Neonatal abstinence syndrome and early childhood morbidity and mortality in Washington state: a retrospective cohort study

Cordelie E. Witt, MD[1,2,3], **Kristina E. Rudd, MD**[1,4], **Pavan Bhatraju, MD**[1,4], **Frederick P. Rivara, MD, MPH**[1,2,5], **Stephen E. Hawes, PhD**[1], and **Noel S. Weiss, MD, DrPH**[1]

[1]Department of Epidemiology, University of Washington, Seattle, WA

[2]Harborview Injury Prevention and Research Center, Seattle, WA

[3]Department of Surgery, University of Washington, Seattle, WA

[4]Division of Pulmonary and Critical Care Medicine, University of Washington, Seattle, WA

[5]Department of Pediatrics, University of Washington, Seattle, WA

Abstract

Objective—To evaluate the association between neonatal abstinence syndrome (NAS) and long-term childhood morbidity and infant mortality.

Study design—We conducted a cohort study of infants born in Washington State during 1990–2008 who were diagnosed with NAS (n=1,900) or were unexposed (n=12,283, frequency matched by birth year). Five-year hospital readmissions and infant mortality were ascertained.

Result—Children with history of NAS had increased risk of readmission during the first five years of life relative to unexposed children; this remained statistically significant after adjustment for maternal age, maternal education, gestational age, and intrapartum smoking status (readmission rates: NAS=21.3%, unexposed=12.7%, aRR 1.54, 95% CI 1.37–1.73). NAS was associated with increased unadjusted infant mortality risk, but this did not persist after adjustment (aRR 1.94, 95% CI 0.99–3.80).

Conclusion—The observed increased risk for childhood hospital readmission following NAS diagnosis argues for development of early childhood interventions to prevent morbidity.

Introduction

Neonatal abstinence syndrome (NAS) is a drug withdrawal syndrome observed in newborns after cessation of fetal exposure to substances taken by the mother during pregnancy or received by the newborn early in life[1, 2]. It may result in a variety of central nervous system, respiratory, metabolic, vasomotor and gastrointestinal disturbances, as classically described

Corresponding author: Cordelie E. Witt, 325 9th Avenue, Box 359960, Seattle, WA, 98104, Phone: 206-744-9482, Fax: 206-744-9962, cwitt@uw.edu.

Conflicts of interest: The authors report no conflicts of interest.

Supplementary information: available at the Journal of Perinatology's website.

by Finnegan et al[3, 4]. The prevalence of NAS is increasing in the US and globally[2, 5, 6], rising in the US from 1.2 cases per thousand live births in 2000 to 3.4 cases per thousand live births in 2009, to 5.8 per thousand live births in 2012[7, 8]. Additionally, the proportion of admissions to the neonatal intensive care unit (NICU) for NAS increased nearly fourfold from 2004 to 2013, from 7 to 27 cases per 1000 admissions[2]. NAS is most commonly related to opioid exposure, but may also result from exposure to psychotropic medications or nonopioid illicit substances[1]. The majority of published research on NAS and/or antenatal opioid exposure focuses on neonatal and perinatal periods[6, 9–18]. Whether these exposures have a long-term effect on childhood morbidity has not been elucidated; however, existing literature indicates that neonatal opioid exposure affects several neurobiologic processes in animal models[19–21] and results in neurocognitive and behavioral issues in humans[13, 22]. Likewise, affected children may grow up in the setting of unstable living situations and other socioeconomic consequences of maternal substance use[13, 23] which may be important mediators for adverse outcomes. Only one prior study, from Australia, assessed longer-term outcomes based on hospital readmissions during childhood; it found that infants born with NAS were more likely to be hospitalized compared to children without NAS, with particularly high risk for maltreatment, trauma, mental health disorders and behavioral disorders[24]. Given substantial differences between the US and Australian healthcare systems in access to care, prenatal and postnatal care pathways, infant outcomes and social resources[24, 25] it is unknown if results from an Australian cohort can be extrapolated to the US population.

Given the rising prevalence of NAS, the current epidemic of prescription drug abuse, and public health concerns related to maternal substance use in the US, it is critical to understand the longer-term implications of NAS. The objectives of this study are to assess whether NAS is associated with (1) childhood morbidity, based on the incidence of hospitalization within the first five years of life, and (2) infant mortality.

Subjects and methods

Study population

This was a population-based retrospective cohort study of singleton infants born in Washington State between 1990 and 2008. Infants were identified using Washington State Vital Statistics birth certificate data. These data were linked to Washington State death certificate data and to hospitalization records from the Washington State Comprehensive Hospital Abstract Reporting System (CHARS), a statewide hospital discharge database which contains *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9) codes for diagnoses and procedures. Data from the birth hospitalization were obtained for both the infant and mother; subsequent hospitalizations from 1990 to 2013 were obtained for the infants. This research was determined to meet exempt status by the Washington State Department of Health Institutional Review Board as all data were de-identified prior to use. As such, informed consent requirements were waived.

The primary exposure was diagnosis of NAS at birth hospitalization, defined by the presence of ICD-9 code 779.5 "drug withdrawal syndrome in newborn" in the infant's linked birth

hospitalization discharge data. The comparison group included a sample of infants without NAS and without maternal diagnosis codes indicating opioid dependence in the mother (maternal ICD-9 diagnosis codes 304.01, "opioid type dependence, continuous" or 304.71, "combinations of opioid type drug with any other, continuous."). A sample of 12,283 unexposed infants, frequency matched to exposed infants by birth year, formed the unexposed cohort for analysis. This sample size provided greater than 99% power to detect a difference given a 0.25% risk of outcome in the unexposed and 1% risk of outcome in the exposed (estimates for infant mortality), as well as greater than 99% power given a 10% risk of outcome in the unexposed and 15% risk in the exposed (estimates for readmission).

Exclusion criteria were designed *a priori*. We excluded non-singleton infants, those with recorded gestational age < 32 weeks or > 45 weeks by obstetric best estimate, or babies of mothers already included in the study with another infant. Exclusions on the basis of gestational age were to exclude improbable data points as well as infants who might otherwise be at a substantially elevated risk of morbidity. Infants of mothers already in the study were uncommon, but were excluded because they introduced statistical challenges of non-independence of events.

Secondary analyses

Two secondary analyses were performed. First, we analyzed the portion of the exposed infants for whom NAS appeared to result from exposure to maternal opioids. This sub-cohort included infants with NAS as defined above, who also had presence of at least one of the following additional diagnosis codes: infant diagnosis code 760.72, "narcotics affecting fetus/newborn via placenta or breast milk"; maternal diagnosis codes 304.01, "opioid type dependence, continuous"; or maternal diagnosis code 304.71, "combinations of opioid type drug with any other, continuous." This group was included because opioid-related NAS is of particular public health and clinical interest. The same unexposed infants described above were used as the comparison group.

Second, we examined the portion of infants with NAS diagnosis who required admission to the neonatal ICU during the birth hospitalization, as a surrogate marker for severe NAS. We compared these infants to both those with NAS who did not require admission to the ICU, as well as to the group of infants without NAS or opioid exposure. Data on neonatal ICU admission was included in the dataset beginning in 2003; thus, these analyses included only births occurring in 2003–2008.

Outcomes

The primary outcome was the occurrence of at least one hospital readmission in the first five years of life (after discharge from the birth hospitalization). Secondary outcomes were infant mortality (death within the first year of life) and reason for readmission. Transfers to another hospital after birth were not included as readmissions. Reason for admission was operationalized by ICD-9 diagnosis codes obtained from CHARS for up to nine diagnoses for each readmission. We utilized ICD-9 code and infant age data for up to the first four readmissions in the first five years of life, which provided data on 94.8% of all readmissions.

The diagnostic categories and ICD-9 ranges used in this study were adapted from ICD-9 categories, as listed in Supplementary Table 1.

Statistical analyses

Potential confounders were chosen *a priori* and included maternal age, maternal cigarette smoking during pregnancy, maternal education, year of birth, maternal race/ethnicity, gestational age, prolonged infant length of stay during the birth hospitalization (more than 3 days), and whether the infant had a concomitant medical condition or congenital anomaly diagnosed during the birth hospitalization. Missing data were omitted from analyses; this was uncommon (0–5.2%) and similar across exposure groups. The exception was for maternal and infant intensive care unit (ICU) admission at birth hospitalization, which were available only for births from 2003–2008.

Demographic data and patient characteristics were compared using Chi square tests for categorical variables. Measures of association between exposure and outcome were assessed using relative risks (RR) and Wald-based 95% confidence intervals (CI) based on Mantel-Haenszel calculations. Final analyses were adjusted for maternal race, maternal education status, maternal smoking status, and gestational age; all other variables thought *a priori* to be potential mediators or confounders (including presence of concomitant medical conditions / congenital anomalies) showed 2% difference between the crude and Mantel-Haenszel adjusted relative risk for readmission. An alpha level of 0.05 was used, with two-sided tests throughout. The data met test-based assumptions for normality and equal variance. Analyses were performed in Stata version 14 (StataCorp, College Station, TX).

Results

The study population included 1,900 infants diagnosed with NAS and 12,283 unexposed infants without NAS or known antenatal opioid exposure.

Maternal and infant characteristics

Demographic and health characteristics differed between exposure groups, as demonstrated in Table 1. Notably, for birth years 2003–2008 when neonatal ICU admission data was available, infants with NAS diagnosis were more likely to be premature, to require ICU care and to have prolonged hospital stays compared to unexposed infants. Mothers of infants with NAS were younger, less likely to have finished high school, more likely to be unemployed, more likely to smoke, and more likely to have Medicaid as the primary maternal payer.

Risk of infant mortality

Infant mortality was 1.00% in the any NAS cohort and 0.29% in the unexposed cohort, as shown in Table 2. These correspond to unadjusted risk ratios of 3.41 (95% CI 1.96, 5.94) for infants with NAS compared to unexposed infants; however, after adjusting for maternal age, maternal education, gestational age, and intrapartum smoking status; the rate of infant death was not significantly elevated.

Risk of readmission

Children with history of NAS diagnosis were significantly more likely than unexposed infants to be readmitted to the hospital in the first five years of life, as shown in Table 2. Over the five year time period, 21.3% of patients with any NAS diagnosis had at least one readmission, compared to 12.7% of unexposed infants with at least one readmission. After adjusting for maternal age, maternal education, gestational age, and intrapartum smoking status, the increased risk of readmission associated with NAS exposure persisted: the adjusted RR for any NAS diagnosis relative to unexposed was 1.54 (95% CI 1.37, 1.73). Given that gestational age is a probable mediator between NAS exposure and rehospitalization, we also performed analyses without adjusting for gestational age and found that the magnitude and direction of the relative risk was similar to that reported above.

Of 2,650 readmissions assessed, 61.1% (n=1,620) occurred in the first year, 17.1% (n=454) occurred in the second year, 10.2% (n=269) occurred in the third year, 6.6% (n=176) occurred in the fourth year, and 4.9% (n=131) occurred in the fifth year.

Reason for readmission

For children with at least one hospital readmission in the first five years of life, reasons for readmission were evaluated for up to the first four readmissions. Table 3 presents data for all diagnostic categories for which there were at least 50 total readmissions, as well as for intentional injuries/child abuse/neglect. Children with history of NAS were more likely than unexposed children to be readmitted for several conditions, including infectious and parasitic diseases, diseases of the nervous system, diseases of the respiratory system, diseases of the digestive system, diseases of skin and subcutaneous tissue, infections and cellulitis, and perinatal conditions. Children with history of NAS had higher unadjusted rates of readmission for injury and poisoning overall, as well as for injuries purposely inflicted by other persons; however, these did not persist after adjustment for maternal race, maternal education, gestational age and intrapartum smoking status.

Secondary analyses

The sub-cohort of infants with NAS and documented exposure to maternal opioids contained 506 infants; as before, the comparison group included 12,238 unexposed infants. As shown in Supplementary Table 2, maternal and infant characteristics differed in a similar pattern to that for the primary analysis. We next considered all-cause infant death; while this occurred in a greater proportion of exposed vs. unexposed infants, there was no statistically significant difference after adjustment for maternal race, maternal education, gestational age and intrapartum smoking status (0.79% in exposed vs. 0.29% in unexposed; aRR 1.60, 95% CI 0.48, 5.31). All-cause readmission was more common in exposed vs. unexposed infants, and the difference was significant after adjustment (21.9%) in exposed vs. 12.7% in unexposed; aRR 1.67, 95% CI 1.38, 2.02). We assessed reasons for readmission in this cohort as well; infants with NAS and documented exposure to maternal opioids were significantly more likely to have readmissions for infectious, neurologic, respiratory, digestive, skin, perinatal conditions or asphyxia after adjustment. Complete data are available in Supplementary Tables 3 and 4.

The sub-cohort of infants with NAS admitted to the neonatal ICU during birth hospitalization from 2003–2008 included 382 infants. We compared these to both unexposed infants (n=6390 from 2003–2008) and to infants with NAS without neonatal ICU admission (n=679). While the proportion of exposed infants sustaining all-cause infant death and all-cause readmission exceeded the proportion in either comparison group, a statistically significant increase persisting after adjustment was present only when comparing the risk of all-cause readmission among exposed infants relative to unexposed infants (26.2% in exposed vs. 12.9% in unexposed; aRR 1.51 (1.24, 1.84). Complete results are shown in Supplementary Table 5.

Discussion

Among infants born in Washington State from 1990 to 2008, children with history of NAS diagnosis were more likely to be readmitted in the first five years of life than unexposed children. We found that this difference was above and beyond the effects of prematurity and major proxies for socioeconomic status (maternal education and race). In contrast, although children with history of NAS had a higher level of infant mortality than unexposed children, this association was no longer statistically significant after adjustment for maternal characteristics and gestational age. Similar patterns were seen in our secondary analysis of infants with NAS and documented exposure to maternal opioids.

Infants in our study with NAS were more likely to be born to mothers who smoked and mothers of lower socioeconomic status as evidenced by proxies of insurance status, unemployment and education. NAS infants were also more often premature, despite that we excluded early preterm infants (<32 weeks) to reduce confounding. While this prematurity data is consistent with several Australian and Swedish studies[24, 26, 27], there is also existing data to suggest that NAS may be less symptomatic in preterm infants[28] or that preterm infants may be less likely to develop NAS[29]. Infants with NAS in our study also had longer lengths of stay at birth hospitalization than unexposed infants and greater likelihood of neonatal ICU admission, which may relate to their need supportive care, potentially including pharmacologic (primarily morphine during the timeframe of this study[30, 31]), or non-pharmacologic interventions[32]. As in other analyses, these patterns were similar in our secondary analysis of infants with NAS and documented exposure to maternal opioids.

Our data showed that NAS was associated with an increased risk of rehospitalization for a wide variety of diagnoses including infectious, neurologic, respiratory and digestive diseases. Previous reports have assessed childhood neurodevelopment in infants with NAS[13, 16] but only a single prior study has evaluated medical conditions across organ systems. A study from Australia found a similarly increased risk of rehospitalization in children with history of NAS compared to unexposed children[24]. Both studies found an increased rate of asthma, respiratory infections and digestive diseases. The Australian study did identify an elevated rate of rehospitalization for mental and behavioral disorders which we did not observe; however, we hypothesize that this difference is because such disorders are not commonly diagnosed in first 5 years of life (their study included up to 13 years of follow up) and when present, are likely to be treated in the outpatient setting. Interestingly, we did not observe a significant increase in adjusted rates of rehospitalization for injury.

Given that the unadjusted relative risks showed a significant differenced but our adjusted relative risks did not, these outcomes may be more strongly associated with environmental and sociodemographic variables, some of which may be collinear with our adjustment variables. We did observe a significant increase in adjusted rates of intentional injury/child abuse/neglect; these findings may be more specific to the NAS population than injury more broadly. Ultimately, it appears that children with history of NAS may have higher risk for readmission for a broad range of diagnoses. Whether this observation results from exposure to unhealthy environments and less preventative care or from biological changes induced by NAS is unclear; regardless these children may benefit from targeted interventions.

The increase in NAS prevalence in the US has led to efforts in healthcare systems to improve care delivered to affected infants[2, 33]; however, interventions have focused on the initial hospitalization rather than the long-term consequences of exposure. Our findings suggest that interventions to address risks and outcomes of infants with NAS should not be limited to this early period; rather, they should extend to at least the first five years of life.

We acknowledge that this study has several limitations. First, we relied on administrative data that may have led to misclassification of children with NAS or opioid abuse. NAS is thought to be under-ascertained in hospital discharge databases, which require ICD-9 code assignment to identify patients[34]. If our unexposed group contained undocumented NAS or opioid exposed cases our measures of association may be attenuated; however, it is also possible that we are capturing only the most severe cases, which may increase our observed measures of association. Likewise, we expect that infant and maternal codes documenting infant exposure to maternal opioids are likely to be underreported. Thus, while our subcohort focusing on these infants is likely to be quite specific, it is likely that many more of those in the any NAS cohort also developed NAS from exposure to maternal opioids. As such, it is not particularly surprising that the results for the two groups are similar. Second, the populations we studied may have differential loss to follow-up, which is important due to the longitudinal nature of our study. Due to different social support or community ties, mothers of children with NAS because of opioid or other substance abuse may be at greater risk to relocate out of Washington State and therefore be lost to follow-up. However, we would expect this differential loss to attenuate our results, since our primary outcome was hospital readmission and migration out of the state would selectively decrease the observed rate of the primary outcome in children born with NAS. Third, we did not have data on the dose of opioids or other substances used by mothers, nor did we have data on treatment during the birth hospitalization for opioid-exposed and NAS infants. Future research would need to explore whether treatment of infants and social work intervention with parents during the birth hospitalization may modify the risk of and reasons for hospital readmission in children with NAS. Fourth, we lacked data on the proportion of patients removed from the home and/or placed into foster care following birth or during early childhood. If more infants with NAS were moved into lower-risk environments, this would be expected to attenuate the observed outcomes. Finally, our ability to examine the potential influence of NAS on infant mortality was limited by the relatively small number of deaths that occurred in the study population.

In conclusion, in this population-based cohort of children born in Washington State from 1990 to 2008, we found substantial increases in the risk of hospital readmission in the first five years of life among children with NAS and among a subcohort of children with NAS and documented exposure to maternal opioids, compared to unexposed infants. Future research should evaluate the biologic pathways affected by these diagnoses, focusing on the diseases for which this study found a greater risk of hospital readmission. As healthcare systems, clinicians and policymakers develop strategies to improve care for patients with antenatal substance exposure, our data suggest that it could be advantageous to extend interventions into at least the early years of childhood.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

References

1. Kocherlakota P. Neonatal abstinence syndrome. Pediatrics. 2014; 134:e547–61. [PubMed: 25070299]

2. 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. [PubMed: 25913111]

3. Finnegan LP, Connaughton JF Jr, Kron RE, Emich JP. Neonatal abstinence syndrome: assessment and management. Addict Dis. 1975; 2:141–58. [PubMed: 1163358]

4. Hudak ML, Tan RC. Neonatal drug withdrawal. Pediatrics. 2012; 129:e540–60. [PubMed: 22291123]

5. Davies H, Gilbert R, Johnson K, Petersen I, Nazareth I, O'Donnell M, et al. Neonatal drug withdrawal syndrome: cross-country comparison using hospital administrative data in England, the USA, Western Australia and Ontario, Canada. Arch Dis Child Fetal Neonatal. 2016; 101:F26–30.

6. 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. [PubMed: 26427919]

7. Patrick SW, Schumacher RE, Benneyworth BD, Krans EE, McAllister JM, Davis MM. Neonatal abstinence syndrome and associated health care expenditures: United States, 2000–2009. J Am Med Assoc. 2012; 307:1934–40.

8. Patrick SW, Davis MM, Lehman CU, Cooper WO. Increasing incidence and geographic distribution of neonatal abstinence syndrome: United States 2009 to 2012. J Perinatol. 2015; 35:667.

9. Beckwith AM, Burke SA. Identification of early developmental deficits in infants with prenatal heroin, methadone, and other opioid exposure. Clinical pediatrics. 2015; 54:328–35. [PubMed: 25189695]

10. Anand KJ, Campbell-Yeo M. Consequences of prenatal opioid use for newborns. Acta Paediatr. 2015; 104:1066–9. [PubMed: 26174725]

11. Bandstra ES, Morrow CE, Mansoor E, Accornero VH. Prenatal drug exposure: infant and toddler outcomes. J Addict Dis. 2010; 29:245–58. [PubMed: 20407980]

12. Cleary BJ, Donnelly JM, Strawbridge JD, Gallagher PJ, Fahey T, White MJ, et al. Methadone and perinatal outcomes: a retrospective cohort study. Am J Obstet Gynecol. 2011; 204:139 e1–9. [PubMed: 21145035]

13. 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. [PubMed: 17728081]

14. McGlone L, Mactier H. Infants of opioid-dependent mothers: neurodevelopment at six months. Early Hum Dev. 2015; 91:19–21. [PubMed: 25460252]

15. Norgaard M, Nielsson MS, Heide-Jorgensen U. Birth and Neonatal Outcomes Following Opioid Use in Pregnancy: A Danish Population-Based Study. Subst Abus. 2015; 9:5–11.

16. Ornoy A, Michailevskaya V, Lukashov I, Bar-Hamburger R, Harel S. The developmental outcome of children born to heroin-dependent mothers, raised at home or adopted. Child Abuse Negl. 1996; 20:385–96. [PubMed: 8735375]

17. 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. [PubMed: 25254116]

18. Hans SL. Developmental consequences of prenatal exposure to methadone. Ann N Y Acad Sci. 1989; 562:195–207. [PubMed: 2742277]

19. Devarapalli M, Leonard M, Briyal S, Stefanov G, Puppala BL, Schweig L, et al. Prenatal Oxycodone Exposure Alters CNS Endothelin Receptor Expression in Neonatal Rats. Drug Res. 2016; 66:246–50.

20. Hays SL, McPherson RJ, Juul SE, Wallace G, Schindler AG, Chavkin C, et al. Long-term effects of neonatal stress on adult conditioned place preference (CPP) and hippocampal neurogenesis. Behav Brain Res. 2012; 227:7–11. [PubMed: 22061798]

21. Sanchez ES, Bigbee JW, Fobbs W, Robinson SE, Sato-Bigbee C. Opioid addiction and pregnancy: perinatal exposure to buprenorphine affects myelination in the developing brain. Glia. 2008; 56:1017–27. [PubMed: 18381654]

22. Nygaard E, Slinning K, Moe V, Walhovd KB. Behavior and Attention Problems in Eight-Year-Old Children with Prenatal Opiate and Poly-Substance Exposure: A Longitudinal Study. PLoS One. 2016; 11:e0158054. [PubMed: 27336798]

23. Sutter MB, Leeman L, Hsi A. Neonatal opioid withdrawal syndrome. Obstet Gynecol Clin North Am. 2014; 41:317–34. [PubMed: 24845493]

24. Uebel H, Wright IM, Burns L, Hilder L, Bajuk B, Breen C, et al. Reasons for Rehospitalization in Children Who Had Neonatal Abstinence Syndrome. Pediatrics. 2015; 136:e811–20. [PubMed: 26371197]

25. Jones PD, Seoane L, Deichmann R, Kantrow C. Differences and similarities in the practice of medicine between australia and the United States of america: challenges and opportunities for the university of queensland and the ochsner clinical school. Ochsner J. 2011; 11:253–8. [PubMed: 21960759]

26. O'Donnell M, Nassar N, Leonard H, Hagan R, Mathews R, Patterson Y, et al. Increasing prevalence of neonatal withdrawal syndrome: population study of maternal factors and child protection involvement. Pediatrics. 2009; 123:e614–21. [PubMed: 19336352]

27. Wurst KE, Zedler BK, Joyce AR, Sasinowski M, Murrelle EL. A Swedish Population-based Study of Adverse Birth Outcomes among Pregnant Women Treated with Buprenorphine or Methadone: Preliminary Findings. Subst Abuse. 2016; 10:89–97. [PubMed: 27679504]

28. Allocco E, Melker M, Rojas-Miguez F, Bradley C, Hahn KA, Wachman EM. Comparison of Neonatal Abstinence Syndrome Manifestations in Preterm Versus Term Opioid-Exposed Infants. Adv Neonatal Care. 2016; 16:329–36. [PubMed: 27611018]

29. Liu WF, Singh K, Faisal M, Li S. Maternal methadone treatment and neonatal abstinence syndrome. Am J Perinatol. 2015; 32:1078–86. [PubMed: 25915141]

30. Nandakumar N, Sankar VS. What is the best evidence based management of neonatal abstinence syndrome? Arch Dis Child Fetal Neonatal Ed. 2006; 91:F463.

31. Osborn DA, Cole MJ, Jeffery HE. Opiate treatment for opiate withdrawal in newborn infants. Cochrane Database Syst Rev. 2002:CD002059. [PubMed: 12137642]

32. Velez M, Jansson LM. The Opioid dependent mother and newborn dyad: non-pharmacologic care. J Addict Med. 2008; 2:113–20. [PubMed: 19727440]

33. Jones HE, Kaltenbach K, Heil SH, Stine SM, Coyle MG, Arria AM, et al. Neonatal abstinence syndrome after methadone or buprenorphine exposure. N Engl J Med. 2010; 363:2320–31. [PubMed: 21142534]

34. Burns L, Mattick RP. Using population data to examine the prevalence and correlates of neonatal abstinence syndrome. Drug Alcohol Rev. 2007; 26:487–92. [PubMed: 17701511]

Table 1

Maternal and infant characteristics among infants with NAS and unexposed infants, Washington State, 1990–2008.

Characteristics	Infants with NAS (n=1,900), %	Unexposed infants (n=12,283), %	P value[a]
Maternal age (years)			<0.001
< 20	4.7%	14.0%	
20 and < 35	79.5%	74.2%	
35	15.8%	11.9%	
Male infant sex	54.6%	51.3%	0.01
Smoking during pregnancy	60.2%	12.2%	<0.001
Maternal education less than high school	37.7%	27.7%	<0.001
Maternal race			<0.001
White	78.4%	71.3%	
Black	6.7%	4.0%	
Hispanic	3.4%	12.7%	
Other or unknown	11.5%	12.0%	
Maternal admission to ICU during birth hospitalization			0.01
Yes	0.6%	0.2%	
No	99.4%	99.8%	
Missing (data not available prior to 2003)	*47.3%*	*49.3%*	
Infant admitted to neonatal ICU during birth hospitalization			<0.001
Yes	39.7%	5.0%	
No	60.3%	95.0%	
Missing (data not available prior to 2003)	*49.4%*	*49.2%*	
Gestational age (weeks) [b]			<0.001
< 34	3.3%	0.8%	
34 and < 37	20.1%	5.6%	
37	76.7%	93.7%	
Concomitant illness diagnosed at birth hospitalization[c]	4.1%	1.8%	<0.001
Infant birth hospitalization length of stay > 3 days	80.7%	11.8%	<0.001
Medicaid as primary maternal payer	61.0%	37.3%	<0.001
Mother unemployed	13.7%	4.8%	<0.001

Footnotes: Abbreviations: NAS = neonatal abstinence syndrome, ICU = Intensive care unit

Percentages for ICU admission (yes/no) are based on non-missing data.

[a] P values derived from Chi square tests

[b] Infants with gestational age <32 weeks, or >45 weeks were excluded

[c] Based on birth certificate data and ICD-9 codes from infant's birth hospitalization discharge data.

Table 2

Association between infant NAS exposure, risk of infant death, and risk of hospital readmission during the first five years of life, Washington State, 1990–2013.

Five-year outcome	Infants with outcome event, n(%)		Risk of diagnosis among infants with NAS, relative to unexposed infants, RR (95% CI)	
	Infants with NAS (n=1900)	Unexposed infants (n=12,283)	Unadjusted relative risk	Adjusted relative risk[a]
All-cause infant death	19 (1.00%)	36 (0.29%)	3.41 (1.96, 5.94)	1.94 (0.99, 3.80)
All-cause readmission	405 (21.3%)	1,558 (12.7%)	1.68 (1.52, 1.85)	1.54 (1.37, 1.73)

Footnotes: Abbreviations: NAS = neonatal abstinence syndrome, RR = relative risk, aRR = adjusted relative risk, CI = confidence interval. Infant death is defined as within the first year of life.

[a] Adjusted relative risks account for maternal race, maternal education, gestational age and intrapartum smoking status.

Table 3

Categories of hospital readmission in the first five years of life among infants with NAS compared to unexposed infants, Washington State, 1990–2013.

Diagnostic categories[a]	Infants with at least one readmission in a given diagnostic category in the first five years of life, n (%)		Risk of diagnosis among infants with NAS, relative to unexposed infants; RR (95% CI)	
	Infants with NAS (n=1,900)	Unexposed infants (n=12,283)	Unadjusted relative risk	Adjusted relative risk[b]
Infectious and parasitic diseases	114 (6.00%)	394 (3.21%)	1.87 (1.53, 2.29)	1.72 (1.35, 2.21)
Diseases of the nervous system	24 (1.26%)	59 (0.48%)	2.63 (1.64, 4.22)	2.07 (1.12, 3.82)
Epilepsy, convulsions	20 (1.05%)	62 (0.50%)	2.09 (1.26, 3.44)	1.80 (0.94, 3.42)
Diseases of the respiratory system	200 (10.53%)	620 (5.05%)	2.09 (1.79, 2.43)	1.59 (1.33, 1.91)
Acute respiratory infections, pneumonia, influenza	58 (3.05%)	208 (1.69%)	1.80 (1.35, 2.40)	1.28 (0.92, 1.77)
Asthma	70 (3.68%)	165 (1.34%)	2.74 (2.08, 3.61)	1.82 (1.29, 2.57)
Diseases of the digestive system	72 (3.79%)	214 (1.74%)	2.18 (1.67, 2.83)	2.07 (1.49, 2.86)
Diseases of the genitourinary system	35 (1.84%)	99 (0.81%)	2.29 (1.56, 3.35)	2.28 (1.49, 3.50)
Diseases of the skin and subcutaneous tissue	53 (2.79%)	106 (0.86%)	3.23 (2.33, 4.48)	3.04 (2.12, 4.36)
Infections and cellulitis	22 (1.16%)	34 (0.28%)	4.18 (2.45, 7.14)	3.57 (2.06, 6.19)
Conditions originating in the perinatal period	86 (4.53%)	386 (3.14%)	1.44 (1.15, 1.81)	1.53 (1.17, 2.00)
Perinatal infections	13 (0.68%)	47 (0.38%)	1.79 (0.97, 3.30)	1.96 (0.99, 3.87)
Asphyxia	13 (0.68%)	46 (0.37%)	1.83 (0.99, 3.38)	1.60 (0.79, 3.25)
Injury and poisoning	17 (0.89%)	56 (0.51%)	1.96 (1.14, 3.37)	1.58 (0.75, 3.31)
Injury purposely inflicted by other persons, neglect, child abuse	6 (0.32%)	6 (0.05%)	6.46 (2.09, 20.02)	4.46 (1.16, 17.15)

Footnotes: Abbreviations: NAS = neonatal abstinence syndrome, aRR = adjusted relative risk, CI = confidence interval.

[a]Diagnostic categories, based on ICD-9 code ranges, were assessed for up to the first four readmissions in the first five years of life, accounting for 94.8% of the total count of readmissions during this timeframe. Diagnoses for which there were at least 50 total occurrences are presented in the table.

[b]Adjusted relative risks accounted for maternal education, gestational age, race and intrapartum smoking.