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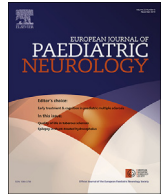


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Perinatal inflammation is associated with social and motor impairments in preterm children without severe neonatal brain injury

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ABSTRACT

Objective: To test the association between exposure to perinatal inflammation – *i.e.* clinical chorioamnionitis or early-onset neonatal infection – in preterm children without severe neonatal brain injury and neurodevelopmental outcome at 30 months of corrected age (CA).

Design: Cross-sectional study from a French regional cohort of clinical follow-up (SEVE Network).

Patients: One hundred sixty-four surviving neonates without severe brain injury – namely, grade III and IV cerebral hemorrhage and cystic periventricular leukomalacia – and without late-onset neonatal inflammation exposure – namely, late-onset neonatal infection and necrotizing enterocolitis –, born at less than 33 weeks of gestational age from November 2011 to June 2015 and enrolled in the SEVE Network.

Main outcome measure: Global developmental quotient (DQ) score of the revised Brunet-Lézine scale and its four indices measured by the same neuropsychologist at 30 months of CA.

Results: After multivariate analysis, exposure to perinatal inflammation was not found significantly associated with a modification of the global DQ score (coefficient -1.7, 95% CI -4.8 to 1.3; $p = 0.26$). Exposure to perinatal inflammation was associated with a decrease of the gross motor function DQ score (coefficient -6.0, 95% CI -9.9 to -2.1; $p < 0.01$) and a decrease of the sociability DQ score (coefficient -5.1, 95% CI -9.2 to -0.9; $p = 0.02$). Language and visuospatial coordination DQ scores were not affected by exposure to perinatal inflammation.

Conclusion: Exposure to perinatal inflammation in preterm children without severe neonatal brain injury is independently associated with decreased motor and social abilities at 30 months of CA.

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Abbreviations: β , linear coefficient.; CA, corrected age.; CI, confidence intervals.; CP, cerebral palsy.; DQ, developmental quotient.; GA, gestational age.; IVH, intraventricular hemorrhage.; MRI, magnetic resonance imaging.; RBL, revised Brunet-Lézine scale.

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1. Introduction

Survival of preterm neonates without severe neonatal morbidity – defined as any of bronchopulmonary dysplasia, severe necrotizing enterocolitis, severe retinopathy of prematurity, grade III and IV cerebral hemorrhage, cystic periventricular leukomalacia – improved over the last two decades [1]. Between 1997 and 2011, the prevalence of cerebral palsy (CP) at two years of corrected age (CA) sharply decreased in French preterm children born less than 34 weeks of gestational age (GA): from 9.0% (95% CI 7.5 to 10.6) to 5.4%

(95% CI 4.2 to 6.8) in children born between 24 and 31 weeks of GA, and from 2.8% (95% CI 1.5 to 4.7) to 0.2% (95% CI 0 to 1.3) in children born between 32 and 34 weeks of GA [2].

In this population of preterm children, perinatal inflammation is a risk factor of severe neonatal brain injuries, such as severe cerebral hemorrhage [3] and cystic periventricular leukomalacia [4] – which are themselves associated with poor neurodevelopmental outcomes [5,6] –, CP [7], and other non-CP neurobehavioral disabilities [8–12]. To our knowledge, there is no study in the current literature determining whether exposure to perinatal inflammation is associated with neurodevelopmental impairment in the specific and growing population of preterm children without severe neonatal brain injury. Interestingly, such perinatal inflammatory conditions are potentially modifiable conditions for which novel therapeutic interventions are a field of intense preclinical and clinical studies [13–18]. We hypothesized that perinatal inflammation – *i.e.* clinical chorioamnionitis or early-onset neonatal infection – in preterm children born at less than 33 weeks of GA without severe neonatal brain injury is associated with a lower global developmental quotient (DQ) score of the revised Brunet-Lézine (RBL) scale at 30 months of CA.

2. Material and methods

STROBE guidelines for observational studies were followed to conduct this study [19].

2.1. Population sample

The SEVE (*Suivi des Enfants Vulnérables sur le Réseau Elena*; www.chu-st-etienne.fr/seve) Network is the French regional cohort of clinical follow-up dedicated to vulnerable children – *i.e.* born either at less than 33 weeks of GA or with neonatal encephalopathy – living in the catchment area of the *Centre Hospitalier Universitaire de Saint-Étienne, France*. Five hundred thirty-seven children among the 570 potentially eligible born between November 2011 and June 2015 were enrolled in the SEVE Network, providing an inclusion rate of 96%. They constitute the population sample of the present study. Each enrolled neonate had a free of charge and standardized clinical follow-up involving pediatricians, general practitioners, physiologists, and neuropsychologists. Data were longitudinally collected in the SEVE database using standardized questionnaires and clinical assessments throughout the follow-up. Among these evaluations, a systematic face-to-face encounter with a specialized neuropsychologist was proposed to all families at 30 months of CA. The present work is a cross-sectional study from our regional cohort of clinical follow-up (SEVE Network).

Exclusion criteria were established risk factors of unfavorable neurodevelopmental outcome in preterm newborns, namely: severe neonatal brain injury – defined as cystic periventricular leukomalacia [6] and grade III and IV cerebral hemorrhage [5] –, neonatal seizures [20], late-onset neonatal inflammation exposure – defined as late-onset neonatal infection [11] and necrotizing enterocolitis [21] –, and genetic abnormality. All these items were mandatory fields prospectively collected on standardized questionnaires in the SEVE database. Cranial ultrasounds were systematically performed in our population sample. Magnetic resonance imaging (MRI) was performed at term equivalent age in all neonates presenting a suspicion of severe brain injury based on clinical symptoms or cranial ultrasound findings, such as grade III and IV cerebral hemorrhage and cystic periventricular leukomalacia. Cerebral hemorrhage was classified in four grades: Grade I, hemorrhage confined to germinal matrix; Grade II, intraventricular hemorrhage (IVH) without ventricular dilation; Grade III, IVH acutely distending the ventricles; Grade IV, venous infarction in

area ipsilateral to IVH [22,23]. Cystic periventricular leukomalacia was defined on MRI by the visualization of diffuse signal abnormality associated with cystic images. Necrotizing enterocolitis was defined by stage II and III enterocolitis, according to Bell's classification [24]. Neonatal seizures were diagnosed by standard electroencephalography. A genetic abnormality was defined by the presence of a pathogenic gene or chromosomal anomaly.

Children were divided into two groups, either non-exposed or exposed to perinatal inflammation. Perinatal inflammation was defined as clinical chorioamnionitis or early-onset neonatal infection. These items were both mandatory in the SEVE database. Clinical chorioamnionitis was defined as maternal fever upper than 38 °C with at least two additional criteria among the following: fetal tachycardia, maternal tachycardia, maternal leukocytosis, uterine tenderness, and foul-smelling amniotic fluid [25]. Neonatal infection was defined by a positive culture collected from a normally sterile site for which clinicians prescribed at least five days of appropriate antibiotics [26]. Early-onset neonatal infection was defined by a neonatal infection with onset within the first 72 h of life; late-onset neonatal infection was defined by a neonatal infection occurring after 72 h of life [26].

Maternal and neonatal items recorded in the SEVE database also included maternal age at delivery, singleton *versus* multiples, antenatal steroids administration, vaginal delivery *versus* cesarean-section, gestational age, birth weight, head circumference at birth, sex, adrenalin administration at birth, Apgar score at 1 and 5 min, surfactant administration, duration of any ventilatory support, postnatal steroids administration, vascular filling or amine use during hospitalization, grade I and II cerebral hemorrhages, feeding at discharge, and parental employment status. Birth weight z scores were calculated according to sex and GA, using the INTERGROWTH-21st International Newborn Size at Birth Standards application version 1.3.5 (intergrowth21.tghn.org).

2.2. Neurodevelopmental assessment

The main endpoint was the global DQ score at the neurodevelopmental evaluation by the RBL scale at 30 months of CA, according to the exposure to perinatal inflammation. The RBL scale is the main scale used to evaluate the psychomotor development of French-speaking children aged from 2 to 30 months of CA in clinical practice and clinical research [27]. It was standardized on a sample of more than 1000 French-speaking children born at term [28,29]. It computes four developmental quotients (DQ) scores – gross motor function, sociability, language, visuospatial coordination –, that permit to calculate a global DQ score. Each DQ score is adjusted and normalized to the CA (in days) with a mean of 100 and a standard deviation (SD) of 15 [28,29]. A non-interpretable RBL was defined by the impossibility to calculate at least one DQ score during the evaluation. To avoid inter-experimenter bias, only neurodevelopmental evaluations performed by the same specialized neuropsychologist of our regional center (MC) were considered.

2.3. Ethics

Written parental consent was required to be enrolled in the SEVE Network. Data collection was approved by the French National Technologies and Civil Liberties Commission (CNIL; authorization No. 1530737). The present study was approved by the Ethical Committee of the Saint-Étienne University Hospital that waived the need for a new parental consent (October 11th, 2018; reference IRBN782018/CHUSTE).

2.4. Statistical analysis

Continuous variables were expressed as mean (standard deviation) when normally distributed or median [interquartile range] when non-normally distributed. Categorical variables were expressed as absolute numbers (percentage).

Children without global DQ score were compared to those with global DQ score using Student t-tests for normally distributed continuous variables, Wilcoxon rank-sum tests for continuous non-normally distributed variables, and chi-square tests or Fisher's exact tests for categorical variables.

The independent associations between exposure to perinatal inflammation and each DQ scores were evaluated using multivariate least-squares linear regressions. Univariate analyses were first performed to screen for potential adjustment covariates and confounders. Variables with p-values <0.10 in univariate analysis – vaginal delivery – and clinically relevant variables – gestational age, birth weight z score, sex, epinephrine at birth, shock during hospitalization, postnatal steroids, cerebral hemorrhage, parental employment status, corrected age at RBL evaluation – were included in the multivariate models as adjustment covariables. In the models, no collinearity – assessed by correlations and by computing variance inflation factors – was found. Assumptions associated with linear regression – linearity, normal distribution of residuals, homoscedasticity – were graphically assessed and respected, and no high leverage patient – defined by a Cook's distance >0.5 [30] – was found. The coefficients of determination (R^2) were computed and displayed, as well as their 95% confidence intervals (CI) estimated by the bootstrap resampling method. Results were expressed as linear coefficients (β) of the exposure to perinatal inflammation for each DQ score with their 95% CI and p-value.

All statistical tests were two-sided, with $p < 0.05$ considered as

statistically significant. Statistical analysis was performed with the R software for statistical computing and graphics, version 3.5.2 (package “car” version 3.0–5).

3. Results

3.1. Population sample

Five hundred thirty-seven children born between November 2011 and June 2015 were enrolled in the SEVE Network. After application of exclusion criteria, 394 remaining children were eligible for the current study. Two hundred and thirty children did not complete the RBL test according to the criteria mentioned above (children without global DQ score), whereas 164 children had a global DQ score (Fig. 1). Children without global DQ score were not clinically different from those with global DQ score, except for multiple pregnancies (Table 1). Among children with global DQ score, perinatal features – except for the mode of delivery –, parental employment status, and corrected age at RBL evaluation were similar between children exposed versus non-exposed to perinatal inflammation (Table 2).

3.2. Neurodevelopmental outcome

The distribution of DQ scores according to the exposition to perinatal inflammation is presented in Fig. 2. After multivariate analysis, exposure to perinatal inflammation was not found significantly associated with a modification of the global DQ score ($\beta -1.7$, 95% CI -4.8 to 1.3; $p = 0.26$) (Table 3). The exposure to perinatal inflammation was associated with a decrease of the gross motor function DQ score ($\beta -6.0$, 95% CI -9.9 to -2.1; $p < 0.01$) and a decrease of the sociability DQ score ($\beta -5.1$, 95% CI -9.2 to -0.9;

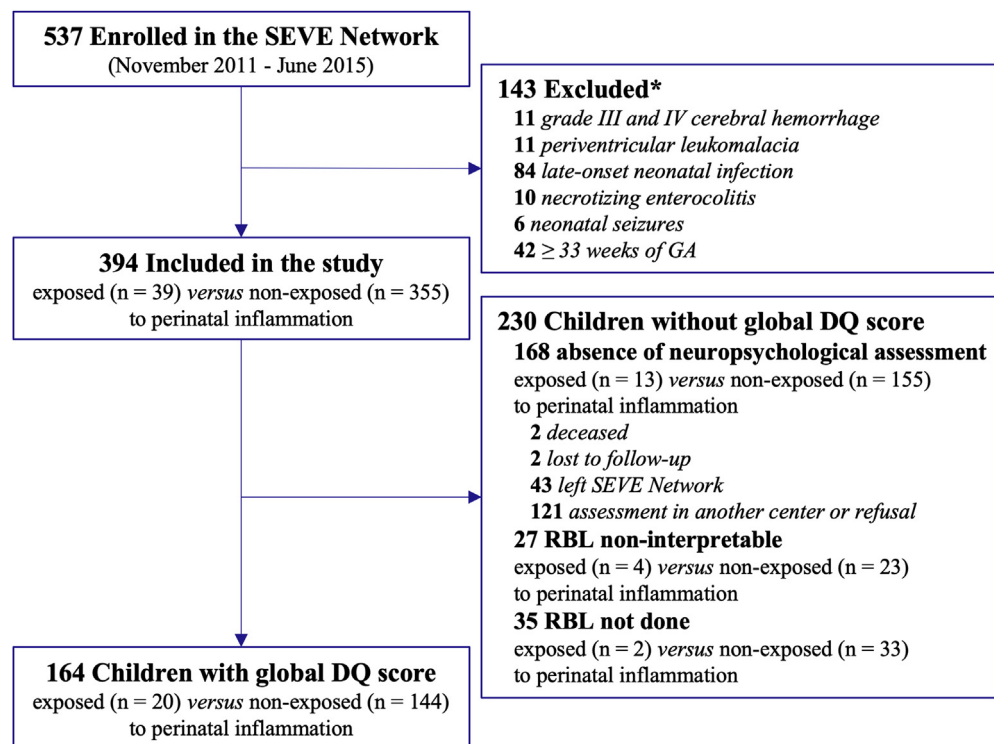


Fig. 1. Flow diagram.

*Absence of genetic abnormality.

Abbreviations: DQ, developmental quotient; GA, gestational age; RBL, revised Brunet-Lézine.

Table 1
Features among children with and without global DQ score.

Features	All children (n = 394)	Children with global DQ score (n = 164)	Children without global DQ score (n = 230)	P values
Perinatal features				
Maternal age, years, mean (SD)	30.0 (5.4)	30.7 (5.3)	29.5 (5.5)	0.02
Multiple pregnancy, n (%) ^a	144 (36.5)	48 (29.3)	96 (41.7)	0.02
Antenatal steroids administration				
Incomplete, n (%)	64 (16.2)	20 (12.2)	44 (19.1)	0.09
Complete, n (%)	253 (64.2)	106 (64.6)	147 (63.9)	
Vaginal delivery, n (%)	106 (27.0)	53 (32.5)	53 (23.0)	0.05
Perinatal inflammation, n (%)				
Chorioamnionitis, n (%)	39 (9.9)	20 (12.2)	19 (8.3)	0.26
EONI, n (%)	15 (3.8)	7 (4.3)	8 (3.5)	0.89
EONI, n (%)	32 (8.1)	18 (11.0)	14 (6.1)	0.12
GA, weeks, mean (SD)	30.5 (2.1)	30.5 (2.0)	30.5 (2.2)	0.97
Birth weight, g, mean (SD)	1433 (398)	1442 (405)	1427 (384)	0.73
Birth weight z score, mean (SD)	-0.12 (0.92)	-0.11 (0.93)	-0.14 (0.91)	0.76
Birth HC, cm, mean (SD)	27.6 (2.5)	27.6 (2.6)	27.6 (2.5)	0.84
Male sex, n (%)	202 (51.3)	80 (48.8)	122 (53.0)	0.46
Epinephrine at birth, n (%)	6 (1.5)	4 (2.4)	2 (0.9)	0.24
Apgar score at 1 min < 7, n (%)	149 (38.5)	64 (39.5)	85 (37.8)	0.81
Apgar score at 5 min < 7, n (%)	28 (7.4)	12 (7.6)	16 (7.2)	1.00
Surfactant administration				
1 dose, n (%)	154 (39.1)	62 (37.8)	92 (40.0)	0.35
2 doses, n (%)	39 (9.9)	21 (12.8)	18 (7.8)	
>2 doses, n (%)	5 (1.3)	1 (0.6)	4 (1.7)	
VS duration, weeks, median [IQR]	2.9 [0.9 to 5.8]	3.2 [0.9 to 5.3]	2.5 [1.0 to 6.0]	0.97
Postnatal steroids, n (%)	14 (3.6)	6 (3.7)	8 (3.5)	1.00
Shock during hospitalization, n (%)				
Vascular filling, n (%)	6 (1.5)	3 (1.8)	3 (1.3)	0.69
Amine use, n (%)	6 (1.5)	3 (1.8)	3 (1.3)	0.69
Cerebral hemorrhage, n (%)	2 (0.5)	1 (0.6)	1 (0.4)	1.00
Grade 1, n (%)	21 (5.3)	8 (4.9)	13 (5.7)	0.91
Grade 2, n (%)	16 (4.1)	7 (4.3)	9 (3.9)	0.66
Grade 2, n (%)	5 (1.3)	1 (0.6)	4 (1.7)	
Feeding at discharge				
Breastfeeding, n (%)	87 (22.4)	34 (21.1)	53 (23.2)	0.56
Artificial, n (%)	222 (57.1)	97 (60.2)	125 (54.8)	
Mixed, n (%)	80 (20.6)	30 (18.6)	50 (21.9)	
Parental employment status				
Both unemployed, n (%)	33 (9.6)	9 (6.1)	24 (12.2)	0.15
One employed, n (%)	82 (23.9)	35 (23.8)	47 (24.0)	
Both employed, n (%)	228 (66.5)	103 (70.1)	125 (63.8)	

Abbreviations: DQ, developmental quotient; EONI, early-onset neonatal infection; GA, gestational age; HC, head circumference; IQR, interquartile range; n (%), number of patients (percentage); SD, standard deviation; VS, ventilatory support.

^a Indicates more than one fetus (i.e., twins, triplets).

$p = 0.02$) (Table 3). We found no association between language or visuospatial coordination DQ scores and the exposure to perinatal inflammation (Table 3).

4. Discussion

In this preterm population sample without severe neonatal brain injury included in a regional cohort of clinical follow-up and assessed with a standardized neuropsychological test at 30 months of CA, we found a significant adjusted association between perinatal exposure to inflammation and poorer social and gross motor abilities.

Numerous studies assessed the association between perinatal inflammation in preterm neonates and severe neurological outcomes, principally CP [7,11,31–33]. Although a meta-analysis found an association between clinical or histological chorioamnionitis and CP [7], this association was inconsistently detected in the most recent observational studies [31]. The incidence of the most severe neurological sequelae is currently decreasing in preterm children [2]. This could restrict the interest of categorical assessments of occurrence of neurodevelopmental anomalies, such as CP, and highlight the value of continuous scales, such as RBL, in order to capture and measure the whole spectrum of sequelae in preterm children.

Few cohort studies assessed the association between

chorioamnionitis in preterm neonates and neurodevelopmental outcomes with continuous scales [8–10,12,34,35]. Among the three studies assessing the exposure to clinical and histological chorioamnionitis [9,10,12], two found that clinical – but not histological – chorioamnionitis was associated with a lower Bayley-III Mental Developmental Index score at 18 months of CA [9,12], and one found that histological – but not clinical – chorioamnionitis was associated with poorer cognitive performances at five years of age [10]. Among the three studies assessing the exposure to histological chorioamnionitis solely [8,34,35], one found an association with a lower Bayley-II Mental Developmental Index score at 18 months of CA [8], and two found no association with motor and cognitive outcomes at 18 months of CA using Bayley-II and -III assessments [34,35]. The main limitation of these works is that report of severe neonatal complications was not exhaustive: occurrence of necrotizing enterocolitis and sepsis were respectively mentioned in one [9] and four [8,9,12,34] of these studies [8–10,12,34,35], although their association with poor neurodevelopmental outcomes is well-established [11,21]. In addition, the samples mixed children with and without severe neonatal brain injuries such as cystic periventricular leukomalacia and severe cerebral hemorrhage (grade III and IV) [8–10,12,34,35], which are associated with poor neurodevelopmental outcomes [5,6]. Hence, to our knowledge, our study is the first to describe the impact of perinatal inflammation on neurodevelopmental outcome in a population

Table 2
Features of children with global DQ score.

Features	Non-exposed to perinatal inflammation (n = 144)	Exposed to perinatal inflammation (n = 20)	P values
Perinatal features			
Maternal age, years, mean (SD)	30.5 (5.1)	32.4 (6.0)	0.14
Multiple pregnancy, n (%) ^a	43 (29.9)	5 (25.0)	0.85
Antenatal steroids administration			
Incomplete, n (%)	16 (11.1)	4 (20.0)	0.24
Complete, n (%)	92 (63.9)	14 (70.0)	
Vaginal delivery, n (%)	41 (28.7)	12 (60.0)	0.01
GA, weeks, mean (SD)	30.5 (2.1)	30.7 (1.8)	0.63
Birth weight, g, mean (SD)	1425 (402)	1562 (419)	0.16
Birth weight z score, mean (SD)	-0.14 (0.94)	0.15 (0.81)	0.14
Birth HC, cm, mean (SD)	27.5 (2.5)	28.4 (2.7)	0.14
Male sex, n (%)	67 (46.5)	13 (65.0)	0.19
Epinephrine at birth, n (%)	2 (1.4)	2 (10.0)	0.07
Apgar score at 1 min < 7, n (%)	56 (39.4)	8 (40.0)	1.00
Apgar score at 5 min < 7, n (%)	9 (6.5)	3 (15.0)	0.18
Surfactant administration			
1 dose, n (%)	52 (36.1)	10 (50.0)	0.59
2 doses, n (%)	19 (13.2)	2 (10.0)	
>2 doses, n (%)	1 (0.7)	0	
VS duration, weeks, median [IQR]	3.2 [0.9 to 5.0]	3.3 [1.6 to 8.1]	0.44
Postnatal steroids, n (%)	5 (3.5)	1 (5.0)	0.55
Shock during hospitalization, n (%)	3 (2.1)	0	1.00
Vascular filling, n (%)	3 (2.1)	0	1.00
Amine use, n (%)	1 (0.7)	0	1.00
Cerebral hemorrhage, n (%)			
Grade 1, n (%)	4 (2.8)	3 (15.0)	0.06
Grade 2, n (%)	1 (0.7)	0	
Feeding at discharge			
Breastfeeding, n (%)	30 (21.3)	4 (20.0)	0.37
Artificial, n (%)	87 (61.7)	10 (50.0)	
Mixed, n (%)	24 (17.0)	6 (30.0)	
Parental employment status			
Both unemployed, n (%)	8 (6.2)	1 (5.3)	0.76
One employed, n (%)	29 (22.7)	6 (31.6)	
Both employed, n (%)	91 (71.1)	12 (63.2)	
RBL evaluation			
Corrected age, months, mean (SD)	31.3 (1.9)	31.7 (2.0)	0.40

Abbreviations: DQ, developmental quotient; GA, gestational age; HC, head circumference; IQR, interquartile range; n (%), number of patients (percentage); RBL, revised Brunet-Lézine; SD, standard deviation; VS, ventilatory support.

^a Indicates more than one fetus (*i.e.*, twins, triplets).

sample of preterm children without such severe brain injury.

Several studies identified neonatal infection in preterm children as a risk factor for CP [11,32,33] or neurodevelopmental impairment, such as lower Bayley-II Mental Developmental Index score at 23 months of CA [32] and lower general cognitive ability at 9 years [36]. However, these studies included more late-onset (range percentage from 81 to 96%) than early-onset neonatal infection (range percentage from 4 to 19%) [11,32,33,36]. In contrast to our work, all these studies did not adjust multivariate analysis on hemodynamic failure [11,32,33,36], which is an established risk factor of death and neurodevelopmental impairment [37].

In line with our results, data from preclinical models showed that perinatal inflammation induced by inactivated or live pathogens – *e.g.* lipopolysaccharide, polyriboinosinic-polyribocytidilic acid, and group B *Streptococcus* – affects the brain development and leads to motor and social impairments without inducing severe brain injuries [38–41]. Altogether, these clinical and preclinical findings support the idea that perinatal inflammation might lead to neurodevelopmental issues affecting gross motor function and behavior without inducing severe neurological impairment such as CP [42].

A limitation of our study is that exposure to clinical chorioamnionitis and early-onset neonatal infection were recorded in the database without detailed diagnostic criteria. Nevertheless, data recording was performed prospectively in the same way in both groups, using the same standardized definition. The use of a

clinical definition of chorioamnionitis instead of a histological definition is another limitation [43], but it meets the most commonly available markers in clinical practice. The high number of patients without global DQ score at 30 months of CA is another limitation. This can be mainly explained by the possibility for parents to consult a neuropsychologist in other centers where RBL scores were not calculated or to decline the neuropsychological consultation. We agree that this may be considered as a convenience sample. However, the features of our population sample of children with global DQ score were similar to those of children without global DQ score (Table 1). Furthermore, as the SEVE Network ensures the clinical follow-up of all preterm children born at less than 33 weeks of GA from the catchment area of the *Centre Hospitalier Universitaire de Saint-Étienne, France*, this network is population-based. In addition, our population sample is comparable to those from other recent French prospective and multicentric studies in terms of maternal and neonatal features [1] and RBL scores [27].

Contributors

AG and HP conceptualized and designed the study. MC performed neuropsychological assessments. AG collected data and drafted the initial manuscript. RC performed statistical analysis. All authors reviewed and revised the manuscript.

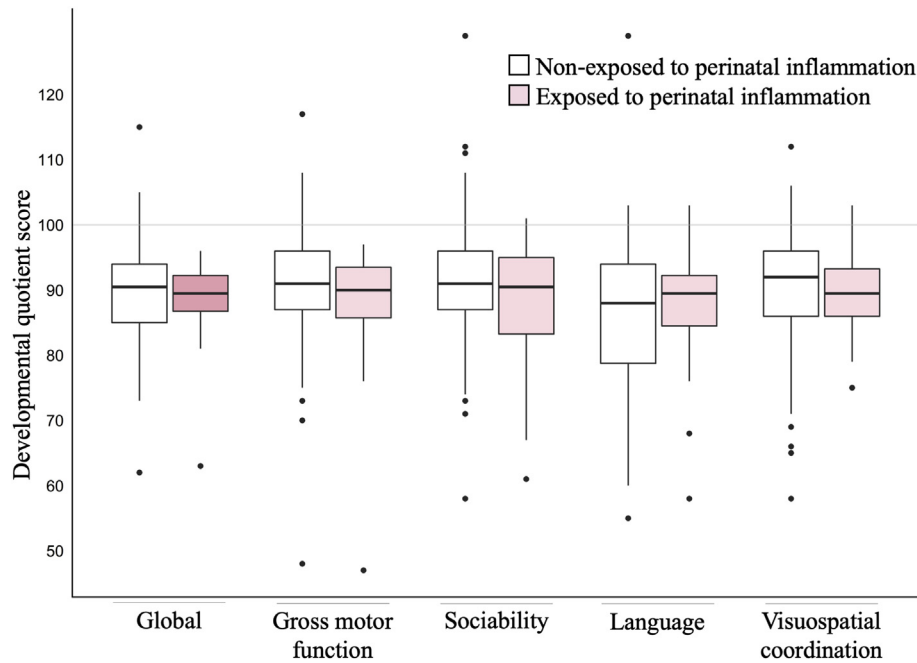


Fig. 2. Distribution of DQ scores at 30 months of corrected age of preterm children exposed versus non-exposed to perinatal inflammation. Horizontal lines mark median, bottom and top boxes borders mark the 25th and 75th percentiles respectively, bottom and top vertical lines mark the 10th and 90th percentiles respectively; dots mark values beyond 10th and 90th percentiles. The normal mean of each DQ score in the general population is 100 with a standard deviation of 15. Abbreviation: DQ, developmental quotient.

Table 3

Association of perinatal inflammation with DQ scores at 30 months of corrected age.

DQ scores	Univariate analysis		Multivariate analysis ^a		
	β (95% CI)	P values	β (95% CI)	P values	R ² (95% CI)
Global	-0.9 (-4.4 to 2.5)	0.59	-1.7 (-4.8 to 1.3)	0.26	0.43 (0.41 to 0.45)
Gross motor function	-4.1 (-8.3 to 0.1)	0.06	-6.0 (-9.9 to -2.1)	<0.01	0.40 (0.38 to 0.42)
Sociability	-3.1 (-7.2 to 1.0)	0.14	-5.1 (-9.2 to -0.9)	0.02	0.48 (0.47 to 0.50)
Language	1.2 (-4.1 to 6.5)	0.66	1.3 (-3.7 to 6.3)	0.61	0.29 (0.28 to 0.30)
Visuospatial coordination	-0.6 (-4.7 to 3.5)	0.77	-0.47 (-4.1 to 3.2)	0.80	0.40 (0.38 to 0.41)

Abbreviations: β , linear coefficient; CI, confidence interval; DQ, developmental quotient; R², coefficient of determination; RBL, revised Brunet-Lézine.

^a Adjusted for vaginal delivery, gestational age, birth weight z score, sex, epinephrine at birth, shock during hospitalization, postnatal steroids, cerebral hemorrhage, parental employment status, corrected age at RBL evaluation.

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Data availability statement

Anonymized data are available from the corresponding authors upon reasonable request.

Declaration of competing interest

The authors have stated that they had no interest which might be perceived as posing a conflict or bias.

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