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Abstract

Objective To assess the association between clinical chorioamnionitis and neurodevelopmental disorders at 5 years of age in children born preterm.

Study design EPIPAGE 2 is a national, population-based cohort study of children born before 35 weeks of gestation in France in 2011. We included infants born alive between 24^{+0} and 34^{+6} weeks following preterm labor (PTL) or preterm premature rupture of membranes (PPROM). Clinical chorioamnionitis was defined as maternal fever before labor (>37.8°C) with at least two of the following criteria: maternal tachycardia, hyperleukocytosis, uterine contractions, purulent amniotic fluid, or fetal tachycardia. The primary outcome was a composite including cerebral palsy, coordination disorders, cognitive disorders, sensory disorders, or behavioral disorders. We also analyzed each of these disorders separately as secondary outcomes. We performed a multivariable analysis using logistic regression models. We accounted for the non-independence of twins and missing data by generalized estimating equation models and multiple imputations, respectively.

Results Among 2927 children alive at 5 years of age, 124 (3%) were born in a context of clinical chorioamnionitis. Overall, 8.2% and 9.6% of children exposed and unexposed respectively to clinical chorioamnionitis had moderate-to-severe neurodevelopmental disorders. After multiple imputations and multivariable analysis, clinical chorioamnionitis was not associated with the occurrence of moderate-to-severe neurodevelopmental disorders (adjusted odds ratio = 0.9, 95%CI: 0.5-1.8).

Conclusion We did not find any association between clinical chorioamnionitis and neurodevelopmental disorders at 5 years of age in children born before 35 weeks of gestation after PTL or PPROM.

Neurodevelopmental disorders, which affect motor, cognitive and behavioral domains, concern up to 3% of children under 5 years of age (1). The leading cause of neurodevelopmental disorders before 5 years of age is preterm birth (2). At 5 years of age, moderate or severe neurodevelopmental disorders affect 12% of children born at 34 weeks of gestation and 28% of children born at 24 weeks (3). These disorders represent a personal and social burden for children, families, societies as well as healthcare and education systems (4,5).

Several studies have investigated the determinants of neurodevelopmental disorders in children born preterm (2,3,6–10). The main risk factor identified was early gestational age (2,3). Fetal growth restriction (FGR) and clinical chorioamnionitis were also found as risk factors (10–16). However, most studies were monocentric, with small samples, and did not differentiate between the different causes of prematurity (10). Indeed, there are distinct clinical pathways leading to preterm birth, with specific obstetrical complications, modes of delivery and neonatal outcomes (17). With FGR, placental insufficiency often leads to medically induced prematurity. In contrast, with clinical chorioamnionitis, inflammation mostly leads to spontaneous prematurity, with more vaginal deliveries and less perinatal mortality than with FGR (17,18). Thus, analyzing all causes of preterm birth together implies a risk of confounding bias because adverse outcomes are induced by different pathways that depend on the cause of prematurity (17–19). Such analysis also seems inappropriate because chorioamnionitis is almost never found in the context of FGR (19).

Clinical chorioamnionitis with elevated fetal cytokine levels may be harmful for the fetus, especially for cerebral white matter (20–23). In previous research, we found an association between clinical chorioamnionitis and cerebral palsy at 2 years of age (24). However, evaluating neurodevelopmental domains at 2 years of age is difficult, especially for the language and behavioral domains (3). A precise assessment of the child's neurodevelopment

at 5 years of age would allow for implementing prevention strategies such as early detection of disorders and specialized care. Indeed, early treatment may limit or even correct subsequent neurodevelopmental sequelae (25,26).

We aimed to investigate the association between clinical chorioamnionitis and neurodevelopmental disorders at 5 years of age in children born preterm.

Methods

This is a secondary analysis of the national prospective population-based EPIPAGE 2 cohort (*Etude épidémiologique sur les petits âges gestationnels*) (27). All births from 22 to 34 weeks of gestation in all maternity units in 25 of 26 French regions in 2011 were eligible for inclusion. Infants alive at 5 years were invited for neurodevelopmental assessment. To obtain reference data for the developmental tests used in the EPIPAGE 2 cohort, a sample of 600 children born at term from the ELFE cohort (*Étude Longitudinale Française depuis l'Enfance*) was assessed with the EPIPAGE 2 follow-up protocol (3). Assessments at 5 years included an interview with parents, a self-administered parental questionnaire, a clinical examination by a pediatrician, and an evaluation by a psychologist. Pediatricians and psychologists were trained to ensure homogeneity in their evaluations. Assessments followed family information and written consent. This study was approved by the National Data Protection Authority (CNIL DR-2016-290) and appropriate ethics committees (Consultative Committee on the Treatment of Data on Personal Health for Research Purposes, reference no. 16.263; Committee for the Protection of People Participating in Biomedical Research, reference 2016- A00333-48) (3).

We included all children born alive between 24^{+0} and 34^{+6} weeks of gestation from singleton or twin pregnancies and born after preterm labor with intact membranes or preterm premature rupture of membranes (PPROM) (Figure 1). We excluded children born after maternal hypertensive disorders, fetal growth restriction, or placental abruption because clinical chorioamnionitis is rare in these contexts of preterm birth (18,19). Children born before 24 weeks were excluded because comfort care was usually provided for these children in France in 2011 (28). We also excluded children with pathologies that could be associated with neurodevelopmental disorders, independent of chorioamnionitis: fetuses with severe congenital malformations, prenatal infections (cytomegalovirus or toxoplasmosis), triple or quadruple pregnancies, and twin pregnancies with twin-twin transfusion syndrome (based on prenatal

ultrasonography findings), or intrauterine fetal death of one co-twin. Finally, we excluded children with missing data for clinical chorioamnionitis.

Clinical chorioamnionitis was defined according to the Gibbs criteria as the presence of maternal fever (> 37.8°C) before labor associated with at least two criteria among maternal tachycardia (> 100 beats/min), hyperleukocytosis (> 15 G/L), uterine pain or contractions, purulent or fetid amniotic fluid, and fetal tachycardia (> 160 beats/min) (29).

Our primary outcome was neurodevelopmental disorders at 5 years, a composite outcome including the presence of cerebral palsy, coordination disorders, sensory impairment, cognitive disorders or behavioral disorders, and classified as no or mild abnormalities versus moderate-to-severe abnormalities (3,30–34). Secondary outcomes were the different items of the composite outcome studied separately. The description and classification of variables used to describe neurodevelopment and classification of neurodevelopmental disabilities are in Table I (available online). Gestational age was determined from early ultrasound assessment and/or last menstrual period.

Statistical Analyses

We performed a descriptive analysis of the population according to clinical chorioamnionitis, using chi-squared test for categorical variables and Student's t-test for continuous variables. Different recruitment periods (used to obtain good power despite the low incidence of extremely preterm births) were considered by weighting: at 24-26 weeks by a factor of 1, at 27-31 weeks by a factor of 1.34 (35/26) and at 32-34 weeks by a factor of 7 (35/5) (27). Logistic regression assessed the association between clinical chorioamnionitis and neurodevelopmental disorders at 5 years. In a first model, we adjusted for only gestational age of birth, as a major prognostic factor of neurodevelopment. In a second model, we used multivariable analysis considering the confounding factors identified after construction of a directed acyclic graph. In addition to gestational age at birth, we adjusted for socio-professional category of the

household, maternal education, maternal country of birth, maternal obesity (defined by body mass index ≥ 30 kg/m^2), smoking during pregnancy, premature rupture of membranes, and multiple pregnancies. We did not adjust for severe neonatal morbidities because they were intermediate factors in the association between clinical chorioamnionitis and neurodevelopment. To account for the non-independence of twins, we used generalized estimating equation models with an independent working correlation structure to study neurodevelopmental disorders. We accounted for missing data during follow-up stages by multiple imputations methods. Missing data were considered missing at random. Variables in the imputation model included both those potentially predicting non-response and those predicting outcomes. We included a large number of predictors to ensure the "missing-at-random" assumption during imputation and for reliability of the imputed results. We generated 50 datasets, imputed with 25 iterations each, and combined the results following Rubin's rules (35). We performed several sensitivity analyses. First, we restricted the population to children born before 32 weeks because clinical chorioamnionitis and neurodevelopmental disorders are more frequent in this subgroup. We performed a second sensitivity analysis using a less restrictive exposure that reflected an underlying inflammatory process: maternal hyperthermia before labor (T° > 37.8°C) or during labor (T° ≥ 38°C). Third, we explored the definition of suspected Triple I including hyperthermia with at least 1 of the following criteria: fetal tachycardia, hyperleukocytosis, or purulent amniotic fluid (36). Finally, we presented the complete cases analyses.

To account for the competitive risk between death and neurodevelopmental disorders, we studied the occurrence of death or moderate-to-severe neurodevelopmental disorders between birth and 5 years of age according to clinical chorioamnionitis (Table IV). Statistical analyses were performed using R.4.0.3 software. All tests were two-sided; $P < 0.05$ was considered statistically significant.

Results

Among 2927 children alive at age 5, 124 (3.0%) were born in the context of clinical chorioamnionitis (Figure 1; Table I). Maternal, obstetric and neonatal characteristics are presented in Table II. Most maternal or obstetric characteristics were similar between children born with and without chorioamnionitis. However, children born with clinical chorioamnionitis (vs those without) more frequently had mothers with obesity, PPROM and birth weight ≤ 1500 g. In addition, the median gestational age was significantly lower for children born with than without clinical chorioamnionitis (31 weeks [interquartile range 29-33] vs 33 weeks [31-34]). Early-onset sepsis was more frequent in children born with than without clinical chorioamnionitis (5.5% vs 1.2%), with no difference in late-onset sepsis (Table I). Finally, the frequency of severe neonatal morbidities did not significantly differ between children born with and without clinical chorioamnionitis (10% vs 5.6%) (Table I).

Compared with children assessed at 5 years, those lost to follow-up more often had younger mothers who were born in countries outside Europe and had lower socio-professional status and children had higher gestational age at birth (Table III, available online). However, the two groups did not differ in exposure to clinical chorioamnionitis (3.0% vs 3.1%), severe neonatal morbidity (5% vs 6%) or outcomes at 2 years, in particular for cerebral palsy (2.1% vs 2.3%) and Ages and Stages Questionnaire score below threshold (35% vs 34%).

Neurodevelopmental Outcomes

Among the 2927 children who survived to 5 years, 1726 had a complete neurodevelopmental assessment. Among children born in the context of clinical chorioamnionitis, 8.2% had moderate-to-severe neurodevelopmental disorders compared with 9.6% of children not born in the context of clinical chorioamnionitis (Table IV). After multiple imputations and

multivariable analysis, we found no association between clinical chorioamnionitis and the occurrence of moderate-to-severe neurodevelopmental disorders (aOR_2 = 0.9, 95% CI: 0.5-1.8). Regarding secondary outcomes, clinical chorioamnionitis was not associated with the occurrence of cerebral palsy, coordination disorders, cognitive impairment or behavioral difficulties (Table IV).

In the delivery room, the mortality rate was higher for children born with than without clinical chorioamnionitis, even after adjustment for gestational age (5.5% vs 1.2%; aOR = 2.5, 95%CI: 1.4-4.6) (Table V). During hospitalization in the neonatal intensive care unit or between discharge and 5 years of age, mortality did not significantly differ between the two groups after adjusting for gestational age at birth. Finally, clinical chorioamnionitis was not associated with the composite outcome: neurodevelopmental disorders or death at 5 years of age after multiple imputations on univariable analysis (25.6% vs 17.1%; OR = 1.5, 95%CI: 0.8-2.6) and after adjustment for gestational age (aOR = 1.1, 95%CI: 0.7-1.8) (Table VI).

Sensitivity Analyses are reported in Table VII (available online)

We found no association between clinical chorioamnionitis and neurodevelopmental disorders for children born before 32 weeks of gestation (aOR_3 = 1.0, 92%CI: 0.5-2.3).

There was no association between hyperthermia before and during labor and neurodevelopmental disorders (aOR_4 = 0.8, 95%CI: 0.4-1.7), nor with coordination disorders (aOR_3 = 1.7, 95%CI: 0.6-4.7; aOR_4 = 1.9, 95%CI: 0.9-4.3). Furthermore, we observed no associations between suspected Triple I and neurodevelopmental disorders (aOR_5 = 0.9, 95%CI: 0.4-2.6). Finally, clinical chorioamnionitis was not associated with moderate-to-severe neurodevelopmental disorders in the complete cases analysis (aOR_6 = 1.2, 95%CI: 0.4-3.6). Thus, the sensitivity analyses showed results similar to the main analysis.

Discussion

Antenatal exposure to clinical chorioamnionitis was not associated with neurodevelopmental disorders at 5 years of age in children born at 24 to 34 weeks of gestation regardless of the model or outcome used.

The potential association between clinical chorioamnionitis and neurodevelopment is controversial. Few small studies have investigated 5-year outcomes according to clinical chorioamnionitis (12–15). Two case–control studies did not find any association between clinical chorioamnionitis and cerebral palsy after 4 years (12,15). Only one study evaluated neurodevelopment at 5 years with the evaluation of cerebral palsy and WPPSI-IV in a cohort of 197 children (14). The authors found no association between clinical chorioamnionitis and neurodevelopmental disorders. Some of these studies chose not to adjust for gestational age at birth, considered an intermediate factor (14). Our choice to adjust for this variable results from our study question: we studied whether, independent of gestational age at birth, clinical chorioamnionitis was an additional risk factor for neurodevelopmental disorders. Therefore, we had to control for gestational age of birth, which is a major prognostic factor of neurodevelopment (2,3,37). A previous study of our group showed an association between clinical chorioamnionitis and cerebral palsy at 2 years of age (aOR = 2.13, 95% CI: 1.12-4.05), which was not confirmed at 5 years of age (24). This reassuring finding mirrors that before age 3: mental and motor development are still intermingled, and delays may not predict impaired development (38). As such, a mild or moderate delay in acquisition at 2 years may evolve favorably at 5 years, either spontaneously or after adequate care such as physiotherapy (38). Moreover, the method of evaluating the child differed between these two follow-up evaluations: cerebral palsy at 5 years was diagnosed by specifically trained teams, whereas at 2 years, it was a declarative diagnosis by the attending physician (3,7).

A major strength of this study is that EPIPAGE 2 is a large national prospective population-based cohort, with 93% participation rate at birth, giving good external validity to our results. Our sample of 2927 children evaluating the consequences of clinical chorioamnionitis at 5 years is one of the largest study so far (10,39). The assessment performed at 5 years was standardized and performed by specifically trained physicians and psychologists. To study the effect of inflammation on the fetus, we included a homogeneous group of patients who differed only by the presence or absence of clinical chorioamnionitis at birth in order to avoid confounding bias due to another underlying cause of fetal morbidity.

Our study should be interpreted in light of its limitations. The proportion of lost to follow-up was about 40% at 5 years of age. To limit the number of children lost to follow-up, we maintain regular contact with families to keep them informed of the study's progress, notably through newsletters. Additionally, we have made several attempts to contact parents of children lost to follow-up by email and phone. We were able to characterize our missing data and found no differences in exposure between our sample and children lost to follow-up. We controlled for this attrition bias by performing multiple imputations. The results of the multiple imputations and the complete cases analysis gave similar ORs, with narrower 95% CIs for the multiple imputations, which reflects the robustness of our results. We used the Gibbs criteria to define clinical chorioamnionitis, first, because it is clearly defined and widely used in previous studies (29,40) and second, because it is useable in current practice in France, unlike the Triple I diagnosis, which requires amniocentesis (36,40). In this study, we chose to differentiate the investigation of clinical chorioamnionitis and histological chorioamnionitis. Indeed, although placental histology serves as a definitive diagnosis for intrauterine inflammation, because it is only available after delivery, it is less applicable to ante-partum decision-making. In this study, we aimed to adopt a clinical perspective. Also, we explored other definitions of the exposure

reflecting underlying inflammation. Even with a broader definition of clinical chorioamnionitis, our results remained coherent.

Theoretically, clinical chorioamnionitis may lead to neurodevelopmental disorders because of inflammation, particularly pro-inflammatory cytokines, in the fetal and neonatal brain (41–44). However, clinical chorioamnionitis represents only a small part of potentially deleterious inflammatory processes (45). To have a more complete representation of the risks of perinatal inflammation on neurodevelopment, these results need confirmation, by considering all the inflammatory processes such as histological chorioamnionitis found on placental histology or early-onset sepsis associated with a strong inflammatory response (45,46). Assessing potential cognitive or behavioral disorders at 5 years of age would allow for early management before entering elementary school. The improvement observed for cerebral palsy between 2 and 5 years of age also encourages us to investigate whether this trend is confirmed at 10 years.

In summary, we did not find any association between exposure to clinical chorioamnionitis and neurodevelopmental disorders at 5 years of age among children born before 35 weeks of gestation. These reassuring results for parents and clinicians need to be confirmed by studying other components of perinatal inflammation.

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Table 2: Maternal, obstetrical and neonatal characteristics according to clinical chorioamnionitis

	Children alive at 5 years N = 2927	Clinical chorioamnionitis		P-value
		No N = 2803 (97.0%) n (%*)	Yes N = 124 (3.0%) n (%*)	
Maternal characteristics				
Age (years) (n = 2927)				0.72
<25	503 (15.2)	479 (15.1)	24 (18.4)	
25-35	1961 (69.0)	1885 (69.1)	76 (65.3)	
>35	463 (15.9)	439 (15.9)	24 (16.3)	
Maternal country of birth (n = 2902)				0.14
Europe	2373 (83.6)	2280 (83.7)	93 (81.8)	
North Africa	209 (6.7)	200 (6.7)	9 (4.6)	
Other African countries	193 (5.8)	180 (5.6)	13 (10.7)	
Other	127 (3.9)	121 (4.0)	6 (2.9)	
Parents' socio-professional category (n = 2782)				0.16
Professional	635 (22.9)	613 (23.0)	22 (22.2)	
Intermediate	577 (21.7)	553 (21.7)	24 (20.9)	
Administrative, public service, self-employed, students	779 (28.2)	751 (28.4)	28 (20.6)	
Service workers	363 (13.4)	348 (13.4)	15 (12.0)	
Manual workers	330 (10.7)	307 (10.4)	23 (20.4)	
Unemployed	98 (3.1)	90 (3.1)	8 (4.0)	
Social security program (n = 2669)				0.47
Social security	2374 (89.2)	2279 (89.4)	95 (83.8)	
Universal health coverage	230 (8.0)	216 (7.9)	14 (12.6)	
State medical aid or none	65 (2.7)	63 (2.7)	2 (3.6)	
Smoking during pregnancy (n = 2832)	631 (20.6)	606 (20.8)	25 (14.4)	0.13
Body mass index $\geq$ 30 kg/m^2 (n = 2695)	353 (12.1)	325 (11.9)	28 (19.2)	<0.001
Obstetric characteristics				
Multiparity (n = 2895)	1332 (45.2)	1263 (45.5)	69 (47.1)	0.76
PPROM (n = 2898)	1247 (42.9)	1158 (42.1)	89 (67.7)	<0.001
Multiple pregnancy (n = 2927)	1083 (38.5)	1046 (38.5)	37 (38.0)	0.93
Antenatal corticosteroids ** (n = 2816)	2244 (74.7)	2146 (74.7)	98 (75.9)	0.80
Cesarean section (n = 2903)	1385 (43.7)	1316 (43.4)	69 (52.3)	0.17
Neonatal characteristics				
Male sex (n = 2927)	1581 (54.9)	1512 (55.0)	69 (53.5)	0.81
Gestational age (weeks) (n = 2927)				<0.001
<28	649 (8.5)	606 (8.2)	43 (18.8)	
28-31	1442 (22.8)	1379 (22.5)	63 (32.7)	
32-34	836 (68.7)	818 (69.4)	18 (48.5)	
Median (IQR) Gestational age (weeks)	33 (31-34)	33 (31-34)	31 (29-33)	0.008
Birth weight (g) (n = 2927)				0.005
<1000	533 (6.9)	502 (6.7)	31 (12.6)	
1000-1500	1034 (19.3)	990 (19.0)	44 (27.2)	
>1500	1360 (73.8)	1311 (74.2)	49 (60.2)	
Severe neonatal morbidity* ** (n = 2775)	324 (5.7)	307 (5.6)	17 (10.0)	0.08
Severe cerebral lesions (n = 2900)	129 (2.4)	119 (4.5)	10 (9.4)	0.07
Necrotizing enterocolitis (n = 2865)	73 (1.5)	70 (1.4)	3 (3.6)	0.22
BPD Moderate-to-severe (n = 2862)	230 (3.1)	219 (3.0)	11 (4.6)	0.21
Early-onset sepsis ** (n = 2785)	49 (1.3)	43 (1.2)	6 (5.5)	0.004
Late-onset sepsis *** (n = 2897)	407 (6.1)	390 (6.1)	17 (7.4)	0.48

PPROM: preterm premature rupture of membranes; IQR: interquartile range; BPD: bronchopulmonary dysplasia

**Percentages were weighted to consider different recruitment periods according to gestational age of birth in the EPIPAGE-2 study (35/35 = 1 for infants born at 22-26 weeks of gestation who were recruited during 35 weeks, 35/26 = 1.34 for infants born at 27-31 weeks recruited during 26 weeks and 35/5 = 7 for infants born at 32-34 weeks recruited only during 5 weeks)*

*** At least one injection*

**** Severe neonatal morbidity: severe cerebral lesions (intraventricular hemorrhage stage 3 or 4 or cystic periventricular leukomalacia) and/or severe bronchopulmonary dysplasia at 36 weeks' postmenstrual age and/or retinopathy of prematurity (stage ≥ 3 or requiring laser treatment) and/or necrotizing enterocolitis (Bell stage ≥ 2)*

***** Early-onset sepsis was defined by a positive blood culture and cerebrospinal fluid occurring before 72 hours of life*

****** Late-onset sepsis was defined by a positive blood culture and at least 5 days of antibiotic therapy occurring ≥ 72 hours of life*

Table 4: Outcomes at 5 years of age according to clinical chorioamnionitis at birth.

	Children alive at 5 years N = 2927	**Clinical chorioamnionitis**				
				Multiple imputations		
		No (n = 2803) N (%*)	Yes (n = 124) N (%*)	**Crude OR (95% CI)**	**Model 1 aOR_1 (95%CI)**	**Model 2 aOR_2 (95%CI)**
Primary outcome						
*Neurodevelopmental disorders***						
Absent–mild	1509 (90.4)	1446 (90.4)	63 (91.8)	1	1	1
Moderate–to-severe	217 (9.6)	208 (9.6)	9 (8.2)	1.1 (0.5-1.8)	1.0 (0.5-1.8)	0.9 (0.5-1.8)
Missing data	*1201*	*1149*	*52*			
Secondary outcomes						
Cerebral palsy at 5 years						
No	1896 (96.7)	1819 (96.7)	77 (96)	1	1	1
Yes	98 (3.3)	92 (3.3)	6 (4.0)	1.2 (0.6-2.7)	1.0 (0.5-2.0)	1.0 (0.5-2.1)
Missing data	*933*	*892*	*41*			
Coordination disorders						
MABC-2						
>5th centile	1372 (95.2)	1320 (95.4)	52 (89.3)	1	1	1
≤5th centile	108 (4.8)	102(4.6)	6 (10.7)	1.9 (0.8-4.8)	1.2 (0.6-2.5)	1.1 (0.5-2.4)
Missing data	*1447*	*1381*	*66*			
Cognitive impairments						
WPPSI-IV*						
≥ -2 SD	1569 (92.4)	1501 (92.4)	68 (94)	1	1	1
< -2 SD	166 (7.6)	159 (7.6)	7 (6)	1.1 (0.4-2.8)	1.0 (0.5-2.0)	0.9 (0.5-1.9)
Missing data	*1192*	*1143*	*49*			
Behavioral difficulties						
SDQ						
≤ 90th centile	1579 (91.3	1512 (91.2)	67 (92.1)	1	1	1
> 90th centile	164 (8.7)	155 (8.8)	9 (7.9)	1.0 (0.4-2.4)	1.3 (0.7-2.4)	1.2 (0.6-2.3)
Missing data	*1184*	*1136*	*48*			

**Percentages and crude ORs weighted to account for different recruitment periods by gestational age at birth*

*** Neurodevelopmental disorders = composite criteria: cerebral palsy or coordination disorders or sensory disorders or cognitive disorders or behavioral disorders.*

Model 1: Adjustment for gestational age at birth + generalized estimating equation (GEE) models

Model 2: Adjustment for gestational age at birth, household socio-professional category, mother's country of birth, mother's level of education, smoking, multiple pregnancy, maternal obesity, preterm premature rupture of membranes + GEE.

OR: odds ratio. aOR: adjusted odds ratio. 95% CI: 95% confidence interval. MABC-2: Movement Assessment Battery, second edition, ELFE cohort reference. WPPSI-IV: Wechsler Preschool and Primary

School Intelligence Scale, fourth edition, ELFE cohort reference. SDQ: Strengths and Difficulties Questionnaire.

Table 5: Death from birth to 5 years of age according to clinical chorioamnionitis at birth.

	Live birth N = 3307	Clinical chorioamnionitis		P-value	OR adjusted for GA (95% CI)
		No (n = 3153) N (%*)	Yes (n = 154) N (%*)		
Death in delivery room				<0.001	
No	3199 (98.7)	3060 (98.8)	139 (94.5)		1
Yes	108 (1.3)	93 (1.2)	15 (5.5)		2.5 (1.4-4.6)
Death in NICU				0.03	
No	2944 (96.7)	2819 (96.8)	125 (94.1)		1
Yes	255 (3.3)	241 (3.2)	14 (5.9)		0.9 (0.5-1.7)
Death between discharge and 5 years of age					
No	2927 (99.4)	2803 (99.4)	124 (99.6)	0.70	1
Yes	17 (0.6)	16 (0.6)	1 (0.4)		1.3 (0.2-9.8)
Death between birth and 5 years of age				<0.001	
No	2927 (94.9)	2803 (95.1)	124 (88.6)		1
Yes	380 (5.1)	350 (4.9)	30 (11.4)		1.3 (0.8-2.1)

GA: gestational age. NICU: neonatal intensive care unit. OR: odds ratio. 95% CI: 95% confidence interval.
**Percentages weighted to consider different recruitment periods according to gestational age of birth*

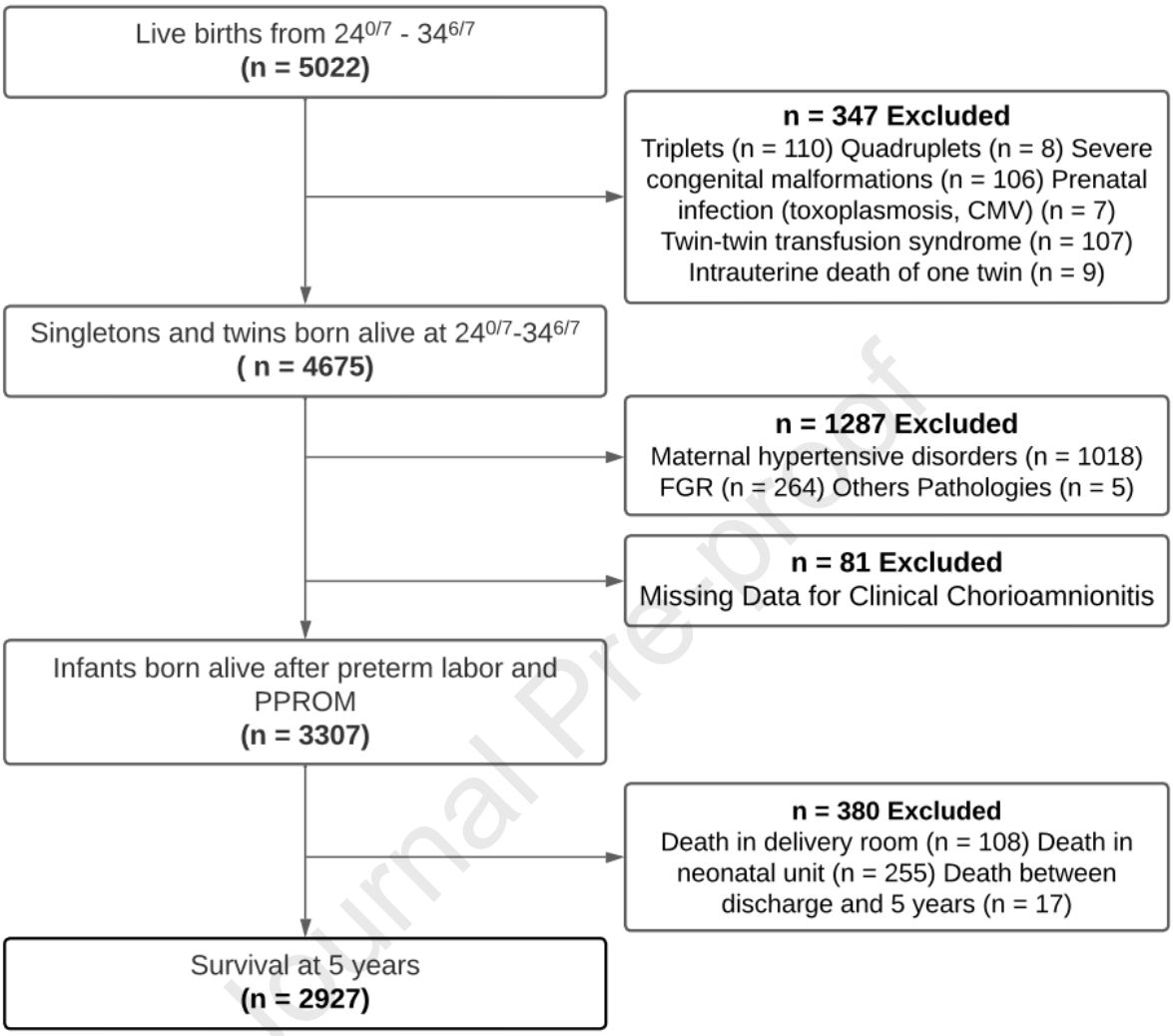
Table 6: Association of clinical chorioamnionitis and neurodevelopmental disorders and/or death at 5 years of age among preterm births, with multiple imputation for outcome

	Respondents at 5 years or dead N = 2163	**Clinical chorioamnionitis**		P-value	Crude OR (95% CI)	OR adjusted for GA (95% CI)
		No N = 2056 (96.5%) N (%*)	Yes N = 107 (3.5%) N (%*)			
Neurodevelopmental disorders or death**				0.04		
No	1509 (82.6)	1446 (82.9)	63 (74.4)		1	1
Yes	597 (17.4)	558 (17.1)	39 (25.6)		1.5 (0.8-2.6)	1.1 (0.7-1.8)
Missing data on neurodevelopmental outcomes	*57*	*52*	*5*			

GA: gestational age. OR: odds ratio. 95% CI: 95% confidence interval.
**Percentages or crude ORs weighted to account for different recruitment periods by gestational age at birth. **Composite criteria: neurodevelopmental disorders (severe or moderate) at 5 years of age or death at 5 years of age*

FIGURE

Figure 1: Flowchart of children in the study



CMV: cytomegalovirus
PPROM: preterm premature rupture of membranes
FGR: fetal growth restriction

Declaration of Interest Statement

We declare no potential, perceived or real conflict of interest relevant to this article.

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