



A Longitudinal Healthcare Use Profile of Children with a History of Neonatal Abstinence Syndrome

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Objective To describe healthcare use over time of children with a history of neonatal abstinence syndrome (NAS) compared with children without NAS.

Study design In this retrospective, longitudinal cohort study, data were obtained from MarketScan Commercial Claims and Encounters database from 2005 to 2014. Children with and without NAS based on *International Classification of Diseases, Ninth Revision* diagnostic codes were followed until 8 years or disenrollment (mean: 35 months). Numbers of claims for inpatient, outpatient, and emergency department encounters; prescription drugs; and costs associated with these encounters were evaluated.

Results Children with NAS had a significantly greater number of claims per year from age 1 to 8 for inpatient hospitalizations (adjusted mean ratio 3.20; 95% CI 1.74-5.90), outpatient encounters (1.23; 1.08-1.41), and emergency department visits (1.46; 1.25-1.70) after we adjusted for confounders. Subsequently, adjusted mean annualized costs were nearly double for all healthcare services in children with NAS (1.86; 1.34-2.60) and >4 times as high as for inpatient hospitalizations (4.34; 2.03-9.30) compared with children without NAS.

Conclusions Children with a diagnosis of NAS have significantly greater rates of healthcare use through age 8 years compared with children without NAS. These findings suggest that children affected by NAS have medical disparities that linger well beyond early infancy. (*J Pediatr* 2019;204:111-7).

The current epidemic of prescription and nonprescription opioid use has resulted in a significant increase in the incidence of neonatal abstinence syndrome (NAS) both in the US and abroad.¹⁻⁶ NAS is a collection of symptoms that occur in newborns as a result of exposure to addictive drugs while in utero.^{7,8} Although the immediate perinatal effects of maternal opioid exposure on fetuses and newborns have been well described, including complications such as growth restriction, preterm birth, and various neurologic and gastrointestinal issues related to withdrawal,⁸⁻¹³ less is known about the long-term outcomes of these newborns as they move into infancy and childhood. Existing literature on cognitive and behavioral sequelae is inconsistent, limited by small numbers of subjects, and includes analysis of patient samples that existed before the era of widespread use and abuse of prescription opioids.¹⁴⁻¹⁷ Although it is impossible to tease out the effects of social and environmental exposures, more recent studies suggest that newborns exposed to opioids in utero may be at increased risk for adverse cognitive, psychomotor, and behavioral outcomes as toddlers and preschoolers.¹⁸⁻²⁰ Furthermore, opioid-exposed newborns may remain susceptible to ongoing challenges into adolescence, with 1 study demonstrating deficient and deteriorating school performance throughout early school years into high school.²¹

Despite our growing knowledge of the long-term neurodevelopmental consequences of in utero drug exposure, there remains a paucity of information on health and medical outcomes of children with NAS. Recent, single-state investigations reveal that admission rates for children during the first 30 days to 5 years are greater for those with NAS compared with unexposed controls, suggesting that these newborns have persistent and lasting health disparities as well.²²⁻²⁴ Although these single-state studies propose additional cause for concern about this vulnerable population, there remains an overall deficiency in knowledge about the healthcare use and medical profile of children with NAS beyond the perinatal period. To address these gaps, we aimed to describe and compare children with NAS with those without NAS through age 8 years, evaluate the number of healthcare encounters (inpatient hospital stays, outpatient evaluations, emergency department [ED] visits) and prescribed medications for children with NAS compared with those without NAS, and evaluate the total number of medical claims and associated medical costs for children with NAS vs those without NAS.

aMR	Adjusted mean ratio
ED	Emergency department
HMO	Health maintenance organization
ICD-9	<i>International Classification of Diseases, Ninth Revision</i>
NAS	Neonatal abstinence syndrome
PPO	Preferred provider organization

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Methods

The MarketScan Commercial Claims and Encounters database (IBM Truven Health Analytics, Ann Arbor, Michigan) consists of reimbursed healthcare claims from a selection of large employers and commercial health plans. Included individuals are covered by private insurance plans across the US, with claims information from >130 payers describing healthcare use and expenditures for >50-million employees and family members per year. Individuals are identified by a unique enrollee identifier and contain information on inpatient, outpatient and prescription drug service use as well as patient age, sex, geographic location, and type of health insurance plan. The medical claims contain *International Classification of Diseases, Ninth Revision* (ICD-9) diagnoses codes and Current Procedural Terminology, Fourth Edition, procedure codes. A claim is defined as any submitted fee for services by the clinician, clinic, or hospital to the insurance company, and, thus, a single encounter may include multiple claims.

MarketScan healthcare data from the years 2005 to 2014 were used to identify children between the ages of 0 and 8 years with initial enrollment during their year of birth. Children with NAS were identified using the ICD-9 code 779.5 (drug withdrawal syndrome in newborn). Among 2 987 660 children eligible for the study, 1479 had a diagnosis of NAS. We randomly selected 10% of children without NAS as the controls ($n = 298\,330$). These controls and all NAS cases formed our study cohort. In addition, we designed a matched cohort study to balance for some potential confounders. Children with NAS were matched one-to-one to controls on sex, age at the end of follow-up, year of birth, US Census region, type of residence, type of insurance, premature birth, and growth restriction.

Demographic characteristics, including age, sex, US Census region (ie, Northeast, North Central, South, and West), type of residence (urban or rural), and type of healthcare plan (health maintenance organization [HMO], preferred provider organization [PPO], and other) were collected. Urban residence was defined by a nonzero metropolitan statistical area code, and rural was defined as residence outside an metropolitan statistical area. PPO and HMO accounted for >80% of the enrollees in the study cohort, and, thus, the remaining 7 types of health plans were bundled into the “other” category. All inpatient and outpatient claims during the birth year were queried to ascertain baseline risk factors. In particular, premature birth was attributed to newborns with ICD-9 codes of 765.0x, 765.1x, and 765.21-29. Intrauterine growth restriction was attributed to newborns with an ICD-9 code of 764.9.

The primary study outcomes were healthcare use, as defined by the numbers of claims related to inpatient hospitalizations, outpatient encounters, ED visits, and medication prescriptions, and costs associated with these healthcare services. In particular, the total number of claims and costs were calculated by bundling all aforementioned healthcare services. Costs are defined as gross payments to a provider

for a service, eligible under the medical plan terms. Costs were adjusted for inflation using the Consumer Price Index for All Urban Consumers: Medical Care and are reported in 2016 US dollars.

Statistical Analyses

By linking the inpatient and outpatient encounter claims databases from 2005 to 2014, we estimated the annualized healthcare use and associated costs for each individual subject. Descriptive analyses were used for exploring cohort demographics and the distributions of annualized use and cost by age. Demographics and healthcare use were compared between children with and without NAS via the χ^2 test/Fisher exact test for categorical variables and t test/Wilcoxon rank-sum test for continuous variables. We considered 2 age groups (birth-1 year and 1-8 years) to calculate average healthcare use trends during infancy and early childhood. Repeated-measures analyses based on generalized estimating equation methods were performed to compare annualized health use and costs between children with NAS and those without. Specifically, negative binomial regression and Gamma regression with log-link function were used in the generalized estimating equation for analyzing use and costs, respectively. The variables included in the models were age group (<1 year vs ≥ 1 year), NAS status, their interaction, and potential confounders (sex, US Census region, residence type, type of healthcare plan, prematurity, and growth restriction). For the analysis of the matched cohort, only age group (<1 year vs ≥ 1 year), NAS status, and their interaction were included in the model. All statistical analyses were performed with SAS, version 9.4, software (SAS Institute, Cary, North Carolina). All statistical tests were 2-sided with $P < .05$ being considered statistically significant.

Results

Of the 299 809 children included in our study, 1479 children had a diagnosis of NAS and 298 330 children without NAS served as controls. All children entered the database during their first year. They were followed for an average of 35 months (NAS: 30 months vs non-NAS: 35 months). **Table I** shows the demographics and clinical characteristics of children with and without NAS. In total, 56.3% of children with NAS were boys compared with 51.4% for children without NAS. The southern US Census region accounted for 38.5% of the total study sample (NAS: 34.4% vs non-NAS: 38.6%), and the Northeast US region had only 15.0% of the cohort (NAS: 22.7% vs non-NAS: 15.0%). PPO was the most common health plan at 62.7% (NAS: 59.6% NAS vs non-NAS: 62.7%) followed by HMO at 16.0% (NAS: 13.2% vs non-NAS: 16.0%). A majority of the sample lived in urban areas (85.5% [NAS: 84.3% vs non-NAS: 85.5%]). In total, 21.4% of children with NAS were born prematurely vs 6.5% of those without NAS. Few children had growth restriction (NAS: 1.8% vs non-NAS: 0.3%).

We observed consistently greater healthcare use among children with NAS from birth to 8 years (**Figure**). During the year

Table I. Demographic and birth characteristics of children with and without NAS

Variables	NAS (%) (n = 1479)	No NAS (%) (n = 298 330)	P value
Sex			.0001
Male	56.3	51.4	
Female	43.7	48.6	
Year of birth			<.0001
2005	4.3	7.5	
2006	5.3	9.4	
2007	4.1	9.6	
2008	8.5	11.5	
2009	6.9	9.5	
2010	11.8	12.2	
2011	18.2	13.7	
2012	15.6	11.3	
2013	17.5	11.0	
2014	7.8	4.5	
Region			<.0001
Northeast	22.7	15.0	
North Central	24.1	24.6	
South	34.4	38.6	
West	15.6	19.6	
Unknown	3.2	2.2	
Health plan			<.0001
HMO	13.2	16.0	
PPO	59.6	62.7	
Other	27.2	21.3	
Residence			.03
Urban	84.3	85.5	
Rural	12.5	12.3	
Unknown	3.2	2.2	
Premature birth	21.4	6.5	<.0001
Growth restriction	1.8	0.3	<.0001

of birth, children with NAS had greater overall numbers of mean healthcare claims (NAS: 103 vs non-NAS: 52) as well as greater medical costs incurred from those claims (\$70 023 vs \$11 913; $P < .0001$). Although use dropped considerably after age 1 year in all children, those with NAS continued to have significantly greater usage rates into toddlerhood and early childhood than those without NAS. Specifically, during age 1-8 years, children with NAS had more overall healthcare claims (annualized average 35 vs 24) and greater costs (\$6927 vs \$2735) than children without NAS. In particular, children with NAS had greater numbers of claims and costs than children without NAS for inpatient hospitalizations (2.1 vs 0.6; \$2425 vs \$458), ED visits (2.1 vs 1.3; \$464 vs \$289), outpatient evaluations (28 vs 21; \$4023 vs \$2091), and prescription drugs (3.9 vs 3.0; \$479 vs \$186), all statistically significant ($P < .0001$).

After the first 3 years, healthcare use and costs progressively increased over time among children with NAS compared with those without NAS who had steady or minimally decreasing use and costs (Figure). Overall, during the age period of 1-8 years, the majority of costs (76.5%) for children without NAS were from outpatient encounters vs 58.1% for children with NAS. In contrast, inpatient hospitalization accounted for much greater costs among those with NAS (\$2425; 35.0%) than those without (\$458; 16.7%) with a between-group (NAS vs non-NAS) cost ratio of 5.3.

After adjusting for potential confounders, we found there were significant interactions between age group and NAS

status (Table II). Although the effects of NAS on healthcare claims and costs were attenuated after 1 year, children with NAS continued to have significantly greater use from age 1 to 8 (adjusted mean ratio [aMR] 1.23 [95% CI 1.08-1.39] for overall claims and 1.86 [1.34-2.60] for overall costs) compared with children without NAS. Most of the covariates also showed significant associations with healthcare claims and costs. In particular, premature birth and growth restriction were strongly associated with greater healthcare use.

Similar results were found for each individual type of health services and the associated costs. During age 1-8 years, healthcare claims and costs remained greater for children with NAS for inpatient hospitalizations (aMR 3.20 [1.74-5.90] for claims; 4.34 [2.03-9.30] for costs); outpatient encounters (claims 1.23 [1.08-1.41]; costs: 1.60 [1.16-2.22]); ED visits (claims: 1.46 [1.23-1.69]; costs: 1.44 [1.23-1.69]), and prescription drugs (claims: 1.26 [1.09-1.46]; costs: 2.01 [1.26-3.22]) (Table III).

The analysis results for the matched cohort confirmed the aforementioned findings. Specifically, during years 1-8, healthcare claims and costs remained greater for children with NAS for inpatient hospitalizations (aMR 6.78 [3.35-13.70] for claims; 8.66 [3.48-21.54] for costs); outpatient encounters (claims: 1.21 [1.04-1.40]; costs: 1.97 [1.33-2.94]); and ED visits (claims: 1.58 [1.29-1.93]; costs: 1.52 [1.21-1.90]) (Table III). However, associations between NAS and prescription drug claims were no longer statistically significant.

As the most substantial differences in healthcare use were found in inpatient hospitalizations, we sought to describe the most frequent diagnoses associated with hospital admission for children with a history of NAS. For infants, the most common diagnoses were "other ill-defined conditions of the perinatal period," which includes the more specific diagnosis of NAS; respiratory conditions; and complications related to prematurity and low birth weight. In contrast, the most frequent inpatient diagnosis for infants without NAS was disorders related to prematurity and low birth weight, accounting for nearly 10% of first-year admission diagnoses. For those children aged 1-8 with a history of NAS, the most frequent diagnoses associated with inpatient claims were general symptoms, asthma, and pericardial disease and patients without NAS were most frequently admitted for pneumonia, general symptoms, and asthma.

Further investigation revealed that well-child and preventative claims accounted for 43.8% of the 5 most frequent encounter codes for infants without a history of NAS, and they only accounted for 26.8% of the codes for infants with NAS. In addition, in children 1-8 years without a diagnosis of NAS, 23.3% of the 5 most frequent diagnostic claims were related to preventative visits and only 8.1% of those claims were related to well-child care in children with history of NAS. These findings indicate that, compared with children without NAS, children with NAS are more often seen for acute care visits and less often seen for preventative checks.

During the first year of life, children with NAS had even greater healthcare use and expenditures (all type claims: 1.66 [1.57-1.76]; costs: 5.27 [4.69-5.92]) than children without NAS.

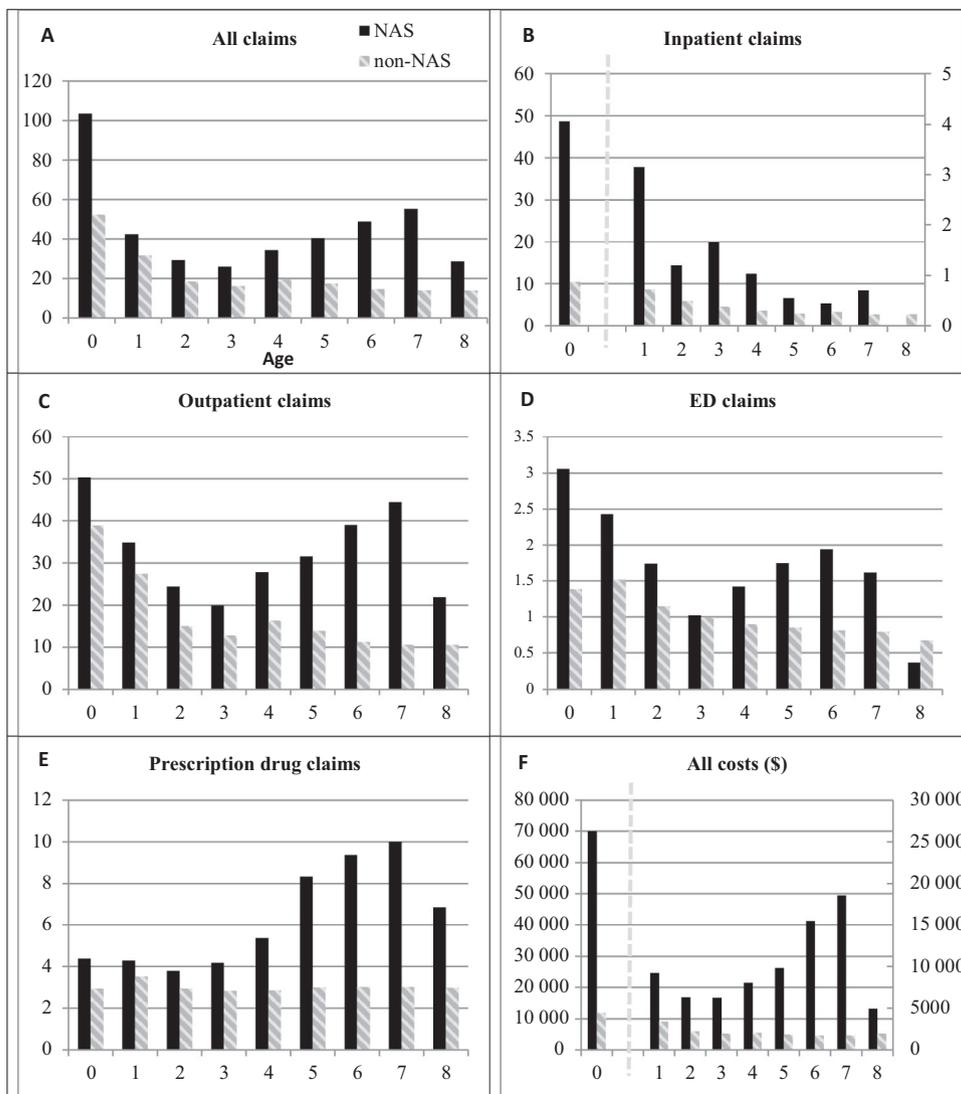


Figure. Healthcare use among children with and without NAS. **A**, Numbers of all-type of medical claims (in-/outpatient; ED; and prescription drugs); **B**, inpatient claims; **C**, outpatient claims; **D**, ED claims; **E**, prescription drug claims; **F**, cost of all-type of medical expenses. Note: Because the inpatient claims (**B**) and all-type costs (**F**) were substantially greater at age 0, secondary y-axes on the right were used for the 1- to 8-year age group. Costs are in 2016 US dollars. All panels: $P < .001$.

We wondered whether the differences in healthcare use and expenditures during year 1 were solely due to the initial birth admission for treatment of withdrawal. Thus, we performed a subgroup analysis specifically evaluating the period of 4-12 months following birth (presumably beyond the time frame of the initial withdrawal treatment). During this period, overall healthcare use and expenditures among infants with NAS remained significantly greater than infants without NAS (aMR for claims: 1.27 [1.19-1.35]); costs: 2.16 [1.98-2.35]). This was also true for each specific type of healthcare service (Table IV; available at www.jpeds.com). In particular, infants with NAS had >4 times as many claims (aMR: 4.21 [1.88-9.44]) and 5 times the incurred costs (5.02 [4.36-5.78]) from inpatient hospitalizations compared with those without NAS. They also

received more services from the ED (claims: 1.80 [1.47-2.19]; costs: 1.65 [1.47-1.87]).

Discussion

This retrospective, longitudinal cohort study provides national information for long-term healthcare use of children with NAS. We found persistently greater rates of healthcare use by children aged 0-8 years with NAS compared with those without NAS. This increased use spanned all healthcare services, including inpatient hospitalizations, outpatient evaluations, and ED visits. The financial burden of this healthcare use is substantial, with a significant increase in costs for

Table II. Multivariable regression for NAS effects on all types of health expenditures in children aged 0-8 years

Variables	Annualized claims		Annualized costs	
	aMR (95% CI)	P value	aMR (95% CI)	P value
NAS (age <1 y)				
Yes	1.66 (1.57-1.76)	<.0001	5.27 (4.69-5.92)	<.0001
No	Reference		Reference	
NAS (age 1-8 y)				
Yes	1.23 (1.08-1.39)	<.0001	1.86 (1.34-2.60)	<.0001
No	Reference		Reference	
Premature birth				
Yes	2.11 (2.07-2.15)	<.0001	7.22 (6.94-7.51)	<.0001
No	Reference		Reference	
Growth retardation				
Yes	1.56 (1.43-1.69)	<.0001	2.55 (2.10-3.11)	<.0001
No	Reference		Reference	
Sex				
Male	1.09 (1.08-1.10)	<.0001	1.18 (1.15-1.21)	<.0001
Female	Reference		Reference	
Region				
Northeast	1.03 (1.02-1.04)	<.0001	0.99 (0.95-1.04)	.71
South	1.09 (1.08-1.10)	<.0001	0.99 (0.96-1.02)	.55
West	0.84 (0.83-0.84)	<.0001	0.92 (0.88-0.96)	.0002
North Central	Reference		Reference	
Residence				
Urban	1.08 (1.06-1.09)	<.0001	1.07 (1.03-1.12)	.0004
Rural	Reference		Reference	
Health plan				
PPO	0.99 (0.98-0.99)	.04	1.08	.01
Other	0.94 (0.93-0.95)	<.0001	1.06	.52
HMO	Reference		Reference	

children with NAS compared with those without NAS over the 8-year study.

As the opioid crisis expands, consideration for the long-term effects of NAS deserves attention. Existing literature suggests that children exposed to opioids in utero are at increased

risk for adverse cognitive, psychomotor, and behavioral outcomes as toddlers and preschoolers¹⁸⁻²⁰ and deficient academic performance in primary school and high school.²¹ Available data on medical outcomes for children with NAS, however, are scant but suggest that hospital readmission rates for these children are greater than unexposed children²²⁻²⁴. Our study, using a national dataset, not only confirms this greater rate of hospital admission but reveals increased outpatient evaluations and ED visits suggesting lasting health disparities among this vulnerable group of children.

The environment in which the fetus grows and develops may have lasting impacts on long-term health. Women with opioid use disorders have greater rates of comorbid conditions such as mental health disorders, physical abuse, polydrug use, undernutrition, chronic illnesses, poor social support and limited prenatal care, all of which are associated with poor perinatal outcomes¹⁰ that may affect subsequent health of opioid-exposed fetuses. Placental insufficiency and fetal growth restriction, placental abruption, and preterm labor are well-described consequences of maternal opioid use, and each are associated with both acute and chronic adverse health outcomes for newborns²⁵⁻²⁸ and may partially explain the increased healthcare use of children with NAS.

More importantly, numerous studies have shown that social and environmental exposures can influence health, cognitive, and behavioral outcomes of children.²⁹ Women with opioid use disorders have high rates of mental health and mood disorders,³⁰ histories of physical and sexual abuse,³¹ and limited social supports. These maternal characteristics may adversely affect the health and wellbeing of their children leading to increased healthcare use by this population.

The findings of our study suggest the need for closer medical follow-up of these vulnerable patients. Children with NAS should have regular visits with their primary care physicians

Table III. Multivariable regression for associations between NAS and healthcare use over the entire study cohort and the matched cohort

Outcomes	aMR (95% CI)			
	Entire cohort*		Matched cohort†	
	<1 y	1-8 y	<1 y	1-8 y
Overall				
All type claims	1.66 (1.57-1.76)	1.23 (1.08-1.39)	1.51 (1.37-1.66)	1.25 (1.06-1.48)
All type costs	5.27 (4.69-5.92)	1.86 (1.34-2.60)	2.86 (2.24-3.67)	2.75 (1.78-4.23)
Inpatient				
Claims	3.91 (3.56-4.29)	3.20 (1.74-5.90)	2.60 (2.10-3.21)	6.78 (3.35-13.70)
Costs	8.88 (7.77-10.16)	4.34 (2.03-9.30)	3.30 (2.47-4.40)	8.66 (3.48-21.54)
Outpatient				
Claims	1.16 (1.11-1.21)	1.23 (1.08-1.41)	1.10 (1.04-1.16)	1.21 (1.04-1.40)
Costs	1.55 (1.42-1.70)	1.60 (1.16-2.22)	1.38 (1.18-1.62)	1.97 (1.33-2.94)
ED				
Claims	1.94 (1.72-2.19)	1.46 (1.25-1.70)	1.94 (1.61-2.33)	1.58 (1.29-1.93)
Costs	2.04 (1.74-2.41)	1.44 (1.23-1.69)	2.07 (1.61-2.65)	1.52 (1.21-1.90)
Prescriptions				
Claims	1.45 (1.33-1.57)	1.26 (1.09-1.46)	0.97 (0.87-1.08)	0.92 (0.75-1.13)
Costs	2.21 (1.35-3.63)	2.01 (1.26-3.22)	1.07 (0.68-1.69)	1.94 (1.11-3.36)

*Adjusted for sex, age bracket (<1; 1-8 years), year of birth, US Census region, type of residence, type of insurance, premature birth, growth restriction.

†Matched on sex, age at the end of follow-up, year of birth, US Census region, type of residence, type of insurance, premature birth, growth retardation and adjusted for age bracket (<1; 1-8 years).

to administer routine well-child care and evaluate for any indication of deteriorating health. Stronger social support and involvement of child welfare systems is necessary to ensure that preventative health maintenance visits are attended. The increased incidence of NAS has overwhelmed the social services systems in some areas,³² and federal funding for the child welfare program has remained stagnant in recent years.³³ As further progress is made in genetics and epigenetics, personalized screening and treatment regimens may help direct resources to those individuals who are most at risk and improve outcomes. Finally, implementing public health and policy changes to provide specific treatment for women of reproductive age with opioid use disorders before becoming pregnant may decrease the incidence of NAS and its subsequent negative health effects. If a woman with an opioid use disorder does become pregnant, optimizing her prenatal care with routine visits, assessment of nutrition, evaluation of social support, and ensuring conversion to opioid-replacement therapy are paramount practices to optimize health outcomes for both mother and baby. Appropriate postnatal, family provisions also should be put in place, including involvement of a case manager, mental health support and substance abuse counseling for the mother, enrollment in parenting classes or in-home instruction, establishment with primary healthcare for both mother and baby, and Early Intervention involvement for the child.³⁴ Successes of the Health Resources and Service Administration and Maternal and Child Health Bureau such as The Healthy Start Program; The Maternal, Infant, and Early Childhood Home Visiting Program; Head Start Programs; and the Supplemental Nutrition Program for Women, Infants, and Children can serve as guidelines for implementation of an effective interventional system targeted at mothers and their children.³⁵

There are several limitations to this study. The use of a national insurance database for research relies on accurate medical diagnosis and procedure coding, and failure to appropriately assign a diagnostic code may lead to inaccurate assessments and conclusions regarding particular patients. In addition, diagnostic codes provide no insight into the type of fetal drug exposure, whether an infant was treated or observed for NAS, the severity of withdrawal, or how the patient's symptoms were managed. In addition, we did not examine or categorize illnesses or reasons for ED visits, nor did we explore the specific drugs prescribed. However, this initial discovery of increased healthcare use by children with NAS is an important finding for policy makers. Another limitation is the fact that we only examined children with a diagnosis of NAS covered by private insurance. We know that >75% of children with NAS have Medicaid insurance coverage at the time of birth.^{1,3} Because Medicaid is a proxy for low socioeconomic status,³⁶ our findings are even more alarming as the affected children in our study, who presumably had greater access to financial and other resources than those covered under Medicaid, still require increased use of the healthcare system. Another limitation is the relatively short follow-up period due to discontinuation of health insurance or censoring at the end of study period. This shorter follow-up has consequently led to a small number of

children examined at age 6-8 years. Although it is difficult to draw firm conclusions based on the limited numbers of patients available for analysis during these later ages, we inferred based on similar trends in the previous years that these children indeed continue to overuse the healthcare system. Finally, we acknowledge that health outcomes are due to multifactorial contributions for which we could not entirely control. However, this investigation, which used a large, national longitudinal database with matching techniques, clearly suggests differences in healthcare use between children with and without NAS and demands further investigation.

Future studies should examine whether similar trends exist among children with Medicaid insurance. In addition, further exploration of the individual illnesses or categories of illness and prescribed medications for which these children seek medical treatment should be considered to better monitor and treat these at-risk children.

In conclusion, children with a diagnosis of NAS in the newborn period have significantly greater rates of healthcare use through age 8 years compared with children without NAS, and these rates increase over time beginning in preschool years. These findings suggest that children affected by NAS have medical issues that linger well beyond early infancy. ■

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References

1. Corr TE, Hollenbeak CS. The economic burden of neonatal abstinence syndrome in the United States. *Addiction* 2017;112:1590-9.
2. Ailes EC, Dawson AL, Lind JN, Gilboa SM, Frey MT, Broussard CS, et al. Opioid prescription claims among women of reproductive age—United States, 2008-2012. *MMWR Morb Mortal Wkly Rep* 2015;64:37-41.
3. Patrick SW, Schumacher RE, Benneyworth BD, Krans EE, McAllister JM, Davis MM. Neonatal abstinence syndrome and associated health care expenditures. *JAMA* 2012;307.
4. 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;35:650-5.
5. Tolia VN, Patrick SW, Bennett MM, Murthy K, Sousa J, Smith PB, et al. Increasing incidence of the neonatal abstinence syndrome in U.S. neonatal ICUs. *N Engl J Med* 2015;372:2118-26.
6. Kocherlakota P. Neonatal abstinence syndrome. *Pediatrics* 2014;134:e547-61.
7. Finnegan LP, Kron RE, Connaughton JF, Emich JP. Assessment and treatment of abstinence in the infant of the drug-dependent mother. *Int J Clin Pharmacol Biopharm* 1975;12:19-32.
8. Hudak ML, Tan RC. Neonatal drug withdrawal. *Pediatrics* 2012;129:e540-60.
9. Patrick SW, Dudley J, Martin PR, Harrell FE, Warren MD, Hartmann KE, et al. Prescription opioid epidemic and infant outcomes. *Pediatrics* 2015;135:842-50.
10. Reddy UM, Davis JM, Ren Z, Greene MF. 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;130:10-28.
11. Whiteman VE, Salemi JL, Mogos MF, Cain MA, Aliyu MH, Salihu HM. Maternal opioid drug use during pregnancy and its impact on perinatal morbidity, mortality, and the costs of medical care in the United States. *J Pregnancy* 2014;2014:906723.
 12. Behnke M, Smith VC. Prenatal substance abuse: short- and long-term effects on the exposed fetus. *Pediatrics* 2013;131:e1009-24.
 13. Logan BA, Brown MS, Hayes MJ. Neonatal abstinence syndrome: treatment and pediatric outcomes. *Clin Obstet Gynecol* 2013;56:186-92.
 14. Ornoy A. The impact of intrauterine exposure versus postnatal environment in neurodevelopmental toxicity: long-term neurobehavioral studies in children at risk for developmental disorders. *Toxicol Lett* 2003;140-141:171-81.
 15. Bunikowski R, Grimmer I, Heiser A, Metze B, Schafer A, Obladen M. Neurodevelopmental outcome after prenatal exposure to opiates. *Eur J Pediatr* 1998;157:724-30.
 16. Hans SL, Jeremy RJ. Postneonatal mental and motor development of infants exposed in utero to opioid drugs. *Infant Ment Health J* 2001;22:300-15.
 17. Moe V. Foster-placed and adopted children exposed in utero to opiates and other substances: prediction and outcome at four and a half years. *J Dev Behav Pediatr* 2002;23:330-9.
 18. Hunt RW, Tzioumi D, Collins E, Jeffery HE. Adverse neurodevelopmental outcome of infants exposed to opiate in-utero. *Early Hum Dev* 2008;84:29-35.
 19. Baldacchino A, Arbuckle K, Petrie DJ, McCowan C. Erratum: neurobehavioral consequences of chronic intrauterine opioid exposure in infants and preschool children: a systematic review and meta-analysis. *BMC Psychiatry* 2015;15:134.
 20. Baldacchino A, Arbuckle K, Petrie DJ, McCowan C. Neurobehavioral consequences of chronic intrauterine opioid exposure in infants and preschool children: a systematic review and meta-analysis. *BMC Psychiatry* 2014;14:104.
 21. Oei JL, Melhuish E, Uebel H, Azzam N, Breen C, Burns L, et al. Neonatal abstinence syndrome and high school performance. *Pediatrics* 2017;139.
 22. 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.
 23. Hwang SS, Diop H, Liu CL, Yu Q, Babakhanlou-Chase H, Cui X, et al. Maternal substance use disorders and infant outcomes in the first year of life among Massachusetts singletons, 2003-2010. *J Pediatr* 2017;191:69-75.
 24. 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;37:1124-9.
 25. McQueen K, Murphy-Oikonen J. Neonatal abstinence syndrome. *N Engl J Med* 2016;375:2468-79.
 26. Temming LA, Dicke JM, Stout MJ, Rampersad RM, Macones GA, Tuuli MG, et al. Early second-trimester fetal growth restriction and adverse perinatal outcomes. *Obstet Gynecol* 2017;130:865-9.
 27. Monier I, Ancel PY, Ego A, Guellec I, Jarreau PH, Kaminski M, et al. Gestational age at diagnosis of early-onset fetal growth restriction and impact on management and survival: a population-based cohort study. *BJOG* 2017;124:1899-906.
 28. Barker DJ. Fetal origins of coronary heart disease. *BMJ* 1995;311:171-4.
 29. Appleton AA, Holdsworth EA, Kubzansky LD. A systematic review of the interplay between social determinants and environmental exposures for early-life outcomes. *Curr Environ Health Rep* 2016;3:287-301.
 30. Benningfield MM, Arria AM, Kaltenbach K, Heil SH, Stine SM, Coyle MG, et al. Co-occurring psychiatric symptoms are associated with increased psychological, social, and medical impairment in opioid dependent pregnant women. *Am J Addict* 2010;19:416-21.
 31. Ouimette PC, Kimerling R, Shaw J, Moos RH. Physical and sexual abuse among women and men with substance use disorders. *Alcohol Treat Q* 2000;18:7-17.
 32. Franca UL, Mustafa S, McManus ML. The growing burden of neonatal opiate exposure on children and family services in Massachusetts. *Child Maltreat* 2016;21:80-4.
 33. Patrick SW, Schiff DM. A public health response to opioid use in pregnancy. *Pediatrics* 2017;139.
 34. Sutter MB, Gopman S, Leeman L. Patient-centered care to address barriers for pregnant women with opioid dependence. *Obstet Gynecol Clin North Am* 2017;44:95-107.
 35. Maternal and Child Health Bureau. Federal Programs to Promote Child Health 2014 [12/13/2017]. <https://mchb.hrsa.gov/chusa14/special-features/federal-programs-promote-child-health.html>. Accessed December 13, 2017.
 36. Rosenbaum S. Medicaid. *N Engl J Med* 2002;346:635-40.

Table IV. Multivariable regression of NAS on health-care use from age 4 to 12 months*

Outcomes	aMR	95% CI	P value
Overall expenditure			
All type claims	1.27	1.19-1.35	<.0001
All type costs	2.16	1.98-2.35	<.0001
Inpatient			
Claims	4.21	1.88-9.44	.0005
Costs	5.02	4.36-5.78	<.0001
Outpatient			
Claims	1.14	1.08-1.21	<.0001
Costs	1.41	1.30-1.53	<.0001
ED			
Claims	1.80	1.47-2.19	<.0001
Costs	1.65	1.47-1.87	<.0001
Prescription drugs			
Claims	1.30	1.17-1.43	<.0001
Costs	1.64	1.49-1.82	<.0001

*Adjusted for sex, year of birth, US Census region, type of residence, type of insurance, pre-mature birth, growth retardation.