HHS Public Access

Author manuscript

Birth Defects Res. Author manuscript; available in PMC 2024 March 18.

Published in final edited form as:

Birth Defects Res. 2021 January 15; 113(2): 144–151. doi:10.1002/bdr2.1811.

Assessing the relationship between neonatal abstinence syndrome and birth defects in Delaware

Khaleel S. Hussaini[1,2], **Dana Drummond**[3], **Louis E. Bartoshesky**[4,5], **Amy Acheson**[6], **Kathleen Stomieroski**[6], **David A. Paul, MD**[4,5], **Russell S. Kirby**[7]

[1]Field Support Branch, Division of Reproductive Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, GA

[2]Division of Public Health, Delaware Department of Health and Social Services, Dover, Delaware

[3]Drug Overdose Surveillance Epidemiologist, Division of Prevention and Community Health, Washington State Department of Health, Tumwater, Washington

[4]Pediatrics, ChristianaCare™, Newark, Delaware

[5]Sidney Kimmel Medical College at Thomas Jefferson University, Philadelphia, Pennsylvania

[6]Center for Women's, Infants' and Children's Health Research, ChristianaCare™, Newark, Delaware

[7]Distinguished Professor and Marrell Endowed Chair, Birth Defects Surveillance ProgramCollege of Public Health, University of South Florida, Tampa, Florida

Abstract

Background: Neonatal abstinence syndrome (NAS) is a withdrawal syndrome in newborns and is frequently caused by maternal opioid use during pregnancy. Our study examines whether NAS is associated with birth defects in Delaware.

Methods: We conducted a retrospective analysis of linked Delaware birth certificate data (BCD), hospital discharge data (HDD), and birth defects registry (BDR) data to examine the association between NAS and birth defects for all hospital births to Delaware residents from 2010 to 2017. Birth defects data were abstracted from medical records from Delaware's BDR. We used International Classification of Diseases Ninth and Tenth Revision Clinical Modification (ICD-9-CM/ICD-10-CM) 779.5 and P96.1 codes to determine NAS using HDD and excluded iatrogenic cases of NAS. We estimated crude and adjusted odds ratio with 95% confidence intervals (CIs).

Results: During 2010–2017, there were 2,784 cases of birth defects and 1,651 cases of NAS in Delaware. Among infants with a diagnosis of NAS, 56 also had a birth defect (3.4%), similar to 2,728 birth defects among 79,636 infants without a diagnosis of NAS (3.4%). We found no

Correspondence: Khaleel S. Hussaini, Delaware Department of Health and Social Services, Division of Public Health, 417 Federal Street, Dover, DE 19901. khaleel.hussaini@delaware.gov.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention, the Delaware Department of Health Social Services, Division of Public Health, and the Christiana Care Health System.

CONFLICT OF INTEREST

The authors have nothing to disclose.

statistically significant association between an NAS diagnosis and birth defects (adjusted odds ratios = 1.0; 95% CI: 0.8–1.3).

Conclusions: Our multiyear state-wide study using linked BCD, HDD, and BDR data for Delaware did not show a statistically significant association between infants diagnosed with NAS and birth defects, overall.

Keywords

birth certificate data; birth defects; birth defects registry; data linkage; hospital discharge data; neonatal abstinence syndrome; opioid use disorder

1 | BACKGROUND

Nationwide, opioid use disorder during pregnancy quadrupled, from 1.5 cases per 1,000 delivery hospitalizations to 6.5 per 1,000 delivery admissions between 1998 and 2014 (Haight, Ko, Tong, Bohm, & Callaghan, 2018; Maeda, Bateman, Clancy, Creanga, & Leffert, 2014). The most recent estimates suggest that during 2008–2012, there was an increase in the percentage of Medicaid-enrolled women who filled at least one opioid prescription during pregnancy (Ailes et al., 2015). Neonatal abstinence syndrome (NAS) is a withdrawal syndrome in newborns frequently caused by maternal opioid use through in utero exposure during pregnancy (Patrick et al., 2012; Patrick, Davis, Lehmann, & Cooper, 2015). Jansson and Velez noted that “exposures such as cocaine, nicotine, SSRIs (selective serotonin reuptake inhibitors), and polydrugs can potentiate the infant’s expression of opioid-induced NAS” (Jansson & Velez, 2012, p. 253). A newborn’s presentation of NAS varies and may be influenced by factors that include licit and illicit exposures as well as maternal physiology, epigenetic modifications, and genetic predisposition (Jansson & Velez, 2012).

Negative effects of opioid use during pregnancy on pregnancies, fetuses, and newborns are well-documented. NAS affected infants are more likely to experience adverse neonatal outcomes such as preterm birth (<37 weeks of gestation) and low birthweight (<2,500 g or 5 pounds, 8 oz)—a major risk factor for infant mortality—than infants without NAS (Anand & Campbell-Yeo, 2015; Lind et al., 2015; McQueen & Murphy-Oikonen, 2016; Nørgaard, Nielsson, & Heide-Jørgensen, 2015; Reddy et al., 2017; Stover & Davis, 2015). However, the relationship between NAS and birth defects is not clear. In 2016, a national expert panel identified the need to better understand the factors that increase the risk for NAS and birth defects such as, the type of substance used, polydrug use, dosage, and the gestational age of exposure to maternal opioids (Reddy et al., 2017).

A recent systematic review of 30 studies of maternal opioid use during pregnancy and teratogenicity of opioids found that 17 out of 30 studies had reported statistically significant associations between maternal opioid use and birth defects (Lind et al., 2017), with inconsistent results by type of birth defect. The National Birth Defects Prevention Study found that therapeutic opioid use was reported by 2.6% of 17,449 case mothers and 2.0% of 6,701 control mothers (Broussard et al., 2011). Treatment was associated with congenital heart defects (conoventricular septal defects, atrioventricular septal defects, hypoplastic left

heart syndrome), spina bifida, or gastroschisis in infants (Broussard et al., 2011; Short et al., 2019). Data on the prevalence of NAS among Delaware births are limited. The earliest publication with estimates of NAS in Delaware reported a 94% increase in the incidence between 2010 and 2015, from 11.9 to 23.0 cases per 1,000 births (Hussaini, 2017). In addition, Delaware's 2012 and 2013 NAS rates (17.8 and 18.5 cases per 1,000 births, respectively) (Hussaini, 2017) were three times that of the 2012 U.S. rate (5.8 cases per 1,000 births) (Patrick, Dudley, et al., 2015; Patrick, Davis, et al., 2015). The primary objective of this study is to evaluate the association between infants diagnosed with NAS and birth defects in Delaware from 2010 to 2017.

2 | METHODS

2.1 | Data and sample

Three data sources were used for this analysis: (a) birth certificate data (BCD); (b) hospital discharge data (HDD); and (c) birth defects registry (BDR) data. We used Delaware BCD collected by the Office of Vital Statistics, HDD for all Delaware licensed hospitals that include all non-federal facilities collected quarterly based on the uniform claims and billing dataset (UB-82 or successor form) for all hospital inpatient discharges, and the BDR data for 2010–2017.

The BDR was established in 1997, by the Delaware Division of Public Health (DPH); data are collected through medical record review of each potential case by trained BDR abstractors with ascertainment of prevalence for approximately 100 specified birth defects (Acheson et al., 2016). The Delaware BDR abstractors review medical records on every child who is born in Delaware to a Delaware resident, and who has a suspected birth defect. Cases are identified from hospital discharge records, birth hospitals' records, reports from maternal fetal medicine specialists, and discharge records up to 1 year of age. Case ascertainment of birth defects is consistent with recommendations from the Centers for Disease Control and Prevention (CDC), and from the National Birth Defects Prevention Network (Acheson et al., 2016). The Institutional Review Boards at Delaware's birth hospitals and within DPH reviewed and approved the data collection process.

We used the Delaware BCD that contains unique identifiers (such as hospital identifiers, medical record numbers, first name, last name, date of birth, etc.) to linkHDD data that contains information on all newborns (e.g., discharges, length of stay, procedures, etc.) and identified all hospital births to Delaware residents (2010–2017). Records from the BDR were then linked to the linked BCD-HDD data to form the database for this study. Figure 1 outlines the study selection procedure for identification of this cohort. Hospital births from the BCD for Delaware residents served as the denominator (n = 82,190). Of the 82,190 hospital births during 2010–2017 in Delaware, 81,287 (~99%) of the records were matched.

2.2 | Measures

Our outcome variable from the linked BCD, HDD, and BDR data was a dichotomous measure of whether an infant had a birth defect or not (yes/no). We ascertained NAS cases in HDD using International Classification of Diseases—Ninth Revision

Clinical Modification (ICD-9-CM) diagnosis of 779.5 and ICD-10-CM diagnosis of P96.1 excluding iatrogenic cases of NAS very low birth weight, intraventricular hemorrhage, periventricular leukomalacia, necrotizing enterocolitis, spontaneous intestinal perforation, or bronchopulmonary dysplasia similar to Patrick et al. (2012)and Patrick, Davis, et al. (2015)), and the current tier II definitions from the Council of State and Territorial Epidemiologists (Council for State and Territorial Epidemiologists, 2019). From the linked BCD and HDD data, our primary exposure variable was a dichotomous measure (yes/no) of whether an infant was diagnosed with NAS for all hospital births, which we used as a surrogate for maternal exposure to opioids.

Covariates were maternal characteristics (i.e., age, education, non-Hispanic categorization of race/ethnicity, insurance status, county of residence, trimester of prenatal care, smoking during pregnancy, and maternal body mass index) and whether infant birth was a singleton or multiple birth from BCD.

2.3 | Statistical analysis

We estimated crude prevalence rates for birth defects and NAS per 1,000 hospital live births in Delaware residents during 2010–2017. We assessed trends in NAS using the Cochran–Armitage trend test. We used chi square tests for dichotomous and categorical variables to assess differences in our exposure NAS and non-NAS infants. We calculated crude odds ratio (cORs) and adjusted odds ratios (aORs) and 95% confidence intervals (CIs) based on a priori risk factors (i.e., plurality, maternal age, maternal education, maternal race/ethnicity, insurance status at delivery, county of residence, prenatal care, cigarette use, and pre-pregnancy body mass index) for birth defects and NAS. All tests were two-sided with alpha at .05 level of significance. All analyses were carried out using SAS v9.4 (SAS Institute, Inc., Cary, NC). Because missing data ranged between 0.1 and 3%, well-below the 5% threshold to conduct any imputation (Dong & Peng, 2013; Jakobsen, Gluud, Wetterslev, & Winkel, 2017; Schafer, 1999; Tabachnick & Fidell, 2012), we used listwise deletion for missing data. For a sensitivity analysis, we also conducted multiple imputations to assess if our estimates from listwise deletion differed from imputed data.

3 | RESULTS

Among 81,287 linked hospital births in Delaware during 2010–2017, there were 2,784 cases of birth defects and 1,651 cases of NAS. The 2010–2017 NAS rate in Delaware was 20.3 per 1,000 births (95% CI, 19.3–21.3). Delaware's NAS rates increased over 100% from 11.8 per 1,000 births in 2010 to 29.3 per 1,000 hospital births in 2017, a statistically significant increase ($z = 10.08$; $p < .0001$). The 2010–2017 rate for birth defects in Delaware was 34.2 per 1,000 births (95% CI, 35.3–38.6). The 2010–2017 rate for birth defects declined during this period in Delaware.

Table 1 presents characteristics of newborns with NAS compared with all other hospital births. There were differences between mothers who delivered NAS-affected infants and mothers whose infants were not diagnosed with NAS. A higher proportion of mothers who delivered NAS-affected infants were younger (i.e., <29 years of age 63 vs. 58%); had lower levels of education (i.e., high school or below 70 vs. ~44%); were non-Hispanic white

(81 vs. ~52%); had Medicaid as the payer of the delivery (~84 vs. 48%); and resided in New Castle County (63 vs. 60%). About one in three mothers who delivered NAS-affected infants had either no prenatal care or had prenatal care beginning in the second or third trimester. About 70% of the mothers who delivered an NAS-affected infant had smoked during pregnancy. A lower proportion of mothers who delivered an NAS-affected infant had BMI levels classified as overweight or obese as compared to non-NAS mothers.

Table 2 displays birth defects prevalence among infants with and without NAS. Among the 1,651 infants who had a diagnosis of NAS, 56 had a birth defect (~3.4%). Among the 79,636 infants not diagnosed with NAS, 2,728 (3.4%) had a birth defect. We found no statistically significant association between NAS and any birth defects in either our cOR (cOR = 1.0; 95% CI: 0.8–1.3) and or aOR (aOR = 0.9; 95% CI: 0.6–1.1) models. Sensitivity analysis from multiple imputations indicated negligible difference in the parameter estimates and our findings did not change.

4 | DISCUSSION

The main finding of our investigation is that infants with an NAS diagnosis are no more likely to have a birth defect than infants born without an NAS diagnosis. As NAS is a significant public health concern, our data showing a lack of association with birth defects is reassuring. Our finding is consistent with the systematic review of Lind et al. (2017) that found no clear evidence associating opioid use with congenital anomalies. However, in a recently published Canadian study of over a million births spanning 24 years 1989–2013, Auger et al. (2018) found that NAS was associated with birth defects and the association was strongest for central nervous system defects. Their study utilized discharge records to ascertain both birth defects and NAS.

Determining a specific cause for birth defect is often difficult (Bérard, Zhao, & Sheehy, 2017; Feldkamp, Carey, Byrne, Krikov, & Botto, 2017; Holbrook & Rayburn, 2014; Källén, Borg, & Reis, 2013; Naeye, Blanc, Leblanc, & Khatamee, 1973; Oliveira & Fett-Conte, 2013; Tinker et al., 2015) and in 75–80% of the cases of birth defects, causes are unknown (Holbrook & Rayburn, 2014;Oliveira & Fett-Conte, 2013; Tinker et al., 2015). For instance, Feldkamp et al.'s (2017) population-based study on the etiology and clinical manifestation of birth defects, found that of the 5,000 cases reviewed, approximately 80% of the cases were attributed to an "unknown etiology," and only 20% could be assigned a "definite cause".Of those with a definite cause, chromosomal or genetic conditions accounted for 95%, teratogens accounted for 4%, and twinning accounted for the remainder (Feldkamp et al., 2017).

The timing of opioid exposure, the type of opioids, the dose (i.e., quantity) are important to assess the levels of opioid exposure during organogenesis (i.e., phase of embryonic development) and/or later in the pregnancy. The current tests to detect fetal exposure to licit and illicit drugs include: radioimmunoassay and enzyme immuno-assay tests (i.e., drug screens), urine toxicology, and meconium and umbilical cord analyses (Jones et al., 2015; Price, Collier, & Wright, 2018) and as such, these drug screens test for exposure late in pregnancy.

The results of our study should be interpreted in the context noted above, the birth defect etiologies, and the emerging research on NAS. Study limitations include ascertainment of NAS cases based only on discharge data for hospital births utilizing ICD-9-CM and ICD-10-CM codes, with all the coding issues incumbent in the use of these data (Patrick et al., 2012). Second, NAS diagnosis served as a surrogate to measure maternal opioid exposure and the timing of exposure was not available in the dataset and therefore, susceptible to misclassification. For instance, in our sample over 70% of the women smoked during pregnancy and both tobacco and prescribed medications such as SSRIs can cause NAS (Jansson & Velez, 2012). Further, opioid use, whether (licit or illicit), may lead to NAS among 50–80% of opioid-exposed infants, as not all exposures result in an NAS diagnosis (Jones, Chisolm, Jansson, & Terplan, 2013; Patrick, Dudley, et al., 2015). A relatively small number of defects were noted among NAS-affected infants, limiting statistical power for exploring specific birth defects potentially related to maternal opioid exposure. Finally, in our dataset, we were unable to account for other confounders (e.g., maternal medications such as SSRIs) that may be associated with some birth defects (Auger et al., 2018). Despite these limitations, our study is population-based, and utilized birth defects data collected by active case-finding. In particular, our study uses existing surveillance systems such as discharge data, BCD, and BDR data to understand the association between NAS and birth defects and found that infants with an NAS diagnosis are no more likely to have a birth defect than infants born without an NAS diagnosis. Future studies in the United States, may incorporate larger population-based datasets, enhanced surveillance systems, additional measures of the opioid exposure such as the timing and dose of opioid exposure, and identify specific substances to understand the teratogenicity.

5 | CONCLUSION

Our multiyear state-wide study using linked BC, hospital discharge, and BDR data for Delaware did not show a statistically significant association between infants diagnosed with NAS and birth defects, overall.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are not publicly available due to privacy or ethical restrictions. Data are subject to state and local regulatory laws.

REFERENCES

Acheson A, Vaidy A, Stomieroski K, Thompson DR, Maiden KM, Ehrenthal DB, … Bartoshesky LE (2016). Surveillance of ventricular septal defects in Delaware. Birth Defects Research: Part A, Clinical and Molecular Teratology, 106(11), 888–893. 10.1002/bdra.23574 [PubMed: 27891775]

Ailes EC, Dawson AL, Lind JN, Gilboa SM, Frey MT, Broussard CS, … Centers for Disease Control and Prevention (CDC). (2015). Opioid prescription claims among women of reproductive age—United States, 2008–2012. MMWR. Morbidity and Mortality Weekly Report, 64(2), 37–41. [PubMed: 25611168]

Anand KJ, & Campbell-Yeo M (2015). Consequences of prenatal opioid use for newborns. Acta Paediatrica, 104(11), 1066–1069. 10.1111/apa.13121 [PubMed: 26174725]

Auger N, Luu TM, Healy-Profitós J, Gauthier A, Lo E, & Fraser WD (2018). Correlation of neonatal abstinence syndrome with risk of birth defects and infant morbidity. Journal of Studies on Alcohol and Drugs, 79(4), 553–560. [PubMed: 30079870]

Bérard A, Zhao JP, & Sheehy O (2017). Antidepressant use during pregnancy and the risk of major congenital malformations in a cohort of depressed pregnant women: An updated analysis of the Quebec Pregnancy Cohort. BMJ Open, 7(1), e013372. 10.1136/bmjopen-2016-013372

Broussard CS, Rasmussen SA, Reefhuis J, Friedman JM, Jann MW, Riehle-Colarusso T, … National Birth Defects Prevention Study. (2011). Maternal treatment with opioid anal-gesics and risk for birth defects. American Journal of Obstetrics and Gynecology, 204(4), 314.e311–314.e311. 10.1016/j.ajog.2010.12.039

Council for State and Territorial Epidemiologists. (2019) Standardized surveillance for diseases or conditions, revised. Retrieved from https://cdn.ymaws.com/www.cste.org/resource/resmgr/ps/2019ps/19-MCH-01_NAS_updated_5.7.19.pdf

Dong Y, & Peng CY (2013). Principled missing data methods for researchers. Springerplus, 2(1), 222. 10.1186/2193-1801-2-222 [PubMed: 23853744]

Feldkamp ML, Carey JC, Byrne JLB, Krikov S, & Botto LD (2017). Etiology and clinical presentation of birth defects: Population based study. BMJ, 357, j2249. 10.1136/bmj.j2249 [PubMed: 28559234]

Haight SC, Ko JY, Tong VT, Bohm MK, & Callaghan WM (2018). Opioid use disorder documented at delivery hospitalization—United States, 1999–2014. MMWR. Morbidity and Mortality Weekly Report, 67(31), 845–849. 10.15585/mmwr.mm6731a1 [PubMed: 30091969]

Holbrook BD, & Rayburn WF (2014). Teratogenic risks from exposure to illicit drugs. Obstetrics and Gynecology Clinics of North America, 41(2), 229–239. 10.1016/j.ogc.2014.02.008 [PubMed: 24845487]

Hussaini KS (2017). Neonatal abstinence syndrome: Delaware, 2010–2015. Research Brief. Retrieved from https://dethrives.com/reports

Jakobsen JC, Gluud C, Wetterslev J, & Winkel P (2017). When and how should multiple imputation be used for handling missing data in randomised clinical trials—A practical guide with flowcharts. BMC Medical Research Methodology, 17(1), 162. 10.1186/s12874-017-0442-1 [PubMed: 29207961]

Jansson LM, & Velez M (2012). Neonatal abstinence syndrome. Current Opinion in Pediatrics, 24(2), 252–258. 10.1097/MOP.0b013e32834fdc3a [PubMed: 22227786]

Jones HE, Chisolm MS, Jansson LM, & Terplan M (2013). Naltrexone in the treatment of opioid-dependent pregnant women: Common ground. Addiction (Abingdon, England), 108 (2), 255–256. 10.1111/add.12071 [PubMed: 23331881]

Jones JT, Jones M, Jones B, Sulaiman K, Plate C, & Lewis D (2015). Detection of codeine, morphine, 6-monoacetylmorphine, and meconin in human umbilical cord tissue: Method validation and evidence of in utero heroin exposure. Therapeutic Drug Monitoring, 37(1), 45–52. 10.1097/FTD.0000000000000104 [PubMed: 24901495]

Källén B, Borg N, & Reis M (2013). The use of central nervous system active drugs during pregnancy. Pharmaceuticals (Basel), 6(10), 1221–1286. 10.3390/ph6101221 [PubMed: 24275849]

Lind JN, Interrante JD, Ailes EC, Gilboa SM, Khan S,Frey MT, … Broussard CS (2017). Maternal use of opioids during pregnancy and congenital malformations: A systematic review. Pediatrics, 139(6), e20164131. 10.1542/peds.2016-4131 [PubMed: 28562278]

Lind JN, Petersen EE, Lederer PA, Phillips-Bell GS,Perrine CG, Li R, … Centers for Disease Control and Prevention (CDC). (2015). Infant and maternal characteristics in neonatal abstinence syndrome—selected hospitals in Florida, 2010–2011. MMWR. Morbidity and Mortality Weekly Report, 64(8), 213–216. [PubMed: 25742381]

Maeda A, Bateman BT, Clancy CR, Creanga AA, & Leffert LR (2014). Opioid abuse and dependence during pregnancy: Temporal trends and obstetrical outcomes. Anesthesiology, 121 (6), 1158–1165. 10.1097/ALN.0000000000000472 [PubMed: 25405293]

McQueen K, & Murphy-Oikonen J (2016). Neonatal abstinence syndrome. The New England Journal of Medicine, 375(25), 2468–2479. 10.1056/NEJMra1600879 [PubMed: 28002715]

Naeye RL, Blanc W, Leblanc W, & Khatamee MA (1973). Fetal complications of maternal heroin addiction: Abnormal growth, infections, and episodes of stress. The Journal of Pediatrics, 83(6), 1055–1061. 10.1016/s0022-3476(73)80550-5 [PubMed: 4757521]

Nørgaard M, Nielsson MS, & Heide-Jørgensen U (2015). Birth and neonatal outcomes following opioid use in pregnancy: A Danish population-based study. Substance Abuse, 9(Suppl 2), 5–11. 10.4137/SART.S23547

Oliveira CI, & Fett-Conte AC (2013). Birth defects: Risk factors and consequences. Journal of Pediatric Genetics, 2(2), 85–90. 10.3233/PGE-13052 [PubMed: 27625844]

Patrick SW, Davis MM, Lehmann CU, & Cooper WO (2015). Increasing incidence and geographic distribution of neonatal abstinence syndrome: United States 2009 to 2012. Journal of Perinatology, 35(8), 650–655. 10.1038/jp.2015.36 [PubMed: 25927272]

Patrick SW, Dudley J, Martin PR, Harrell FE, Warren MD, Hartmann KE, … Cooper WO (2015). Prescription opioid epidemic and infant outcomes. Pediatrics, 135(5), 842–850. 10.1542/peds.2014-3299 [PubMed: 25869370]

Patrick SW, Schumacher RE, Benneyworth BD, Krans EE,McAllister JM, & Davis MM (2012). Neonatal abstinence syndrome and associated health care expenditures: United States, 2000–2009. Jama, 307(18), 1934–1940. 10.1001/jama.2012.3951 [PubMed: 22546608]

Price HR, Collier AC, & Wright TE (2018). Screening pregnant women and their neonates for illicit drug use: Consideration of the integrated technical, medical, ethical, legal, and social issues. Frontiers in Pharmacology, 9, 961. 10.3389/fphar.2018.00961 [PubMed: 30210343]

Reddy UM, Davis JM, Ren Z, Greene MF, & Opioid Use in Pregnancy, Neonatal Abstinence Syndrome, and Childhood Outcomes Workshop Invited Speakers. (2017). Opioid use in pregnancy, neonatal abstinence syndrome, and childhood outcomes: Executive summary of a joint workshop by the Eunice Kennedy Shriver National Institute of Child Health and Human Development, American College of Obstetricians and Gynecologists, American Academy of Pediatrics, Society for Maternal-Fetal Medicine, Centers for Disease Control and Prevention, and the March of Dimes Foundation. Obstetrics and Gynecology, 130(1), 10–28. 10.1097/AOG.0000000000002054 [PubMed: 28594753]

Schafer JL (1999). Multiple imputation: A primer. Statistical Methods in Medical Research, 8(1), 3–15. 10.1177/096228029900800102 [PubMed: 10347857]

Short TD, Stallings EB, Isenburg J, O'Leary LA, Yazdy MM, Bohm MK, … Reefhuis J (2019). Gastroschisis trends and ecologic link to opioid prescription rates—United States, 2006–2015. MMWR. Morbidity and Mortality Weekly Report, 68 (2), 31–36. 10.15585/mmwr.mm6802a2 [PubMed: 30653484]

Stover MW, & Davis JM (2015). Opioids in pregnancy and neonatal abstinence syndrome. Seminars in Perinatology, 39(7), 561–565. 10.1053/j.semperi.2015.08.013 [PubMed: 26452318]

Tabachnick BG, & Fidell LS (2012). Using multivariate statistics (6th ed.). Boston, MA: Pearson Education.

Tinker SC, Gilboa S, Reefhuis J, Jenkins MM, Schaeffer M, & Moore CA (2015). Challenges in studying modifiable risk factors for birth defects. Current Epidemiology Reports, 2(1), 23–30. 10.1007/s40471-014-0028-y [PubMed: 26236577]

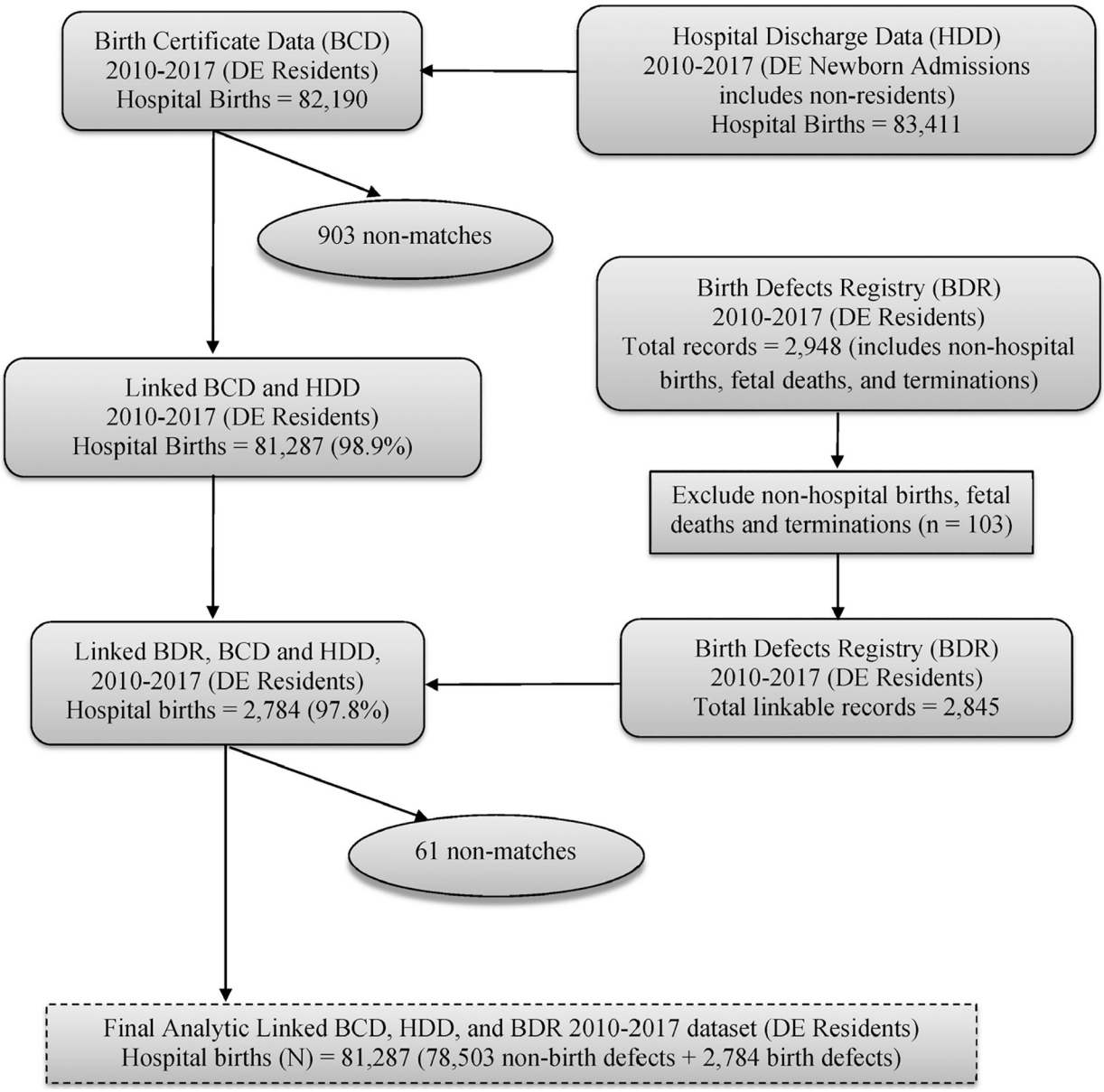

FIGURE 1.

Study selection and data linkage for identification of a cohort of newborns with neonatal abstinence syndrome (surrogate measure for maternal opioid exposure) and birth defects, Delaware, 2010–2017

TABLE 1

Characteristics of newborns with and without a diagnosis of NAS, in Delaware, 2010–2017

	Total (N = 81,287)[a]		
Maternal and infant characteristics[a]	**Birth with NAS (n = 1,651)**	**Birth without NAS (n = 79,636)**	p [b]
Plurality			
Singleton	1,624 (98.4%)	77,032 (96.7%)	.0002
Multiple birth	27 (1.6%)	2,604 (3.3%)	
Maternal age (years)			
<20	33 (2.0%)	5,457 (6.9%)	<.0001
20–24	402 (24.4%)	17,478 (22.0%)	
25–29	602 (36.5%)	23,409 (29.4%)	
30–34	449 (27.2%)	21,415 (26.9%)	
> = 35	165 (10.0%)	11,877 (14.9%)	
Maternal education			
<9 years of schooling	51 (3.1%)	4,361 (5.5%)	<.0001
9–11 years of schooling	402 (24.4%)	9,931 (12.5%)	
High school graduate	705 (42.7%)	20,560 (25.8%)	
1–3 years of college	424 (25.7%)	21,090 (26.5%)	
>3 years of college	49 (3%)	23,259 (29.2%)	
Unknown/refused	20 (1.2%)	435 (0.6%)	
Maternal race and ethnicity			
White (non-Hispanic)	1,337 (81.0%)	41,237 (51.8%)	<.0001
Black (non-Hispanic)	218 (13.2%)	21,976 (27.6%)	
Hispanic	75 (4.5%)	11,442 (14.4%)	
Other	19 (1.2%)	4,954 (6.2%)	
Unknown/missing	2 (0.1%)	27 (~0.0%)	
Insurance status at delivery			
Medicaid	1,380 (83.6%)	38,548 (48.4%)	<.0001
Non-Medicaid	271 (16.4%)	41,088 (51.6%)	
Maternal county of residence			
Kent	263 (15.9%)	16,412 (20.6%)	<.0001

Birth Defects Res. Author manuscript; available in PMC 2024 March 18.

Maternal and infant characteristics[a]	Total (N = 81,287)[a] Birth with NAS (n = 1,651)	Birth without NAS (n = 79,636)	p [b]
New Castle	1,032 (62.5%)	47,218 (59.3%)	
Sussex	356 (21.6%)	16,006 (20.1%)	
Prenatal care initiation			
No prenatal care	59 (6.7%)	1,229 (2.5%)	<.0001
First trimester	548 (62.6%)	37,592 (75.1%)	
Second trimester	190 (21.7%)	8,260 (16.5%)	
Third trimester	52 (5.9%)	2,204 (4.4%)	
Unknown/missing	26 (3.0%)	781 (1.6%)	
Smoking during pregnancy			
Yes	1,149 (69.6%)	7,908 (9.9%)	<.0001
No	499 (30.2%)	44,532 (90.0%)	
Unknown/missing	3 (0.2%)	23 (0.1%)	
Pre-pregnancy BMI (kg/m^2) [c]			
Underweight (<18.5)	58 (6.6%)	2,273 (4.5%)	<.0001
Normal weight (18.5 to <25.0)	434 (49.6%)	21,505 (43%)	
Overweight (25.0 to <30.0)	217 (24.8%)	12,690 (25.4%)	
Obese (> = 30.0)	145 (16.6%)	12,776 (25.5%)	
Unknown/missing	21 (2.4%)	822 (1.6%)	

Abbreviations: BC, birth certificate; BDR, birth defects registry; BMI, body mass index; HDD, hospital discharge data; NAS, neonatal abstinence syndrome.

[a] Linked BC, HDD, and BDR data for 2010–2017.

[b] p-Value calculated from chi-square test for difference between NAS exposure groups.

[c] BMI is defined as the body mass divided by the square of the body height, expressed in mass in kilograms and height in meters.

TABLE 2

Birth defects among infants with and without NAS in Delaware, 2010–2017

Exposure/outcome	Birth defect	No birth defect	Total	cOR[b] (95% CI)	aOR[c] (95% CI)
NAS[a]	56 (3.4%)	1,595 (96.6%)	1,651	1.0 (0.8–1.3)	0.9 (0.6–1.1)
Non-NAS	2,728 (3.4%)	76,908 (96.6%)	79,636		
Total	2,784 (3.4%)	78,503 (96.6%)	81,287		

Abbreviations: aOR, adjusted odds ratio; BMI, body mass index; CI, confidence interval; cOR, crude odds ratio; NAS, neonatal abstinence syndrome.

[a]NAS measured using ICD-9-CM/ICD-10-CM codes 779.5 and P96.1.

[b]cOR with 95% CI.

[c]aOR with 95% CI. Adjusted a priori for plurality, maternal age, maternal education, maternal race/ethnicity, insurance status at delivery, county of residence, trimester of prenatal care initiation, cigarette use during pregnancy, and pre-pregnancy BMI.