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Intersection of Maternal Disability Status, Prescription Opioid Use Before And During Pregnancy, and Adverse Birth Outcomes

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INTERSECTION OF MATERNAL DISABILITY STATUS, PRESCRIPTION OPIOID USE BEFORE AND DURING PREGNANCY, AND ADVERSE BIRTH OUTCOMES

by

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DEDICATION

This dissertation is dedicated to my eighteen year old self, who started college bright eyed and bushy tailed, to my twenty year old self, who believed in herself when things did not go according to plan, to my twenty three year old self, who moved to South Carolina with two suitcases and twenty dollars in her pocket, to my twenty five year old self, who stayed in South Carolina after she got her first public health job and started dating a guy she met online, and to my twenty eight year old self, who began her (fully funded!) PhD journey, while working full-time. This dissertation is also dedicated to my village: my husband, Drew; my sister, Ally; my best friends, Amanda, Lara, Rachel, and Bryn; my mom, Teri, and her partner, Michael; my dad, Stephen, and his fiancée, Joyce; my grandparents; extended family and friends; and my colleagues past and present. In addition, I dedicate this dissertation to Dr. Simon Body, my supervisor at Brigham and Women's Hospital, without whom I would have never pursued graduate training in epidemiology. Finally, I dedicate this dissertation to Dr. Harley Davis and Georgia Mjartan, my supervisors at the South Carolina Department of Health and Environmental Control and South Carolina First Steps, respectively. Without the trust and mentorship of these two incredible women, I could not have achieved my dream while maintaining my full-time roles improving the lives of South Carolinians.

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ABSTRACT

Nationally, individuals with disability, like those with chronic health conditions, have higher rates of opioid use and misuse and are prescribed higher dosages than those without disability. Because opioid agonists and antagonists can cross the placenta rapidly, there is biological plausibility that they may have an impact on birth outcomes. Therefore, monitoring prescription opioid use, particularly among pregnant women, is of great public health importance. While evidence for the impact of opioid use on preterm birth and low birthweight are conflicting; findings are consistent that opioid use during pregnancy is associated with a higher risk of small for gestational age, neonatal abstinence syndrome, admission to the neonatal intensive care unit (NICU), as well as longer length of stay in the hospital.

To date, only one study has compared prescription opioid use during pregnancy between women with and without disability, which was done among Tennessee Medicaid beneficiaries between 1995 and 2009. My dissertation links hospital discharge, pharmacy, and birth certificate data from South Carolina Medicaid beneficiaries, who had a live birth between 2008 and 2017. Disability was defined through diagnostic codes to group the women into categories of discrete pathology, i.e., intellectual and developmental disabilities (IDD), inflammatory conditions, longstanding physical disability, and psychiatric conditions, which is a unique feature of my research. The aims of my dissertation are to answer: (1) are pregnant women with disability prescribed opioids more and at higher dosages than those without disability?; (2) is prescription

opioid use during pregnancy a mediator of the relationship between the interaction of chronic pain and disability status and low birthweight, preterm birth, and small for gestational age?; (3) is the cumulative dosage of prenatal opioid prescriptions or the interaction of chronic pain and disability status associated with neonatal abstinence syndrome, admission to the neonatal intensive care unit, and length of stay in the hospital?

Are Pregnant Women with Disability Prescribed Opioids More and At Higher Dosages Than Those Without Disability?

Yes. Bivariate analyses and adjusted negative binomial regression were utilized to obtain adjusted rate ratios for total opioid prescriptions and total morphine milligram equivalents (MME) during pregnancy per live birth, comparing those with disability to those without. Overall, those with disability had a significantly higher adjusted rate ratio of total opioid prescriptions (aRR: 2.36; 95% CI: 2.21-2.52) and total MME (aRR: 2.29; 95% CI: 2.07-2.52) during pregnancy per live birth than those without disability.

Is Prescription Opioid Use During Pregnancy a Mediator of the Relationship Between the Interaction of Chronic Pain and Disability Status and Low Birthweight, Preterm Birth, and Small For Gestational Age?

No. Adjusted causal mediation and logistic regression analyses were utilized to disentangle the relationship between maternal disability and chronic pain status and adverse birth outcomes, whether the relationship is mediated by prescription opioid use during pregnancy. Those with disability and chronic conditions with pain symptoms had 52% higher odds (95% confidence interval (CI): 1.43-1.62) of preterm birth, 33% higher odds (95% CI: 1.24-1.42) of low birthweight, and 8% higher odds (95% CI: 1.02-1.15),

than those with neither disability nor conditions with chronic pain symptoms. Prescription opioid use did not mediate the association between disability and adverse birth outcomes.

Is The Cumulative Dosage of Prenatal Opioid Prescriptions or the Interaction of Chronic Pain and Disability Status Associated with Neonatal Abstinence Syndrome, Admission to the Neonatal Intensive Care Unit, and Length Of Stay In The Hospital?

Yes and no. Using logistic and Poisson regression models, a 10-unit increase in cumulative, prenatal morphine milligram equivalents (MME) was associated with 2.2% higher odds of NAS (95% confidence interval (CI): 1.7%-2.6%), after adjustment. All levels of conditions of disability overall and pain symptoms were significantly associated with increased odds of NAS. A 10-unit increase in cumulative, prenatal MME was associated with 0.02% higher rate of LOS per live birth, after adjustment. An increase in cumulative, prenatal MME was not associated with increased odds of NICU admission, after adjustment.

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CHAPTER 1

INTRODUCTION

This dissertation is presented as three separate manuscripts, one of which has been previously submitted to a peer-reviewed journal. To tie the three manuscripts together, an introduction and literature review precede the manuscripts, and a conclusion succeeds them.

1.1 Historical Context

In October 2017, then acting secretary of the US Department of Health and Human Services (HHS), Eric Hargan declared a public health emergency for the national opioid crisis[1]. Since 1999, three waves of the opioid epidemic have taken place in the US[2]. The first wave from 1999-2010 was characterized by an increase in prescription opioid overdose deaths; the second, from 2010-2013, saw an increase in heroin overdose deaths; the third started in 2013 and is characterized by an increase in mortality due to synthetic opioids[2]. Early in 2017, HHS revealed a "five-point opioid strategy: improve access to prevention, treatment, and recovery support services; target the availability and distribution of overdose-reversing drugs; strengthen public health data reporting and collection; support cutting-edge research on addiction and pain; advance the practice of pain management"[1]. At the end of 2017, South Carolina Governor Henry McMaster declared a similar public health emergency for the state, as it has a high rate of opioid-related mortality[3].

1.2 Literature Review

Nationally, the prevalence of opioid use disorder per 1,000 delivery hospitalizations increased from 1.5 in 1999 to 6.5 in 2014[4]. As recently as 2019, 6.6% of women across 34 US jurisdictions reported prescription opioid use during pregnancy[5]. Those prescribed opioids are at increased risk of opioid misuse, substance use disorder, overdose, and overdose death[6,7]; all of which are preventable outcomes[8].

Therefore, monitoring prescription opioid use and its impact, particularly among pregnant women, is of great public health importance. Because opioid agonists and antagonists can cross the placenta rapidly[9], there is biological plausibility that they have an impact on birth outcomes. Opioid use, either prescription or illicit, during pregnancy is related to adverse neonatal and maternal outcomes, like delayed prenatal care[10], maternal death[11], minor congenital malformations[12], and neonatal abstinence syndrome[13].

While, evidence for the impact of prenatal opioid use on preterm birth (gestational age <37 weeks)[14–20] and low birthweight (birthweight <2,500 grams)[14,17,19–21] are conflicting; findings are consistent that opioid use during pregnancy is associated with a higher risk of small-for-gestational age (sex-specific composite measure of birthweight and gestational age)[15–18,21], NICU admission[18,22,23], longer LOS[11,17], and NAS[14,17,18,23–27], which is characterized by in utero exposure to opioids, benzodiazepines, or barbiturates, in addition to poor sleep or feeding, high-pitched or excessive crying, among other signs[28]. Further, there is evidence that opioid prescriptions used for medication-assisted treatment (MAT) of opioid use disorder have differing magnitudes, when compared to each other, of increased risk for NAS[19,20], reduced gestational age[20], and reduced birthweight[20]. Through healthy pregnancy practices, like adequate prenatal care, these adverse birth outcomes are potentially preventable[29].

Despite historical attitudes that women with disability experience challenges with conception, study findings show no difference in prevalence of sexual activity, prevalence of contraception use, desire to have a baby, or risk of abortion, when comparing women with disability to those without[30,31]. Evidence for the relationship between maternal disability and adverse birth outcomes are mixed, which may be attributed to the variety of disability definitions used in the literature.

Disability defined using self-report activity limitations is associated with a higher likelihood of preterm birth and low birthweight[32]. There is evidence from surveys that those with longstanding physical disability, like spinal cord injury and cerebral palsy, are at higher risk for low birthweight[33,34]. However, in population-based cohorts for specific longstanding physical disabilities, like multiple sclerosis, the condition was not associated with an increased risk of low birthweight[35]. Cohort studies of women with inflammatory conditions, like ankylosing spondylitis, psoriatic arthritis, and rheumatoid arthritis, have found an association between the condition and increased risk of preterm birth[36,37] and low birthweight[38]. Further, from administrative data, retrospective studies have found an association between psychiatric conditions and adverse birth outcomes, particularly for schizophrenia and low birthweight and SGA[39,40].

Nationally, individuals with disability, like those with chronic health conditions, have higher rates of opioid use and misuse. Additionally, adults with disability are prescribed higher doses of opioids than those who experience less specific pain and those without disability[41–47]. Longstanding physical disability and many inflammatory conditions are associated with chronic pain, which is an indicator for opioid prescribing[48,49]. Further, both activity limiting disability and chronic pain are associated

with prescription opioid use[42–44,50]. The relationship between disability and opioid use prevalence and dosage differs by the type of disability, and it may be additionally impacted by social isolation or general health status[43].

There is evidence that these adverse birth outcomes have short- and long-term impacts on the whole family. Shortly after birth, NAS is related to an increase in stress hormones for both mom and baby[51] and admission to the NICU and increased LOS are related to family stress and disruptions in bonding between the infant and parents[52]. NAS has been associated with an increased risk of neurodevelopmental issues in infancy[53] and not meeting well-child visit recommendations at fifteen months[54]. There is also evidence for impacts later on in childhood, such as having a complex chronic condition at age five[54], meeting criteria for disability and needing therapeutic services at school (ages three through eight)[55], and difficulties (emotional and behavioral) at age nine[56]. Low birthweight, preterm birth, and SGA are associated with increased risk of infant mortality[57], increased risk of not being ready for school at kindergarten entry[58], and increased risk of chronic conditions in middle adulthood[59]. There is also evidence that mothers with a preterm infant are more likely to have a subsequent preterm birth[60]. Having an infant with these adverse birth outcomes has also been associated with short- and long-term parent outcomes, like posttraumatic stress disorder[52], chronic and postpartum depression[61,62] and anxiety[61].

1.3 Statement of the Problem

There is a gap in the literature for evidence of increased risks of adverse birth outcomes among those with disability with increased risk of opioid use, like longstanding physical disability, inflammatory conditions, psychiatric conditions, and other conditions with pain symptoms[22,23,42–44,50,52,63]. These subgroups and those with disability broadly have

higher rates of opioid use, potential for opioid misuse, and are prescribed higher dosages than their counterparts without these conditions[41–44,50,63]. Further, those with disability often experience less than optimal prenatal care[64–67], which may limit the amount of monitoring they receive from a clinician for their prenatal opioid intake, compared to those without disability.

To date, one study (Epstein et al 2013)[42], which used Tennessee Medicaid birth data from 1995 – 2009, exists that investigated the intersection of these factors. As prescribing patterns, public health surveillance, and policies have changed since then, it is time for a similar study that uses more recent data. Further, Epstein et al (2013) only looked at opioid use during pregnancy, so the current study additionally considers opioid use before pregnancy, as well as includes the dosage of the opioid prescriptions. Similarly, Epstein et al (2013) defined disability using the Medicaid eligibility criteria, which does not allow for differentiation by disability type. The current study defines disability using diagnostic codes and differentiates by disability type for all analyses. Finally, Epstein et al (2013) did not look at the association with birth outcomes.

1.4 Aims and Hypotheses

This dissertation uses data from Medicaid beneficiaries, who had a live birth from 2008-2017 in South Carolina. The aims of this dissertation are to answer: (1) are pregnant women with disability prescribed opioids more and at higher dosages than those without disability?; (2) is prescription opioid use during pregnancy a mediator of the relationship between the interaction of chronic pain and disability status and low birthweight, preterm birth, and small for gestational age?; (3) is the cumulative dosage of prenatal opioid prescriptions or the interaction of chronic pain and disability status associated with

neonatal abstinence syndrome, admission to the neonatal intensive care unit, and length of stay in the hospital?

The objective of the first paper was to understand the difference in opioid prescribing during pregnancy over time by disability status. We hypothesized that those with disability would be prescribed opioids more frequently and at higher dosages than their counterparts without disability during pregnancy and that this remained stable over the time period of interest.

The objective of the second paper was to disentangle the relationship between the interaction of chronic pain and disability status and low birthweight, preterm birth, and small for gestational age, whether the relationship is mediated by prenatal prescription opioid use. We hypothesized that opioid use during pregnancy mediates the association between the interaction of chronic pain and disability status and preterm birth, low birthweight, and small for gestational age.

The objective of the third paper was to understand the association between cumulative dosage of prenatal opioid prescriptions, the interaction of chronic pain and disability status, and neonatal abstinence syndrome (NAS), admission to the neonatal intensive care unit (NICU), and length of stay (LOS) in the hospital. We hypothesize that an increase in cumulative prescribed morphine milligram equivalents (MME) during pregnancy will be associated with an increased risk of having an infant with NAS or a NICU admission and a longer LOS, for Medicaid beneficiaries, after controlling for known risk factors. We further hypothesize that this risk will be highest for those with disability (physical, inflammatory, or psychiatric) and chronic conditions with pain symptoms than those without. Finally, we hypothesize that those with chronic conditions

with pain symptoms and physical disabilities or inflammatory conditions would have higher risk of having an infant with NAS or a NICU admission and a longer LOS, compared to women with chronic conditions with pain symptoms and psychiatric conditions or women without disability, controlling for other known risk factors.

CHAPTER 2

ARE PREGNANT WOMEN WITH DISABILITY PRESCRIBED OPIOIDS MORE AND AT HIGHER DOSAGES THAN THOSE WITHOUT DISABILITY?: A RETROSPECTIVE COHORT STUDY OF SOUTH CAROLINA MEDICAID BENEFICIARIES[1]

[1]Richard CL, Love BL, Boghossian N, Hardin J, McDermott S. As submitted to *Disability and Health Journal* (Disability and Substance Use Disorders Special Supplement Issue) on July 11, 2021.

2.1 Abstract

Background: Nationally, individuals with disability have higher rates of opioid use and misuse and are prescribed higher doses than those without disability. Opioid prescriptions during pregnancy are associated with adverse birth outcomes.

Objective: To understand the difference in opioid prescribing during pregnancy over time by disability status among Medicaid beneficiaries who gave birth from 2008-2017 in South Carolina.

Methods: Data from hospital discharges, vital records, and pharmacy were linked to determine the mother's disability status, opioid prescriptions filled during pregnancy, and other maternal characteristics. Disability status was characterized into physical disability, inflammatory conditions, intellectual and developmental disabilities (IDD), and psychiatric conditions. Bivariate analyses and negative binomial regression were utilized to obtain adjusted rate ratios for total opioid prescriptions and total morphine milligram equivalents (MME) during pregnancy per live birth. Models were adjusted for chronic pain status. The final analytic sample included 319,752 births to 224,838 mothers.

Results: Almost 7% of the births were to mothers with at least one type of disability. Overall, those with disability had a significantly higher adjusted rate ratio of total opioid prescriptions (aRR: 2.36; 95% CI: 2.21-2.52) and total MME (aRR: 2.29; 95% CI: 2.07-2.52) during pregnancy per live birth than those without disability. These findings were seen across all the diagnostic groups, except IDD, where there were no significant differences.

Conclusions: The current study found that women with physical, inflammatory, and psychiatric disability were prescribed more opioids and at higher dosages during pregnancy than their counterparts without disability, after adjusting for chronic pain status.

2.2 Background

Nationally, individuals with disability are prescribed higher doses of opioids than those without disability[41–47]. The relationship between disability and opioid use may be impacted by social isolation[43], general health status[43], chronic pain[45,50], and work injury[45]. Opioid prescribing and dosage differ by disability type[42,44]. There is evidence that those with physical disability[44,47], inflammatory conditions[44,47], and those with poor physical and mental health[45,46], are at an elevated risk of being prescribed opioids.

Those prescribed opioids are at increased risk of opioid misuse, substance use disorder, overdose, and overdose death[6,7]. A study in Australia found that 46.6% of opioid users would develop an opioid use disorder in their lifetime[7]. The transition from prescription opioid use to substance use disorder can take place over a small period of time, shortening the time for possible intervention[7]. Therefore, monitoring prescription opioid use, particularly among pregnant women, is of great public health importance. Because opioid can cross the placenta rapidly[9], there is biological plausibility that they may have an impact on birth outcomes. While evidence for the impact of opioid use on preterm birth[14–20] and low birth weight[14,17,19–21] are conflicting; findings are consistent that opioid use during pregnancy is associated with a higher risk of small-for-gestational age[15–18,21], neonatal abstinence syndrome[17,19,20], admission to the neonatal intensive care unit[17–19], as well as longer length of stay in the hospital[14,17,19–21].

To date, only one study has compared prescription opioid use during pregnancy between women with and without disability, which was done among Tennessee Medicaid beneficiaries between 1995 and 2009[42]. The objective of the current study is to examine opioid prescription among specific diagnostic groups of disabled women insured through Medicaid who gave birth between 2008 and 2017 in South Carolina. We hypothesized that those with disability would be prescribed opioids more frequently and at higher dosages than their counterparts without disability during pregnancy and that this remained stable over the time period of interest.

2.3 Methods

Data from South Carolina resident births from January 1, 2008 through December 31, 2017 were obtained (n=359,049). Hospital discharge data (inpatient, emergency department, and outpatient surgery) from the mothers associated with these births were obtained from January 1, 2007 through December 31, 2017 and were utilized to determine the pregnant woman's status of disability[44,68,69] and other chronic conditions with pain symptoms[70]. The diagnoses and relevant International Classification of Disease (ICD) 9/10 codes included to define the four disability groups are outlined in appendix table 2.1. Disability is a qualifying event for Medicaid coverage, so appendix tables A.1 and A.2 also include the prevalence for each diagnosis of those on Medicaid due to their disability. The ICD-9/10 codes to define other chronic conditions with pain symptoms are displayed in appendix table A.3. ICD-9 codes were used until September 30, 2015. On October 1, 2015, ICD-10 codes were used. The disability diagnostic groups with an elevated risk of opioid prescribing of interest were physical disability; inflammatory conditions; intellectual and developmental disabilities (IDD); and psychiatric conditions.

The diagnostic groups were not mutually exclusive. Overall disability status was defined as having at least one of the conditions in the diagnostic groups or being blind or deaf. There were 46 total women who were blind or deaf, so they were included in the overall disability definition. Disability status, diagnostic group, and chronic pain status from the pregnant woman's hospital discharge data were linked to the birth certificate data.

Medicaid pharmacy data were obtained between January 1, 2007 and December 31, 2017 from fee for service and managed care and were utilized to determine prescription drugs dispensed before and during pregnancy. Prescriptions were grouped based on their American Hospital Formulary Service Pharmacologic-Therapeutic Classification codes into opioids and prescriptions associated with opioid prescribing (appendix table A.3). A crosswalk from the Centers for Disease Control and Prevention was utilized to calculate the morphine milligram equivalents (MME) for each opioid prescription[71]. To account for extreme MME values[72], which were likely coding errors, observations two standard deviations greater than the mean were excluded from analysis (MME >2977.28; <1% of prescriptions). Using hospital discharge data from the newborn's birth hospitalization, the birth date was estimated, and the date of conception was estimated with the estimated birth date and the estimated gestational age. The time periods of interest were defined as before pregnancy (one year before estimated conception) and during pregnancy (estimated conception to estimated birth date). The prescription dispense date was then utilized to determine whether the prescription was filled before or during pregnancy. Only the month and year of the prescription dispense date were available, so the fifteenth day of the month was imputed for each prescription. The prescription drug data from the pregnant women were linked to the birth certificate

data. Although pregnancy is a qualifying event for Medicaid, women were included in the sample regardless of whether they were on Medicaid before their pregnancy or not.

For the analytic sample, only singleton births with an estimated date of birth were included to ensure that each infant included was exposed to all the opioid prescription dispensed. The final analytic sample included 319,752 unique births to 224,838 unique pregnant women (figure 2.1). As the current study used administrative, de-identified data, it was deemed exempt from Institutional Review Board review at the University of South Carolina.

Other covariates of interest were obtained from the birth certificate. Previous live births were categorized as 0, 1, and 2+. Maternal education level was categorized as: less than high school; high school graduate; some college/two-year degree; four-year degree or higher. Maternal age, any tobacco use during pregnancy, and the Kotelchuck Index[73] were also obtained. The Kotelchuck Index is a measure of how early and frequent prenatal care was accessed and is categorized into inadequate, intermediate, adequate, and adequate plus[73]. Any unknown data were set to missing for the analyses. Missing/unknown data were as follows: chronic pain (n = 7,150); previous live births (n=109); tobacco use (n = 203); Kotelchuck (n = 723); maternal education level (n = 894).

For all analyses, SAS 9.4 was used[74]. To understand the demographic distribution differences between those with and without disability, bivariate analyses were used. Negative binomial regression models with robust variance estimators were used because of the high frequency of zeroes for the outcomes of interest and to account for multiple infants in the sample born to the same women. These models were used to obtain

adjusted prevalence rate ratios of opioid prescriptions and cumulative MME during pregnancy per live birth, when comparing those with disability to those without across diagnostic groups. The directed acyclical graph (DAG) of the general association of interest (derived from DAGitty[75]) is displayed in figure 2.2. Models were adjusted for chronic pain status, as informed by the DAG. To understand the impact of time, two approaches were undertaken. The first was to additionally adjust for birth year as a covariate in the negative binomial models and interpret the beta coefficient of the time variable. The second was to stratify the adjusted negative binomial models by birth year.

2.4 Results

There were 21,855 infants (6.8%) born to women with disability; 2,762 (0.9%) to women with physical disability; 3,490 (1.1%) to women with inflammatory conditions; 931 (0.3%) to women with IDD; 14,679 (4.6%) to women with psychiatric conditions (table 2.1). Of those with disability, 37.4% of them qualified for Medicaid due to their disability (results not displayed). It is noteworthy that the smallest disability group was mothers with IDD, and this group had the lowest proportion of opioid prescriptions during pregnancy. Overall, 7.5% of the sample were dispensed at least one opioid prescription during pregnancy, and 9.6% were dispensed at least one opioid prescription before pregnancy.

Our findings showed that compared to those without disability, those with disability had a significantly higher adjusted rate of opioid prescriptions and a higher rate of total MME across diagnostic groups before or during pregnancy, except for those with IDD (table 2.2). Overall, those with disability had a 2.36 (95% confidence interval (CI): 2.21-2.52) times higher adjusted prevalence rate ratio of total opioid prescriptions and a

2.29 (95% CI: 2.07-2.52) times higher adjusted prevalence rate ratio of total opioid MME during pregnancy per live birth than their counterparts without disability, after adjusting for other chronic conditions with pain symptoms.

After adjustment, the average prevalence rate ratio of opioid prescriptions and of total MME filled during pregnancy per live birth significantly decreased by 12.9% (95% CI: 12.0-13.7%; figure 2.3) and 22.6% (95% CI: 21.7-23.5%; figure 2.4), respectively for each one-year increase in time, when comparing those with disability to those without. Across each diagnostic group, the average decrease in the prevalence rate ratio was very similar for the adjusted models.

As shown in figure 2.3, those with disability had a significantly higher adjusted rate of total opioid prescriptions during pregnancy per live birth in 2008 than their counterparts without disability (aRR:1.98; 95% CI: 1.75-2.23). The rate ratio remained significant for each year throughout the study period, peaking in 2017. This varied by diagnostic group. The adjusted prevalence rate ratio for psychiatric conditions was significantly higher across all birth years for total opioid prescriptions dispensed (figure 3). Similarly, as shown in figure 2.4, in 2008, those with disability had a significantly higher adjusted rate of total opioid MME during pregnancy per live birth than their counterparts without disability (aRR: 1.78; 95% CI: 1.54-2.06). The rate ratio remained significant for each year throughout the study period for disability overall but varied by diagnostic group.

2.5 Discussion

The current study provides evidence that those with disability were prescribed opioids more frequently and at higher dosages than their counterparts without disability during pregnancy. Further, opioid prescribing patterns remained stable from 2008 to 2017 for total prescriptions during pregnancy per live birth overall, but not for total MME during pregnancy per live birth. The prevalence of filling an opioid prescription in the current study was 7.5% during pregnancy and 9.6% before pregnancy, which is lower than what has been reported in previous studies. In a Tennessee Medicaid beneficiary study from 1995 to 2009, the prevalence of filling an opioid prescription during pregnancy was 29%[42]. This difference is most likely attributable to national trends of opioid prescribing peaking in 2010[76]. One national study reported a 13% net reduction in opioid prescribing from 2006 to 2017[76].

One policy strategy to reducing opioid prescribing is establishment of Prescription Drug Monitoring Programs (PDMPs), which exist in almost every state[47]. PDMPs are administered and regulated at the state-level[47]. In 2006, the South Carolina Prescription Monitoring Act established the prescription monitoring program for controlled substances, which was operational in 2008[3,77]. Theoretically, this increased surveillance and reporting would impact prescribing patterns similarly across all groups. However, there is evidence that PDMPs do not reduce opioid prescribing for those with physical disability or inflammatory conditions, compared to those without[47]. The current study supports this finding.

In the study of Tennessee Medicaid beneficiaries, Epstein et al found that those with disability had an opioid prescription rate 1.14 times that of those without disability (95% CI: 1.11-1.16), after adjusting for birth year, age group, race, ethnicity, educational attainment, gravidity, and urbanicity of residence[42]. The current study only adjusted for other chronic conditions with pain symptoms and only included live births. This distinction, as well as the way we defined disability (Medicaid definition vs. ICD codes), may explain why the current study found a higher adjusted rate ratio (aRR: 2.36; 95% CI: 2.21-2.52). The current study found a prevalence of opioid prescription during pregnancy of 7.5%. This is lower than Epstein et al, which was 29.0% (1995-2009)[42], but it is higher than other recent studies that range from 4% among women in Ontario, Canada (2013-2018)[27]; 4.5% among women in Sweden (2007-2013)[78]; and 6.6% among women in the US (self-reported; 2019)[79].

The main strength of the current study is the use of administrative data, which helps limit selection bias that may occur when using other methods of recruiting study participants with disability[80]. The use of several ICD-9/10 codes to define disability also allowed the current study to look at the diagnostic groups separately. In the literature, the definition of disability varies. It has been defined by self-report with validated questionnaires[30,43,81,82], health insurance definitions, e.g. Medicare[41] or Medicaid[42], or by diagnoses in medical or billing records[44,68,69,83,84]. Typical disability groups included in studies from diagnostic codes are physical disability and intellectual and developmental disabilities (IDD)[44,68,69,83,84]. As these conditions have different biological origins and social and health implications, combining them can obscure results. Inclusion of those with IDD, along with other diagnostic groups, like in the current study, can add to a

study's face validity. In the current study, there was no significant difference seen for those with IDD, compared to those without, in the adjusted rate ratio of total opioid prescriptions and total MME during pregnancy per live birth. This finding is not unexpected, as there is limited evidence for why those with IDD would have more chronic pain or an elevated risk of opioid use than the general population[85].Another strength of the use of ICD-9/10 codes was that chronic pain status could be obtained, which was not done in previous studies, and it is an indication for opioid prescribing. The use of administrative data also enabled opioid prescribing to be defined as prescriptions filled and to adjust for other prescriptions filled that are associated with opioids, which limited the impact of reporting and social desirability biases. Finally, since the administrative data were from a ten-year period, the sample size was high.

Our study has several limitations. The current study is of Medicaid beneficiaries, which limits the generalizability of our findings. Since these women are insured, they are potentially more likely to access health care regularly and prenatal care earlier and at a more adequate frequency during pregnancy than the general population, which includes uninsured or underinsured individuals. By accessing health care more, they are more likely to receive prescriptions. An additional limitation is the definition of disability, which was defined using data from inpatient, emergency department, and outpatient surgery encounters. While chronic conditions, like those used in the current study's definition of disability, should be captured in the ICD 9/10 codes at each encounter, there is a possibility that only the most severe chronic conditions were captured. This would leave those with less severe disabilities misclassified as without disability. However, since the current study encompasses encounters over a ten-year period, the authors

believe the impact of this potential misclassification is minimized. Another limitation of the current study is related to the definition of chronic pain, which was determined through a set of diagnostic codes (appendix table A.3). This method could have introduced some unmeasured confounding as it may not be holistic enough to capture all elements of chronic pain that increase the likelihood of being prescribed an opioid. One study found that the optimal assessment of chronic pain should include intensity, other perceptual qualities, distribution throughout the body, and temporal features, and this should be incorporated into clinical protocols[86]. The diagnoses used in the current study most likely do not incorporate this assessment in a standard way. Another limitation is lack of data on prescription opioid misuse or illicit use. The authors had initially hoped to do a sensitivity analysis with opioid antagonists, which includes naloxone and naltrexone, as a proxy for illicit use. However, only seven prescriptions of opioid antagonists were found in the Medicaid pharmacy data, which may be because those administered in emergency situations are not captured in this data source. Passed in 2015, the South Carolina Overdose Prevention Act allowed prescribers to give standing orders for "opioid antidotes" to first responders and gave pharmacists the ability to prescribe them directly to family members[3,87]. This increased access to these opioid antagonists will help prevent opioid overdose deaths, but their use may not be detected in the Medicaid pharmacy record of the person who received the drug. The final limitations of the current study are related to the data sources. Since three administrative data sources were used (hospital discharge, pharmacy, and vital records for Medicaid beneficiaries), it is difficult to determine the overall data quality and its impact on inference drawn from the analytic sample.

In the current study, those with psychiatric conditions had the highest adjusted rate ratio among the diagnostic groups for number of prescriptions and cumulative dosage of opioids during pregnancy, compared to their counterparts without psychiatric conditions. Those with psychiatric conditions may have limited work opportunities or be more likely to work highly physical jobs, where health and safety are not prioritized, which increases the likelihood for work-related injuries[45]. These work-related injuries and subsequent, somewhat elusive pain are associated with an increased risk of opioid prescribing and misuse[45]. Additionally, psychiatric conditions, like anxiety and depression, have a high rate of co-occurrence with chronic pain, which is an indicator for opioid prescribing[88]. Those with psychiatric conditions are more likely to be socially isolated and to have poor physical health, which are also associated with an increased risk of opioid prescription misuse[43,45,46].

The American College of Obstetricians and Gynecologists recommends early universal screening of pregnant women for prescription opioid use and misuse[89]. If the screening tools affirm use or misuse, then brief intervention and referral to treatment are recommended[89]. For women with chronic pain, alternative therapies to opioid prescription are recommended, like physical therapy or behavioral health interventions[89]. Policies that encourage pregnant women, particularly those with disabilities, to seek drug treatment could improve maternal and child outcomes[23]. In South Carolina, a positive drug test for either the mother or the child, unless it is for "medical treatment", is proof that a "newborn child is an abused or neglected child"[90]. The state code does not explicitly state whether medication-assisted treatment for a substance use disorder is an allowable "medical treatment," for which a newborn would not be considered neglected

or abused[90]. Like South Carolina, drug use during pregnancy is considered child abuse in 22 other states and the District of Columbia[91].

Despite its limitations, the current study fills a gap in the literature for an up-to-date understanding of the relationship between disability diagnostic groups and opioid prescribing, particularly in the face of policy changes that South Carolina has undergone in response to the opioid epidemic[3]. It is important to understand this relationship as deaths related to prescription opioids have decreased nationally, and there is an increase in deaths related to use of synthetic/illicit opioids[92]. Surveillance of these trends, particularly among subpopulations, is needed to mitigate other potential consequences of opioid use and misuse during pregnancy, like adverse birth outcomes.

2.6 Conclusions

The current study found that women with physical disability, inflammatory conditions, and psychiatric conditions were prescribed more opioids and at higher dosages during pregnancy than their counterparts without disability. Further, the number of opioid prescriptions per live birth was significantly higher for those with disability across the time period of interest, compared to those without. Total MME per live birth was significantly higher for those with disability from 2008 through 2011 but was non-significant overall from 2012 through 2017. Understanding opioid prescribing in pregnant women, particularly among those with disability, is of great public health importance, as opioid use during pregnancy is associated with an increased risk of adverse birth outcomes.

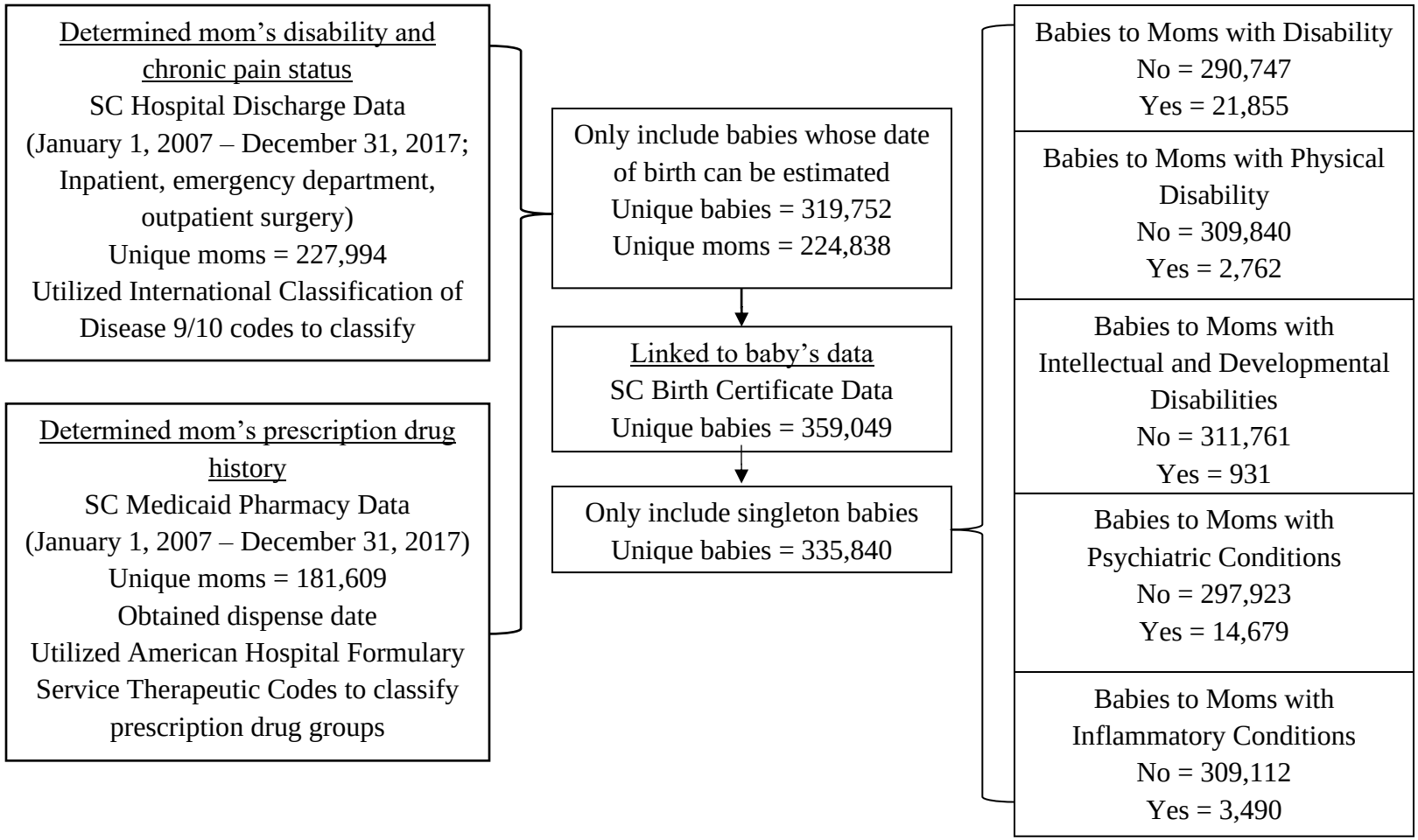

Figure 2.1. Data linkages from hospital discharge, pharmacy, and birth certificate data from South Carolina Medicaid beneficiaries who gave birth from 2008-2017 and exclusions made to obtain analytic sample; disability groups not mutually exclusive

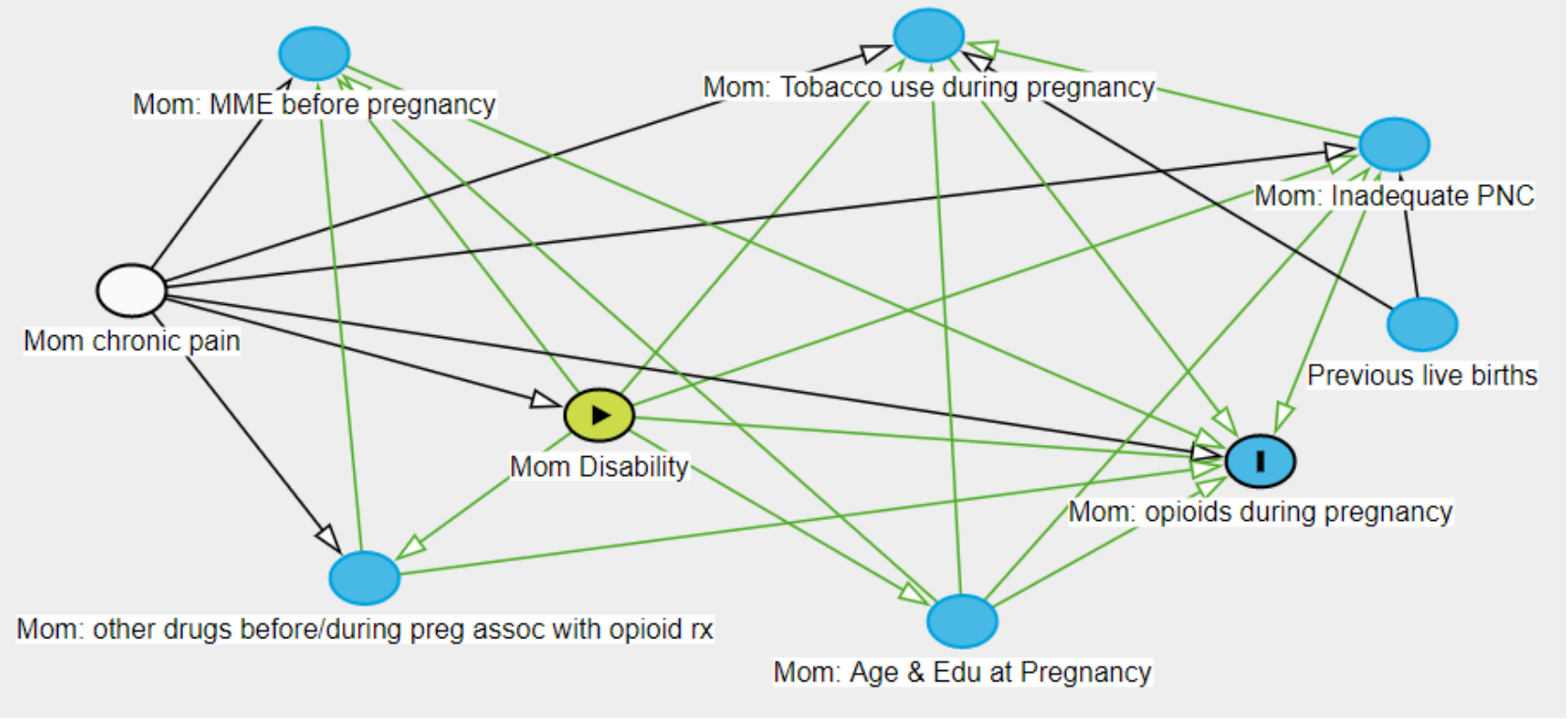

Figure 2.2. Directed acyclical graph (derived from DAGitty) of the association between maternal disability status and prescription opioids during pregnancy

Table 2.1. Demographic distribution of births by mom's disability status and diagnostic group (diagnostic groups not mutually exclusive; total sample n = 319,752)

	Overall		Disability		Physical Disability		Inflammatory Conditions		Intellectual and Developmental Disability		Psychiatric Conditions	
	n	%	n	%	n	%	n	%	n	%	n	%
Overall	319,752	100.0%	21,855	6.8%	2,762	0.9%	3,490	1.1%	931	0.3%	14,679	4.6%
Opioid prescription(s) during pregnancy	23,929	7.5%	3,568	16.3%	411	14.9%	539	15.4%	80	8.6%	2,544	17.3%
Opioid prescription(s) before pregnancy	30,664	9.6%	5,350	24.5%	632	22.9%	782	22.4%	168	18.0%	3,778	25.7%
Any chronic pain diagnosis	69,016	21.6%	11,022	50.4%	1,387	50.2%	1,630	46.7%	355	38.1%	7,665	52.2%
Previous live births												
None	124,010	38.8%	6,588	30.1%	868	31.4%	1,067	30.6%	364	39.1%	4,286	29.2%
One	97,140	30.4%	6,690	30.6%	849	30.7%	1,050	30.1%	266	28.6%	4,527	30.8%
Two or more	98,493	30.8%	8,570	39.2%	1,043	37.8%	1,373	39.3%	301	32.3%	5,861	39.9%
Tobacco use during pregnancy	49,615	15.5%	6,305	28.8%	531	19.2%	719	20.6%	98	10.5%	4,973	33.9%
Kotelchuck Index												
Inadequate	77,701	24.3%	5,167	23.6%	647	23.4%	716	20.5%	253	27.2%	3,548	24.2%
Intermediate	20,342	6.4%	1,504	6.9%	182	6.6%	199	5.7%	71	7.6%	1,054	7.2%
Adequate	81,728	25.6%	5,078	23.2%	688	24.9%	764	21.9%	212	22.8%	3,410	23.2%
Adequate plus	139,258	43.6%	10,057	46.0%	1,233	44.6%	1,805	51.7%	393	42.2%	6,638	45.2%

Maternal education level												
Less than high school	85,962	26.9%	8,007	36.6%	863	31.2%	930	26.6%	403	43.3%	5,824	39.7%
High school	105,189	32.9%	7,195	32.9%	964	34.9%	1,166	33.4%	362	38.9%	4,697	32.0%
Some college	107,936	33.8%	6,030	27.6%	831	30.1%	1,243	35.6%	141	15.1%	3,818	26.0%
4 year college degree or more	19,771	6.2%	555	2.5%	95	3.4%	143	4.1%	19	2.0%	295	2.0%
Drugs associated with opioid prescribing (before/during pregnancy)	60,223	18.8%	11,296	51.7%	1,011	36.6%	1,250	35.8%	320	34.4%	8,731	59.5%
Birth year												
2008	35,647	11.1%	2,315	10.6%	353	12.8%	342	9.8%	87	9.3%	1,538	10.5%
2009	33,895	10.6%	2,313	10.6%	316	11.4%	369	10.6%	85	9.1%	1,544	10.5%
2010	32,838	10.3%	2,346	10.7%	281	10.2%	371	10.6%	87	9.3%	1,602	10.9%
2011	31,985	10.0%	2,389	10.9%	296	10.7%	346	9.9%	83	8.9%	1,666	11.3%
2012	31,439	9.8%	2,332	10.7%	297	10.8%	399	11.4%	87	9.3%	1,553	10.6%
2013	30,876	9.7%	2,329	10.7%	309	11.2%	372	10.7%	67	7.2%	1,580	10.8%
2014	31,323	9.8%	2,337	10.7%	258	9.3%	367	10.5%	90	9.7%	1,626	11.1%
2015	30,731	9.6%	2,272	10.4%	282	10.2%	343	9.8%	94	10.1%	1,554	10.6%
2016	30,401	9.5%	1,791	8.2%	204	7.4%	308	8.8%	95	10.2%	1,184	8.1%
2017	29,703	9.3%	1,374	6.3%	163	5.9%	260	7.4%	148	15.9%	799	5.4%

Maternal age, mean (SD)	25.1	5.5	24.6	5.5	24.7	5.5	25.2	5.5	24.5	5.7	24.5	5.5
Cumulative MME during pregnancy, mean (SD)	86.0	174.6	118.4	282.8	137.4	474.2	127.4	228.3	63.8	84.4	115.2	253.0
Cumulative MME before pregnancy, mean (SD)	100.3	202.7	137.8	302.7	152.3	446.2	159.8	359.6	80.5	107.6	133.7	262.8

Table 2.2. Adjusted prevalence rate ratios (aRR) of total opioid prescriptions and total morphine milligram equivalents (MME) during pregnancy per live birth by overall disability and diagnostic group (n = 319,752)

	Total Opioid Prescriptions Per Live Birth aRR (95% CI)	Total MME Per Live Birth aRR (95% CI)
Disability overall	2.36 (2.21-2.52)	2.29 (2.07-2.52)
Disability diagnostic groups		
Physical disability	1.70 (1.44-2.00)	2.23 (1.60-3.11)
Inflammatory conditions	2.04 (1.78-2.34)	2.11 (1.71-2.61)
Intellectual and developmental disability	0.93 (0.67-1.30)	0.82 (0.59-1.13)
Psychiatric conditions	2.46 (2.28-2.67)	2.24 (2.00-2.51)

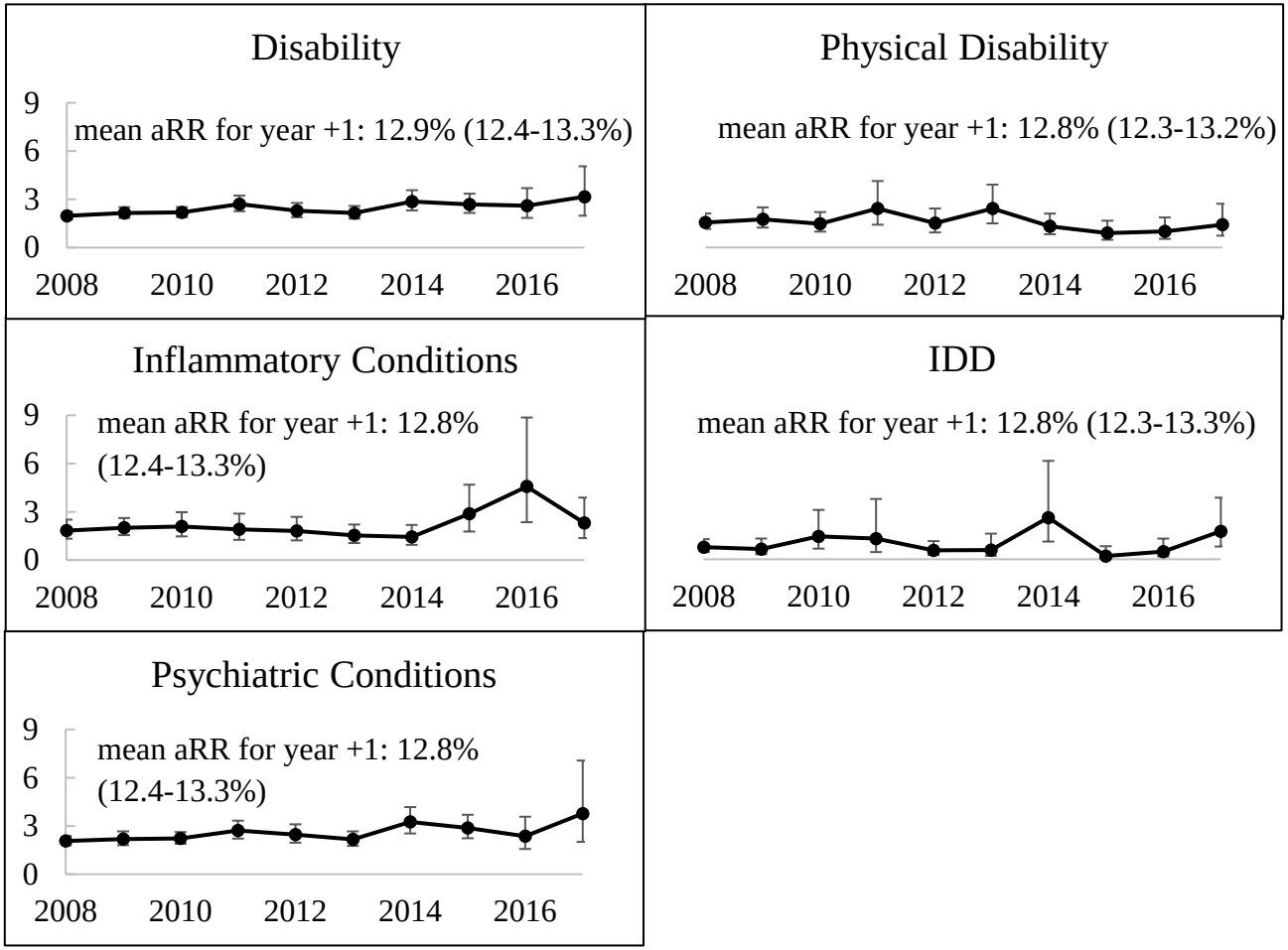

Figure 2.3. Adjusted prevalence rate ratio of total opioid prescriptions dispensed per live birth by birth year comparing those with disability to those without (without is referent; n=319,752 live births; IDD = intellectual and developmental disabilities; dot = adjusted prevalence rate ratio; error bar = 95% confidence interval)

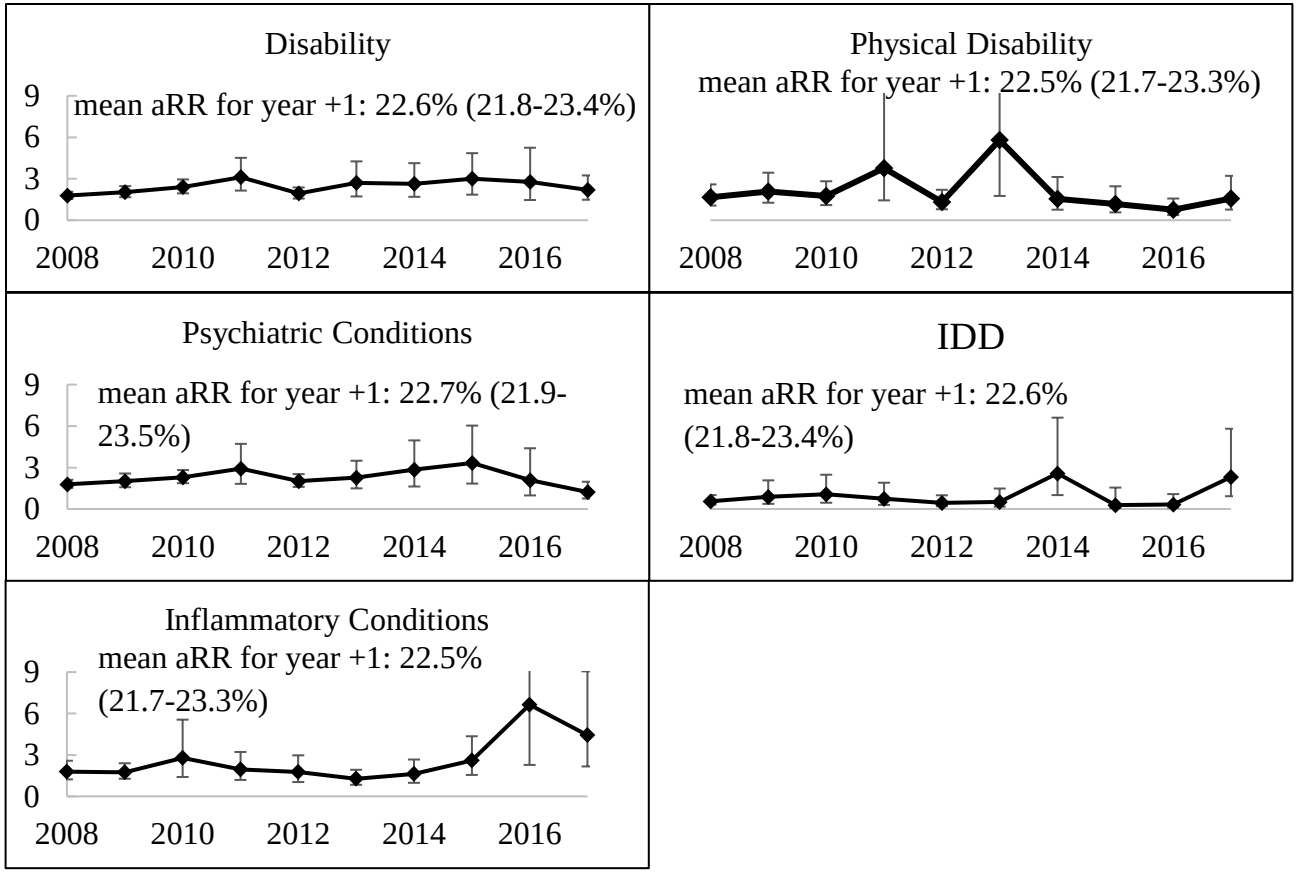

Figure 2.4. Adjusted prevalence rate ratio of morphine milligram equivalents dispensed per live birth by birth year comparing those with disability to those without (without is referent; n=319,752 live births; IDD = intellectual and developmental disabilities; dot = adjusted prevalence rate ratio; error bar = 95% confidence interval)

CHAPTER 3

MATERNAL DISABILITY AND ADVERSE BIRTH OUTCOMES: IS PRESCRIPTION OPIOID USE DURING PREGNANCY A MEDIATOR? A RETROSPECTIVE COHORT STUDY OF SOUTH CAROLINA MEDICAID BENEFICIARIES[2]

[2]Richard CL, Boghossian N, Love BL, Hardin J, McDermott S. To be submitted to *Maternal and Child Health Journal.*

3.1 Abstract

Objectives: There is evidence that maternal disability is associated with an increased risk of adverse birth outcomes, which may be explained by differences in prescription opioid use. The study aimed to understand if the relationship between maternal disability status and adverse birth outcomes is mediated by prescription opioid use during pregnancy.

Methods: Hospital, pharmacy, and vital records were linked for South Carolina Medicaid beneficiaries, who gave birth between 2008-2017. Clinical data were used to define maternal disability and chronic conditions with pain symptoms. Pharmacy data were used to calculate morphine milligram equivalents (MME) during pregnancy and other prescriptions related to adverse birth outcomes and opioid prescribing. Vital records data were used to define covariates and outcomes: preterm birth (<37 weeks gestation); low birthweight (<2,500 grams); small for gestational age (SGA). Logistic regression and causal mediation analyses were used. A sensitivity analysis of nulliparous women was included.

Results: The final sample included 306,446 infants. The prevalence of disability + chronic pain + overall was 3.2%. Those with disability and chronic conditions with pain symptoms had 52% higher odds (95% confidence interval (CI): 1.43-1.62) of preterm birth, 33% higher odds (95% CI: 1.24-1.42) of low birthweight, and 8% higher odds (95% CI: 1.02-1.15), than those with neither disability nor conditions with chronic pain symptoms. Prescription opioid use did not mediate the association between disability and adverse birth outcomes.

Discussion: Obstetricians should be trained in how to best support pregnant women with disabilities to deliver optimal care.

3.2 Objectives

Despite historical misconceptions that women with disability experience challenges with conception, study findings show no difference in prevalence of sexual activity, prevalence of contraception use, desire to have a baby, or risk of abortion, when comparing women with disability to those without[30,31]. Evidence for the relationship between maternal disability and adverse birth outcomes is mixed, which may be attributed to the variety of disability definitions used in the literature.

Disability defined using self-report activity limitations is associated with a higher likelihood of preterm birth and low birthweight[32]. There is evidence from surveys that those with longstanding physical disability, like spinal cord injury and cerebral palsy, are at higher risk for low birthweight[33,34]. However, in population-based cohorts for specific longstanding physical disabilities, like multiple sclerosis, the condition was not associated with an increased risk of low birthweight[35]. Cohort studies of women with inflammatory conditions, like ankylosing spondylitis, psoriatic arthritis, and rheumatoid arthritis, have found an association between the condition and increased risk of preterm birth[36,37] and low birthweight[38]. Further, from administrative data, retrospective studies have found an association between psychiatric conditions and adverse birth outcomes, particularly for schizophrenia and low birthweight and small for gestational age, or SGA[39,40].

Longstanding physical disability and many inflammatory conditions are associated with chronic pain[48,49], and both activity limiting disability and chronic pain are associated with prescription opioid use, which can lead to opioid misuse[42–44,50].

Overall, evidence for the impact of opioid use on preterm birth, low birthweight, and small for gestational age (SGA) are conflicting depending on how the exposure of opioid use is defined[14–17,27]. Opioids can cross the placenta[9], so there is biologic plausibility that opioid exposure may be on the causal pathway between maternal disability status and an increased risk of adverse birth outcomes[9].

The current study utilizes administrative data from South Carolina Medicaid beneficiaries to understand the relationship between disability status and adverse birth outcomes and if it is mediated by prescription opioid use. The authors hypothesized that opioid use during pregnancy mediates the association between disability and the adverse birth outcomes of interest (preterm birth, low birthweight, and SGA).

3.3 Methods

The cohort consists of South Carolina Medicaid beneficiaries, who gave birth between 2008 and 2017. The sample was obtained by linking hospital discharge (from inpatient, outpatient, and emergency department records), pharmacy, and vital records data (figure 3.1). Data were obtained from the South Carolina Integrated Data Warehouse and linked by a unique identifier established by the Office of Revenue and Fiscal Affairs. Sample exclusions were multiples (n=23,209); neonates whose date of birth could not be estimated (n=16,088); women whose data could not be linked to a birth record (n=7,150); neonates born to mothers with intellectual or developmental disabilities (n=931); neonates who were born to women with an indicator of opioid misuse (n=5,225; definition appendix table C.1). The final sample included 306,446 neonates born to 214,446 women.

Hospital discharge data from inpatient, outpatient, and emergency department records were used to determine mom's disability status and other chronic conditions with pain symptoms via International Classification of Disease 9/10 codes (appendix table C.1). The disability diagnostic groups of interest were longstanding physical disability, inflammatory conditions, and psychiatric conditions. Those with intellectual or developmental disability were excluded from the study due to no association with prescription opioids in a previous study. Overall disability status was determined if the mom was in any one of these three groups, and the groups were not mutually exclusive. The exposure was defined as a composite measure of disability status and status of other chronic conditions with pain symptoms (appendix table C.1). Those with disability and other chronic conditions with pain symptoms (Disability + Chronic Pain +) were compared to those without disability or other chronic conditions with pain symptoms (Disability – Chronic Pain –).

Medicaid pharmacy data were used to obtain the mediator of interest, total morphine milligram equivalents (MME) prescribed during pregnancy. Prescription opioids were included based on their American Hospital Formulary Service Therapeutic Codes: opiate agonists (28:08.08); opiate partial agonists (28:08.12); opioid antagonists (28:10). During pregnancy was defined as between the estimated date of last menses and estimated date of birth. Total MME were calculated utilizing the total dose per day (calculated from strength per unit, number of units, and total supply) and a reference obtained from the Centers for Disease Control and Prevention[71]. Extreme values defined as greater than two standard deviations from the mean (2,977.28) were excluded. Less than 1% of all opioid prescriptions met this definition of extreme values.

Data on adverse birth outcomes were obtained from birth certificates. These outcomes were dichotomized. Low birthweight was defined as <2,500 grams; preterm birth was defined as <37 weeks gestation; and SGA was defined using the age-sex specific cut offs described in Alexander et al (1996)[93].

SAS 9.4 was used for all statistical analyses[74]. We first conducted bivariate analyses to summarize the distribution of the outcomes, various pregnancy circumstances, and maternal attributes among the disability + chronic pain groups (table 3.1). The Kotelchuck Index is a composite measure of the frequency of prenatal care visits and how early in the pregnancy prenatal care was accessed[73]. Other medications prescribed during pregnancy were explored, including those associated with adverse birth outcomes and with opioid prescribing (appendix table C.2).

To measure the association between disability + chronic pain and the adverse birth outcomes, logistic regression models were obtained (table 3.2). To measure the association between disability + chronic pain and MME during pregnancy (continuous) and adverse birth outcomes and MME during pregnancy (continuous), Student's t-tests were obtained to understand whether there was a significant difference in the mean MME during pregnancy between the groups of interest (table 3.3).

Then, we utilized mediation analyses to explore whether total MME during pregnancy mediated the association between disability status/group + chronic pain and the adverse birth outcome. We employed PROC CAUSALMED in SAS 9.4[74] for the mediation analyses, which uses the approach described in Vanderweele (2014)[94]. The outcome was modeled under a binomial distribution, and the mediator, opioid use during pregnancy, was modeled at its naturally occurring level (zero). The association was

measured on the multiplicative, odds ratio scale because the outcome was dichotomous. For this relationship, the total effect is equal to the product of the natural direct effect and the natural indirect effect. These effects are displayed as odds ratios and summarized using the associated 95% confidence intervals in table 3.4. The detailed directed acyclical graph (DAG) of the overall approach derived from DAGitty[75] is displayed in figure 4.2. The DAG showed no biasing pathways or confounding, so models were not adjusted for any factors. Sensitivity analyses were performed using nulliparous women only (n = 118,649).

3.4 Results

The prevalence of disability + chronic pain + groups were rare (overall: 3.2%; longstanding physical disability: 0.4%; inflammatory: 0.5%; psychiatric conditions: 2.2%) in the analysis sample. Across groups, there was a high prevalence of women who were white, had low educational attainment, had previous live births, used tobacco during pregnancy, had a Kotelchuck Index of 'adequate plus', were overweight or obese, and were prescribed drugs that were associated with birth outcomes or opioid prescribing (table 3.1).

Table 3.2 shows the association between disability + chronic pain + groups and adverse birth outcomes. Those with disability overall and chronic conditions with pain symptoms had 1.52 times higher odds (95% confidence interval (CI): 1.43-1.62) of preterm birth, than their counterparts with neither disability nor chronic conditions with pain symptoms. Similar findings for preterm birth were seen across all disability groups for all women and the nulliparous sample (table 3.2). Those with disability overall and chronic conditions with pain symptoms had 1.33 times higher odds (95% CI: 1.24-1.42)

of a low birthweight infant, compared to their counterparts with neither disability nor chronic conditions with pain symptoms. Similar findings for low birthweight were seen for all women and nulliparous women for longstanding physical disability, inflammatory conditions, but not psychiatric conditions. Those with disability and chronic conditions with pain symptoms had 1.08 times higher odds of having a small for gestational age infant (95% CI: 1.02-1.15), than their counterparts with neither disability nor chronic conditions with pain symptoms. Similar findings for SGA were seen for all women and nulliparous women for inflammatory conditions, but not longstanding physical disability or psychiatric conditions (table 3.2).

Table 3.3 shows the differences in mean MME during pregnancy between disability groups and birth outcomes. Those with neither disability nor chronic conditions with pain symptoms received 67.06 MME, on average, during pregnancy (95% CI: 65.38-68.74), compared to those with both disability and chronic conditions with pain symptoms, who received 111.20 MME, on average, during pregnancy (103.00-119.30). This finding is similar across all disability diagnostic groups. Those who had a preterm birth received 87.96 MME, on average, during pregnancy (95% CI: 82.58-93.34); while those without a preterm birth received 77.58 MME, on average, during pregnancy (95% CI: 75.71-79.45). There were no differences in average MME during pregnancy for levels of low birthweight or SGA. For nulliparous women, there were differences seen in average MME during pregnancy between levels of disability overall, psychiatric conditions, and preterm birth.

Table 3.4 displays the results of the mediation analysis. For disability overall and chronic conditions with pain symptoms 6.79% of the association with preterm birth was

mediated by MME during pregnancy (95% CI: 2.48-11.10%). Similarly, for inflammatory conditions and chronic conditions with pain symptoms 5.04% of the association with preterm birth was mediated by MME during pregnancy (95% CI: 1.02-9.07%). Finally, for psychiatric conditions and chronic conditions with pain symptoms 5.52% of the association with preterm birth was mediated by MME during pregnancy (95% CI: 0.20-10.83). For nulliparous women, there was no mediation by total MME during pregnancy for disability and chronic conditions with pain symptoms and its association with adverse birth outcomes.

3.5 Discussion

Overall, opioid use during pregnancy does not mediate the association of disability and adverse birth outcomes. The current study does provide evidence of an association between longstanding physical disability, inflammatory conditions, and psychiatric disability and adverse birth outcomes. The findings of the current study align with some of the literature; although as definitions of disability vary widely, the ability to compare the magnitude of the effects from the current study is limited.

The first strength of the study is the use of multiple administrative data sources, which allowed us to obtain a high sample size and detailed data on each mother and infant. These administrative data sources were leveraged to categorize women into disability diagnostic groups, which are pathologically distinct. They were also utilized to obtain the total MME during pregnancy, chronic conditions with pain symptoms, and other prescriptions associated with birth outcomes and opioid prescribing. Similarly, another strength of using administrative data is that the current study excluded women with an indicator of opioid misuse, considering the lack of data related to illicit drug use.

The final strength was the use of causal mediation analysis, which allowed for inference to be made about the causal pathway between disability and the adverse birth outcomes of interest[94]. While there are specific mediation analyses for pharmacoepidemiology[95], the current study violates the key assumption of this model that disease-free people are not exposed to the drug of interest. For the current study, the exposure was a composite of disability and chronic conditions with pain symptoms to reduce the likelihood of unmeasured confounding from disease severity for the association of disability and opioids that may occur if disability were the exposure alone.

The greatest limitation of the current study is the restricted generalizability. The cohort was derived from South Carolina Medicaid beneficiaries, so the women included in this study were at or below 194% of the federal poverty level at some point during their pregnancy. Further, disability and pregnancy are qualifying events for Medicaid coverage, so women with disability are more likely to be covered by Medicaid before their pregnancy than their counterparts without disability. This may contribute to those with disability having better access to family planning and/or having higher rates of pregnancy intention. This may also lead to information bias in the current study as those with disability are more likely to have been covered by Medicaid throughout their entire pregnancy and, therefore, are more likely to have a more opioid prescriptions in the pharmacy data.

Another limitation to the current study is the temporality of disability and chronic conditions with pain symptoms. Records were not obtained over each woman's entire life, so the temporality of the disability diagnosis and the diagnosis of conditions with chronic pain is unknown. This limitation also lends to the possibility of misclassification

for undiagnosed chronic pain or disability conditions that impact activities of daily living that could lead to opioid prescribing, particularly early in the time of interest. This misclassification would put exposed women into the unexposed group, which would bias the results toward the null.

Further, opioid use only included prescription opioids dispensed, so the current study assumes that the opioids were taken as prescribed, and there was no differential misclassification of illicit opioid or other street drug use. Another limitation is the impact of survivorship bias, which may underestimate the magnitude of the associations as only live births were included in the current study. The final limitation to the current study is the lack of information from the administrative data about the severity of disability. If the severity of disability were available, the likelihood of unmeasured confounding between opioids and disability would be greatly reduced.

While there is no evidence that prescription opioid use during pregnancy is on the causal pathway between disability status and adverse birth outcomes, there is evidence for an association between disability and adverse birth outcomes. There is evidence that women with disabilities experience prenatal care differently than their counterparts without disability. Qualitative studies examining the barriers to optimal prenatal care for women with disability have shown that the ideal experiences for these women were with well-informed doctors about disability, as well as clinical offices that had mobility-assistance equipment[64,65,67]. For those with longstanding physical disability, perhaps there is a treatment of the injury or mobility limitation, like other prescriptions, that is the reason for the increased odds of preterm birth and low birthweight. For those with inflammatory conditions, perhaps there is an auto-immune explanation for the increased

odds of these adverse birth outcomes. Further, for those with psychiatric conditions, perhaps malnutrition or tobacco use explain the increased odds of adverse birth outcomes. These potential mechanisms warrant future study. There is also a possibility that the women with disability and chronic conditions with pain symptoms in the current study did not have their chronic pain adequately addressed or treated, which could lead to the increased odds of adverse birth outcomes. There is evidence that some pain management strategies are inadequate, particularly for those conditions where the source of the pain is undetermined[44].

In conclusion, obstetricians should be trained to deliver optimal care to support pregnant women with longstanding physical disability, psychiatric conditions, and inflammatory conditions that meets their unique needs.

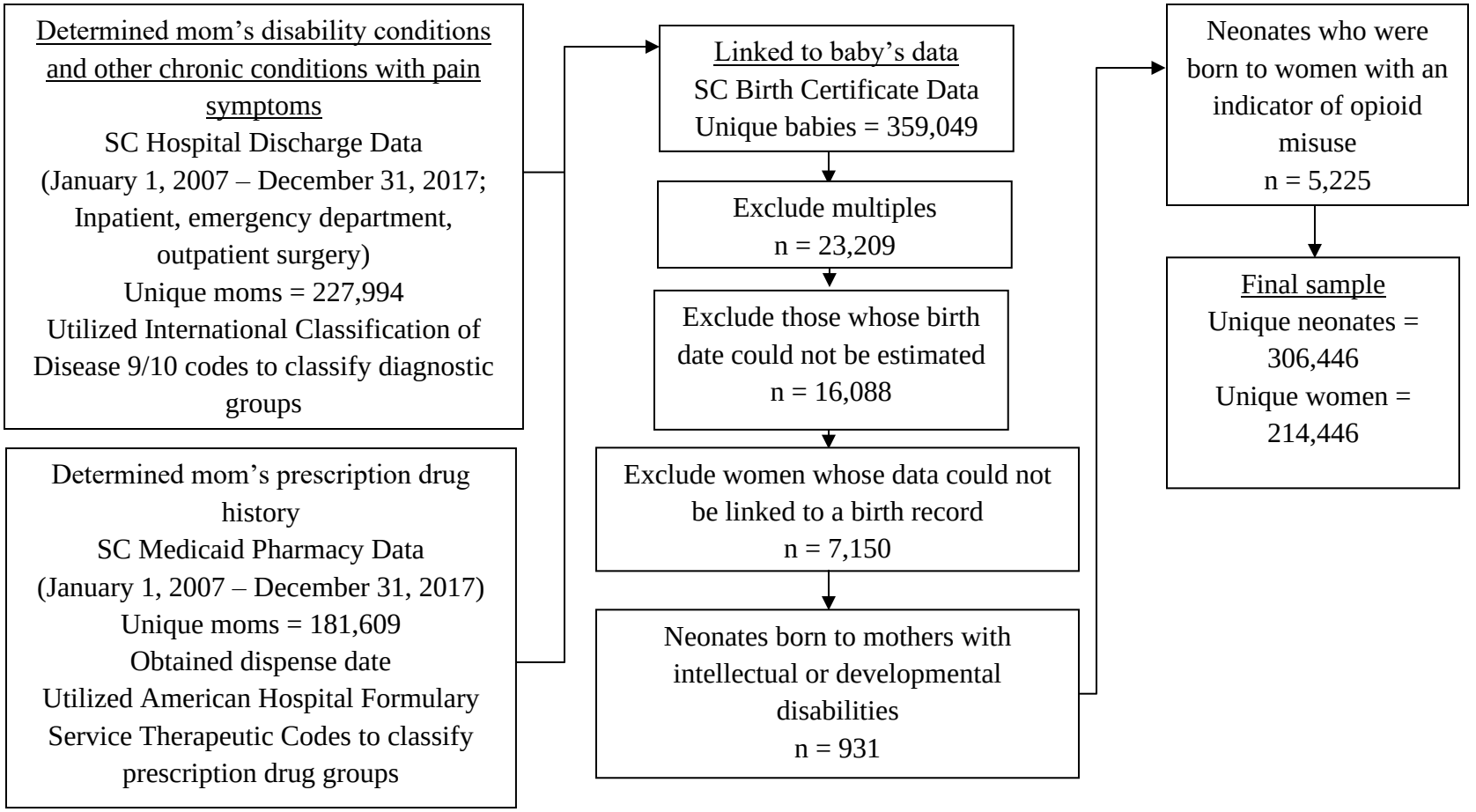

Figure 3.1. Data sources and sample exclusions for measuring the mediation of prescription opioid use during pregnancy of the association of disability and chronic pain and adverse birth outcomes for South Carolina Medicaid beneficiaries who gave birth from 2008 through 2017

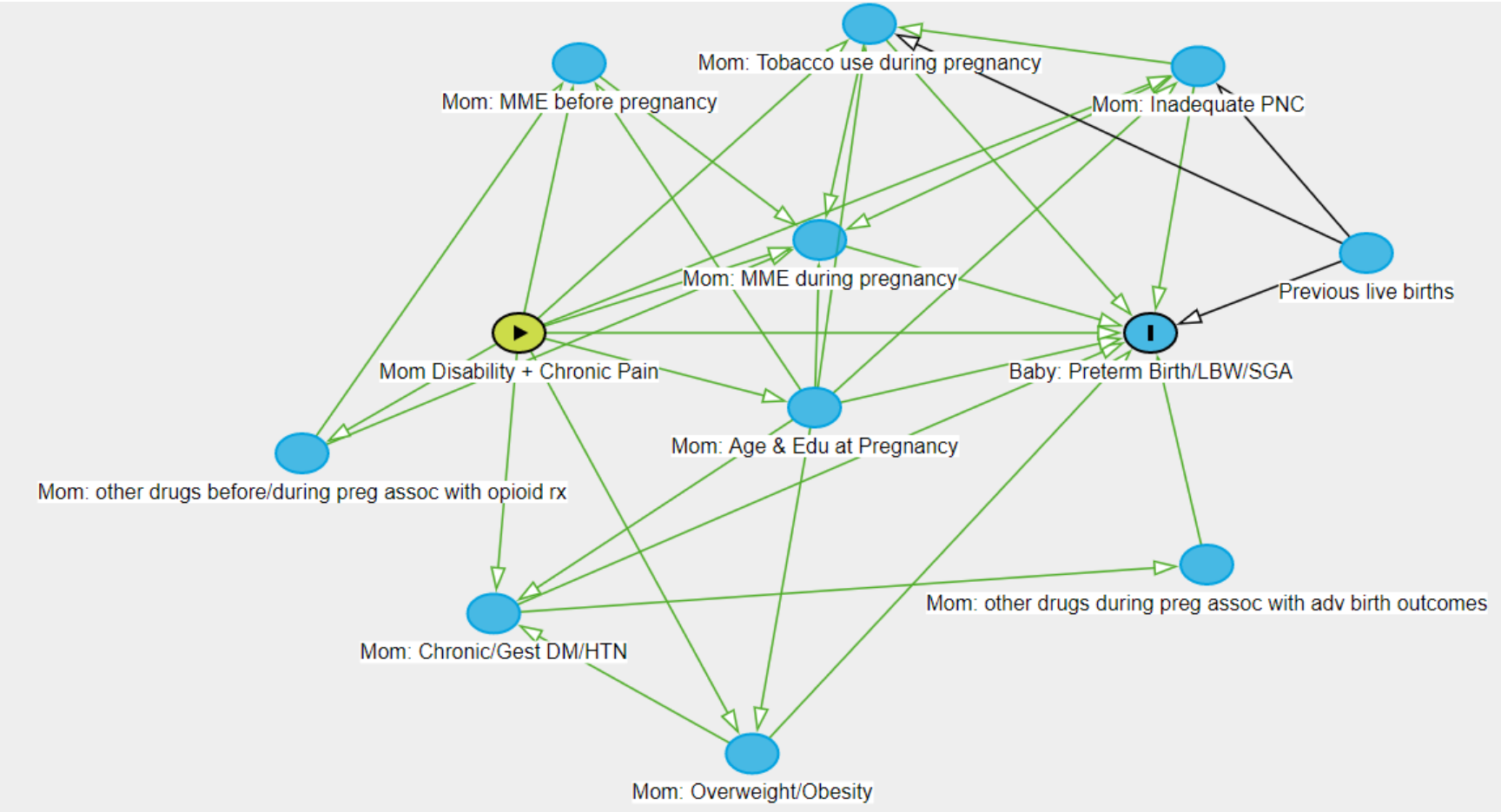

Figure 3.2. Directed acyclical graph (made using DAGitty) for causal mediation analysis of opioid use during pregnancy mediating the association of disability/chronic pain and adverse birth outcomes (PNC: prenatal care; Gest DM/HTN: Gestational Diabetes Mellitus or Hypertension; LBW: low birthweight; SGA: small for gestational age)

Table 3.1. Distribution of the outcomes, various pregnancy circumstances, and maternal attributes among the disability + chronic pain groups

	Overall		Disability + Conditions with Chronic Pain Symptoms		Longstanding Physical Disability + Conditions with Chronic Pain Symptoms		Inflammatory Conditions + Conditions with Chronic Pain Symptoms		Psychiatric Conditions + Conditions with Chronic Pain Symptoms	
	n	%	n	%	n	%	n	%	n	%
Overall	306,446	100%	9,672	3.2%	1,300	0.4%	1,535	0.5%	6,868	2.2%
Outcomes of interest										
Preterm birth (<37 weeks)	28,011	9.1%	1,216	12.6%	160	12.3%	215	14.0%	847	12.3%
Low birthweight (<2500 grams)	24,950	8.1%	978	10.1%	138	10.6%	189	12.3%	660	9.6%
Small-for-gestational age	38,081	12.4%	1,264	13.1%	184	14.2%	231	15.0%	859	12.5%
Potential confounders: categorical										
Maternal race										
White	163,393	53.3%	5,935	61.4%	597	45.9%	836	54.5%	4,527	65.9%
Black	137,747	44.9%	3,649	37.7%	694	53.4%	686	44.7%	2,273	33.1%
Other	5,185	1.7%	84	0.9%	8	0.6%	13	0.8%	65	0.9%
Hispanic/Latino	33,411	10.9%	288	3.0%	49	3.8%	50	3.3%	189	2.8%
Maternal education level										
Less than high school	82,981	27.1%	3,681	38.1%	446	34.3%	415	27.0%	2,834	41.3%
High school	101,667	33.2%	3,172	32.8%	436	33.5%	538	35.0%	2,205	32.1%
Some college	103,001	33.6%	2,613	27.0%	395	30.4%	530	34.5%	1,698	24.7%
4 year college degree or more	17,945	5.9%	177	1.8%	19	1.5%	46	3.0%	112	1.6%

Previous live births										
None	118,649	38.7%	2,505	25.9%	368	28.3%	398	25.9%	1,749	25.5%
One	93,146	30.4%	3,009	31.1%	412	31.7%	469	30.6%	2,137	31.1%
Two or more	94,547	30.9%	4,153	42.9%	518	39.8%	668	43.5%	2,979	43.4%
Tobacco use during pregnancy	46,062	15.0%	2,820	29.2%	241	18.5%	346	22.5%	2,246	32.7%
Kotelchuck Index										
Inadequate	74,268	24.2%	1,932	20.0%	247	19.0%	266	17.3%	1,424	20.7%
Intermediate	19,421	6.3%	669	6.9%	106	8.2%	107	7.0%	458	6.7%
Adequate	78,336	25.6%	2,208	22.8%	309	23.8%	336	21.9%	1,570	22.9%
Adequate plus	133,729	43.6%	4,841	50.1%	632	48.6%	824	53.7%	3,402	49.5%
Risk factors										
Prepregnancy diabetes	3,147	1.0%	165	1.7%	25	1.9%	18	1.2%	122	1.8%
Gestational diabetes	16,525	5.4%	499	5.2%	58	4.5%	75	4.9%	369	5.4%
Prepregnancy hypertension	8,388	2.7%	324	3.3%	58	4.5%	52	3.4%	217	3.2%
Gestational hypertension	18,421	6.0%	652	6.7%	86	6.6%	104	6.8%	462	6.7%
Prepregnancy BMI category										
Underwight (<18.5)	13,813	4.5%	439	4.5%	48	3.7%	61	4.0%	333	4.8%
Normal weight (18.5-<25.0)	110,748	36.1%	3,247	33.6%	448	34.5%	531	34.6%	2,279	33.2%
Overweight (25.0-<30.0)	75,171	24.5%	2,302	23.8%	301	23.2%	378	24.6%	1,631	23.7%
Obese (30.0+)	100,672	32.9%	3,492	36.1%	475	36.5%	541	35.2%	2,484	36.2%
Drugs associated with adverse birth outcomes (before or during pregnancy)	33,858	11.0%	2,560	26.5%	334	25.7%	395	25.7%	1,844	26.8%
Drugs associated with opioid prescribing (before or during pregnancy; Central Nervous System agents)	57,490	18.8%	5,728	59.2%	604	46.5%	717	46.7%	4,428	64.5%
Continuous variables (mean (SD))										

Birthweight	3,209.04	537.08	3,153.81	542.01	3,134.02	534.50	3,114.82	563.43	3,165.45	538.66
Gestational age	38.47	1.77	38.17	1.78	38.19	1.79	38.05	1.85	38.19	1.76
Total MME before pregnancy	93.16	152.13	133.65	218.91	118.62	159.19	161.32	297.02	130.52	207.60
Total MME during pregnancy	78.77	132.78	111.16	184.12	94.69	140.38	139.93	230.40	107.79	178.43
Maternal age in years	25.05	5.51	24.41	5.36	24.27	5.30	25.14	5.38	24.28	5.35

Table 3.2. Logistic regression modeling association of disability + chronic pain + (compared to disability – chronic pain –) and adverse birth outcomes

	Total Sample n = 306,446			Nulliparous Only n = 118,649		
	OR	95% CI		OR	95% CI	
Preterm birth						
Disability + Chronic Pain +	1.52	1.43	1.62	1.37	1.20	1.55
LPD + Chronic Pain +	1.47	1.25	1.74	1.61	1.18	2.18
IC + Chronic Pain +	1.70	1.47	1.97	1.79	1.35	2.38
PSY + Chronic Pain +	1.48	1.37	1.59	1.21	1.03	1.42
Low birthweight						
Disability + Chronic Pain +	1.33	1.24	1.42	1.23	1.08	1.40
LPD + Chronic Pain +	1.47	1.25	1.74	1.42	1.04	1.94
IC + Chronic Pain +	1.64	1.41	1.91	1.66	1.25	2.20
PSY + Chronic Pain +	1.25	1.15	1.35	1.09	0.93	1.28
SGA						
Disability + Chronic Pain +	1.08	1.02	1.15	1.12	1.00	1.24
LPD + Chronic Pain +	1.18	1.01	1.38	1.27	0.97	1.65
IC + Chronic Pain +	1.27	1.10	1.46	1.36	1.07	1.75
PSY + Chronic Pain +	1.02	0.95	1.10	1.03	0.90	1.17
LPD: longstanding physical disability; IC: inflammatory conditions; PSY: psychiatric conditions; SGA: small for gestational age						

Table 3.3. Results of t-test for average total morphine milligram equivalents of prescribed opioids during pregnancy between disability groups and adverse birth outcomes

	Total Sample n = 306,446			Nulliparous Only n = 118,649		
	Mean	95% CI		Mean	95% CI	
Disability – Chronic Pain –	67.06	65.38	68.74	64.43	61.77	67.09
Disability + Chronic Pain +	111.20	103.00	119.30	90.78	76.30	105.30
LPD – Chronic Pain –	67.88	66.16	69.59	65.06	62.28	67.84
LPD + Chronic Pain +	94.69	77.09	112.30	79.02	55.83	102.20
IC – Chronic Pain –	67.83	66.14	69.53	65.37	62.58	68.15
IC + Chronic Pain +	139.90	114.20	165.60	99.56	52.83	146.30
PSY – Chronic Pain –	67.40	65.71	69.09	64.35	61.73	66.98
PSY + Chronic Pain +	107.80	98.46	117.10	91.91	74.83	109.00
Not preterm birth	77.58	75.71	79.45	69.14	66.55	71.73
Preterm birth	87.96	82.58	93.34	81.56	72.05	91.07
Not low birthweight	78.34	76.47	80.20	69.80	67.18	72.42
Low birthweight	82.72	77.20	88.24	75.80	66.97	84.64
Not SGA	78.65	76.79	80.52	71.04	68.23	73.86
SGA	79.50	74.21	84.78	67.42	61.79	73.06
LPD: longstanding physical disability; IC: inflammatory conditions; PSY: psychiatric conditions; SGA: small for gestational age						

Table 3.4. Causal mediation analysis of total morphine milligram equivalents of opioids prescribed during pregnancy mediating the association of disability + chronic pain and adverse birth outcomes

	Total effect			Natural Direct effect			Natural Indirect effect			% mediated		
Total Sample n = 306,446	OR	95% CI		OR	95% CI		OR	95% CI		Estimate	95% CI	
Disability + Chronic Pain +												
Low birthweight	1.02	1.01	1.04	1.02	1.01	1.04	1.00	1.00	1.00	3.74	-5.78	13.27
Preterm birth	1.06	1.04	1.07	1.05	1.04	1.07	1.00	1.00	1.01	6.79	2.48	11.10
SGA	0.99	0.97	1.01	0.99	0.97	1.01	1.00	1.00	1.00	4.99	-21.09	31.07
LPD + Chronic Pain +												
Low birthweight	1.02	0.98	1.06	1.02	0.98	1.06	1.00	1.00	1.00	1.84	-6.80	10.48
Preterm birth	1.06	1.02	1.10	1.05	1.01	1.09	1.00	1.00	1.00	3.49	-0.50	7.48
SGA	0.99	0.95	1.04	0.99	0.95	1.04	1.00	1.00	1.00	7.98	-35.96	51.92
IC + Chronic Pain +												
Low birthweight	1.09	1.05	1.13	1.09	1.05	1.13	1.00	1.00	1.00	0.95	-3.34	5.24
Preterm birth	1.11	1.07	1.15	1.11	1.07	1.14	1.01	1.00	1.01	5.04	1.02	9.07
SGA	1.03	0.99	1.07	1.03	0.99	1.07	1.00	0.99	1.00	-8.01	-28.87	12.85
PSY + Chronic Pain +												
Low birthweight	1.01	0.99	1.02	1.01	0.99	1.02	1.00	1.00	1.00	0.21	-22.59	23.02
Preterm birth	1.04	1.03	1.06	1.04	1.02	1.06	1.00	1.00	1.00	5.52	0.20	10.83
SGA	0.98	0.96	1.00	0.98	0.97	1.00	1.00	1.00	1.00	2.61	-11.27	16.49
Nulliparous Only n = 118,649												
Disability + Chronic Pain +												
Low birthweight	1.02	0.99	1.05	1.02	0.99	1.05	1.00	1.00	1.00	7.15	-9.02	23.32
Preterm birth	1.03	1.00	1.06	1.03	1.00	1.06	1.00	1.00	1.01	15.11	-2.60	32.82
SGA	1.01	0.97	1.05	1.01	0.97	1.05	1.00	1.00	1.00	-12.77	-76.96	51.41

LPD + Chronic Pain +												
Low birthweight	1.01	0.94	1.10	1.01	0.93	1.09	1.00	1.00	1.00	10.49	-57.29	78.27
Preterm birth	0.98	0.91	1.06	0.98	0.91	1.06	1.00	1.00	1.01	-14.19	-88.13	59.76
SGA	1.02	0.93	1.12	1.02	0.93	1.12	1.00	1.00	1.00	-5.96	-40.14	28.23
IC + Chronic Pain +												
Low birthweight	1.05	0.98	1.13	1.05	0.98	1.13	1.00	1.00	1.01	5.39	-5.06	15.84
Preterm birth	1.12	1.05	1.21	1.12	1.04	1.20	1.01	1.00	1.01	4.95	-0.24	10.14
SGA	1.07	0.97	1.17	1.07	0.98	1.17	1.00	0.99	1.00	-5.00	-15.14	5.15
PSY + Chronic Pain +												
Low birthweight	1.02	0.98	1.05	1.01	0.98	1.05	1.00	1.00	1.00	12.68	-20.12	45.49
Preterm birth	1.02	0.98	1.05	1.01	0.98	1.05	1.00	1.00	1.01	25.46	-23.75	74.67
SGA	1.00	0.96	1.04	1.00	0.96	1.04	1.00	1.00	1.00	-	-	-
LPD: longstanding physical disability; IC: inflammatory conditions; PSY: psychiatric conditions; SGA: small for gestational age; OR: odds ratio; CI: confidence interval												

CHAPTER 4

CUMULATIVE PRESCRIPTION OPIOID USE DURING PREGNANCY, THE INTERACTION OF CHRONIC CONDITIONS WITH PAIN SYMPTOMS AND DISABILITY, AND ADVERSE BIRTH OUTCOMES[3]

[3]Richard CL, Love BL, Boghossian N, Hardin J, McDermott S. To be submitted to *Journal of Opioid Management*.

4.1 Abstract

Objective: To understand the association between cumulative, prenatal prescription opioid use and neonatal abstinence syndrome (NAS), admission to the neonatal intensive care unit (NICU), and length of stay (LOS) in the hospital and how it differs by chronic conditions of disability and/or those associated with pain symptoms

Design: Retrospective cohort

Setting: South Carolina

Participants: Medicaid beneficiaries with a live birth from 2008-2017

Main Outcome Measures: NAS, NICU admission, increased LOS

Results: A 10-unit increase in cumulative, prenatal morphine milligram equivalents (MME) is associated with 2.2% higher odds of NAS (95% confidence interval (CI): 1.7%-2.6%), after adjustment. All levels of conditions of disability overall and pain symptoms are significantly associated with increased odds of NAS. A 10-unit increase in cumulative, prenatal MME is associated with 0.02% higher rate of LOS per live birth, after adjustment. An increase in cumulative, prenatal MME was not associated with increased odds of NICU admission, after adjustment.

Conclusions: The current study lends to a call for policies that encourage pregnant women to seek drug treatment and for a model that ensures a comprehensive approach continuity of care between drug treatment, obstetrics, and professionals caring for women with disability and/or conditions with pain symptoms.

Key Words: Disability, Pain, Pregnancy, Medicaid, Neonatal Outcomes

4.2 Background

Nationally, the prevalence of opioid use disorder per 1,000 delivery hospitalizations increased from 1.5 in 1999 to 6.5 in 2014[4]. As recently as 2019, 6.6% of women across 34 US jurisdictions reported prescription opioid use during pregnancy[5]. Opioid use, either prescription or illicit, during pregnancy is related to adverse neonatal and maternal outcomes, like delayed prenatal care[10], maternal death[11], minor congenital malformations[12], and neonatal abstinence syndrome[13]. Neonatal abstinence syndrome (NAS) is characterized by in utero exposure to opioids, benzodiazepines, or barbiturates, in addition to poor sleep or feeding, high-pitched or excessive crying, among other signs[28].

Consistent with the clinical definitions, findings are reliable that prenatal opioid exposure, compared to no exposure, is associated with a higher risk of NAS[14,17,18,23–26]. Further, there is evidence that opioid prescriptions used for medication-assisted treatment of opioid use disorder, like methadone and buprenorphrine, have differing magnitudes of increased risk for NAS, when compared to each other[19,20]. Admission to the neonatal intensive care unit (NICU) and an increased length of stay (LOS) in the hospital is significantly higher among infants with NAS[96]. Similarly, findings are consistent that prenatal opioid exposure, compared to no exposure, is associated with a higher risk of NICU admission[18,22,23] and longer LOS[11,17].

Shortly after birth, NAS is related to an increase in stress hormones for both mom and baby[51] and admission to the NICU and increased LOS are related to family stress and disruptions in bonding between the infant and parents[52]. While the causal pathways are not clear, there is evidence that these adverse birth outcomes have short- and long-term

impacts on the whole family. NAS has been associated with an increased risk of neurodevelopmental issues in infancy[53] and not meeting well-child visit recommendations at fifteen months[54]. There is also evidence for impacts later on in childhood, such as having a complex chronic condition at age five[54], meeting criteria for disability and needing therapeutic services at school (ages three through eight)[55], and difficulties (emotional and behavioral) at age nine[56]. Having an infant with these adverse birth outcomes has also been associated with short- and long-term parent outcomes, like posttraumatic stress disorder[52], chronic and postpartum depression[61,62] and anxiety[61].

There is evidence that mothers with chronic depression[52] or mental health disorders[22,23], compared to the general population, are at higher risk of these adverse birth outcomes and opioid use. However, there is a gap in the literature for evidence of increased risks of these adverse birth outcomes among those with other chronic conditions that are associated with higher risk of opioid use, like longstanding physical disability, inflammatory conditions, and other conditions with pain symptoms[42–44,50,63]. These subgroups and those with disability broadly have higher rates of opioid use, potential for opioid misuse, and are prescribed higher dosages than their counterparts without these conditions[41–44,50,63]. Further, those with disability often experience less than optimal prenatal care[64–67], which may limit the amount of monitoring they receive from a clinician for their prenatal opioid intake, compared to those without disability.

Therefore, the current study aims to understand the association between cumulative prescription opioid use during pregnancy and NAS, NICU admission, and length of stay (LOS) in the hospital. We hypothesize that an increase in cumulative prescribed morphine milligram equivalents (MME) during pregnancy will be associated

with an increased risk of having an infant with NAS or a NICU admission and a longer LOS, for Medicaid beneficiaries, after controlling for known risk factors. We further hypothesize that this risk will be highest for those with disability (physical, inflammatory, or psychiatric) and chronic conditions with pain symptoms than those without. Finally, we hypothesize that those with chronic conditions with pain symptoms and physical disabilities or inflammatory conditions would have higher risk of having an infant with NAS or a NICU admission and a longer LOS, compared to women with chronic conditions with pain symptoms and psychiatric conditions or women without disability, controlling for other known risk factors.

4.3 Methods

Data from clinical records, pharmacy claims, and birth certificates were linked for South Carolina Medicaid beneficiaries who gave birth from 2008 through 2017. Clinical records were obtained from inpatient, outpatient, and emergency department discharges. The following were excluded from the analysis sample: non-singleton babies (n = 23,209); babies whose date of birth could not be estimated (n = 16,088); babies to moms with intellectual disabilities (n=931); babies to moms with no or unknown opioid prescriptions during pregnancy (n = 295,894); moms missing disability or chronic conditions with pain symptoms status (n = 23); moms with indicators of opioid misuse (n=1,304; definition in appendix table C.1). The remaining sample was 22,493 babies (figure 4.1). For analyses of NICU admission and length of stay, babies with high-risk conditions (definition in appendix table C.1) were excluded from the sample (n = 5,365; figure 4.1), which resulted in a sample of 17,128 babies. These high-risk conditions were selected as they

appeared in the list of top fifteen causes of infant mortality in South Carolina from 2008-2017[97,98].

Prescription opioid use during pregnancy was obtained through pharmacy records, and those included were based on their American Hospital Formulary Service Therapeutic Codes: opiate agonists (28:08.08); opiate partial agonists (28:08.12); opioid antagonists (28:10). During pregnancy was defined as between the estimated date of last menses and estimated date of birth. Cumulative morphine milligram equivalents (MME) over the entire pregnancy were calculated utilizing a reference obtained from the Centers for Disease Control and Prevention[71]. Extreme or missing values of MME were marked as missing; extreme was defined as greater than two standard deviations from the mean (2,977.28). Less than 1% of all opioid prescriptions met this definition of extreme. For the current study, cumulative prescription opioid use during pregnancy was continuous.

Hospital discharge records via International Classification of Disease (ICD) codes 9/10 were used to obtain disability status overall, disability diagnostic group (longstanding physical disability; inflammatory conditions; psychiatric conditions), and status of other conditions with associated chronic pain symptoms (table 4.1). Other covariates of interest were obtained from the birth certificate: Kotelchuck index[73]; tobacco use during pregnancy; previous live births (0, 1, 2+); maternal race, ethnicity, age, and educational attainment. Kotelchuck index[73] is a measure of utilization and adequacy of prenatal care.

The outcomes of interest were obtained from the hospital discharge records for both mom and baby. Diagnosis of neonatal abstinence syndrome (NAS) was obtained through age two, using diagnostic codes (ICD-9: 779.5; ICD-10: P96.1). Both admission

to the neonatal intensive care unit (NICU) and length of stay were calculated across all newborn hospitalizations associated with the delivery hospitalization. Length of stay was a continuous, discrete count of days for modelling purposes but was dichotomized into ≤2 days (median) or more than 2 days for descriptive statistics.

As described in the directed acyclical graphs derived from DAGitty[75] (figures 4.2 and 4.3), logistic regression models for the association of cumulative prescription opioid use during pregnancy and NAS and NICU admission were adjusted for maternal age and educational attainment; inadequate prenatal care (defined by the Kotelchuck index); tobacco use during pregnancy; previous live births; and the interaction of disability (overall and by group) and other conditions with chronic pain symptoms. Poisson regression models for the association of cumulative prescription opioid use during pregnancy and length of stay were adjusted for the same covariates as the models for NAS and NICU admission.

SAS 9.4 was utilized for all analyses[74]. Bivariate analyses were utilized to describe each sample. Adjusted odds ratios and related 95% confidence intervals (CIs) were obtained from the logistic regression models. Adjusted rate ratios and related 95% CIs were obtained from the Poisson regression models.

4.4 Results

NAS and NICU admission were rare outcomes with 0.6% and 0.4% of the samples experiencing each, respectively. Infants with NAS had a higher prevalence of moms with disability overall, inflammatory conditions, psychiatric conditions, other conditions with chronic pain symptoms, less than adequate prenatal care, tobacco use during pregnancy, had two or more previous live births, and who identified as white, compared to those

without NAS. Infants who were admitted to the NICU had a higher prevalence of moms with disability overall, psychiatric conditions, not having other chronic conditions with pain symptoms, tobacco use during pregnancy, and who identified as white, compared to those who were not admitted to the NICU. The demographic distribution for infants with an above median length of stay compared to those with a length of stay two days or less were relatively homogenous (table 4.1).

For those with disability overall, a 10-unit increase in cumulative MME during pregnancy was associated with 2.2% increased odds of NAS (95% CI: 1.7%-2.6%). This finding was consistent across the disability groups. While there were no dose response relationships observed across levels of disability and other chronic conditions with pain symptoms, this interaction was significantly associated with increased odds of NAS. Across disability groups, those with other chronic conditions with pain symptoms without disability had increased odds of NAS (disability overall: aOR: 2.220; 95% CI: 1.457-3.382), compared to those with neither other chronic conditions with pain symptoms nor disability (table 4.2). There were no differences observed for the association between a 10-unit increase in cumulative MME during pregnancy or the interaction of disability and chronic pain and NICU admission for disability overall or any disability diagnostic group (table 4.2).

For those with disability overall, a 10-unit increase in cumulative MME during pregnancy was associated with a 0.2% increased rate of length of stay per live birth (95% CI: 0.1%-0.2%). This finding was consistent across the disability groups. Those with disability overall, but without other chronic conditions with pain symptoms had a 5.7% increased rate of length of stay per live birth (95% CI: 0.06%-11.1%), compared to those

with neither disability nor other chronic conditions with pain symptoms. This finding was also observed for those with psychiatric conditions. Women with inflammatory conditions and other chronic conditions with pain symptoms had a 12.4% increase rate of length of stay per live birth (95% CI: 3.4%-22.2%), compared to those with neither inflammatory nor other chronic conditions with pain symptoms (table 4.3).

4.5 Discussion

Prescription opioid use during pregnancy is associated with increased odds of NAS and increased rate of length of stay, after adjusting for confounders and the interaction of disability and other chronic conditions with pain symptoms. Overall, whether disability and other chronic conditions with pain symptoms are both present or either are present does not make a difference in the interaction's association with NAS or length of stay, but it is significantly associated with increased odds of both outcomes. Prenatal prescription opioid use was not associated with an increased risk of NICU admission for neither disability overall nor any disability diagnostic group and their interaction with other conditions with chronic pain.

Literature is limited on the association of cumulative MME during pregnancy and the adverse birth outcomes of interest, as well as for differences by maternal disability and chronic pain status. The current study aligns with evidence that prescription opioid use during pregnancy is associated with increased risk of NAS, when adjusted for risk factors[24–26], and this risk increases as the dosage of opioids increases[24]. Since the current study excluded those with opioid use disorder, it is difficult to compare to Ma et al (2020), which found that women with mental health conditions and opioid use disorder[23] are at increased risk of having an infant with NAS and NICU admission[23].

Existing studies utilized a combination of claims data[11,23,25,26,99] (mostly, Medicaid[23–25]), birth certificate[14,22,25], and hospital discharge data[14,22], but none of these studies linked these three data sources together like the current study does. While there are concerns about the reliability of administrative data, particularly birth certificate data[14,100,101], this is limited in the current study as the main exposure and outcomes of interest were derived from the clinical and pharmacy data. However, interpretation of the current study is contingent on the assumption that the opioids were taken as prescribed. Further, by using several administrative data sources, the current study encompassed ten years of live births, during a period where surveillance of opioid prescribing increased[3,102].

Another strength is the use of ICD 9/10 codes for the definition of disability overall, disability diagnostic groups, conditions with chronic pain symptoms, high-risk conditions of the infant, and the outcome of NAS (through age two). While there is no standard case definition for NAS, studies have found high positive predictive value (ranging from 91.0%-98.2%) of the ICD 9/10 codes for identifying this condition[103,104], which were used to define the NAS outcome for this study through age two. By utilizing pharmacy records, the authors were able to calculate cumulative MME during pregnancy, and it remained a continuous variable in all models. The final strength was the inclusion of the interaction between disability and conditions with chronic pain symptoms, which is a unique feature of the current study.

Limitations to the current study include lack of data on illicit opioid use that could lead to an underestimation of the measures of association, which is a common limitation of other studies[24–26]. However, since the current study excluded mothers with indicators

of opioid misuse, the authors believe the impact of this lack of information is limited and, therefore, would not introduce any sizable unmeasured confounding. Other limitations are the lack of information on the severity of disability or NAS and the unclear temporality between the onset of disability, conditions with chronic pain symptoms, and opioid use. Several researchers call for the need to use an assessment tool for measuring NAS severity[24,25], like the Finnegan Scale, to limit diagnosis bias and improve the reliability of NAS codes in claims data[14,26]. Typically, these assessment tools are time-intensive, necessitate a high-level of training, and require assessment by two professionals simultaneously[105], so their scalability for widespread use is questionable. The final limitation is the generalizability of the findings, as the sample was exclusively focused on women receiving Medicaid benefits in a non-expansion state. If the current study were done in a state with expanded Medicaid eligibility, the demographics of the sample would be different since the income eligibility criteria would be higher, and the sample size would be larger as more women could be included in any exposure group, as well as would have pharmacy records. However, it is likely that more women without disability would be included in the study than those with disability. Therefore, the current study may be an overestimate of the associations that would be observed in an expansion state.

There is evidence that lowering dosages of opioids towards the end of pregnancy[24] or use of non-opioid therapies would lower risk of these adverse birth outcomes, as recommended by the American College of Obstetricians and Gynecologists[89]. Adverse outcomes associated with prenatal opioid use are directly

related to significant increases in Medicaid expenditures over the past two decades[13,106–109], so decreasing these risks in the population will also ease the burden on the public insurance system, as well as decrease short- and long-term impacts of these outcomes that lead to future complications related to stress[51], reduced bonding[52], and anxiety[61].

One barrier to reducing the short- and long-term impacts of these outcomes is a lack of continuity of care or comprehensive approaches either within the NICU[52,110] or between drug treatment and obstetrics[111]. Since 1999, three large birth hospitals in Dublin, Ireland have had a Drug Liaison Midwife, who coordinates care between obstetrics and addiction services[111]. This model reduces stigma, which is another cited barrier to reducing the impacts of these outcomes[110], and suggests a benefit for not only the infant and the mother, but also for the health care system broadly[111]. However, this model is dependent on women accepting drug treatment or misusing prescription opioids to the point of needing drug treatment[111].

Policies that encourage pregnant women to seek drug treatment could improve maternal and child outcomes[23]. In South Carolina, a positive drug test for either the mother or the child, unless it is for "medical treatment", is proof that a "newborn child is an abused or neglected child"[90]. The state code does not explicitly state whether medication-assisted treatment for a substance use disorder is an allowable "medical treatment," for which a newborn would not be considered neglected or abused[90]. Like South Carolina, drug use during pregnancy is considered child abuse in 22 other states and the District of Columbia[91].

The current study lends to a call for a model that ensures a comprehensive approach continuity of care between drug treatment, obstetrics, and professionals caring

for women with disability and/or conditions with pain symptoms. Two-generation approaches, like whole family supports in the NICU[52], should be taken to address the complex needs of those with disability and/or conditions with pain symptoms and their infants, particularly for those women who are prescribed opioids during pregnancy.

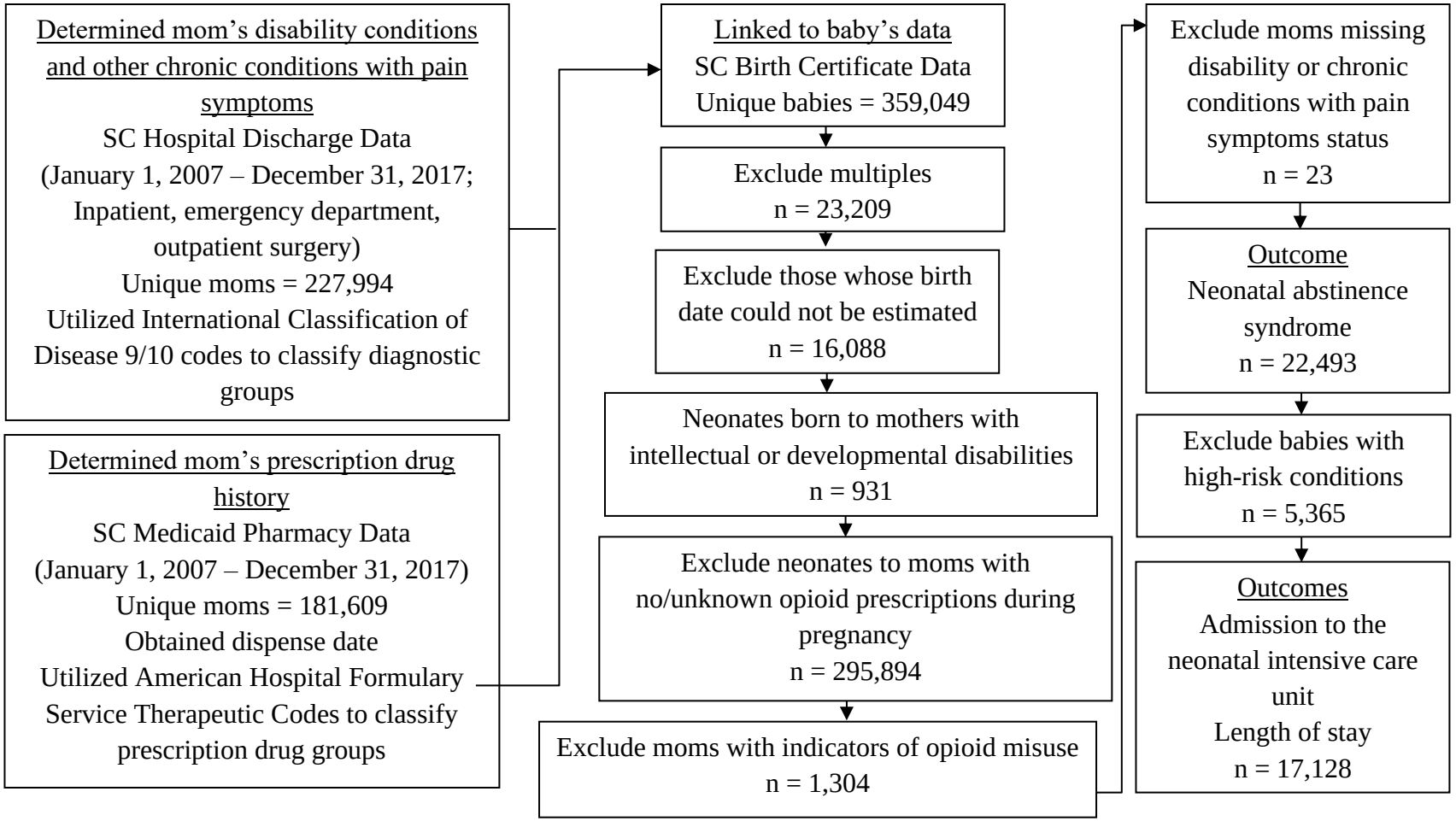

Figure 4.1. Data linkages from hospital discharge, pharmacy, and birth certificate data from South Carolina Medicaid beneficiaries who gave birth from 2008-2017 and exclusions made to obtain analytic sample for neonatal abstinence syndrome, admission to the neonatal intensive care unit, and length of stay

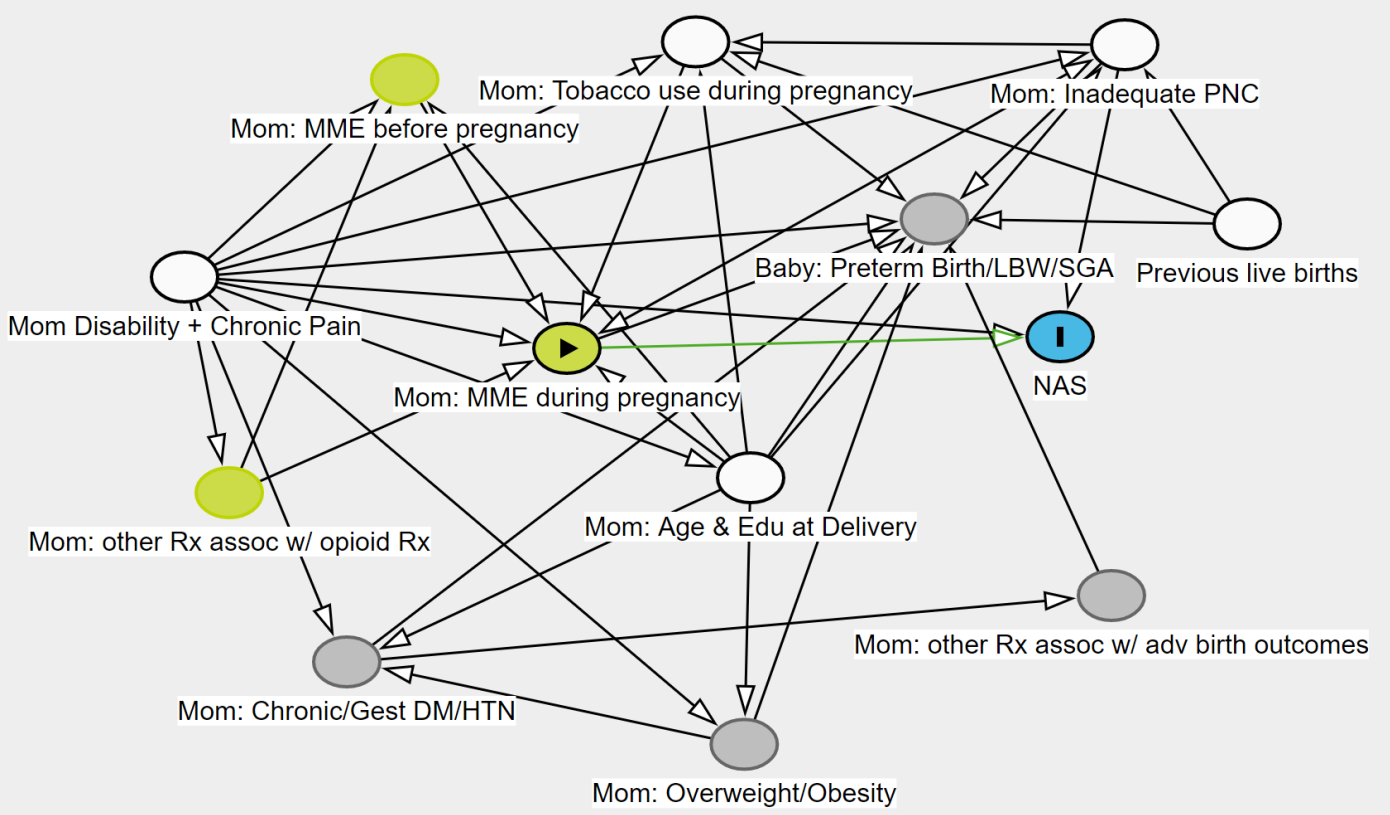

Figure 4.2. Directed acyclical graph (derived from DAGitty) of association between cumulative morphine milligram equivalents (MME) during pregnancy and neonatal abstinence syndrome (NAS) – model adjusted for: interaction of disability and other conditions with pain symptoms; tobacco use during pregnancy; inadequate prenatal care (PNC; measured with the Kotelchuck Index); previous live births; mom age and education (edu) at delivery

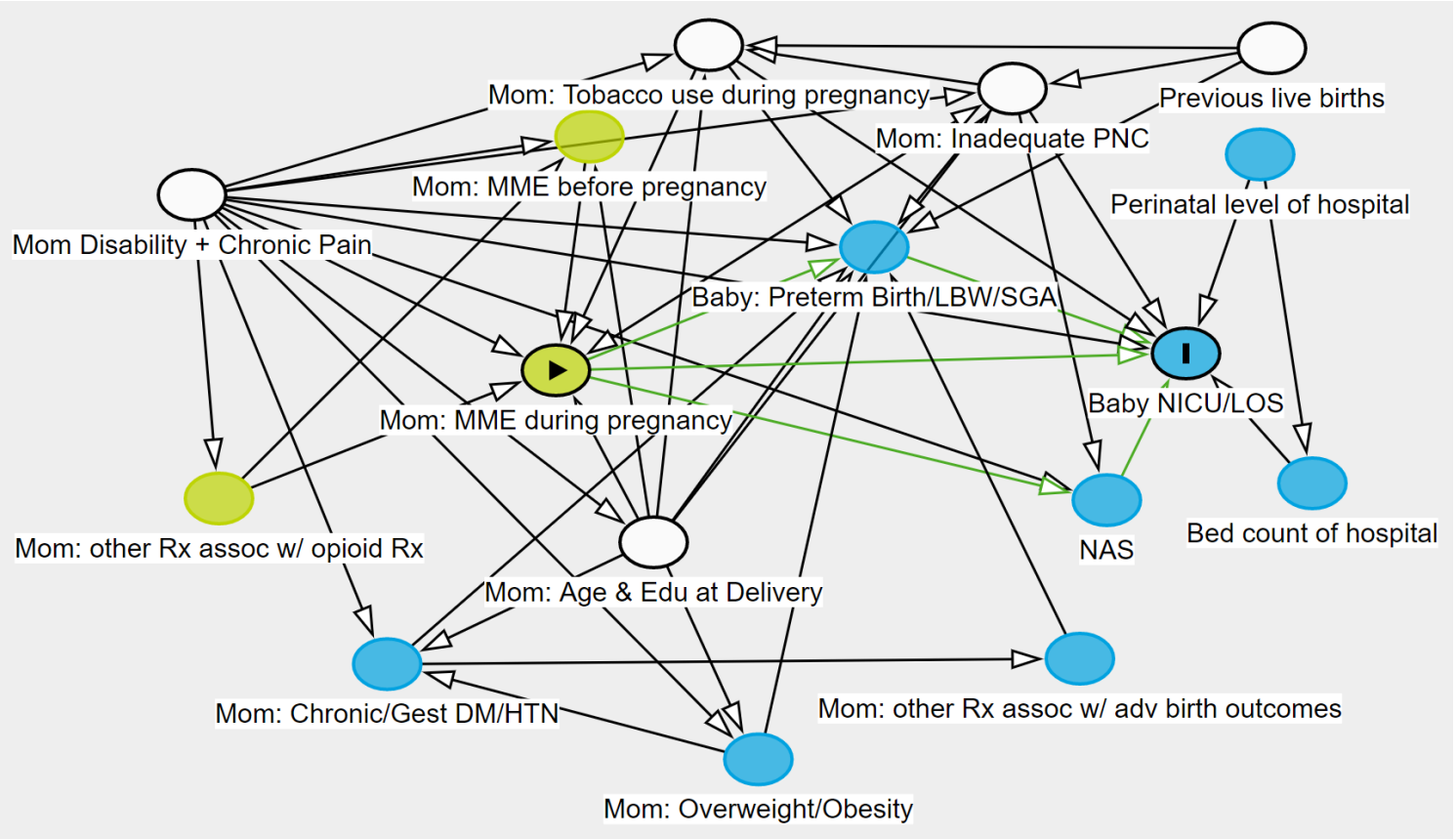

Figure 4.3. Directed acyclical graph (derived from DAGitty) of association between cumulative morphine milligram equivalents (MME) during pregnancy and admission to the neonatal intensive care unit (NICU) and increased length of stay (LOS) – model adjusted for: interaction of disability and other conditions with pain symptoms; tobacco use during pregnancy; inadequate prenatal care (PNC; measured with the Kotelchuck Index); previous live births; mom age and education (edu) at delivery

Table 4.1. Demographic and risk factor distribution by outcomes of interest (neonatal abstinence syndrome (NAS); neonatal intensive care unit (NICU) admission; length of stay)

	NAS (n = 22,493)				NICU Admission (n = 17,128)				Length of Stay (median; n = 17,128)			
	No		Yes		No		Yes		≤2 Days		>2 Days	
	n	%	n	%	n	%	n	%	n	%	n	%
Overall	22,351	99.4%	142	0.6%	17,066	99.6%	62	0.4%	12,681	74.0%	4,447	26.0%
Prescription opioid use during pregnancy (cumulative MME (mean, SD))	77.7	120.0	283.0	494.1	77.9	122.4	90.7	120.8	76.4	112.5	82.3	146.8
Maternal age (mean, SD)	25.0	5.3	27.2	5.0	24.9	5.2	24.3	4.2	24.8	5.1	25.4	5.6
Disability												
No	19,365	86.6%	98	69.0%	14,907	87.3%	50	80.6%	11,116	87.7%	3,841	86.4%
Yes	2,986	13.4%	44	31.0%	2,159	12.7%	12	19.4%	1,565	12.3%	606	13.6%
Longstanding physical disability												
No	21,968	98.3%	141	99.3%	16,801	98.4%	60	96.8%	12,491	98.5%	4,370	98.3%
Yes	383	1.7%	1	0.7%	265	1.6%	2	3.2%	190	1.5%	77	1.7%
Inflammatory conditions												
No	21,855	97.8%	131	92.3%	16,724	98.0%	60	96.8%	12,432	98.0%	4,352	97.9%
Yes	496	2.2%	11	7.7%	342	2.0%	2	3.2%	249	2.0%	95	2.1%

Psychiatric conditions												
No	20,233	90.5%	110	77.5%	15,508	90.9%	54	87.1%	11,550	91.1%	4,012	90.2%
Yes	2,118	9.5%	32	22.5%	1,558	9.1%	8	12.9%	1,131	8.9%	435	9.8%
Chronic conditions with pain symptoms												
No	12,874	57.6%	48	33.8%	9,971	58.4%	40	64.5%	7,346	57.9%	2,665	59.9%
Yes	9,477	42.4%	94	66.2%	7,095	41.6%	22	35.5%	5,335	42.1%	1,782	40.1%
Kotelchuck index												
Inadequate	4,297	19.2%	54	38.0%	3,251	19.0%	6	9.7%	2,370	18.7%	887	19.9%
Intermediate	1,278	5.7%	11	7.7%	1,017	6.0%	8	12.9%	776	6.1%	249	5.6%
Adequate	5,139	23.0%	25	17.6%	4,188	24.5%	16	25.8%	3,138	24.7%	1,066	24.0%
Adequate Plus	11,584	51.8%	49	34.5%	8,585	50.3%	32	51.6%	6,377	50.3%	2,240	50.4%
Tobacco use during pregnancy												
Yes	5,932	26.5%	84	59.2%	4,628	27.1%	22	35.5%	3,556	28.0%	1,094	24.6%
No	16,398	73.4%	56	39.4%	12,427	72.8%	40	64.5%	9,116	71.9%	3,351	75.4%
Maternal education												
Less than high school	6,756	30.2%	47	33.1%	5,180	30.4%	13	21.0%	3,920	30.9%	1,273	28.6%
High school diploma/equivalent	7,966	35.6%	51	35.9%	6,104	35.8%	21	33.9%	4,563	36.0%	1,562	35.1%
Some college	6,984	31.2%	36	25.4%	5,308	31.1%	28	45.2%	3,892	30.7%	1,444	32.5%
College degree or higher	597	2.7%	6	4.2%	440	2.6%	0	0.0%	283	2.2%	157	3.5%
Previous live births												

None	6,886	30.8%	22	15.5%	5,187	30.4%	21	33.9%	3,682	29.0%	1,526	34.3%
One	7,055	31.6%	49	34.5%	5,466	32.0%	19	30.6%	4,146	32.7%	1,339	30.1%
Two or more	8,400	37.6%	69	48.6%	6,404	37.5%	22	35.5%	4,847	38.2%	1,579	35.5%
NAS	-	-	-	-	68	0.4%	0	0.0%	10	0.1%	58	1.3%
NICU admission	199	0.89%	0	0.0%	-	-	-	-	4	0.0%	58	1.3%
Length of stay (>2 days)	7,552	33.8%	129	90.9%	4,389	25.7%	58	93.6%	-	-	-	-
Length of stay (mean, SD)	3.2	3.5	10.2	7.3	2.3	1.2	5.6	3.6	1.9	0.4	3.6	1.7

Table 4.2. Prevalence of characteristics among each outcome and adjusted odds ratios (with associated 95% confidence intervals) by disability overall and diagnostic group for neonatal abstinence syndrome and admission to the neonatal intensive care unit

	Disability Overall		Longstanding Physical Disability		Inflammatory Conditions		Psychiatric Conditions	
	%	OR (95% CI)	%	OR (95% CI)	%	OR (95% CI)	%	OR (95% CI)
Neonatal abstinence syndrome (through age two)*								
Cumulative MME during pregnancy (increase by 10 units)		1.022 (1.017-1.026)		1.022 (1.018-1.027)		1.022 (1.017-1.026)		1.022 (1.018-1.026)
Chronic Pain-Disability Status								
Chronic Pain + Disability +	24.7	3.692 (2.273-5.999)	0.7	0.999 (0.135-7.385)	5.6	5.014 (2.258-11.134)	18.3	3.474 (2.055-5.875)
Chronic Pain + Disability -	41.6	2.220 (1.457-3.382)	65.5	2.339 (1.624-3.37)	60.6	2.328 (1.596-3.396)	47.9	2.246 (1.505-3.353)
Chronic Pain - Disability +	6.3	2.136 (1.003-4.548)	0.0	-	2.1	3.820 (1.069-13.648)	4.2	1.877 (0.77-4.574)
Chronic Pain - Disability -	27.5	1.000 (Referent)	33.8	1.000 (Referent)	31.7	1.000 (Referent)	29.6	1.000 (Referent)
Admission to the neonatal intensive care unit (any birth-related hospitalization)*								
Cumulative MME during pregnancy (increase by 10 units)		1.007 (0.992-1.022)		1.007 (0.992-1.022)		1.007 (0.992-1.021)		1.007 (0.992-1.022)

Chronic Pain-Disability Status								
Chronic Pain + Disability +	12.9	1.358 (0.621-2.97)	3.2	2.584 (0.614-10.872)	0.0	-	9.7	1.339 (0.556-3.224)
Chronic Pain + Disability -	22.6	0.615 (0.33-1.148)	32.3	0.686 (0.397-1.182)	35.5	0.796 (0.467-1.357)	25.8	0.636 (0.352-1.148)
Chronic Pain - Disability +	6.5	1.421 (0.501-4.026)	0.0	-	3.2	4.121 (0.971-17.482)	3.2	0.964 (0.231-4.033)
Chronic Pain - Disability -	58.1	1.000 (Referent)	64.5	1.000 (Referent)	61.3	1.000 (Referent)	61.3	1.000 (Referent)
*Adjusted for mom disability + chronic pain, mom age and education at delivery, inadequate prenatal care (measured by the Kotelchuck index), tobacco use during pregnancy, previous live births								

Table 4.3. Adjusted rate ratios and associated 95% confidence intervals by disability overall and diagnostic group for length of stay (all birth-related hospitalizations)*

	Disability Overall			Longstanding Physical Disability			Inflammatory Conditions			Psychiatric Conditions		
	aRR	95% CI		aRR	95% CI		aRR	95% CI		aRR	95% CI	
Cumulative MME during pregnancy (increase by 10 units)	1.002	1.001	1.002	1.002	1.001	1.002	1.002	1.001	1.002	1.002	1.001	1.002
Chronic Pain-Disability Status												
Chronic Pain + Disability +	1.031	0.995	1.069	1.022	0.928	1.125	1.124	1.034	1.222	1.013	0.971	1.056
Chronic Pain + Disability -	0.999	0.977	1.021	1.000	0.980	1.021	0.997	0.976	1.017	1.005	0.983	1.027
Chronic Pain - Disability +	1.057	1.006	1.111	0.944	0.817	1.090	0.974	0.867	1.095	1.098	1.036	1.163
Chronic Pain - Disability -	1.000	Ref	Ref	1.000	Ref	Ref	1.000	Ref	Ref	1.000	Ref	Ref
*Adjusted for mom disability + chronic pain, mom age and education at delivery, inadequate prenatal care (measured by the Kotelchuck index), tobacco use during pregnancy, previous live births; aRR: adjusted rate ratio; CI: confidence interval												

CHAPTER 5

CONCLUSION

The aims of this dissertation were to answer: (1) are pregnant women with disability prescribed opioids more and at higher dosages than those without disability?; (2) is prescription opioid use during pregnancy a mediator of the relationship between the interaction of chronic pain and disability status and low birthweight, preterm birth, and small for gestational age?; (3) is the cumulative dosage of prenatal opioid prescriptions or the interaction of chronic pain and disability status associated with neonatal abstinence syndrome, admission to the neonatal intensive care unit, and length of stay in the hospital?

5.1 Are Pregnant Women with Disability Prescribed Opioids More and at Higher Dosages Than Those Without Disability?

Chapter 2 provides evidence that those with disability were prescribed opioids more frequently and at higher dosages than their counterparts without disability during pregnancy. Further, opioid prescribing patterns remained stable from 2008 to 2017 for total prescriptions during pregnancy per live birth overall, but not for total MME during pregnancy per live birth. The prevalence of filling an opioid prescription in chapter 2 was 7.5% during pregnancy and 9.6% before pregnancy, which is lower than what has been reported in previous studies. In Epstein et al (2013), from 1995 to 2009, the prevalence of

filling an opioid prescription during pregnancy was 29%[42]. This difference is most likely attributable to national trends of opioid prescribing peaking in 2010[76]. One national study reported a 13% net reduction in opioid prescribing from 2006 to 2017[76].

5.2 Is Prescription Opioid Use During Pregnancy a Mediator of the Relationship Between the Interaction of Chronic Pain and Disability Status and Low Birthweight, Preterm Birth, and Small for Gestational Age?

Reported in chapter 3, opioid use during pregnancy does not mediate the association of disability and adverse birth outcomes. Chapter 3 does provide evidence of an association between longstanding physical disability, inflammatory conditions, and psychiatric disability and adverse birth outcomes. The findings of chapter 3 align with some of the literature; although as definitions of disability vary widely, the ability to compare the magnitude of the effects from the current study is limited.

5.3 Is the Cumulative Dosage of Prenatal Opioid Prescriptions or the Interaction of Chronic Pain and Disability Status Associated with Neonatal Abstinence Syndrome (NAS), Admission to The Neonatal Intensive Care Unit (NICU), And Length Of Stay In The Hospital?

In chapter 4, prescription opioid use during pregnancy is associated with increased odds of NAS and increased rate of length of stay, after adjusting for confounders and the interaction of disability and other chronic conditions with pain symptoms. Overall, whether disability and other chronic conditions with pain symptoms are both present or either are present does not make a difference in the interaction's association with NAS or length of stay, but it is significantly associated with increased odds of both outcomes. Prenatal prescription opioid use was not associated with an increased risk of NICU

admission for neither disability overall nor any disability diagnostic group and their interaction with other conditions with chronic pain.

Literature is limited on the association of cumulative MME during pregnancy and the adverse birth outcomes of interest, as well as for differences by maternal disability and chronic pain status. Chapter 4 aligns with evidence that prescription opioid use during pregnancy is associated with increased risk of NAS, when adjusted for risk factors[24–26], and this risk increases as the dosage of opioids increases[24]. Since the current study excluded those with opioid use disorder, it is difficult to compare to Ma et al (2020), which found that women with mental health conditions and opioid use disorder[23] are at increased risk of having an infant with NAS and NICU admission[23].

5.4 Common Strengths

The main strength of all three studies is the use of administrative data, which helps limit selection bias that may occur when using other methods of recruiting study participants with disability[80]. The use of several ICD-9/10 codes to define disability also allowed the three studies to look at the diagnostic groups separately. In the literature, the definition of disability varies. It has been defined by self-report with validated questionnaires[30,43,81,82], health insurance definitions, e.g. Medicare[41] or Medicaid[42], or by diagnoses in medical or billing records[44,68,69,83,84]. Typical disability groups included in studies from diagnostic codes are physical disability and intellectual and developmental disabilities (IDD)[44,68,69,83,84]. As these conditions have different biological origins and social and health implications, combining them can obscure results. Another strength of all three studies through the use of ICD-9/10 codes was that data on other conditions with pain symptoms (an indication for opioid prescribing) and indicators for opioid misuse

(chapters 3 and 4) could be obtained. The use of administrative data also enabled opioid prescribing to be defined as prescriptions filled and to adjust for other prescriptions filled that are associated with opioids, which limited the impact of reporting and social desirability biases. Finally, since the administrative data were from a ten-year period, the sample size was high.

5.5 Common Limitations

The three studies have several common limitations. The first limitation is generalizability. South Carolina's population has a high proportion of individuals living with disability. Estimates from the 2015 Behavioral Risk Factor Surveillance System show that the prevalence of disability in SC (25.8%) was significantly higher than the US median (22.2%)[112]. The three studies were limited to Medicaid beneficiaries. South Carolina is a non-expansion state, meaning the income eligibility requirements are more stringent. Disability and pregnancy are qualifying events for Medicaid coverage, so women with disability are more likely to be covered by Medicaid before their pregnancy than their counterparts without disability. This may contribute to those with disability having better access to family planning and/or having higher rates of pregnancy intention. This may also lead to information bias in the three studies as those with disability are more likely to have been covered by Medicaid throughout their entire pregnancy and, therefore, are more likely to have a more opioid prescriptions in the pharmacy data. If the current study were done in a state with expanded Medicaid eligibility, the demographics of the sample would be different since the income eligibility criteria would be higher, and the sample size would be larger as more women could be included in any exposure group, as well as would have pharmacy records. However, it is likely that more women without

disability would be included in the study than those with disability. Therefore, chapters 3 and 4 may be an overestimate of the associations that would be observed in an expansion state.

Another limitation of the studies is related to the proxy used for chronic pain (other conditions with pain symptoms), which was determined through diagnostic codes. This method could have introduced some unmeasured confounding as it may not be holistic enough to capture all elements of chronic pain that increase the likelihood of being prescribed an opioid. One study found that the optimal assessment of chronic pain should include intensity, other perceptual qualities, distribution throughout the body, and temporal features, and this should be incorporated into clinical protocols[86]. The diagnoses used in the current study most likely do not incorporate this assessment in a standard way.

Further, opioid use only included prescription opioids dispensed, so the three studies assume that the opioids were taken as prescribed, and there was no differential misclassification of illicit opioid or other street drug use. Another limitation is the impact of survivorship bias, which may underestimate the magnitude of the associations as only live births were included in the current study. The final limitation to the current study is the lack of information from the administrative data about the severity of disability. If the severity of disability were available, the likelihood of unmeasured confounding between opioids and disability would be greatly reduced.

Another limitation is lack of data on prescription opioid misuse or illicit use. The authors had initially hoped to do a sensitivity analysis with opioid antagonists, which includes naloxone and naltrexone, as a proxy for illicit use. However, only seven

prescriptions of opioid antagonists were found in the Medicaid pharmacy data, which may be because those administered in emergency situations are not captured in this data source. Passed in 2015, the South Carolina Overdose Prevention Act allowed prescribers to give standing orders for "opioid antidotes" to first responders and gave pharmacists the ability to prescribe them directly to family members[3,87]. This increased access to these opioid antagonists will help prevent opioid overdose deaths, but their use may not be detected in the Medicaid pharmacy record of the person who received the drug. In chapters 3 and 4, women with indicators of opioid misuse were excluded, so the authors believe the impact from this lack of data was limited.

The final limitations of the current study are related to the data sources. Since three administrative data sources were used (hospital discharge, pharmacy, and vital records for Medicaid beneficiaries), it is difficult to determine the overall data quality and its impact on inference drawn from the analytic sample. Other limitations include the lack of temporality between the disability diagnoses and chronic pain diagnoses and that the birth dates for the newborns were estimated.

5.6 Policy and Practice Implications

One policy strategy to reducing opioid prescribing is establishment of Prescription Drug Monitoring Programs (PDMPs), which exist in almost every state[47]. PDMPs are administered and regulated at the state-level[47]. In 2006, the South Carolina Prescription Monitoring Act established the prescription monitoring program for controlled substances, which was operational in 2008[3,77]. Theoretically, this increased surveillance and reporting would impact prescribing patterns similarly across all groups. However, there is evidence that PDMPs do not reduce opioid prescribing for those with

longstanding physical disability or inflammatory conditions, compared to those without[47]. Chapter 2 supports this finding.

There is evidence that lowering dosages of opioids towards the end of pregnancy[24] or use of non-opioid therapies would lower risk of these adverse birth outcomes, as recommended by the American College of Obstetricians and Gynecologists[89]. Adverse outcomes associated with prenatal opioid use are directly related to significant increases in Medicaid expenditures over the past two decades[13,106–109], so decreasing these risks in the population will also ease the burden on the public insurance system, as well as decrease short- and long-term impacts of these outcomes that lead to future complications related to stress[51], reduced bonding[52], and anxiety[61].

One barrier to reducing the short- and long-term impacts of these outcomes is a lack of continuity of care or comprehensive approaches either within the NICU[52,110] or between drug treatment and obstetrics[111]. Since 1999, three large birth hospitals in Dublin, Ireland have had a Drug Liaison Midwife, who coordinates care between obstetrics and addiction services[111]. This model reduces stigma, which is another cited barrier to reducing the impacts of these outcomes[110], and suggests a benefit for not only the infant and the mother, but also for the health care system broadly[111]. However, this model is dependent on women accepting drug treatment or misusing prescription opioids to the point of needing drug treatment[111].

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The findings of chapters 3 and 4 lend to a call for a model that ensures a comprehensive approach continuity of care between drug treatment, obstetrics, and professionals caring for women with disability and/or conditions with pain symptoms. Two-generation approaches, like whole family supports in the NICU[52], should be taken to address the complex needs of those with disability and/or conditions with pain symptoms and their infants, particularly for those women who are prescribed opioids during pregnancy.

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APPENDIX A

SUPPLEMENTAL TABLES FOR CHAPTER 2

Table A.1. International Classification of Disease 9 Codes for Diagnostic Groups (frequency among live births (n=319,752))

Diagnosis description	**Codes**	**Frequency**	**% of births**	**Frequency qualified for Medicaid because of disability**	**Proportion of those identified that are on Medicaid for disability**
Physical disability		2480	0.8%	249	10.0%
Multiple sclerosis	340	228	0.1%	53	23.2%
Spinal cord injury	952	642	0.2%	27	4.2%
Spina bifida (includes Arnold-Chiari syndrome)	756	658	0.2%	32	4.9%
Cerebral Palsy (including diplegic, hemiplegic, quadriplegic, monoplegic, unspecified, and athetoid)	343.0, 343.1, 343.2, 343.3, 343.4, 343.8, 343.9, 333.71	92	0.0%	56	60.9%
Stroke	433, 434, 436	433	0.1%	48	11.1%

Traumatic brain injury	800-801, 803-804, 851-854	429	0.1%	35	8.2%
Inflammatory conditions		3088	1.0%	179	5.8%
Ankylosing spondylitis	720	449	0.1%	20	4.5%
Rheumatoid arthritis	714	464	0.1%	57	12.3%
Systemic lupus erythematosus	710	1016	0.3%	81	8.0%
Psoriatic arthritis	696	1173	0.4%	24	2.0%
Intellectual and developmental disabilities		587	0.2%	266	45.3%
Down Syndrome	758	0	0.0%	0	0.0%
Chromosomal Anomalies and Autosomal Deletion Syndromes	758.1, 758.2, 758.31, 758.32, 758.33, 758.39	86	0.0%	4	4.7%
Fragile X Syndrome	759.83	25	0.0%	3	12.0%
Lesch Nyhan Syndrome	277.2	0	0.0%	0	0.0%
Tuberous Sclerosis	759.5	0	0.0%	0	0.0%
Prader-Willi Syndrome	759.81	0	0.0%	0	0.0%
Pervasive Developmental Disorders (including Autistic Disorder)	299.00, 299.01, 299.10, 299.11, 299.80, 299.81, 299.90, 299.91	121	0.0%	75	62.0%
Moderate-to-Profound Intellectual Disability	318.0, 318.1, 318.2	164	0.1%	97	59.1%
Mild Intellectual Disability	317	151	0.0%	82	54.3%
Unspecified Intellectual Disability	319	3	0.0%	0	0.0%

Cerebral Degenerations Manifest in Childhood	330.0, 330.1, 330.2, 330.3, 330.8, 330.9	16	0.0%	0	0.0%
Fetal Alcohol Syndrome	760.71	41	0.0%	9	22.0%
Psychiatric conditions		14327	4.5%	1659	11.6%
Schizophrenia	295	543	0.2%	251	46.2%
Other psychoses (including bipolar/manic depressive, depressive psychosis)	296	13862	4.3%	1439	10.4%
Other disabilities, included in overall disability definition					
Legal blindness	369.4	33	0.0%	16	48.5%
Deaf or hearing loss	389.0-389.9	1034	0.3%	174	16.8%

Table A.2. International Classification of Disease 10 Codes for Diagnostic Groups (frequency among live births (n=319,752))

Diagnosis description	**Codes**	**Frequency**	**% of births**	**Frequency qualified for Medicaid because of disability**	**Proportion of those identified that are on Medicaid for disability**
Physical disability		305	0.1%	49	16.1%
Multiple sclerosis	G35	87	0.0%	13	14.9%
Spinal cord injury	S14.101A, S14.102A, S14.103A, S14.104A	4	0.0%	0	0.0%
Spina bifida (includes Arnold-Chiari syndrome)	Q05, Q76, Q07	108	0.0%	12	11.1%
Cerebral Palsy (including diplegic, hemiplegic, quadriplegic, monoplegic, unspecified, and athetoid)	G80.1, G80.2, G80.0, G80.8, G80.9, G80.3	42	0.0%	21	50.0%
Stroke	I67.89, I65.1, IGG.09, I66.19, I66.29	54	0.0%	2	3.7%
Traumatic brain injury	S02.0XXA, S02.101A, S02.102A, S02.109A, S02.91XA, S06.330A, S06.6X0A, S06.360A, S06.890A	10	0.0%	1	10.0%
Inflammatory conditions		419	0.1%	34	8.1%

Ankylosing spondylitis	M08.1, M45	11	0.0%	0	0.0%
Rheumatoid arthritis	M05, M06	159	0.0%	17	10.7%
Systemic lupus erythematosus	M32	238	0.1%	17	7.1%
Psoriatic arthritis	L40.5	10	0.0%	0	0.0%
Intellectual and developmental disabilities		360	0.1%	105	29.2%
Down Syndrome	Q91.7	7	0.0%	0	0.0%
Chromosomal Anomalies and Autosomal Deletion Syndromes	Q91.3, Q93.4, Q93.81, Q93.88, Q93.3, Q93.7, Q93.89	20	0.0%	0	0.0%
Fragile X Syndrome	Q99.2	17	0.0%	0	0.0%
Lesch Nyhan Syndrome	E79.1, E79.8	1	0.0%	0	0.0%
Tuberous Sclerosis	Q85.1	1	0.0%	0	0.0%
Prader-Willi Syndrome	Q87.1	8	0.0%	1	0.0%
Pervasive Developmental Disorders (including Autistic Disorder)	F84.0, F84.3, F84.5, F84.8, F84.9	10	0.0%	10	100.0%
Moderate-to-Profound Intellectual Disability	F72, F73	100	0.0%	37	37.0%
Mild Intellectual Disability	F70	67	0.0%	47	70.1%
Unspecified Intellectual Disability	F79	102	0.0%	12	11.8%

Cerebral Degenerations Manifest in Childhood	E75.02, E75.19, E75.4, G93.89, G93.9, F84.2, G31.81, G31.82, G31.9	6	0.0%	0	0.0%
Fetal Alcohol Syndrome	P04.3, Q86.0	34	0.0%	9	26.5%
Psychiatric conditions		29	0.0%	6	20.7%
Schizophrenia	F20.89	16	0.0%	6	37.5%
Other psychoses (including bipolar/manic depressive, depressive psychosis)	F30.10	13	0.0%	0	0.0%
Other disabilities, included in overall disability definition					
Legal blindness	H54.8	14	0.0%	14	100.0%
Deaf or hearing loss	H91.0-H91.X, H90.0-H90.A	335	0.1%	65	19.4%

Table A.3. American Hospital Formulary Service Therapeutic (AHFS) Codes for prescription drug groups (unique cases are unique moms with each component in analytic sample; total moms = 224,838) and International Classification of Disease (ICD) Codes for chronic conditions with pain symptoms

Prescription drug group	**AHFS Therapeutic code**	**Unique cases of Rx before/during pregnancy**
Opioids		
Opiate agonists	28:08.08	40,663
Opiate partial agonists	28:08.12	795
Opioid antagonists	28:10	7
Prescriptions associated with opioid prescribing		
Other Nonsteroidal Anti-inflammatory Agents	28:08.04	35,322
Barbiturates	28:12.04	8
Benzodiazepines	28:12.08	1,352
Anticonvulsants, Miscellaneous	28:12.92	4,046
Antidepressants	28:16.04	21,697
Antipsychotics	28:16.08	1,723
Anxiolytics, Sedatives, and Hypnotics	28:20	0
Antimanic Agents	28:28	2,027
Chronic Conditions with Pain Symptoms	**ICD-9 Codes**	**ICD-10 Codes**
Chronic pain syndrome	338.4	G89.4
Fibromyalgia	729.1	M79.7
Irritable bowel syndrome	564.1	K58.0, K58.1, K58.2, K58.8, K58.9
Interstitial cystitis/Bladder pain syndrome	595.1, 595.3	N30.10, N30.30
Vulvodynia	625.71, 625.79, 625.70	N94.810, N94.818, N94.819
Migraine	346.XX (exclude 346.60, 346.62 (cerebral infarct) and 346.20, 346.21 (cyclical vomiting))	G43.XXX (exclude G43.6- and G43.A-)
Chronic tension-type headache	339.1	G44.201
Tension headache	307.81	G44.209
Tension type/stress headache	339.11	G44.211, G44.219
Tension-vascular headache	339.12	G44.221, G44.229

Temporomandibular disorder	524.60, 524.62, 524.63, 830.0	M26.60, M26.62, M26.63, S03.0XXA
Chronic low back pain	724.2, 724.3, 780.71	M54.5, M54.40, M54.41, M54.42, R53.82
Endometriosis with pain	617.0 with 608.9, 625.9, 789.09, 625.3, or 625.0	N80.XXX and (R10.2 or N94.4 or N94.5 or N94.6 or N94.10 or N94.11 or N94.12 or N94.19)

APPENDIX B

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APPENDIX C

SUPPLEMENTAL TABLES FOR CHAPTER 3

Table C.1. International Disease Classification (ICD) 9/10 codes used for disability diagnostic groups, chronic conditions with pain symptoms, and indicators of opioid misuse

Diagnosis description	**ICD-9 Codes**	**ICD-10 Codes**
Longstanding physical disability		
Multiple sclerosis	340	G35
Spinal cord injury	952	S14.101A, S14.102A, S14.103A, S14.104A
Spina bifida (includes Arnold-Chiari syndrome)	756	Q05, Q76, Q07
Cerebral Palsy (including diplegic, hemiplegic, quadriplegic, monoplegic, unspecified, and athetoid)	343.0, 343.1, 343.2, 343.3, 343.4, 343.8, 343.9, 333.71	G80.1, G80.2, G80.0, G80.8, G80.9, G80.3
Stroke	433, 434, 436	I67.89, I65.1, IGG.09, I66.19, I66.29
Traumatic brain injury	800-801, 803-804, 851-854	S02.0XXA, S02.101A, S02.102A, S02.109A, S02.91XA, S06.330A, S06.6X0A, S06.360A, S06.890A
Inflammatory conditions		
Ankylosing spondylitis	720	M08.1, M45
Rheumatoid arthritis	714	M05, M06
Systemic lupus erythematosus	710	M32
Psoriatic arthritis	696	L40.5

Psychiatric conditions		
Schizophrenia	295	F20.89
Other psychoses (including bipolar/manic depressive, depressive psychosis)	296	F30.10
Chronic conditions with pain symptoms		
Chronic pain syndrome	338.4	G89.4
Fibromyalgia	729.1	M79.7
Irritable bowel syndrome	564.1	K58.0, K58.1, K58.2, K58.8, K58.9
Interstitial cystitis/Bladder pain syndrome	595.1, 595.3	N30.10, N30.30
Vulvodynia	625.71, 625.79, 625.70	N94.810, N94.818, N94.819
Migraine	346.XX (exclude 346.60, 346.62 (cerebral infarct) and 346.20, 346.21 (cyclical vomiting))	G43.XXX (exclude G43.6- and G43.A-)
Chronic tension-type headache	339.1	G44.201
Tension headache	307.81	G44.209
Tension type/stress headache	339.11	G44.211, G44.219
Tension-vascular headache	339.12	G44.221, G44.229
Temporomandibular disorder	524.60, 524.62, 524.63, 830.0	M26.60, M26.62, M26.63, S03.0XXA
Chronic low back pain	724.2, 724.3, 780.71	M54.5, M54.40, M54.41, M54.42, R53.82
Endometriosis with pain	617.0 with 608.9, 625.9, 789.09, 625.3, or 625.0	N80.XXX and (R10.2 or N94.4 or N94.5 or N94.6 or N94.10 or N94.11 or N94.12 or N94.19)
Indicators of opioid misuse		
Opioid abuse/use disorder	304.00-304.03, 304.70-304.73, 305.50-305.53	F11.10, F11.120-D11.122, F11.129, F11.14, F11.150, F11.151, F11.159, F11.181, F11.182, F11.188, F11.19-F11.29, F11.90-F11.99

Opioid overdose	965.00-965.02, 965.09, 970.1, E850.0-E850.2	T40.0X1A-T40.694D
Adverse effects of opioids	E935.0-E935.2, E940.1	T40.0X5A-T40.695D

Table C.2. American Hospital Formulary Service Therapeutic (AHFS) Codes for prescription drug groups (unique cases are unique moms with each component in analytic sample; total moms = 224,291)

Prescription drug group	**AHFS Therapeutic code**
Prescriptions associated with opioid prescribing	
Other Nonsteroidal Anti-inflammatory Agents	28:08.04
Barbiturates	28:12.04
Benzodiazepines	28:12.08
Anticonvulsants, Miscellaneous	28:12.92
Antidepressants	28:16.04
Antipsychotics	28:16.08
Anxiolytics, Sedatives, and Hypnotics	28:20
Antimanic Agents	28:28
Prescriptions associated with adverse birth outcomes	
Tetracyclines	08:12.24
Nucleosides and Nucleotides	08:18.32
HMG-COA Reductase Inhibitors	24:06.08
Angiotensin-Converting Enzyme Inhibitors	24:08.44.04
Antineoplastic Agents	10:00.00
Coumarin Derivatives	20:12.04.08
Antibacterials	52:04.04
Prostaglandins	56:28.28
Androgens	68:08.00
Skin and Mucous Membrane Agents, Miscellaneous	84:92
Biologic Response Modifiers	92:20
Other Miscellaneous Therapeutic Agents	92:92.00

APPENDIX D

SUPPLEMENTAL TABLES FOR CHAPTER 4

Table D.1. International Disease Classification (ICD) 9/10 codes used for disability diagnostic groups, chronic conditions with pain symptoms, indicators of opioid misuse, and high risk conditions of the infant

Diagnosis description	**ICD-9 Codes**	**ICD-10 Codes**
Longstanding physical disability		
Multiple sclerosis	340	G35
Spinal cord injury	952	S14.101A, S14.102A, S14.103A, S14.104A
Spina bifida (includes Arnold-Chiari syndrome)	756	Q05, Q76, Q07
Cerebral Palsy (including diplegic, hemiplegic, quadriplegic, monoplegic, unspecified, and athetoid)	343.0, 343.1, 343.2, 343.3, 343.4, 343.8, 343.9, 333.71	G80.1, G80.2, G80.0, G80.8, G80.9, G80.3
Stroke	433, 434, 436	I67.89, I65.1, IGG.09, I66.19, I66.29
Traumatic brain injury	800-801, 803-804, 851-854	S02.0XXA, S02.101A, S02.102A, S02.109A, S02.91XA, S06.330A, S06.6X0A, S06.360A, S06.890A
Inflammatory conditions		
Ankylosing spondylitis	720	M08.1, M45
Rheumatoid arthritis	714	M05, M06
Systemic lupus erythematosus	710	M32
Psoriatic arthritis	696	L40.5
Psychiatric conditions		
Schizophrenia	295	F20.89
Other psychoses (including bipolar/manic depressive, depressive psychosis)	296	F30.10

Chronic conditions with pain symptoms		
Chronic pain syndrome	338.4	G89.4
Fibromyalgia	729.1	M79.7
Irritable bowel syndrome	564.1	K58.0, K58.1, K58.2, K58.8, K58.9
Interstitial cystitis/Bladder pain syndrome	595.1, 595.3	N30.10, N30.30
Vulvodynia	625.71, 625.79, 625.70	N94.810, N94.818, N94.819
Migraine	346.XX (exclude 346.60, 346.62 (cerebral infarct) and 346.20, 346.21 (cyclical vomiting))	G43.XXX (exclude G43.6- and G43.A-)
Chronic tension-type headache	339.1	G44.201
Tension headache	307.81	G44.209
Tension type/stress headache	339.11	G44.211, G44.219
Tension-vascular headache	339.12	G44.221, G44.229
Temporomandibular disorder	524.60, 524.62, 524.63, 830.0	M26.60, M26.62, M26.63, S03.0XXA
Chronic low back pain	724.2, 724.3, 780.71	M54.5, M54.40, M54.41, M54.42, R53.82
Endometriosis with pain	617.0 with 608.9, 625.9, 789.09, 625.3, or 625.0	N80.XXX and (R10.2 or N94.4 or N94.5 or N94.6 or N94.10 or N94.11 or N94.12 or N94.19)
Indicators of opioid misuse		
Opioid abuse/use disorder	304.00-304.03, 304.70-304.73, 305.50-305.53	F11.10, F11.120-D11.122, F11.129, F11.14, F11.150, F11.151, F11.159, F11.181, F11.182, F11.188, F11.19-F11.29, F11.90-F11.99
Opioid overdose	965.00-965.02, 965.09, 970.1, E850.0-E850.2	T40.0X1A-T40.694D
Adverse effects of opioids	E935.0-E935.2, E940.1	T40.0X5A-T40.695D
High-risk conditions of the infant		
Septicemia	038	A40-A41
Diseases of the circulatory system	390–434,436–459	I00-I99
Newborn affected by maternal complications of pregnancy	761	P01
Newborn affected by complications of placenta, cord and membranes	762	P02

Disorders related to short gestation and low birth weight, not elsewhere classified	765	P07
Intrauterine hypoxia and birth asphyxia	768	P20-P21
Respiratory distress of newborn	769	P22
Atelectasis	770.4-770.5	P28.0-P28.1
Bacterial sepsis of newborn	771.8	P36
Neonatal hemorrhage	772	P50-P52,P54
Necrotizing enterocolitis of newborn	777.5	P77
Congenital malformations, deformations and chromosomal abnormalities	740-759	Q00-Q99