Subclinical and Overt Newborn Opioid Exposure: Prevalence and First-Year Healthcare Utilization

Zana Percy, BS[1,2], Cole Brokamp, PhD[3,4], Jennifer M. McAllister, MD[3,5], Patrick Ryan, PhD[2,3,4], Scott L. Wexelblatt, MD[3,5], and Eric S. Hall, PhD[3,5,6]

Objectives To categorize newborn infants in Hamilton County, Ohio by late pregnancy fetal opioid exposure status and to assess their first-year healthcare utilization.

Study design We used a population-based cohort of 41 136 live births from 2014-2017 and analyzed healthcare encounters in the first year of life from electronic health records. We prospectively assessed for the presence of opioids in maternal urine collected at delivery and for a diagnosis of newborn neonatal abstinence syndrome (NAS). At birth, infants were classified as unexposed to opioids, exposed to opioids and diagnosed with NAS, or subclinically exposed to opioids (exposure that did not result in NAS).

Results The prevalence of newborn opioid exposure was 37 per 1000 births. The duration of the hospital birth encounter was significantly longer for infants with subclinical exposure compared with unexposed infants (10% increase; 95% CI, 7%-13%). However, duration for infants with subclinical exposure was shorter compared to those with NAS. Neither subclinical exposure nor NAS was associated with total emergency department visits. Subclinical exposure was associated with increased odds of having at least 1 hospitalization in the first year. However, the total length of stay for hospitalizations was 82% that of the unexposed group (95% CI, 75%-89%). Infants with NAS had a 213% longer total length of stay compared with the unexposed group (95% CI, 191%-237%).

Conclusions Subclinical and overt opioid exposure among newborn infants was associated with increased first-year healthcare utilization. From 2014 to 2017, this cost the Hamilton County healthcare system an estimated $1 109 452 for longer birth encounters alone. *(J Pediatr 2020;222:52-8)*.

The opioid epidemic has become a public health crisis in the US, but opioid use among pregnant women remains understudied for several reasons. Self-reporting of illicit drug use during pregnancy is unreliable,[1] and most delivery hospitals in the US perform drug testing only on suspicion of newborn exposure (ie, risk-based screening) rather than implementing a universal testing protocol.[2] Others have shown that neonatal abstinence syndrome (NAS), also known as neonatal opioid withdrawal syndrome (NOWS), is on the rise in the US; between 2000 and 2013, the incidence of NAS increased from 1.2 to 6 per thousand live-born infants.[3-5]

A meta-analysis described associations between in utero opioid exposure and adverse neurobehavioral and visual outcomes in children aged <3 years but interpreted the results with caution owing to inherent limitations and biases of the included studies.[6] Another review reported associations between maternal opioid use and congenital malformations and recommended that future studies include comparison groups of truly unexposed children to allow for valid conclusions.[7] Previous work has been unable to accurately differentiate exposed and unexposed newborns from hospital records, because infants with "subclinical" exposure, who do not experience severe withdrawal and are not diagnosed with NAS, are not retrospectively identifiable. Thus, infants with subclinical exposure may be misclassified as unexposed controls in studies of opioid use during pregnancy, biasing any findings of those studies.

We conducted a population-based cohort study of infants whose mothers were universally tested for opioids at birth, allowing us to differentiate infants with subclinical opioid exposure from truly unexposed infants. The objectives of this study were to calculate the prevalence of late-pregnancy fetal opioid exposure and to determine how subclinical and overt (ie, NAS) opioid exposure

CCHMC	Cincinnati Children's Hospital Medical Center
DAG	Directed acyclic graph
ED	Emergency department
ICD	*International Classification of Diseases*
NAS	Neonatal abstinence syndrome
SES	Socioeconomic status
ZIP	Zero-inflated Poisson

From the [1]Medical Scientist Training Program, [2]Department of Environmental Health, and [3]Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH; and [4]Division of Biostatistics and Epidemiology, [5]Perinatal Institute, and [6]Division of Biomedical Informatics, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

The patient cohort was obtained from the Cincinnati regional Maternal and Infant Data Hub, supported by the National Center for Advancing Translational Sciences of the National Institutes of Health through the Center for Clinical and Translational Science and Training at the University of Cincinnati (5UL1TR001425-02). This work was also supported by a University of Cincinnati Medical Scientist Training Program Grant supported by the National Institutes of Health (2T32GM063483-1). The authors declare no conflicts of interest.

https://doi.org/10.1016/j.jpeds.2020.03.052

were associated with healthcare utilization, including the duration of the initial birth encounter, number of emergency department (ED) visits, time to first ED visit, and total length of stay during hospitalizations in the first year of life. We hypothesized that infants exposed to opioids would have increased healthcare utilization compared with their unexposed peers.

Methods

We examined 41 136 live births in 2014-2017 in a population-based cohort of infants with a residential address at birth within Hamilton County, Ohio. Each infant received newborn services from a physician affiliated with Cincinnati Children's Hospital Medical Center (CCHMC) at 1 of 13 regional delivery hospitals representing 94.6% of the 43 467 county resident births during the period as reported by the Ohio Department of Health.[8] CCHMC physician billing records generated during newborn encounters, as well as electronic health records collected during subsequent CCHMC hospital encounters, are integrated within the Maternal and Infant Data Hub, a regional population-based perinatal research repository.[9]

CCHMC cares for 99% of the 0- to 14-year-old children who receive inpatient care in Hamilton County and 81% of the children who receive emergency care, ensuring nearly complete hospital utilization data for the cohort.[10] We analyzed first-year hospital encounters for each child in the study, including admissions and urgent care and ED visits. We excluded infants who had died in the first year of life (n = 183) or had unknown health insurance type (n = 7; owing to the difficulty of modeling this covariate when these patients were included), resulting in a final sample size of 40 966.

Exposure to opioids was assessed for each newborn infant by maternal urine testing using an immunoassay. Urine samples were collected immediately on admission to labor and delivery to avoid the detection of medications administered during the labor process. When opioids were detected by immunoassay, confirmation was obtained with mass spectrometry.

All infants were assessed for NAS as part of the standard of care during their birth encounter, and NAS diagnoses were recorded using the *International Classification of Diseases* (ICD), *Ninth* or *Tenth Revision* (ICD-9/10) codes (ICD-9: 779.5; ICD-10 P96.1). Furthermore, the assignment of the NAS diagnosis was standardized within the region and represents only infants who receive pharmacologic treatment (including a stringent pharmacologic weaning protocol) for the management of severe opioid withdrawal symptoms.[11] If maternal urine tested positive for opioids, the infant were automatically hospitalized for 72-96 hours for observation. Infants managed exclusively with nonpharmacologic measures, such as swaddling, skin-to-skin care, or breastfeeding, were classified as subclinically exposed to opioids and were not diagnosed with NAS. We classified the infants into 3 mutually exclusive groups: unexposed group, opioid-exposed infants without NAS (subclinical exposure group), and opioid-exposed infants with NAS diagnosis (NAS group).

Health care utilization was abstracted from hospital billing data. We assessed the duration of the birth encounter (including any hospital transfers before homebound discharge), total ED visits in the first year of life, time to first ED visit in the first year of life beginning after discharge from the birth encounter, and total inpatient length of stay in the first year of life not including the birth encounter.

To address confounding, we selected covariates a priori using a directed acyclic graph (DAG) based on the defined levels of opioid exposure and hospital utilization outcomes (**Figure 1**; available at www.jpeds.com). DAGs are used to visually represent causal pathways between exposure and outcome and aid the selection of model covariates to prevent overadjustment or underadjustment and collider stratification bias.[12] We adjusted statistical models for infant race, ethnicity, gestational age category (full-term, ≥37 weeks; late preterm, <37-≥34 weeks; or preterm, <34 weeks), insurance type, presence of a complex chronic condition, and presence of neonatal intensive care unit admission during the initial birth encounter. Complex chronic conditions were defined based on ICD-10 codes and the Pediatric Complex Chronic Condition Classification System version 2.[13] For the total ED visits and time to first ED visit models, we created partially adjusted models that excluded demographic covariates (race, ethnicity, and insurance type) to assess for the effect of physiological variables only. We created another DAG considering socioeconomic status (SES) factors as our exposure and determined that we could adjust for the same confounders to estimate the direct effect of these SES factors on ED utilization (**Figure 2**; available at www.jpeds.com). The model for duration of birth encounter also included the delivery route (vaginal vs cesarean) as a covariate. The final variables included in models were obtained from the Cincinnati Maternal and Infant Data Hub.

Statistical Analyses

Univariate differences among the 3 exposure groups were tested using the Kruskal-Wallis test. We used multivariable Poisson regression to model the length of the initial birth encounter and multivariable Cox proportional hazards regression to model the time to the first ED visit. For total ED visits and total length of inpatient stay, we used multivariable zero-inflated Poisson (ZIP) regression models to account for the large number of infants with no ED visits or inpatient stays. The zero-inflated assumption was verified using Vuong nonnested tests.[14] ZIP models assume that the data are generated through 2 distinct distributions. The first is whether a count is zero or nonzero, modeled using a logistic distribution. The second is the magnitude of all of the nonzero counts, modeled using a Poisson distribution. Thus, a ZIP model produces both an OR for a zero count and a risk ratio for the multiplicative change in the nonzero count.

Because we considered opioid exposure to be a nonordered categorical variable with 3 levels (no exposure,

subclinical exposure, and NAS-level exposure), we were able to extract separate ORs for subclinical exposure and NAS-level exposure, both compared with the baseline of no exposure. Because polysubstance exposures and genetic factors are believed to play crucial roles in the presentation and severity of NAS, the type, extent, and duration of in utero opioid exposure alone cannot fully predict the severity of an infant's withdrawal.[15] Models were fitted using only nonmissing covariate data, and a previous study of this cohort showed that race and ethnicity data were missing completely at random.[16]

We used R version 3.6.1 for all data analysis,[17] including the packages *pscl*[18,19] for ZIP models, *survival*[20] for Cox proportional hazards models, and *survminer*[20] for the generation of survival curves.

Results

Of the 40 966 infants born between 2014 and 2017, 39 469 (96.3%) were not exposed to opioids, 1066 (2.6%) had subclinical opioid exposure, and 431 (1.1%) had NAS. Of the 183 excluded patients who died in the first year, 176 (96.2%) were unexposed, 6 (3.3%) had subclinical exposure, and 1 (0.5%) was diagnosed with NAS (n = 1). All 7 patients who were excluded due to unknown insurance type were unexposed.

Table I presents the hospital utilization outcomes and sociodemographic factors of the cohort by exposure status. There were statistically significant differences among the 3 exposure groups for all outcome variables and covariates except infant sex. Infants with subclinical exposure and those with NAS were more likely than unexposed infants to have public insurance, to be admitted to the neonatal intensive care unit, and to have a complex chronic condition. Infants with subclinical exposure were more likely than both unexposed infants and infants with NAS to be born preterm, and infants with NAS were more likely than both unexposed and subclinically exposed infants to be born late preterm ($P < .001$ for both). For comparison, Table I also provides sociodemographic data for US births in 2017.

Subclinical exposure to opioids was associated with a 10% longer birth encounter compared with infants without

Table I. Cohort outcomes and sociodemographic information by exposure group, 2014-2017

Variable	Unexposed	Subclinical	NAS	*P* value	US births in 2017*
Total infants, n (%)	39 469 (96.3)	1066 (2.6)	431 (1.1)		3 855 500
Total LOS >0, %†	8.1	12.5	19.0	<.001	
Duration of birth encounter, d, %				<.001	
25th percentile	2	3	11		
Median	2	4	15		
75th percentile	3	5	21		
Total ED visits >0, %	40.1	48.5	46.9	<.001	
Time to first ED visit, d, n‡				.024	
25th percentile	44	38	48		
Median	122	97	118		
75th percentile	227	212	220		
Female sex, %	48.8	50.6	50.1	.46	48.8
Race, %				<.001	
White	26.1	22.9	5.8		51.7
Black	12.0	12.7	12.3		14.5
Other	22.1	22.4	21.6		33.8
Unknown	39.8	42.0	60.3		–
Ethnicity, %				<.001	
Hispanic	6.0	2.8	3.3		23.3
Non-Hispanic	84.8	88.5	90.0		76.7
Unknown ethnicity	9.2	8.7	6.7		–
Term status, %				<.001	
Full-term	86.4	79.8	74.7		90
Late preterm	7.5	12.3	19.3		7.2
Preterm	2.9	5.7	4.9		2.8
Unknown	3.2	2.2	1.2		–
Health insurance, %				<.001	
Public	46.5	75.8	75.4		46.4
Private	43.8	12.9	7.4		49.1
Self-pay	9.7	11.4	17.2		4.1
Delivery method, %				.10	
Vaginal	68.5	65.7	74.5		68.2
Cesarean	31.5	34.3	25.5		31.8
NICU stay, %				<.001	
Yes	8.0	20.3	67.5		–
Unknown	1.1	1.1	4.2		–
Complex chronic condition	18.6	24.1	26.5	<.001	–

LOS, length of stay; *NICU*, neonatal intensive care unit.
**National Vital Statistics Reports* 67:8, November 7, 2018.
†Total LOS does not include initial hospitalization at birth.
‡Only patients with an ED visit in the first year of life are included in these calculations.

Table II. Total ED visits in first year of life (ZIP model) results and time to first ED visit (Cox proportional hazards model)

	Total ED visits								
	Odds of having at least 1 ED visit			Number of nonzero ED visits			Time to first ED visit		
Model	OR	95% CI	*P* Value	RR	95% CI	*P* Value	HR	95% CI	*P* Value
Fully adjusted									
Subclinical	1.18	0.98-1.48	.09	0.99	0.92-1.06	.66	1.11	1.01-1.21	.02
NAS	1.00	0.73-1.38	.997	1.04	0.91-1.18	.57	0.99	0.83-1.17	.90
Unadjusted									
Subclinical	1.43	1.23-1.64	<.001	1.05	0.98-1.12	.17	1.31	1.21-1.44	<.001
NAS	0.95	0.73-1.25	.70	0.97	0.85-1.10	.58	0.95	0.80-1.11	.50
Partially adjusted									
Subclinical	1.37	1.18-1.59	<.001	1.03	0.96-1.10	.48	1.26	1.16-1.38	<.001
NAS	0.93	0.70-1.25	.66	0.97	0.85-1.10	.59	0.93	0.79-1.10	.40

RR, risk ratio; *HR*, hazard ratio.
The reference is unexposed infants. Fully adjusted models include infant race, ethnicity, term status, insurance type, complex chronic condition, and NICU stay. Partially adjusted models include term status, complex chronic condition, and NICU stay and do not include demographic covariates race, ethnicity, or insurance type.

opioid exposure (95% CI, 7%-13%; $P < .001$). NAS was associated with a 94% longer birth encounter (95% CI, 88%-101%; $P < .001$).

To assess the association between prenatal opioid exposure and ED utilization, we created multivariable ZIP and Cox proportional hazards models for total ED visits and time to first ED visit, respectively (Table II). Neither the logistic portion nor the Poisson portion of the fully adjusted ZIP model showed a significant association between in utero opioid exposure and the number of ED visits in the first year of life. In the fully adjusted time to first ED visit model, there was a significantly increased hazard for subclinical exposure (hazard ratio, 1.11; 95% CI, 1.01-1.21; $P = .02$).

Before adjusting for any covariates, subclinical exposure was associated with increased odds of having at least 1 ED visit in the first year of life compared with the unexposed group ($P < .001$), and increased hazard for time to first ED visit ($P < .001$) (Table II). NAS was not significantly associated with these outcomes. When the models were adjusted with a partial set of covariates (gestational age category, complex chronic condition, and neonatal intensive care unit stay), the results were very similar to those for the unadjusted models, indicating that these variables do not account for the differences between the simple and fully adjusted models (Table II). Figure 3 shows the unadjusted survival curves for time to first ED visit in the first year. The rates of first-year ED visits were 40.1% in the unexposed group, 48.5% in the subclinical exposure group, and 46.9% in the NAS group.

To assess associations between in utero opioid exposure and rates of first-year hospitalizations, we used a ZIP model. In the logistic portion of the adjusted model, subclinical exposure was associated with a 30% greater odds of having at least 1 hospital admission (95% CI, 6%-59%; $P = .01$) compared with unexposed infants, and NAS exposure was associated with 28% greater odds ($P = .13$). From the Poisson portion of the adjusted model, we expect the total length of stay of the subclinical exposure group to be 82% of that of the unexposed group (95% CI, 75%-89%; $P < .001$) and the total length of stay of the NAS group to be 213% of that of the unexposed group (95% CI, 191%-237%; $P < .001$).

Discussion

In this population-based cohort of 40 966 infants born between 2014 and 2017 in Hamilton County, Ohio, 37 infants per 1000 births were born exposed to opioids. This is roughly 5 times greater than the previous national estimate for 2014 based on ICD code diagnoses of 6.5-8 per 1000 for NAS alone.[3,4]

After adjustment for factors that covary with opioid exposure, subclinical opioid exposure among newborn infants was associated with a 10% longer length of stay during the birth encounter, and infants with overt signs of opioid withdrawal who were diagnosed with NAS had a 94% longer length of stay during the birth encounter. During the 4-year study period, the increased duration of birth encounters directly attributable to in utero opioid exposure translated to an additional 1024 days of hospitalization across Hamilton County.

In our cohort, a maternal urine sample testing positive for opioids triggered a 72- to 96-hour mandatory hospital observation period for the infant for observation of opioid withdrawal. The unadjusted median length of stay at the birth encounter for infants with subclinical exposure was 4 days, compared with 2 days for unexposed infants, so most of their observed additional stay was likely due to the mandatory observation period. Infants with NAS had an unadjusted median length of stay of 15 days; additional medical needs complicated their birth encounters. The observed median length of stay for infants with NAS in our cohort is similar to that previously reported in the US[21] and Canada.[22]

Opioid exposure was not associated with differences in total ED encounters in fully adjusted models, but the subclinical exposure group had an 11% longer time to first ED encounter in the first year of life. We are unable to explain

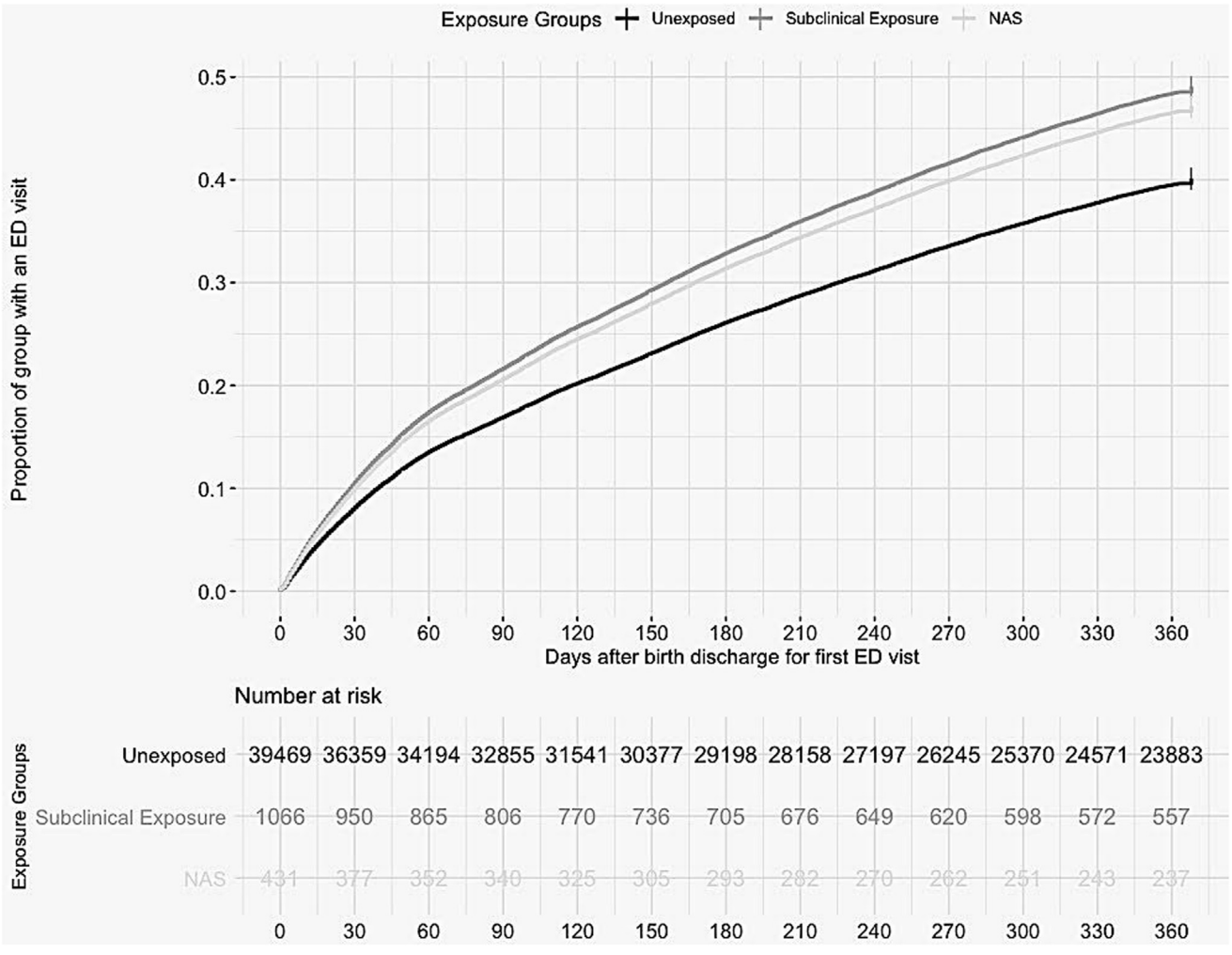

Figure 3. Unadjusted survival curves of time to first ED visit by exposure group.

why subclinical exposure, but not NAS exposure, was associated with increased time to first ED encounter. However, we hope that future research in this understudied group of infants with subclinical opioid exposure will help elucidate our results.

In the unadjusted ZIP model, subclinical exposure was associated with 43% increased odds of having at least 1 ED visit in the first year. To test the hypothesis that SES factors were driving the unadjusted ED utilization results, we created a partially adjusted ZIP model that did not include race, ethnicity, or insurance type and compared this partially adjusted model with the unadjusted model. The estimates from the unadjusted and the partially adjusted models were very similar, leading us to conclude that SES variables were driving the associations seen in the unadjusted ED utilization results. Others have also explored the relationship between ED utilization and SES. For example, Schlinchting et al explored trends in ED utilization rates and found that children with public insurance had 55% increased odds of visiting the ED compared with those with private insurance, and that non-Hispanic white children were less likely than children of other races or ethnicities to visit the ED.[23]

Subclinical opioid exposure at birth was associated with increased odds of hospitalization in the first year. However, for the subgroup of infants who were hospitalized, the total length of stay was shorter than that of the unexposed infants with at least 1 hospital stay. The longer length of stay among unexposed infants may be due to a higher proportion of hospitalizations for low-acuity illness in the subclinical exposure group compared with the unexposed group. Because the subclinical exposure group was more likely to experience hospitalization, they might have had different types of illnesses than their unexposed peers.

Patrick et al followed infants born with NAS in New York and observed that these infants were 149% more likely to be readmitted within 30 days of discharge compared with their uncomplicated full-term peers after adjusting for covariates.[24] In contrast, we found that NAS was not associated with increased odds of hospitalization; however, we considered the entire first year of life. In addition, we were able to study subclinical exposure, which was associated with

increased odds of hospitalization, and we considered the total length of stay experienced by each exposure group in the first year of life.

Although we are confident that we have correctly identified our exposed and unexposed groups owing to the universal maternal testing in Hamilton County, these classifications do not represent exposure during the full gestational period. Our drug testing likely only captured a window of several days before delivery, so we cannot consider earlier exposure; however, we speculate that a positive test result at delivery is more likely than a negative test result to represent exposure during pregnancy, which could occur in mothers who used opioids earlier in pregnancy and stopped before delivery.

Another limitation of this study is that we were unable to differentiate between illicit and prescribed opioids (including medication-assisted treatment) exposure. We would expect these 2 groups of mothers to have different healthcare utilization behaviors, and there may be residual confounding by type of opioid use.[25] For example, in utero exposure to illicit opioids may have different physiological effects on infants than prescribed opioids,[26] but mothers with illicit use also may be less likely to seek prenatal care.[27] Other drugs of abuse, when detected by our universal testing protocols, were not differentiated in billing records; this precluded analysis of these exposures as additional confounding factors.

Although this study assumed that all children in the cohort remained in the study area for the first year of life, we were unable to verify that apparent nonutilization was not due to residential mobility out of Hamilton County. However, another study of Cincinnati children found that residential mobility was low, with only 6.5% moving in the first year of life, and that families who did move did so only approximately 2 miles from their previous residence.[28] Although we only were able to assess healthcare encounters that occurred at CCHMC, this represented 90% of all encounters and 99% of hospitalizations in the county.

To estimate the opioid cost burden to the county health care system from the increased length of the birth encounter, we calculated the additional length of stay from adjusted risk estimates and assumed a cost per day of $1084.[21] During the 4-year study period, opioid exposure in newborns was associated with increased healthcare utilization in the first year of life, which cost the county healthcare system a total of $1 109 452.

Our data show that infants born exposed to opioids in Hamilton County, Ohio had an increased length of stay during the hospital birth encounter, increased odds of hospitalization, and an increased length of stay during hospitalizations in the first year of life.

The universal maternal drug testing program in Hamilton County allowed us to distinguish infants who were exposed to opioids but did not have clinically significant NAS, a subclinical group that previously has been difficult to identify and study. We found that infants with subclinical exposure to opioids had increased healthcare utilization in the first year of life compared with unexposed infants, suggesting that this population may require closer observation either in the delivery hospital or through primary care. Although our results may be generalizable to areas with similar population demographics and opioid use rates, it is difficult to fully consider differences in culture and healthcare access, as well as other unmeasured confounders that may exist between study areas. Therefore, our results should be interpreted with caution until they can be replicated in other locations. Further research is also needed to follow long-term health outcomes for infants with subclinical opioid exposure. ■

Submitted for publication Jan 7, 2020; last revision received Mar 9, 2020; accepted Mar 20, 2020.

Reprint requests: Eric S. Hall, PhD, 3333 Burnet Avenue, Cincinnati, OH 45229. E-mail: ehall3@geisinger.edu

References

1. Chiandetti A, Hernandez G, Mercadal-Hally M, Alvarez A, Andreu-Fernandez V, Navarro-Tapia E, et al. Prevalence of prenatal exposure to substances of abuse: questionnaire versus biomarkers. Reprod Health 2017;14:137.
2. Wexelblatt SL, Ward LP, Torok K, Tisdale E, Meinzen-Derr JK, Greenberg JM. Universal maternal drug testing in a high-prevalence region of prescription opiate abuse. J Pediatr 2015;166:582-6.
3. Haight SC, Ko JY, Tong VT, Bohm MK, Callaghan WM. Opioid use disorder documented at delivery hospitalization—United States, 1999-2014. MMWR Morb Mortal Wkly Rep 2018;67:845-9.
4. 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:e20173520.
5. Patrick SW, Davis MM, Lehman CU, Cooper WO. Increasing incidence and geographic distribution of neonatal abstinence syndrome: United States 2009 to 2012. J Perinatol 2015;35:650-5.
6. Monnelly VJ, Hamilton R, Chappell FM, Mactier H, Boardman JP. Childhood neurodevelopment after prescription of maintenance methadone for opioid dependency in pregnancy: a systematic review and meta-analysis. Dev Med Child Neurol 2019;61:750-60.
7. Lind JN, Interrante JD, Ailes EC, Gilboa SM, Khan S, Frey MT, et al. Maternal use of opioids during pregnancy and congenital malformations: a systematic review. Pediatrics 2017;139:e20164131.
8. Ohio Department of Health. Ohio Public Health Information Warehouse: Ohio live births 2019. http://publicapps.odh.ohio.gov/EDW/DataCatalog. Accessed December 11, 2019.
9. Hall ES, Greenberg JM, Muglia LJ, Divekar P, Zahner J, Gholap J, et al. Implementation of a regional perinatal data repository from clinical and billing records. Matern Child Health J 2018;22:485-93.
10. Beck AF, Riley CL, Taylor SC, Brokamp C, Kahn RS. Pervasive income-based disparities in inpatient bed-day rates across conditions and subspecialties. Health Aff (Millwood) 2018;37:551-9.
11. Hall ES, Wexelblatt SL, Crowley M, Grow JL, Jasin LR, Klebanoff MA, et al. A multicenter cohort study of treatments and hospital outcomes in neonatal abstinence syndrome. Pediatrics 2014;134:e527-34.
12. Shrier I, Platt RW. Reducing bias through directed acyclic graphs. BMC Med Res Methodol 2008;8:70.
13. Feudtner C, Feinstein JA, Zhong W, Hall M, Dai D. Pediatric complex chronic conditions classification system version 2: updated for ICD-10 and complex medical technology dependence and transplantation. BMC Pediatr 2014;14:199.
14. Vuong QH. Likelihood ratio tests for model selection and non-nested hypotheses. Econometrica 1989;57:307-33.
15. Logan BA, Brown MS, Hayes MJ. Neonatal abstinence syndrome: treatment and pediatric outcomes. Clin Obstet Gynecol 2013;56:186-92.
16. Brokamp C, Beck AF, Goyal NK, Ryan P, Greenberg JM, Hall ES. Material community deprivation and hospital utilization during the first year

of life: an urban population-based cohort study. Ann Epidemiol 2019;30:37-43.
17. R Core Team. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2019. https://www.R-project.org/. Accessed December 11, 2019.
18. Zeileis A, Kleiber C, Jackman S. Regression models for count data in R. J Stat Softw 2008;27:1-25.
19. Jackman S. pscl: classes and methods for R developed in the political science computational laboratory. United States Studies Centre, University of Sydney; 2017. https://github.com/atahk/pscl/. Accessed December 11, 2019.
20. Therneau TM. A package for survival analysis in R. https://cran.r-project.org/package=survival. Accessed December 11, 2019.
21. Corr TE, Hollenbeak CS. The economic burden of neonatal abstinence syndrome in the United States. Addiction 2017;112:1590-9.
22. Filteau J, Coo H, Dow K. Trends in incidence of neonatal abstinence syndrome in Canada and associated healthcare resource utilization. Drug Alcohol Depend 2018;185:313-21.
23. Schlichting LE, Rogers ML, Gjelsvik A, Linakis JG, Vivier PM. Pediatric emergency department utilization and reliance by insurance coverage in the United States. Acad Emerg Med 2017;24:1483-90.
24. Patrick SW, Burke JF, Biel TJ, Auger KA, Goyal NK, Cooper WO. Risk of hospital readmission among infants with neonatal abstinence syndrome. Hosp Pediatr 2015;5:513-9.
25. Jansson LM, Velez ML, McConnell K, Spencer N, Tuten M, Jones H, et al. Maternal buprenorphine treatment and infant outcome. Drug Alcohol Depend 2017;180:56-61.
26. Hulse GK, Milne H, English DR, Holman CD. The relationship between maternal use of heroin and methadone and infant birth weight. Addiction 1997;92:1571-9.
27. Chen CY, Wang IA, Fang SY, Huang N, Tsay JH, Chang SH. Inadequate prenatal care utilization among women with and without methadone-treated opioid use disorders in Taiwan. Int J Drug Policy 2019;67:1-8.
28. Brokamp C, Lemasters GK, Ryan PH. Residential mobility impacts exposure assessment and community socioeconomic characteristics in longitudinal epidemiology studies. J Expo Sci Environ Epidemiol 2016;26:428-34.

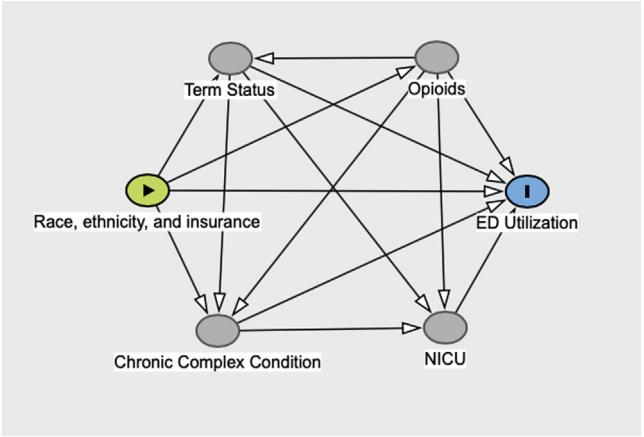

Figure 1. Directed acyclic graph for potential confounders in the relationship between opioid exposure and healthcare utilization.

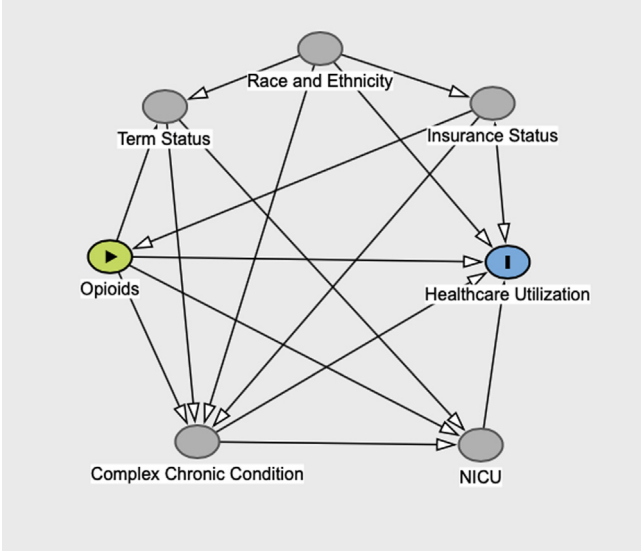

Figure 2. Directed acyclic graph for the relationship between socioeconomic factors and ED utilization with potential confounders.