

Neonatal Abstinence Syndrome in North Carolina: Incidence and Characteristics among Infants and Mothers

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BACKGROUND Neonatal abstinence syndrome (NAS) is a complex disorder characterized by withdrawal symptoms secondary to *in utero* exposure to drugs capable of producing physical dependence. The objective of this study was to determine the incidence of NAS, as well as infant and maternal characteristics associated with NAS in North Carolina (NC).

METHODS This retrospective, cross-sectional, observational study used the State Inpatient Database (SID) to compare the incidence rates of NAS for NC for the year 2016 to historical data (years 2000 to 2013). A multivariable logistic regression model including available co-variables of interest was constructed.

RESULTS Overall NAS incidence rate (IR) for NC was found to be 9.7 per 1,000 live births, a 32.3-fold increase since 2000 (IR=0.3 in 2000). The multivariable logistic regression model suggested race group (both black [OR 0.11; 95% CI: 0.08, 0.16] and 'other' [OR 0.43; 95% CI: 0.31, 0.61] vs white), ethnicity [OR 0.43; 95% CI: 0.31, 0.61], insurance group (both 'other/self-pay' [OR 0.35; 95% CI: 0.24, 0.52] and 'private insurance' [OR 0.07; 95% CI: 0.05, 0.10] vs Medicaid/Medicare), region (Piedmont [OR 0.62; 95% CI: 0.50, 0.79] vs Mountain), income quartile (both 4th [OR 0.45; 95% CI: 0.26, 0.79] and 3rd [OR 0.70; 95% CI: 0.50, 0.96] vs 1st), county population size (50k-249k [OR 0.54; 95% CI: 0.34, 0.86] vs ≥ 1 million), birth weight [OR 0.87; 95% CI: 0.78, 0.98], and length of stay [OR 1.23; 95% CI: 1.20, 1.26] as potentially important predictors of NAS.

LIMITATIONS Only hospitals providing data to the SID for 2016 were included and ICD-9 codes, in use at the time of data collection, were used.

CONCLUSIONS The incidence of NAS has increased in NC in 2016 compared to prior years spanning back to 2000. Specific infant and maternal characteristics including race, ethnicity, payer type, geographic region, county population, parental income status, birth weight, and length appear to be associated with an infant bearing the diagnosis of NAS.

Neonatal Abstinence Syndrome (NAS) is a medical condition in infants born to a mother who used substances during the pregnancy that are capable of producing withdrawal, including prescribed medications taken correctly, medications being misused, illicit substances, or with medication-assisted treatment. Infants with NAS exhibit a range of withdrawal signs and symptoms representing neonatal neurobehavioral dysregulation within the first few days of life. While NAS is most commonly associated with *in utero* opioid exposure, other substances known to produce physical dependence have been associated with an abstinence syndrome. The pathophysiology of NAS and factors that influence its severity are not completely understood. However, altered levels of neurotransmitters such as norepinephrine, dopamine, and serotonin are presumed to play a significant role [1].

In the United States, there has been a reported increase in maternal use of opioid products. [2] Several factors need to be considered when assessing the increased use by mothers, including legitimate pain relief, medication-assisted treatment for opioid use disorders, illicit reasons, and the legality of procurement. In these situations, the developing fetus is exposed to the opioid substances *in utero* which establishes the possibility for the development of NAS upon birth. Prior medical literature has established an association

between the rise in maternal use of opioids to an increased incidence of NAS [3-5]. The objective of this study was to determine the incidence of NAS, as well as infant and maternal characteristics associated with NAS in the state of North Carolina.

Study Methodology

This study utilized the North Carolina State Inpatient Database (SID), part of the Healthcare Cost and Utilization Project (HCUP), administered by the Agency for Healthcare Research and Quality (AHRQ). [6]. Information contained in the SID is compiled from inpatient discharge records from hospitals in individual participating states. The SID provides a unique view of inpatient care from ~97% of community hospital discharges at a statewide level on an annual basis [6]. Community hospitals, as defined by American Hospital Association (AHA), include "all nonfederal, short-term, general and other specialty hospitals, excluding hospital units

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of institutions.” Included among community hospitals are academic medical centers and specialty hospitals such as obstetrics, gynecology, ear nose throat, short-term rehabilitation, orthopedic, and pediatric hospitals. Some community hospitals may not be included in the SID because their data were not provided by the data source [7]. SID contains information related to over 100 different variables including insurance type, diagnosis, procedures, admission status, demographics, expected payment source, total charges, and length of stay [6].

We utilized data contained in the SID for North Carolina for the year 2016 under a data use agreement with HCUP. We utilized 2016 SID data because it was the latest data available at the time of the study. A subject was categorized as having NAS when an ICD-10 code of P96.1, P96.2, or P04.4 was reported. Subjects missing data for key variables of interest were excluded at the discretion of the investigators.

The endpoint for all analyses was the incidence of NAS. The incidence rate in North Carolina was computed based

on the 2016 SID data and a plot was created to compare the 2016 NAS incidence to prior years using a published report from the Centers for Disease Control and Prevention (CDC) that also utilized the SID [5]. Details on the covariates utilized in the CDC study can be found in references 6-9.

Demographics and participant characteristics were summarized by NAS (yes vs. no). A multivariable logistic regression model was constructed to evaluate the predictive value of each independent variable, adjusting for covariates of interest available in the database, on NAS. These covariates, along with all variables included in the model, can be found in Table 2. Odds ratios (ORs) with corresponding 95% CIs for each level of each variable included in the model, in comparison to each variable’s reference group, were generated and reported. As this was a retrospective, hypothesis generating study, no adjustments for multiple comparisons were made. In addition, following current recommended best practices against significance testing, statistical significance was not reported for any results [10]. All analyses were generated using SAS version 9.4 [11].

TABLE 1.
Maternal and Infant Characteristics by NAS Status in North Carolina in 2016 (N = 115,637)

Characteristic		NAS (%) ^a (N = 1,120)	No NAS (%) ^a (N = 114,517)
Sex of Infant:	Female	540 (0.96)	55,730 (99.04)
	Male	579 (0.98)	58,744 (99.02)
Infant Race:	Other ^b	81 (0.37)	21,712 (99.63)
	Black	85 (0.35)	24,479 (99.65)
	White	857 (1.52)	55,516 (98.48)
Infant Ethnicity:	Hispanic or Latino	22 (0.18)	12,231 (99.82)
	Non-Hispanic or Latino	935 (1.13)	82,057 (98.87)
Primary Payer:	Other ^c	80 (0.73)	10,854 (99.27)
	Private	68 (0.14)	48,761 (99.86)
	Medicaid/Medicare	971 (1.75)	54,671 (98.25)
NC Resident:	No	21 (0.63)	3,321 (99.37)
	Yes	1,099 (0.98)	111,196 (99.02)
NC Region:	Coastal	340 (1.14)	29,370 (98.86)
	Piedmont	479 (0.66)	72,144 (99.34)
	Mountain	280 (2.81)	9,682 (97.19)
Zip Income: ^d	4th Quartile	38 (0.29)	13,281 (99.71)
	3rd Quartile	108 (0.49)	21,495 (99.51)
	2nd Quartile	395 (1.06)	36,797 (98.94)
	1st Quartile	564 (1.34)	41,535 (98.66)
County Size: ^e	Non metro/micropolitan	103 (1.71)	5,910 (98.29)
	Micropolitan (10k-49k)	220 (1.33)	16,351 (98.67)
	Metro (50k-249k)	84 (0.78)	10,658 (99.22)
	Metro (250k-999k)	494 (1.29)	37,689 (98.71)
	Central/Fringe (≥1M)	218 (0.49)	43,857 (99.51)
Length of Stay (weeks) [Median; Mean (± SD)]		1.43; 2.22 (± 2.72)	0.29; 0.49 (± 1.22)
Birthweight (kilograms) [Median; Mean (± SD)]		2.91; 2.93 (± 1.02)	3.30; 3.25 (± 0.68)

SD: Standard Deviation

^aTotals for any variables that do not sum to the column total are due to missing characteristic variable data; Percentages displayed are row percentages in order to display the proportion with NAS across the levels of each variable.

^b‘Other’ includes Hispanic, Asian or Pacific Islander, Native American, and ‘Other’

^c‘Other’ includes Self-Pay/No Charge/Other

^dBased on median household income; 1st quartile is the lowest income level.

^e‘Non metro/micropolitan’ - counties that are not classified as ‘Metro’, ‘Micropolitan’ or ‘Central/Fringe’

TABLE 2.
Multivariable Logistic Regression Model for NAS in North Carolina in 2016

Variables ^a	Adjusted Odds Ratio (95% Wald Confidence Limits)
Race: Other ^b vs White	0.43 (0.31, 0.61)
Race: Black vs White	0.11 (0.08, 0.16)
Ethnicity: Hispanic/Latino vs Non-Hispanic/Latino	0.16 (0.08, 0.30)
Insurance: Other ^c vs Medicare/Medicaid	0.35 (0.24, 0.52)
Insurance: Private vs Medicare/Medicaid	0.07 (0.05, 0.10)
Region: Coastal vs Mountain	0.80 (0.61, 1.05)
Region: Piedmont vs Mountain	0.62 (0.50, 0.79)
Income Quartile: 4th vs 1st ^d	0.45 (0.26, 0.79)
Income Quartile: 3rd vs 1st	0.70 (0.50, 0.96)
Income Quartile: 2nd vs 1st	0.90 (0.73, 1.09)
County: Not metro/micro vs 'Central' & 'Fringe' ≥1 million	1.31 (0.89, 1.94)
County: Micropolitan vs 'Central' & 'Fringe' ≥1 million	0.95 (0.70, 1.31)
County: Metro 50k-249k vs MSA County ≥1 million	0.54 (0.34, 0.86)
County: Metro 250k-999k vs MSA County ≥1 million	0.92 (0.71, 1.21)
Length of Stay (weeks)	1.23 (1.20, 1.26)
Birthweight (kilograms)	0.87 (0.78, 0.98)

Multivariable logistic regression model to predict NAS (Yes vs. No)

^aReference group listed last in each row.

^bIncludes Hispanic, Asian or Pacific Islander, Native American, and 'Other'

^cIncludes Self-pay, No charge and 'Other'

^d1st quartile is the lowest income level.

Results

A total of 115,637 live births were reported in 2016 in North Carolina in the SID database. Of these live births, 1,120 were NAS cases. Figure 1 displays the annual NAS incidence rate for 2016 compared to historical data (2000 to 2013) previously reported by the Center for Disease and Control, demonstrating a persistent increase in the annual incidence rate from 0.3 per 1000 births in the year 2000 to 9.7 per 1000 births in the year 2016.

Table 1 provides demographic information and maternal/infant characteristics for births by NAS status ('yes' vs. 'no'). NAS incidence was similar for both female (0.96%) and male (0.98%) infants. Incidence of NAS was higher in the white race group (1.52%) than in either the black or 'other' race groups (0.35% and 0.37%, respectively), and higher for infants of non-Hispanic/Latino ethnicity (1.13%).

Geographically, nearly all NAS cases were residents of North Carolina with the remaining percentage of cases being nonresidents and obtaining medical care in North Carolina hospitals. The incidence of NAS for North Carolina residents (0.98%) was higher than non-residents (0.63%). The incidence of NAS within the three general geographic regions of North Carolina was as follows: the Piedmont (0.66%), Coastal (1.14%) and Mountain (2.81%). When looking at county population, NAS incidence was highest in counties with the smallest population, 'non-metro or micropolitan' (1.71%) and 'micropolitan' (1.33%), while counties with a population >1,000,000 (which include only two counties: Mecklenburg and Wake) had the lowest incidence (0.49%).

Examining economic and financial factors, the incidence

of NAS was highest for infants with a primary payment method of Medicaid/Medicare (1.75%). Income status of the parent was reported in quartiles and the incidence of NAS was greatest in the 1st income quartile (the lowest income level, 1.34%). The incidence rate of NAS for the 2nd income quartile was 1.06%, the 3rd quartile was 0.49%, and 4th income quartile was 0.29%.

We also observed that infants diagnosed with NAS tended to weigh less at birth (median [mean] 2.91 kg [2.93 kg] versus 3.30 kg [3.25 kg]) and had longer lengths of hospital stay (median [mean] 1.43 weeks [2.22 weeks] versus 0.29 weeks [0.49 weeks]) than those who did not have NAS, respectively.

A multivariable logistic regression model (Table 2) was constructed to assess the relationship between NAS and the available predictor variables of interest, including race, ethnicity, birth weight, infant payer, length of hospital stay, county/region of residence, county population size, and zip income quartile. Adjusting for the covariates of interest available in the database, the OR estimates and associated 95% confidence intervals for each level of each variable as compared to the reference level suggest that the odds of infants being diagnosed with NAS in North Carolina in 2016 were lower in the 'other' (OR 0.43; 95% CI: 0.31, 0.61) and 'black' (OR 0.11; 95% CI: 0.08, 0.16) race groups as compared to white race group, in Hispanic/Latinos as compared to Non-Hispanic/Latinos (OR 0.16; 95% CI: 0.08, 0.30), for those with 'other' (OR 0.35; 95% CI: 0.24, 0.52) or private insurance (OR 0.07; 95% CI: 0.05, 0.10) as compared to those with Medicaid/Medicare, for those in the Piedmont region as compared to the Mountain region of the state (OR 0.62;

95% CI: 0.50, 0.79), for those in the 4th (OR 0.45; 95% CI: 0.26, 0.79) and 3rd (OR 0.70; 95% CI: 0.50, 0.96) income quartile as compared to the 1st, for those in areas with a population of 50,000 to 249,000 as compared to areas with a population of more than a million (OR 0.54; 95% CI: 0.34, 0.86) and for those with lower birthweight (OR 0.87; 95% CI: 0.78, 0.98). Further, the odds of infants being diagnosed with NAS in North Carolina in 2016 were higher for those with a longer length of stay in the hospital (OR 1.23; 95% CI: 1.20, 1.26).

Discussion

Neonatal abstinence syndrome (NAS) is a complex medical condition that is associated with the mother's use of medications capable of producing withdrawal. [2-5]. Despite the shift that many NC hospitals in caring for opioid exposed infants post-delivery, there no universal screening policy for NC hospitals to follow regarding suspected substance exposed pregnancies/infants.

The incidence of NAS in NC has been reported as 0.3 per 1,000 hospital births for the year 2000 to 6.4 per 1,000 hospital births in 2013 [5]. Our study was designed consistent with the reported design and methodology of Ko et al [5]. Both studies utilized the State Inpatient Database from HCUP, in-hospital births, and identified NAS using appropriate ICD codes.

Annual incident rates are depicted in Figure 1. It was our objective to determine the incidence of NAS using more current (2016) data for comparison to these historical data. We determined the incidence rate of NAS in North Carolina increased to 9.7 per 1,000 hospital births for the year 2016 (Figure 1). Our confidence in this finding is based on the fact

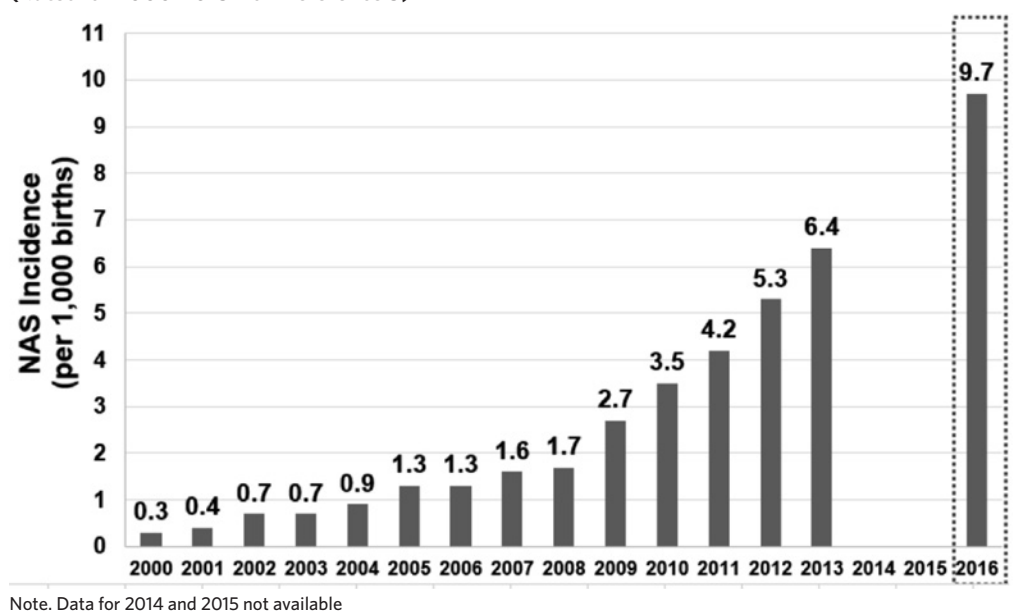
that our study methodology, including the data source (SID), is similar to the historical data used for comparison. The growing incidence in NAS across the nation has been attributed to increases in opioid prescribing rates, prevalence of illicit opioid use, and coding practices [5]. We also believe these reasons may account for the persistent increase in NAS in North Carolina.

The state of North Carolina is the 28th largest and 9th most populous of the 50 United States. The state is generally divided into three main regions; the Atlantic coastal plain, occupying the eastern portion, the central Piedmont region, and the Mountain region in the west that is part of the Appalachian Mountains. In addition to geographical diversity, North Carolina has broad economic diversity with multiple urban areas and broad rural regions.

We found significant geographic variation in NAS. Our findings suggest the Appalachian Mountain region of North Carolina had a substantially higher burden of NAS in 2016 as compared to the Piedmont region. The Appalachian Mountain region had a NAS incidence rate nearly three times higher than the statewide rate. Our findings were also consistent with work performed by Erwin et al [14] in the Tennessee Appalachian region, a border state of North Carolina. These investigators stated the Appalachian region has been associated with health disparities and widespread health care issues [14].

Our study also demonstrates a disparity of NAS incidence amongst based upon residential location and economic quartile. Our data revealed that NAS is more prevalent in rural counties and zip codes with the lowest median household incomes as compared to such areas with higher median household incomes. We determined that infants covered by

FIGURE 1.
Neonatal Abstinence Syndrome (NAS) Incidence Rates per 1,000 Hospital Births in North Carolina
(Rates for 2000-2013 from reference 5)



social insurance (Medicare/Medicaid) were significantly at higher risk for NAS as compared to both private and 'other' forms of insurance. This finding is consistent with other findings demonstrating social insurance is financially responsible for ~80% of NAS-related annual charges [5].

There are limitations to all studies, including this study. This was an observational study using retrospective data. Hospital sites providing data was ~96%. In addition, the diagnosis of NAS historically was made using ICD-9 coding, which has been supplanted with the ICD-10 coding convention.

In consideration of the growing NAS incidence, public health resources should focus on preventative screening and educational programs to decrease use of opioids amongst pregnant females. Such programs should focus in areas of North Carolina that are burdened with higher incident rates of NAS. Targeting the Appalachian Mountain region, rural areas, and lower income households may be most effective.

Conclusion

The findings of this study demonstrate the highest incident rate of NAS on record at 9.7 per 1,000 hospital births in North Carolina in 2016. This rate is consistent with the steady increase observed since the year 2000. Public health efforts in North Carolina should consider infant and maternal characteristics associated with the likelihood of NAS particularly considering the diversity of North Carolina. In addition, prevention efforts may need to focus on smaller rural communities. Appropriate opioid prescribing, maternal drug screening, streamlined reporting and guidelines for NAS diagnosis, as well as state and national monitoring programs are areas to focus on. NCMJ

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