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Infant Mortality Associated With Prenatal Opioid Exposure

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IMPORTANCE Knowledge of health outcomes among opioid-exposed infants is limited, particularly for those not diagnosed with neonatal opioid withdrawal syndrome (NOWS).

OBJECTIVES To describe infant mortality among opioid-exposed infants and identify how mortality risk differs in opioid-exposed infants with and without a diagnosis of NOWS compared with infants without opioid exposure.

DESIGN, SETTING, AND PARTICIPANTS A retrospective cohort study of maternal-infant dyads was conducted, linking health care claims with vital records for births from January 1, 2010, to December 31, 2014, with follow-up of infants until age 1 year (through 2015). Maternal-infant dyads were included if the infant was born in Texas at 22 to 43 weeks' gestational age to a woman aged 15 to 44 years insured by Texas Medicaid. Data analysis was performed from May 2019 to October 2020.

EXPOSURE The primary exposure was prenatal opioid exposure, with infants stratified by the presence or absence of a diagnosis of NOWS during the birth hospitalization.

MAIN OUTCOMES AND MEASURES Risk of infant mortality (death at age <365 days) was examined using Kaplan-Meier and log-rank tests. A series of logistic regression models was estimated to determine associations between prenatal opioid exposure and mortality, adjusting for maternal and neonatal characteristics and clustering infants at the maternal level to account for statistical dependence owing to multiple births during the study period.

RESULTS Among 1 129 032 maternal-infant dyads, 7207 had prenatal opioid exposure, including 4238 diagnosed with NOWS (mean [SD] birth weight, 2851 [624] g) and 2969 not diagnosed with NOWS (mean [SD] birth weight, 2971 [639] g). Infant mortality was 20 per 1000 live births for opioid-exposed infants not diagnosed with NOWS, 11 per 1000 live births for infants with NOWS, and 6 per 1000 live births in the reference group ($P < .001$). After adjusting for maternal and neonatal characteristics, mortality in infants with a NOWS diagnosis was not significantly different from the reference population (odds ratio, 0.82; 95% CI, 0.58-1.14). In contrast, the odds of mortality in opioid-exposed infants not diagnosed with NOWS was 72% greater than the reference population (odds ratio, 1.72; 95% CI, 1.25-2.37).

CONCLUSIONS AND RELEVANCE In this study, opioid-exposed infants appeared to be at increased risk of mortality, and the treatments and supports provided to those diagnosed with NOWS may be protective. Interventions to support opioid-exposed maternal-infant dyads are warranted, regardless of the perceived severity of neonatal opioid withdrawal.

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Supplemental content

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In 2019, an estimated 9.5 million adults in the US misused opioids, and 1.6 million had an opioid use disorder (OUD).[1] The increasing prevalence of OUD among pregnant women has resulted in a corresponding increase in the number of infants exposed to opioids in utero and, in turn, the number who experience neonatal opioid withdrawal.[2-4] Neonatal opioid withdrawal syndrome (NOWS) is diagnosed in approximately 20 000 newborns in the US each year, with neurologic and gastrointestinal symptoms presenting along a continuum of disease severity.[5,6] Hospital stays for infants with NOWS average 16 to 19 days, with national health care costs exceeding $500 million annually.[2,3,5-7] Eighty percent of these costs are borne by Medicaid.[5,6]

Recognizing this substantial burden of disease, several research and quality improvement initiatives have aimed to improve the hospital-based care of infants with NOWS and support maternal-infant dyads in their transitions home following hospital discharge.[8-11] However, 2 knowledge gaps persist. First, given our clinical focus on NOWS, we know little about birth outcomes in opioid-exposed infants who are not diagnosed with opioid withdrawal; outside of clinical trials, even knowledge about the incidence of NOWS following prenatal opioid exposure is lacking. Second, our understanding of infants' health outcomes following hospital discharge is limited, a gap highlighted in 3 systematic reviews and a joint statement by the National Institute of Child Health and Human Development, the American College of Obstetrics and Gynecology, the American Academy of Pediatrics, and the Centers for Disease Control and Prevention.[2,12-14] Infant mortality is a widely accepted indicator of population health but has been the focus of very few studies in opioid-exposed infants.[15-17]

To address these knowledge gaps, we investigated infant mortality in a large cohort of infants with prenatal opioid exposure, examining how survival differed in infants with and without a diagnosis of NOWS compared with infants without opioid exposure.

Key Points

Question What is the risk of mortality in opioid-exposed infants, and is mortality associated with neonatal opioid withdrawal syndrome?

Findings In this cohort study of more than 1 million maternal-infant dyads, the odds of mortality in infants with a history of neonatal opioid withdrawal syndrome was not significantly different from the reference population in adjusted analyses. In contrast, the odds of mortality in opioid-exposed infants not diagnosed with neonatal opioid withdrawal syndrome was 72% greater than the reference population.

Meaning The findings of this study suggest that programs and policies to support women with opioid use disorder and their infants are warranted, regardless of perceived severity of neonatal opioid withdrawal.

Methods

Population and Data Set

We conducted a population-based, retrospective cohort study using the Texas Neonatal Intensive Care Project data set developed by Texas Health and Human Services. Texas Medicaid is the primary payer for 1 of 18 births in the US each year, and more than 50% of all births in the state.[18] This data set links (1) maternal and infant professional and facility health care claims and encounters, (2) enrollment files, (3) birth certificate data, and (4) infant mortality data for all Medicaid-insured newborns born between January 1, 2010, and December 31, 2014. The data set includes maternal health care claims/encounters during pregnancy and reflects infant mortality through December 31, 2015. We excluded infants born outside of Texas (n = 1151); infants missing a facility or professional claim within 2 days of birth unless they had died within 48 hours of birth, making claim generation less likely (n = 122 883); infants with a birth weight less than 400 g (n = 932); mothers younger than 15 years or older than 44 years (n = 3452); and infants born less than 22 weeks or greater than 43 weeks of gestational age (n = 957). The institutional review boards of Texas Health and Human Services and Dartmouth College provided study approval and granted a waiver of consent for research that involves no more than minimal risk.

Primary Exposure and Maternal-Infant Characteristics

Our primary exposure was prenatal opioid exposure, with infants stratified based on the presence or absence of a NOWS diagnosis during the birth hospitalization. We defined prenatal opioid exposure as (1) a maternal *International Classification of Diseases, 9th Revision, Clinical Modification* (*ICD-9-CM*) diagnosis of OUD documented in at least 1 health care encounter during pregnancy or the birth hospitalization using a previously developed algorithm (eTable 1 in the Supplement),[19-21] (2) a *Current Procedural Terminology* code for methadone delivery during the prenatal period (eTable 1 in the Supplement), or (3) an infant diagnosis of NOWS, documented in any claims position during the birth hospitalization. NOWS was defined using the *ICD-9-CM* designation of drug withdrawal syndrome in newborn (code 779.5), which has been shown to have a high positive predictive value.[22] The reference population was all other infants meeting the above-described inclusion criteria.

From infant birth certificates we determined maternal age, maternal-reported race/ethnicity, educational attainment, marital status, parity (number of births ≥24 weeks' gestational age), smoking during pregnancy, receipt of prenatal care (reported as a binary yes/no variable as well as by number of prenatal visits), mode of delivery (vaginal or cesarean delivery) and plurality (singleton or multiple birth). From enrollment files we determined the number of months of maternal Medicaid enrollment during pregnancy. From maternal health care claims we determined the presence of co-occurring substance abuse and mental illness using established *ICD-9-CM*–based algorithms,[19,23,24] and calculated the Obstetric Comorbidity Index, a validated index that identifies and enumerates 20 maternal health conditions in a single score.[25,26] Regarding birth outcomes, we examined (1) preterm birth, defined as birth at less than 37 weeks' gestational age as recorded on the

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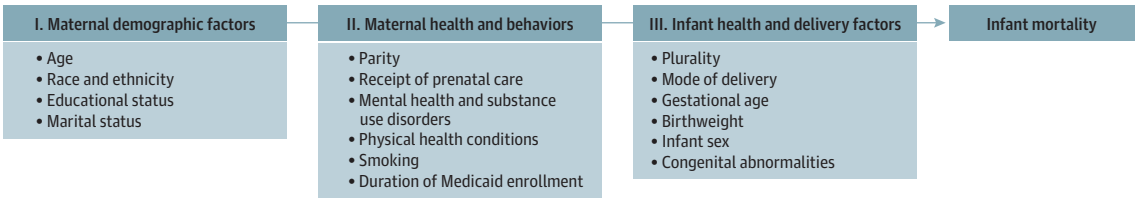
Figure 1. Factors Examined in Regression Models Given Hypothesized Associations With Infant Mortality



birth certificate; (2) small for gestational age, defined as a birth weight of less than the 10th percentile for gestational age and sex using the INTERGROWTH-21st standards[27,28]; and (3) congenital abnormalities, identified using a previously established diagnostic algorithm.[29,30] To reduce the risk of ascertainment bias given differential birth hospitalization lengths of stay in infants with and without NOWS, diagnostic codes for congenital abnormalities were required to occur on 2 separate dates and at least once following discharge from the birth hospitalization.

Outcomes

Our primary outcome was infant mortality, defined as death before age 365 days as identified on health care claims or vital records. We classified the underlying cause of death using *International Statistical Classification of Disease, 10th Revision* (*ICD-10*) cause-of-death codes, applying the Lavista Ferres et al[31] algorithm for sudden unexplained infant death, which includes code R95 (sudden infant death syndrome), code R99 (ill-defined and unknown cause), or code W75 (accidental suffocation or strangulation in bed), and the Nakamura et al[32] classification scheme for all other causes of infant mortality (excluding sudden infant death syndrome from the Nakamura et al congenital abnormalities category to report mutually exclusive causes of death). To avoid reporting cell sizes less than 11, we report causes of death due to (1) sudden unexplained infant death, (2) prematurity or congenital abnormalities and related causes, and (3) other or unknown causes (including obstetric conditions, birth asphyxia, infections, and other external causes).

Statistical Analysis

Statistical analysis was performed from May 2019 to October 2020. We first calculated individual-level summary statistics to examine differences in maternal and infant characteristics and birth outcomes across the 3 exposure groups, using χ^2 tests for categorical variables and analysis of variance for continuous variables. To examine differences in risk of infant mortality, we created Kaplan-Meier curves and tested for statistical differences in these curves using log-rank tests. Because NOWS is typically diagnosed between 2 and 5 days of life, opioid-exposed infants who died before age 5 days may have been less likely to receive this diagnosis (survivorship bias). Therefore, as a sensitivity analysis, we repeated these analyses contingent upon survival until 5 days.

To further examine the association between prenatal opioid exposure and infant mortality, we developed a series of logistic regression models that we estimated using generalized estimating equations to account for the repeated measures made among women with multiple infants born during the study period. We favored fixed time outcomes over time-to-event analyses owing to evidence of nonproportional hazards and no observable censoring of infant mortality during the follow-up period. In the first model we adjusted for maternal sociodemographic factors, in the second model we added factors related to maternal health and behaviors (excluding maternal substance use disorders, given the high rate of co-occurrence of these disorders with opioid exposure), and in the third model we added factors related to the infant and mode of delivery (**Figure 1**). All covariates were selected a priori based on established or hypothesized associations with infant mortality. All models included a variable to indicate those missing a maternal-infant link.

Three variables in our models that adjusted for maternal health and behaviors (mental health diagnoses, Obstetric Comorbidity Index, and duration of Medicaid enrollment) were missing for 185 140 infants whose claims could not be linked to their mothers (eTable 2 in the Supplement), and 17 873 maternal-infant dyads were missing data regarding receipt of prenatal care. To account for these missing data, we used multiple imputation to create 10 imputed data sets, replacing missing values with imputed values informed by maternal age at birth, race/ethnicity, educational attainment, and marital status.

We conducted several sensitivity analyses to evaluate the robustness of our findings using the multiply imputed data sets described above. First, to account for potential survivorship bias in NOWS diagnosis, we repeated our logistic regression models contingent upon survival until age 5 days. Second, we repeated these analyses using only maternal-infant dyads with linked infant and maternal claims. Third, recognizing that women with and without a documented OUD diagnosis may differ in observed and unobserved characteristics, we repeated our analysis limited to maternal-infant dyads with documented maternal OUD. Fourth, recognizing that approximately 1% of infants with NOWS develop withdrawal symptoms due to iatrogenic factors, we repeated our models excluding those with a birth weight less than 1500 g or with any of the following complex neonatal diagnoses: intraventricular hemorrhage, periventricular leukomalacia, necrotizing enterocolitis, spontaneous intestinal perforation, or bronchopulmonary dysplasia.[22,33] Fifth, given that infant mortality may be associated with the hospital of birth, we estimated a companion series of regression models including a random effect for

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birth hospital instead of using generalized estimating equations. Sixth, as an alternative approach to account for confounding that is more robust to outcome model misspecification, we calculated a propensity score for opioid-exposed infants to measure the predicted probability of receiving a NOWS diagnosis using a logistic regression model, including characteristics shown in Figure 1 as predictors. We then accounted for differences in the propensity of a NOWS diagnosis using inverse probability weighting (trimming weights at the 90th percentile), thereby avoiding the need to adjust for these factors in the infant mortality models.[34]

Analyses were conducted using SAS, version 9.3 (SAS Institute Inc) and Stata, version 16 (StataCorp LLC) software. All statistical testing was 2-sided, with $P < .05$ considered statistically significant.

Results

Following application of the above-described eligibility criteria, our sample included 1 129 032 maternal-infant dyads. Of these, 7207 had prenatal opioid exposure, including 4238 diagnosed with NOWS (3.8 per 1000 live births) (mean [SD] birth weight, 2851 [624] g) and 2969 who did not receive a NOWS diagnosis (2.6 per 1000 live births) (mean [SD] birth weight, 2971 [639] g).

In total, 62.0% of the maternal cohort was Hispanic, 21.0% was non-Hispanic White, and 14.1% was non-Hispanic Black; mean (SD) age was 25.4 (5.8) years (**Table 1**). Opioid exposure was most frequently observed in women who were non-Hispanic White (3062 [42.5%]), were unmarried (5386 [74.7%]), and had smoked during pregnancy (2452 [34.0%]). Women with prenatal opioid exposure also had considerably higher rates of mental illness (5158 [81.2%]) and substance use disorders (4952 [77.9%]) than women in the reference group (mental illness, 125 639 [13.4%]; substance use disorders, 33 965 [3.6%]). In evaluating rates of preterm delivery, small for gestational age, and congenital abnormalities, we observed a stepwise pattern in which infants diagnosed with NOWS were most likely to have experienced these birth outcomes, followed by opioid-exposed infants without NOWS, with the lowest rates observed in the reference population. In contrast, the infant mortality rate was highest in opioid-exposed infants without NOWS (20 per 1000 live births), compared with 11 per 1000 live births in infants with a history of NOWS, and 6 per 1000 live births in the reference group infants ($P < .001$) (**Table 2**).

Figure 2 illustrates differences in survival over time; opioid-exposed infants had significantly lower estimated survival probabilities than the reference population (survival during infancy in the reference group: 99.4%; 95% CI, 99.4%-99.5%; in the NOWS group: 98.9%; 95% CI, 98.5%-99.2%; in the opioid-exposed without NOWS group: 98.0%; 95% CI, 97.4%-98.5%; log-rank $P < .001$). The divergence of the curves for the 2 opioid-exposed groups at age 2 days raised concerns for potential survivorship bias in the NOWS group. In our sensitivity analysis beginning at age 5 days, the differences between the estimated survival probabilities remained and were most marked during the postneonatal period (survival during infancy in the reference group: 99.6%; 95% CI, 99.6%-99.6%; in the NOW group: 98.9%; 95% CI, 98.6%-99.2%; in the opioid-exposed without NOW group: 98.5%; 95% CI, 98.0%-98.9%; log-rank $P < .001$).

In our unadjusted analysis, infants with NOWS had a 2.01 (95% CI, 1.51-2.68) greater odds of mortality compared with the reference population, and opioid-exposed infants without NOWS had an odds of mortality 3.58 (95% CI, 2.76-4.63) times greater than the reference population (**Table 3**). Adjustment for maternal sociodemographic characteristics attenuated these findings. After adjusting for maternal health and behavioral characteristics, the odds of mortality were no longer significantly elevated in infants with a history of NOWS (odds ratio, 1.17; 95% CI, 0.88-1.56) but remained elevated in opioid-exposed infants without NOWS (odds ratio, 2.08; 95% CI, 1.57-2.76). After adding neonatal and delivery characteristics to the model, the odds of mortality in opioid-exposed infants without NOWS remained 72% higher than the reference population. Our models directly comparing mortality in opioid-exposed infants with and without NOWS illustrate that infants diagnosed with NOWS had significantly decreased odds of mortality that were independent of observed maternal sociodemographic and health characteristics, as well as birth weight, gestational age, and congenital abnormalities.

Our sensitivity analyses yielded similar results, demonstrating the robustness of these findings in analyses beginning at age 5 days (eTable 3 and eTable 4 in the Supplement), when limiting opioid-exposed maternal-infant dyads to those with a maternal diagnosis of OUD (eTable 5 in the Supplement), when excluding infants with risk factors for iatrogenic NOWS (eTable 6 in the Supplement), when modeled using mixed-effect logistic regression including a random effect for birth hospital (eTable 7 in the Supplement), and when limiting our analysis to maternal-infant dyads for whom we had a successful linkage of maternal and infant claims (eTable 8 in the Supplement).

Discussion

Opioid-exposed infants not diagnosed with NOWS represented more than 40% of the opioid-exposed cohort and appear to be at particularly increased risk of death despite having lower rates of prematurity, small for gestational age, and congenital abnormalities than infants diagnosed with NOWS. After adjusting for maternal and infant characteristics, the odds of mortality in infants diagnosed with NOWS were not greater than the reference population. In contrast, opioid-exposed infants not diagnosed with NOWS had a substantially increased odds of mortality unexplained by observable factors.

Although 3 systematic reviews indicate a substantial gap in our knowledge regarding outcomes following hospital discharge for opioid-exposed infants,[12-14] a small number of studies[15,16] have reported that infants with a history of neonatal abstinence syndrome are at increased risk of mortality. One population-based study in the US found that infants with a history of neonatal abstinence syndrome had 3.4 times the unadjusted risk of mortality relative to the reference

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Table 1. Maternal Sociodemographic, Health, and Behavior Characteristics, and Infant Birth Outcomes

Characteristic	No. (%)			*P* value
	Prenatal opioid exposure			
	With NOWS (n = 4238)	Without NOWS (n = 2969)	Reference group (n = 1 121 825)	
Maternal age, mean (SD), y	27.2 (5.3)	26.3 (5.4)	25.4 (5.8)	<.001
Maternal race/ethnicity				
Hispanic	2107 (49.7)	1083 (36.5)	696 334 (62.1)	<.001
Non-Hispanic White	1617 (38.2)	1445 (48.7)	234 474 (20.9)	
Non-Hispanic Black	460 (10.9)	394 (13.3)	157 932 (14.1)	
Non-Hispanic other race	54 (1.3)	47 (1.6)	33 085 (3.0)	
Maternal educational level				
<High school	1743 (41.1)	999 (33.7)	381 347 (34.0)	<.001
High school completed	1472 (34.7)	1111 (37.4)	398 160 (35.5)	
≥Some college	1023 (24.1)	859 (28.9)	342 318 (30.5)	
Marital status, % married	1015 (24.0)	806 (27.2)	437 989 (39.0)	<.001
Parity				
1	3339 (78.8)	2316 (78.0)	948 625 (84.6)	<.001
2	753 (17.8)	544 (18.3)	153 620 (13.7)	
≥3	146 (3.5)	109 (3.7)	19 580 (1.8)	
Smoking during pregnancy	1501 (35.4)	951 (32.0)	93 232 (8.3)	<.001
Maternal mental illness[a]				
Depressive disorders	583 (16.9)	807 (27.8)	33 183 (3.5)	<.001
Anxiety disorders	545 (15.8)	623 (21.5)	28 171 (3.0)	<.001
Bipolar and related disorders	345 (10.0)	476 (16.4)	13 528 (1.4)	<.001
Schizophrenia spectrum and other psychotic disorders	83 (2.4)	154 (5.3)	3218 (0.3)	<.001
Trauma and stress-related disorders	183 (5.3)	253 (8.7)	12 262 (1.3)	<.001
Other mental illness	271 (7.9)	441 (15.2)	18 252 (2.0)	<.001
Maternal substance use disorders[a]				
Alcohol	128 (3.7)	203 (7.0)	4048 (0.4)	<.001
Amphetamines	179 (5.2)	267 (9.2)	1989 (0.2)	<.001
Cannabis	368 (10.7)	542 (18.7)	12 197 (1.3)	<.001
Cocaine	399 (11.6)	347 (12.0)	2967 (0.3)	<.001
Other[b]	1627 (47.1)	1523 (52.5)	20 810 (2.2)	<.001
Obstetric Comorbidity Index, mean (SD)[a]	1.9 (2.0)	2.3 (2.1)	0.7 (1.3)	<.001
Receipt of prenatal care				
Yes[c]	3295 (77.8)	2679 (90.2)	1 064 157 (94.9)	<.001
No. of visits, mean (SD)[c]	8.4 (4.4)	9.3 (4.1)	10.3 (3.6)	<.001
Delivery method, % cesarean delivery	1719 (40.6)	1163 (39.2)	381 755 (34.0)	<.001
Multiple gestation	85 (2.0)	83 (2.8)	28 247 (2.5)	<.001
Medicaid enrollment, months, mean (SD)*	6.5 (2.7)	7.3 (2.2)	6.4 (3.0)	<.001
Infant sex, % female	1914 (45.2)	1428 (48.1)	548 270 (48.9)	<.001
Gestational age, mean (SD)	37.4 (2.8)	37.7 (2.8)	38.3 (2.1)	<.001
Gestational age, wk				<.001
≤36	1072 (25.3)	554 (18.7)	122 000 (10.9)	
37-41	3007 (71.0)	2315 (78.0)	950 841 (84.8)	
>41	159 (3.8)	100 (3.4)	48 984 (4.4)	
Birth weight, mean (SD), g	2851 (624)	2971 (639)	3208 (570)	<.001
Small for gestational age (%)	555 (13.4)	285 (9.8)	55 429 (5.0)	<.001
Congenital abnormalities	591 (14.0)	283 (9.5)	71 861 (6.4)	<.001
Missing maternal health care claims	784 (18.5)	68 (2.3)	185 140 (16.5)	<.001

[a] Excluded from analysis are women for whom health care claims were not available, as indicated in the final row of the table.

[b] Includes hallucinogens and other substance use disorders contained in the Healthcare Cost and Utilization Project diagnostic algorithm.[19]

[c] Missing for 17 873 (1.58%) of maternal-infant dyads.

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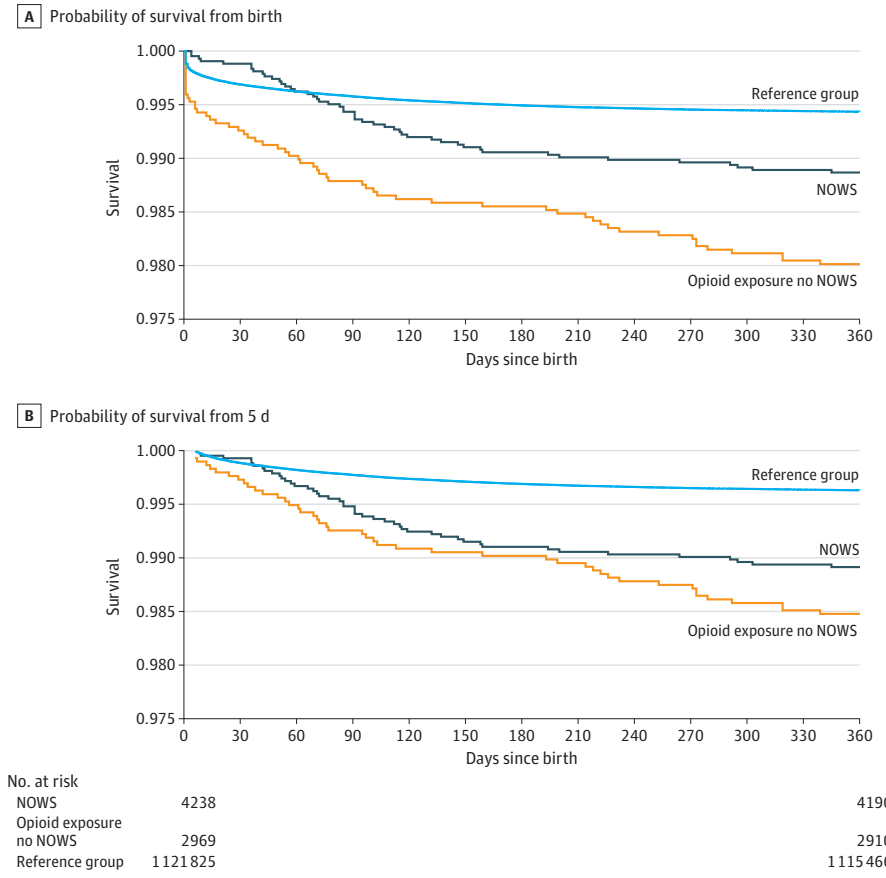
Table 2. Infant Mortality and Characteristics Among Opioid-Exposed Infants vs the Reference Group

Characteristic	Prenatal opioid exposure		Reference group (n = 1 121 825)	*P* value
	With NOWS (n = 4238)	Without NOWS (n = 2969)		
Infant mortality (deaths/1000 live births), No.	48 (11)	59 (20)	6359 (6)	<.001
Age at death, mean (SD), days	107.4 (83.5)	98.1 (107.0)	60.0 (82.2)	<.001
Mortality following discharge from birth hospitalization, No. (%)	42 (87.5)	46 (78.0)	4791 (75.3)	<.001
Cause of death, No. (%)				
Sudden unexplained infant death	13 (27.1)	15 (25.4)	1231 (19.4)	.19
Prematurity, congenital anomalies, and related conditions	13 (27.1)	22 (37.3)	2680 (42.1)	
Other/unknown	22 (45.8)	22 (37.3)	2448 (38.5)	

Abbreviation: NOWS, neonatal opioid withdrawal syndrome.

Figure 2. Probability of Survival During Infancy



Probability of survival beginning at birth (A) and beginning at age 5 days (B) in opioid-exposed infants with and without a history of neonatal opioid withdrawal syndrome (NOWS) diagnosis and in the reference population. Log-rank *P* < .001 for both analyses. Because the availability of mortality data from vital records did not depend on Medicaid enrollment, there was no observable censoring of infants at risk. Mortality among infants who moved out of the state may not be identified, but this variable was not available in the data set.

population,[15] and a Canadian study observed a mortality rate of 12.2 per 1000 live births among opioid-exposed infants—a rate almost 3 times their national average.[16] Our findings add to this literature and provide insight into causes of death. In the present cohort, approximately 1 in 4 deaths among opioid-exposed infants were due to sudden unexplained infant death, consistent with a number of studies indicating relatively higher rates of sudden unexplained infant death in substance-exposed infants.[35-38]

In contrast, previous studies have reported prenatal opioid exposure to be associated with improved survival during the neonatal period, despite higher rates of maternal and infant comorbidities.[17] This pattern of improved neonatal survival has been hypothesized to be due to accelerated lung maturation in opioid-exposed infants, a hypothesis supported by animal studies.[39,40] By stratifying the study population to examine survival separately among opioid-exposed infants with and without a NOWS diagnosis, we observed differences in survival during the first few days of life, suggesting that survivorship bias may contribute to relatively improved neonatal survival in those diagnosed with NOWS. However, even excluding deaths earlier than age 5 days, by which time most

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Table 3. Mortality in Opioid-Exposed Infants, Overall and Stratified According to NOWS Diagnosis

Variable	OR (95% CI)				
	Mortality in opioid-exposed infants vs reference population			Mortality in opioid-exposed infants with vs without NOWS	
	Total[a]	With NOWS[a]	Without NOWS[a]	Standard logistic regression models[a]	Inverse probability-weighted propensity score models
Unadjusted	2.65 (2.19-3.21)	2.01 (1.51-2.68)	3.58 (2.76-4.63)	0.56 (0.38-0.83)	NA
Adjusted for maternal sociodemographic characteristics[b]	2.43 (2.00-2.95)	1.86 (1.39-2.49)	3.24 (2.50-4.20)	0.57 (0.39-0.85)	0.56 (0.38-0.83)
Adjusted for maternal sociodemographic and health characteristics[c]	1.54 (1.26-1.87)	1.17 (0.88-1.56)	2.08 (1.57-2.76)	0.56 (0.37-0.84)	0.51 (0.34-0.76)
Adjusted for maternal sociodemographic and health characteristics, and birth outcomes[d]	1.14 (0.91-1.44)	0.82 (0.58-1.14)	1.72 (1.25-2.37)	0.47 (0.30-0.75)	0.45 (0.30-0.68)

Abbreviations: NA, not applicable; NOWS, neonatal opioid withdrawal syndrome; OR, odds ratio.

[a] Adjusted models account for clustering of infants nested in women with multiple births during the study period.

[b] Model 1: covariates included maternal age (years), maternal race/ethnicity (Hispanic, non-Hispanic White, non-Hispanic Black, non-Hispanic other race), maternal educational level (<high school, high school completed, ≥some college), marital status (binary), and indicator of maternal-infant linkage (binary).

[c] Model 2: covariates included those from model 1 as well as parity (1, 2, or ≥3), smoking during pregnancy (binary), receipt of prenatal care (binary), maternal mental illness diagnoses (depressive disorders, anxiety disorders, bipolar and related disorders, schizophrenia spectrum and other psychotic disorders, trauma and stress-related disorders, and other mental illnesses as identified on the basis of *International Classification of Diseases, 9th Revision, Clinical Modification* codes),[23,24] Obstetric Comorbidity Index (continuous),[25,26] and duration of Medicaid enrollment during pregnancy (months).

[d] Model 3 covariates included those from models 1 and 2 as well as delivery method (vaginal or cesarean delivery), multiple gestation (binary), infant sex, gestational age (continuous), birth weight (continuous), congenital abnormalities (binary).[29,30]

NOWS diagnoses are made, opioid-exposed infants without NOWS demonstrated increased odds of mortality that were independent of prematurity, low birth weight, and congenital abnormalities.

Recent initiatives have focused on improving hospital-to-home transitions for infants with NOWS, including referrals to early intervention, health services, and other community supports.[9,41] Our finding that opioid-exposed infants diagnosed with NOWS had improved survival compared with those who did not receive this diagnosis raises questions about whether enhanced provision of health and social services may have contributed to their improved survival. The postnatal period is one of substantial risk to women with OUD, including increased risks of treatment discontinuation, overdose, and postpartum depression.[42-45] We hypothesize that a NOWS diagnosis and the accompanying care for maternal-infant dyads may support maternal stability in treatment for OUD and concomitant mental health conditions and thereby decrease mortality risk. Although the present analysis cannot test these hypotheses, the increased mortality rate observed in opioid-exposed infants provides justification for enhanced health and community supports for both women and their infants, regardless of whether the infant received a NOWS diagnosis.

Strengths and Limitations

The results of this study should be interpreted in light of its strengths and limitations. Most studies of prenatal opioid exposure conducted to date have focused on predominantly non-Hispanic White populations; the racial and ethnic diversity of our sample adds to this literature. Our linkage of maternal-infant health care claims with vital records provides data for risk adjustment that are typically not available in administrative data sets, including maternal sociodemographic and health characteristics, as well as precise gestational age and birth weight. Limitations of this study include the absence of pharmacy claims data, which prevented us from examining maternal use of medications for OUD or how stability of maternal recovery is associated with infant outcomes, both of which are potential confounding variables and relevant to further understanding of infant mortality. In addition, the identification of modifiable factors potentially associated with infant mortality, such as birth hospital length of stay, postdischarge health care use, and custody status, is beyond the scope of this analysis. Regarding generalizability, Texas had a relatively low NOWS incidence during the study period compared with other US regions.[7] Relatedly, eligibility criteria for Medicaid coverage during pregnancy varies across states, which may influence the generalizability of study findings.[46] Although *ICD-9-CM* and *ICD-10* codes for neonatal drug withdrawal have been shown to have high positive predictive value for clinician-diagnosed NOWS,[22] we do not have data regarding the specific symptoms, toxicologic test results, or clinical scoring for opioid-exposed infants. As with all studies reliant upon health care claims, our findings may be affected by unmeasured confounding. However, even our unadjusted results have clinical and health policy implications.

Conclusions

The findings of our study suggest that opioid-exposed infants are at increased risk of mortality during infancy, and the constellation of treatments and supports provided to infants diagnosed with NOWS may be protective. Clinical interventions, public health programs, and health policy to support women with OUD and their infants appear to be warranted, regardless of the perceived severity of neonatal opioid withdrawal.

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Acquisition, analysis, or interpretation of data: All authors.
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Critical revision of the manuscript for important intellectual content: Schaefer, Wasserman, Moen, O'Malley, Goodman.
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REFERENCES

1. Substance Abuse and Mental Health Services Administration. Key substance use and mental health National Survey on Drug Use and Health (HHS publication No. PEP20-07-01-001, NSDUH series H-55). Published 2020. Accessed February 4, 2021. https://www.samhsa.gov/data/

2. Reddy UM, Davis JM, Ren Z, Greene MF; Opioid Use in Pregnancy, Neonatal Abstinence Syndrome, and Childhood Outcomes Workshop invited speakers. Opioid use in pregnancy, neonatal abstinence syndrome, and childhood outcomes: executive summary of a joint workshop by the Eunice Kennedy Shriver National Institute of Child Health and Human Development, American College of Obstetricians and Gynecologists, American Academy of Pediatrics, Society for Maternal-Fetal Medicine, Centers for Disease Control and Prevention, and the March of Dimes Foundation. *Obstet Gynecol*. 2017;130(1):10-28. doi:10.1097/AOG.0000000000002054

3. Jansson LM, Patrick SW. Neonatal abstinence syndrome. *Pediatr Clin North Am*. 2019;66(2):353-367. doi:10.1016/j.pcl.2018.12.006

4. Opioid use and opioid use disorder in pregnancy: Committee Opinion No. 711. American College of Obstetricians and Gynecologists. *Obstet Gynecol*. 2017;130(2):e81-e94. doi:10.1097/AOG.0000000000002235

5. Winkelman TNA, Villapiano N, Kozhimannil KB, Davis MM, Patrick SW. Incidence and costs of neonatal abstinence syndrome among infants with Medicaid: 2004-2014. *Pediatrics*. 2018;141(4):e20173520. doi:10.1542/peds.2017-3520

6. Strahan AE, Guy GP Jr, Bohm M, Frey M, Ko JY. Neonatal abstinence syndrome incidence and health care costs in the United States, 2016. *JAMA Pediatr*. 2020;174(2):200-202. doi:10.1001/jamapediatrics.2019.4791

7. Patrick SW, Davis MM, Lehmann CU, Cooper WO. Increasing incidence and geographic distribution of neonatal abstinence syndrome: United States 2009 to 2012. *J Perinatol*. 2015;35(8):650-655. doi:10.1038/jp.2015.36

8. Holmes AV, Atwood EC, Whalen B, et al. Rooming-in to treat neonatal abstinence syndrome: improved family-centered care at lower cost. *Pediatrics*. 2016;137(6):e20152929. doi:10.1542/peds.2015-2929

9. Peacock-Chambers E, Leyenaar JK, Foss S, et al. Early intervention referral and enrollment among infants with neonatal abstinence syndrome. *J Dev Behav Pediatr*. 2019;40(6):441-450. doi:10.1097/DBP.0000000000000679

10. Walsh MC, Crowley M, Wexelblatt S, et al; Ohio Perinatal Quality Collaborative. Ohio perinatal quality collaborative improves care of neonatal narcotic abstinence syndrome. *Pediatrics*. 2018;141(4):e20170900. doi:10.1542/peds.2017-0900

11. Wachman EM, Grossman M, Schiff DM, et al. Quality improvement initiative to improve inpatient outcomes for neonatal abstinence syndrome. *J Perinatol*. 2018;38(8):1114-1122. doi:10.1038/s41372-018-0109-8

12. Yeoh SL, Eastwood J, Wright IM, et al. Cognitive and motor outcomes of children with prenatal opioid exposure: a systematic review and meta-analysis. *JAMA Netw Open*. 2019;2(7):e197025. doi:10.1001/jamanetworkopen.2019.7025

13. Conradt E, Flannery T, Aschner JL, et al. Prenatal opioid exposure: neurodevelopmental consequences and future research priorities. *Pediatrics*. 2019;144(3):e20190128. doi:10.1542/peds.2019-0128

14. Maguire DJ, Taylor S, Armstrong K, et al. Long-term outcomes of infants with neonatal abstinence syndrome. *Neonatal Netw*. 2016;35(5):277-286. doi:10.1891/0730-0832.35.5.277

15. Witt CE, Rudd KE, Bhatraju P, Rivara FP, Hawes SE, Weiss NS. Neonatal abstinence syndrome and early childhood morbidity and mortality in Washington state: a retrospective cohort study. *J Perinatol*. 2017;37(10):1124-1129. doi:10.1038/jp.2017.106

16. Brogly SB, Turner S, Lajkosz K, et al. Infants born to opioid-dependent women in Ontario, 2002-2014. *J Obstet Gynaecol Can*. 2017;39(3):157-165. doi:10.1016/j.jogc.2016.11.009

17. Abdel-Latif ME, Bajuk B, Lui K, Oei J; NSW on ACT Neonatal Intensive Care Units' Study (NICUS) Group. Short-term outcomes of infants of substance-using mothers admitted to neonatal intensive care units in New South Wales and the Australian Capital Territory. *J Paediatr Child Health*. 2007;43(3):127-133. doi:10.1111/j.1440-1754.2007.01031.x

18. Texas Health and Human Services. 2010 Natality. Accessed May 14, 2020. https://www.dshs.state.tx.us/chs/vstat/vs10/nnatal.shtm

19. Heslin KC, Elixhauser A, Steiner CA. Hospitalizations involving mental and substance use disorders among adults, 2012. Statistical brief #191. Agency for Healthcare Research and Quality. Published June 2015. Accessed February 4, 2021. https://www.hcup-us.ahrq.gov/reports/statbriefs/sb191-Hospitalization-Mental-Substance-Use-Disorders-2012.jsp

20. Hadland SE, Wharam JF, Schuster MA, Zhang F, Samet JH, Larochelle MR. Trends in receipt of buprenorphine and naltrexone for opioid use disorder among adolescents and young adults, 2001-2014. *JAMA Pediatr*. 2017;171(8):747-755. doi:10.1001/jamapediatrics.2017.0745

21. Hadland SE, Bagley SM, Rodean J, et al. Receipt of timely addiction treatment and association of early medication treatment with retention in care among youths with opioid use disorder. *JAMA Pediatr*. 2018;172(11):1029-1037. doi:10.1001/jamapediatrics.2018.2143

22. Maalouf FI, Cooper WO, Stratton SM, et al. Positive predictive value of administrative data for neonatal abstinence syndrome. *Pediatrics*. 2019;143(1):1-7. doi:10.1542/peds.2017-4183

23. Children's Hospital Association. Mental health disorder codes. Updated September 10, 2019. Accessed September 26, 2019. https://www.childrenshospitals.org/Research-and-Data/Pediatric-Data-and-Trends/2019/Mental-Health-Disorder-Codes

24. Cutler GJ, Rodean J, Zima BT, et al. Trends in pediatric emergency department visits for mental health conditions and disposition by presence of a psychiatric unit. *Acad Pediatr*. 2019;19(8):948-955. doi:10.1016/j.acap.2019.05.132

25. Metcalfe A, Lix LM, Johnson JA, et al. Validation of an obstetric comorbidity index in an external population. *BJOG*. 2015;122(13):1748-1755. doi:10.1111/1471-0528.13254

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26. Bateman BT, Mhyre JM, Hernandez-Diaz S, et al. Development of a comorbidity index for use in obstetric patients. *Obstet Gynecol*. 2013;122(5):957-965. doi:10.1097/AOG.0b013e3182a603bb

27. Papageorghiou AT, Kennedy SH, Salomon LJ, et al; International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st). The INTERGROWTH-21st fetal growth standards: toward the global integration of pregnancy and pediatric care. *Am J Obstet Gynecol*. 2018;218(2S):S630-S640. doi:10.1016/j.ajog.2018.01.011

28. Global Health Network. INTERGROWTH-21st. Standards and tools. Accessed March 21, 2020. https://intergrowth21.tghn.org/standards-tools/

29. Huybrechts KF, Bröms G, Christensen LB, et al. Association between methylphenidate and amphetamine use in pregnancy and risk of congenital malformations: a cohort study from the International Pregnancy Safety Study Consortium. *JAMA Psychiatry*. 2018;75(2):167-175. doi:10.1001/jamapsychiatry.2017.3644

30. Bateman BT, Hernandez-Diaz S, Fischer MA, et al. Statins and congenital malformations: cohort study. *BMJ*. 2015;350:h1035. doi:10.1136/bmj.h1035

31. Lavista Ferres JM, Anderson TM, Johnston R, Ramirez JM, Mitchell EA. Distinct populations of sudden unexpected infant death based on age. *Pediatrics*. 2020;145(1):e20191637. doi:10.1542/peds.2019-1637

32. Nakamura AM, Dove MS, Minnal A, Damesyn M, Curtis MP. Infant mortality: development of a proposed update to the Dollfus classification of infant deaths. *Public Health Rep*. 2015;130(6):632-642. doi:10.1177/003335491513000613

33. Patrick SW, Schumacher RE, Benneyworth BD, Krans EE, McAllister JM, Davis MM. Neonatal abstinence syndrome and associated health care expenditures: United States, 2000-2009. *JAMA*. 2012;307(18):1934-1940. doi:10.1001/jama.2012.3951

34. Lee BK, Lessler J, Stuart EA. Weight trimming and propensity score weighting. *PLoS One*. 2011;6(3):e18174. doi:10.1371/journal.pone.0018174

35. Burns L, Conroy E, Mattick RP. Infant mortality among women on a methadone program during pregnancy. *Drug Alcohol Rev*. 2010;29(5):551-556. doi:10.1111/j.1465-3362.2010.00176.x

36. Hoffman HJ, Damus K, Hillman L, Krongrad E. Risk factors for SIDS. results of the National Institute of Child Health and Human Development SIDS Cooperative Epidemiological Study. *Ann N Y Acad Sci*. 1988;533:13-30. doi:10.1111/j.1749-6632.1988.tb37230.x

37. Durand DJ, Espinoza AM, Nickerson BG. Association between prenatal cocaine exposure and sudden infant death syndrome. *J Pediatr*. 1990;117(6):909-911. doi:10.1016/S0022-3476(05)80133-7

38. Kandall SR, Gaines J, Habel L, Davidson G, Jessop D. Relationship of maternal substance abuse to subsequent sudden infant death syndrome in offspring. *J Pediatr*. 1993;123(1):120-126. doi:10.1016/S0022-3476(05)81554-9

39. Oei JL. After NAS. *Semin Fetal Neonatal Med*. 2019;24(2):161-165. doi:10.1016/j.siny.2019.01.012

40. Taeusch HW Jr, Carson SH, Wang NS, Avery ME. Heroin induction of lung maturation and growth retardation in fetal rabbits. *J Pediatr*. 1973;82(5):869-875. doi:10.1016/S0022-3476(73)80086-1

41. Bordelon C, Wood T, Johnson M, Fogger S. Transition home: safe plan of care for infants with a history of neonatal abstinence syndrome. *J Addict Nurs*. 2020;31(1):60-65. doi:10.1097/JAN.0000000000000325

42. Schiff DM, Nielsen T, Terplan M, et al. Fatal and nonfatal overdose among pregnant and postpartum women in Massachusetts. *Obstet Gynecol*. 2018;132(2):466-474. doi:10.1097/AOG.0000000000002734

43. Wilder C, Lewis D, Winhusen T. Medication assisted treatment discontinuation in pregnant and postpartum women with opioid use disorder. *Drug Alcohol Depend*. 2015;149:225-231. doi:10.1016/j.drugalcdep.2015.02.012

44. Faherty LJ, Matone M, Passarella M, Lorch S. Mental health of mothers of infants with neonatal abstinence syndrome and prenatal opioid exposure. *Matern Child Health J*. 2018;22(6):841-848. doi:10.1007/s10995-018-2457-6

45. Mangla K, Hoffman MC, Trumpff C, O'Grady S, Monk C. Maternal self-harm deaths: an unrecognized and preventable outcome. *Am J Obstet Gynecol*. 2019;221(4):295-303. doi:10.1016/j.ajog.2019.02.056

46. Medicaid.gov. State overviews. Updated October 2020. Accessed August 11, 2020. https://www.medicaid.gov/state-overviews/index.html

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