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Neurodevelopmental outcomes of very low birth weight preterms in preschool childhood: a prospective cohort study

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Abstract

Background Preterm birth is a risk factor for a child's neurological development. Preterm children have unusual neurodevelopmental profiles with executive, visual-motor functions, fine and gross motor skills, language and behavior that affect learning. In this study, we analyzed the neurodevelopmental outcomes of a cohort of very low birth weight infants admitted to the Treviso Neonatal Intensive Care Unit (NICU) between 2014 and 2016 and followed up to preschool childhood.

Method This is a prospective cohort study. Infants were followed at birth and after NICU discharge at two- and four-year follow-ups. The two-year assessment was conducted with Bayley III, and at four years with the Wechsler Preschool and Primary Scale of Intelligence - III scales and Movement Assessment Battery for Children – 2.

Results The cohort consisted of 207 subjects with a mean gestational age of 28.9 weeks, and a mean birth weight of 1097.2 g. At two years of age, children without disabilities were 90 (59.6%), those with minor disabilities 47 (31.1%), and those with major disabilities 14 (9.3%); at four years, 58.4% of children without previous disabilities, presented problems with verbal tests and manual dexterity: aiming, grasping and balance at movement assessment. There was significant alteration in processing speed ($p < 0.001$). Furthermore, there was a strong correlation between processing speed and manual dexterity ($p < 0.001$) and between processing speed and aiming and grasping ($p = 0.0059$).

Conclusions We found that more than half the children free of disability at two years, at four years had deficit often involving the oculo-motor coordination and processing speed. These motor profile alterations limit the expression of cognitive abilities and the achievement of expected school performance, thus resulting in behavioral disorders, typical of preterm children. Early professional follow-up could improve the expected educational outcomes.

Keywords Neurological development, Neurodevelopmental assessment, Disability, Very low birth weight

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Background

The clinical history of preterm infants is characterized by extremely heterogeneous neonatal conditions that predispose over time to outcomes with various degrees of complexity [1, 2].

The care given to preterm newborns in the neonatal intensive care unit (NICU) led to an increase in survival at very low gestational ages (GAs) and neonatal weights, making it necessary to plan a multidisciplinary and continuous follow-up until pre-school childhood [3, 4]. Severe neuromotor, sensorineural and cognitive sequelae are evident in the first years of life, affecting 10–20% of very low birth weight infants (VLBWIs), which occur more frequently at lower GAs [4]. Mild sequelae concerning cognitive, communicative-linguistic, attentional, behavioral delays, gross and fine motor skill delays, which compromise executive functions, memory, and learning, appear to be prominent in pre- and school age [5–11].

Even in children without serious perinatal clinical histories (early neonatal sepsis, severe intraventricular hemorrhage, bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), late neonatal sepsis), there is an alteration of the developmental outcomes in the motor history, [12–14] not associated with brain lesions but with early exposure to the adverse extra-uterine NICU environment, early and repetitive sensory and proprioceptive experiences, which can alter connectivity in the preterm brain [15–17]. These minor motor abnormalities are often overshadowed by other more severe physical and intellectual conditions (low IQ, learning disabilities, attention-deficit/hyperactivity disorder, neuropsychologic deficit, behavior problems). The first step in targeted intervention is to identify and characterize them to initiate adequate management [6, 18].

Misidentification of cognitive problems in school-age children with a history of premature birth has often led to the misdiagnosis of learning disabilities and consequently difficulties in providing appropriate support for the child's abilities.

The objective of this study was to analyze cognitive, motor, attentional and behavioral developmental profiles of VLBWIs at the age of four, in relation to their clinical history and two-year profile, to understand the more common trajectory in the neurodevelopment of VLBWIs.

Methods

This is a single tertiary center prospective cohort study. All infants admitted to our NICU in 2014–2016, and January and February 2017 with a GA of less than 30 weeks, or a neonatal weight of less than 1500 g, were included. Those born with malformation syndromes or genetic disease were excluded. This cohort was assessed prospectively during a four-year follow-up (Fig. 1).

At the age of two years, assessment of the development quotient was conducted with the Bayley III scales: cognitive, linguistic and motor administered through direct interaction with the child; socioemotional and adaptive behavior was provided by parents with a self-administered questionnaire. Disability was defined according to the American Academy of Pediatrics as a major disability [5], given by moderate or severe cerebral palsy with Gross Motor Function Classification System (GMFCS) ≥ 2, Bayley III cognitive scores < 70 and GMFCS ≥ 2, vision with a bilateral deficit < 1/10, permanent hearing loss which does not allow the child to communicate, despite a prostheses or cochlear implant. Minor disability was defined as disorders of the motor and postural sphere (clumsiness and motor coordination disorder), with learning disabilities, behavioral disturbances and pathology of adaptive functions.

At the age of four years, the cognitive assessment was conducted with the Wechsler Preschool and Primary Scale of Intelligence - III scales (WPPSI-III), in particular the verbal subtest to evaluate the knowledge of words and the ability to form verbal concepts, and other sub-performance tests that measure the child's ability to use logical and abstract reasoning and to organize categories, the processing speed to evaluate attention and concentration. Motor assessment was conducted with the Movement Assessment Battery for Children- 2 (mABC 2) scales to detect manual dexterity, aiming, grasping and balance.

In addition, major disability was defined on the WPPSI III and mABC 2 scales with a total IQ score of less than 70 on the first and second scales, along with minor disability and a total IQ score between 70 and 89. Scales have always been administered by neuropsychologists in the Follow-up Service.

All parents gave informed consent, with the study approved by the Clinical Trials Ethics Committee of the Azienda ULSS2 Marca Trevigiana, No. 958 / CE Brand.

Statistical analysis

Quantitative variables were summarized with mean and standard deviation, and categorical variables with count and percentage of subjects in each category.

The perinatal outcomes potential predictors of disability at 2 and 4 years were evaluated with a univariate cumulative logit model. The outcomes found to be statistically significant at the 5% level, were then considered in a multivariate model with backward selection. The association between gestational age categorized (23–25, 26–27 and ≥ 28 wks) and the centile neonatal weight (< 10° / ≥ 10°) with Bayley scale components at 2 years and the WPPSI III and mABC 2 at 4 years, was evaluated with Kruskall-Wallis test in case of quantitative outcome, with chi-square or Fisher's exact test in case of categorical outcomes. The comparison of the three-gestational

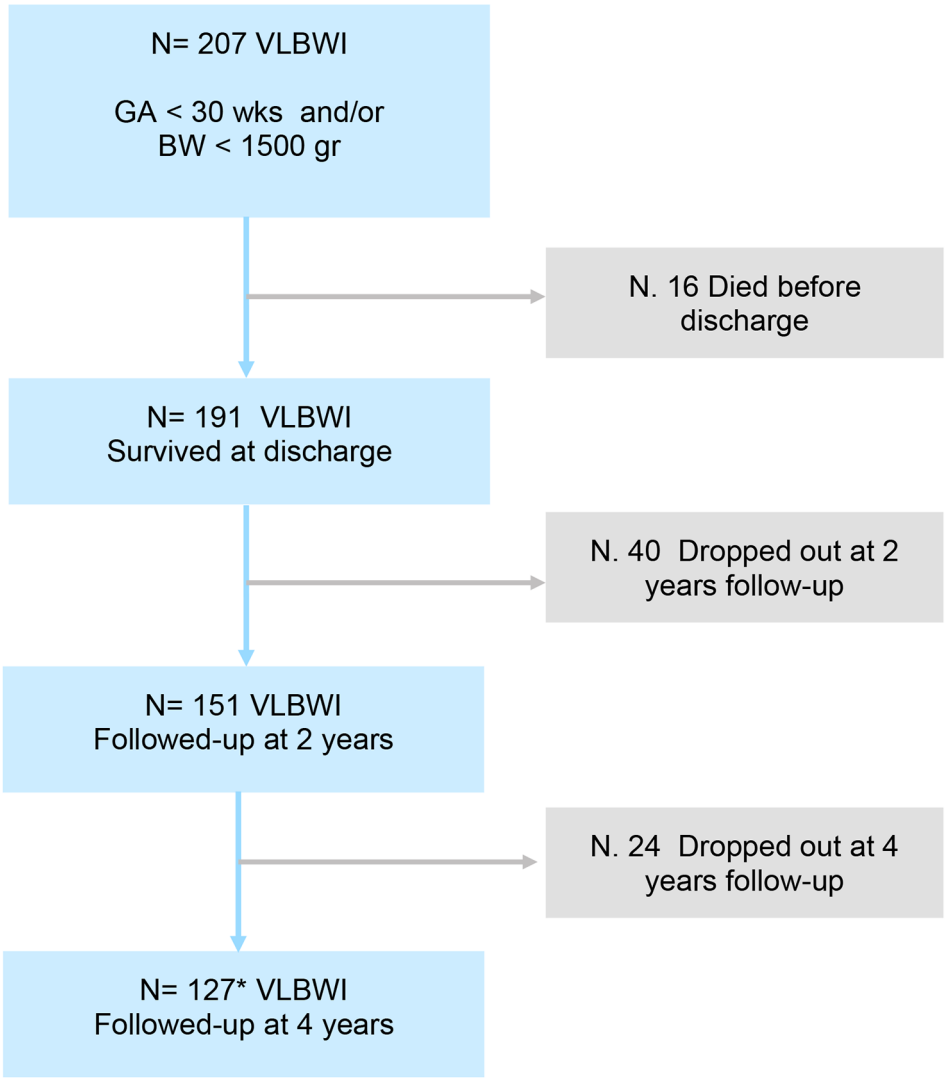

Fig. 1 Study Flow chart
*3 VLBW not evaluated at 2 years

age group was followed by pairwise comparison in case of statistical significance at the 5% level.

The correlation between the ability to process information quickly (IVE) of the WPPSI III scale with manual dexterity (DM) and the ability to grasp and aim (ME) using the mABC 2 scale, was evaluated with the Spearman rank correlation test. The level of statistical significance was set at the 5% level.

The statistical analysis was performed with SAS 9.4 (SAS Institute Inc., Cary, NC, USA) for Windows.

Results

The cohort including 207 VLBWIs was followed until 2021. Characteristics and perinatal outcomes of the population discharged and followed up to two years are reported in Table 1.

Patients discharged from the NICU were n=191 (mortality 7.7%); 20.9% of children did not continue with controls up to 24 months and another 15.9% did not complete the four-year assessment. Drop-outs were mainly due to inability of families to join the high-risk follow-up program, or for transferring to other facilities, going abroad, or for refusal.

Follow-up visits, comprehensive evaluations included neurodevelopmental, pediatric, auxological, nutritional, respiratory, and other special evaluations as needed were tailored to the needs of each individual child and his/her family.

Results at the two years follow up

The cohort of children evaluated at two years (n=151) showed no disability in 90 of them (59.6%), a minor

Table 1 Perinatal characteristics and discharge outcomes of the VLBWI population and followed-up at 2 years

	Study population N. 207	**VLBW follow up at 2 years N. 151**
	Mean (DS)/n (%)	**Mean (DS)/n (%)**
Gestational Age (weeks)	28.9 (2.6)	28.9 (2.4)
Birth weight (gr)	1097.2 (281.7)	1101.3 (262.2)
- Percentile	39.3 (27.7)	40.8 (27.0)
- Z score	-0.5 (1.1)	-0.4 (1.0)
Head Circumference (cm)	26.4 (2.3)	26.5 (2.2)
- percentile	45.9 (27.1)	47.8 (26.5)
- Z score	-0.1 (1.0)	-0.1 (1.0)
APGAR score at 5'	8 (1.8)	8.1 (1.6)
Inborn	178 (86.0)	130 (86.1)
Male	107 (51.7)	077 (51.0)
Prenatal steroids	194 (93.7)	146 (96.7)
Cesarean Section	161 (77.8)	114 (75.5)
Respiratory distress	148 (75.1)	118 (78.1)
BPD at 36 weeks	54 (28.1)	036 (23.8)
O2 at home	14 (7.3)	012 (7.9)
PDA	73 (37.8)	60 (39.7)
EOS	13 (6.3)	010 (6.6)
LOS	36 (17.7)	030 (19.9)
NEC	15 (6.7)	11 (7.3)
PVL	10 (5.2)	007 (4.6)
IVH	28 (14.8)	22 (14.6)
IVH ≥ 3	6 (3.5)	3 (2.0)
ROP	42 (27.8)	38 (25.2)
ROP ≥ 2	13 (6.8)	011 (7.3)
Length of stay (days)	61.5 (29.0) *	65.2 (29.0) **
Deaths before discharge or after	16 (7.7)	0 (0)

Patent ductus arteriosus (PDA), Early onset sepsis (EOS), Late onset sepsis (LOS), Necrotizing enterocolitis (NEC), Periventricular leukomalacia (PVL), Intraventricular hemorrhage (IVH), Severe intraventricular hemorrhage (IVH ≥ 3), Retinopathy of prematurity (ROP), Severe retinopathy of prematurity (ROP ≥ 2).

*Excluded patients died

**One missing

Mean and standard deviation (SD) for quantitative variables, number, and percentage of subjects for categorical variables

disability in 47 (31.1%) and a major disability in 14 children (9.3%) according to the definition described in the Methods. Disability at two years resulted associated in the following neonatal outcomes and perinatal complications: early neonatal sepsis ($p=0.0377$), grade ≥ 3 intraventricular hemorrhage ($p=0.0245$), BPD ($p=0.0130$), ROP ($p=0.0342$), late neonatal sepsis ($p=0.0180$), and length of hospitalization ($p<0.0001$) (Table 2). Using multivariate analysis, only the length of stay was seen as predictive.

At two years, the Bayley motor scale resulted worse in the lowest GA groups ($p=0.0282$). No statistically significant difference emerged in the distribution of disability classes at two years between AGA (Adequate for Gestational Age and SGA (Small for Gestational Age) classes, defined as birth weight less than the 10th percentile, according to World Health Organization charts ($p=0.4282$) (Table 3).

Results at the four years follow up

Assessment at four-years, 127 out of 151 children followed until two years were evaluated, showing major disability in 25 (19.7%), a minor disability in 60 (47.2%), or no disability in 42 (33.1%). Statistical analysis showed that the disability was only associated with BPD ($p=0.0441$) and length of hospitalization ($p=0.0077$) (Table 2). Using multivariate analysis, only the length of stay was seen as predictive. Even at age four, considering AGA and SGA groups, there was no difference in the incidence of disabilities ($p=0.2689$) (Table 4).

Considering the results of the cognitive (WPPSI-QI TOT) and motor assessments (mABC 2 TOT) in relation to GA groups, progressively worse performance was noted in relation to reduction of the GA (Table 4).

The analysis of the conjoint distribution of disability at age of two and four years revealed how children without disabilities at the age of two (n=77, 62.1%)

Table 2 Association of the degree of disability at 2 and 4 years and outcomes at discharge

	Disability at 2 years (n = 151)					Disability at 4 years (n = 127)				
	No (N = 90)	Minor (N = 47)	Major (N = 14)	OR (95% CI)	p- value	No (N = 42)	Minor (N = 60)	Major (N = 25)	OR (95% CI)	p-value
BPD 36 wks N (%)										
Presence vs. Absence	16 (17.8)	13 (27.7)	07 (50.0)	2.511 (1.214; 5.194)	**0.0130**	05 (11.9)	16 (26.7)	08 (32.0)	2.258 (1.022; 4.991)	**0.0441**
PVL N (%)										
Presence vs. Absence	04 (4.4)	01 (2.1)	02 (14.3)	1.608 (0.379; 6.828)	0.5197	01 (2.4)	05 (8.3)	00 (0.0)	1.000 (0.215; 4.662)	1.0000
IVH N (%)										
1–2 vs. 0	09 (10.0)	05 (10 0.6)	05 (35.7)	2.525 (1.006; 6.340)	**0.0245**	04 (9.5)	06 (10.0)	06 (24.0)	2.258 (0.833; 6.119)	0.2683
3–4 vs. 0	0 (0)	2 (4.3)	1 (7.1)	9.641 (1.078; 86.193)		00 (0 0.0)	02 (3.3)	00 (0.0)	1.582 (0.114; 21.958)	
ROP N (%)										
1 vs. 0	16 (17.8)	15 (31.9)	06 (42.9)	2.515 (1.221; 5.181)	**0.0342**	09 (21.4)	15 (25.0)	06 (24.0)	1.136 (0.526; 2.454)	0.9319
2 vs. 0	00 (0.0)	01 (2.1)	00 (0.0)	5.038 (0.128; 198.734)		00 (0.0)	01 (1.7)	00 (0.0)	1.470 (0.036; 59.260)	
EOS N (%)										
Presence vs. Absence	01 (1.1)	09 (19 0.1)	00 (0.0)	3.622 (1.076; 12.196)	**0.0377**	02 (4.8)	03 (5.0)	02 (8.0)	1.448 (0.346; 6.059)	0.6123
LOS N (%)										
Presence vs. Absence	13 (14.4)	11 (23.4)	06 (42 0.9)	2.536 (1.173; 5.481)	**0 0.0180**	06 (14.3)	12 (20.0)	06 (24.0)	1.545 (0.669; 3.571)	0.3083
Total Length of stay (day) Mean (SD)										
Per day of increase	57.4 * (21 0.2)	71.1 (30.1)	95.0 (43 0.6)	1.028 (1.016; 1.040)	**< 0.0001**	56.6 (28.5)	66.6 (23.2)	72.4 (29.1)	1.017 (1.005; 1.031)	**0.0077**

*1 Missing

ORs and 95% CI obtained with univariate ordinal logistic regression

Table 3 Distribution of disability and scores on Bayley III assessments by gestational age group and centile neonatal weight at 2 years of age

	Gestational age class					Centile neonatal weight			
	23–25 (N = 15)	26–27 (N = 40)	≥ 28 (N = 96)	Total (N = 151)	P Value	< 10° (SGA) (N = 28)	≥ 0° (AGA) (N = 123)	Total (N = 151)	P Value
Missing	00 (00.0%)	00 (00.0%)	00)	00 (00.0%)	0.0576	00 (00.0%)	00 (00.0%)	00 (00.0%)	0.4282
0 no disability	04 (26.7%)	25 (62.5%)	61 (63.5%)	90 (59.6%)		14 (50.0%)	76 (61.8%)	90 (59.6%)	
1 minor disability	08 (53.3%)	11 (27.5%)	28 (29.2%)	47 (31.1%)		10 (35.7%)	37 (30.1%)	47 (31.1%)	
2 major disability	03 (20.0%)	04 (10.0%)	07 (7.3%)	14 (9.3%)		04 (14.3%)	10 (08.1%)	14 (09.3%)	
Cog Compos									
N (N Missing)	15 (0)	35 (5)	86 (10)	136 (15)		27 (1)	109 (14)	136 (15)	
Mean (SD)	98.0 (11.9)	98.1 (9.6)	101.5 (11.4)	100.3 (11.1)	0.1035	98.3 (13.5)	100.8 (10.4)	100.3 (11.1)	0.4138
Lang compos									
N (N Missing)	13 (2)	29 (11)	79 (17)	121 (30)		21 (7)	100 (23)	121 (30)	
Mean (SD)	95.1 (10.8)	92.6 (10.5)	95.6 (11.1)	94.8 (10.9)	0.5028	91.7 (11.9)	95.5 (10.7)	94.8 (10.9)	0.1701
Motor compos									
N (N Missing)	14 (1)	31 (9)	82 (14)	127 (24)		24 (4)	103 (20)	127 (24)	
Mean (SD)	89.5 (7.6)	96.1 (12.1)	97.2 (9.4)	96.1 (10.2)	**0.0282**	93.2 (8.4)	96.8 (10.5)	96.1 (10.2)	0.1038
Social compos									
N (N Missing)	10 (5)	19 (21)	75 (21)	104 (47)		17 (11)	87 (36)	104 (47)	
Mean (SD)	96.5 (10.0)	106.3 (18.5)	103.8 (25.0)	103.6 (22.9)	0.3789	103.2 (24.0)	103.6 (22.8)	103.6 (22.9)	0.7543
GAC compos									
N (N Missing)	10 (5)	20 (20)	75 (21)	105 (46)		17 (11)	88 (35)	105 (46)	
Mean (SD)	93.1 (18.8)	100.0 (10.3)	97.0 (24.7)	97.2 (22.1)	0.3871	94.3 (28.3)	97.8 (20.9)	97.2 (22.1)	0.0689

Table 4 Distribution of disability and scores on WPPSI and mABC 2 assessments by year gestational age group and centile neonatal weight at 4 years of age

	Gestational Age					Centile neonatal weight			
	23–25 (N = 13)	26–27 (N = 35)	≥ 28 (N = 79)	Total (N = 127)	P Value	< 10° (SGA) (N = 26)	≥ 10° (AGA) (N = 101)	Total (N = 127)	P Value
Missing	00 (00.0%)	00 (00.0%)	01 (01.3%)	01 (00.8%)		01 (03.8%)	00 (00.0%)	01 (00.8%)	
0 no disability	05 (38.5%)	08 (22.9%)	28 (35.9%)	41 (32.5%)		07 (28.0%)	34 (33.7%)	41 (32.5%)	
1 minor disability	05 (38.5%)	17 (48.6%)	38 (48.7%)	60 (47.6%)		10 (40.0%)	50 (49.5%)	60 (47.6%)	
2 major disability	03 (23.1%)	10 (28.6%)	12 (15.4%)	25 (19.8%)	0.3775	08 (32.0%)	17 (16.8%)	25 (19.8%)	0.2344
ICV - WPPSI									
N (N Missing)	10 (3)	28 (7)	64 (15)	102 (25)		20 (6)	82 (19)	102 (25)	
Mean (SD)	113.6 (8.0)	109.2 (9.9)	115.1 (10.9)	113.3 (10.6)	**0.0170**	113.9 (12.9)	113.2 (10.1)	113.3 (10.6)	0.4777
IVP- WPPSI									
N (N Missing)	10 (3)	28 (7)	67 (12)	105 (22)		20 (6)	85 (16)	105 (22)	
Mean (SD)	107.8 (8.6)	107.6 (16.3)	112.0 (12.8)	110.4 (13.6)	0.1992	110.7 (14.5)	110.4 (13.4)	110.4 (13.6)	0.8959
IVE- WPPSI									
N (N Missing)	10 (3)	28 (7)	67 (12)	105 (22)		20 (6)	85 (16)	105 (22)	
Mean (SD)	81.8 (18.9)	81.0 (15.4)	83.1 (19.3)	82.4 (18.1)	0.8216	83.1 (19.8)	82.2 (17.8)	82.4 (18.1)	0.9381
QI TOT- WPPSI									
N (N Missing)	10 (3)	28 (7)	64 (15)	102 (25)		20 (6)	82 (19)	102 (25)	
Mean (SD)	109.1 (8.5)	107.2 (13.7)	113.5 (13.0)	111.3 (13.0)	**0.0508**	112.4 (14.8)	111.1 (12.6)	111.3 (13.0)	0.6276
DM - mABC									
N (N Missing)	10 (3)	28 (7)	67 (12)	105 (22)		20 (6)	85 (16)	105 (22)	
Mean (SD)	9.9 (4.5)	8.6 (2.8)	11.9 (4.1)	10.8 (4.1)	**0.0013**	11.5 (4.0)	10.7 (4.1)	10.8 (4.1)	0.4270
ME- mABC									
N (N Missing)	10 (3)	26 (9)	66 (13)	102 (25)		20 (6)	82 (19)	102 (25)	
Mean (SD)	6.4 (2.4)	7.8 (3.7)	9.1 (3.7)	8.5 (3.7)	**0.0291**	8.3 (3.5)	8.5 (3.8)	8.5 (3.7)	0.8783
E- mABC									
N (N Missing)	10 (3)	27 (8)	67 (12)	104 (23)		20 (6)	84 (17)	104 (23)	
Mean (SD)	13.8 (5.3)	15.5 (4.7)	16.6 (4.0)	16.1 (4.3)	**0.0499**	16.4 (4.5)	16.0 (4.3)	16.1 (4.3)	0.5170
TOT- mABC									
N (N Missing)	10 (3)	26 (9)	66 (13)	102 (25)		20 (6)	82 (19)	102 (25)	
Mean (SD)	10.6 (4.3)	11.5 (4.1)	14.4 (4.5)	13.3 (4.6)	**0.0031**	13.8 (4.8)	13.2 (4.6)	13.3 (4.6)	0.5812

Definitions: ICV = verbal tests, IVP = ability of logical and abstract reasoning and the ability to organize categories, IVE = processing speed, IQ = intellectual quotient, DM = manual dexterity, ME = aiming and grasping, E = balance

developed impairments at the age of four in 58.4% of cases ($p<0.0001$) (Fig. 2).

Statistical analysis revealed significant correlation between processing speed and manual dexterity with Spearman's coefficient = 0.47 ($p<0.0001$) and between processing speed and aiming and grasping with Spearman's coefficient = 0.27 ($p<0.0001$). Modest processing speed scores also correlated with modest scores in manual dexterity and the ability to aim and grasp (Fig. 3).

Discussion

The results of our study show that the neurodevelopmental assessment at the age of two is not indicative of the neurodevelopmental profile at pre-school age. This is mostly due to poor processing speed which impacts the total cognitive score with WPPSI scales.

We confirm how perinatal clinical history (neonatal sepsis, grade ≥ 3 IVH, BPD, ROP and length of hospitalization) significantly influence the degree of disability

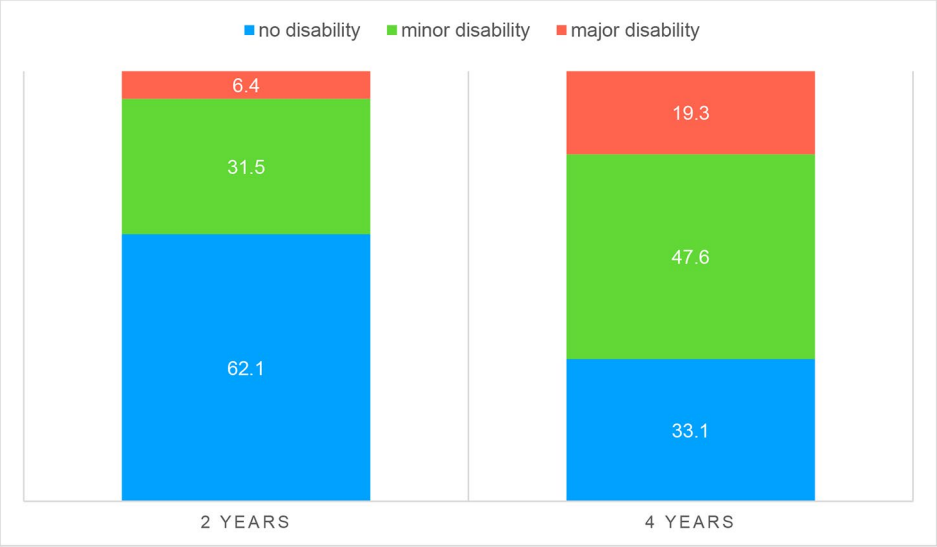

Fig. 2 Disability distribution at 2 and 4 years (n = 124 with both evaluations)

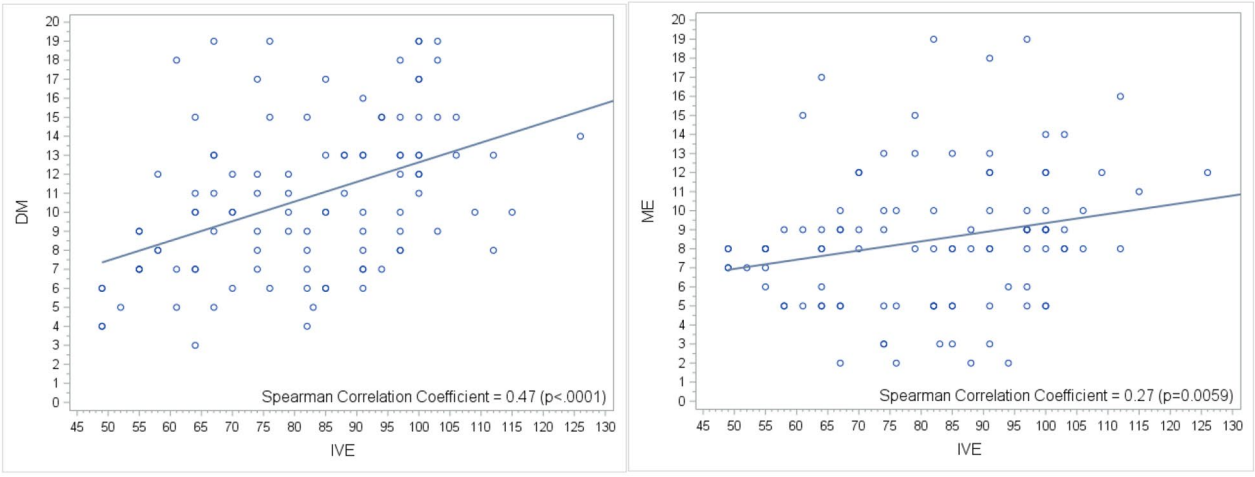

Fig. 3 Correlation between processing speed (IVE) and manual dexterity (DM) (A) processing speed (IVE) and aiming and grasping (ME) (B)

at two years, while at four years the neurodevelopmental outcome is compromised by BPD and the length of hospitalization.

According to our results, Do et al. confirmed that perinatal risk factors became less impacting on disabilities in the long-term, as the environment acquires an even greater influence [19]. In contrast, the study based on the EPIPAGE-2 cohort showed that at five years, only GA correlated with the neurodevelopment outcome [20].

Length of hospital stay and gestational age are strictly related and define the complexity of the perinatal phase. Furthermore, our analysis excluded a correlation between SGA children and neurodevelopmental outcomes, as already extensively described [20].

We demonstrated a clear shift in the incidence of disabilities at the four-year evaluations: about half of children completely free from disability at two years of age, showed a disability related to fine motor skills that impacted an alteration in processing speed at four years. This evidence is confirmed by numerous studies in the literature, however without clarifying the reasons for the increase in disability at preschool age. One study conducted in Taiwan on ~6,000 children, born between 2002 and 2009, found that one-fifth of VLBW preterm children with abnormal neurodevelopmental outcomes at 5 years had normal or borderline neurologic and developmental assessments at 2 years. [21].

In a recent Swedish study as well, 22% of preterm infants, examined at 2.5 years without problems, had cognitive impairments first detected at 6.5 years [22].

We should stress that the use of the Bayley III scales administered to two-year children may not be predictive of the preschool outcome, as it describes the development reached at that time and cannot account for environmental factors or the social and cultural level of the parents, which significantly determines early childhood development [23–26].

Based on stratified results by groups of GA, at two years the motor deficit of the composite type (fine and gross) is related to lower GA and it is confirmed at four years in all the sub scales of mABC 2. This was also reported by a Swedish study, conducted in a cohort of 400 children born at fewer than 27 GA evaluated at 6.5 years: motor coordination disorder was present in 37% and borderline motor function was present in 15%. In these children are more likely to have behavioral and intellectual comorbidity. It is necessary to identify motor disorders correctly as early as possible and reduce the negative impact that they may have for future learning [14]. Moreover, much of the literature over the past ten years has found that fine motor disorders closely affect the quality of life in premature children [27, 28]; for this reason, the need to extend follow-up to at least preschool age is reiterated [11, 24].

In our study, an impaired neurodevelopmental profile was observed as early as age four in children who showed no disability at age two, specifically due to low processing speed leading to a lower total cognitive score on the WPPSI. In fact the processing speed is linked to handling information quickly, along with implications for attention, memory, and academic results. A close correlation was sought between processing speed wih the WPPSI scale and scores with mABC 2 assessments, confirming that low processing speed scores correlate with low scores in manual dexterity, as well as aiming and grasping. This suggests that attentional capacity may not be the primary cognitive problem, but a motor impairment and a difficulty with oculo-motor coordination in the assessment. Children with oculo-motor impairment have less cognitive results and this does not reflect their true abilities. Therefore, for proper assessment of school learning problems, it is necessary to conduct a careful follow-up on all cognitive, motor and behavioral aspects as early as possible to detect the real problem. This allows intervention with appropriate neuropsychological techniques and thus improves school performance.

Strengths and limitations of our study

One limit of the present study is the high number of dropouts due to poor parental adherence or transferring to another venue before the conclusion of the assessment. The strength is a standardized follow-up program for national and international recommendations and stable professional roles, reducing individual variability in the evaluation itself.

Conclusions

Alterations in the fine motor profile (oculo-motor coordination, hand coordination, grasp and fine movement) may limit the expression of cognitive abilities and the achievement of expected academic results and cause behavioral disorders, typical of premature births. This study reiterates the need for careful and prolonged follow-up at least until pre-school age, to identify developmental abnormalities correctly, so that proper treatment can be started as early as possible.

Abbreviations

AGA	Adequate for Gestational Age
BPD	Bronchopulmonary Dysplasia
CESC	Clinical Trials Ethics Committee
GA	Gestational Age
GMFCS	Gross Motor Function Classification System
DCD	Motor Coordination Disorder
E	Balance
EOS	Early Onset Sepsis
ICV	Verbal Compréhension Index
IQ	Intelligence Quotient
IVE	Processing Speed Index
IVH	Intraventricular Hemorrhage
IVP	Performance Speed index
LOS	Late Onset Sepsis
mABC	Movement Assessment Battery for Children
ME	Aiming and Grasping
MD	Manual Dexterity
NEC	Necrotizing Enterocolitis
NICU	Neonatal Intensive Care Unit
PDA	Patent Ductus Arteriosus
PVL	Periventricular leukomalacia
ROP	Retinopathy of prematurity
SD	Standard Deviation
SGA	Small for Gestational Age
VLBWIs	Very Low Birth Weight Infants
WPPSI	Wechsler Preschool Primary Scale Intelligence

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Authors' contributions

N.B. conceptualized and designed the study, drafted the initial manuscript, and revised the manuscript; C.B., F.DO. A.G. and P.L. led the data acquisition and interpretation; AC.F. made statistical analysis and revised the manuscript; C.B., F.DO. A.G and P.L. made substantial contributions to the conception of the study, interpretation of the data, and reviewed the manuscript. All authors have read and agreed to the published version of the manuscript.

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Data Availability

The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was conducted in accordance with the Declaration of Helsinki and approved by the Clinical Trials Ethics Committee (CESC) of the Azienda ULSS2 Marca Trevigiana, No. 958 / CE Brand. Written informed consent was obtained from the parents of enrolled children.

Consent for publication
Written informed consent for data publication was obtained from the parents of enrolled children.

Competing interests
All of the authors had no personal, financial, commercial, or academic conflicts of interest separately.

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References

1. Ream MA, Lehwald L. Neurologic consequences of Preterm Birth. Curr Neurol Neurosci Rep. 2018 Jun;18(8):48.
2. Younge N, Goldstein RF, Bann CM, Hintz SR, Patel RM, Smith PB, et al. Survival and neurodevelopmental outcomes among Periviable Infants. N Engl J Med. 2017;Feb16376(7):617–28.
3. Barfield WD. Public Health Implications of very Preterm Birth. Clin Perinatol. 2018 Sep;45(3):565–77.
4. Pascal A, Govaert P, Oostra A, Naulaers G, Ortibus E, Van den Broeck C, et al. Neurodevelopmental outcome in very preterm and very-low-birthweight infants born over the past decade: a meta-analytic review. Dev Med Child Neurol. 2018 Apr;60(4):342–55.
5. Follow up Care of High-Risk Infants. Pediatrics. 2004;114(supplement5):1377–97. http://pediatrics.aappublications.org/content/114/Supplement_5/1377.full.html.
6. Allotey J, Zamora J, Cheong-See F, Kalidindi M, Arroyo-Manzano D, Asztalos E, et al. Cognitive, motor, behavioral and academic performances of children born preterm: a meta-analysis and systematic review involving 64061 children. BJOG. 2018 Jan;125(1):16–25.
7. Delobel-Ayoub M, Arnaud C, White-Koning M, Casper C, Pierrat V, Garel M, et al. Behavioral problems and cognitive performance at 5 years of age after very preterm birth: the EPIPAGE Study. Pediatrics. 2009 Jun;123(6):1485–92.
8. Kaul F, Johansson Y, Månsson M, Stjernqvist J, Farooqi K, Serenius A. Cognitive profiles of extremely preterm children: full-scale IQ hides strengths and weaknesses. Acta Paediatr. 2021 Jun;110(6):1817–26.
9. Ahn D-H, Min A, Kim K, Kim KA, Oh MY, Lee HJ, et al. Cognitive function, emotional and behavioral problems, and temperament of premature children. Soa Chongsonyon Chongsin Uihak. 2019;Jan130(1):34–41.
10. Bos AF, Van Braeckel KNJA, Hitzert MM, Tanis JC, Roze E. Development of fine motor skills in preterm infants. Dev Med Child Neurol. 2013 Nov;55 Suppl4:1–4.
11. Schnider B, Disselhoff V, Held U, Latal B, Hagmann CF, Wehrle FM. Executive function deficits mediate the association between very preterm birth and behavioral problems at school-age. Early Hum Dev 2020 Jul; 146:105076.
12. Akazawa K, Chang L, Yamakawa R, Hayama S, Buchthal S, Alicata D, et al. Probabilistic maps of the white matter tracts with known associated functions on the neonatal brain atlas: application to evaluate longitudinal developmental trajectories in term-born and preterm-born infants. NeuroImage. 2016 Mar;128:167–79.
13. Marlow N, Wolke D, Bracewell MA, Samara M, EPICure Study Group. Neurologic and developmental disability at six years of age after extremely preterm birth. N Engl J Med. 2005;Jan6(1):9–19.
14. Bolk J, Farooqi A, Hafström M, Åden U, Serenius F. Developmental Coordination Disorder and its Association with Developmental Comorbidities at 6.5 years in apparently healthy children born extremely Preterm. JAMA Pediatr. 2018;Aug1172(8):765–74.
15. Duncan AF, Matthews MA. Neurodevelopmental outcomes in early childhood. Clin Perinatol. 2018 Sep;45(3):377–92.
16. Tooley UA, Bassett DS, Mackey AP. Environmental influences on the pace of brain development. Nat Rev Neurosci. 2021 Jun;22(6):372–84.
17. Cheong JLY, Burnett AC, Treyvaud K, Spittle AJ. Early environment and long-term outcomes of preterm infants. J Neural Transm (Vienna). 2020 Jan;127(1):1–8.
18. Williams J, Lee KJ, Anderson PJ. Prevalence of motor-skill impairment in preterm children who do not develop cerebral palsy: a systematic review. Dev Med Child Neurol. 2010 Mar;52(3):232–7.
19. Do CHT, Kruse AY, Wills B, Sabanathan S, Clapham H, Pedersen FK, et al. Neurodevelopment at 2 years corrected age among vietnamese preterm infants. Arch Dis Child. 2020 Feb;105(2):134–40.
20. Larroque B, Ancel P-Y, Marret S, Marchand L, André M, Arnaus C, et al. Neurodevelopmental disabilities and special care of 5-year-old children born before 33 weeks of gestation (the EPIPAGE study): a longitudinal cohort study. Lancet. Mar 2008;8(9615):813–20.
21. Lin C-Y, Hsu C-H, Chang J-H. Neurodevelopmental outcomes at 2 and 5 years of age in very-low-birth-weight preterm infants born between 2002 and 2009: a prospective cohort study in Taiwan. Pediatr Neonatol. 2020 Feb;61(1):36–44.
22. Kaul YF, Naseh N, Strand Brodd K, Böhm B, Holmström G, Hellström-Westas L. Average 2.5-year neurodevelopmental test results in children born very preterm did not rule out cognitive deficits at 6.5 years of age. Acta Paediatr. 2021 Mar;110(3):846–54.
23. Kilbride HW, Aylward GP, Doyle LW, Singer LT, Lantos J. Prognostic neurodevelopmental testing of preterm infants: do we need to change the paradigm? J Perinatol. 2017 May;37(5):475–9.
24. Pascal A, Govaert P, Oostra A, Naulaers G, Ortibus E, Van den Broek C. Neurodevelopmental outcome in very preterm and very-low-birthweight infants born over the past decade: a meta-analytic review. Dev Med Child Neurol. 2018 Apr;60(4):342–55.
25. Spittle AJ, Spencer-Smith MM, Eeles AL, Lee KJ, Lorefice LE, Anderesen PJ, et al. Does the Bayley-III Motor Scale at 2 years predict motor outcome at 4 years in very preterm children? Dev Med Child Neurol. 2013 May;55(5):448–52.
26. Wong HS, Edwards P. Nature or nurture: a systematic review of the effect of socio-economic status on the developmental and cognitive outcomes of children born preterm. Matern Child Health J. 2013 Nov;17(9):1689–700.
27. Feder KP, Majnemer A, Bourbonnais D, Platt R, Blayney M, Synnes A. Handwriting performance in preterm children compared with term peers at age 6 to 7 years. Dev Med Child Neurol. 2005 Mar;47(3):163–70.
28. Shih H-N, Tsai W-H, Chang S-H, Lin C-Y, Hong R-B, Hwang Y-S. Chinese handwriting performance in preterm children in grade 2. PLoS ONE. 2018;Jun19(6):e0199355.

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