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Original Research

Hypoxic-Ischemic Encephalopathy and Perinatal Exposure to Infection and Inflammation Increase the Risk of Cerebral Palsy: A Real-World Analysis Using Epic Cosmos

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Abstract

Background and Objectives: Cerebral palsy (CP) is the leading cause of childhood disability. Both neonatal hypoxic-ischemic encephalopathy (HIE) and perinatal infection and inflammation (PII) increase the risk of developing CP. However, interactive or additive contributions of HIE and PII on the risk of developing CP are not understood. The aim of this study was to examine the interactive effects of HIE and PII, operationalized as pyrexia during labor, chorioamnionitis, or neonatal sepsis, on the risk of CP.

Methods: We conducted a population-based retrospective cohort study using Epic Cosmos. Birthing parent-infant dyads who delivered between 2017 and 2022 and had at least two follow-up visits for the child between 1-24 and 13-36 months were included. All exposures and outcomes were defined by ICD-10-CM code. CP had to be diagnosed by 36 months. We determined the additive effects of HIE and pyrexia during labor, chorioamnionitis, and neonatal sepsis on the risk of CP. Log-binomial regressions were used to obtain rate ratios (RR) with 95% confidence intervals (CI) and interactions on the additive scale. Multiplicative interactions were computed using relative excess risk due to interaction (RERI).

Results: A total of 2,611,562 birthing parent-infant dyads were included in the analysis. HIE was associated with an elevated risk of CP (RR_{adj} = 49.1, 95% CI: 44.7-53.8). PII increased the risk of both HIE (pyrexia during labor: RR_{adj} = 2.8, 95% CI: 2.3-3.3; chorioamnionitis: RR_{adj} = 5.0, 95% CI: 4.7-5.4; neonatal sepsis: RR_{adj} = 19.9, 95% CI: 18.6-21.3) and CP (pyrexia during labor: RR = 1.5, 95% CI: 1.1-2.0; chorioamnionitis: RR = 1.7, 95% CI: 1.5-1.9; neonatal sepsis: RR_{adj} = 9.7, 95% CI: 8.7-10.8). Interaction analyses revealed an additive effect of HIE and neonatal sepsis on CP risk (16.5, 95% CI: 2.4-30.6, p = 0.0107). Surprisingly, HIE with chorioamnionitis had a lower risk of CP (RR_{adj} = 39.0, 95% CI: 31.0-49.2), compared to HIE alone (RR_{adj} = 50.7, 95% CI: 46.0-55.8).

Discussion: Exposure to PII was associated with increases in HIE and CP risks. These results suggest that the effect of HIE on CP risk may be modulated by the HIE etiology and severity of PII.

Keywords: *Cerebral palsy, Hypoxic-ischemic encephalopathy, Perinatal infection and inflammation, Neonatal sepsis.*

1. Introduction

Perinatal infection and inflammation (PII); such as maternal fever, chorioamnionitis, and neonatal sepsis; and hypoxic-ischemic encephalopathy (HIE) are known risk factors for developing cerebral palsy (CP).[1–4] For example, the risk of CP has been shown to increase 9-fold in offspring exposed to intrapartum fever,[5] 4-fold in those exposed to clinical chorioamnionitis,[6,7] and 8-fold with early-onset neonatal sepsis.[8] HIE has also consistently been linked to a marked increase in CP risk,[9] with up to 30% of moderate HIE survivors and almost all severe HIE survivors experiencing some form of neurodevelopmental impairment.[10] However, the interactive effect between PII and HIE on the risk of CP is debated.[11]

Immune activation in neonates with PII may lower their tolerance for hypoxia, making them more vulnerable to HIE.[12] This is supported by epidemiological investigations showing that PII increases the risk of HIE, however, the physiologic mechanisms underlying this risk remain unknown. Pyrexia during labor,[13,14] chorioamnionitis,[14–17] and neonatal sepsis[18,19] have each been associated with greater risk of HIE. Indeed, approximately 40% of neonates with HIE are born to mothers with chorioamnionitis.[15] Thus, PII increases the risk of HIE, which, in turn, increases the risk of CP.

It has been suggested that co-occurring PII and HIE may result in worse neonatal outcomes that are less amenable to mitigation than HIE alone.[20] In newborn rats, the detrimental effects of PII-related HIE on the brain could not be reversed by standard HIE treatment protocols. In low- and middle-income countries, where infection is more prevalent, the same intervention strategies that are used in high-income countries did not improve outcomes for HIE patients (Hypothermia for Moderate or Severe Neonatal Encephalopathy in Low and Middle-Income Countries (HELIX) trial).[22] We speculate that HIE when induced by or occurring together with PII is different than HIE without PII, which could explain the lack of efficacy of standard HIE interventions and overall more severe patient outcomes.

By contrast, other studies have found co-occurring PII and HIE to be associated with better neurodevelopmental outcomes than HIE alone. Secondary analysis from the High-Dose Erythropoietin for Asphyxia and Encephalopathy trial (HEAL trial)[24] revealed that neonates with chorioamnionitis had less severe background pattern abnormalities on EEG within 24 hours of birth and less central injury patterns on brain MRI.[11] Central injury patterns are associated with adverse long-term outcomes[26] and are more commonly observed after perinatal sentinel events, such as placental abruption or uterine rupture.[26] In the HEAL trial, HIE patients with cooccurring chorioamnionitis had a lower rate of sentinel events supporting the idea that subacute HIE etiologies, such as PII, result in less severe deep brain injury and better outcomes.[11] However, this trial is somewhat limited given a population of only 500 neonates who all received therapeutic cooling, and may not reflect the diverse population outside of major academic centers.

We hypothesized that PII would worsen the risk of CP in neonates with HIE. The current study sought to determine the interactive effect of PII on CP risk in neonates with HIE. While HIE and PII are well-established independent risk factors of CP, some studies suggest that HIE with PII leads to worse outcomes than HIE alone, while others have demonstrated better outcomes than HIE alone. Using Epic Cosmos, we conducted a large-scale population-based investigation of CP risks in infants with a) HIE, b) PII, and c) both HIE and PII.

2. Methods

Epic Cosmos Dataset

We conducted a retrospective cohort study using Epic Cosmos (Epic Corporation, Verona, Wisconsin); a dataset created in collaboration with a community of health systems using Epic representing more than 310 million patient records from over 2,358 hospitals and 52.5 thousand clinics as of October 2026. The community represents patients from all 50 states, D.C., Canada, Lebanon, and Saudi Arabia, though this study is limited to patients from the U.S.

The study included all deliveries with a live birth outcome that occurred between January 1, 2017, and December 31, 2022, at hospitals participating in Cosmos, for which linkage between infant and birthing parent charts could be performed and at least one visit before 24 months of age and at least one subsequent visit between ages 1 and 3 years, with weight recorded, were available. This follow-up timeframe was deemed suitable for capturing the majority of CP outcomes given the typical age at CP diagnosis.[28] Infants with a gestational age of less than 35 weeks or more than 44 weeks were excluded from the analysis.

The final dataset was stored in the Epic Cosmos Data Science Virtual Machine (DSVM) on 4/4/2026 and reflects the data that was available in Epic Cosmos on this date. The study protocol was reviewed by the Institutional Review Board at Nemours Children's Health and deemed non-human subjects research given the de-identified nature of the data.

Variable Definitions

Outcome and exposure variables were defined by ICD-10-CM code. HIE was required to be documented in the delivery hospitalization record and was categorized by severity: mild HIE (ICD-10-CM: P91.61), moderate HIE (ICD-10-CM: P91.62), severe HIE (ICD-10-CM: P91.63), or unspecified HIE (ICD-10-CM: P91.60). CP included all types and severity levels and could be documented at any encounter through age 36 months (ICD-10-CM: G80.*). Pyrexia during labor (ICD-10-CM: O75.2) and chorioamnionitis (ICD-10-CM: O41.12*) had to be recorded by their ICD-10-CM code in the delivery hospitalization record. Finally, neonatal sepsis was defined as ICD-10-CM code P36* in the delivery hospitalization record or within 1 week of birth.

Potential Confounders

Rate ratio models were adjusted for a priori specified confounders (Figure 1). Maternal age was identified as a potential confounder for rate ratios of CP [29,30] and HIE [15,29], while primigravida status was adjusted for in rate ratios of HIE.[30,31] We also accounted for a causal relationship between pyrexia during labor[32,33] and chorioamnionitis [33,34] on neonatal sepsis in the current analysis.

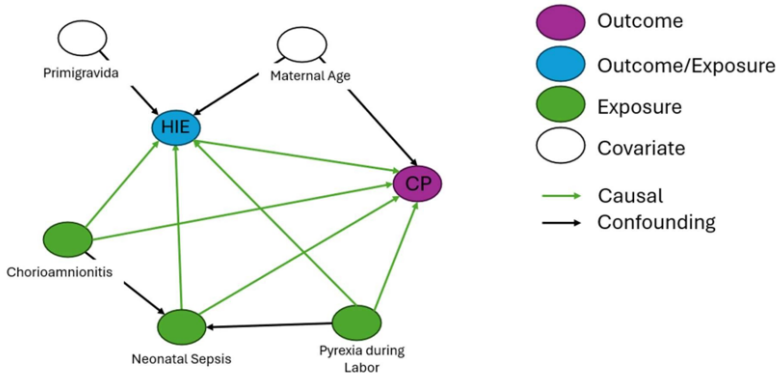


Figure 1. Directed acyclic graph (DAG) illustrating the assumed causal relationship between exposures, outcomes, and potential confounders.

Statistical Analysis

Cohort demographics and clinical characteristics were summarized and stratified by HIE and PII status, using mean (standard deviation) for continuous measures and count (proportion) for categorical measures. Next, the rate of CP was calculated as events per 1,000 live births, comparing HIE severity levels to no HIE. Log binomial regression was used to estimate unadjusted and adjusted rate ratios. Adjusted analyses accounted for potentially confounding variables, specifically for maternal age and PII.

Similarly, the rate of HIE and the rate of CP per 1,000 live births were calculated, comparing each PII exposure to infant-birthing parent dyads without the respective exposure. Log binomial regression was used to estimate unadjusted and adjusted rate ratios. Adjusted analyses accounted for potentially confounding variables (Figure 1). Specifically, CP rates were adjusted for maternal age, and HIE rates were adjusted for both maternal age and primigravida status. CP and HIE rates by neonatal sepsis were additionally adjusted for pyrexia during labor and chorioamnionitis.

Interaction analyses were performed for HIE and each PII exposure, e.g., pyrexia during labor, chorioamnionitis, and neonatal sepsis. For each analysis, the CP rate per 1,000 live births was calculated separately and jointly in order to estimate a) the joint effect of HIE and each PII diagnosis, b) the effect of each PII diagnosis only, and c) the effect of HIE only, compared to infants with no HIE or PII. Log-binomial regression was used to investigate interaction on the multiplicative scale and relative excess risk due to interaction (RERI) was used to investigate interaction on the additive scale.[35] Adjusted analyses accounted for potential confounders; specifically, for primigravida, maternal age, and other PII diagnoses.

Infant mortality was reported for each exposure group and broken down by demise during the birth encounter and during the first 3 years of life. We also provided the number of infants per group that were noted alive at or after age 3. This information was only available for patients who were not lost in the dataset or who died at a Cosmos participating institution.

Sensitivity Analysis

Sensitivity analyses were conducted to evaluate a) potential selection bias arising from requiring a follow-up visit between 24 and 36 months of age and b) the effect of defining pyrexia during labor by diagnosis code rather than by temperature range (e.g., ≥ 100.4 F). Potential selection bias due to the 24 to 36-month follow-up requirement was assessed by comparing the demographic and clinical characteristics of the selected cohort (e.g., follow-up requirement) to those of the non-selected cohort (e.g., no follow-up requirement). Propensity scores were then estimated for each of the covariates using logistic regression models. Post weighting balance of covariates was quantified in terms of unadjusted standardized mean difference (SMD). An SMD of 0.1 was defined as balanced. The analysis steps described above were then repeated for the ("normalized") selected cohort with inverse probability of selection weights (IPSWs). To explore the effect of using diagnosis codes to define pyrexia during labor (primary definition) compared to temperature from vitals (secondary definition), the analysis was run again with the secondary definition of pyrexia during labor.

3. Results

3.1 Cohort Characteristics

A total of 2,611,562 birthing parent-infant dyads were included in the analysis (Table 1.1). Birthing parents had a mean age of 30.6 years (SD = 5.7). The self-reported racial and ethnic distribution of birthing parents was as follows: < 1% American Indian or Alaska Native, nonHispanic (N = 10,110); 4% Asian, non-Hispanic (N = 78,170); 15% Black or African American, non-Hispanic (N = 324,228); < 1% Native Hawaiian or Other Pacific Islander, non-Hispanic (N = 6,366); 52% White, non-Hispanic (N = 1,119,417); 1% Other Race, non-Hispanic (N = 30,904); 10% Multiple Races, non-Hispanic (N = 217,755); and 17% Hispanic or Latino (N = 378,927).

Race and ethnicity data were missing for 445,685 birthing parents. Most patients identified English as their primary language (76%, N = 1,987,673). Spanish was the primary language for 5% (N = 142,323) of the population, and 18% (N = 480,051) reported a primary language other than English or Spanish. Additionally, 27% of birthing parents were primigravida (N = 704,286), while 73% were not primigravida (N = 1,907,214). Gravidity information was missing for 62 dyads.

Miscellaneous or other insurance, including unspecified or unknown insurance, Medicare Advantage, Medicare Replacement, Tricare, Worker's Compensation, Veteran's Affairs, and third-party liability insurance, was the most frequently reported payer type, accounting for 77% of patients (N = 1,987,445), followed by Medicaid (23%, N = 585,267). Less than 1% of parentinfant dyads were covered by Medicare (N = 8,524), and 1% were self-pay (N = 13,013). An additional 17,313 dyads were classified as having other or unknown insurance coverage. Vaginal delivery occurred in 69% of births (N = 1,781,643), whereas 31% of babies were delivered via cesarean section (N = 800,927). Fewer than 1% of deliveries were categorized as other (N = 104), and delivery mode was missing for 28,888 records. Deliveries occurred between 2017 and 2022: 304,094 (12%) in 2017, 357,570 (14%) in 2018, 406,620 (16%) in 2019, 458,119 (18%) in 2020, 514,816 (20%) in 2021, and 568,828 (22%) in 2022.

Among infants, 48% were female (N = 1,252,356) and 52% were male (N = 1,359,086), and infant sex was missing or listed as 'other' in 120 cases. Mean gestational age was 38.6 weeks (SD = 1.3). The self-reported race and ethnicity of infants was < 1% American Indian or Alaska Native, non-Hispanic (N = 8,545); 3% Asian, non-Hispanic (N = 69,595); 13% Black or African American, non-Hispanic (N = 312,705); < 1% Native Hawaiian or Other Pacific Islander, nonHispanic (N = 5,781); 47% White, non-Hispanic (N = 1,140,702); 2% Other Race, non-Hispanic (N = 37,052); 16% Multiple Races, non-Hispanic (N = 386,923); and 19% Hispanic or Latino (N = 465,064). Race and ethnicity data were missing for 185,195 infants.

The number of infants with a diagnosis of HIE was 6,292 (0.24%). Additionally, 4.9% of babies were exposed to perinatal inflammation or infection (N = 127,222), including pyrexia during labor (0.5%, N = 13,810), chorioamnionitis (3.6%, N = 94,635), and neonatal sepsis (0.7%, N = 18,777). Finally, a total of 4,803 babies received a diagnosis of cerebral palsy (0.18%).

Cohort Characteristics Stratified by HIE Severity

The birthing-parent infant cohort was stratified by HIE severity (Table 1.2). A total of 6,292 infants had HIE (0.2% or 2.4:1000), while 2,605,270 infants were not diagnosed with HIE. Among infants with HIE, 1,163 had mild HIE (18%), 2,559 had moderate HIE (41%), 1,055 had severe HIE (17%), and 1,515 had HIE of unspecified severity (24%).

The sub-cohorts were compared in terms of demographic and delivery characteristics. Higher severity HIE groups tended to have a greater proportion of non-Hispanic Black or African American birthing parents (severe HIE: N = 229, 26%) and infants (severe HIE: N = 204, 20%) and a lower proportion of non-Hispanic White birthing parents (severe HIE: N = 385, 43%) and infants (severe HIE: N = 396, 39%), compared to dyads with no HIE [birthing parents: Black or African American (N = 323,175, 15%), White (N = 1,116,964, 52%), infants: Black or African American (N = 311,723, 13%), White (N = 1,138,260, 47%)]. Dyads with HIE had a greater proportion of C-sections (severe HIE: N = 708, 68%), primigravida (severe HIE: N = 376, 36%), and male infant sex (severe HIE: N = 490, 54%) compared to dyads with no HIE (C-sections: N = 797,274, 31%, primigravida: N = 701,810, 27%, male infant sex: N = 1,355,369, 52%).

Cohort Characteristics Stratified by PII

The birthing-parent infant cohort was stratified by perinatal inflammation and infection (Table 1.3). A total of 127,222 infants had exposure to perinatal inflammation or infection (4.9%), while 2,484,340 did not. Among dyads with perinatal inflammation or infection, 13,810 had pyrexia during labor (11%), 94,635 had chorioamnionitis (74%), and 18,777 had neonatal sepsis (15%).

The sub-cohorts were compared in terms of demographic and delivery characteristics. A greater proportion of dyads with pyrexia during labor were primigravida (N = 7,528, 55%), compared to dyads without pyrexia during labor (N = 696,758, 27%).

Compared to dyads without chorioamnionitis, those with chorioamnionitis had lower proportions of non-Hispanic White birthing parents (with chorioamnionitis: N = 28055, 35%; no chorioamnionitis: N = 1,091,362, 52%) and infants (with chorioamnionitis: N = 27006, 30%; no chorioamnionitis: N = 1,113,696, 48%), Miscellaneous/Other insurance coverage (with chorioamnionitis: N = 66,280, 70%; no chorioamnionitis: N = 1,921,165, 77%), and vaginal deliveries (with chorioamnionitis: N = 55,990, 60%; no chorioamnionitis: N = 1,725,653, 69%). Conversely, higher proportions of birthing parents (with chorioamnionitis: N = 21,934, 27%; no chorioamnionitis: N = 256,993, 17%) and infants were Hispanic or Latino (with chorioamnionitis:

N = 26,414, 30%; no chorioamnionitis: N = 438,650, 19%), were covered by Medicaid (with chorioamnionitis: N = 27,136, 29%; no chorioamnionitis: N = 558,131, 22%), delivered by csection with chorioamnionitis: N = 37,467, 40%; no chorioamnionitis: N = 763,460, 31%), and were primigravida (with chorioamnionitis: N = 46,292, 49%; no chorioamnionitis: N = 657,994, 26%).

Compared to dyads without neonatal sepsis, a lower proportion of dyads with sepsis had birthing parents (with neonatal sepsis: N = 6,708, 43%; no neonatal sepsis: N = 1,112,709, 52%) and infants who were non-Hispanic White (with neonatal sepsis: N = 6,860, 39%; no neonatal sepsis: N = 1,133,842, 47%), had a vaginal delivery (with neonatal sepsis: N = 10,596, 57%; no neonatal sepsis: N =1,771,047, 69%), and had female infant sex (with neonatal sepsis: N =1,244,519, 48%; no neonatal sepsis: N = 7,837, 42%). A greater proportion of dyads with neonatal sepsis were primigravida (with neonatal sepsis: N = 6,697, 36%; no neonatal sepsis: N = 697,589, 27%).

3.2 Risk of CP increases with increasing HIE severity

As expected, the rate of CP increased with increasing HIE severity (Table 2). The rate of CP in infants without HIE was 1.7 (95% CI: 1.6 - 1.7) per 1,000 live term births. The rate of CP per 1,000 live term births increased with increasing severity of HIE (mild: 20.6, 12.5 - 28.8; moderate: 57.8, 48.8 - 66.9; severe: 334.6, 306.1 - 363.1; unspecified: 93.7, 79.1 - 108.4). An HIE diagnosis of any severity was associated with a rate of 106.0 (95% CI: 98.4 - 113.6) CP cases per 1,000 live term births.

Compared to no HIE, the unadjusted CP rate ratio increased with HIE severity, ranging from 12.5 (95% CI: 8.2 - 18.1) in infants with mild HIE and 35.0 (95% CI: 29.7 - 40.9) in infants with moderate HIE to 202.5 (95% CI: 184.7 - 221.2) in infants with severe HIE. Infants with HIE of unspecified severity had a CP rate ratio of 56.7 (95% CI: 48.1 - 66.2).

Overall, the rate ratio of CP in infants with HIE was 64.2 (95% CI: 59.3 - 69.3), compared to infants without HIE. Rate ratios remained high even after adjustment for a priori specified confounders, e.g., maternal age, pyrexia during labor, chorioamnionitis, and neonatal sepsis: mild HIE: 10.9 (95% CI: 7.1 - 15.8), moderate HIE: 28.7 (95% CI: 24.3 - 33.7), severe HIE: 148.8 (95% CI: 133.1 - 165.7), and unspecified HIE: 47.2 (95% CI: 39.9 - 55.3). The adjusted rate ratio of CP after HIE of any severity was 49.1 (95% CI: 44.7 - 53.8).

Table 1.1. Birthing Parent-Infant Dyad Cohort Characteristics

	Total
Birthing Parent Age (Years)	
Mean (SD)	30.6 (5.7)
Missing	86
Birthing Parent Race and Ethnicity	
American Indian or Alaska Native, non-Hispanic	10110 (0%)
Asian, non-Hispanic	78170 (4%)
Black or African American, nonHispanic	324228 (15%)
Native Hawaiian or Other Pacific Islander, non-Hispanic	6366 (0%)
White, non-Hispanic	1119417 (52%)
Other Race, non-Hispanic	30904 (1%)
Multiple Races, non-Hispanic	217755 (10%)
Hispanic or Latino	378927 (17%)
Missing	445685
Insurance Type	
Medicaid	585267 (23%)
Medicare	8524 (0%)
Miscellaneous/Other	1987445 (77%)
Self-Pay	13013 (1%)
Missing	17313
Preferred Language	
English	1987673 (76%)
Spanish	142323 (5%)
Other Language	480051 (18%)
Delivery Year	
2017	304094 (12%)
2018	357570 (14%)
2019	406620 (16%)
2020	458119 (18%)
2021	514816 (20%)
2022	568828 (22%)
Delivery Method	
C-Section	800927 (31%)
Vaginal	1781643 (69%)
Other/Missing	28992
Primigravida	
No	1907214 (73%)
Yes	704286 (27%)
Missing	62

Table 1.1. Continued...

Gestational Age (Weeks)	
Mean (SD)	38.6 (1.3)
Infant Race and Ethnicity	
American Indian or Alaska Native, non-Hispanic	8545 (0%)
Asian, non-Hispanic	69595 (3%)
Black or African American, nonHispanic	312705 (13%)
Native Hawaiian or Other Pacific Islander, non-Hispanic	5781 (0%)
White, non-Hispanic	1140702 (47%)
Other Race, non-Hispanic	37052 (2%)
Multiple Races, non-Hispanic	386923 (16%)
Hispanic or Latino	465064 (19%)
Missing	185195
Infant Sex	
Female	1252356 (48%)
Male	1359086 (52%)
Other/Missing	120
Diagnoses	
HIE	6292 (0.2%)
Pyrexia During Delivery	13810 (0.5%)
Chorioamnionitis	94635 (3.6%)
Neonatal Sepsis	18777 (0.7%)
CP	4803 (0.2%)
Total	2611562

Table 1.1. Birthing parent-infant dyad cohort characteristics, including number, percentage, and standard deviation (SD, where applicable) for birthing parent age, birthing parent race and ethnicity, insurance type, preferred language, delivery year, mode of delivery, primigravida, gestational age, infant race and ethnicity, infant sex, and diagnoses.

Table 1.2. Birthing Parent-Infant Dyad Cohort Characteristics Stratified by HIE Severity.

	No HIE (N = 2605270)	**HIE (N = 6292)**			
		Mild HIE (N = 1163)	Moderate HIE (N= 2559)	Severe HIE (N = 1055)	Unspecified HIE (N = 1515)
Birthing Parent Age (Years)					
Mean (SD)	30.6 (5.68)	30.8 (6.11)	30.5 (6.08)	30.4 (6.03)	30.7 (5.97)
Missing	76-85	0	10 or fewer	0	0
American Indian or Alaska Native, non-Hispanic	10090 (0%)	10 or fewer (≤ 1%)	10 or fewer (≤ 1%)	10 or fewer (≤ 1%)	10 or fewer (≤ 1%)
Asian, non-Hispanic	77944 (4%)	47 (5%)	112 (5%)	30 (3%)	37 (3%)
Black or African American, non-Hispanic	323175 (15%)	164 (17%)	411 (19%)	229 (26%)	249 (20%)

Table 1.2. Continued...

Native Hawaiian or Other Pacific Islander, non-Hispanic	6323 (0%)	10 or fewer (≤ 1%)	27 (1%)	11 (1%)	10 or fewer (≤ 1%)
White, non-Hispanic	1116964 (52%)	508 (51%)	970 (45%)	385 (43%)	590 (46%)
Other Race, non-Hispanic	30829 (1%)	16 (2%)	26 (1%)	13 (1%)	20 (2%)
Multiple Races, non-Hispanic 217229 (10%)	217229 (10%)	76 (8%)	214 (10%)	79 (9%)	157 (12%)
Hispanic or Latino	378031 (17%)	171 (17%)	370 (17%)	142 (16%)	213 (17%)
Missing	444685	Suppressed	Suppressed	Suppressed	Suppressed
Insurance Type					
Medicaid	583657 (23%)	284 (25%)	658 (26%)	301 (29%)	367 (24%)
Medicare	8482 (0%)	10 or fewer (≤ 1%)	10 or fewer (≤ 1%)	10 or fewer (≤ 1%)	12 (1%)
Miscellaneous/ Other	1982890 (77%)	847 (74%)	1857 (73%)	733 (70%)	1118 (75%)
Self-Pay	12989 (1%)	8482 (0%)	12 (0%)	10 or fewer (≤ 1%)	10 or fewer (≤ 1%)
Missing	17252	Suppressed	Suppressed	Suppressed	Suppressed
Preferred Language					
English	1984017 (76%)	893 (77%)	1942 (76%)	821 (78%)	1182 (78%)
Spanish	142050 (5%)	68 (6%)	149 (6%)	56 (5%)	74 (5%)
Other Language	479203 (18%)	202 (17%)	468 (18%)	178 (17%)	259 (17%)
Delivery Year					
2017	303675 (12%)	104 (9%)	205 (8%)	110 (10%)	165 (11%)
2018	357009 (14%)	136 (12%)	301 (12%)	124 (12%)	205 (14%)
2019	405941 (16%)	151 (13%)	380 (15%)	148 (14%)	225 (15%)
2020	457283 (18%)	196 (17%)	437 (17%)	203 (19%)	271 (18%)
2021	513734 (20%)	277 (24%)	581 (23%)	224 (21%)	293 (19%)
2022	567628 (22%)	299 (26%)	655 (26%)	246 (23%)	356 (23%)

Table 1.2. Continued...

Delivery Method					
C-Section	797274 (31%)	652 (57%)	1473 (59%)	708 (68%)	820 (55%)
Vaginal	1779119 (69%)	489 (43%)	1034 (41%)	327 (32%)	674 (45%)
Other/Missing	28877	22	52	20	21
Primigravida					
No/Missing	1903460 (72%)	684 (59%)	1519 (59%)	679 (64%)	934 (62%)
Yes	701810 (27%)	479 (41%)	1040 (41%)	376 (36%)	581 (38%)
Gestational Age (Weeks)					
Mean (SD)	38.6 (1.31)	38.6 (1.62)	38.4 (1.63)	38.3 (1.63)	38.4 (1.58)
Infant Race and Ethnicity					
American Indian or Alaska Native, non-Hispanic	8527 (0%)	10 or fewer (≤ 1%)	10 or fewer (≤ 1%)	10 or fewer (≤ 1%)	10 or fewer (≤ 1%)
Asian, non-Hispanic	69413 (3%)	37 (3%)	93 (4%)	18 (2%)	34 (2%)
Black or African American, non-Hispanic	311723 (13%)	168 (15%)	394 (16%)	204 (20%)	216 (15%)
Native Hawaiian or Other Pacific Islander, non-Hispanic	5747 (0%)	10 or fewer (≤ 1%)	22 (1%)	10 or fewer (≤ 1%)	10 or fewer (≤ 1%)
White, non-Hispanic	1138260 (47%)	505 (46%)	966 (40%)	396 (39%)	575 (40%)
Other Race, non-Hispanic	36947 (2%)	17 (2%)	47 (2%)	17 (2%)	24 (2%)
Multiple Races, non-Hispanic	385820 (16%)	147 (13%)	430 (18%)	191 (19%)	335 (23%)
Hispanic or Latino	463975 (19%)	211 (19%)	456 (19%)	175 (17%)	247 (17%)
Missing	184858	Suppressed	Suppressed	Suppressed	Suppressed
Infant Sex					
Female	1249783 (48%)	463 (40%)	1016 (40%)	490 (46%)	604 (40%)
Male	1355369 (52%)	700 (60%)	1543 (60%)	555-564 (53%)	901-910 (60%)
Other/Missing	118	0 (0%)	0 (0%)	10 or fewer (≤ 1%)	10 or fewer (≤ 1%)

Table 1.2. Birthing parent-infant dyad cohort characteristics stratified by HIE severity, including number, percentage, and standard deviation (SD, where applicable) for birthing parent age, birthing parent race and ethnicity, insurance type, preferred language, delivery year, mode of delivery, primigravida, gestational age, infant race and ethnicity, infant sex, and diagnoses.

Table 1.3. Birthing Parent-Infant Dyad Cohort Characteristics Stratified by Maternal Infection/Inflammation and Neonatal Sepsis

	Pyrexia During Labor		Chorioamnionitis		Neonatal Sepsis	
	No (N = 2597752)	Yes (N = 13810)	No (N = 2516927)	Yes (N = 94635)	No (N = 2592785)	Yes (N = 18777)
Birthing Parent Age (Years)						
Mean (SD)	30.6 (5.68)	29.1 (5.58)	30.6 (5.67)	29.3 (5.87)	30.6 (5.68)	30.0 (5.97)
Missing	86	0	76-85	10 or fewer	76-85	10 or fewer
Birthing Parent Race and Ethnicity						
American Indian or Alaska Native, non-Hispanic	10051 (0%)	59 (1%)	9661 (0%)	449 (1%)	9995 (0%)	115 (1%)
Asian, non-Hispanic	77487 (4%)	683 (6%)	73243 (4%)	4927 (6%)	77352 (4%)	818 (5%)
Black or African American, non-Hispanic	322708 (15%)	1520 (13%)	310018 (15%)	14210 (18%)	321580 (15%)	2648 (17%)
Native Hawaiian or Other Pacific Islander, nonHispanic	6326 (0%)	40 (0%)	5888 (0%)	478 (1%)	6239 (0%)	127 (1%)
White, non-Hispanic	1114055 (52%)	5362 (47%)	1091362 (52%)	28055 (35%)	1112709 (52%)	6708 (43%)
Other Race, non-Hispanic	30755 (1%)	149 (1%)	29427 (1%)	1477 (2%)	30610 (1%)	294 (2%))
Multiple Races, nonHispanic	216473 (10%)	1282 (11%)	208642 (10%)	9113 (11%)	216153 (10%)	1602 (10%)
Hispanic or Latino	376598 (17%)	2329 (20%)	256993 (17%)	21934 (27%)	375474 (17%)	3453 (22%)
Missing	443299	2386	431693	13992	442673	3012
Insurance Type						
Medicaid	582471 (23%)	2796 (20%)	558131 (22%)	27136 (29%)	580790 (23%)	4477 (24%)
Medicare	8493 (0%)	31 (0%)	8222 (0%)	302 (0%)	8442 (0%)	82 (0%)
Miscellaneous/ Other	1976590 (77%)	10855 (79%)	1921165 (77%)	66280 (70%)	1973452 (77%)	13993 (75%)
Self-Pay	12952 (1%)	61 (0%)	12668 (1%)	345 (0%)	12942 (1%)	71 (0%)
Missing	17246	67	16741	572	17159	154
Preferred Language						
English	1978411 (76%)	10444 (76%)	1918876 (76%)	69979 (74%)	1974877 (76%)	13978 (74%)
Spanish	141626 (5%)	771 (6%)	133726 (5%)	8671 (9%)	141032 (5%)	1365 (7%)

Table 1.3. Continued...

Other Language	477715 (18%)	2595 (19%)	464325 (18%)	15985 (17%)	476876 (18%)	3434 (18%)
Delivery Year						
2017	302632 (12%)	1627 (12%)	294010 (12%)	10249 (11%)	301416 (12%)	2843 (15%)
2018	355716 (14%)	2059 (15%)	345283 (14%)	12492 (13%)	354718 (14%)	3057 (16%)
2019	404467 (16%)	2378 (17%)	392396 (16%)	14449 (15%)	403700 (16%)	3145 (17%)
2020	455896 (18%)	2494 (18%)	441688 (18%)	16702 (18%)	455304 (18%)	3086 (16%)
2021	512585 (20%)	2524 (18%)	496523 (20%)	18586 (20%)	511818 (20%)	3291 (18%)
2022	566456 (22%)	2728 (20%)	547027 (22%)	22157 (23%)	565829 (22%)	3355 (18%)
Delivery Method						
C-Section	796461 (31%)	4466 (33%)	763460 (31%)	37467 (40%)	793065 (31%)	7862 (43%)
Vaginal	1772420 (69%)	9223 (67%)	1725653 (69%)	55990 (60%)	1771047 (69%)	10596 (57%)
Other/Missing	28,871	122	27814	1178	28673	319
Primigravida						
No/Missing	1900994 (73%)	6282 (45%)	1858933 (74%)	48343 (51%)	1895196 (73%)	12080 (64%)
Yes	696758 (27%)	7528 (55%)	657994 (26%)	46292 (49%)	697589 (27%)	6697 (36%)
Gestational Age (Weeks)						
Mean (SD)	38.6 (1.31)	39.1 (1.25)	38.6 (1.30)	39.0 (1.37)	38.6 (1.30)	38.2 (1.67)
Infant Race and Ethnicity						
American Indian or Alaska Native, non-Hispanic	8492 (0%)	53 (0%)	8169 (0 %)	376 (0%)	8447 (0%)	98 (1%)
Asian, non-Hispanic	69029 (3%)	566 (4%)	65342 (3%)	4253 (5%)	68875	720 (4%)
Black or African American, non-Hispanic	311212 (13%)	1493 (12%)	299496 (13%)	13209 (15%)	310127 (13%)	2578 (15%)
Native Hawaiian or Other Pacific Islander, nonHispanic	5750 (0%)	31 (0%)	5334 (0%)	447 (1%)	5668 (0%)	113 (1%)
White, non-Hispanic	1135302 (47%)	5400 (42%)	1113696 (48%)	27006 (30%)	1133842 (47%)	6860 (39%)

Table 1.3. Continued...

Other Race, non-Hispanic	36871 (2%)	181 (1%)	35508 (2%)	1544 (2%)	36775 (2%)	277 (2%)
Multiple Races, nonHispanic	384653 (16%)	2270 (18%)	371261 (16%)	15662 (18%)	384065 (16%)	2858 (16%)
Hispanic or Latino	462253 (19%)	2811 (22%)	438650 (19%)	26414 (30%)	460886 (19%)	4178 (24%)
Missing	184190	1005	179471	5724	184100	1095
Infant Sex						
Female	1245854 (48%)	6502 (47%)	1208627 (48%)	43729 (46%)	1244519 (48%)	7837 (42%)
Male	1351778 (52%)	7308 (53%)	130818013081 89 (52%)	50896-50905 (54%)	134813813481 47 (52%)	10930-10939 (58%)
Other/Missing	120	0 (0%)	110-119	10 or fewer	110-119	10 or fewer

Table 1.3. Birthing parent-infant dyad cohort characteristics stratified by perinatal infection and inflammation, including number, percentage, and standard deviation (SD, where applicable) for birthing parent age, birthing parent race and ethnicity, insurance type, preferred language, delivery year, mode of delivery, primigravida, gestational age, infant race and ethnicity, infant sex, and diagnoses.

Table 2. CP Rate Ratio by HIE Severity.

Exposure		CP Events	Live Births	Rate per 1000 Live Term Births	Unadjusted RR (95% CI)	Adjusted RR* (95% CI)
HIE						
	No	4304	2605270	1.7 (1.6, 1.7)	1.00 (Ref)	1.00 (Ref)
	Mild	24	1163	20.6 (12.5, 28.8)	12.5 (8.2, 18.1)	10.9 (7.1, 15.8)
	Moderate	148	2559	57.8 (48.8, 66.9)	35.0 (29.7, 40.9)	28.7 (24.3, 33.7)
	Severe	353	1055	334.6 (306.1, 363.1)	202.5 (184.7, 221.2)	148.8 (133.1, 165.7)
	Unspecified	142	1515	93.7 (79.1, 108.4)	56.7 (48.1, 66.2)	47.2 (39.9, 55.3)
	Any	667	6292	106.0 (98.4, 113.6)	64.2 (59.3, 69.3)	49.1 (44.7, 53.8)

* Adjusted for maternal age, pyrexia during delivery, chorioamnionitis, and neonatal sepsis.

Table 2. Number of CP outcomes and number of live term births for each HIE severity category. The rate of CP for each HIE severity level was computed per 1,000 live term births. Additionally, the table shows rate ratios of CP with 95% confidence intervals for each HIE severity level compared to the no HIE group ("Unadjusted RR 95% CI"). The results were adjusted for maternal age, pyrexia during labor, chorioamnionitis, and neonatal sepsis ("Adjusted RR 95% CI").

3.3 Risk of HIE increases with directness of PII

The rate of HIE was higher in infants with a diagnosis of PII (Table 3.1). Birthing parent-infant dyads with pyrexia during labor had a HIE rate of 7.7 (95% CI: 6.2 - 9.1) per 1,000 live term births, while those without pyrexia during labor had a rate of 2.4 cases (95% CI: 2.3 - 2.4). Infants with chorioamnionitis had a HIE rate of 11.5 (95% CI: 10.8 - 12.2) compared to 2.1 (95% CI: 2.0 - 2.1) in infants without chorioamnionitis. Finally, infants with sepsis had a HIE rate of 57.9 per 1,000 live term births (95% CI: 54.5 - 61.2), while those without sepsis had a rate of 2.0 per 1,000 (95% CI: 2.0 - 2.1).

The corresponding rate ratios were 3.2 (95% CI: 2.6 - 3.9) for dyads with pyrexia during labor compared to no pyrexia during labor, 5.6 (95% CI: 5.2 - 5.9) for infants with chorioamnionitis compared to no chorioamnionitis, and 28.8 (95% CI: 27.0 - 30.7) for infants with neonatal sepsis compared to no sepsis. After adjustment for primigravida, the rate ratio of HIE showed a modest attenuation towards the null for dyads with pyrexia during labor relative to dyads without pyrexia during labor (RR = 2.8; 95% CI: 2.3 - 3.3) and for dyads with chorioamnionitis relative to dyads without chorioamnionitis (RR = 5.0; 95% CI: 4.7 - 5.4). The rate ratio of HIE for patients with neonatal sepsis compared to those without neonatal sepsis was 19.9 (95% CI: 18.6 - 21.3) after further adjustment for pyrexia during labor and chorioamnionitis, indicating a significant attenuation toward the null but remaining of large magnitude.

3.4 Risk of CP increases with directness of PII

The rate of CP was higher in infants with a diagnosis of perinatal inflammation or infection (Table 3.2). Birthing parent-infant dyads with pyrexia during labor had a CP rate of 2.8 per 1,000 live term births (95% CI: 1.9 - 3.7), while those without pyrexia during labor had a rate of 1.9 cases (95% CI: 1.8 - 2.0). Infants with chorioamnionitis had a CP rate of 3.1 (95% CI: 2.8 - 3.5) compared to 1.9 (95% CI: 1.8 - 1.9) in infants without chorioamnionitis. Finally, infants with sepsis had a CP rate of 18.2 per 1,000 live term births (95% CI: 16.3 - 20.1), while those without sepsis had a rate of 1.8 per 1,000 (95% CI: 1.7 - 1.8).

The corresponding rate ratios were 1.5 (95% CI: 1.1 - 2.0) for dyads with pyrexia during labor compared to no pyrexia during labor, 1.7 (95% CI: 1.5 - 1.9) for infants with chorioamnionitis compared to no chorioamnionitis, and 10.2 (95% CI: 9.1 - 11.4) for infants with neonatal sepsis compared to no sepsis. The rate ratio of CP for patients with neonatal sepsis compared to those without neonatal sepsis was 9.7 (95% CI: 8.7 - 10.8) after further adjustment for pyrexia during labor and chorioamnionitis, indicating a modest attenuation toward the null.

3.5 Interaction between HIE and Pyrexia during Labor on CP Risk

Results revealed no interaction between HIE (A) and pyrexia during labor (B) on the rate of CP in this cohort (see Table 4.1). After adjusting for primigravida, maternal age, chorioamnionitis, and neonatal sepsis, there is further attenuation of interaction measures and rate ratios toward the null (see Table 4.2).

Compared to the common referent (e.g., No HIE/No Pyrexia during Labor, A=0/B=0, "unexposed group"), the RR of CP in dyads with no HIE and pyrexia during labor (A=0/B=1) was 1.1 (95% CI: 0.69 - 1.5; adjusted: 1.0, 0.65 - 1.5), the RR of CP in dyads with HIE and no pyrexia during labor (A=1/B=0) was 63.8 (95% CI: 58.9 - 69.0; adjusted: 48.9, 44.6 - 53.7), and the RR of CP in dyads with HIE and pyrexia during labor (A=1/B=1) was 85.7 (95% CI: 53.6 - 137.1; adjusted: 61.2, 38.2 - 97.9). The RR of CP in dyads with joint HIE and pyrexia during labor is increased compared to the RR associated with either HIE or pyrexia during labor alone.

Amongst dyads without HIE, the RR of CP with pyrexia during labor compared to without pyrexia during labor was 1.1 (95% CI: 0.69 - 1.5; adjusted: 1.0, 0.65 - 1.5). Amongst dyads with HIE, the RR of CP with pyrexia during labor compared to without pyrexia during labor was 1.3 (95% CI: 0.84 - 2.2; adjusted 1.3, 0.78 - 2.0). In sum, within strata of HIE (A), no increased risk was observed for dyads with pyrexia during labor compared to without pyrexia during labor, e.g., confidence intervals cross null.

Conversely, amongst dyads without pyrexia during labor, the RR of CP with HIE compared to without HIE was 63.8 (95% CI: 58.9 - 69.0; adjusted: 48.9, 44.6 - 53.7). Amongst dyads with pyrexia during labor, the RR of CP with HIE compared to without HIE was 80.8 (95% CI: 43.6 - 149.6; adjusted: 61.3, 33.2 - 113.1). In sum, within strata of pyrexia during labor (B), higher overall point estimates were observed. However, the overlap in the confidence intervals indicates that there is insufficient evidence to conclude that pyrexia during labor modifies the effect of HIE on the rate of CP.

Measures of interaction on additive (21.8; 95% CI: -18.6 - 62.3; p = .145; adjusted: 12.3; 95% CI: -16.4 - 41.0; p = .2) and multiplicative scale (1.3; 95% CI: 0.66 - 2.3; p = .457; adjusted: 1.3; 95% CI: 0.66 - 2.3; p = .473) both cross null with p > 0.5, which leads to the conclusion of no evidence of interaction between HIE and pyrexia during labor on CP rate.

Table 3.1. HIE Rate Ratio by Perinatal Inflammation/Infection.

Exposure		HIE Events	Live Births	Rate per 1000 Live Term Births	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
Pyrexia During Labor						
	No	6186	2597752	2.4 (2.3, 2.4)	1.00 (Ref)	1.00 (Ref)
	Yes	106	13810	7.7 (6.2, 9.1)	3.2 (2.6, 3.9)	2.8 (2.3, 3.3)*
Chorioamnionitis						
	No	5203	2516927	2.1 (2.0, 2.1)	1.00 (Ref)	1.00 (Ref)
	Yes	1089	94635	11.5 (10.8, 12.2)	5.6 (5.2, 5.9)	5.0 (4.7, 5.4)*
Neonatal Sepsis						
	No	5205	2592785	2.0 (2.0, 2.1)	1.00 (Ref)	1.00 (Ref)
	Yes	1087	18777	57.9 (54.5, 61.2)	28.8 (27.0, 30.7)	19.9 (18.6, 21.3)**

* Adjusted for primigravida

** Adjusted for primigravida, pyrexia during delivery, and chorioamnionitis

Table 3.1. Number of HIE outcomes and number of live term births for each perinatal inflammation/infection diagnosis, e.g., pyrexia during labor, chorioamnionitis, and neonatal sepsis. The rate of HIE for each of the diagnoses was computed per 1,000 live term births. Additionally, the table shows rate ratios of HIE with 95% confidence intervals for each diagnosis compared to the respective unexposed group ("Unadjusted RR 95% CI"). Pyrexia during labor and chorioamnionitis results were adjusted for primigravida, while neonatal sepsis RR of HIE was further adjusted for pyrexia during labor and chorioamnionitis ("Adjusted RR 95% CI").

Table 3.2. CP Rate Ratio by Perinatal Inflammation/Infection.

Exposure		CP Events	Live Births	Rate per 1000 Live Term Births	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
Pyrexia During Labor						
	No	4932	2597752	1.9 (1.8, 2.0)	1.00 (Ref)	--
	Yes	39	13810	2.8 (1.9, 3.7)	1.5 (1.1, 2.0)	
Chorioamnionitis						
	No	4,676	2516927	1.9 (1.8, 1.9)	1.00 (Ref)	--
	Yes	295	94635	3.1 (2.8, 3.5)	1.7 (1.5, 1.9)	
Neonatal Sepsis						
	No	4629	2592785	1.8 (1.7, 1.8)	1.00 (Ref)	1.00 (Ref)
	Yes	342	18777	18.2 (16.3, 20.1)	10.2 (9.1, 11.4)	9.7 (8.7, 10.8)

* Adjusted for pyrexia during delivery and chorioamnionitis

Table 3.2. Number of CP outcomes and number of live term births for each perinatal inflammation/infection diagnosis, e.g., pyrexia during labor, chorioamnionitis, and neonatal sepsis. The rate of CP for each of the diagnoses was computed per 1,000 live term births. Additionally, the table shows rate ratios of CP with 95% confidence intervals for each diagnosis compared to the respective unexposed group ("Unadjusted RR 95% CI"). The rate ratio of CP for dyads with neonatal sepsis was adjusted for pyrexia during labor and chorioamnionitis ("Adjusted RR 95% CI").

3.6 Interaction between HIE and Chorioamnionitis on CP Risk

Amongst infants with HIE (A), we observed lower point estimates for CP in those who also had chorioamnionitis (B), compared to HIE patients without chorioamnionitis (see Table 5.1). This difference was enhanced after adjustment for confounders (Table 5.2). We also show a submultiplicative interaction between HIE and chorioamnionitis on CP rate, which reached statistical significance after adjustment.

Compared to the common referent (e.g., No HIE/No chorioamnionitis A=0/B=0, "unexposed group"), the RR of CP in dyads with no HIE and chorioamnionitis (A=0/B=1) was 1.2 (95% CI: 1.0 - 1.4; adjusted: 1.1, 0.95 - 1.3), the RR of CP in dyads with HIE and no chorioamnionitis (A=1/B=0) was 63.8 (95% CI: 59.7 - 70.7; adjusted: 50.7, 46.0 - 55.8), and the RR of CP in dyads with HIE and chorioamnionitis (A=1/B=1) was 62.7 (95% CI: 52.5 - 74.9; adjusted: 43.3, 35.9 - 52.3). Thus, the RR of CP in dyads with joint HIE and chorioamnionitis is slightly decreased compared to the RR associated with HIE and no chorioamnionitis without reaching significance as indicated by overlapping confidence intervals.

Amongst dyads without HIE, the RR of CP with chorioamnionitis compared to without chorioamnionitis was 1.2 (95% CI: 1.0 - 1.4; adjusted: 1.1, 0.95 - 1.3). Amongst dyads with HIE, the RR of CP with chorioamnionitis compared to without chorioamnionitis was 1.0 (95% CI: 0.80 - 1.2; adjusted: 0.90, 0.71 - 1.0). In sum, within strata of HIE (A), no increased risk was observed for dyads with chorioamnionitis compared to without chorioamnionitis, e.g., confidence intervals cross null.

Conversely, amongst dyads without chorioamnionitis, the RR of CP with HIE compared to without HIE was 65.0 (95% CI: 59.7 - 70.7; adjusted: 50.7; 46.0 - 55.8). Amongst dyads with chorioamnionitis, the RR of CP with HIE compared to without HIE was 52.6 (95% CI: 41.9, 66.0; adjusted: 39.0, 31.0 - 49.2). In sum, the RR of patients with HIE compared to no HIE was lower amongst dyads with chorioamnionitis compared to amongst dyads with no chorioamnionitis. However, it is not possible to conclude a modification of the effect of HIE on CP rate by chorioamnionitis due to overlapping confidence intervals.

Results revealed a sub-multiplicative interaction between HIE (A) and chorioamnionitis (B) on the rate of CP after adjustment for primigravida, maternal age, pyrexia during labor, and neonatal sepsis (0.77; 95% CI: 0.60 - 0.98; p = .0336). No evidence of an interaction between HIE and chorioamnionitis was observed on the additive scale before (-2.5; 95% CI: -14.6 - 9.6; p = .657) or after adjustment for a priori confounders (-7.5; 95% CI: -16.1 - 1.1; p = .957). Likewise, there was no evidence of a multiplicative interaction in the unadjusted analysis (0.81; 95% CI: 0.63 - 1.0; p = .0861).

3.7 Interaction between HIE and Neonatal Sepsis on CP Risk

Results revealed a super-additive and a sub-multiplicative interaction between HIE (A) and neonatal (B) on the rate of CP in this cohort (see Table 6.1). The results remain mostly unchanged after adjusting for primigravida, maternal age, chorioamnionitis, and pyrexia during labor (see Table 6.2).

Compared to the common referent (e.g., No HIE/No neonatal sepsis A=0/B=0, "unexposed group"), the RR of CP in dyads with no HIE and neonatal sepsis (A=0/B=1) was 6.9 (95% CI: 6.0 - 8.0; adjusted: 7.0, 6.0 - 8.0), the RR of CP in dyads with HIE and no neonatal sepsis (A=1/B=0) was 62.9 (95% CI: 57.6 - 68.6; adjusted: 64.0, 58.5 - 69.8), and the RR of CP in dyads with HIE and neonatal sepsis (A=1/B=1) was 85.2 (95% CI: 73.1 - 99.3; adjusted: 86.4, 74.0 - 100.9). The RR of CP in dyads with joint HIE and neonatal sepsis is increased compared to the RR associated with either HIE or neonatal sepsis alone.

Amongst dyads without HIE, the RR of CP with neonatal sepsis compared to without neonatal sepsis was 6.9 (95% CI: 6.0 - 8.0; adjusted: 7.0, 6.0 - 8.0). Amongst dyads with HIE, the RR of CP with neonatal sepsis compared to without neonatal sepsis was 1.4 (95% CI: 1.1 - 1.6; adjusted: 1.4, 1.1 - 1.6). In sum, amongst dyads without HIE the effect of neonatal sepsis on CP rate is greater than the effect of neonatal sepsis amongst dyads with HIE.

Conversely, amongst dyads without neonatal sepsis, the RR of CP with HIE compared to without HIE was 62.9 (95% CI: 57.6 - 68.6; adjusted: 64.0; 58.5 - 69.8). Amongst dyads with neonatal sepsis, the RR of CP with HIE compared to without HIE was 12.3 (95% CI: 10.0 - 15.1; adjusted: 12.4, 10.1 - 15.2). In sum, amongst dyads without neonatal sepsis, the effect of HIE on CP rate is greater than the effect of HIE amongst dyads with neonatal sepsis.

Results revealed a super-additive interaction between HIE and neonatal sepsis on the rate of CP before (16.3; 95% CI: 2.5 - 30.1; p = .0105) and after adjustment for primigravida, maternal age, pyrexia during labor, and chorioamnionitis (16.5; 95% CI: 2.4 - 30.6; p = .0107). This indicates that the joint presence of both factors produces more excess risk than individual RRs would sum to. On the multiplicative scale, the results show evidence of a negative interaction both on unadjusted (0.20; 95% CI: 0.16 - 0.24; p < .001) and adjusted analyses (0.19; 95% CI: 0.15 - 0.24; p < .001). This indicates that the joint risk ratio is smaller than the result of multiplying the RRs of HIE and neonatal sepsis individually.

3.8 Infant Mortality

By age 3, 63% of infants (N = 3,530,748) in this study were known to be alive and less than 0.001% of infants (N = 16,667) were known to be deceased. The remaining 36% of infants (N = 2,022,095) were lost in the dataset (see Table 7).

Mortality for infants without HIE or PII was 0.2% (N = 13,470). Dyads with pyrexia during labor also had an infant mortality rate of 0.2% without HIE (N = 62) and 10% with HIE (N = 16). Chorioamnionitis with HIE had a mortality rate of 5.8% (N = 173) and chorioamnionitis without HIE had a mortality rate of 0.3% (N = 728). Infants with neonatal sepsis and HIE had the highest mortality rate at 10.5% (N = 251), while infants with neonatal sepsis and no HIE had a mortality rate of 2.3% (N = 999). HIE alone was associated with a mortality rate of 7.7% (N = 976).

The percentage of infants who were lost in the dataset ranged from 16% to 36%. Infants without HIE or PII were lost in the dataset in 36% of cases (N = 1,937,736). Dyads with pyrexia during labor and HIE had a lost in the dataset rate of 16% (N = 25) and those with pyrexia during labor and no HIE had a lost in the dataset rate of 34% (N = 9,471). Chorioamnionitis with HIE had a lost in the dataset rate of 27% (N = 440) and chorioamnionitis without HIE had a lost in the dataset of 35% (N = 62,744). Infants with neonatal sepsis and HIE had the lowest lost in the dataset rate at 24% (N = 322), while infants with neonatal sepsis and no HIE had a lost in the dataset rate of 33% (N = 9,358). HIE alone was associated with a lost in the dataset rate of 27% (N = 1,983).

4. Sensitivity Analysis

4.1.1 Selected vs. Non-Selected Cohorts

Differences in terms of demographic and clinical characteristics of the selected vs. non-selected cohorts appeared to be minimal and did not raise concerns regarding selection bias (Table 8.1). Further, there were no significant differences in prevalence of pyrexia during labor (selected: N = 13810, 0.5% vs. non-selected: 13265, 0.48%), chorioamnionitis (selected: N = 94635, 3.6% vs. non-selected: 83351, 3%), and neonatal sepsis (selected: N = 18777, 0.7% vs. non-selected: 17595, 0.64%). However, the selected study cohort showed almost double the prevalence of HIE compared to the non-selected cohort (selected: N = 6292, 0.2% vs. non-selected: 3564, 0.13%).

IPSWs were computed in order to confirm that results from the main analysis hold when the characteristics of the selected cohort are normalized to match those of the non-selected cohort. IPSWs ranged from 0.62 to 2.6, with a mean weight of 1. The adjusted effective sample size for non-selected and selected cohorts was 2,715,123 and 2,578,044, respectively. Unadjusted standardized mean differences (SMD) for all covariates were below the standard 0.1 SMD threshold of imbalance. After adjustment, all covariates had an SMD of 0.

4.1.2 CP Rate by HIE Severity

There was modest attenuation of all rate ratios as a result of adding IPSWs to the selected cohort (Table 8.2). The same incremental increase in unadjusted and adjusted RR of CP with increasing HIE severity was observed.

The unadjusted RRs of CP for each HIE severity level were as follows: mild HIE: 12.6, 8.4 - 18.7 (vs. no IPSWs: 12.5, 8.2 - 18.1), moderate HIE: 35.3, 30.1 - 41.5 (vs. no IPSWs: 35.0, 29.7 - 40.9), severe HIE: 205.9, 188.1 - 225.3 (vs. no IPSWs: 202.5, 184.7 - 221.2), and unspecified HIE: 56.8, 48.3 - 66.6 (vs. no IPSWs: 56.7, 48.1 - 66.2). The adjusted rate ratio of CP after HIE of any severity was 64.9, 60.0 - 70.2 (vs. no IPSWs: 64.2, 59.3 - 69.3). The adjusted RRs of CP for each HIE severity level were as follows: mild HIE: 10.7, 7.2 - 16.0 (vs. no IPSWs: 10.9, 7.1 - 15.8), moderate HIE: 28.1, 23.6 - 33.5 (vs. no IPSWs: 28.7, 24.3 - 33.7), severe HIE: 142.8, 125.3 - 162.6 (vs. no IPSWs: 148.8, 133.1 - 165.7), and unspecified HIE: 45.9, 38.6 - 54.6 (vs. no IPSWs: 47.2, 39.9 - 55.3). The adjusted rate ratio of CP after HIE of any severity was 47.9, 43.0 - 53.5 (vs. no IPSWs: 49.1, 44.7 - 53.8). Adding IPSWs to the selected cohort does not meaningfully change the conclusions regarding the unadjusted or adjusted RRs of CP by HIE severity (compare Table 2).

4.1.3 HIE Rate by PII

Adding IPSWs to the selected cohort resulted in a modest attenuation of HIE rate ratios toward the null. As before, the rate of HIE was higher in infants with perinatal exposure to inflammation/infection (Table 8.3).

The unadjusted rate ratios were 3.3, 2.7 - 3.9 (vs. no IPSW: 3.2, 2.6 - 3.9) for dyads with pyrexia during labor compared to no pyrexia during labor, 5.7, 5.3 - 6.1 (vs. no IPSW: 5.6, 5.2 - 5.9) for infants with chorioamnionitis compared to no chorioamnionitis, and 30.1, 28.2 - 32.1 (vs. no IPSW: 28.8, 27.0 - 30.7) for infants with neonatal sepsis compared to no sepsis. The corresponding adjusted rate ratios were 3.3, 2.7 - 3.9 (vs. no IPSW: 2.8, 2.3 - 3.3) for dyads with pyrexia during labor compared to no pyrexia during labor, 5.7, 5.3 - 6.1 (vs. no IPSW: 5.0, 4.7 - 5.4) for infants with chorioamnionitis compared to no chorioamnionitis, and 30.1, 28.2 - 32.1 (vs. no IPSW: 19.9, 18.6 - 21.3) for infants with neonatal sepsis compared to no sepsis. The IPSWs did not meaningfully change the conclusions from Table 3.1.

4.1.4 CP Rate by PII

Adding IPSWs to the selected cohort resulted in a modest increase rate ratios of CP for neonatal sepsis, while the rate ratios of CP for pyrexia during labor and chorioamnionitis did not meaningfully change (Table 8.4).

The unadjusted rate ratios were 1.4, 1.0 - 2.0 (vs. no IPSW: 1.5, 1.1 - 2.0) for dyads with pyrexia during labor compared to no pyrexia during labor, 1.6, 1.4 - 1.8 (vs. no IPSW: 1.7, 1.5 - 1.9) for infants with chorioamnionitis compared to no chorioamnionitis, and 9.6, 8.6 - 10.8 (vs. no IPSW: 10.2, 9.1 - 11.4) for infants with neonatal sepsis compared to no sepsis. The rate ratio of CP for patients with neonatal sepsis compared to those without neonatal sepsis was 9.3, 8.3 - 10.4 (vs. no IPSW: 9.7, 8.7 - 10.8) after further adjustment for pyrexia during labor and chorioamnionitis. The IPSWs did not meaningfully change the conclusions from Table 3.2.

4.1.5 Interaction between HIE and Perinatal Infection/Inflammation on CP Rate

The conclusions drawn from interaction analyses did not change as a result of adding IPSWs.

There was no interaction between HIE and pyrexia during labor on either the additive or the multiplicative scale. Adding IPSWs caused a modest attenuation further toward the null (Table 8.5). There was a significant sub-multiplicative interaction between HIE and chorioamnionitis, which, despite a modest attenuation toward the null, did not change after IPSWs were added (Table 8.6). Finally, the super-additive interaction between HIE and neonatal sepsis and the submultiplicative interaction between HIE and neonatal sepsis remained significant (Table 8.7).

4.2 Assessment of Pyrexia: DX Code vs. Temperature Range

4.2.1 Cohort Characteristics

The study cohort was stratified by pyrexia during labor, defined by a maternal body temperature of at least 100.4 °F (Table 9.1). Per this definition, a total of 87,007 (3.3%) birthing parent-infant dyads were affected by pyrexia during labor, while 2,524,555 dyads were not affected by pyrexia during labor (96.7%). By contrast, only 13,810 dyads (0.5%) were identified as having pyrexia during labor based on the diagnosis code definition. Compared to dyads without pyrexia during labor, those with pyrexia during labor had lower proportions of nonHispanic White birthing parents (pyrexia during labor: N = 29,369; 40%; no pyrexia during labor:

N = 109,004; 52%) and infants (pyrexia during labor: N = 29388; 36%; no pyrexia during labor: N = 1,111,314; 47%), and vaginal delivery (pyrexia during labor: N = 55,386; 64%; no pyrexia during labor: N = 1,726,257; 69%). Conversely, dyads with pyrexia during labor had higher proportions of Hispanic or Latino birthing parents (pyrexia during labor: N = 18,134; 25%; no pyrexia during labor: N = 360,793; 17%) and infants (pyrexia during labor: N = 21,885; 27%; no pyrexia during labor: N = 443,179; 19%), and C-section deliveries (pyrexia during labor: N = 30,704; 36%; no pyrexia during labor: N = 770,223; 31%). A greater proportion of dyads with pyrexia during labor were primigravida (with neonatal sepsis: N = 47,409; 54%; no neonatal sepsis: N = 656,877; 26%).

4.2.2 CP Rate by HIE Severity

The effect of changing the definition of pyrexia during labor from diagnosis code to maternal temperature criteria on adjusted rate ratios of CP by HIE severity was minimal (Table 9.2). The same incremental increase in adjusted RR of CP with increasing HIE severity was observed. The adjusted RRs of CP for each HIE severity level were as follows: mild HIE: 10.9, 7.1 - 15.9 (vs. primary definition: 10.9, 7.1 - 15.8), moderate HIE: 28.9, 24.4 - 33.9 (vs. primary definition:

28.7, 24.3 - 33.7), severe HIE: 148.8, 132.3 - 164.9 (vs. primary definition: 148.8, 133.1 - 165.7), and unspecified HIE: 47.4, 40.1 - 55.5 (vs. primary definition: 47.2, 39.9 - 55.3). The adjusted rate ratio of CP after HIE of any severity was 49.2, 44.8 - 53.9 (vs. primary definition: 49.1, 44.7 - 53.8). The alternate definition of pyrexia during labor does not change the conclusions regarding the RR of CP by HIE severity.

4.2.3 HIE Rate by Pyrexia during Labor

The rate of HIE was higher in dyads with a diagnosis of pyrexia during labor regardless of definition (Table 9.3) compared to dyads without pyrexia during labor. Birthing parent-infant dyads with pyrexia during labor as defined by maternal temperature had an unadjusted RR of HIE of 4.2 (95% CI: 3.9 - 4.6) and an adjusted RR of HIE of 3.7 (95% CI: 2.4 - 4.0). By contrast, the primary definition of pyrexia during labor resulted in an unadjusted RR of HIE of 3.2 (95% CI: 2.6 - 3.9) and an adjusted RR of HIE of 2.8 (95% CI: 2.3 - 3.3). The RR of HIE for dyads with vs. without neonatal sepsis adjusted for pyrexia during labor per the temperature definition was

19.8 (95% CI: 18.5 - 21.3), compared to 19.9 (95% CI: 18.6 - 21.3) when adjusted for pyrexia during labor per the diagnosis code definition. These RRs are modestly greater than the ones associated with pyrexia during labor per the primary definition, with no meaningful change in conclusions.

4.2.4 CP Rate by Pyrexia during Labor

The rate of CP was higher in dyads with a diagnosis of pyrexia during labor both per diagnosis code definition and per maternal temperature definition (Table 9.4). Results showed no meaningful difference in terms of rate of CP and unadjusted RR of CP between primary (rate: 2.8, 1.9 - 3.7; unadjusted RR: 1.5, 1.1 - 2.0) and secondary definitions of pyrexia during labor (rate: 2.4, 2.1 - 2.7; unadjusted RR: 1.3, 1.1 - 1.5).

4.2.5 Interaction HIE x Pyrexia during Labor on CP Rate

Within strata of HIE, point estimate moves away from null toward lower risk of CP with pyrexia during labor compared to no pyrexia during labor. No change in conclusions for within strata of pyrexia during labor or measures of interaction (Table 9.5).

After full adjustment, point estimates move away from null toward lower risk of CP with pyrexia during labor compared to no pyrexia during labor. No change in conclusions for within strata of pyrexia during labor or measures of interaction (Table 9.6).

Table 4.1. Unadjusted interaction between HIE and Pyrexia during Labor on the Rate of CP.

	No HIE (A = 0)		HIE (A = 1)		RR (95% CI) for A = 1 vs A = 0, within strata of B
	N with/without outcome	RR (95% CI)	N with/without outcome	RR (95% CI)	
No Fever (B = 0)	4280/2591566	1.0 (Ref)	652/6186	63.8 (58.9, 69.0)	63.8 (58.9, 69.0)
Fever (B = 1)	24/13704	1.1 (0.69, 1.5)	15/106	85.7 (53.6, 137.1)	80.8 (43.6, 149.6)
RR (95% CI) for B = 1 vs. B = 0, within strata of A		1.1 (0.69, 1.5)		1.3 (0.84, 2.2)	
Measure of interaction on additive scale:	21.8 (-18.6, 62.3)	p = 0.145			
Measure of interaction on multiplicative scale:	1.3 (0.66, 2.3)	p = 0.457			

Table 4.1. The table shows: a) the number of patients for each combination of strata A (HIE) and B (pyrexia during labor) that developed CP and the number of those who did not ("N with/without outcome"). b) rate ratios of CP with 95% confidence intervals ("RR 95% CI") for each of the exposure groups (A=0/B=1; A=1/B=0; A=1/B=1), compared to the unexposed group (A=0/B=0). c) rate ratios of CP with 95% confidence intervals for dyads exposed to B (B=1) compared to dyads unexposed to B (B=0), separately for dyads in each stratum of exposure A (A=0 and A=1; "RR 95% CI for B = 1 vs. B = 0, within strata of A"). Conversely, the table shows rate ratios of CP with 95% confidence intervals for dyads exposed to A (A=1) compared to dyads unexposed to A (A=0), separately for dyads in each stratum of exposure B (B=0 and B=1; "RR 95% CI for B = A vs. A = 0, within strata of B") d) measures of interaction on additive and multiplicative scale with 95% confidence intervals and p values.

Table 4.2. Adjusted interaction between HIE and Pyrexia during Labor on the Rate of CP.

	No HIE (A = 0)		HIE (A = 1)		RR (95% CI) for A = 1 vs A = 0, within strata of B
	N with/without outcome	RR (95% CI)	N with/without outcome	RR (95% CI)	
No Fever (B = 0)	4280/2591566	1.0 (Ref)	652/6186	48.9 (44.6, 53.7)	48.9 (44.6, 53.7)
Fever (B = 1)	24/13704	1.0 (0.65, 1.5)	15/106	61.2 (38.2, 97.9)	61.3 (33.2, 113.1)
RR (95% CI) for B = 1 vs. B = 0, within strata of A		1.0 (0.65, 1.5)		1.3 (0.78, 2.0)	
Measure of interaction on additive scale:	12.3 (-16.4, 41.0)	p = 0.2			
Measure of interaction on multiplicative scale:	1.3 (0.66, 2.3)	p = 0.473			

* Adjusted for primigravida, maternal age, chorioamnionitis, and neonatal sepsis

Table 4.2. This table is identical to Table 4.1, except that the results are adjusted for a priori specified confounders, including primigravida, maternal age, chorioamnionitis, and neonatal sepsis.

Table 5.1. Unadjusted interaction between HIE and Chorioamnionitis on the Rate of CP

	No HIE (A = 0)		HIE (A = 1)		RR (95% CI) for A = 1 vs A = 0, within strata of B
	N with/without outcome	RR (95% CI)	N with/without outcome	RR (95% CI)	
No Chorio (B = 0)	4121/2511724	1.0 (Ref)	555/5203	65.0 (59.7, 70.7)	65.0 (59.7, 70.7)
Chorio (B = 1)	183/93546	1.2 (1.0, 1.4)	112/1089	62.7 (52.5, 74.9)	52.6 (41.9, 66.0)
RR (95% CI) for B = 1 vs. B = 0, within strata of A		1.2 (1.0, 1.4)		1.0 (0.80, 1.2)	
Measure of interaction on additive scale:	-2.5 (-14.6, 9.6)	p = 0.657			
Measure of interaction on multiplicative scale:	0.81 (0.63, 1.0)	p = 0.0861			

Table 5.1. The table shows: a) the number of patients for each combination of strata A (HIE) and B (chorioamnionitis) that developed CP and the number of those who did not ("N with/without outcome"). b) rate ratios of CP with 95% confidence intervals ("RR 95% CI") for each of the exposure groups (A=0/B=1; A=1/B=0; A=1/B=1), compared to the unexposed group (A=0/B=0). c) rate ratios of CP with 95% confidence intervals for dyads exposed to B (B=1) compared to dyads unexposed to B (B=0), separately for dyads in each stratum of exposure A (A=0 and A=1; "RR 95% CI for B = 1 vs. B = 0, within strata of A"). Conversely, the table shows rate ratios of CP with 95% confidence intervals for dyads exposed to A (A=1) compared to dyads unexposed to A (A=0), separately for dyads in each stratum of exposure B (B=0 and B=1; "RR 95% CI for B = A vs. A = 0, within strata of B") d) measures of interaction on additive and multiplicative scale with 95% confidence intervals and p values.

Table 5.2. Adjusted interaction between HIE and Chorioamnionitis on the Rate of CP.

	No HIE (A = 0)		HIE (A = 1)		RR (95% CI) for A = 1 vs A = 0, within strata of B
	N with/without outcome	RR (95% CI)	N with/without outcome	RR (95% CI)	
No Chorio (B = 0)	4121/2511724	1.0 (Ref)	555/5203	50.7 (46.0, 55.8)	50.7 (46.0, 55.8)
Chorio (B = 1)	183/93546	1.1 (0.95, 1.3)	112/1089	43.3 (35.9, 52.3)	39.0 (31.0, 49.2)
RR (95% CI) for B = 1 vs. B = 0, within strata of A		1.1 (0.95, 1.3)		0.90 (0.71, 1.0)	
Measure of interaction on additive scale:	-7.5 (-16.1, 1.1)	p = 0.957			
Measure of interaction on multiplicative scale:	0.77 (0.60, 0.98)	p = 0.0336**			

* Adjusted for primigravida, maternal age, pyrexia during labor, and neonatal sepsis

** Significance level p < 0.05

Table 5.2. This table is identical to Table 5.1, except that the results are adjusted for a priori specified confounders, including primigravida, maternal age, pyrexia during labor, and neonatal sepsis.

Table 6.1. Unadjusted interaction between HIE and Neonatal Sepsis on the Rate of CP.

	No HIE (A = 0)		HIE (A = 1)		RR (95% CI) for A = 1 vs A = 0, within strata of B
	N with/without outcome	RR (95% CI)	N with/without outcome	RR (95% CI)	
No Sepsis (B = 0)	4109/2587580	1.0 (Ref)	520/5205	62.9 (57.6, 68.6)	62.9 (57.6, 68.6)
Sepsis (B = 1)	195/17690	6.9 (6.0, 8.0)	147/1087	85.2 (73.1, 99.3)	12.3 (10.0, 15.1)
RR (95% CI) for B = 1 vs. B = 0, within strata of A		6.9 (6.0, 8.0)		1.4 (1.1, 1.6)	
Measure of interaction on additive scale:	16.3 (2.5, 30.1)	p = 0.0105*			
Measure of interaction on multiplicative scale:	0.20 (0.16, 0.24)	p < 0.001*			

* Significance level p < 0.05

Table 6.1. The table shows: a) the number of patients for each combination of strata A (HIE) and B (neonatal sepsis) that developed CP and the number of those who did not ("N with/without outcome"). b) rate ratios of CP with 95% confidence intervals ("RR 95% CI") for each of the exposure groups (A=0/B=1; A=1/B=0; A=1/B=1), compared to the unexposed group (A=0/B=0). c) rate ratios of CP with 95% confidence intervals for dyads exposed to B (B=1) compared to dyads unexposed to B (B=0), separately for dyads in each stratum of exposure A (A=0 and A=1; "RR 95% CI for B = 1 vs. B = 0, within strata of A"). Conversely, the table shows rate ratios of CP with 95% confidence intervals for dyads exposed to A (A=1) compared to dyads unexposed to A (A=0), separately for dyads in each stratum of exposure B (B=0 and B=1; "RR 95% CI for B = A vs. A = 0, within strata of B") d) measures of interaction on additive and multiplicative scale with 95% confidence intervals and p values.

Table 6.2. Adjusted interaction between HIE and Neonatal Sepsis on the Rate of CP.

	No HIE (A = 0)		HIE (A = 1)		RR (95% CI) for A = 1 vs A = 0, within strata of B
	N with/without outcome	RR (95% CI)	N with/without outcome	RR (95% CI)	
No Sepsis (B = 0)	4109/2587580	1.0 (Ref)	520/5205	64.0 (58.5, 69.8)	64.0 (58.5, 69.8)
Sepsis (B = 1)	195/17690	7.0 (6.0, 8.0)	147/1087	86.4 (74.0, 100.9)	12.4 (10.1, 15.2)
RR (95% CI) for B = 1 vs. B = 0, within strata of A		7.0 (6.0, 8.0)		1.4 (1.1, 1.6)	
Measure of interaction on additive scale:	16.5 (2.4, 30.6)	p = 0.0107**			
Measure of interaction on multiplicative scale:	0.19 (0.15, 0.24)	p < 0.001**			

* Adjusted for primigravida, maternal age, pyrexia during labor, and chorioamnionitis

** Significance level p < 0.05

Table 6.2. This table is identical to Table 6.1, except that results are adjusted for a priori specified confounders, including primigravida, maternal age, pyrexia during labor, and chorioamnionitis.

Table 7. Infant mortality data by HIE and PII exposure category.

Group	Total	Neonatal Mortality	Mortality by Age 3	Mortality	Alive by Age 3	Lost to Follow-Up
Maternal fever without HIE	27975	12	49	61 (0.2%)	18455 (66%)	9471 (34%)
Maternal fever with HIE	157	10 or fewer	10 or fewer	16 (10%)	116 (74%)	25 (16%)
Chorioamnionitis without HIE	176992	237	491	728 (0.3%)	113757 (64%)	62744 (35%)
Chorioamnionitis with HIE	1642	77	96	173 (5.8%)	1106 (67%)	440 (27%)
Neonatal Sepsis without HIE	28069	366	633	999 (2.3%)	18078 (64%)	9358 (33%)
Neonatal Sepsis with HIE	1339	110	141	251 (10.5%)	876 (65%)	322 (24%)
HIE alone	7276	419	557	976 (7.7%)	4736 (65%)	1983 (27%)
No HIE or maternal fever, chorio, neonatal sepsis	5321621	3218	10261	13479 (0.2%)	3373624 (63%)	1937736 (36%)

Table 7. Mortality for different HIE and PII exposure groups. Death was noted when infant was marked deceased at the initial delivery hospitalization visit (Neonatal Mortality) or if the patient died at a Cosmosparticipating institution, e.g., in-patient or emergency department (Mortality by Age 3). If a patient had a visit at a Cosmos-participating institution at 3 years of age, they were confirmed alive (Alive by Age 3). All remaining patients either died at another institution or were not seen within 2 years of turning 3 (Lost to Follow-Up).

Table 8.1. Comparison of birthing parent-infant dyad demographic and clinical characteristics for selected and non-selected cohort.

	Study Cohort	Not Selected Dyads
Birthing Parent Age (Years)		
Mean (SD)	30.6 (5.7)	30.9 (5.8)
Missing	86	165
Birthing Parent Race and Ethnicity		
American Indian or Alaska Native, non-Hispanic	10110 (0%)	12893 (1%)
Asian, non-Hispanic	78170 (4%)	131611 (6%)
Black or African American, nonHispanic	324228 (15%)	382951 (16%)
Native Hawaiian or Other Pacific Islander, non-Hispanic	6366 (0%)	11838 (0%)
White, non-Hispanic	1119417 (52%)	1132066 (47%)
Other Race, non-Hispanic	30904 (1%)	47362 (2%)
Multiple Races, non-Hispanic	217755 (10%)	214130 (9%)
Hispanic or Latino	378927 (17%)	458832 (19%)
Missing	445685	350058
Insurance Type		
Medicaid	585267 (23%)	588805 (22%)
Medicare	8524 (0%)	7364 (0%)
Miscellaneous/Other	1987445 (77%)	2082437 (77%)
Self-Pay	13013 (1%)	29895 (1%)
Missing	17313	33240
Preferred Language		
English	1987673 (76%)	2149257 (78%)
Spanish	142323 (5%)	188694 (7%)
Other Language	480051 (18%)	403790 (15%)
Delivery Year		
2017	304094 (12%)	374416 (14%)
2018	357570 (14%)	437264 (16%)
2019	406620 (16%)	457842 (17%)
2020	458119 (18%)	458181 (17%)

Table 8.1. Continued...

2021	514816 (20%)	485950 (18%)
2022	568828 (22%)	528088 (19%)
Delivery Method		
C-Section	800927 (31%)	844134 (31%)
Vaginal	1781643 (69%)	1868450 (69%)
Other/Missing	28992	29157
Primigravida		
No	1907214 (73%)	2047625 (75%)
Yes	704286 (27%)	694073 (25%)
Missing	62	43
Gestational Age (Weeks)		
Mean (SD)	38.6 (1.3)	38.7 (1.30)
Infant Race and Ethnicity		
American Indian or Alaska Native, non-Hispanic	8545 (0%)	12430 (0%)
Asian, non-Hispanic	69595 (3%)	124221 (5%)
Black or African American, nonHispanic	312705 (13%)	388610 (15%)
Native Hawaiian or Other Pacific Islander, non-Hispanic	5781 (0%)	11004 (0%)
White, non-Hispanic	1140702 (47%)	1179679 (45%)
Other Race, non-Hispanic	37052 (2%)	75978 (3%)
Multiple Races, non-Hispanic	386923 (16%)	316195 (12%)
Hispanic or Latino	465064 (19%)	525314 (20%)
Missing	185195	108310
Infant Sex		
Female	1252356 (48%)	1369998 (50%)
Male	1359086 (52%)	1371358 (50%)
Other/Missing	120	385
Diagnoses		
HIE	6292 (0.2%)	3564 (0.13%)
Pyrexia During Delivery	13810 (0.5%)	13265 (0.48%)
Chorioamnionitis	94635 (3.6%)	83351 (3%)
Neonatal Sepsis	18777 (0.7%)	17595 (0.64%)
CP	4803 (0.2%)	
Total	2611562	2741741

Table 8.1. Selected vs. non-selected birthing parent-infant dyad cohort characteristics, including number, percentage, and standard deviation (SD, where applicable) for birthing parent age, birthing parent race and ethnicity, insurance type, preferred language, delivery year, mode of delivery, primigravida, gestational age, infant race and ethnicity, infant sex, and diagnoses.

Table 8.2. CP Rate Ratio by HIE Severity with IPSW.

Exposure		Rate per 1000 Live Term Births	Unadjusted RR (95% CI)	Adjusted RR* (95% CI)
HIE				
	No	1.6 (1.6, 1.7)	1.00 (Ref)	1.00 (Ref)
	Mild	20.6 (12.4, 28.9)	12.6 (8.4, 18.7)	10.7 (7.2, 16.0)
	Moderate	58.0 (48.9, 67.1)	35.3 (30.1, 41.5)	28.1 (23.6, 33.5)
	Severe	338.1 (309.4, 366.9)	205.9 (188.1, 225.3)	142.8 (125.5, 162.6)
	Unspecified	93.2 (78.6, 107.9)	56.8 (48.3, 66.6)	45.9 (38.6, 54.6)
	Any	106.6 (99.0, 114.3)	64.9 (60.0, 70.2)	0.9 (43.0, 53.5)

* Adjusted for maternal age, pyrexia during delivery (secondary definition), chorioamnionitis, and neonatal sepsis

Table 8.2. Number of CP outcomes and number of live term births for each HIE severity category with IPSW. The rate of CP for each HIE severity level was computed per 1,000 live term births. Additionally, the table shows rate ratios of CP with 95% confidence intervals for each HIE severity level compared to the no HIE group ("Unadjusted RR 95% CI"). The results were adjusted for maternal age, pyrexia during labor (by secondary definition), chorioamnionitis, and neonatal sepsis ("Adjusted RR 95% CI").

Table 8.3. HIE Rate Ratio by Perinatal Inflammation/Infection with IPSW.

Exposure		Rate per 1000 Live Term Births	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
Pyrexia During Labor				
	No	1.8 (1.8, 1.9)	1.00 (Ref)	1.00 (Ref)
	Yes	5.9 (4.8, 7.1)	3.3 (2.7, 3.9)	2.8 (2.3, 3.4)*
Chorioamnionitis				
	No	1.6 (1.6, 1.6)	1.00 (Ref)	1.00 (Ref)
	Yes	9.1 (8.6, 9.6)	5.7 (5.3, 6.1)	5.1 (4.8, 5.5)*
Neonatal Sepsis				
	No	1.5 (1.5, 1.6)	1.00 (Ref)	1.00 (Ref)
	Yes	46.4 (43.6, 49.1)	30.1 (28.2, 32.1)	21.0 (19.4, 22.7)**

* Adjusted for primigravida

** Adjusted for primigravida, pyrexia during delivery, and chorioamnionitis

8.3. Number of HIE outcomes and number of live term births for each perinatal inflammation/infection diagnosis with IPSWs, e.g., pyrexia during labor, chorioamnionitis, and neonatal sepsis. The rate of HIE for each of the diagnoses was computed per 1,000 live term births. Additionally, the table shows rate ratios of HIE with 95% confidence intervals for each diagnosis compared to the respective unexposed group ("Unadjusted RR 95% CI"). Pyrexia during labor and chorioamnionitis results were adjusted for primigravida, while neonatal sepsis RR of HIE was further adjusted for pyrexia during labor and chorioamnionitis 847 ("Adjusted RR 95% CI").

Table 8.4. CP Rate Ratio by Perinatal Inflammation/Infection with IPSW.

Exposure		Rate per 1000 Live Term Births	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
Pyrexia During Labor				
	No	1.8 (1.8, 1.9)	1.00 (Ref)	--
	Yes	2.6 (1.8, 3.4)	1.4 (1.0, 2.0)	
Chorioamnionitis				
	No	1.8 (1.7, 1.9)	1.00 (Ref)	--
	Yes	2.8 (2.5, 3.2)	1.6 (1.4, 1.8)	
Neonatal Sepsis				
	No	1.7 (1.7, 1.8)	1.00 (Ref)	--
	Yes	16.7 (14.9, 18.5)	9.6 (8.6, 10.8)	

*Adjusted for pyrexia during delivery and chorioamnionitis

Table 8.4. Number of CP outcomes and number of live term births for each perinatal inflammation/infection diagnosis with IPSW, e.g., pyrexia during labor, chorioamnionitis, and neonatal sepsis. The rate of CP for each of the diagnoses was computed per 1,000 live term births. Additionally, the table shows rate ratios of CP with 95% confidence intervals for each diagnosis compared to the respective unexposed group ("Unadjusted RR 95% CI"). The rate ratio of CP for dyads with neonatal sepsis was adjusted for pyrexia during labor and chorioamnionitis ("Adjusted RR 95% CI").

Table 8.5. Adjusted interaction between HIE and Pyrexia during Labor on the Rate of CP with IPSW.

	No HIE (A = 0)		HIE (A = 1)	RR (95% CI) for A = 1 vs A = 0, within strata of B
	RR (95% CI)		RR (95% CI)	
No Fever (B = 0)	1.0 (Ref)		47.8 (43.1, 53.0)	47.8 (43.1, 53.0)
Fever (B = 1)	1.0 (0.66, 1.5)		58.4 (33.8, 100.9)	47.2 (29.1, 112.1)
RR (95% CI) for B = 1 vs. B = 0, within strata of A	1.0 (0.66, 1.5)		1.2 (0.71, 2.1)	
Measure of interaction on additive scale:	10.6 (-21.2, 42.4)	p = 0.257		
Measure of interaction on multiplicative scale:	1.2 (0.59, 2.3)	p = 0.6053		

* Adjusted for primigravida, maternal age, chorioamnionitis, and neonatal sepsis.

Table 8.5. This table is identical to Table 4.2, except that IPSW weights are added.

Table 8.6. Adjusted interaction between HIE and Chorioamnionitis on the Rate of CP with IPSW.

	No HIE (A = 0)		HIE (A = 1)	RR (95% CI) for A = 1 vs A = 0, within strata of B
	RR (95% CI)		RR (95% CI)	
No Chorio (B = 0)	1.0 (Ref)		49.6 (44.5, 55.1)	49.6 (44.5, 55.1)
Chorio (B = 1)	1.1 (0.93, 1.3)		41.2 (33.2, 51.2)	37.8 (29.2, 49.0)
RR (95% CI) for B = 1 vs. B = 0, within strata of A	1.1 (0.93, 1.3)		0.83 (0.67, 1.0)	
Measure of interaction on additive scale:	-8.4 (-17.9, 1.1)	p = 0.958		
Measure of interaction on multiplicative scale:	0.76 (0.58, 0.99)	p = 0.0492**		

* Adjusted for primigravida, maternal age, pyrexia during labor, and neonatal sepsis

** Significance level $p < 0.05$

Table 8.6. This table is identical to Table 5.2, except that IPSW weights are added.

Table 8.7. Adjusted interaction between HIE and Neonatal Sepsis on the Rate of CP with IPSW.

	No HIE (A = 0)		HIE (A = 1)	RR (95% CI) for A = 1 vs A = 0, within strata of B
	RR (95% CI)		RR (95% CI)	
No Sepsis (B = 0)	1.0 (Ref)		64.7 (58.5, 71.4)	64.7 (58.5, 71.4)
Sepsis (B = 1)	6.9 (6.0, 8.0)		87.1 (73.0, 104.0)	12.5 (10.0, 15.7)
RR (95% CI) for B = 1 vs. B = 0, within strata of A	6.9 (6.0, 8.0)		1.4 (1.1, 1.6)	
Measure of interaction on additive scale:	16.4 (0.15, 32.6)	p = 0.0239		
Measure of interaction on multiplicative scale:	s0.19 (0.15, 0.25)	p < 0.001**		

*Adjusted for primigravida, maternal age, pyrexia during labor, and chorioamnionitis ** Significance level $p < 0.05$

Table 8.7. This table is identical to Table 6.2, except that IPSW weights are added.

Table 9.1. Comparison of birthing parent-infant dyad demographic and clinical characteristics for dyads with vs. without pyrexia during labor (per either definition)

	Pyrexia during Labor (Temp.)	
	No (N = 2,524,555)	Yes (N = 87,007)
Birthing Parent Age (Years)		
Mean (SD)	30.6 (5.67)	29.1 (5.68)
Missing	77-86	10 or fewer
Birthing Parent Race and Ethnicity		
American Indian or Alaska Native, non-Hispanic	9819 (0%)	291 (0%)
Asian, non-Hispanic	73260 (4%)	4910 (7%)
Black or African American, nonHispanic	313650 (15%)	10578 (15%)
Native Hawaiian or Other Pacific Islander, non-Hispanic	6008 (0%)	358 (0%)
White, non-Hispanic	1090048 (52%)	29369 (40%)
Other Race, non-Hispanic	29634 (1%)	1270 (2%)
Multiple Races, non-Hispanic	209837 (10%)	7918 (11%)
Hispanic or Latino	360793 (17%)	18134 (25%)
Missing	431506	14179
Insurance Type		
Medicaid	564152 (22%)	21115 (24%)
Medicare	8368 (0%)	156 (0%)
Miscellaneous/Other	1922630 (77%)	64815 (75%)
Self-Pay	12690 (1%)	323 (0%)
Missing	16715	598
Preferred Language		
English	1924050 (76%)	64805 (74%)
Spanish	135821 (5%)	6576 (8%)
Other Language	464684 (18%)	15626 (18%)
Delivery Year		
2017	293220 (12%)	11039 (13%)
2018	345232 (14%)	12543 (14%)
2019	392696 (16%)	14149 (16%)
2020	443318 (18%)	15072 (17%)

Table 9.1. Continued..

2021	498801 (20%)	16308 (19%)
2022	551288 (22%)	17896 (21%)
Delivery Method		
C-Section	770223 (31%)	30704 (36%)
Vaginal	1726257 (69%)	55386 (64%)
Other/Missing	2875	917
Primigravida		
No/Missing	1867678 (74%)	39598 (46%)
Yes	656877 (26%)	47409 (54%)
Gestational Age (Weeks)		
Mean (SD)	38.6 (1.31)	39.1 (1.26)
Infant Race and Ethnicity		
American Indian or Alaska Native, non-Hispanic	8296 (0%)	249 (0%)
Asian, non-Hispanic	65377 (3%)	4218 (5%)
Black or African American, nonHispanic	302772 (13%)	9933 (12%)
Native Hawaiian or Other Pacific Islander, non-Hispanic	5472 (0%)	309 (0%)
White, non-Hispanic	1111314 (47%)	29388 (36%)
Other Race, non-Hispanic	35707 (2%)	1345 (2%)
Multiple Races, non-Hispanic	373015 (16%)	13908 (17%)
Hispanic or Latino	443179 (19%)	21885 (27%)
Missing	179423	5772
Infant Sex		
Female	1211922 (48%)	40434 (46%)
Male	1312510-1312519 (52%)	46562-46571 (54%)
Other/Missing	109-118	10 or fewer

Table 9.1. Cohort characteristics for birthing parent-infant dyad with vs. without pyrexia during labor (secondary definition), including number, percentage, and standard deviation (SD, where applicable) for birthing parent age, birthing parent race and ethnicity, insurance type, preferred language, delivery year, mode of delivery, primigravida, gestational age, infant race and ethnicity, infant sex, and diagnoses.

Table 9.2. CP Rate Ratio by HIE Severity

Exposure		CP Events	Live Births	Rate per 1000 Live Term Births	Unadjusted RR (95% CI)	Adjusted RR* (95% CI)
HIE						
	No	4304	2605270	1.7 (1.6, 1.7)	1.00 (Ref)	1.00 (Ref)
	Mild	24	1163	20.6 (12.5, 28.8)	12.5 (8.2, 18.1)	10.9 (7.1, 15.9)
	Moderate	148	2559	57.8 (48.8, 66.9)	35.0 (29.7, 40.9)	28.9 (24.4, 33.9)
	Severe	353	1055	334.6 (306.1, 363.1)	202.5 (184.7, 221.2)	148.8 (132.3, 164.9)
	Unspecified	142	1515	93.7 (79.1, 108.4)	56.7 (48.1, 66.2)	47.4 (40.1, 55.5)
	Any	667	6292	106.0 (98.4, 113.6)	64.2 (59.3, 69.3)	49.2 (44.8, 53.9)

*Adjusted for maternal age, pyrexia during delivery (secondary definition), chorioamnionitis, and neonatal sepsis

Table 9.2. Number of CP outcomes and number of live term births for each HIE severity category. The rate of CP for each HIE severity level was computed per 1,000 live term births. Additionally, the table shows rate ratios of CP with 95% confidence intervals for each HIE severity level compared to the no HIE group ("Unadjusted RR 95% CI"). The results were adjusted for maternal age, pyrexia during labor (by secondary definition), chorioamnionitis, and neonatal sepsis ("Adjusted RR 95% CI").

Table 9.3. HIE Rate Ratio by Perinatal Inflammation/Infection

Exposure		HIE Events	Live Births	Rate per 1000 Live Term Births	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
Pyrexia During Labor						
	No	5490	2524555	2.2 (2.1, 2.2)	1.00 (Ref)	1.00 (Ref)
	Yes	802	87007	9.2 (8.6, 9.9)	4.2 (3.9, 4.6)	3.7 (3.4, 4.0)*
Neonatal Sepsis						
	No	5205	2592785	2.0 (2.0, 2.1)	1.00 (Ref)	1.00 (Ref)
	Yes	1087	18777	57.9 (54.5, 61.2)	28.8 (27.0, 30.7)	19.8 (18.5, 21.3)**

* Adjusted for primigravida

** Adjusted for primigravida, pyrexia during delivery (secondary definition), and chorioamnionitis

Table 9.3. Number of HIE outcomes and number of live term births for pyrexia during labor (secondary 898 definition) and neonatal sepsis. The rate of HIE for each of the diagnoses was computed per 1,000 live 899 term births. Additionally, the table shows rate ratios of HIE with 95% confidence intervals for each diagnosis 900 compared to the respective unexposed group ("Unadjusted RR 95% CI"). Pyrexia during labor RR of HIE 901 was adjusted for primigravida, while neonatal sepsis RR of HIE was further adjusted for pyrexia during labor 902 (secondary definition) and chorioamnionitis ("Adjusted RR 95% CI").

Table 9.4. CP Rate Ratio by Perinatal Inflammation/Infection.

Exposure		CP Events	Live Births	Rate per 1000 Live Term Births	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
Pyrexia During Labor						
	No	4763	2524555	1.9 (1.8, 2.0)	1.00 (Ref)	
	Yes	208	87007	2.4 (2.1, 2.7)	1.3 (1.1, 1.5)	

Table 9.4. Number of CP outcomes and number of live term births for pyrexia during labor (secondary 906 definition). The rate of CP was computed per 1,000 live term births. Additionally, the table shows the rate 907 ratio of CP with 95% confidence intervals for pyrexia during labor compared to the unexposed group 908 ("Unadjusted RR 95% CI").

Table 9.5. Unadjusted interaction between HIE and Pyrexia during Labor on the Rate of CP.

	No HIE (A = 0)		HIE (A = 1)		RR (95% CI) for A = 1 vs A = 0, within strata of B
	N with/without outcome	RR (95% CI)	N with/without outcome	RR (95% CI)	
No Fever (B = 0)	4176/2519065	1.0 (Ref)	587/5490	64.5 (59.3, 70.0)	64.5 (59.3, 70.0)
Fever (B = 1)	128/86205	0.90 (0.75, 1.1)	80/802	60.2 (48.8, 74.2)	67.2 (51.3, 88.1)
RR (95% CI) for B = 1 vs. B = 0, within strata of A		0.90 (0.75, 1.1)		0.93 (0.75, 1.2)	
Measure of interaction on additive scale:	-4.2 (-17.7, 9.2)	p = 0.73			
Measure of interaction on multiplicative scale:	1.0 (0.78, 1.4)	p = 0.778			

Table 9.5. This table is identical to Table 4.1, except that pyrexia during labor is defined by temperature 914 (secondary definition).

Table 9.6. Adjusted interaction between HIE and Pyrexia during Labor on the Rate of CP.

	No HIE (A = 0)		HIE (A = 1)		RR (95% CI) for A = 1 vs A = 0, within strata of B
	N with/without outcome	RR (95% CI)	N with/without outcome	RR (95% CI)	
No Fever (B = 0)	4176/2519065	1.0 (Ref)	587/5490	49.3 (44.8, 54.2)	49.3 (44.8, 54.2)
Fever (B = 1)	128/86205	0.77 (0.63, 0.94)	80/802	37.2 (29.2, 47.4)	48.2 (36.6, 63.4)
RR (95% CI) for B = 1 vs. B = 0, within strata of A		0.77 (0.63, 0.94)		0.75 (0.59, 0.96)	
Measure of interaction on additive scale:	-11.9 (-21.1, -2.7)	p = 0.994			
Measure of interaction on multiplicative scale:	0.98 (0.74, 1.3)	p = 0.873			

* Adjusted for primigravida, maternal age, chorioamnionitis, and neonatal sepsis

Table 9.6. This table is identical to Table 4.2, except that pyrexia during labor is defined by temperature (secondary definition).

5. Discussion

The current study investigated the impact of PII on CP risk in infants with HIE. All types of PII examined here were independently associated with an increased risk of CP. In combination with HIE, intrapartum fever and neonatal sepsis further elevated the risk of CP compared to HIE patients without the respective PII exposure. Infants with both HIE and chorioamnionitis had a lower risk of CP than those with HIE alone.

5.1 HIE increases the risk of CP

The incidence of HIE in our cohort was approximately 0.2% or 2.4:1000 infants, which is only slightly higher than previous reports of 0.5-1.9 per 1,000 term births in the US in recent years.[52,53] The proportion of infants with HIE may be slightly overrepresented in this study due to healthy infants being lost to follow-up and excluded from analysis.

In our analysis of 2,611,562 infant-birthing parent dyads, HIE significantly increased CP risk. Across all severity levels combined, the risk increase was approximately 50-fold, with CP risk ratios rising with increasing HIE severity. Severe HIE was associated with an approximately 150fold increase in CP rate ratio, even after adjustment for potential confounders. Mild and moderate HIE were also linked to significant increases in CP risk, although the magnitude of these increases was not as large as observed for severe HIE. The adjusted rate ratios showed an almost 30-fold increase in CP risk for moderate HIE, and even mild HIE was associated with more than a 10-fold increase in CP risk. When severity of HIE was not available, e.g., unspecified HIE, we observed a 47-fold increase in CP risk.

The stepwise increase in CP risk with greater HIE severity observed here is consistent with previous reports demonstrating higher rates of CP among infants with moderate or severe HIE than among those with mild HIE.[10,36,37] Myaka-Gama et al. (2026) found that 21.4% of infants with severe HIE compared to 7.6% of infants with moderate HIE had received a CP diagnosis by 1 year of age. Similarly, AlMuqbil et al. (2023) showed a significant association between severe HIE and CP as well as an overall higher prevalence of adverse neurodevelopmental outcomes in patients with more severe cases of HIE. MRI abnormalities, including watershed, global, white matter, and basal ganglia or thalamus lesions, have been most commonly observed in infants with severe HIE.

5.2 Pyrexia during Labor increases the risk of HIE and CP

In this study, pyrexia during labor was associated with an almost 3-fold increased risk of HIE and a 1.5-fold increased risk of CP. These findings align with previous work demonstrating increases in both HIE [13,38] and CP risks in infants exposed to intrapartum fever.[37] It has been shown that both infectious and non-infectious hyperthermia induces neutrophilic infiltration of the placenta that can lead to elevated levels of proinflammatory cytokines and activation of native glial cells in the fetus.[39] This inflammatory state may render the fetal brain more susceptible to hypoxia, effectively lowering the threshold for HIE in infants exposed to maternal fever.[2,40,41] Although point estimates suggest an increased risk of CP in febrile patients with HIE compared to non-febrile patients with HIE, the difference between their respective rate ratios was not statistically significant.

5.3 Chorioamnionitis increases the risk of HIE and CP but does not increase the risk of CP in HIE patients

Our study identified chorioamnionitis as an independent risk factor for CP. Specifically, we observed that infants exposed to chorioamnionitis had a 1.7-fold higher risk of developing CP, which is consistent with previous studies reporting a positive association between the two conditions.[5,6,42,43]

Chorioamnionitis may increase the risk of CP through direct and indirect mechanisms. Infectioninduced fetal inflammatory response leads to pro-inflammatory cytokine and chemokine release that, if crossing the blood-brain barrier, can damage white matter structures and activate native microglia.[44] Additionally, the infection-sensitized brain is consequently more susceptible to other insults, such as asphyxia that may not typically result in brain damage.[19,40] Chorioamnionitis can impair placental function and fetal oxygen delivery, increasing the chances of a hypoxic-ischemic event occurring. Higher odds of the event occurring coupled with a lower threshold for the event to result in brain damage should lead to a higher rate of HIE among patients exposed to chorioamnionitis.[6,45,46] Indeed, in this investigation, chorioamnionitis was associated with a 5-fold increase in HIE risk, which, in turn, is a large risk factor for CP.

Interestingly however, amongst infants with HIE, the presence of chorioamnionitis did not significantly change the risk of developing CP. In fact, the rate of CP among infants with cooccurring HIE and chorioamnionitis was slightly lower than that among infants with HIE alone (RR_{adj} = 0.9; 95% CI: 0.71-1.0) and the sub-additive interaction between HIE and chorioamnionitis indicated that their joint effect on CP risk was smaller than the sum of their individual effects. This finding is concordant with the results from the HEAL trial, which demonstrated better neurodevelopmental outcomes at 2 years among infants exposed to chorioamnionitis in a cohort of patients with moderate and severe HIE.[11] The reduced risk of CP in patients with both HIE and chorioamnionitis suggests that the impact of HIE on CP risk may depend on the underlying etiology of the hypoxic-ischemic event. Unlike chorioamnionitis, perinatal sentinel events such as placental abruption or uterine rupture cause HIE via an acute severe disruption in cerebral oxygen flow[15], potentially leading to more severe encephalopathy and poorer long-term outcomes. This is supported by the HEAL trial, which found different and less severe brain injury patterns in HIE patients exposed to chorioamnionitis.[11] In addition to HIE associated with chorioamnionitis potentially being less severe than HIE arising from other etiologies, the overwhelming impact of HIE on CP risk may obscure the contribution of other risk factors.

5.4 Neonatal sepsis increases the risk of HIE and CP and further increases the risk of CP in HIE patients

Neonatal sepsis is a systemic inflammatory response to infection that occurs within the first 72 hours of life.[19,47] It initiates a complex, multifactorial mechanism involving blood-brain barrier disruption, hemodynamic instability, and mitochondrial dysfunction, which increases vulnerability to hypoxic-ischemic insult and promotes a self-perpetuating cycle of neuroinflammation and neuronal damage.[48–50]

Indeed, we found that neonatal sepsis was associated with a 20-fold increase in risk of HIE and a 10-fold increase in risk of CP. Previous work has found similar patterns of elevated rates of HIE [18,19] and CP in patients with culture-confirmed and probable sepsis.[8,50] Furthermore, we determined that the risk of CP was greater in infants with both neonatal sepsis and HIE, compared to those with neonatal sepsis or HIE only. The combined effect of neonatal sepsis and HIE was significantly greater than the sum of their individual effects. Thus, our work suggests that sepsis-associated hypoxic ischemic encephalopathy constitutes a significant threat to neurodevelopment.

5.5 Strengths, limitations, and future directions

The current study used a very large dataset of more than 2.5 million paired mother-baby dyads representing patients from all 50 US states. The size of our cohort allowed us to perform rigorous and comprehensive statistical analyses, including interactions between HIE and different types of PII. To our knowledge, this is the first study able to provide this level of analytical detail. Another important strength of our study is that we were able to capture and link patients' visits across Cosmos-participating institutions. Thus, it was possible to perform linkage between a patient's birth encounter at the delivery hospital and follow-up appointments in another healthcare setting, e.g., a well-child visit at a pediatric hospital at which a cerebral palsy diagnosis would be recorded. This Cosmos capability greatly limits the number of patients lost to follow-up and missed CP diagnoses. Finally, this study was able to collect important pre- and perinatal history from the birthing parent's chart that may not have been available in the infant's record, since Cosmos allows for infant and birthing parent charts to be linked. Thus, the current investigation leverages a unique opportunity for fine-grained statistical analysis of exposures and outcomes derived from the charts of different individuals, e.g., mother and baby. Even a large multi-center retrospective or prospective study would likely not be able to match the amount of data that our study is based on.

The study has several limitations. The follow up time frame we used in this study has the potential to miss children who received a later CP diagnosis, potentially due to loss of follow up, change in providers, or milder symptoms. In addition, our study excludes neonates who were stillborn or died outside of a Cosmos participating institution, but might otherwise be included in the CP cohort, had they lived. Our study also excluded those individuals who did not follow up at a Cosmos participating site within 36 months of birth; though our sensitivity analysis suggests this contributed minimal selection bias.

Another limitation of the study is the use of diagnosis codes to measure outcomes. Diagnosis codes are constructed primarily for billing purposes and can be used inconsistently in complex clinical contexts and across institutions. The diagnosis of neonatal encephalopathy is the more appropriate initial terminology for neonates with evidence of metabolic acidosis at birth and an abnormal neurologic exam until a definitive diagnosis can be made via additional testing. Hypoxic ischemic encephalopathy is a diagnosis that can result from neonatal encephalopathy when signs of hypoxia or ischemia are seen on brain MRI. Given the lack of discrete clinical data available when using such a large dataset, we relied on the diagnosis of HIE in the medical record. Future research should evaluate the number of neonates with neonatal encephalopathy and the conversion to HIE with interaction by PII. Such an analysis is more feasible via retrospective case:control cohort analysis or prospective analysis, however, the time burden required for these studies is substantially higher and with a significantly lower number of individuals available for such a study.

Similarly, analysis of the impact of PII is also limited by the accuracy of diagnostic codes attributed in the medical record for such events, and variation in how diagnosis codes for sepsis are used between hospitals may impact the analysis on the impact of neonatal sepsis. Clinical vs histological chorioamnionitis cannot be straightforwardly discriminated using the Cosmos dataset and are grouped together in this analysis. In addition, maternal fever is a criteria included in the diagnosis of chorioamnionitis, so there may be some overlap between the clinical population of pyrexia during labor and chorioamnionitis in this study. Future studies should remove dyads with both pyrexia during labor and chorioamnionitis from the pyrexia during labor group.

6. Conclusion

The current study examined the impact of PII on CP risk in infants with HIE using a large dataset of paired birthing parent-infants dyads obtained through Epic Cosmos. Analyses revealed that both PII, operationalized as maternal fever, chorioamnionitis, and neonatal sepsis, and HIE were independently associated with an increase in risk of CP. When occurring in combination with HIE, maternal fever and neonatal sepsis further increased CP risk, while chorioamnionitis decreased CP risk. Future work should seek to elucidate the cellular and molecular mechanisms involved in infection/inflammation-sensitized brain injury.

Disclosures

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