




Early factors associated with risk of developmental coordination disorder in very preterm children: A prospective area-based cohort study in Italy

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Abstract

Background: Developmental coordination disorder (DCD) is a motor disorder of unknown aetiology that may have long-term consequences on daily activities, and psychological and physical health. Studies investigating risk factors for DCD have so far provided inconsistent results.

Objectives: To assess, using a parent-report screening tool, risk of DCD in school-age very preterm children born in Italy, and investigate the associated early biomedical and sociodemographic factors.

Methods: A prospective area-based cohort (804 children, response rate 73.4%) was assessed at 8–11 years of age in three Italian regions. Perinatal data were abstracted from medical records. DCD risk was measured using the Italian-validated version of the Developmental Coordination Disorder Questionnaire (DCDQ-IT). For this study, children with cognitive deficit (i.e. intelligence quotient <70), cerebral palsy, severe vision and hearing disabilities, and other impairments affecting movement were excluded. A total of 629 children were analysed. We used inverse probability weighting to account for loss to follow-up, and multilevel, multivariable modified Poisson models to obtain adjusted risk ratio (aRR) and 95% confidence interval (CI). Missing values in the covariates were imputed.

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Results: 195 children (weighted proportion 31.8%, 95% CI 28.2, 35.6) scored positive on the DCDQ-IT, corresponding to the 15th centile of the reference Movement-ABC test. Factors associated with overall DCD risk were male sex (aRR 1.35, 95% CI 1.05, 1.73), intrauterine growth restriction (aRR 1.45, 95% CI 1.14, 1.85), retinopathy of prematurity (aRR 1.62, 95% CI 1.07, 2.45), and older maternal age at delivery (aRR 1.39, 95% CI 1.09, 1.77). Complete maternal milk feeding at discharge from the neonatal unit and higher parental socio-economic status were associated with decreased risk.

Conclusions: Both biomedical and sociodemographic factors increase DCD risk. These findings can contribute to elucidating the origins of this disorder, and assist in the identification of children at risk for early referral and intervention.

KEYWORDS

developmental coordination disorder, early diagnosis, risk factors, very preterm birth

1 | BACKGROUND

Developmental coordination disorder (DCD) is a condition of unknown aetiology¹ characterised by a level of motor performance substantially lower than expected for chronological age and motor skill learning opportunities, which significantly interferes with daily activities and is not explained by intellectual disability or other known medical conditions or diseases such as visual, neurological or physical impairments.² The onset of symptoms occurs during the developmental period.² The reported prevalence in the general paediatric population is about 5%–6%,¹ but can range from 12% to over 50% in children born preterm.^{3–8} Males are 2–7 times more likely to be affected compared with females.^{1,3–7}

Although the diagnosis is rarely made before 5–6 years of age, the onset can generally be traced back to early childhood, with difficulties in the acquisition of motor skills such as walking, use of common tools, catching an object, riding a bicycle, drawing and handwriting, leading in time to disadvantage in home tasks, recreational activities, and school curriculum.¹ DCD children have a mean intelligence quotient in the average range, yet they are more likely to have school outcomes poorer than peers.⁹ They tend to engage in fewer physical and group activities,¹⁰ with negative consequences on their self-esteem, mental¹¹ and physical¹² health, social relations, and overall quality of life.¹³ The difficulties encountered by these children may be increased by the presence of co-morbidities such as attention deficit and hyperactivity disorder, learning disabilities, and specific language impairment.¹⁴ The few available longitudinal studies suggest that, although remission is possible, in a substantial proportion of cases the problems in motor coordination continue to adolescence⁸ and even adulthood,¹⁵ and may substantially affect academic, professional, and emotional life.

Previous studies have investigated risk factors for DCD in the ante-, peri-, and neonatal periods, but results have been inconsistent. While males are generally found at higher risk,^{1,4–7} a recent

Synopsis

Study question

What factors are associated with risk of developmental coordination disorder in very preterm children?

What's already known

Developmental coordination disorder is a condition of unknown aetiology, more frequent in males and preterm children. Inadequate motor skills lead to disadvantages in school education, home tasks, and leisure activities, with impact on mental and physical health. Previous studies investigating risk factors have provided inconsistent results.

What this study adds

In children born very preterm, both biomedical (intrauterine growth restriction, antepartum haemorrhage, and retinopathy of prematurity) and sociodemographic (older maternal age and smoking in pregnancy) variables are associated with increased risk of developmental coordination disorder. Full maternal milk feeding at discharge and higher socio-economic status are associated with lower risk.

review states that this applies to the general paediatric population only.¹⁶ Associations were reported between DCD and pregnancy exposures, such as active^{4,17–19} and passive^{20,21} maternal smoking, and with medical conditions including threatened abortion before 20 weeks,²² infection/inflammation,^{23,24} fetal distress during labour^{22,25} and intrauterine growth restriction,^{4,26} although this latter was not always confirmed¹⁴ or explored²² in subsequent studies.

Neonatal morbidities, including seizures,²² prolonged jaundice,²² disruption of brain white matter,²⁷ retinopathy of prematurity,²³ and bronchopulmonary dysplasia,²² or treatments such as postnatal steroids^{3,25} were reported to increase the risk of DCD. The impact of sociodemographic factors such as younger²⁸ and older²² maternal age, low²⁹ and high⁶ parental education, maternal unemployment,²⁸ and high professional status⁴ was also reported and attributed to related perinatal conditions, or to the potential to modify environmental variables directly affecting child motor development.³⁰

Neuroimaging research suggests that DCD is related to brain pathology, and recently, Dewey et al²⁷ documented reduced volumes in white matter and total brain tissues, particularly in areas associated with motor functions such as the cerebellum, corpus callosum, thalamus, and basal ganglia, together with alterations in the microstructural organisation of brain white matter, possibly reflecting reduced myelination and axonal size.

Overall, however, despite the large number of studies carried out, most often with very preterm or low-birthweight children, research findings are not yet conclusive and, as noted by a recent review, “surprisingly little is known about the aetiology of DCD.”¹⁶

This study aimed to investigate the biological, medical, and sociodemographic factors associated with DCD risk assessed at school age. We focussed on very preterm (VP, i.e. <32 weeks of gestational age) children because of the higher frequency of DCD in this population and the availability of data from a prospective area-based VP cohort followed up to school age in Italy.

2 | METHODS

2.1 | Cohort selection

The ACTION (Accesso alle Cure e Terapie Intensive Ostetrico-Neonatali—access to intensive obstetrical and neonatal care) follow-up project is an area-based prospective cohort study including all very preterm infants born in 2003–2005 in five Italian regions, with follow-up at 2 years of corrected age.³¹ In three of the regions (Friuli-Venezia Giulia, Toscana, and Lazio), a second wave of follow-up was carried out at school age (mean 9.2 years, standard deviation 0.7) to assess general health, cognitive and neuropsychological development, and motor functions including the risk of DCD.

Out of 1350 newborns admitted to neonatal intensive care units (NICUs) in these regions, 1103 were discharged alive (Figure 1). There were eight documented deaths before school age, leaving 1095 children eligible for follow-up. At school age, 158 children could not be traced, and for 133, parents refused participation. Thus, we collected information on 804 children (response rate 73.4%). In accordance with the DCD diagnostic criteria² for this study, we excluded children with cerebral palsy and other physical conditions limiting movement such as shorter limb; severe vision and hearing disabilities; and cognitive deficit, defined as full-scale intelligence quotient (FSIQ) <70. In 65 cases, the parent-report questionnaire used to

assess DCD risk was missing or incomplete in some of the domains, precluding computation of the total score. We were able to impute 21 cases using the average of the completed questions within the same domain. Thus, 629 children were available for the analysis.

2.2 | Measurements and data collection

Maternal and neonatal data were abstracted from clinical records using a data collection form with agreed definitions. GA was recorded as the best obstetrical estimate using information on the last menstrual period and ultrasound measurements. Small-for-gestational-age (SGA) status was defined as birthweight <10th percentile using European intrauterine references.³² Recorded morbidities in NICU included intraventricular haemorrhage (IVH) grades 3–4, periventricular leucomalacia (PVL), retinopathy of prematurity (ROP) stages 3–4, and bronchopulmonary dysplasia (BPD), defined as oxygen supplementation at 36 weeks' postmenstrual age.

School-age follow-up was carried out in 4 hospital sites (2 in Friuli-Venezia Giulia, 1 in Tuscany, and 1 in Lazio). Information on the child's health, including the presence and severity of cerebral palsy, data on vision and hearing, and use of aids were collected according to agreed definitions. We used the Italian-validated version of the Kaufman Assessment Battery for Children, second edition (KABC-II), to measure cognitive development (Mental Processing Index, MPI, equivalent to FSIQ). Values below the minimum were used to impute cases with missing assessment but documented severe cognitive deficit ($n = 5$).

The risk of DCD was assessed using the Developmental Coordination Disorder Questionnaire,³³ Italian-validated version (DCDQ-IT).³⁴ This 15-item parent-report tool describes child motor abilities in three separate areas (Control during Movement, Fine Motor/Handwriting, and General Coordination) using a set of positive affirmations (e.g. “Your child throws a ball in a controlled and accurate fashion”). Parents are asked to provide their assessment according to a 5-point Likert scale (from 1, “not at all similar to your child,” to 5 “completely similar to your child”), in comparison with same-age peers. The individual item scores are added to compute three area subscores and a total score (range 15–75), with higher values indicating no suspect/risk of DCD. Based on the total score, each child can be classified as “indicated, or suspected, DCD” versus “probably not DCD,” according to the age-specific (5–7, 8–9, and 10–15 years) cut-offs.

The validation of the Italian version (DCDQ-IT) was carried out using the Movement Assessment Battery for Children (MABC, 1st edition) as reference standard. In a first study carried out on a clinical sample,³⁴ the DCDQ-IT showed a sensitivity of 88% (95% CI 69, 97%) and a specificity of 96% (95% CI 86, 99%), while a second one based on a community sample led to lower values, that is 73% and 70%, respectively, for the age 8–10 years.³⁵

For this study, the questionnaire was completed by the parents in paper form at the time of the hospital visit.

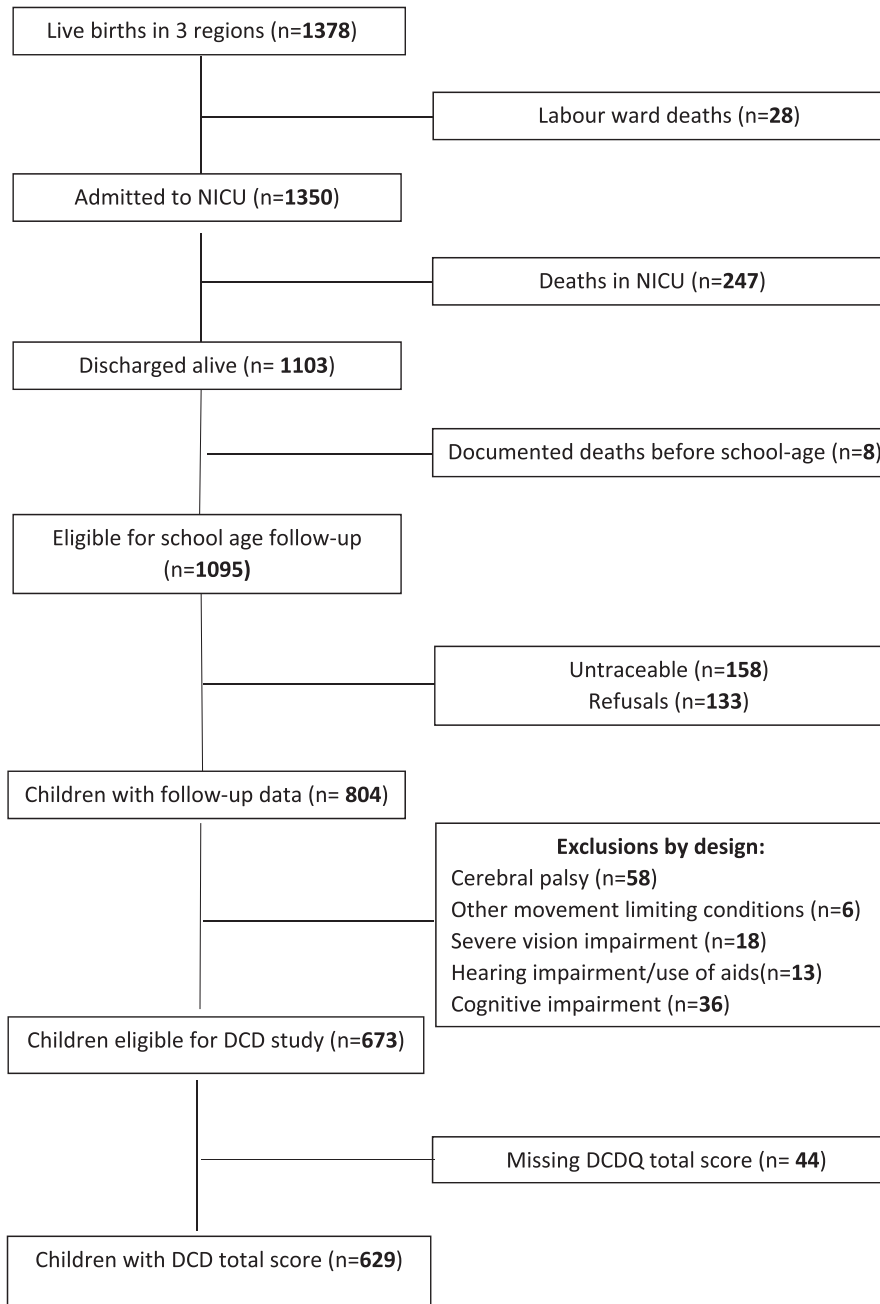


FIGURE 1 Flow chart of the study cohort

2.3 | Outcomes

The main outcome was the proportion of children at risk for DCD in the cohort, based on the DCDQ-IT results. Secondary outcomes were the proportion of children at risk in the three DCD domains of Control during Movement, Fine motor/Handwriting, and General Coordination.

2.4 | Statistical analysis

We used the Italian cut-offs on DCDQ-IT corresponding to the 15th percentile of the MABC reference standard in the validation study³⁵ to identify the children at risk for DCD in our very preterm population. We carried out uni- and multivariable analyses to explore

the relation between potential predictors and indicated DCD status. Variables considered for inclusion in the analyses were region, GA, SGA status, multiple births, pregnancy complications, child sex, Apgar score at 5', severe morbidities in NICU (intraventricular haemorrhage—IVH—stages 3–4; periventricular leucomalacia—PVL; any sepsis and/or necrotising enterocolitis—NEC; retinopathy of prematurity—ROP—stages 3–4; and bronchopulmonary dysplasia—BPD), feeding at discharge from NICU, and child age at DCDQ assessment. Sociodemographic variables were maternal country of birth (Italy or otherwise), age at delivery, and any maternal smoking in pregnancy as reported by the mother at the 2-year follow-up. The education and professional level of both parents were used to compute Hollingshead's composite index as a measure of household socio-economic status (SES).³⁶

We used multilevel modified Poisson regression analysis³⁷ to obtain unadjusted and adjusted risk ratios (RRs) and 95% CIs of scoring positive at the 15th percentile cut-off. Maternal identification code was included as random effect to take into account correlation within multiple births. To account for the missing cases due to loss to follow-up, all analyses used inverse probability weights³⁸ to attribute a higher weight to subjects with characteristics of non-responders (Table S1). Variables associated with the main or any of the secondary outcomes were retained in the final models.

As sensitivity analysis, we present all tables without IPW (Tables S2–S5).

Data analysis was carried out with STATA 17.0 SE (Stata Corporation, College Station, Texas).

2.4.1 | Missing data

Missing values in covariates were all <5%, with the exception of any sepsis or NEC (16%) and maternal antenatal smoking (17%). We carried out multiple imputations with chained equations (MICE).³⁹ Data were assumed to be “missing at random.” Fifty data sets were imputed, using all variables included in the model as predictor or outcome.

2.5 | Ethics approval

The school-age follow-up study (Prot. RF-2009-1511846) was approved by the Ethics Committee at the coordinating institute, Paediatric Hospital Bambino Gesù, IRCCS, on 9 May 2012 (Prot. N. 282 LB). Ethics Committees in Toscana and Friuli-Venezia Giulia confirmed the approval. Written parental consent was obtained at the recruitment of the cohort and at follow-up.

3 | RESULTS

Table 1 shows the characteristics of the study population. The proportions are weighted to account for loss to follow-up. Overall, more than half of the children were males, and almost one third was born from multiple births; 27.9% were SGA, defined as birthweight by gestational age <10th centile. Over 80% had a mother born in Italy, and in 37.1% of the children, maternal age was ≥35 years at delivery. A story of maternal smoking in pregnancy was reported for about 11% of the children. Hollingshead's composite index allowed to group children as belonging to low (36.8%), intermediate (35.0%), and high (28.2%) SES, respectively.

Overall, 195 children (weighted proportion 31.8%, 95% CI 28.2, 35.6) scored <15th centile reference cut-off, indicating risk of DCD. Figures stratified by sex and by DCDQ domain are shown in Table 2. In all domains, risks were higher for males.

Table 3 shows the weighted distribution of DCD risk, overall and by domain, by the characteristics of the study population, together with univariable RRs and 95% confidence intervals.

TABLE 1 Characteristics of the study population by developmental coordination disorder risk (weighted proportions, column)

	Total (N = 629)		Not at risk for DCD (n = 434)		At risk for DCD (n = 195)	
	N	%	n	%	n	%
Child variables:						
Child sex						
Female	278	43.6	211	47.5	67	35.3
Male	351	56.4	223	52.5	128	64.7
Gestational age, weeks						
<28	131	19.3	92	19.6	39	18.6
≥28	498	80.7	342	80.4	156	81.4
Birthweight by GA						
≥10th percentile	454	72.1	327	75.4	127	65.1
<10th percentile	175	27.9	107	24.6	68	34.9
Multiple births						
No	442	72.6	307	73.2	135	71.3
Yes	187	27.4	127	26.8	60	28.7
Apgar at 5 min						
0–6	110	17.3	76	17.0	34	17.9
7–10	517	82.7	357	83.0	160	82.1
Any sepsis and/or NEC						
No	434	80.9	304	80.0	130	82.9
Yes	96	19.1	71	20.0	25	17.1
Severe brain damage ^a						
No	595	95.1	417	95.9	178	93.3
Yes	28	4.9	16	4.1	12	6.7
Retinopathy of prematurity stages 3–4						
No	602	96.4	420	97.7	182	93.6
Yes	22	3.6	10	2.3	12	6.4
Bronchopulmonary dysplasia						
No	590	93.8	411	94.9	179	91.3
Yes	39	6.2	23	5.1	16	8.7
Feeding at discharge						
Mixed/full formula	469	76.7	307	73.0	162	84.8
Maternal milk only	158	23.3	125	27.0	33	15.2
Child age at DCD assessment, y						
8–9	413	65.8	289	66.8	124	63.5
10–11	216	34.2	145	33.2	71	36.5
Parental variables						
Maternal age						
<35 years	384	62.9	279	66.0	105	56.2
≥35 years	241	37.1	152	34.0	89	43.8
Maternal country of birth						
Italy	516	83.7	353	83.6	163	84.0
Other	113	16.3	81	16.4	32	16.0

(Continues)

TABLE 1 (Continued)

	Total (N = 629)		Not at risk for DCD (n = 434)		At risk for DCD (n = 195)	
	N	%	n	%	n	%
	Pregnancy hypertensive disorders					
No	493	80.0	343	80.1	150	79.8
Yes	128	20.0	88	19.9	40	20.2
Antepartum haemorrhage						
No	543	86.8	380	87.8	163	84.7
Yes	78	13.2	51	12.2	27	15.3
PROM						
No	447	71.6	314	72.3	133	70.2
Yes	177	28.4	119	27.7	58	29.8
Any smoking in pregnancy						
No	469	88.9	337	91.4	132	83.5
Yes	53	11.1	30	8.6	23	16.5
Maternal education						
Upper secondary or more	458	70.6	332	74.9	126	61.5
Lower secondary or less	166	29.4	99	25.1	67	38.5
Paternal education						
Upper secondary or more	380	60.3	270	62.7	110	55.0
Lower secondary or less	230	39.7	150	37.3	80	45.0
Maternal occupation						
Manager/professional	89	13.3	63	13.5	26	12.8
White-collar worker	242	38.5	186	43.5	56	27.6
Manual worker	98	16.3	58	13.6	40	22.1
Unemployed/housewife	192	31.9	122	29.4	70	37.5
Paternal occupation						
Manager/professional	166	26.4	120	27.6	46	24.1
White-collar worker	292	48.3	197	48.2	95	48.5
Manual worker	108	19.3	71	18.4	37	21.2
Unemployed	32	6.0	22	5.8	10	6.2
Hollingshead's SES index						
Low	211	36.8	133	33.7	78	43.5
Medium	219	35.0	153	35.6	66	33.7
High	185	28.2	139	30.7	46	22.8
Region						
FVG	98	14.8	71	15.5	27	13.1
Lazio	325	53.7	212	50.9	113	59.8
Tuscany	206	31.5	151	33.6	55	27.1

^aIntraventricular haemorrhage grades III–IV and/or periventricular leucomalacia/porencephaly.

TABLE 2 Risk for developmental coordination disorder by child sex (weighted proportions and 95% CIs)

	Total	At risk for DCD	
	N	n	% (95% CI)
Total DCD			
Female	278	67	25.7 (20.7, 31.2)
Male	351	128	36.5 (31.6, 41.8)
Control during movement			
Female	278	85	31.4 (26.0, 37.1)
Male	351	124	35.7 (30.8, 40.9)
Fine motor/handwriting			
Female	278	59	22.3 (17.9, 28.0)
Male	351	153	44.2 (39.0, 49.6)
General coordination			
Female	278	59	23.5 (18.6, 28.8)
Male	351	117	33.2 (28.5, 38.5)

The results of multivariable analysis are presented in Table 4. Male sex was confirmed to be a risk factor, particularly in the Fine motor/Handwriting domain (aRR 1.87, 95% CI 1.43, 2.43), but showed no association with Control during Movement. Also, previous ROP (aRR 1.62, 95% CI 1.07, 2.45), SGA (aRR 1.45, 95% CI 1.14, 1.85), and maternal age at delivery ≥ 35 years (aRR 1.39, 95% CI 1.09, 1.77) were associated with overall DCD risk. Smoking in pregnancy and antepartum haemorrhage increased DCD risk in the Control during Movement (1.39, 95% CI 0.98, 1.96) and General Coordination (aRR 1.73, 95% CI 1.27, 2.36) domains, respectively. Exclusive maternal milk feeding at discharge from NICU, high SES index, and, for Control during Movement only, older child age were associated with lower DCD risk.

4 | COMMENT

4.1 | Principal findings

In this area-based study of school-age VP children, we found an overall proportion of DCD risk of 31.8%, consistent with the results of the literature.^{7,8} Both antenatal factors (older maternal age, antepartum haemorrhage, and smoking in pregnancy) and child variables (male sex, SGA, and ROP stages 3–4) were associated with increased DCD risk, overall and/or in specific domains. Full maternal milk feeding at discharge from the neonatal unit and high family SES were associated with decreased risk. Gestational age was not related to DCD risk in our data, most likely because of our study restriction to VP births only.⁵

4.2 | Strengths of the study

The strengths of this study are the relatively large size and the area-based prospective recruitment of the cohort. The response rate was satisfactory for this type of study, and availability of baseline data

TABLE 3 Distribution of developmental coordination disorder risk, overall and by domain, by the characteristics of the study population (weighted proportions and risk ratios)^a

	Total DCD		Control during movement		Fine motor/handwriting		General coordination		
	Total (N = 629)	At risk (n = 195)	Risk ratio (95% CI)	At risk (n = 209)	Risk ratio (95% CI)	At risk (n = 212)	Risk ratio (95% CI)	At risk (n = 176)	Risk ratio (95% CI)
	n	n (%)	(95% CI)	n (%)	(95% CI)	n (%)	(95% CI)	n (%)	(95% CI)
Child variables									
Child sex									
Female	278	67 (25.7)	1.00 (Reference)	85 (31.4)	1.00 (Reference)	59 (22.3)	1.00 (Reference)	59 (23.5)	1.00 (Reference)
Male	351	128 (36.5)	1.42 (1.10, 1.83)	124 (35.7)	1.14 (0.90, 1.43)	153 (44.2)	1.98 (1.52, 2.58)	117 (33.2)	1.41 (1.07, 1.87)
Gestational age, weeks									
<28	131	39 (30.7)	1.00 (Reference)	45 (36.2)	1.00 (Reference)	42 (32.7)	1.00 (Reference)	44 (35.6)	1.00 (Reference)
≥28	498	156 (32.1)	1.04 (0.77, 1.41)	164 (33.2)	0.92 (0.69, 1.21)	170 (35.1)	1.07 (0.80, 1.44)	132 (27.4)	0.77 (0.57, 1.03)
Birthweight by GA									
≥10th percentile	454	127 (28.7)	1.00 (Reference)	141 (31.8)	1.00 (Reference)	144 (32.7)	1.00 (Reference)	118 (27.2)	1.00 (Reference)
<10th percentile	175	68 (39.8)	1.39 (1.09, 1.76)	68 (38.8)	1.22 (0.96, 1.55)	68 (39.6)	1.21 (0.96, 1.52)	58 (33.3)	1.22 (0.93, 1.60)
Multiple births									
No	442	135 (31.3)	1.00 (Reference)	152 (34.4)	1.00 (Reference)	145 (33.7)	1.00 (Reference)	131 (30.6)	1.00 (Reference)
Yes	187	60 (33.3)	1.06 (0.81, 1.40)	57 (32.0)	0.93 (0.70, 1.24)	67 (37.3)	1.11 (0.84, 1.46)	45 (24.5)	0.80 (0.56, 1.13)
Apgar at 5 min									
0-6	110	34 (32.9)	1.00 (Reference)	39 (37.8)	1.00 (Reference)	39 (37.7)	1.00 (Reference)	35 (32.4)	1.00 (Reference)
7-10	517	160 (31.6)	0.96 (0.71, 1.30)	169 (33.0)	0.87 (0.66, 1.15)	172 (34.0)	0.90 (0.68, 1.20)	141 (28.2)	0.87 (0.64, 1.20)
Any sepsis and/or NEC									
No	434	130 (30.5)	1.00 (Reference)	137 (32.1)	1.00 (Reference)	135 (31.7)	1.00 (Reference)	117 (27.3)	1.00 (Reference)
Yes	96	25 (26.6)	0.87 (0.60, 1.27)	30 (31.1)	0.97 (0.69, 1.36)	32 (34.7)	1.09 (0.80, 1.50)	29 (31.4)	1.15 (0.81, 1.63)
Severe brain damage									
No	595	178 (30.7)	1.00 (Reference)	193 (33.0)	1.00 (Reference)	199 (34.6)	1.00 (Reference)	159 (27.7)	1.00 (Reference)
Yes	28	12 (42.3)	1.38 (0.86, 2.20)	11 (39.6)	1.20 (0.73, 1.97)	9 (30.1)	0.87 (0.48, 1.56)	12 (41.6)	1.50 (0.93, 2.42)
Retinopathy of prematurity stage 3-4									
No	602	182 (31.1)	1.00 (Reference)	195 (33.1)	1.00 (Reference)	198 (34.1)	1.00 (Reference)	162 (27.9)	1.00 (Reference)
Yes	22	12 (56.3)	1.81 (1.22, 2.68)	13 (57.5)	1.73 (1.18, 2.55)	13 (57.2)	1.68 (1.14, 2.48)	13 (60.9)	2.18 (1.52, 3.14)
Bronchopulmonary dysplasia									
No	590	179 (31.0)	1.00 (Reference)	192 (33.0)	1.00 (Reference)	199 (34.7)	1.00 (Reference)	161 (28.3)	1.00 (Reference)
Yes	39	16 (44.6)	1.44 (0.99, 2.10)	17 (45.1)	1.37 (0.93, 2.01)	13 (34.1)	0.98 (0.61, 1.57)	15 (38.4)	1.36 (0.87, 2.11)

(Continues)

TABLE 3 (Continued)

	Total DCDD		Control during movement		Fine motor/handwriting		General coordination	
	Total (N = 629)	At risk (n = 195)	At risk (n = 209)	Risk ratio (95% CI)	At risk (n = 212)	Risk ratio (95% CI)	At risk (n = 176)	Risk ratio (95% CI)
	n	n (%)	n (%)		n (%)		n (%)	
Feeding at discharge								
Mixed/full formula	469	162 (35.2)	166 (35.7)	1.00 (Reference)	178 (38.8)	1.00 (Reference)	143 (31.3)	1.00 (Reference)
Maternal milk only	158	33 (20.7)	43 (27.3)	0.59 (0.42, 0.83)	34 (21.0)	0.54 (0.39, 0.76)	33 (21.2)	0.68 (0.48, 0.95)
Child age at follow-up, y								
8-9	413	124 (30.7)	154 (37.6)	1.00 (Reference)	132 (32.9)	1.00 (Reference)	108 (26.8)	1.00 (Reference)
10-11	216	71 (33.9)	55 (26.5)	1.10 (0.86, 1.42)	80 (38.1)	1.16 (0.90, 1.49)	68 (33.1)	1.24 (0.94, 1.63)
Parental variables								
Maternal age								
<35 years	384	105 (28.4)	113 (30.1)	1.00 (Reference)	127 (34.1)	1.00 (Reference)	102 (27.9)	1.00 (Reference)
≥35 years	241	89 (37.5)	95 (40.0)	1.32 (1.04, 1.68)	84 (35.6)	1.04 (0.82, 1.33)	74 (30.8)	1.10 (0.84, 1.45)
Maternal country of birth								
Italy	516	163 (31.9)	177 (34.2)	1.00 (Reference)	174 (34.5)	1.00 (Reference)	145 (28.4)	1.00 (Reference)
Other	113	32 (31.3)	32 (31.6)	0.98 (0.70, 1.38)	38 (35.3)	1.02 (0.75, 1.39)	31 (31.5)	1.11 (0.78, 1.57)
Pregnancy Hypertensive Disorders								
No	493	150 (31.5)	166 (34.8)	1.00 (Reference)	167 (35.3)	1.00 (Reference)	135 (28.5)	1.00 (Reference)
Yes	128	40 (31.9)	40 (30.5)	1.01 (0.75, 1.36)	42 (32.9)	0.93 (0.69, 1.25)	37 (29.7)	1.04 (0.75, 1.46)
Antepartum haemorrhage								
No	543	163 (30.8)	178 (33.3)	1.00 (Reference)	185 (35.2)	1.00 (Reference)	140 (26.5)	1.00 (Reference)
Yes	78	27 (36.6)	28 (37.7)	1.19 (0.85, 1.65)	24 (32.1)	0.91 (0.64, 1.30)	32 (43.2)	1.63 (1.20, 2.22)
PROM								
No	447	133 (31.0)	147 (33.5)	1.00 (Reference)	146 (34.0)	1.00 (Reference)	121 (28.0)	1.00 (Reference)
Yes	177	58 (33.1)	59 (34.3)	1.07 (0.82, 1.39)	64 (36.8)	1.08 (0.84, 1.39)	52 (30.5)	1.09 (0.82, 1.46)
Any smoking in pregnancy								
No	469	132 (28.7)	145 (31.3)	1.00 (Reference)	146 (31.7)	1.00 (Reference)	126 (27.6)	1.00 (Reference)
Yes	53	23 (45.7)	25 (49.4)	1.59 (1.14, 2.23)	23 (43.2)	1.36 (0.96, 1.92)	18 (35.2)	1.28 (0.86, 1.90)
Hollingshead SES index								
Low	211	78 (37.4)	79 (38.1)	1.00 (Reference)	79 (38.7)	1.00 (Reference)	71 (34.6)	1.00 (Reference)
Medium	219	66 (30.5)	69 (31.0)	0.81 (0.61, 1.08)	78 (36.3)	0.94 (0.71, 1.23)	53 (24.8)	0.71 (0.52, 0.99)
High	185	46 (25.6)	55 (30.4)	0.68 (0.50, 0.94)	48 (26.6)	0.69 (0.50, 0.95)	48 (26.5)	0.76 (0.55, 1.06)

TABLE 3 (Continued)

Region	Total (N = 629)	Total DCD		Control during movement		Fine motor/handwriting		General coordination					
		At risk (n = 195)	n (%)	Risk ratio (95% CI)	At risk (n = 209)	n (%)	Risk ratio (95% CI)	At risk (n = 212)	n (%)	Risk ratio (95% CI)	At risk (n = 176)	n (%)	Risk ratio (95% CI)
FVG	98	27 (28.2)		1.00 (Reference)	30 (31.2)		1.00 (Reference)	30 (30.7)		1.00 (Reference)	25 (25.8)		1.00 (Reference)
Lazio	325	113 (35.4)		1.25 (0.87, 1.80)	127 (39.2)		1.25 (0.89, 1.77)	119 (37.5)		1.22 (0.86, 1.73)	95 (30.3)		1.17 (0.79, 1.76)
Tuscany	206	55 (27.4)		0.97 (0.64, 1.45)	52 (25.8)		0.83 (0.55, 1.24)	63 (31.7)		1.03 (0.70, 1.52)	56 (28.1)		1.09 (0.70, 1.68)

^aRisk ratios were computed using modified Poisson univariable models. Random effect: maternal identification code.

allowed us to use IPW to adjust for loss to follow-up. The proportion of missing values in covariates was below 5% except for antenatal smoking, and multiple imputations were used to retain all cases in multivariable analyses.

4.3 | Limitations of the data

The main limitation of this study is the use of a parental questionnaire for the assessment of DCD. However, after standardised motor tests, DCDQ is considered one of the best tools to determine whether a child may have the disorder or is unlikely to be affected.⁴⁰ It was translated into several languages, and studies using it are included in systematic reviews.¹⁶ A second limitation is the use of maternal reported smoking in pregnancy, without biological marker measurement to verify the exposure. Although previous studies have validated self-reported smoking by pregnant women,⁴¹ others have not.⁴² Misclassification of smokers into non-smokers cannot be excluded, but would likely lead to underestimation of the association with the outcome.

4.4 | Interpretation

Consistent with most previous research, we found that males had higher DCD risk compared with females. Male sex has since long been linked to worse perinatal outcomes, including neurological and developmental disabilities.⁴³ The underlying mechanisms are poorly understood, and the male disadvantage has been attributed to a general biological or genetic vulnerability, partly linked to the single X chromosome. More recently, sex-related genetic polymorphisms in the genes encoding proinflammatory cytokines have been reported,⁴⁴ as well as differences in the DNA methylation placental profile, suggesting that male fetuses might be more vulnerable to epigenetic processes affecting neurodevelopment.⁴⁵

Our results regarding the role of SGA are consistent with those first described in the Danish National Birth cohort,⁴ as well as with the review by Murray et al.²⁶ who reported a higher risk of motor impairment among SGA children born preterm. Differences in the definition of SGA may in part explain the inconsistencies with other studies.¹⁴ Similar to the Danish cohort study,⁴ we used an intrauterine reference,³² which provides a better estimate of fetal growth restriction, particularly for very preterm children.⁴⁶

Despite the exclusion of children with severe visual impairments, we found that previous ROP was the strongest predictor of DCD risk in our population. Previous studies have linked ROP to non-visual developmental disabilities, especially in the cognitive and motor areas,⁴⁷ even in case of favourable vision outcomes and independently of acquired major brain injury.^{48,49} Involvement of the macula area of the retina has been especially linked to subsequent non-visual disability.⁴⁷ Neuroimaging data have shown associations between ROP, developmental impairment, and brain abnormalities such as reduced volumes⁴⁹ and maturational delay of the brain white

TABLE 4 Factors associated with developmental coordination disorder risk: results of multivariable analysis (weighted data)^a

	Total DCD	Control during movement	Fine motor/handwriting	General coordination
	aRR (95% CI)	aRR (95% CI)	aRR (95% CI)	aRR (95% CI)
Child sex				
Female	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Male	1.35 (1.05, 1.73)	1.11 (0.88, 1.39)	1.87 (1.43, 2.43)	1.35 (1.03, 1.77)
Birthweight by GA				
≥10 percentile	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
<10 percentile	1.45 (1.14, 1.85)	1.24 (0.97, 1.58)	1.22 (0.97, 1.54)	1.35 (1.03, 1.77)
Antepartum haemorrhage				
No	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Yes	1.27 (0.92, 1.76)	1.19 (0.86, 1.65)	0.93 (0.66, 1.32)	1.73 (1.27, 2.36)
ROP (grade 3–4)				
No	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Yes	1.62 (1.07, 2.45)	1.70 (1.13, 2.55)	1.33 (0.87, 2.05)	2.02 (1.39, 2.93)
Feeding on discharge				
Artificial milk partial/complete	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Maternal milk only	0.66 (0.47, 0.93)	0.82 (0.61, 1.11)	0.61 (0.43, 0.85)	0.74 (0.52, 1.05)
Maternal age at delivery				
<35 years	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
≥35 years	1.39 (1.09, 1.77)	1.36 (1.07, 1.72)	1.10 (0.87, 1.39)	1.19 (0.91, 1.56)
Smoking in pregnancy				
No	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Yes	1.33 (0.92, 1.91)	1.39 (0.98, 1.96)	1.17 (0.83, 1.65)	1.11 (0.74, 1.68)
Hollingshead's SES index				
Low	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Medium	0.82 (0.62, 1.08)	0.82 (0.62, 1.08)	0.97 (0.74, 1.26)	0.74 (0.54, 1.01)
High	0.72 (0.52, 0.99)	0.82 (0.60, 1.11)	0.75 (0.54, 1.03)	0.84 (0.60, 1.18)
Age at DCDQ assessment, y				
8–9	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
10–11	1.08 (0.84, 1.38)	0.70 (0.53, 0.92)	1.12 (0.88, 1.41)	1.20 (0.92, 1.57)

^aMultivariable multilevel modified Poisson regression analysis based on imputed data (50 imputations). Random effect: maternal identification code. aRR is adjusted risk ratio.

matter, particularly in the posterior regions, optic radiations, and posterior limbs of the internal and external capsule, where the primary visual and motor pathways are housed.⁴⁸ These findings suggest that a common cause may lead to impaired neurovascular and neural development in the retina and in the brain. One postulated mechanism involves the anabolic hormone insulin-like growth factor 1 (IGF-1), whose low levels after preterm birth may impair brain growth and maturation, as well as normal angiogenesis, leading in the retina to the pathologic revascularisation, which is the hallmark of ROP.^{48,50} Postnatal systemic inflammation with activation of proinflammatory cytokines was also proposed as common cause,⁵¹ either by itself or in combination with IGF-1 deficiency.⁵² Inflammation can exert an influence also before birth.⁵³ Antenatal haemorrhage, which is considered a marker of inflammation, was associated in our study with increased risk of General Coordination problems.

As with other developmental outcomes,⁵⁴ we found that socio-economic variables such as maternal age, smoking in pregnancy, parental education, and occupational profession may be important in shaping the neuropsychological profile of a child, and in our study were associated with risk of motor problems even when controlling for biomedical factors. The root of these relations may be both socio-economic and educational, linked to the level of home affordances,³⁰ opportunities for motor activities, training, and outdoor leisure time, as well as to more active parenting practices and stimulating environment.⁵⁵

While the effect of maternal smoking on intrauterine growth is well known, its role in developmental disorders, and specifically DCD, has been less researched. We found that both SGA and smoking were independently associated with increased DCD risk, although in different domains, with only smoking affecting

Control during Movement. These findings are consistent with previous research showing a relation between antenatal smoking and motor difficulties,¹⁷ even when cotinine markers were used^{18,20} and when socio-economic factors and alcohol intake were taken into account.¹⁹ Cigarette smoke contains several harmful substances that can cross the placenta and affect the child prenatally.⁵⁶ Nicotine binds to receptors of several organs, including the brain. The cerebellum, which is particularly rich in nicotine receptors, is responsible for general coordination of movements and body balance, and has been implicated in the pathogenesis of DCD.²⁷

The benefits of breast feeding on the child health and development, including cognition, have been largely discussed in the literature, providing justification for including this variable in our analyses. Belfort et al.⁵⁷ found that, in infants below 30 weeks of GA, breastmilk intake in the first 28 days of life was associated with greater brain deep nuclear grey matter at term equivalent age, and better motor and cognitive performance at 7 years of age. However, these findings were not replicated by subsequent studies,^{55,58} which did not identify any feeding associated differences in the achievement of motor milestones in very preterm infants. Our study found that, adjusting for maternal age, smoking in pregnancy, and SES index, maternal milk feeding at discharge from the neonatal unit was associated with lower DCD risk, particularly overall and in the Fine Motor/Handwriting domains. Proposed mechanisms linking breast feeding with brain development are the nutritional properties of breastmilk,⁵⁷ and possibly the quality of mother–infant relation that may be enhanced by breast feeding.^{55,57} Recently, the report by Kar et al.⁵⁹ of an association between breast-feeding exclusivity and duration and brain global and regional white matter microstructure has provided additional support to the link between breast feeding and infant motor development.

5 | CONCLUSIONS

Our study confirms the high risk of DCD in children born very preterm and highlights the association with both biomedical and socio-economic variables. The pattern of associations differs according to the specific motor domains. General coordination appears to be influenced mainly by biomedical factors (sex, SGA, antepartum haemorrhage, and a history of severe ROP), while Control during Movement is affected also by maternal age and smoking in pregnancy. The identification of these factors and their differential distribution across motor domains, together with the accumulating findings of neuroimaging studies, can contribute to elucidating the aetiopathogenetic mechanisms of DCD, as well as to the discussion about possible different DCD subtypes. Additionally, they may alert parents, teachers, and physicians to suspect DCD when an association between these risk factors and motor problems is present, referring the child for specialist assessment and early intervention, rather than dismissing the issue as mere clumsiness that will be overgrown with time.

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AUTHOR CONTRIBUTIONS

Stefania Zoia and Marina Biancotto drafted the manuscript. Alessandra Valletti and Laura Montelisciani carried out statistical analysis; Ileana Croci was in charge of the database management. Fabio Voller and Franca Rusconi in Tuscany, Marco Carrozzi and Valeria Chiandotto in Friuli Venezia Giulia, and Domenico di Lallo, Barbara Caravale and Stefano Vicari in Lazio contributed to the preparation of the study instruments and to the coordination of data collection. Marina Cuttini initiated the study, provided overall project coordination, supervised statistical analysis and finalized the manuscript. All Authors critically reviewed the manuscript for important aspects and approved the final version.

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SUPPORTING INFORMATION

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