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ORIGINAL ARTICLE

Perinatal risk factors for developmental coordination disorder in children born extremely preterm

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Abstract

Aim: Children born extremely preterm frequently have developmental coordination disorder (DCD). We aimed to evaluate perinatal risk factors for DCD.

Methods: Swedish national cohort study including 226 children born before 27 gestational weeks without major neurodevelopmental disabilities at 6.5 years. Outcome was DCD, defined as ≤5th percentile on the Movement Assessment Battery for Children-Second Edition. Perinatal risk factors were evaluated using multivariable logistic regression.

Results: DCD was present in 84/226 (37.2%) children. Of the risk factors known at 40 weeks gestation, independent and significant risk factors for DCD were: mother's age at delivery (odds ratio [OR] 1.73, 95% confidence interval [CI] 1.07–2.80); pre-eclampsia (2.79, 1.14–6.80); mother born in a non-Nordic country (2.23, 1.00–4.99); gestational age per week increase (0.70, 0.50–0.99) and retinopathy of prematurity (2.48, 1.26–4.87). Of factors known at discharge, postnatal steroids exposure (2.24,

Abbreviations: BPD, bronchopulmonary dysplasia; CI, confidence intervals; CRIB, Clinical Risk Index for Babies; DCD, developmental coordination disorder; EPT, extremely preterm infants; EXPRESS, Extremely Preterm Infants in Sweden Study; IVH, intraventricular haemorrhage; MABC-2, Movement Assessment Battery for Children–Second Edition; ORs, odds ratios; PDA, patent ductus arteriosus; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity; SD, standard deviation.

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1.13–4.46) and mechanical ventilation (1.76, 1.06–2.09) were independent risk factors when added to the model in separate analyses.

Conclusion: The risk of DCD in children born extremely preterm was multifactorial and associated with gestational age largely mediated by ROP, maternal factors, pre-eclampsia, administration of postnatal steroids and mechanical ventilation. These risk factors are common among children born extremely preterm, contributing to their high risk of DCD.

KEYWORDS
developmental coordination disorder, perinatal, preterm, risk factors

1 | INTRODUCTION

Developmental coordination disorder (DCD) describes motor coordination problems that are not explained by other neurodevelopmental impairments and affect an individual's daily life and/or academic achievements.[1] Children born preterm have an increased risk of DCD and up to 6–8 times increased risk for DCD has been reported, compared to children born at term.[2]

Several studies have reported risk factors for cerebral palsy in preterm children. However, the associations with perinatal and neonatal factors are less well described for risk of DCD, especially for children born at the limit of viability. Associations with several perinatal variables have been reported in very preterm children, such as male sex, low gestational age, the administration of postnatal steroids and moderate to severe white matter injury.[3,4] The risk for these neonatal morbidities increased with decreasing gestational age, which means that infants born EPT are particularly vulnerable.

The Extremely Preterm Infants in Sweden Study (EXPRESS), which forms the basis for this study, is a large national cohort of children born at <27 weeks of gestation. We have previously reported a 37% rate of DCD among extremely preterm children in the EXPRESS cohort at 6.5 years of age and a 5.5% rate of DCD in the EXPRESS control group.[5]

The aim of this study was to expand on that research, by evaluating the associations between gestational age and perinatal and neonatal risk factors with DCD in children from the EXPRESS cohort at 6.5 years.

Key Notes

- This Swedish nationwide population-based cohort study describes the associations between perinatal risk factors in children born extremely preterm and developmental coordination disorder (DCD), a motor impairment that affects children who do not have major neurodevelopmental disabilities and which has a negative impact on their daily lives.
- There were 84 of 226 children born extremely preterm that had DCD.
- The DCD risk was multifactorial and was associated with several risk factors.

2 | PATIENTS AND METHODS

2.1 | Study population

The EXPRESS cohort includes all children born in Sweden before 27+0 gestational weeks, between 1 January 2004 and 31 March 2007. The recruitment, follow-up procedures and neurodevelopmental outcomes until 6.5 years of age have been reported previously.[5–11] There were 462 children who were alive at 6.5 years of age and 441 (95.0%) of the parents provided consent. These 441 children were followed up at 6.5 years of age alongside 371 controls born at 37–41 gestational weeks.[6] The background characteristics at 6.5 years have previously been reported for both the children born extremely preterm and the controls and were similar in the children born extremely preterm who were or were not followed up.[6] A paediatrician clinically assessed the 441 children at 6.5 years of age: 382 in person and 59 by reviewing their medical records. Two hundred and seventy-four children who were free of cerebral palsy and any cognitive, visual or hearing impairment formed the present study population.

2.2 | Measures

2.2.1 | Perinatal, neonatal and sociodemographic data

Perinatal and neonatal data for the EXPRESS cohort were collected at birth and prospectively during the first 180 days of hospitalisation or until discharge. Gestational age was based on ultrasound screening before 20 postmenstrual weeks in 95% of cases. Administration of antenatal steroids was defined as at least one dose of betamethasone prior to delivery. Pre-eclampsia was defined, according to standard

criteria, and patent ductus arteriosus (PDA) as a symptomatic PDA that required pharmacological treatment, surgical ligation or both. Small for gestational age was a birth weight of <2 SD below the Swedish intrauterine growth standard. Intraventricular haemorrhage (IVH) was defined according to Papile and periventricular leukomalacia (PVL) according to de Vries; a brain injury was IVH and/or PVL. Bronchopulmonary dysplasia (BPD) was defined as the need for supplemental oxygen at 36 weeks postmenstrual age and severe BPD if the need for oxygen was ≥30% at 36 weeks postmenstrual age. Sepsis was defined as clinical symptoms combined with a positive blood culture and necrotising enterocolitis was defined according to Bell's criteria. Retinopathy of prematurity (ROP) was defined according to the International Classification for Retinopathy of Prematurity. The Clinical Risk Index for Babies (CRIB) score evaluates the infant's mortality risk during the first hours of life and was used as a proxy for the severity of neonatal illness. References for the aforementioned definitions can be found in the original EXPRESS study report.[7]

2.2.2 | Assessment at 6.5 years of uncorrected age

The children underwent a medical clinical examination, psychological tests and had their motor and ophthalmological function assessed at 6.5 years of uncorrected age. The parents answered questionnaires including demographic data. Cognitive impairment was defined as less than−2 standard deviations (SDs) on the Wechsler Intelligence Scale for Children-Fourth Edition, compared with the means and SDs of the controls in the EXPRESS study. For children with missing test results, information on cognitive impairment was collected from medical charts or from the physical examination of the child. Visual and hearing impairment was defined as any visual or hearing impairment.

2.2.3 | Definition of DCD

The child's motor performance was assessed with the Movement Assessment Battery for Children-Second Edition (MABC-2), which is a standardised test of motor function that has demonstrated high reliability and validity in children.[12] It measures gross motor function by assessing ball skills in three different tasks, balance in three different tasks and fine motor function by assessing manual dexterity in three different tasks. According to the manual, a total test result of ≤5th percentile indicates definitive motor problems and a result between the 6th and the 15th percentile indicates borderline motor problems. To avoid false positives, we used the fifth percentile as a cut-off for defining DCD. Since MABC-2 results have been reported to vary between different countries and contexts, we expressed the results relative to the EXPRESS control group, as previously described.[5] We operationalised the Diagnostic and Statistical Manual of mental disorders-fifth edition (DSM-5) diagnostic criteria for DCD[13] to include only children who were free from neurodevelopmental impairments (cerebral palsy, cognitive impairment, visual impairment or hearing impairment).

2.2.4 | Ethical approval

The parents provided written informed consent and the study was approved by the regional ethics review board of Lund, Sweden (DNR 42/2004, 2009/9).

2.2.5 | Statistics

We compared the background characteristics between the children with and without MABC-2 data using the Student's *t*-test, the Mann–Whitney *U* test, the chi-square test and the Fisher's exact test, as appropriate.

Univariable logistic regression with odds ratios (ORs) and 95% confidence intervals (CIs) and Student's *t*-test with mean difference was used to evaluate any associations between gestational age, potential risk factors (specified in Table 1) and DCD. Variables with a *p*-value <0.2 and/or deemed clinically relevant, were sequentially entered into a stepwise multivariable regression model in chronological order. The six timepoints were factors that were known at birth, 5 min after birth, 12 h after birth, 1 week after birth, at 40 weeks of postmenstrual age and when the child was discharged home. We retained factors with *p*-values of <0.2 in the model until the final time point, whereas factors with *p*-values ≥0.2 were eliminated. Pseudo R2 (Nagelkerke) was used to estimate the variance explained by the final model.

Data were missing for some children on maternal education ($n = 1$), pre-eclampsia ($n = 12$), amnionitis ($n = 12$), a CRIB score ≥ 10 ($n = 7$), BPD ($n = 19$) and ROP ($n = 1$), and these children were excluded from the univariable analyses. Missing data on pre-eclampsia, the CRIB score, BPD and ROP were coded as absent in the multivariable analyses, because the sensitivity analyses showed almost identical risk estimates for the respective unknown groups compared to the condition absent groups. All the analyses were performed using SPSS, version 25.0 (IBM Corp). The SPSS complex samples design was applied to account for any correlations among multiple births. A two-sided *p*-value of <0.05 and a confidence interval that did not cross 1.0 was considered statistically significant.

3 | RESULTS

3.1 | Study group

Of 274 children born EPT in the study population, 226 had complete MABC-2 data at 6.5 years of age (Figure 1). The characteristics of children with and without MABC-2 data are reported in Table 1. With one exception, the findings were similar: mothers of children with MABC-2 data were more likely to be born in a Nordic country. We have previously reported the prevalence of DCD in 229 children born EPT from the EXPRESS cohort and the background characteristics of the term controls. This study excluded three EPT children, because they were too old when they

TABLE 1 Characteristics of eligible children born extremely preterm at <27 weeks of gestation without neurodevelopmental disabilities: cerebral palsy and/or intellectual, visual or hearing impairment. Compared with and without MABC-2 results.

Perinatal characteristics	Children with MABC-2 data *n* = 226	Eligible children without MABC-2 data *n* = 48	*p*-value
Gestational age, weeks, mean (SD)	25.1 (0.94)	25.1 (1.00)	0.82
Birth weight, grams, mean (SD)	799 (170)[a]	823 (176)[a]	0.39
Birth weight z-score, mean (SD)	−0.82 (1.19)[a]	−0.61 (1.23)[a]	0.28
Pre-eclampsia, *n* (%)	30/214 (14.0)	5/46 (20.0)	0.82
Amnionitis, *n* (%)	30/214 (14)	9/45 (20.0)	0.36
Small for gestational age, *n* (%)	39/226 (17)	7/48 (14.6)	0.83
Male sex, *n* (%)	113/226 (50)	24/48 (50.0)	1.00
Caesarean section, *n* (%)	142/226 (63)	25/48 (52.0	0.19
Antenatal steroids, *n* (%)	211/226 (93.4)	46/48 (95.8)	0.75
Multiple birth, *n* (%)	45/226 (19.9)	13/48 (27.1)	0.33
Primiparity, *n* (%)	142/226 (62.8)	31/48 (64.6)	0.87
APGAR score at 5 min <7, *n* (%)	65/226 (28.8)	19/48 (39.6)	0.17
Clinical Risk Index for Babies score > 10, *n* (%)	12/219 (5.5)	4/48 (8.3)	0.50
Neonatal characteristics			
Days of mechanical ventilation, median (range)	9 (0–49)[a]	7 (0–66)[a]	0.94
Postnatal steroids, *n* (%)	41/226 (18.1)	13/48 (27.2)	16.5
Bronchopulmonary dysplasia, *n* (%)	128/207 (61.8)	29/42 (69.0)	0.48
Severe bronchopulmonary dysplasia, *n* (%)	41/207 (19.8)	9 /42 (21.4)	0.83
Sepsis, *n* (%)	103/226 (45.6)	24/48 (50.0)	0.63
Necrotising enterocolitis, *n* (%)	13/226 (5.8)	1/48 (2.0)	0.48
Patent ductus arteriosus, treated, *n* (%)	128/226 (56.6)	27/48 (56.3)	1.00
Patent ductus arteriosus, ligated, *n* (%)	54/226 (23.9)	13/48 (27.1)	0.71
Retinopathy of prematurity ≥ stage 3, *n* (%)	59/225 (26.2)	9/48 (18.8)	0.36
Intraventricular haemorrhage grade 1–2, *n* (%)	66/226 (29.2)	8/47 (17.0)	0.11
Intraventricular haemorrhage stage 3–4, *n* (%)	11/226 (4.9)	1/47 (2.1)	0.70
Periventricular leukomalacia, *n* (%)	7/226 (3.1)	2/48 (4.2)	0.66
Breastmilk at discharge *n* (%)	129/226 (57.1)	21/48 (43.8)	0.25
No breastmilk	73/202 (36.1)	22/45 (48.9)	
Partly fed breastmilk	49/202 (24.3)	10/22 (22.2)	
Exclusively fed breastmilk	80/202 (39.6)	13/45 (28.9)	
Maternal characteristics			
Mother's age at delivery, *n* (%)			
<25 years	31/226 (13.7)	5/48 (10.4)	0.22
25–34 years	134/226 (59.3)	24/48 (50.0)	
≥35 years	61/226 (27.0)	19/48 (39.6)	
Maternal education, *n* (%)			
≤9 years	15/225 (6.7)	4/30 (13.3)	0.43
10–11 years	13/225 (5.8)	2/30 (6.7)	
12–13 years	75/225 (33.3)	11/30 (36.7)	
14–15 years	65/225 (28.9)	5/30 (16.7)	
16 years	22/225 (9.8)	5/30 (16.7)	
17 years	35/225 (15.6)	3/30 (10.0)	
Mother born in a non-Nordic country, *n* (%)	33/226 (14.6)	18/48 (37.5)	<0.001

Note: Differences between proportions were evaluated with chi-square tests; differences between mean values with student's *t*-test. The difference between days on mechanical ventilation was obtained by Mann–Whitney *U* test.

Abbreviation: SD: standard deviation.

[a]*n* values were 226 and 48 respectively.

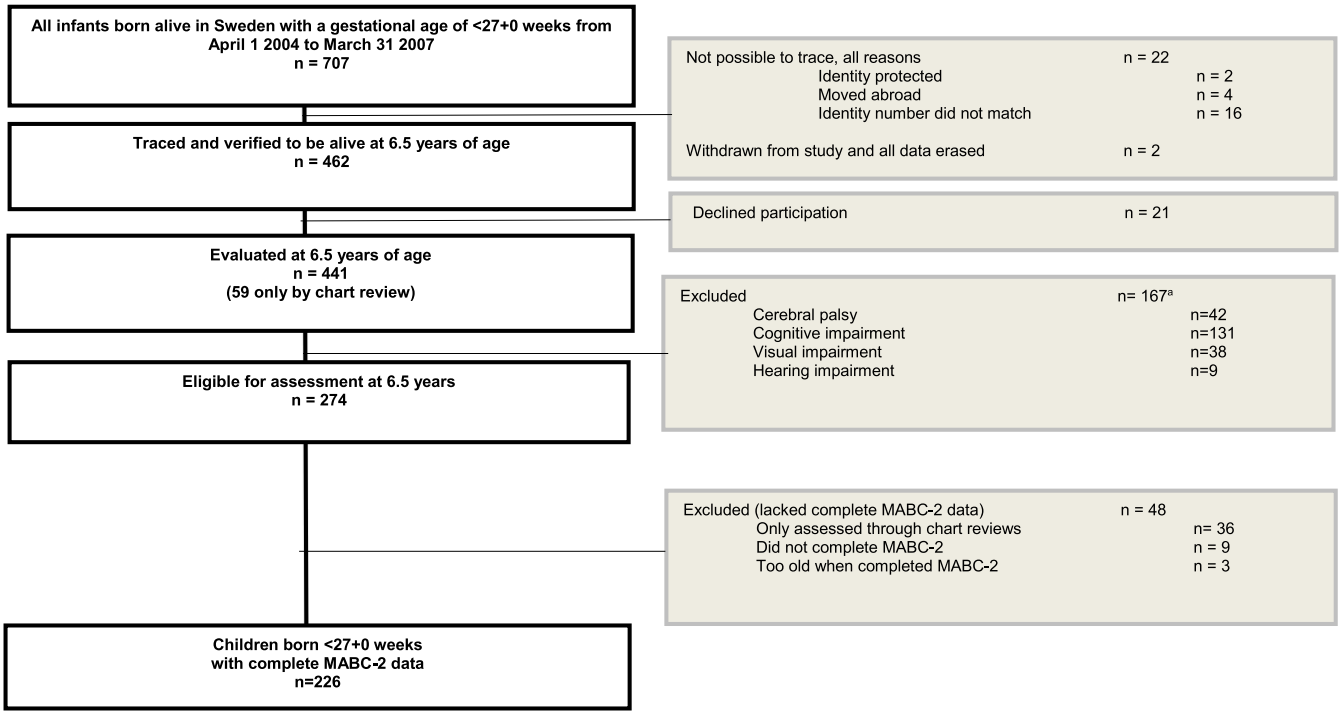

FIGURE 1 Study population.

performed the MABC-2. This left us with a study group of 226 children.

3.2 | Prevalence of DCD

Of the 226 children born EPT, 84 (37.2%) had DCD. The baseline characteristics of the children with and without DCD are presented in Table 2.

3.3 | Association between potential risk factors and DCD in children born EPT

The variables that had a $p < 0.2$ in the univariable analyses included the mother's age at the time of EPT birth, gestational age at birth, birth weight, Apgar score of <7 at 5 min, a CRIB score ≥ 10, PDA, ROP ≥ stage 3, BPD, receipt of any postnatal steroids and duration of mechanical ventilation (Table 2). These factors were entered sequentially into the multivariable regression model. We also entered factors that were considered clinically relevant, namely pre-eclampsia, mother born in a non-Nordic country, male sex, the child's birth weight z-score and any brain injury or sepsis.

Table 3 presents the results of the multivariable analysis. Significant variables before, during and up to 5 min after the birth were the mother's age at the time of the birth, pre-eclampsia and gestational age. Adding the CRIB score at 12 h did not have any impact on the associations. At the time point of 40 weeks postmenstrual age PDA, brain injury, ROP ≥stage 3, BPD and sepsis were added to the model. Mother's age, whether she was born in a non-Nordic country, pre-eclampsia and ROP ≥stage 3 were significant. The effect of gestational age at birth was attenuated but remained significant. At the time point discharge home, administration of postnatal steroids and mechanical ventilation were added one at a time and analysed separately. Both were significant in separate analyses but the association between administration of postnatal steroids and DCD weakened when both factors were analysed in conjunction. The association of ROP, pre-eclampsia, maternal factors and mechanical ventilation remained with DCD remained in the final model at discharge, whereas the association between gestational age at birth and DCD weakened.

4 | DISCUSSION

This nationwide cohort study investigated perinatal risk factors for DCD in children born EPT during 2004–2007. Children included in the study group were followed up at 6.5 years of age and did not have cerebral palsy or cognitive and/or visual and hearing impairments.

We found that the maternal factors including pre-eclampsia and infant factors ROP, mechanical ventilation, receipt of postnatal steroids and gestational age at birth contributed to the risk of DCD either at 40 weeks of postmenstrual age or at discharge home.

Even though gestational age was a strong risk factor at 1 week of age, the association was considerably attenuated when neonatal morbidities were included at 40 weeks of postmenstrual age. Gestational age is strongly associated with the risk for neonatal morbidities, such as PDA, ROP, BPD and the duration of mechanical

TABLE 2 Baseline characteristics and univariable analysis of potential risk factors for DCD in children born extremely preterm at <27 weeks of gestation, without a diagnosis of cerebral palsy or cognitive or visual impairment or hearing impairment at 6.5 years of age.

	DCD *n* = 84	No DCD *n* = 142	Odds ratio or mean difference (95% CI)	*p*-value
Factors known before birth				
Mother's age at delivery				0.09
<25 years	7/84 (8.3)	24/142 (17)		
25–35 years	49/84 (58.3)	85/142 (60)		
>35 years	28/84 (33.3)	33/142 (23)		
Pre-eclampsia, *n* (%)	16/81 (19.8)	14/133 (10.5)	2.09 (0.96–4.56)	0.06
Amnionitis, *n* (%)	8/81 (9.9)	22/133 (16.5)	0.55 (0.23–1.31)	0.18
Antenatal steroids, *n* (%)	78/84 (92.9)	133/142 (93.7)	0.88 (0.30–2.57)	0.81
Primipara, *n* (%)	55/84 (65.5)	87/142 (61.3)	1.11 (0.86–1.43)	0.41
Mother born in a non-Nordic country, *n* (%)	16/84 (19.0)	17/142 (12.0)	1.73 (0.82–3.64)	0.15
Maternal education[a]	–	–		0.95
≤9 years	6/83 (7.2)	9/142 (6.3)		
10–11 years	5/83 (6.0)	8/142 (5.6)		
12–13 years	28/83 (33.7)	47/142 (33.0)		
14–15 years	22/83 (26.5)	43/142 (30.2)		
16 years	7/83 (8.4)	15/142 (10.6)		
≥17 years	15/83 (18.1)	20/142 (14.0)		
Factors known at birth				
Male sex, *n* (%)	48/84 (57.1)	65/142 (45.8)	1.58 (0.92–2.72)	0.10
Gestational age, weeks, mean (SD)[a]	24.8 (0.96)	25.3 (0.90)	0.42 (0.17–0.67)	**0.001**
22 weeks, *n* (%)	1/84	0	0.62 (0.46–0.83)	**0.007**
23 weeks, *n* (%)	6/84 (7.1)	8/142 (5.6)		
24 weeks, *n* (%)	22/84 (26.2)	19/142 (13.4)		
25 weeks, *n* (%)	32/84 (38.1)	44/142 (31.0)		
26 weeks, *n* (%)	23/84 (27.4)	71/142 (50.0)		
Birth weight, grams, mean (SD)	758[b] (160)	823[b] (172)	64.64 (19.20–110.08)	**0.005**
Birth weight z-score, mean (SD), per SD increase[a]	−0.89[b] (1.28)	−0.78[b] (1.15)	0.93 (0.74–1.16)	0.50
Small for gestational age, *n* (%)	18/84 (21.4)	21/142 (14.8)	1.57 (0.78–3.16)	0.20
Caesarean section, *n* (%)	48/84 (57.1)	94/142 (66.2)	0.68 (0.39–1.19)	0.17
Multiple birth, *n* (%)	17/84 (20.2)	28/142 (19.7)	1.03 (0.53–2.03)	0.93
APGAR score at 5 min <4, *n* (%)	5/84 (6.0	8/142 (5.6)	1.06 (0.34–3.35)	0.92
APGAR score at 5 min <7, *n* (%)	31/84 (36.9)	34/142 (23.9)	1.86 (1.03–3.34)	**0.04**
Factors known 12 h after birth				
Clinical Risk Index for Babies score > 10, *n* (%)	9/82 (11.0)	3/137 (2.2)	5.51 (1.45–20.98)	**0.01**
Factors known at 40 weeks of postmenstrual age				
Patent ductus arteriosus, *n* (%)	56/84 (66.7)	72/142 (50.7)	1.94 (1.11–3.41)	**0.02**
Intraventricular haemorrhage grade 1–2, *n* (%)	25/84 (29.8)	41/142 (28.9)	1.04 (0.58–1.89)	0.89
Brain injury (intraventricular haemorrhage grade 3–4 and/or periventricular leukomalacia), *n* (%)	9/84 (10.7)	8/142 (5.6)	2.01 (0.74–5.43)	0.17
Retinopathy of prematurity ≥ stage 3, *n* (%)	33/84 (39.3)	26/141 (18.4)	2.86 (1.55–5.27)	**0.001**

TABLE 2 (Continued)

	DCD $n = 84$	No DCD $n = 142$	Odds ratio or mean difference (95% CI)	p-value
Bronchopulmonary dysplasia (BPD), per category increase[a]	–	–		**<0.001**
No BPD, *n* (%)	21/78 (26.9)	58/129 (45.0)		
Mild BPD (<30% oxygen at 36 weeks), *n* (%)	36/78 (46.2)	51/129 (39.5)		
Severe BPD (>30% oxygen at 36 weeks), *n* (%)	21/78 (26.9)	20/129 (15.5)		
Sepsis, verified, *n* (%)	43/84 (51.2)	60/142 (42.3)	1.43 (0.83–2.47)	0.19
Factors known at discharge home				
Necrotising enterocolitis, *n* (%)	7/84 (8.3)	6/142 (4.2)	2.06 (0.67–6.35)	0.21
Administration of postnatal steroids, *n* (%)	26/84 (31.0	15/142 (10.6)	3.80 (1.87–7.70)	**<0.001**
Days of mechanical ventilation, per category increase[a]	–	–		**<0.001**
0–7 days, *n* (%)	29/84 (35)	88/142 (62)		
8–28 days, *n* (%)	41/84 (49)	43/142 (30)		
>28 days, *n* (%)	14/84 (17)	11/142 (8)		
Breastmilk				0.41
No breastmilk	27/73 (35.1)	46/129 (35.7)		
Partly fed breastmilk	21/73 (28.8)	28/129 (21.7)		
Exclusively fed breastmilk	25/73 (34.2)	55/129 (42.6)		
Age at MABC-2 assessment				
Age at MABC-2 assessment, months, median (range) and per month increase[a]	79[b] (75–85)	79[b] (74–85)	0.92 (0.79–1.07)	0.26

Abbreviations: CI, Confidence interval; MABC-2, Movement Assessment Battery for Children-Second Edition; SD, Standard deviation.

[a]Analysed as a continuous variable. The remaining variables analysed as categorical variables.

[b]No missing data.

Bold values are statistically significant of $p < 0.05$.

ventilation, that is, to factors that are causally and more directly related to outcom.[14] Moreover, the effect of gestational age may also have been less prominent in our cohort because the gestational age range was narrow, at 22–26 weeks.

Boys born preterm tend to have a higher risk of neonatal mortality, morbidity and adverse neurodevelopmental outcomes than preterm girls.[15] However, our study found that the increased risk for DCD was not statistically significant in boys. It is possible that this could be partly explained by the fact that we excluded children with neurodevelopmental impairments. Other studies have reported conflicting results. Some studies on preterm infants have found an increased risk for DCD in boys,[4,16,17] but others have not.[18] With the exception of preterm birth, male sex is the only risk factor that has been consistently shown to be associated with DCD in the general population.[19]

Pre-eclampsia was significantly associated with DCD in our study. This condition has been shown to increase the risk of intrauterine growth restriction and being born small for gestational age, which are risk factors for neonatal morbidities, and adverse neurodevelopment in extremely preterm children. Pre-eclampsia and maternal hypertension have also been reported previously to increase the risk for adverse motor development.[20] It should be noted that we found no association between birth weight z-scores and the risk of DCD.

We found that the receipt of postnatal steroids and duration of mechanical ventilation were significant risk factors for DCD in univariable analyses and also in the multivariable model when these factors were added one at a time in separate analyses. Research has shown that the administration of postnatal steroids has been associated with impaired motor function.[17,21] Likewise, prolonged mechanical ventilation has been reported to be associated with low motor scores, altered white matter maturation and brain stem development alterations in preschool children born very preterm.[22]

As postnatal steroids are recommended for children with lung disease and/or prolonged mechanical ventilation, it becomes difficult to distinguish which of these risk factors are most important for the development of motor impairment and DCD. Moreover, infants with prolonged mechanical ventilation often have multiple neonatal morbidities including BPD, which further complicates the efforts to identify the independent effects of mechanical ventilation. Retinopathy of prematurity ≥ stage 3 was significantly associated

TABLE 3 Multivariable analysis with odds ratios (ORs), confidence intervals (CI) and p-values from stepwise multivariable analysis, showing the association between perinatal risk factors and Developmental Coordination Disorder (DCD) at different time points in 226 children born EPT.

	Factors known before birth	Factors known at birth	Factors known 5 min after birth	Factors known 12 h after birth	Factors known 1 week after birth
Mother's age at delivery, per category increase	1.67 (1.03–2.69) 0.04	1.73 (1.06–2.83) 0.03	1.74 (1.07–2.81) 0.02	1.75 (1.07–2.84) 0.03	1.78 (1.10–2.87) 0.02
Pre-eclampsia	2.43 (1.08–5.46) 0.03	2.93 (1.13–7.62) 0.03	2.84 (1.22–6.62) 0.03	2.58 (1.09–6.14) 0.03	2.91 (1.24–6.78) 0.01
Mother born in a non-Nordic country	1.85 (0.89–3.84) 0.10	1.88 (0.86–4.11) 0.12	1.81 (0.84–3.92) 0.13	1.86 (0.85–4.08) 0.12	1.80 (0.84–3.85) 0.13
Male sex		1.69 (0.95–3.00) 0.07	1.69 (0.95–3.02) 0.08	1.77 (0.93–2.96) 0.08	1.71 (0.96–3.07) 0.07
Gestational age, per week increase		0.58 (0.42–0.82) 0.01	0.59 (0.43–0.82) 0.002	0.63 (0.45–0.88) 0.01	0.62 (0.45–0.87) 0.01
Birth weight z-score, 1 per SD increase		1.01 (0.76–1.35) 0.93*			
Apgar score < 7 at 5 min			1.74 (0.93–3.25) 0.08	1.61 (0.86–3.04) 0.14	1.67 (0.89–3.15) 0.11
CRIB score > 10				2.49 (0.56–11.0) 0.23*	
Patent ductus arteriosus					1.63 (0.89–3.00) 0.11
Pseudo R^2,[a]	0.07	0.15	0.17	0.18	0.18
	Factors known at 40 postmenstrual weeks	**Factors known at 40 postmenstrual weeks**	**Factors known at discharge**	**Factors known at discharge home**	**Factors known at discharge home[d]**
	Intermediate analysis	**Final analysis**	**Intermediate analysis[b]**	**Intermediate analysis[c]**	**Final analysis**
Mother's age at delivery, per category increase	1.76 (1.08–2.87) 0.02	1.73 (1.07–2.80) 0.03	1.71 (1.06–2.77) 0.03	1.81 (1.10–2.96) 0.02	1.76 (1.08–2.88) 0.02
Pre-eclampsia	2.82 (1.14–6.96) 0.03	2.79 (1.14–6.80) 0.02	3.02 (1.23–7.44) 0.02	2.70 (1.08–6.76) 0.03	2.83 (1.13–7.08) 0.03
Mother born in a non-Nordic country	2.25 (1.00–5.04) 0.05	2.23 (1.00–4.99) 0.05	2.27 (1.01–5.08) 0.05	2.32 (1.02–5.21) 0.04	2.35 (1.06–5.24) 0.04
Male sex	1.64 (0.90–2.94) 0.10	1.65 (0.92–2.96) 0.09	1.63 (0.90–2.93) 0.11	1.61 (0.89–2.90) 0.10	1.57 (0.88–2.84) 0.13
Gestational age, per week increase	0.74 (0.52–1.06) 0.10	0.70 (0.50–0.99) 0.046	0.79 (0.55–1.12) 0.18	0.85 (0.58–1.24) 0.40*	
Birth weight z-score per 1 SD increase					
Apgar score < 7 at 5 min	1.75 (0.92–3.32) 0.09	1.81 (0.97–3.40) 0.06	1.61 (0.86–3.03) 0.14	1.89 (1.00–3.57) 0.05	1.74 (0.91–3.23) 0.09
CRIB score > 10					
Patent ductus arteriosus	1.48 (0.79–2.81) 0.22*				
Brain injury (IVH 3–4 and/or PVL)	1.26 (0.40–3.92) 0.69*				
Retinopathy of prematurity ≥ stage 3	2.34 (1.17–4.68) 0.02	2.48 (1.26–4.87) 0.01	2.24 (1.13–4.46) 0.02	2.25 (1.14–4.42) 0.02	2.19 (1.10–4.34) 0.03
BPD, per category increase	1.42 (0.95–2.14) 0.09	1.44 (0.96–2.16) 0.08	1.40 (0.93–2.12) 0.11	1.39 (0.92–2.09) 0.12	1.40 (0.92–2.11) 0.11

TABLE 3 (Continued)

	Factors known at 40 postmenstrual weeks	Factors known at 40 postmenstrual weeks	Factors known at discharge	Factors known at discharge home	Factors known at discharge home[d]
	Intermediate analysis	Final analysis	Intermediate analysis[b]	Intermediate analysis[c]	Final analysis
Septicaemia	1.05 (0.55–2.02) 0.88*				
Any administration of postnatal steroids			2.40 (1.13–5.12) 0.02		2.05 (0.92–4.58) 0.08
Mechanical ventilation, per category increase				1.76 (1.06–2.94) 0.03	1.69 (1.01–2.82) 0.046
Pseudo R^2,[a]	0.23	0.22	0.25	0.25	0.26

Note: Days of mechanical ventilation are categorised as 0–7 days, 8–28 days or >28 days.

Abbreviations: CRIB, Clinical Risk Index for Babies; IVH, Intraventricular haemorrhage; MABC-2, Movement Assessment Battery for Children-Second Edition assessment BPD, Bronchopulmonary dysplasia, categorised as none, mild (<30% oxygen at 36 weeks) or severe (>30% oxygen at 36 weeks postmenstrual age); PVL, Periventricular leukomalacia.

*Factor eliminated on account of p-value ≥0.20.

[a]Obtained by SPSS complex samples (G. CW. *Sampling techniques (3rd edition)*: John Wiley and sons; 1977).

[b]Factor 'administration of postnatal steroids' was added.

[c]Factor 'administration of postnatal steroids' was removed and factor 'mechanical ventilation per category increase' was added.

[d]Factors 'administration of postnatal steroids' and 'mechanical ventilation per category increase' are both included.

with DCD, as reported by others.[16,23] Retinopathy of prematurity has been associated with delayed maturation of white matter and smaller brain volumes,[24] that is, with factor that are also related to impaired motor outcome and DCD.[25]

Studies have shown that adverse neurodevelopment in preterm infants depended on both medical risks and social factors,[17,26] and we found an association between having a mother born in a non-Nordic country and DCD. However, other social, cultural and/or genetic factors could have contributed to that result. Likewise, increasing maternal age was also associated with DCD in the multivariable model.

Our univariable analyses showed that PDA was associated with the risk of DCD, but the multivariable analyses did not. This was in line with other studies that did not report PDA as a significant predictor.[4,17]

We did not find any association between brain injuries that were defined by ultrasound and DCD. This concurs with research showing that brain injuries are strongly associated with cerebral palsy—which was an exclusion criterion in our study—but not with DCD.[27]

The prevalence of DCD in very preterm children has been consistently reported to be higher than in the term population. For example, a meta-analysis from 2011, which included the same fifth percentile on the MABC-2 cut-off as our study, reported an odds ratio of 6 for DCD in very preterm children compared to controls.[2] More than one-third of children born EPT in our study had DCD, as previously reported.

Preterm birth seems to affect motor function in numerous ways, as it directly affects the motor areas in the growing brain. One follow-up study of very preterm children found alternations in brain connectivity linked to motor function at 12 years of age.[28] Being aware of the potential risk factors for DCD could help clinicians to identify children at risk at an early stage. It could also optimise early interventions and follow-up support for individual children.

5 | STRENGTHS AND LIMITATIONS

The strengths of our study included the prospective, nationwide, population-based cohort study design. The follow-up rate was high and the dropout analyses showed large similarities between the children who were and were not assessed. This suggests that our findings have high generalisability to other populations of children who are born EPT and receive the same level of neonatal care. All the tests that were used were standardised and validated.

Our study also had some limitations. As previously described,[5] we chose the fifth percentile cut-off in order to ensure that we only studied children with significant motor impairment. This was important because we lacked information on how the children's motor impairments affected their daily life. Others have used less than the 15th percentile,[3,23] which includes children with borderline motor problems,[12] and some studies used other tests with different cut-off points.[29] We do not know whether these differences might lead to identifying different risk factors.

Even though the children had reached school age, they were still young, and we do not know if DCD always lasts until adolescence and throughout adult life in children born extremely preterm. It is possible that motor problems will decrease or become more pronounced as children grow older. We used a stepwise regression model in an attempt to explore risk factors at different timepoints, but there could be a risk that the age when we introduced the factors into the model could have led to bias. Collinearity between the risk factors could have influenced the results.

6 | CONCLUSIONS

The risk of DCD in children born EPT was multifactorial and associated with gestational age largely mediated by ROP, maternal factors, pre-eclampsia, the administration of postnatal steroids and mechanical ventilation. Many of the risk factors are common among children born extremely preterm, contributing to the high prevalence of DCD found in this population.

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CONFLICT OF INTEREST

The authors have no potential conflicts of interest relevant to this article to disclose.

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