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ORIGINAL ARTICLE

Being born extremely preterm with low-grade intraventricular haemorrhage had no impact on brain volumes or neurodevelopment in later childhood

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Abstract

Aim: Our aim was to investigate the impact that low-grade intraventricular haemorrhage (IVH) had on neonatal morbidities, brain volumes and neurodevelopmental outcomes in children born extremely preterm (EPT) and compare them with children born EPT without low-grade IVH.

Methods: This prospective cohort study was carried out in Stockholm, Sweden. It focused on 103 children born EPT from 2004 to 2007, at less than 27 weeks of gestation, without major brain injuries. The group with low-grade IVH, defined as grades I–II, were compared with children born EPT without IVH. Around half (45%) underwent MRI scans at 10 years of age and 55% had neurodevelopmental assessments at 12 years.

Results: The low-grade IVH group was sicker during the neonatal period than the children born EPT without IVH. They had lower gestational ages at birth, more days on mechanical ventilation, a higher incidence of necrotising enterocolitis and were more likely to need surgical ligation of patent ductus arteriosus. However, they did not have significantly smaller brain volumes at 10 years of age or worse neurodevelopmental outcomes at 12 years of age.

Conclusion: Brain volumes or neurodevelopment were not affected in children born EPT with low-grade IVH, compared to children born EPT without IVH.

Abbreviations: EPT, extremely preterm; IVH, intraventricular haemorrhage; MABC-2, Movement Assessment Battery for Children, Second Edition; MRI, magnetic resonance imaging; VMI, visual motor integration; WISC-V, Wechsler Intelligence Scale for Children, Fifth Edition.

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KEYWORDS
extremely preterm, low-grade intraventricular haemorrhage, magnetic resonance imaging, neonatal morbidities, neurodevelopmental outcomes

1 | INTRODUCTION

Children born extremely preterm (EPT), at less than 28 weeks of gestation, risk complications due to preterm birth. These include intraventricular haemorrhage (IVH), white and grey matter injuries and neurodevelopmental impairment.[1–4] IVH is graded from I to IV[4] and studies have shown that 20–35% of preterm infants had low-grade IVH, namely grades I–II.[5,6] Studies on the impact that low-grade IVH has on the brain development and neurodevelopmental outcomes of these children are needed. Low-grade IVH in children born preterm has been associated with reduced cortical volume at term age and reduced cerebellar volume, which may be associated with neurodevelopmental impairment later in life.[7–9] EPT birth occurs during the rapid development of the cerebellum, which plays an important role in both cognition and motor skills.[10,11] When cerebellar growth is disturbed by preterm birth, this may damage the cerebellar and result in neurodevelopmental impairment.[11] However, studies on the impact of low-grade IVH on neurodevelopmental outcomes in children born preterm have shown different results. Some studies have reported more problems with neurodevelopmental outcomes in children with low-grade IVH from 2 to 14 years of age than in those children born EPT without IVH.[12–15] Meanwhile, other studies have reported no association with neurodevelopmental outcomes between 2 and 18 years of age.[16–18]

This study focused on children born EPT and the influence of low-grade IVH on white and grey matter of the brain and neurodevelopment during late childhood. Our aim was to examine three potential issues related to children born EPT with low-grade IVH and to compare them with children born EPT without IVH. The first was whether they were sicker and had more complications in the neonatal period. The second was whether they had lower grey and white matter volumes in the cerebrum and cerebellum at 10 years of age. The third was whether they had poorer neurodevelopmental outcomes at 12 years of age.

2 | MATERIALS AND METHODS

2.1 | Study population

This prospective cohort study focused on 103 children with low-grade, or no, IVH, who were born EPT between 1 January 2004 and 31 March 2007 in Stockholm, Sweden (Figure 1). We excluded those with major brain injuries, namely moderate or severe white matter injuries, grey matter injuries and/or high-grade IVH. The study population was a sub-cohort of the Extremely Preterm Infants in Sweden Study and included children born before 27 weeks of gestation. Low-grade IVH was defined as grades I–II.

Key notes

- We compared the impact that low-grade intraventricular haemorrhage (IVH) had on children born extremely preterm (EPT) with children born EPT without IVH.
- Nearly half (45%) of the cohort underwent magnetic resonance imaging at 10 years of age and 55% had neurodevelopmental assessments at 12 years.
- The IVH neonates were sicker than the children born EPT without IVH, but they did not have significantly smaller brain volumes or worse neurodevelopmental outcomes.

2.2 | Procedure

A trained neonatologist performed cranial ultrasounds during the children's hospital stays, as part of the clinical routine following EPT birth. IVH was scored and assessed according to Papile.[4] Magnetic resonance imaging (MRI) brain scans were performed at term age to detect possible white matter, grey matter and cerebellar injuries.

2.3 | Cranial ultrasound

Ultrasound scans were carried out to detect IVH during the first 3 days after birth and then at least once a week until the infant reached 27 weeks of age. They were then carried out once every 2 weeks and at term-equivalent age. Scans were performed more frequently if pathology was found. Infants with no IVH, or low-grade IVH, were included. Grade I was subependymal haemorrhage and grade II was intraventricular haemorrhage without dilatation.[4]

2.4 | MRI acquisition

The MRI scanning protocol, scoring and grading at term age was carried out according to Inder et al.[3] and has previously been described.[19] The imaging was carried out using a Philips Intera 1.5-T MRI system (Philips International, New York, USA), with a T1-weighted turbo spin echo: TE/TR/Flip = 9 ms/600 ms/90°, voxel = 0.7 × 0.7 × 4 mm, ETL = 3, FOV = 180 mm.[19]

The second MRI was performed at 10 years of age, using a Sigma 3.0-T MR scanner (GE HealthCare Technologies Inc., Illinois, USA) at the Karolinska University Hospital, Sweden. The MRI protocol included a sagittal 3D-T1 weighted with a BRAVO SPGR sequence: time to inversion = 400 ms, field of vision = 240 × 240 mm^2,

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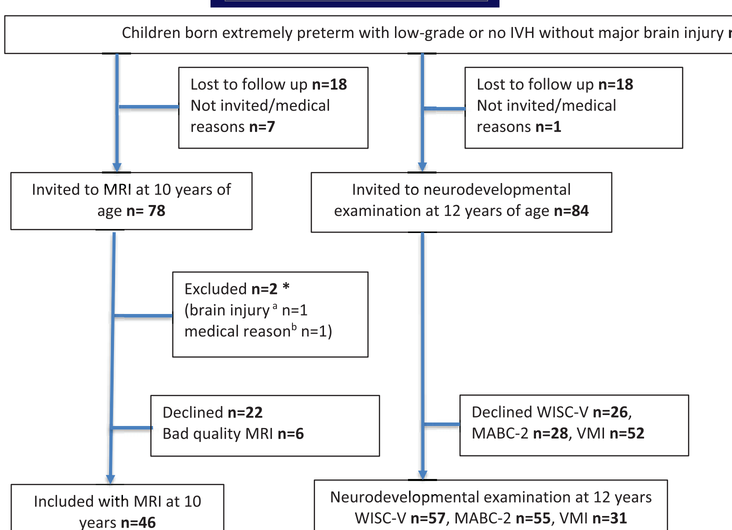

FIGURE 1 The study population.

flip angle = 12°, voxel size $1 \times 0.938 \times 0.938\,mm^3$ and slice thickness = 1.0 mm. The MRI protocol also included a diffusion tensor imaging multi-shell acquisition: TR = 6300 ms, TE = 72 ms, FOV = $220 \times 220\,mm^2$, slice thickness = 2.3 mm, 4b = 0, 30 b = $1000 s/mm^2$ and 60b = $2500\,s/mm^2$. The images were also visually assessed for brain injuries by the same neuroradiologist, who was blinded to their IVH status.

2.5 | Imaging pre-processing and processing

The cerebrum and cerebellum were segmented into grey and white matter from the three-dimension T1-weighted MRI images, using FreeSurfer version 7.2.0 (Harvard University, Massachusetts, USA).[20] The procedures used to pre-process and process the T1 high-resolution images included intensity non-uniformity correction, skull stripping and affine transformation to a Montreal Neurological Institute template. They also included intensity normalisation, removal of non-brain tissue, linear and nonlinear transformations to a probabilistic brain atlas and labelling of subcortical and allocortical structures. The right label for each single voxel was determined using spatial localisation priors. Cerebral and cerebellar volumes were automatically extracted into white matter and cortexes (Figures 2 and 3).

2.6 | Neurodevelopmental outcome at 12 years

A psychologist, blinded to the children's IVH status, examined them using the Weschler Intelligence Scale for Children—Fifth Edition (WISC-V).[21] This includes five index scores: processing speed, working memory, verbal comprehension, visual spatial and the fluid reasoning index. The full-scale intelligence quotients were then calculated from the index scores, with a mean of 100 ± 15.[21]

Motor performance was evaluated by a physiotherapist, blinded to the children's IVH status, using the Movement Assessment Battery for Children, Second Edition (MABC-2).[22] This is a standardised tool, with high validity and reliability, which is often used in clinical and research practice. The test includes three subtests: manual dexterity, ball skills and balance. An age-adjusted total score and standard scores are calculated from the raw scores of the three different subtests. A higher score indicates better performance and the mean standard score is 10.[22]

Visual motor integration (VMI) was examined by a psychologist with the Beery-Buktenica Developmental Test of Visual-Motor Integration, Sixth Edition.[23] Children are asked to use a pen and paper to copy 24 geometrical shapes. An age-adjusted standard score is calculated from the raw scores, depending on how many shapes the child can copy. The mean is set at 100 ± 15 points.

All these tests were carried out during a 1-day study-related appointment. The same psychologist tested the WISC-V and then the VMI. After a break, the physiotherapist examined motor performance.

2.7 | Statistical analysis

SPSS version 26.0 (IBM Corp, New York, USA) was used for the statistical analysis. Fisher's exact test, the Chi-square test or the Chi-square test for trend were used for the categorical outcomes. The student's *t*-test or Mann–Whitney *U*-test were used for continuous data, in order to identify differences in brain volume and neurodevelopmental outcomes between the groups of children born EPT, with and without low-grade IVH. The WISC-V index score, the MABC-2 standard scores and the visual motor integration standard score were used for the neurodevelopmental outcome analysis. Gestational age was used as a covariate in the general linear model analysis, with white matter, grey matter of

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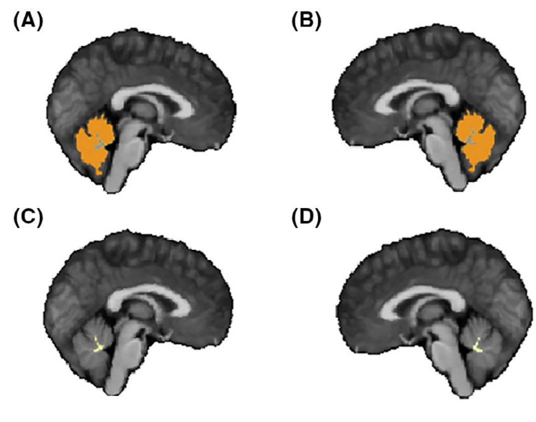

FIGURE 2 Automatic segmented volumes of cerebellum.

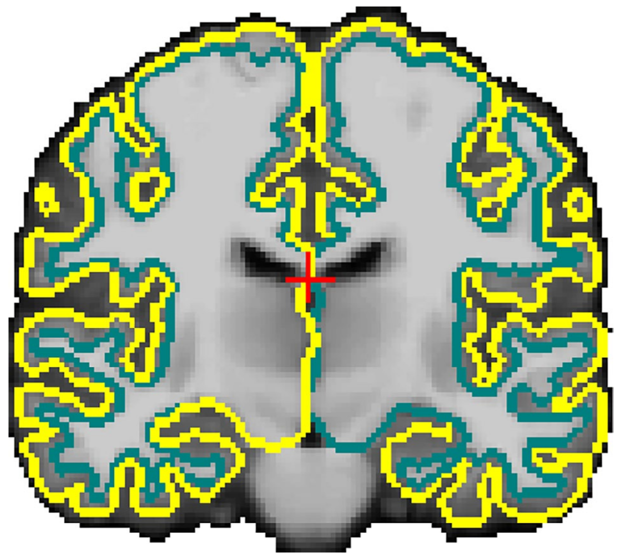

FIGURE 3 Automatic segmented grey and white matter volume of cerebrum.

the cerebrum and cerebellar volume as the dependent variables. The statistical significance level was set at a two-sided p value of less than 0.05.

2.8 | Ethics

The study was carried out in accordance with the Declaration of Helsinki and approved by the regional ethics committee in Stockholm (04–889/2, 2010/850–31/1, 2014/1035–32 and 2016/17). Written, informed consent was obtained from the parents of all the participants at each stage of the process.

3 | RESULTS

We invited 78 of the 103 children born EPT to undergo MRI brain scans at 10 years of age, as 18 were lost to follow-up and seven were not invited for medical reasons (Figure 1). The detailed characteristics of the 46 children who participated are presented in Table 1 and this shows that 15 had low-grade IVH and 31 did not. Two of the 46 children had not had an MRI brain scan at term age, because their parents declined. The median age (range) when the term scans were carried out was 40.4 (39.3–42.3) weeks of gestation in the children with IVH and 40.6 (39.3–45.3) weeks in the children born EPT without IVH. Their median age (range) at the time of the second scans were 10.1 (9.1–11.8) years in the low-grade IVH group and 10.3 (9–11.4) years in the children born EPT without low-grade IVH.

At 12 years of age, 84 of the 103 children were invited to undergo a neurodevelopmental assessment, as 18 were still lost to follow up and one was not invited for medical reasons (Figure 1).

Of these, 68% underwent the WISC-V, 65% the MABC-2 and 37% the VMI. Tables S1–S3 compare the characteristics of the children who took part, by whether they had low-grade IVH or no IVH.

There were no significant differences between the groups. The sub-group who underwent the WISC-V assessment were significantly more likely to undergo surgical ligation for patent ductus arteriosus if they had low-grade IVH than children born EPT without IVH ($p = 0.046$ [Table S1]). Those who underwent the MABC-2 assessments were significantly more likely to undergo surgical ligation for patent ductus arteriosus ($p = 0.004$) and spend more days on mechanical ventilation ($p = 0.04$) if they had low-grade IVH than the children born EPT without IVH (Table S2). Children with IVH who underwent the VMI assessment were born at a significantly lower gestational age ($p = 0.01$), spent more days on mechanical ventilation ($p = 0.02$) and were more likely to receive surgical ligation for patent ductus arteriosus ($p = 0.03$) than the children born EPT without IVH (Table S3).

3.1 | Perinatal characteristics

The low-grade IVH group were born at a lower gestational age, spent more days on mechanical ventilation, had a higher incidence of necrotising enterocolitis and were more likely to undergo surgical ligation for patent ductus arteriosus than the children born EPT without low-grade IVH (Table 1).

3.2 | Brain volumes

At 10 years of age, there were no significant differences between the groups in the white matter in the cerebrum or cerebellum, the cortex of the cerebrum or cerebellum or the total cerebellar volume. These results remained the same after adjusting for gestational age (Table 2).

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TABLE 1 Characteristics and magnetic resonance imaging findings in the 46 children born extremely preterm who had brain scans at 10 years of age.

	No IVH $n=31$	IVH (I-II) $n=15$	*p* Value
Perinatal			
Birth weight (g), mean ± SD	864 ± 151	841 ± 146	0.64
Gestational age at birth, weeks, median (range)	26.1 (23.6–26.6)	25.2 (23.1–26.6)	0.03
Male sex, *n* (%)	17 (55)	5 (33)	0.22
Small for gestational age, *n* (%)	2 (6)	0 (0)	1.00
Antenatal steroids, *n* (%)	30 (97)	13 (87)	0.24
BPD, oxygen at age 36 weeks, *n* (%)	7 (23)	7 (47)	0.17
Mechanical ventilation (days), median (range)	2 (0–41)	12 (0–43)	0.02
Necrotising enterocolitis Bell's grade 2–3, *n* (%)	2 (6)	4 (27)	0.04
Patent ductus arteriosus, treated with ibuprofen, *n* (%)	19 (61)	10 (67)	1.00
Patent ductus arteriosus, surgical ligation, *n* (%)	5 (16)	8 (53)	0.01
Postnatal steroids, *n* (%)	3 (10)	1 (7)	1.00
Retinopathy of prematurity, laser treatment, *n* (%)	3 (10)	3 (20)	0.38
Sepsis, *n* (%)	18 (58)	13 (87)	0.09
Magnetic resonance imaging at term age ($n=44$)[a]			
Mild white matter abnormality, *n* (%)	12 (39)	5 (33)	0.75
Magnetic resonance imaging at 10 years of age			
Age at scan, years, median (range)	10.3 (9–11.4)	10.0 (9.1–11.3)	0.93
Cerebellar injury, *n*	0	0	—
Intracranial volume, mean (cm^3) ± SD	1402.9 ± 105.1	1356.6 ± 96.9	0.16

Note: Significant value, $p<0.05$. Sepsis was defined as positive blood cultures or a clinical picture of sepsis in association with an elevated C-reactive protein or leucocyte count.

Abbreviations: BPD, bronchopulmonary dysplasia; SD, standard deviation.

[a]Two children did not have MRI scans at term age as the parents declined.

TABLE 2 Differences in volume (cm^3) in brain regions at 10 years of age between 46 children born extremely preterm with and without low-grade IVH.

	No IVH $n=31$	IVH (I-II) $n=15$	*p* Value	Adjusted *p* value[a]
Cerebrum region mean ± SD				
Total grey matter	742.7 ± 58.1	713.5 ± 60.6	0.13	0.16
Total white matter	402.8 ± 47.5	386.7 ± 43.3	0.26	0.37
Cerebellum region mean ± SD				
Right-side white matter	12.9 ± 1.2	12.3 ± 1.9	0.21	0.46
Right-side cortex	58.4 ± 5.4	55.9 ± 4.9	0.14	0.30
Left-side white matter	13.6 ± 1.4	13.0 ± 1.6	0.23	0.45
Left-side cortex	58.3 ± 5.9	55.0 ± 4.9	0.06	0.14
Total cerebellum	143.6 ± 12.3	136.7 ± 11.2	0.07	0.19

Note: Significant value, $p<0.05$.

Abbreviation: SD, standard deviation.

[a]Adjusted for gestational age.

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3.3 | Neurodevelopmental outcomes

At 12 years of age, the low-grade IVH group performed significantly better in the processing speed index than the children born EPT without low-grade IVH There were no significant differences in working memory, verbal comprehension, visual spatial, and the fluid reasoning index of the WISC-V (Table 3). In addition, there were no significant differences between the groups in the MABC-2 subtest or total scores or the VMI results (Table 3).

3.4 | Non-participants

There were no differences in neonatal characteristics between the children in the study and dropout groups (Table S4).

4 | DISCUSSION

Children born EPT with low-grade IVH were sicker than the children born EPT without low-grade IVH during the neonatal period. They had a lower gestational age at birth, more days on mechanical ventilation, a higher incidence of necrotising enterocolitis and were more likely to undergo surgical ligation for patent ductus arteriosus. The low-grade IVH group did not have a smaller volume of cerebrum or cerebellum at 10 years of age than the children born EPT without low-grade IVH and there were no differences in neurodevelopmental outcomes at 12 years of age between the groups.

IVH appears in children born preterm due to a disturbance in the cerebral blood flow and the underdevelopment of the vulnerable germinal matrix.[24] Padilla et al. found that subjects with low-grade IVH had reduced cerebellar volumes at term age than those born EPT without IVH.[25] Others studies have reported similar results at term age in children born preterm with IVH.[8,11] Despite this, studies on the impact of low-grade IVH on brain growth during childhood have been scarce. The current study found that when children born EPT with low-grade IVH reached 10 years of age, their MRI scans did not show significantly reduced volumes in the cerebrum or cerebellum than children born EPT without IVH. Studies have also described the mechanism of white matter injuries and reported that IVH damaged the oligodendrocyte progenitors and disturbed the cortical layers in the grey matter.[26,27] However, we did not found any influence of low-grade IVH on the cerebral volumes of children born EPT and could speculate that those who showed reduced cerebellar volume at term age subsequently caught up during infancy and childhood.

There have been inconsistent results regarding the impact of low-grade IVH on neurodevelopmental outcomes.[12–18,28] Our study found that neurodevelopment did not differ in children born EPT with and without low-grade IVH when they reached 12 years of age. This was in line with Payne et al., who reported on neurodevelopmental outcomes around 2 years of age.[29] In contrast, Patra et al.[13] found differences in neuromotor outcomes at around 2 years of age when they studied EPT-born children with and without low-grade IVH.[13] However, Patra et al. only used the mental developmental index of the Bayley Scales of Infant Development—Second Edition when their subjects were 2 years of age.[13] Only a few studies have presented findings on the influence of low-grade IVH and outcomes in later childhood. Hollebrandse et al.[14] found a higher risk of cerebral palsy in children born EPT with low-grade IVH when they reached 8 years of age than children born EPT without IVH. But they did not find differences in cognitive function, or overall motor function, using the WISC-III or WISC-IV and MABC or MABC-2 respectively. However,

TABLE 3 Neurodevelopmental outcomes at 12 years of age in children born extremely preterm with and without low-grade IVH.

Outcome assessment			*p* Value
WISC-V index score mean ± SD	No IVH *n* = 34	IVH (I-II) *n* = 23	
Verbal comprehension	99 ± 17	104 ± 16	0.21
Visual spatial	90 ± 16	97 ± 17	0.10
Fluid reasoning	94 ± 15	95 ± 14	0.69
Working memory	88 ± 15	94 ± 17	0.14
Processing speed	90 ± 14	99 ± 17	0.02
Full-scale intelligence quotient	92 ± 16	98 ± 15	0.15
MABC-2 standard score mean ± SD	No IVH *n* = 34	IVH (I-II) *n* = 21	
Total score	8 ± 4	8 ± 3	0.84
Manual dexterity	8 ± 3	9 ± 3	0.46
Aiming and catching	9 ± 4	8 ± 4	0.42
Balance	9 ± 4	8 ± 4	0.64
Visual motor integration standard score mean ± SD	No IVH *n* = 19	IVH (I-II) *n* = 12	
	88 ± 19	91 ± 14	0.65

Note: Significant value, $p < 0.05$.

Abbreviations: MABC-2, Movement Assessment Battery for Children, Second Edition; SD, Standard deviation; WISC-V, Weschler Intelligence Scale for Children, Fifth Edition.

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it is not clear whether they adjusted the data for other brain abnormalities.[14] In contrast, Campbell et al.[16] did not find any association between IVH and motor or cognitive outcomes when children born EPT reached 10 years of age.[16] Similarly, Ann et al.[28] did not find any correlation between low-grade IVH and cognition when children who were born preterm reached 18 years of age.[28]

4.1 | Strengths and limitations

One strength of this study was that the cohort received regular ultrasound assessments after they were born. They also had MRI assessments at term age and 10 years of age and their neurodevelopment was comprehensively assessed at 12 years of age. This meant that we were able to specifically focus on low-grade IVH, defined as grades I–II, and exclude major brain injuries that could have affected the results. Ultrasound is routinely performed to detect IVH in children born EPT. The clinical significance of finding low-grade IVH, and its possible influence on neurodevelopment, is important, especially when talking to parents. Being born EPT carries a risk of poorer neurodevelopmental outcomes, but this study shows that the outcomes were not worse for children born EPT with low-grade IVH than for children born EPT without IVH.

Another strength of the study was that we used standardised, automatic segmentation algorithms that reduce the influence of human bias, due to manual segmentation of the brain. Automatic segmentation can produce errors, but we visually assessed the images after segmentation and this meant that the risk was limited.

The major limitation of this study was the sample size and the risk for type II errors. A higher sample size could have highlighted differences in brain volumes and outcomes. Nevertheless, the mean values for brain volumes, WISC-V, MABC-2 and VMI scores were quite similar between the two groups. We were limited by the high attrition rates that are common in long-term follow-up studies. There were also specific difficulties in obtaining high-quality scans from children born EPT, who may have had other health and developmental issues that could have affected their scan quality and participation. This means that it is possible that minor effects on brain volume and neurodevelopment went undetected. Despite these limitations, our sample size was in the same range as previous studies that pointed to the negative effects of low-grade IVH.[30] Another limitation was that we did not adjust for resilience factors during childhood, such as other health conditions and training motor and cognitive skills that may have influenced neurodevelopment at 12 years of age. Including a control group of term-born children in the study could have strengthened it. Finally, more studies are needed to confirm our results.

5 | CONCLUSION

The aim of this prospective study was to compare the neonatal characteristics and outcomes of Swedish children who were born EPT, with and without low-grade IVH. The low-grade IVH group was sicker during the neonatal period than the children born EPT without IVH and had more complications. They were born at lower gestational ages, spent more days on mechanical ventilation, had a higher incidence of necrotising enterocolitis and were more likely to undergo surgical ligation for patent ductus arteriosus. However, they did not have significantly smaller brain volumes at 10 years of age or worse neurodevelopmental outcomes at 12 years of age.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The data are available from the corresponding author upon reasonable request.

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