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ARTICLE

Histological chorioamnionitis and developmental outcomes in very preterm infants

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Abstract

Objective To characterize the association of histological chorioamnionitis (HCA) with neurodevelopmental outcomes in children born at <30 weeks gestation.

Study design This retrospective cohort study included infants born 2006–2012 in whom placental histopathology, neonatal outcomes, and Bayley-III assessment at age 2 years were available. We assessed the association of HCA exposure with cognitive, language, and motor delay with logistic regression models adjusted for gestational age, sex, small for gestational age and brain injury.

Results Of 1353 infants, 985 had histological and neonatal data available, and 708 infants had Bayley-III assessments. HCA-exposed infants were at higher risk of some neonatal adverse outcomes, and stage of HCA correlated with low Apgar score and early-onset sepsis. Exposure to HCA was not associated with neurodevelopmental outcomes in adjusted models including stage of HCA.

Conclusions Exposure to HCA, especially higher stage, was associated with neonatal morbidity but not with adverse neurodevelopmental outcomes at 2 years of age.

Introduction

Preterm births account for the majority of neonatal morbidity and mortality worldwide [1]. Chorioamnionitis – inflammation and neutrophil infiltration of the placental chorionic disk, chorionic and amniotic membranes, and umbilical cord – is a frequent antecedent of preterm birth and is inversely correlated with gestational age (GA) [2]. It reflects the presence of intact microbes or microbial ligands, together with maternal inflammatory mediators, in the amniotic fluid and fetal circulation. The resulting activation of the fetal immune system is detectable as increased levels of inflammatory markers in cord blood, cerebrospinal fluid, and peripheral blood of the newborn [3, 4]. This systemic inflammatory response is associated with increased risk of neonatal morbidity (including early-onset sepsis, intraventricular hemorrhage, and chronic lung disease) and mortality, and may result in structural brain injury, with adverse long-term effects [5–10]. Data on the association between chorioamnionitis and neurodevelopmental outcomes in very preterm infants are conflicting. This may partly reflect methodological heterogeneity, specifically the diagnostic criteria for chorioamnionitis (clinical vs. histological), the

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gestational and postnatal ages of the study population, methods and age of developmental assessment, and outcome definitions [6, 11, 12].

In this study we aimed to characterize the relationship between histological chorioamnionitis (HCA) and standardized neurodevelopmental outcomes in very preterm infants, with adjustment for covariates that are common in this population and may contribute to developmental impairment. We hypothesized that exposure to HCA would be predictive of adverse neonatal and neurodevelopmental outcomes, with more severe HCA having the strongest evidence of association.

Materials and methods

This single center retrospective cohort study was approved by the institutional Human Research Ethics Committee of King Edward Memorial Hospital for Women (project #4360), the only tertiary perinatal center in Western Australia (current population 2.58 million). The electronic records of all infants born between 1 January 2006, and 31 December 2012 with a gestational age (GA) of 22 + 0 to 29 + 6 weeks delivered at or transferred to the study center were assessed for availability of placental histology, neonatal, and developmental follow-up data. Infants with major congenital malformations or chromosomal aberrations associated with adverse neurodevelopmental outcomes were excluded (Fig. 1).

Placental histology was performed as part of routine clinical care from pregnancies delivering <30 weeks' GA

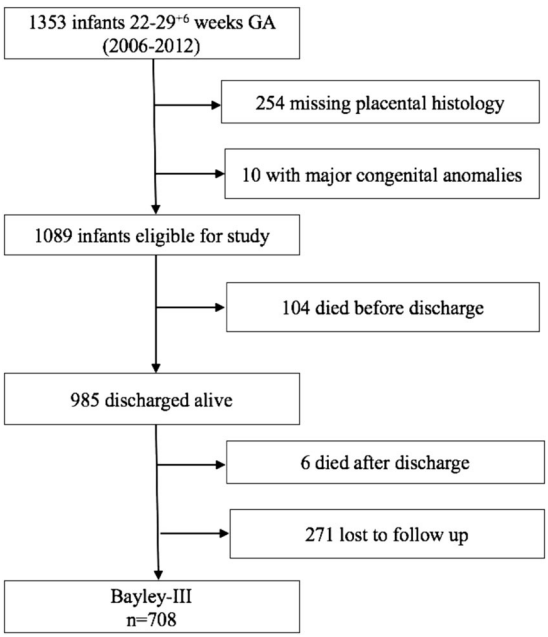

Fig. 1 Study flowchart

and reviewed by a single senior placental histopathologist who was blinded to clinical outcomes. Sections of the chorioamniotic membranes, umbilical cord, chorionic plate, and placenta were analyzed by one perinatal pathologist throughout the study period, using an adaptation of a widely accepted semi-quantitative scoring system, as previously described [13, 14]. Presence and degree of maternal inflammation was defined by neutrophilic infiltration of the cellular chorion, of the membranes or the chorionic plate. Fetal inflammation was defined by neutrophilic infiltration from the fetal vessels into the umbilical vessels or the chorionic plate vessels. Funisitis was defined as inflammation of the umbilical cord arising from the fetal vessels [15, 16]. Microbes causing chorioamnionitis are fastidious and microbiological culture of the placenta is neither routine nor standardized [17] and consequently, histologic examination remains the diagnostic gold standard [10]. Due to the aforementioned limitations, placental microbiological data were not included in the analyses.

A birth weight <10th percentile was defined as small for gestational age. Neonatal sepsis was defined by a positive culture (blood, cerebrospinal fluid and/or urine) plus antibiotic therapy for at least 5 days. Sepsis was classified by postnatal age at onset: early-onset sepsis (EOS) occurring <72 h and late-onset sepsis (LOS) occurring ≥72 h. Only cases of necrotizing enterocolitis (NEC) classified as Bell's stage II or higher were included [18]. Brain injury was defined as intraventricular hemorrhage (IVH) grade 3 or higher, and/or periventricular leukomalacia on routine cranial ultrasound scans [19, 20]. Bronchopulmonary dysplasia was defined as a supplementary oxygen requirement at age 36 weeks postmenstrual age [21]. Retinopathy of prematurity (ROP) was defined as grade 3 or higher [22]. Socio-Economic Indexes For Areas of Relative Advantage-Disadvantage (SEIFA) score based on postcodes was used as an indicator of maternal socioeconomic status, with statewide decile data available from 2006 onwards (Australian Bureau of Statistics) [23].

Developmental assessment at 24 months corrected age. The Bayley Scales of Infant and Toddler Development 3rd edition (Bayley-III) is used in the Neonatal Follow-up Program to review development of infants at 24 months corrected age. This is offered to infants born <31 weeks gestation and/or with a birthweight <1250 g. This state-wide program has follow-up rates of ~80 and 50% at 24 months for children residing in metropolitan and rural areas, respectively. The Bayley-III scales were used to assess developmental progress of infants at 24 months corrected age, individually administered under standardized conditions by a small team of trained psychologists. The cognitive, language and motor scales were submitted for analysis. The test norms for the Bayley-III fit a normal curve, with a mean of 100 and standard deviation of 15. The receptive

Table 1 Neonatal characteristics among neonates with and without Bayley III assessment data

Characteristic	Neonates with Bayley III $N = 708$		Neonates without Bayley III $N = 271$		p-value
Gestational age (w)	27.1	(±1.8)	27.3	(±1.9)	0.21
Birthweight (g)	972.0	(±278.6)	982.4	(±279.2)	0.60
Birthweight z-score	0.02	(±0.86)	−0.08	(±0.82)	0.01
SGA	63	(8.9)	27	(10.0)	0.61
Male gender	370	(52.3)	160	(59.0)	0.06
Multiple birth	179	(25.3)	64	(23.6)	0.59
Outborn	33	(4.7)	23	(8.5)	0.02
Ethnicity					
Caucasian	562	(79.8)	161	(60.1)	<0.001
Aboriginal	32	(4.5)	77	(28.7)	
Other	110	(15.6)	30	(11.2)	
SEIFA[a] (lowest 2 quintiles)	77	(11.6)	67	(29.9)	<0.001
Antenatal steroids					
None	45	(6.4)	25	(9.2)	0.2
Incomplete	193	(27.3)	64	(23.6)	
Complete	470	(66.4)	182	(67.2)	
Antenatal antibiotics	416	(58.8)	151	(55.7)	0.39
Cesarean section	418	(59.0)	152	(56.1)	0.40
Apgar <7 at 5 min	161	(22.7)	63	(23.2)	0.87
Intubation	503	(71.0)	179	(66.1)	0.13
PDA	434	(61.3)	146	(53.9)	0.03
CLD	187	(26.4)	64	(23.6)	0.37
Postnatal dexamethasone	44	(6.2)	21	(7.7)	0.39
IVH grade III–IV	33	(4.7)	16	(5.9)	0.43
ROP stage III–IV	42	(5.9)	18	(6.6)	0.68
ROP treatment	43	(6.1)	17	(6.3)	0.91
NEC stage II–III	26	(3.7)	11	(4.1)	0.78
PVL	8	(1.1)	6	(2.2)	0.23
EOS					
None	437	(61.7)	153	(56.5)	0.14
Clinical	253	(35.7)	114	(42.1)	
Confirmed	18	(2.5)	4	(1.5)	
LOS					
None	396	(55.9)	155	(57.2)	0.67
Clinical	135	(19.1)	45	(16.6)	
Confirmed	177	(25.0)	71	(26.2)	

Data summarised as mean (±sd) or n (%)

SGA small for gestational age, *SEIFA* Socio-Economic Indexes For Areas of Relative Advantage-Disadvantage, *PDA* patent ductus arteriosus, *CLD* chronic lung disease, *IVH* intraventricular hemorrhage, *ROP* retinopathy of prematurity, *NEC* necrotizing enterocolitis, *PVL* periventricular leukomalacia, *EOS* early-onset sepsis, *LOS* late-onset sepsis

[a]SEIFA data available on 666 neonates with Bayley III and 224 without Bayley III

communication, expressive communication, fine motor, and gross motor subscales also produce age-standardized scores with a mean of 10 and standard deviation of 3.

Developmental delay was defined from Bayley-III scores as follows: Scores falling between >1–2 standard deviations below the mean (i.e. composite score <85) represented a mild delay in developmental progress, scores >2–3 standard deviations below the mean (i.e. composite score <70) were considered to represent moderate to severe delay. Infants who could not be assessed due to severe impairments/delay were assigned a composite score of 40 (4 SD below the normative mean and below any achievable score).

The raw scores of the Bayley-III were initially submitted for analysis of group differences, with adjustment for age at assessment. Binary outcomes were subsequently submitted using age-standardized scores (composite and scaled scores) for group comparison of delay. Adjusted composite scores, by a factor of 7 standard points, was submitted for analysis, acknowledging the recognized overestimation of developmental composite scores of the Bayley-III [24–26]. However, adjusted composite scores did not alter the pattern of results and thus only standardized scores of the Bayley-III are reported.

Statistical analysis

Continuous data were summarised with means and standard deviations (SD) and categorical data as frequency distributions. Comparisons of continuous data between neonates with and without placental histology were made using the independent t-test; comparisons between severity of HCA groups (none, mild, and severe) utilized one-way ANOVA; and categorical comparisons were made using the Chi-square test or Fisher exact test. Logistic regression analysis was conducted to assess the effect of HCA exposure on cognitive, language and motor delay, defined as a standard composite score <85 (1 SD below the mean). Severity of HCA was initially assessed univariately, then with a priori adjustments for covariates known to be associated with poor neurodevelopmental outcomes in preterm infants including GA, sex, and SGA, and then in a model that included brain injury (IVH and/or periventricular leukomalacia).

The semiquantitiative staging system of HCA implies that a mild maternal response is the least inflammatory cellular response affecting the fetus, through severe maternal reponse to fetal reaction in the fetal vessles of the chorionic plate and cord to funisitis. The clinical outcomes were examined according to this grading system, and as the numbers allowed, also by collapsing the groups to funisitis, HCA, and no HCA.

Additional covariates included in univariate and multivariable predictive models were socioeconomic status, multiple birth, Apgar score, chronic lung disease, postnatal

Table 2A Baseline clinical characteristics and neonatal outcomes based on severity of histological chorioamnionitis

Characteristic	No HCA $N = 562$		Mild HCA $N = 208$		P* No vs mild	Severe HCA $N = 319$		P* No vs severe
Gestational age (w)	27.5	(±1.7)	26.7	(±2.0)	<0.001	26.4	(±1.9)	<0.001
Birthweight (g)	949.8	(±291.0)	995.0	(±303.6)	0.05	925.5	(±270.8)	0.23
Birthweight *z*-score	−0.29	(±0.99)	0.30	(±0.78)	<0.001	0.14	(±0.65)	<0.001
SGA	102	(18.1)	7	(3.4)	<0.001	7	(2.2)	<0.001
Male	321	(57.1)	109	(52.4)	0.24	162	(50.8)	0.07
Multiple birth	184	(32.7)	45	(21.6)	0.003	41	(12.9)	<0.001
SEIFA ($n = 996$) (lowest 2 quintiles)	74	(14.2)	40	(21.1)	0.03	42	(14.7)	0.84
Antenatal steroids								
None	51	(9.1)	14	(6.7)	0.12	21	(6.6)	0.26
Incomplete	147	(26.2)	69	(33.2)		76	(23.8)	
Complete	364	(64.8)	125	(60.1)		222	(69.6)	
Antenatal antibiotics	227	(40.4)	140	(67.3)	<0.001	256	(80.3)	<0.001
Pre-eclampsia	199	(27.9)	3	(1.3)	<0.001	–	–	<0.001
Caesaerean section	425	(75.6)	82	(39.4)	<0.001	122	(38.2)	<0.001
Apgar <7 at 5 min	114	(20.3)	54	(26.0)	0.09	111	(34.8)	<0.001
Delivery room intubation	371	(66.0)	163	(78.4)	0.001	245	(76.8)	0.001
PDA	334	(59.4)	125	(60.1)	0.87	190	(59.6)	0.97
CLD	132	(23.5)	43	(20.7)	0.41	83	(26.0)	0.4
Postnatal dexamethasone	45	(8.0)	14	(6.7)	0.55	24	(7.5)	0.8
IVH grade III–IV	31	(5.5)	24	(11.5)	0.004	33	(10.3)	0.01
ROP stage III–IV	27	(4.8)	11	(5.3)	0.78	23	(7.2)	0.14
ROP treatment	26	(4.6)	15	(7.2)	0.16	20	(6.3)	0.29
NEC Stage II–III	31	(5.5)	10	(4.8)	0.7	12	(3.8)	0.25
PVL	7	(1.2)	3	(1.4)	0.83	8	(2.5)	0.16
EOS								
None	355	(63.2)	142	(68.3)	0.01	158	(49.5)	<0.001
Clinical	200	(35.6)	58	(27.9)		149	(46.7)	
Confirmed	7	(1.2)	8	(3.8)		12	(3.8)	
LOS								
None	321	(57.1)	126	(60.6)	0.24	183	(57.4)	0.9
Clinical	105	(18.7)	28	(13.5)		56	(17.6)	
Confirmed	136	(24.2)	54	(26.0)		80	(25.1)	
Mortality								
Before discharge	56	(10.0)	21	(10.1)	0.96	27	(8.5)	0.46
Before follow up	2	(0.4)	1	(0.5)	1.000	3	(0.9%)	0.36

Data represent mean (± sd) or number (%), as appropriate.

SGA small for gestational age, *SEIFA* Socio-Economic Indexes For Areas of Relative Advantage–Disadvantage, *PDA* patent ductus arteriosus, *CLD* chronic lung disease, *IVH* intraventricular hemorrhage, *ROP* retinopathy of prematurity, *NEC* necrotizing enterocolitis, *PVL* periventricular leukomalacia, *EOS* early-onset sepsis, *LOS* late-onset sepsis

*p-values < 0.025 ($\alpha = 0.05/2$) are considered statistically significant when the Bonferroni correction is applied

dexamethasone, necrotizing enterocolitis, and neonatal sepsis. Univariate and adjusted effects were summarized as odds ratios (OR), adjusted OR (aOR), and 95% confidence intervals (CI). Strength of association between neurodevelopmental delay models were assessed using the area under the curve (AUC) constructed using probabilities generated from both the

Table 2B Neonatal outcomes based on presence of maternal with or without fetal histological chorioamnionitis and funisitis

	No HCA $N = 562$		Maternal HCA alone $N = 131$		HCA with fetal reaction $N = 171$		HCA with fetal reaction and funisitis $N = 225$		
	N	%	*N*	%	*N*	%	*N*	%	*P*
Apgar <7 at 5 mins	114	20.3	28	21.4	59	34.5 ($p < 0.001$)	78	34.7 ($p < 0.001$)	<0.001
Delivery room intubation	371	66.0	99	75.6 ($p = 0.04$)	139	81.3 ($p < 0.001$)	170	75.6 ($p = 0.01$)	<0.001
CLD	132	23.5	23	17.6	42	24.6	61	27.1	0.23
PDA	334	59.4	79	60.3	104	60.8	132	58.7	0.97
NEC	31	5.5	7	5.3	4	2.3	11	4.9	0.4
ROP III–IV	27	4.8	10	7.6	5	2.9	19	8.4	0.06
Brain injury	36	6.4	16	12.2 ($p = 0.02$)	25	14.6 ($p = 0.001$)	24	10.7 ($p = 0.04$)	0.004
EOS (any)	207	36.8	38	29.0	63	36.8	126	56.0 ($p < 0.001$)	<0.001
LOS (any)	241	42.9	51	38.9	73	42.7	94	41.8	0.87
Mortality	56	10.0	17	13.0	17	9.9	14	6.2	0.19

Data represent mean (±sd) or number (%), as appropriate. *P*-values are inserted where statistically significant pairwise comparisons occurred between no HCA and the respective category. *P*-values<0.017 ($\alpha = 0.05/3$) are considered statistically significant when the Bonferroni correction is applied.

PDA patent ductus arteriosus, *CLD* chronic lung disease, *brain injury* intraventricular hemorrhage (IVH) grade 3 or higher, and/or periventricular leukomalacia, *ROP* retinopathy of prematurity, *NEC* necrotizing enterocolitis, *EOS* early-onset sepsis, *LOS* late-onset sepsis

adjusted and multivariable predictive models.

Sample size calculation: Of 1353 births at 22 to 29 + 6 weeks gestation from 2006 and 2012, ~60% (*n*~800) were expected to attend follow-up. A sample size of $n = 800$ gives 80% power to detect odds ratios of 1.6–1.7, reflecting differences in estimated baseline rates from 13 to 21% (cognitive delay) and 21 to 30% (language delay) when the prevalence of HCA is 48%, and with adjustment for other covariates in the logistic regression model [24]. A sample size of 708 allowed us to detect, with 80% power, differences in actual rates from 7 to 14% and 28 to 38% for cognitive and language delay respectively. Statistical analysis was performed using SPSS 20.0 (IBM Corp, Armonk, NY) and *p*-values <0.05 were considered statistically significant.

Results

1353 infants born between 22–29 + 6 weeks GA and cared for at King Edward Memorial Hospital NICU between January 2006 to December 2012 were assessed for availability of relevant data (Fig. 1). Two hundred and fifty four infants were excluded as placental histology was not performed and a further ten were excluded with major congenital or chromosomal anomalies. One-hundred and four (9.6%) infants died before discharge from hospital, leaving 985 infants discharged alive with available placental histology. Of these 708 children attended Bayley-III assessments. Of these, 56 infants were born at other hospitals and transported to the tertiary center. Children who did and did not attend Bayley-III assessments had similar neonatal characteristics, except for non-attendance associated with being outborn, Aboriginal ethnicity and with lower socio-economic status (Table 1)

Neonatal outcomes

Placental histology was available in 1089 infants, of which 527 (48.4%) showed evidence of HCA. Combined maternal and fetal HCA was observed in 380 (34.9%) placentae, maternal HCA alone in 131 (12%) and fetal HCA alone in only 8 (0.7%). Funisitis was observed in 225 (20.7%) placentae, invariably with concomitant HCA.

Infants exposed to HCA were born at lower GA, more likely to be singleton and to be born via spontaneous vaginal delivery. These infants also had lower Apgar scores, were more likely to require intubation at birth, develop EOS, receive postnatal intravenous antibiotics and have high grade IVH (Tables 2A and 2B). The presence of HCA was not associated with risk of neonatal mortality univariately, nor after adjustment for covariates including antenatal steroid exposure, multiple birth, gestational age, small for gestational age, Apgar score <7 at 5 min, IVH and EOS. Short term outcomes among the sub groups of HCA showed low Apgar scores were more likely among neonates with fetal inflammation; intubation in delivery room and IVH/PVL more common among neonates any inflammation (fetal or maternal), and EOS more likely among neonates with fetal inflammation and funisitis (Table 2B).

Table 3 Developmental outcomes at corrected age 2 years. Categorical standard composite scores (scores <85 indicative of delay) are described by exposure to HCA. Raw continuous scores were also analysed with an adjustment for corrected age with no substantive change in results. Unadjusted results are presented in the table

	No HCA		Mild HCA		Severe HCA		
Bayley III	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	*p*-value
Raw scores							
Age (months)	371	24.2 (±1.2)	146	23.9 (±1.4)	191	24.2 (±1.7)	0.03
Cognitive	369	62.9 (±5.9)	142	63.2 (±5.8)	190	62.3 (±5.6)	0.33
Receptive language	349	25.1 (±6.4)	136	25.0 (±5.9)	181	24.4 (±5.8)	0.38
Expressive language	345	26.3 (±7.6)	132	26.1 (±7.7)	175	26.1 (±6.7)	0.95
Fine motor	358	39.6 (±3.3)	142	39.3 (±3.3)	186	39.7 (±3.9)	0.5
Gross motor	347	54.1 (±5.3)	136	54.1 (±4.4)	182	54.0 (±4.3)	0.98
Composite scores	*N*	*N* (%)	*N*	*N* (%)	*N*	*N* (%)	
Cognitive delay	369	23 (6.2)	143	10 (7.0)	190	13 (6.8)	0.94
Language delay	344	91 (26.5)	133	39 (29.3)	177	50 (28.2)	0.8
Motor delay	344	30 (8.7)	136	12 (8.8)	183	13 (7.1)	0.79

Neurodevelopmental outcomes

Of 979 infants with placental histology who survived to age 2 years, 708 were assessed using the Bayley-III, at a mean corrected age of 24.1 ± 1.4 months. Of those with Bayley-III assessments, 337 (47.6%) were exposed to HCA; a similar incidence to the overall cohort, and consistent with the results of our previous report [14]. There were no differences in raw scores for cognitive, language, or motor subscale scores between infants with or without HCA exposure (Table 3), nor did we observe any effects of severity or stage of HCA.

There was no evidence of association between HCA exposure and cognitive, language or motor delay, defined by standard composite scores <85, on univariate analyses or after a priori adjustments (GA, SGA, sex, and brain injury) (Table 4). Analysis of modified composite scores were similar to results for standard composite scores shown in Table 4 (data for modified scores not shown).

Logistic regression was used to derive alternative sets of risk factors predictive of neurodevelopmental delay. In addition to a priori risk factors considered in the adjusted models, the alternative multivariable predictive models for cognitive, language, and motor delay included; cognitive delay: gestational age (aOR 0.77, 95% CI 0.64–0.92), male sex (aOR 2.82, 95% CI 1.41–5.64), SGA (aOR 2.49, 95% CI 1.04–5.97), brain injury (aOR 4.27, 95% CI 1.76–10.38), and postnatal dexamethasone (aOR 2.33, 0.96–5.63); language delay: gestational age (aOR 0.85, 95% CI 0.76–0.95), male sex (aOR 2.51, 95% CI 1.73–3.76), multiple birth (aOR 1.65, 95% CI 1.11–2.46), CLD (aOR 1.77, 95% CI 1.17–2.70), and brain injury (aOR 1.96, 95% CI 0.95–4.07); motor delay: gestational age (aOR 0.81, 95% CI 0.69–0.95), male sex (aOR 1.81, 95% CI 1.01–3.27), SGA (aOR 2.53, 95% CI 1.14–5.59), and brain injury (aOR 3.48, 95% CI 1.45–8.36).

Areas under the curve were similar between the adjusted and multivariable predictive models for each outcome; cognitive delay: AUC 0.708 and 0.753, language delay: AUC 0.682 and 0.676, and motor delay: both AUC 0.687 for the predictive and adjusted models respectively. Additional risk factors including multiple birth, Apgar <7 at 5 min, sepsis, CLD and postnatal dexamethasone did not alter the findings.

Discussion

In this single center cohort study of preterm infants born before 30 weeks' GA, we found no evidence of an association between HCA and early childhood neurodevelopmental outcomes. We used the Bayley-III as a widely employed parameter of developmental outcome and assessed the effects of HCA by severity, both in univariable analyses and those adjusted for important covariates.

In addition to inducing preterm labor and delivery, chorioamnionitis often results in systemic fetal and neonatal inflammation that are plausibly associated with developmental sequelae in early childhood [27, 28]. The incidence of both HCA and adverse neurodevelopmental outcomes in this study are in keeping with those reported in similar high-risk preterm infant populations [29]. In our cohort, there was no association between exposure to HCA and poorer neurodevelopmental outcomes; these findings are in line with some recent reports [30–32]. In contrast, other studies report an association between chorioamnionitis and adverse neurodevelopmental outcomes and a meta-analysis of chorioamnionitis and cerebral palsy indicated increased risk in preterm infants with HCA [33]. These divergent findings may reflect differences in study design, including (i) type and sample size of cohort, (ii) gestational age of study population, (iii) outcome measures, and (iv) the definitions

Table 4 Univariate and adjusted results for the effect of HCA exposure and severity on developmental delay (standard composite scores <85)

				Univariate			Adjusted[a]			Adjusted[b]		
	N	*N* (%) delayed of total tested	(%) delayed of risk group	OR	95% CI	*p*-value	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Cognitive delay	702	46 (6.6)										
Any HCA	333	23 (3.3)	(6.9)	1.12	(0.61–2.03)	0.72	0.95	(0.48–1.89)	0.88	0.86	(0.43–1.74)	0.68
HCA												
None	369	23 (3.3)	(6.2)	1.00			1.00			1.00		
Mild	143	10 (1.4)	(7.0)	1.13	(0.52–2.44)	0.75	1.05	(0.46–2.43)	0.91	0.96	(0.41–2.25)	0.92
Severe	190	13 (1.9)	(6.8)	1.11	(0.55–2.23)	0.78	0.88	(0.40–1.94)	0.74	0.79	(0.35–1.79)	0.58
Language delay	654	180 (27.5)										
Any HCA	310	89 (13.6)	(28.7)	1.12	(0.79–1.58)	0.52	0.98	(0.67–1.43)	0.90	0.94	(0.64–1.39)	0.77
HCA												
None	344	91 (13.9)	(26.5)	1.00			1.00			1.00		
Mild	133	39 (6.0)	(29.3)	1.15	(0.74–1.80)	0.53	1.06	(0.66–1.70)	0.81	1.03	(0.64–1.66)	0.91
Severe	177	50 (7.6)	(28.2)	1.10	(0.73–1.64)	0.66	0.91	(0.58–1.43)	0.69	0.88	(0.56–1.39)	0.58
Motor delay	663	55 (8.3)										
Any HCA	319	25 (3.8)	(7.8)	0.89	(0.51–1.55)	0.68	0.79	(0.43–1.48)	0.47	0.73	(0.39–1.37)	0.33
HCA												
None	344	30 (4.5)	(8.7)	1.00			1.00			1.00		
Mild	136	12 (1.8)	(8.8)	1.01	(0.50–2.04)	0.97	0.98	(0.46–2.07)	0.96	0.91	(0.43–1.95)	0.81
Severe	183	13 (2.0)	(7.1)	0.80	(0.41–1.58)	0.52	0.66	(0.31–1.40)	0.28	0.60	(0.28–1.29)	0.19

[a]Adjusted for GA, SGA and gender.

[b]Adjusted for [1] and 'brain injury' (IVH/PVL)

used for exposures and outcomes and control for confounding factors such as social indices.

The fetal host responses to antenatal inflammatory stimuli are incompletely characterized. Responses differ between individuals and are influenced by the nature and duration of the inflammatory exposure, immunologic maturity and other factors. Some early complications of preterm birth linked to poorer neurodevelopmental outcomes are also associated with HCA exposure, particularly reduced GA, low Apgar score, EOS, brain injury, and possibly CLD. The individual contributions and etiologic pathways are ill-defined but likely to partly reflect shared biological mechanisms [28, 34, 35].

Antenatal steroids have broad anti-inflammatory actions and may impact on inflammation-related clinical outcomes, while their association with neurodevelopmental outcomes in the setting of chorioamnionitis remains uncertain. Administration of steroids to women in preterm labor is routine care and improves neonatal outcomes, including in infants with HCA exposure, although placental histology appears unchanged [36]. In our cohort, over 90% of mothers received antenatal steroids; variation in steroid exposure between centers may also contribute to reported differences in neurodevelopmental outcomes.

Additional established risk factors for adverse long-term neurodevelopmental outcomes, such as male sex, intrauterine growth restriction, and postnatal steroids, are not causally related to HCA [35]. It is possible that the main deleterious consequence of HCA exposure is preterm birth per se and subsequent adverse outcomes stem from biological immaturity of the infant, rather than directly from the more proximal exposure to perinatal inflammation. Alternatively, there may be a modest independent contribution of HCA to overall risk of adverse neurodevelopmental outcomes, but this is not discernable from the larger effect sizes associated with preterm birth and related morbidity and the relatively modest sample size of most studies. Moreover it is possible that severe chorioamnionitis, which is associated with stillbirth, may introduce a survival bias, such that only infants affected by less severe HCA in utero survive [37].

While findings on the effects of HCA exposure on neurodevelopmental outcomes are variable, several studies highlight the association between infection-related inflammation in early life and increased risk for brain injury and developmental delay and/or disability [10, 38–40]. The apparent differential effects of ante- and early postnatal inflammation may be partly due to the lower virulence and inflammatory potential of the most common pathogens in HCA (Mycoplasma and Ureaplasma spp, which may occur without positive microbiology using standard techniques), in contrast to the etiological agents and consequent inflammation from neonatal sepsis.

Our study has several strengths, including a contemporaneous post-surfactant era cohort that was treated at the sole regional tertiary perinatal center serving a defined population. Further strengths include routine reporting of semiquantitative placental histology, availability of clinical data collected routinely for relevant outcomes, and developmental assessment by commonly used outcome measures performed by a small team of psychologists blinded to HCA exposure. Placental histology was scored without reference to any outcome parameter. Our study has some unavoidable limitations, including the lack of laboratory markers supporting the presence, magnitude, and duration of fetal and neonatal inflammation, although these routine markers generally lack sensitivity and specificty for HCA [41]. Data on maternal infection during earlier stages of the pregnancy were not available. Approximately one quarter of infants did not attend developmental assessment, and given the limited resources for routine follow up and the vast geographical area of Western Australia, this is an unvoidable limitation. Children from disadvantaged backgrounds and of rural residence were more likely to miss developmental assessments, leading to inevitable selection bias. The overall rates of routine follow up described are in line with recent reports [42]. Results from this single center study may not be generalizable and warrant replication. This includes developmental assessment later in childhood as we cannot exclude HCA may increase the risk of impairment at advanced stages of development. While our sample size allowed adjustment for important covariates, there may be other unmeasured confounders.

In conclusion, this retrospective cohort study indicates that exposure to HCA increases risk of neonatal morbidity, but is not associated with adverse neurodevelopmental outcomes. Further studies should focus on identifying other modifiable factors.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Blencowe H, Cousens S, Oestergaard MZ, Chou D, Moller AB, Narwal R, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. Lancet. 2012;379:2162–72. (9832)
2. Lahra MM, Jeffery HE. A fetal response to chorioamnionitis is associated with early survival after preterm birth. Am J Obstet Gynecol. 2004;190:147–51.(1)

3. Hecht JL, Fichorova RN, Tang VF, Allred EN, McElrath TF, Leviton A. Relationship between neonatal blood protein concentrations and placenta histologic characteristics in extremely low GA newborns. Pediatr Res. 2011;69:68–73.(1)
4. Leviton A, Hecht JL, Allred EN, Yamamoto H, Fichorova RN, Dammann O. Persistence after birth of systemic inflammation associated with umbilical cord inflammation. J Reprod Immunol. 2011;90:235–43.(2)
5. Soraisham AS, Trevenen C, Wood S, Singhal N, Sauve R. Histological chorioamnionitis and neurodevelopmental outcome in preterm infants. J Perinatol. 2013;33:70–5.(1)
6. von Ehrenstein OS, Neta GI, Andrews W, Goldenberg R, Goepfert A, Zhang J. Child intellectual development in relation to cytokine levels in umbilical cord blood. Am J Epidemiol. 2012;175:1191–9.(11)
7. Hatfield T, Wing DA, Buss C, Head K, Muftuler LT, Davis EP. Magnetic resonance imaging demonstrates long-term changes in brain structure in children born preterm and exposed to chorioamnionitis. Am J Obstet Gynecol. 2011;205:384 e1–8.(4)
8. Rovira N, Alarcon A, Iriondo M, Ibanez M, Poo P, Cusi V, et al. Impact of histological chorioamnionitis, funisitis and clinical chorioamnionitis on neurodevelopmental outcome of preterm infants. Early Hum Dev. 2011;87:253–7.(4)
9. Shatrov JG, Birch SC, Lam LT, Quinlivan JA, McIntyre S, Mendz GL. Chorioamnionitis and cerebral palsy: a meta-analysis. Obstet Gynecol. 2010;116:387–92.(2 Pt 1)
10. Leviton A, Allred EN, Kuban KC, Hecht JL, Onderdonk AB, O'Shea TM, et al. Microbiologic and histologic characteristics of the extremely preterm infant's placenta predict white matter damage and later cerebral palsy. the ELGAN study. Pediatr Res. 2010;67:95–101.
11. Ylijoki M, Ekholm E, Haataja L, Lehtonen L. Is chorioamnionitis harmful for the brain of preterm infants? A clinical overview. Acta Obstet Gynecol Scand. 2012;91:403–19.
12. Pugni L, Pietrasanta C, Acaia B, Merlo D, Ronchi A, Ossola MW, et al. Chorioamnionitis and neonatal outcome in preterm infants: a clinical overview. J Matern Fetal Neonatal Med. 2016;29:1525–9.
13. Redline RW, Faye-Petersen O, Heller D, Qureshi F, Savell V, Vogler C. Amniotic infection syndrome: nosology and reproducibility of placental reaction patterns. Pediatr Dev Pathol. 2003;6:435–48.
14. Strunk T, Doherty D, Jacques A, Simmer K, Richmond P, Kohan R, et al. Histologic chorioamnionitis is associated with reduced risk of late-onset sepsis in preterm infants. Pediatrics. 2012;129:e134–41.
15. Kim CJ, Romero R, Chaemsaithong P, Chaiyasit N, Yoon BH, Kim YM. Acute chorioamnionitis and funisitis: definition, pathologic features, and clinical significance. Am J Obstet Gynecol. 2015;213:S29–52. (4 Suppl)
16. Khong TY, Mooney EE, Ariel I, Balmus NC, Boyd TK, Brundler MA, et al. Sampling and definitions of placental lesions: amsterdam placental workshop group consensus statement. Arch Pathol Lab Med. 2016;140:698–713.
17. Hendson L, Russell L, Robertson CM, Liang Y, Chen Y, Abdalla A, et al. Neonatal and neurodevelopmental outcomes of very low birth weight infants with histologic chorioamnionitis. J Pediatr. 2011;158:397–402.
18. Bell MJ, Ternberg JL, Feigin RD, Keating JP, Marshall R, Barton L, et al. Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. Ann Surg. 1978;187:1–7.
19. Schmidt B, Asztalos EV, Roberts RS, Robertson CM, Sauve RS, Whitfield MF, et al. Impact of bronchopulmonary dysplasia, brain injury, and severe retinopathy on the outcome of extremely low-birth-weight infants at 18 months: results from the trial of indomethacin prophylaxis in preterms. JAMA. 2003;289:1124–9.
20. Papile LA, Munsick-Bruno G, Schaefer A. Relationship of cerebral intraventricular hemorrhage and early childhood neurologic handicaps. J Pediatr. 1983;103:273–7.
21. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. Am J Respir Crit Care Med. 2001;163:1723–9.
22. Chen ML, Guo L, Smith LE, Dammann CE, Dammann O. High or low oxygen saturation and severe retinopathy of prematurity: a meta-analysis. Pediatrics. 2010;125:e1483–92.
23. Pink B. Socio-economic indexes for areas (SEIFA). Australian Bureau of Statistics. Canberra; 2013.
24. Anderson PJ, De Luca CR, Hutchinson E, Roberts G, Doyle LW. Victorian Infant Collaborative Group Underestimation of developmental delay by the new Bayley-III Scale. Arch Pediatr Adolesc Med. 2010;164:352–6.
25. Moore T, Johnson S, Haider S, Hennessy E, Marlow N. Relationship between test scores using the second and third editions of the Bayley Scales in extremely preterm children. J Pediatr. 2012;160:553–8.
26. Silveira RC, Filipouski GR, Goldstein DJ, O'Shea TM, Procianoy RS. Agreement between Bayley Scales second andthird edition assessments of very low-birth-weight infants. Arch Pediatr Adolesc Med. 2012;166:1075–6.
27. Dammann O, Leviton A. Intermittent or sustained systemic inflammation and the preterm brain. Pediatr Res. 2014;75:376–80.
28. O'Shea TM, Allred EN, Dammann O, Hirtz D, Kuban KC, Paneth N, et al. The ELGAN study of the brain and related disorders in extremely low gestational age newborns. Early Hum Dev. 2009;85:719–25.
29. Chawla S, Natarajan G, Shankaran S, Pappas A, Stoll BJ, Carlo WA, et al. Association of neurodevelopmental outcomes and neonatal morbidities of extremely premature infants with differential exposure to antenatal steroids. JAMA Pediatr. 2016;170:1164–72.
30. Huetz N, Triau S, Leboucher B, Sentilhes L, Hanf M, Nguyen S, et al. Association of severe placental inflammation with death prior to discharge and cerebral palsy in preterm infants. BJOG. 2016;123:1956–63.
31. van Vliet EO, de Kieviet JF, van der Voorn JP, Been JV, Oosterlaan J, van Elburg RM. Placental pathology and long-term neurodevelopment of very preterm infants. Am J Obstet Gynecol. 2012;206:489 e1–7.(6)
32. Schlapbach LJ, Ersch J, Adams M, Bernet V, Bucher HU, Latal B. Impact of chorioamnionitis and preeclampsia on neurodevelopmental outcome in preterm infants below 32 weeks gestational age. Acta Paediatr. 2010;99:1504–9.
33. Shi Z, Ma L, Luo K, Bajaj M, Chawla S, Natarajan G, et al. Chorioamnionitis in the Development of Cerebral Palsy: A Meta-analysis and Systematic Review. Pediatrics Jun 2017;139(6) e20163781; https://doi.org/10.1542/peds.2016-3781.
34. Jacobsson B, Hagberg G, Hagberg B, Ladfors L, Niklasson A, Hagberg H. Cerebral palsy in preterm infants: a population-based case-control study of antenatal and intrapartal risk factors. Acta Paediatr. 2002;91:946–51.
35. Linsell L, Malouf R, Morris J, Kurinczuk JJ, Marlow N. Prognostic factors for poor cognitive development in children born very preterm or with very low birth weight: a systematic review. JAMA Pediatr. 2015;169:1162–72.
36. Sawady J, Mercer BM, Wapner RJ, Zhao Y, Sorokin Y, Johnson F, et al. The National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network Beneficial Effects of Antenatal Repeated Steroids study: impact of repeated doses of antenatal corticosteroids on placental growth and histologic findings. Am J Obstet Gynecol. 2007;197:281 e1–8.(3)
37. Reddy UM, Goldenberg R, Silver R, Smith GC, Pauli RM, Wapner RJ, et al. Stillbirth classification--developing an international consensus for research: executive summary of a National

Institute of Child Health and Human Development workshop. Obstet Gynecol. 2009;114:901–14.
38. Bright HR, Babata K, Allred EN, Erdei C, Kuban KCK, Joseph RM, et al. Neurocognitive outcomes at 10 years of age in extremely preterm newborns with late-onset bacteremia. J Pediatr. 2017;187:43–9.
39. Allred EN, Dammann O, Fichorova RN, Hooper SR, Hunter SJ, Joseph RM, et al. Systemic inflammation during the first postnatal month and the risk of attention deficit hyperactivity disorder characteristics among 10 year-old children born extremely preterm. J Neuroimmune Pharmacol. 2017;12:531–43.
40. Dammann O, Allred EN, Fichorova RN, Kuban K, O'Shea TM, Leviton A, et al. Duration of systemic inflammation in the first postnatal month among infants born before the 28th week of gestation. Inflammation. 2016;39:672–7.
41. Howman RA, Charles AK, Jacques A, Doherty DA, Simmer K, Strunk T, et al. Inflammatory and haematological markers in the maternal, umbilical cord and infant circulation in histological chorioamnionitis. PLoS ONE. 2012;7:e51836.
42. Gnanendran L, Bajuk B, Oei J, Lui K, Abdel-Latif ME, Network N. Neurodevelopmental outcomes of preterm singletons, twins and higher-order gestations: a population-based cohort study. Arch Dis Child Fetal Neonatal Ed. 2015;100:F106–14.