

Neonatal Abstinence Syndrome and Maternal Substance Use in Wisconsin, 2009-2014

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ABSTRACT

Introduction: Increasing rates of neonatal abstinence syndrome (NAS), most commonly linked to maternal opioid use, are a growing concern within clinical and public health domains.

Objectives: The study aims to describe the statewide burden of NAS and maternal substance use, focusing on opioids in Wisconsin from 2009 to 2014.

Methods: Trends in NAS and maternal substance use diagnosis rates were calculated using Wisconsin's Hospital Discharge Data. Demographic and payer characteristics, health service utilization, and clinical outcomes were compared for newborns with and without NAS. Demographic and payer characteristics were compared between women with and without substance use identified at time of delivery.

Results: Rates of NAS and maternal substance use, most notably opioid use, increased significantly between 2009 and 2014. The majority of newborns diagnosed with NAS, and women identified with substance use, were non-Hispanic, white, and Medicaid-insured. Disproportionate rates of NAS and maternal opioid use were observed in American Indian/Alaska Native and Medicaid populations compared to white and privately insured groups, respectively. Women age 20-29 years had the highest rates of opioid use compared to the reference group (10-19 years). Odds of adverse clinical outcomes and levels of health service utilization were significantly higher for newborns with NAS.

Conclusions: Similar to trends nationally, our findings show an increase in maternal opioid use and NAS rates in Wisconsin over time, with disproportionate effects in certain demographic groups. These findings support the need for targeted interventions in clinical and public health settings aimed at prevention and burden reduction of NAS and maternal substance use in Wisconsin.

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BACKGROUND

The use of drugs during pregnancy, both illicit and prescribed, can lead to negative consequences for mothers and newborns. Of particular concern amidst the current epidemic of opioid use and abuse in the United States is the increasing number of infants born with physical dependence to opioids taken by the mother.¹⁻⁴ Known as neonatal abstinence syndrome (NAS), this condition encompasses a constellation of behavioral and physiological signs and symptoms characterized by neurological over-activity, feeding difficulties, and respiratory problems, which can result in significant medical treatment, prolonged hospital stays, and increased costs in the days and weeks following birth.⁵ Clinical manifestations of NAS depend on various factors influencing the newborn's intrauterine drug exposure, including the type, dose, frequency, and metabolism of the drug used by the mother.⁶ In addition to NAS, these newborns experience higher rates of prematurity and poor fetal growth.^{1,3-6} There is also evidence of increased risks for

certain birth defects and associated neurobehavioral and developmental problems later into childhood.^{7,8}

NAS can result from in utero exposure to prescription opioid pain medications, heroin, methadone, and buprenorphine used for opioid addiction treatment, benzodiazepines, barbiturates, amphetamines, cocaine, marijuana, and alcohol.^{6,9} The 2012-2013 National Survey on Drug Use and Health reported that 5.4% of pregnant women age 15 to 44 years old used illicit drugs.¹⁰ Opioid use during pregnancy rose nearly 2.5-fold between 2001 and 2009 within a nationally representative sample of inpatient hospital discharges.¹¹ Looking at all women reproductive age, on average 27.7% of privately insured and 39.4% of Medicaid-enrolled women filled a prescription for an opioid

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pain medication annually in 2008-2012.¹² Given that negative effects of substance exposure can occur during the unrecognized first weeks of pregnancy, and that half of all US pregnancies are unplanned, the growing use and misuse of opioids in women of reproductive age presents potential risks for mother and infant.¹³

Previous reports indicate that Wisconsin's rates of opioid prescribing, use, and abuse are similar to rising national trends.¹⁴ To date, quantification of NAS and maternal substance use in the state has been limited. The objectives of this study are to describe the statewide burden of NAS in Wisconsin from 2009 to 2014, including perinatal outcomes, hospital utilization trends, and differences across demographic and payer groups between newborns with and without a NAS diagnosis, and to describe the statewide burden of maternal substance use identified at time of delivery in Wisconsin from 2009 to 2014, including differences across demographic and payer groups comparing mothers identified with and without substance use.

METHODS

Data Source

Wisconsin's inpatient Hospital Discharge Data (HDD) was used to identify maternal delivery hospitalizations and hospitalizations of newborns up to 28 days after delivery in Wisconsin facilities from 2009 to 2014. The HDD contains all hospital admission-discharge encounters for facilities located in Wisconsin and includes demographic information for patients, procedure and diagnosis codes, length of hospital stay, discharge status, and billing information (eg, payer and hospital charges). Delivery hospitalizations among newborns and mothers were analyzed separately. Hospitalization records for Wisconsin residents receiving care in a neighboring state and within federal Veterans Affairs hospitals are not included in the inpatient HDD.

This study used nonidentifiable patient data and was considered exempt per the Wisconsin Department of Public Health Institutional Review Board criteria.

Study Population

Newborns—Newborn hospitalizations (referred to as newborns in subsequent text) with a NAS diagnosis were identified using the *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* diagnosis code 779.5 (drug withdrawal syndrome in newborn). Newborns were included if they were age 0-28 days at the onset of hospitalization; a range chosen based on current knowledge of possible withdrawal symptom onset for the substances most commonly associated with NAS.⁶ The 0-28 day timeframe allowed for capturing newborns experiencing NAS shortly after birth and those who presented with NAS after being discharged.

Neonatal abstinence syndrome can occur due to iatrogenic causes from hospital therapies required for other complications

in the newborn period unrelated to maternal drug use. Based on a 2012 study by Patrick et al, newborns with select diagnoses associated with iatrogenic causes of NAS were excluded. These included very low birth weight (<1,500g, ICD-9-CM 765.0, 764.01-764.05, V213.1-V213.3), gestational age less than 24 weeks (ICD-9-CM 765.21), intraventricular hemorrhage (ICD-9-CM 772.1), periventricular leukomalacia (ICD-9-CM 779.7), necrotizing enterocolitis (ICD-9-CM 777.5), spontaneous intestinal perforation (ICD-9-CM 777.6), or bronchopulmonary dysplasia (ICD-9-CM 770.7).¹

The comparison group of newborns without NAS included newborns born within, or en route to, the hospital during the study timeframe. The same exclusion criteria for iatrogenic causes of NAS were applied to this population to ensure comparable groups.

Delivering Mothers—Delivery hospitalizations (referred to as mothers in subsequent text) with a live birth were identified using methods described by Kuklina et al.¹⁵ Any record containing delivery-related procedure codes (V 720-1, V724, V726, V729, V736, V740-2, V744, V7221, V7229, V7231, V7239, V7251, V7253-54, V7271, V7279, V7322, V7359, or V7499), Medicare Severity Diagnosis-Related group codes (765-768 and 774-775 or ICD-9-CM code 650) were included. Encounters with abortive or abnormal pregnancy outcome codes (ICD-9-CM 630.x, 639.x, 750.x, 690.1x, 695.1x, and 749.1x) were excluded to ensure capture of only live births.

Measures

Newborn Substance Exposure—The ICD-9-CM does not allow for identification of a specific substance of exposure within the 779.5 NAS code. Therefore, newborn substance exposure type was identified by searching for codes associated with a specific drug exposure in the newborn's hospital record.³ If a substance exposure code was identified without a concurrent diagnosis of NAS, the newborn was excluded as a NAS case due to limitations in confirming if the newborn suffered clinical symptoms meeting criteria for NAS.

Maternal Substance Use—Maternal substance use was captured by searching for select ICD-9-CM codes associated with maternal substance use identified during the delivery hospitalization, mirroring the technique used by Creanga et al.³ Mothers were classified broadly as substance-using (any substance) or non-substance using. Substance-using mothers included those with ICD-9-CM codes in the hospitalization record for broad drug types, eg, opioid (including heroin, methadone, and opioid analgesic), psychotropic (sedative, hypnotic, and tranquilizers), stimulant, cocaine, cannabis, alcohol, tobacco, other, unspecified, and polydrug. Illicit versus prescribed use could not be ascertained with ICD-9-CM coding.

Demographic Characteristics—Newborn demographic data examined included race, ethnicity, and sex. Maternal demographic data examined were race; ethnicity; and age, categorized as 10-19, 20-29, 30-39, and 40-45 years. Race was classified as white, black, American Indian/Alaska Native, and Asian or Pacific Islander. Ethnicity classification was Hispanic or non-Hispanic. Race and ethnicity were presented separately due to a large proportion of missing race or ethnicity data for some outcomes.

Payer Source—Primary payer for each hospitalization was categorized as private, Medicaid, or other (self-pay, Medicare, or uninsured).

Newborn Health Care Utilization—Two measures were collected: length of stay (LOS) and total hospital charges, defined as the total facility fee reported within the hospital discharge record.

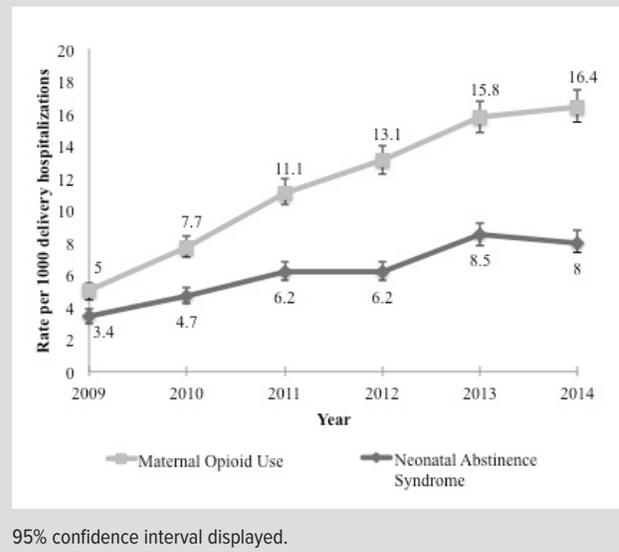
Newborn Clinical Outcomes—Five outcomes were examined: low birth weight (1500g-2500g; ICD-9-CM 764.0-764.2, 764.9, 765.0-765.1), prematurity (24-37 weeks gestation; ICD-9-CM 765.1-765.2), feeding difficulties (ICD-9-CM 779.3), respiratory distress syndromes (ICD-9-CM 769, 770), and seizures (ICD-9-CM 779.0, 780.3).^{1,3,16} The HDD does not provide a continuous measure of birth weight, thus this outcome was treated as a dichotomous variable.

Statistical Analysis

NAS rates were calculated by year as the rate of NAS diagnoses per 1,000 delivery hospitalizations. A chi-squared test for linear trend was used to examine significant trends over time. Descriptive statistics for demographic characteristics and payer source were generated for newborns with and without a diagnosis of NAS, and mothers with substance use, opioid use, and no substance use. For newborns, rates of NAS per 1,000 delivery hospitalizations were calculated within each demographic group, and rate ratios (RR) were computed using a reference group within each demographic or payer category. Logistic regression was used to examine adverse clinical outcomes in newborns with NAS compared to newborns without NAS. For continuous health care utilization measures (LOS and total charges), the groups were compared using Student's t-test for continuous variables.

Maternal substance use and opioid use rates were calculated by year as the rate of mothers with substance or opioid use identified at time of delivery per 1,000 delivery hospitalizations. A chi-squared test for linear trend was used to examine significant maternal substance and opioid use trends over time. Rates of any substance use and of opioid use per 1,000 delivery hospitalizations were calculated for each demographic and payer group. Rate ratios were computed using a reference group within each demographic and payer category. *P*-values of 0.05 were considered statistically significant for all comparisons and statistical tests. All analyses were conducted in SAS 9.4. (SAS Institute Inc, Cary, North Carolina).

Figure 1. Rate of Neonatal Abstinence Syndrome and Maternal Opioid Use Among Delivery Hospitalizations in Wisconsin, 2009-2014



RESULTS

Newborn Results

A total of 2,361 newborns were diagnosed with NAS between 2009 and 2014. The rate of NAS per 1,000 delivery hospitalizations increased significantly during this time period (*P* for trend <0.05), Figure 1. Ninety-two percent (n=2182) of NAS cases were diagnosed during the delivery hospitalization. ICD-9-CM codes for a specific substance of exposure were identified in only 17.4% (n=412) of NAS-affected newborns. Of these identified exposures, opioids comprised 70.9% of cases.

Mean LOS for newborns diagnosed with NAS was significantly longer compared to newborns without NAS (16.4 days, SD=16.1 vs 2.8 days, SD=4.9, *P*<0.001). Mean hospital charges were also significantly higher for newborns diagnosed with NAS compared to unaffected newborns (\$44,929, SD=58,971 vs \$5,864, SD=22,644, *P*<0.001).

NAS rates by demographic and payer group are presented in Table 1. The majority of newborns with a NAS diagnosis were non-Hispanic (73.8%), white (68.2%), and Medicaid-insured (82.0%). Rates of NAS were higher in males and non-Hispanic newborns. Compared to white newborns, the NAS rate was lower in black and “other” race categories, but higher in American Indian/Alaska Native newborns. Compared to privately insured newborns, the NAS rate was higher for Medicaid and other-insured groups.

The proportion of newborns with and without NAS experiencing adverse clinical outcomes is presented in Table 2. Compared to newborns without a NAS diagnosis, newborns with NAS had significantly higher odds of low birth weight, prematurity, feeding difficulties, seizures, and respiratory distress syndrome.

Table 1. Demographic Characteristics and Payer Source for Delivery Hospitalizations of Newborns With and Without Neonatal Abstinence Syndrome (NAS) in Wisconsin, 2009-2014

	Delivery Hospitalizations Without NAS No. (%)	Delivery Hospitalizations With NAS No. (%)	NAS Rate Per 1,000 (95% CI)	Rate Ratio ^a (95% CI)
Sex^b				
Female	188,589 (48.8)	1,030 (43.6)	5.4 (5.1, 5.7)	Ref
Male	198,014 (51.2)	1,331 (56.3)	6.7 (6.3, 7.1)	1.2 (1.1, 1.3)
Ethnicity^c				
Non-Hispanic	285,121 (75.0)	1,772 (73.8)	6.2 (5.9, 6.5)	Ref
Hispanic	27,403 (4.6)	109 (7.1)	4.0 (3.3, 4.7)	0.6 (0.5, 0.8)
Race^d				
White	258,773 (66.9)	1,612 (68.2)	6.2 (5.9, 6.5)	Ref
Black	33,757 (8.7)	162 (6.9)	4.8 (4.1, 5.5)	0.8 (0.7, 0.9)
Asian/Pacific Islander	13,279 (3.4)	8 (0.3)	0.6 (0.2, 1.0)	0.1 (0.0, 0.2)
American Indian/Alaskan Native	3,936 (1.0)	76 (3.2)	18.9 (14.6, 23.2)	3.1 (2.4, 3.9)
Other	18,279 (4.7)	68 (2.9)	3.7 (2.8, 4.6)	0.6 (0.5, 0.8)
Payer				
Private insurance	207,528 (53.7)	294 (12.4)	1.4 (1.2, 1.6)	Ref
Medicaid	161,089 (41.7)	1,938 (82.0)	11.9 (11.4, 12.4)	8.4 (7.4, 9.5)
Other	18,012 (4.7)	129 (5.5)	7.1 (5.9, 8.3)	5.0 (4.1, 6.2)

^aRate ratios represent the rate of NAS in each group compared to the rate of NAS in the reference group

^bMissing for 26 delivery hospitalizations (<0.5%).

^cMissing for 74,585 delivery hospitalizations (19.1%).

^dMissing for 59,040 delivery hospitalizations (15.2%).

Table 2. Proportions and Odds of Clinical Outcomes for Delivery Hospitalizations of Infants with NAS in Wisconsin, 2009-2014

	Delivery Hospitalizations Without NAS No. (%)	Delivery Hospitalizations With NAS No. (%)	Rate Ratio ^a (95% CI)
Low birth weight	18,981 (4.9)	349 (14.8)	3.4 (3.0, 3.8)
Prematurity	27,983 (7.2)	411 (17.4)	2.7 (2.4, 3.0)
Feeding difficulties	14,257 (3.7)	470 (19.9)	6.5 (5.9, 7.2)
Seizures	389 (0.1)	21 (0.9)	8.9 (5.7, 13.8)
Respiratory distress syndrome	31,815 (8.2)	677 (28.7)	4.5 (4.1, 4.9)

^aOdds ratios represent the odds of a clinical outcome for NAS.

Maternal Results

Rates of any substance use per 1,000 delivery hospitalizations increased from 83.0 in 2009 to 96.5 in 2014. Tobacco was the leading substance identified (mean 4814 users per year [range 4658-5015]), followed by opioids, polydrug (defined as >1 substance), cannabis, unspecified substances, cocaine and alcohol (Figure 2). Opioid use rates per 1,000 delivery hospitalizations increased 3.3-fold over the study period (Figure 1, *P* for trend <0.001). Rates of cannabis and polydrug use were the only other substance categories to increase between 2009 and 2014, and to a smaller degree than opioids, 2.1-fold and 2.0-fold, respectively.

Maternal substance and opioid use rates by demographic and payer groups are presented in Table 3. The majority of women

with any substance use were non-Hispanic (93.4%), white (79.5%), and Medicaid-insured (70.2%). Compared to women age 10 to 19, the rate of any maternal substance use was higher in women age 20 to 29, and lower in women age 30 to 39 and age 40 to 55 years. Compared to white women, rates of any maternal substance use were higher in black and American Indian/Alaska Native women, but lower in Asian/Pacific Islander and “other” race women. Medicaid-insured and “other”-insured women had higher rates of any maternal substance use versus privately insured women. Similar comparisons of rates between demographic groups were observed for maternal opioid use with the exception of age. Compared to the reference age group (10 to 19 years), the rate of maternal opioid use was higher in women age 20 to 29, and also in women age 30 to 39 and 40 to 55 years.

DISCUSSION

This study found increasing rates of NAS and maternal substance use, particularly for opioids, in Wisconsin between 2009 and 2014. Although analyzing mothers and newborns separately restricts causal inferences, the parallel rising trends for both findings is supportive of an association. There was a slight decline in the NAS rate in 2014; however, this was not statistically different from the rate in 2013. The decline could represent a true plateau in the number of cases or be an outlier within a continued upward trend. It also might

signal improvements in the prenatal management of substance-using mothers, in particular given the 4% rise in maternal opioid use rates observed from 2013 to 2014.

The higher incidence of poor perinatal outcomes in newborns with NAS certainly contributes to the observed increased health service utilization for these newborns. These adverse outcomes must be interpreted cautiously. Some outcomes measured are clinical criteria used within symptom scoring tools to make a diagnosis of NAS, and therefore are expected to be more common in newborns with this diagnosis.^{5,6} Causal links between poor clinical outcomes and substance use by the mother should be considered within the context of other potential confounding risk factors, which were not explored in the present analysis. These include

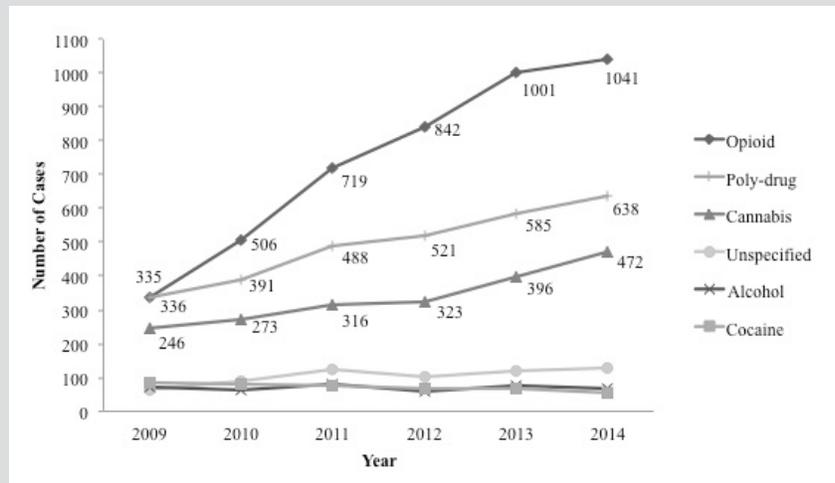
the impact of other clinical conditions from which the newborn may be suffering, as well as maternal factors such as stress, other substances used, general health, mental health disorders, socioeconomic status, and characteristics of prenatal care, which could contribute to poor newborn outcomes.^{16,17}

The study's findings support anecdotal reports of increasing NAS and maternal opioid use observed by clinical and public health practitioners across the state. Further, the analysis highlights populations with the highest burden of NAS and maternal substance use (eg, non-Hispanic, White, and Medicaid-insured newborns and women), while identifying subgroups disproportionately affected by these issues (eg, American Indian and Alaska Native, non-Hispanic, and Medicaid-insured newborns and women; women aged 20-29 years old). Wisconsin's findings are comparable to descriptive analyses from other states, including Tennessee, Ohio, Washington, and Florida, suggesting a need for additional research, prevention and treatment investments, and nonpunitive policy initiatives targeting substance exposure during pregnancy and associated impact on newborns at the state and national levels.^{1,3,9,17,18}

There are several limitations of this study. ICD-9-CM code limitations, as well as variations in practice across clinical settings, complicate the determination of a "best" definition of NAS for accurately identifying cases caused by maternal substance use. Some studies have included a broader array of codes to capture NAS (eg, 760.7x, noxious influences affecting fetus or newborn via placenta or breast milk).^{3,18} For this analysis a more conservative definition was used to improve specificity at the risk of underestimating the true burden of NAS.

The number of NAS-diagnosed newborns lacking a specific substance exposure code, as well as the newborns identified with only an opioid exposure code but no NAS code, also may be a product of coding obstacles and practice variations. The latter group may contain missed NAS cases. Further challenges arise when trying to exclude newborns with NAS due to iatrogenic causes. The array of exclusion diagnoses used in this analysis, while informed by previous studies, is not comprehensive.^{1,3,4,9} Without additional clinical information, there could be misclassification of newborns with and without NAS due to maternal substance use. Future studies should build upon existing analyses to improve case ascertainment for NAS, including accurate identification of substance exposure and appropriate exclusions for iatrogenic causes to ensure appropriate classification of cases.

Figure 2. Maternal Substance Use Identified During Delivery Hospitalization in Wisconsin, 2009-2014



Tobacco use not shown due to scale.
Hallucinogen, heroin, psychotropic, stimulant and other not shown (<50 cases per year).

The reliance on ICD-9-CM codes captured at time of delivery to identify maternal substance use also may underestimate the use rates. The episode of hospital care at time of delivery is only one snapshot within a longer prenatal course during which substance use may have affected pregnancy. Fear of reporting substance use due to the potential consequences, and the absence of universal substance use screening protocols during delivery hospitalization could result in missed cases. Future work using linked data sets, such as HDD and birth certificate data, and exploration of the clinical record could aid in associating newborn outcomes from specific maternal exposures, provide additional variables of interest (eg, maternal education), and enable more complex regression analysis using continuous variables (eg, birth weight). A better understanding of clinical coding and screening practices also may ensure more comprehensive and consistent surveillance.

Incomplete variables within the dataset, such as missing information for race (15.2%) and ethnicity (19.1%) in newborns, could misrepresent the burden and disproportionate risk of NAS across groups. Missing data is one potential explanation for the discordance in risks observed for NAS and maternal substance use within racial groups. Although black newborns had a decreased risk of NAS compared to white newborns, there was an increased risk of any maternal substance use, and specifically opioid use, in black women compared to white women. Other factors that could affect findings across different demographic groups include disparate screening, reporting, prescribing, or management practices. Previous literature, for example, has shown that providers are less likely to prescribe opioids to some minority groups compared to whites presenting with similar medical problems.¹⁹ Inclusion of birth certificate data in future analyses may help overcome the

Table 3. Maternal Demographic Characteristics and Payer Source for Delivery Hospitalizations With and Without Substance Use in Wisconsin, 2009-2014

	Delivery Hospitalizations Without Substance Use No. (%)	Delivery Hospitalizations With Substance Use No. (%)	Substance Use Rate Per 1,000 (95% CI)	Rate Ratio ^a (95% CI)	Delivery Hospitalizations With Opioid Use No. (%)	Opioid Use Rate Per 1,000 (95% CI)	Rate Ratio ^a (95% CI)
Age (years)^b							
0 to 19	23,835 (6.7)	2,752 (8.1)	103.5 (99.6, 107.4)	Ref	169 (3.8)	6.4 (5.4, 7.4)	Ref.
20 to 29	184,247 (51.9)	22,210 (65.0)	107.6 (106.2, 109.0)	1.0 (1.0, 1.1)	2,719 (61.2)	13.2 (12.7, 13.7)	2.1 (1.8, 2.4)
30 to 39	138,675 (39.1)	8,721 (25.5)	59.2 (58.0, 60.4)	0.6 (0.5, 0.6)	1,477 (33.2)	10.0 (9.5, 10.5)	1.6 (1.3, 1.8)
40 to 55	8,049 (2.3)	498 (1.5)	58.3 (53.2, 63.4)	0.6 (0.5, 0.6)	79 (1.8)	9.2 (7.2, 11.2)	1.5 (1.1, 1.9)
Ethnicity^c							
Non-Hispanic	309,075 (87.1)	31,935 (93.4)	93.6 (92.6, 94.6)	Ref	4,124 (92.8)	12.1 (11.7, 12.5)	Ref.
Hispanic	32,333 (9.1)	1,050 (3.1)	31.5 (29.6, 33.4)	0.3 (0.3, 0.4)	211 (4.8)	6.3 (5.4, 7.2)	0.5 (0.5, 0.6)
Race^d							
White	270,777 (76.3)	27,178 (79.5)	91.2 (90.1, 92.3)	Ref	3,476 (78.2)	11.7 (11.3, 12.1)	Ref.
Black	35,934 (10.1)	4,225 (12.4)	105.2 (102.0, 108.4)	1.2 (1.1, 1.2)	558 (12.6)	13.9 (12.7, 15.1)	1.2 (1.1, 1.3)
Asian or Pacific Islander	15,453 (4.4)	421 (1.2)	26.5 (24.0, 29.0)	0.3 (0.3, 0.3)	45 (1.0)	2.8 (2.0, 3.6)	0.2 (0.2, 0.3)
American Indian/Alaskan Native	3,864 (1.1)	1,066 (3.1)	216.2 (203.2, 229.2)	2.4 (2.2, 2.5)	134 (3.0)	27.2 (22.6, 31.8)	2.3 (2.0, 2.8)
Other	18,249 (5.1)	592 (1.7)	31.4 (28.9, 33.9)	0.3 (0.3, 0.4)	114 (2.6)	6.1 (5.0, 7.2)	0.5 (0.4, 0.6)
Payer							
Private insurance	211,382 (59.6)	8,696 (25.4)	39.5 (38.7, 40.3)	Ref	1,400 (31.5)	6.4 (6.1, 6.7)	Ref
Medicaid	131,440 (37.1)	23,985 (70.2)	154.3 (152.3, 156.3)	3.9 (3.8, 4.0)	2,858 (64.3)	18.4 (17.7, 19.1)	2.9 (2.7, 3.1)
Other	11,988 (3.4)	1,500 (4.4)	111.2 (105.6, 116.8)	2.8 (2.7, 3.0)	186 (4.2)	13.8 (11.8, 15.8)	2.2 (1.9, 2.5)

^aRate ratios represent the rate of substance use or opioid use in each group compared to the rate of substance use or opioid use in the reference group.

^bMissing for 9 women with no substance use (<0.5%) and 9 women with no opioid use (<0.5%).

^cMissing for 13,401 women with no substance use (3.8%), 1,197 women with substance use (3.5%), and 109 women with opioid use (2.5%).

^dMissing for 10,533 women with no substance use (3.0%), 700 women with substance use (2.1%), and 117 women with opioid use (2.6%).

gaps in newborn demographic information observed in this study.

Despite these limitations, this study describes the growing burden of NAS and maternal substance use, particularly of opioids, in Wisconsin. The findings, supplemented by a growing body of literature showing the potential negative impacts of NAS and maternal opioid use during and beyond the perinatal period, provide evidence for targeted investments in clinical, public health, and policy initiatives aimed at all levels of prevention and care for mothers and newborns, paying particular attention to those populations with the highest burdens and risks. Early interventions, ideally preventing an opioid-affected pregnancy in the first place, should be top priority.

The ever-growing public health conversation and heightened clinical awareness of NAS and maternal opioid use may help overcome some of the aforementioned challenges of this study through increased diligence in screening, diagnosis, and documentation. Some states have developed universal substance screening procedures for delivering mothers and infants, mandated reporting policies, and statewide real-time surveillance mechanisms to better capture maternal substance use and subsequent newborn impacts.^{9,18} Wisconsin has not implemented such strategies, making up-to-date and accurate monitoring more challenging. Conversations between clinical providers, policy decision-makers, public health professionals, and community organizations can lead to improved surveillance approaches, better interventions

for substance-using mothers and their children, and prevention strategies that will be essential to ensure the best birth outcomes possible in light of increasing opioid use in Wisconsin and across the nation.

Funding/Support: This study was supported in part by an appointment to the Applied Epidemiology Fellowship Program administered by the Council of State and Territorial Epidemiologists (CSTE) and funded by the Centers for Disease Control and Prevention (CDC) Cooperative Agreement Number 1U38OT000143-02. The Wisconsin Partnership Program, in support of the University of Wisconsin Preventive Medicine Residency Program, provided additional funding.

Financial Disclosures: None declared.

Planners/Reviewers: The planners and reviewers for this journal CME activity have no relevant financial relationships to disclose.

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