ARTICLE

Association between pharmacologic treatment and hospital utilization at birth among neonatal opioid withdrawal syndrome mother-infant dyads

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OBJECTIVE: We linked mother-baby dyads to explore associations between maternal medication-assisted therapy (MAT) and infants' pharmacologic treatment on birth hospital utilization for infants with NOWS.
METHODS: We extracted singleton infant and maternal delivery discharges from PHIS hospitals with large volumes of deliveries for 2016–2019. We matched newborns with NOWS to maternal delivery discharges by hospital, day of birth, mode of delivery, and ZIP code. We examined the association between maternal MAT, infants' pharmacologic treatment, and hospital utilization at birth.
RESULTS: We included $N = 146$ mother-baby dyads from six hospitals (74% match rate). Among matched dyads, 51% received maternal MAT, 60% pharmacotherapy (37% both). Infants treated non-pharmacologically and born to mothers receiving MAT had the shortest stays vs. infants without pharmacotherapy or MAT (RR = 0.29; 95% CI: 0.25–0.35).
CONCLUSIONS: These findings underscore the importance of adequate perinatal treatment for opioid use disorder to improve outcomes for mothers and infants with opioid exposure.

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INTRODUCTION

The incidence of neonatal opioid withdrawal syndrome (NOWS), also known as neonatal abstinence syndrome (NAS), has increased dramatically over the past two decades, mirroring the opioid epidemic in the United States with large geographical variation [1–5]. With no standardized treatment protocol, there is wide variation in neonatal treatment ranging from treatment with pharmaceutical agents including opioids, phenobarbital and clonidine, to non-pharmaceutical interventions including maternal rooming-in, encouraging breastfeeding, and other non-pharmacologic bundles [6–14]. A growing literature suggests that otherwise well infants diagnosed with NOWS historically treated with pharmacotherapy can often be managed conservatively with non-pharmacologic comfort measures, resulting in reductions in length of stay, NICU utilization, and postnatal opioid exposure [6, 10, 12, 13, 15–18]. Prior studies have demonstrated large variation in choice of NOWS treatment both regionally and at the hospital-level [7, 13, 19, 20].

Maternal treatment for opioid use disorder in pregnancy varies, however the American Congress of Obstetricians and Gynecologists, Substance Abuse and Mental Health Services Administration, and the World Health Organization recommend referral for opioid-assisted methadone therapy for pregnant women [21–24]. Treatment choice (i.e., methadone vs. opioid agonists) or illicit opioid use during pregnancy is associated with differences in neonatal outcomes including severity of NOWS symptoms, length of stay, need for neonatal pharmacologic treatment, head circumference and growth [25–30]. A recent study using Massachusetts state-level data linking mothers and infants found maternal medication-assisted therapy (MAT) is associated with increased odds of infants' pharmacologic treatment and longer and higher acuity birth hospitalizations [13].

Prior studies demonstrating significant variation in infants' hospital utilization at birth and pharmacologic treatment using large geographically diverse administrative data cohorts have been unable to link infants to mothers to examine the impact of maternal MAT [3, 7, 19]. In 2019, Honein, et al. published a call to action to improve public health surveillance for mothers and infants exposed to opioids, in part by facilitating linkage between maternal and infant data in order to adequately address gaps in care throughout the perinatal period and examine both short and long term outcomes for infants [31].

Given the limitations of prior NOWS studies using large geographically diverse administrative billing datasets, we sought to link maternal and infant discharges forming mother-baby dyads for infants with NOWS using data from pediatric tertiary care birthing hospitals across the United States. Our aim for this analysis was to use the linked data to examine the effect of perinatal maternal medication-assisted therapy on infants' pharmacologic treatment, birth hospitalization length of stay, NICU use, total costs, and revisits for infants diagnosed with NOWS.

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METHODS

Study design

Using administrative data from the Pediatric Health Information System (PHIS) on inpatient discharges from tertiary care pediatric birthing hospitals, we identified infants diagnosed with NOWS and matched to maternal delivery discharges to form mother-infant dyads. Using matched dyads, we examined associations between maternal medication-assisted therapy, infants' pharmacologic treatment for NOWS, utilization during birth hospitalization, inpatient readmissions, and emergency department (ED) visits.

Patient selection criteria and matching

To link maternal and infant discharges forming mother-baby dyads for infants with NOWS, we applied a recently described, unvalidated deterministic matching algorithm [32].

We identified singleton infants diagnosed with NOWS born at PHIS hospitals and discharged from January 1, 2016 to December 31, 2019 along with maternal delivery discharges for singleton deliveries during the same time period. We restricted the sample to singleton births as multiples would have been excluded during the matching process. As a tertiary care children's hospital database, only a subset of PHIS hospitals has large volumes of routine deliveries and submit their maternity discharge data for inclusion in PHIS. We restricted our analysis to PHIS hospitals with any NOWS birth discharges and those submitting large volumes of maternity discharges (>5000) to PHIS during the study time period. Six PHIS hospitals were included representing regions across the United States including West, Midwest, South and East.

Infants with NOWS were identified by diagnosis code (International Classification of Diseases 10th Revision code P96.1: neonatal withdrawal symptoms from maternal use of drugs of addiction). Maternal singleton delivery discharges were identified by delivery ICD-10 procedure codes with a corresponding ICD-10 diagnosis code specifying single liveborn infant as the outcome of birth (Z37.0: Single live birth). We identified mode of delivery by ICD-10 procedure codes for maternal discharges and ICD-10 diagnosis codes for infants (Z38.00: single liveborn infant, delivered vaginally; Z38.01: single liveborn infant, delivered by cesarean). Date of delivery was extracted from the date of delivery procedure for maternal discharges and date of birth for infants. Infants were matched to maternal discharges within hospitals by date of birth/delivery, mode of delivery, and ZIP code. Prior to matching, maternal and infant discharges were de-duplicated by hospital, day of delivery/birth, mode of delivery and ZIP code to ensure the infants were matched to the correct maternal discharge. Additional details on the matching algorithm including diagnosis and procedure codes to identify infant and maternal discharges are described in Hahn, et al. [32].

After matching, we excluded infants with mechanical ventilation, extracorporeal membrane oxygenation (ECMO), congenital or genetic abnormalities, and any surgical procedure during the birth admission using flags available in PHIS based on ICD-10 diagnosis and procedure codes. We excluded infants with extreme prematurity (<32 weeks) or extremely low birthweight (<1500 grams) by diagnosis codes or gestational age and birthweight, if recorded. Similar to prior studies of infants with NOWS, these exclusions were chosen to limit other comorbidities associated with higher resource utilization during birth admission and increased readmission risk [3, 7, 19, 33].

Measures

Maternal medication-assisted therapy (MAT) was determined by pharmacy billing codes for methadone, buprenorphine or other opioid agonists during delivery hospitalization. Our definition for infants' pharmacologic treatment was based on the 2020 AAP guidelines and determined by pharmacy billing codes for opioids, phenobarbital and/or clonidine during the birth hospitalization [14]. The combination of maternal MAT and infants' pharmacologic treatment was used to construct a 4-category variable identifying dyads: infant treated with pharmacologic treatment whose mother received MAT; infant with pharmacologic treatment whose mother did not receive MAT; infant without pharmacologic treatment whose mother received MAT; and infant without pharmacologic treatment whose mother did not receive MAT.

Measures of resource utilization collected during birth hospitalization included length of stay (LOS), neonatal intensive care unit (NICU) use and total costs for infants. Length of stay and costs were also collected for maternal discharges. Costs are provided by PHIS and are derived from charges converted to costs according to hospital-specific ratios, adjusted for geographic variation using Centers for Medicare and Medicaid Services wage and price index and standardized to eliminate between and within-hospital cost variation for individual items or services and has been described in detail elsewhere [34, 35]. We also examined inpatient readmissions within 30-, 60- and 90-days of discharge and emergency department (ED) visits within 7- and 30-days of discharge. Readmissions and revisits during the same time periods were also examined for mothers.

Additional sociodemographic predictors included maternal age, maternal and infant race and ethnicity, maternal and infant insurance payor, and median household income based on ZIP code. Given low frequencies for racial and ethnic groups other than White, we combined Black/African American, Hispanic/Latinx, and another race and ethnicity in adjusted analyses. Income was divided into categories based on tertiles of income in the U.S [36]. Maternal diagnosis of opioid use disorder (OUD) was identified by diagnosis code (ICD-10 F11: opioid related disorders). Diagnosis codes were also used to identify other substance use disorders (SUD) including alcohol, cannabis, cocaine, other stimulants, and hallucinogens (ICD-10 F10; F12-F16; F18-F19); polysubstance use disorder was defined as a diagnosis for OUD in combination with another SUD. Maternal nicotine dependence was identified by diagnosis code (ICD-10 F17).

Statistical analysis

We report mean (standard deviation) or median (interquartile range) for continuous variables and frequency (percent) for categorical variables. We compared mother-baby dyads with infants on pharmacological treatment to those not on pharmacological treatment and mothers receiving MAT to those not receiving MAT on infant and maternal sociodemographic factors, clinical characteristics, hospital utilization, readmissions, and revisits. Chi-square or Fisher's exact test was used to assess for differences in categorical variables; *T*-test or Wilcoxon signed-rank test was used for continuous variables. We used logistic regression to examine the association between maternal MAT and infants' pharmacologic treatment. We examined the association between the combination of maternal MAT and infants' pharmacologic treatment with NICU admission during birth hospitalization, birth LOS, and birth hospitalization costs using Poisson regression, logistic regression and gamma regression analyses, respectively. We examined the interaction between maternal MAT and infants' pharmacologic treatment, NICU use, birth LOS and costs. Regression models adjusted for infants' race and ethnicity, sex, insurance payor, and birthweight. We report odds ratios (OR) for logistic regression predicting NICU admission while risk ratios (RR) are reported for Poisson and gamma regression models predicting LOS and costs. All analyses were performed using SAS version 9.4 (SAS Institute, Inc.; Cary, NC) and $P < 0.05$ were considered statistically significant.

RESULTS

A total of 234 singleton birth discharges for infants diagnosed with NOWS and 96 181 maternal singleton delivery discharges were extracted from six PHIS hospitals from 2016–2019, including at least one hospital in the West, Midwest, South, and East. Following de-duplication and matching, we identified a matching maternal discharge for $N = 174$ infants with an overall match rate of 74%, ranging from 64% to 90% by hospital. After additional exclusions of infants with extreme prematurity or low birthweight, respiratory support, congenital abnormalities or surgical procedures during admission, $N = 146$ matched mother-infant dyads were included in the final analysis (ranging from 11–64 by hospital).

The dyads included 74 (51%) mothers that received MAT during delivery hospitalization and 88 (60%) infants that received pharmacotherapy during birth hospitalization. Among mothers on MAT, 91% received methadone and 9% buprenorphine. Virtually all infants treated pharmacologically received opioids (99%) and 10% also received a second-line agent phenobarbital and/or clonidine. Only one infant received phenobarbital alone. Overall, 54 (37%) infants with NOWS were treated pharmacologically and born to mothers receiving MAT; 34 (23%) with pharmacotherapy, no maternal MAT; 20 (14%) no pharmacotherapy, with maternal MAT; and 38 (26%) no pharmacotherapy, no maternal MAT.

Table 1. Maternal and infant characteristics by medication assisted therapy (MAT) among mother-baby dyads for infants with NOWS from 6 PHIS hospitals ($N = 146$).

	***n* (%)**			***p*-value**
	Overall ($N = 146$)	**MAT ($n = 74$)**	**No MAT ($n = 72$)**	
Maternal sociodemographic characteristics				
Age (years), mean (SD)	29.5 (4.9)	29 (4.2)	30 (5.4)	0.23
Race and ethnicity				
White, non-Hispanic	88 (60%)	51 (69%)	37 (51%)	0.001
Black/African American, non-Hispanic	15 (10%)	3 (4%)	12 (17%)	
Hispanic/Latinx	18 (12%)	3 (4%)	15 (21%)	
Another, non-Hispanic	3 (2%)	2 (3%)	1 (1%)	
Unknown	22 (15%)	15 (20%)	7 (10%)	
Insurance payor				
Commercial/Private	25 (17%)	10 (14%)	15 (21%)	0.15
Public	119 (82%)	64 (86%)	55 (76%)	
Other	2 (1%)	0 (0%)	2 (3%)	
Median household income				
<$40,000	61 (42%)	27 (36%)	34 (47%)	0.11
$40,000–$89 999	75 (51%)	42 (57%)	33 (46%)	
$90,000 or more	7 (5%)	5 (7%)	2 (3%)	
Unknown	3 (2%)	0 (0%)	3 (4%)	
Maternal clinical characteristics				
Mode of delivery				
Vaginal	83 (57%)	44 (59%)	39 (54%)	0.52
Cesarean	63 (43%)	30 (41%)	33 (46%)	
Diagnosis for opioid use disorder	89 (61%)	65 (88%)	24 (33%)	<0.001
Polysubstance use disorder	24 (16%)	15 (20%)	9 (13%)	0.21
Nicotine dependence	51 (35%)	32 (43%)	19 (26%)	0.03
Maternal hospital utilization				
Length of stay (days), median (IQR)	3 (2)	3 (2)	3 (2)	0.78
Total cost ($), median (IQR)	10,588 (5190)	11,044 (5033)	10,354 (4777)	0.26
Infant clinical characteristics				
Gestational age (weeks), mean (SD) ($N = 112$)	38.0 (1.8)	38.3 (1.8)	37.8 (1.8)	0.19
Preterm (<37 weeks) ($N = 112$)	20 (18%)	9 (17%)	11 (19%)	0.75
Birthweight (grams), mean (SD)	2964 (509)	2957 (458)	2971 (560)	0.87
Birthweight category				
Low (1501–2500 grams)	26 (18%)	10 (14%)	16 (22%)	0.17
Normal (>2500 grams)	120 (82%)	64 (86%)	56 (78%)	
Pharmacologic treatment (PT)	88 (60%)	54 (73%)	34 (47%)	0.002
Opioids (among those on PT)	87 (99%)	54 (100%)	33 (97%)	0.39
Phenobarbital (among those on PT)	5 (6%)	4 (7%)	1 (3%)	0.64
Clonidine (among those on PT)	7 (8%)	6 (11%)	1 (3%)	0.24
Infant hospital utilization				
Length of stay (days), median (IQR)	14 (18)	19 (19)	9 (13)	<0.001
Length of stay category				
4 days or less	8 (5%)	1 (1%)	7 (10%)	0.006
5–9 days	49 (34%)	19 (26%)	30 (41%)	
10–14 days	20 (14%)	10 (14%)	10 (14%)	
15 or more days	69 (47%)	44 (59%)	25 (35%)	
NICU admission	108 (74%)	60 (81%)	48 (67%)	0.05
Total cost ($), median (IQR)	34,327 (46 165)	47,042 (44,745)	20,998 (33,616)	<0.001

Table 1. continued

	n (%)			*p*-value
	Overall (*N* = 146)	**MAT (*n* = 74)**	**No MAT (*n* = 72)**	
Infant revisits				
Inpatient readmissions				
Within 30-days	6 (4%)	4 (5%)	2 (3%)	0.68
Within 60-days	7 (5%)	4 (5%)	3 (4%)	0.99
Within 90-days	8 (5%)	5 (7%)	3 (4%)	0.72
Emergency department visits				
Within 7-days	4 (3%)	1 (1%)	3 (4%)	0.36
Within 30-days	6 (4%)	3 (4%)	3 (4%)	0.99
Maternal revisits				
Inpatient readmissions				
Within 30-days	4 (3%)	1 (1%)	3 (4%)	0.36
Within 60-days	5 (3%)	2 (3%)	3 (4%)	0.68
Within 90-days	5 (3%)	2 (3%)	3 (4%)	0.68
Emergency department visits				
Within 7-days	5 (3%)	3 (4%)	2 (3%)	0.99
Within 30-days	9 (6%)	6 (8%)	3 (4%)	0.49

SD standard deviation, *IQR* interquartile range.

Sociodemographic and clinical characteristics for dyads by maternal MAT are presented in Table 1. There were no significant differences by MAT in maternal sociodemographic factors, mode of delivery, maternal hospital utilization, gestational age, or birthweight. Mothers who were Black/African American or Hispanic/Latinx were less likely to receive MAT relative to White mothers; 57% of White mothers received MAT compared to only 20% among Black/African American mothers and 17% Hispanic/Latinx mothers ($p = 0.001$). Overall 61% of mothers had a diagnosis of OUD, and those mothers were more likely to receive MAT ($p < 0.001$). Infants born to mothers receiving MAT were more likely to be treated pharmacologically (73% vs. 47%; $p = 0.002$). Median LOS was over twice as long for infants born to mothers receiving MAT (19 days vs. 9 days; $p < 0.001$) with 59% staying 15 days or longer compared to 35% among those born to mothers without MAT ($p = 0.006$). Infants whose mother was receiving MAT were also slightly more likely to be admitted to the NICU ($p = 0.05$). Median total costs were over twice as high for infants born to mothers receiving MAT ($47,042 vs. $20,998; $p < 0.001$). Inpatient readmissions for both infants and mothers were infrequent and did not differ significantly by maternal MAT.

Infants' sociodemographic and clinical factors, maternal factors, and hospital utilization by infants' pharmacologic treatment are reported in Table 2. There was no association between pharmacologic treatment and sociodemographic factors, mode of delivery, or maternal age. Pharmacologic treatment was associated with slightly older gestational age ($p = 0.02$) but there was no significant difference in birthweight ($p = 0.09$). Infants born to mothers with a diagnosis for OUD or polysubstance use disorder were more likely to be treated pharmacologically (both $p = 0.01$). Infants born to mothers receiving buprenorphine were less likely to receive pharmacologic treatment compared to those whose mother received methadone for MAT (33% vs. 83%; $p < 0.001$). Infants' pharmacologic treatment was associated with higher utilization including longer birth LOS (median 20 days vs. 6 days; $p < 0.001$), higher NICU utilization (83% vs. 60%; $p = 0.002$) and higher costs (median $51 911 vs. $10 467; $p < 0.001$) compared to infants treated without pharmacotherapy. Inpatient readmissions and ED revisits were relatively infrequent with no significant difference by pharmacologic treatment.

In unadjusted analysis, infants born to mothers receiving MAT had higher odds of receiving pharmacologic treatment (OR = 3.02, 95% CI: 1.51–6.02). Adjusting for sociodemographic factors and birthweight, maternal MAT was associated with 2.53 times the odds of infant pharmacologic treatment (95% CI: 1.23–5.15; Fig. 1). Infants' race and ethnicity, sex, insurance payor, median household income and birthweight were not associated with infant pharmacologic treatment.

Unadjusted associations between the combination of maternal MAT and infants' pharmacologic treatment and infant hospital utilization are reported in Table 3. NICU utilization, infants' length of stay and total costs differed significantly by the combination of maternal MAT and infants' pharmacologic treatment ($p = 0.01$; $p < 0.001$; and $p < 0.001$, respectively). In unadjusted models, the interaction between maternal MAT and infants' pharmacologic treatment was significant for LOS and costs but not for NICU use ($p < 0.001$, $p = 0.02$, and $p = 0.52$, respectively) therefore subsequent models included the four-category combination between maternal MAT and infants' pharmacologic treatment.

Adjusting for infants' sociodemographic factors and birthweight, utilization differed significantly by the combination of infants' pharmacologic therapy and maternal MAT (Fig. 2). Infants treated with pharmacotherapy and born to mothers receiving MAT were more likely to be admitted to the NICU, had longer stays, and higher costs compared to those without MAT or pharmacotherapy ($p = 0.02$, Fig. 2A; $p < 0.001$, Fig. 2B; and $p < 0.001$, Fig. 2C, respectively). After adjusting for sociodemographic factors and birthweight, infants born to mothers receiving MAT but who were not treated pharmacologically had the shortest LOS vs. infants without pharmacotherapy and no maternal MAT (RR = 0.29; 95% CI: 0.25–0.35; Fig. 2B). Similarly, costs were lowest in infants treated without pharmacotherapy born to mothers receiving MAT (RR = 0.20; 95% CI: 0.14–0.27; Fig. 2C). There was no association between sociodemographic factors or birthweight and NICU use (Fig. 2A) while Black/African American, Hispanic/Latinx or another race infants, and those with public insurance were associated with longer LOS (Fig. 2B), and public insurance and lower birthweight were associated with higher costs (Fig. 2C).

Table 2. Sociodemographic factors, clinical characteristics, maternal characteristics and hospital utilization among infants with NOWS from 6 PHIS hospitals ($N = 146$).

	***n* (%)**			***p*-value**
	Overall ($N = 146$)	**Pharmacologic treatment ($n = 88$)**	**No pharmacologic treatment ($n = 58$)**	
Sociodemographic characteristics				
Race and ethnicity				
White, non-Hispanic	78 (53%)	48 (55%)	30 (51%)	0.18
Black/African American, non-Hispanic	16 (11%)	7 (8%)	9 (16%)	
Hispanic/Latinx	21 (14%)	12 (13%)	9 (16%)	
Another, non-Hispanic	11 (8%)	5 (6%)	6 (10%)	
Unknown	20 (14%)	16 (18%)	4 (7%)	
Male sex	59 (40%)	33 (38%)	26 (45%)	0.38
Insurance payor				
Commercial/Private	20 (14%)	10 (11%)	10 (17%)	0.48
Public	124 (85%)	77 (88%)	47 (81%)	
Other	2 (1%)	1 (1%)	1 (2%)	
Median household income				
<$40,000	61 (42%)	42 (48%)	19 (33%)	0.18
$40,000–$89 999	75 (51%)	40 (45%)	35 (60%)	
$90,000 or more	7 (5%)	5 (6%)	2 (3%)	
Unknown	3 (2%)	1 (1%)	2 (3%)	
Maternal characteristics				
Maternal age (years), *mean (SD)*	29.5 (4.9)	29.5 (4.7)	29.5 (5.2)	0.92
Diagnosis for opioid use disorder	89 (61%)	61 (69%)	28 (48%)	0.01
Polysubstance use disorder	24 (16%)	20 (23%)	4 (7%)	0.01
Nicotine dependence	51 (35%)	32 (36%)	19 (33%)	0.65
Medication-assisted therapy (MAT)	74 (51%)	54 (61%)	20 (34%)	.002
Methadone (among those on MAT)	59 (80%)	49 (91%)	10 (50%)	<.001
Buprenorphine (among those on MAT)	15 (20%)	5 (9%)	10 (50%)	<.001
Clinical Characteristics at Birth				
Mode of delivery				
Vaginal	83 (57%)	50 (57)	33 (57)	0.99
Cesarean	63 (43%)	38 (43)	25 (43)	
Gestational age (weeks), mean (SD) ($N = 112$)	38.0 (1.8)	38.4 (1.6)	37.5 (2.0)	0.02
Preterm (<37 weeks) ($N = 112$)	20 (18%)	9 (13%)	11 (27%)	0.06
Birthweight (grams), mean (SD)	2964 (509)	3021 (524)	2877 (478)	0.09
Birthweight category				
1501–2 500 grams	26 (18%)	13 (15)	13 (22)	0.24
>2500 grams	120 (82%)	75 (85)	45 (78)	
Hospital utilization				
Length of stay (days), median (IQR)	14 (18)	20 (13)	6 (3)	<0.001
Length of stay category				
4 days or less	8 (5%)	1 (1%)	7 (12%)	<0.001
5–9 days	49 (34%)	10 (11%)	39 (67%)	
10–14 days	20 (14%)	13 (15%)	7 (12%)	
15 or more days	69 (47%)	64 (73%)	5 (9%)	
NICU admission	108 (74%)	73 (83%)	35 (60%)	0.002
Total standardized cost ($), median (IQR)	34,327 (46,165)	51,911 (30,022)	10,467 (12,052)	<0.001

Table 2. continued

	n (%)			*p*-value
	Overall (*N* = 146)	**Pharmacologic treatment (*n* = 88)**	**No pharmacologic treatment (*n* = 58)**	
Revisits				
Inpatient readmissions				
Within 30-days	6 (4%)	3 (3%)	3 (5%)	0.68
Within 60-days	7 (5%)	4 (5%)	3 (5%)	0.99
Within 90-days	8 (5%)	4 (5%)	4 (7%)	0.71
Emergency department visits				
Within 7-days	4 (3%)	1 (1%)	3 (5%)	0.30
Within 30-days	6 (4%)	3 (3%)	3 (5%)	0.68

SD standard deviation, *IQR* interquartile range.

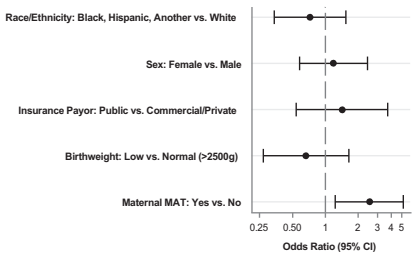

Fig. 1 Adjusted associations between maternal MAT and infants' pharmacologic treatment. Among $N = 146$ infants diagnosed with NOWS from 6 PHIS hospitals. Odds ratios (OR) and 95% confidence intervals (CI) from logistic regression.

DISCUSSION

Using data from six pediatric tertiary care birthing hospitals in the United States, we linked infant births and maternal discharges forming mother-baby dyads to explore the impact of maternal medication-assisted therapy on neonatal treatment and utilization during birth hospitalization for infants with NOWS. Overall, we found a matching maternal delivery discharge for nearly three-quarters of NOWS births and within-hospital match rates as high as 90%, similar to previously reported match rates using this methodology in PHIS as well as other studies using both deterministic and probabilistic methods to link mother-baby dyads in administrative data [32, 37–40]. Results from the matched dyads indicate maternal MAT is strongly associated with infants' pharmacologic treatment and a moderator of the relationship between infants' pharmacologic treatment and hospital utilization at birth.

We found maternal MAT was the strongest predictor of infants' pharmacologic treatment which is in turn associated with longer stays and higher costs. The association between maternal MAT and infants' need for pharmacotherapy has been demonstrated previously and has important implications for MAT in pregnancy that warrant further study [13]. Despite the potential for more severe NOWS symptoms, the benefits far outweigh the risks and MAT is recommended for the health and safety of both mother and baby although studies of long-term outcomes are limited [13, 21–24]. In our cohort, just over half of mothers received MAT at the time of delivery which indicates a major opportunity for improving access to MAT during pregnancy. As a period of high contact with the healthcare system, pregnancy represents a unique opportunity for opioid use disorder treatment initiation and should be leveraged to improve access rather than reinforcing stigma for these mothers, thereby improving outcomes for both mothers and infants [23].

We found that infants born to mothers who did not receive MAT had shorter stays, lower costs, and were less likely to be admitted to the NICU. Mothers without MAT may be more likely to have perinatal exposure to illicit opioids (e.g., heroin) which are metabolized quicker than methadone and have been associated with less severe NOWS symptoms, and therefore less likely to require pharmacologic treatment [13]. However, we were unable to ascertain maternal exposure to illicit or non-prescribed opioids in order to explore this further in this cohort.

Interestingly, in our cohort 61% of mothers had a diagnosis of OUD and of those 73% were receiving MAT while a small percentage *without an OUD diagnosis* received MAT (16%). There are a number of possibilities that may explain infants with NOWS diagnosis born to mothers without OUD diagnosis including: under-coding of maternal OUD, therapeutic exposure to opioids during pregnancy for other conditions (e.g., chronic pain management, post-surgical analgesia), and maternal exposure to drugs other than opioids. Prior studies have shown that maternal OUD is frequently under-coded for a variety of reasons and may be related to hospital practice, stigma, and bias [41]. A recent study using data from four states indicated that 20% more newborns receive opioid-related diagnoses than mothers, with pronounced discordance by race and ethnicity [41]. Therapeutic exposure to opioids in pregnancy is not recommended although relatively common with prevalence of prescribed opioid exposure during pregnancy estimated at 15% in the United States [1, 21–24], which may explain at least some proportion of the mothers in our cohort without an OUD diagnosis. While it is possible that infants born to mothers without an OUD diagnosis *or* MAT were withdrawing from another substance, this is unlikely to explain the discrepancy. The diagnosis code used to identify NOWS (ICD-10 P96.1) is specific to maternal exposure to drugs of addiction rather than iatrogenic withdrawal (captured by ICD-10 P96.2), though non-specific to type of drug. However, prior studies have shown high sensitivity and positive predictive value between infants' NOWS diagnosis code and maternal opioid exposure specifically, with withdrawal from other substances rarely resulting in a NOWS diagnosis [42, 43]. Additionally, numerous studies using administrative data have relied on this code to identify NOWS in the absence of other clinical information to characterize opioid exposure [7, 19, 33]. Given this and our exclusion of infants likely to have post-natal therapeutic exposure to opioids (e.g., mechanically ventilated or undergoing surgical procedures during admission), infants' pharmacologic treatment with opioids is an additional proxy for maternal opioid exposure as treatment with

Table 3. Unadjusted associations between maternal MAT, infants' pharmacologic treatment and infants' birth hospitalization utilization among infants with NOWS from 6 PHIS hospitals ($N = 146$).

	Maternal MAT		No Maternal MAT		*p*-value
	Infant		Infant		
	Pharmacologic Treatment ($n = 54$)	No Pharmacologic Treatment ($n = 20$)	Pharmacologic Treatment ($n = 34$)	No Pharmacologic Treatment ($n = 38$)	
NICU admission, *n* (%)[a]	47 (87%)	13 (65%)	26 (76%)	22 (58%)	0.01
Length of stay (days), median (IQR)[b]	23.5 (14.0)	6.0 (3.5)	16.5 (12.0)	6.0 (3.0)	<0.001
Total cost ($), median (IQR)[c]	57,144 (32,925)	11,109 (10,742)	41,489 (26,747)	9553 (12,092)	<0.001

MAT medication-assisted therapy, *IQR* interquartile range.
[a]*p*-value from chi-square test.
[b]*p*-value from unadjusted Poisson regression.
[c]*p*-value from unadjusted gamma regression.

opioids is unlikely in the absence of in-utero opioid exposure. We performed a sensitivity analysis excluding infants whose opioid exposure was uncertain ($n = 28$ without maternal MAT, OUD diagnosis or infants' pharmacologic treatment) and results did not change substantially.

Though costs and LOS were highest among infants treated pharmacologically whose mothers received MAT, those born to mothers with MAT and treated without pharmacotherapy had shorter lengths of stay, lower costs, and lower NICU admission rates after adjusting for sociodemographic factors and birthweight. These findings complement the existing literature indicating that adequate perinatal treatment for opioid use disorder in the absence of infants' pharmacotherapy is associated with reduced hospital utilization and improved birth outcomes [26–28]. We found just over a quarter of infants whose mother received MAT were treated *without* the use of pharmacotherapy; three-quarters of whom were from a single hospital demonstrating persistent practice variation consistent with the geographic and hospital variation reported previously [7, 19, 20]. Emerging evidence indicates infants with NOWS who are treated conservatively and without pharmacotherapy have similar or better outcomes to their pharmacologically-treated counterparts, along with additional benefits including decreased hospital utilization and eliminating post-natal opioid exposure with no increase in readmissions [6, 9, 10, 12, 15–18]. Shorter stays and less NICU use for these infants would translate to direct benefits to the healthcare system in terms of costs while facilitating increased maternal presence thereby improving maternal-infant bonding in the critical neonatal period as long stays, especially in the NICU, have been shown to disrupt bonding, parental confidence and breastfeeding [6, 8–10, 12, 15, 16, 18].

Similar to other studies of maternal opioid use disorder and infants with NOWS, there were few Black/African American or Hispanic/Latinx mothers in our cohort [7, 19, 44, 45]. However, we found Black/African American and Hispanic/Latinx mothers were much less likely to receive MAT compared to White mothers while there was no disparity evident in infants' pharmacologic treatment. To investigate this disparity further, we performed an exploratory analysis examining the association between race and ethnicity and maternal MAT in the sample of all maternal delivery discharges (unmatched) for mothers with an OUD diagnosis at our six included PHIS hospitals. Among 277 maternal delivery discharges with OUD, 46% received MAT. Among White mothers, 50% received MAT compared to 24% among Black/African American mothers and 39% among Hispanic/Latinx mothers ($p = 0.001$). This analysis is limited as race and ethnicity collected for administrative billing purposes may not accurately or completely reflect self-identified race, but is an important first step in examining disparities using available data. Though PHIS is not the optimal data source to examine this question as it is primarily a database for pediatric encounters, these findings provide a glimpse into the persistent and pervasive racial and ethnic disparity in access to perinatal opioid treatment demonstrated in prior studies [44, 45], and paralleling disparities in access to other healthcare services including opioid and substance abuse treatment throughout the lifecourse [46–48].

Limitations

This study has a number of limitations. First, this analysis relied on administrative billing data which may be incomplete with regard to comorbidities or other clinical factors, and/or sociodemographic factors, race and ethnicity in particular. Infants with NOWS were identified by birth discharge diagnosis codes which may under- or over-estimate incidence. Although there is no alternative to identify NOWS in the context of administrative data, diagnosis codes have shown high positive predictive value compared to gold-standard clinical diagnosis of NOWS and as noted above, have been applied in a number of prior NOWS

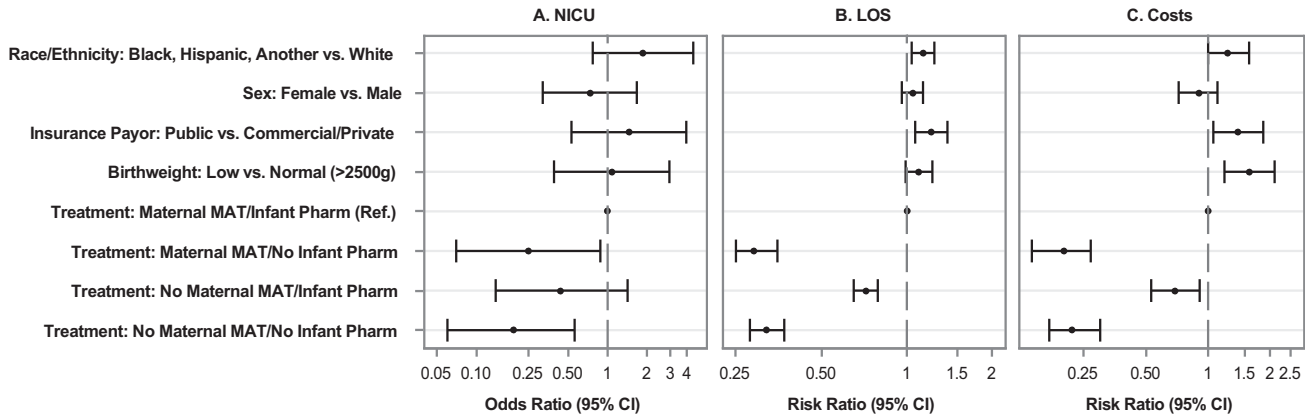

Fig. 2 Adjusted associations between maternal MAT and infants' pharmacologic treatment on utilization during birth hospitalization. Among $N = 146$ infants diagnosed with NOWS at 6 PHIS hospitals. Adjusted odds ratios (OR) and 95% confidence intervals (CI) from logistic regression for (**A**) NICU use. Adjusted risk ratios (RR) and 95% CI from Poisson regression for (**B**) length of stay (LOS). Adjusted RR and 95% CI from gamma regression for (**C**) total costs.

studies using PHIS data [7, 19, 33, 43, 49]. The sample of $N = 146$ infants with NOWS included in our analysis was relatively small resulting in wide confidence intervals, particularly for the less common combinations of maternal MAT and infants' pharmacotherapy. However, we found a significant difference in NICU use, LOS, and costs by maternal MAT and infants' pharmacologic treatment despite the limited sample size. Future studies using large data sources with matched mother-baby dyads are needed to increase precision of our estimates.

The limitations of the matching methodology have been described in detail previously [32]. Importantly, our sample of hospitals was limited to a subset of PHIS hospitals with large volumes of routine deliveries who were also submitting maternal delivery data for inclusion in PHIS. While all regions in the United States except the Northeast were represented, this sample of hospitals is not representative of all PHIS hospitals and may not be generalizable to other delivery hospitals e.g., non-PHIS tertiary care adult hospitals or community hospitals. As described previously and given the limitations of PHIS data [32], we were unable to validate matched dyads, however the de-duplication process should minimize the likelihood of an incorrect match. Despite the inability to validate matched dyads, the rates of maternal MAT and association with infants' pharmacologic treatment are similar to recent estimates using linked state-level data [13]. This, in addition to the innate characteristics of the deterministic matching algorithm used, provides evidence for the high likelihood of correctly matched dyads.

In addition, readmissions and ED revisits are underestimated as only those to the same PHIS hospital are included; revisits to other tertiary care or community hospitals are not captured in PHIS. It is difficult to estimate the likelihood of returning to the PHIS birth hospital versus a non-PHIS hospital as that may depend upon geographical factors including urbanicity, regionalization of care, and distance from the PHIS hospital as well as severity of illness, reason for revisit, hospital census, and insurance status. However, readmission and ED revisit estimates for both infants and mothers in our cohort are similar to previously reported estimates using other data sources [33, 50–53]. Our definition for maternal MAT was limited to in-hospital therapy received during the delivery discharge and we were unable to determine dose which has been associated with severity of NOWS symptoms [54]. There is no information available in PHIS to determine treatment or type of MAT received during the course of pregnancy prior to the hospital encounter for delivery. Maternal exposure to illicit or non-prescribed opioids at the time of or prior to delivery is also not available in PHIS. Mothers who were not receiving MAT at the time of delivery may be more likely to have exposure to illicit drugs. Finally, though we examined pharmacologic treatment for NOWS using pharmacy billing codes, we were unable to explore the impact of non-pharmacologic treatments like breastfeeding, rooming-in, and promoting skin-to-skin as these are not coded in administrative data.

Despite these limitations, PHIS allows for timely analysis of hospital utilization in addition to robust estimates of cost. PHIS clinical data releases are lagged by mere months in contrast to state-level data which are often difficult to link and may not be available for years [31, 53]. These findings add to the body of literature examining hospital utilization for infants with NOWS specifically using PHIS data and allow for incorporating maternal characteristics at delivery.

CONCLUSIONS

We found maternal medication-assisted therapy is the strongest predictor of infants with NOWS receiving pharmacologic treatment. Infants treated without the use of pharmacotherapy whose mothers received MAT had substantially shorter birth lengths of stay at lower cost, with no increase in readmissions. These findings underscore the importance of adequate perinatal treatment for opioid use disorder to improve outcomes and reduce hospital utilization for mothers and infants with opioid exposure.

DATA AVAILABILITY

The datasets analyzed in this study are not publicly available as they were acquired through the Pediatric Health Information System which prohibits data sharing outside of its member hospitals.

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AUTHOR CONTRIBUTIONS

CEM conceptualized and designed the study and planned the analyses with input from PDH, AO, PM, and DAG. With input from CEM, PDH acquired and analyzed the data. CEM, PDH, PM and DAG reviewed and interpreted statistical output. PDH and CEM drafted the initial manuscript. All authors reviewed and revised the manuscript. All authors approved the final manuscript as submitted.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL

The authors declare no competing interests.This study was performed in accordance with the Declaration of Helsinki. This study used de-identified administrative billing data and was considered not human subjects research by the Institutional Review Board at Boston Children's Hospital.

ADDITIONAL INFORMATION

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