Title

Risk factors for neonatal encephalopathy in late preterm and term singleton births in a large California birth cohort

Journal

Journal of Perinatology, 42(3)

ISSN

0743-8346

Authors

Bandoli, Gretchen
Suttner, Denise
Kiernan, Elizabeth
et al.

Publication Date

2022-03-01

DOI

10.1038/s41372-021-01242-z

Peer reviewed

Published in final edited form as:

J Perinatol. 2022 March ; 42(3): 341–347. doi:10.1038/s41372-021-01242-z.

Risk factors for neonatal encephalopathy in late preterm and term singleton births in a large California birth cohort

Gretchen Bandoli, PhD[1], **Denise Suttner, MD**[1,2], **Elizabeth Kiernan, MPH**[1], **Rebecca J Baer, MPH**[1,3], **Laura Jelliffe-Pawlowski, PhD**[3], **Christina D Chambers, PhD MPH**[1]

[1]Department of Pediatrics, University of California San Diego, La Jolla California

[2]Rady Children's Hospital, San Diego CA

[3]Preterm Birth Initiative, University of California San Francisco

Abstract

Objectives.—The objective was to investigate maternal and pregnancy characteristics associated with neonatal encephalopathy (NE).

Study design.—We queried an administrative birth cohort from California between 2011–2017 to determine the association between each factor and NE with and without hypothermia treatment.

Results.—From 3 million infants born at 35 or more weeks of gestation, 6,857 cases of NE were identified (2.3 per 1,000 births), 888 (13%) which received therapeutic hypothermia. Risk factors for NE were stronger among cases receiving hypothermia therapy. Substance-related diagnosis, preexisting diabetes, preeclampsia, and any maternal infection were associated with a two-fold increase in risk. Maternal overweight/obesity, nulliparity, advanced maternal age, depression, gestational diabetes or hypertension, and short or long gestations also predicted NE. Young maternal age, Asian race and Hispanic ethnicity, and cannabis related diagnosis lowered risk of NE.

Conclusions.—By disseminating these results, we encourage further interrogation of these perinatal factors.

Introduction

Neonatal encephalopathy (NE) describes a complex condition of neurologic dysfunction in infants born at 35 or more weeks of gestation.[1] NE is a critical problem with the potential for life-long sequelae, including motor and cognitive impairment. In developed

Corresponding author: Gretchen Bandoli, PhD, 9500 Gilman Drive, MC 0828, La Jolla, CA 92093, 858-246-1733, gbandoli@health.ucsd.edu.

Contributors statements

Drs. Bandoli conceptualized the design and analysis for the study, performed the analysis, drafted and revised the manuscript.

Drs. Suttner and Chambers conceptualized the design and analysis for the study, drafted and revised the manuscript.

Ms. Kiernan coordinated the literature review, contributed to the drafting and revision of the manuscript.

Ms. Baer managed the database for the study, cleaned and prepared data for the analysis, and contributed to the drafting and revision of the manuscript.

Dr. Jelliffe-Pawlowski assisted in conceptualizing the parent study, and critically reviewed and revised the manuscript.

Conflict of interest

The authors have no competing financial interests in relation to this work

countries, NE is estimated to occur in 3–4 of 1000 live births.[2,3] Known causes for NE include hypoxia-ischemia, metabolic, inflammatory, thromboembolic, and genetic factors.[4,5] Historically, NE and hypoxic ischemic encephalopathy (HIE) were used synonymously. Neonatal HIE is an intrapartum cause-specific subset of NE whereby disruption of perfusion or oxygen leads to cerebral injury. Treatment with hypothermia is a standard of care for newborns diagnosed with moderate to severe HIE based on a number of criteria. Estimates vary widely for the proportion of cases of NE where HIE was a contributing factor, ranging from 30–80%.[2,4–6]

Importantly, in a substantial number of NE cases, including those appropriately ascribed to HIE, the cause of NE is unclear or incompletely classified without consideration for contributing prenatal or maternal conditions. In cases where hypoxia-ischemia has occurred, the proximal event may be only one factor among other unrecognized antenatal events predisposing the neonate to injury.[7] It is essential to identify maternal predictive factors for intrapartum or unknown cause NE at the outset of prenatal care or in the preconception period, alerting parents and clinicians to increased risk that may potentially be mitigated by intervention. A number of studies have examined risk factors for NE, although only a handful specifically assessed prenatal risk factors, had robust sample sizes and importantly, evaluated risk factors with multivariable analyses.[8–17] Of these, a relatively narrow range of prenatal risk factors were typically assessed, resulting in the need for additional investigation.

The objective of this study was to identify maternal and prenatal risk factors associated with unspecified and intrapartum NE. From an administrative birth cohort consisting of approximately 3 million births, we assessed the independent associations of maternal sociodemographic, clinical and pregnancy characteristics with the risk of NE.

Materials and methods

This retrospective cohort was comprised of pregnancies that resulted in live-born singleton births in California between 2011–2017. Birth certificates, maintained by California Vital Statistics, were linked to hospital discharge, emergency department, and ambulatory surgery records maintained by the California Office of Statewide Health Planning and Development. These databases contain detailed information on maternal and infant characteristics and hospital discharge diagnoses. Hospital discharge, emergency department, and ambulatory surgery files provided diagnoses codes based on the *International Classification of Diseases, 9th Revision*, Clinical Modification (ICD-9) and *International Classification of Diseases, 10th Revision*, Clinical Modification (ICD-10) as reported to the California Office of Statewide Health Planning and Development by the hospitals.[18] The study dataset consists of discharge records (maternal: one year prior to the birth through delivery; infant: first year of life) linked to the infant's birth certificate. In general, approximately 85% of birth records are successfully linked to discharge records for the study cohort. The study was approved by the University of California San Diego Human Research Protections Program and the Committee for the Protection of Human Subjects within the Health and Human Services Agency of the State of California.

Outcome and exposure variables

Unspecified and intrapartum NE was identified from ICD-9 and ICD-10 codes during the birth admission: hypoxic ischemic encephalopathy (768.7, P91.6), other and unspecified NE in newborn (779.1, P91.81, P91.82, P91.88), birth asphyxia (768.5, 768.6, 768.9, P21.0), and other specified brain damage due to birth injury (767.0, 768.7, P11.1, P11.2). Codes were chosen based on previous literature,[9,10,19] and to be inclusive of all cases classified as birth-related or unspecified by the clinician. Therapeutic hypothermia during the birth admission was identified from ICD procedure codes (99.81, 6A4Z0ZZ, 6A4Z1ZZ). Stratification based on hypothermia was performed to identify a group at particular risk for poor neurodevelopmental outcome. Maternal and prenatal factors were identified from hospital discharge records recorded during pregnancy or the delivery episode. A full list of data sources and ICD codes are available in Supplemental Table 1.

Statistical analysis

Based on the American College of Obstetricians and Gynecologists (ACOG) definition of NE, we limited the cohort to births that occurred at or beyond 35 weeks of gestation.[1] To assess heterogeneity in risk factors by severity and cause, as proxied by therapeutic hypothermia, we stratified NE diagnosis by receipt of therapeutic hypothermia, and compared each stratum to infants with no NE diagnosis. We first assessed the univariate association between each risk factor and NE stratum with chi-square and Fisher's exact tests where necessary. Subsequently, for variables with univariate chi-square probability ≤ 0.05 and a cell count of at least 5, we performed multivariable regression. Log-linear regression was used to estimate risk ratios for each stratum of NE (compared with no NE diagnosis) with all variables in a single model. The vast majority of cases (97%) were attributed to HIE, birth injury or birth asphyxia. To determine whether 'other and unspecified NE' influenced results, we performed a sensitivity analysis where we removed the cases of 'other and unspecified NE' without overlapping codes for HIE, injury or asphyxia and repeated all models. In all analyses missing variables were left as such, and complete case analysis was performed. All analyses were conducted in SAS, version 9.4 (SAS Institute), and statistical significance was set at $p<0.05$.

Results

There were 3,161,875 births in the State of California between 2011–2017 which were able to be linked to hospital discharge summaries. From these, there were 3,067,069 singleton births, of which 2,994,892 occurred at 35 or greater weeks of gestation. From the cohort, 6,857 described cases of NE were identified (2.3 per 1,000 births), of which 888 (13%) received therapeutic hypothermia. Of 5,969 NE cases without therapeutic hypothermia, 9.5% had ICD codes for asphyxia, 41.7% had codes for HIE, 4.0% had codes for other and unspecified NE in newborn, and 48.2% had codes specific to birth injury (not mutually exclusive; Supplemental Table 2). When limited to NE cases with therapeutic hypothermia, almost all (96.1%) had ICD codes indicating HIE.

Univariate analyses

In univariate analyses, NE without hypothermia was associated with maternal race/ethnicity, body mass index, prenatal care, payer source, parity, mental health conditions, alcohol, cannabis, and other substance related diagnosis during pregnancy, nicotine, preexisting diabetes (Type I or II), hypertension, asthma, inflammatory bowel disease, maternal stroke and migraine (Table 1). The majority of pregnancy complications were associated with having an infant with NE, including gestational diabetes, preeclampsia or gestational hypertension, and any infection during pregnancy. Finally, birth at 35–38 weeks or greater than 40 weeks was also associated with NE. When assessing NE with therapeutic hypothermia, most of the same variables were identified, with the exception of alcohol use, maternal stroke and migraine. Additionally, maternal age and rheumatoid arthritis were associated with NE with therapeutic hypothermia, which was not observed in the strata without hypothermia.

Multivariable analyses

We first assessed these factors among infants with NE who did not receive therapeutic hypothermia (Table 2). Infants born to women who were overweight or obese, had less than adequate prenatal care, were nulliparous, had bipolar disorder or a substance related diagnosis, had preexisting diabetes, gestational diabetes or hypertension, preeclampsia, any infection in pregnancy, or who had a pregnancy at the short (35–38 weeks) or long (>40 weeks) end of the gestational range all had an increased risk of NE. Infants born to women who identified as Hispanic or Asian were at lower risk of NE. While most associations were modest, preexisting diabetes was associated with more than a doubling of risk (adjusted risk ration (aRR) 2.42, 95% CI 2.02, 2.91). Maternal stroke, which was associated with NE in univariate analyses, was not included in multivariable analyses due to a cell size less than 5.

In the group of infants treated with hypothermia, we examined maternal factors and compared these to infants with no NE diagnosis (Table 3). In this subset, advanced maternal age, maternal overweight/obesity, sub-adequate prenatal care, public insurance, nulliparity, maternal depression or substance related diagnosis, preexisting diabetes and asthma were all independently associated with this NE group. The following pregnancy complications were also independently associated with the risk of NE in this group: gestational diabetes, preeclampsia, gestational hypertension, and any infection during pregnancy. Compared with pregnancies of 39–40 weeks, shorter and longer gestations both predicted NE that received hypothermia therapy. Cannabis related diagnosis was associated with a lower risk of NE in this group, as was young maternal age and Hispanic ethnicity. A handful of associations had risk estimates greater than 2.0, including substance related diagnosis (aRR 2.63, 95% CI 1.96, 3.53), preexisting diabetes (aRR 2.11, 95% CI 1.49, 2.98), preeclampsia (aRR 2.48, 95% CI 2.07, 2.97) and any maternal infection during pregnancy (aRR 2.33, 95% CI 2.07, 2.63). Rheumatoid arthritis was omitted from multivariable analysis due to low prevalence.

Comparing results between the models of NE with and without hypothermia therapy, there were no variables that stood out in contrast to each other. Generally, the variables in the

model of NE with hypothermia therapy were directionally the same as the NE model without hypothermia, just stronger in their associations with the outcome.

Sensitivity analysis

From all cases of NE identified by ICD codes, only 220 (210 from NE without hypothermia therapy and 10 from NE with hypothermia therapy) had codes for 'other and unspecified NE' (Supplemental Table 2). When these cases were removed from the NE strata and moved to the reference group, there was no notable change to the results in risk factors or magnitude of the estimated risk (results not shown).

Discussion

The etiology of NE is not always clear and is often multifactorial. Although historically research has focused on adverse intrapartum risk factors for NE, there is great interest in elucidating maternal and prenatal risk factors that can serve as intervention targets to reduce the incidence of this important disorder. To date, this is the largest assessment of characteristics associated with unspecified and intrapartum NE. In this birth cohort of over 6,000 cases of code-specific NE (2.3 per 1,000 births), we identified multiple prenatal risk factors, which confirmed findings in smaller studies and identified a few novel factors. Preexisting diabetes, and in the subset who received therapeutic hypothermia, maternal substance related diagnosis, preeclampsia and any maternal infection during pregnancy each were associated with a two-fold increased risk of NE. To a lesser degree, having a mother who was overweight/obese, nulliparous, had select mental health conditions, had gestational diabetes or hypertension, or with a gestation less than 39 weeks or greater than 40 weeks also predicted NE. Young maternal age, Hispanic ethnicity, as well as a cannabis related diagnosis in pregnancy were associated with reduced risk of NE with hypothermia therapy in multivariable analysis. Several factors, including maternal education, nicotine use, alcohol related diagnosis, anxiety, inflammatory bowel disease, and migraines were not associated with NE in multivariable analyses.

Given the inconsistencies in diagnosing NE, some researchers rely on ICD codes,[9,10,17] and others rely on disparate clinical criteria such as the use of therapeutic hypothermia and Apgar scores, Thompson score or neuroimaging findings.[8,11–15] Further, many studies select specifically at HIE as opposed to other relevant NE codes,[8,11,13,15] potentially eliminating a significant number of affected children. This heterogeneity may limit direct comparisons between studies; however, many of the features identified in our analysis have been previously noted. For clarity in comparisons with previous studies that follow, we note whether the study was specific to NE or HIE.

In a population-based cohort in Sweden, similar to this study, nulliparity, gestations greater than 40 weeks, and hypertensive disorders all were associated with the risk of severe HIE.[8] In a very similar study to ours, researchers assessed risk factors for NE (identified from ICD codes) from an administrative cohort from Washington state (with data from 1994–2002).[10] There, researchers found public insurance was associated with NE, but education was not, similar to our findings. In addition, nulliparity and preeclampsia were also associated with

increased risk of NE in univariate analysis, while prenatal tobacco use was not.[10] Of note, in their study, neither young maternal age, Hispanic ethnicity, nor Asian race were associated with reduced risk of NE as we observed in our cohort. In a population-based study from Australia in the mid-1990s[14] at least a doubling of risk of HIE was observed with advanced maternal age, public insurance, maternal hypertension, preeclampsia, gestational length greater than 40 weeks, and no (vs. some) alcohol consumption. Finally, in a large Swedish cohort study,[17] nulliparity was the only maternal variable that was significantly associated with severe to moderate HIE in multivariable analyses. In contrast to our results, neither preeclampsia, gestational age, nor gestational diabetes predicted the outcome, although only 76 cases were identified, resulting in low statistical power.

Our finding of any infection during pregnancy as a risk factor has also been noted by others. Among 45 infants with HIE not attributed to sentinel events, urinary tract infection during pregnancy was associated with a 2-fold increase risk of HIE.[16] Similarly, in a retrospective cohort study,[15] unexplained HIE cases were associated with nulliparity and intrauterine infection (histologic funisitis but not chorioamnionitis). The authors suggest that fetal inflammation may augment the mechanism by which hypoxia ischemia leads to more significant injury. Our finding of preexisting diabetes and the 2-fold increased risk of NE, both with and without hypothermia therapy, has also been noted elsewhere. In a large Swedish cohort, authors found 2–3 fold increased odds of HIE with maternal Type I and Type II diabetes, independent of obesity.[20] Further, their findings for Type 1 diabetes, but not Type II, remained after limiting to women without hypertension and infants who were not born premature or low birth weight. The latter is interesting in light of our univariate findings of a 5-fold increased risk of NE with the autoimmune disease rheumatoid arthritis. In one study of neonatal arterial ischemic stroke (NAIS), a known cause of NE, maternal autoimmune disease was associated with NAIS, although the diseases studied (Type I diabetes and others) did not include rheumatoid arthritis.[21] Our univariate finding should be more rigorously queried in a sample that includes more women with rheumatoid arthritis, and further work analyzing autoimmune conditions and neonatal encephalopathy may be warranted.

To our knowledge, we are the first to report a decreased risk of NE with cannabis use (which was only observed in our strata with therapeutic hypothermia). The reduced risk of NE with hypothermia therapy among those prenatally exposed to cannabis did not move below the null until adjustment for substance use. This finding was unexpected and warrants further investigation. Finally, with respect to our univariate findings of maternal stroke, the rarity of the outcome prohibited multivariable analysis. However, the unadjusted prevalence was 6 times greater among infants with NE. Given that the risk factors for stroke include preeclampsia, hypertension, diabetes and substance use,[22] stroke may be a mediator between these factors and NE. This question would need to be formally analyzed with a mediation analysis in a dataset with a higher prevalence of maternal stroke than was observed in our data set.

There are clinical and research implications to these findings. Expansion of our understanding of documented risk factors allows for interventions that may impact the incidence or severity of NE. We have identified numerous factors associated with an

increased risk of NE, although most are relatively modest in strength. Some of these factors have been noted before but not in this large of a dataset. Others, like the decreased risk with cannabis related diagnosis, are more difficult to interpret and require additional research. Further, as it is almost certain that some of these factors interact with each other, analyses employing machine learning may further elucidate how factors working in concert result in NE to build predictive models that can help clinicians better identify pregnancies at high risk of NE. Additionally, a limitation of including all variables in one model is that some results may encompass the total effect, while others that have mediators also in the model are estimating the direct (unmediated) effects.[23] It is important for researchers interested in specific risk factors to plan out multivariable analyses *a priori* to estimate specific pathways of interest. As such, these estimates should be interpreted as associations as opposed to causal estimates.

By querying a large, diverse birth cohort of approximately 3 million births, we were able to analyze multiple risk factors for unspecified or intrapartum NE. Our research should be considered in light of the limitations. Our administrative cohort relies on ICD codes, and does not have data such as clinical characteristics documented in medical charts. In a validation study of ICD9 codes for NE,[19] the majority of which were used in our study as well, the codes were not very reliable in meeting ACOG criteria for HIE. However, the sample of cases used in that analysis was small and relied on ICD9 codes from the 1999 version, which have been updated both with newer ICD9 codes and for ICD10 codes. Additionally, to increase sensitivity, we excluded codes such as '770.88: hypoxemia' or '775.81: other acidosis of the newborn,' and were transparent with the included ICD codes in order to encourage reproducibility. Further, to address potential misclassification due to the use of ICD codes, we stratified NE models by infants who received therapeutic hypothermia, which resulted in stronger estimates among the cases, which were overwhelmingly comprised of infants diagnosed with HIE. We also removed 'unspecified or other NE' from models with no change to results. Nonetheless, in the absence of universally accepted criteria, even clinical criteria differ widely between studies, affecting the ability to interpret the literature as a whole. Further, administrative data provides an incomplete capture of diagnosis and procedure codes, and thus our prevalence estimates are lower than other estimates that relied on different data sources.[24] Consequently, we are more likely to have misclassified individuals as unexposed who did in fact have NE or receive therapeutic hypothermia, which may underestimate the true risk. Another consideration of the risk estimates is that in some cases, the cause of NE is known and completely unrelated to prenatal events. Including cases like these would attenuate our effect estimates. However, we felt that it was important to include all birth related NE cases as the majority of the time, the cause is unclear or may be incorrectly ascribed to proximal events. Additionally, the reliance on ICD codes and birth records for demographic factors and comorbidities can lead to misclassification, which would likely be non-differential and bias results towards the null. Further, some variables such as substance related diagnoses are known to be under-reported in hospital discharge summaries and likely represent disordered use. Finally, we have not considered the fetal genome, which very likely contributes to NE risk either through direct genetic susceptibility,[25] or through interaction with the factors we analyzed.[26]

In conclusion, we replicated and expanded findings for prenatal characteristics associated with NE. By expanding documented risk factors, researchers may further elucidate etiologic pathways of NE. Additionally, clinicians may consider these risk factors in the early identification of women at a greater risk of having an infant with NE.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors wish to thank Joe Gleeson, MD for his valuable comments on the project.

Funding

This analysis was funded by the San Diego Study of Mothers and Infants at the University of California San Diego and the Rady Children's Institute for Genomic Medicine. Gretchen Bandoli is funded by a NIH award (1 K01 AA027811-01). No funders/sponsors participated in this work.

Abbreviations

ACOG	American College of Obstetricians and Gynecologists
HIE	Hypoxic ischemic encephalopathy
ICD	International Classification of Diseases
NE	Neonatal encephalopathy

References

1. American College of Obstetricians and Gynecologists. Neonatal Encephalopathy and Neurologic Outcome. 2nd ed. American College of Obstetrics and Gynecologists: Washington, DC, 2019 doi:10.1097/01.AOG.0000445580.65983.d2.
2. Kurinczuk JJ, White-Koning M, Badawi N. Epidemiology of neonatal encephalopathy and hypoxic-ischaemic encephalopathy. Early Hum. Dev 2010; 86: 329–338. [PubMed: 20554402]
3. Badawi N, Kurinczuk JJ, Keogh JM, Alessandri LM, O'Sullivan F, Burton PR et al. Intrapartum risk factors for newborn encephalopathy: the Western Australian case-control study. BMJ 1998; 317: 1554–1558. [PubMed: 9836653]
4. Molloy EJ, Bearer C. Neonatal encephalopathy versus Hypoxic-Ischemic Encephalopathy. Pediatr Res 2018; 84: 574. [PubMed: 30214023]
5. Aslam S, Strickland T, Molloy EJ. Neonatal Encephalopathy: Need for Recognition of Multiple Etiologies for Optimal Management. Front. Pediatr 2019; 7: 142. [PubMed: 31058120]
6. Volpe JJ. Neonatal encephalopathy: An inadequate term for hypoxic-ischemic encephalopathy. Ann. Neurol 2012; 72: 156–166. [PubMed: 22926849]
7. Martinello K, Hart AR, Yap S, Mitra S, Robertson NJ. Management and investigation of neonatal encephalopathy: 2017 update. Arch. Dis. Child. Fetal Neonatal Ed 2017; 102: F346–F358. [PubMed: 28389438]
8. Liljestrom L, Wikstrom AK, Agren J, Jonsson M. Antepartum risk factors for moderate to severe neonatal hypoxic ischemic encephalopathy: a Swedish national cohort study. Acta Obstet Gynecol Scand 2018; 97: 615–623. [PubMed: 29450878]
9. Blume HK, Li CI, Loch CM, Koepsell TD. Intrapartum fever and chorioamnionitis as risks for encephalopathy in term newborns: A case-control study. Dev Med Child Neurol 2008; 50: 19–24. [PubMed: 18173624]

10. Blume HK, Loch CM, Li CI. Neonatal encephalopathy and socioeconomic status: population-based case-control study. Arch Pediatr Adolesc Med 2007; 161: 663–8. [PubMed: 17606829]
11. Martinez-Biarge M, Diez-sebastian J, Wusthoff CJ, Cowan FM. Antepartum and Intrapartum Factors Preceding Neonatal Hypoxic-Ischemic Encephalopathy. Pediatrics 2013; 132. doi:10.1542/peds.2013-0511.
12. Tann CJ, Nakakeeto M, Willey BA, Sewegaba M, Webb EL, Oke I et al. Perinatal risk factors for neonatal encephalopathy: an unmatched case-control study. Arch Dis Child Fetal Neonatal Ed 2018; 103: F250–F256. [PubMed: 28780500]
13. Liljestrom L, Wikstrom A-K, Jonsson M. Obstetric emergencies as antecedents to neonatal hypoxic ischemic encephalopathy, does parity matter? Acta Obstet Gynecol Scand 2018; 97: 1396–1404. [PubMed: 29978451]
14. Ellis M, de l Costello AM, Murphy DJ, Badawi N, Kurinczuk JJ, Stanley FJ et al. Antepartum risk factors for newborn encephalopathy. BMJ. 1999; 318: 1414.
15. Novak CM, Eke AC, Ozen M, Burd I, Graham EM. Risk Factors for Neonatal Hypoxic-Ischemic Encephalopathy in the Absence of Sentinel Events. Am J Perinatol 2018; 36: 27–33. [PubMed: 29579759]
16. Parker SJ, Kuzniewicz M, Niki H, Wu YW. Antenatal and Intrapartum Risk Factors for Hypoxic-Ischemic Encephalopathy in a US Birth Cohort. J Pediatr 2018; 203: 163–169. [PubMed: 30270166]
17. Lundgren C, Brudin L, Wanby AS, Blomberg M. Ante- and intrapartum risk factors for neonatal hypoxic ischemic encephalopathy. J Matern Neonatal Med 2018; 31: 1595–1601.
18. Baer RJ, Rogers EE, Partridge JC, Anderson JG, Morris M, Kuppermann M et al. Population-based risks of mortality and preterm morbidity by gestational age and birth weight. J Perinatol 2016; 36: 1008–1013. [PubMed: 27467566]
19. Vance GA, Niederhauser A, Chauhan SP, Magann EF, Dahlke JD, Muraskas JK et al. Does the International Classification of Disease (ICD-9) code accurately identify neonates who clinically have hypoxic-ischemic encephalopathy? Gynecol Obstet Invest 2011; 71: 202–206. [PubMed: 21160147]
20. Cnattingius S, Lindam A, Persson M. Risks of asphyxia-related neonatal complications in offspring of mothers with type 1 or type 2 diabetes: the impact of maternal overweight and obesity. Diabetologia 2017; 60: 1244–1251. [PubMed: 28409211]
21. Martinez-Biarge M, Cheong JLY, Diez-Sebastian J, Mercuri E, Dubowitz LMS, Cowan FM. Risk factors for neonatal arterial ischemic stroke: The importance of the intrapartum period. J Pediatr 2016; 173: 62–68.e1. [PubMed: 27049002]
22. Sells CM, Feske SK. Stroke in Pregnancy. Semin Neurol 2017; 37: 669–678. [PubMed: 29270940]
23. Bandoli G, Palmsten K, Chambers CD, Jelliffe-pawlowski LL, Baer RJ, Thompson CA. Revisiting the Table 2 fallacy : A motivating example examining preeclampsia and preterm birth. Paediatr Perinat Epidemiol 2018; 32: 390–397. [PubMed: 29782045]
24. Kracer B, Hintz SR, Van Meurs KP, Lee HC. Hypothermia therapy for neonatal hypoxic ischemic encephalopathy in the state of California. J Pediatr 2014; 165: 267–273. [PubMed: 24929331]
25. Bruun TUJ, Desroches CL, Wilson D, Chau V, Nakagawa T, Yamasaki M et al. Prospective cohort study for identification of underlying genetic causes in neonatal encephalopathy using whole-exome sequencing. Genet Med 2018; 20: 486–494. [PubMed: 28817111]
26. Harteman JC, Groenendaal F, Benders MJ, Huisman A, Blom HJ, De Vries LS. Role of thrombophilic factors in full-term infants with neonatal encephalopathy. Pediatr Res 2013; 73: 80–86. [PubMed: 23128422]

Table 1.

Maternal and infant characteristics of infants born at 35 weeks or more in California (2011–2017)

	No NE or therapeutic hypothermia (n=2,988,035)		NE without therapeutic hypothermia (n=5,969)			NE with therapeutic hypothermia (n=888)		
	N	%	N	%	p value	N	%	p value
Maternal characteristics Race/ethnicity					<0.0001			<0.0001
White	796,918	26.7	1,878	31.5		296	33.3	
Hispanic	1,464,920	49.0	2,588	43.4		341	38.4	
Black	144,228	4.8	367	6.1		57	6.4	
Asian	434,786	14.6	788	13.2		115	13.0	
Other, multiple or unknown	147,183	4.9	348	5.8		79	8.9	
Age					0.52			0.001
<18	50,104	1.7	98	1.6		10	1.1	
18–34	2,335,264	78.2	4,632	77.6		655	73.8	
35+	602,558	20.2	1,239	20.8		223	25.1	
Missing	109	0.0	0	0.0		0	0.0	
Education					0.13			0.004
<12th grade	511,083	17.1	975	16.3		115	13.0	
missing	126,505	4.2	315	5.3		67	7.5	
Body mass index					0.002			0.03
Under/normal weight	1,471,961	49.3	2,792	46.8		396	44.6	
Overweight	749,622	25.1	1,539	25.8		238	26.8	
Obese	643,669	21.5	1,357	22.7		212	23.9	
Missing	122,783	4.1	281	4.7		42	4.7	
Prenatal care					0.002			0.03
Inadequate	314,005	10.5	687	11.5		109	12.3	
Intermediate	416,576	13.9	883	14.8		141	15.9	
Adequate	2,192,581	73.4	4,246	71.1		614	69.1	
Missing	64,873	2.2	153	2.6		24	2.7	
Payer					<0.0001			0.05
Private	1,425,551	47.7	3,061	51.3		442	49.8	
Public	1,418,839	47.5	2,710	45.4		418	47.1	

	No NE or therapeutic hypothermia (n=2,988,035)		NE without therapeutic hypothermia (n=5,969)			NE with therapeutic hypothermia (n=888)		
	N	%	N	%	p value	N	%	p value
Other	143,645	4.8	198	3.3		28	3.2	
Nulliparous	1,151,327	38.5	2,936	49.2	<0.0001	472	53.2	<0.0001
Mental health								
Anxiety	96,036	3.2	272	4.6	<0.0001	50	5.6	<0.0001
Depression	75,945	2.5	221	3.7	<0.0001	53	6.0	<0.0001
Bipolar disorder	27,867	0.9	116	1.9	<0.0001	20	2.3	<0.0001
Substance use								
Alcohol related diagnosis	5,826	0.2	25	0.4	<0.0001	3	0.3	0.33
Substance related diagnosis[1]	57,040	1.9	214	3.6	<0.0001	53	6.0	<0.0001
Cannabis related diagnosis	34,211	1.1	116	1.9	<0.0001	18	2.0	0.01
Nicotine	88,820	3.0	249	4.2	<0.0001	46	5.2	0.0001
Comorbidities								
Preexisting diabetes	25,619	0.9	129	2.2	<0.0001	21	2.4	<0.0001
Preexisting hypertension	59,817	2.0	173	2.9	<0.0001	27	3.0	0.03
Asthma	156,753	5.2	393	6.6	<0.0001	77	8.7	<0.0001
Systemic lupus erythematosus	4,263	0.1	8	0.1	0.86	0	0.0	0.26
Rheumatoid arthritis	3,711	0.1	10	0.2	0.34	4	0.5	0.006
Inflammatory Bowel Disorder	31,738	1.1	94	1.6	0.0001	13	1.5	0.24
Maternal Stroke	310	0.0	4	0.1	<0.0001	0	0.0	0.76
Migraine	40,558	1.4	110	1.8	0.001	16	1.8	0.25
Pregnancy complications								
Gestational diabetes	312,939	10.5	728	12.2	<0.0001	120	13.5	0.003
Preeclampsia	106,130	3.6	385	6.4	<0.0001	92	10.4	<0.0001
Gestational hypertension	96,673	3.2	255	4.3	<0.0001	59	6.6	<0.0001
Any infection in pregnancy	306,395	10.3	838	14.0	<0.0001	203	22.9	<0.0001
Gestational weeks at delivery					<0.0001		0.0	<0.0001
35–38 weeks	876963	29.3	2012	33.7		287	32.3	
39–40 weeks	1878211	62.9	3282	55.0		482	54.3	
>40 weeks	232861	7.8	675	11.3		119	13.4	

[1]Diagnosis indicating use or disordered use of opioids, sedatives, hypnotic or anxiolytics, cocaine or other stimulants, and hallucinogens

Table 2.

Multivariable log-linear regression estimates for prenatal risk factors of neonatal encephalopathy without therapeutic hypothermia

	aRR, 95% CI
Maternal characteristics	
Race/ethnicity	
White	Reference
Hispanic	0.77 (0.72, 0.83)
Black	0.97 (0.86, 1.10)
Asian	0.82 (0.75, 0.89)
Other, multiple or unknown	0.95 (0.85, 1.07)
Body mass index	
Under/normal weight	Reference
Overweight	1.12 (1.05, 1.19)
Obese	1.11 (1.04, 1.20)
Prenatal care	
Adequate	Reference
Intermediate	1.08 (1.00, 1.16)
Inadequate	1.12 (1.03, 1.22)
Payer	
Private	Reference
Public	0.94 (0.88, 1.00)
Other	0.73 (0.62, 0.85)
Nulliparous	1.51 (1.43, 1.59)
Mental health	
Anxiety	1.09 (0.95, 1.25)
Depression	1.07 (0.92, 1.25)
Bipolar disorder	1.53 (1.25, 1.89)
Substance use	
Alcohol related diagnosis	0.98 (0.62, 1.55)
Substance related diagnosis	1.58 (1.29, 1.94)
Cannabis related diagnosis	0.89 (0.65, 1.21)
Nicotine	1.03 (0.89, 1.19)
Comorbidities	
Preexisting diabetes	2.42 (2.02, 2.91)
Preexisting hypertension	1.02 (0.87, 1.21)
Asthma	1.04 (0.93, 1.16)
Inflammatory Bowel Disease	0.96 (0.72, 1.28)
Migraine	1.06 (0.87, 1.30)
Pregnancy complications	
Gestational diabetes	1.24 (1.14, 1.34)
Preeclampsia	1.41 (1.26, 1.58)

	aRR, 95% CI
Gestational hypertension	1.16 (1.02, 1.33)
Any infection in pregnancy	1.30 (1.20, 1.40)
Gestational weeks at delivery	
36–38 weeks	1.24 (1.17, 1.31)
39–40 weeks	Reference
>40 weeks	1.44 (1.32, 1.57)

Table 3.

Multivariable log-linear regression estimates for prenatal risk factors of neonatal encephalopathy with therapeutic hypothermia

	aRR, 95% CI
Maternal characteristics	
Race/ethnicity	
White	Reference
Hispanic	0.69 (0.61, 0.79)
Black	0.84 (0.67, 1.06)
Asian	0.86 (0.73, 1.01)
Other, multiple or unknown	1.14 (0.90, 1.44)
Age	
<18	0.57 (0.34, 0.94)
18–34	Reference
35+	1.44 (1.27, 1.63)
Education	
<12th grade	1.13 (0.96, 1.33)
Body mass index	
Under/normal weight	Reference
Overweight	1.18 (1.04, 1.34)
Obese	1.18 (1.04, 1.35)
Prenatal care	
Adequate	Reference
Intermediate	1.18 (1.03, 1.35)
Inadequate	1.15 (0.98, 1.35)
Payer	
Private	Reference
Public	1.13 (1.00, 1.27)
Other	0.82 (0.61, 1.10)
Nulliparous	1.80 (1.62, 2.01)
Mental health	
Anxiety	0.96 (0.75, 1.22)
Depression	1.65 (1.29, 2.10)
Bipolar disorder	1.03 (0.70, 1.52)
Substance use	
Substance related diagnosis	2.63 (1.96, 3.53)
Cannabis related diagnosis	0.44 (0.28, 0.70)
Nicotine	0.90 (0.69, 1.17)
Comorbidities	
Preexisting diabetes	2.11 (1.49, 2.98)
Preexisting hypertension	0.75 (0.54, 1.04)
Asthma	1.33 (1.11, 1.59)

	aRR, 95% CI
Pregnancy complications	
Gestational diabetes	1.25 (1.07, 1.46)
Preeclampsia	2.48 (2.07, 2.97)
Gestational hypertension	1.76 (1.43, 2.17)
Any infection	2.33 (2.07, 2.63)
Gestational age at birth	
35–38 weeks	1.07 (0.95, 1.20)
39–40 weeks	Reference
>40 weeks	1.77 (1.52, 2.06)