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

3

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17

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21 **Abstract**

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

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

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

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

33 **Results:** After multivariate analysis, exposure to perinatal inflammation was not found significantly
34 associated with a modification of the global DQ score (coefficient -1.7, 95% CI -4.8 to 1.3; $p = 0.26$).
35 Exposure to perinatal inflammation was associated with a decrease of the gross motor function DQ score
36 (coefficient -6.0, 95% CI -9.9 to -2.1; $p < 0.01$) and a decrease of the sociability DQ score (coefficient -
37 5.1, 95% CI -9.2 to -0.9; $p = 0.02$). Language and visuospatial coordination DQ scores were not affected
38 by exposure to perinatal inflammation.

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

41

42 **Keywords:** prematurity, chorioamnionitis, early-onset neonatal infection, development, revised
43 Brunet-Lézine scale.

44 **Abbreviations**

45 β , linear coefficient.

46 CA, corrected age.

47 CI, confidence intervals.

48 CP, cerebral palsy.

49 DQ, developmental quotient.

50 GA, gestational age.

51 IVH, intraventricular hemorrhage.

52 MRI, magnetic resonance imaging.

53 RBL, revised Brunet-Lézine scale.

54 **1. Introduction**

55 Survival of preterm neonates without severe neonatal morbidity – defined as any of bronchopulmonary
56 dysplasia, severe necrotizing enterocolitis, severe retinopathy of prematurity, grade III and IV cerebral
57 hemorrhage, cystic periventricular leukomalacia – improved over the last two decades.¹ Between 1997
58 and 2011, the prevalence of cerebral palsy (CP) at two years of corrected age (CA) sharply decreased in
59 French preterm children born less than 34 weeks of gestational age (GA): from 9.0% (95% CI 7.5 to
60 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%
61 (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

62 In this population of preterm children, perinatal inflammation is a risk factor of severe neonatal brain
63 injuries, such as severe cerebral hemorrhage³ and cystic periventricular leukomalacia⁴ – which are
64 themselves associated with poor neurodevelopmental outcomes^{5,6} –, CP⁷, and other non-CP
65 neurobehavioral disabilities.^{8–12} To our knowledge, there is no study in the current literature determining
66 whether exposure to perinatal inflammation is associated with neurodevelopmental impairment in the
67 specific and growing population of preterm children without severe neonatal brain injury. Interestingly,
68 such perinatal inflammatory conditions are potentially modifiable conditions for which novel therapeutic
69 interventions are a field of intense preclinical and clinical studies.^{13–18} We hypothesized that perinatal
70 inflammation – *i.e.* clinical chorioamnionitis or early-onset neonatal infection – in preterm children born
71 at less than 33 weeks of GA without severe neonatal brain injury is associated with a lower global
72 developmental quotient (DQ) score of the revised Brunet-Lézine (RBL) scale at 30 months of CA.

73

74 **2. Material and methods**

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

76

77 **2.1. Population sample**

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

90
91 **Exclusion criteria were established risk factors of unfavorable neurodevelopmental outcome in preterm**
92 **newborns, namely: severe neonatal brain injury – defined as cystic periventricular leukomalacia⁶ and**
93 **grade III and IV cerebral hemorrhage⁵ –, neonatal seizures²⁰, late-onset neonatal inflammation exposure**
94 **– defined as late-onset neonatal infection¹¹ and necrotizing enterocolitis²¹ –, and genetic abnormality.**
95 **All these items were mandatory fields prospectively collected on standardized questionnaires in the**
96 **SEVE database. Cranial ultrasounds were systematically performed in our population sample. Magnetic**
97 **resonance imaging (MRI) was performed at term equivalent age in all neonates presenting a suspicion of**
98 **severe brain injury based on clinical symptoms or cranial ultrasound findings, such as grade III and IV**
99 **cerebral hemorrhage and cystic periventricular leukomalacia. Cerebral hemorrhage was classified in four**

100 grades: Grade I, hemorrhage confined to germinal matrix; Grade II, intraventricular hemorrhage (IVH)
101 without ventricular dilation; Grade III, IVH acutely distending the ventricles; Grade IV, venous
102 infarction in area ipsilateral to IVH.^{22,23} Cystic periventricular leukomalacia was defined on MRI by the
103 visualization of diffuse signal abnormality associated with cystic images. Necrotizing enterocolitis was
104 defined by stage II and III enterocolitis, according to Bell's classification.²⁴ Neonatal seizures were
105 diagnosed by standard electroencephalography. A genetic abnormality was defined by the presence of a
106 pathogenic gene or chromosomal anomaly.

107
108 Children were divided into two groups, either non-exposed or exposed to perinatal inflammation.
109 Perinatal inflammation was defined as clinical chorioamnionitis or early-onset neonatal infection. These
110 items were both mandatory in the SEVE database. Clinical chorioamnionitis was defined as maternal
111 fever upper than 38°C with at least two additional criteria among the following: fetal tachycardia,
112 maternal tachycardia, maternal leukocytosis, uterine tenderness, and foul-smelling amniotic fluid.²⁵
113 Neonatal infection was defined by a positive culture collected from a normally sterile site for which
114 clinicians prescribed at least five days of appropriate antibiotics.²⁶ Early-onset neonatal infection was
115 defined by a neonatal infection with onset within the first 72 hours of life; late-onset neonatal infection
116 was defined by a neonatal infection occurring after 72 hours of life.²⁶

117
118 Maternal and neonatal items recorded in the SEVE database also included maternal age at delivery,
119 singleton *versus* multiples, antenatal steroids administration, vaginal delivery *versus* cesarean-section,
120 gestational age, birth weight, head circumference at birth, sex, adrenalin administration at birth, Apgar
121 score at 1 and 5 minutes, surfactant administration, duration of any ventilatory support, postnatal
122 steroids administration, vascular filling or amine use during hospitalization, grade I and II cerebral

123 hemorrhages, feeding at discharge, and parental employment status. Birth weight z scores were
124 calculated according to sex and GA, using the INTERGROWTH-21st International Newborn Size at
125 Birth Standards application version 1.3.5 (*intergrowth21.tghn.org*).
126

127 **2.2. Neurodevelopmental assessment**

128 The main endpoint was the global DQ score at the neurodevelopmental evaluation by the RBL scale at
129 30 months of CA, according to the exposure to perinatal inflammation. The RBL scale is the main scale
130 used to evaluate the psychomotor development of French-speaking children aged from 2 to 30 months of
131 CA in clinical practice and clinical research.²⁷ It was standardized on a sample of more than 1000
132 French-speaking children born at term.^{28,29} It computes four developmental quotients (DQ) scores –
133 gross motor function, sociability, language, visuospatial coordination –, that permit to calculate a global
134 DQ score. Each DQ score is adjusted and normalized to the CA (in days) with a mean of 100 and a
135 standard deviation (SD) of 15.^{28,29} A non-interpretable RBL was defined by the impossibility to
136 calculate at least one DQ score during the evaluation. To avoid inter-experimenter bias, only
137 neurodevelopmental evaluations performed by the same specialized neuropsychologist of our regional
138 center (MC) were considered.
139

140 **2.3. Ethics**

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

146

147 **2.4. Statistical analysis**

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

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

154 The independent associations between exposure to perinatal inflammation and each DQ scores were
155 evaluated using multivariate least-squares linear regressions. Univariate analyses were first performed to
156 screen for potential adjustment covariates and confounders. Variables with p-values <0.10 in univariate
157 analysis – vaginal delivery – and clinically relevant variables – gestational age, birth weight z score, sex,
158 epinephrine at birth, shock during hospitalization, postnatal steroids, cerebral hemorrhage, parental
159 employment status, corrected age at RBL evaluation – were included in the multivariate models as
160 adjustment covariables. In the models, no collinearity – assessed by correlations and by computing
161 variance inflation factors – was found. Assumptions associated with linear regression – linearity, normal
162 distribution of residuals, homoscedasticity – were graphically assessed and respected, and no high
163 leverage patient– defined by a Cook's distance >0.5³⁰ – was found. The coefficients of determination
164 (R^2) were computed and displayed, as well as their 95% confidence intervals (CI) estimated by the
165 bootstrap resampling method. Results were expressed as linear coefficients (β) of the exposure to
166 perinatal inflammation for each DQ score with their 95% CI and p-value.

167 All statistical tests were two-sided, with $p < 0.05$ considered as statistically significant. Statistical
168 analysis was performed with the R software for statistical computing and graphics, version 3.5.2
169 (package “car” version 3.0-5).

170

171 **3. Results**

172 **3.1. Population sample**

173 Five hundred thirty-seven children born between November 2011 and June 2015 were enrolled in the
174 SEVE Network. After application of exclusion criteria, 394 remaining children were eligible for the
175 current study. Two hundred and thirty children did not complete the RBL test according to the criteria
176 mentioned above (children without global DQ score), whereas 164 children had a global DQ score
177 (**Figure 1**). Children without global DQ score were not clinically different from those with global DQ
178 score, except for multiple pregnancies (**Table 1**). Among children with global DQ score, perinatal
179 features – except for the mode of delivery –, parental employment status, and corrected age at RBL
180 evaluation were similar between children exposed *versus* non-exposed to perinatal inflammation (**Table**
181 **2**).

182

183 **3.2. Neurodevelopmental outcome**

184

185 The distribution of DQ scores according to the exposition to perinatal inflammation is presented in
186 **Figure 2**. After multivariate analysis, exposure to perinatal inflammation was not found significantly
187 associated with a modification of the global DQ score ($\beta -1.7$, 95% CI -4.8 to 1.3; $p = 0.26$) (**Table 3**).
188 The exposure to perinatal inflammation was associated with a decrease of the gross motor function DQ
189 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 -

190 9.2 to -0.9; $p = 0.02$) (**Table 3**). We found no association between language or visuospatial coordination
191 DQ scores and the exposure to perinatal inflammation (**Table 3**).

192

193 **4. Discussion**

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

198

199 Numerous studies assessed the association between perinatal inflammation in preterm neonates and
200 severe neurological outcomes, principally CP.^{31,7,11,32,33} Although a meta-analysis found an association
201 between clinical or histological chorioamnionitis and CP,⁷ this association was **inconsistently detected in**
202 **the most** recent observational studies.³¹ The incidence of the most severe neurological sequelae is
203 currently decreasing in preterm children.² This could restrict the interest of categorical assessments of
204 occurrence of neurodevelopmental anomalies, such as CP, and highlight the value of continuous scales,
205 such as RBL, in order to **capture and measure the whole spectrum of sequelae in preterm children.**

206

207 Few cohort studies assessed the association between chorioamnionitis in preterm neonates and
208 neurodevelopmental outcomes with continuous scales.^{8-10,12,34,35} Among the three studies assessing the
209 exposure to clinical and histological chorioamnionitis,^{9,10,12} two found that clinical – but not histological
210 – chorioamnionitis was associated with a lower Bayley-III Mental Developmental Index score at 18
211 months of CA,^{9,12} and one found that histological – but not clinical – chorioamnionitis was associated
212 with poorer cognitive performances at five years of age.¹⁰ Among the three studies assessing the

213 exposure to histological chorioamnionitis solely,^{8,34,35} one found an association with a lower Bayley-II
214 Mental Developmental Index score at 18 months of CA,⁸ and two found no association with motor and
215 cognitive outcomes at 18 months of CA using Bayley-II and -III assessments.^{34,35} The main limitation of
216 these works is that report of severe neonatal complications was not exhaustive: occurrence of
217 necrotizing enterocolitis and sepsis were respectively mentioned in one⁹ and four^{8,9,12,34} of these
218 studies,^{8-10,12,34,35} although their association with poor neurodevelopmental outcomes is well-
219 established.^{11,21} In addition, the samples mixed children with and without severe neonatal brain injuries
220 such as cystic periventricular leukomalacia and severe cerebral hemorrhage (grade III and IV),^{8-10,12,34,35}
221 which are associated with poor neurodevelopmental outcomes.^{5,6} Hence, to our knowledge, our study is
222 the first to describe the impact of perinatal inflammation on neurodevelopmental outcome in a
223 population sample of preterm children without such severe brain injury.

224

225 Several studies identified neonatal infection in preterm children as a risk factor for CP^{11,32,33} or
226 neurodevelopmental impairment, such as lower Bayley-II Mental Developmental Index score at 23
227 months of CA³² and lower general cognitive ability at 9 years.³⁶ However, these studies included more
228 late-onset (range percentage from 81 to 96%) than early-onset neonatal infection (range percentage from
229 4 to 19%).^{11,32,33,36} In contrast to our work, all these studies did not adjust multivariate analysis on
230 hemodynamic failure,^{11,32,33,36} which is an established risk factor of death and neurodevelopmental
231 impairment.³⁷

232

233 In line with our results, data from preclinical models showed that perinatal inflammation induced by
234 inactivated or live pathogens – *e.g.* lipopolysaccharide, polyriboinosinic-polyribocytidilic acid, and
235 group B *Streptococcus* – affects the brain development and leads to motor and social impairments

236 without inducing severe brain injuries.³⁸⁻⁴¹ Altogether, these clinical and preclinical findings support the
237 idea that perinatal inflammation might lead to neurodevelopmental issues affecting gross motor function
238 and behavior without inducing severe neurological impairment such as CP.⁴²

239

240 A limitation of our study is that exposure to clinical chorioamnionitis and early-onset neonatal infection
241 were recorded in the database without detailed diagnostic criteria. Nevertheless, data recording was
242 performed prospectively in the same way in both groups, using **the same** standardized definition. **The**
243 **use of a clinical definition of chorioamnionitis instead of a histological definition is another limitation,**⁴³
244 **but it meets the most commonly available markers in clinical practice.** The high number of patients
245 without global DQ score at 30 months of CA is another limitation. This can be mainly explained by the
246 possibility for parents to consult a neuropsychologist in other centers where RBL scores were not
247 calculated or to decline the neuropsychological consultation. We agree that this may be considered as a
248 convenience sample. However, the features of our population sample of children with global DQ score
249 were similar to those of children without global DQ score (**Table 1**). Furthermore, as the SEVE Network
250 ensures the clinical follow-up of all preterm children born at less than 33 weeks of GA from the
251 catchment area of the *Centre Hospitalier Universitaire de Saint-Étienne, France*, this network is
252 population-based. In addition, our population sample is comparable to those from other recent French
253 prospective and multicentric studies in terms of maternal and neonatal features¹ and RBL scores.²⁷

254 **Contributors**

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

258

259 **Competing interest**

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

261

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266

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269

270 **Data availability statement**

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

272

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401 **Tables**

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

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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
Amine use, n (%)	2 (0.5)	1 (0.6)	1 (0.4)	1.00
Cerebral hemorrhage, n (%)				
Grade 1, n (%)	21 (5.3)	8 (4.9)	13 (5.7)	0.91
Grade 1, 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)	

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

405

Abbreviations: DQ, developmental quotient; EONI, early-onset neonatal infection; GA, gestational age; HC, head

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circumference; IQR, interquartile range; n (%), number of patients (percentage); SD, standard deviation; VS,

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ventilatory support.

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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

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

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.

416 **Table 3. Association of perinatal inflammation with DQ scores at 30 months of corrected age.**
 417

DQ scores	Univariate analysis		Multivariate analysis*		
	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)

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

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

423

424 **Figure legends**

425 **Figure 1. Flow diagram.**

426 *Absence of genetic abnormality.

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

428

429 **Figure 2. Distribution of DQ scores at 30 months of corrected age of preterm children exposed**

430 **versus non-exposed to perinatal inflammation.** Horizontal lines mark median, bottom and top boxes

431 borders mark the 25th and 75th percentiles respectively, bottom and top vertical lines mark the 10th and

432 90th percentiles respectively; dots mark values beyond 10th and 90th percentiles. The normal mean of

433 each DQ score in the general population is 100 with a standard deviation of 15.

434 Abbreviation: DQ, developmental quotient.

537 Enrolled in the SEVE Network

(November 2011 - June 2015)

143 Excluded*

11 *grade III and IV cerebral hemorrhage*

11 *periventricular leukomalacia*

84 *late-onset neonatal infection*

10 *necrotizing enterocolitis*

6 *neonatal seizures*

42 ≥ 33 weeks of GA

394 Included in the study

exposed (n = 39) *versus* non-exposed (n = 355)
to perinatal inflammation

230 Children without global DQ score

168 absence of neuropsychological assessment

exposed (n = 13) *versus* non-exposed (n = 155)
to perinatal inflammation

2 *deceased*

2 *lost to follow-up*

43 *left SEVE Network*

121 *assessment in another center or refusal*

27 RBL non-interpretable

exposed (n = 4) *versus* non-exposed (n = 23)
to perinatal inflammation

35 RBL not done

exposed (n = 2) *versus* non-exposed (n = 33)
to perinatal inflammation

164 Children with global DQ score

exposed (n = 20) *versus* non-exposed (n = 144)
to perinatal inflammation

