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Health outcomes in children with prenatal opioid exposure with and without neonatal abstinence syndrome in the first seven years of life: An observational cohort study

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Abstract

Introduction: Prenatal opioid exposure (POE) is a major public health consequence of the opioid epidemic. Long-term health outcomes associated with POE remain unclear, especially for children with POE without a diagnosis of neonatal abstinence syndrome (NAS). Here, we aimed to describe the health outcomes of children with POE and with POE and NAS compared to unexposed children during the first 7 years of life.

Design: In this retrospective observational cohort study, children born between 2015 and 2022 were identified from the Maternal and Infant Data Hub (MIDH), a data repository that continuously integrates maternal, neonatal, and pediatric records from two academic medical centers and one pediatric hospital system in the Midwest, USA.

Methods: International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10 CM) chapters A00-N99 served as outcomes of interest. Annual incidence and crude incidence rate ratios were calculated to explore descriptive differences between the exposed and unexposed groups.

Results: The study included 22,002 children, 20,130 (91.5%) of whom were unexposed and 1872 (8.5%) were exposed. Of the 1872 exposed children, 371 (19.8%) received a diagnosis of NAS (POE + NAS) and 1501 were in the POE-NAS group. Across all 7 years, exposed children had a higher incidence of diagnoses in most ICD-10 CM chapters compared to unexposed children. A consistently higher incidence rate ratio of diagnosis was observed in both POE-NAS and POE + NAS groups (vs. unexposed) related to mental and behavioral disorders, eye diagnoses, and diseases of the musculoskeletal system and gastrointestinal systems.

Conclusions: POE is associated with an increased risk of diagnoses in a number of ICD-10 CM chapters throughout childhood. These findings underscore the need for early screening and targeted interventions to support exposed children and improve their well-being. Further research is required to explore underlying mechanisms and develop preventive measures for at-risk populations.

Clinical Relevance: Understanding the conditions more often diagnosed in children with prenatal opioid exposure will help to improve care provided to this population.

As a result of study findings, nurses who provide care to children with prenatal opioid exposure can prioritize their assessments and allocate time, resources, and education toward areas more likely to be affected.

KEYWORDS
incidence rate ratio, long-term health outcomes, maternal infant data hub, neonatal abstinence syndrome, prenatal opioid exposure

INTRODUCTION

Prenatal opioid exposure (POE) has become a growing public health concern due in large part to the opioid epidemic that has affected many parts of the world. POE refers to the exposure of a fetus to licit or illicit opioids while in utero. One of the most well-known and immediate consequences of POE is neonatal abstinence syndrome (NAS), sometimes stated as neonatal opioid withdrawal syndrome or NOWS. NAS refers to the withdrawal symptoms that are sometimes present and can vary in severity in newborns exposed in utero to opioids, including irritability, tremors, difficulty feeding, and respiratory problems (Patrick et al., 2020). NAS is commonly used as a proxy for POE in epidemiological surveillance, and according to 2018 data from the United States (US), about seven newborns are diagnosed with NAS for every 1000 newborn hospital stays (Hirai et al., 2021).

Beyond NAS, preterm birth and low birthweight are both well documented, immediate outcomes associated with POE (Azuine et al., 2019). Conversely, the long-term health outcomes of children with POE are not as well understood, and this is an area in which research is still ongoing (Bann et al., 2023). Many children with POE develop and function normally, but there is evidence to suggest that exposed children may be at increased risk for certain health issues as they age (Arter et al., 2020; Rees et al., 2020). The extent to which these outcomes occur varies significantly between studies.

While there are unequivocal reasons to perform studies that investigate causal links between POE and long-term health, there is also value in performing descriptive studies to better equip clinicians with knowledge regarding health outcomes of children with POE. We are now in the fourth wave of the opioid epidemic (Manchikanti et al., 2022), and many children have already been exposed. Parents and caregivers of children with POE have already expressed concern and feelings of unpreparedness about their child's health and development needs as they age (Reichelt, 2021).

Moreover, little is known about the health outcomes of children with POE who do not receive a NAS diagnosis (Hall et al., 2019). The presence of a NAS diagnosis is commonly used to identify children with POE in research studies. However, not all children with POE receive a NAS diagnosis, thus limiting the generalizability of study results using NAS as a proxy for POE only to children with POE and NAS.

The objective of this study was to elucidate the incidence and crude incident rate ratio of health outcomes of children with POE during their first 7 years of life, while distinguishing between those with and without a NAS diagnosis, using a regional maternal infant data hub. This study does not attempt to link causality of outcomes to POE but serves to fill gaps in critical knowledge by describing the most common diagnoses observed in exposed children compared with unexposed children.

DESIGN

A retrospective, observational cohort study was performed using a regional dataset, the Maternal and Infant Data Hub (MIDH), to describe age-specific outcomes of children with POE and with POE and NAS compared to unexposed children within the dataset in the first 7 years of life.

MATERIALS AND METHODS

The MIDH continuously integrates maternal, neonatal, and pediatric records to produce a data repository, originating from two academic medical centers and one pediatric hospital system in the Midwest region of the US (Hall et al., 2018). Inpatient and outpatient maternal and child electronic health care records are integrated and linked to physician billing records, US census data, home visiting program data, and state vital records using validated probabilistic and deterministic approaches utilizing patient identifier fields (Hall et al., 2018). The MIDH is structured using the Observational Medical Outcomes Partnership data model (Stang et al., 2010). Once linked, a de-identified dataset was produced and made available to the research team, which included maternal and child diagnoses, procedures, medications, vital signs, laboratory results, gestational age and birthweight, and length of hospital stay. Procedures followed were in accordance with the ethical standards of the university and review was completed prior to the start of the study. The University's Internal Review Board (IRB) determined that this study was not research involving human subjects as defined by DHHS, DOJ, and FDA. Data are available upon written request to study authors.

Cohort selection

Children born in the Midwest region of the US between 2015 and 2022 with data in the MIDH were included in this study. A total of 312 children were excluded from the analysis because (1) ICD codes

were not in the dataset; (2) birthweight was >9000 gm; (3) they received a diagnosis for NAS without evidence of opioid exposure, indicating exposure to substances other than opioids. After exclusion criteria were applied, remaining children were categorized as belonging to one of three exposure groups: unexposed, exposed without a NAS diagnosis (POE–NAS), and exposed with a NAS diagnosis (POE + NAS).

Children were not excluded from analysis based on potential confounding factors (Feudtner et al., 2014), as the purpose of this study is to describe the incidence and incidence rate ratio of health outcomes of children with POE + NAS and POE–NAS compared with unexposed children in the first 7 years of life, and not to infer causal relationships between exposure and health outcomes. Preterm birth is commonly used as an exclusion criterion in epidemiological studies exploring child outcomes, but it is also a well-established outcome of prenatal opioid exposure (Graeve et al., 2022). Excluding children from analysis based on a factor associated with the exposure introduces a risk of sampling bias (Razaz et al., 2023).

Exposure

Prenatal opioid exposure encompasses the use of opioid medications for pain management or opioid use disorder treatment, the improper consumption of prescription or illicit opioid drugs, and exposure to a combination of opioids and other potentially harmful substances. The identification of POE in children included in this study was based on laboratory values and ICD-10-CM codes from the mother and child. Children were categorized as POE–NAS if their record contained one or both of the following: a positive toxicology result for opioids or metabolites during pregnancy or the birth hospitalization from the mother or child, the mother's diagnosis of opioid use or disorder during pregnancy or the birth hospitalization (see Table 1. Opioid Diagnoses), or the child's diagnosis indicating opioid exposure (i.e., ICD-10-CM codes P04.14 or P04.49). Children were categorized as POE + NAS if they received the diagnosis code P96.1 or F11.23 in addition to identification as prenatally opioid exposed. Exposure criteria are detailed in Figure 1.

Outcomes

Child health outcomes of interest for this study consisted of International Classification of Diseases and Related Health Problems, 10th Revision, Clinical Modification (ICD-10 CM) chapter codes. Specifically, the first 14 ICD-10 CM chapters (A00-N99), which comprise diseases and injury to body systems, were the outcomes of interest. The broadest level of ICD 10-CM code was used as the outcome of interest due to the exploratory and descriptive nature of this study. Each child's medical record was examined during each year of life through the last data pull in 2022. For each ICD 10-CM chapter (A00-N99) in each of the first 7 years of life, we determined whether the child had received at least one code in that chapter or not. Children who had not lived long enough to be considered for an age group were not counted (received an "NA") for the year of life under consideration.

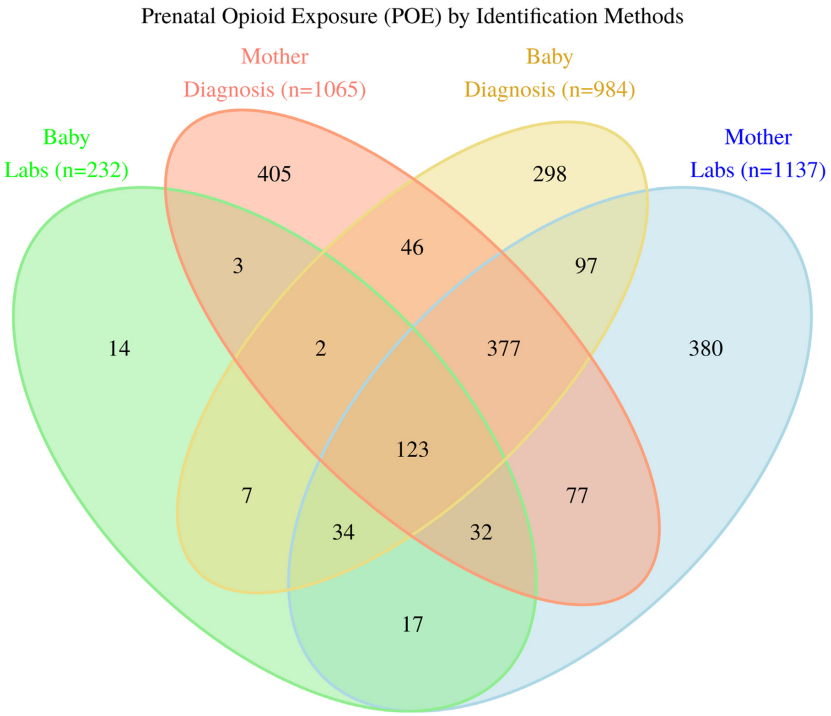

FIGURE 1 Flow chart for the process of identification of Prenatal Opioid Exposure (POE). Overlap of colors indicates children who were identified as POE through multiple methods.

Statistical analysis

Sample characteristics for the three groups (unexposed, POE–NAS, POE + NAS) can be found in Table 1. The crude incidence rate ratio (IRR) and 95% confidence interval (CI) between POE–NAS versus unexposed and POE + NAS versus unexposed were calculated on the 14 ICD-10 CM chapters (A00-N99) in each of the first 7 years of life. The complete view of all incidences, IRR and 95% CI by exposure group, year, and ICD-10 CM chapters can be found in Table 2. A brief summarized version of just the IRR by year and ICD-10 CM chapter can be found in Table 3a and 3b. The crude IRR was calculated by using the median-unbiased estimation method in the epitools R package (R Studio Team, 2020). Table production was performed using the tableone package (Yoshida, 2019); data manipulation was performed using the data table (Dowle & Srinivasan, 2018), and tidyr packages (Wickham & Henry, 2020). In all tables, if any row contained a cell with a frequency of less than 5, the corresponding frequency, incidence and/or IRR was replaced with a hyphen (-) to ensure the deidentification of the results.

RESULTS

Of the 22,314 children with records included in the MIDH, 22,002 (98.6%) were included in the analysis. Of those children, 20,130 (91.5%) were unexposed and 1872 (8.5%) were exposed. Of the 1872 exposed children, 371 (19.8%) also received a diagnosis of NAS (POE + NAS) and 1501 (80.2%) did not receive a diagnosis of NAS (POE–NAS). Sample characteristics differed between exposure groups. Mothers of children in the POE-NAS group had the lowest income and fraction with a high school education, and highest deprivation index and percentage who identified as Black or African American of all study groups. Children with POE–NAS had the lowest birthweight and were most often born at a gestational age of 34 weeks or before. Mothers of children in both exposed groups were less likely to be Hispanic, Latino, or of Spanish origin compared to unexposed children. Children with POE + NAS had the longest NICU length of stay, highest percentage with public insurance and who identified as White or Caucasian of all study groups. Notably, the differences between groups related to maternal self-report of race were most pronounced between those who identified as White and Black. The unexposed group comprised 33.7% Black and 43.6% White children. The POE–NAS group comprised 39.3% Black and 52% White children. However, the POE + NAS group comprised 5.9% Black and 89.5% White children.

The incidence and IRR of diagnoses in each of the ICD-10 CM chapters A00-N99 were descriptively compared among the three exposure groups in each of the first 7 years of life. Children from both exposure groups received higher incidence of diagnoses in most years and in most chapters compared to unexposed children. The exception to this is the POE + NAS group in Year 7, when there were not enough children in the sample who received diagnoses to perform statistical analyses in most chapters. For all study groups, incidence of diagnosis was rare, occurring in <5% of the sample half of the time. Incidence of diagnosis was highest in Year 1 for all study groups in all ICD-10 CM chapters except F01-F99: Mental, behavioral, and neurodevelopmental disorders and H60-H95: Diseases of the ear and mastoid process. A summary of results of all children receiving a diagnosis within ICD-10-CM chapters A00-N99 categorized by exposure status and year of life can be found in Table 2 and will be discussed below.

A00-B99: Certain infectious and parasitic diseases

Incidence of diagnosis in this chapter was one of the most common and was high for all groups, ranging from 17 to 35%, in the first 2 years of life. A decrease in incidence was observed in each group as the children aged, except for the POE + NAS group in Year 6, who experienced an increase. The incidence of diagnosis occurred 1.36 to 1.55 times more often (95% CI 0.85, 2.08; 1.10, 2.12) in the POE–NAS group compared with the unexposed group in Years 1–6. There were no major differences in IRR between the POE + NAS and unexposed groups after Year 1.

C00-D49: Neoplasms

Incidence of diagnosis was rare, occurring in <5% of children in all study groups and years.

D50-D89: Diseases of the blood and blood-forming organs and certain disorders involving immune mechanism

Incidence of diagnosis in this chapter was rare, occurring in <5% of children in all study groups and years, except for the NAS–POE group in Year 1 ($n = 103$, 6.9%).

E00-E89: Endocrine, nutritional, and metabolic diseases

Incidence of diagnosis in this chapter was rare, occurring in <5% of children in all study groups and years, except Year 1, where exposed groups received diagnoses 1.38 (POE–NAS: 95% CI 1.00, 1.86) and 2.31 (POE + NAS: 95% CI 1.37, 3.63) times more often than the unexposed group.

F01-F99: Mental, behavioral, and neurodevelopmental disorders

Diagnoses in this chapter were more common in exposed groups every year compared with unexposed. Every year except Year 5, the POE + NAS group had the highest incidence rates compared to unexposed and POE–NAS groups. Notably, the POE + NAS group had a

TABLE 1 Maternal and child demographics.

		Opioid exposure status		
	Overall	Unexposed	POE–NAS[a]	POE + NAS[b]
Characteristic	***N* = 22,002**	***N* = 20,130**	***N* = 1501**	***N* = 371**
Continuous variables	**Mean (SD)**			
Mothers age at delivery in years	28 (6)	28 (6)	29 (6)	29 (5)
Birthweight (grams)	3012 (709)	3037 (700)	2728 (767)	2762 (619)
Missing	38	35	3	0
Infant NICU length of stay (days)	6 (11)	5 (11)	8 (15)	18 (13)
Missing	184	149	27	8
Fraction with high school education	0.87 (0.09)	0.87 (0.09)	0.85 (0.09)	0.86 (0.08)
Missing	5657	5181	360	116
Median income	52,664 (28,961)	53,207 (29,204)	46,383 (26,217)	48,925 (21,998)
Missing	5657	5181	360	116
Deprivation index	0.40 (0.17)	0.40 (0.17)	0.44 (0.17)	0.42 (0.15)
Missing	5657	5181	360	116
Categorical variables	***N* (%)**			
Mother's ethnicity				
Hispanic, Latino, or of Spanish origin	2894 (13%)	2808 (14%)	82 (5.5%)	–[c]
Not Hispanic, Latino, or Spanish origin	18,994 (86%)	17,220 (86%)	1412 (94%)	362 (98%)
Unknown	114 (0.5%)	102 (0.5%)	7 (0.5%)	5 (1.3%)
Mother's race				
American Indian or Alaska Native	29 (0.1%)	26 (0.1%)	–	–
Asian	1010 (4.6%)	990 (4.9%)	20 (1.3%)	–
Black or African American	7390 (34%)	6778 (34%)	590 (39%)	22 (5.9%)
Hispanic	2649 (12%)	2579 (13%)	67 (4.5%)	–
Multiracial	303 (1.4%)	278 (1.4%)	17 (1.1%)	8 (2.2%)
Native Hawaiian or Pacific Islander	39 (0.2%)	39 (0.2%)	–	–
White or Caucasian	9898 (45%)	8786 (44%)	780 (52%)	332 (89%)
Other	615 (2.8%)	589 (2.9%)	23 (1.5%)	3 (0.8%)
Unknown	69 (0.3%)	65 (0.3%)	–	–
Baby's biological sex				
Male	11,264 (51%)	10,305 (51%)	771 (51%)	188 (51%)
Female	10,733 (49%)	9820 (49%)	730 (49%)	183 (49%)
Unknown	5 (<0.1%)	5 (<0.1%)	–	–
Baby insurance type				
Private	7414 (34%)	7165 (36%)	223 (15%)	26 (7.0%)
Public	14,310 (65%)	12,704 (63%)	1264 (84%)	342 (92%)
Self-pay	278 (1.3%)	261 (1.3%)	14 (0.9%)	–
Complex chronic condition status				
Yes	3984 (18%)	3538 (18%)	346 (23%)	100 (27%)
No	18,018 (82%)	16,592 (82%)	1155 (77%)	271 (73%)
Gestational age				
34 weeks or below	2141 (9.8%)	1818 (9.0%)	268 (18%)	55 (15%)
35 weeks and above	19,817 (90%)	18,276 (91%)	1226 (82%)	315 (85%)
Missing	44	36	7	1

[a]POE–NAS: Children with prenatal opioid exposure without a diagnosis for neonatal abstinence syndrome.
[b]POE + NAS: Children with prenatal opioid exposure with a diagnosis for neonatal abstinence syndrome.
[c]Categories with valid frequency <5 is represented with dash (–).

TABLE 2 Frequency, incidence rate, IRR, and 95% CI by exposure group for each year and ICD-10 CM chapter.

	Overall	Unexposed	POE–NAS[a]	POE–NAS vs. unexposed	POE + NAS[b]	POE + NAS vs. unexposed
	N (%)	*N* (%)	*N* (%)		*N* (%)	
ICD-10-CM chapter	Total *N* = 22,002	Group *N* = 20,130	*N* = 1501	IRR (95% CI)	*N* = 371	IRR (95% CI)
A00-B99: Certain infectious and parasitic diseases						
Year 1	5422 (24.6)	4796 (23.8)	496 (33.0)	1.37 (1.22, 1.54)	130 (35.0)	1.37 (1.07, 1.72)
Year 2	3664 (18.0)	3246 (17.5)	347 (24.1)	1.44 (1.26, 1.64)	71 (19.8)	0.78 (0.53, 1.10)
Year 3	1692 (10.0)	1483 (9.7)	180 (13.7)	1.41 (1.16, 1.70)	29 (9.0)	0.91 (0.55, 1.43)
Year 4	936 (6.9)	798 (6.5)	115 (9.8)	1.48 (1.15, 1.88)	23 (8.9)	1.04 (0.52, 1.84)
Year 5	469 (4.6)	399 (4.4)	59 (6.0)	1.55 (1.1, 2.12)	11 (5.4)	0.86 (0.26, 2.01)
Year 6	245 (3.5)	203 (3.3)	32 (4.6)	1.36 (0.85, 2.08)	10 (6.9)	1.15 (0.28, 3.02)
Year 7	72 (1.9)	59 (1.8)	9 (2.2)	0.91 (0.27, 2.26)	–	–
C00-D49: Neoplasms						
Year 1	563 (2.6)	508 (2.5)	38 (2.5)	1.22 (0.77, 1.84)	17 (4.60)	1.46 (0.57, 2.99)
Year 2	244 (1.2)	216 (1.2)	21 (1.5)	1.58 (0.80, 2.81)	7 (2.00)	1.31 (0.2, 4.11)
Year 3	103 (0.6)	91 (0.6)	9 (0.7)	1.75 (0.60, 4.06)	–	–
Year 4	67 (0.5)	60 (0.5)	6 (0.5)	1.12 (0.17, 3.82)	–	–
Year 5	41 (0.4)	36 (0.4)	5 (0.5)	1.61 (0.23, 5.83)	–	–
Year 6	28 (0.4)	25 (0.4)	–	–	–	–
Year 7	5 (0.1)	–	–	–	–	–
D50-D89: Diseases of the blood and blood-forming organs and certain disorders involving immune mechanism						
Year 1	967 (4.4)	851 (4.2)	103 (6.9)	1.86 (1.35, 2.51)	13 (3.5)	0.92 (0.32, 1.98)
Year 2	657 (3.2)	581 (3.1)	68 (4.7)	1.54 (1.08, 2.12)	8 (2.2)	0.37 (0.06, 1.15)
Year 3	486 (2.9)	426 (2.8)	55 (4.2)	1.16 (0.75, 1.73)	5 (1.5)	0.24 (0.01, 1.06)
Year 4	299 (2.2)	252 (2.1)	43 (3.7)	1.33 (0.77, 2.13)	–	–
Year 5	174 (1.7)	141 (1.6)	29 (3.0)	1.74 (0.94, 2.96)	–	–
Year 6	65 (0.9)	54 (0.9)	9 (1.3)	1.37 (0.40, 3.49)	–	–
Year 7	21 (0.6)	18 (0.6)	–	–	–	–
E00-E89: Endocrine, nutritional, and metabolic diseases						
Year 1	2016 (9.2)	1829 (9.1)	146 (9.7)	1.38 (1.00, 1.86)	41 (11.1)	2.31 (1.37, 3.63)
Year 2	661 (3.3)	583 (3.1)	64 (4.5)	1.52 (1.03, 2.17)	14 (3.9)	0.88 (0.27, 2.05)
Year 3	435 (2.6)	372 (2.4)	51 (3.9)	1.17 (0.66, 1.92)	12 (3.7)	1.08 (0.26, 2.83)
Year 4	318 (2.3)	281 (2.3)	33 (2.8)	1.43 (0.83, 2.29)	–	–
Year 5	203 (2.0)	172 (1.9)	27 (2.7)	1.51 (0.78, 2.66)	–	–
Year 6	138 (2.0)	122 (2.0)	14 (2.0)	1.14 (0.47, 2.33)	–	–
Year 7	75 (2.0)	61 (1.9)	14 (3.4)	2.42 (1.08, 4.86)	–	–
F01-F99: Mental, behavioral, and neurodevelopmental disorders						
Year 1	821 (3.7)	677 (3.4)	89 (5.9)	2.04 (1.38, 2.91)	55 (14.8)	8.50 (5.74, 12.16)
Year 2	1755 (8.6)	1520 (8.2)	163 (11.3)	1.16 (0.89, 1.48)	72 (20.1)	2.45 (1.69, 3.43)
Year 3	1899 (11.2)	1620 (10.6)	212 (16.1)	1.41 (1.14, 1.72)	67 (20.7)	2.18 (1.54, 3.00)
Year 4	1431 (10.5)	1225 (10.1)	168 (14.4)	1.46 (1.18, 1.80)	38 (14.7)	1.51 (0.94, 2.29)
Year 5	1028 (10.0)	870 (9.6)	134 (13.6)	1.59 (1.25, 1.98)	24 (11.8)	1.04 (0.52, 1.84)
Year 6	554 (7.9)	461 (7.5)	75 (10.7)	1.25 (0.88, 1.73)	18 (12.4)	1.98 (0.98, 3.52)
Year 7	184 (4.9)	148 (4.5)	27 (6.6)	1.67 (0.98, 2.70)	9 (9.6)	1.57 (0.37, 4.16)

TABLE 2 (Continued)

ICD-10-CM chapter	Overall *N* (%) Total *N* = 22,002	Unexposed *N* (%) Group *N* = 20,130	POE–NAS[a] *N* (%) *N* = 1501	POE–NAS vs. unexposed IRR (95% CI)	POE + NAS[b] *N* (%) *N* = 371	POE + NAS vs. unexposed IRR (95% CI)
G00-G99: Diseases of the nervous system						
Year 1	1220 (5.5)	1081 (5.4)	111 (7.4)	0.98 (0.63, 1.45)	28 (7.5)	1.43 (0.65, 2.68)
Year 2	713 (3.5)	637 (3.4)	62 (4.3)	1.00 (0.55, 1.65)	14 (3.9)	0.96 (0.23, 2.50)
Year 3	618 (3.6)	538 (3.5)	62 (4.7)	1.15 (0.67, 1.82)	18 (5.6)	1.82 (0.71, 3.74)
Year 4	489 (3.6)	407 (3.3)	69 (5.9)	1.59 (1.00, 2.40)	13 (5.0)	2.08 (0.81, 4.3)
Year 5	338 (3.3)	271 (3.0)	53 (5.4)	1.73 (1.03, 2.74)	14 (6.9)	2.56 (0.89, 5.64)
Year 6	210 (3.0)	168 (2.7)	36 (5.1)	1.85 (0.94, 3.30)	6 (4.1)	0.00 (0.00, 2.77)
Year 7	83 (2.2)	67 (2.1)	14 (3.4)	1.73 (0.57, 4.16)	–	–
H00-H59: Diseases of the eye and adnexa						
Year 1	3007 (13.7)	2659 (13.2)	255 (17.0)	1.06 (0.86, 1.29)	93 (25.1)	2.56 (1.94, 3.30)
Year 2	1905 (9.4)	1678 (9.1)	159 (11.1)	1.04 (0.81, 1.31)	68 (19.0)	2.37 (1.67, 3.24)
Year 3	1198 (7.1)	1044 (6.8)	114 (8.6)	1.11 (0.83, 1.44)	40 (12.4)	2.18 (1.41, 3.20)
Year 4	893 (6.6)	767 (6.3)	100 (8.6)	1.37 (1.03, 1.80)	26 (10.0)	1.77 (0.99, 2.90)
Year 5	659 (6.4)	569 (6.3)	75 (7.6)	1.11 (0.78, 1.53)	15 (7.4)	0.67 (0.20, 1.55)
Year 6	394 (5.6)	329 (5.4)	50 (7.1)	1.25 (0.82, 1.82)	15 (10.3)	2.41 (1.14, 4.42)
Year 7	127 (3.4)	109 (3.3)	14 (3.4)	0.82 (0.34, 1.66)	–	–
H60-H95: Diseases of the ear and mastoid process						
Year 1	3524 (16.0)	3163 (15.7)	285 (19.0)	1.24 (1.07, 1.43)	76 (20.5)	1.11 (0.8, 1.49)
Year 2	3854 (19.0)	3438 (18.6)	331 (23.0)	1.28 (1.11, 1.46)	85 (23.7)	1.34 (1.01, 1.73)
Year 3	1934 (11.4)	1725 (11.2)	164 (12.4)	1.09 (0.89, 1.33)	45 (13.9)	1.18 (0.77, 1.71)
Year 4	1029 (7.6)	901 (7.4)	111 (9.5)	1.25 (0.96, 1.60)	17 (6.6)	1.04 (0.54, 1.79)
Year 5	526 (5.1)	465 (5.1)	53 (5.4)	1.07 (0.73, 1.52)	8 (3.9)	0.95 (0.33, 2.05)
Year 6	337 (4.8)	295 (4.8)	37 (5.3)	1.27 (0.82, 1.87)	–	–
Year 7	95 (2.5)	84 (2.6)	9 (2.2)	0.66 (0.20, 1.61)	–	–
I00-I99: Diseases of the circulatory system						
Year 1	1096 (5.0)	958 (4.8)	111 (7.4)	1.77 (0.99, 2.92)	27 (7.3)	2.59 (0.91, 5.69)
Year 2	333 (1.6)	295 (1.6)	32 (2.2)	1.80 (0.61, 4.16)	6 (1.7)	1.72 (0.07, 7.78)
Year 3	211 (1.2)	185 (1.2)	24 (1.8)	0.86 (0.13, 2.84)	–	–
Year 4	131 (1.0)	111 (0.9)	18 (1.5)	0.00 (0.00, 3.78)	–	–
Year 5	89 (0.9)	74 (0.8)	14 (1.4)	1.00 (0.04, 5.09)	–	–
Year 6	50 (0.7)	42 (0.7)	5 (0.7)	0.00 (0.00, 3.35)	–	–
Year 7	15 (0.4)	14 (0.4)	–	–	–	–
J00-J99: Diseases of the respiratory system						
Year 1	7280 (33.1)	6539 (32.5)	591 (39.4)	1.20 (1.08,1.33)	150 (40.4)	1.09 (0.86, 1.36)
Year 2	5449 (26.8)	4880 (26.3)	457 (31.8)	1.18 (1.05, 1.33)	112 (31.3)	1.10 (0.84, 1.39)
Year 3	3148 (18.5)	2774 (18.1)	302 (22.9)	1.21 (1.04, 1.40)	72 (22.3)	1.17 (0.84, 1.57)
Year 4	1989 (14.6)	1739 (14.3)	218 (18.6)	1.19 (0.99, 1.43)	32 (12.4)	0.81 (0.48, 1.27)
Year 5	1226 (11.9)	1049 (11.5)	148 (15.1)	1.43 (1.15, 1.75)	29 (14.2)	0.97 (0.52, 1.64)
Year 6	715 (10.2)	616 (10.0)	84 (12.0)	1.12 (0.83, 1.47)	15 (10.3)	0.65 (0.23, 1.39)
Year 7	217 (5.8)	186 (5.7)	25 (6.1)	1.26 (0.75, 1.99)	6 (6.4)	0.76 (0.12, 2.38)

(Continues)

TABLE 2 (Continued)

ICD-10-CM chapter	Overall *N* (%) Total *N* = 22,002	Unexposed *N* (%) Group *N* = 20,130	POE–NAS[a] *N* (%) *N* = 1501	POE–NAS vs. unexposed IRR (95% CI)	POE + NAS[b] *N* (%) *N* = 371	POE + NAS vs. unexposed IRR (95% CI)
K00-K95: Diseases of the digestive system						
Year 1	4745 (21.6)	4216 (20.9)	412 (27.4)	1.23 (1.07, 1.41)	117 (31.5)	1.70 (1.33, 2.15)
Year 2	2371 (11.7)	2113 (11.4)	206 (14.3)	1.15 (0.94, 1.39)	52 (14.5)	1.24 (0.83, 1.78)
Year 3	1399 (8.2)	1239 (8.1)	136 (10.3)	1.13 (0.87, 1.43)	24 (7.4)	0.80 (0.41, 1.38)
Year 4	1007 (7.4)	868 (7.1)	125 (10.7)	1.46 (1.13, 1.85)	14 (5.4)	0.94 (0.45, 1.70)
Year 5	710 (6.9)	591 (6.5)	103 (10.5)	1.80 (1.38, 2.33)	16 (7.8)	1.09 (0.46, 2.12)
Year 6	400 (5.7)	341 (5.5)	44 (6.3)	1.16 (0.76, 1.69)	15 (10.3)	2.06 (0.93, 3.90)
Year 7	141 (3.7)	119 (3.7)	18 (4.4)	1.14 (0.55, 2.10)	–	–
L00-L99: Diseases of the skin and subcutaneous tissue						
Year 1	5399 (24.5)	4825 (24.0)	435 (29.0)	1.26 (1.11, 1.42)	139 (37.5)	1.55 (1.24, 1.91)
Year 2	3047 (15.0)	2700 (14.6)	278 (19.3)	1.33 (1.14, 1.54)	69 (19.3)	1.30 (0.94, 1.75)
Year 3	1637 (9.6)	1455 (9.5)	160 (12.1)	1.26 (1.03, 1.54)	22 (6.8)	0.77 (0.43, 1.25)
Year 4	977 (7.2)	856 (7.0)	113 (9.7)	1.29 (1.00, 1.64)	8 (3.1)	0.38 (0.12, 0.89)
Year 5	644 (6.3)	560 (6.2)	77 (7.8)	1.50 (1.13, 1.95)	7 (3.4)	0.45 (0.11, 1.16)
Year 6	311 (4.4)	274 (4.5)	34 (4.9)	1.14 (0.74, 1.69)	–	–
Year 7	96 (2.6)	82 (2.5)	13 (3.2)	1.15 (0.50, 2.26)	–	–
M00-M99: Diseases of the musculoskeletal system and connective tissue						
Year 1	2276 (10.3)	1886 (9.4)	189 (12.6)	1.21 (0.93, 1.56)	201 (54.2)	10.35 (8.53, 12.44)
Year 2	1260 (6.2)	1075 (5.8)	128 (8.9)	1.24 (0.9, 1.66)	57 (15.9)	3.03 (1.97, 4.42)
Year 3	768 (4.5)	671 (4.4)	77 (5.8)	0.92 (0.58, 1.38)	20 (6.2)	1.50 (0.68, 2.82)
Year 4	522 (3.8)	446 (3.7)	58 (5.0)	1.10 (0.68, 1.68)	18 (6.9)	2.61 (1.29, 4.65)
Year 5	349 (3.4)	292 (3.2)	47 (4.8)	1.46 (0.91, 2.22)	10 (4.9)	1.50 (0.45, 3.54)
Year 6	204 (2.9)	169 (2.7)	30 (4.3)	1.09 (0.53, 2.00)	–	–
Year 7	69 (1.8)	62 (1.9)	6 (1.5)	0.72 (0.17, 2.00)	–	–
N00-N99: Diseases of the genitourinary system						
Year 1	1990 (9.0)	1787 (8.9)	159 (10.6)	0.91 (0.70, 1.16)	44 (11.9)	1.08 (0.64, 1.68)
Year 2	794 (3.9)	710 (3.8)	70 (4.9)	0.95 (0.63, 1.37)	14 (3.9)	0.62 (0.19, 1.45)
Year 3	426 (2.5)	366 (2.4)	53 (4.0)	1.47 (0.93, 2.21)	7 (2.2)	1.17 (0.36, 2.75)
Year 4	360 (2.6)	310 (2.5)	39 (3.3)	0.89 (0.49, 1.48)	11 (4.2)	1.29 (0.39, 3.04)
Year 5	290 (2.8)	243 (2.7)	40 (4.1)	1.69 (1.05, 2.59)	7 (3.4)	1.32 (0.31, 3.47)
Year 6	162 (2.3)	135 (2.2)	20 (2.9)	1.13 (0.55, 2.07)	7 (4.8)	2.08 (0.49, 5.55)
Year 7	53 (1.4)	41 (1.3)	9 (2.2)	3.65 (1.39, 8.53)	–	–

Note: Categories with valid frequency <5 is represented with dash (–).

[a]POE–NAS: Children with prenatal opioid exposure without a diagnosis for neonatal abstinence syndrome.

[b]POE + NAS: Children with prenatal opioid exposure with a diagnosis for neonatal abstinence syndrome.

rate of diagnoses that was 8.5 (95% CI 5.74, 12.16) times higher than that of the unexposed in Year 1. Trends for this chapter differed from others, as the incidence of diagnoses peaked in Year 3, and >5% of exposed children received diagnoses every year, which only occurred in one other chapter (J00-J99: Diseases of the Respiratory System).

G00-G99: Diseases of the nervous system

Incidence of diagnosis in this chapter was higher in exposed children each year but was uncommon in all groups and years (ranging from <5% to 7.5%) compared to other chapters.

TABLE 3A POE–NAS versus unexposed incident rate ratio (IRR).[a,b]

ICD-10-CM chapters	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7
A00-B99: Certain infectious and parasitic diseases	1.37	1.44	1.41	1.48	1.55	1.36	0.91
C00-D49: Neoplasms	1.22	1.58	1.75	1.12	1.61	–	–
D50-D89: Diseases of the blood and blood-forming organs and certain disorders involving immune mechanism	1.86	1.54	1.16	1.33	1.74	1.37	–
E00-E89: Endocrine, nutritional, and metabolic diseases	1.38	1.52	1.17	1.43	1.51	1.14	2.42
F01-F99: Mental, behavioral, and neurodevelopmental disorders	2.04	1.16	1.41	1.46	1.59	1.25	1.67
G00-G99: Diseases of the nervous system	0.98	1	1.15	1.59	1.73	1.85	1.73
H00-H59: Diseases of the eye and adnexa	1.06	1.04	1.11	1.37	1.11	1.25	0.82
H60-H95: Diseases of the ear and mastoid process	1.24	1.28	1.09	1.25	1.07	1.27	0.66
I00-I99: Diseases of the circulatory system	1.77	1.8	0.86	0	1	0	–
J00-J99: Diseases of the respiratory system	1.2	1.18	1.21	1.19	1.43	1.12	1.26
K00-K95: Diseases of the digestive system	1.23	1.15	1.13	1.46	1.8	1.16	1.14
L00-L99: Diseases of the skin and subcutaneous tissue	1.26	1.33	1.26	1.29	1.5	1.14	1.15
M00-M99: Diseases of the musculoskeletal system and connective tissue	1.21	1.24	0.92	1.1	1.46	1.09	0.72
N00-N99: Diseases of the genitourinary system	0.91	0.95	1.47	0.89	1.69	1.13	3.65

Note: Categories with valid frequency <5 is represented with dash (–).

[a]Incident rate ratios (IRR) are calculated using median-unbiased estimation. IRRs are calculated for each year individually. Calculations were completed in R using the epitools package.

[b]Table shading indicates deviations above 1, meaning that the exposed group had higher incidence than the unexposed group.

H00-H59: Diseases of the eye and adnexa

Incidence of diagnosis in this chapter was common in Years 1–6 and highest in Year 1 for all study groups. Incidence was higher in exposed children compared with unexposed children every year. In Years 1–3 and 6, POE + NAS received diagnoses more than twice as often as unexposed.

H60-H95: Diseases of the ear and mastoid process

Incidence of diagnosis in this chapter was common in Years 1–4 and highest in Year 2 for all study groups. Incidence was higher in exposed children in Years 1–6, but a decrease in incidence was observed in every group each year between Years 2 and 7.

I00-I99: Diseases of the circulatory system

Incidence of diagnosis in this chapter was rare, occurring in <5% of children in all study groups each year, except for Year 1, where approximately 7% of both exposed groups received a diagnosis.

J00-J99: Diseases of the respiratory system

Incidence of diagnosis in this chapter was the most common for all study groups compared to other ICD 10-CM chapters. In Year 1, 32.5–40.4% of children across groups received a diagnosis. Diagnosis rates decreased for all groups as the children aged but were still common (>5% of children diagnosed) in Year 7. Incidence was higher for exposed children every year compared to the unexposed group.

K00-K95: Diseases of the digestive system

Incidence of diagnosis in this chapter was common in Years 1–6 and was highest in Year 1, ranging from 20.9 to 30.5%, for all study groups. A decrease in incidence was observed in all groups in Years 1–3. In Years 4–7, a decrease in incidence was observed for unexposed, but incidence rates remained similar in Years 3–5 for POE–NAS before decreasing in Years 6–7. The NAS + POE group experienced an increase in incidence between Years 4–6. IRR was moderately higher in the POE–NAS and POE + NAS groups compared to the unexposed groups in Years 1, 4, 5, and Years 1, 2, and 6, respectively.

TABLE 3B POE + NAS versus unexposed incident rate ratio (IRR).[a,b]

ICD-10-CM chapters	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7
A00-B99: Certain infectious and parasitic diseases	1.37	0.78	0.91	1.04	0.86	1.15	–
C00-D49: Neoplasms	1.46	1.31	–	–	–	–	–
D50-D89: Diseases of the blood and blood-forming organs and certain disorders involving immune mechanism	0.92	0.37	0.24	–	–	–	–
E00-E89: Endocrine, nutritional, and metabolic diseases	2.31	0.88	1.08	–	–	–	–
F01-F99: Mental, behavioral, and neurodevelopmental disorders	8.5	2.45	2.18	1.51	1.04	1.98	1.57
G00-G99: Diseases of the nervous system	1.43	0.96	1.82	2.08	2.56	0	–
H00-H59: Diseases of the eye and adnexa	2.56	2.37	2.18	1.77	0.67	2.41	–
H60-H95: Diseases of the ear and mastoid process	1.11	1.34	1.18	1.04	0.95	–	–
I00-I99: Diseases of the circulatory system	2.59	1.72	–	–	–	–	–
J00-J99: Diseases of the respiratory system	1.09	1.1	1.17	0.81	0.97	0.65	0.76
K00-K95: Diseases of the digestive system	1.7	1.24	0.8	0.94	1.09	2.06	–
L00-L99: Diseases of the skin and subcutaneous tissue	1.55	1.3	0.77	0.38	0.45	–	–
M00-M99: Diseases of the musculoskeletal system and connective tissue	10.35	3.03	1.5	2.61	1.5	–	–
N00-N99: Diseases of the genitourinary system	1.08	0.62	1.17	1.29	1.32	2.08	–

Note: Categories with valid frequency <5 is represented with dash (–).

[a]Incident rate ratios (IRR) are calculated using median-unbiased estimation. IRRs are calculated for each year individually. Calculations were completed in R using the epitools package.

[b]Table shading indicates deviations above 1, meaning that the exposed group had higher incidence than the unexposed group.

L00-L99: Diseases of the skin and subcutaneous tissue

Incidence of diagnosis in this chapter was common for all study groups in Years 1–3 and for unexposed and POE–NAS in Years 4–5. Incidence was most common in Year 1 with 24–37.5% of all children receiving a diagnosis. Exposed groups had higher incidence than unexposed in Years 1–5, and incidence was rare for all groups in Years 6–7.

M00-M99: Diseases of the musculoskeletal system and connective tissue

Incidence of diagnosis in this chapter was common in Years 1–2 and highest in Year 1 for all study groups. The POE + NAS group had markedly higher incidence rates and IRRs compared to the unexposed and POE–NAS groups in Years 1 and 2. The IRRs ranged from 10.35 in Year 1 to 3.03 in Year 2. Incidence declined for all groups as the children aged so that in Years 5–7, diagnosis was rare.

N00-N99: Diseases of the genitourinary system

Incidence of diagnosis in this chapter was rare, occurring in <5% of children in all study groups each year except Year 1, where incidence ranged from 8.9 to 11.9%, with the highest incidence occurring in the exposed groups.

DISCUSSION

In the present study, we examined the health outcomes of children in each year of life through the first 7 years according to opioid exposure status and NAS diagnosis. Several differences in sample characteristics and health outcomes were found between groups. Regarding demographics, the distribution of the sample according to maternal self-reported race in the unexposed and POE–NAS groups closely aligned with the US Census Bureau reported demographics for the region, 50.4% White and 39.6% Black (2023). However, differences were pronounced in the POE + NAS group, with a much higher proportion of White children (89.5%) and much lower proportion of Black children (5.9%). The difference in NAS diagnoses between Black

and White children identified in this dataset has also been reported in other studies using regional and national US datasets (Ramphul et al., 2020; Decker et al., 2023; Dookeran et al., 2023). Exploring the factors influencing this disparity in NAS diagnoses was outside the scope of this study. However, this is a pressing finding requiring further investigation, considering the results of a recent population-based, retrospective cohort study that associated POE–NAS with higher infant mortality compared to POE + NAS and the reference population (Leyenaar et al., 2021). Differences between groups related to other sample characteristics were also noted. While it is appreciated that these differences can influence health outcomes, we did not control for them, as we are not inferring casual relationships between exposure and health outcomes. Rather, we are reporting on diagnoses more often observed in children with POE in the first 7 years of life to increase clinicians' awareness and surveillance to improve early identification and mitigation of long-term issues.

Exposed children (both POE–NAS and POE + NAS) in this study consistently received diagnoses in each chapter more often than unexposed children. Incidence of diagnoses was highest in Year 1 for all study groups in all chapters, except for chapters F01-F99: mental, behavioral, and neurodevelopmental disorders and H60-H95: diseases of the ear and mastoid process, where diagnoses for all groups peaked in Year 3. Notably, the most pronounced differences in rates of diagnoses were observed between the POE + NAS and unexposed groups in Year 1 related to musculoskeletal and connective tissue disorders (IRR 10.35 (8.53, 12.44)) and mental, behavioral, and neurodevelopmental disorders (IRR 8.50 (5.74, 12.16)). Musculoskeletal findings are consistent with prior research, where muscle/joint tightness, tremors, torticollis, and musculoskeletal congenital anomalies were observed more often in exposed children (Boggess & Payne, 2022; Wen et al., 2021; Yeoh et al., 2019). Mental, behavioral, and neurodevelopmental disorder findings are also consistent with prior research (Arter et al., 2022; Azuine et al., 2019; Conradt et al., 2019), where conduct disorder, emotional disturbance, and ADHD were more often observed in exposed children. Children with POE + NAS were also approximately twice as likely to receive eye diagnoses in most years compared with unexposed children. These findings are consistent with prior, longitudinal research indicating that POE is strongly associated with the risk of ocular muscle disorders (Auger et al., 2020).

The POE–NAS group also had elevated IRRs compared to the unexposed group. Most pronounced differences were observed in Year 7 related to genitourinary disorders (IRR 3.65 (1.39, 8.53)) and endocrine, nutritional, and metabolic diseases (IRR 2.42 (1.08, 4.86)). Kelty and Hulse (2017) similarly noted an increase in genitourinary disorders in exposed children, which they attributed to the elevated rates of genitourinary birth abnormalities observed in their population. Findings from the current study related to differences in rates of endocrine, nutritional, and metabolic diagnoses between the unexposed and POE–NAS groups are novel in that no other study has examined these outcomes in children past the infancy stage. However, it has recently been posited that growth trajectories of infants with POE may involve excessive catch-up growth, which increases the risk for adiposity and obesity as they age (Yen & Davis, 2022). While differences in incidence rates between the POE–NAS and unexposed groups were not as pronounced as differences between the POE + NAS and unexposed groups, the POE–NAS group still received diagnoses more often than unexposed children in each of the 7 years related to E00-E89: Endocrine, Nutritional, and Metabolic Diseases; F01-F99: Mental, Behavioral, and Neurodevelopmental Disorders; J00-J99: Diseases of the Respiratory System; K00-K95: Diseases of the Digestive System; and L00-L99: Diseases of the Skin and Subcutaneous Tissue. The study data support the implementation of protocols to screen children with POE–NAS for diagnoses related to these systems using validated tools.

Several limitations should be acknowledged. There is potential that some of the children in the dataset were misclassified based on exposure status, as currently, no evidence-based practice guidelines exist to standardize the process of identifying POE (Jansson & Patrick, 2019). To minimize misclassification based on exposure status, multiple data points were used as exposure indicators rather than just one. Loss of follow-up is also a potential limitation. Since outcomes of interest in this study were ICD-10 CM codes, it is difficult to discern whether a missing datapoint was due to a child not receiving the diagnosis code under consideration or if the child no longer accessed care in the network. Lastly, there were less data available for children in the older age groups than in the younger age groups (e.g., there were 1 year of data on 7-year-old children compared with 7 years of data on 1-year-old children in the dataset). As such, after categorizing the sample by exposure status, analysis in the older age groups was somewhat limited by a small sample size.

We previously published findings of a study that examined individual ICD-9 and ICD-10 codes in children in the first 3 years of life (Arter et al., 2021) that was constrained by three limitations: the challenge of aligning ICD-9 and ICD-10 coding systems, the granularity of individual ICD codes, and a short analysis period (3 years). In contrast, the current study distinguishes itself by exclusively focusing on ICD-10 codes, utilizing chapter-level diagnoses instead of individual codes, and extending the analysis period to encompass the first 7 years of life. These refinements enhance the robustness and comprehensiveness of our investigation into the impact of prenatal opioid exposure on children's health outcomes.

Overall, the present study findings provide evidence that POE is associated with various diagnoses throughout the first 7 years of life. The higher incidence rates of diagnoses in exposed children, particularly related to mental and behavioral disorders, eye diagnoses, and diseases of the musculoskeletal system and gastrointestinal systems raise concerns about the potential long-term health impacts associated with prenatal opioid exposure.

CONCLUSION

Study results provide valuable information for nurses and highlight the importance of early screening, intervention, and support

for children with POE to address their specific health needs and improve their overall well-being as they grow. Study findings can assist nurses in focusing their assessments of children with POE in areas with higher incidence rates and rate ratios, including the musculoskeletal, genitourinary, and vision systems, as well as mental health and nutrition, to ensure early identification of issues. Study findings can also inform patient and family education related to potential issues for which to monitor at home between health care visits in each of the first 7 years of life. Addressing the needs of this high-risk, vulnerable population early and coordinating connections to appropriate services is critical to mitigating the impact of poor health outcomes associated with POE. Moving forward, the results of this study will be used to determine specific ICD-10 CM chapters on which to focus our next study, better understanding subpopulations of children with POE and with POE and NAS. Future studies will also explore specific diagnoses within chapters to better understand what is driving the higher incidence of diagnosis in some chapters compared to others.

CLINICAL RESOURCES

American Academy of Pediatrics Clinical Report: Neonatal Opioid Withdrawal Syndrome. https://publications.aap.org/pediatrics/article/146/5/e2020029074/75310/Neonatal-Opioid-Withdrawal-Syndrome.

Substance Use and Mental Health Disorders: Supporting Kinship Families. https://ncsacw.acf.hhs.gov/training/videos-and-webinars/supporting-kinship-families-webinar/.

Neonatal Opioid Withdrawal Syndrome: A Guide for Families. https://static1.squarespace.com/static/5e8f4e2a4eaf8154a7c9c939/t/64c00679d46fca63f460a775/1690306174120/23opqc_NOWS_patient_guide23_FINAL....pdf.

Disrupting Stigma: How Understanding, Empathy, and Connection Can Improve Outcomes for Families Affected by Substance Use and Mental Disorders. https://cwlibrary.childwelfare.gov/discovery/delivery/01CWIG_INST:01CWIG/1218764930007651.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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