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Perinatal Hypoxic-Ischemic Encephalopathy: Incidence over Time Within a Modern US Birth Cohort

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ABSTRACT

Background. Recent studies suggest that the incidence of perinatal hypoxic-ischemic encephalopathy (HIE) may be increasing in developed countries. However, this observed increase may be due to increased ascertainment and increased treatment with therapeutic hypothermia rather than an increase in disease burden. In a US population-based cross-sectional study, we determined the incidence of perinatal HIE over time.

Methods. The study population included all 289,793 liveborn infants ≥ 35 weeks gestational age born at 15 Kaiser Permanente Northern California hospitals between 2012 and 2019. Perinatal HIE was defined as the presence of both neonatal acidosis (i.e., cord blood pH <7 or base deficit ≥10, or base deficit ≥10 on first infant gas) and neonatal encephalopathy confirmed by medical record review. Hospital discharge diagnoses of HIE were determined by extracting ICD diagnostic codes for HIE assigned upon hospital discharge.

Results. The population incidence of perinatal HIE was 1.7 per 1,000. Although the incidence of perinatal HIE did not change significantly, both hospital discharge diagnoses of HIE and treatment with therapeutic hypothermia increased significantly during the study period. The sensitivity and positive predictive value of a hospital discharge diagnosis of HIE for identifying perinatal HIE confirmed by chart review were 72% and 79%, respectively.

Conclusions. During the study years, the incidence of perinatal HIE remained stable despite increases in hospital discharge diagnoses of HIE and in the use of therapeutic hypothermia. Our findings underscore the importance of applying stringent diagnostic criteria when diagnosing this complex condition.

Keywords: Hypoxic-ischemic encephalopathy, neonates, therapeutic hypothermia, incidence, time trends.

Introduction.

Perinatal hypoxic-ischemic encephalopathy (HIE) occurs in 1 to 3 per 1000 births in developed countries[1, 2] and accounts for 22% of neonatal deaths worldwide.[3] It is a condition caused by acute lack of blood flow or oxygen to the neonate around the time of birth. Newborn infants with perinatal HIE present with significant acidosis reflecting the recent hypoxic-ischemic insult, combined with clinical signs of neonatal encephalopathy such as reduced level of consciousness or poor tone. Survivors of perinatal HIE may develop long-term disabilities such as cerebral palsy and cognitive impairment.[4]

Although the burden of HIE in developed countries are amongst the lowest in the world,[2, 5] some studies have reported an increase in HIE diagnoses since the adoption of therapeutic hypothermia.[6, 7] Between 2010 and 2012, Kracer et al. reported a 23% increase in infants admitted to California neonatal intensive care units who were diagnosed with HIE.[6] Similarly, in the UK, Azzopardi et al reported an increase in the rate of HIE registration during the implementation of therapeutic hypothermia between 2006 and 2011.[7] However, other studies have reported stable rates of HIE in recent decades.[8, 9]

Previous HIE incidence studies have used inconsistent case definitions, have not been population-based, or have ascertained HIE by analyzing hospital discharge ICD diagnosis codes.[1, 10, 11] The validity of ICD codes for HIE has never been studied, as most large administrative datasets do not contain the individual-level clinical data that are necessary to validate the diagnosis of HIE, namely blood gas and neurologic examination findings.[9, 12] In a population-based modern US birth cohort, we identified neonates with HIE using specific criteria for acidosis and neurologic signs of encephalopathy that were documented prospectively by the treating clinicians and confirmed by detailed medical records review. We further set out to determine the change in incidence of perinatal HIE over time.

Methods

In a cross-sectional study, we identified all live births ≥ 35 weeks gestational age born between January 1, 2012 and July 31, 2019 at 15 Kaiser Permanente Northern California (KPNC) hospitals. We excluded infants with major congenital anomalies or genetic conditions. KPNC is an integrated healthcare system serving over 4.3 million members, representing approximately 40% of the insured population in the region. The sociodemographic distribution of the KPNC membership is broadly similar to the local and state-wide California population, though the extremes of the income distribution are underrepresented.[13, 14] Study procedures were approved by the institutional review boards at the Kaiser Foundation Research Institute and the University of California, San Francisco.

We defined perinatal HIE as the presence of both neonatal acidosis and neonatal encephalopathy (NE). *Neonatal acidosis* was defined as cord blood pH <7 or base deficit ≥10, or a base deficit ≥10 on the first infant gas before 2 hours of age. We excluded cord gases with a pCO2<25mmHg as these are likely erroneous and due to air bubbles. *Neonatal encephalopathy* was defined as a documented abnormal Sarnat exam[15] between 1 and 6 hours of age that either 1) persisted beyond 6 hours of age, or 2) was accompanied by seizures (i.e., electrographic or focal-clonic),[16] or 3) was treated with active therapeutic hypothermia. At KPNC, eligibility for therapeutic hypothermia is based on clinical inclusion criteria adopted from the NICHD hypothermia trial.[17]

We first extracted all blood gas results from the KPNC laboratory database. For infants who met criteria for neonatal acidosis, we then determined if they also had neonatal encephalopathy by reviewing the newborn medical records of all those with a documented abnormal "enhanced neurologic exam" which is a templated modified Sarnat exam[15] that KPNC clinicians are prompted to perform whenever an infant is born with a 10 minute Apgar score<7 or a base deficit ≥10. To ensure that all infants with perinatal HIE were identified, we further reviewed the neonatal medical records of any infant with both neonatal acidosis as defined above and at least one of the following perinatal complications: base deficit ≥16; 5-minute Apgar <7 and admission to the neonatal intensive care unit; death within 72 hours of age; treatment with therapeutic hypothermia; HIE or seizures documented in the KPNC Neonatal Minimum Data Set;[18] or receipt of phenobarbital, phenytoin, fosphenytoin or levetiracetam within 72 hours of age.

For all infants in the study population, we collected the following electronically available demographic information from existing KPNC perinatal datasets:[18, 19] maternal age; self-reported maternal race; neighborhood deprivation index (NDI),[20] a composite score in which higher values indicate more socioeconomically disadvantaged neighborhood characteristics; multiple gestation; infant sex; and gestational age. To identify infants who received a hospital discharge diagnosis of HIE, we performed an electronic search for all newborns who received a diagnosis of HIE based on the following diagnostic codes: ICD-9 768.5-768.7 or 768.9; ICD-10 P21.0 or P91.60–P91.63.

We calculated the sensitivity, positive predictive value, and exact binomial 95% CI of a hospital discharge diagnoses of HIE for predicting the presence of perinatal HIE confirmed on chart review. Incidence estimates were obtained via multiple logistic regression and adjusted for the change in demographic covariates over time: maternal race/ethnicity, maternal age, gestational age modeled as a spline given nonlinearity, neighborhood deprivation index, and multiple gestation. Robust standard errors were calculated using sandwich estimators to account for the correlation of subjects within hospitals. For the

adjusted estimates, the trend across calendar years was modeled under the assumption of a linear trend after more flexible restricted cubic splines trends were assessed and dismissed due to a lack of improvement in model fit. Trends across calendar year in adjusted incidence for perinatal HIE, HIE by ICD codes, and therapeutic hypothermia were assessed as adjusted effects and via marginal-effect estimation.[21] For marginal effects, the estimated incidence of the targeted outcome for each subject was obtained by fixing covariates at their observed values and varying calendar years. The predicted probabilities (of each incidence outcome for each year) were obtained from the fitted model and averaged across subjects to obtain the expected incidence for a given calendar year. Inference using Wald tests were obtained and focused on the adjusted slope coefficient for calendar year as well as the contrast between the marginal incidence at the beginning and end of the study period. All *P* values assumed two-sided tests and results were considered statistically significant for $P<0.05$. All analyses were conducted in Stata, release 17 (StataCorp LLC).

Results

Among all 289,793 infants in the study cohort (Figure 1), 4,370 (15.1 per 1,000) had neonatal acidosis. Among neonates with acidosis, 1,200 underwent chart review to assess the presence of perinatal HIE as they had either an abnormal enhanced neurologic exam or a perinatal complication. We confirmed the presence of perinatal HIE in 503 infants, providing a population incidence of 1.7 per 1,000. In the same study period, 1.6 per 1,000 received a hospital discharge diagnosis of HIE and 1.4 per 1,000 were treated with therapeutic hypothermia.

The incidence of perinatal HIE varied from 1.3 to 2.1 per 1,000 during the eight-year study period (Figure 2), but no significant increase in incidence over time was identified (P=0.26). In contrast, there was a significant increase in hospital discharge diagnoses of HIE from 1.4 in the first 2 years to 1.8 per 1,000 in the last 2 years (P =0.03). There was also an increase in the use of active therapeutic hypothermia from 1.2 in the first 2 years to 1.7 per 1,000 in the last 2 years (P=0.005). We also observed an increase in the percentage of infants who underwent blood gas analysis (from 17.8% to 23.5%, P<0.001), as well as a significant increase in the incidence of neonatal acidosis (from 1.3% to 1.7 %, P<0.001) diagnosed across the study period (Supplement 1).

After adjusting for changes in the demographic factors of race, maternal age, neighborhood deprivation index, multiple gestation, and gestational age over time, we again found that there was no significant increase in the incidence of perinatal HIE (P =0.20), while both hospital discharge diagnoses of HIE (P= 0.01) and the use of therapeutic hypothermia (P=0.003) increased significantly over the study period.

Among infants with perinatal HIE, the proportion receiving therapeutic hypothermia increased over time from 63% in 2012 to 78% in 2019 (P= 0.02).

A total of 457 infants received a hospital discharge diagnosis of HIE. Of these, 360 (79%) were confirmed by chart review to meet criteria for perinatal HIE (Table 1). Among the 97 infants who received a hospital discharge diagnosis of HIE but who did not have perinatal HIE, 69 (71%) did not meet criteria for neonatal acidosis, and 65 (67 %) did not meet study criteria for neonatal encephalopathy. A total of 37 (38%) neonates with a hospital discharge diagnosis of HIE had neither evidence of acidosis nor neonatal encephalopathy.

Among the 503 infants with perinatal HIE confirmed on record review, 143 (28%) did not receive a clinical diagnosis of HIE. A hospital discharge diagnosis of HIE had a sensitivity of 72% (95% CI 67-76%) and a positive predictive value of 79% (95% CI 75-82%) for identifying perinatal HIE. The positive predictive value of a hospital discharge diagnosis of HIE remained stable over time, while the sensitivity improved from 61% (95% CI 54-68%) before 2014 to 77% (95% CI 71-83%) after 2017.

The clinical characteristics of the 503 infants with perinatal HIE are summarized in Table 2. Among infants with perinatal HIE, 361 (72%) received active therapeutic hypothermia. An additional 39 infants without perinatal HIE also received active therapeutic hypothermia; among these infants, 25 (82%) did not meet criteria for neonatal acidosis on blood gas analysis, 7 (18%) had no blood gas analysis performed, and 11 (28%) did not meet study criteria for neonatal encephalopathy. Three infants with neither acidosis nor encephalopathy nonetheless received therapeutic hypothermia for a postnatal arrest.

The incidence of perinatal HIE varied by demographic factors (Table 3). Infants born to mothers ≥35 years of age demonstrated a significantly higher incidence of perinatal HIE, as did male infants and late preterm or post-term infants. In contrast, infants born to Hispanic mothers exhibited a lower incidence of perinatal HIE than infants born to white mothers.

Discussion

We report the first population-based study of perinatal HIE to incorporate individual medical record review and to examine the validity of hospital discharge diagnoses of HIE by ICD codes. We found that the sensitivity (72%) and positive predictive value (78%) of a clinical diagnosis of HIE were modest for identifying true perinatal HIE confirmed on record review. Our findings reflect a general lack of consensus regarding the definition of HIE.[23, 24] Importantly, neonatal acidosis is a biomarker of hypoxia-

ischemia that plays a critical role in distinguishing perinatal HIE from other causes of neonatal encephalopathy; yet studies of HIE do not always require a low blood pH or high base deficit to make a diagnosis.[25-27] Similarly, clinical centers that do not require evidence of significant acidosis for eligibility for therapeutic hypothermia[28] may tend to over-diagnose HIE in some cases.
At KPNC, although the decision to cool is based on a protocol adopted from one of the largest cooling trials,[17] clinical criteria allow some infants to be cooled despite the lack of significant acidosis, thus potentially over-diagnosing perinatal HIE in some cases.

Although hospital discharge diagnoses of HIE increased during the study period, the incidence of perinatal HIE as defined by strict clinical criteria and confirmed on record review remained unchanged. However, the proportion of neonates in the study cohort who received therapeutic hypothermia increased during this time period, as did the proportion of neonates with perinatal HIE who received therapeutic hypothermia. These findings further suggest that the observed increase in hospital discharge diagnoses of HIE reflects an increase in case ascertainment in the setting of an effective therapy, as opposed to a true increase in incidence. The rising proportion of infants who underwent blood gas analyses further supports a change in diagnostic practices over time, as does the increased sensitivity of hospital discharge diagnoses of HIE for identifying perinatal HIE.

Although the terms “HIE” and “neonatal encephalopathy” are often used interchangeably,[1, 10, 29] it is important to distinguish perinatal HIE from other causes of neonatal encephalopathy because it evokes a different underlying pathogenic mechanism and a different approach to treatment and prevention.[30, 31] Therapeutic hypothermia is a proven treatment for perinatal HIE,[32] but not for all cases of neonatal encephalopathy which can result from genetic, metabolic, and infectious etiologies. Similarly, studies that focus on detecting hypoxia-ischemia during labor and delivery using novel electronic fetal monitoring analytic techniques[33] may more successfully predict perinatal HIE than the more heterogeneous condition referred to as neonatal encephalopathy.

Our study has limitations. We may not have identified all infants with perinatal HIE since KPNC does not perform universal cord gas screening, and only 21% of the study population underwent cord or newborn blood gas analysis before two hours of age. However, 91% of infants with a 5-minute Apgar score <7 had an available blood gas. While we did not differentiate between mild, moderate, and severe HIE, we likely captured the full spectrum of HIE severity rather than just infants with moderate to severe HIE who would require therapeutic hypothermia. However, because our definition of perinatal HIE

excludes infants with encephalopathy that resolved within six hours of age, we may have under-estimated the incidence of perinatal HIE by excluding the mildest cases.

Conclusion. The incidence of perinatal HIE remained stable over the past decade. Almost one in five infants who received a hospital discharge diagnosis of HIE lacked evidence of neonatal acidosis, a key clinical factor distinguishing perinatal HIE from other causes of neonatal encephalopathy. Future studies should include neonatal acidosis in the definition of perinatal HIE, to avoid misdiagnosing this complex condition.

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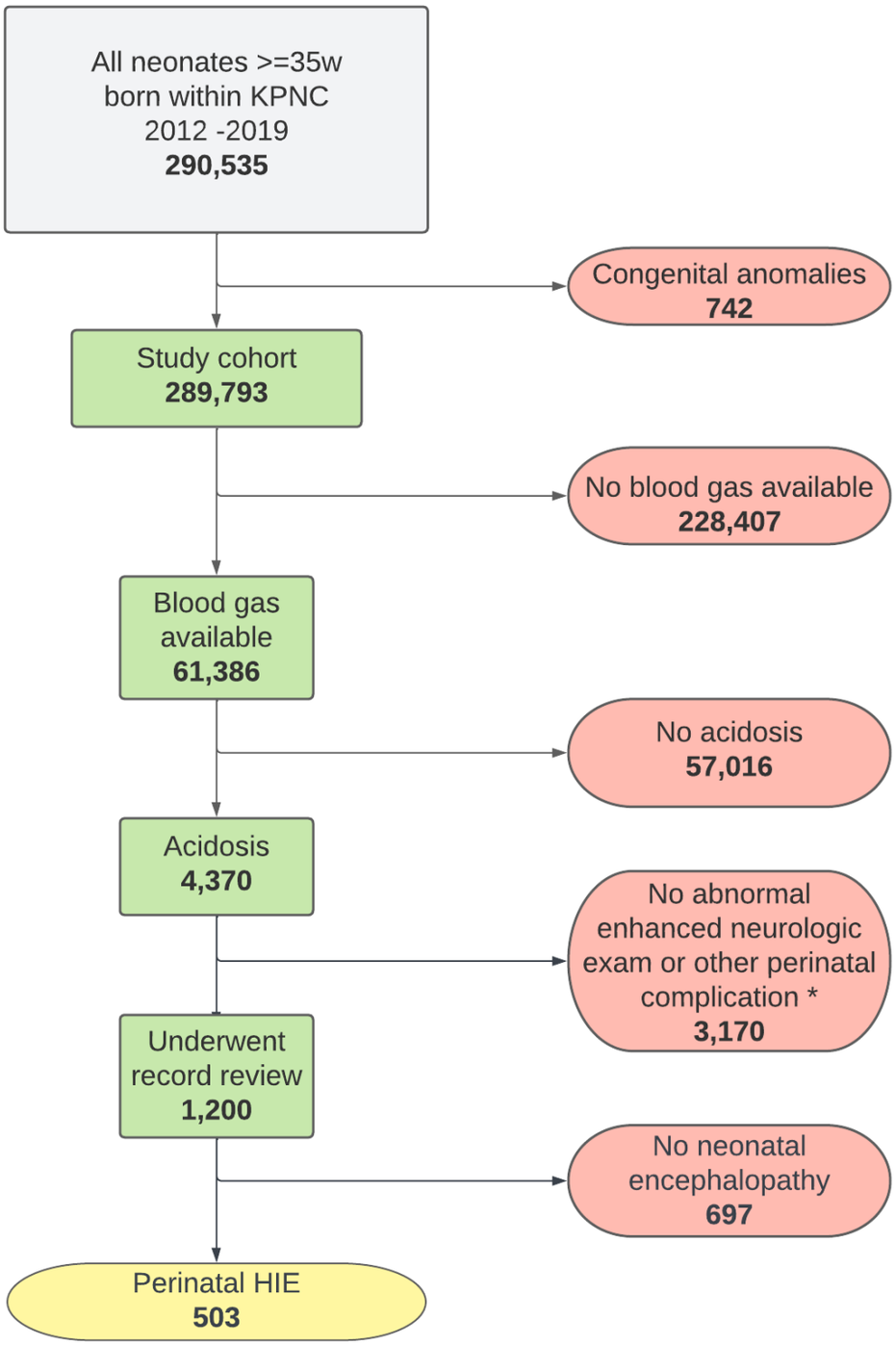
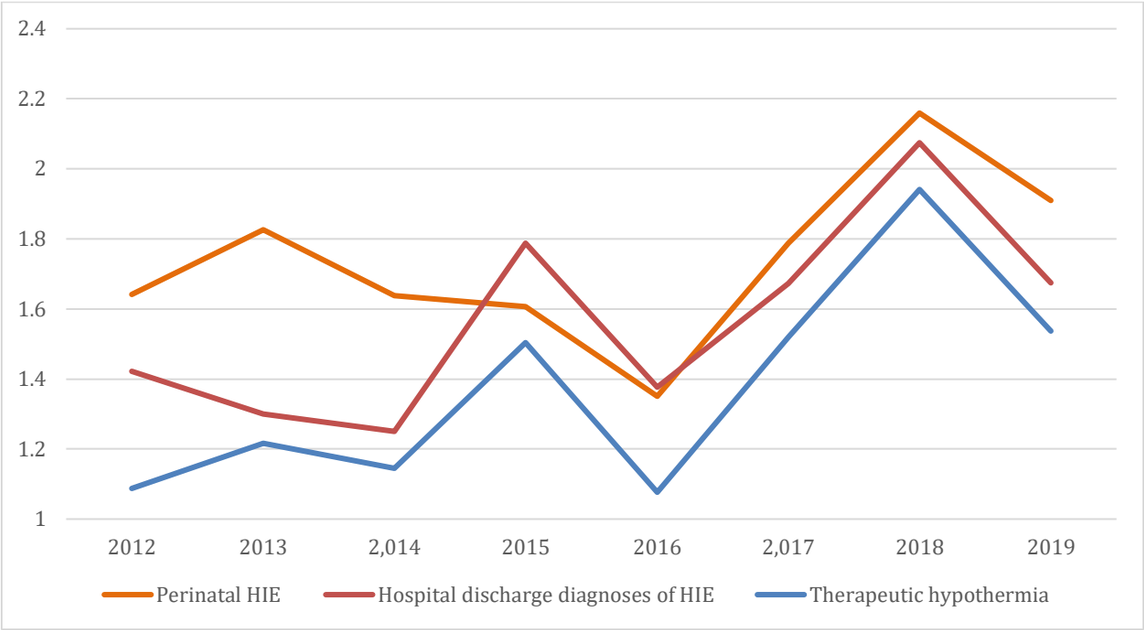
Figure 1: Flow diagram of the study population.



* Perinatal complication includes base deficit ≥16; 5-minute Apgar <7 and admission to the neonatal intensive care unit; death within 72 hours of age; treatment with therapeutic hypothermia; HIE or seizures documented in the KPNC Neonatal Minimum Data Set;[18] or receipt of phenobarbital, phenytoin, fosphenytoin or levetiracetam within 72 hours of age.

Figure 2: Population incidence of perinatal HIE, hospital discharge diagnoses of HIE, and therapeutic hypothermia between 2012 and 2019*.



*Test of trend: perinatal HIE, p=0.26; hospital discharge diagnosis of HIE, p=0.03; active therapeutic hypothermia, p=0.005.

Table 1. Relationship between hospital discharge diagnoses of HIE, and perinatal HIE confirmed by record review, in a US birth cohort in 2012-2019.

		Perinatal HIE*		
		Yes	No	
Hospital discharge diagnosis of HIE*	Yes	360	97	457
	No	143	289,193	289,336
		503	289,290	289,793

*Hospital discharge diagnosis of HIE is defined as receiving a diagnosis of HIE (ICD-9 768.5-768.7 or 768.9; ICD-10 P21.0 or P91.6) upon hospital discharge. Perinatal HIE is defined as the presence of both neonatal acidosis and neonatal encephalopathy confirmed on record review. Sensitivity = 72%; specificity= 99.8%; negative predictive value = 99.9%; positive predictive value = 79%.

Table 2. Clinical characteristics of 503 infants with perinatal HIE within a large US birth cohort.

	N	%
Cord pH, mean ± SD	7.06 ± 0.17	
Cord base deficit[a], mean ± SD	11.3 ± 5.6	
Worst infant gas base deficit[a], mean ± SD	16.1 ± 5.5	
Resuscitation		
Bag mask positive pressure ventilation	448	89.1%
Intubation in delivery room	235	46.7%
Chest compressions	124	24.7%
5 minute Apgar		
0-3	171	34.0%
4-6	248	49.3%
7-10	84	16.7%
10 minute Apgar		
0-3	58	11.5%
4-6	192	38.2%
7-10	243	48.3%
Active therapeutic hypothermia	361	71.8%
Seizures (electrographic or focal clonic)	128	25.4%
Acute brain injury on MRI	109	21.7%
Neonatal death at < 28 days of age	34	6.8%
Length of hospital stay, median (IQR)	8.0 (5.4-11.8)	

Table 3: Population incidence of perinatal HIE over time among demographic subgroups

	Total	HIE	Incidence (per 1,000 liveborn – 95% CI)	RR	95% CI
Birth year					
2012	34,421	57	1.65 (1.02-2.29)	Reference	
2013	34,242	63	1.84 (1.35-2.32)	1.11	0.80-1.54
2014	36,489	60	1.64 (1.25-2.04)	0.99	0.67-1.48
2015	38,636	63	1.63 (1.17-2.10)	0.98	0.72-1.34
2016	40,012	54	1.35 (0.72-1.98)	0.81	0.48-1.37
2017	40,321	72	1.79 (1.09-2.48)	1.07	0.69-1.67
2018	41,230	88	2.13 (1.69-2.57)	1.29	0.93-1.76
2019	24,442	46	1.88 (1.39-2.38)	1.14	0.76-1.68
Maternal age, years					
<20	9,786	24	2.45 (1.19-3.72)	1.49	0.95-2.33
20-34	219,589	362	1.65 (1.31-1.99)	Reference	
>=35	60,418	117	1.94 (1.50-2.36)	1.17	1.03-1.34
Maternal race					
White	108,877	211	1.94 (1.48-2.40)	Reference	
Asian	71,199	123	1.73 (1.28-2.17)	0.89	0.69-1.14
Black	18,551	39	2.10 (1.07-3.13)	1.08	0.69-1.71
Hispanic	74,801	95	1.27 (0.97-1.57)	0.66	0.52-0.82
Multiracial/ Other	12,182	27	2.22 (1.24-3.19)	1.14	0.76-1.73
Missing	4,183	8	1.91 (0.71-3.12)	0.99	0.51-1.90
Neighborhood deprivation index					
1st quartile (least deprived)	72,570	132	1.82 (1.27-2.37)	Reference	
2nd quartile	72,358	142	1.97 (1.42-2.50)	1.08	0.81-1.44
3rd quartile	72,427	117	1.62 (1.28-1.95)	0.89	0.69-1.15
4th quartile (most deprived)	72,182	111	1.54 (1.09-1.98)	0.85	0.57-1.24
Multiple gestation					
Singelton	281,993	492	1.75 (1.38-2.11)	Reference	
Multiple	7,800	11	1.41 (0.77-2.05)	0.81	0.50-1.31
Infant Sex					
Female	141,674	198	1.40 (1.10-1.70)	Reference	
Male	148,119	305	2.06 (1.59-2.53)	1.47	1.23-1.76
Infant gestational age					
Late preterm (35-36 weeks)	14,770	47	3.19 (2.18-4.18)	2.1	1.54-2.85
Term (37-40 weeks)	241,369	366	1.52 (1.18-1.85)	Reference	
Post-term (≥ 41 weeks)	33,654	90	2.67 (1.94-3.41)	1.76	1.37-2.26

SUPPLEMENT 1: Blood gas and acidosis by study year

	2012 N=34,421		2013 N=34,242		2014 N=36,489		2015 N=38,636		2016 N=40,012		2017 N=40,321		2018 N=41,230		2019 N=24,442	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Blood gas	6,117	17.8%	6,190	18.1%	7,174	19.7%	8,274	21.4%	9,092	22.7%	9,269	23.0%	9,527	23.1%	5,743	23.5%
Acidosis	460	1.3%	459	1.3%	504	1.4%	506	1.3%	611	1.5%	727	1.8%	697	1.7%	406	1.7%