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Trends, Patterns, and Maternal Characteristics of Opioid Prescribing During Pregnancy in a Large Population-based Cohort Study

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Abstract

Background: Opioid use during pregnancy has been associated with adverse maternal and infant health outcomes. Prescription drug monitoring programs (PDMP) provide a population-based source of prescription data. We linked statewide PDMP and birth certificate data in Tennessee (TN) to determine patterns of prescription opioid and benzodiazepine use during pregnancy.

Methods: We constructed a cohort of 311,217 live singleton births from 2013 to 2016 with prescription history from 90 days before pregnancy to birth. Descriptive statistics were used to describe opioid prescription patterns during pregnancy overall, by maternal characteristics and by year. Multivariable logistic regression models estimated adjusted odds ratios and 95% confidence intervals for factors associated with prescription use.

Results: The prevalence of prescription use during pregnancy was 14.1% for opioid analgesics, 1.6% buprenorphine for medication-assisted treatment, and 2.6% for benzodiazepines. The prevalence of opioid analgesic use decreased from 16.6% (2013) to 11.8% (2016) ($p_{trend}<$ 0.001). About 25% used for >7 and 9.7% for >30 days' supply. The most common types were hydrocodone (9.3%), codeine (3.4%), and oxycodone (2.9%). In adjusted models, lower

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Contributors

All authors contributed to the design of the study. SN, SK and SM acquired the data for the study and the IRB approval. SN completed the first full draft of the manuscript and conducted the primary analyses using the linked dataset. All authors contributed to the data creation and validation, analysis, interpretation, and manuscript writing. All authors have contributed to and approved the final manuscript for publication.

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education, lower income, pre-pregnancy obesity and smoking during pregnancy were associated with increased odds of any opioid and opioid analgesic use.

Conclusion(s): Despite the encouraging trend of decreasing use of prescription opioid analgesics, the overall prevalence remained close to 12% with many women using for long durations. Use was associated lower socioeconomic status, obesity, and prenatal smoking. Findings highlight the need for maternal education and resources, and provider support for implementation of evidence-based care.

Keywords

maternal opioid use; cohort; descriptive epidemiology; pregnancy; cohort; opioid prescribing; prescription drug monitoring programs

1. Introduction

Opioid use during pregnancy has adverse short and long-term consequences on both maternal and infant health (Azuine et al., 2019; McQueen and Murphy-Oikonen, 2016; Norgaard et al., 2015; Patrick et al., 2015; Patrick et al., 2012; Sujan et al., 2019; Whiteman et al., 2014; Yazdy et al., 2015). Opioids can cross the placenta and have been associated with preterm birth and reduced birthweight (Ross et al., 2015; Yazdy et al., 2015). A systematic review of prenatal opioid exposure and long-term cognitive and motor outcomes at six years of age or older found lower motor scores and lower cognitive tests based on data from 26 studies that utilized age-appropriate standardized tests and included non-exposed children as a comparison group (Yeoh et al., 2019). Neonatal abstinence syndrome, a drug-withdrawal syndrome diagnosed after birth in infants, is largely a consequence of prenatal opioid use and can result in substantial infant morbidity, and potentially adverse long-term health outcomes (Maguire et al., 2016; Yazdy et al., 2015).

A *Morbidity and Mortality Weekly Report* article from August 2018 reported the national prevalence of opioid use disorder (OUD) during pregnancy increased from 1.5 to 6.5 cases per 1,000 hospital deliveries during 1994 to 2014 (Haight et al., 2018). A study of women of reproductive age (15–44 years) using Truven Health's MarketScan Commercial Claims and Encounters and Medicaid data reported that about 39.4% of women with Medicaid had at least one opioid prescription claim compared to 28% of women with private insurance during 2008 to 2012 (Ailes et al., 2015). Opioids may be used during pregnancy for treatment for pain, both acute and chronic, as well as for treatment for opioid use disorder. The American College of Obstetricians and Gynecologists (ACOG) recommends that prescription opioids for pain be avoided, and specifically states "…practice goals include strategies to avoid or minimize the use of opioids for pain management, highlighting alternative pain therapies such as nonpharmacologic (e.g., exercise, physical therapy, behavioral approaches), and nonopioid pharmacologic treatments" (ACOG, 2017). ACOG also recommends a careful discussion on the risks and benefits of treatment options with patients. For women with OUD, opioids for treatment during pregnancy, such as buprenorphine for medication-assisted treatment (MAT), are recommended to improve both maternal and infant outcomes, as compared to withdrawal or no treatment (ACOG, 2017).

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To date, studies of prescription opioid use during pregnancy have been focused on Medicaid-only populations, used insurance claims data with limited information on maternal factors, or been based on self-report that may be subject to social desirability bias and usually precludes information on drug types and duration (Bateman et al., 2014; Desai et al., 2014; Elliott et al., 2018; Epstein et al., 2013; Ko et al., 2020; Kroll-Desrosiers et al., 2016; Metz et al., 2018). Prescription drug monitoring programs (PDMP) are a key tool used to fight the opioid epidemic and provide a population-based source of prescription data. However, no studies have been conducted to link PDMP and birth certificate (BC) data to enable population-based studies of prescribing during pregnancy with detailed prescription information to evaluate patterns of use. Our study had two objectives. First, we described the prevalence of opioid prescriptions used preconceptionally and during pregnancy, including opioid analgesics and buprenorphine for MAT overall and by year among all women with a resident live birth in Tennessee (TN). We also evaluated specific types of opioids and prescription characteristics (e.g., days' supply), and benzodiazepine prescription use. Second, we evaluated associations between maternal factors and prescription opioid use during pregnancy.

2. Materials and methods

2.1. Cohort study design and data sources

We conducted a population-based retrospective cohort study of linked maternal and infant data from TN's Birth Statistical Files (2013–2016) and the Controlled Substance Monitoring Database (CSMD) (2012–2016), two TN Department of Health (TDH) data sources. The TDH Institutional Review Board for human subjects research approved this study using these two TDH data sources. Data linkage and validation was conducted at TDH. All data analyses were conducted at TDH.

2.1.1. Controlled Substances Monitoring Database (2012–2016).—The CSMD is TN's PDMP which, provides data on schedule II-V controlled substances dispensed since 2012. The major drug classes collected include opioids, benzodiazepines, muscle relaxants, and stimulants. Prescription information includes date filled, days' supply, quantity, and national drug code number (NDC). Patient information includes names, address, and date of birth (DOB). The Centers for Disease Control and Prevention (CDC) and the National Center for Injury Prevention and Control provides an annually updated file to assign specific drug types using the NDC, which was used to determine opioid and benzodiazepine drug types for the study (CDC, 2021).

2.1.2. TN Live Birth Statistical Files (2013–2016).—The TN Live Birth Statistical Files include BC data for all TN live births, regardless of residence status, and for live births to TN residents who delivered at an out-of-state hospital. The TN BC data follows the National Center for Health Statistics standards for data items and data quality (CDC, 2019). Data collected includes maternal and infant name, address, maternal and infant DOB, maternal demographics (education, household income, race, ethnicity) and pregnancy characteristics (e.g., smoking during pregnancy and pre-pregnancy weight and height), and infant birth characteristics (e.g., birthweight, length of gestation, and sex).

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2.2. Data linkage methodology

We have developed methods for linking statewide public health datasets described in detail previously (Nechuta et al., 2020). Briefly, identifiers used for data linkage approaches included first and last name, DOB, and address. The CSMD does not contain a unique identifier, such as social security number. We cleaned and standardized names and geocoded addresses. Address data was geocoded using ArcGIS, version 10.6 (ESRI, Redlands, CA), with a minimum match score of 85 and a spelling sensitivity of 80. To link PDMP and birth data, we used a fuzzy matching/probabilistic linkage approach (sensitivity values of 85 for both names and DOB) using SAS Data Management Studio software (SAS, 2016). This approach has been identified as the most accurate (balancing false positive and false negative matches) based on our previous work. For more details, see: (Nechuta et al., 2020). As this approach is not strictly deterministic, false positives are a concern. Therefore, we identified potentially incorrect matches among all prescribing record and birth record linkages (n=262,866) and manually reviewed all potentially incorrect matches (n=5,154). Among these 5,154, 39% were classified as true false positives and excluded.

2.3. Maternal and infant characteristics

Maternal characteristics from the live birth data files included maternal age at delivery in years (<20, 20–24, 25–29, 25–34, ≥35), maternal education (< high school (HS), HS, some college, ≥college graduate), maternal race (white, Black, other racial groups), household income (<$10,000, $10,000-<25,000, $25,000–50,000, $≥50,000), prenatal care (none, received during first trimester, received (unknown timing), parity (0 live births, 1 live birth, 2 live births, ≥3 live births), number of pregnancies (0, 1, 2, ≥3), smoking during first trimester (no, yes), smoking during second trimester (no, yes), smoking during third trimester (no, yes), total cigarettes per day during pregnancy (none, <10, ≥10), weeks of gestation based on the clinical estimate (weeks), infant birthweight (grams), infant sex (female, male), maternal height, and maternal pre-pregnancy weight. We created a categorical length of gestation variable using established cut-points (WHO, 2018), including very preterm (<32 weeks), preterm (32-<37 weeks), term (37–41 weeks), and post-term (≥42 weeks). Birthweight was categorized based on established cutpoints (Blencowe et al., 2019) and considering sample size (<2,500g, 2,500-<2,977g, 2,977-<3,260g, 3,260-<3,572g, ≥ 3,572g). Maternal weight and height were used to create pre-pregnancy body mass index (BMI), categorized using established cutpoints (Weir and Jan, 2021) with the exception of the underweight category, for which the midpoint of 21.5kg/m^2 was used due to small samples sizes for those <18.5kg/m^2 (<21.5kg/m^2, 21.5-<24.99 kg/m^2, 24.99-<29.99 kg/m^2, ≥30 kg/m^2).

2.4. Prescription characteristics

Opioid use based on prescription fills in the PDMP database was defined as any type, opioid analgesics, and buprenorphine for MAT. Throughout this paper, “use” refers to filling a prescription for brevity. We also classified opioid analgesic use further by type including hydrocodone, oxycodone short-acting (SA), tramadol SA, and codeine. Women who filled any benzodiazepines prescription were defined as any benzodiazepine use. We also classified based on the top three types of benzodiazepines: alprazolam, diazepam, and clonazepam. We examined use overall and by type any time during pregnancy, in specific

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trimesters, and then in the 90 days before pregnancy. We also evaluated the number of prescription fills and duration of use based on days' supply during pregnancy. Illicit drug use is not captured in PDMP data.

2.5. Final analytic sample

Figure 1 describes all the study exclusions both before and after linkage to the CSMD. After exclusions due to missing data for key linkage and analytic variables and non-eligible births and prescriptions, there were 311,217 live singleton births for linkage to the prescription record. Opioid exposure included live singleton births to women who were TN residents with at least one or more days' supply for a filled opioid prescription during pregnancy (47,399 births). Unexposed included live singleton births to women who were TN residents with no prescription fills of at least 1 days' supply during pregnancy (n= 249,113). Non-opioid controlled substance (CS) use included live singleton births to women who were TN residents with at least one or more days' supply of a filled CS that was not an opioid during pregnancy (n=14,705 births). We included these as a separate group to enable the comparisons of characteristics of births with non-opioid CS use during pregnancy with prescription opioid use and no exposures to any prescribed CS during pregnancy.

2.6. Statistical analysis

Descriptive statistics (percentages, frequencies) were used to describe maternal and infant characteristics by opioid exposure history during pregnancy (any opioid use, any non-opioid CS use, no opioid or other CS prescription use). Descriptive statistics were also used to describe prescription patterns by year, by type of opioid (and benzodiazepines), and by duration of use. P-values for trends were calculated using Cochran-Armitage trend test. Age and further-adjusted multivariable logistic regression models were used to estimate adjusted odds ratios (ORs) and 95% confidence intervals (CIs). P-values less than 0.05 and CIs excluding 1.0 were considered statistically significant. Data management and statistical analyses were conducted using SAS version 9.4 (Cary, North Carolina), Microsoft SQL Server Management Studio Version 17 (Redmond, Washington), and SAS Data Management Studio version 2.7 (Cary, North Carolina).

3. Results

The study population included live births during 2013 to 2016 in TN defined by prescription use during pregnancy. Table 1 shows maternal and infant characteristics for women who filled an opioid during pregnancy, women who filled any other CS during pregnancy and women who did not fill a prescription for a CS during pregnancy. Comparing women with any opioid use to those with no opioid or CS use during pregnancy, a lower percentage of women with any opioid use completed college (12.3% college graduate vs. 27.7%) and were of higher income ≥ $50,000 (15.0% vs. 27.8%). Comparing women with any opioid use to those with no opioid or CS use during pregnancy, a higher percentage of women were Black (24% vs. 20.6%), had more previous live births and/or pregnancies (≥ 3: 27.5% vs. 18.4%), self-reported smoking during pregnancy ≥ 10 cigarettes per day (27.4% vs. 9.5%), had a preterm birth (10.1% vs. 7.3%), and had a lower birthweight infant (10.1% >2,500 vs. 6.8%).

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Table 2 displays the prevalence of opioid and benzodiazepine prescription use before pregnancy and during pregnancy. Opioids for pain with < 1% prevalence of use anytime during pregnancy were not included due to small sample size (oxycodone LA, oxymorphone SA, oxymorphone LA, hydromorphone, tramadol LA, methadone, fentanyl, morphine SA/LA). Use of any opioids during pregnancy was 15.2% (14.1% for opioid analgesic use; 1.6% for buprenorphine for MAT use). The most common type of opioid analgesic used during pregnancy was hydrocodone (9.3%), followed by codeine (3.4%), oxycodone SA (2.9%), and tramadol SA (1.2%). Use of opioids, regardless of type, tended to decrease from first to third trimester, except for buprenorphine for MAT and codeine. The prevalence of benzodiazepine use during pregnancy was 2.6%. We also looked at any use during pregnancy (regardless of trimester) for the three most common types of benzodiazepines used in this population. The prevalence of any use during pregnancy by type was as follows: alprazolam (1.2%), clonazepam (0.7%), and diazepam (0.5%).

Figure 2 shows patterns over time for the prevalence of opioid analgesics, buprenorphine for MAT, and benzodiazepine overall and by trimester. The prevalence of use of opioid analgesics during pregnancy decreased from 2013 to 2016, from 16.6% in 2013 (any time during pregnancy) to 11.8% in 2016 ($p_{trend} < 0.001$). Use of buprenorphine for MAT increased from 2013 (1.1%) to 2016 (1.9%) ($p_{trend} < 0.001$). Use of benzazepines during pregnancy decreased from 2013 (2.8%) to 2016 (2.4%) ($p_{trend} < 0.001$). Overall, these patterns did not vary by trimester of use.

Figure S1 shows patterns over time for the prevalence of types of benzodiazepines among those with at least one prescription day of benzodiazepine use during pregnancy (n=8,270). The patterns over time differed by type of benzodiazepine. Prescription use during pregnancy decreased for alprazolam (50.4% in 2013 and 43.6% in 2016), increased for diazepam (25.2% in 2013 and 31.9% in 2016) and showed no change for clonazepam (17% in 2013 and 17.4% in 2016).

Table 3 displays prescription characteristics for women who had at least one prescription day of opioid use during pregnancy in the cohort. The mean number of fills during pregnancy was 2.2 for opioid analgesics and 17.1 for buprenorphine for MAT. The median days' supply was 5 for opioid analgesics and 150 for buprenorphine for MAT. Among women who used opioids for pain, 25% had a days' supply longer than 7 days, and 9.7% had a days' supply longer than 30 days. Looking at type of opioid analgesics, the percentage of women with days' supply longer than 30 days was highest for tramadol SA (16.4%), followed by oxycodone SA (13.2%), hydrocodone (8.6%), and codeine (1.7%). Among women who used buprenorphine for MAT, almost all (98%) had a days' supply of 7 days or more and close to half (47%) had a days' supply > 30 days. Among women who used benzodiazepines during pregnancy, 88% had a days' supply of 7 days or more and 65% had a days' supply > 30 days.

Table 4 displays results from multivariable logistic regression models to evaluate factors associated with prescription opioid use during pregnancy for any opioids and for opioid analgesics alone (sample size was too small to evaluate predictors of buprenorphine for MAT use). In models adjusted for maternal age, birth year, and maternal characteristics

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(further-adjusted models), lower education was associated with increased odds of prescription opioid use during pregnancy (further-adjusted ORs (95% CIs): 2.42 (2.31–2.53), 2.38 (2.30–2.47), 2.09 (2.02–2.17) for < HS education, HS education, and some college, respectively, compared to college graduate). Black race (compared to white race) was associated with increased odds of prescription opioid use during pregnancy, further-adjusted OR (95% CI): 1.12 (1.09–1.15). Lower household income (vs. ≥$50,000) was associated with increased odds of opioid use during pregnancy (further-adjusted ORs (95% CIs): 1.87 (1.80–1.95), 1.59 (1.53–1.65), 1.17 (1.13–1.16) for < $10,000, $10,000-<$25,000, and $25,000-$50,000, respectively). Pre-pregnancy BMI ≥ 30 kg/m^2 (compared to BMI 21.5–24.99 kg/m^2) was associated with increased odds of opioid use during pregnancy, further-adjusted OR (95% CI): 1.19 (1.15–1.22). Smoking during pregnancy was associated with increased odds of opioid use during pregnancy (further-adjusted ORs (95% CIs): 1.61 (1.52–1.70) and 2.65 (2.58–2.72) for < 10 (vs. none) and ≥ 10 cigarettes per day, respectively. These associations were similar when looking at only opioid use for pain (excluding women who only used buprenorphine for MAT).

4. Discussion

In this large cohort study of trends and patterns of prescription opioid use during pregnancy, we found that while opioid analgesic use decreased over time, the prevalence of use remained high (~12%). Further, over 25% used opioids analgesics for longer than 7 days, and 10% for longer than 30 days during pregnancy. The most common types of opioids used included hydrocodone SA, codeine, oxycodone SA and tramadol SA. These finding highlight the need for support of health care providers to implement evidence-based care (Klaman et al., 2017; Pritham and McKay, 2014), both among pregnant women and among women who may become pregnant. In addition, education on the risks of prescription opioids and benzodiazepines during pregnancy and resources for alternative approaches for chronic pain treatment are warranted.

In our study, we also found that prescription opioid use was associated with lower education (< HS or HS), lower income (<$10,000), pre-pregnancy obesity, and smoking during pregnancy. The association of illicit opioid use and OUD with smoking and lower socioeconomic status is well-known (Clemans-Cope et al., 2019; Creanga et al., 2012; Metz et al., 2018). Less is known, however, regarding associations with prescription opioids use. Our findings suggest that women receiving prescription opioids during pregnancy are a high-risk and vulnerable group, with multiple risk factors for adverse maternal and infant outcomes. As these women are interacting with the health care system to receive a prescription, this is an important opportunity to link women to education and supportive resources to prevent adverse outcomes. Further, most women received prenatal care in our study and started prenatal care in the first trimester. This is a key opportunity for education and support for women of lower socioeconomic status who are at risk for adverse birth outcomes due to substance use, life stressors, and environmental factors.

Previous studies using claims or other administrative data have evaluated opioid prescribing patterns during pregnancy in Medicaid only (Desai et al., 2014; Epstein et al., 2013) or commercially insured populations (Bateman et al., 2014; Elliott et al., 2018), as well as

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among veterans (Kroll-Desrosiers et al., 2016). Desai and colleagues used Medicaid data to examine trends in opioid use from 2000 to 2007 in a retrospective cohort (Desai et al., 2014). They found 21.6% of pregnant women filled at least one prescription during pregnancy and that use increased over time from 2000 to 2007. A second retrospective cohort study focused on Medicaid enrollees examined trends in opioid analgesic prescription use from 1995 to 2009 and found a higher overall proportion of women who filled at least one opioid prescription during pregnancy (29%) (Epstein et al., 2013). This study also reported the most common types of opioids used were hydrocodone, codeine, oxycodone, and propoxyphene. An older study by Bateman et al. (2014) used commercial claims data from 2005 to 2011 and found a prevalence of about 14.4% for filling of one or more opioid prescriptions during pregnancy (Bateman et al., 2014). A second retrospective cohort study using claims data from the upper midwestern region of the United States reported a lower prevalence during pregnancy, with only 7.5% filling opioid prescriptions (Elliott et al., 2018). The lower prevalence could be due to that at least 5 days' supply was needed for a prescription to be included. Lastly, a study using administrative and electronic health record data on female Veterans during 2001–2010 reported that about 10% of women filled a prescription for an opioid during pregnancy (Kroll-Desrosiers et al., 2016). This study among Veterans did not find an association between sociodemographic factors and use, with the exception of that being married (versus not married) was associated with prescription opioid use.

We also examined as a secondary aim the prevalence and prescribing trends for benzodiazepine use during pregnancy. Prescription opioids and benzodiazepine may be used concurrently as anxiety and other mood disorders are more prevalent among those who use opioids (Sun et al., 2017). A recent systematic review of 14 studies found that benzodiazepine use during pregnancy was associated with increased risk of several adverse perinatal outcomes, including preterm birth, low birth weight, and admission to the neonatal intensive care unit (Grigoriadis et al., 2020). While prevalence of benzodiazepine use was low overall during pregnancy in our study, the unclear risks associated with use highlight the need for continued public health surveillance to monitor trends and patterns of use, and more research to understand long-term effects of in-utero exposure on infant and child health outcomes.

4.1. Strengths and limitations

This is the first study to link PDMP and BC data to provide population-based data on opioids and benzodiazepine prescription patterns and trends during pregnancy. We built upon our experience in data linkage (Nechuta et al., 2020; Nechuta et al., 2018) to utilize two population-based statewide public health data sources with careful approaches considering missed matches and false positives. The study was large and covered four years of live births, and all filled prescriptions for prescribed opioids in the state of TN among women who had a live birth outcome. The CSMD includes all prescription fills for opioid analgesics and for buprenorphine for MAT. Further, we were able to evaluate type and duration of opioids used, and patterns by trimester and maternal demographics and characteristics.

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This study also has several limitations. First, we may have underestimated use that results in adverse outcomes as we only were able to include women with live births as birth certificate data is for live births only in the United States. Therefore, our study was unable to include women with miscarriages and fetal deaths. Future studies that collect accurate data on these outcomes could be informative. Second, we did not have information on indication of use for opioid analgesics, which could have helped with interpretations of findings, such as high doses observed or use of hydrocodone or oxycodone during pregnancy. The linkage of surveillance data sources to electronic health records and insurance claims data to provide information on patient diagnoses and medical history could potentially address this issue in future studies (Rivera et al., 2020). Third, while buprenorphine for MAT is the preferred treatment for OUD during the study time frame (Goodman, 2011), we are not capturing all opioid treatment use in our study. The CSMD does capture all prescriptions filled for opioid analgesics, however, prescriptions for methadone are not captured, as these are dispensed from federal treatment centers that are not required to report to the CSMD. Fourth, data is on prescriptions filled, and we do not know for sure how the drugs were used and do not have information on illicit use.

4.2. Future research and public health implications

Despite a downward trend in prescription opioids during pregnancy, given the unclear and potentially adverse safety profile of opioid analgesic during pregnancy, and recommendations by clinical experts including ACOG, more work is needed to reduce use through education and providing safer alternatives to manage acute and chronic pain. As unplanned pregnancy is more common among women of lower socioeconomic status, education and resources targeting women of reproductive age who may become pregnant and either have OUD or a chronic pain condition or other morbidity that may result in a prescription for an opioid or benzodiazepine is critically needed. Continued surveillance is needed to monitor trends in prescription use among pregnant women. Future research among both pregnant women and providers to understand barriers to alternative therapies, linkage to evidence-based care, and education are needed. Additional linkage of the population-based surveillance data sources used in this study with administrative data (such as insurance claims data) or electronic health records to provide diagnoses and medical history information during pregnancy and postpartum are needed to support future research on opioid use during pregnancy in association with maternal and child health outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ACOG	American College of Obstetricians and Gynecologists
BC	Birth certificate
BMI	Body mass index
CDC	Centers for Disease Control and Prevention
CIs	Confidence intervals
CS	Controlled substance
CSMD	Controlled Substance Monitoring Database
DOB	Date of birth
HS	High school
MAT	Medication-assisted treatment
NDC	National drug code number
ORs	Odds ratios
OUD	Opioid use disorder
PDMP	Prescription Drug Monitoring Programs
SA	Short-acting
TN	Tennessee
TDH	Tennessee Department of Health
U.S.	United States

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Highlights

- No study has linked PDMP and birth certificate data.
- This can provide population-based data on prenatal opioid prescribing patterns.
- Prenatal opioid prescriptions decreased over time, but prevalence was still 12%.
- Opioid use was associated with lower education and income, obesity, and smoking.

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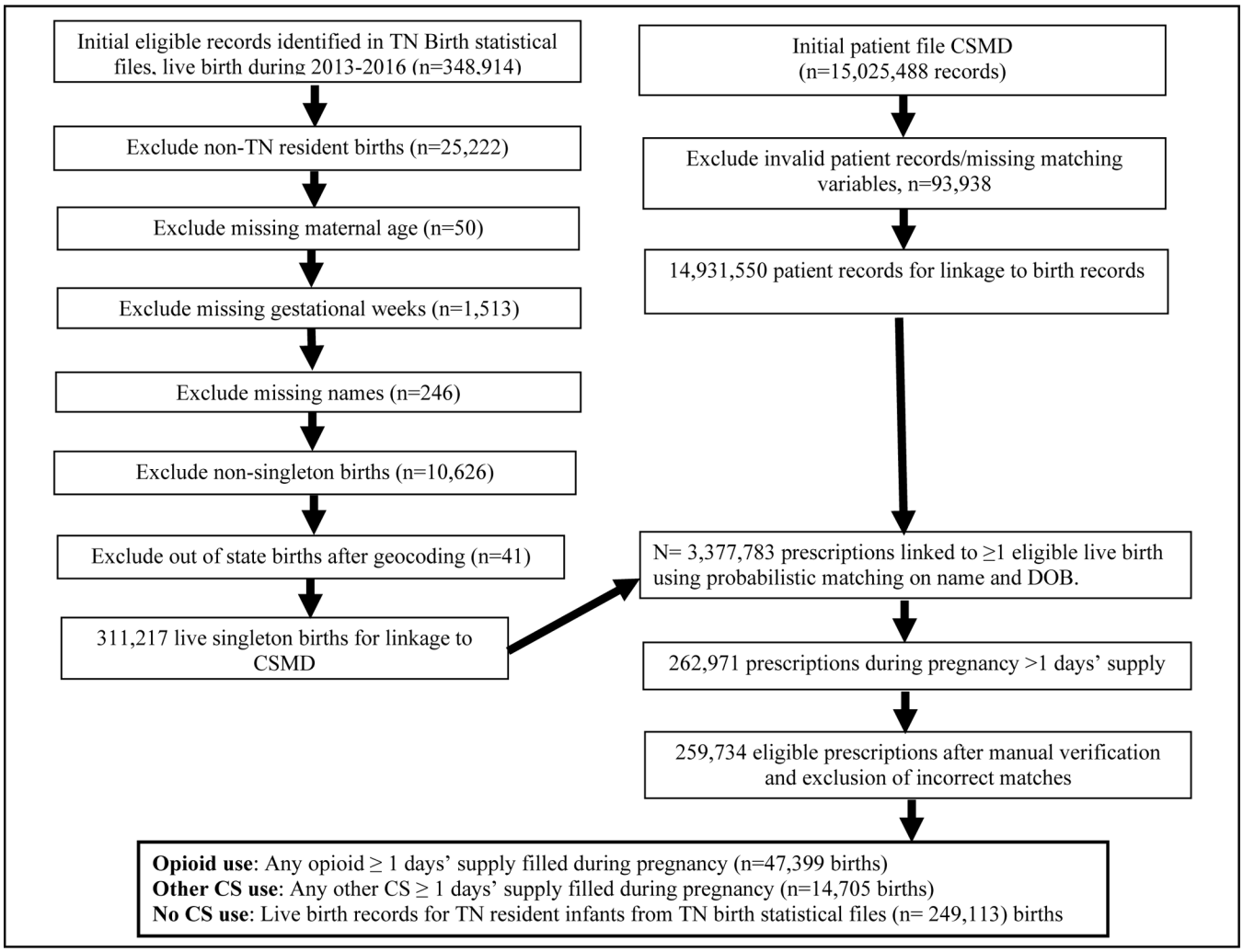

Figure 1.
Study design and final analytic sample

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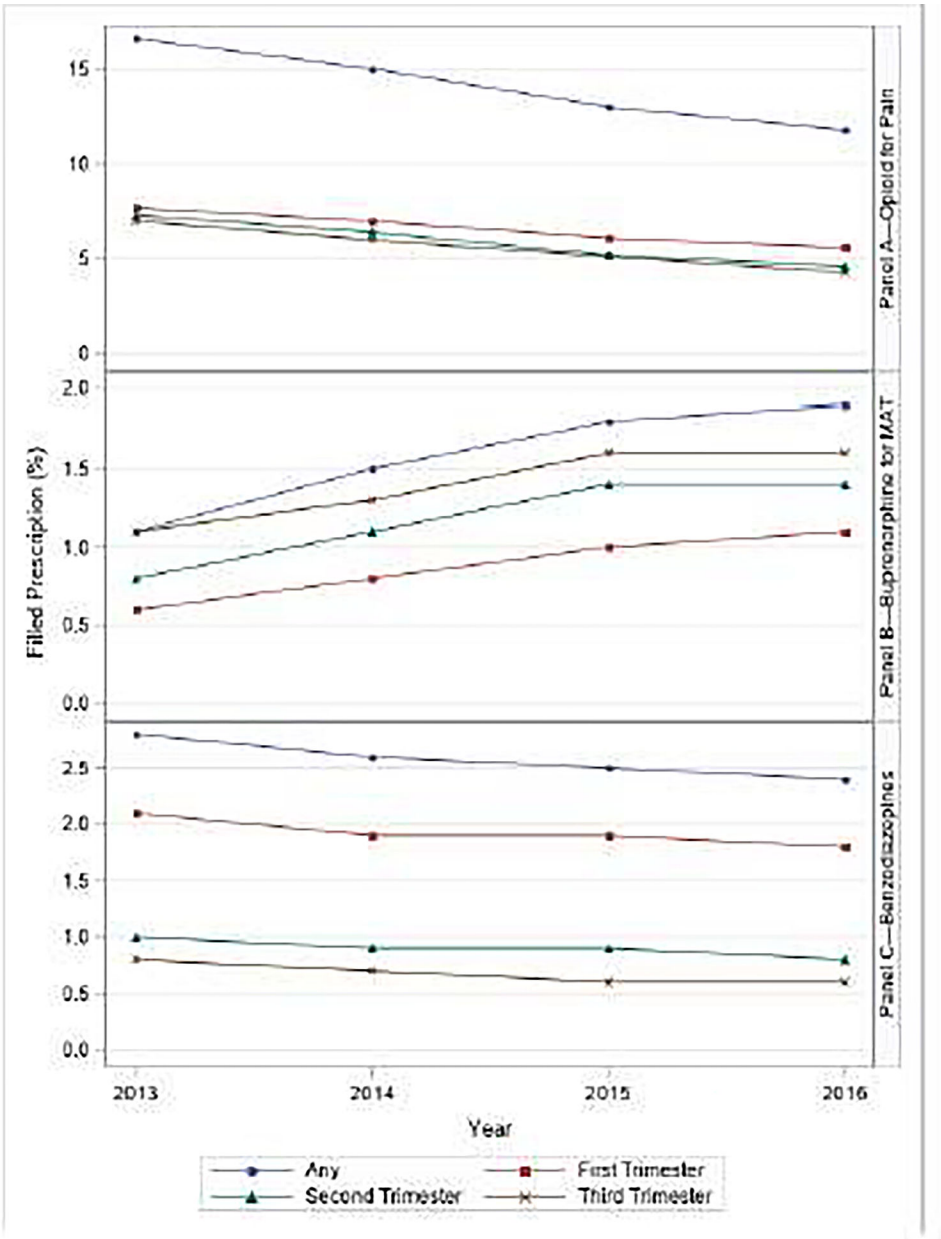

Figure 2.
Prevalence of opioid and benzodiazepine use during pregnancy in TN by year, 2013–2016

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Table 1.

Study population characteristics by prescription opioid exposure history during pregnancy (n=311,217)

	Any prescription opioid use (n=47,399)		Any non-opioid controlled substance prescription use (n=14,705)		No opioid or controlled substance prescription use[a] (n=249,113)		P-values[b]
Maternal age at delivery (years), n (%)							
< 20	3,463	(7.3)	682	(4.6)	21,471	(8.6)	
20–24	14,262	(30.1)	2,775	(18.9)	67,707	(27.2)	
25–29	15,167	(32.0)	4,322	(29.4)	73,600	(29.5)	
25–34	9,842	(20.8)	4,392	(29.9)	57,782	(23.2)	
≥ 35	4,665	(9.8)	2,534	(17.2)	28,553	(11.5)	<0.001
Missing							
Maternal education, n (%)							
< High School	7,958	(16.8)	1,082	(7.4)	37,123	(15.0)	
High School	17,415	(36.9)	3,254	(22.2)	67,666	(27.3)	
Some college	16,073	(34.0)	5,360	(36.5	74,428	(30.0)	
≥ College graduate	5,815	(12.3)	4,974	(33.9)	68,751	(27.7)	<0.001
Missing	138		35		1,145		
Maternal race, n (%)							
White	34,384	(72.8)	12,612	(86.1)	168,350	(68.0)	
Black	11,355	(24.0)	1,562	(10.7)	50,979	(20.6)	
Other	1,510	(3.2)	479	(3.3)	28,356	(11.5)	<0.001
Missing	150		52		1,428		
Household income, n (%)							
< $10,000	12,114	(25.6)	1,554	(10.6)	39,864	(16.0)	
$10,000–< 25,000	10,469	(22.1)	2,026	(13.8)	42,944	(17.2)	
$25,000–50,000	7,395	(15.6)	2,737	(18.6)	44,668	(17.9)	
≥ $50,000	7,126	(15.0)	5,646	(38.4)	69,277	(27.8)	
Missing	10,295	(21.7)	2,742	(18.7)	52,360	(21.0)	<0.001
Prenatal care, n (%)							
None	747	(1.6)	101	(0.7)	3,812	(1.5)	
Any	46,300	(98.4)	14,529	(99.3)	243,308	(98.5)	<0.001
Missing	352		75		1,993		
Prenatal care, n (%)							
None	747	(1.6)	101	(0.7)	3,812	(1.5)	
No	29,852	(63.5)	10,773	(73.6)	160,662	(65.0)	
Yes	12,885	(27.4)	2,799	(19.1)	65,017	(26.3)	
Received, unknown timing	3,563	(7.6)	957	(6.5)	17,629	(7.1)	<0.001
Missing	352		75		1,993		
Parity, n (%)							

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	Any prescription opioid use (n=47,399)		Any non-opioid controlled substance prescription use (n=14,705)		No opioid or controlled substance prescription use[a] (n=249,113)		P-values[b]
0	14,459	(31.0)	5,592	(38.6)	101,705	(41.5)	
1	15,137	(32.4)	5,014	(34.6)	77,745	(31.7)	
2	9,609	(20.6)	2,500	(17.2)	39,011	(15.9)	
≥ 3	7,461	(16.0)	1,398	(9.6)	26,644	(10.9)	<0.001
Missing	733		201		4,008		
Pre-pregnancy BMI (kg/m^2), n (%)							
< 21.5	10,884	(23.6)	2,907	(20.2)	57,862	(24.1)	
21.5–< 24.99	10,753	(23.3)	3,590	(25.0)	64,868	(27.0)	
24.99–< 29.99	10,953	(23.7)	3,704	(25.8)	58,088	(24.2)	
≥ 30 kg/m^2	13,587	(29.4)	4,164	(29.0)	59,313	(24.7)	<0.001
Missing	1,222		340		8,982		
Smoking during first trimester, n (%)							
No	32,857	(69.9)	12,448	(85.2)	219,787	(88.7)	
Yes	14,151	(30.1)	2,170	(14.8)	27,875	(11.3)	<0.001
Missing	391		87		1,451		
Smoking during second trimester, n (%)							
No	34,088	(72.5)	12,761	(87.3)	22,4037	(90.5)	
Yes	12,909	(27.5)	1,859	(12.7)	23,596	(9.5)	<0.001
Missing	402		85		1,480		
Smoking during third trimester, n (%)							
No	34,699	(73.9)	12,898	(88.3)	22,5472	(91.1)	
Yes	12,288	(26.2)	1,716	(11.7)	22,111	(8.9)	<0.001
Missing	412		91		1,530		
Total cigarettes per day during pregnancy, n (%)							
None	32,496	(69.1)	12,370	(84.6)	218,858	(88.4)	
<10	1,648	(3.5)	383	(2.6)	5,308	(2.1)	
≥10	12,880	(27.4)	1,870	(12.8)	23,533	(9.5)	<0.001
Missing	375		82		1,414		
Length of gestation, n (%)							
Very preterm (< 32 weeks)	802	(1.7)	192	(1.3)	3,350	(1.3)	
Preterm (32–< 37 weeks)	4,790	(10.1)	1,263	(8.6)	18,100	(7.3)	
Term (37–41 weeks)	41,713	(88.0)	13,227	(90.0)	226,994	(91.1)	
Postterm (≥ 42 weeks)	94	(0.2)	23	(0.2)	669	(0.3)	<0.001
Infant sex, n (%)							
Female	23,049	(48.6)	7,192	(48.9)	121,669	(48.8)	

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	Any prescription opioid use (n=47,399)		Any non-opioid controlled substance prescription use (n=14,705)		No opioid or controlled substance prescription use[a] (n=249,113)		P-values[b]
Male	24,350	(51.4)	7,513	(51.1)	127,441	(51.2)	0.5244
Missing	1				3		
Birthweight (grams), n (%)							
< 2,500	4,760	(10.1)	1,009	(6.9)	16,820	(6.8)	
2,500–< 2977	10,309	(21.8)	2,257	(15.4)	41,459	(16.7)	
2977–< 3260	10,354	(21.9)	2,869	(19.6)	51,300	(20.7)	
3260–< 3572	10,805	(22.9)	3,768	(25.7)	63,428	(25.6)	
≥ 3572	10,997	(23.3)	4,759	(32.5)	75,192	(30.3)	<0.001
Missing[c]	174		43		914		

[a] No opioid or controlled substance prescription use means no fills for prescribed opioids or other controlled substances during pregnancy.

[b] P-values were derived from chi-square analysis comparing the any prescription opioid use group with the no opioid/controlled prescription use group. The Pearson Chi-square test statistic used for nominal variables and Mantel-Haenszel was used for ordinal variables.

[c] Missing also includes birthweights <400 grams.

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Table 2.

Prevalence of prescription opioids and benzodiazepine use before and during pregnancy overall and by trimester in TN (2013–2016), n=311,217[a]

	Pre-pregnancy Use		First Trimester		Second Trimester		Third Trimester		Any use during pregnancy	
Opioids (any type), n (%)										
No	306,134	(98.4)	288,425	(92.7)	289,675	(93.1)	289,832	(93.1)	263,818	(84.8)
Yes	5,083	(1.6)	22,792	(7.3)	21,542	(6.9)	21,385	(6.9)	47,399	(15.2)
Opioid analgesics, n (%)										
No	307,296	(98.7)	290,746	(93.4)	292,922	(94.1)	293,745	(94.4)	267,293	(85.9)
Yes	3,921	(1.3)	20,471	(6.6)	18,295	(5.9)	17,472	(5.6)	43,924	(14.1)
Buprenorphine for MAT, n (%)										
No	310,040	(99.6)	308,531	(99.1)	307,583	(98.8)	307,002	(98.7)	306,303	(98.4)
Yes	1,177	(0.4)	2,686	(0.9)	3,634	(1.2)	4,215	(1.4)	4,914	(1.6)
Any benzodiazepines, n (%)										
No	307,544	(98.8)	305,210	(98.1)	308,423	(99.1)	309,082	(99.3)	303,190	(97.4)
Yes	3,673	(1.2)	6,007	(1.9)	2,794	(0.9)	2,135	(0.7)	8,027	(2.6)
Hydrocodone, n (%)										
No	308,937	(99.3)	297,486	(95.6)	299,920	(96.4)	301,034	(96.7)	282,359	(90.7)
Yes	2,280	(0.7)	13,731	(4.4)	11,297	(3.6)	10,183	(3.3)	28,858	(9.3)
Oxycodone SA, n (%)										
No	311,128	(100.0)	307,628	(98.9)	307,829	(98.9)	307,454	(98.8)	302,148	(97.1)
Yes	987	(0.3)	3,589	(1.2)	3,388	(1.1)	3,763	(1.2)	9,069	(2.9)
Tramadol SA, n (%)										
No	310,682	(99.8)	308,987	(99.3)	310,389	(99.7)	310,458	(99.8)	307,602	(98.8)
Yes	535	(0.2)	2,230	(0.7)	828	(0.3)	759	(0.2)	3,615	(1.2)
Codeine, n (%)										
No	310,230	(99.7)	308,242	(99.0)	306,704	(98.6)	307,046	(98.7)	300,719	(96.6)
Yes	89	(0.0)	2,975	(1.0)	4,513	(1.5)	4,171	(1.3)	10,498	(3.4)

Abbreviations: medication assisted treatment (MAT), short-acting (SA)

[a]The reference group for this table includes all women who did not fill an opioid during pregnancy to estimate use of prescription opioids during pregnancy among all women with a live birth in TN during the study years.

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Table 3.

Prescription characteristics for women had at least one prescription day of opioids use during pregnancy in TN (2013–2016), n=47,399[a]

	Number of fills	Day supply	Days' supply >7		Days' supply >30	
	Mean (SD)	Median (IQR)	n	(%)	n	(%)
Opioid, any type (n=47,399)						
No	-	-	32,091	(67.7)	41,027	(86.6)
Yes	3.82 (7.5)	5.0 (3–17)	15,308	(32.3)	6,372	(13.4)
Opioids for pain (n=43,924)						
No	-	-	32,821	(74.7)	39,686	(90.4)
Yes	2.2 (2.81)	5.0 (3–10)	11,103	(25.3)	4,238	(9.7)
Buprenorphine for MAT (n=4,914)						
No	-	-	114	(2.3)	2,618	(53.3)
Yes	17.1 (16.1)	150 (67–252)	4,800	(97.7)	2,296	(46.7)
Benzodiazepine (n=4,540)						
No	-	-	555	(12.2)	1,576	(34.7)
Yes	4.7 (5.3)	60 (30–150)	3,985	(87.8)	2,964	(65.3)
Type of opioids for pain						
Hydrocodone (n=28,858)						
No	-	-	22,852	(79.2)	26,380	(91.4)
Yes	1.9 (2.1)	4.0 (2–8)	6,006	(20.8)	2,478	(8.6)
Codeine (n=10,498)						
No	-	-	8,574	(81.7)	10,318	(98.3)
Yes	1.3 (0.96)	4.0 (3–7)	1,924	(18.3)	180	(1.7)
Oxycodone SA (n=9,069)						
No	-	-	6,389	(70.5)	7,875	(86.8)
Yes	2.0 (2.6)	5.0 (3–10)	2,680	(29.6)	1,194	(13.2)
Tramadol SA (n=3,615)						
No	-	-	2,115	(58.5)	3,024	(83.7)
Yes	1.6 (1.1)	5.0 (3–15)	1,500	(41.5)	591	(16.4)

Abbreviations: medication assisted treatment (MAT), short-acting (SA)

[a]Table is among women who had at least one days' supply for an opioid during pregnancy. For the days' supply percentages, percentages are among the group that received at least one of the types of prescriptions (that is the denominator includes women who had a least one prescription day for that type of prescription).

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Table 4.

Maternal demographics and characteristics in association with prescription opioid use, n=311,217[a]

	Any prescription opioid[b] (n=311,217)				Opioid prescription analgesics only [b,c] (n=307,782)			
	Age and delivery year-adjusted		Further-adjusted[d]		Age and delivery year-adjusted		Further-adjusted[d]	
	OR	95% CI	OR	95% CI				
Maternal education								
< High School	3.02	(2.90–3.12)	2.42	(2.31–2.53)	2.70	(2.60–2.80)	2.24	(2.14–2.34)
High School	3.46	(3.35–3.46)	2.38	(2.30–2.47)	3.10	(3.02–3.23)	2.21	(2.13–2.30)
Some college	2.69	(2.60–2.77)	2.09	(2.02–2.17)	2.53	(2.45–2.61)	1.98	(1.92–2.06)
≥ College graduate	1.00	(reference)	1.00	(reference)	1.00	(reference)	1.00	(reference)
Maternal race								
White	1.00	(reference)	1.00	(reference)	1.00	(reference)	1.00	(reference)
Black	1.13	(1.10–1.15)	1.12	(1.09–1.15)	1.24	(1.21–1.27)	1.19	(1.16–1.22)
Other	0.28	(0.26–0.29)	0.30	(0.28–0.32)	0.30	(0.29–0.32)	0.32	(0.30–0.33)
Household income								
< $10,000	3.31	(3.20–3.42)	1.87	(1.80–1.95)	3.02	(2.94–3.12)	1.74	(1.67–1.82)
$10,000–< 25,000	2.58	(2.50–2.67)	1.59	(1.53–1.65)	2.34	(2.30–2.46)	1.51	(1.45–1.58)
$25,000–50,000	1.69	(1.63–1.75)	1.17	(1.13–1.21)	1.64	(1.58–1.70)	1.16	(1.11–1.20)
≥ $50,000	1.00	(reference)	1.00	(reference)	1.00	(reference)	1.00	(reference)
Pre-pregnancy BMI								
< 21.5	1.13	(1.10–1.17)	1.05	(1.02–1.09)	1.07	(1.04–1.11)	1.02	(0.99–1.05)
21.5–< 24.99	1.00	(reference)	1.00	(reference)	1.00	(reference)	1.00	(reference)
24.99–< 29.99	1.13	(1.10–1.16)	1.06	(1.03–1.09)	1.17	(1.14–1.20)	1.10	(1.06–1.13)
≥ 30 kg/m^2	1.37	(1.33–1.40)	1.19	(1.15–1.22)	1.46	(1.42–1.50)	1.26	(1.22–1.30)
Total cigarettes per day during pregnancy								
None	1.00	(reference)	1.00	(reference)	1.00	(reference)	1.00	(reference)
< 10	2.03	(1.92–2.15)	1.61	(1.52–1.70)	1.92	(1.81–2.03)	1.54	(1.45–1.63)
≥ 10	3.54	(3.45–3.62)	2.65	(2.58–2.72)	2.98	(2.90–3.05)	2.29	(2.23–2.36)

[a] Models exclude missing data by maternal factor as applicable (see Table 1 for the number by variable). The exception is for household income, where missing data on income was include as an indicator variable.

[b] Reference groups include all women in the study population who did not fill an opioid of any type during pregnancy.

[c] Excludes women who only filled buprenorphine for MAT and did not use opioids for pain during pregnancy.

[d] Adjusted for birth year, maternal age, maternal education (when applicable), number of live births, maternal race (when applicable), pre-pregnancy BMI (when applicable), and total cigarettes per day (when applicable).