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Perinatal Health in North Dakota: Emerging Issues

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To the Graduate Council:

I am submitting herewith a dissertation written by Grace N. Njau entitled "Perinatal Health in North Dakota: Emerging Issues." I have examined the final electronic copy of this dissertation for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy, with a major in Comparative and Experimental Medicine.

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Perinatal Health in North Dakota: Emerging Issues

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DEDICATION

This dissertation is dedicated to my daughter Eden, my sister Esther, my mom Elizabeth, and my grandmother Esther. I am eternally grateful to and for you.

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ABSTRACT

Preterm birth, newborn screening refusal, and postpartum depression represent three emerging areas of concern that have not been previously been investigated in North Dakota. Their potential impact creates significant social, behavioral, and economic burdens. Although various studies have investigated preterm birth and postpartum depression, newborn screening refusal in the United States has not been previously investigated to the best of my knowledge. In alignment with the role of Title V of the Social Security Act (Maternal and Child Health) Programs to conduct ongoing statewide needs assessments, the objectives of these studies were to investigate and identify predictors of preterm birth, newborn screening refusal and postpartum depression.

The study used data from the North Dakota (ND) Pregnancy Risk Assessment Monitoring System, the ND Newborn Screening Program, and the ND Division of Vital Records. Factor-specific prevalence and confidence intervals of potential predictors were computed. Logistic regression models were used to investigate and identify predictors of preterm birth and postpartum depression. Since newborn screening refusal is a rare outcome (<10% prevalence), multivariable Firth logistic regression was used to investigate maternal and provider predictors of newborn screening refusal. Adjusted odds ratios (AOR) and their 95% Confidence Intervals were computed for all identified significant predictors of preterm birth, newborn screening refusal, and postpartum depression. Relevant models' goodness-of-fit was evaluated using the Hosmer-Lemeshow test.

The identified significant ($p < 0.05$) predictors of preterm birth (maternal hypertension, premature rupture of membranes, prior preterm birth, rural residence, multiple gestation, maternal age ≥ 35, multiple gestation and < 9 prenatal care visits); newborn screening refusal (homebirths, non-credentialed birth attendants, refusal of Hepatitis B vaccine, and fewer prenatal care visits); and postpartum depression (unintended pregnancies, high childhood adversity, American Indian race, and history of depression), offer useful insight into the epidemiology of these emerging issues in North Dakota.

Ongoing evaluation and the implementation of health programs and policies that allow women to plan pregnancies, access preconception care and prenatal care, and access to behavioral health services prior to, during, and after pregnancy will remain invaluable in mitigating these three emerging issues, thereby aiding in reducing their burden.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ACEs: Adverse Childhood Experiences

ACOG: American College of Obstetricians and Gynecologists

BMI: Body Mass Index

CDC: Centers for Disease Control and Prevention

CNM: Certified Nurse Midwife

CPM: Certified Professional Midwife

DO: Doctor of Osteopathic Medicine

EPDS: Edinburgh Postnatal Depression Screening

HDN: Hemolytic Disease of the Newborn

HPSA: Health Professional Shortage Area

HRSA: Health Resources & Services Administration

IRB: Internal Review Board

MCH: Maternal and Child Health

MD: Medical Doctor

NBS: Newborn Screening

ND: North Dakota

NDDoH: North Dakota Department of Health

PDSS: Postpartum Depression Screening Scale

PHQ-9: Patient Health Questionnaire 9

PKU: Phenylketonuria

PPD: Postpartum Depression

PRAMS: Pregnancy Risk Assessment Monitoring System

PPROM: Preterm Premature Rupture of Membranes

PROM: Premature Rupture of Membranes

PTB: Preterm Birth

RUSP: Recommended Uniform Screening Panel

SCID: Structured Clinical Interview for DSM Disorders

WHO: World Health Organization

U.S: United States

CHAPTER 1

Introduction

Life expectancy in the United States increased by over 30 years between 1900 and 1999 and this substantial improvement in years of life gained is largely attributable to advances in public health [1]. Poor perinatal health outcomes, such as infant and maternal mortality, decreased by over 95% over this time period, making the innovation in and implementation of public health practices and policies specific to these populations one of the primary drivers of the increased life expectancy [1]. Despite these momentous advances in medical and socio-economic factors in the United States, women during the perinatal period, continue to face various challenges and emerging issues that may lead women and infants to experience adverse outcomes. These poor outcomes are cross-cutting through various subpopulations with significant disparities amongst certain demographic, socio-economic, and geographic subpopulations.

Title V of the 1935 Social Security Act, commonly known as Title V, is the longest standing federal program aimed at improving the condition of mothers, women, and children through funding to individual states [2]. This program, administered by the Maternal and Child Health Bureau (MCHB), identifies areas of national performance and outcomes related to the maternal and child health populations. The MCHB then charges states with implementing needs assessments that further identify current and emerging areas of concern in the maternal and child health population domains, which include the women/maternal populations, perinatal/infant populations, child population, adolescent population, and children with special healthcare needs.

Extensive research has shown that exposure to certain risk factors in early infancy can have lifelong implications that remain significantly more difficult to mitigate later in life, if at all. Such is the case for infants born preterm, infants who are not appropriately screened for genetic and metabolic disorders, and infants born to women who experience postpartum depression [1, 3-12]. Of significance to note is, first, preterm birth is the leading cause of neonatal mortality globally and represents one of the persistent public health burdens estimated to cost the United States $26 billion dollars annually [13]. Secondly, the success of public health preventative measures, especially in the maternal and child population, is dependent on trust in the medical infrastructure to deliver efficacious screening, diagnosis, and treatment options. Such is the case for newborn screening - the largest genetic screening program in the United States. Newborn screening programs identify approximately 12,000 infants annually that are at high risk of severe morbidity and mortality if otherwise not treated [14-16]. Third, perinatal population health outcomes are heavily intertwined with maternal mental health and specifically with postpartum depression. Since poor attachment capacity and the emotional wellbeing of new mothers can have adverse lifelong implications starting in infancy for most children, the burden of postpartum depression is an emerging and concerning issue for this population [17-21]. Examining these perinatal issues through the maternal lens, and at the state level where strategies are implemented and evaluated, offers insight into identifying upstream predictors and present opportunities for public health mitigation.

In alignment with the core mission of Title V — examining emerging issues among the maternal and perinatal populations — the objectives of these studies were to investigate and

identify predictors of preterm birth (Chapter 2), newborn screening refusal (Chapter 3), and postpartum depression (Chapter 3) in North Dakota.

This dissertation is divided into five chapters. The first chapter includes the introduction to the study and literature review. Chapters 2, 3, and 4 describe the methods and findings of studies each addressing the above objectives. Lastly, chapter 5 provides a summary of the conclusions and recommendations of this study.

1.1 Literature Review

1.1.1 Preterm Birth

1.1.1.1 Biology, Etiology, and Symptoms

Preterm birth is defined as a birth occurring before 37 weeks gestation. Globally, approximately 15 million infants are born premature, representing almost 11% of all births annually [22, 23]. Approximately 4.1% of the global preterm births occur at less than 28 weeks gestation, 11.3% occur between 28 and 31 weeks, and 54.7% occur at between 32 and 36 weeks [24-26]. Preterm birth can be either spontaneous or medically induced. Medically induced preterm birth, also known as iatrogenic preterm birth, refers to induction of labor or caesarean delivery prior to 37 weeks, that is triggered by a clinician due to maternal severe morbidity or fetal indications, such as severe congenital malformation or threat of stillbirth [22, 27-29]. About 30-35% of the medically induced preterm births are due to maternal and fetal complications [27, 29, 30]. Severe maternal morbidity, such as eclampsia or cholestasis of pregnancy, may lead to the induced delivery of a premature infant to preserve the life of both mother and baby [10, 24,

26, 31-34]. Additionally, preterm premature rupture of membranes (PPROM) due to mechanical injury or other spontaneous factors is also a leading cause of induced preterm birth [35-37]. Nearly 75% of preterm births are spontaneous with between 40-45% occurring with intact membranes and between 20 and 30% occurring after PPROM. The mechanisms and etiology of preterm birth remain poorly understood. Approximately 40% of preterm births are estimated to be attributable to maternal infections and inflammatory conditions [27, 29, 30].

Preterm birth is most frequently preceded by preterm labor, in what is known as spontaneous preterm birth. Preterm labor, the precursor for spontaneous preterm birth, is most often characterized by uterine contractions that happen six or more times in an hour, with or without any other symptoms [11, 36, 38]. Other indicators of preterm labor include lower abdominal menstrual-like cramps, dull backache felt below the waistline that may or may not be or be constant, pelvic pressure, abdominal cramping with or without diarrhea, and increase or change in vaginal discharge such as change into a mucous, watery, or bloody discharge [31, 39, 40].

Certain maternal health conditions and risk behaviors have been shown to increase the likelihood of preterm birth. Gestational hypertensive diseases, defined as blood pressure of above 120/80mmHG is a significant predictor of both spontaneous and induced preterm birth [10, 31, 32, 34, 41]. Tobacco use is another known predictor and one that is also associated with risks of gestational hypertension. Other maternal risk factors include history of preterm birth in a previous pregnancy, older maternal age, premature rupture of membranes (PROM), and plural pregnancies (twins or more). Notably, plural pregnancies in the United States are an increasing trend, as is higher maternal age at first pregnancy and at delivery. The utilization of assisted

reproductive technologies is a known predictor and contributor to this trend and has also been found to be independently associated with preterm birth [42-44].

1.1.1.2 Diagnoses and Treatment/Management

Various methods and biomarkers are utilized in making a diagnosis of preterm labor. According to the American College of Obstetricians and Gynecologists (ACOG), preterm labor is typically diagnosed when a change in cervical dilation is found after contractions start [40]. In addition to a physical exam, other tests may be administered to confirm this status. Firstly, an ultrasound exam may be utilized to establish gestational age and estimate infant maturity. Secondly, the fetal fibronectin test may be administered to test for the ability of the amniotic sac to stay connected to the inside of the uterus [36, 40, 45, 46].

There are no definitive treatments for preterm labor. However, preterm labor does not always result in a preterm birth. Advances in maternal and fetal medicine provide few but significant therapeutic options to manage spontaneous preterm labor [36, 40, 45]. These methods most commonly entail attempts to delay delivery. This is especially critical in the event of extreme prematurity (less than 28 weeks) and very preterm infants (27 to 32 weeks), where the likelihood of neonatal death is much higher due to underdeveloped lung capacity in the neonate. The primary treatments administered serve three core functions: 1) assisting in organ maturation, 2) reducing the risk of maternal and infant complications, such as sepsis, and 3) attempting to delay progression of labor [47-49]. The therapeutics utilized include corticosteroids to hasten fetal lung, brain, and digestive organ development, and magnesium sulphate to reduce the risk of cerebral palsy and neuromuscular complications [45, 47, 50, 51]. The main group of therapeutics

utilized to slow the progression of preterm labor are tocolytics. These are medications that are typically administered to a woman in preterm labor with the goal of delaying delivery by up to 48 hours [49, 51, 52]. This critical time window offered by tocolytics is meant to allow for the action of the other medications utilized to assist in fetal organ development and the reduction of neuromuscular complications. Tocolytic use is controversial due to the increased risk of maternal hypotension, pulmonary edema, and hypoglycemia, among others [52, 53]. Therefore, this use is determined by the attending provider after an extensive examination of risks and benefits.

1.1.1.3 Burden of Preterm Birth

Preterm birth is the leading cause of neonatal mortality globally and in the United States [54, 55]. For many infants who do survive, additional risks of severe morbidity and lifelong disability persist thereby making preterm birth a significant burden [13, 56].

1.1.1.3.1 Global Burden of Preterm Birth

Globally, approximately 15 million babies are born premature, representing 11% of all births annually. One in 15 of these premature infants die each year due to complications of prematurity [29, 30, 56]. Preterm birth remains the leading cause of perinatal deaths and all deaths for children under the age of 5. According to the World Health Organization (WHO), infants born premature account for 16% of all deaths in children under the age of 5 and 35% of all deaths among newborn babies [22, 29, 55]. For the preterm babies who survive, severe morbidity as a result of being born premature may include several complications. These complications may include respiratory distress syndrome, sepsis, seizures, and cerebral palsy

which represent significant medical and socioeconomic impact to affected families and communities [11-13].

As of 2014, it was estimated that, between 60 and 80% of all preterm births globally occur in South Asia and Sub-Saharan Africa. Interestingly, an analysis of World Health Organization accumulated data from various countries across all economic indices found that preterm birth rates were increasing or not improving in certain high-income countries, including the United States. India, China and Nigeria ranked in the top 3 of countries with the highest number of preterm births. Among these 3 countries, between 800,000 to 3.5 million preterm birth cases were reported in 2014, representing nearly a third of all preterm births globally [24, 26]. The United States ranked 7th in this global ranking, with 383, 257 babies born premature. Global prevalence of preterm birth varies and is estimated to range from a high of 18.1% in Malawi to a low of 5.5% in Ireland. Survival rates also vary globally, with nearly 50% of infants born at 24 weeks surviving in developed countries. In low-income countries, survival rates only start to show significant improvement at 32 weeks, where half of the neonates born premature are reported to survive [24-26]. Access to higher levels of care and medical technology explain some of the observed disparity [10, 11, 25].

Mitigating preterm birth remains critical and aligns with the WHO Sustainable Development Goal of ensuring healthy lives and promoting wellbeing for all at all ages by reducing preterm-related mortality and morbidity by 2030 [25, 57, 58]. It is also worth noting that readily available global data on preterm birth incidence, prevalence and trends are limited due to differences in surveillance systems by the various jurisdictions [25].

1.1.1.3.2 Burden of Preterm Birth in the United States

According to the Centers for Disease Control and Prevention (CDC), approximately 10.2% of infants were born preterm in the United States in 2020 [54]. Geographically, this prevalence ranged from a low of 7.6% in Vermont to a high of 14.2% in Mississippi. Alongside Mississippi, the states with the highest prevalence included Alabama (12.9%), Louisiana (12.9%), West Virginia at (12.0%), and South Carolina at (11.8%). The five lowest-ranked states were Vermont (7.62%) followed by Oregon (8.2%), New Hampshire (8.4%), Idaho (8.5%), and Washington (8.6%). At 9.9%, North Dakota ranked in 23rd among all U.S. states [54].

Notably, between 2010 and 2020, preterm birth prevalence in the United States has ranged from 10.0% in 2010 to the current estimated prevalence of preterm birth rate of 10.1% [10, 33, 34]. This slight increase in preterm birth in the United States is especially puzzling given the magnitude of investments in public health made to improve this burden. Additionally, the declining fertility rates in the United States have not resulted in the anticipated decrease in preterm birth rates. One suspected driver of preterm birth in the United States is the increase in births to women over the age of 35, which are significantly associated with increased maternal comorbidities, and assisted reproductive technologies that are also associated with the likelihood of plural pregnancies [42-44]. It is also worth noting that maternal comorbidities, plural pregnancies, and artificial reproductive technologies are known independent risk factors of preterm birth [10, 43, 44].

In addition to the medical and public health impact of preterm birth, in the United States, preterm birth is estimated to cost approximately $26 billion dollars annually [13]. According to an analysis by the Institute of Medicine, this high economic toll is largely attributable to the high

costs of neonatal intensive care unit costs and maternal care. Early intervention, special education services, and lost pay for affected individuals make up approximately 30% of these costs. This trifecta of medical, public health and socioeconomic burden [11-13] highlights the need to continue investigations into preterm birth and its predictors that are modifiable.

1.1.1.3.3 Burden of Preterm Birth in North Dakota

Approximately 12,000 infants are born in North Dakota each year. North Dakota's preterm birth rate is comparable to that of the greater United States with about 1 in 10 infants born premature annually. North Dakota typically ranks in the 50th percentile of states ranking in prematurity [54]. Between 2010 and 2020, North Dakota's prematurity prevalence ranged from 9.7% in 2010 to 9.9% in 2020, indicating a marginal increase. Over the course of the decade, the prevalence has been as low as 8.4%, in 2015 [59], but since then, this prevalence continued to increase, thereby making premature births one of the areas of concern for the state's maternal and child health population [54, 59].

1.1.1.4. Temporal Trends in Preterm Birth Rates

The estimation of global preterm birth rate trends is limited due to the differences in surveillance systems across various countries and jurisdictions. The WHO Member States databases of national civil registration and vital statistics provides the most consistent estimates to date. However only 38 member countries are considered to have high-quality data on preterm births as of 2014. Therefore, there are no reliable known comparison rates that demonstrate overall global trends in prematurity. In an analysis of this database by Chawanpaiboon and

others, the global prevalence of preterm birth was estimated to be 9.8% (95% CI [8.3,10.9%]) and increased to 10.6% (95% CI [9.0,12.0]), between 1990 and 2014 [26].

In a second estimate of global trends, between 1990 and 2010, the estimated preterm birth prevalence in 1990 were 7.2% amongst developed nations, 7.7% in Latin America, and 8.9% among Caribbean countries [29]. By 2010, all three groups reported higher prevalence of 8.6% among developed countries, 8.4% in Latin America and 11.2% in Caribbean countries [25, 29].

In the United States between 1989 and 2020, preterm birth rates remained largely unchanged at 10.4% and only decreasing to 10.1% [27]. Marginal increases and decreases over the same time period were observed with minimal sustainable improvements in the burden of the condition. While North Dakota consistently ranks at or near the 50th percentile of preterm birth rates, between 2010 and 2020, North Dakota's prematurity prevalence ranged from 9.7% in 2010 to 9.9% in 2020, representing a 2% increase [54, 59].

Globally and in the United States, public health initiatives have not been successful in significantly reducing the prevalence of preterm birth. Given these marginal-to-no improvements the need to further investigate this issue in local jurisdictions and to identify risk reduction opportunities remains critical.

1.1.1.5 Socio-demographic Determinants of Preterm Birth

1.1.1.5.1 Demographic Factors

In the United States, disparities persist in the prevalence of preterm birth rates across different subpopulations. Preterm birth has been shown to be associated with maternal race, with minority races, African American and American Indian, especially, being at higher risk of

preterm birth [10, 25, 33, 54, 60]. Black/African American women in the United States are over 1.5 times more likely to experience preterm birth compared to non-Hispanic White women. In 2020, for example, the prevalence of preterm birth among black infants was 14.2%, 11.6% among American Indians/Alaska Natives, and 9.2% among White infants. Asian and Pacific Islanders had the lowest prevalence of preterm birth at 8.8% [54]. Notably, women of minority races in the United States are more likely to have lower incomes, be less educated, and have higher rates of medical comorbidities such as gestational hypertension that may lead to higher risk of preterm birth [10, 60, 61].

Maternal age is another known predictor of preterm birth and appears to follow a U-curve distribution with teenage women (younger than age 20) having a higher prevalence of preterm birth, and those over the age of 35 having the highest prevalence of preterm birth. Estimates from the United States between 2018 and 2020 indicated that among those younger than age 20, the preterm birth rate was 10.4% compared to 9.6 amongst those ages 20-29, 10.3% among those aged 30-39 and 14.4% among those over the age of 40 [59]. A rise in the prevalence of first-time motherhood among those aged 35 and older is one suspected driver of preterm birth prevalence. This is especially significant given the known association between medical comorbidities as maternal age increases [41, 62]. For example, compared to those between 25-29, gestational hypertension is 1.22 times higher among women between ages 35 and 39.9 years of age, and 1.63 times higher among those 40 to 44.9 years of age [63]. A review of the literature by Taddei and others suggests that age-induced oxidative stress that is further exacerbated by the increased cardiac output that pregnancy demands, partially explains why gestational hypertensive diseases

are more prevalent among older mothers [64]. Notably, gestational hypertensive diseases are the leading cause of severe maternal morbidity, necessitating induced preterm birth [63].

1.1.1.5.2 Socioeconomic Factors.

While age and maternal race appear to be the most significant contributors to preterm birth, they tend to be largely intertwined with socioeconomic status of women. These factors include maternal income and education, insurance status, rurality, and childhood adversity [10, 33, 34, 41, 60, 63].

Maternal education has significant implications in birth outcomes, as demonstrated in various studies [38, 65-67]. In one prospective cohort of 75,296 European infants, researchers found that there was a nearly 50% higher risk of preterm birth and low birth weight among women who had low education compared to those with higher education. In another 10-year cohort study of Quebec infants, Luo and others found that women with less than a community college education had nearly 1.5 times higher odds of preterm birth (OR 1.48, 95% CI [1.44,.152]), in comparison to women who had completed community college or higher [68]. These higher odds are likely attributable to poor access to healthcare and other resources for women given that less-educated women may not have resources, such as pre-conception and prenatal care, readily accessible to them. Additionally, given the significant overlap of maternal education, income, insurance status, and higher stress levels, women with low socioeconomic status remain at high risk [38, 65-67]. In studies that specifically isolate the role of maternal income and preterm birth, inequalities in income, as measured by annual changes in the GINI

coefficient, appear to play a significant role in higher preterm birth rates amongst affected populations [61].

Rurality is another known risk factor for preterm birth. In the United States, women living in rural areas are likely to be less educated, more likely to smoke, and have less access to prenatal care in the first trimester [69]. Access to healthcare services during the pre-pregnancy period, through avenues such as telemedicine and local public health units, could improve access for rural populations and ensure management of other risk factors of preterm birth, such as hypertension and pre-gestational diabetes [70]. A trend analysis of births from 2012 to 2018 conducted by the Southwest Rural Health Research Center examined singleton deliveries by rural status. While preterm birth in the United States from 2012 to 2018 was more prevalent in southern states, residing in a rural county was identified as an independent risk factor of preterm birth among all women [71]. Utilization of healthcare services has been shown to be negatively associated with rurality and with poor birth outcomes among women residing in rural areas of the United States [72]. For a primarily rural state like North Dakota, further identifying areas of geographical concerns remains paramount to improving preterm birth incidence.

1.1.2 Newborn Screening Refusal

1.1.2.1 Newborn Screening Definition and History

Newborn screening is the largest genetic screening program in the United States, serving nearly 4 million newborns each year since its initial inception and implementation in the 1960s [8, 73, 74]. Newborn screening identifies infants who have or are at high risk for certain genetic, endocrine, and metabolic disorders [7, 75, 76]. Newborn screening programs also screen for

hearing loss and critical congenital heart defects. These tests are conducted between 24 and 48 hours after delivery using a dried bloodspot and other non-invasive tools and are typically administered prior to discharge from a birthing facility [6, 8, 73, 77] .

Globally, the newborn conditions screened for fall under six broad categories which include: Organic acid metabolism disorders, Fatty acid oxidation disorders, Amino acid metabolism disorders, Endocrine disorders, Hemoglobin disorders and a sixth category of "other" conditions, such as hearing loss and Cystic Fibrosis [8, 75, 76] . Given the ease of administration, low cost of access, and near universal acceptance, newborn screening is considered 1 of the 10 CDC Public Health Wins of the 20th century [7]. This minimally invasive procedure in the early perinatal period has prevented immeasurable severe mortality and morbidity in children [7, 75, 78].

Newborn Screening in the United States began with Robert Guthrie's invention of the PKU test in the early 1960s. Once mass screening pilots and further validation tests were completed, by the mid-1970s, all 50 states were participating in some form of newborn screening. The invention and accessibility of tandem mass spectrometry revolutionized newborn screening potential for disorders to screen, the timeliness of results, and the ability for states and jurisdictions to conduct follow up of cases for early intervention [73, 76, 78].

By 1965, 32 American states had enacted newborn screening laws, almost all making it compulsory. Newborn screening became commonplace in the United States, then globally, soon after the validation of Robert Guthrie's test for phenylketonuria (PKU), a metabolic disorder that when identified early and treated with a specialized diet, results in minimal if any intellectual disability in the affected infant [73, 79-81]. Infants who do not receive this special diet are at risk

of irreversible brain damage and intellectual disability. Since the 1970s, the accessibility and wide use of tandem mass spectrometry in state hygienic labs allowed for the screening of dozens more conditions simultaneously, thereby streamlining the newborn screening process with its built-in efficiencies. Due to the success of the state programs, and emerging technology, by the 1990s and 2000, public health advocates continued to identify and add conditions to the screening panel, allowing for early detection of dozens of conditions [8, 73, 80, 82].

Prior to the public health uptake of newborn screening, gaps in access to timely confirmatory testing and early interventions were responsible for thousands of premature deaths in children and immeasurable years of life and quality of life years lost [8, 73, 83]. Given the rarity of conditions screened for, the success of newborn screening is heavily dependent on acceptance and utilization by the populations who are unlikely to receive any direct benefit. Refusal or hesitancy due to lack of trust, and other barriers, in newborn screening procedures represents an emerging area of interest in public health research.

1.1.2.2 Newborn Screening Globally

Globally, PKU remains the most frequently screened for condition due to the historical validation and wide accessibility of tools necessary to implement a newborn screening program. In a global survey of newborn screening procedures by Pellegrino and others, extensive newborn screening that is comparable to the dozens of disorders screened for in the United States, is mostly available in developed countries [84, 85]. Conditions most frequently screened for varied and reflected available resources and likelihood of disorders in specific populations. For example, while PKU screening is near universal in Europe, Congenital Hypothyroidism is

especially screened for in Latin America and Asia Pacific [85]. In North America, both Canada and the United States have fairly similar newborn screening services that are state/province-level administered with each state determining eligibility and refusal criteria. Other developed countries such as Australia and New Zealand offer screening panels that are comparable to the United States and Canada. [73, 79-81]

1.1.2.3 Newborn Screening in the United States

Newborn screening in the United States is one of the most successful public health programs with near 100% coverage in all states and jurisdictions [73, 74, 84]. Successful implementation of newborn screening programs ensures that approximately 12,000 children each year that receive a positive screen are referred for additional diagnostic and treatment options. Early intervention presents unique opportunities for follow-up services that can help mitigate the severity of the detected condition [7, 73].

The Health Resources Services Administration (HRSA) oversees the formal recommendation process for conditions that are to be added to the screening panel. In the 1960s, only PKU screening was available nationwide; by 2020, there were 35 conditions on the Recommended Uniform Screening Panel (RUSP) [8, 75, 76, 78]. For a disorder to be included in the RUSP, a series of criteria must be met. First, the condition must be detectable in the newborn period prior to the beginning of symptoms. Secondly, effective treatment must be available for the condition. Lastly, conditions to be added to the RUSP must withstand a rigorous scientific review of the condition itself, the mechanism and ability to detect it, and the efficacy of treatment options available. Given the intensity of the review process, the addition of new

conditions to the RUSP takes at least a year and the implementation of screening for the condition must then be executed by each state [8].

Newborn screening programs in the United States typically involves three core entities: 1) medical system/birthing facilities that collect the necessary samples and administer the pulse oximetry and hearing tests soon after a birth; 2) public health laboratories that conduct the testing and validate results; and 3) the local or state public health agencies that conduct surveillance, patient follow-up and implement quality improvement processes. Most conditions screened for require accuracy in specimen collection and timely follow-up to prevent severe morbidity [86]. It is therefore critical to have policies and practices in place that foster public trust and allow for maximum reach for all newborns.

1.1.2.3.1 Newborn Screening Policies and Practices in the United States

All 50 states, the District of Columbia and the Commonwealth of Puerto Rico participate in newborn screening. However, there are no federal laws regulating newborn screening. State mandates require that all newborns be screened for at least 29 to 35 conditions that are in the RUSP [8, 73, 74]. These policies are the primary drivers in ensuring that of the approximately 4 million infants born in the United States, over 99% of them utilize newborn screening services [74].

Given the sensitivity of newborn screening practices and critical need for early and timely intervention, each state has its own policies on newborn screening refusal. Following a survey of all newborn screening programs in the United States, Therrell and others found that 33 of the 50 state programs permitted parental refusal on religious grounds, 12 allowed for refusal

on religious or other grounds, 5 did not allow refusal, and only one state (New Hampshire) did not have any policy on opting in or out. Consent process to screening also differed by states, with states such as Wyoming and Maryland requiring parents to actively consent for their child to participate [87]. Other states such as North Dakota have a passive consent process, whereby all newborns are screened unless a parent refuses. A written refusal is usually required to document the dissent. For almost all states additional protections exist on the use of newborn screening specimens for research or other purposes [9, 88]. States like Colorado and Florida, for example, define genetic material as personal property, therefore, medical facilities and public health personnel are only allowed access to newborn screening information for service delivery or birth defect surveillance. Privacy is paramount to public trust in newborn screening and some states, such as, California, Utah and Florida, have explicit penalties for violation of newborn screening laws and regulations.

Other policy considerations include privacy and confidentiality of specimens and data and the usage of collected information. One limitation of having each state administer their own newborn screening program is that the various laws and regulations in each state/jurisdiction do not allow for uniform policies to track refusals and cases of non-screening [9, 88]. Therefore, as more conditions are added to the RUSP and emerging concerns on privacy invasion and ownership of leftover genetic materials remain under scrutiny, newborn screening rates may see future declines [89].

1.1.2.4 Newborn Screening in North Dakota

Newborn screening in North Dakota is defined and allowed under Chapter 25-17 of North Dakota's Century Code [90]. This segment of state law defines what is considered newborn screening and its core components. Currently, North Dakota screens for nearly 50 conditions; these include the 29 RUSP conditions and other state added conditions of concern [91].

1.1.2.4.1 Newborn Screening Refusal Legislation in North Dakota

As outlined in Chapter 25-17-02 of North Dakota's Century Code, newborn screening is required for all infants born in the state of North Dakota [92]. The legislation states, "A responsible clinician shall provide the parents and guardians of a newborn written information on the nature of newborn screening and confirmatory-diagnostic testing. The parents or guardians of a newborn may object to screening after receiving the written information. A newborn may not be subject to screening to which the newborn's parents or guardians object. In the case of an objection, the responsible clinician shall record the objection in a document signed by the parents or guardians and shall submit the document to the department". Therefore, if parents do not accept newborn screening services, their dissent must be documented and reported to the North Dakota Department of Health [93].

1.1.2.5 Socio-demographic Determinants of Newborn Screening Refusal

Newborn screening refusal is an emerging phenomenon, and one that has not been well documented. In the United States, for example, this could be attributable to the lack of federal

law regulating newborn screening, and with each state administering its own program, uniform data and historical trends have not been assessed. For states that do require active dissent, there are no reported formal tracking processes or publicly available datasets that would allow for an examination of newborn screening refusal [9, 88].

1.1.2.5 Socio-Demographic Factors

Newborn screening refusal is a rare event that has not been extensively studied in the United States or globally. One French study on Cystic Fibrosis screening found that the introduction of parental informed consent processes that included education to the parents led to an over 75% reduction in the refusal rate in one screening center from 0.8% to 0.2% [94]. In an examination of neonatal hypoglycemia screening in one center by Palmaccio and others, found that parents cited concerns of pain while administering the heel stick, not wanting separation between mother and baby and a perception of "over-medicalizing birth and newborn care" as the primary reasons behind declining the service. Interestingly, these concerns were easily mediated through individual parental education[95]. In a single center Nigerian study by Olusanya and others that involved a two-step perinatal hearing screening process, found no differences between women who delivered their babies out of a hospital setting compared to those who delivered in a hospital (OR: 1.62; 95% CI: 0.98-2.70) [96].

1.1.3 Postpartum Depression

1.1.3.1 Condition Biology, Etiology, and Symptom

Postpartum depression, which affects approximately 1 in 7 women globally, includes minor or major depression that occurs in the first 12 months after a delivery [97-99]. Globally, 20% of maternal mortality is attributable to suicide, which is most commonly proceeded by depression [97, 98]. Postpartum depression is characterized by depressed maternal mood, excessive crying, difficulty bonding with the baby, intense irritability, hopelessness, and severe anxiety, among other symptoms. Suicidal ideation and suicide are also common among women in the severe modes of postpartum depression [97, 98, 100-103].

The etiology of postpartum depression is still under investigation. However, there are three proposed pathways [104-106]: 1) The levels of maternal reproductive hormones. Evidence indicates that women suffering from postpartum depression may be differentially sensitive to the effects of gonadal steroids. This is evidenced by differences observed in women with a history of postpartum depression versus those without a history. In one study by Bloch and others, researchers observed a significant increase in depressive symptoms among women with a history of postpartum depression after simulating two excess hormones (estradiol and progesterone) among women in both categories in an attempt to measure their effect. This study was instrumental in demonstrating the role of these two gonadal hormones in postpartum depression and their interaction effect when in combination with history of postpartum depression [107]. Another known reproductive hormonal contributor to postpartum depression is lower levels of oxytocin, which have been shown to be a predictor of postpartum depression as well as severity of symptoms, especially in those with depression history pre-pregnancy. 2) Increased levels of

stress hormones such as the placental corticotropin releasing hormone and other neuroendocrine factors of the hippocampus-pituitary axis, while not used for diagnostic purposes, are known biomarkers of postpartum depression. 3) Neurosteroid levels, specifically allopregnanolone, a metabolite of progesterone, have been shown to be lower in major depressive disorder and are then increased following antidepressant treatment. Other factors include higher levels of β-endorphin, platelet serotonin reduction, increased monoamine oxidase-A density, and lower vitamin D levels [104-106].

1.1.3.2 Diagnoses and Treatments

Screening for postpartum depressive symptoms can be conducted utilizing several tools. The most commonly utilized screening and diagnostic questionnaires [21, 100-102, 108] include the Edinburgh Postnatal Depression Scale (EPDS) and the Patient Health Questionnaire (PHQ-9). Women who scoreless than 10 are categorized as not having postpartum depression. Standard cutoff scores for the EPDS and PHQ-9 are utilized to categorize postpartum depression as mild, moderate or severe. For the EPDS, the cut offs are for possible depressive disorder are 7-13 for mild, 14-18 for moderate and 19-30 for severe depression. For the PHQ-9, these cutoffs are 5-9 for mild depression, 10-14 for moderate, 15-19 for moderately severe, and 20-27 for severe depression [21, 100-102, 108]. For women who endorse self-harm ideation or score in the severe range (a score of 19 or more on the EPDS or a score of 15 or more on the PHQ-9) on the screening tools, are usually referred for emergency treatment. The PHQ-9 and the EPDS tend to be highly concordant with moderate to strong agreement in their ability to detect depression (kappa >0.6) [109]. Other less frequently used screening and diagnostic tools with similar criteria

include the Postpartum Depression Screening Scale (PDSS) and the Structured Clinical Interview for DSM Disorders (SCID) [110-115].

While there are no standard guidelines on the frequency of screening, typically, most providers administer the screen at the first postpartum visit or upon request from the woman or other provider [102, 110, 116]. Risk assessments are also typically conducted for women who score near or at the clinical thresholds of the screening tools, for example, women with a PHQ-9 Score of 8 or 9. These assessments could include questioning on other known predictors of postpartum depression, such as family history of depression, prior episodes of depression, depression during pregnancy, and past psychiatric history. Current life events such as marital status, maternal coping mechanisms, maternal childhood adverse experiences, financial difficulties, and infant temperament may be instrumental in making a final diagnosis and referral to specialty care [98, 117].

For women who are diagnosed with mild to moderate depression (EPDS or PHQ-9 score range of 7-19 or 5-19, respectively), treatment options vary. These treatments or recommendations may include supportive interventions, such as self-help activities, extra follow-up visits, and if deemed necessary through a risk-benefit analysis, antidepressant prescription may be dispensed.

For women with severe postpartum depression (more than 19 on either the PHQ-9 or EPDS), specialty care referral for psychosocial and pharmacotherapy treatments is recommended. Women who report suicidal ideation and attempts or harm to others may be referred for emergency room and inpatient treatment upon screening by provider. Since postpartum depression may last up-to a year in some women, follow up visits are typically

necessary depending on the patient disposition across the spectrum of mild to severe postpartum depression [17, 18, 20, 21, 102, 118].

1.1.1.3 Disease Burden

1.1.1.3.1 Global Burden of Postpartum Depression

Several studies have attempted to map the global prevalence of perinatal and postpartum depression. These studies consistently show that postpartum depression is a heavy burden to women, families, and their communities and warrants further investigation into predictors, prevention, and treatment strategies [119-122]. In one such meta-analysis on the global prevalence of postpartum depression, sub-Saharan Africa had the highest prevalence of postpartum depression with almost 40% of women reporting symptoms (39.96%, 95% CI [27.81, 53.48]) [122]. The Oceania region had the lowest estimated prevalence of 11% (95% CI [9.27,13.25], $p < 0.01$) [122]. Southern Asian countries reported a prevalence of 22% (22.32%, 95% CI [18.48,26.70]), closely followed by South America at a prevalence of 22% (95% CI [19.78, 23.76]). Western Asian, North America, Eastern Europe and Southern Europe countries all reported prevalences of between 16% and 20% countries. Northern Europe, West Africa and South-East Asia reported prevalences of approximately 14%. Amongst individual countries, Afghanistan reported the highest prevalence at 61% while Denmark had the lowest at 6.5% The United States reports a prevalence of approximately 13% annually [21].

1.1.1.3.2 Postpartum Depression in the United States

Approximately 13% of postpartum women reported experiencing postpartum depression symptomology in the United States [21]. Mississippi had the highest prevalence (23%) followed by West Virginia (19.4%). North Dakota ranked 20th out of the 31 states with available data. The same study reported higher prevalence of postpartum depression among Black Non-Hispanic women, American Indian/Alaska Native, those who were 19 years of age or less and those who had a high school education or less. Women who participated in publicly funded programs such as the Women, Infants and Children Program (WIC) and Medicaid were also more likely to experience symptoms compared to those that did not. Tobacco use, having less than a college education, history of depression, and those with a history of intimate partner violence were significantly more likely to report postpartum depression symptoms [21].

1.1.3.4 Temporal Trends

The Prevalence of postpartum depression is on the rise in the United States. In one analysis by Bauman and others assessing temporal trends in reported postpartum depression across 16 states, the reported prevalence showed a small but significant increase between 2012 and 2018 (0.22%, $p < 0.05$) [100]. This increase is troubling given the declining trend of postpartum depression that was previously observed in 13 participating states, from an estimated high of 14.8% in 2004 to a low of 9.8% in 2012. In another examination of severe postpartum depression requiring mental health hospitalization comparing data from California and Florida, between 2006 and 2011 California reported a 29% increase in the rate of postpartum depression hospitalizations from a low of 8 per 10,000 to 10.9 per 10,000 [123]. Florida observed a near

50% increase in postpartum depression hospitalizations from a low of 8.2 per 10,000 to 14.0 per-10,000. Given the increasing trend of depressive disorders observed across various populations in the United States, identifying population at risk is of grave importance [124-126].

1.1.3.5 Socio-demographic Determinants of Postpartum Depression

1.1.3.5.1 Demographic Factors

Extensive research indicates postpartum depression is significantly associated with family history of depression, prior episodes of major depression, depression during pregnancy, and past psychiatric history [3, 4, 119-121, 127]. Other predictors include level of psychosocial supports, marital relationship, unintended pregnancy, current stressful life events, trauma and other adverse childhood experiences and the maternal ability to cope with problems [3, 119-121]. Notably, the more risk factors one has, the higher the likelihood of postpartum depression [3]. It is worth noting that infant characteristics such as temperament, health status, and presence of special needs, are also known risk factors [3, 4, 119].

1.1.3.5.2 Socioeconomic Factors

Maternal education, and household income are known contributors to postpartum depression [3, 119, 120, 128]. Countries with higher wealth inequality based on the GINI Index had higher levels of postpartum depression. As Holbrook and others found, approximately 41% of the cross-national variation in postpartum depression prevalence was explained by wealth inequality [128]. There is conflicting evidence on the significance of rural residence as a predictor of postpartum depression. Nidey and others found the odds of postpartum depression

among women residing in rural areas to be 21% higher compared to urban residing women (*OR* = 1.21, 95% CI[1.05, 1.41]) [129]. By contrast, Collins and others found that women in rural Appalachia were less likely to experience postpartum depression compared to those who resided in the urban or suburban areas [130]. Additionally, a 2010 meta-analysis of rural residing women and postpartum depression, found that, while the predictors of depression were not significantly different between rural and urban residing women, family sizes of 2 or more young children were an additional risk factor for depression among rural residing women [131].

1.1.5 Role of Title V/Maternal and Child Health Public Programs in Addressing Emerging Issues in the Perinatal Population

1.1.5.1 Needs Assessments

Title V of the Social Security Act is the longest standing federal legislation and program in support of women, children and families in the United States [2]. Since its first authorization in 1935, this federal-state partnership provides funding to states to prioritize critical activities that mitigate adverse population-level outcomes affecting women, mothers and children. [2, 132, 133]. As defined in section 501(a)(1) of the Title V legislation, the Maternal and Child Health Block Grant enables each state to:

1) Provide and assure access to health services for mothers and children

2) Improve perinatal health especially in relation to reducing infant mortality and the prevalence of preventable diseases in children

3) Provide access to comprehensive family-centered, community-based services for children with special healthcare needs [2].

The Health Resources Services Administration (HRSA) defines and categorizes the maternal and child health population into five domains: maternal health (pregnant women and women ages 15-44), perinatal/infant health (ages 0-1), child health (ages 1-11), adolescent health (ages 12-17), and children with special healthcare needs (ages 1-21) populations [134, 135]. To further identify the health risk behaviors and outcomes for these five populations, and receive funds to address said issues, all states must conduct ongoing needs assessments and set priorities that align with the national performance and outcome priorities. National outcomes measures for each relevant population are established by HRSA every five years. For a health outcome to be set as a national priority, it must be recognized as a sentinel health marker for maternal and child health, such as preterm birth or infant mortality; the condition must be considered important for monitoring due to emergence or rising incidence, such as the case for postpartum depression and developmental screening; and the issue must also be recognized as a necessity in propelling the maternal and child health population health forward [135]. Surveillance and research of these issues is then mandated and considered for prioritization in relation to Title V policies and legislation at national and local levels [134].

Needs assessments serve a critical piece in the establishment of state and national performance and outcome measures. These assessments are systematic processes that identify the current status of an issue, set goals and establish priorities [136], and are often characterized as the process to determine the gap between the targeted state and the actual state [137]. The fundamental outcome of needs assessment processes is to describe what is currently being observed and how these findings compare to the ideal or achievable goals. Given the emergence of new challenges in the perinatal population or the resurgence of persistent adverse outcomes,

needs assessments through a thorough examination of data and the literature remain a core component of establishing areas of investment and improvement in the maternal and child health realm.

1.1.5.2 Partnerships & Community Engagement

Perinatal morbidity and mortality are key indicators of a nation's health status and the basis of attempts to improve outcomes is in engaging community partnerships [1, 134, 135, 138]. In perinatal populations, the intersection of healthcare entities, public health agencies, and local organizations is paramount for successful implementation of programs serving women and children. As such, there are various frameworks of community engagement in the maternal and child health populations that serve the purpose of assisting in the implementation of maternal and child health initiatives. Established models of community engagement, such as, the Ladder of Community Participation are especially effective for state-level driven initiatives that must be adopted in smaller local jurisdictions since they operate by engaging stakeholders at each step [139] .

The Ladder of Community Participation, for example, includes seven strategies: initiation and direction of action, education of the community, initial community consultation, extensive community consultation, bridging of community members and health departments, power-sharing of the participating entities, and lastly community driven action. State-based perinatal quality collaboratives (PQCs) also serve as innovation hubs of engaging partners and communities. Through active networks of providers, hospitals, birthing facilities, and local and state health departments, PQCs embody the seven strategies listed above in improving perinatal

health outcomes through continuous quality improvements around topics of significance. According to the CDC, PQCs were first established in 1997 in the United States and over the course of their existence and expansion, they have been instrumental in leading significant improvements in nosocomial infections in newborns, maternal hypertension, severe maternal morbidity, among other issues [138, 140, 141]. Since PQCs operate on a state-by-state basis, they are more able to quickly identify and address emerging issues as they arise, and they serve as one of the stakeholders privy to findings of the North Dakota Title V needs assessments. For the three emerging issues under investigation in this study, PQCs are ideal in examining these findings and resource mapping to help improve outcomes.

1.1.5.3 Policy Development

The creation of, advocacy for, and utilization of policies, plans and laws that impact health of relevant populations are two of the 10 Essential Public Health Services outlined by the CDC [142]. There are various policies nationally and globally that have been implemented to prevent adverse outcomes in the perinatal population with conflicting results. In preterm birth prevention, healthcare policy is primarily shaped by guidelines and expertise of the national bodies representing the relevant key stakeholders. The American College of Obstetricians and Gynecologists (ACOG) through their practice bulletins provides a synthesis of the medical literature and recommendations of practice for providers that become standards of practice. Specific guidelines and policies on the management of prevention of preterm birth include:
1) Risk assessment policies for providers caring for women with a threatened preterm birth [143].

2) Guidelines on the diagnostic procedures of preterm birth [32].

3) Guidelines on the use of progesterone and cervical cerclage [144].

4) Guidelines on the use of low-dose aspirin for the prevention of severe maternal hypertensive diseases necessitating preterm birth [145], among others.

Continuous timely and appropriate screening for and treatment of postpartum depression and the prevention of severe maternal morbidity are among the emerging issues of policy and guidelines that ACOG has prioritized [31]. Other recent examples of effective and promising public health policies include the legal protection of smoke-free policies in the reduction of preterm birth. In one meta-analysis by Been and others on the impact of smoke-free legislation and perinatal health, in four studies of over 1.3 million individuals, a 10.4% reduction in the prevalence of preterm birth was observed between 2008 and 2013 [146].

Additionally, cost of services is a commonly cited policy concern among women in relation to access to health services for themselves and their newborns. Policies that mitigate this could have significant impact in increasing access and utilization of preventive services [147-150]. Policies that reduce financial burden on at-risk populations may significantly improve the burden of at-risk populations, especially those with low household incomes [88, 150, 151]. Recent examples include the state expansion of Medicaid coverage under the Affordable Care Act [147-149]. This was a critical change in federal health policy given that approximately 50% of births in the United States are covered by Medicaid [148]. This federal-state program that insures individuals with income levels that range from between 138% to 380% of the Federal Poverty Level, has been instrumental in ensuring access to prenatal and postpartum care among low income women in the United States.

For states like North Dakota and 36 others, the expansion of postpartum Medicaid under the Affordable Care Act offered low-income women the ability to continue coverage past 60 days postpartum [147-149]. While children are typically enrolled in Medicaid right at birth, thereby allowing them to access the critical services that may be urgently necessary due to preterm birth or newborn screening, this expansion of benefit for the perinatal population is especially critical for access and utilization of services such as postpartum depression, inter-conception care, and long-acting reversible contraception [147-149]. Identifying the predictors of these three key emerging issues could help mitigate the poor outcomes associated with them and significantly improve the health of North Dakota's perinatal population.

CHAPTER 2

2.0 Investigation of Predictors of Preterm Birth among North Dakota Women

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Running Head: Predictors of Postpartum Depression in North Dakota

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2.1 Abstract

Preterm birth, a leading cause of neonatal morbidity and mortality, represents approximately 10% of births in both North Dakota (ND) and the United States annually. Therefore, it is critical to reduce its burden. This study investigated predictors of preterm birth among women in ND.

Methods*:* Data from the 2017-2019 ND Pregnancy Risk Assessment Monitoring System were used for the study. Factor-specific prevalence and confidence intervals of potential predictors were computed. Logistic models were used to investigate and identify predictors of preterm birth.

Of the 30,565 births during the study period, 8.5% were preterm. There were significant associations between odds of preterm birth and plurality (adjusted odds ratio [AOR] = 95.6; $p < 0.0001$), maternal hypertension (AOR = 6.1; $p < 0.0001$), premature rupture of membranes (AOR=15.0; $p < 0.0001$), prior preterm birth (AOR = 6.0; $p < 0.0001$), and rural county of residence (AOR = 1.7; $p = 0.019$). Additionally, the odds of preterm birth were twice as high among women who were ≥ 35 years old at the time of delivery (AOR = 2.0; $p = 0.043$) compared to those who were 20-34 years. Finally, the odds of preterm birth among women who attended < 9 prenatal care visits were nearly three times that of those who attended 9-11 visits (AOR = 2.8; $p < 0.0001$). Surprisingly, there was no association ($p = 0.35$) between preterm birth and the adverse childhood experiences score.

Access to regular and appropriate prenatal visits as well as screening for maternal risk factors of preterm birth remain critical in ensuring early detection and management of the identified risk factors and hence in reduction/elimination of the problem.

2.2 Background

Preterm birth refers to a birth occurring before 37 weeks of gestation. Premature infants are at higher risk of severe neonatal and infant disorders such as chronic lung disease, metabolic disorders, and developmental delays. Preterm birth is the leading cause of neonatal mortality, accounting for over 50% of perinatal deaths globally [23, 152, 153]. In the United States, approximately 1 in 10 infants were born premature in 2019 [54, 154, 155].

While the rate of preterm birth in the United States was on a declining trend between 2007 (10.4%) and 2014 (9.5%), nationally, prevention efforts have largely failed to decrease this rate to a level significantly lower than the 9.5% prevalence recorded in 2018 [54, 154]. Southern states, including Mississippi, Arkansas, Alabama, and Louisiana, are among the most poorly ranked states, with each reporting over 12% of their births being premature. North Dakota ranks in the bottom 20th percentile of states, with approximately 9% of births being premature in 2018. However, initiatives to significantly improve this outcome have also not been successful [54].

In the United States, preterm births are estimated to cost over $26 billion each year. These costs are largely related to maternal and neonatal medical and healthcare costs, early intervention services for the children born premature, special education services, and loss of work and pay for individuals who have premature births [28, 156]. Understanding the socioeconomic and medical predictors of preterm birth as well as any potential effect modifiers is critically important for guiding mitigation strategies to curb the problem. Unfortunately, not much has been done to investigate these issues in North Dakota and yet this information is critically important for evidence-based health programs aimed at reducing preterm birth in the

state [23, 28, 152, 157]. Therefore, the objective of this study was to investigate predictors of preterm birth among North Dakota women who had live births between 2017 and 2019.

2.3 Methods

2.3.1 Ethics Approval

This study was reviewed and approved by the North Dakota Department of Health (NDDoH) Institutional Review Board (IRB) and the University of Tennessee IRB (IRB Number: 21-06599-XM).

2.3.2 Study Area

The study area included all 53 counties of North Dakota, which had a population of 779,094 in 2020. The racial distribution of the state is 81.7% White, 5.0% American Indian/Native American, 3.4% Black, 1.7% Asian, and 5.4% two or more races. Approximately 4.3% of the residents are of Hispanic ethnicity [158]. Women of reproductive age (15-44) make up 19% of the state's total population. Approximately 11% of North Dakotans lived below the Federal Poverty Line in 2019, with about 11% of women of reproductive age (15-44) reporting having no health insurance coverage in 2017 [159]. Between 2017 and 2019 there were a total of 31,815 births to North Dakota residents that occurred within the state. The study population included the cohort of live births occurring among North Dakota residents based on weighted responses to the North Dakota Pregnancy Risk Assessment Monitoring System (PRAMS) [155, 160].

2.3.3 Data Sources & Management

Data for this study were acquired from the North Dakota PRAMS Program which is a collaborative population-based surveillance system by the U.S. Centers for Disease Control and Prevention (CDC) and the North Dakota Department of Health (NDDoH) [155]. The core CDC PRAMS was established in 1987 and monitors maternal attitudes, behaviors, experiences, and outcomes before, during, and immediately after pregnancy. The North Dakota PRAMS Program data used in this study was initiated in 2017. North Dakota utilizes the standard PRAMS data collection methodology which has been described in detail elsewhere [160]. Briefly, a stratified random sample of women identified in the birth certificate dataset is invited to participate in the survey. In the North Dakota PRAMS, approximately 14.8% of women with a live birth were sampled between 2017 and 2019 [160]. The North Dakota PRAMS' response rate was 70.2% in 2017, 59.9% in 2018, and 59.1% in 2019. These response rates were above the CDC-required 55% response threshold for a weighted statewide representative sample [155, 160].

The PRAMS questionnaire covers an array of topics on maternal behaviors and experiences. It includes questions on smoking, substance abuse, prenatal care and other healthcare provider access, insurance status, and information covered by healthcare providers during healthcare visits. The questionnaire also contains questions on healthcare outcomes, such as preterm birth, maternal diabetes, hypertension, and behavioral health. States participating in the CDC PRAMS Program are permitted to add questions to the core survey that reflect emerging or state-relevant needs. Due to interest among stakeholders in the state, North Dakota added the adverse childhood experiences (ACEs) module of questions [161, 162].

2.3.3.1 Outcome variable, preterm birth

Preterm birth was defined as live births occurring before 37 weeks of gestation. A dichotomous preterm birth variable was created by categorizing gestation period into births before 37 weeks as preterm, and those 37 weeks and after as term births.

2.3.3.2 Potential predictors of preterm birth

Data on the potential predictors of preterm birth from the ND PRAMS dataset included: maternal race categorized as American Indian, White, and other races; maternal age classified as < 20, 20-34, and ≥ 35 years at the time of birth; and plural births categorized as plural (2 or more neonates) or not (singleton). Additional maternal characteristics included insurance type used to pay for the birth (North Dakota Medicaid or non-Medicaid); marital status (infant born "in wedlock" or not, according to self-reported status on the birth certificate); rural or urban maternal residence using the county classification system outlined by the North Dakota Center for Rural Health [163]; frequency of prenatal care visits (< 9, 9-11, > 11 visits); hypertension during pregnancy (defined as blood pressure at or above 130/80 millimeters of mercury), including women who self-reported chronic hypertension, pre-eclampsia, and eclampsia; prior preterm birth (yes or no); and rupture of the amniotic sac before active labor, also known as premature rupture of membranes (PROM; yes or no) . The cumulative ACE score was computed by summing responses (Yes = 1, No = 0) to the 10 ACE module Yes/No questions (Table 2.1) included in the ND PRAMS survey [161, 162] (for a possible maximum score of 10). Totals of ≥ 4 were categorized as having a high ACE score, which is consistent with

Table 2.1: Childhood Adversity Module, North Dakota Pregnancy Risk Assessment Monitoring System 2017, 2018, 2019

Question/ Statement	Options	No	Yes
71. While you were growing up, during your first 18 years of life:	a. Were your parents ever separated or divorced?	☐	☐
	b. Did you live with anyone who was a problem drinker or alcoholic or who used street drugs?	☐	☐
	c. Was a household member depressed or mentally ill, or did a household member attempt suicide?	☐	☐
	d. Did a household member go to prison?	☐	☐
	e. Did an adult or person at least 5 years older than you ever touch or fondle you or have you touch their body in a sexual way **OR** attempt or actually have oral, anal, or vaginal intercourse with you?	☐	☐
72. While you were growing up, during your first 18 years of life, did any of the following things happen often or very often?	a. Did a parent or other adult in the household swear at you, insult you, put you down, or humiliate you **OR** act in a way that made you afraid that you might be physically hurt?	☐	☐
	b. Did a parent or other adult in the household push, grab, slap, or throw something at you **OR** ever hit you so hard that you had marks or were injured?	☐	☐
	c. Did you feel that no one in your family loved you or thought you were important or special **OR** your family didn't look out for each other, feel close to each other, or support each other?	☐	☐
	d. Did you feel that you didn't have enough to eat, had to wear dirty clothes, and had no one to protect you **OR** your parents were too drunk or high to take care of you or take you to the doctor if you needed it?	☐	☐
	e. Was your mother or stepmother pushed, grabbed, slapped, or had something thrown at her **OR sometimes, often, or very often** kicked, bitten, hit with a fist, or hit with something hard **OR ever** repeatedly hit at least a few minutes or threatened with a gun or knife?	☐	☐

extant studies that showed graduated increases in risks of poor outcomes with the highest risks being observed among those having ACE scores of ≥ 4 [164-168].

2.3.4 Statistical Analyses

2.3.4.1 Descriptive Statistics

All statistical analyses were performed in SAS 9.4 [169]. Since the data were from a complex survey, all analyses involved specification of both the strata variable (STRATUMC) and the sampling weight variable (WTANAL). Thus, weighted crude and factor-specific percentages of preterm birth and their 95% confidence intervals (95% CI) were calculated for all categorical variables using PROC SURVEYFREQ in SAS [169].

2.3.4.2 Predictors of Prematurity among North Dakota Women with a Live Birth

The first step in the investigation of predictors of preterm birth involved assessing univariable associations between each of the identified potential predictor variables and preterm birth (Figure 2.1). To adjust for the complex survey design used to collect study data, both the univariable and multivariable analyses utilized PROC SURVEY LOGISTIC of SAS [169], specifying the strata variable (STRATUMC) and the sampling weight variable (WTANAL). Potential predictors that had *p*-values ≤ 0.20 based on the univariable analysis were assessed in the 2nd step which involved building a multivariable logistic model using a backwards elimination approach. Only variables with *p*-values ≤ 0.05 were retained in the final main-effects multivariable model.

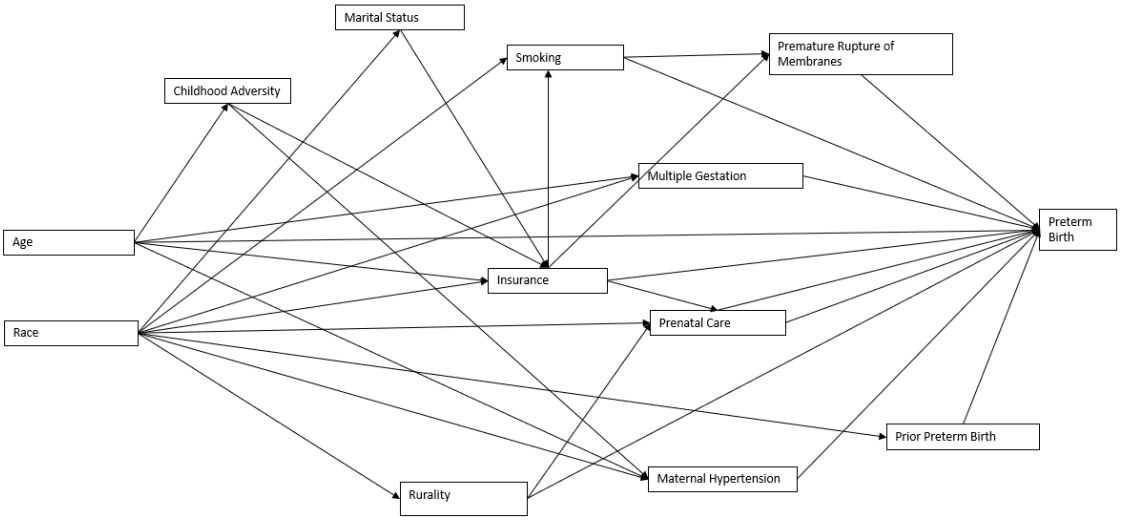

Figure 2.1: Conceptual model representing predictors of prematurity among women in North Dakota, 2017-2019.

Confounding variables were evaluated by observing the changes of parameter estimates of variables in the model before and after removal of a suspected confounding variable from the model. If the parameter estimates of any variable in the model increased or decreased by ≥ 20% after removal of the suspected confounding variable from the model, then that variable was considered an important confounder and retained in the model regardless of its *p*-value. Biologically plausible two-way interaction terms were also assessed. No confounders or interaction terms were identified. Odds ratios and their 95% confidence intervals were generated for all variables retained in the final model.

2.4 Results

2.4.1 Descriptive Statistics & Simple Associations

There were 2,600 preterm births in North Dakota during the study period, representing 8.5% of all births. The prevalence of preterm birth was significantly ($p < 0.0001$) higher among women who had pregnancies resulting in the delivery of two or more babies (72.4%) compared to those who had single births (7.7%). Women who had hypertension had a significantly ($p < 0.0001$) higher prevalence of preterm birth (19.1%) than those who did not have hypertension (7.5%). The prevalence of preterm birth was significantly ($p < 0.0001$) higher among women who had PROM (51.4%) than those who did not (6.8%). The prevalence of preterm birth was significantly ($p<0.0001$) higher among women who had at least one prior preterm birth (27.4%) than among women who did not (7.7%). American Indian women had a significantly ($p = 0.0017$) higher prevalence of preterm birth (13.1%) compared to White women (8.3%) and women of all other races (6.5%). Women who smoked during their first trimester had a

significantly ($p = 0.0300$) higher prevalence of preterm birth (11.6%) compared to women who did not (7.8%). Finally, and not surprisingly, women who had < 9 prenatal visits during their pregnancy had a significantly ($p < 0.0001$) higher prevalence of preterm birth (20.7%) than those who had the recommended 9-11 visits (8.7%) as well as those who had > 11 visits (3%). Although women who had four or more adverse childhood experiences had a seemingly higher prevalence of preterm birth (9.9%) than those who had less than four (8.2%), these differences were not statistically significant ($p = 0.350$) (Table 2.2).

2.4.2 Predictors of Preterm Birth among North Dakota Women with a Live Birth

The results of the assessments of the univariable associations indicate that a total of 9 variables were identified as potential predictors of preterm birth based on a relaxed alpha of 0.2 (Table 2.3). However, the final multivariable logistic model identified 7 statistically significant predictors, including plural births, hypertension, premature rupture of membranes, prior preterm birth, age ≥ 35 years at the time of delivery, rural residence and number of prenatal visits (Table 2.3). Women with plural births (twins or more) had 95.6 times higher odds of preterm birth (AOR = 95.6; 95% CI [25.6, 356.3]; $p < 0.0001$) than those with singleton pregnancies (Table 2.4). The odds of preterm birth among women who had hypertension were 6.1 times higher (AOR = 6.1; 95% CI [3.5, 11.0]) than those of women who did not have hypertension. Women who experienced PROM also had higher odds of preterm birth (AOR = 15.0; 95% CI [8.3, 27.2]) compared to those that did not. Additionally, the odds of preterm birth were higher among women who experienced prior preterm birth (AOR = 6.0; 95% CI [3.0, 11.7]) compared to those that did not have a history of preterm birth (Table 2.4).

Table 2.2: Demographic Characteristics and Health Status of North Dakota Residents who had Live Births between 2017 and 2019

Maternal Characteristics	Preterm Birth	Percent	95% CI[1]	Term Births	Percent	95% CI[1]	*p*-value
Births	2600	8.5	(7.1, 9.9)	27965	91.5	(90.1, 92.9)	
Plural Births							<0.0001
Yes	269	72.4	(52.3, 92.5)	102	35.9	(7.5, 47.7)	
No	2331	7.7	(6.3, 9.1)	27862	92.3	(90.9, 93.7)	
Hypertension During Pregnancy							<0.0001
Yes	524	19.1	(12.3, 26.0)	2216	80.9	(74.0, 87.7)	
No	2076	7.5	(6.0, 8.8)	25749	92.5	(91.1, 94.0)	
PROM[2]							<0.0001
Yes	596	51.4	(38.0, 64.8)	596	48.6	(35.2, 62.0)	
No	2004	6.8	(5.5, 8.1)	27335	93.2	(91.9, 94.5)	
Prior Preterm Birth							<0.0001
Yes	357	27.4	(15.9, 39.0)	946	72.6	(61.0, 84.1)	
No	2243	7.7	(6.3, 9.1)	27019	92.3	(9.07, 93.7)	
Insurance Type							0.3200
Medicaid	723	9.7	(6.7, 12.7)	6714	90.3	(87.3, 93.3)	
Private	1591	8.0	(6.3, 9.8)	18210	92.0	(90.2, 93.7)	
Married							0.0500
Yes	1512	7.5	(5.8, 9.1)	18713	92.5	(90.8, 94.2)	
No	1088	10.5	(7.8, 13.2)	9251	89.5	(86.8, 92.2)	
Adverse Childhood Experiences Score							0.3500
<4	2028	8.2	(6.6, 9.8)	22747	91.8	(90.2, 93.3)	
≥4	572	9.9	(6.4, 13.3)	1904	90.1	(86.7, 93.6)	
Race							0.0017
American Indian	354	13.1	(10.7, 15.6)	2341	86.9	(84.4, 89.3)	
White	1993	8.3	(6.6, 10.0)	21958	91.7	(90.0, 93.4)	
Other races	252	6.5	(2.4, 10.5)	3666	93.5	(89.5, 97.6)	
Age							0.0150
<20	61	5.6	(1.0, 10.2)	1020	94.4	(89.8, 98.9)	
20-34	1985	7.8	(6.3, 9.3)	23502	92.2	(90.7, 93.7)	
≥35	554	13.9	(8.9, 18.9)	3444	86.1	(81.1, 91.1)	
Geography of Residence							0.1600
Rural	1197	7.7	(5.8, 9.6)	14284	92.3	(90.4, 94.1)	
Urban	1403	9.3	(7.1, 11.5)	13680	90.7	(88.5, 92.9)	
Smoking 1st Trimester							0.0300
Yes	769	11.6	(8.1, 15.0)	5886	88.4	(85.0, 91.9)	
No	1817	7.8	(6.1, 9.3)	21842	92.3	(90.7, 93.9)	
Prenatal Care Visits							<0.0001
≤8	1169	20.7	(15.9, 25.4)	4488	79.3	(74.6, 84.1)	
9-11	961	8.7	(6.2, 11.2)	10107	91.3	(88.8, 93.8)	
>11	372	3.0	(1.6, 4.3)	12219	97.0	(95.7, 98.4)	

[1]95% Confidence Interval, [2]PROM: Premature Rupture of Membranes

Table 2.3: Univariable Associations of Preterm Birth and Potential Predictors among North Dakota Residents who had Live Births between 2017 and 2019

Maternal Characteristics	Odds Ratio	95% CI[1] Lower Limit	95% CI[1] Upper Limit	*p*-value
Plural Births				
Yes	27.8	10.4	74.3	<0.0001
No (referent)				
Hypertension During Pregnancy				
Yes	3.1	1.9	5.0	<0.0001
No (referent)				
PROM[2]				
Yes	13.0	7.3	23.2	<0.0001
No (referent)				
Prior Preterm Birth				
Yes	5.2	2.8	9.7	<0.0001
No (referent)				
Race				0.0017
American Indian	1.7	1.0	2.3	0.002
Other races	0.8	0.4	1.5	0.124
White (referent)				
Age				0.013
<20	0.6	0.2	1.7	0.111
≥35	1.9	1.2	3.1	0.008
20-34 (referent)				
Geography of Residence				
Rural	1.3	0.9	1.9	0.019
Urban (referent)				
Smoking 1st Trimester				
Yes	1.6	1.05	2.4	0.030
No (referent)				
Prenatal Care Visits				<0.0001
<9 Visits	2.8	1.8	4.3	<0.0001
>11	0.3	0.2	0.5	<0.0001
9-11 (referent)				

[1]95% Confidence Interval
[2]PROM: Premature Rupture of Membranes

Table 2.4: Predictors of Preterm Birth among North Dakota Residents who had Live Births between 2017 and 2019

Maternal Characteristics	Adjusted Odds Ratio	95% CI[1] Lower Limit	95% CI[1] Upper Limit	*p*-value
Plural Births				
Yes	95.6	25.6	356.3	<0.0001
No (referent)				
Hypertension During Pregnancy				
Yes	6.1	3.5	11.0	<0.0001
No (referent)				
PROM[2]				
Yes	15.0	8.3	27.2	<0.0001
No (referent)				
Prior Preterm Birth				
Yes	6.0	3.0	11.7	<0.0001
No (referent)				
Age				0.013
<20	0.3	0.1	1.3	0.111
≥35	2.0	1.1	3.5	0.008
20-34 (referent)				
Geography of residence				
Rural	1.7	1.1	2.6	0.019
Urban (referent)				
Prenatal Care Visits				<0.0001
<9	2.8	1.8	4.3	<0.0001
>11	0.3	0.2	0.5	<0.0001
9-11 (referent)				

[1]95% Confidence Interval
[2]PROM: Premature Rupture of Membranes

The odds of preterm birth were twice as high among women who were 35 years or older at the time of delivery (AOR = 2.0; 95% CI [1.1, 3.5]; $p = 0.043$) compared to those who were 20-34 years old at time of birth. Rural women of North Dakota had nearly twice the odds of preterm birth (AOR = 1.7; 95% CI [1.1, 22.6]; $p = 0.02$) of those residing in urban counties. No significant interactions were identified.

2.5 Discussion, Strengths, Limitations & Conclusions

This study examined predictors of preterm birth in North Dakota between 2017 and 2019. The findings of this study are consistent with those of previous studies that have reported significant associations between risks of preterm birth and plurality, maternal hypertension, PROM, prior preterm birth, maternal age, rural residence, and number of prenatal care visits [38, 66, 67, 170]. ACEs and maternal race were not significantly associated with preterm birth in this study.

The current study found that the odds of premature birth were much higher for plural pregnancies compared to single pregnancies. This is in agreement with reports from other studies that have reported that plural pregnancies are associated with preterm birth as well as older maternal age, maternal hypertension, and PROM [67, 152, 170, 171]. The rate of plural pregnancies, especially twins, has been increasing in the United States, from 23.1 per 1,000 live births in 1991 to 33.2 per 1,000 live births in 2009 [172]. This trend is largely attributable to older maternal age and the growth in the utilization of assisted reproductive technologies, which substantially increase the likelihood of plural births [172]. Considering the risks associated with plural pregnancies, The American College of Obstetricians and Gynecologists recommend

adequate prenatal care to assist in managing other known risk factors, such as hypertension, so as to reduce the risk of perinatal mortality [173].

Hypertension during pregnancy remains a leading predictor of both poor maternal birth outcomes and high risk of cardiovascular disease for women and infants [156, 174, 175]. The risks associated with hypertension during pregnancy have been documented in several studies around the world. In Iran, maternal hypertension was associated with a more than 7-fold increase in the odds of preterm birth (*OR* = 7.3, CI[2.1, 25.4]) [152]. In a cohort study of singleton Canadian births between 2012 and 2016, hypertensive women had a nearly 4-fold risk of preterm birth compared to those who were not (adjusted risk ratio [aRR] = 3.81; 95% CI [3.6, 4.1]). Notably, the study found that women diagnosed with pre-pregnancy hypertension that progressed to preeclampsia during pregnancy had a nearly 45-fold risk of preterm birth compared to those who did not (aRR = 45.40; 95% CI [36.7, 52.0]). It is critical to encourage women with hypertension who plan to become pregnant to engage in pre-pregnancy counselling and hypertension management [175]. Adherence to prenatal care recommendations is also critical in enabling prompt diagnosis and management among women who develop hypertension during pregnancy in order to mitigate unfavorable maternal and infant health outcomes [157]. Unfortunately, management of hypertension with antihypertensives among women planning for pregnancy has proven to be especially challenging because some of these medications are known to cause abnormal fetal development [176]. More studies are needed to better understand the effectiveness and safety of different mitigation strategies to reduce risk and improve pregnancy outcomes.

Given the high risks of preterm birth among women with history of hypertension prior to pregnancy, primary prevention of hypertension among women of reproductive age is essential. Focusing on pre-conception counseling for women of reproductive age is important since approximately 45% of pregnancies are not planned [171]. Pre-conception counseling provides an important window for prevention and clinical management of hypertension [175]. It also allows for discussion about family planning and education about effective methods of pregnancy prevention.

The results of the current study concur with extant studies that have identified history of preterm birth as a risk factor for subsequent preterm birth [66, 67]. In the Preterm Prediction Study by Mercier and others, there was a nearly 3-fold increase in the odds of preterm birth among women who had prior preterm birth, compared to those who had no history of preterm birth [177]. In our study, the associated odds were even higher (AOR = 6.1, 95% CI [3.5,11.0]). Women with a prior history of preterm birth should be educated as to their risk for subsequent preterm birth. During pregnancy, providers should screen women at risk of recurrent preterm birth to optimize the ability of women to seek timely care with maternal and fetal medicine specialists for intervention [170] . This is especially critical in rural areas where advanced specialties like maternal and fetal medicine are rare [66, 72, 170]

Approximately 8.5% of the deliveries in this study were preterm birth, and 22.9% of these preterm births were complicated by PROM. While the etiology of PROM is largely unknown, established risk factors include maternal infection, placental abruption, injury, and invasive procedures such as amniocentesis [152, 156, 178]. Given the largely unknown etiology

of this phenomenon, individuals that experience PROM represent a population in need of further investigations.

The current study found that the age-specific preterm birth rates followed a J shape. The preterm birth rates among women < 20 years old were similar to the rates among those who were 20-34 years old, followed by a higher rate among those ≥ 35 years old. Our results differ from a 2018 analysis of maternal age and the risk of preterm birth among 165,282 Canadian births, which found a U-curve distribution based on age: higher rates of preterm birth among women < 20 years old, lower risk among the 20-34 year old women, and then a slow but consistently high risk of prematurity at ≥ 35 years old. Strong significance was especially persistent at > 40 years of age [179]. The researchers proposed that the high risk of prematurity with advanced maternal age could be explained by increases in the frequency of chronic hypertension, pre-gestational diabetes, and other maternal comorbidities in conjunction with advanced maternal age.

In an examination of age-related risk for adverse outcomes among more than 220,000 births occurring in Finland between 2005 and 2015, the age threshold for high-risk comorbidities varied. Women 28 years of age and older were at high risk of preterm birth, women 33 years of age and older were at high risk for hypertension during pregnancy, and those 38 years of age and older were at high risk for severe hypertensive diseases of pregnancy [180]. Given the notable trend of delayed childbearing, especially in developed countries, prevention and intervention strategies aimed at mitigating medical comorbidities, such as hypertension and diabetes, must remain a priority [180].

The findings of the current study are consistent with a trend analysis of births from 2012 to 2018 conducted by the Southwest Rural Health Research Center that examined singleton

deliveries by rural status. That study found that, while most preterm birth in the United States from 2012 to 2018 occurred primarily in the rural southern states, rurality was an independent risk factor of preterm birth among all women [71]. Utilization of healthcare services has been shown to be negatively associated with rurality and with poor birth outcomes among women residing in rural areas of the United States [72]. Since fewer prenatal visits and lower access to care during delivery are linked to negative outcomes, there is a need to further explore the medical gaps among women living in rural areas. Millions of people in the United States live in areas designated as primary care health professional shortage areas [181]. Access to healthcare services during the pre-pregnancy period, through avenues such as telemedicine and local public health units, could improve access for rural populations and ensure management of other risk factors of preterm birth, such as hypertension and pre-gestational diabetes [70].

While maternal ACE score did not show a significant association with preterm birth in this study, this is an area that deserves further research. Traumatic, chronic stressors are known to induce a considerable physiological response based on the body's fundamental need to maintain homeostasis [166, 182, 183]. When the duration of exposure to or levels of stress surpass an individual's normal threshold, poor health outcomes such as preterm birth may reasonably be expected to occur. In a 2016 prospective study of 2,303 pregnant women recruited from 137 clinical practices in Connecticut and Massachusetts, Smith *et al* administered the Early Trauma Inventory Self Report Short Form to participants. In addition to the high risk of high blood pressure during pregnancy, for each additional early trauma reported, gestational age decreased by 0.063 gestational weeks and gestational weight decreased by 0.042 grams [183].

Though maternal race was not significantly associated with preterm birth in the final model developed in this study, racial disparities in preterm birth are a persistent public health problem in the United States [60]. Preterm birth data from 2018 to 2020 reported by the March of Dimes show that Black women had the highest average percentage of live births that were preterm (14.2%) followed by American Indian/Alaska Native women (11.6%); White women (9.2%) and Asian/Pacific Islander women (8.8%) [59]. The definitive causes of racial disparities in preterm birth are not exactly known, but many proposed social and medical factors provide biologically plausible explanations [60, 184, 185]. Addressing implicit bias among healthcare providers is one strategy being employed to improve the healthcare experiences of Black, Indigenous, and other people of color, which could lead to better pre-conception health among women of reproductive age as well as completion of more prenatal care visits and better management of risks for preterm birth [60, 184, 185].

2.5.1 Strengths and Limitations

This is one of the first studies that has investigated predictors of preterm birth in North Dakota. It is also one of a few studies within a growing body of work exploring the association between childhood adversity and poor maternal outcomes. With response rates ranging from 59.1% to 70.2% for the three years of data utilized for this study, we are confident in the generalizability of our findings to women in North Dakota, including those who live in rural areas and/or identify as Native American. Another key strength of the study was the utilization of clinically reported data for the outcome of interest (gestational age at delivery) which minimizes self-reporting bias. Other PRAMS elements, such as the ACEs module, are self-reported during

the post-partum period, hence some self-reporting and/or recall bias is to be expected. Additionally, the birth certificate information and the PRAMS dataset do not encompass all known predictors. For example, clinical-level questions on known mechanical risk factors, such as amniocentesis procedures and placental complications, are not included in the PRAMS survey or birth certificate. Thus, this analysis was limited to the available population-level variables. These limitations notwithstanding, the findings of this study are important in guiding future studies and public health efforts to address preterm birth.

2.5.2 Conclusions

Several maternal and medical risk factors identified in this study and others continue to be a challenge in reducing the odds of severe neonatal morbidity and mortality associated with prematurity, hence this remains a research area worth revisiting. Given the notable trend of delayed childbearing, especially in developed countries, prevention strategies aimed at reducing medical comorbidities that appear to be strongly associated with age should be considered a priority. A notable factor that was associated with lower odds of preterm birth was larger numbers of prenatal visits. Healthcare providers play a critical role in managing conditions such as hypertension and multiple gestation, hence for women at potential risk, encouraging early initiation and adherence to prenatal care continues to be a priority.

2.6 Availability of data and materials

Data were provided by the North Dakota PRAMS, a project of the North Dakota Department of Health, and the CDC of the U.S. Health and Human Services Department. This

report does not represent the official views of the CDC or of the North Dakota Department of Health.

CHAPTER 3

3.0 Investigation of Predictors of Newborn Screening Refusal in a Large Birth Cohort in North Dakota, USA

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Running Head: Predictors of Postpartum Depression in North Dakota

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My contributions to this paper included literature review, study design, data acquisition and management, analysis, interpretation

3.1 Abstract

The objective of this study was to identify maternal and provider predictors of newborn screening (NBS) refusal in North Dakota between 2011 and 2014. Records of 40,440 live resident births occurring in North Dakota between 2011 and 2014 were obtained from the North Dakota Department of Health and included in the study. Factor-specific percentages of NBS refusals and 95% confidence intervals were computed for each predictor. Since the outcome is rare, multivariable Firth logistic regression was used to investigate maternal and provider predictors of NBS refusal. Model goodness-of-fit test was evaluated using the Hosmer–Lemeshow test. All analyses were conducted in SAS 9.4. Of the 40,440 live births, 135 (0.33%) were NBS refusals. 97% of the refusals were to white women, 94% were homebirths, and 93% utilized state non-credentialed birth attendants. The odds of NBS refusals were significantly higher among non-credentialed birth attendants ($p < 0.0001$), homebirths ($p < 0.0001$), and among those that refused Hepatitis B vaccination (HBV) at birth ($p = 0.047$). On the other hand, odds of NBS refusals were significantly ($p < 0.0001$) lower among women that had more prenatal visits. This study provides preliminary evidence of association between NBS refusal and provider type, home births, and HBV refusal. Additional studies of obstetric providers, home births and women are needed to improve our understanding of the reasons for NBS refusal to better deliver preventive services to newborns.

Significance: *What is already known on this subject?* Although newborn screening (NBS) tests enhance early identification of newborns with potentially fatal and/or debilitating disorders, North Dakota state law allows parents to refuse NBS for any reason. While most studies on parental refusal of preventive services have focused on childhood vaccinations, little is known on

parental refusal of preventive services during infancy. *What this study adds?* North Dakota NBS and Vital Records data were utilized to identify maternal and provider predictors of NBS refusal. Study findings reveal that homebirths, refusal of Hepatitis B vaccine and non-credentialed providers were associated with NBS refusal.

3.3 Background

Newborn screening (NBS) refers to tests conducted on newborns for early detection of potentially fatal and/or debilitating disorders that can be identified through a few blood drops collected within a few days of life. With over 4 million newborns screened for congenital disorders each year in the United States (US), NBS remains the largest genetic screening program in the country [83]. Since the inception of the first screening test for Phenylketonuria (PKU) in the early 1960s, NBS has expanded to incorporate the screening for dozens of conditions, including but not limited to: amino acid disorders, fatty acid oxidation disorders, and endocrine disorders. As a result, over 6000 infants with genetic and/or metabolic disorders are detected through NBS tests each year. These screenings allow for timely confirmatory diagnoses, referral, and treatment to avoid severe diseases or death [7, 75, 78]. In the United States, NBS is state-administered, with individual states taking ultimate responsibility in determining disorders to screen for, standards of practice, and the informed consent process on whether parents can opt-in or opt-out of NBS [73, 75]Some states, such as Alaska and Hawaii, allow refusal of NBS services only for religious reasons; while others like North Dakota (ND) and Minnesota allow parents to refuse NBS for any reason [91]. In ND, under ND Century Code (NDCC) § 25-17-02, parents who choose to refuse NBS are provided educational information on NBS by the

attending care provider present at birth. The attending providers are required to submit a signed refusal form to the ND NBS Program [90, 92, 186]. Despite the well-established clinical efficacy of NBS [14, 187], the rate of parental refusal of NBS in ND has continued to rise. Given the important interaction that pregnant women have with their obstetric providers prior to, during, and after pregnancy, obstetric providers may play a critical role regarding how new mothers approach preventive measures, such as NBS [76, 188, 189]. With these issues in mind, the objective of this study was to identify maternal and provider predictors of NBS refusal.

3.3 Methods

3.3.1 Study Area

The study area included all 53 counties of ND which had a population ranging from 685,476 to 739,904 between 2011 and 2014, thereby remaining the fastest growing state in the nation. The racial distribution of ND is 87.9% White, 5.5% American Indian/Native American and 6.6% all other races. Approximately 3.6% of the residents are of Hispanic ethnicity [190, 191] . The study population included the cohort of live births occurring among ND residents between 2011 and 2014.

3.3.2 Conceptual Model for the Potential Predictors NBS

Predictors of NBS refusal are not well understood, therefore, our conceptual model showing the potential predictors of NBS refusal that guided our epidemiological/statistical modelling is shown in Figure 3.1. This model is based on parental refusal literature, specifically, immunization refusal studies which have largely shown that parental vaccine refusal in the US is

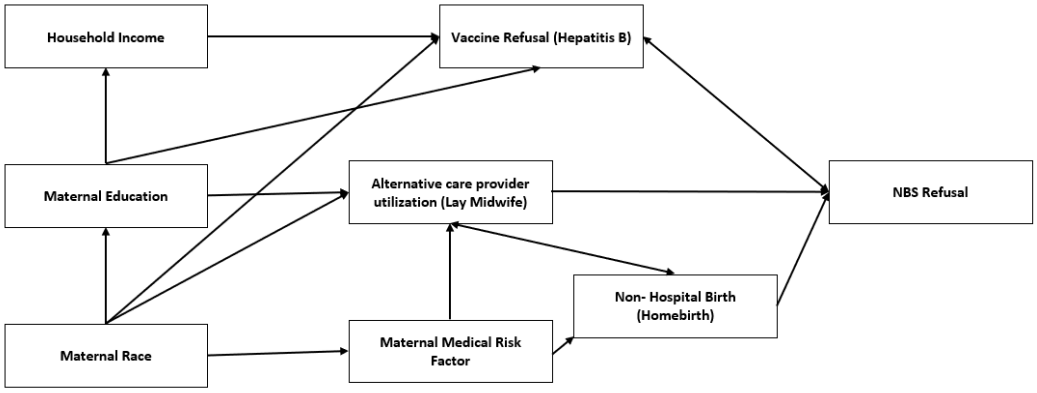

Figure 3.1: Proposed conceptual model showing predictors of newborn screening refusal in North Dakota.

associated with higher income and educational levels, parental race, and regular use of alternative providers (such as chiropractors and naturopaths) [16, 192-197]. Other maternal characteristics included in the conceptual model were maternal medical risk factors that have been identified by other studies as part of the criteria used by alternate obstetric providers, specifically midwives, in selecting low-risk clients for home or out-of-hospital births [198]. Hepatitis B vaccination (HBV) at birth was included in the conceptual model because it was hypothesized that women who refuse preventive care like HBV for their infants would be more likely to refuse other preventive procedures like NBS compared to those who did not refuse the vaccine.

3.3.3 Data Sources and Management

NBS and birth certificate data were obtained for all births and NBS refusals occurring between 2011 and 2014 from the NDDoH. NBS refusal was defined as an infant whose parent or guardian had a written NBS refusal form signed and returned to the ND NBS Program.

3.3.3.1 Predictor Data

Data on potential predictors of NBS refusal were obtained from the birth certificate database. The variables extracted from this database included the maternal and infant health related predictors presented in Table 3.1. Maternal socio-economic predictors such as maternal race, education, insurance status, and marital status were also obtained from the birth certificate database. Information on birth attendant credentialing was also obtained from the birth certificate database and assigned to two distinct categories. The first category consisted of birth attendants

Table 3.1. Demographic characteristics, by NBS status, of mothers of babies born in North Dakota between 2011 and 2014

Characteristic	NBS* refused	Percent	95% CI**	Non-refusal	Percent	95% CI**	Significant association
ND-born resident births (all)	135	0.33	(0.28, 0.39)	40,305	99.67	(99.61, 99.72)	
Provider type							
Non-ND credentialed	126	93.28	(88.97, 98.09)	91	0.44	(0.18, 0.27)	< 0.001
ND-credentialed	8	5.97	(1.91, 10.03)	40,129	99.56	(99.50, 99.63)	
Other/missing	**1**	0.75		85			
Place of birth							
Hospital/clinic	8	5.93	(1.89, 9.96)	40,003	99.33	(99.26, 99.41)	
Home birth	127	94.07	(90.04, 98.11)	268	0.67	(0.59, 0.74)	< 0.001
Socio-demographic factorsMaternal race							
White	114	96.61	(93.30, 99.92)	33,385	85.28	(84.93, 85.63)	< 0.0001
Black/African American	***	***	(***,**)	1198	3.06	(2.89, 3.23)	
American Indian	***	***	(***,***)	3774	9.64	(9.35, 9.93)	
Asian/NH/PI	***	***	(***,***)	791	2.02	(1.88, 2.16)	
Missing	**17**			1157			
Maternal age groups							
<35	113	83.70	(77.39, 90.01)	36,273	90.00	(89.70, 90.29)	
>35	22	16.29	(9.99, 22.61)	4032	10.00	(9.71, 10.29)	0.01
Marital status							
In Wedlock	118	87.41	(81.74, 93.08)	27,154	67.15	(66.93, 67.85)	
Out of Wedlock	17	12.59	(6.92, 18.26)	13,136	32.48	(32.14, 33.06)	< 0.001
Maternal education							
< Associate degree	84	69.42	(61.09, 77.75)	20,528	51.423	(50.94, 51.92)	< 0.0001
≥ Associate degree	37	30.48	(22.25, 38.91)	19,383	48.57	(48.08, 49.06)	
Missing	14			394			
Maternal WIC enrollment							
Yes	5	4.07	(0.53, 7.60)	10,678	27.49	(27.04, 27.92)	
No	118	95.94	(92.40, 99.47)	28,172	72.51	(72.07, 72.96)	
Missing	12			1455			
Payer/insurance status							
Third party payor	9	8.04	(2.92, 13.14)	25,099	62.18	(61.92, 62.86)	
Self-pay	103	76.30	(69.03, 83.56)	976	6.90	(6.65, 7.14)	< 0.0001
Other	23	17.04	(10.61, 23.46)	2776	2.42	(2.28, 2.58)	
Missing	0			77			
Maternal and infant medical risk factors	6.05		(5.61, 6.48)	10.67		(10.64, 10.71)	< 0.0001
Median number of prenatal visits							
Infant breastfed at birth							
Yes	134	99.26	(97.79, 100.00)	30,757	79.86	(79.46, 80.26)	< 0.0001
No	***	***	***	7758	20.14	(19.74, 20.54)	
Hepatitis B vaccine refusal							
Yes	80	59.26	(50.86, 67.65)	2900	7.20	(6.94, 7.44)	< 0.0001
No	55	40.74	(32.35, 49.14)	37,405	92.8	(92.55, 93.06)	
Precipitous delivery							
Yes	11	8.15	(3.53, 12.76)	959	2.38	(2.23, 2.53)	< 0.0001
No	124	91.85	(87.24, 96.47)	39,346	97.60	(97.5, 97.8)	

Table 3.1 Continued

Characteristic	NBS* refused	Percent	95% CI**	Non-refusal	Percent	95% CI**	Significant association
Previous C-section							
Yes	5	3.70	(0.48, 6.93)	5359	13.25	(12.96, 13.63)	
No	130	96.30	(93.07, 99.52)	34,946	86.70	(86.37, 87.03)	0.003
Maternal tobacco use							
Yes	***	***	(***,***)	4791	11.89	(11.57, 12.20)	
No	132	97.78	(95.26, 100.00)	35,514	88.11	(87.80, 88.43)	0.003

*Newborn screening

**95% confidence intervals

***Censored cases (i.e. cells with < 5 subjects)

who were licensed and overseen by a professional board in ND [186, 199] . This category included birth attendants who self-reported as medical doctors (MD), Doctor of Osteopathic Medicine (DO), or certified nurse midwives (CNM). The second category consisted of providers who identified themselves as an "other midwife" or "lay midwife". "certified professional midwives" (CPM) were also included in the non-credentialed category since they are not recognized or overseenby either the board of nursing or board of medicine in ND [186, 199]. Registered and licensed provider names are publicly available in ND through the ND Board of Medicine and Board of Nursing websites. Therefore, missing credential information in the birth records were cross-referenced with the two licensing boards' websites to complete any missing provider credential information. The NBS Program also maintains a log of known lay midwives in the state. This was used to complete missing information on lay midwives. These combined efforts of identifying providers through the birth certificate database, the NBS lay midwives' log and the ND Boards of Nursing and Medicine, resulted in the correct classificationof over 98% of all the births and the corresponding credential status of their birth attendants. Information on household income is not collected on the NDbirth certificate. However, NDDoH collects informationon women who participate in the public benefit programfor low-income families called "Women, Infants and Children (WIC) Program" (North Dakota Department of Health, 2016). Therefore, participation in the WIC program, was used as a proxy indicator of low household income. A binaryvariable indicating low household income (yes/no) was created based on participation in the WIC program. Women participating in the WIC program in ND also receive maternal education and counselling sessions on maternal and childhealth issues. Therefore,

these variables along with maternal race, were considered as potential confounders and included in subsequent analyses.

3.3.4 Statistical Analyses

3.3.4.1 Descriptive Statistics

Data were analyzed using SAS 9.4. Percentages and 95% confidence intervals were calculated for all categorical variables. Tests for normality (Kolmogorov–Smirnov) were conducted on the continuous variable, number of prenatal visits. Median and interquartile ranges were calculated for the two continuous variables since they were non-normally distributed.

3.3.4.2 Logistic Regression Model

Given the limited body of literature specific to NBS refusal, and utilizing the conceptual model shown in Figure 3.1, modelbuilding process was initiated by first assessing simple associations between predictor variables and NBS refusal using univariable Firth logistic regression models. All potential predictor variables that had univariable associations at an alpha-level of 0.10 level were considered for inclusion in the multivariable Firth logistic model which was then fit to the data using backwards elimination procedure. Firth logistic models were chosen for these data because the maximum likelihood estimation of the usual/ordinary logistic regression suffers from small-sample bias. Since there were small sample sizes associated with NBS, the Firth logistic regression provides better estimates than the usual/ordinary logistic regression models for these data [200].The advantage of the Firth model is that it uses penalized likelihood to reduce small-sample bias in maximum likelihood estimation [201]. In case of logistic regression, penalized likelihood also has the advantage of producing finite, consistent estimates of regression

parameters in situations when maximum likelihood estimates do not exist due to complete or quasi-complete separation [201, 202].Confounding was assessed by examining whether the removal of a variable from the model resulted in a change of > 20% in the coefficients of any of the other variables already in the model. Two-way interaction term between home births and provider type was assessed for significance in the final model. Hosmer–Lemeshow test was used to assess goodness-of-fit of the final model.

3.4 Results

3.4.1 Descriptive Analyses

Births eligible to participate in this study ranged from a low of 9211 in 2011, to a high of 11,005 in 2014, for a total of 40,440 births over the study period. The number of cases of NBS refusals ranged from a low of 23 in 2011 to a high of 47 in 2014, representing an over 100% increase in the count of cases of NBS refusal. The risk of NBS refusal over the same time period ranged from a low of 2.5 per 1000 live births in 2011 to a high of 4.3 per 1000 live births in 2014. As shown in Table 3.1, 0.33% (135/40,440) newborns had an NBS filed with the NDDoH. 93% of all NBS refusals were from women utilizing non-credentialed birth attendants compared to only 0.44% of non-credentialed providers among those who did not refuse NBS. Moreover, 94% of NBS refusals were associated with births occurring at home, compared to 0.7% of births occurring at home among those that did not refuse NBS. Note worth is the 157 homebirths attended by credentialed providers, none of which were NBS refusals. Approximately 97% of NBS refusals were to white women and, as expected from the racial distribution in ND, they also represented the majority in the non-refusal category at 85.2%. Interestingly, while about 90% of

births among those accepting NBS were paid for by a third-party payer, 76.3% of the NBS refusals paid for their delivery out of pocket. Additionally, 59.3% of NBS refusals also refused HBV compared to only 7.2% among those not refusing NBS.

3.4.2 Firth Logistic Model Results

The effective analytic sample size used in the Multivariable Firth logistic regression was 37,559 new births, 121 of which were NBS refusals. Thus, the final Firth model used 93% (37,559/40,440) of all live births in the registry and 90% (121/135) of NBS refusal cases in the registry. Thus, the proportion of missing data is relatively small and is not expected to adversely affect study findings. Moreover, none of the categorical variables included in the final model had cell sizes < 5. Based on the findings from the multiple Firth logistic model, deliveries attended by non-credentialed birth attendants had significantly higher odds of NBS refusal compared to those attended by a credentialed provider ($p < 0.0001$) . Deliveries occurring at home also had significantly higher odds of NBS refusal compared to those occurring at birthing facilities ($p < 0.0001$). Infants who had recorded Hepatitis B vaccine refusals had significantly higher odds of NBS refusal, compared to those that did not ($p = 0.047$). The odds of NBS refusal were significantly ($p = 0.02$) higher among infants born to women participating in WIC compared to those not participating in WIC. Babies born to women who had more prenatal visits had significantly ($p < 0.0001$) lower odds of NBS refusal than those with fewer visits. Interestingly, although both non-credentialed providers ($p < 0.0001$) and homebirths ($p < 0.0001$) were significantly associated with higher odds of NBS refusal, no significant interaction between provider type and homebirths was observed indicating that the two variables work through

different biological pathways in affecting NBS refusals. The Hosmer–Lemeshow goodness-of-fit test indicated that the model fit the data well ($\chi 2 = 4.23$; $p = 0.84$).

3.5 Discussion, Strengths & Limitations

This study investigated predictors of NBS refusal and is the first of its kind to focus on maternal and provider determinants of NBS refusal and hence a scarcity of studies with which to compare the findings of our study. The rate of NBS refusal in ND was 0.33%, which is comparable to the 0.22% refusal rate of vitamin K prophylaxis in newborns, observed in Canada [16]. In our study, NBS refusal was higher among those utilizing non-credentialed providers and those that had homebirths. The fact that homebirths and provider type were both statistically significant in the final model suggests both are independent predictors of NBS refusal. Thus, the association between provider type and NBS refusal is not due to confounding by homebirths because if that was the case, there would be no significant association between provider type and NBS after controlling for homebirths in the model. If all the effects of provider type on NBS refusal was mediated through homebirths, then we would expect provider type to not have a significant association with NBS refusal when home birth is added to the model. However, in our case both were significant in the final model implying that provider type has an independent association with NBS refusal (independent of home births). Additionally, since the interaction between homebirths and provider type was non-significant it implies the predictors do not modify the effect of each other (Table 3.2). The association between NBS refusal and parental refusal of HBV is consistent with report from other studies evaluating the predictors of parental refusal of preventive services, such as, vitamin K prophylaxis, which have found that nonhospital births and those utilizing midwives had higher risk of vitamin K refusal [16, 193, 203].

Table 3.2: Results of Firth logistic regression model assessing predictors of newborn screening refusal in North Dakota, 2011–2014

Prediction	Coefficient estimate	95% Confidence Interval	$\chi 2$	*p*-value
Intercept	-2.5	-3.3 to -1.7	36.1	<0.0001
Non-credentialed provided (Lay midwife)				
Yes	2.4	1.8 – 3.0	64.8	<0.0001
No	-		-	-
Home Births				
Yes	1.6	1.0-2.2	26.3	<0.0001
No	-		-	-
Participated in Women, Infants and Children program				
Yes	0.7	0.1 – 1.3	5.7	0.017
No	-		-	-
Number of prenatal visits	-0.3	-0.4 to -1.2	35.8	<0.0001
Hepatitis B Vaccine refusal				
Yes	0.3	0.004 – 0.6	3.9	0.047
No	-		-	-

* $\chi 2$ – Chi Square

In their 2016 study on reasons for parental refusal of newborn vitamin K prophylaxis, for example, Hamrick, and others, reported that out-of-hospital births (birthing centers) had higher incidence of vitamin K refusal compared to those who had hospital deliveries [203]. They also reported that parents who refused vitamin K were also more likely to refuse other prophylactic treatments such as Hepatitis B vaccine and erythromycin eye ointment for their newborns compared to those that did not refuse vitamin K. A key difference between our study and the one by Hamrick and co-workers was that birthing centers included in the latter investigation were staffed by only state-licensed practitioners (either certified nurse midwives or nurse practitioners). Sahni and others, in their 2014 study, also examined parental vitamin K prophylaxis refusal and reported that midwife deliveries had over eight-times [risk ratio (RR)=8.4, 95% confidence interval (CI) 6.5–11.0] higher risk of vitamin K refusal compared to non-midwife deliveries. They also reported that home births had almost five-times (RR=4.9, 95% CI 3.8–6.4) higher risk of vitamin K refusal than nonhome births [16]. Given that non-credentialed providers in ND can only offer their services to women who choose to deliver at home, it is important to identify unique characteristics that lead women to choose homebirths. Boucher et al. investigated why women in the US deliver at home. The majority of respondents in their study were white women (87%) and most were married (91%). Additionally, 24% cited that the "desire to avoid medical interventions, routine procedures, and interferences" were their main criteria for choosing homebirth [204]. This implies that women choosing homebirths are likely to refuse medical interventions (e.g., NBS) and are likely to seek providers likely to accommodate these preferences. In this study, women refusing NBS were generally healthier during their pregnancies than those who accepted NBS, as evidenced by the lower percentages of

maternal health related risk factors, including smoking status, and histories of previous poor outcomes compared to those who did not refuse NBS. Those refusing NBS also had fewer prenatal visits, and were more likely to utilize non-credentialed birth attendants compared to those who did not refuse NBS. These findings are consistent with findings from other studies that reported that midwives tend to select homebirth clients who have low medical risks [198]. This study found lower odds of NBS refusal among women who had more prenatal visits indicating the importance of following the recommendations of the American College of Obstetricians and Gynecologists on providing educational information to pregnant women on NBS during multiple prenatal visits [76, 188]. Given that the disorders screened for through NBS have the potential to cause severe morbidity and/or mortality, NBS refusal poses a unique challenge. New born screening is a multi-factorial process that can impose barriers to parents and providers alike [74, 75, 80, 83]. The process starts with the "education of parents and professionals; screening, which includes specimen collection, submission, and testing; follow-up of abnormal and unsatisfactory test results; confirmatory testing and diagnosis; medical management and periodic evaluation; and system quality assurance" [74, 75, 80, 83]. Future studies and efforts in NBS program planning should attempt to identify areas of improvement through each step, in order to encourage parents and providers alike to promote and accept NBS. Additionally, while NBS may not face safety concerns, storage of genetic material through the dried blood spot by state entities has raised ethical concerns for NBS programs. Most states, including ND, offer parents and legal guardians the option of retaining the dried bloodspot card after the screening has been conducted [84, 91, 92].Therefore, it is imperative for obstetric providers to fully inform new parents on all their options prior to and after NBS to alleviate these concerns and potentially minimize refusals.

3.5.1 Strengths

This study is the first of its kind to link NBS and birth certificate data in the U.S., and utilize this information to identify maternal and provider predictors of NBS refusal. Moreover, the ability to distinguish and include home births in this analysis was a key strength compared to recent similar studies, such as the vitamin K refusal study by Sahni and others, which attempted to study parental refusal issues, and cited this as a limitation [16] . Additionally, ND birth certificate data utilizes both self-reported variables, and variables extracted directly from maternal medical records by a medical certifier, hence minimizing self-reporting bias in the medical risk factor data. Furthermore, as demonstrated by Shoendorf and others, in their evaluation of vital statistics data to study perinatal health, use of these data is effective in minimalizing selection bias of samples and allows for study results that are representative of the birth population of interest [205].

3.5.2 Limitations

Since this was a retrospective study using secondary data, the predictors that could be investigated were limited to those available in the databases. Moreover, certain predictor were self-reported and hence prone underreporting bias. Additionally, some births may occur partially at home and completed at a hospital. Missing data in key variables was another study weakness. However, the proportion of missing data was relatively small and hence is not expected to adversely affect study findings. The fact that NBS refusal is a rare event also presented modeling challenges of small-sample bias. However, this was addressed using Firth logistic model that

reduces small-sample bias. The small sample sizes may also affect the precision of the estimates. Thus, while this study is quite novel the findings should be interpreted with caution and further investigations are warranted to help strengthen the evidence. Lastly although the Health Department requires NBS refusal forms to be completed, there is no active tracking process for ensuring that parents that refuse NBS actually return the forms. These limitations notwithstanding, the findings of this study provide very useful information to guide future studies to help improve our understanding of the problem and hence improve provision of preventive services for newborns.

3.5.3 Conclusions

The results of this study have been successful in providing preliminary evidence of the association between NBS refusals and both homebirths and provider type. Since NBS refusal has the potential to increase the chances of an infant's disorder being diagnosed late potentially resulting in complications or death, it is an area worth serious attention. Future studies will need to identify sub-populations that may have higher rates of NBS refusal and explore patient and provider perspectives regarding NBS. They will also need to identify ways of addressing the problem in these populations.

3.6 Compliance with Ethical Standards & Acknowledgements

Conflict of interest: The authors declare that they have no conflicts of interest. Ethical approval This study was reviewed and approved as exempt by both the ND Department of Health (NDDoH) (Approval Number: ND-014-42016) and the University of Tennessee,

Knoxville Institutional Review Boards (IRB) (Approval Number: UTK IRB-17- 04027-XM). Thus, the study has been performed in accordance with ethical standards laid down in the 1964 Helsinki Declaration and its later amendments. No identifying information was available in study data and all results are presented in aggregated form to ensure study subjects cannot be identified.

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CHAPTER 4

4.0 Predictors of Postpartum Depression among North Dakota Women

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Running Head: Predictors of Postpartum Depression in North Dakota

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4.1 Abstract

Postpartum depression (PPD) affects 13.2% of postpartum women in the United States. The United States Preventative Services Task Force identified it as one of the emerging public health burdens with significant gaps in knowledge and that warrant further surveillance. Not much is known about its medical and socioeconomic risk factors in North Dakota (ND) and yet this is useful information for health programs and policy. Therefore, this study investigated predictors of PPD among women that had live births in ND.

Data from the 2017-2019 ND Pregnancy Risk Assessment Monitoring System (PRAMS) were used for the study. Since the PRAMS data are based on a complex survey, all analyses involved specification of both strata and sampling weight variables. Therefore, weighted crude and factor-specific prevalence proportions of PPD and 95% confidence intervals (CI) were computed. A conceptual model and survey logistic regression were used to investigate and identify predictors of PPD. Adjusted odds ratios (AOR) and their 95% CI were computed for all identified significant predictors of PPD.

There were 3,763 reported cases of PPD in North Dakota during the study period, representing 12.5% of all births. Women with unintended pregnancies had significantly ($p < 0.0001$) higher prevalence of PPD (17%) than those that did not (9%). The prevalence of PPD was significantly ($p < 0.0001$) higher among women who reported adverse childhood experiences (ACE) score ≥ 4 (20.4%), compared to those with ACE < 4 (10.7%). The odds of PPD among American Indian women was double (AOR = 2.0; 95% CI[1.4, 2.8]) that of White women, while the odds among women of all other races were nearly 3 times (AOR = 2.7; 95% CI [1.4, 5.1]) those of White women. Women that had unintended pregnancies had 1.7 times

higher odds of PPD (AOR = 1.7; 95% CI [1.2, 2.6]) than those who had intended pregnancies. Women with an ACE score ≥ 4 had nearly double the odds of PPD (AOR = 1.8; 95% CI [1.2, 2.6]) of those with ACE score < 4. Finally, the odds of PPD among women with history of depression were almost four times (AOR = 3.9; 95% CI [2.5, 5.9]) those of women with no history of depression.

The identified predictors of PPD offer useful insight into the epidemiology of the condition in North Dakota. Given the persistence of PPD as a public health challenge, prevention strategies aimed at reducing its burden should be considered a priority. Health programs and policies that allow women to plan pregnancies and to access behavioral health services prior to, during, and after pregnancy will remain invaluable in mitigating PPD.

4.2 Background

Globally, postpartum depression (PPD) affects approximately 10-15% of postpartum women annually, with depressive symptoms lasting more than 6 months in approximately 25% of the cases [99]. Postpartum depression can occur within days and up to a year after giving birth. However, cases of PPD lasting up to four years post-delivery have been reported [99]. Estimating the true prevalence of the problem remains challenging due to limited screening by providers and underreporting by women [114] who are reluctant to disclose feelings of depression for fear of stigmatization and that they might be considered “bad parents” [113]. Often, the symptoms of PPD are minimized by both the patient and health care provider and considered to be a normal result of childbirth [115].

Untreated postpartum depression has been shown to have significant detrimental impacts on both women and children. Studies have shown that postpartum depression is associated with lower breastfeeding initiation rates, poor bonding with the infant, behavioral disorders in children, and in extreme cases, maternal suicidal ideation [97, 103, 117]. Most concerning is the fact that suicide, which is most commonly preceded by severe depression [206], is associated with approximately 20% of all postpartum deaths in the United States [97, 207, 208].

In 2019, the United States Preventative Services Task Force (USPTF) identified PPD as one of the emerging public health burdens with significant gaps in knowledge and that warrant further surveillance [103]. The severity of poor outcomes to both the women and children [99, 103, 177, 209-211] led the USPTF to recommend the prioritization of the identification of at-risk populations, investigation of modifiable risk factors among women at high risk of PPD, and the evaluation of modes of healthcare delivery and evidence-based interventions to improve outcomes.

For rural states, such as North Dakota, where data and mental healthcare providers are scarce, prevention, early detection through surveillance efforts, and early intervention to minimize the impacts of PPD are critical [181]. Unfortunately, most previous studies of PPD have been conducted in clinical settings and yet population-level studies that allow for anonymous self-reporting of PPD are invaluable for determining the burden of the problem and identification of its risk factors [100, 101, 108]. The information obtained from such population-level studies are critically important for guiding not only future research but also targeted surveillance efforts as well as allocation of resources for prevention, control, and treatment of PPD. Therefore, the objective of this study was to investigate and identify predictors of PPD

among North Dakota women in order to inform public health programs geared towards curbing the problem.

4.3 Methods

4.3.1 Ethics Approval

This study was reviewed and approved by the North Dakota Department of Health (NDDoH) Institutional Review Board (IRB) and the University of Tennessee IRB (IRB Number: UTK IRB-21-06599-XM).

4.3.2 Study Area

All 53 counties of North Dakota, which had a population of 762,062 in 2019, were included in the study. North Dakota's racial composition in 2019 was 87.0% White, 5.5% American Indian/Native American, and 7.5% all other races [158]. Approximately 4% of the residents were of Hispanic ethnicity. The median household income in North Dakota during the study period ranged from $61,843 in 2017 to $64, 894 in 2019 [158, 159]. The study population included the cohort of live births (30,565 total births) occurring among North Dakota residents from 2017 to 2019 based on weighted responses to the North Dakota Pregnancy Risk Assessment Monitoring System (ND PRAMS).

4.3.3 Data Sources & Management

Data for this study were obtained from the ND PRAMS, a population-based surveillance system designed by the Centers for Disease Control and Prevention (CDC) in collaboration with

the North Dakota Department of Health [155]. The ND PRAMS Program conducts surveillance on maternal attitudes, behaviors, experiences, and outcomes. Survey questions are used to collect data focusing on critical time periods preceding pregnancy, during pregnancy and in the postpartum period, which are known to affect perinatal outcomes. Since 2017, North Dakota has employed the standard PRAMS data collection methodology, described in detail elsewhere [155, 162]. Briefly, a stratified random sample of women identified in the birth certificate dataset is invited to participate in the survey. In the North Dakota PRAMS, approximately 14.8% of the women that had live births were sampled between 2017 and 2019. The North Dakota PRAMS' response rate was 70.2% in 2017, 59.9% in 2018, and 59.1% in 2019 [155, 162]. These response rates were well above the 55% threshold for a weighted countrywide representative sample [155].

The North Dakota PRAMS questionnaire covers an array of topics on maternal behaviors and experiences. It includes questions on smoking, body mass index, substance abuse, childhood adversity, prenatal care and other healthcare provider access, insurance status, and information covered by healthcare providers during healthcare visits. The questionnaire also contains questions on healthcare outcomes, such as, postpartum depression, hypertension, and diabetes [162].

4.3.3.1 Outcome Variable, Post-partum Depression

Postpartum depression was defined based on responses to two questions: "Since your baby was born, how often have you felt down, depressed, or hopeless?" and "Since your new baby was born, how often have you had little interest or little pleasure in doing things?" Women

who responded that they “often” or “always” experienced these symptoms to at least one of these questions were classified as experiencing symptoms of PPD. Those who responded “sometimes” “rarely” or “never” to both of these questions were classified as not having PPD [100, 160].

4.3.3.2 Potential Predictors of Postpartum Depression

Potential predictors of postpartum depression investigated included: maternal race (American Indian, White, and all other races), maternal age (<20, 20-34 and 35+ years old), insurance status used to pay for birthing expenses (Medicaid vs non-Medicaid), maternal education (associate degree and above vs less than an associate degree), annual household income during the year preceding the pregnancy (<$24,000, $24,001-$40,000, $40,001 to $60,000 and >$60,000), pregnancy intention (unintended pregnancy vs intended pregnancy), and married (Yes/No). Women reporting any form of diabetes during pregnancy, including pre-existing Type 1 or Type 2 diabetes, and gestational diabetes, were categorized accordingly (Yes/No). Other maternal characteristics assessed included first trimester smoking status, body mass index, self-reported history of depression, rurality of county of residence, and frequency of prenatal care visits (<9, 9-11, 12+). To calculate the cumulative ACE Score, responses (Yes = 1; No = 0) to the 10 questions in the Adverse Childhood Experiences Module of the ND PRAMS survey were summed (for a possible maximum total score of 10). Women with total score ≥ 4 were categorized as having a high ACE score otherwise they were categorized as having low score [161, 165, 166, 212, 213].

4.3.4 Statistical Analyses

4.3.4.1 Descriptive Statistics

Statistical analyses were performed in SAS 9.4 [169] and SPSS 25 [214]. The ND PRAMS dataset is based on a complex survey, hence all analyses involved specification of both the strata variable (STRATUMC) and the sampling weight variable (WTANAL). Weighted crude and factor-specific percentages of PPD and their 95% confidence intervals (95% CI) were computed for all categorical variables using PROC SURVEYFREQ in SAS. Bivariate correlations were assessed in SPSS 25 [214] with the Complex Survey Analysis Plan function using the strata variable STRATUMC and sampling weight variable WTANAL.

4.3.4.2 Predictors of Postpartum Depression among North Dakota Women with Live Births

The conceptual model used to guide the construction of the multivariable logistic regression model used to investigate predictors of PPD is shown in Figure 4.1. This investigation was initiated first, by the assessment of univariable associations between each of the potential predictors in Figure 4.1 and postpartum depression. PROC SURVEY LOGISTIC, specifying the strata variable (STRATUMC) and the sampling weight variable (WTANAL), were utilized in the univariable and multivariable analyses to adjust for the complex survey design. Two-way Spearman rank correlation analyses were performed on all potential predictor variables that had $p \leq 0.2$ in the univariable analyses. Only one of a pair of highly correlated variables ($r > 0.7$) were retained for further assessment in the subsequent multivariable model. The decision regarding which of a pair of highly correlated variables to retain for further investigation was based on biological and statistical considerations. All potential predictors that had p-values ≤

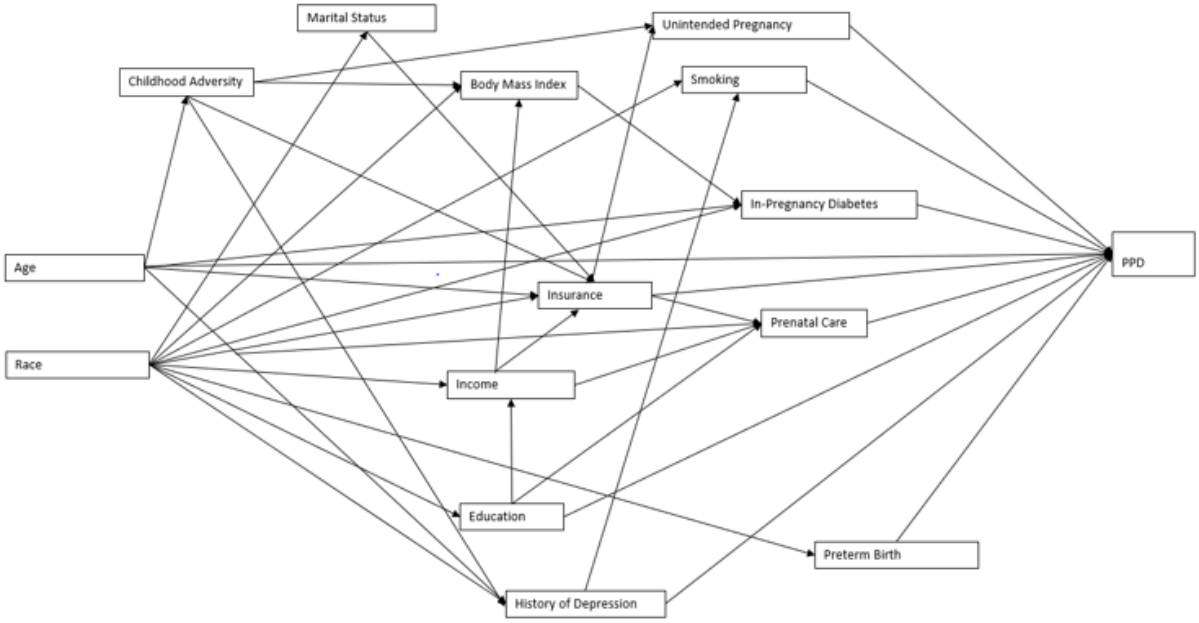

Figure 4.1: Conceptual model showing potential predictors of postpartum depression (PPD) among women in North Dakota, 2017-2019.

0.20 from the univariable model analyses and that were retained based on the correlation analyses were included in the multivariable logistic model building process using a manual backwards elimination approach. Only variables with *p*-values ≤ 0.05 were retained in the final main-effects multivariable model. Confounding variables were evaluated by observing the changes of parameter estimates of variables in the model before and after removal of a suspected confounding variable from the model. If the parameter estimates of any variable increased or decreased by ≥ 20% after removal of the suspected confounding variable from the model, then that variable would be considered an important confounder and retained in the model regardless of its *p*-value. Biologically plausible two-way interaction terms were also assessed. No confounders or interaction terms were identified. Odds ratios and their 95% confidence intervals were generated for all variables retained in the final model. F-adjusted mean residual was used to assess goodness-of-fit of the final model [215].

4.4 Results

4.4.1 Descriptive Statistics & Simple Associations

There were 3,763 reported cases of PPD in North Dakota between 2017 and 2019, representing 12.5% of all live births (Table 4.1). The prevalence of PPD was significantly ($p < 0.0001$) higher among minority women than their White counterparts. For instance, the prevalence was 21.2% among American Indian women and 22.0% among women of other races, while it was 10.1% among White women. With a prevalence of 21.4%, teenagers had significantly ($p = 0.049$) higher prevalence of PPD compared to women ages 20-34 (12.5%) and those over the age of 35 (10.4%). Women who had unintended pregnancies had a significantly (*p*

= < 0.0001) higher prevalence of PPD (17%) compared to those that had intended pregnancies (9%). The prevalence of PPD was significantly (p = < 0.0001) higher among women who had an ACE score ≥4 (20.4%) compared to those with ACE score < 4 (10.7%). Women reporting less than $24,000 annual household income reported significantly (p < 0.0001) higher prevalence of PPD (21.3%) compared to women reporting more than $60,000 household income (6.9%). Married women reported a significantly (p < 0.0001) lower prevalence of PPD (9.9%) compared to those who were not married (17.8%). Women who had ≤ 8 prenatal visits during their pregnancy had significantly (p = 0.0005) higher prevalence of PPD (18.5%) than those who had > 11 visits (8.9%). The prevalence of PPD was also significantly (p = 0.012) higher among women who reported smoking during their first trimester (18%) compared to those who did not (11%) (Table 4.1).

4.4.2 Predictors of Postpartum Depression among North Dakota Women with a Live Birth

A total of 12 potential predictors had univariable associations with PPD based on a relaxed alpha of 0.2 (Table 4.2). However, based on the final multivariable logistic model, there were only 4 statistically significant predictors based on an alpha of 0.05. These included maternal race, unintended pregnancy, ACE score and maternal history of depression (Table 4.3). The odds of PPD among American Indian women was 2 times (AOR = 2.0, 95% CI [1.4, 2.8]) that of White women while the odds among women of all other races were nearly 3 times (AOR = 2.7; 95% CI [1.4, 5.1]) those of White women. Women that had unintended pregnancies had 1.7 times higher odds of PPD (AOR = 1.7; 95% CI [1.2, 2.6]) than those who had intended pregnancies (Table 4.3).

Table 4.1: Selected Characteristics of Women with Post-partum Depression in North Dakota, 2017- 2019

Maternal Characteristic	PPD[1] Frequency	PPD Percent	Lower limit of the 95% CI[2]	Upper limit of the 95% CI[2]	*p*-Value
Births	3763	12.5	10.8	14.3	
Maternal Race					<0.0001
American Indian	548	21.2	18.2	24.2	
White	2399	10.1	8.2	12.0	
Other	815	22.0	15.0	29.0	
Maternal Age Groups					0.049
<20	229	21.4	10.1	32.7	
20-34	3134	12.5	10.6	14.4	
≥35	400	10.4	5.7	15.0	
Unintended Pregnancy					<0.0001
Yes	2070	17	13.9	20.2	
No	1585	9	7.0	11.0	
Maternal BMI[3]					0.0187
Underweight (<18.5)	85	23.6	0.5	46.8	
Normal Weight (18.5-24.9)	1027	8.9	6.4	11.4	
Overweight (25.0-29.9)	1362	16.1	12.4	19.8	
Obese (≥30)	1274	13.4	10.2	16.5	
History of Depression					<0.0001
Yes	1361	26.6	20.8	32.3	
No	2339	9.5	7.8	11.2	
ACE[4] Score					<0.0001
<4	2597	10.7	8.9	12.5	
≥4	1165	20.4	15.5	25.3	
In-Pregnancy Diabetes					0.06
Yes	481	18.2	10.6	25.8	
No	3210	11.8	10.0	13.6	
Insurance					<0.0001
Medicaid	1474	20.4	16.1	24.8	
Other	1949	10	8.0	12.0	
Education					<0.0001
College	950	6.4	4.6	8.1	
Less than College	2813	18.7	15.7	21.7	
Income					<0.0001
<$24,000	1749	21.3	17.2	25.5	
$24,001-$40,000	383	17.7	9.6	25.8	
$40,001-$60,000	344	2.6	6.0	15.8	
>$60,000	942	6.9	5.0	9.0	
Married					0.0001
Yes	1971	9.9	7.9	11.9	
No	1792	17.8	14.3	21.3	
Prenatal Care Visits	0.0005				
≤8	999	18.5	13.8	23.2	
9-11	1279	11.6	8.8	14.5	
>11	1112	8.9	6.6	11.3	
Preterm Birth					0.95
Yes	317	12.4	6.6	18.2	
No	3445	12.6	10.7	14.4	
Maternal Smoking During 1st Trimester					0.012
Yes	1182	18.0	13.7	22.3	
No	2556	11.0	9.1	12.1	

[1]Post-partum depression
[2]95% Confidence Interval (Lower and Upper Limits)
[3]BMI Body Mass Index
[4]Adverse Childhood Experiences

Table 4.2: Results of Univariable Assessments of the Associations of Postpartum Depression and Potential Predictors among Women with Live Births in North Dakota, 2017-2019

Maternal Characteristics	Un-adjusted OR	Lower limit of the 95% CI[1]	Upper limit of the 95% CI[1]	*p*-Value
Maternal Race				<0.0001
American Indian	2.4	1.8	3.2	0.018
Other	2.0	1.2	3.4	0.320
White (referent)				
Maternal Age				0.013
<20	2.2	1.1	4.4	0.014
≥35	0.8	0.5	1.4	0.06
20-34 (referent)				
Unintended Pregnancy				
Yes	2.2	1.6	3.1	<0.0001
No (referent)				
BMI[2]				0.0187
Underweight (<18.5)	4.0	1.1	14.9	0.111
Overweight (25.0-29.9)	1.9	1.2	3.0	0.852
Obese (≥30)	1.5	0.9	2.3	0.295
Normal Weight (18.5-24.9) (referent)				
History of Depression				
Yes	4.3	2.9	6.3	<0.0001
No (referent)				
ACE[3]				
≥4	2.4	1.7	3.5	<0.0001
<4 (referent)				
Insurance				
Medicaid	2.2	1.5	3.2	<0.0001
Other (referent)				
Income				0.0187
<$24,000	3.7	2.5	5.6	<0.0001
$24,001-$40,000	2.4	1.2	4.7	0.3421
$40,001-$60,000	1.4	0.7	2.6	0.1995
>$60,000 (referent)				
Education				
No College	3.6	2.5	5.3	<0.0001
College (referent)				
Married				
No	2.0	1.4	2.8	<0.0001
Yes (referent)				
Prenatal Care Visits				0.0005
<9 Visits	1.8	1.2	2.8	0.0002
>11	0.8	0.5	1.2	0.038
9-11 (referent)				
Maternal Smoking During 1st Trimester				<0.0001
Yes	2.0	1.4	2.9	
No (referent)				

Table 4.3: Results of the Final Model Showing Predictors of Postpartum Depression among Women with Live Births in North Dakota, 2017-2019

Maternal Characteristics	AOR	Lower Limit of the 95% CI[1]	Upper Limit of the 95% CI[1]	*p*-Value
Maternal Race				<0.0001
American Indian	2.0	1.4	2.8	
Other	2.7	1.4	5.1	
White (referent)				
Unintended Pregnancy				
Yes	1.7	1.2	2.6	0.0067
No (referent)				
ACE[2] Score				
≥4	1.8	1.2	2.6	0.0063
<4 (referent)				
History of Depression				
Yes	3.9	2.5	5.9	<0.0001
No (referent)				

[1]95% Confidence Interval
[2]Adverse Childhood Experiences

Women with ACE score ≥ 4 had nearly 2 times higher odds of PPD (AOR = 1.8; 95% CI [1.2, 2.6]) than those with ACE score < 4. Women with a history of depression during pregnancy had nearly 4 times higher odds of PPD (AOR: 3.9; 95% CI [2.5, 5.9]) than those with no history of depression. No significant interactions or important confounders were identified. There was no evidence that the final multivariable logistic model did not fit the data well (F-adjusted mean residual = 0.81; $p = 0.61$).

4.5 Discussion

This study identified predictors of PPD among North Dakota women who had live births between 2017 and 2019. This is the first study of its kind in North Dakota, and one of the few in the United States, with a representative cohort of American Indian women.

The findings of this study are consistent with those of other studies that reported significant associations between PPD and unintentional pregnancy, adverse childhood experiences, maternal race, and maternal history of depression [100, 108, 115-117, 164]. Low socioeconomic status (SES) was not a significant predictor of PPD in this study. These findings provide further insight for health programs aimed at reducing inequities and burden of PPD in North Dakota.

The current study found that women with unintended pregnancies had significantly higher odds of PPD compared to those with intended pregnancies. This is consistent with findings from other studies which reported that pregnancy intention was a significant predictor of PPD [99, 100, 115, 116, 216-218]. One such analysis of 688 women at 3 months postpartum, and 550 women at 12 months postpartum, by Mercier and others [177] found that risk of depression

was significantly higher among women with unintended pregnancies at both 3 months postpartum (risk ratio [RR] = 2.1; 95% CI [1.2, 3.6]), and at 12 months postpartum (RR = 3.6; 95% CI [1.8, 7.1]) [177]. The findings from the current study are also consistent with those of a meta-analysis conducted by Qiu and others which included a total of thirty studies involving 65,454 participants [219]. Qiu and co-workers reported that women with unintended pregnancies were at significantly higher odds of developing PPD (OR = 1.53; 95% CI [1.35, 1.74]; $p < 0.0001$) than those who had intended pregnancies. These findings and those of the current study are especially meaningful given that approximately half of all pregnancies in the United States and North Dakota are unintended [171]. These higher odds of PPD among those with unintended pregnancies present opportunities for providers to screen women for pregnancy intention and offer appropriate resources in the postpartum period to address this adverse outcome early in the postpartum period [220, 221].

The findings of the current study concur with a small but growing body of research that has investigated Adverse Childhood Experiences (ACEs) and their associations with PPD. One such analysis of 1,994 women by Racine and others, found that after adjusting for social support, maternal childhood adversity was a strong predictor of depression during pregnancy, and especially in the postpartum period, with odds of PPD ranging from 1.12 to 1.54 [210]. Similarly, Brody and others, in their study of exposure of Danish women (129,439 childbirths occurring between January 1980 and December 1998) to eight types of childhood adversities, reported that women who had two adversities had higher hazards of postpartum psychiatric diagnosis (Hazard Ratio [HR]: 1.88, 95% CI [1.51, 2.36]), compared to those with no adversity [112]. In another study involving 1,257 Swedish women, Angerud and others found that while

PPD appeared to have a dose-response relationship with childhood adversity, significantly higher risks were only established at an ACE Score of 5 [164]. One key difference between the current study and the studies by Angerud et al and Brody et al was that the current study used a cumulative ACE Score of 4 to differentiate between high and low adversity. Most ACE studies use the classification used in the current study to distinguish between high and low adversity [167, 168, 222, 223]. Addressing the persistent poor outcomes amongst those affected by childhood adversity remains a challenge to the public health system. In addition to early prevention, screening women for childhood adversity during prenatal care could provide an avenue for early identification of women who may be at high risk of PPD [210, 224].

In agreement with reports from a number of other studies, the current study found a significant association between maternal history of depression and PPD. In a Canadian randomized control trial of 1,403 women seeking support during pregnancy, Davey and others screened women at eight weeks postpartum for depression and its severity [110]. After adjusting for demographic, obstetric, and other psychosocial factors, maternal history of depression was associated with more than two-fold increase in the odds of PPD (OR = 2.27; 95% CI [1.42, 3.63]). Other studies, including a systematic review of antenatal risk factors of PPD by Robertson and colleagues, included over 3,700 participants and reported higher odds PPD among women who reported a history of depression with effect sizes ranging from moderate to strong [225]. O'Hara and Swain in their meta-analysis of risk factors of PPD examined 77 studies and also reported a moderate effect size of the strength of association between maternal history of depression and PPD [111]. Given this well-established association between pre-pregnancy depression and PPD, public health programs aimed at reducing the burden of PPD should

consider reaching women with a history of depression prior to, during, and after pregnancy for appropriate screening and treatment [113, 216, 226].

Women from minority racial and ethnic groups in the United States have been reported to be especially susceptible to PPD [218, 227, 228]. The results of the current study are consistent with these reports. Postpartum depression among American Indian women, who represent approximately 1% of all annual births in the United States, remains an understudied public health burden [217]. In North Dakota, American Indian women represent about 9% of annual births, and as evidenced by the results of this study, they had significantly higher prevalence of PPD than their White counterparts. Generational trauma, poverty, and childhood adversity have been reported to affect American Indian women leading to increased vulnerability to PPD [211, 217, 229]. Culturally appropriate public health education targeted towards minority women, and providers, could contribute to improvements in the utilization of appropriate screening and treatment for PPD by this segment of the population [218, 230, 231].

In contrast to the findings of this study, previous studies have reported that women of low SES were more likely to experience PPD [226, 227, 231, 232]. Goyal and others found that women with low incomes, less than college education, unmarried or unemployed were 11 times more likely to experience PPD symptoms compared to those with none of these risk factors [232]. Mayberry and others also found that low SES women were at higher risks of PPD, compared to those of higher SES [233]. Though there was no association between SES and PPD in this study, it is an issue worth further exploration. Suffice it to say that ensuring equitable access to prevention, screening and treatment services for women, regardless of their SES, must remain a priority. This is especially critical in states like North Dakota where over 60% of the

counties are designated by the Health Resources and Services Agency as Mental Health Professional Shortage Areas [181].

4.5.1 Strengths and limitations

This is the first study to investigate predictors of PPD in North Dakota. It is also one of a few studies with a representative sample of American Indian women. The Pregnancy Risk Assessment Monitoring System (PRAMS) remains the primary source of population-based surveillance on maternal behaviors, experiences, and outcomes, and with response rates ranging from 59.1% to 70.2% for the three years of data used for this study, we are confident in the generalizability of the study's findings to women in North Dakota. However, this study is not without limitations. Since a number of the variables used in the study are self-reported, some self-reporting and/or recall bias is to be expected. Additionally, the birth certificate information and the PRAMS dataset do not encompass all known predictors. Thus, this analysis was limited to the available population-level variables.

4.5.2 Conclusions

The maternal risk factors of PPD identified in this study offer some useful insight into the epidemiology of the condition in North Dakota. Given the persistence of PPD as a public health challenge for new mothers, families, and public health professionals, prevention strategies aimed at reducing its burden should be considered a priority. Programs and policies that allow women to plan pregnancies, such as pre-conceptual counselling, and to access behavioral health services prior to, during, and after pregnancy will remain invaluable in mitigating PPD.

4.6 Availability of data and materials

All data are available within the article and supporting documents. The data were provided by the North Dakota Pregnancy Risk Assessment and Monitoring System (PRAMS), a project of the North Dakota Department of Health, and the CDC of the U.S. Health and Human Services Department. This report does not represent the official views of the CDC or of the North Dakota Department of Health.

CHAPTER 5

5.0 Summary, Discussions, and Conclusions

To my knowledge, this is the first study to investigate emerging issues of concern and their predictors in North Dakota. Several factors were identified as significant predictors of the three adverse outcomes of interest. These findings present opportunities for public health action and directions for further exploration.

First, in the early perinatal period, significant predictors of preterm birth were plural births, hypertension, premature rupture of membranes, prior preterm birth, maternal age of ≥35 years, and rurality of residence. These findings were consistent with various other studies examining the odds of preterm birth and present opportunities for the provision of better risk assessment among women with histories of preterm birth and those who may have chronic diseases prior to pregnancy. This study further provided insight into the association between maternal age and higher odds of preterm birth. As maternal age at first and subsequent births continues to increase in the United States, screening for chronic diseases and communication of risk should be encouraged for women. Providers serving these women should be concise in their delivery of risk communication and in offering services that will lead women to enter pregnancy in optimum health. Notably, accessibility to healthcare services remains a challenge in primarily rural states such as North Dakota. This study further highlights a previously unknown inequity of higher odds of preterm birth among North Dakotan women living in rural areas. Opportunities for easier healthcare access for these women should remain a priority, especially given the high odds of preterm birth among women with fewer than 8 prenatal visits.

Secondly, in the perinatal period 24 to 48 hours after delivery, this investigation found that significantly higher odds of newborn screening refusal were associated with home births, use of a lay midwife for delivery, refusal of the administration of the Hepatitis B vaccine to the infant and fewer number of prenatal care visits. Refusal of preventive services, while rare, presents an additional challenge to public health and medical professionals. It is especially concerning that newborn screening refusal was also associated with the Hepatitis B vaccine, providing further evidence in how early parental vaccine hesitancy may emerge. As Title V/Maternal and Child Health Programs create new initiatives, building back trust in effective public health strategies will remain critical. Moreover, given the critical timeliness required of newborn screening, refusal has the potential to increase the chances of an infant's disorder being diagnosed late, potentially resulting in complications or death. This is an area worth serious attention and future studies will need to identify subpopulations that may have higher rates of NBS refusal. Exploring patient and provider perspectives regarding newborn screening and other perinatal preventive services is another area worth further investigating.

Thirdly, in the postpartum period of up to 9 months, this investigation found that significantly higher odds of postpartum depression in North Dakota were associated with unintentional pregnancy, high adverse childhood experiences, American Indian maternal race, and maternal history of depression. These findings further illuminate the need for risk assessments prior to pregnancy on issues such as history of, and pre-existing depression as well as adverse childhood experiences. This study also showed higher odds of postpartum depression among American Indian women, who represent the largest minority group in North Dakota yet are underrepresented in perinatal research. Health equity is one of the cornerstones of Title V

programs and these findings present opportunities to further focus on this subpopulation for additional investigation and resource allocation to mitigate postpartum depression. That unintended pregnancies were associated with postpartum depression was especially concerning, given that nearly 50% of births in the United States are unintentional. Family planning services and education is one avenue that should be utilized to reduce the prevalence of unintended pregnancies and consequently postpartum depression. Given the severe morbidity to women, children, and families associated with postpartum depression, resources around screening, diagnosis and treatment must be prioritized to improve maternal wellbeing.

This study has a number of strengths. Firstly, the utilization of the North Dakota Pregnancy Risk Assessment Monitoring System (PRAMS), which is the primary source of population-based surveillance on maternal behaviors, experiences, and outcomes in the United States. With response rates ranging from 59.1% to 70.2% for the three years of data used for this study, there is high confidence in the generalizability of the preterm birth and postpartum depression studies' findings to women in North Dakota. Secondly, the investigation of newborn screening refusal was the first of its kind in the United States. Although the prevalence of refusal was low, using the Firth logistic model effectively reduced the small sample bias in model estimates. Thirdly, this investigation of newborn screening refusal was also the first of its kind to link newborn screening, clinician credential, facility type, and birth certificate data in the investigation of maternal and provider predictors of newborn screening refusal. Previous studies in this area were also limited in the ability to distinguish homebirths from hospital births. The utilization of the entire North Dakota birth cohort database in this study allowed investigators to make this distinction and further illuminate the significance of place of birth as a predictor of

newborn screening refusal. Therefore, the data and methods utilized for this investigation are important additions in shaping the future processes of similar needs assessments.

Over the course of this investigation, there were a few barriers identified. Firstly, several variables, such as the adverse childhood experience questions from the North Dakota PRAMS database utilized to investigate the predictors of preterm birth and postpartum depression, were self-reported, hence some self-reporting and/or recall bias is to be expected. Second, the birth certificate database and the PRAMS dataset do not encompass all known predictors for postpartum depression and preterm birth. For example, clinical-level questions on known mechanical risk factors of preterm birth, such as amniocentesis procedures and placental complications, are not included in the PRAMS survey or birth certificate. Thus, all analyses were limited to the available population-level variables. The ability to gather data from other sources, such as electronic medical records or claims datasets, may fill this gap and allow the inclusion of other variables in future studies.

The findings of this study highlight several areas for further research and program planning that could help mitigate the observed outcomes. These include the call to propensity and investment of public health programs to: 1) Enact programs and policies that allow for uniform documentation of refusal of preventative services, such as newborn screening; 2) Examine the barriers to utilization of prenatal care services in medically underserved communities; 3) Implement initiatives around pre-conception counseling that could aid in the screening and treatment of issues such as pre-existing depression and maternal hypertension, especially as maternal age at first birth increases; and 4) Implement educational programs on the

risks of recurrence of preterm birth among those with a history of a prior preterm birth and the likelihood of postpartum depression among women with a history of depression.

In conclusion, this investigation was instrumental in describing and identifying the significant predictors of emerging perinatal morbidity issues of preterm birth, newborn screening refusal, and postpartum depression among North Dakotan women with a live birth. The Title V of the Social Security Act provides resources and a unique opportunity for states like North Dakota to continue to examine needs and trends, build partnerships, and implement programs and policies that allow emerging issues in the maternal and child health issues to be addressed through further research and resource allocations. These findings are especially valuable in guiding targeted efforts that would allow for health improvements in the perinatal period and likely lead to health improvements across the life course.

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