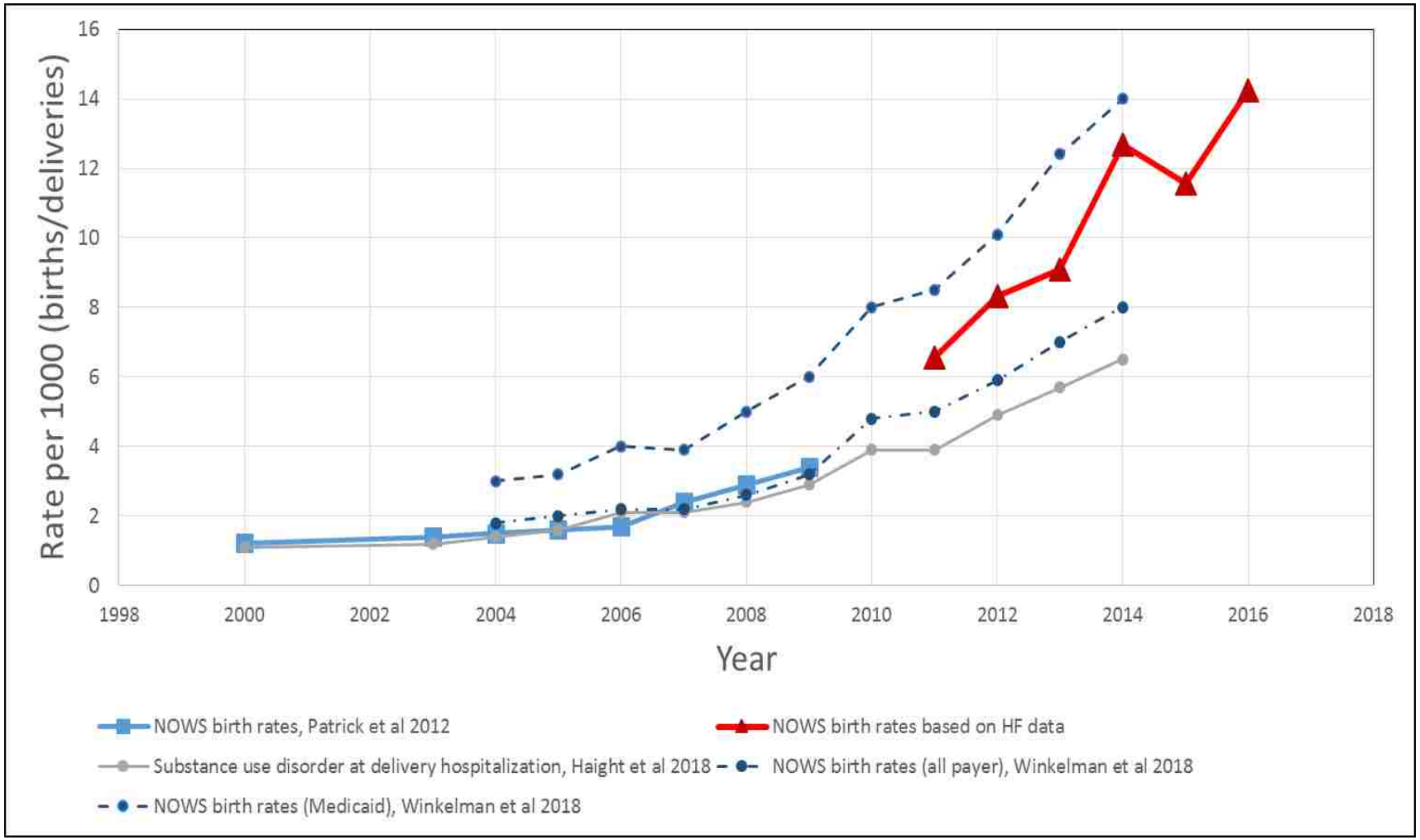
The trends and geographic distribution of NOWS births matched the growing opioid epidemic in the US. Between 2011 and 2016, the incidence of NOWS increased approximately four fold in several census divisions in the US. Results from our analysis show that rates of NOWS are consistently above 15 per 1000 births and reach up to, and over, 30 per 1000 births in New England, Middle Atlantic, East South Central, and South Atlantic regions. In contrast, during the same period, the rates of late preterm birth remained relatively constant at approximately 6 per 100 births.

The growing rate of NOWS reflects the ongoing opioid epidemic in the US. Increasing rates of opioid prescription across the U.S. has been shown by previous reports.[108-111]. Data has recently shown a peak in illicit opioid use (heroin and other synthetic opioids) in the northeast U.S. around the year 2015, dramatically increasing the opioid overdose rates in large swaths of communities across that region.[112] The increase in illicit opioid use and misuse of prescription opioids in the general population was matched by an increase in opioid use during pregnancy, which closely correlates to increase in the rates of NOWS. Using the Healthcare Cost and Utilization project (HCUP) Kids data,

Patrick et al. reported a three-fold increase in the rates of NOWS between the years 2009 and 2012 across the US.[43,113]

Figure 10 shows the rates of NOWS derived from our findings compared to the previous studies. Patrick et al. reported an increase in the rates of NOWS from approximately 1.2 per 1000 births in the year 2000 to approximately 3.5 per 1000 births in the year 2009.[25] A similar growth of substance use disorder in mothers at delivery was reported by Haight et al.[114] Additionally, the rates of NOWS reported by Winkelman et al[113] show significant overlap with the estimates reported by Patrick et al. (years 2004-2009). The rates of NOWS observed in our study were significantly higher compared to the rates reported by Winkelman et al. during the same study period. The denominator used for the estimate of NOWS rates in our study is a subset of the total number of births that actually occurred, which can cause the rates of NOWS to be potentially overestimated. Additionally, the hospitals/health centers that were included in the study are not specifically weighted to represent total national births, which may also cause the rates obtained in our study to be different than previous estimates.

Figure 10: Comparison of estimates of NOWS birth with results from existing literature



There is a wide variability in the prescribing patterns of opioids across different states in the US, which has led to significant variability in the incidence of NOWS across the country. The geographic variability in NOWS incidence in our study are in accord with findings from previous studies and matches the variation in the incidence of opioid epidemic in the US.[43,115] These reports show that the rates of opioid use are closely related to the rates of NOWS, and policies that address the opioid epidemic could lead to lower rates of NOWS.

Infants with NOWS differed significantly in terms of their baseline characteristics compared to uncomplicated births and late preterm births. A higher proportion of infants diagnosed with NOWS were Caucasian (79%) compared to late preterm birth and uncomplicated births (53% and 57%, respectively). This difference in the rates of NOWS reflects the difference in rates of opioid use, which has been reported to be higher in non-Hispanic Whites.[111] Our study also showed that Medicaid covered a majority of NOWS cases (approximately 69%). Previous studies have reported similar findings, with one study reporting up to 80% of the NOWS related payments were covered by Medicaid.[44] Furthermore, our study shows that a majority of the NOWS births occurred in medical centers/hospitals with a bed size of 300 or more. Infants with NOWS usually require a greater level of medical attention, pharmacological management, and higher rates of admission to the NICU to manage symptoms related to NOWS. This would require admission to large hospital systems where these services are available, thus reflecting the difference in the birthing hospital.

As expected, there were significant differences in healthcare utilization in infants who were diagnosed with NOWS at birth compared to both control groups. If in utero

exposure to opioids is confirmed, the patients are required to stay in the hospital for an extended observation period (ranging from 72 to 96 hours) to examine the symptoms of NOWS. Infants who are diagnosed with NOWS require significant pharmacologic and non-pharmacologic management of the symptoms, which prolongs their hospital stay. For infants requiring pharmacologic treatment, the LOS depends upon the severity of NOWS, the amount of opioid treatment required to manage the symptoms, and any additional complications present at birth. Similar to findings from previous studies, our study showed that the average LOS for infants diagnosed with NOWS is approximately 15 days.

The amount of additional care required for NOWS is also reflected in the average cost of the management of NOWS. There was a significant difference in cost (total charges) for NOWS births compared to uncomplicated births (approximate median charges: $24,900 vs. $3,100). The cost of management of late preterm birth was similar to NOWS, as similar degrees of medical attention were needed for both groups. Furthermore, respiratory problems, sepsis, and feeding difficulties were common in the late preterm group. These conditions require greater medical attention and specialized care, which leads to longer hospital stays and higher cost of treatment.

Post-discharge health care utilization in infants with NOWS showed consistent trends over different measures of healthcare utilization. There was an increase in the rates of post-discharge health care utilization in the NOWS group between the years 2011 and 2013 (from 8.5% to 13% for any composite visit and from 2.1% to 6.7% for any 30-day composite visit), whereas the post-discharge rates in the late preterm group and uncomplicated birth group remained fairly constant. This could have probably been

because of the surge in the incidence of NOWS in that period while there were not enough measures available in the hospitals to effectively diagnose and manage infants with NOWS.

Our study found that approximately 4% of infants with NOWS had hospital readmission, compared to about 1.5% of the two control groups. Patrick et al. reported that the overall one-year readmission rates in infants with NOWS was approximately 7.5% compared to 4% in controls.[36] While absolute readmission rates for the NOWS group in our study were lower than that reported by Patrick et al., the ratio of readmission between the NOWS and uncomplicated birth groups was approximately the same. Infants with NOWS had significantly higher odds of hospital readmission compared to controls for both one-year (OR: 1.7, 95% C.I. 1.3-2.2) and 30-day rehospitalizations (OR: 1.9 95% C.I.: 1.3-2.6). Similar findings were reported by Patrick et al. 2015 (30-day rehospitalization: OR: 2.5, 95% C.I.: 1.8-3.6)[36], Hwang et al. (OR: 1.1: 95% C.I.: 1.04-1.2)[116] and Liu et al. (adjusted mean ratio: 4.2, 95% C.I.: 1.9-9.7)[117]. Using the Zero-inflated Poisson regression models, consistent results were observed in the incidence rates of rehospitalizations for the NOWS groups compared to the uncomplicated birth group. This evidence suggests increased rehospitalization during the period surrounding the first year of life for the NOWS group.

We observed higher rates of emergency department visits in the NOWS group compared to the uncomplicated birth group, though, not as pronounced as the difference in rehospitalizations between the groups. In the adjusted model, a marginally significant association was observed for 30-day emergency department visits. Liu et al. reported an adjusted mean ratio of 1.8 (95% C.I.: 1.5-2.2) for emergency department visit claims in the ages between 4 and 12 months.[117] Hwang et al. reported lower odds of emergency

department visits in infants born to mothers with substance use disorders compared to controls.[116] However that study was not specific to withdrawal syndrome related to opioids, which could have contributed to differences in the estimates of emergency department visits.

The differences in the estimates of post-discharge health care utilization may have been observed due to a multitude of reasons. First, the selection criteria of NOWS group in our study was significantly different compared to Patrick et al. study. Our study applied additional exclusion criteria to the NOWS group, such as LOS less than three days or more than 60 days. Patrick et al. had reported that NOWS infants with LOS less than seven days had comparatively higher rates of rehospitalization than those who had longer hospital stays (up to 28 days). Our study excluded those who did not have hospital stays of more than or equal to three days, which may have led to the differences between the two studies. Second, the differences in effect size may also stem from where the infants may seek care for health related problems. Since the information for any utilization is only captured when the infant visits a center that specifically uses the CERNER EHR system, information about all post-discharge visits may not be available. Assuming that the choice of accessing a health center for emergency visit is random across the study groups (i.e. the probability of choosing a health center that utilizes CERNER EHR is the same for NOWS group and uncomplicated birth group), the effect size will be biased towards the null. Therefore, we can speculate that the association between NOWS and emergency department visits has been underestimated.

In comparison to mostly “unplanned” visits, such as emergency department visits or rehospitalizations, the proportion of infants who had outpatient visits was similar in the

NOWS group compared to the uncomplicated birth group. In the adjusted model, there was no significant association between outpatient visit and diagnosis of NOWS. Additionally, the absolute prevalence of any outpatient visit in NOWS group was lower than the uncomplicated birth group. Liu et al. reported adjusted mean ratio of 1.1 (95% C.I.: 1.1-1.2) claims for outpatient claims in infants diagnosed with NOWS.[117] It should be noted that the Liu et al. study was based on the analysis of commercial claims data. Since approximately 80% of the initial NOWS related birth costs are covered by Medicaid, population-based study of infants who had commercial insurance could contribute to these differences in findings. Furthermore, there is evidence of lower rates of child health services use in infants born to mothers with substance use disorder.[86] It is likely that in the NOWS group, the higher number of emergency department visits and rehospitalization, could be due to lack of or insufficiently planned routine health-care visits (e.g.: outpatient visits and well-baby visits). Other possible reasons could be constraints on access to care such as distance, availability of appointments.

A multitude of factors can affect emergency department or rehospitalization visits after discharge in the first year of the infant's life.[41,118-122] These factors range from initial length of hospital stay following birth, the type of insurance used, the infant's sex, and socioeconomic factors. In addition, the presence of certain medical conditions at birth, such as preterm birth, feeding difficulties, jaundice, convulsions, sepsis and respiratory problems, are also known to increase the risk of emergency department visits and readmissions to a health care facility. These factors were adjusted in the multivariable models in our study. Factors relating to the infants family such as maternal health, socio-economic status, nutrition, and social support mechanism are also factors that could

potentially affect the health of an infant. The lack of these information in our study warrants additional research.

In sub-group analysis, there were minor differences between the NOWS group and the late preterm group regarding health care utilization. The NOWS group had marginally lower hospital readmissions (adjusted OR: 0.8, 95% C.I.: 0.6-0.98) and any composite visits (adjusted OR: 0.8, 95% C.I.: 0.6-0.98). Furthermore, we examined the effect of difference in inclusion criteria across NOWS and late preterm group. After excluding infants with LOS less than 3 days from the late preterm, group we observed some changes in the differences in the estimates of effect size. However, the direction of association remained the same.

The evidence suggests that during the one-year follow-up period, the NOWS and late preterm group had similar profiles regarding health care utilization. While the etiology and management protocols for these two groups varies, these groups face similar medical problems during their initial stay in the hospital. Thus, inclusion of late preterm birth as a control group in this study is justified. The evidence suggests that regardless of the etiology, early life medical conditions potentially lead to higher levels of health care utilization in the formative years of an infant's life.

5.2: Discussion for Specific Aim 2

There is limited evidence regarding the impact of NOWS severity on long-term health care utilization. The severity of NOWS was determined by several factors, including the need for pharmacological management of NOWS, length of hospital stay following

birth, need for the administration of second line agents (e.g.: phenobarbital), and additional medical conditions.

Approximately 35% of the infants received pharmacological treatment for NOWS. In our study, this was defined as receiving any methadone, morphine, tincture of opium, or phenobarbital. Previous studies have reported a wide variation regarding the need for pharmacological treatment for infant's with NOWS. Research indicates this number ranges from 15% to 90%.[37,115,123] Varying definitions of what constitutes "pharmacological management of NOWS," (e.g.: if phenobarbital or clonidine were considered pharmacological treatment) could be a possible reason for this variation. While minor differences in demographic variables were observed in the Treated-For-NOWS and Not-Treated-For-NOWS groups, there were significant differences in the NOWS severity measures between the two groups. Those infants who received pharmacologic treatment for NOWS had longer LOS and higher costs related to their initial hospital stay than those who did not. Additionally, a higher proportion of those who received pharmacologic treatment had respiratory problems, convulsions, feeding difficulties, and sepsis, thereby requiring more treatment during their initial stay.

A significantly higher proportion of infants in the Treated-For-NOWS group had emergency department visits within 30-days of discharge (10% vs. 6.2%, $p<0.001$) as well as any composite visits (13% vs. 9%, $p <0.001$), compared to those in the Not-Treated-For-NOWS group. Higher number of emergency department visits could have potentially driven this difference. These differences were not sustained in the adjusted model, which suggests that these associations were confounded by other factors.

LOS, administration of other adjunctive therapies, and the presence of medical conditions (respiratory problems, feeding difficulties) were considered as severity measures of NOWS. These severity measures could potentially affect post-discharge healthcare utilization in infants with NOWS. This assessment was based on the hypothesis that severity of NOWS could translate to higher health care utilization later in life. Previous research has shown that the LOS at time of birth, has a non-linear effect on post-discharge hospitalization in infants with NOWS.[36] Similarly, other studies examining this impact for those born prematurely, reported the potential of unmeasured confounding in the use of LOS as a predictor for rehospitalization and had utilized time of birth as an instrumental variable to predict a 7-day readmission.[124] In our study, we explored various designs to explore the effects of LOS on hospital post-discharge healthcare utilization. Linear model as described in the results section did not show a significant effect on post-discharge health care utilization based on LOS at birth. Next, we explored the quadratic form, equally spaced quantiles, and the cubic splines to examine LOS in the hospital at birth as a predictor for post-discharge health care utilization. These forms generally showed a non-linear effect, with increasing probability of rehospitalization observed until the LOS was 20 days. This could have been due to the fact that very short LOS could lead to poor management of NOWS. Average LOS of around 15-20 days could mean that proper care was provided to the infants thereby lowering the chances of post-discharge health care utilization. Considerable variability in the risk of post-discharge health care utilization was observed across the models when LOS exceeded 20 days. Longer lengths of stay (greater than 20 days) could mean that there were other medical conditions or that the NOWS symptoms were very severe. This could potentially lead to higher post-discharge health care

utilization after the discharge. These findings are fairly consistent with the estimates reported by Patrick et al.[36] Additional information regarding the medications and medical conditions diagnosed during the initial stay following birth were available in our study. These factors could be adjusted in full models, however, we chose to use the linear form of the variables in our statistical models.

We also examined additional diagnostic codes received by those in the NOWS group and found that there was a consistent effect on post-discharge healthcare utilization regarding the presence or absence of respiratory problems in the NOWS group. It is likely that infants in the NOWS group with respiratory problems, require further management and health care services after their discharge for this medical condition. Feeding difficulties, jaundice, and sepsis showed a minor impact on post-discharge healthcare utilization. The medical conditions we used as factors potentially leading to readmission in the hospital have been shown by studies to be common causes for readmission in the hospital following birth for the general population. It is likely that the presence of diagnostic codes for these conditions, resulted in the proper management of these conditions, and minimized their long-term effects. In our study, we only included infants with NOWS who remained in the hospital for at least three days following birth. That criterion allowed sufficient time of observation in order to diagnose, or rule out, medical conditions that could lead to higher rates of early rehospitalization or emergency department visits.

Overall, analysis of factors relating to NOWS severity showed limited association with post-discharge healthcare utilization during a follow-up period of one-year. This finding may have been observed due to multiple reasons. First, the presence of the

diagnostic codes for medical conditions, or pharmaceutical treatment, could imply that the condition was managed efficiently during the initial hospital stay. Thus, the likelihood of early health care utilization, either through an emergency department visit within 30 days or rehospitalization within 30 days, would be limited to extraneous conditions that would not be specific to NOWS. Furthermore, while the NOWS group had higher health care utilization overall, it is possible this is due to other conditions not directly related with NOWS. Examination of reasons for follow up health care encounters in infants with NOWS after the age of 15 days (average LOS for infants with NOWS) were revealed that conditions, such as acute upper respiratory tract infection, bronchitis, and cough, were common in the post-discharge visits. However, there was an association between the composite measure of NOWS severity (first principal component) and post-discharge health care utilization. As principal component analysis reduces the different measures of NOWS severity into uncorrelated composite measures, these composite measures can serve as better predictors in the regression models.

It is to be noted that across all the analysis, there were significant effect of infant sex and insurance status on post-discharge healthcare utilization. Male infants had significantly higher rates of hospitalization but not emergency department visits. In addition, infants whose initial visits were covered through Medicaid had higher health care utilization. The increased utilization could be due to comparatively lower out-of-pocket costs. It could also be considered a marker for poor socioeconomic condition, which could lead to poor health of the infant, thereby increasing the risk of post-discharge health care utilization.

5.3: Limitations of the study

Our study has several limitations. The primary limitation is the reliance on hospital administrative databases for the diagnosis of a medical conditions.[125-127] Diagnostic codes are used for administrative/reimbursement purposes, and are not primarily intended for research purposes. However, the wealth of data collected during patients' encounters with a health care system, combined with the sheer volume of the data generated in the process, make these administrative databases a "gold-mine" for researchers. The findings, however, should be interpreted with an awareness of the limitations of these databases.

As with any retrospective data analysis, the findings of this study rely on the accuracy of the databases. Infants who show symptoms of withdrawal syndrome are assigned the ICD-9-CM code 779.5 (ICD-10-CM: P96.1). ICD-9-CM code 779.5 refers to "Drug withdrawal syndrome in newborn" and ICD-10-CM code refers to "Neonatal withdrawal symptoms from maternal use of drugs of addiction". These codes are not specific to just opioid exposure. Thus, there is a likelihood of potential misclassification regardless of the exposure; it is possible that infants who were not exposed to prenatal opioids, were included in the study as those who were exposed, and led to an erroneous estimate of the effect size. It is important to note that withdrawal syndrome is primarily attributed to opioids due to the high prevalence of opioid use in the United States. Previous studies have noted that the use of the diagnostic codes for identification of infants with NOWS, has a high positive predictive value (91% for ICD-9-CM code and 98.2% for ICD-10-CM)[93]. Furthermore, the use of LOS in the hospital following birth as an additional criterion leads to increased accuracy in diagnosing NOWS.

Second, this study is based on the analysis of clinical data, therefore detailed information on maternal health, socioeconomic status, marital status, maternal education, breastfeeding, and substance abuse is lacking. Type and intensity of maternal opioid exposure could be significant in predicting long-term health care utilization in infants with NOWS. There is no direct link between mother and infant records within the HF database, thus making this type of analysis difficult. Poor maternal health, social, and economic problems can lead to adverse health outcomes in infants, which could lead to increased health-care utilization in terms of emergency visits and rehospitalizations. Additionally, the same factors could impact the general care of the infant. For example, a missed general health-care appointment because of poor care or resources could cause greater health care utilization in term of emergency department visits and rehospitalization in the long run. A majority of infants born with a diagnosis of NOWS, have mothers who are either active substance users or managed on a maintenance therapy. In general, risk factors such as poor social support network, stigma for the society, lack of economic means, unstable housing, abuse, poor nutrition, behavioral health disorders, anxiety, depression, alcohol use, and infectious diseases (HIV/HCV) are prevalent in these populations.[8,128-131] These factors, in combination with limited resources for the care of the infant, may lead to poor health, and increase the chances of health care utilization which could have been potentially avoided.

Third, there are limitations to the estimates of the amount of treatment received by the infant during their hospital stay for NOWS. Initially, we sought to quantify the amount of opioids the infant received for management of withdrawal symptoms during their initial hospital stay. There were limitations in the database regarding quantification of medications, such as oral morphine for the management of NOWS, as the solution has to

be diluted several times (up to 0.04 mg/ml from original concentration of 10mg/5ml or 5mg/5ml) before administration. While the information on the strength and timing of administration of morphine and methadone was available, there was no reliable information on dilution or the strength of the medication administered to the infants. Furthermore, there is no consensus on conversion of methadone to morphine equivalents, specifically in relation to management of NOWS. Conversion factors range from 1:3 to 1:4 for lower doses, but the variability in conversion increases as the dose increases.[132]

Fourth, a simple Poisson model does not account for the dependency of outcomes. For example, infants who had an emergency department visit are more likely to have subsequent department visits because of their medical condition. The assumption of independence in Poisson models is violated by these recurrent events. Additionally, when examining all three groups (NOWS, late preterm births, and uncomplicated births), a majority of the infants in the study had no emergency visits or rehospitalizations within 30-days of discharge. This leads to a high number of zero values in the outcome variable. We addressed this problem by the utilization of Zero-inflated Poisson as a robust alternative to Poisson regression.

Fifth, errors relating to censoring of data because they accessed care in different health care centers whereby their information was not captured in the Cerner HealthFacts database could bias the results in our study. It is likely that a fraction of a sample across all the study groups who required service from a healthcare center whether it may be emergency department visits or hospital readmission may seek care in institutions that do not use the CERNER EHR system. While there is a probability that this absence could lead to underestimation of the actual number of visits, the effect on the odds ratio of these events

in NOWS group compared to controls would be minimal. This is based on the assumption that infants would seek care from healthcare institutions irrespective of the EHR being utilized at that institution.

Based on the results of our study and previous studies, let us assume that the rate of rehospitalization across during the follow up period in the NOWS group and the uncomplicated birth group is 4% and 2%, respectively. Based on this hypothetical data, the OR would be 2.04. Assuming that only 75% of these visits are captured in CERNER system, the observed OR would be 2.03. Even at a rate of 25% of these events occurring in a health care system that uses CERNER EHR, the observed OR would approximate 2.01. While the estimates of post-discharge health care observed in our study were lower than observed elsewhere, they were proportionately similar across the study groups. Given that the probability of seeking care at any given hospital is random across study groups, the observed effect size is very robust.

Finally, generalizability of the study might be limited. However, our dataset spans hospitals and health care centers across the United States, and covers a wide range of demographics. Previous studies were either limited geographically, [35,36,116] or, did not include a majority of the infants who present with NOWS[117]. HF database covers over 500 health centers across the United States, thus, increasing our study's generalizability compared to previous studies.

Even in the light of the above limitations, we believe that our study contributes to the existing literature relating to long-term health care utilization in infants with NOWS. By using a measure of the severity of NOWS as a predictor of future health care utilization, we have added another dimension to the study of effects of opioid withdrawal. We believe

that the findings of this study can lead to the formulation of policy that will ensure proper follow-up and evaluation of these infants. In this era of the opioid use epidemic in the United States, we believe that this study can contribute to the overall understanding of the long-term effects of prenatal opioid exposure.

5.4: Implications of the study

As the opioid crisis expands long-term effects of NOWS warrant greater attention. There are conflicting reports of the long-term impact of NOWS. Recent studies on infants born to women who were on MAT showed no difference in development in their early childhood compared to infants who were not exposed to prenatal opioids.[84,85] Existing literature also suggests a variety of risks for infants with NOWS such as cognitive, behavioral deficits at young age, and poor school performance when these infants reach older age.[83] There is limited data on post-discharge health care service utilization in infants who were diagnosed with NOWS.[36,117] Our study shows consistent evidence of increased rehospitalization in infants with NOWS compared to uncomplicated birth infants in the one-year follow-up period after discharge. However, impact of NOWS on emergency department visits, and outpatient visits, is still inconsistent across studies.

The results from our study showed that the rates of post-discharge health care utilization were not specific to the severity of NOWS. While certain diagnoses at birth were related to increased post-discharge health care utilization the association was not consistent. The principal component analysis in our study where the severity of NOWS was transformed into uncorrelated components showed consistent association with post-discharge health care utilization. Hence, a scaled measure of NOWS severity could be vital

in predicting post-discharge health care utilization. Maternal substance use, poor nutrition, lack of social support, and poor pre/postnatal care may also lead to higher health care needs for these infants. Numerous studies have shown the impact of environment and family on the health of an infant.[133] Women with substance use disorders have high rates of mental health disorders and unemployment, and are more likely to have a history of abuse, poor nutrition, and limited social support.[8,86,128,129] These forces, in combination with the effects of opioid exposure and subsequent withdrawal effects, may contribute to higher health care needs and thus, health care utilization for these infants.

Hospital readmission and emergency department visits are costly to tax-payers, disruptive to patients and their families, and may increase stress and financial hardships for patients and families as well. Closer follow-up and management of infants with NOWS is needed to minimize emergency department visits and unplanned rehospitalization. Providing additional resources and a comprehensive care environment could lead to improved health outcomes in infants with NOWS. It is recommended that these infants have regular well-child visits for evaluation of any signs of medical condition that could warrant proper medical care.

5.5: Future research

Our study shows that infants with NOWS have a higher risk of post-discharge health care utilization compared to controls. Based on this piece of evidence, a two-pronged approach to future research is suggested. First, research should be focused towards reducing "preventable and unplanned" health-care utilization events and improving regular check-up/follow-up visits in infants who are either diagnosed with NOWS or experienced

in-utero exposure to opioids. Research aimed at improving the mental and physical needs of the mother is also recommended, as improvement in her health may translate to improvement in the infant's health. Providing improved social support, ensuring ease of access to health services, such as treatment for OUD, counseling, proper nutrition, and arrangement for proper housing, may lead to increased stability in the surrounding environment of the infant. Studies focusing on implementation of these interventions and their effectiveness on improving the infant health outcomes are necessary.

Second, future research could benefit by addressing the limitations of our study. We were not able to link maternal health information to infant data. Maternal health information could be key in further explaining post-discharge health care utilization. Furthermore, a greater focus on the future impact of the exposure to opioids within the context of NOWS management, is merited. Our study could not explore dose-response relationship of opioids in relation to post-discharge healthcare utilization. Detailed examination of these treatments could reveal unexplained variations in the outcomes of our study (or infants born with NOWS).

Our study did not specifically evaluate the reasons for post-discharge healthcare utilization. Little is known about the reasons what specific events or conditions results in emergency visits or rehospitalization. Examining the causes of these health care utilization events could help guide policy in creating policies to minimize unnecessary hospital readmissions and/or emergency room visits. There would also be additional benefit of following up these infants for a longer period of time to examine their health outcomes in adulthood. Other avenues of research include study of long-term economic impact of increased post-discharge health care utilization. Additionally, cost-effectiveness analysis

of difference measures of NOWS management (e.g. ESC or institution specific methods of care) would help facilitate adoption of these measures.

Understanding how NOWS affects an infant holds the key to promoting policies and interventions that can improve health outcomes. We believe that this study provides a greater understanding of the long-term effects of NOWS. We hope this study serves as a guide for future research in improving the lives of infants diagnosed with NOWS at birth.

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