# The Burden of Neonatal Abstinence Syndrome, Opioids, and COVID-19 in Wisconsin

Peter Johnson MD, MS; Erwin Cabacungan, MD; Ke Yan, PhD; Mahua Dasgupta, MS; Jennifer Broad, MPH; Madeline Kemp, MPH; Kelsey Ryan, MD

## ABSTRACT

**Introduction:** Wisconsin experienced overlapping and accelerating epidemics of opioid use and COVID-19 after March 2020. We hypothesized that Wisconsin neonatal abstinence syndrome rates increased after March 2020 alongside other markers of opioid burden.

**Methods:** Retrospective cohort analysis examined deidentified Wisconsin census, birth certificate, death certificate, hospital discharge, Prescription Drug Monitoring Program, emergency medical service run, and COVID-19 diagnosis records spanning January 1, 2019, through December 31, 2021. January 2019 through March 2020 was considered before the onset of COVID-19 (pre); April 2020 through December 2021 was considered post-onset of COVID-19 (post). Wisconsin Department of Health Services guidelines defined 5 Wisconsin regions. Rates pre- to post-onset were compared with $P$ values < 0.05 considered statistically significant.

**Results:** From January 2019 through December 2021, 190 072 infants were born in Wisconsin, of which 1205 were diagnosed with neonatal abstinence syndrome. Statewide opioid-associated deaths, emergency medical service runs, and emergency department visits all increased from the pre- to post-onset periods. Per-person Prescription Drug Monitoring Program rates decreased in both the total population and childbearing-age females (15-44 years), and statewide deaths in childbearing-age females increased significantly ($P < 0.001$). Statewide monthly neonatal abstinence syndrome incidence rates did not change significantly (6.68/1000 births to 6.10/1000 births; $P = 0.16$) but decreased significantly in the most populous Southeastern Region (8.13/1000 births to 6.37/1000 births; $P = 0.02$) of the state.

**Conclusions:** Opioid-associated morbidity and mortality increased in Wisconsin during the study period, including among females age 15 to 44 years. Despite increased opioid burden, neonatal abstinence syndrome incidence decreased in the Southeastern Region. Ongoing neonatal abstinence syndrome and opioid analysis may benefit from region-based contextualization.

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**Author Affiliations:** Medical College of Wisconsin (MCW), Milwaukee, Wisconsin (Johnson); Department of Pediatrics, MCW, Milwaukee, Wis (Cabacungan, Ryan); Quantititive Health Sciences, MCW, Milwaukee, Wis (Yan, Dasgupta); Wisconsin Department of Health Services, Madison, Wisconsin (Broad, Kemp); Centers for Disease Control and Prevention/CSTE Applied Epidemiology Fellowship Program, Madison, Wis (Kemp).

**Corresponding Author:** Peter Johnson, MD, MS, Children's Corporate Center, 999 N 92nd St, Suite C410, PO Box 1997, Wauwatosa, WI 53226; email pjohnson@mcw.edu; ORCID ID 0000-0002-1688-7967

## INTRODUCTION

Neonatal abstinence syndrome (NAS) is a clinical syndrome affecting newborns who are prenatally exposed to substances – classically opioids – and who subsequently experience withdrawal symptoms after birth.[1] Rates of opioid use in pregnant people and rates of NAS in infants have increased with the accelerating opioid epidemic in the United States.[2,3] Substance use disorder significantly contributes to pregnancy-associated maternal morbidity and mortality.[4,5] In addition, newborns affected by NAS are more likely to experience prolonged hospitalizations, higher average medical costs, and increased readmission rates within 30 days of discharge.[6-8]

This at-risk population of mother-infant dyads has demonstrated unequal distribution across geography, race, and income, with neonates experiencing NAS presenting disproportionately from rural areas, lower incomes, and with public insurance.[9-11] Recent efforts to identify associations between county-level factors that increase community risk of opioid-associated health care events and NAS suggest associations with higher rates of mental health hospitalizations, mental health professional shortages, unemployment, property crime, and poverty, underscoring the connection between social determinants of health and opioid use.[12,13] This clustering of increased resource needs in areas of higher resource scarcity may amplify inequality in health care accessibility and utilization, thereby potentially compound-

ing the risks of the opioid epidemic – and other epidemics – to mother and infant.

Wisconsin historically has exhibited increasing maternal opioid use and NAS rates similar to trends seen nationally.[14] Wisconsin also has exhibited geographic variation in counties experiencing the burden of both the opioid epidemic and NAS incidence rates.[15] The most recent statewide summary of county rates of NAS was published in 2015, presenting county-level rates of NAS per 1000 births during 2009-2014. In that report, the state's northernmost counties experienced the highest NAS rates, despite the population centers concentrated in the Eastern and Southeastern Regions of the state.

In March 2020, the onset of the COVID-19 pandemic drastically changed how patients sought and received health care, including pregnancy-related care and opioid treatment. Treatment of opioid use disorder relies on regularly scheduled clinician-patient meetings and tight regulation of opioid agonist dispensation, which were heavily affected by social distancing protocols, decreased in-person clinic availability, and the expansion of telehealth.[16,17] COVID-19 also changed the experience of giving birth in the health care setting, including strict visitor guidelines, maternal rooming-in practices, and concerns with viral transmission and breastfeeding.[18,19] A 2022 study by Racine et al demonstrated that after the onset of COVID-19 in Wisconsin, an increased percentage of mothers presented in active labor, presented at or after 41 weeks, and mother-infant dyads had shorter hospital lengths of stay.[20] Nationally, the proportion of infants born outside of a hospital increased.[21]

Wisconsin observed an increase in the suspected opioid burden after the onset of the COVID-19 pandemic in the state.[22] Prior trends would suppose that this would cause an increase in opioid use among childbearing-age females and a subsequent increase in NAS infants. However, no studies have examined whether this association has been disrupted by changes in health care access and delivery caused by COVID-19.

This investigation aimed to identify if regional and statewide NAS incidence rates also changed after the onset of the COVID-19 pandemic in Wisconsin. We hypothesized that the burden of the opioid epidemic in Wisconsin increased after the onset of the COVID-19 pandemic, specifically among childbearing-age females (15-44 years), and that NAS incidence rates also increased.

## METHODS

### Study Design

This retrospective cohort analysis examined regional disease burdens of NAS and opioid use in Wisconsin before and after the onset of the COVID-19 pandemic. COVID-19 onset was defined as March 2020, corresponding with Wisconsin's first identified positive cases. January 2019 through March 2020 was considered prior to onset of COVID-19 (pre); April 2020 through December 2021 was considered post-onset of COVID-19 (post). This retrospective project was approved and informed consent was waived by the Medical College of Wisconsin Institutional Review Board and the Wisconsin Department of Health Services (DHS) Data Governance Board as there is no identification or interaction with subjects.

Deidentified data from January 1, 2019, through December 31, 2021, were obtained from databases administered by the Wisconsin DHS; totaled by month, year, and associated Wisconsin county; and aggregated by region for analysis. Data were excluded if a county association could not be identified. Five regions (Northern, Northeastern, Southeastern, Southern, and Western) were defined by DHS Region by County guidelines.[23] Regional aggregation prevented unintended identification of individuals when county counts were small, increased statistical reliability, and facilitated compliance with the DHS Data Governance Board recommendation for suppression of case counts less than 5.

### Data Sources

***Wisconsin Population:*** Overall population data for Wisconsin were obtained through the Wisconsin Interactive Statistics on Health portal.[24] These data are based on the yearly estimates provided for Wisconsin from the US Census Bureau. Variables of interest included year, county of residence, age, and sex. Childbearing-age females were defined as ages 15 to 44 years to maintain alignment with other maternal and child health literature.[24]

***Birth Certificates:*** The birth certificate database is maintained by the Wisconsin Vital Records Office and includes all finalized birth certificates for Wisconsin residents. Extracted birth certificate variables included infant date of birth, maternal county of residence at time of birth, infant death at birth, and birth outside a health care facility, with less than 1% of records excluded for missing county information. The county of an infant's birth is ascribed to the maternal county of residence at the time of birth.

***Death Certificates:*** The death records database also is maintained by the Wisconsin Vital Records Office, with coding of the underlying and contributing causes of death completed by the National Center for Health Statistics. Variables of interest included date of death, county of residence, age and sex at death, underlying or contributing causes of death, and pregnancy status at time of death. Infant mortality was defined as death prior to 1 year of age. Deaths were ascribed to the county of residence of the deceased. Two percent of records extracted from the death records database were excluded for missing county information.

***Hospital Records:*** The hospital records database collects legally required billing documentation at the time of discharge from Wisconsin inpatient, emergency department (ED), surgery, or observational visits (Wis Stat § 153.05). Hospital discharge data are also collected from Iowa and Minnesota health care facilities for Wisconsin residents. Variables of visit included date of visit, county of residence, date of birth, sex, age at visit, and princi-

**Table 1.** Change in Wisconsin Population Characteristics Following COVID-19 Onset

| Region (% population) | Statewide | | | Northern (8.4%) | | | Northeastern (21.6%) | | | Southeastern (36.6%) | | | Southern (19.8%) | | | Western (13.7%) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Population Characteristics** | **Pre** | **Post** | ***P*** | **Pre** | **Post** | ***P*** | **Pre** | **Post** | ***P*** | **Pre** | **Post** | ***P*** | **Pre** | **Post** | ***P*** | **Pre** | **Post** | ***P*** |
| **Population total** | 5 839 299 | 5 835 721 | | 490 400 | 490 272 | | 1 260 328 | 1 259 054 | | 2 133 382 | 2 134 136 | | 1 156 110 | 1 154 363 | | 799 078 | 797 896 | |
| Birth rate per 1000 persons | 0.91 | 0.90 | 0.43 | 0.80 | 0.77 | 0.14 | 0.87 | 0.85 | 0.46 | 0.96 | 0.92 | 0.08 | 0.87 | 0.87 | 0.88 | 0.86 | 0.87 | 0.54 |
| Death rate per 1000 persons | 0.79 | 0.89 | **0.004**[a] | 0.93 | 1.06 | **0.03**[a] | 0.82 | 0.92 | **0.03**[a] | 0.77 | 0.88 | **0.002**[a] | 0.71 | 0.79 | **0.02**[a] | 0.78 | 0.89 | **0.004**[a] |
| % Childbearing population (15-44 F)[b] | 16.31% | 16.33% | **<0.001**[a] | 14.52% | 14.54% | 0.24 | 16.23% | 16.25% | **0.03**[a] | 18.54% | 18.57% | 0.13 | 16.23% | 16.26% | **0.01**[a] | 16.92% | 16.93% | 0.18 |
| Infant deaths per 1000 births | 5.82 | 5.47 | 0.38 | 5.36 | 5.63 | 0.84 | 7.04 | 4.81 | **0.01**[a] | 6.54 | 6.80 | 0.66 | 4.28 | 4.84 | 0.42 | 5.27 | 4.49 | 0.47 |
| Births occurring outside a hospital per 1000 | 32.27 | 37.55 | **<0.001**[a] | 41.03 | 47.01 | 0.12 | 24.37 | 31.10 | **<0.001**[a] | 11.50 | 14.24 | **0.001**[a] | 47.19 | 50.90 | 0.14 | 80.89 | 88.10 | 0.06 |

[a]Denotes *P* value < 0.05

[b]Denotes unpaired *t* test with counties as unit (N).

Abbreviations: pre, prior to COVID-19 onset; post, post COVID-19 onsent; *P*, *P* value; y, year-old; F, females.

pal and diagnosis codes, with 4% of records excluded for missing county information. ED visits and hospitalizations were tallied by individual's county of residence.

***Prescription Drug Monitoring Program (PDMP):*** The Wisconsin PDMP is a legally required administrative database that monitors the dispensation of controlled substances from pharmacies to Wisconsin residents (Wis Stat § 153.87). Variables of interest obtained from the Wisconsin PDMP database included date of dispensing, county of residence, age and sex at dispensing, and drug category (this analysis selected for opioids), with 2% of records excluded for missing county data. PDMP dispensations were attributed to the county of residence of the prescription recipient. Of note, buprenorphine- and methadone-containing prescription dispensations were not included. Additionally, monitoring of gabapentin began on September 1, 2021, in the Wisconsin PDMP. However, gabapentin is not classified as an opioid by the Wisconsin PDMP; thus, this change is assumed to have minimal impact on this opioid-focused analysis.[25]

***Wisconsin Ambulance Run Data System (WARDS):*** WARDS gathers "emergency medical service (EMS) run" reports from first responders for all 911 call responses. EMS run reports describe preliminary treatment in the field, whether or not they resulted in transport or hospitalizations. Variables of interest included date of incident, county of incident, age and sex at incident, call type, primary and secondary complaint and impression, and incident narrative, with no excluded records. EMS runs were ascribed to the county where the incident occurred.

***Wisconsin Electronic Disease Surveillance System (WEDSS):*** COVID-19 is a reportable condition in Wisconsin, meaning that all laboratory-confirmed cases and clinical diagnoses are legally required to be reported to WEDSS (Wis Stats § 252.05). These reports are then consolidated at the individual level so that the number of cases may be ascertained. Variables of interest included date of diagnosis, county of residence, and indicator of COVID-19. The county variable was required for receipt of the data, so it is not possible to determine how many cases were excluded; however, since it is a reportable condition, it may be that no cases were missing county information.

## Variable Definitions

***NAS:*** NAS cases were identified by querying statewide hospital inpatient discharge records for *International Classification of Diseases, Tenth Revision, Clinical Modification* (ICD-10-CM) code P96.1 Neonatal Abstinence Syndrome, which is diagnosed within the first 28 days of life. Each unique infant was identified to ensure that infants experiencing multiple hospitalizations for NAS were not counted more than once. NAS cases were tallied by county of birth, which is based on county of residence of the mother listed on the birth certificate. Then, the incidence rate of NAS was calculated for each Wisconsin region by dividing the number of NAS cases by the number of total births occurring within that region within the identified time frame and reported as a rate per 1000 births.

***Opioid Burden:*** The overall population burden of the opioid epidemic was characterized by multiple deidentified measures. PDMP data provided the number of opioid prescriptions dispensed by county of residence of recipient, which was then reported per 1000 persons residing in the county or region. Opioid poisoning or overdose was determined from inpatient and

**Table 2.** Change in Wisconsin Opioid Burden Following COVID-19 Onset

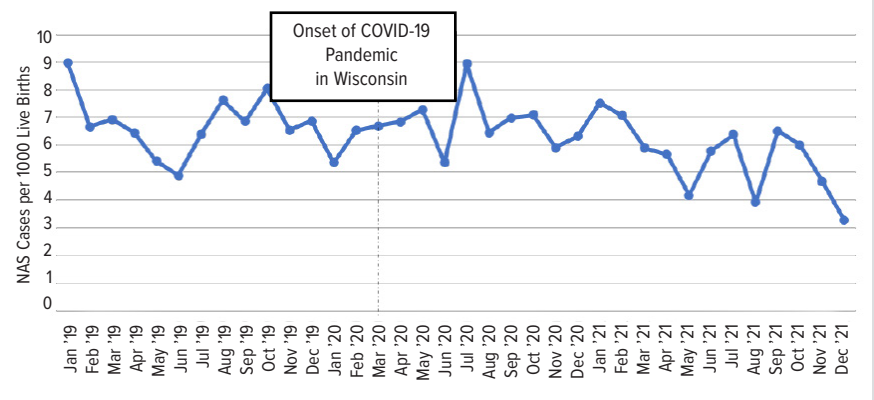
| Region (% population) | Statewide | | | Northern (8.4%) | | | Northeastern (21.6%) | | | Southeastern (36.6%) | | | Southern (19.8%) | | | Western (13.7%) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Opioid Burden** | **Pre** | **Post** | ***P*** | **Pre** | **Post** | ***P*** | **Pre** | **Post** | ***P*** | **Pre** | **Post** | ***P*** | **Pre** | **Post** | ***P*** | **Pre** | **Post** | ***P*** |
| **Population total** | 5 839 299 | 5 835 721 | | 490 400 | 490 272 | | 1 260 328 | 1 259 054 | | 2 133 382 | 2 134 136 | | 1 156 110 | 1 154 363 | | 799 078 | 797 896 | |
| Opioid deaths per 1000 deaths | 33.96 | 43.90 | **<0.001[a]** | 16.87 | 21.13 | 0.15 | 19.43 | 28.15 | **<0.001[a]** | 49.90 | 68.85 | **<0.001[a]** | 41.63 | 42.91 | 0.75 | 18.39 | 21.26 | 0.40 |
| Opioid deaths per 1000 deaths in 15-44 y F | 375.34 | 452.80 | **0.03[a]** | 249.85 | 229.61 | 0.82 | 230.65 | 463.43 | **0.001[a]** | 430.68 | 530.94 | **0.04[a]** | 502.09 | 429.17 | 0.24 | 215.46 | 317.57 | 0.14 |
| Opioid ED rates per 1000 ED visits | 1.47 | 1.93 | **<0.001[a]** | 1.00 | 1.17 | 0.15 | 0.90 | 1.70 | **<0.001[a]** | 1.78 | 2.04 | 0.10 | 1.97 | 2.73 | **<0.001[a]** | 1.00 | 1.39 | **0.005[a]** |
| Opioid ED rates per 1000 ED visits in 15-44 y F | 1.55 | 2.02 | **0.002[a]** | 1.56 | 1.87 | 0.24 | 1.04 | 2.18 | **<0.001[a]** | 1.67 | 1.80 | 0.52 | 1.99 | 2.73 | **0.01[a]** | 1.24 | 1.61 | 0.14 |
| Opioid suspected EMS rates per 1000 EMS visits | 11.25 | 14.75 | **<0.001[a]** | 7.08 | 9.04 | **0.007[a]** | 8.55 | 12.23 | **<0.001[a]** | 13.10 | 17.18 | **<0.001[a]** | 13.25 | 16.19 | **0.01[a]** | 7.85 | 10.55 | **<0.001[a]** |
| Opioid suspected EMS rates per 1000 EMS visits in 15-44 y F | 20.21 | 26.50 | **<0.001[a]** | 21.35 | 26.43 | 0.14 | 20.57 | 30.83 | **<0.001[a]** | 19.42 | 24.94 | **<0.001[a]** | 23.59 | 30.66 | **0.004[a]** | 18.57 | 22.83 | 0.08 |
| Opioid inpatient rates per 1000 hospitalizations | 2.04 | 1.93 | 0.25 | 1.60 | 1.43 | 0.26 | 1.65 | 1.49 | 0.34 | 2.49 | 2.43 | 0.66 | 2.24 | 1.86 | **0.02[a]** | 1.29 | 1.51 | 0.09 |
| Opioid inpatient rates per 1000 hospitalizations in 15-44 y F | 2.13 | 2.07 | 0.71 | 2.63 | 2.30 | 0.63 | 1.89 | 1.57 | 0.30 | 2.33 | 2.46 | 0.64 | 1.89 | 1.97 | 0.87 | 1.94 | 1.61 | 0.42 |
| Averaged opioid prescriptions per 1000 persons | 44.46 | 40.25 | **<0.001[a]** | 48.68 | 41.70 | **<0.001[a]** | 44.35 | 40.05 | **<0.001[a]** | 47.25 | 42.74 | **<0.001[a]** | 42.07 | 38.64 | **<0.001[a]** | 38.09 | 35.34 | **<0.001[a]** |
| Averaged opioid prescriptions per 1000 persons in 15-44 y F | 27.02 | 24.03 | **<0.001*** | 29.87 | 26.60 | **<0.001[a]** | 28.73 | 25.65 | **<0.001[a]** | 28.05 | 24.55 | **<0.001[a]** | 25.78 | 13.32 | **0.001*** | 21.82 | 19.79 | **<0.001[a]** |
| NAS births per 1000 births | 6.68 | 6.10 | 0.16 | 8.57 | 10.32 | 0.24 | 7.17 | 7.10 | 0.95 | 8.13 | 6.37 | **0.02[a]** | 4.78 | 4.74 | 0.97 | 4.48 | 4.54 | 0.94 |

[a]Denotes *P* value < 0.05.

Abbreviations: pre, prior to COVID-19 onset; post, post COVID-19 onset; *P*, *P* value; y, year-old; F, females; ED, emergency department; EMS, emergency medical services; NAS, neonatal abstinence syndrome.

ED hospital discharge data (ICD-10-CM code of T40.0-T40.4 or T40.6), death certificates (cause of death code X40-X44, X60-64, X85 or Y10-Y14 and an opioid use code in any of the contributing causes of death fields), and ambulance run data (suspected case defined by presence of key words within the incident narrative). The number of opioid-related EMS, ED, and inpatient visits was tallied by county and reported as a rate per 1000 of their respective events. Death certificates citing opioids were reported as a rate per 1000 death certificates from residents of that county or region.

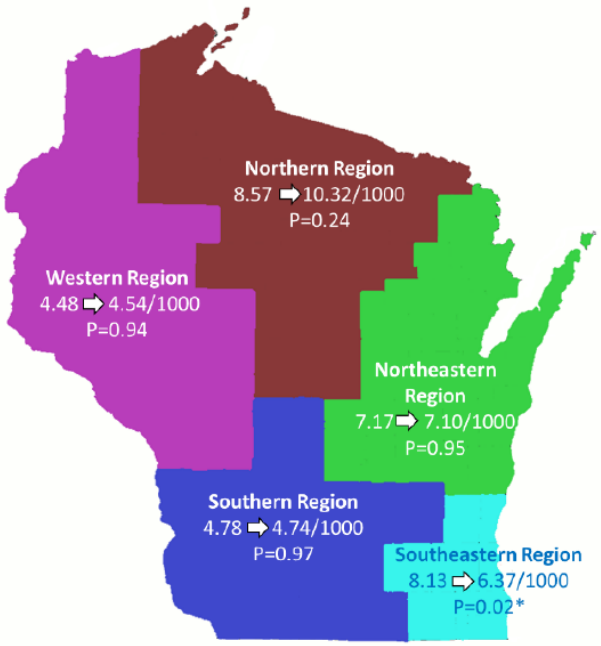
**Figure 1.** Neonatal Abstinence Syndrome (NAS) in Wisconsin, January 2019 – December 2021




Wisconsin statewide monthly rate of NAS decreased but did not significantly change January 2019 – March 2020 vs April 2020 – December 2021 (6.68 to 6.10 per 1000 births, *P* = 0.16).

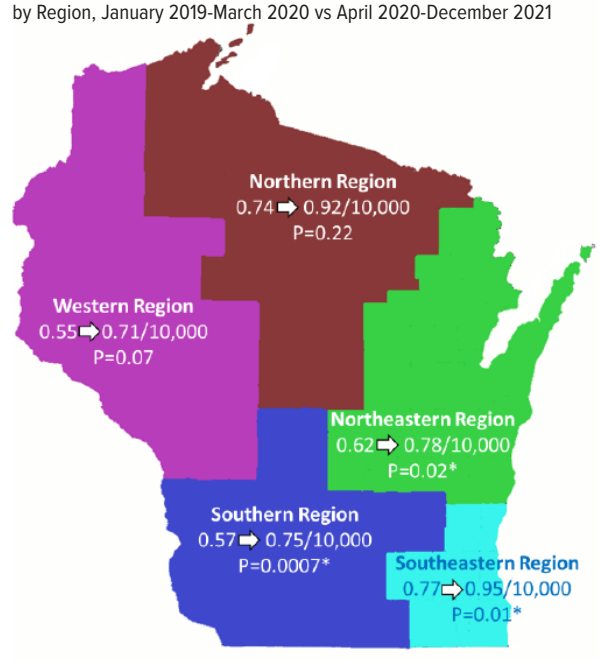
**Figure 2.** Regional Neonatal Abstinence Syndrome Incidence and All-cause Mortality Rates in Childbearing-Age Females

**2A.** Change in Regional rates of NAS in Wisconsin per 1000 Births, January 2019-March 2020 vs April 2020-December 2021




The statewide NAS rate did not significantly change (6.68 vs 6.10 per 1000 births $P=0.16$. $P$ values obtained via unpaired $t$ test.
*Denotes statistical significance of $P<0.05$.

**2B.** Average Rate of Death in Childbearing Age Females (Age 15-45 Years) per 10 000 Females of Childbearing Age in Wisconsin per Month by Region, January 2019-March 2020 vs April 2020-December 2021




Statewide death rates in this population increased from 0.67 to 0.84 per 10 000 ($P=0.0002$). $P$ values obtained via unpaired $t$ test.
*Denotes statistical significance of $P<0.05$.

*COVID-19:* COVID-19 cases were determined by surveillance reporting of laboratory findings of SARS-CoV-2 genetic material and death certificate coding. COVID-19 deaths were defined as those coded U071 in the underlying or contributing causes of death fields.

### Statistical Analysis

Trends in outcomes were plotted over time at statewide and regional levels. Incidence rates of NAS and opioid burden were aggregated and averaged into monthly rates for the two periods (pre- and post-onset of COVID-19). The pre- and post-onset rates were considered independent and were then compared using $t$ test with months as unit of analysis. The exception to this was in the percent childbearing-age population; as they are not completely independent, a paired $t$ test was used with counties as the unit of analysis. $P$ values $<0.05$ were considered statistically significant. The analysis utilized SAS version 9.4 (Cary, North Carolina).

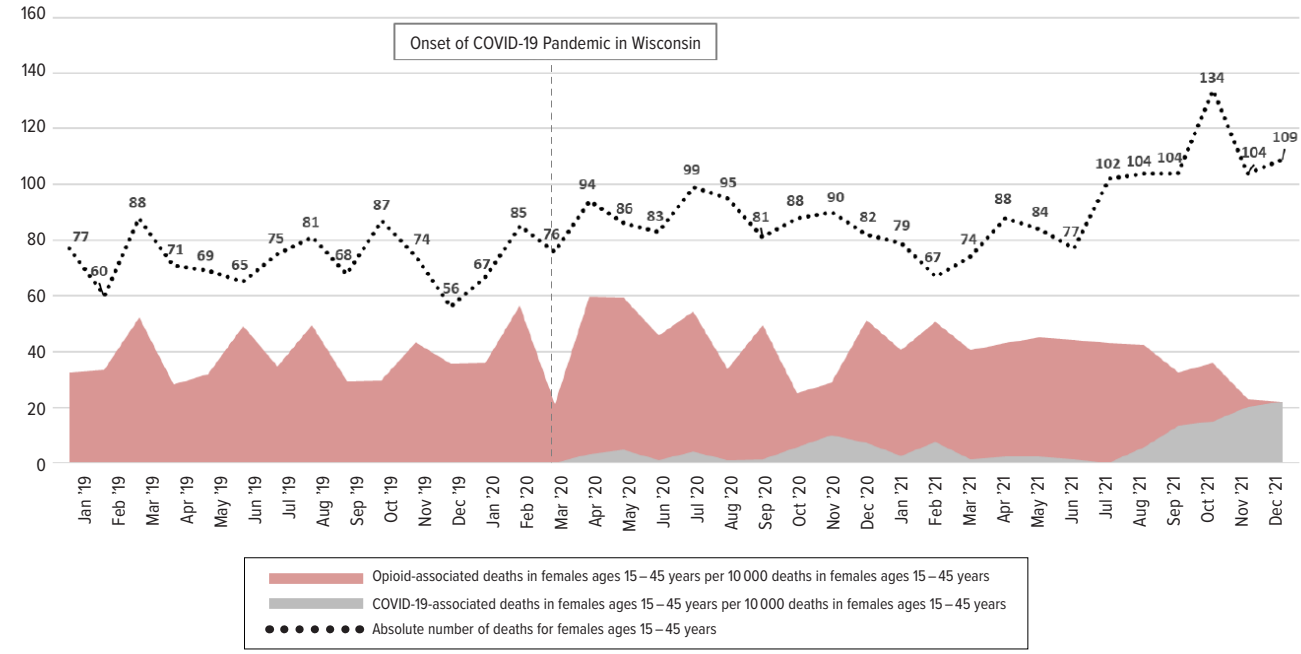
## RESULTS

During the study period, 190 087 infants were born in Wisconsin, of which 1205 were diagnosed with NAS. Table 1 summarizes changes in statewide and regional population characteristics and birth rates following COVID-19 onset. Although the statewide birth rate did not change significantly during the study period, an increased proportion of births occurred outside of a health care facility (32.3 vs 37.6 per 1000 births, $P<0.001$).

The statewide total death rate increased significantly (0.79 to 0.89 deaths per 1000 persons, $P=0.004$), as did opioid-associated death rates (33.96 to 43.9 opioid-related deaths per 1000 deaths, $P<0.001$) (Table 2). However, statewide per-person PDMP opioid prescriptions decreased significantly (44.46 to 40.25 opioid prescriptions per 1000 persons, $P<0.001$), while the proportion of opioid-related EMS and ED visits increased (11.25 to 14.75 opioid-related EMS visits per 1000 EMS visits, $P<0.001$; 1.47 to 1.93 opioid-related ED visits per 1000 ED visits, $P<0.001$). Similarly, among the subgroup of childbearing-age, there was a significant increase in statewide opioid-associated deaths (375.34 to 452.8 opioid-related deaths per 1000 deaths in females 15-44 years, $P=0.03$), EMS runs (20.21 to 26.5 opioid-related EMS runs per 1000 EMS runs in females 15-44 years, $P<0.001$), and ED visits (1.55 to 2.02 opioid-related ED visits per 1000 ED visits in females 15-44 years, $P=0.02$), while there was a significant decrease in PDMP per-person rates (27.02 to 24.03 opioid-related prescriptions per 1000 persons, $P<0.001$).

Monthly NAS rates in Wisconsin are shown in Figure 1. The statewide monthly NAS incidence rate did not change significantly during the study period, although it decreased (6.68 to 6.1 NAS births per 1000 births, $P=0.16$). Regional NAS incidence and all-cause mortality rates in childbearing-age females are shown in Figures 2A and 2B, respectively. The Southeastern Region experienced a significant decrease in NAS presentations (8.13 to 6.37

**Figure 3.** Deaths in Females Ages 15 – 45 years in Wisconsin, January 2019 – December 2021




Statewide rates of death in females ages 15 – 45 years with opioid-related or COVID-19-related primary or underlying cause of death. The number of deaths in this population associated with both opioid use and COVID-19 were suppressed due to low case count.

NAS births per 1000 births, $P = 0.02$), while the other regions experienced no significant change. The Southeastern, Southern, and Northeastern Regions experienced a significant increase in all-cause mortality among childbearing-age females – Southeastern: 0.77 to 0.95 deaths per 10 000 childbearing-age females, $P = 0.01$; Southern: 0.57 to 0.75 deaths per 10 000 childbearing-age females, $P < 0.001$; Northern: 0.62 to 0.78 deaths per 10 000 childbearing-age females, $P = 0.02$. Statewide opioid-associated and COVID-19 deaths over time in females of childbearing-age are shown in Figure 3. Deaths of childbearing-age females with both opioids and COVID-19 listed as underlying or contributing cause had a case count of less than 5 and were the only data suppressed in compliance with DHS policy.

## DISCUSSION

This is the first study in Wisconsin to describe the overlapping effects of the COVID-19 pandemic and opioid epidemic on population rates and NAS diagnoses. These results suggest that although the burden of the opioid epidemic increased after the onset of the COVID-19 pandemic in both the statewide population and in childbearing-age females, statewide NAS rates did not significantly increase (Table 2). Furthermore, the NAS rate unexpectedly decreased in the populous Southeastern Region of the state.

Prior studies have identified an increased opioid burden in response to the COVID-19 pandemic within Wisconsin.[22] Our analysis also demonstrates a statistically significant increase in multiple markers of opioid-related burden, such as an increased proportion of opioid-associated deaths, EMS visits, and ED visits across Wisconsin after the onset of the COVID-19 pandemic. We further report that increased opioid-associated deaths, EMS runs, and ED visits were observed in childbearing-age females. Identifying these trends for childbearing-age females is paramount to understanding the circumstances of the population that most directly impacts NAS diagnosis rates. Interestingly, these patterns occurred in the setting of decreased per-person PDMP opioid prescription counts in both the overall population and in childbearing-age females.

NAS is a lagging indicator of the burden of the opioid epidemic, as it requires a pregnancy to result in delivery before the diagnosis can be made. NAS statewide incidence rates did not significantly change after the onset of the COVID-19 pandemic. However, a statistically significant decrease in NAS occurred in the Southeastern Region (Figure 2A). This is particularly notable as this region contains more than one-third of the state's population and the highest proportion of childbearing-age females (Table 1). The change in NAS rates in the Southeastern Region deserves more detailed contextualization in future studies, including recognition of the differential impact of COVID-19 and opioid-related disease burden across this racially, ethnically and economically diverse regional population.

The juxtaposition of trends in childbearing-age females and infants reveals multiple factors that deserve consideration. An increased proportion of births occurred outside of a health care

facility after March 2020, which may falsely depress NAS rates, as newborn infants born outside of a health care facility may not undergo screening and diagnosis as they would during a birth hospitalization. Also, those pregnant people who received inpatient delivery and postnatal care did so in a transformed health care system after onset of the COVID-19 pandemic.[17-21] Whether statistically significant changes in disease detection rates reflect changes in the disease or the health care system will require longer-term and more nuanced study.

Separately, mortality increased in childbearing-age females, with an increased proportion of deaths associated with opioid use. Though much attention during this period focused on the potential increased risk of death caused by COVID-19 infection, COVID-19 deaths in childbearing-age females only approached levels of opioid-associated deaths in the last months of the study period (Figure 3). This finding demonstrates the opioid epidemic's burden across Wisconsin even before the COVID-19 pandemic. Increased rates of death associated with opioid use in childbearing-age females may reduce NAS rates by interrupting current or preventing future pregnancies that could result in infants at risk of NAS. This potential impact across Wisconsin, and specifically in the Southeastern Region, deserves dedicated examination.

While this analysis provides insight into opioid burden, birth rates, death rates, and NAS rates before and after the COVID-19 pandemic, the implications are limited by the observational nature of this study. Although we speculate an interplay between these population trends, we cannot demonstrate causality. Additionally, this study aggregates time frames before and after the onset of the COVID-19 pandemic, which may obscure distinct and rapidly changing circumstances. Further study is needed to interrogate potential links between childbearing and pediatric NAS populations and requires an analysis of outcomes over time to examine possible longer-term effects. Expanding the inclusion time frame of analysis would allow for examination of subsequent evolutions or "waves" in the COVID-19 pandemic that occurred after December 2021 and may also better capture longer-term effects, such as changes in pregnancy-associated overdose deaths and NAS diagnoses.[4] Analysis of maternal mortality and NAS risk per pregnancy over a longer study period and stratified for other potential confounders of geographic distribution, such as socioeconomic status, race, and ethnicity, is necessary to interpret the changes in maternal and neonatal outcomes described in this work.

## CONCLUSIONS

Multiple markers of the burden of the opioid epidemic increased after onset of the COVID-19 pandemic in Wisconsin, including in childbearing-age females. Statewide NAS rates, however, did not increase. Instead, the most populous Southeastern Region of Wisconsin experienced a significant decrease in NAS incidence after the onset of COVID-19. This pattern coincides with a significant increase in deaths of childbearing-age females and a significant increase in births occurring outside of health care facilities in this region. Contextualizing NAS incidence within regional trends may help inform more effective statewide responses to the overlapping epidemics of opioid use and COVID-19.

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**Availability of Data and Material:** Study materials available upon request.

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