Distribution Agreement

Signature:

________________________________ _______________

Daisy Fernandez Date

Opioid prescription patterns among pregnant women on Medicaid in Montana

and effect on adverse birth outcomes

By

Daisy Fernandez

Master of Public Health

Epidemiology

Julie A. Gazmararian, PhD, MPH

Committee Chair

K. Alaine Broadaway, PhD

Committee Member

Opioid prescription patterns among pregnant women on Medicaid in Montana

and effect on adverse birth outcomes

By

Daisy Fernandez

Bachelor of Arts

Columbia University in the City of New York

2015

<u>Thesis Committee:</u>

Julie A. Gazmararian, PhD, MPH

Committee Chair

K. Alaine Broadaway, PhD

Committee Member

An abstract of

a thesis submitted to the Faculty of the

Rollins School of Public Health of Emory University

in partial fulfillment of the requirements for the degree of

Master of Public Health

in Epidemiology

2018

Abstract

Opioid prescription patterns among pregnant women on Medicaid in Montana

and effect on adverse birth outcomes

By Daisy Fernandez

Background: The last two decades have seen an increase in prescription of opioids among pregnant women. Nonetheless, the association between opioid prescription in pregnancy and adverse birth outcomes is unclear. Further, prescription patterns among Medicaid-enrolled pregnant women in Montana have yet to be explored. This study identifies opioid prescription patterns among pregnant women on Medicaid in Montana, while exploring the association between opioid prescription, preterm birth and small for gestational age (SGA). This work also provides a look at patterns among Medicaid-enrolled American Indian and Alaska Native pregnant mothers in Montana, for which information on opioid prescription is limited.

Methods: Through a retrospective cohort study of 6,947 Medicaid claim records, the prenatal opioid prescription patterns of women in Montana who delivered from 2009 to 2015 were assessed. Additionally, the association between opioid prescription during pregnancy and adverse birth outcomes was analyzed.

Results: From 2009 to 2015, 28.5% of women on Medicaid were prescribed an opioid during pregnancy. The average age of mothers who received a prescription was 24.9 years (SD: 5.4) and most were white, did not smoke during pregnancy, and had a high school diploma. Similarly, the average age for mothers who did not receive a prescription was 24.1 (SD: 5.8) and most were also white, did not smoke, and had a high school diploma. Of the sample, 21.8% had a preterm birth and 11.1% had a SGA birth. Additionally, 25.9% of American Indian or Alaska Native mothers were prescribed an opioid during pregnancy. Lastly, among mothers who had a preterm birth, the odds of having an opioid prescribed during pregnancy was 1.20 (95% CI: 1.06-1.37). No association was found between opioid prescription and SGA.

Conclusion: Over a quarter of women on Medicaid in Montana were prescribed an opioid during pregnancy. This is alarming given that opioid prescription during pregnancy was found to be associated with preterm birth. These results push for further research on the safety of opioid use during pregnancy and encourage medical providers to proceed with caution when prescribing opioids to mothers until more comprehensive information on the effects of opioid use during pregnancy is available.

Opioid prescription patterns among pregnant women on Medicaid in Montana and effect on adverse birth outcomes

By

Daisy Fernandez

Bachelor of Arts

Columbia University in the City of New York

2015

<u>Thesis Committee:</u>

Julie A. Gazmararian, PhD, MPH

Committee Chair

K. Alaine Broadaway, PhD

Committee Member

A thesis submitted to the Faculty of the

Rollins School of Public Health of Emory University

in partial fulfillment of the requirements for the degree of

Master of Public Health

in Epidemiology

2018

Acknowledgements

Thanks to Drs. Gazmararian and Broadaway for serving as advisors and providing mentorship throughout the thesis process. Thanks to Todd Koch and Laura Williamson for providing insight in regards to data collection methodology and analysis. Finally, thanks to the Montana Department of Public Health and Human Services for providing the data used in this analysis.

Table of Contents

CHAPTER I: Background and Literature Review

Prescription opioids have long been used to treat cancer-related pain, but can also be used to treat other chronic and temporary pain of ranging severity. As states across the United States have relaxed their opioid prescription laws over the past two decades, the use of opioids for non-cancer related pain has increased dramatically (1). From 2000 to 2009, there was a 35% increase in the number of opioids prescribed in the United States, a spike which has contributed to the opioid epidemic that the country is now experiencing (2). The increase in prescription of opioids is associated with a higher overdose mortality rate, an increase in emergency room visits for non-medical opioid consumption, an increased risk of neonatal abstinence syndrome (NAS) among infants exposed in utero, and an increased rate of opioid addiction (3). Therefore, identifying individuals who are more likely to use opioids may help explain disparities in health outcomes between individuals who use opioids and those who do not.

In the United States, opioid use is disproportionately higher among Medicaid enrollees than among privately insured individuals (4). A 2015 study found that Medicaid enrollees were prescribed an average of 6.3 opioids in 2010 and that about 40% of these enrollees had at least one indicator of potential inappropriate use or prescribing (defined as overlapping opioid prescriptions, overlapping opioid and benzodiazepine prescriptions, long acting/extended release opioids for acute pain, and high daily doses) (4). This is a stark contrast from privately insured individuals who were prescribed an average of 3.3 opioids in 2009; of these, 25% had one or more indicators of potential inappropriate use or prescribing of opioids (5). There is also disproportionate opioid use among Medicaid-enrolled women compared to those that are privately insured; between 2008 and 2012, about 39% of Medicaid insured and 28% of privately insured women between the age of 15 and 44 filled an opioid prescription each year (6). Moreover, while women make up 54% of the Medicaid population, 74% of enrollees with at least one opioid prescription were female, indicating that women comprise the largest proportion of opioid users on Medicaid (4). These results suggest that the burden of adverse outcomes related to opioid use falls disproportionately on Medicaid-enrolled individuals, particularly women of reproductive age, as opioid use is more most prevalent among this population.

The prescription of opioid drugs to pregnant women has also increased over the last two of decades. Most pregnant women use prescription opioids to treat such issues as abdominal pain, lower back pain, headaches, joint pain, and migraines (7). Additionally, opioid dependent women may need methadone or buprenorphine maintenance therapy to manage their addiction throughout pregnancy (8). Similar to the general American population, opioid prescriptions are more prevalent among Medicaid-enrolled pregnant women than those privately insured (7). Between 2000 and 2007, about 22% of Medicaid-enrolled pregnant women filled an opioid prescription at some point in their pregnancy (7). Meanwhile between 2005 and 2011, about 14% of privately insured pregnant women were dispensed an opioid during pregnancy (9). Across 46 U.S. states and the District of Columbia, the proportion of Medicaid-enrolled women who filled an opioid prescription during pregnancy increased from 19% in 2000 to 23% in 2007 (7).

Although research shows a consistently higher prevalence of opioid prescription among pregnant women on Medicaid than among those enrolled in private insurance, meaningful regional variations in opioid prescriptions among pregnant women in general have been observed across the nation (7, 9). For example, in Utah, 42% of women on

Medicaid were prescribed an opioid during pregnancy, compared to less than 10% in Oregon (7). Meanwhile, for women enrolled in private insurance, opioid prescription varied from less than 11% in the Northeast to more than 20% in the South (9). Such variation suggest that state-specific analyses of opioid prescription may be more beneficial for understanding the patterns of opioid use in different parts of the country.

I. Demographics of pregnant women using opioids during pregnancy

In a 2014 nationwide analysis of opioid use among pregnant women on Medicaid, 21.6% of women filled a prescription between 2000 and 2007 (7). The mean age of mothers in this study was 24 (SD: 5.8) and the racial breakdown was 40% White, 34% Black, 16% Hispanic, and 11% other races (7). Among women who filled an opioid prescription, the mean age was 24.3 (SD: 5.3) and the breakdown was 53% white, 30% black, 10% Hispanic and 7% other races, while among women who did not fill a prescription the mean age was lower (23.9 (SD: 5.9)) and the racial breakdown was 36% White, 35% Black, 18% Hispanic, and 12% other races (7). Similarly, in an independent study of women from Tennessee, opioid use during pregnancy was more likely among women who were 21 years of age or older, white, non-Hispanic, prima gravid, and with less than a high school education (10). Thus, while the prevalence of opioid use among pregnant women may vary across states, maternal characteristics (such as racial breakdown and age) seem to be more consistent across the country.

Current literature on opioid use among pregnant women mainly focuses on racial differences between White, Black and Hispanic populations, leaving a gap in knowledge when it comes to opioid use patterns among Native Americans, as the latter often makes up only a small portion of the samples considered. Only two identified sources reported prenatal opioid use among American Indian and Alaska Native populations. One study in Wisconsin found that about 3% of American Indian and Native American mothers who delivered between 2009 and 2014 had used opioids. However, this study used the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes to identify maternal substance abuse at the time of delivery (instead of throughout the duration of pregnancy) and included both illicit and prescribed opioid use (11). This study also found that the rate of opioid use was higher among American Indian and Alaska Native mothers (27.2 (95% CI: 22.6-31.8)) than among White mothers (11.7 (95% CI: 11.3-12.1)) (11). In contrast, one 2017 community assessment report in Montana found that among the Blackfeet Indian Reservation in northwest Montana, 31% of women who delivered at one of the Blackfeet medical facilities tested positive for opioids at delivery (12). Note that both studies report American Indian and Alaskan Native maternal opioid use (both illicit and prescribed) at time of hospitalization for delivery, not opioid prescription patterns. No study was found that described opioid prescription among American Indians. The ten-fold difference in opioid use between these two studies and the absence of any study that assesses opioid prescriptions patterns among Native Americans in the United States point to the need for more extensive and comprehensive research that explores the statewide and nationwide opioid trends observed among the American Indian and Alaska Native population.

II. Current knowledge on the association between opioids and adverse birth outcomes

The increase in the prescription of opioids among pregnant mothers on Medicaid is alarming considering that many of the adverse birth outcomes of opioid use during pregnancy have not been extensively researched, making it difficult to fully comprehend the impact that opioids have on mothers and newborns. Opioids used during pregnancy may be detected in the umbilical cord and placenta, indicating that opioids can cross the placental barrier and reach the fetus during pregnancy (8). However, it is not clear how opioids may affect a developing fetus or the pregnant mother, as pregnant women tend to be excluded from clinical studies. Certain adverse birth outcomes such as NAS and neural tube defects have been more extensively researched than others; illicit and prescription use of opioids during pregnancy have been found to result in a higher rate of NAS, while opioid use during pregnancy was found to be associated with an elevated risk of neural tube defects (13, 14). Additionally, early fetal exposure to opioids may lead to teratogenic effects and congenital birth defects (10). Specifically, the National Birth Defects Prevention Study found that septal defects and spina bifida were associated with maternal codeine use, and a study in Denmark found an association between opioid use, fetal loss, and intrauterine growth restrictions (15, 16). When combined with illicit drug use and additional risk factors such as cigarette and alcohol use, opioid use can further increase the risk of these adverse prenatal and infant outcomes (17).

Limited and often contradictory research exists for other adverse birth outcomes. Particularly for preterm birth and SGA, research does not agree on whether an association exists and if so, what that effect is. Several studies have found a positive, statistically significant association between opioid use during pregnancy and preterm birth (18-21). For example, a large study in Ireland (n=61,030) found that methadone was associated with preterm birth (OR: 2.5, 95% CI: 2.0-3.1) (20). However, a study (n=2,748) in Connecticut and Massachusetts found no association between opioid use and preterm birth among pregnant women (22). Further, it may be the case that the association between opioids and preterm birth is dependent on the type of opioid used during pregnancy; a 2010 study found that infants exposed to buprenorphine during gestation are less likely to be preterm birth when compared to infants exposed to methadone (OR: 0.4, 95% CI: 0.1-2.8), although the association was not found to be statistically significant (23). Similarly, results for the association between opioid use during pregnancy and SGA have also been inconsistent; one 2012 study found that infants exposed to opioids in vitro were more likely to be SGA (11.5%) compared to those who were unexposed (7.8%) (22). This association was also noted in other studies (16, 20). However, a 2013 cohort study in Sweden found no association between opioid use during pregnancy and SGA (24). The limited number of studies available for these two adverse birth outcomes and the inconsistent results provided indicate that further research is needed to clarify the relationship between opioid use during pregnancy and SGA and/or preterm birth.

III. Opioid use among pregnant women in Montana

Very little is known about opioid prescription patterns among Medicaid-enrolled pregnant women in Montana, as this state was previous excluded in a national study on opioid use during pregnancy due difficulty linking maternal Medicaid claims to infant outcomes (7). States surrounding Montana experience a rate of prescription opioid dispensing ranging from 10% to more than 30% for pregnant women on Medicaid (7). Meanwhile, for privately insured women in Montana, the rate is between 17% to 21% (9). Additional research is needed to determine how Montana's opioid prescription patterns compare to those observed in neighboring states and those found among Montana's privately insured pregnant women.

IV. Montana demographics

One million people live in Montana and of these about 33% are considered low income (i.e. fall below 200% of the federal poverty limit) (25). Montana is predominantly White (89%), with a small (yet larger than that in many other states across the United States) American Indian and Alaska Native population (6%), and an even smaller Hispanic or Latino population (3%) (26). In terms of Medicaid eligibility, pregnant women at or below the 157% federal poverty limit are eligible for Medicaid and are covered for up to 60 days postpartum (27). Of the adult population enrolled in Medicaid, 55% are women, 70% are white and 21% are Native American (27).

V. Federal and state policies overlooking opioid prescriptions

As of 2016, 49 Medicaid programs across the United States (including Montana’s Medicaid program) have implemented Patient Review and Restriction Programs (PRRs), managed care, or both as a response to the opioid epidemic (28). Through PRRs individuals who are suspected of over-utilizing opioids are designated one provider and/or pharmacy. Additionally, Montana’s Medicaid program has incorporated a preferred drug list; any drug that is not on this list requires prior authorization to be prescribed (27). Montana’s Medicaid program has also adopted a Prescription Drug Monitoring Program (PDMP)—a database for identifying individuals who may be misusing opioid—and quantity limits on opioid dispensing (29). Through these policies and regulations, Montana’s Medicaid program is attempting to combat the opioid epidemic by alerting providers of patients who may be misusing opioids before opioid use results in adverse outcomes.

VI. Project objectives and significance

There is a gap in knowledge when it comes to identifying the demographics of mothers on Medicaid who take opioids during pregnancy in Montana. Additionally, existing literature on the association between maternal opioid use during pregnancy on small for gestational age and on preterm birth has been contradicting and limited. This study tackles these gaps by examining opioid prescription patterns among pregnant women in Montana—a state for which there is currently no published research on opioid use among Medicaid-enrolled pregnant women—and by providing additional insight into the association between opioid use and preterm birth and SGA. The objectives of this analysis were to: (1) compare the patterns of opioid prescription among pregnant women on Medicaid in Montana to that observed across the United States, (2) identify opioid prescription patterns among Medicaid-enrolled American Indian and Alaska Native women in Montana—a population for which opioid prescription information is mostly lacking—and, (3) examine the association between opioid use during pregnancy, small for gestational age and preterm birth.

CHAPTER II: Manuscript

Introduction

The opioid crisis has quickly become one of the most critical public health concerns in the United States. As is the case among the general American population, the prescription of opioid drugs among pregnant women has seen an increased over the last two decades. In fact, opioid prescriptions are more prevalent among Medicaid-enrolled pregnant women than those who are privately insured (7). Between 2000 and 2007, about 22% of Medicaid-enrolled pregnant women filled an opioid prescription at some point in their pregnancy (7). Meanwhile between 2005 and 2011, about 14% of privately insured pregnant women were dispensed an opioid during pregnancy (9). The prevalence of opioid prescription for both privately insured pregnant women and pregnant women enrolled on Medicaid significantly varies by state (7, 9). In Montana, the prevalence of opioid dispensing during pregnancy was found to be between 17 and 21% among privately insured women (9). However, to date there are no published comparable values for opioid prescription among pregnant women on Medicaid in Montana.

Current literature on opioid use among pregnant women mainly focuses on racial differences between White, Black and Hispanic populations, leaving a gap in knowledge regarding opioid use patterns among Native Americans, as the latter often makes up only a small portion of the samples considered. Only two identified sources reported prenatal opioid use among American Indians and Alaska Native populations. One study in Wisconsin found that about 3% of American Indian and Native American mothers who delivered between 2009 and 2014 had used opioids (11). However, this study used International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes to identify maternal substance abuse at the time of delivery (instead of throughout the duration of pregnancy) and included both illicit and prescribed opioid use (11). Only focusing on ICD-9-CM codes at the time of delivery may result in biased results, as opioid exposure during the rest of pregnancy is not captured. This study also found that the rate of opioid use was higher among American Indian and Alaska Native mothers (27.2 (95% CI: 22.6-31.8)) than among White mothers (11.7 (95% CI: 11.3-12.1)) (11). In contrast, one 2017 community assessment report in Montana found that among the Blackfeet Indian Reservation in northwest Montana, 31% of women who delivered at one of the Blackfeet medical facilities tested positive for opioids at delivery (12). Note that both studies report American Indian and Alaskan Native maternal opioid use (both illicit and prescribed) at time of hospitalization for delivery, not opioid prescription patterns. No study was found that described opioid prescription among American Indians. The ten-fold difference in opioid use between these two studies and the absence of any study that assesses opioid prescriptions patterns among Native Americans in the United States point to the need for more extensive and comprehensive research that explores the statewide and nationwide opioid trends observed among the American Indian and Alaska Native population.

While studies have found a clear association between opioid use and some adverse birth outcomes such as neonatal abstinence syndrome, for other outcomes such as preterm birth and small for gestation age, research does not agree on whether an association exists and if so, what that effect is. Some studies have found a positive, statistically significant association between opioid use during pregnancy and preterm birth (18-21), while others have found no association between preterm birth and opioid use during pregnancy or differing association depending on opioid type (22, 23). Results for the association between opioid use during pregnancy and SGA have been similarly inconsistent (16, 20, 22, 24).

The objectives of this analysis are threefold: (1) to compare the patterns of opioid prescription among pregnant women on Medicaid in Montana to that observed across the United States, (2) to identify opioid prescription patterns among Medicaid-enrolled American Indian and Alaska Native women in Montana—a population for which opioid prescription information is mostly lacking—and, (3) to examine the association between opioid use during pregnancy, preterm birth, and small for gestational age. In this way, this work can help clarify the relationship between opioid use and these two adverse birth outcomes to help guide future research focusing on opioid use during pregnancy.

Methods

I. Study population and data sources

A retrospective cohort study was conducted using data from Montana's Medicaid program. Medicaid claim records from a total of 7,389 pregnant women were linked to birth records for infants born from 2009 to 2015 by the Montana Department of Public Health and Human Services. From the linked records, a de-identified dataset containing only mothers who were on Medicaid throughout the entire duration of their pregnancy was obtained. Observations with missing or "NA" values listed for the exposure of interest (i.e. opioid prescription at any point during pregnancy), for any of the potential confounders (i.e. maternal age, parity, maternal smoking status, maternal alcohol use, maternal race, and maternal education), or for any variables needed to calculate the outcomes of interest (e.g. gestational age at birth and birthweight) were excluded from the final dataset. Missing or "NA" values constituted about 3.6% of the original dataset (n=267). Additionally, observations with gestational age less than 22 weeks were ineligible for this analysis and were excluded, as were observations where maternal race was categorized as "Other/Multiple." The latter only comprised 1.4% of the total data, making it difficult and unreliable to analyze this group alone. The remaining dataset was inspected for implausible values of birthweight using corrected United States Birth Weight References (30); birthweight values more than ± three standard deviations from the mean birthweight for respective sex were regarded as implausible (n=58) and were removed. After data cleaning, a total of n=6,947 observations were carried forward to the descriptive and analytic portion of the study (Figure 1). A summary of the variables used in this study is provided in the Appendix (Table 1).

II. Exposure, outcomes and covariates of interest

Opioid prescription status during pregnancy was evaluated as the exposure of interest; observations with an opioid prescription indicated at any point during pregnancy were coded as exposed (1) and those with no opioid prescriptions during pregnancy were coded as unexposed (0). The outcomes of interest for this study were preterm birth and SGA; each outcome's association with opioid prescription during pregnancy was evaluated separately. For the preterm analysis, births between 22 and 36 gestational weeks inclusively, were coded as preterm (1) while observations with a gestational week of 37 or greater were considered term births (0). Given that there is no lower bound of preterm birth that is consistently used across the literature, 22 weeks of gestation was used as the cut-off point to distinguish between spontaneous abortions (miscarriages) and preterm births. Unfortunately, previous studies often do not agree on the lower bound for gestational age when determining preterm birth status, an issue which may play a role in comparing study results (18-20). However, providing a lower bound of 22 weeks helps eliminate any outcome misclassification issues. Meanwhile for the SGA analysis, birth weights below the 10th percentile for sex-specific gestational age were coded as SGA births (1) while all other births were considered not SGA (0) (30).

Based on previous literature, potential confounders were considered as part of this analysis (Appendix Figure 1). Maternal race was coded as either American Indian and Alaska Native (1) or White (0) based on how maternal race was reported on birth records. Medicaid record. Reported alcohol use during pregnancy and maternal smoking status during pregnancy were coded as either yes (1) or no (0). Maternal education level had four levels and was coded as no degree (1), high school diploma (2), some college (3), or

Associate Degree or higher (0). Meanwhile, maternal age was coded as less than 20 (1), 20-24 (2), 25-29 (0), 30-34 (3), 35-39 (4), and older than 40 years of age (5). Finally, parity was coded as zero (0), one (1), two (2), three (3), four (4), or five or more (5).

III. Analysis

First, time trends by year were determined for mothers on Medicaid in Montana who received an opioid prescription during pregnancy. Next, descriptive statistics were calculated to compare demographics of all mothers in the sample who were prescribed an opioid during pregnancy versus those who were not, and for American Indian or Alaska Native mothers who were prescribed opioids during pregnancy compared to those who were not. Chi-square tests were conducted to determine if proportional differences for the demographic characteristics considered were significantly different by exposure status. Similarly, t-tests were conducted to determine if differences in average maternal age were significantly different by exposure status.

The last portion of the statistical analysis for this study was divided into two parts; one examined the association between opioid prescription during pregnancy and preterm birth and the other between opioid prescription during pregnancy and SGA. Odds ratios were calculated to allow comparability of this study's results with those obtained by past studies. The initial logistic regression models for each analysis were as follows:

(a) logit P(PRETERM=1) = α + β1(OpioidPrescriptionStatus) + γ1(MaternalRace) + γ2(AlcoholUse) + γ3(MaternalSmokingStatus) + γ4(Education1) + γ5(Education2) + γ6(Education3) + γ7(MaternalAge<20) + γ8(MaternalAge20-24) + γ9(MaternalAge30-34) + γ10(MaternalAge35-39) + γ11(MaternalAge40+) + γ12(Parity1) + γ13(Parity2) + γ14(Parity3) + γ15(Parity4) + γ16(Parity5)

(b) $\text{logit } P(SGA=1) = \alpha + \beta1(\text{OpioidPrescriptionStatus}) + \gamma1(\text{MaternalRace}) + \gamma2(\text{AlcoholUse}) + \gamma3(\text{MaternalSmokingStatus}) + \gamma4(\text{Education1}) + \gamma5(\text{Education2}) + \gamma6(\text{Education3}) + \gamma7(\text{MaternalAge<20}) + \gamma8(\text{MaternalAge20-24}) + \gamma9(\text{MaternalAge30-34}) + \gamma10(\text{MaternalAge35-39}) + \gamma11(\text{MaternalAge40+}) + \gamma12(\text{Parity1}) + \gamma13(\text{Parity2}) + \gamma14(\text{Parity3}) + \gamma15(\text{Parity4}) + \gamma16(\text{Parity5})$

Note: Dummy variables were made manually for all nominal variables including maternal education level and parity. Maternal age was categorized into six age bands, as this grouping scheme seemed to best follow the trend in risk ratio estimates for the association between maternal age and the outcomes of interest when maternal age was kept as a continuous variable. The reference categories used for the analyses were as follows:

- Maternal race = White
- Maternal alcohol use during pregnancy = no
- Maternal smoking status = no
- Education = Associate Degree or Higher
- Parity = 0
- Maternal age = 25-29

A) Collinearity Assessment

The first step towards reaching the final models for this analysis was to determine if collinearity was an issue between any two of the potential confounders. Collinearity was identified by Condition Indices (CI) greater than 30 combined with a Variance Decomposition Proportions (VDPs) higher than 0.5. Specifically, any two variables with

CIs above 30 and similar VDPs (but not associated with the intercept) were considered to be involved in a collinearity issue.

The collinearity assessment for both the preterm birth and the SGA analysis revealed no collinearity problems; no CIs were greater than 30. For both the preterm and SGA analyses, only one VDP associated with the largest CI was higher than 0.5 (i.e. maternal age). Thus, no two variables fulfilled the definition specified previously for collinearity and no predictors were consequently dropped.

B) Variable Screening

The relationship between each potential confounder, each outcome of interest (i.e. preterm birth and SGA), and opioid prescription during pregnancy was assessed by obtaining odd ratio estimates for the relationship between potential confounders and each outcome, and risk ratio estimates for the relationship between potential confounders and the exposure. The results from the variable screening processes are summarized in the Appendix (Table 2). Maternal use of alcohol during pregnancy had a weak/moderate association with opioid prescription during pregnancy, preterm birth and SGA. Alcohol use also had the widest confidence intervals out of all potential confounders considered. Similarly, maternal age had a weak association with the outcomes of interest and had the largest confidence intervals of all the potential confounders. For these reasons, alcohol use during pregnancy and maternal age were excluded from the analysis. The following models were included in the confounding assessment and were considered the full models for this analysis:

(a) $\text{logit } P(\text{PRETERM}=1) = \alpha + \beta 1(\text{OpioidPrescriptionStatus}) + \gamma 1(\text{MaternalRace}) + \gamma 2(\text{MaternalSmokingStatus}) + \gamma 3(\text{Education1}) + \gamma 4(\text{Education2}) + \gamma 5(\text{Education3}) + \gamma 6(\text{Parity1}) + \gamma 7(\text{Parity2}) + \gamma 8(\text{Parity3}) + \gamma 9(\text{Parity4}) + \gamma 10(\text{Parity5})$

(b) $\text{logit } P(\text{SGA}=1) = \alpha + \beta 1(\text{OpioidPrescriptionStatus}) + \gamma 1(\text{MaternalRace}) + \gamma 2(\text{MaternalSmokingStatus}) + \gamma 3(\text{Education1}) + \gamma 4(\text{Education2}) + \gamma 5(\text{Education3}) + \gamma 6(\text{Parity1}) + \gamma 7(\text{Parity2}) + \gamma 8(\text{Parity3}) + \gamma 9(\text{Parity4}) + \gamma 10(\text{Parity5})$

C) Confounding Assessment

To assess confounding, OR estimates were obtained from all possible model combinations derived from the full models. These OR estimates were compared to those obtained using the full model to determine whether any of the four variables considered (i.e. maternal smoking status, parity, maternal race and maternal education level) were confounders in the analysis. The results of the confounding assessment for both the preterm birth and the SGA analyses are summarized in the Appendix (Table 3 and Table 4, respectively). Although all OR estimates for the preterm birth analysis are within 10% of the full model OR estimate, Model 9, 14 and the Crude Model provide an OR that lays on the 10% boundary from the full model OR. Thus, the final model should include both maternal smoking status and parity as potential confounders. The Model 1, 3 and 6 all include these variables; however, Model 1 provides a slightly narrower 95% confidence interval for the OR estimate. Thus, Model 1 was chosen as the final model for the preterm birth analysis.

On the other hand, the full model was kept as the final model for the SGA analysis, given that all models were within 10% of the full model OR and that all had similar 95% confidence interval widths. The final models used for both analyses are included below.

(a) $\text{logit } P(\text{PRETERM}=1) = \alpha + \beta 1(\text{OpioidPrescriptionStatus}) + \gamma 2(\text{MaternalSmokingStatus}) + \gamma 3(\text{Education1}) + \gamma 4(\text{Education2}) + \gamma 5(\text{Education3}) + \gamma 6(\text{Parity1}) + \gamma 7(\text{Parity2}) + \gamma 8(\text{Parity3}) + \gamma 9(\text{Parity4}) + \gamma 10(\text{Parity5})$

(b) $\text{logit } P(\text{SGA}=1) = \alpha + \beta 1(\text{OpioidPrescriptionStatus}) + \gamma 1(\text{MaternalRace}) + \gamma 2(\text{MaternalSmokingStatus}) + \gamma 3(\text{Education1}) + \gamma 4(\text{Education2}) + \gamma 5(\text{Education3}) + \gamma 6(\text{Parity1}) + \gamma 7(\text{Parity2}) + \gamma 8(\text{Parity3}) + \gamma 9(\text{Parity4}) + \gamma 10(\text{Parity5})$

All analyses were conducted in SAS 9.4 (SAS Institute Inc. North Carolina). This study was declared exempt from IRB review and approval by the Emory International Review Board.

Results

Medicaid claim records for 6,947 pregnant women in Montana who delivered between 2009 and 2015 were linked to the corresponding birth records and met study inclusion criteria. Of these, 1,978 pregnant women on Medicaid (28.5%) received an opioid prescription at some point during pregnancy. In 2009, 27.8% of pregnant women on Medicaid in Montana were prescribed an opioid compared to 24.1% in 2015 (Figure 1). Additionally, the mean age of mothers who received an opioid prescription during pregnancy was 24.9 (SD: 5.4) and most of these mothers were white (73.3%), did not smoke during pregnancy (58.2%) and had a high school diploma (40.7%). Similarly, the average age for mothers who did not receive a prescription was 24.1 (SD: 5.8) and most of these mothers were also white (69.6), did not smoke (69.7), and had a high school diploma (40.3). Of the sample, 21.8% mothers had a preterm birth and 11.1% had a SGA birth during the study period. Among women who were prescribed an opioid during pregnancy, 25.3% had a preterm birth, and 11.7% delivered a SGA infant, compared to 20.5% and 10.9% among women who were not prescribed an opioid (Table 1).

Among the 2,040 American Indian or Alaska Native mothers in the sample, 25.9% were prescribed an opioid during pregnancy. This is significantly lower than the 29.5% of white mothers who received an opioid prescription ($p = 0.003$). Most American Indian or Alaska Native mothers who were prescribed an opioid during pregnancy, did not smoke (59.5%), and had a mean age of 25.3 (SD: 5.7). On the other hand, among American Indian and Alaska Native mothers who were not prescribed an opioid, the proportion of mothers who did not smoke during pregnancy (71.1%) was higher than among those who were prescribed an opioid ($p<0.0001$) and these mothers had a lower average age (23.4 (SD: 5.7)) (Table 2).

For mothers who had a preterm birth, the odds of having an opioid prescribed during pregnancy after adjusting for maternal smoking status, maternal education level and parity was 1.20 (95% CI: 1.06-1.37) the odds of not having an opioid prescription during pregnancy. Meanwhile, for women who delivered an infant that was SGA, the odds of having an opioid prescribed during pregnancy was not found to be statistically and significantly different from the odds of not having an opioid prescription during pregnancy (OR: 1.02, 95% CI: 0.86-1.20) regardless of whether the crude or adjusted model was used (Table 3).

Discussion

This study provides the first evaluation of opioid prescription patterns among pregnant women in Montana on Medicaid. Although the years of this study differ from a comparable national study (2009-2015 versus 2000-2007), the demographics of Montana women who were prescribed opioids during their pregnancy resembles prescription patterns that were seen across the United States. Nationally, 21.6% of pregnant women on Medicaid received an opioid prescription, versus 28.5% of Montana mothers (7). Although it is possible that some of the differences observed may be due to differences in measurement of the exposure (here, the exposure was defined as any opioid prescription during pregnancy, whereas other studies looked at filled opioid prescriptions), it is unlikely that this can entirely explain the difference between Montana's figures and those seen across the country. The difference between Montana percentages and national percentages could be due to differences in racial breakdown: most women in this study (71%) were White, while in the national study, 40% were White and 29% of these mothers received a prescription during pregnancy. Additionally, the percent of women receiving an opioid prescription in Montana is similar to that seen in states neighboring Montana; in Washington, Idaho and Wyoming, the rate of filled opioid prescriptions during pregnancy among women on Medicaid is greater than 30%, while in North Dakota the rate is between 20-30% (7). Meanwhile, the average age of women on Medicaid that received an opioid prescription (24.9±5.4) was found to be within one standard deviation of the national average (24.3±5.3) (7). These results support the idea that the demographic patterns of mothers who are more likely to be prescribed opioids during pregnancy are consistent between Montana and the rest of the United States, while the rate of opioid prescription in Montana mirrors that seen in neighboring states.

The present study provides the first published overview of opioid prescription trends observed among American Indian and Alaska Native women who are enrolled in Medicaid in Montana. In Montana, almost 27% of Native American women on Medicaid between 2009 and 2015 were prescribed opioids during pregnancy. Nonetheless, a previous report found that 31% women in Montana's Blackfeet Indian Reservation were found to have opioids in their systems at delivery (12). These differences may indicate that opioid prescription and use patterns vary during different points in pregnancy for this subpopulation. Additionally, in this sample, only 2.2% of American Indian and Alaska Native mothers reported drinking alcohol during pregnancy. However, other studies have found a much higher rate of alcohol use during pregnancy among Native populations. For example, a 2017 meta-analysis found the prevalence of alcohol use during pregnancy among the Aboriginal population in the United States to be 42.9% (30). This difference may suggest underreporting of alcohol use among Native American mothers in this sample and thus should be explored further. Nonetheless, these results provide preliminary opioid prescription patterns among American Indian and Alaska Native population that can help guide future studies and policies that focus on this population.

As expected, the proportion of pregnant women on Medicaid in Montana with an opioid prescription is higher than that among privately insured pregnant women in the state; among privately insured women, the proportion is between 16.6 and 20.5% (versus 28.5% among women on Medicaid) (9). These results support other published research (9) that suggests a higher rate of opioid prescription among less financially advantaged mothers (who tend to be enrolled in Medicaid) than among more financially advantaged mothers (who tend to be privately insured).

When it comes to opioid prescription patterns across time, the proportion of women who were prescribed opioids fluctuated throughout the seven-year study period considered. Thus, given that there is no clear trend in opioid prescription rates in the years between 2009 and 2015, additional data is needed to more comprehensively describe Montana's opioid prescription patterns. Specifically, data for the years directly before 2009 and after 2015 are needed to understand whether the rate of opioid prescription among pregnant women on Medicaid changes when taking a more holistic view of the data.

Similar to previous studies, an association between opioid prescription during pregnancy and preterm birth was found in this study, although the association was smaller than what has been reported in other studies. While in this study, the odds ratio was found to be 1.2 (95% CI: 1.1-1.4), a study looking specifically at the association between methadone and preterm birth found the odds ratio to be 2.5 (95% CI: 2.0-3.1) (20). This may be a result of classifying opioid exposure during pregnancy as receiving any opioid prescription regardless of opioid type. It is possible that the effect of opioids strongly associated with preterm birth may have been masked by opioids that have a smaller association with this outcome.

For the SGA analysis, no association was found between opioid prescription during pregnancy and SGA. Considering that the literature does not agree on the association between SGA and opioid use during pregnancy, these findings confirm the need to consider the effect of opioids on SGA by opioid type in future studies. Thus, this work does not rule out an association between opioid use during pregnancy and SGA but instead, it provides more insight on how the association between these two variables can be studied more accurately in the future.

There are at least four strengths to this study. First, this study provides the first look at opioid prescription patterns among pregnant women on Medicaid in Montana, fulfilling a gap currently present in this area of research. Secondly, the large sample size used for this analysis and the limited number of observations that were excluded due to missing values reduces variability in the data and provides more reliable results. Thirdly, the large sample of American Indian and Alaska Native mothers used in this study allowed for a closer look at opioid prescription patterns within the Native population. Lastly, this analysis provides both crude and adjusted measures of association for the relationship between opioid prescription and preterm birth/SGA, which helped identify the role that potential confounders have on the association of interest.

Nonetheless, the work provided in this study is not devoid of limitations. There are at least three limitations that may prevent this study from being completely generalizable to other populations. First, given that only birth records and Medicaid data were available, opioid prescriptions were used as a proxy for opioid use during pregnancy. This may pose a problem, as women who were prescribed an opioid may not have filled the prescription or they may not have taken the opioid altogether. Second, from these results it is not clear if opioid use during pregnancy contributes to preterm birth or if an underlying condition is increasing the risk of preterm birth and leading to the use of opioids during pregnancy (i.e. other sources of confounding may be affecting the association between preterm birth and opioid use during pregnancy). Third, instead of looking at the effect that individual types of opioids may have on adverse birth outcomes, the prescription of opioids was studied as a whole. In the future, it may be beneficial to obtain specific information on the type of opioid and timing of dose administered during pregnancy.

This study provides an overview of opioid prescription patterns for pregnant women on Medicaid in Montana overall, as well as a more detailed look at patterns among the American Indian and Alaska Native population. This research provides the first snapshot of opioid prescription trends over time for mothers on Medicaid in Montana. Future studies should work on using this information as a stepping stone towards more elaborate research to identify the populations most burdened by opioid use during pregnancy. Additionally, the preterm birth and SGA analyses provided here offer another look at whether these adverse birth outcomes may be associated with opioid use during pregnancy. Although this work is not conclusive, it provides additional information for researchers and providers who are attempting to interpret the role that opioid use during pregnancy may play in the risk of developing adverse birth outcomes.

References

(1) Manchikanti L, Helm II S, Fellows B, Janata JW, Pampati V, Grider JS, Boswell MV. (2012). Opioid Epidemic in the United States. *Pain Physician*, 15(3S), ES9-ES38.

(2) Kenan K, Mack K, Paulozzi L. (2012). Trends in Prescriptions for Oxycodone and Other Commonly Used Opioids in the United States, 2000–2010. *Open Medicine*, 6(2), e41-e47.

(3) Kolodny A, Courtwright DT, Hwang CS, Kreiner P, Eadie JL, Clark TW, Alexander GC. (2015). The Prescription Opioid and Heroin Crisis: A Public Health Approach to an Epidemic of Addiction. *Annual Review of Public Health*, 36, 559–574.

(4) Mack K, Zhang K, Paulozzi L, Jones C. (2015). Prescription Practices Involving Opioid Analgesics Among Americans with Medicaid, 2010. *Journal of Health Care for the Poor and Underserved*, 26(1), 182-198.

(5) Liu Y, Logan JE, Paulozzi LJ, Zhang K, Jones CM. (2013). Potential Misuse and Inappropriate Prescription Practices Involving Opioid Analgesics. *The American Journal of Managed Care*, 19(8), 648-665.

(6) Ailes EC, Dawson AL, Lind JN, Gilboa SM, Frey MT, Broussard CS, Honein MA. (2015). Opioid Prescription Claims Among Women of Reproductive Age — United States, 2008–2012. *Morbidity and Mortality Weekly Report*, 64(3), 37-41.

(7) Desai RJ, Hernandez-Diaz S, Bateman BT, Huybrechts KF. (2014). Increase in Prescription Opioid Use During Pregnancy Among Medicaid-Enrolled Women. *Obstetrics & Gynecology*, 123(5), 997-1002.

(8) Yazdy MM, Desai, RJ, Brogly SB. (2015). Prescription Opioids in Pregnancy and Birth Outcomes: A Review of the Literature. *Journal of Pediatric Genetics*, 4(2), 56-70.

(9) Bateman BT, Hernandez-Diaz S, Rathmell JP, Seeger JD, Doherty M, Fischer MA, Huybrechts KF. (2014). Patterns of Opioid Utilization in Pregnancy in a Large Cohort of Commercial Insurance Beneficiaries in the United States. *Anesthesiology*, 120(5), 1216-1224.

(10) Epstein RA, Bobo WV, Martin PR, Morrow JA, Wang W, Chandrasekhar R, Cooper, WO. (2014). Increasing Pregnancy-Related Use of Prescribed Opioid Analgesics. *Annals of Epidemiology*, 23(8), 498-503.

(11) Atwell KA, Weiss HB, Gibson C, Miller R, Corden TE. (2016). Neonatal Abstinence Syndrome and Maternal Substance Use in Wisconsin 2009-2014. *Wisconsin Medical Journal*, 115(6), 287-293.

(12) Indian Health Service. (2017). Chart Review of All Deliveries in One Calendar Year (Undisclosed), 2013-2017. Billings, MT: IHS Billings Area Office.

(13) Creanga AA, Sabel JC, Ko JY, Wasserman CR, Shaprio-Mendoza CK, Taylor P, Barfield W, Cawthon L, Paulozzi LJ. (2012). Maternal Drug Use and its Effect on Neonates: A Population-Based Study in Washington State. *Obstetrics & Gynecology*, 119(5), 924–33.

(14) Yazdy MM, Mitchell AA, Tinker SC, Parker SE, Werler MM. (2015). Periconceptional Use of Opioids and the Risk of Neural Tube Defects. *Obstetrics & Gynecology*, 122(2), 838-844.

(15) Broussard CS, Rasmussen SA, Reefhuis J, Friedman JM, Jann MW, Riehle-Colarusso T, Honein MA. (2011). National Birth Defects Prevention Study. Maternal Treatment with Opioid Analgesics and Risk for Birth Defects. *American Journal of Obstetrics & Gynecology*, 204(4), 314.e1–314.e11.

(16) Nørgaard M, Nielsson MS, Heide-Jørgensen U. (2015). Birth and Neonatal Outcomes Following Opioid Use in Pregnancy: A Danish Population-Based Study. *Substance Abuse: Research and Treatment*, 9(S2), 5-11.

(17) Hand DJ, Short VL, Abatemarco DJ. (2016). Substance Use, Treatment, and Demographic Characteristics of Pregnant Women Entering Treatment for Opioid Use Disorder Differ by United States Census Region. *Journal of Substance Abuse Treatment*, 76, 58-63.

(18) Kelly L, Dooley J, Cromarty H, Cromarty H, Minty B, Morgan, A, Madden S, Hopman, W. (2011). Narcotic-Exposed Neonates in a First Nations Population in Northwestern Ontario: Incidence and Implications. *Canadian Family Physician*, 57(11), e441-e447.

(19) Dryden C, Young D, Hepburn M, Mactier H. (2009) Maternal Methadone Use in Pregnancy: Factors Associated with the Development of Neonatal Abstinence Syndrome and Implications for Healthcare Resources. *British Journal of Obstetrics & Gynaecology*, 116(5), 665–671.

(20) Cleary BJ, Donnelly JM, Strawbridge JD, Paul JG, Fahey T, White MJ, Murphy DJ. (2011) Methadone and Perinatal Outcomes: A Retrospective Cohort Study. *American Journal of Obstetrics & Gynecology*, 204(2), 139.e1–139.e9.

(21) Sharpe C, Kuschel C. (2004). Outcomes of Infants Born to Mothers Receiving Methadone for Pain Management in Pregnancy. *Archives of Disease in Childhood. Fetal Neonatal Edition*, 89(1), F33–F36.

(22) Smith MV, Costello D, Yonkers KA. (2015). Clinical Correlates of Prescription Opioid Analgesic Use in Pregnancy. *Maternal and Child Health Journal*, 19(3):548–556.

(23) Jones HE, Kaltenbach K, Heil SH, (2010). Neonatal Abstinence Syndrome After Methadone or Buprenorphine Exposure. *New England Journal of Medicine*, 363(24): 2320–2331.

(24) Källén B, Borg N, Reis M. (2013). The Use of Central Nervous System Active Drugs During Pregnancy. *Pharmaceuticals*, 6, 1221-1286.

(25) The Henry J. Kaiser Family Foundation. (2017). Medicaid in Montana. Retrieved from http://files.kff.org/attachment/fact-sheet-medicaid-state-MT .

(26) U.S. Census Bureau (2010). Profile of General Population and Housing Characteristics: 2010. Retrieved from http://ceic.mt.gov/Documents/PopulationProjections/Census2010Profiles/State%20Profiles/Census2010_DP1_Montana.pdf .

(27) Department of Public Health and Human Services-Montana. (2017). Montana Department of Public Health and Human Services Report to the 2017 Legislature: State Fiscal Years 2015/2016. Retrieved from

https://dphhs.mt.gov/Portals/85/Documents/biennialreports/FINAL%20PRINTED%20%201-7-17%202017%20MEDICAID%20REPORT.pdf .

(28) Welch J, Cohn A. (2016). Curbing Prescription Drug Abuse with Patient Review and Restriction Programs. 1-26. Retrieved from http://www.pewtrusts.org/~/media/assets/2016/03/curbing_prescription_drug_abuse_with_patient_review_and_restriction_programs.pdf .

(29) Hernandez AA, Moore JE. (2017). Addressing the Opioid Epidemic in Medicaid Managed Care for Women and Newborns. Institute for Medicaid Innovation. Retrieved from http://www.medicaidinnovation.org/_images/content/5._Addressing_the_Opioid_Epidemic_in_Medicaid_Managed_Care_for_Women_and_Newborns_.pdf

(30) Talge NM, Mudd LM, Sikorskii A, Basso O. (2014). United States Birth Weight Reference Corrected for Implausible Gestational Age Estimates. *Pediatrics*, 133, 844-853.

(31) Popova S, Lange S, Probst C, Parunashvili N, Rehm J. (2017). Prevalence of Alcohol Consumption During Pregnancy and Fetal Alcohol Spectrum Disorders Among the General and Aboriginal Populations in Canada and the United States. *European Journal of Medical Genetics*, 60(1), 32-48.

Figures and Tables

Figure 1. Study population used to identify the patterns of opioid prescription among pregnant women on Medicaid in Montana and to analyze the association between opioid prescription and preterm birth/small for gestational age.

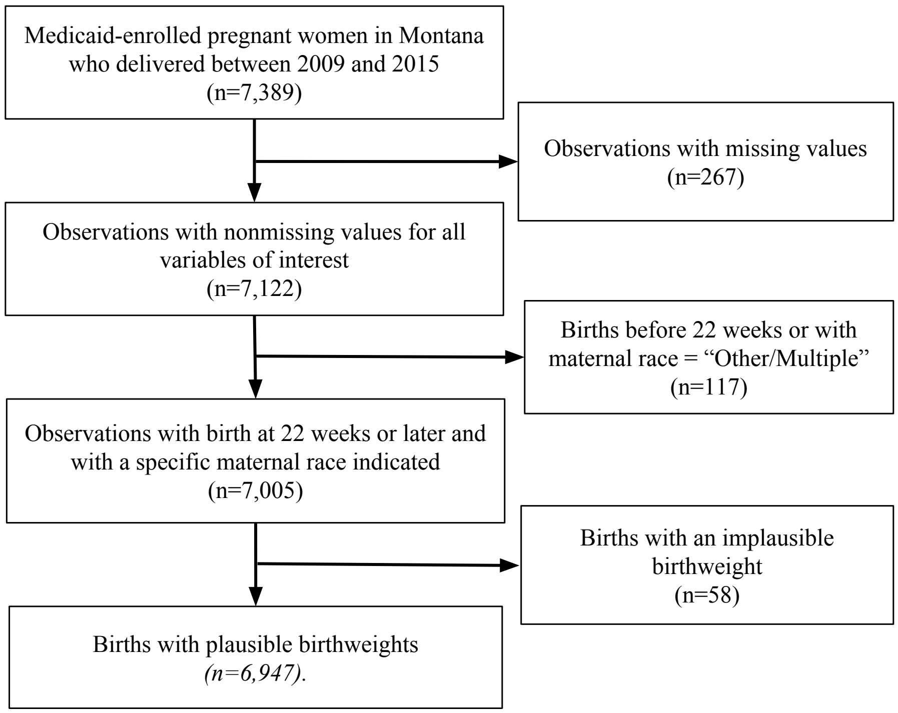
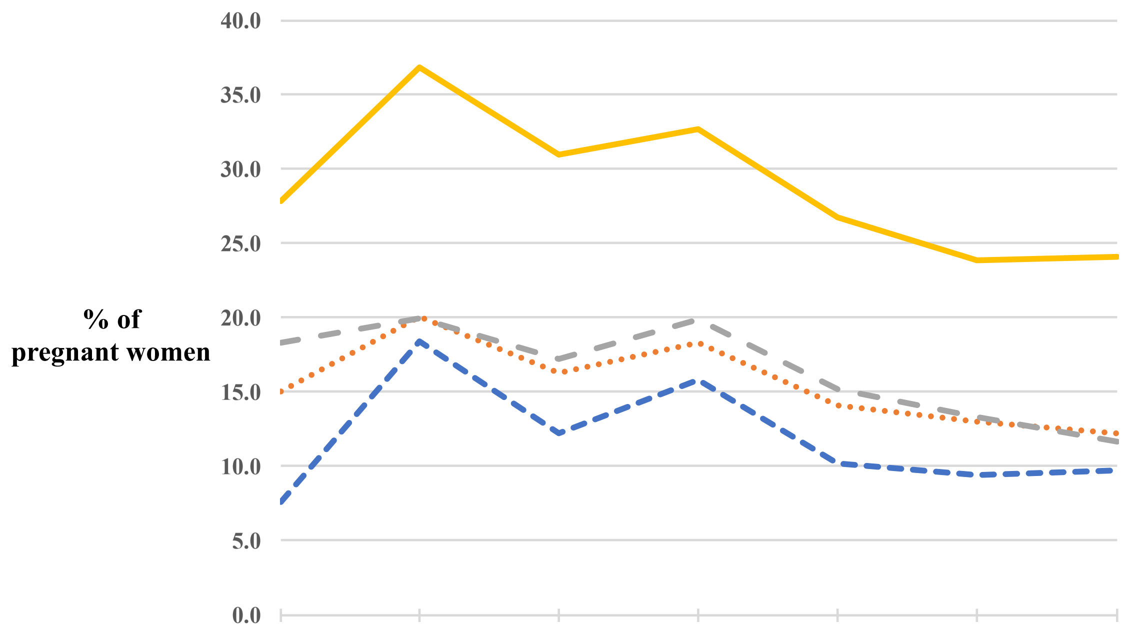


Figure 2. Proportion of pregnant women on Medicaid in Montana who were prescribed an opioid, 2009-2015 (n=6,947).



	2009		2010		2011		2012		2013		2014		2015		All	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
First trimester	63	7.6	167	18.4	112	12.3	131	15.8	97	10.2	102	9.5	142	9.8	814	11.7
Second trimester	125	15.1	182	20.1	148	16.2	153	18.4	134	14.1	140	13.0	177	12.2	1,059	15.2
Third trimester	152	18.4	181	20.0	157	17.2	165	19.9	144	15.1	143	13.3	169	11.7	1,111	16.0
Any time during pregnancy	230	27.8	334	36.9	283	31.1	272	32.7	254	26.7	257	23.9	348	24.1	1,978	28.5

Table 1. Demographic characteristics of mothers on Medicaid in Montana (2009-2015) by opioid prescription status.

	Eligible Births (n=6,947) No. (%)	Opioid Prescribed during Pregnancy (n=1,978) No. (%)	No Opioid Prescribed during Pregnancy (n=4,969) No. (%)	p-value[a]
Preterm				p<0.0001
Yes	1,516 (21.8)	500 (25.3)	1,016 (20.5)	
No	5,431 (78.2)	1,478 (74.7)	3,953 (79.5)	
SGA				0.3565
Yes	773 (11.1)	231 (11.7)	542 (10.9)	
No	6,174 (88.9)	1,747 (88.3)	4,427 (89.1)	
Average Maternal Age (SD)	24.3 (5.7)	24.9 (5.4)	24.1 (5.8)	p<0.0001
Maternal Race				0.0025
White	4,907 (70.6)	1,449 (73.3)	3,458 (69.6)	
American Indian/Alaska Native	2,040 (29.4)	529 (26.7)	1,511 (30.4)	
Mother used alcohol during pregnancy				0.3488
Yes	134 (1.9)	43 (2.2)	91 (1.8)	
No	6,813 (98.1)	1,935 (97.8)	4,878 (98.2)	
Mother smoked during pregnancy				p<0.0001
Yes	2,334 (33.6)	827 (41.8)	1,507 (30.3)	
No	4,613 (66.4)	1,151 (58.2)	3,462 (69.7)	
Maternal Education Level				0.0040
No Degree	2,210 (31.8)	617 (31.2)	1,593 (32.1)	
High School Diploma	2,805 (40.4)	804 (40.7)	2,001 (40.3)	
Some College	1,395 (20.1)	434 (21.9)	961 (19.3)	
Associate Degree or Higher	537 (7.7)	123 (6.2)	414 (8.3)	
Parity				p<0.0001
0	2,069 (29.8)	412 (20.8)	1,657 (33.3)	
1	2,146 (30.9)	624 (31.6)	1,522 (30.6)	
2	1,393 (20.1)	467 (23.6)	926 (18.6)	
3	733 (10.6)	262 (13.3)	471 (9.5)	
4	342 (4.92)	128 (6.5)	214 (4.3)	
5+	264 (3.8)	85 (4.3)	179 (3.6)	

[a]T-test used for maternal age comparison. Chi-quared tests used for all other characteristics.

Table 2. Characteristics of American Indian/Alaska Native mothers on Medicaid in Montana (2009-2015) by opioid prescription status.

	Eligible Births	**Opioid Prescribed during Pregnancy**	**No Opioid Prescribed during Pregnancy**	
	(n=2,040)	**(n=529)**	**(n=1,511)**	
	No. (%)	**No. (%)**	**No. (%)**	**p-value**[a]
Preterm				0.0585
Yes	475 (23.3)	139 (26.3)	336 (22.2)	
No	1,565 (76.7)	390 (73.7)	1,175 (77.8)	
SGA				0.1308
Yes	183 (9.0)	56 (10.6)	127 (8.4)	
No	1,857 (91.0)	473 (89.4)	1,384 (91.6)	
Average Maternal Age (SD)	23.7 (5.8)	25.3 (5.7)	23.4 (5.7)	p<0.0001
Mother used alcohol during pregnancy				0.5659
Yes	45 (2.2)	10 (1.9)	35 (2.3)	
No	1,995 (97.8)	519 (98.1)	1,476 (97.7)	
Mother smoked during pregnancy				p<0.0001
Yes	649 (31.8)	213 (40.3)	436 (28.9)	
No	1,391 (68.2)	316 (59.5)	1,075 (71.1)	
Maternal Education Level				0.2719
No Degree	879 (43.1)	209 (39.5)	670 (44.3)	
High School Diploma	625 (30.6)	175 (33.1)	450 (29.8)	
Some College	373 (18.3)	100 (18.9)	273 (18.1)	
Associate Degree or Higher	163 (8.0)	45 (8.5)	118 (7.8)	
Parity				p<0.0001
0	559 (27.4)	88 (16.6)	471 (31.2)	
1	518 (25.4)	132 (25.0)	386 (25.5)	
2	403 (19.8)	127 (24.0)	276 (18.3)	
3	263 (12.9)	90 (17.0)	173 (11.4)	
4	165 (8.1)	56 (10.6)	109 (7.2)	
5+	132 (6.5)	36 (6.8)	96 (6.4)	

[a]T-test used for maternal age comparison. Chi-quared tests used for all other characteristics.

Table 3. Adjusted and crude odds ratios for the association between opioid prescription during pregnancy and two adverse birth outcomes (preterm birth and SGA).

Model	**Preterm Birth** **OR (95% CI)**	**SGA** **OR (95% CI)**
Crude	1.32 (1.16 - 1.49)	1.08 (0.92 - 1.27)
Adjusted	1.20 (1.06 - 1.37)[a]	1.02 (0.86 - 1.20)[b]

[a] Adjusted for maternal smoking status, maternal education level, and parity
[b] Adjusted for maternal race, maternal smoking status, maternal education level, and parity

CHAPTER III: Public Health Implications

In the United States, opioid prescription has been increasing and is leading towards a country-wide epidemic. Research to date shows that opioid use during pregnancy is also increasing, although opioid prescription patterns among pregnant women vary considerably across regions and may even vary from state to state. This increase in opioid prescription among pregnant women is particularly alarming given that the effect of opioid use during pregnancy on adverse birth outcomes is poorly understood. This becomes even more concerning in states where opioid prescription patterns are unknown, among communities where trends are understudied, and among populations that are experiencing higher rates of health disparities. Ultimately, the burden of opioid use among such populations remains poorly understood and prevent researchers and providers from identifying individuals most at-risk for adverse outcomes that result from opioid use during pregnancy. Such is the case for the Medicaid population in Montana, where statewide opioid prescription patterns have not been studied and where the American Indian and Alaska Native population has a larger presence than in other parts of the country. Through this study, the patterns of opioid prescription among pregnant Medicaid-enrollees in Montana were identified, with particular attention to the trends observed among the American Indian and Alaska Native population. Additionally, the relationship between opioid prescription during pregnancy, preterm birth, and small for gestational age (two birth outcomes that have shown mixed results when evaluated for their association to opioid use during pregnancy in previous studies) were also explored.

These study findings reveal that overall, demographic patterns in Montana among Medicaid-enrolled mothers are similar to those seen across the United States.

Furthermore, when it comes to the trends in the proportion of pregnant women who were prescribed opioids, Montana's figures closely mirror what is seen in neighboring states. These results can help guide future research to identify why opioid prescription is higher among certain subpopulations. In this way, statewide and nationwide interventions can reach the most at-risk populations and direct tax-payer money in a way that will benefit the highest risk populations. These results support the need to examine opioid prescribing patterns among pregnant women on Medicaid at the regional level, instead of focusing on nationwide patterns, particularly when looking at the proportion of pregnant women who are prescribed opioids. Alternatively, looking at country-wide trends may provide policy guidance that may prove to be inappropriate or unsuccessful in states that do not strictly follow national trends.

Among the 2,040 American Indian or Alaska Native mothers in the sample, slightly more than one-quarter were prescribed an opioid during pregnancy. This is lower than the almost one-third of white mothers who were prescribed an opioid. These patterns provide a first look at how opioid use among the American Indian and Alaska Native population compares to that observed among other subpopulations in similar studies. Targeted data on opioid prescription patterns among subpopulations in the United States can help public health officials better serve their communities and develop comprehensive opioid use guidelines.

The preterm birth and SGA analyses of this study also provide guidance for how future studies considering these two adverse birth outcomes should consider opioid exposure. These results contribute to the already existing literature that indicate a positive association between opioid use during pregnancy and preterm birth and no association between opioid use during pregnancy and SGA. However, rather than providing conclusive results on the relationship between these variables, these results encourage researchers in this field to consider alternate ways of measuring opioid use during pregnancy to ascertain the effect that different types of opioids have on adverse birth outcomes.

While there are still many gaps in knowledge when it comes to opioid use during pregnancy, research in this field is actively growing. To benefit the women who are more likely to use opioids during pregnancy and to develop adverse birth outcomes, more detailed research is needed to identify the reasons why these mothers use opioids. This research should look at differences in age, race, education level and geographic location to determine whether there are patterns among mothers who share certain demographic characteristics. These results may help policy makers develop recommendations that are sensitive to the experiences of the most-at-risk mothers and that will prove to be the most beneficial to this population.

APPENDIX: Additional Figures and Tables

Table 1. Variables obtained from Medicaid claim data and vital records that were used for this analysis.

From Birth Records (2009 – 2015)	
Variable	Description
Unique Identifier	Unique identifier for each woman in the dataset
BIRTHY4	Year of delivery
Race	Coded as White, AIAN, other
Ethnicity	Coded as Hispanic/non-Hispanic
Maternal age	Age of mother at time of delivery
Maternal Education	Mother's highest diploma/degree
Parity	Previous number of live births (combining now living & now dead births)
BGESTAT	Gestational age at birth
BWTGRMS	Gestational weight in grams
pregsmoke	Binary measure of any smoking during pregnancy as reported by mothers
BDRINKA	Alcohol use during pregnancy (yes, no, unknown)
BSEXA	Coded as Male/Female
From Medicaid Data (2009-2015)	
Variable	Description
OpioidScript1T	Number of opioid scripts during 1st trimester
OpioidScript2T	Number of opioid scripts during 2nd trimester
OpioidScript3T	Number of opioid scripts during 3rd trimester
AnyOpioid	Were opioids prescribed at any point during pregnancy?

Figure 1. Potential confounders of the association between opioid prescription and preterm birth/SGA, according to current literature.

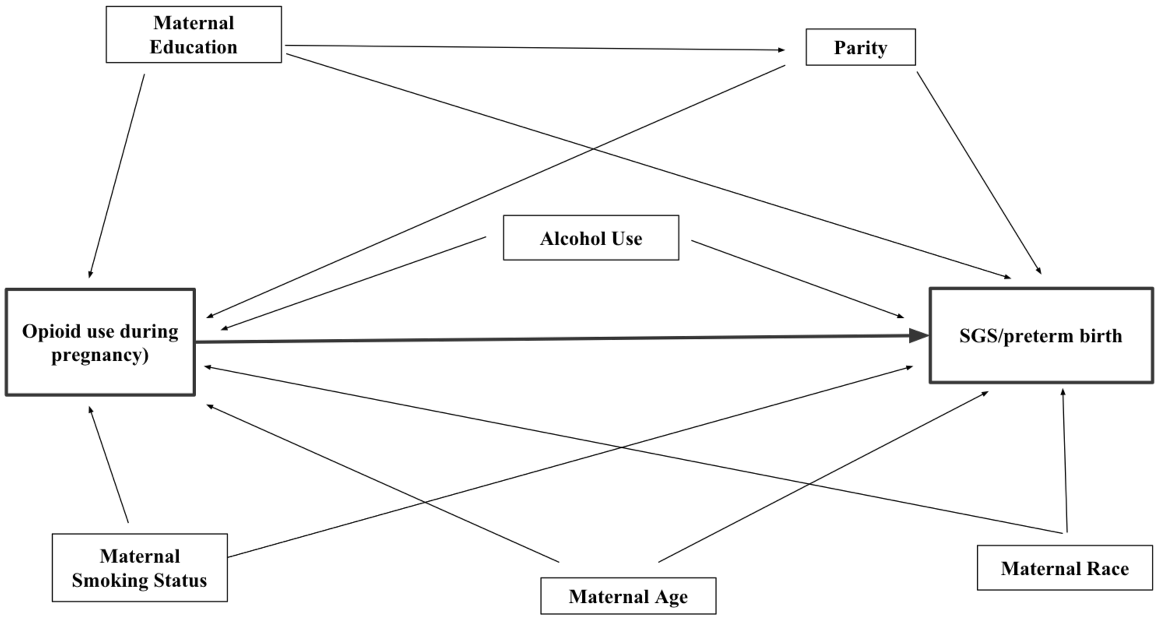


Table 2. Assessment of potential confounders via variable screening.

Covariate	Opioid Prescribed During Pregnancy OR	Lower Limit	Upper Limit	Width	Association	Preterm Birth RR	Lower Limit	Upper Limit	Width	Association	Conclusion	SGA RR	Lower Limit	Upper Limit	Width	Association	Conclusion
Maternal Race					Weak/ Moderate					Weak	Include					Moderate	Include
White[b]	1.00					1.00						1.00					
American Indian/Alaska Native	0.84	0.74	0.94	1.26		1.10	1.00	1.21	1.21			0.75	0.64	0.87	1.37		
Mother smoked during pregnancy					Strong					Weak	Include					Strong	Include
No[b]	1.00					1.00						1.00					
Yes	1.65	1.48	1.84	1.24		1.12	1.02	1.23	1.20			1.81	1.58	2.06	1.30		
Maternal age, years					Strong/ Moderate					Weak	EXCLUDE					Weak	EXCLUDE
25-29[b]	1.00					1.00						1.00					
<20	0.52	0.45	0.61	1.35		0.71	0.62	0.81	1.31			1.02	0.84	1.23	1.46		
20-24	0.86	0.75	0.98	1.31		0.92	0.82	1.03	1.26			1.04	0.87	1.24	1.43		
30-34	0.85	0.71	1.01	1.41		1.09	0.95	1.26	1.32			1.05	0.84	1.32	1.57		
35-39	0.67	0.51	0.88	1.72		1.25	1.03	1.51	1.46			1.25	0.92	1.70	1.85		
40+	0.93	0.56	1.54	2.75		1.24	0.86	1.80	2.09			0.90	0.44	1.85	4.19		
Maternal use of alcohol during pregnancy					Weak					Weak/ Moderate	EXCLUDE					Weak/ Moderate	EXCLUDE
No[b]	1.00					1.00						1.00					
Yes	1.19	0.83	1.71	2.07		1.20	0.90	1.60	1.78			1.35	0.90	2.03	2.27		
Maternal Education Level					Moderate/ Strong					Weak	Include					Moderate/ Strong	Include
Associate Degree or Higher	1.00					1.00						1.00					
No Degree	1.30	1.04	1.63	1.56		0.98	0.81	1.17	1.44			1.72	1.26	2.37	1.89		
High School Diploma	1.35	1.09	1.68	1.54		1.06	0.89	1.26	1.42			1.55	1.13	2.12	1.88		
Some College	1.52	1.21	1.92	1.59		1.02	0.84	1.23	1.46			1.21	0.86	1.71	1.98		
Parity					Strong					Strong	Include					Moderate	Include
0	1.00					1.00						1.00					
1	1.65	1.43	1.90	1.33		1.23	1.08	1.40	1.30			0.85	0.72	1.00	1.39		
2	2.03	1.74	2.37	1.36		1.54	1.34	1.76	1.31			0.79	0.65	0.96	1.47		
3	2.24	1.86	2.68	1.44		1.80	1.55	2.09	1.35			0.89	0.71	1.13	1.59		
4	2.41	1.88	3.07	1.63		2.19	1.84	2.61	1.42			0.85	0.62	1.18	1.91		
5+	1.91	1.44	2.53	1.75		2.11	1.73	2.56	1.48			0.63	0.41	0.96	2.34		

[a]Opioid prescribed at any point during pregnancy vs. no opioids prescribed during pregnancy

[b]Reference group

Table 3. Confounding assessment for the association between opioid prescription and preterm birth analysis.

Model	Variables Included in the Model	Variable dropped	OR	CI 95%	CI WIDTH	Within 10%?	confounding?
Full	Opioid Prescription Status Maternal Race Maternal Smoking Status Education Level Parity	none	1.21	1.06 - 1.37	1.29	--	--
1	Opioid Prescription Status Maternal Smoking Status Education Level Parity	Maternal Race	1.20	1.06 - 1.37	1.29	YES	NO
2	Opioid Prescription Status Maternal Race Education Level Parity	Maternal Smoking Status	1.22	1.07 - 1.38	1.28	YES	NO
3	Opioid Prescription Status Maternal Race Maternal Smoking Status Parity	Education Level	1.21	1.07 - 1.37	1.29	YES	NO
4	Opioid Prescription Status Maternal Race Maternal Smoking Status Education Level	Parity	1.30	1.15 - 1.48	1.28	YES	NO
5	Opioid Prescription Status Education Level Parity	Maternal Race, Maternal Smoking Status	1.21	1.07 - 1.37	1.28	YES	NO
6	Opioid Prescription Status Maternal Smoking Status Parity	Maternal Race, Education Level	1.21	1.06 - 1.37	1.29	YES	NO
7	Opioid Prescription Status Maternal Smoking Status Education Level	Maternal Race, Parity	1.30	1.15 - 1.47	1.28	YES	NO
8	Opioid Prescription Status Maternal Race Parity	Maternal Smoking Status, Education Level	1.22	1.08 - 1.38	1.28	YES	NO
9	Opioid Prescription Status Maternal Race Education Level	Maternal Smoking, Parity	1.32	1.17 - 1.50	1.28	YES	NO
10	Opioid Prescription Status Maternal Race Maternal Smoking Status	Education Level, Parity	1.31	1.15 - 1.48	1.28	YES	NO
11	Opioid Prescription Status Parity	Maternal Race, Maternal Smoking Status, Education	1.21	1.07 - 1.38	1.29	YES	NO
12	Opioid Prescription Status Education Level	Maternal Race, Maternal Smoking Status, Parity	1.32	1.16 - 1.49	1.28	YES	NO
13	Opioid Prescription Status Maternal Smoking Status	Maternal Race, Education Level, Parity	1.30	1.15 - 1.47	1.28	YES	NO
14	Opioid Prescription Status Maternal Race	Maternal Smoking Status, Education Level, Parity	1.32	1.17 - 1.50	1.28	YES	NO
Crude	Opioid Prescription Status	Maternal Race, Maternal Smoking Status, Education Level, Parity	1.32	1.16 - 1.49	1.28	YES	NO

Table 4. Confounding assessment for the association between opioid prescription and SGA analysis.

Model	Variables Included in the Model	Variable dropped	OR	CI 95%	CI WIDTH	Within 10%?	confounding?
Full	Opioid Prescription Status Maternal Race Maternal Smoking Status Education Level Parity	none	1.02	0.86 - 1.20	1.38	--	--
1	Opioid Prescription Status Maternal Smoking Status Education Level Parity	Maternal Race	1.03	0.87 - 1.22	1.40	YES	NO
2	Opioid Prescription Status Maternal Race Education Level Parity	Maternal Smoking Status	1.08	0.92 - 1.28	1.39	YES	NO
3	Opioid Prescription Status Maternal Race Maternal Smoking Status Parity	Education Level	1.02	0.86 - 1.21	1.40	YES	NO
4	Opioid Prescription Status Maternal Race Maternal Smoking Status Education Level	Parity	0.99	0.84 - 1.17	1.40	YES	NO
5	Opioid Prescription Status Education Level Parity	Maternal Race, Maternal Smoking Status	1.10	0.93 - 1.30	1.39	YES	NO
6	Opioid Prescription Status Maternal Smoking Status Parity	Maternal Race, Education Level	1.03	0.87 - 1.22	1.40	YES	NO
7	Opioid Prescription Status Maternal Smoking Status Education Level	Maternal Race, Parity	1.00	0.85 - 1.18	1.40	YES	NO
8	Opioid Prescription Status Maternal Race Parity	Maternal Smoking Status, Education Level	1.10	0.93 - 1.30	1.39	YES	NO
9	Opioid Prescription Status Maternal Race Education Level	Maternal Smoking, Parity	1.07	0.90 - 1.26	1.39	YES	NO
10	Opioid Prescription Status Maternal Race Maternal Smoking Status	Education Level, Parity	0.99	0.84 - 1.16	1.38	YES	NO
11	Opioid Prescription Status Parity	Maternal Race, Maternal Smoking Status, Education	1.11	0.94 - 1.31	1.39	YES	NO
12	Opioid Prescription Status Education Level	Maternal Race, Maternal Smoking Status, Parity	1.08	0.92 - 1.27	1.38	YES	NO
13	Opioid Prescription Status Maternal Smoking Status	Maternal Race, Education Level, Parity	1.00	0.84 - 1.18	1.39	YES	NO
14	Opioid Prescription Status Maternal Race	Maternal Smoking Status, Education Level, Parity	1.07	0.91 - 1.26	1.39	YES	NO
Crude	Opioid Prescription Status	Maternal Race, Maternal Smoking Status, Education Level, Parity	1.08	0.92 - 1.27	1.39	YES	NO